DIFFERENTIAL DIAGNOSIS IN ONCOLOGY

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BCC AND SCC (SOME EASY; OTHERS NOT)
EPIDEMIOLOGY AND CLINICAL PRESENTATION

INTRODUCTION

- Non-melanoma skin cancer (NMSC) represents the most frequently observed malignancy amongst Caucasians
- UV light exposure is the major risk factor for development
- Other risk factors include: exposure to ionizing radiation, arsenic or organic chemicals; human papillomavirus infection; immunosuppression; and genetic predisposition
- Surgery is the mainstay of treatment, but immunomodulators, photodynamic therapy, and drugs that address genetic defects show promise

OVERALL EPIDEMIOLOGY

- Caucasians most affected
- Exact incidence of NMSCs difficult to obtain due to limited reporting to state cancer registries
- Positive correlation observed with latitude and average annual UV exposure
- Under 40 years old, majority of NMSC is found in women
- However, sharp increase for men for NMSC after 60 years old, leading women in 2-3:1 ratio by age 80

SQUAMOUS CELL CARCINOMA (SCC) EPIDEMIOLOGY

- Increasing age, male sex, and previous history of actinic keratoses noted as risks for developing invasive SCC
- Incidence increases significantly after 60 years old
- Majority are located on head/neck, upper extremities
- Mortality from SCC is higher in whites, older persons, and men
- Males have a 3:1 greater SCC mortality than women
- In darker skin, associated with chronic irritation, scar, or injury
- SCCs on ear, lip, genitalia associated with higher risk of death

BASAL CELL CARCINOMA (BCC) EPIDEMIOLOGY

- BCC most common skin cancer in humans
- More common in males, with male to female ration of 1.5-2:1
- Risk factors for development: Increasing age, Caucasian race, male gender (2x than women)
- Mortality from BCC quite rare, usually in immunocompromised or with patients with basal cell nevus syndrome
- Metastatic BCC usually with aggressive histopathologic patterns, including morpheaform, infiltrative, metatypical, and basosquamous
- Perineural involvement is also sign of aggressive disease
- Metastases involve regional lymph nodes, lungs, bone and skin

RISK FACTORS: ULTRAVIOLET (UV) EXPOSURE

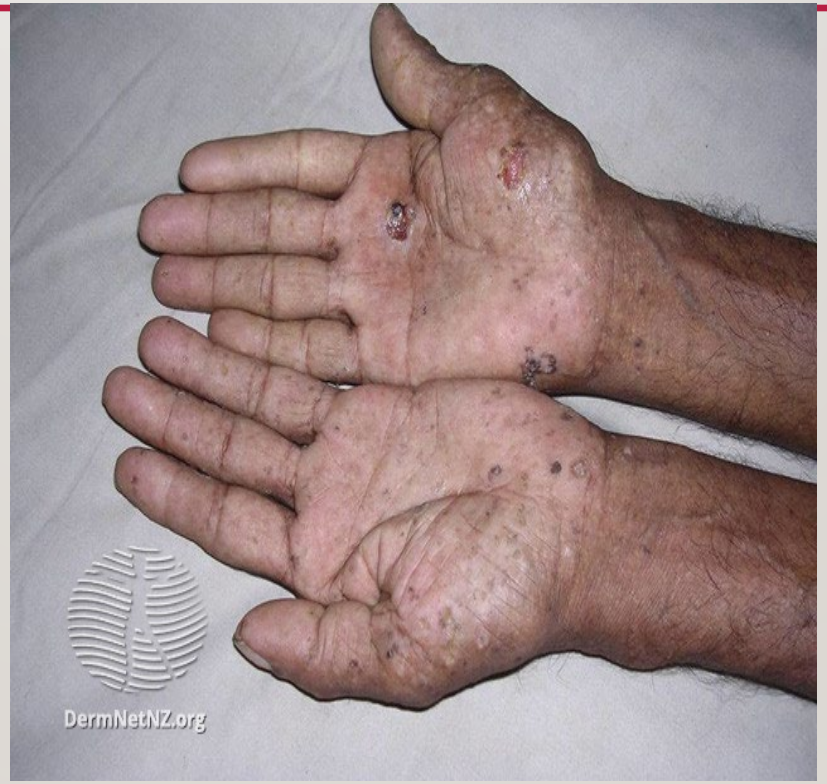
- UV exposure is the predominant cause of NMSC development
- BCC has higher risk with intermittent intense episodes of UV exposure and sunburns at any age
- SCC usually related to cumulative long-term UV exposure and childhood sunburns
- Incidence is inversely proportional to latitude
- Artificial sources of UV radiation, intentional tanning shown to increase risk of SCC and BCC development, even after adjusting for sunburn history and sun exposure
- Red hair, light skin, poor ability to tan, freckling are risk factors

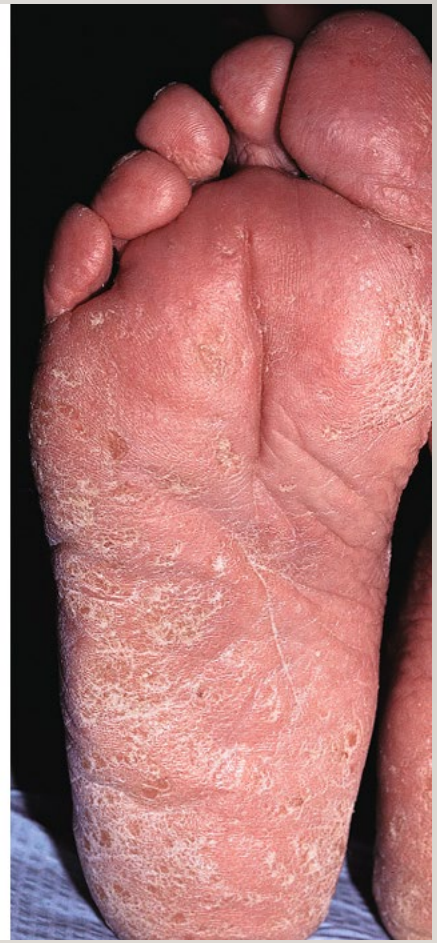
RISK FACTORS: MEDICATIONS/WORK EXPOSURE

- PUVA has a significant dose related-risk of SCC and BCC after 100 treatments
  - PUVA immunosuppression may also play a role
- Exposure to ionizing radiation leads to a threefold increased risk of NMSC, risk is in proportion to radiation dose
- Pilots, sailors, locomotive engineers, agricultural workers at increased risk of NMSC development

RISK FACTORS- CHEMICAL EXPOSURE

- Usually located on arms in multiples
- Pesticides, asphalt, tar, polycyclic aromatic hydrocarbons, typically result in SCC
- Arsenic exposure results in palmoplantar arsenical keratosis and BCCs with latency of 20-40 years

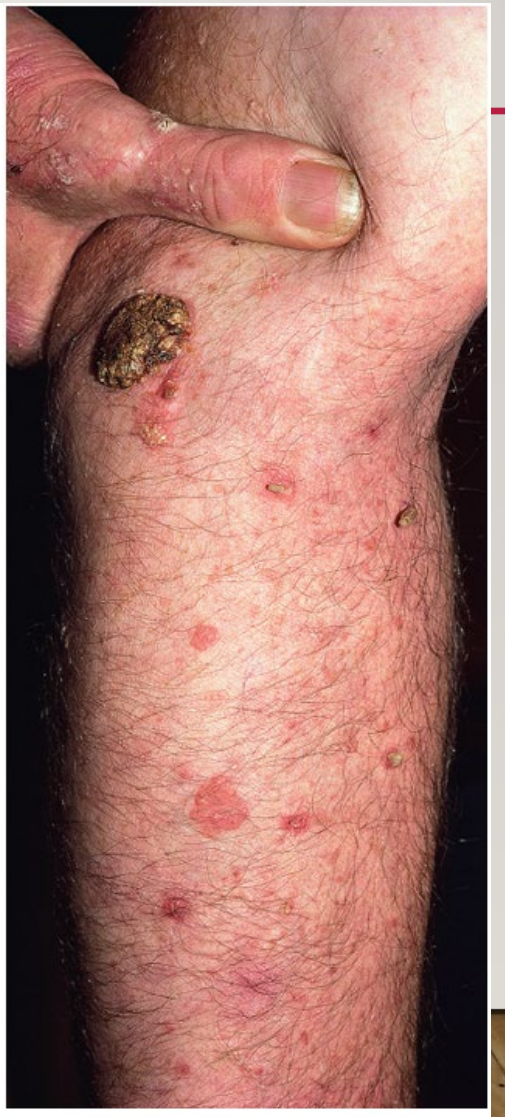




Arsenical keratoses on palms and soles

RISK FACTORS- IMMUNOSUPPRESSION

- BCC risk 5-10 times higher with organ transplant recipients
- SCC risk 40-250 times higher with organ transplant recipients
- Skin type, cumulative sun exposure, age at transplant, length of immunosuppression impact NMSC development
- SCC pathogenesis: decreased immunity, direct carcinogenic effect immunosuppressive medications, HPV, UV light
- More likely to have numerous lesions, more local/regional recurrences and metastases
- HPV DNA in 70-90% SCCs in this population

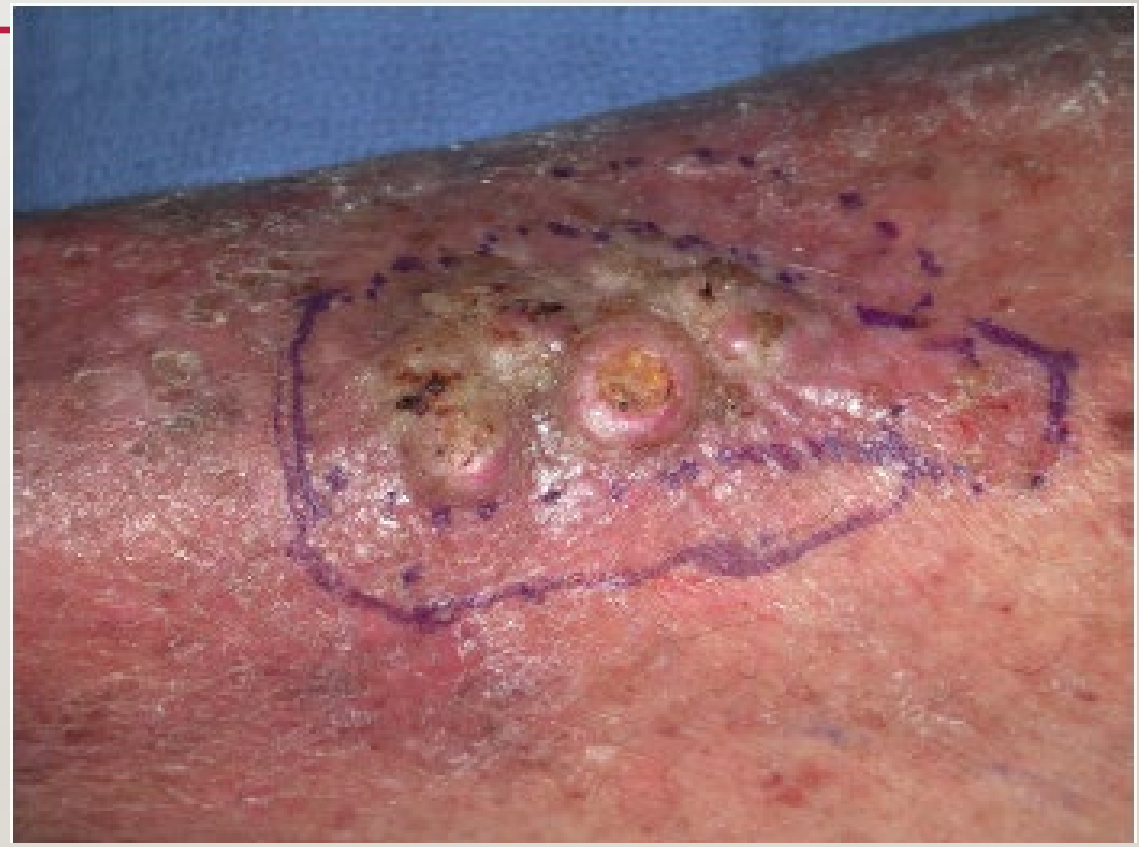


Multiple SCCs in renal transplant patient

Andrews' Diseases of the Skin by James et al.

TRANSPLANT PATIENTS

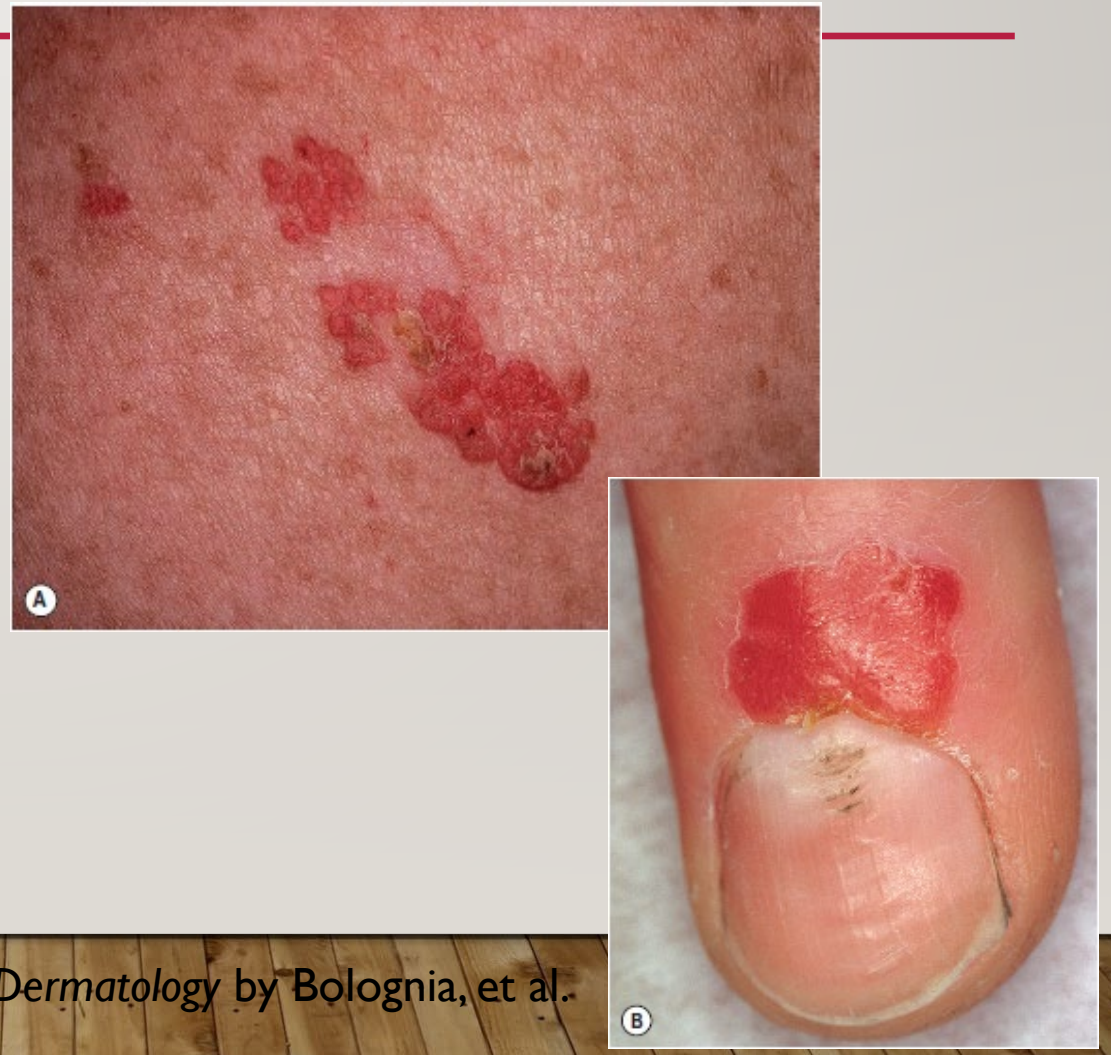
- Of renal transplant patients, 5% died from skin cancer
- Of heart transplant patients, 27% died of skin cancer
- 2/3 skin cancer related deaths in transplant patients were from SCC
- Hematopoietic transplants usually do not encounter this marked increased risk of skin cancer, unless received long-term voriconazole



Dermatology by Bolognia, et al.

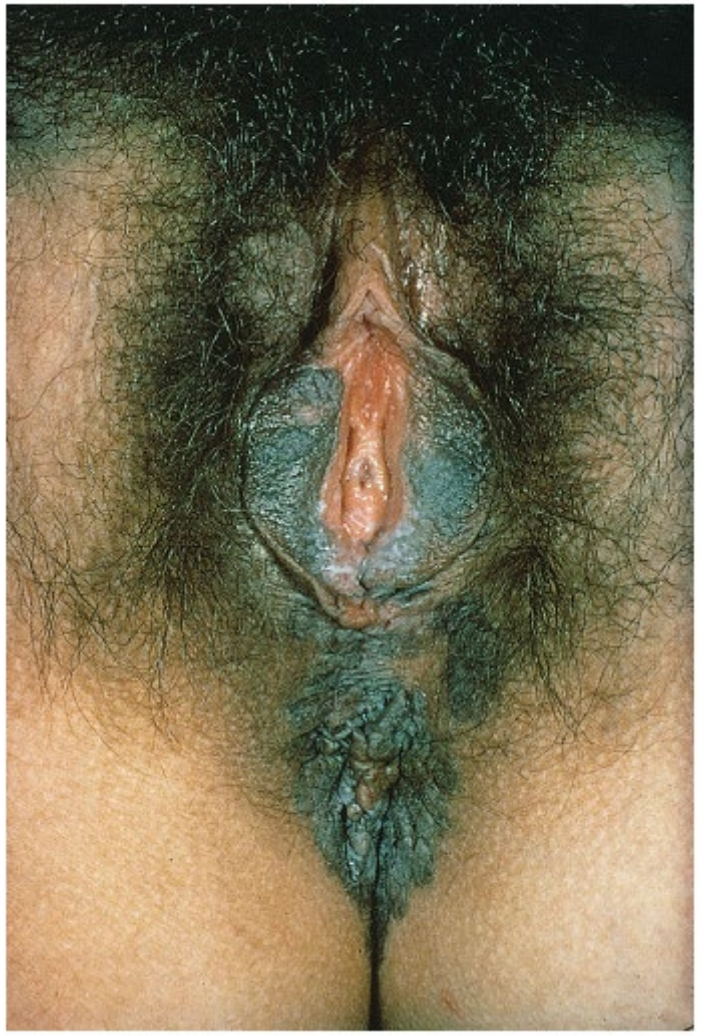
CLINICAL FEATURES: SCC IN SITU

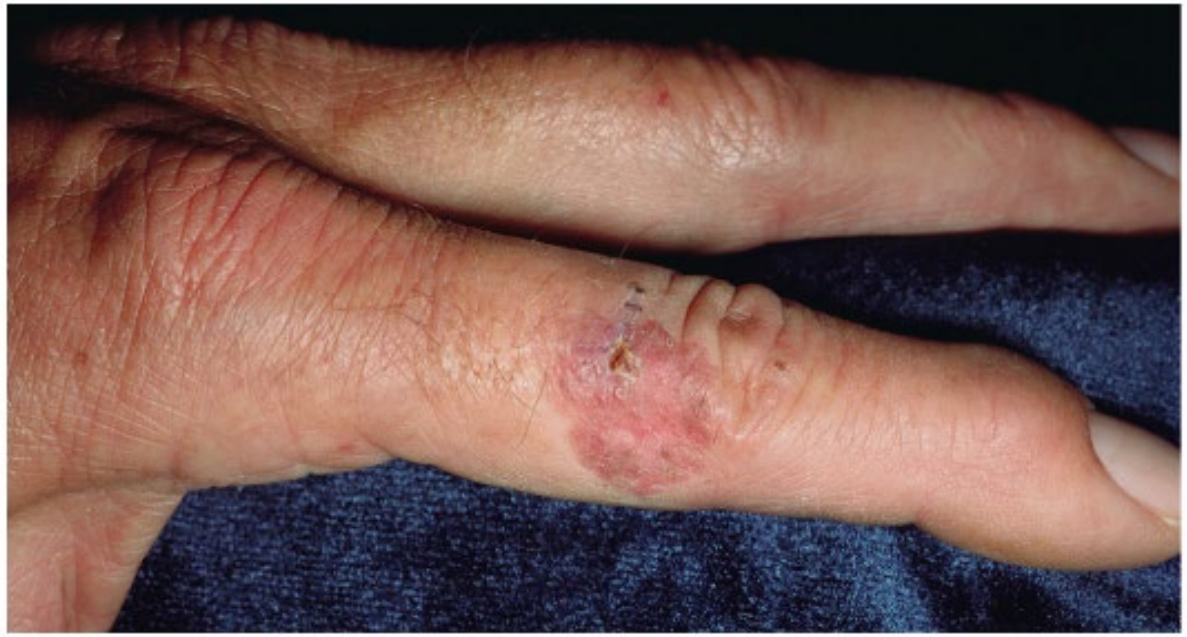
- Also known as Bowen's disease
- Presents as erythematous scaly patch or slightly elevated plaque on sun-exposed skin
- May arise de novo or from an existing AK
- Rarely becomes invasive
- Can be difficult to tell SCC in situ apart from AK, superficial BCC, psoriasis, or chronic eczema
- Arsenical SCC in situ: located on non-sun exposed areas; multiple lesions with hyperpigmentation
- Bowenoid papulomatosis: SCC in situ arising from genital warts with HPV 16, 18

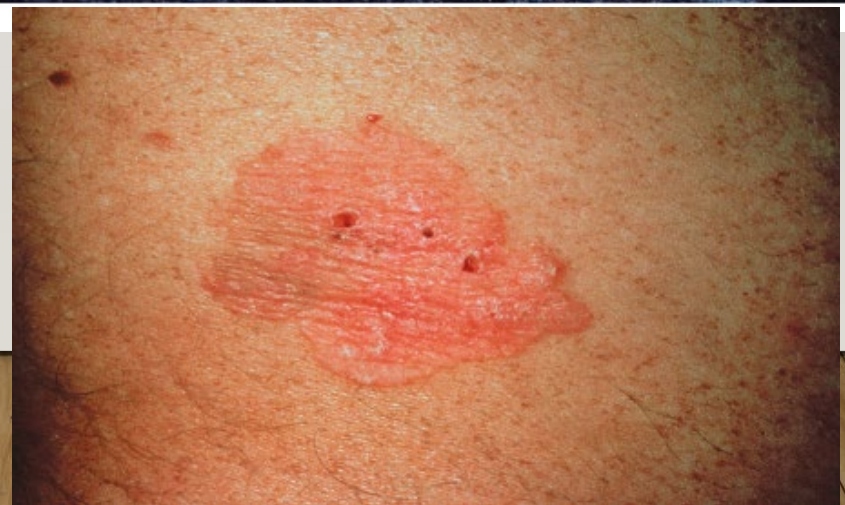


Dermatology by Bolognia, et al.

BOWEN'S DISEASE: CLINICAL IMAGES



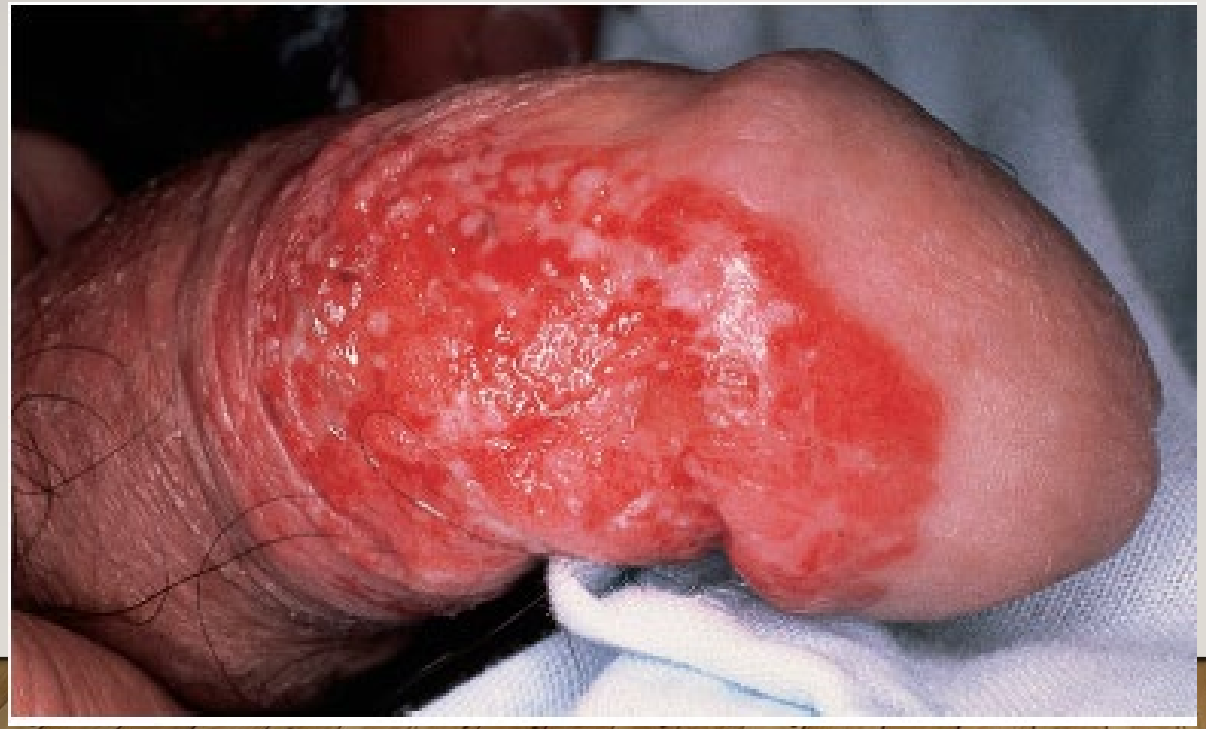




Andrews' Diseases of the Skin by James et al.

SCCIS: SUBTYPES

- Erythroplasia of Queyrat
  - Subtype of SCCIS on penile shaft and glans



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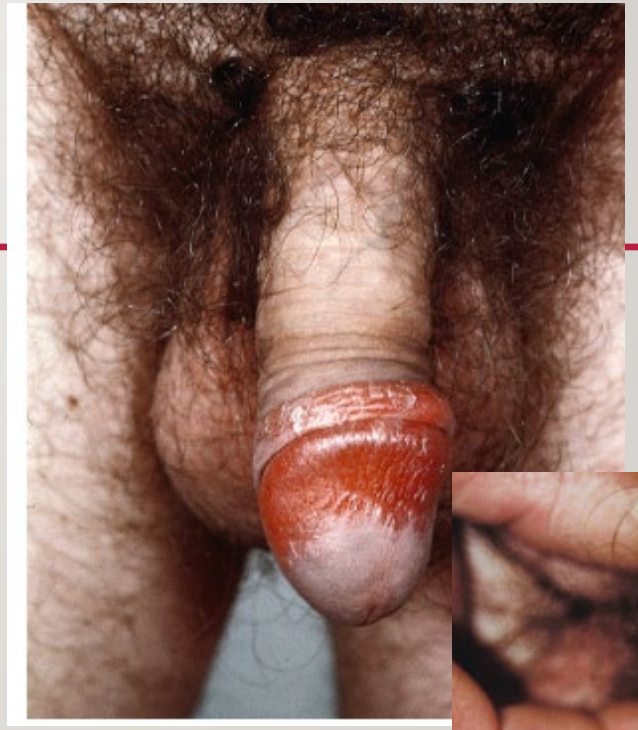
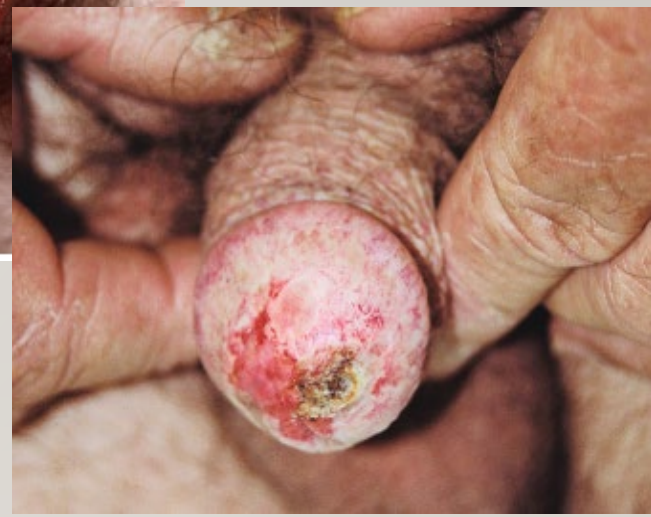
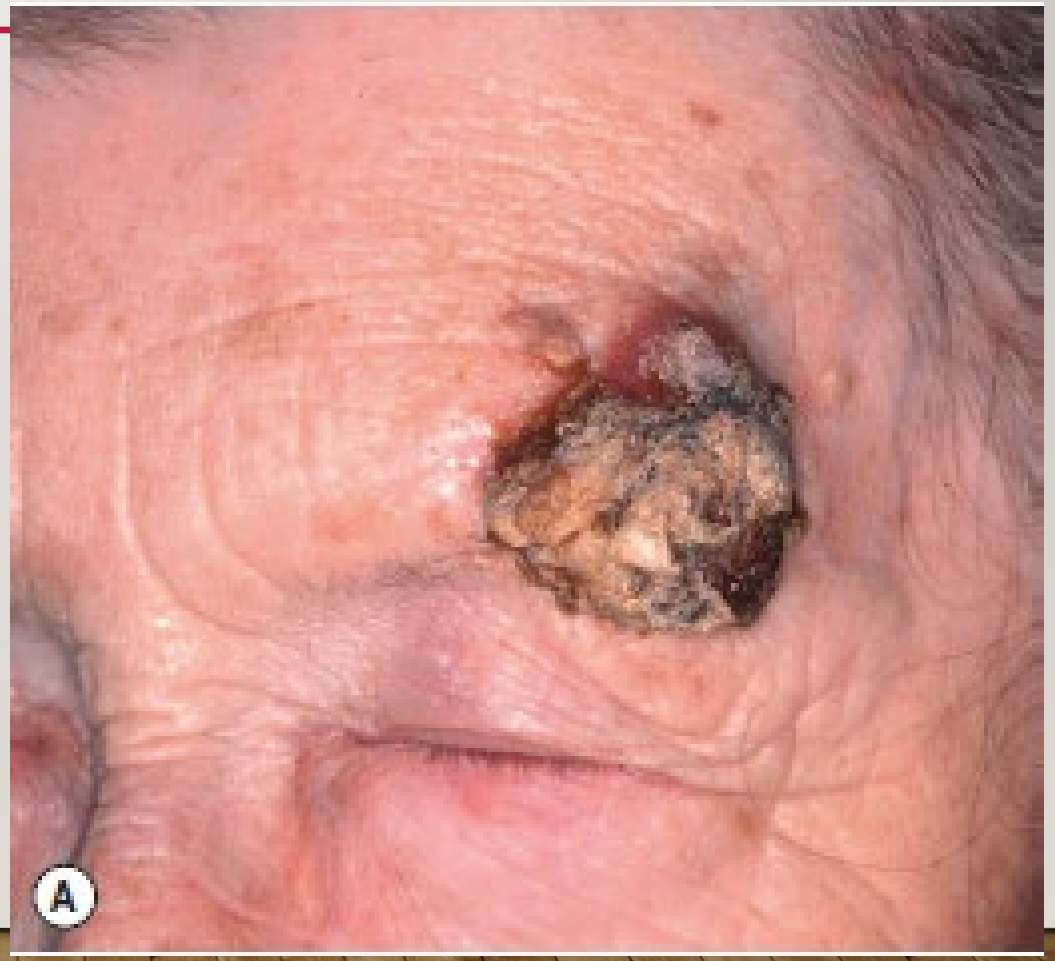




Andrews' Diseases of the Skin by James et al.

INVASIVE SCC CLINICAL FEATURES

- Most common locations: bald scalp, face, neck, extensor forearms, dorsal hands and shins
- Usually papulonodular, but can often be exophytic or papillomatous
- Can have hyperkeratosis, crusting, and ulceration
- May enlarge slowly or rapidly and can be accompanied by pain



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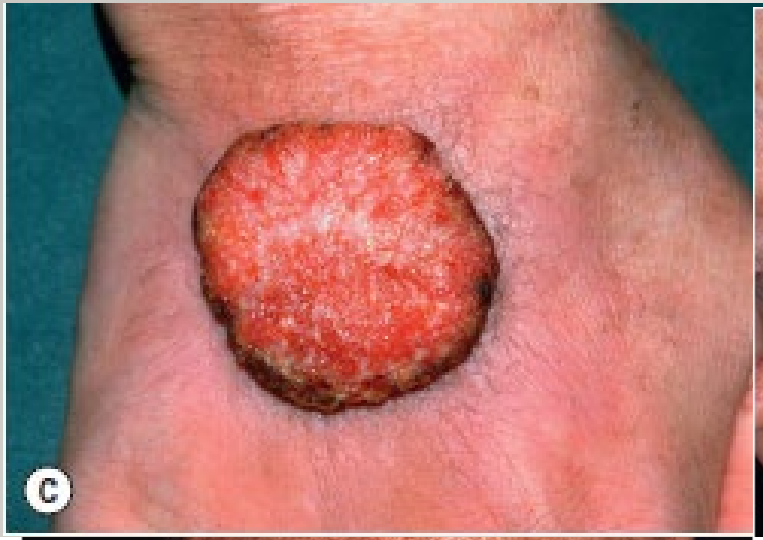
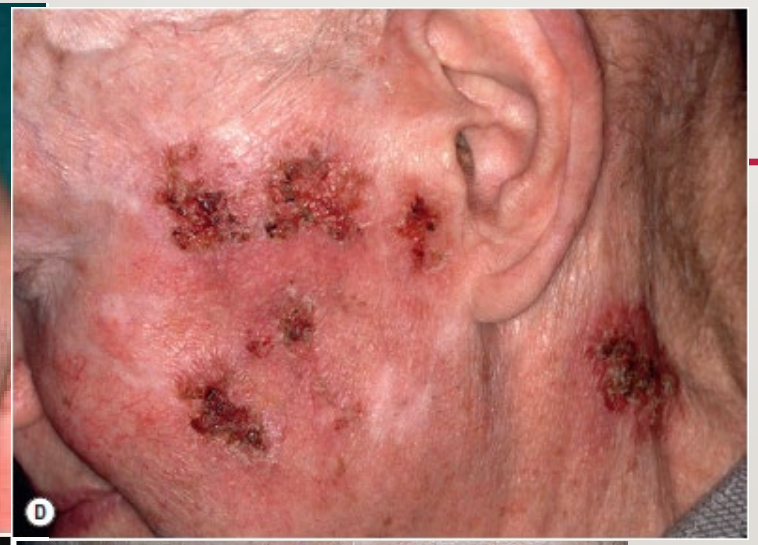
INVASIVE SCC: CLINICAL IMAGES





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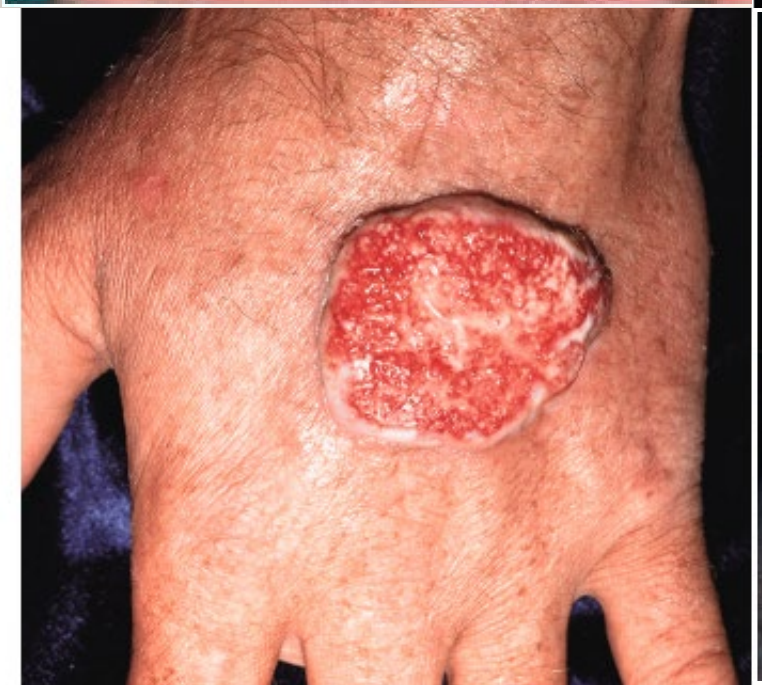
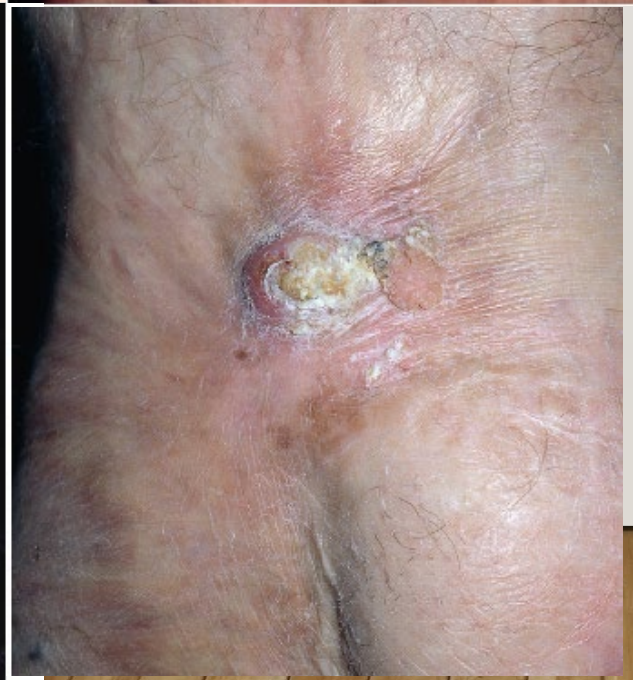
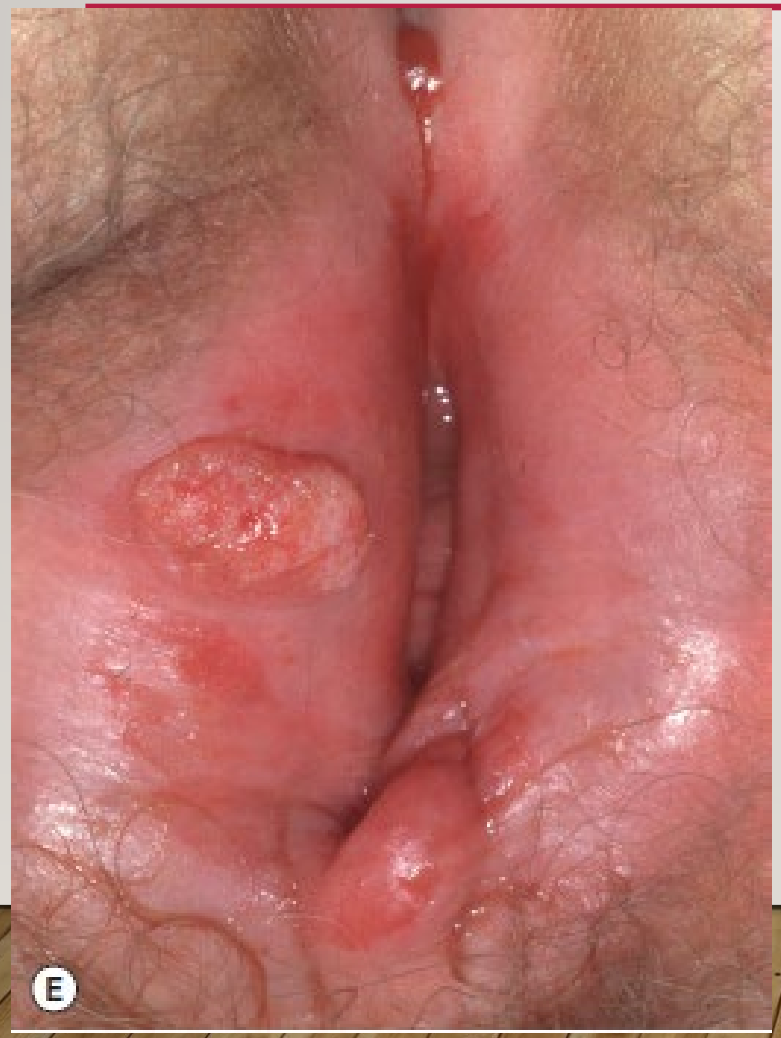
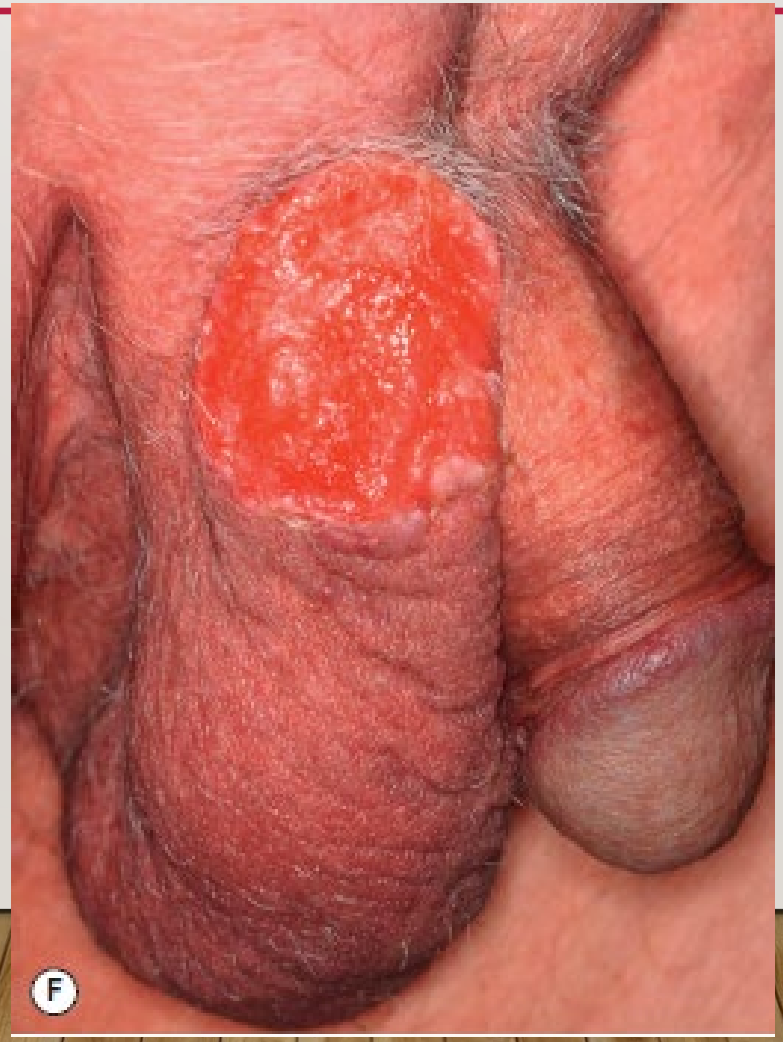




Andrews' Diseases of the Skin by James et al.

INVASIVE SCC: CLINICAL IMAGES





Given location, likely HPV-induced

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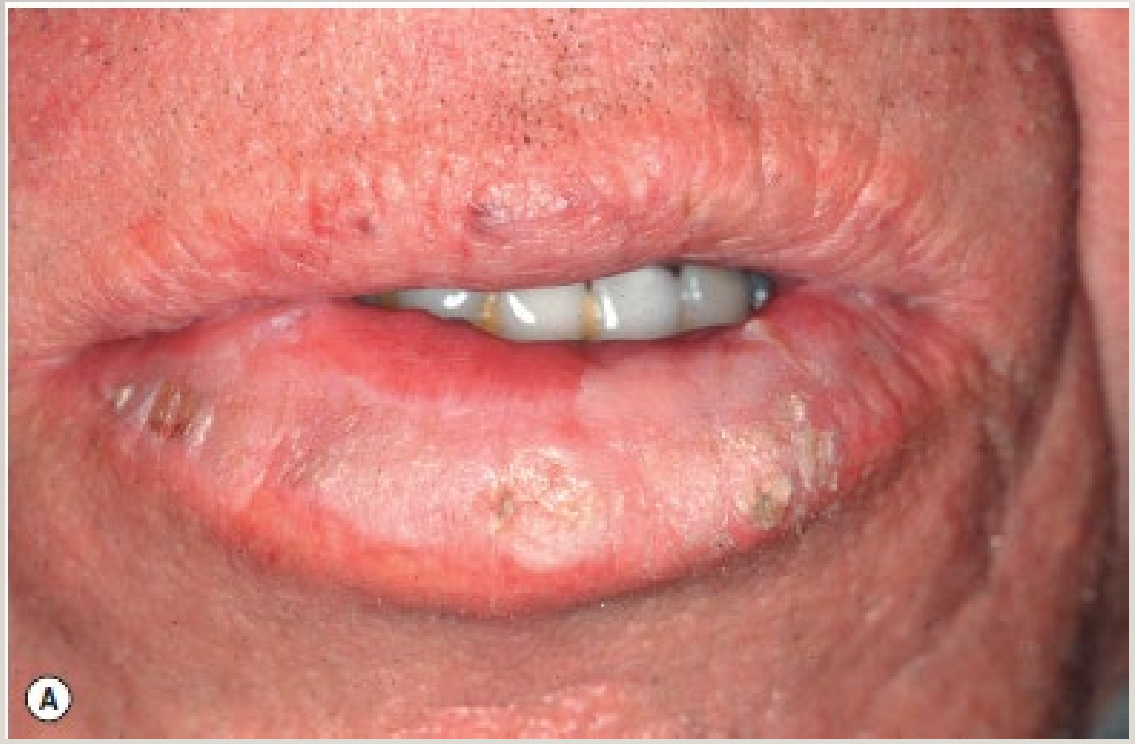
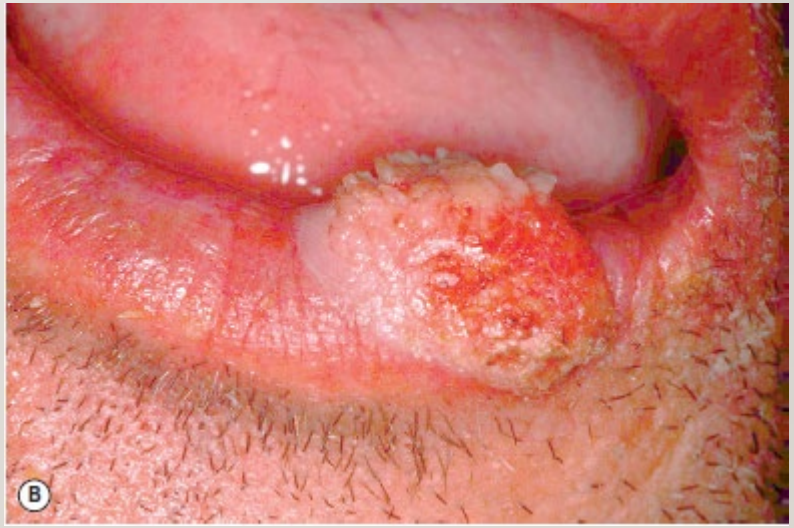
INVASIVE SCC: CLINICAL IMAGES





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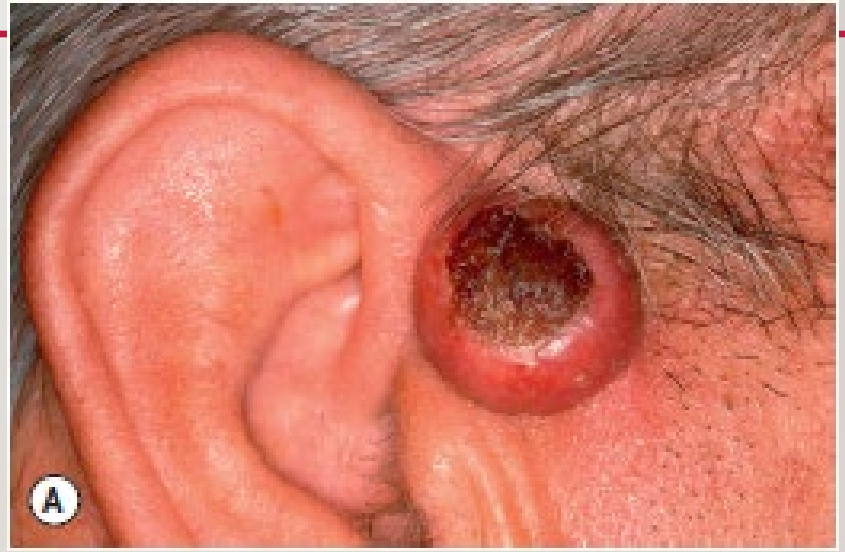
KERATOACANTHOMAS (KAS)

- Debate if this is a benign entity vs variant of SCC
  - Largely treated as SCC
- Rapidly enlarging papule, sharply circumscribed, crateriform nodule with keratotic core over a few weeks
- May resolve slowly over months to leave an atrophic scar
- Ferguson-Smith and Gryzbowski syndromes represent inherited conditions leading to the development of multiple KAs



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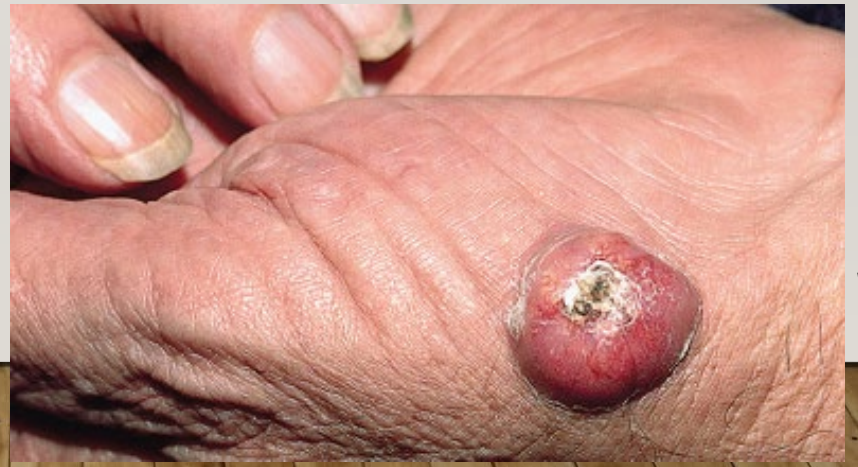

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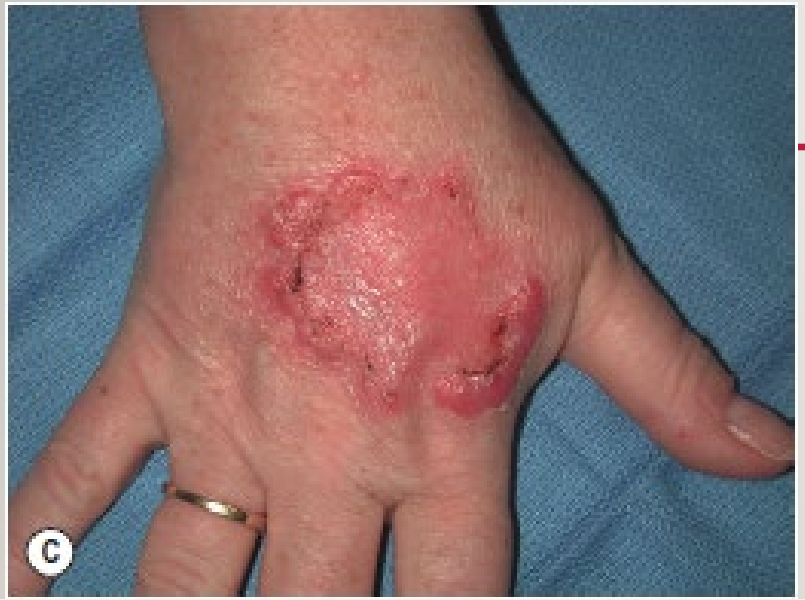
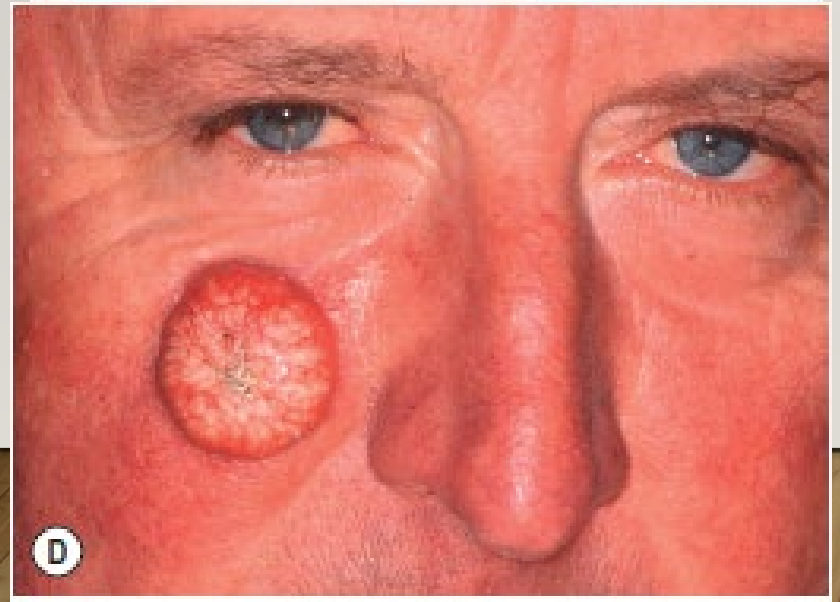
KAS: CLINICAL IMAGES





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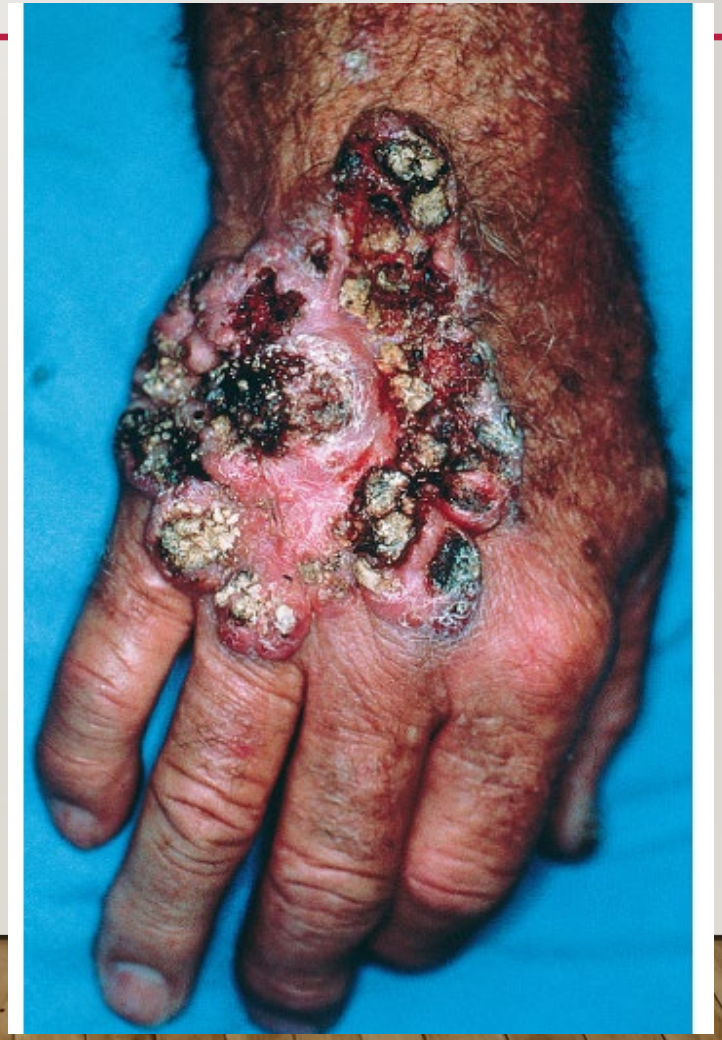


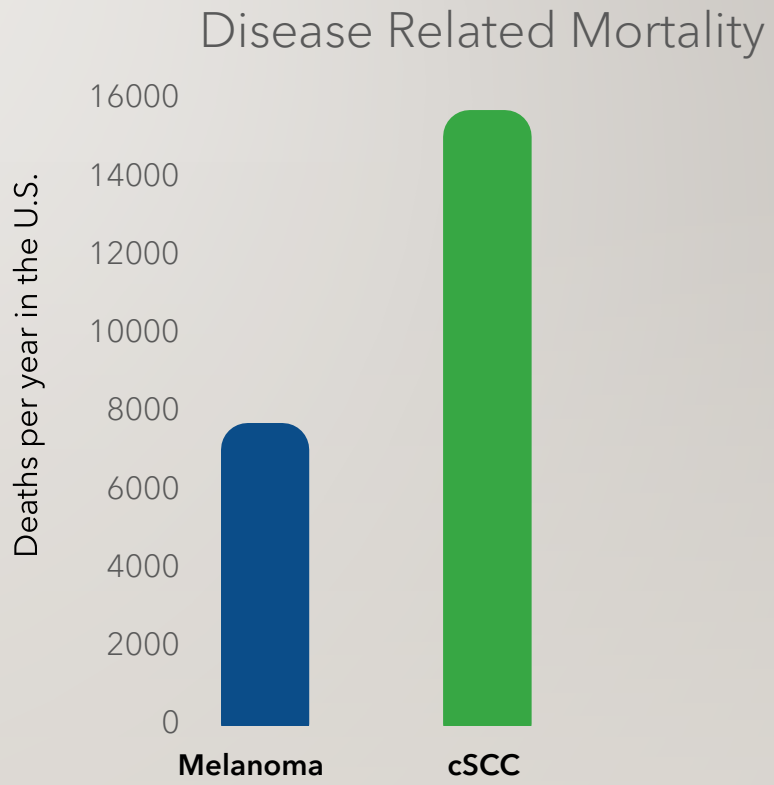
Andrews' Diseases of the Skin by James et al.

Cutaneous squamous cell carcinoma is an emerging problem in the U.S.

- **Managing SCC is a significant clinical issue as deaths from SCC are now estimated to exceed those from melanoma**

- **Because cancer treatment plans and their outcomes are guided by risk for metastasis, prognostic accuracy has direct implications on patient management**

- **Unlike melanoma, breast and other common cancers, SCC patient care has not been personalized with risk predicting gene expression profile (GEP) tests**



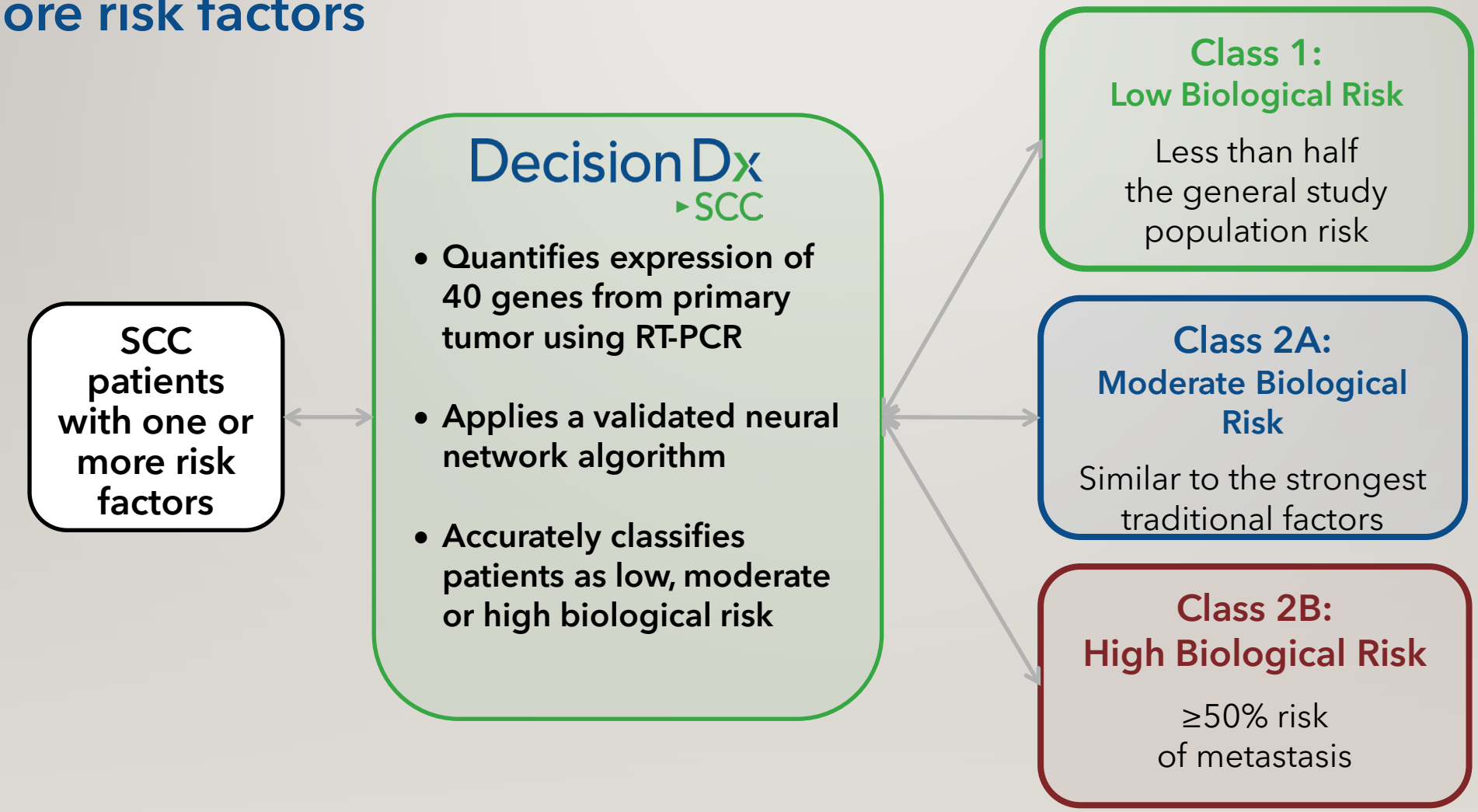
SEER data release 2015; Mansouri et al. *JAMA Dermatol* 2017

Current cutaneous squamous cell carcinoma (SCC) staging fails to identify >30% of cases who will go on to experience metastasis

	Under-Staged % of metastases occurring in patients deemed low risk by staging	Over-staged % of high-risk cases without metastasis over-called by staging
Study	**Patients with metastatic outcomes staged as T1/T2a**	**Patients without metastatic outcomes staged as T2b/T3**
Tschetter 2020	60.0%	94.1%
Ruiz 2019	30.4%	74.6%
Marrazzo 2018	22.6%	83.4%
Canueto 2018	39.1%	73.1%
Haisma 2016	51.9%	64.3%
Karia 2014	31.3%	76.1%
Jambusaria 2013	16.0%	61.8%
Median	31.3%	74.6%
Average	35.9%	75.3%
Comprehensive	35.1%	75.7%

Clinical Validity and Intended Use

DecisionDx-SCC predicts metastatic risk for SCC patients with one or more risk factors



Considerations for integrating DecisionDx-SCC into practice

- **Expert panel of Mohs surgeons, surgical oncologists, and a radiation oncologist from academic medical centers and community practices.**

- **The panel focused on decision-making points where information from testing can inform the clinical management of patients with high-risk CSCC.**

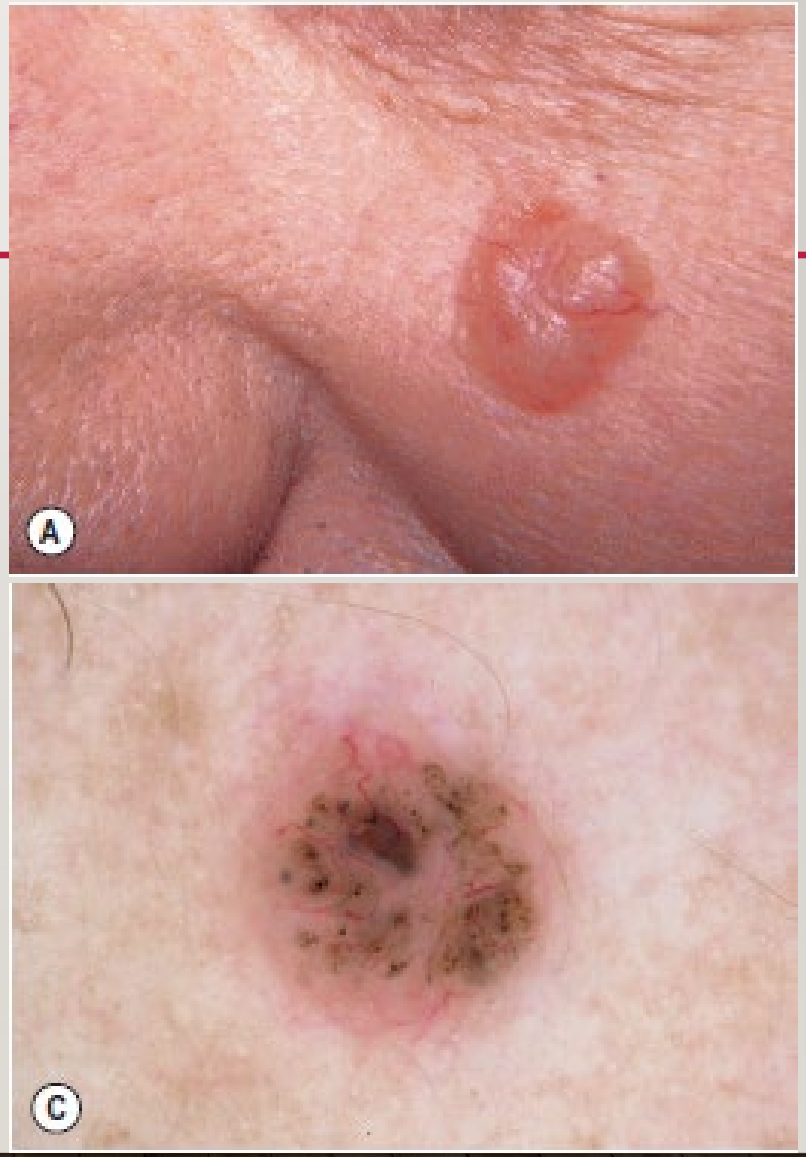
- **These decision points included:**
  1) nodal evaluation: imaging and sentinel lymph node biopsy (SLNB),
  2) adjuvant radiation therapy (ART), and
  3) follow-up and surveillance.

SCC: METASTASIS

- SCC in chronically sun exposed areas have relatively indolent behavior with low metastatic rate <5%
- There is a strong correlation between tumor thickness and metastasis
- Secondary risk factors for metastasis include immunosuppression, location on lips or ear
- SCCs genitalia and perianal area more aggressive, higher risk of metastasis
- Immunosuppressed patients at much higher risk

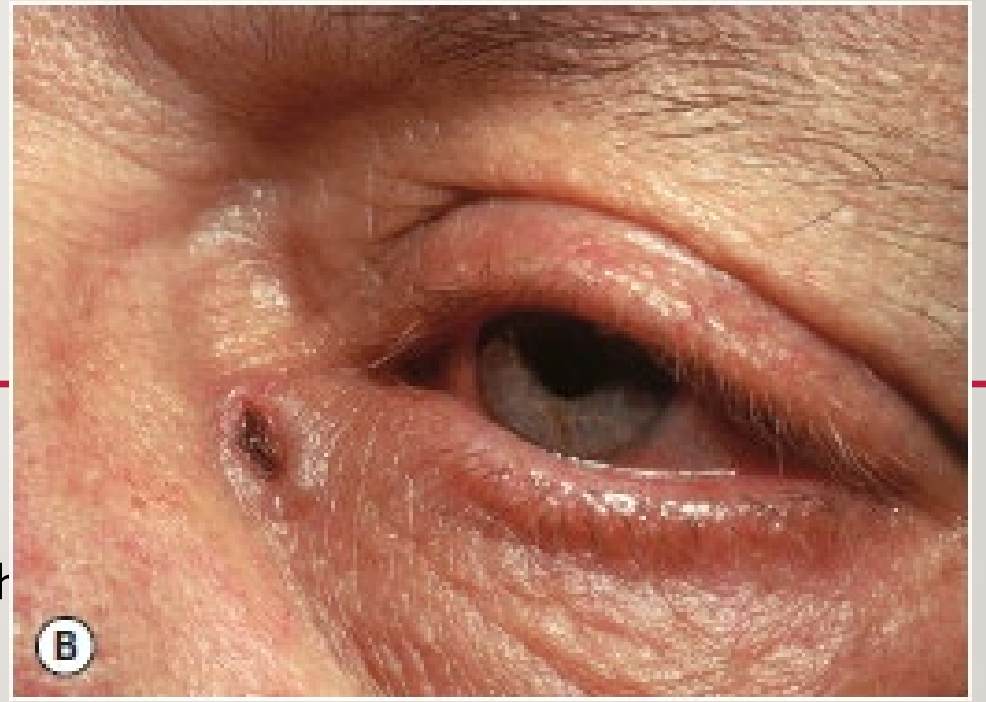
BCC
CLINICAL FEATURES

- Tumor arising in sun-damaged skin
- Rarely on palms and soles or mucous membranes
- 4 major distinctive clinicopathologic types
  - 1) Nodular
  - 2) Superficial
  - 3) Morpheaform
  - 4) Fibroepithelial
- Can be combination lesions, often ulcerate
- May have pigmented BCCs, melanin in tumors
  - More common in darker skin



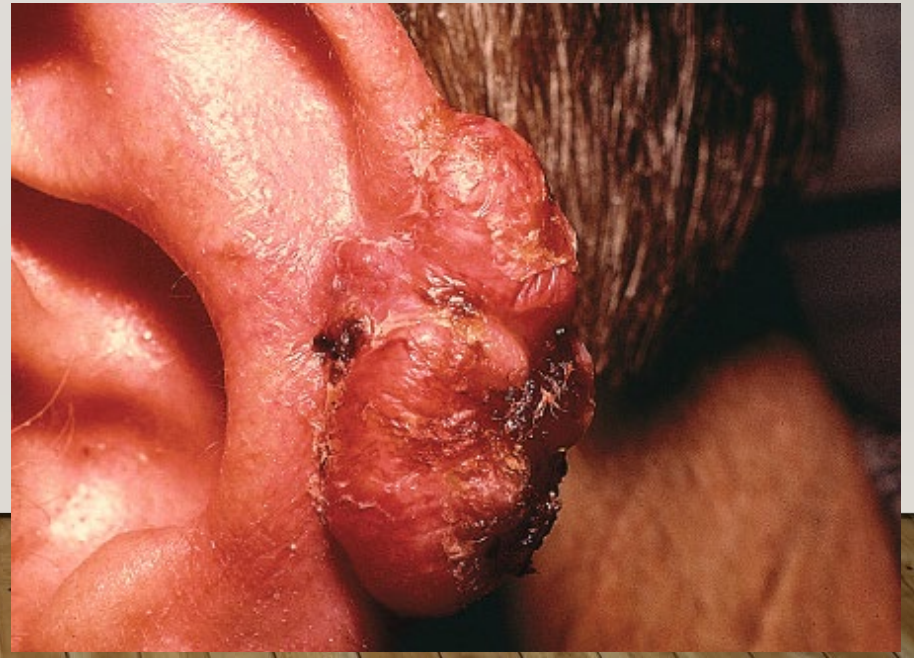
Dermatology by Bolognia, et al.

NODULAR BCC



Dermatology by Bolognia, et al.

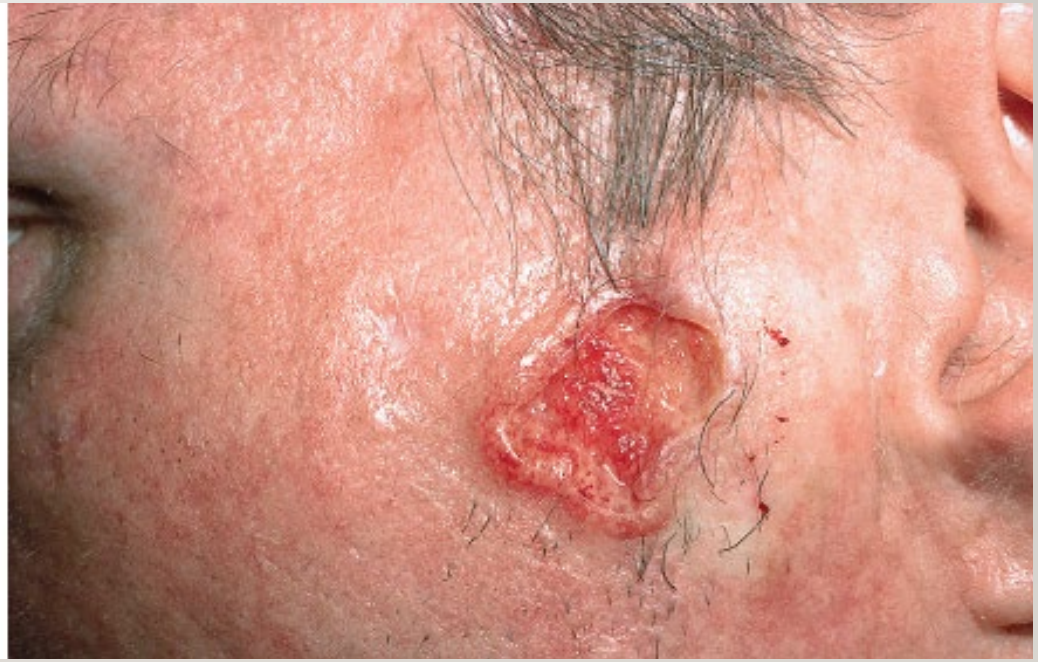
- Most common subtype
- Presents as shiny, pearly papule with arborizing telangiectasias
- Tumor can enlarge and ulcerate, often with elevated rolled borders



Andrews' Diseases of the Skin by James et al.

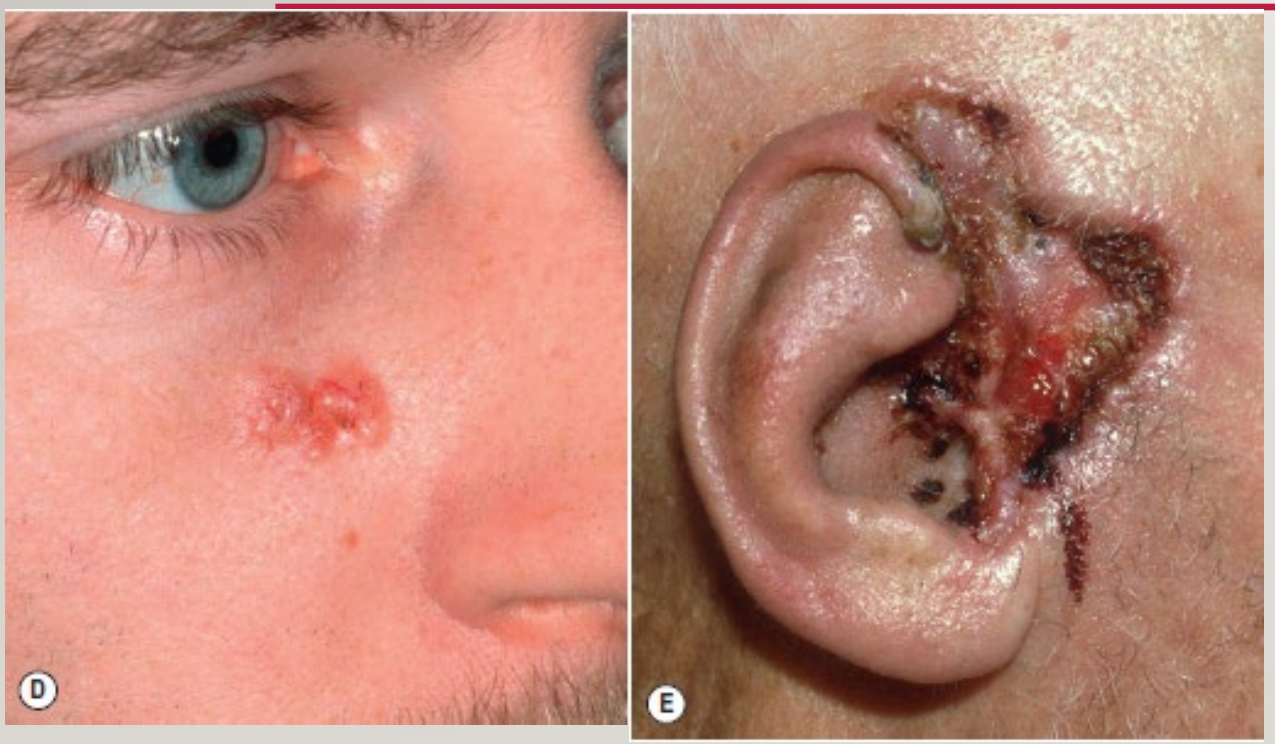
NODULAR BCC SUBTYPES

- Basosquamous Carcinoma
  - Histologic features of both BCC/SCC
  - May behave more like SCC,
    - greater likelihood of recurrence after treatment and metastasis
- Micronodular BCCs
  - Destructive behavior, subclinical spread, high rates of recurrence and potential for metastasis



Basosquamous subtype
Andrews' Diseases of the Skin by James et al.

BCC
CLINICAL IMAGES



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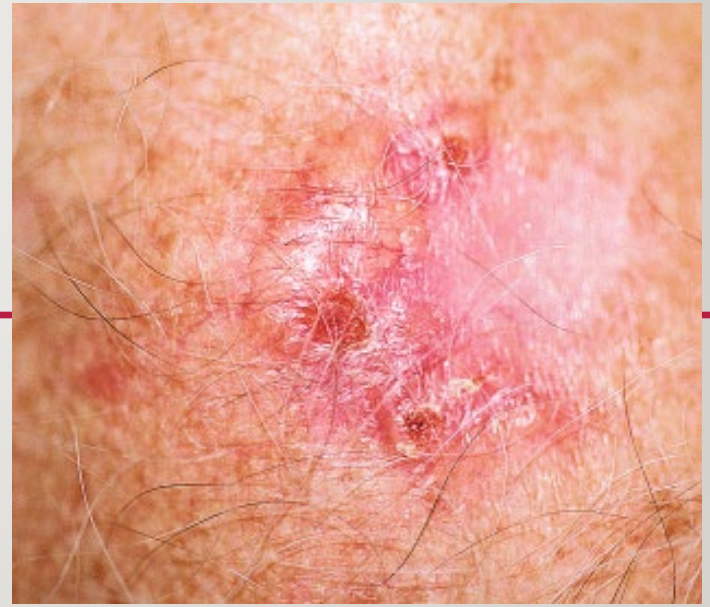
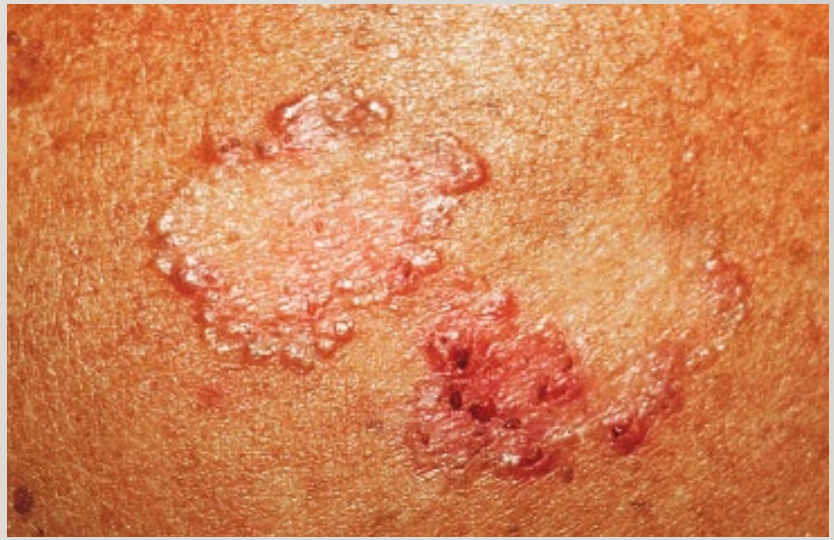


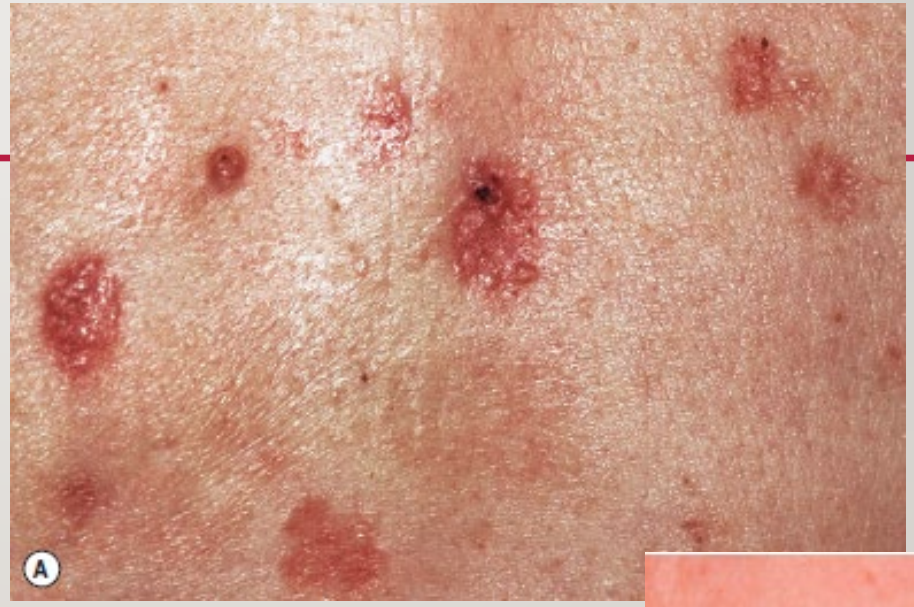


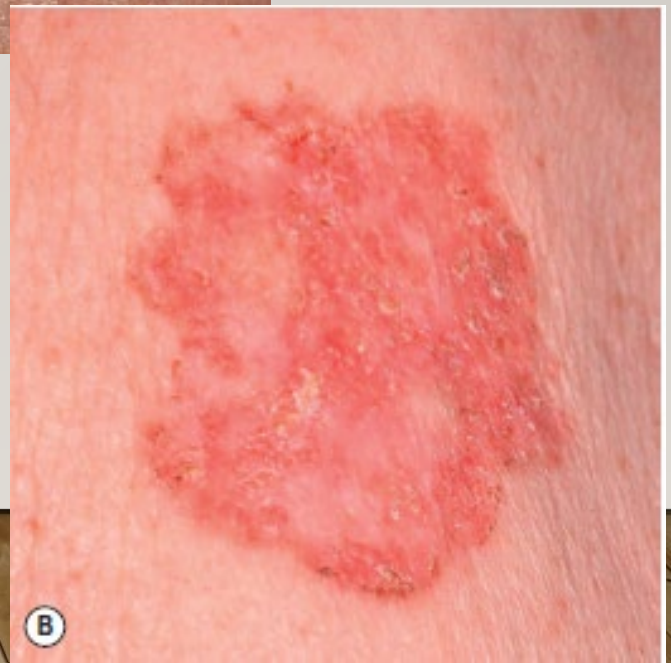
Andrews' Diseases of the Skin by James et al.

SUPERFICIAL BCC

- Well-circumscribed, erythematous macule/patch or thin papule/plaque
- Usually displays focal scale/crusts, thin rolled border, atrophy and hypopigmentation
- Most common subtype in younger patients
- Trunk + extremities more common location

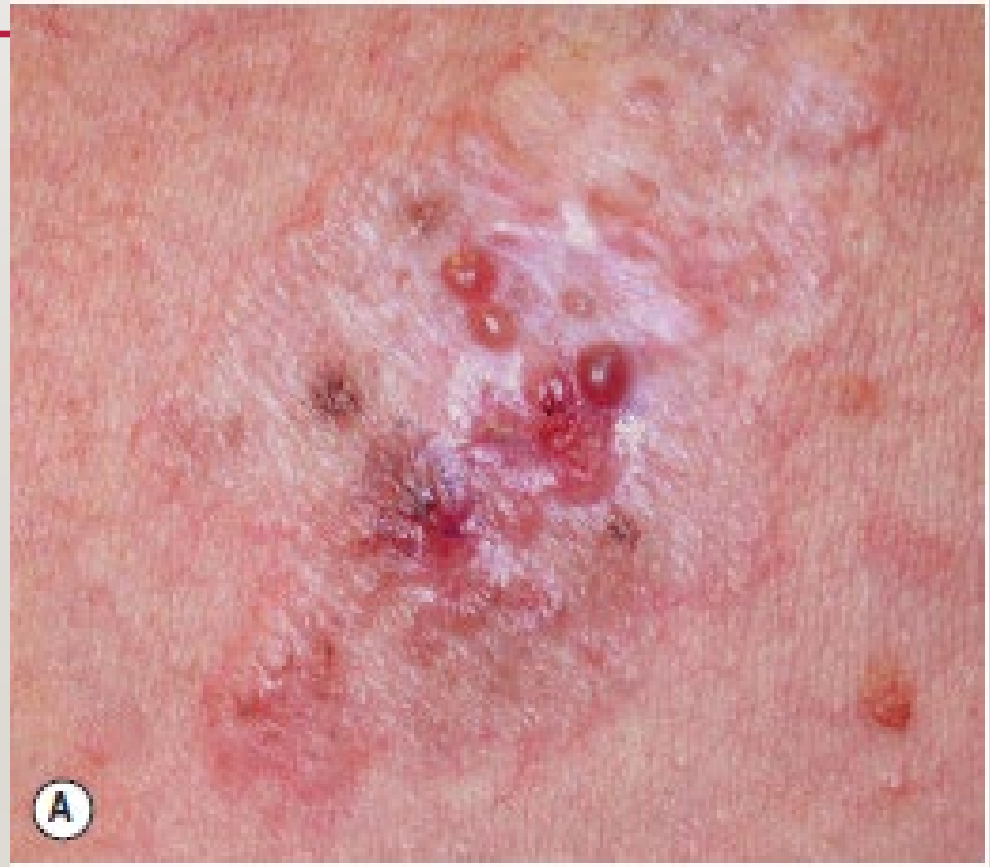
Dermatology by Bolognia, et al.





MORPHEAFORM BCC

- Less common subtype
- Slightly elevated to even depressed area of induration
- Light pink to white in color with ill-defined borders
- Similar to scar or plaque of morphea
- Telangiectasias often present
- Behavior is usually more aggressive with extensive local destruction



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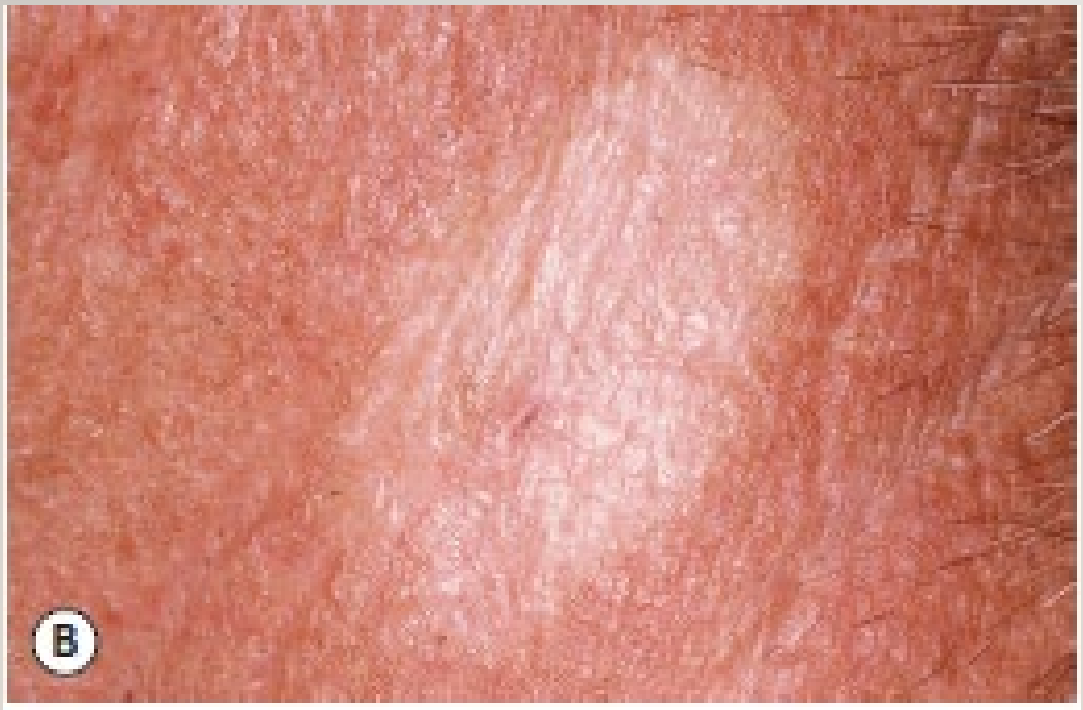
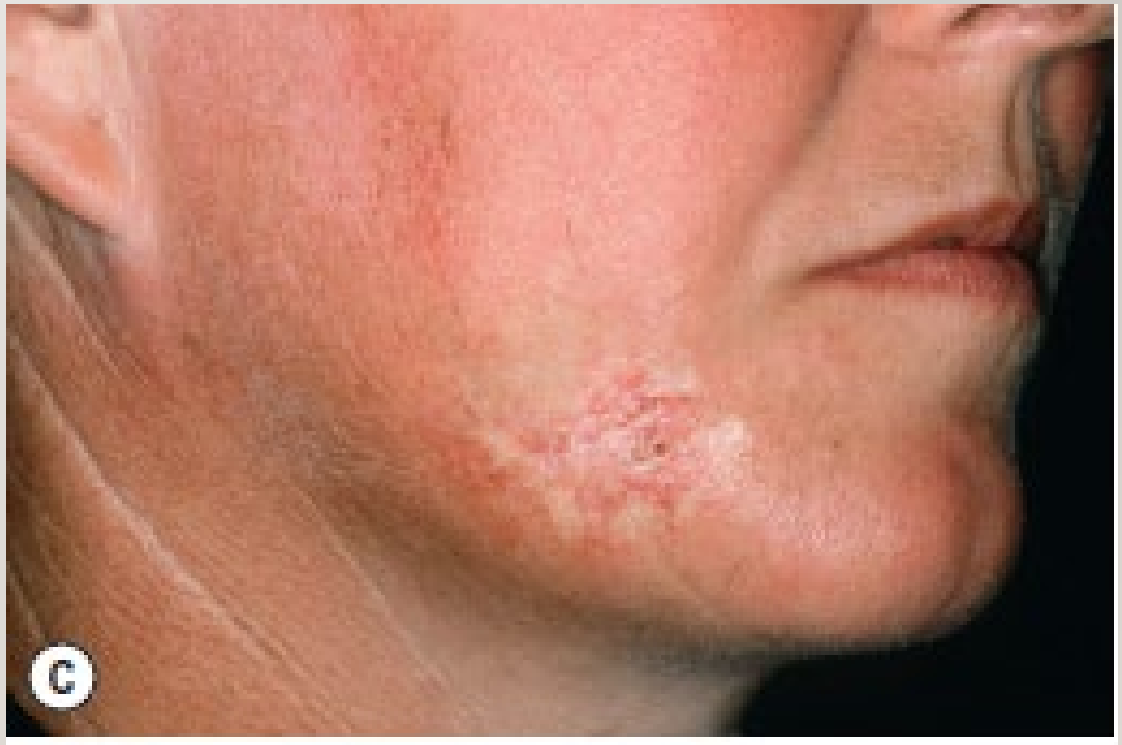
MORPHEAFORM BCC





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BCC: METASTASIS

- 1:1000 to 1:35000 rate of metastasis (exceedingly rare)
- Most common progression: Lymph node then lung and bone metastasis

NMSK: MULTIPLE APPROACHES

- Mohs Micrographic Surgery (Mohs)
- Other Destructive Methods
- Superficial Radiation Therapy (SRT)
- Difficult BCC –Hedgehog Pathway Inhibitors (vismodegib and sonidegib).
- Difficult SCC – PD1Inhibtors (cemiplimab)