Cutaneous squamous cell carcinoma represents one of the most common malignancies in humans. The malignant tumour arises from suprabasal epidermal keratinocytes that invade the dermis and together with basal cell carcinoma, forms the most common malignancies of skin to affect humans. But unlike basal cell carcinoma that is thought to arise de novo, this non-melanoma skin cancer is thought to evolve from precursor lesions of actinic keratosis (AK) and Bowen’s disease. The clinical appearance is highly variable but a strong suspicion must be kept in mind if a non-healing lesion presents, specially on sun exposed areas. Histopathological evidence helps in establishing the diagnosis. While a multitude of treatment options are available, prevention in patients with predispositions should attract more attention.

Definition and Epidemiology of Squamous Cell Carcinoma

Cutaneous squamous cell carcinoma is a non-melanoma skin cancer arising from the
suprabasal epidermal keratinocytes.

Non-melanoma skin cancers are the most common type of skin cancers affecting humans. SCC is the **second most common non-melanoma skin cancer** following basal cell carcinoma. It is seen most frequently in sun exposed areas in people aged more than 40 years. White males are more likely to be affected by this cancer, however SCC is the most common skin cancer in patients with darker skin types.

### Classification of Squamous Cell Carcinoma

#### Precursor lesions

- Actinic keratosis (AK)
- SCC in situ (Bowen's disease)

#### Direct exposure to the sun

- SCC (invasive SCC)
- Clear cell SCC
- Spindle cell SCC
- SCC with single cell infiltrates

#### Unrelated to sun exposure

- De novo SCC
- Verrucous carcinoma
- LELCS (lymphoepithelioma-like carcinoma of skin)

### Etiology and Pathogenesis of Squamous Cell Carcinoma

SCC is associated with both **acquired** and **genetic risk factors**.

### Predisposing factors

**Precursor lesions**
Most SCCs develop from precursor lesions - AK or Bowen's disease.

**UV exposure**
- Predominant risk factor
- Linear relationship between UV exposure and SCC incidence
- Incidence of SCC doubles with every 8-10 degree decline in latitude
- Highest incidence at equator

**Ionizing radiation**
Patients susceptible to **sunburns** are more at risk for developing SCC.

**Environmental carcinogens**
- Other than anthramine and 3-methylcholanthrene, chemical carcinogens generally produce more SCC than BCC
- Alcohol and smoking are associated with SCC of the oral cavity

**Chronic immunosuppression**
- Patients on long term corticosteroid, azothioprine or cyclosporine therapy found to be susceptible to SCC
- 18-fold rise in patients with renal transplant
- More aggressive behaviour in patients with HIV, leukaemia, lymphoma

**Human papilloma virus**
- Verruca pus carcinoma is associated with many variants of HPV
- SCC of head, neck and periungual region are associated with HPV

**Thermal factors**
Chronic heat exposure is also a risk factor.

**Scars and underlying diseases**
- Associated with burns and chronic infection
- Vaccination scars are more associated with BCC than SCC

**Genodermatoses**
- Variety of heritable diseases predispose to SCC
- Xeroderma pigmentosum, dystrophic form of epidermolysis bullosum, epidermodysplastic verruciferous, oculocutaneous albinism, etc.

**Molecular aspects**

**Genetic alterations**
- Chromosomal deletions in chromosomes 3,7,9,11
- Involvement of p53 tumor suppression genes

**Involvement of p53 genes**
- **Apoptosis** of keratinocytes with UV damage is regulated by p53 tumor suppressors, which are a defense against malignant transformation
- Loss of function of p53 leads to increased resistance of UV damaged cells to apoptosis; they proliferate and survive better - increasing the risk for SCC
Other apoptotic regulators

- Bcl-2 inhibition in vulvar SCC
- Bcl-XL in tumor invasion and metastasis
- Bax in SCC tongue

Clinical Manifestations of Squamous Cell Carcinoma

Development from precursor lesions

![Image: “Actinic keratoses are precancerous lesions common on sun-exposed areas of the skin. They can assume many different appearances, but this image shows a very common presentation of AKs on a balding head.” by Future FamDoc – Own work. License: CC BY-SA 4.0]

Actinic keratosis

- Multiple lesions
- Pin point to over 2cm in size
- Ill defined borders
- Rough gritty texture

Bowen’s disease

- Isolated lesions
- Variable size
- Sharply demarcated lesions
- Scaling papules or plaques that are non-pruritic

The development of tenderness, induration, erosion, increased scaling or enlarging diameter indicate evolution into SCC.

Morphologies of SCC

SCC can present in many different ways. The most common presentation is a firm, erythematous, keratotic plaque or papule, however, ulcers, thick cutaneous horns or modules are not uncommon.

In periungual location, the abscess or verrucous form of SCC are more commonly seen. As the tumor progressively invades, it loses the free character and fixes to the
underlying tissue. In the head and neck region, **enlarged lymph nodes** are indicative of tumor **metastasis**.

Usual **sites of presentation** include **oral cavity** (involving palate and tongue), and more commonly, the **lower lip**, as well as the genital region (most common site being anterior labia majora of vulva).

**Keratocanthoma** is a clinical subtype of SCC, which usually spontaneously resolves but can also be locally aggressive and destructive. The hallmark feature is its rapid growth, over several centimeters in a matter of weeks followed by spontaneous resolution over a period of months. The usual presentation for this is an elderly patient presenting with a large, smooth, dome shaped verrucous lesion with a central keratotic crater on the extremities.

### Investigations for Squamous Cell Carcinoma

**Biopsy**

The diagnosis of SCC is always made with biopsy. In elevated lesions, **punch biopsy** is performed while in flat lesions or lesions with minimal elevation (less than 1mm), **superficial shave technique** is adequate and also minimizes wound size and scarring.

**Depth of the biopsy** should be sufficient to distinguish between in situ carcinoma and invasive SCC.

**What to expect in the histopathological report?**

- The hallmark of SCC is **extension of atypical keratinocytes** beyond the basement membrane and into the dermis.
- **Absence of connection** between epidermis and tumor cells indicates metastatic SCC.
- Clues to underlying etiology, for example, presence of scar tissue indicates recurrent SCC, while solar elastosis and keratinocyte atypia indicates actinically derived SCC. These clues hold important implications for treatment and prognosis.

### Differential diagnosis

- **Bowen’s disease** may have an **eczematous appearance** and at first sight may be mistaken for eczema, psoriasis or lichen simplex. These lesions are however pruritic, a finding characteristically absent in Bowen’s disease.
- For **verrucous lesions** - warts, seborrhoeic keratosis, AK, chromomycosis, metastatic SCC, Merkel cell carcinoma
- For **ulcerative lesions** - trauma, BCC, herpes virus infection
- For **pigmented lesions** - melanoma

### Management of Squamous Cell Carcinoma

Selection of the best modality of treatment for SCC is based on an assessment of risk factors for recurrence and **metastasis**.

**Non-excisional ablative techniques**
Electrodesiccation and curettage
- Liquid nitrogen cryotherapy
- Carbon dioxide laser
- Intralesional chemotherapy
- Photodynamic therapy
- Superficial technique
- Do not allow histological margin control
- **Status:** to be used in situ disease only, in special circumstances. Inappropriate for invasive SCC.

**Surgical techniques**

Conventional surgical excision:

- **Treatment of choice for primary SCC**
  - Recommended margins – 4mm for low risk lesions with depth less than 2mm

Mohs microscopically controlled surgery (MMCS):

- Allows for minimal tissue destruction
- **Indications of MMCS**
  - History of radiation at site
  - Involvement of nerve, muscle, or bone
  - Immunosuppression
  - Recurrent tumor
  - Infiltrative SCC
  - Important tissue preservation sites (lip, eyelid, nasal tip, ear, genitalia)
  - Verrucous carcinoma

**Radiation**

- Used for superficially invasive to moderate risk lesions, particularly in lesions
of external auditory canal

- As adjuvant therapy:
  - To excisional surgery in residual microscopic disease
  - Perineural SCC
- As prophylaxis against metastatic disease

Prevention of Squamous Cell Carcinoma

Patients with a prior history of non-melanoma skin cancer or with any of the predisposing factors as mentioned above must receive regular complete skin examinations.

Sun protection

It is the most effective method of prevention. Includes regular application of sunscreen, proper clothing, wearing sunglasses and avoiding exposure to sun during peak hours.

Treatment of precursor lesions

A variety of treatment options are available for management of AK. While isolated lesions can be treated with liquid nitrogen cryotherapy, multiple lesions are treated with a course of 5-fluorouracil.

Other preventive measures

- Use of condoms and vaccination to prevent the transmission of HPV
- Decrease alcohol consumption
- Smoking cessation
- Use of low dose retinoids and interferons as systemic chemopreventive agents, for example Accutane
- Topical application of DNA repair enzymes in liposomes
- Topical immune modifiers that stimulate cutaneous immunity to kill malignant cells

References

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msdmanuals.com

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