Malignant Skin Tumors

Malignant tumor

- A tumor is an abnormal mass of tissue - growth of which exceeds & is uncoordinated with that of normal tissue with capacity to *metastasize* to lymph nodes and other organs
- Deals chiefly with the malignant tumors arising from epidermal cells

- Basal cell carcinoma
- Squamous cell carcinoma
- Malignant melanoma

Basal cell carcinoma (BCC)

- The most common cancers in humans
- All BCCs - Mutations activating the *Hedgehog signaling* pathway
- Exposure to UV light
- Associated with *PTCH1* gene mutation in most cases
- BCCs are locally destructive but *rarely* metastatic
- BCCs - primarily treated by surgical excision, electrodesiccation & curettage, Mohs micrographic surgery and topical agents

Epidemiology

- BCC - The most common cancer in humans
- Estimated - >3 million new cases occur each year in the USA
- Men - affected slightly more often than are women
- Tumors - More frequent in patients older than 60 years of age
- Majority of BCCs- located on the head and neck

Risk factors

- Risk factors for BCC - ultraviolet radiation (UVR) exposure, light hair and eye color, northern European ancestry and inability to tan
- BCC is rare in dark skin - the inherent photoprotection of melanin & melanosomal dispersion

Clinical Features

- Subtypes

➢Nodular BCC - the most common clinical subtype

➢Pigmented BCC - a subtype of nodular BCC that exhibits increased melanization

➢Superficial BCC - most commonly on the trunk

➢Morpheaform (sclerosing/infiltrating) BCC - an aggressive growth variant

➢Basosquamous carcinoma - a form of aggressive growth BCC; can be confused with squamous cell carcinoma (SCC)

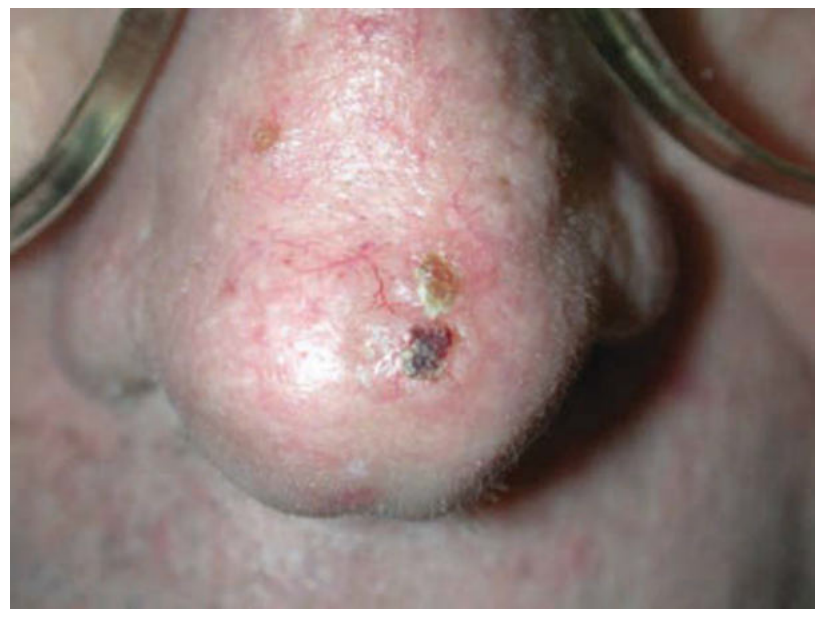
➢Fibroepithelioma of Pinkus

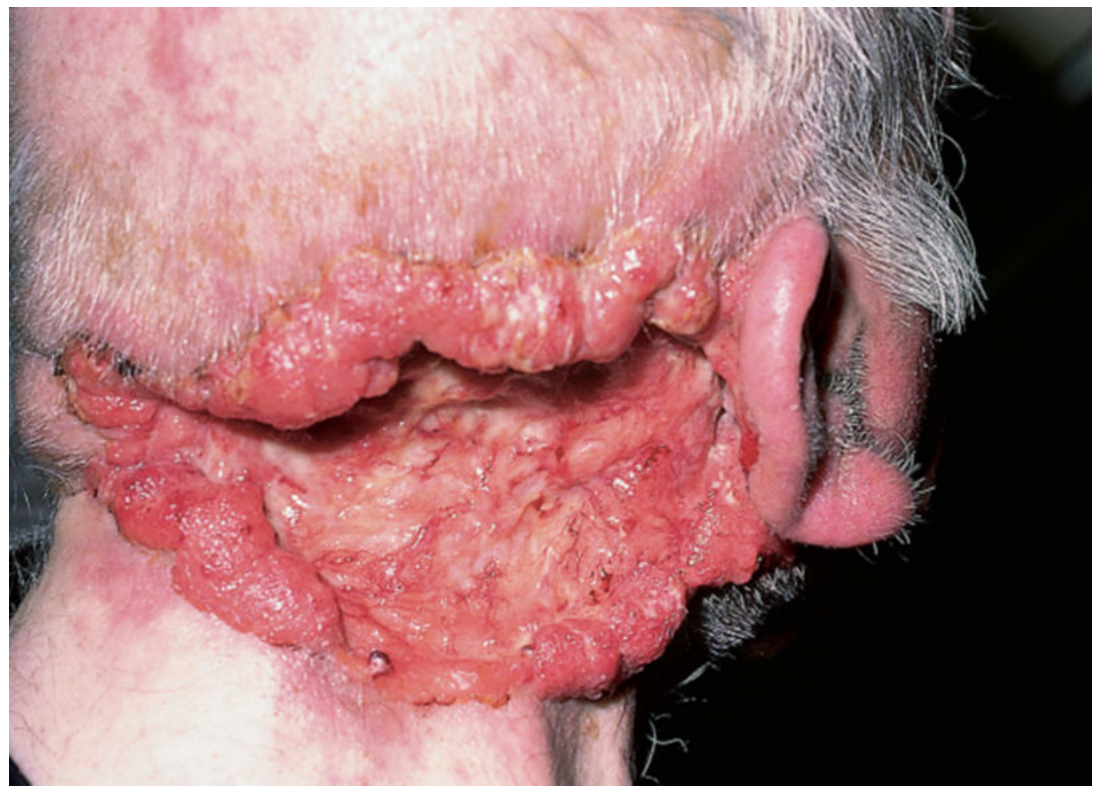
Clinical Features

- Presence of any nonhealing lesion → Should raise the suspicion of skin cancer
- BCC - usually on sun-exposed areas of the head & neck
- Can occur anywhere on the body
- Commonly seen features - translucency, ulceration, telangiectasias, and the presence of a rolled border
- Characteristics - Differ for different clinical subtypes

Nodular BCC

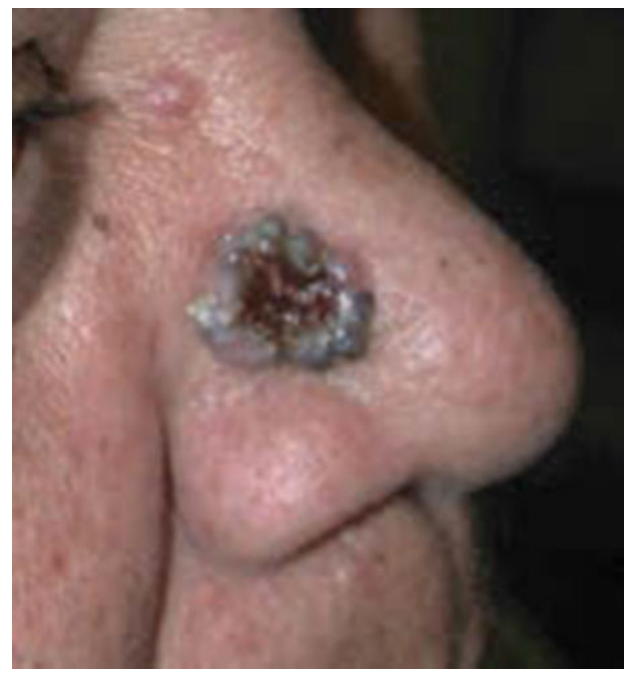
- The most common clinical subtype
- Occurs most often on the sunexposed areas of the head & neck
- Appears as a translucent papule or nodule
- Usually telangiectasias and often a rolled border
- Larger lesions with central necrosis - referred to by the historical term '*rodent ulcer*'





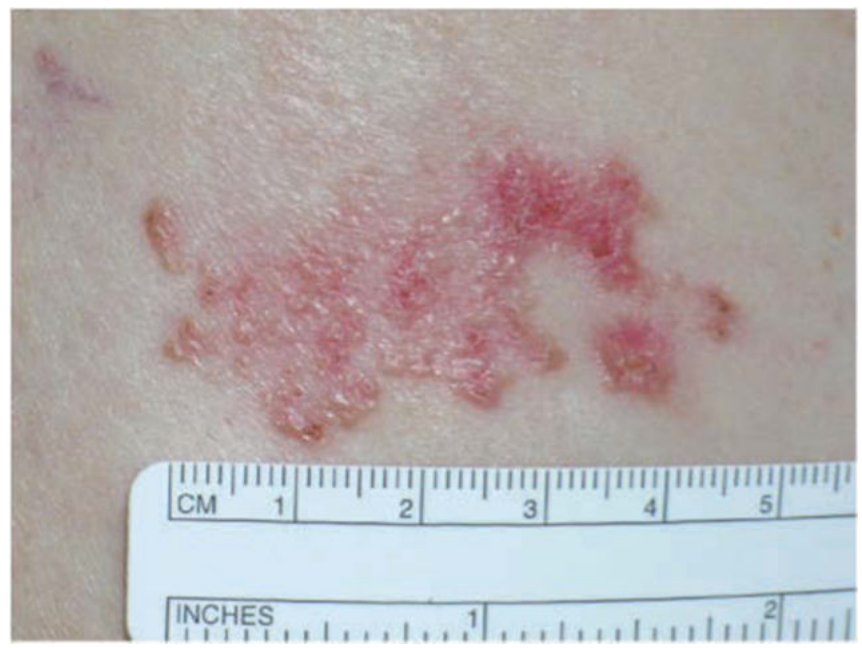
Pigmented BCC

- A subtype of nodular BCC – exhibits increased melanization
- Pigmented BCC - Presents as a hyperpigmented, translucent papule



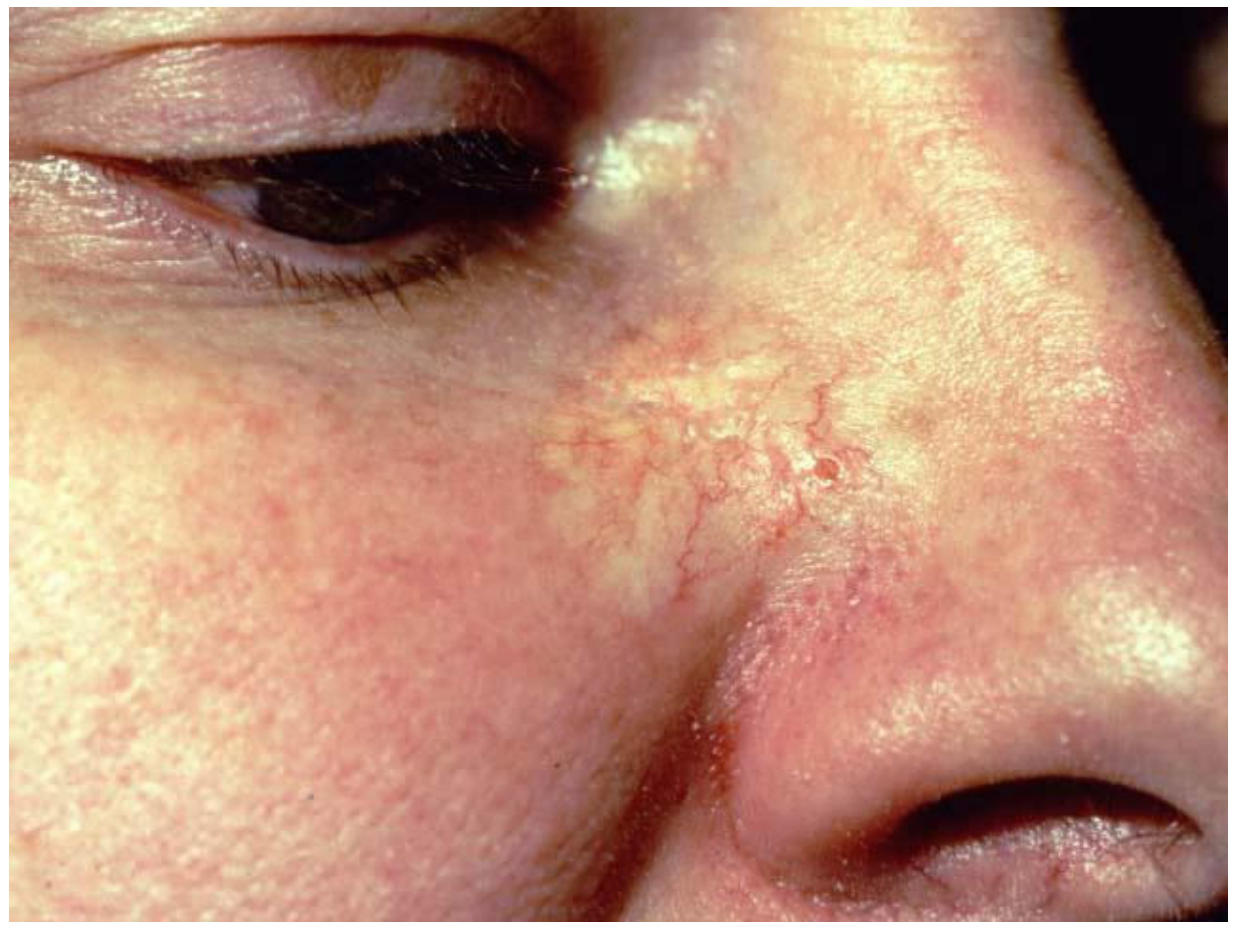
Superficial BCC

- Superficial BCC - most commonly on the trunk
- Appears as - a well-demarcated erythematous patch
- The DD nummular (discoid) dermatitis
- An isolated patch of "*eczema*" that does not respond to treatment - raise suspicion for superficial BCC



Morpheaform BCC

- An aggressive growth variant
- Lesions of morpheaform BCC - have an ivorywhite appearance
- May resemble a scar or a small lesion of morphea
- The appearance of scar tissue [in the absence of trauma/ previous surgical procedure or the appearance of atypical-appearing scar tissue at a previously treated lesion] - alert for possibility of morpheaform BCC
- The extent - often larger than the clinical appearance



Basosquamous carcinoma

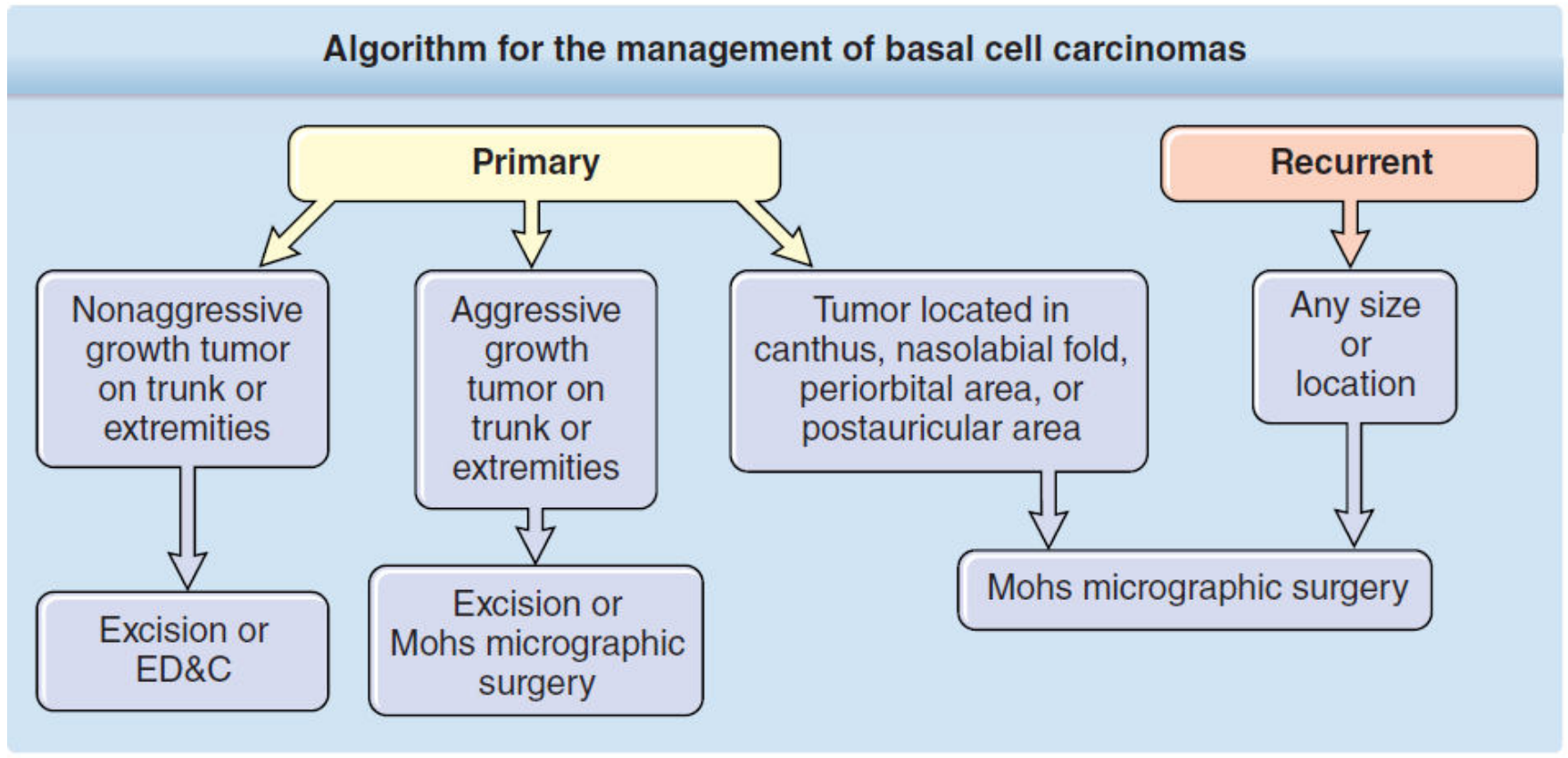
- A form of aggressive growth BCC
- Can be confused with squamous cell carcinoma (SCC)
- Histologically - Shows both basal cell and SCC differentiation in a continuous fashion

Diagnosis

- Diagnosis - Accurate interpretation of the skin biopsy results
- The preferred method of biopsy - shave biopsy, punch biopsy
- Punch biopsy - Useful for flat lesions of morpheaform BCC & for recurrent BCC occurring in a scar
- During biopsy - adequate tissue

Management

- Management of BCC - guided by anatomic location & histological features
- Approaches include standard surgical excision or destruction by various other physical modalities, Mohs micrographic surgery (MMS) topical chemotherapy
- Best chance to cure - Through 'adequate initial treatment' → recurrent tumors are more likely to be resistant to further treatments
- May cause further local destruction



Algorithm for the management of basal cell carcinomas. ED&C, electrodesiccation and curettage.

Mohs micrographic surgery

- Developed in 1938 by Frederic E. Mohs, a general surgeon
- A microscopically controlled surgery used to treat common types of skin cancer
- During the surgery, after each removal, the tissue is examined for cancer cells
- Provides informed decision for additional tissue removal
- Improves prognosis - After 5 years, MMS-treated BCCs recurred in 1.4% of primary & 4% of recurrent tumors
- Preferred treatment for any BCC where tissue conservation is desired

- Standard surgical excision
- Curettage & desiccation
- Cryosurgery
- Imiquimod (5% cream)
- 5-Fluorouracil
- Photodynamic therapy (PDT)

Squamous cell carcinoma (SCC)

- SCC - second most common skin cancer, in immunocompetent after basal cell carcinoma
- The most common skin cancer - in immunosuppressed organ transplantation recipients
- Majority of SCC - present with early-stage disease
- Prognosis - excellent in the majority of cases
- Risk of developing metastasis from SCC is *generally* low

Risk factors

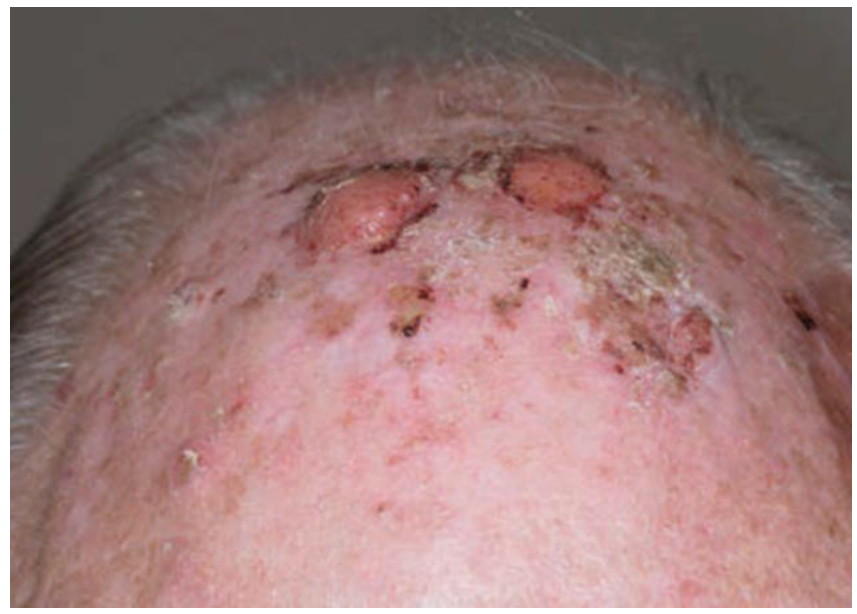
- Ultraviolet radiation (both UVB and UVA) – most important environmental risk factor for the development of SCC with a strong dose-response association
- Genetic predisposition - potentiate the risk of environmental factors such as UVR
- Clinical skin phenotypes - Light complexion (as in photo types I, II)
- Physical & chemical carcinogens- *Arsenic*, used in various medications, tainted wine and unprocessed well water may stimulate skin carcinogenesis; *Cutting oils* - a risk of SCC development in certain industrial occupations; SCC on the scrotum of chimney sweeps - attributed to chronic exposure to *ash & polycyclic aromatic hydrocarbons* derived from carbon compounds (e.g. coal tar)
- Immunosuppression including iatrogenic (e. g. solid organ transplantation recipients, with autoimmune or rheumatoid disease), Hematopoietic stem cell transplantation, Infection with HIV/AIDS
- Viral infection – HPVs
- Chronic inflammation & chronic injury of the skin – chronic ulcers (Marjolin's), burn scars & radiation dermatitis
- Chronic inflammatory disorders - discoid lupus erythematodes, mucosal & hypertrophic lichen planus, lichen sclerosus & dystrophic epidermolysis bullosa

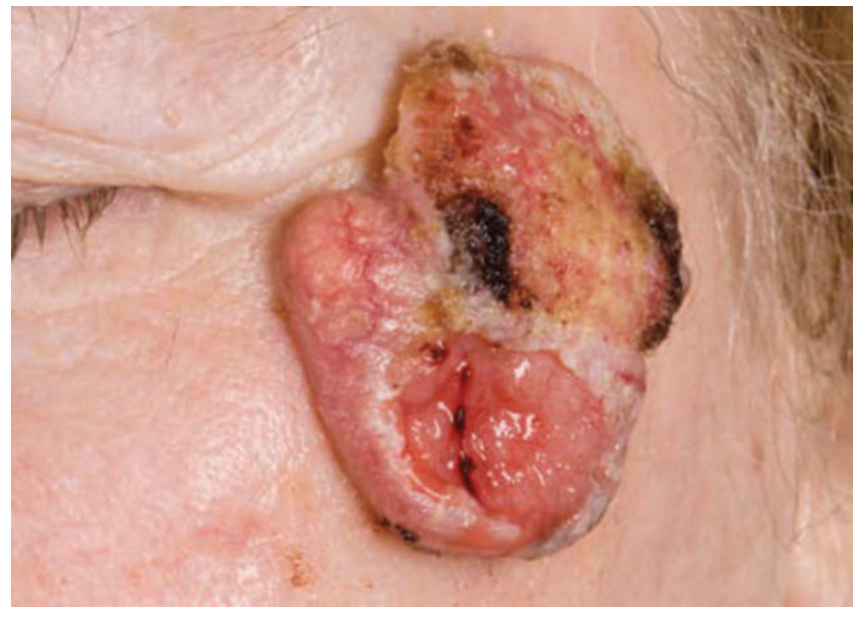
Epidemiology

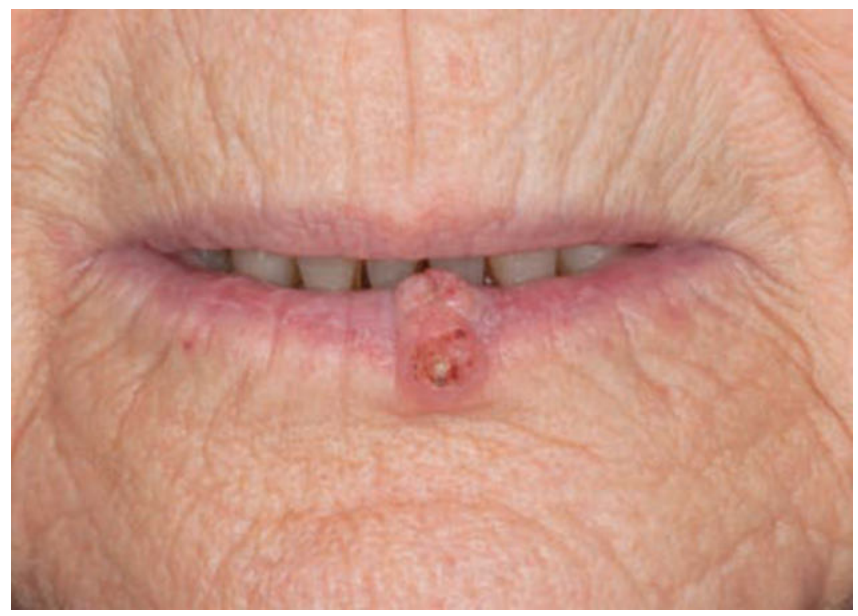
- SCC incidence - increases with age; most patients =/> 60
- Higher in men than in women
- Sun-sensitive individuals with red hair, blue eyes & fair complexion - higher risk than individuals with darker pigmentation
- Race- Australians, exposed to very high, long-term UVR levels – more likely to develop SCC than other populations

Clinical Features

- Variable & depends on the histologic subtype and location
- Typically, SCCs arise on sun-exposed areas
- The face, head, and neck region & the forearms & dorsum of the hands
- The typical clinical finding – includes slowly enlarging, firm, skin-colored to erythematous plaques or nodules
- Marked hyperkeratosis
- Ulceration, exophytic or infiltrative growth patterns - seen

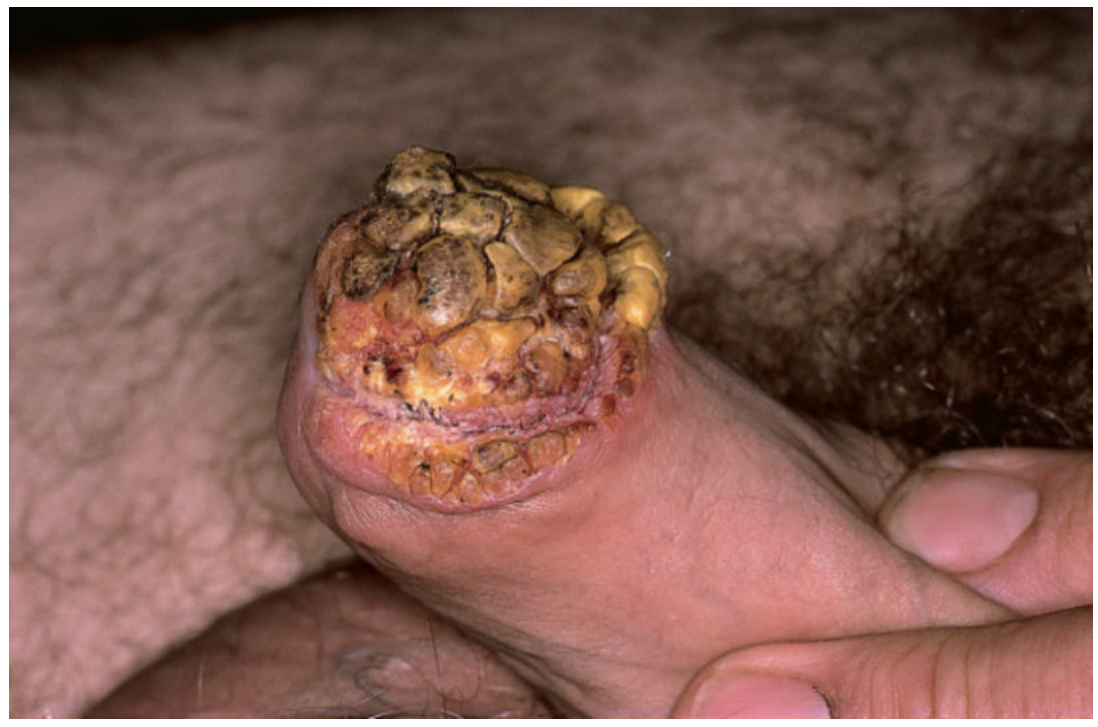






Verrucous SCC

- Verrucous SCC - a slowly growing ulcerated plaque or an exophytic cauliflower-like slowly growing tumor
- <u>Typical locations</u>
- Oral cavity (oral florid papillomatosis)
- Genitoanal region (giant condyloma acuminatum; Buschke-Löwenstein)
- Plantar skin (epithelioma cuniculatum)
- Amputation stumps
- Less common than other forms of invasive SCC



Diagnosis

- The standard pathology report to indicate:
- Histologic subtype (acantholytic, spindle cell, verrucous, or desmoplastic type)
- Grade of differentiation (G1 to G4)
- Maximum vertical tumor diameter in millimeters
- Extent of dermal invasion (Clark level)
- Presence or absence of perineural, vascular, or lymphatic invasion
- Information about whether the margins are free or not

Treatment

- Treatment modality for the primary lesion - major determinant for the risk of local recurrence
- Ideal management - *local* tumor control along with maximal *preservation* of function and cosmesis

Surgical excision

- Surgery excision - preferably microscopically controlled surgery (Mohs surgery) - primary mode of therapy
- For localized lesions - cure rate of 95%
- SCC - local *in-transit* metastasis- may be removed by wide surgical excision or treated by irradiation of a wide field around the primary lesion
- Treatment of nodal metastasis - lymph node dissection, radiation, or a combination of both

Other therapies

- Topical therapeutic treatments- e.g. imiquimod, topical or intralesional 5-fluoruracil, cryotherapy & PDT – Lack of evidence for the efficacy
- Radiation therapy - patient preference and other factors, e.g. problematic locations for surgery

- Limited data on the efficacy of chemotherapy for *metastatic* SCC
- Standard options in metastatic or unresectable disease – systemic platinum-based chemotherapeutic regimens, 5-fluorouracil/capecitabine, or monotherapy/chemotherapy with methotrexate

Prognosis

- Majority of SCCs- low risk
- If early stage- result in a high cure rate with excellent prognosis
- Prognosis for locally advanced SCC at the time of diagnosis & patients with progressive disease after first-line surgical therapy - usually poor
- A poorer outcome of *immunosuppressed* patients with advanced disease

Melanoma

- Melanoma (Gr. *melas* [dark], *oma* [tumor]) - malignant tumor arising from melanocytic cells
- Can occur anywhere where melanocytes are found
- The most frequent type - cutaneous melanoma
- Also at the mucosal, the uveal, or even the meningeal membrane
- 10% melanomas – detected by lymph node metastases [with so-called “unknown primary”]

Epidemiology

- Rising incidence worldwide - Countries with white inhabitants, with highest incidence rates in Australia (35 new cases/year/100,000)
- North America (21.8 new cases/100,000)
- Europe (13.5 new cases/100,000)
- Median age - for melanoma diagnosis is 63 years with 15% being <45 years
- Melanoma – Accounts for only 4% of all skin cancer diagnoses in the USA
- Responsible for 75% of skin cancer deaths

Risk factors

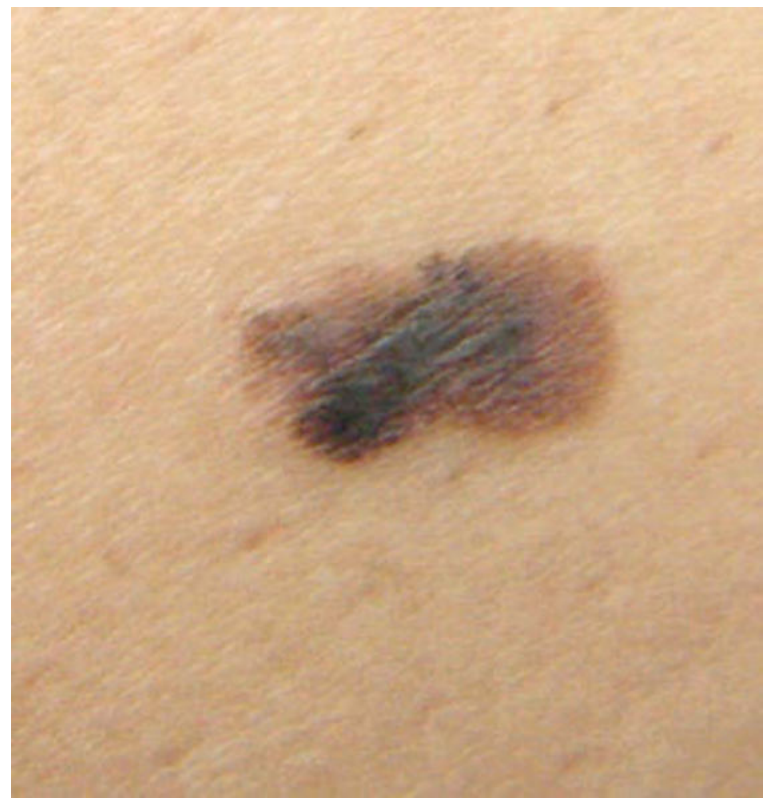
- History of sunburns and/or heavy sun exposure
- Fitzpatrick skin phototypes I & II
- Blue or green eyes, blonde or red hair, fair complexion
- >100 typical nevi, or any atypical nevi
- Prior personal or family history of melanoma
- *p16* mutation

Clinical Features

- Subtypes
  - ➢Superficial spreading melanoma
  - ➢Nodular melanoma
  - ➢Lentigo maligna
  - ➢Lentigo maligna melanoma
  - ➢Acral lentiliginous melanoma
  - ➢Desmoplastic melanoma
  - ➢Mucosal melanoma

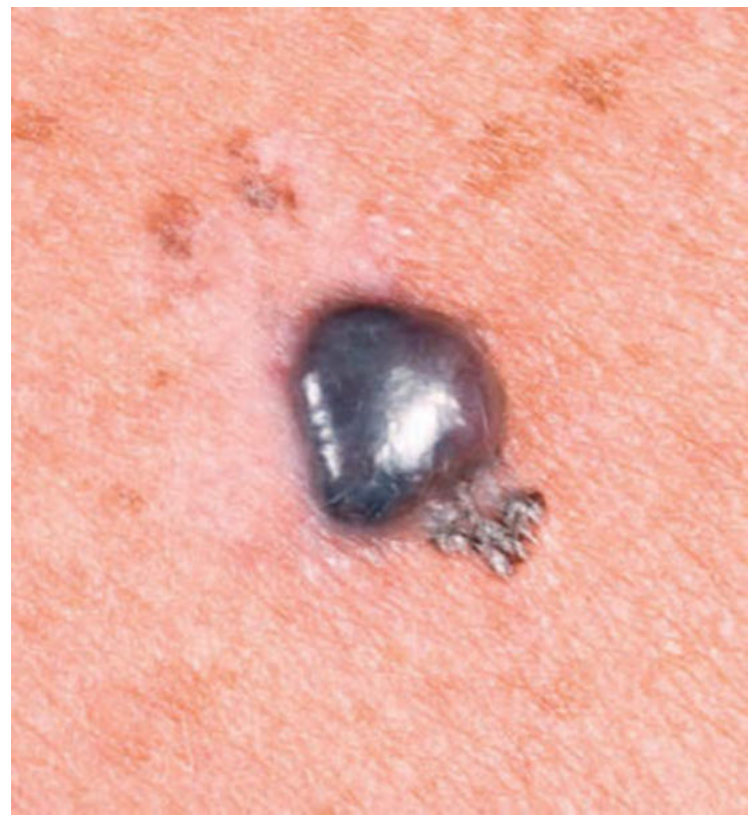
Superficial spreading melanoma

- Most common subtype, accounting for approximately 70%
- Most common on intermittently sunexposed areas
- The lower extremity of women; the upper back of men
- Irregular borders and irregular pigmentation
- May present subtly as a discrete focal area of darkening
- Varying shades of brown typify most melanocytic lesions
- Also aspects of dark brown to black, blue-gray, red, and gray-white (which may represent regression) may be found



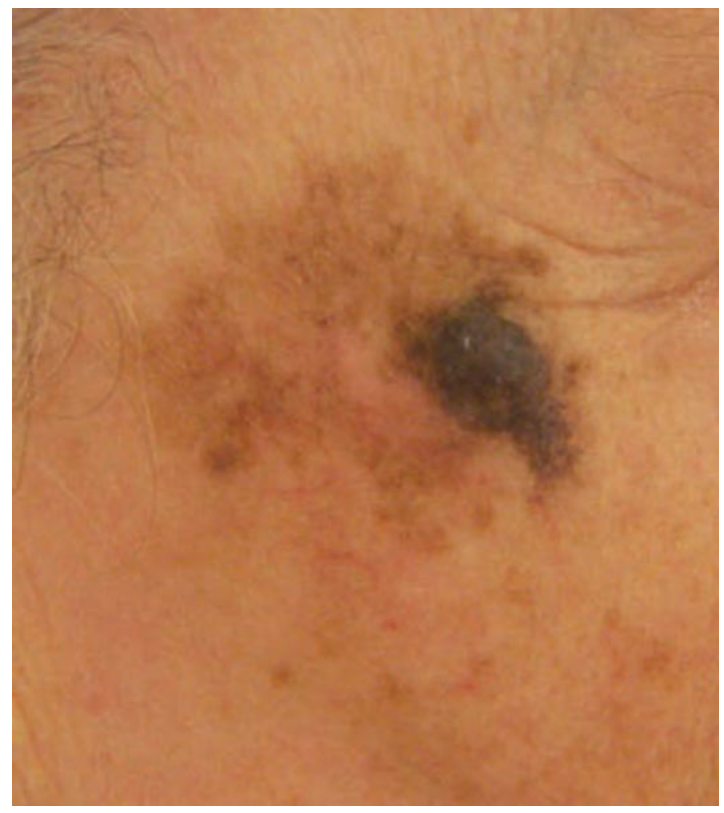
Nodular melanoma

- Approximately 15%-30% of all melanomas
- The trunk - the most common site
- Remarkable for rapid evolution - often arising over several weeks to months
- May lack an apparent radial growth phase
- Typically appears as a uniformly dark blue-black or bluish-red raised lesion
- 5% are amelanotic



Lentigo maligna & Lentigo maligna melanoma

- Lentigo maligna - melanoma *in situ* with a prolonged radial growth phase
- Eventually becomes invasive → Lentigo maligna melanoma
- Diagnosed most commonly in the seventh to eighth decades (uncommon before the age 40)
- Most common location - the chronically sun-exposed face, on the cheeks and nose in particular
- Clinical appearance - flat, slowly enlarging, brown, freckle-like macule with irregular shape & differing shades of brown and tan



Complications

- Usually based on metastatic disease - symptoms associated with the affected organ
- Pain (any metastases)
- Convulsion (brain metastases)
- Instabilities, # - (bone metastases)
- Later - symptoms associated with progression of the disease & death in the palliative setting
- Cutaneous changes - localized or diffuse hypo- or hyperpigmentation
- Development of a melanoma-associated vitiligo [an accompanying *autoimmune* disease against melanocytes] - in 4%; associated with a better prognosis

Diagnosis

- Early detection - the key to improve prognosis
- Melanoma - Change in color and increase in size (or a new lesion) are the 2 most common *early* characteristics noticed by patients that may be useful in discriminating between melanoma and other benign lesions
- Physical examination
- Dermascopy

- Pathology- *Excisional* skin biopsy
- Large lesion and/or located on anatomic areas such as the palm/sole, digit, face, or ear, an *incisional* skin biopsy *may* be performed
- Lymph node examination f/b USG/excisional biopsy
- Tomographic investigations like computed tomography (CT), magnetic resonance imaging (MRI) & positron emission tomography (PET) - generally not recommended at the stage of primary melanoma - rate of false positive findings is far too high (8%-15%), e.g. unspecific lung lesions

Management

- The standard of therapy - wide local excision (WLE)
- The purpose - to prevent local recurrence due to subclinical persistent disease
- The risk of satellite metastases - related to primary melanoma thickness
- Current recommendations on the clinical margins - depending on the Breslow thickness of the primary
  - For melanoma *in situ* - a 0.5-1-cm margin
  - For melanoma <1±mm Breslow depth –a 1-cm margin
  - For melanoma 1 to 2±mm thick - a 1- to 2-cm margin
  - For melanoma >2±mm thick - a 2-cm margin is recommended
- Wider excisions with up to 5-cm margins - *not* show a benefit for local recurrence rate
- Standard of therapy for macroscopic (stage IIIB/IIIC) lymph nodes – CLND of the involved regional basin
- Uncontrolled nodal disease - Major cause of melanoma-related morbidity with a significant high negative impact on QoL
- CLND for regional metastatic melanoma - associated with long-term survival

Adjuvant therapy

- Adjuvant therapy - for patients with surgically resected disease who are at high risk for relapse such as those with thick primary melanomas or nodal disease
- Interferon-alpha
- Anti-CTLA-4 antibody (ipilimumab) – an immune checkpoint blocker
- Adjuvant radiotherapy after CLND

Treatment algorithm		
	Surgery	**Systemic treatment**
Stage I/II	**Wide local excision** • In situ (0.5 cm) • ≤2 mm (1 cm) • >2 mm (2 cm)	**Consider adjuvant treatment** • Low-dose interferon for high-risk primary
Stage III	**Complete lymph-node dissection (CLND)** • Stage IIIB/C	**Adjuvant treatment** • Immune checkpoint blocker (nivolumab, pembrolizumab, ipilimumab)
Stage IV	**Consider metastasectomy** • Stolitary metastasis	**Immune checkpoint blocker** • Ipilimumab + nivolumab • PD-1 antibody monotherapy **Targeted Therapy** • BRAF/MEK inhibition (BRAF mutation) • Consider KIT inhibition (KIT mutation)