Non-Melanoma Skin Cancer

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I have no relevant conflicts of interest

Overview

- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC)
  - Incidence
  - Risk Factors
  - Clinical Presentation
  - Treatment

Non-melanoma skin cancer

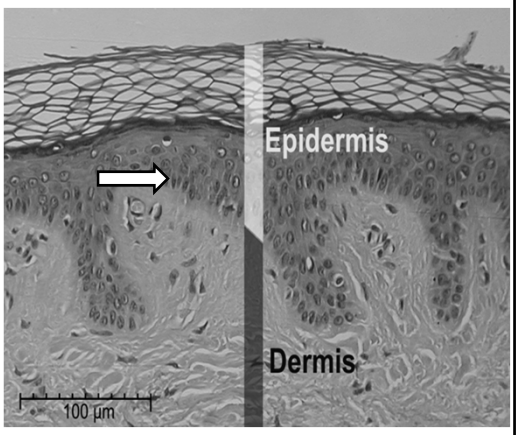
BCC/SCC and "Other" Tumors (Non-inclusive list)

- Atypical fibroxanthoma
- Dermatofibrosarcoma protuberans
- Microcystic adnexal carcinoma
- Merkel cell carcinoma
- Extramammary Paget's Disease
- Superficial cutaneous leiomyosarcoma
- Other apocrine and eccrine neoplasms

Basal Cell Carcinoma (BCC)

Basal Cell Carcinoma: Background

- Derived from non-keratinizing cells of the basal layer of the epidermis
- Is the most common skin cancer (4:1 SCC; 20:1 melanoma)
- Generally grows slowly
- If allowed to remain on the skin can become locally destructive
- Rarely metastasize



Basal Cell Carcinoma: Epidemiology

- The most common malignancy
- Rogers HW et al. Arch Dermatol, 2010
  - Estimated that 3.5 million non-melanoma skin cancers (NMSC) occurred in 2.5 million individuals in the United States in 2006
- 75-80% of NMSC are BCC (≈2.8 million)
- 20-25% of NMSC are SCC (≈0.7 million)
- Estimated lifetime risk of BCC in the white population is 33–39% for men and 23–28% for women.

Basal Cell Carcinoma: Risk Factors

- Ultraviolet light (UVL) exposure
- Male sex
- Light hair and eye color
- Northern European ancestry
- Inability to tan

Basal Cell Carcinoma: Pathogenesis

- Sun exposure
- Personal history of non-melanoma skin cancer
- Family history of non-melanoma skin cancer
- Skin type
- Gene Mutations
- Exposure to artificial UV light
- Immunosuppression
- Ionizing radiation
- Arsenic
- Genetic syndromes (Nevoid basal cell carcinoma syndrome, Bazex syndrome, etc.)

⇦ After initial skin cancer diagnosis, the risk of developing another BCC
  At 3 years is 30%
  At 5 years is 50%

BCC: Pathogenesis – Sun exposure

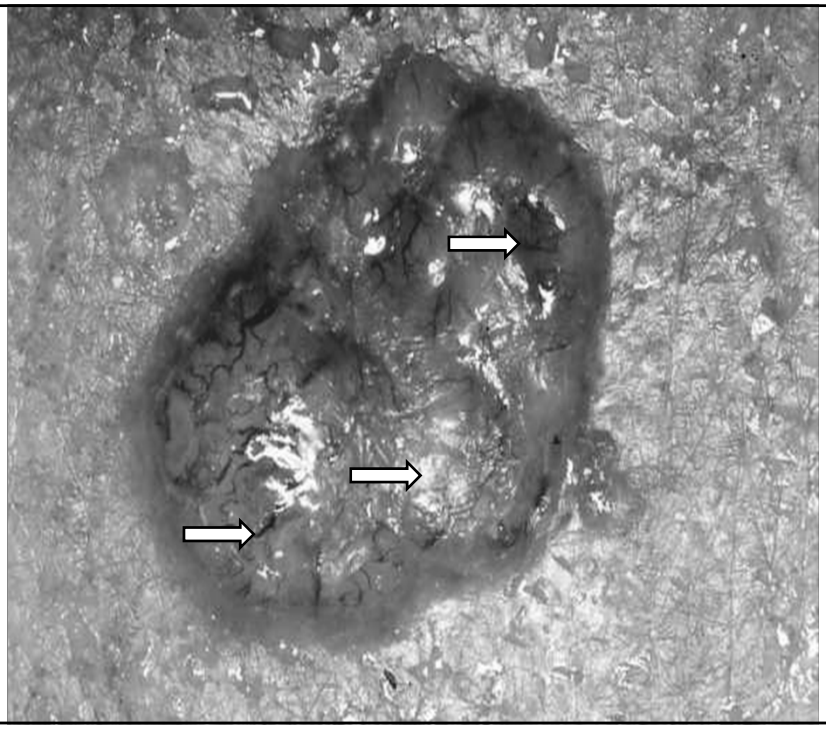
- Key etiologic agent
- Particularly UVB spectrum (290nm-320nm)
  - Induces mutations in tumor suppressor genes
  - Some studies suggest intense periods of light exposure can be particularly damaging
- Increased rates seen in tanning bed users and those who receive iatrogenic light therapy (PUVA)

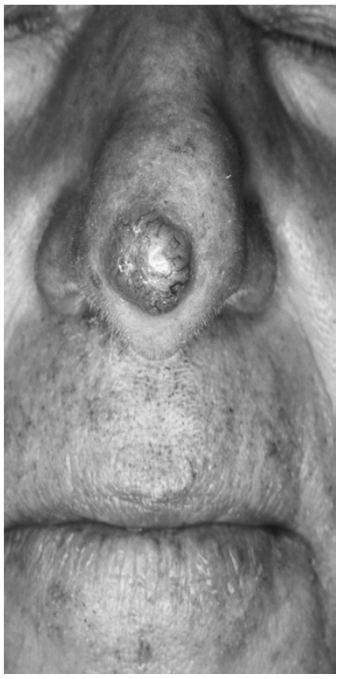
Basal Cell Carcinoma: Clinical Presentation

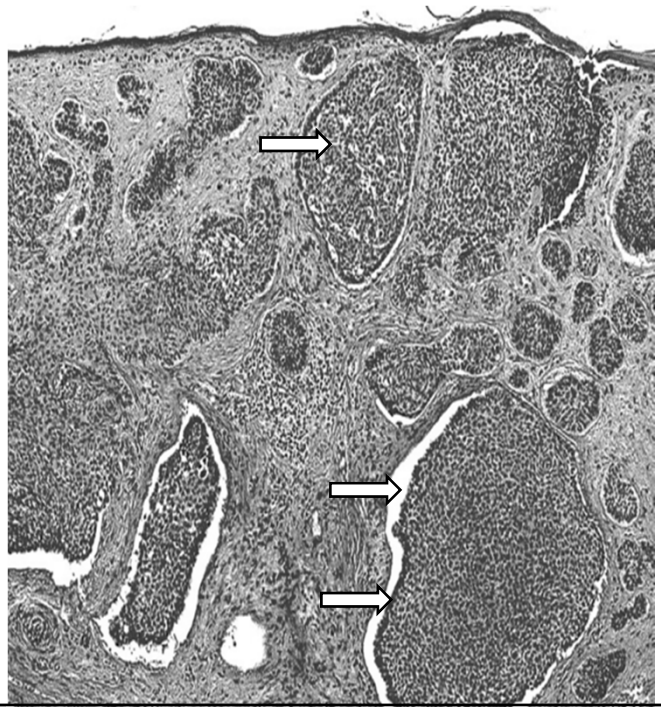
- Lesion that bleeds easily
- Lesion that does not heal
- Oozing or crusting spots in a lesion
- Scar-like lesion without having injured the area
- Irregular blood vessels in or around the lesion

Basal Cell Carcinoma: Nodular Type

- Approximately 50% of all BCC
- Primarily on the head and neck
- Key to clinical diagnosis:
  - Arborizing telangiectasias
  - Pearly luminescence
  - Ulcerate when larger
  - Bleed easily
- May have brown, blue, purple color (pigmented BCC)

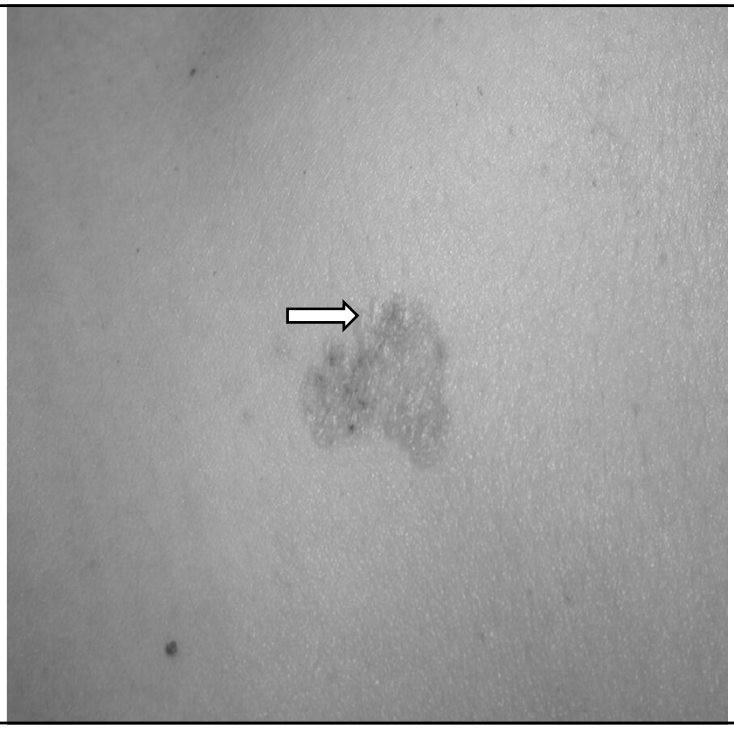


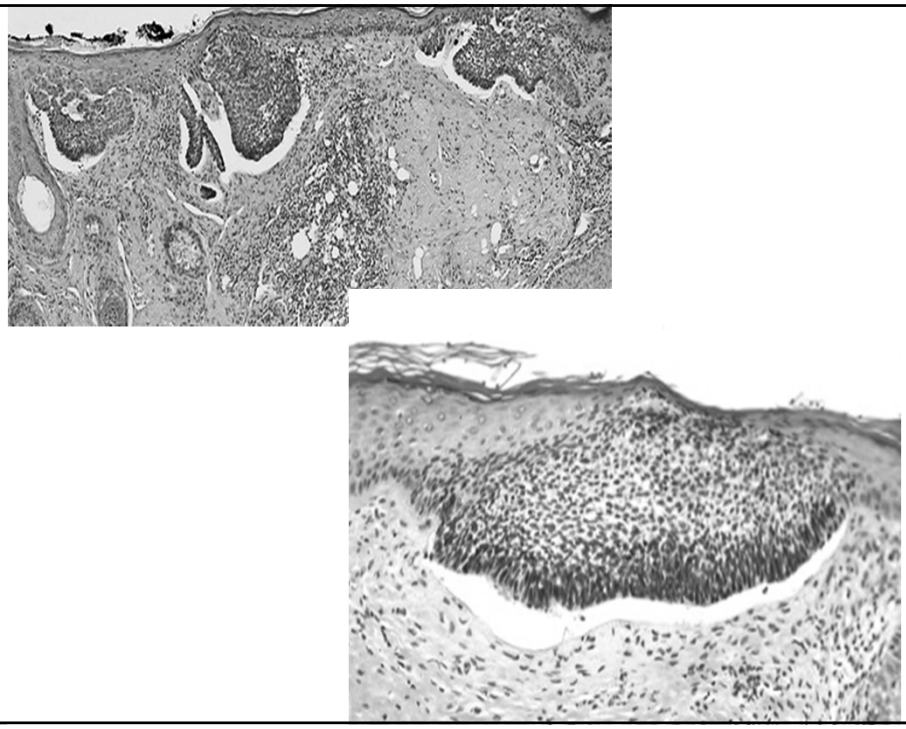




Basal Cell Carcinoma: Superficial Type

- More frequently on the trunk and extremities
- Often confused with eczema, psoriasis, or tinea in its early stages
- Keys to clinical diagnosis:
  - Pink plaque non-responsive to standard interventions
  - Thread like border that has characteristic clinical finding of BCC

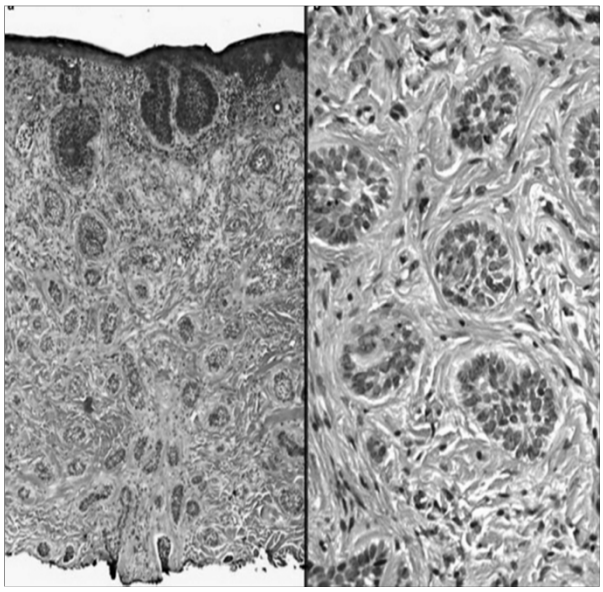


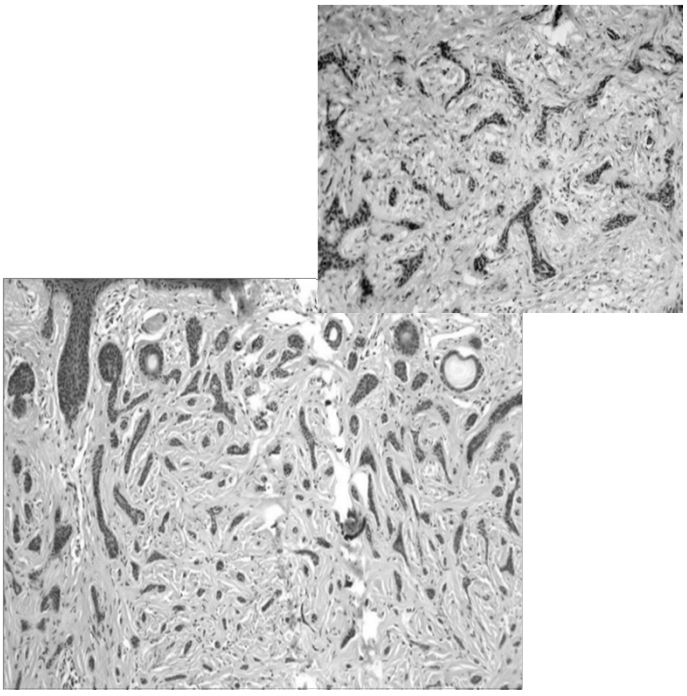


Basal Cell Carcinoma: Morpheaform and Micronodular Type

- Morpheaform BCC
  - Often presents as a pink to ivory plaque
  - A more difficult clinical diagnosis
- Micronodular BCC
  - May present as macules, papules or slightly elevated plaques
  - May be difficult to differentiate from nodular BCC

- **Main issue with both subtypes is subclinical spread

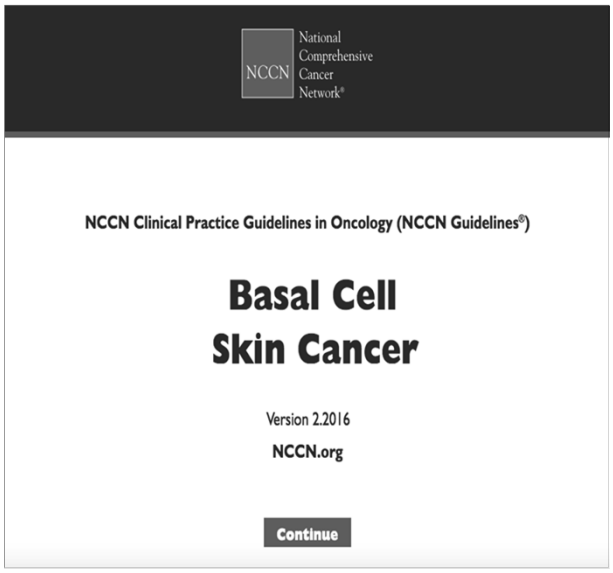




Basal Cell Carcinoma: Biological Behavior

- Local Invasion
  - Generally a slow growing tumor
  - Rate of doubling estimated between 6 and 12 months
- Metastasis
  - Occurs only rarely; rates varying from 0.0028% to 0.55%
  - Lymph nodes and lung were the most common sites involved

Basal Cell Carcinoma: Treatment



BCC: Current Treatment Options

- **Standard Excision**
- **Curettage with electrodessication**
- **Curettage alone**
- **Curettage with topical therapy**
- **Cryosurgery**
- **Photodynamic therapy**
- **Ablative laser (continuous CO2)**
- **Imiquimod**
- **Intralesional interferon-α-2b**
- **Mohs Micrographic Surgery**
- **Vismodegib**

BCC: Risk Factors for Recurrence

H&P	Low Risk	High Risk
Location/Size	Area L < 20mm Area M < 10mm Area H < 6mm	Area L > 20mm Area M > 10mm Area H > 6mm
Borders	Well defined	Poorly defined
Primary vs Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Pathology		
Subtype	Nodular, superficial	Aggressive growth pattern*
Perineural involvement	(-)	(+)

Area H = Mask areas of the face (central face, eyelids, eyebrows, periorbital, nose, lips (cutaneous and vermillion), chin, mandible, preauricular, and postauricular skin/sulci, temple, ear), genitalia, hands, and feet
Area M = cheeks, forehead, scalp, and neck
Area L = trunk and extremities
*** Morpheaform, sclerosing, or micronodular features in any portion of the tumor**

BCC: Current Treatment Options

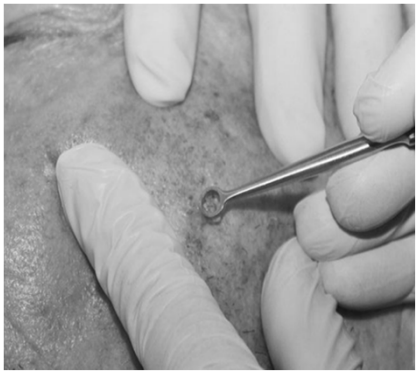
- The goal of primary treatment of basal cell skin cancer:
  ① Cure of the tumor
  ② Maximal preservation of function
  ③ Maximal preservation of cosmesis
  ④ Cost

Surgical Excision for BCC

- The most common treatment modality for BCC
- Reported 5-year recurrence rates of 3.2 – 10% for primary BCC, and 17% for recurrent BCC
- Rowe et al, J Dermatol Surg Oncol, 1989
  - Reviewed all studies on BCC treatment from 1947 to 1989 (included 106 studies)
- General margin is 4mm
  - For non-high risk BCC; for larger BCC (>2cm) the appropriate margin is so variable it is difficult to make a margin recommendation

Basal Cell Carcinoma: Electrodessication and Curettage

- **Good for:**
  - **Well defined BCC**
  - **Areas with low risk for recurrence**
- **Advantages**
  - **High clearance rate in appropriate BCCs**
  - **Fast, no suture removal**
- **Disadvantages**
  - **If extends to subcutaneous tissue, must perform excisional procedure**
  - **Potentially more apparent scar**
  - **No margin assessment**



BCC: 5-year cure rates for primary BCC, Meta-analysis

Treatment Modality	5-year cure rate* ^
Surgical excision	90%
Electrodessication and curettage	92%
Radiation	91%
Cryotherapy	92%
All non-MMS	91%
MMS	99%

***Rowe DE, Carroll RJ, Day LC: Long-term recurrence rates in previously untreated (primary) basal cell carcinoma – implications for patient follow-up. J Dermatol Surg Oncol 1989; 15:315-328.**
^The 5-year cure rates for recurrent BCC was 90-92% with MMS, and 80% with all non-MMS modalities

Basal Cell Carcinoma: Mohs Surgery Pivotal BCC Treatment Papers

- "Basal Cell Carcinoma Treated with Mohs Surgery"
  - Leibovitch I et al, *J Amer Acad Dermatol*, 2005
  - Prospective multicenter interventional case series
  - 3370 patients completed the 5 year follow-up
  - Primary outcome measure: Recurrence @ 5 years
  - Recurrence, Primary tumors: 1.4%
  - Recurrence, Recurrent tumors: 4%

Basal Cell Carcinoma: Mohs Surgery Pivotal BCC Treatment Papers

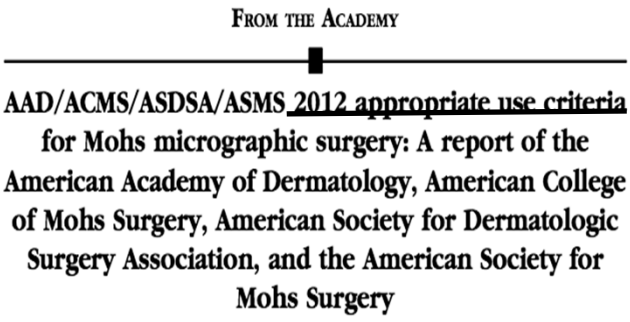
- There are several large or prospective studies that have looked at MMS for BCC

Table VII. Comparative clinical and 5-year recurrence data on Mohs micrographic surgery for basal cell carcinoma

	Mohs [25,26]	Robins [27]	Julian and Bowers [28]	Current Study
Study years	NA	1965-1980	1981-1995	1993-2002
Tumor location	Head	Head	Head	Mainly head and neck
Overall No. of tumors with 5-y follow-up (primary/secondary)	8643 (7257/1386)	2960 (NA)	228 (NA)	3370 (1886/ 1484)
Overall 5-y recurrence (primary/secondary)	1.0% (0.7%/3.2%)	2.6% (1.8%/3.4%)	3.8% (1.7%/4.8%)	2.6% (1.4%/ 4.0%)
NA, Not available				

BCC: Treatment

- **The higher cure rates associated with MMS could likely be applied to all BCCs; however, from a practical standpoint, low-risk BCCs are generally well managed with non-MMS modalities**



FROM THE ACADEMY

AAD/ACMS/ASDSA/ASMS 2012 appropriate use criteria for Mohs micrographic surgery: A report of the American Academy of Dermatology, American College of Mohs Surgery, American Society for Dermatologic Surgery Association, and the American Society for Mohs Surgery

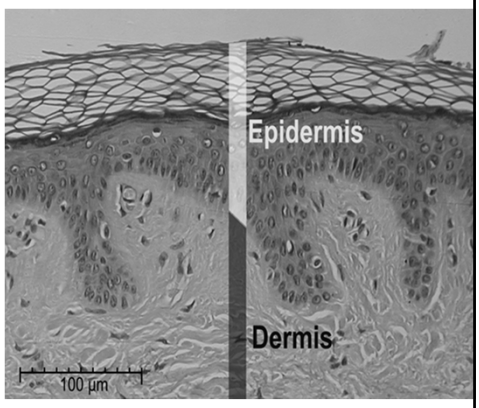
BCC: Key Points

- **The most common malignancy in humans**
- **Multifactorial in origin**
- **If left without treatment, can be very destructive**
- **Many treatment modalities available, and appropriate patient selection will deliver most effective care**

Cutaneous Squamous Cell Carcinoma (cSCC)

cSCC: Background

- Malignancy arising from epithelial keratinocytes
- Second most common cutaneous malignancy behind BCC
- Incidence is increasing



cSCC: Epidemiology

- The second most common cutaneous malignancy
- Rogers HW et al. Arch Dermatol, 2010
  - Estimated that 3.5 million non-melanoma skin cancers (NMSC) occurred in 2.5 million individuals in the United States in 2006
- 75-80% of NMSC are BCC (≈2.8 million)
- 20-25% of NMSC are SCC (≈0.7 million)

cSCC: Epidemiology

- Incidence is increasing
  - 1976 to 1989: incidence was 39 per 100,000 in women and 63 per 100,000 in men in the United States
  - 1990 to 1992: incidence was 100 per 100,000 for women and 191 per 100,000 for men in the United States
  - Possible factors:
    - increased UV exposure, ozone depletion
    - increased prevalence of human papillomavirus (HPV)
    - ionizing radiation
    - genetics
    - immunosuppression

cSCC: Pathogenesis, UV exposure

- Cumulative sun exposure is believed to be the most important factor contributing to the development of SCC
  - Majority of SCCs occurring on sun-exposed skin
- Incidence doubles with every 8-10 degree decline in latitude in high-risk populations
- UVB (290–320 nm) is more carcinogenic in SCC development than is UVA (320–400 nm)
  - majority of UVB-induced damage to DNA is repaired
  - Xeroderma pigmentosa patients have defective excision repair mechanisms of thymidine dimer base pairs and therefore display greater photosensitivity and higher incidence of SCC development.

cSCC: Pathogenesis, Other factors

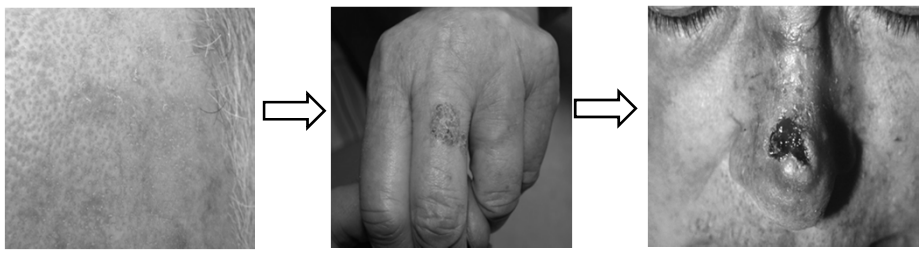
- Myriad of other risk factors
- Chronic dermatoses, chronic scars, and exogenous chemicals
- Personal and family history of SCC
- Human Papillomavirus
  - Inhibits p53 tumor suppressor gene
  - May also inhibit cell apoptosis
  - Estimated to be involved in the pathogenesis of up to 90% of NMSCs in immunocompromised individuals and up to 50% of NMSCs in immunocompetent individuals

cSCC: Pathogenesis, Immunosuppression

- Many forms off immunosuppression lead to increased rates of NMSC, particularly SCC
- Of particular concern are solid organ transplant (SOT) patients
  - SCC:BCC ratio in normal population is 1:4
  - SCC:BCC ratio in SOT is 4:1
  - Amount of immunosuppression is important
    - Highest rates in heart transplant patients
  - Type of immunosuppression is important
    - Higher rates with azathioprine than cyclosporine

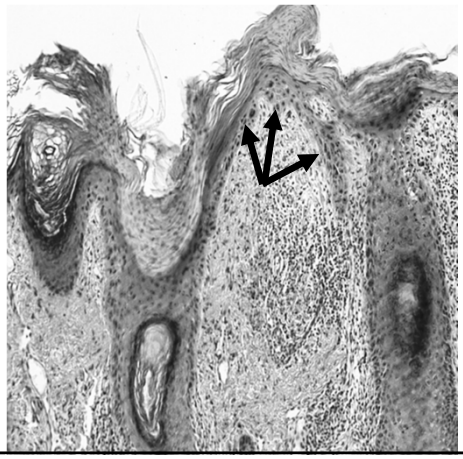
cSCC: Clinical Presentation

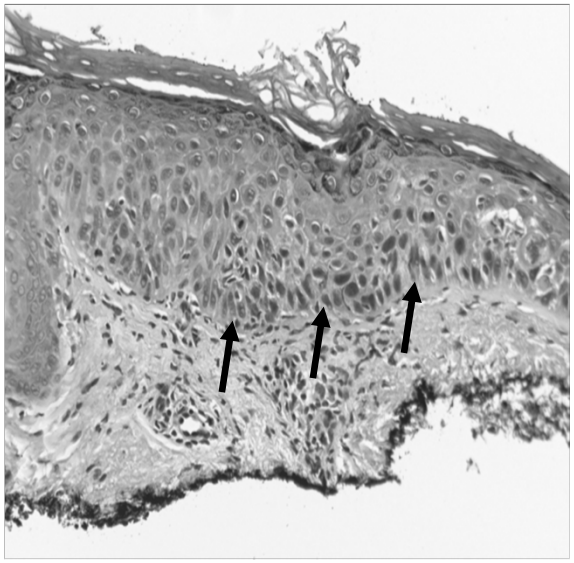
- Presents with a variety of clinical features
  - Can range from indolent to very aggressive
- Progression from actinic keratosis to squamous cell carcinoma in situ (SCCIS) to invasive squamous cell carcinoma (SCC)
  - Many invasive SCC are believed to evolve de novo



cSCC: Actinic Keratoses

- **Atypical proliferation of keratinocytes at the basal layer (lowest layer) of the epidermis**

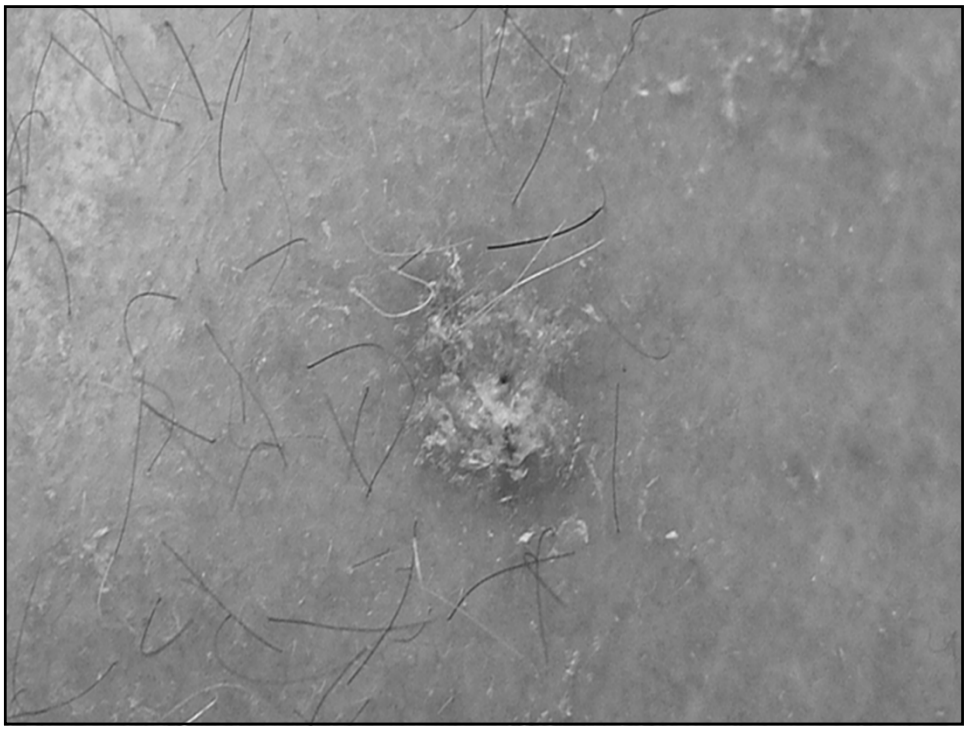




cSCC: Actinic Keratoses

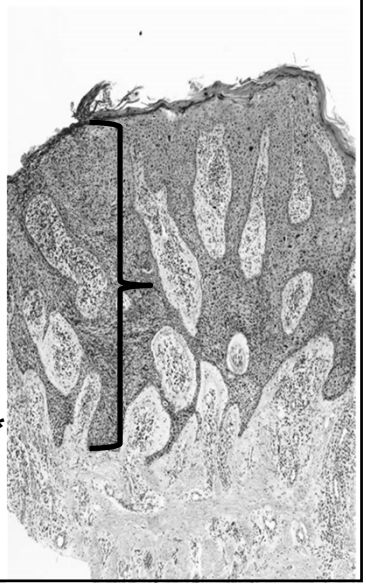
- More acceptance that these can be precursor lesion to SCCIS and SCC
- Controversy about rate of transformation
  - Difficult to assess in a controlled trial
  - One study show a per year transformation rate of 0.075% to 0.096% per lesion per year
    - Thus, patient with 7.7 AKs, average number for an affected person, invasive SCC would develop at a rate of 10.2% over 10 years if left untreated*

*Reviewed in Fu W, Cockerell CJ. The actinic (solar) keratosis: a 21st-century perspective. Arch Dermatol. 2003 Jan;139(1):66-70.

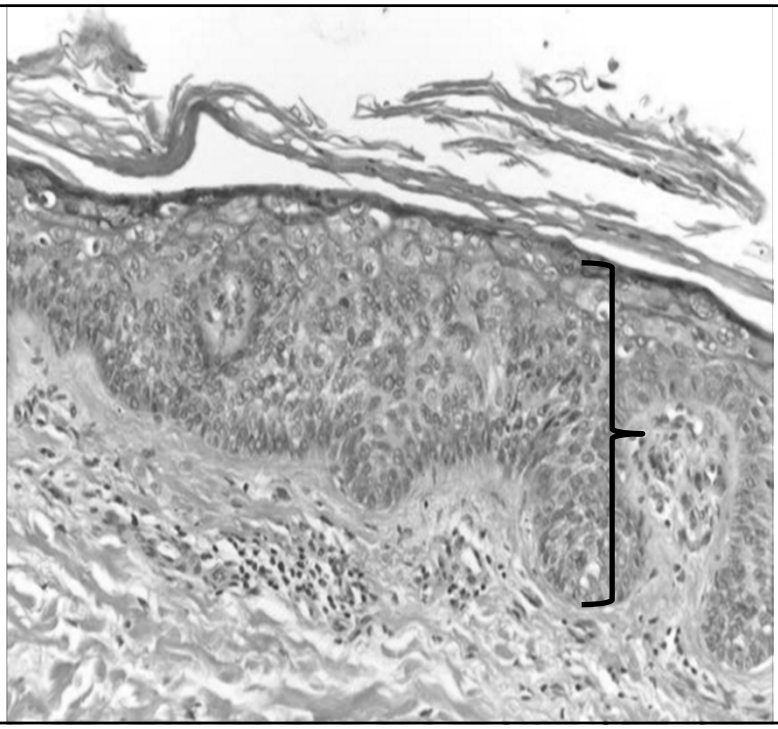


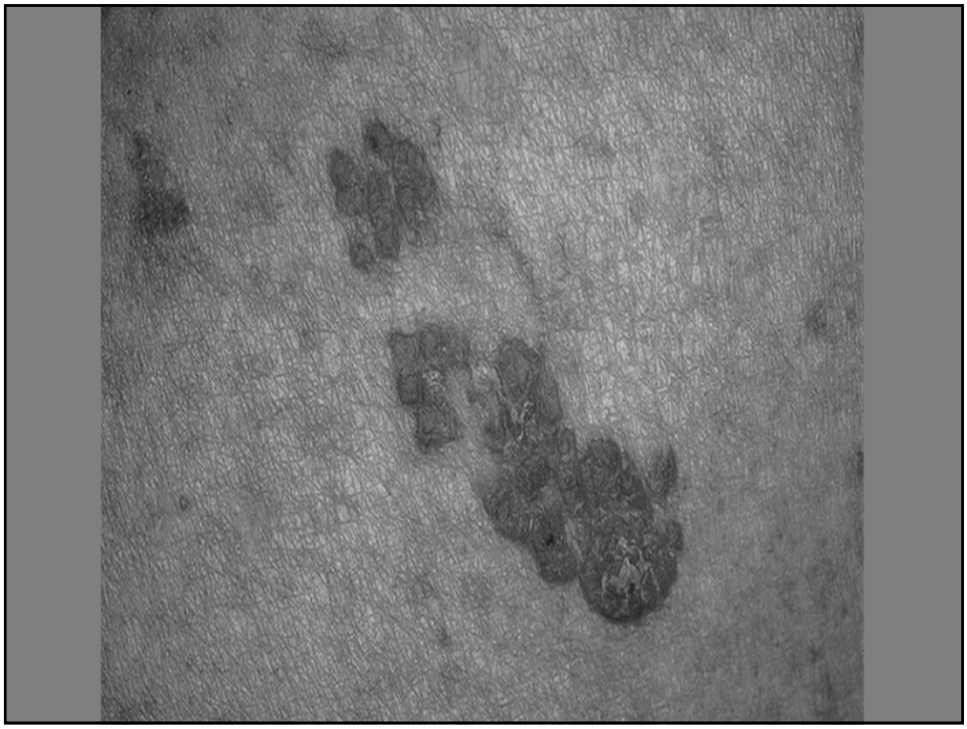
cSCC: Squamous Cell Carcinoma In-Situ (SCCIS)

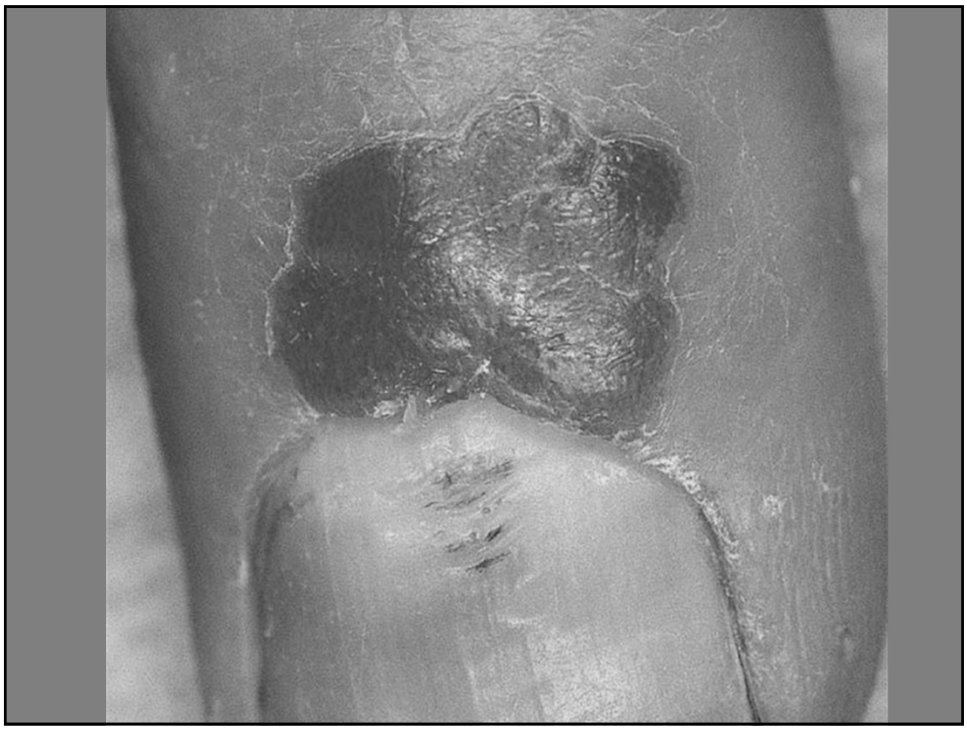
- Also known as Bowen's Disease
- Proliferation of atypical keratinocytes throughout the epidermis
- May arise from an AK or de novo
- Rate of transformation estimated to be between 3-8%*



*Cox NH, Eedy DJ, Morton CA; Therapy Guidelines and Audit Subcommittee, British Association of Dermatologists. Guidelines for management of Bowen's disease: 2006 update. Br J Dermatol. 2007 Jan;156(1):11-21.

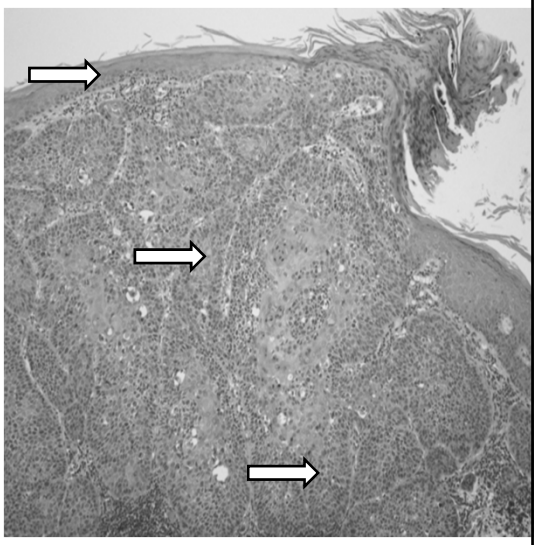






cSCC: Invasive Squamous cell carcinoma (SCC)

- Malignant proliferation of keratinocytes that involves the dermis
- May develop from AK, SCCIS or de-novo

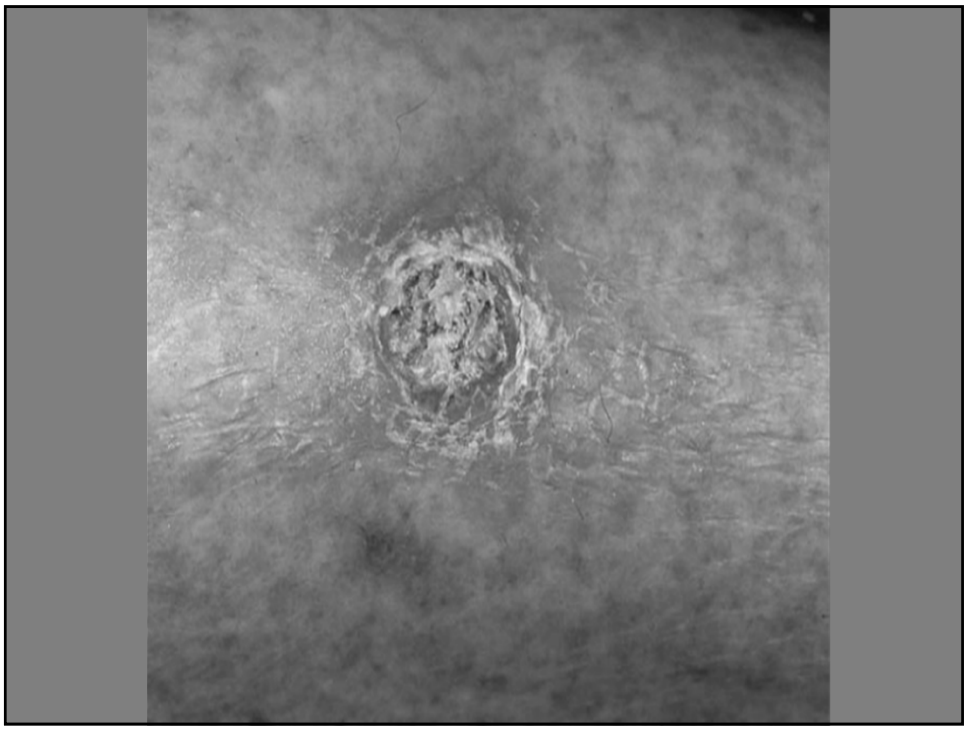


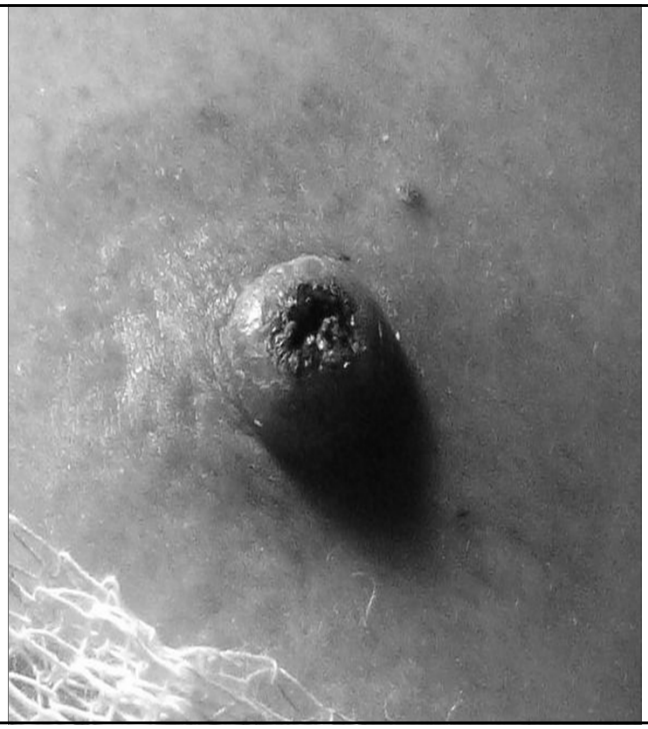
cSCC: Invasive Squamous cell carcinoma (SCC)

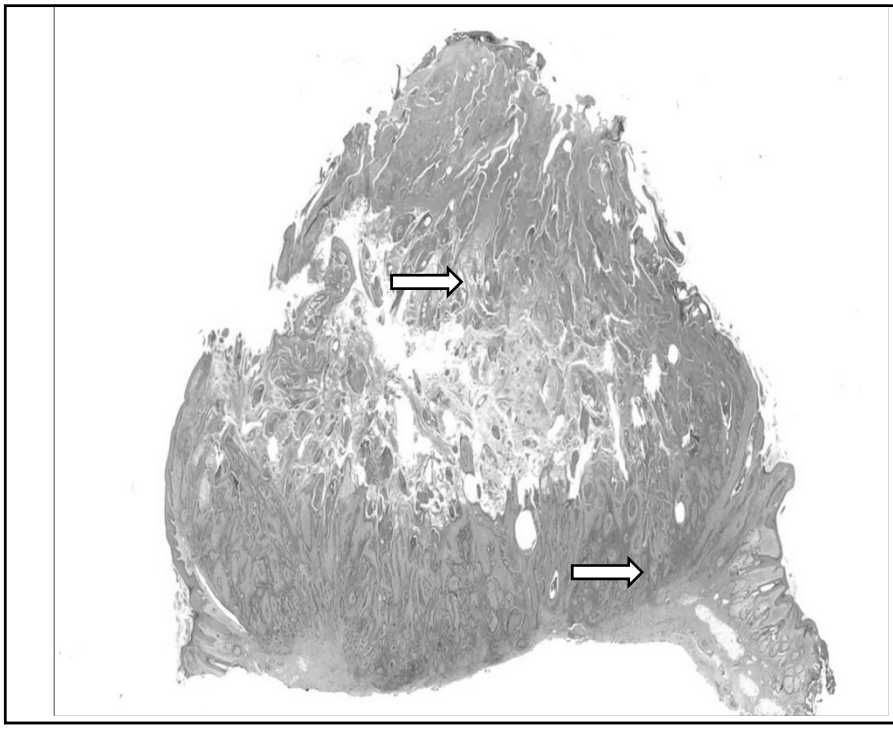
- Particular sites carry certain risks
  - Higher metastasis rate of SCC on the lip, ear, and temple
  - Periungual SCC have higher local recurrence rates, but low metastatic rates
  - Marjolin's Ulcer (SCC in a chronic wound) have higher metastasis rates
- A few of the subtypes
  - Keratoacanthoma
    - Characterized by rapid growth, and involution in some instances
  - Verrucous Carcinoma
    - Buschke–Löwenstein tumor, epithelioma cuniculatum, Ackerman tumor
    - Related to HPV types 6 and 11
    - Considered a low grade SCC; anaplastic change has been seen with radiation

cSCC: Invasive Squamous cell carcinoma (SCC)

- **Clinical findings:**
  - **Can present as keratotic, non-healing papules, plaques or nodules**
  - **Most commonly on sun exposed skin**
  - **SCC-Keratoacanthoma type presents as a nodule with a central keratotic core**







cSCC: Staging

- **For SCC, the rate of Local Recurrence and Metastasis must be considered**
- **Most patients have a low risk for lymph node or distant metastasis**
- **If at a high-risk for these, consideration for further work-up considered**
  - **Lymph node evaluation**
  - **Imaging**

Risk Factors for Cutaneous Squamous Cell Carcinoma Recurrence, Metastasis, and Disease-Specific Death A Systematic Review and Meta-analysis

Agnieszka K. Thompson, MD; Benjamin F. Kelley, MD; Larry J. Prokop, MLS; M. Hassan Murad, MD, MPH; Christian L. Baum, MD

Outcome	Risk Factor	No. of Studies	Risk Ratio	(95% CI)	*P* Value
Metastasis	Invasion beyond subcutaneous fat	5	11.21	3.59-34.97	<.01
	Breslow thickness >2 mm	3	10.76	2.55-45.31	<.01
	Breslow thickness >6 mm	2	6.93	4.02-11.94	<.01
	Diameter >20 mm	8	6.15	3.56-10.65	<.01
	Poor differentiation	18	4.98	3.30-7.49	<.01
	PNI	12	2.95	2.31-3.75	<.01
	Temple	7	2.82	1.72-4.63	<.01
	Ear	13	2.33	1.67-3.23	<.01
	Lip	13	2.28	1.54-3.37	<.01
	Immunosuppression	6	1.59	1.07-2.37	.02
	Cheek	5	1.30	0.61-2.77	.49

JAMA Dermatol. **2016;152(4):419-428. doi:10.1001/jamadermatol.2015.4994.**

Table 3. Summary of the AJCC, UICC, and BWH Tumor Staging Systems[a]

Tumor Staging System	Definition
AJCC	
T1	Tumor ≤2 cm in greatest dimension, with <2 high-risk factors[b]
T2	Tumor >2 cm in greatest dimension or with ≥2 high-risk factors[b]
T3	Tumor with invasion of orbit, maxilla, mandible, or temporal bones
T4	Tumor with invasion of other bones or direct perineural invasion of skull base
UICC	
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm in greatest dimension
T3	Tumor with invasion of deep structures (eg, muscle, cartilage, bone [excluding axial skeleton], orbit)
T4	Tumor with invasion of axial skeleton or direct perineural invasion of skull base
BWH	
T1	0 High-risk factor[c]
T2a	1 High-risk factor
T2b	2-3High-riskfactors
T3	≥4 High-risk factors or bone invasion

Abbreviations: AJCC, American Joint Committee on Cancer; BWH, Brigham and Women's Hospital; T, tumor stage from TNM staging system; UICC, Union for International Cancer Control.

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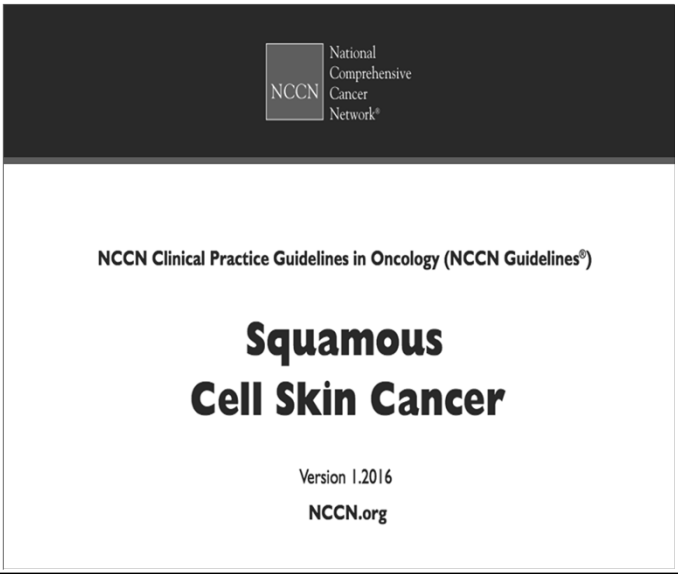
Squamous Cell Carcinoma: Treatment



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- Photodynamic therapy
- Radiation therapy
- Imiquimod/topical chemotherapeutics
- Intralesional fluorouracil or methotrexate (KA subtype)
- Mohs Micrographic Surgery
- Oral chemotherapy

SCC: Current Treatment Options

- The goal of primary treatment of squamous cell skin cancer:

① Cure of the tumor

② Maximal preservation of function

③ Maximal preservation of cosmesis

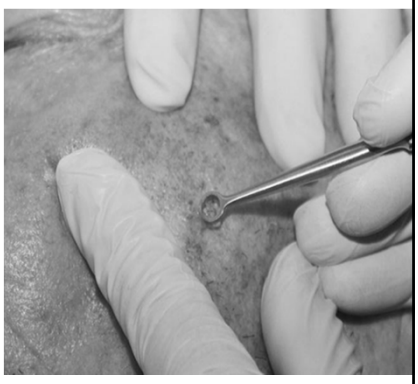
④ Cost

Surgical Excision for SCC

- One of the most common treatment modality for SCC
- Reported 5-year recurrence rates of around 7% for primary SCC, and 23% for recurrent SCC
- General margin is 4mm

Squamous Cell Carcinoma: Electrodessication and Curettage

- Good for:
  - SCCIS, very minimally invasive SCC*
  - Areas with low risk for recurrence
- Advantages
  - High clearance rate in appropriate SCCs
  - Fast, no suture removal
- Disadvantages
  - If there is perifollicular involvement, higher rate of recurrence
  - No margin assessment
  - Potentially more apparent scar



SCC: Risk Factors for Recurrence

H&P	Low Risk	High Risk
Location/Size	Area L < 20mm Area M < 10mm Area H < 6mm	Area L > 20mm Area M > 10mm Area H > 6mm
Borders	Well defined	Poorly defined
Primary vs Recurrent	Primary	Recurrent
Immunosuppression	(-)	(+)
Site of prior RT	(-)	(+)
Rapidly Growing Tumor	(-)	(+)
Neurologic Symptoms	(-)	(+)
Pathology		
Degree of Differentiation	Well differentiated	Moderately or poorly differentiated
Depth: Thickness or Clark Level	<2mm or I, II, III	≥2mm or IV, V
Adenoid (acantholytic), adenosquamous, or desmoplastic	(-)	(+)
Perineural involvement	(-)	(+)

SCC: 5-year cure rates for primary SCC, Meta-analysis

Treatment Modality	5-year cure rate* ^
Surgical excision	92%
Electrodessication and curettage	96%
Radiation	90%
Cryotherapy	N/A%
All non-MMS	92%
MMS	97%

***Rowe DE, Carroll RJ, Day LC: Long-term recurrence rates in previously untreated (primary) basal cell carcinoma – implications for patient follow-up. J Dermatol Surg Oncol 1989; 15:315-328.**

SCC: Treatment: When to Consider MOHS

- One or more risk factors
- Tumors of any size in certain high-risk sites
  - Lip SCC
  - Ear SCC
  - Nail Unit SCC

SCC: Key Points

- The second most common skin cancer in humans
- Multifactorial in origin
- If left without treatment, can be locally destructive and progress to regional and distant metastasis
- Many treatment modalities available, and appropriate patient selection will deliver most effective care