

Squamous Cell Carcinoma

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Squamous cell carcinoma at the junction between the corner of the mouth and cheeks

It is estimated that there are between 900,000 and 1,200,000 new skin cancers each year in the United States. 80% of these cases are Basal Cell Carcinomas & 20% are Squamous Cell Carcinomas, which is roughly about 250,000 new cases each year in the US only.

Squamous cell carcinoma is the second most common type of skin cancer. It arises from plate-like cell layer in the epidermis and is due to extensive sun exposure. Squamous cell carcinoma can metastasize if is not treated.

Etiology

Neoplastic is generated from the squamous cell layer of the epithelium upon stimulation by irritants. Those irritants (or known as risk factors) are stochastic in nature and it is hard to specify a specific dose or quantity at which the neoplastic tissue starts to generate. DNA damage by irritants is the most probable cause of neoplastic tissue generation.

Squamous cell carcinoma is typically found on areas often exposed to the sun, such as the scalp, face and neck, however, it can develop on other parts of the body including the mucous membrane and the genitalia.

Although researchers know what causes many cases of squamous cell carcinoma – most notably, excessive exposure to ultraviolet radiation – studies are still underway to determine how this type of cancer develops in parts of the body that are seldom or never exposed to sunlight. Past studies show that nearly 95 percent of all non-melanoma skin cancers are the direct result of DNA changes that occur in the skin after cells are damaged by UVA or UVB rays, and scientists continue to investigate the possible causes of the remaining 5 percent.

Through ongoing studies, researchers are also investigating the exact changes that occur within the body after squamous cells are damaged by UV exposure. Currently, with regard to what causes squamous cell carcinoma, medical professionals know that:

- Healthy skin regenerates itself every few days. As old cells die, they are pushed to the surface of the skin by the new cells developing underneath. The old cells are then sloughed off.

- When squamous cells sustain DNA damage, the cells aren't able to regulate their own growth as they normally should. Abnormal cells can accumulate without dying off and create bumps or sores on the skin.

Risk factors

Many risk factors associated with squamous cell carcinoma have a direct link to UV exposure. For instance:

1. Tobacco

- Patients with smoking habits are at a much higher risk of developing SCCs.

2. UV Exposure

- Extended exposure to UV radiations may introduce mutations in the DNA of the squamous cell layer promoting SCC.
- Males are nearly three times more likely to develop squamous cell carcinoma than females, which may be partially attributed to their comparatively higher tendency to spend time outdoors without adequate sun protection.
- Use of tanning beds. People who use indoor tanning beds have an increased risk of squamous cell carcinoma of the skin.

3. History of precancerous lesions, sunburns or SCC

- A personal history of precancerous skin lesions. Having a precancerous skin lesion, such as **actinic keratosis** or **Bowen's disease**, increases your risk of squamous cell carcinoma of the skin.
- A history of sunburns. Having had one or more blistering sunburns as a child or teenager increases your risk of developing squamous cell carcinoma of the skin as an adult. Sunburns in adulthood also are a risk factor.
- A personal history of skin cancer. If you've had squamous cell carcinoma of the skin once, you're much more likely to develop it again.

4. Racial susceptibility

- Fair skin. Anyone, regardless of skin color, can get squamous cell carcinoma of the skin. However, having less pigment (melanin) in your skin provides less protection from damaging UV radiation.
- If you have blond or red hair and light-colored eyes and you freckle or sunburn easily, you're much more likely to develop skin cancer than is a person with darker skin.

5. Age

- Older adults are more frequently diagnosed with squamous cell carcinoma than younger individuals, presumably due to the cumulative effects of UV exposure over a person's lifetime.
- People with an inherited condition known as xeroderma pigmentosum have an extreme sensitivity to sunlight and are also very susceptible to cellular damage caused by UVA and UVB rays.

6. Genetically Susceptible and Infected individuals

- People with psoriasis and other inflammatory skin diseases often receive ultraviolet light-based treatments, which can increase their risk of developing skin cancer in the future.
- Rare genetic disorder. People with xeroderma pigmentosum, which causes an extreme sensitivity to sunlight, have a greatly increased risk of developing skin cancer.
- Weakened immune system. People with weakened immune systems have an increased risk of skin cancer. This includes people who have leukemia or lymphoma and those who take medications that suppress the immune system, such as those who have undergone organ transplants.

Additional risk factors include exposure to large amounts of arsenic, coal tar or other carcinogenic chemicals; chronic ulcers and a history of radiation therapy for previous cancers. Also, a person who has already been diagnosed with skin cancer has an elevated risk of developing a second skin cancer during his or her lifetime.

Epidemiology

- It commonly affects men > 60 years
- Incidence: More than one million cases each year in the U.S alone.
- About 15,000 people die each year as a result of nonmelanoma skin cancer, mostly metastatic SCC.
- It has been estimated that a Caucasian male born in 1994 has a 9% to 14% chance of developing an SCC within his lifetime. The estimates for white women range from 4% to 9%.
- Fair-skinned phenotype, excessive cumulative overexposure to UV radiation, advancing age, outdoor vocation, or avocation, and sunbelt latitudes.
- The highest risk factors are the presence of Actinic Keratosis or a previous nonmelanoma skin cancer
- Immunosuppressed patients and patients receiving long-term photochemotherapy (PUVA) are especially predisposed to the development of SCCs.
- Countries or Cities near the equator are of higher frequency of developing SCCs.
- High-risk SCCs for metastases and death are those that grow rapidly, become larger than 2 cm, invade deeply and reach a thickness of at least 6 mm, have been treated previously, or are located in high-risk areas such as the vermilion lip, the ear, and the columella of the nose. Patients who are immunocompromised are more predisposed to the development of metastases.

Clinical Presentation

SCCs may occur on all areas of the body, including the mucous membranes and genitals, but are most common in areas frequently exposed to the sun, such as the rim of the ear, lower lip, face, balding scalp, neck, hands, arms and legs. The skin in these areas often reveals telltale signs of sun damage, including wrinkles, pigment changes, freckles, “age spots,” loss of elasticity and broken blood vessels.



Figure 1: SCC a of the buccal mucosa.

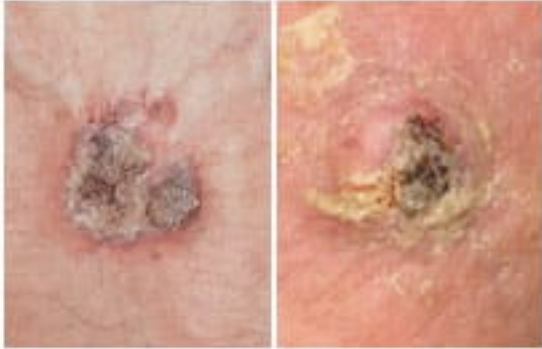
SCCs can often look like scaly patches, open sores, warts or elevated growths with a central depression; they may crust or bleed. They can become disfiguring and sometimes deadly if allowed to grow.

Signs and Symptoms

Skin cancers often do not cause bothersome symptoms until they have grown quite large. Then they may itch, bleed, or even hurt. But typically they can be seen long before they reach this point. Squamous cell carcinoma are usually easy to find early, during a thorough skin examination by a dermatologist. Regular examination of the skin for any new or unusual growths, or changes in the size, shape or color of an existing spot, is key to finding and treating these cancers early.

General warning signs of skin cancer include a new spot or growth that increases in size, or a sore that doesn't heal within two months. In addition, common signs of squamous cell carcinomas include:

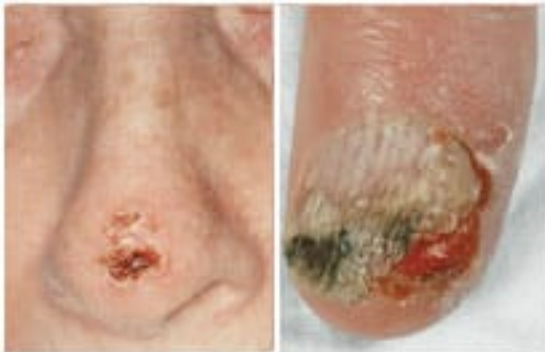
- Persistent, thick, scaly patches that may bleed.
- It can be a white-ish or reddish lesion.
- A growing lump with a rough scaly or crusty surface, Slow-growing flat reddish patch.
- Raised growths or lumps, sometimes with a lower area in the center.
- Wart-like growths and sometimes have open sores with a raised border.
- The skin around them typically shows signs of sun damage such as wrinkling, pigment changes and loss of elasticity.



(a) Persistent, scaly red patch with irregular borders that sometimes crusts or bleeds.



(b) An elevated growth with a central depression that occasionally bleeds. It may rapidly increase in size.



(c) An open sore that bleeds or crusts and persists for weeks.

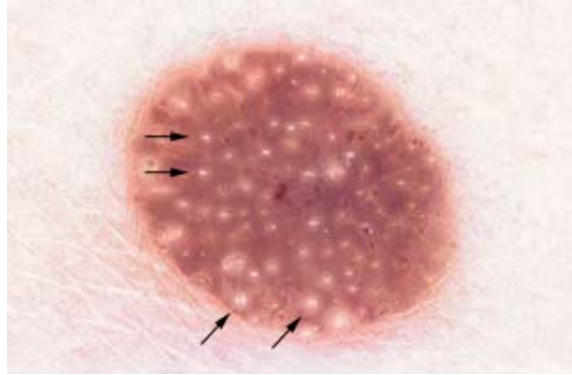


(d) A wart-like growth that crusts and occasionally bleeds.

Differential diagnosis

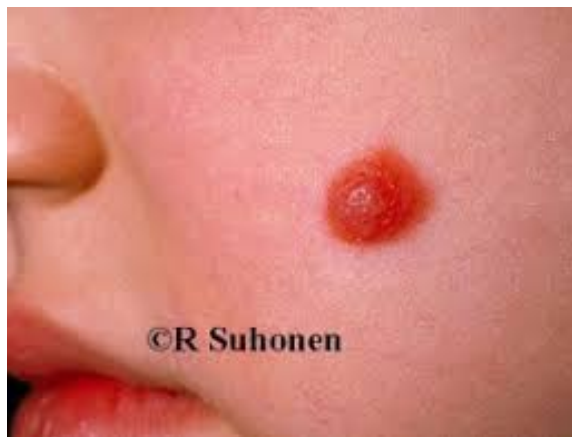
Squamous cell carcinoma usually has some similarities with:

1. Mature melanocytic nevus:



- Type of vessels: comma
- Distribution: regular
- Additional criteria:
 - a. Comedo-like openings/milia-like cysts
 - b. Terminal hair
 - c. Residual brown pigmentation

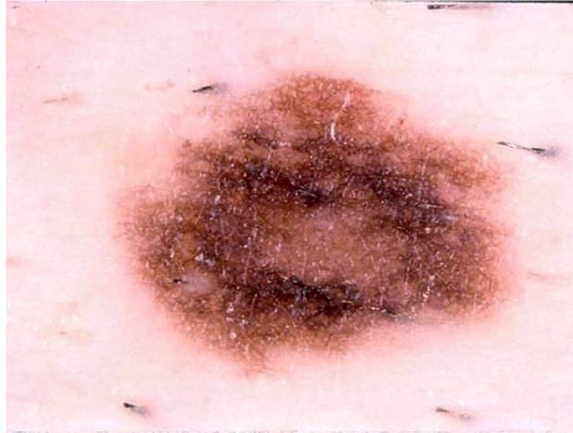
2. Spitz nevus:



A Spitz nevus (also known as an epithelioid and spindle-cell nevus, benign juvenile melanoma, and “Spitz’s juvenile melanoma”) is a benign melanocytic nevus, a type of skin lesion, affecting the epidermis and dermis.

- Type of vessels: dotted
- Distribution: regular
- Additional criteria:
 - a. Pink background
 - b. Melanocytic criteria:
 - c. Inverted network
 - d. Chrysalis structures

3. Dysplastic nevus:



These are unusual benign moles that may resemble melanoma. People who have are at increased risk of developing single or multiple melanomas. The higher the number of these moles someone has, the higher the risk. Those who have 10 or more have 12 times the risk of developing melanoma compared to the general population.

- Type of vessels: dotted and comma
- Distribution: regular/irregular
- Additional criteria:
 - Melanocytic criteria

4. Melanoma:



- Type of vessels:
 - a. Thin tumors (<1 mm): dotted vessels
 - b. Intermediate tumors (1-2mm): dotted and linear irregular vessels
 - c. Thick tumors: polymorphous vessels
- Distribution: irregular
- Additional criteria:
 - a. Atypical melanocytic criteria
 - b. Chrysalis structures

5. **Clear cell acanthoma:**



- Type of vessels: dotted
- Distribution: string of pearls
- Additional criteria: Erythematous background

6. **Basal cell carcinoma:**



Basal cell carcinoma is the most common form of skin cancer, affecting approximately one million Americans each year. More than one out of every three new cancers are skin cancers, and the vast majority are basal cell carcinomas. Basal cell carcinomas are easily treated in their early stages. The larger the tumor has grown, however, the more extensive the treatment needed.

- Type of vessels: telangiectasia
- Distribution: branching
- Additional criteria
 - a. Blue-grey nests and ovoid globules
 - b. Maple leaf-like areas
 - c. Wheel spoke areas
 - d. Ulceration

Diagnosis

Squamous cell carcinoma can be diagnosed by the following procedures:

1. Skin Examination
 - Examination of abnormal spots or bumps in the skin
2. Biopsy
 - **Shave biopsy:** A sterile razor blade is used to “shave off” the abnormal-looking growth
 - **Punch biopsy:** A special instrument called a punch or a trephine is used to remove a circle of tissue from the abnormal-looking growth
 - **Excisional biopsy:** A scalpel is used to remove the entire growth

Patient is also most probably going to have a history of:

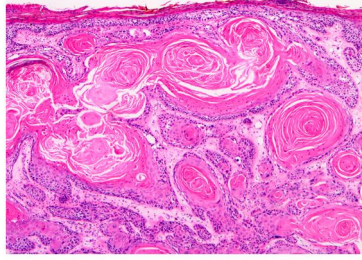
- Smoking habit
- Exposure to UV either by sunlight or artificially
- Precancerous lesion

Types of squamous cell carcinoma:

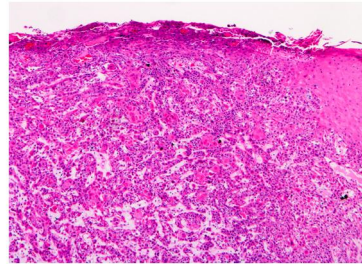
- Verrucous squamous-cell carcinoma
- Clear Cell SCC
- Spindle cell squamous cell carcinoma
- Adenoid/pseudoglandular squamous cell carcinoma
- Intraepidermal squamous cell carcinoma
- Large cell keratinizing squamous cell carcinoma
- Large cell non-keratinizing squamous cell carcinoma
- Lymphoepithelial carcinoma
- Papillary squamous cell carcinoma
- Papillary thyroid carcinoma
- Small cell keratinizing squamous cell carcinoma
- Spindle cell SCC

Histopathology

- Squamous cell carcinoma is a malignant epithelial tumor which originates in epidermis.
- Tumor cells destroy the basement membrane and form sheets or compact masses which invade the subjacent connective tissue (dermis).
- Tumor cells show signs of epithelial dysplasia.
- Tumor cells may surround and destroy blood vessels, and may invade the lumina of vein or lymphatics.
- In well differentiated carcinomas, tumor cells are pleomorphic/atypical, but resembling normal keratinocytes from prickly layer (large, polygonal, with abundant eosinophilic (pink) cytoplasm and central nucleus). Their disposal tends to be similar to that of normal epidermis: immature/basal cells at the periphery, becoming more mature to the centre of the tumor masses. Tumor cells transform into keratinized squamous and form round nodules with concentric, laminated layers, called “cell nests” or “epithelial/keratinous pearls”. The surrounding stroma is reduced and contains inflammatory infiltrate (lymphocytes).
- Poorly differentiated squamous carcinomas contain more pleomorphic cells and no keratinization. (H&E, ob. x10)



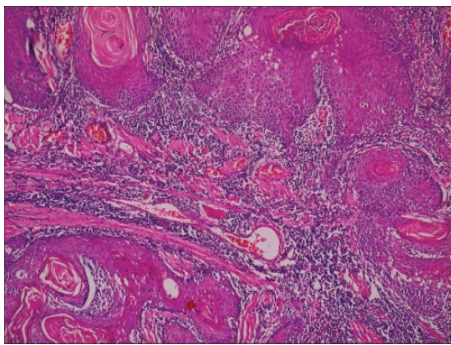
(a) Well-differentiated lesions show prominent keratinization and may form “pearl-like” structures where dermal nests of keratinocytes attempt to mature in a layered fashion (40x).



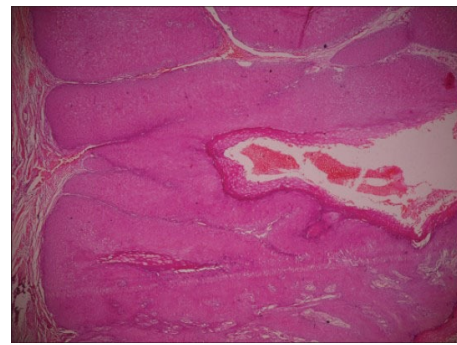
(b) Moderately differentiated lesions of SCC show much less organization and maturation with significantly less keratin formation (40x).

Variants

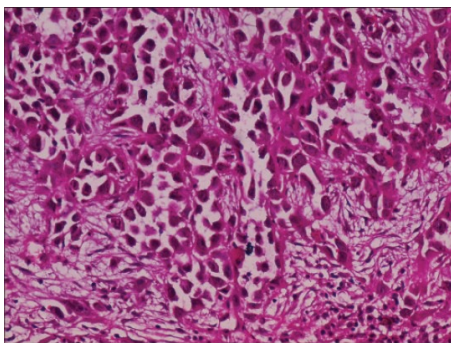
Conventional SCC and variants of SCC frequently arise within the oral cavity. Precise histopathological diagnosis can help the clinician to plan accurate treatment, as the prognosis of each of them differs considerably.



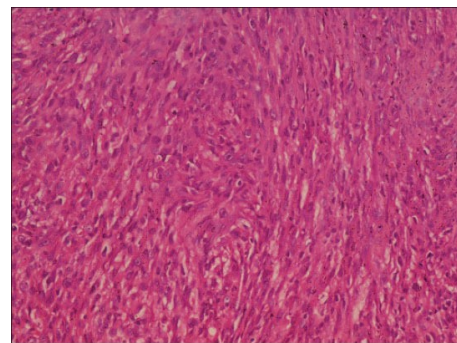
1. **Conventional Squamous Cell Carcinoma:** Conventional oral squamous cell carcinoma-malignant epithelial islands showing keratin pearl formation.



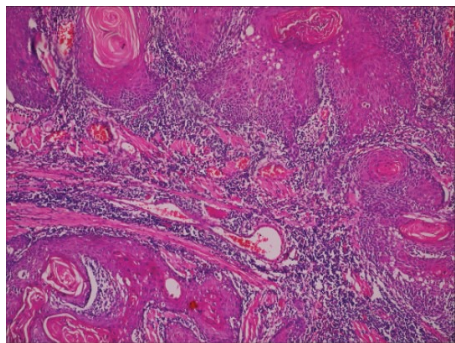
2. **Verrucous Carcinoma:** Verrucous carcinoma-broad bulbous pushing rete ridges with parakeratotic plugging.



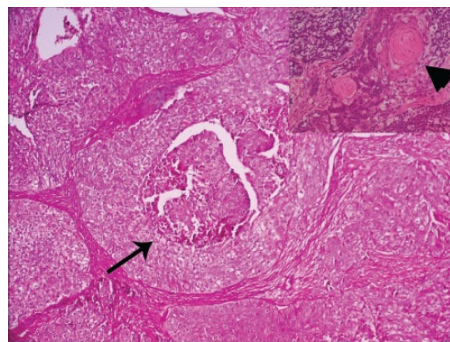
3. **Adenoid squamous cell carcinoma:** Adenoid squamous cell carcinoma -pseudoglandular pattern with acantholytic tumor cells.



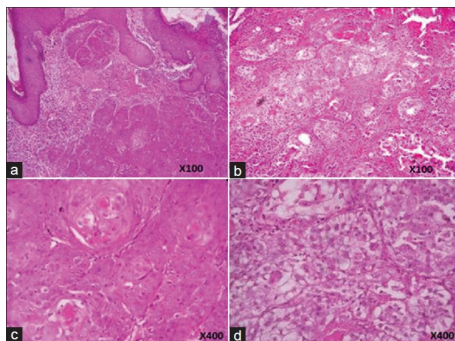
4. **Spindle cell carcinoma:** Spindle cell carcinoma-malignant epithelial cells showing spindling/sarcomatoid appearance.



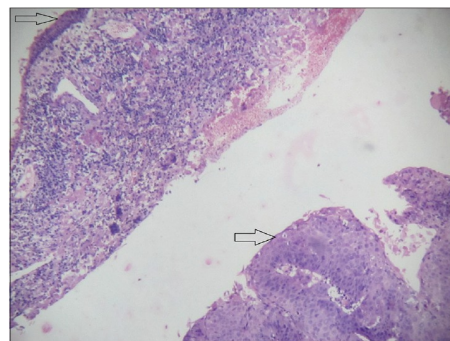
5. **Adenosquamous carcinoma:** Adenosquamous carcinoma-biphasic tumor showing true glandular differentiation (arrowhead) along with squamous differentiation (arrow) (H&E stain, $\times 100$). Inset depicts alcian blue positive mucin secretion ($\times 400$). Characterized histopathologically by a combination of adenocarcinoma and squamous cell carcinoma. The adenoid (glandular) pattern includes mucous production has been demonstrated.



6. **Basaloid squamous cell carcinoma:** Basaloid squamous cell carcinoma biphasic tumor showing basaloid malignant islands with peripheral palisading and comedonecrosis (arrow) (H&E stain, $\times 100$). Inset depicts squamous differentiation with keratin pearl formation (arrowhead) (H&E stain, $\times 100$)



7. **Clear variant of squamous cell carcinoma:** is a rare variant of SCC of skin in which ultraviolet radiation has been suggested as possible etiology. Features of malignant epithelial neoplasm composed of islands of large oval to polyhedral malignant squamous cells with eosinophilic to amphophilic cytoplasm and vesicular nuclei and there were areas showing clear cell differentiation and isolated areas of keratin pearl formation. The hydropic degeneration of neoplastic cells and the accumulation of intracellular fluid and not the accumulation of glycogen, lipid, or mucin, results in its clear cell appearance.



8. **Transitional Cell Carcinoma (Lymphoepithelioma):** H and E stain, $\times 40$. Section shows the tissue lined by a respiratory type of epithelium (marked with arrow) and papillary projections formed by nonkeratinizing squamous cells (marked with arrow).

Tumor Grading

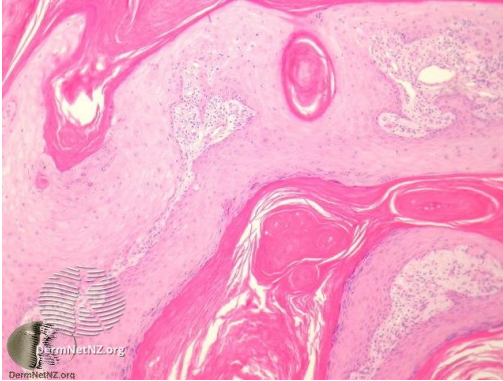
Histopathological Grading Systems for Oral Squamous Cell Carcinoma:

1. Broder's System (1927)
2. Anneroth et al (1987)
3. Bryne's invasive front grading (1989, 1992)
4. Jakobbson et al (1973)
5. Fisher (1975)
6. Lund et al (1975)

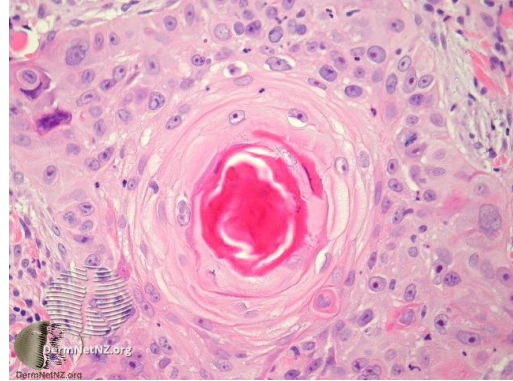
7. Willen et al (1975)
8. Crissman et al (1980)

Broder's System (1927)

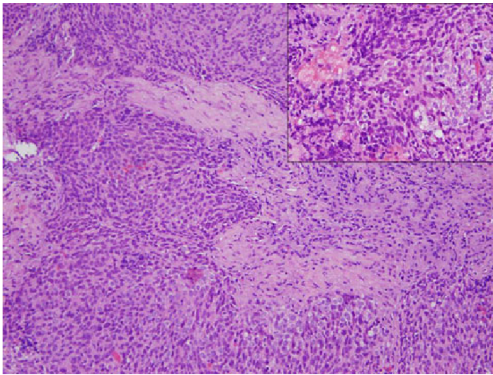
Accordingly, tumors were graded on the basis of degree of differentiation and keratinization of tumor cells into:



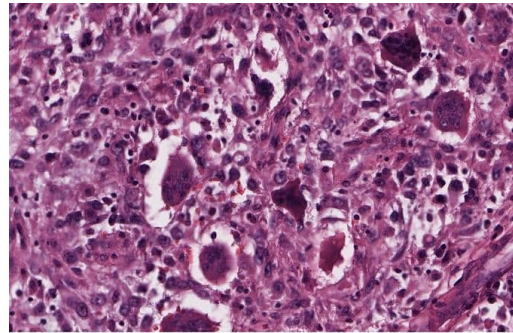
(a) **Grade I:** Well differentiated tumors – 75-100% of cells are differentiated



(b) **Grade II:** Moderately differentiated tumors – 50-75% of cells are differentiated



(c) **Grade III:** Poorly differentiated tumors – 25-50% of cells are differentiated



(d) **Grade IV:** Anaplastic tumor – 0-25% of cells are differentiated

Staging

Clinical staging of squamous cell carcinoma is done by the TNM system. The extent of the Tumor (**T**), lymph nodes involvement (**N**), metastasis (**M**).

- The size and extent of the primary lesion.
- The degree of infiltration of the primary lesion.
- Presence or absence of metastases to regional lymph nodes.
- Whether ipsilateral nodes only or contralateral nodes are also involved.
- Whether or not the involved nodes are fixed.
- Presence or absence of distant metastases.

T:

- **T0**: No evidence of primary tumor.
- **Tis**: Carcinoma in situ
- **T1**: < 2cm in its greatest diameter.
- **T2**: > 2cm < 4cm.
- **T3**: > 4cm
- **T4**: > 4cm & extended to adjacent structures (bone, sinuses & skin)
- **T4a**: Can be surgically resected
- **T4b**: Can't be surgically resected

N:

- **N0**: No L.N involved.
- **N1**: Palpable but not fixed (ipsilateral).
- **N2**: Palpable but not fixed (contralateral).
- **N3**: Fixed L.N (ipsilateral, contralateral or bilateral)

M:

- **M0**: No metastasis.
- **M1**: Metastasis present.

Tumor Markers

Serum levels of six tumor markers:

- Carcinoembryonic antigen (CEA)
- Squamous cell carcinoma antigen (SCCA)
- Immunosuppressive acidic protein (IAP)
- Alpha-fetoprotein (AFP)
- Ferritin (FER),
- Carbohydrate antigen 19-9 (CA 19-9)

were simultaneously measured in 29 patients with primary squamous cell carcinoma (SCC) of the oral cavity to determine their significance. The positive rates were 34.5% for CEA, 41.4% for SCCA, 51.7% for IAP, 0% for AFP, 10.3% for FER, and 6.9% for CA 19-9 in patients with oral SCC. Therefore, CEA, SCCA, and IAP levels, of which the positive rates were significantly different ($P < 0.01$) from those of control patients without oral cancer, were considered to be of diagnostic value. The sensitivity (69.0%) and accuracy (90.3%) of the combination assay with these three tumor markers proved to be higher than those obtained with individual

markers. A combination assay with CEA, SCCA, and IAP could be useful for the screening of patients with oral cancer.

Complications

Untreated squamous cell carcinoma of the skin can destroy nearby healthy tissue, spread to the lymph nodes or other organs, and may be fatal, although this is uncommon. The risk of aggressive squamous cell carcinoma of the skin may be increased in cases where the cancer:

- Is particularly large or deep
- Involves the mucous membranes, such as the lips
- Occurs in a person with a weakened immune system, such as someone who takes anti-rejection medications after an organ transplant or someone who has chronic leukemia

Treatment of SCCs

There are several types of treatment available for squamous cell carcinoma.

Treatment Options

A) Surgery

Surgery may be used to treat squamous cell carcinoma or actinic keratosis. Types of surgery include:

1. Mohs Microscopic Surgery The doctor removes the cancer from the skin in thin layers and each layer is analyzed under a microscope during surgery for cancer cells. The doctor continues to remove one layer at a time until removing a layer with no evidence of cancer cells. This allows the surgeon to be certain the entire growth is removed and avoid taking an excessive amount of surrounding healthy skin.
2. Simple Excision The doctor removes the skin cancer and some of the healthy tissue around it. In this procedure, your doctor cuts out the cancerous tissue and a surrounding margin of healthy skin. Your doctor may recommend removing additional normal skin around the tumor in some cases (wide excision). To minimize scarring, especially on your face, consult a doctor skilled in skin reconstruction.

B) Radiation Therapy

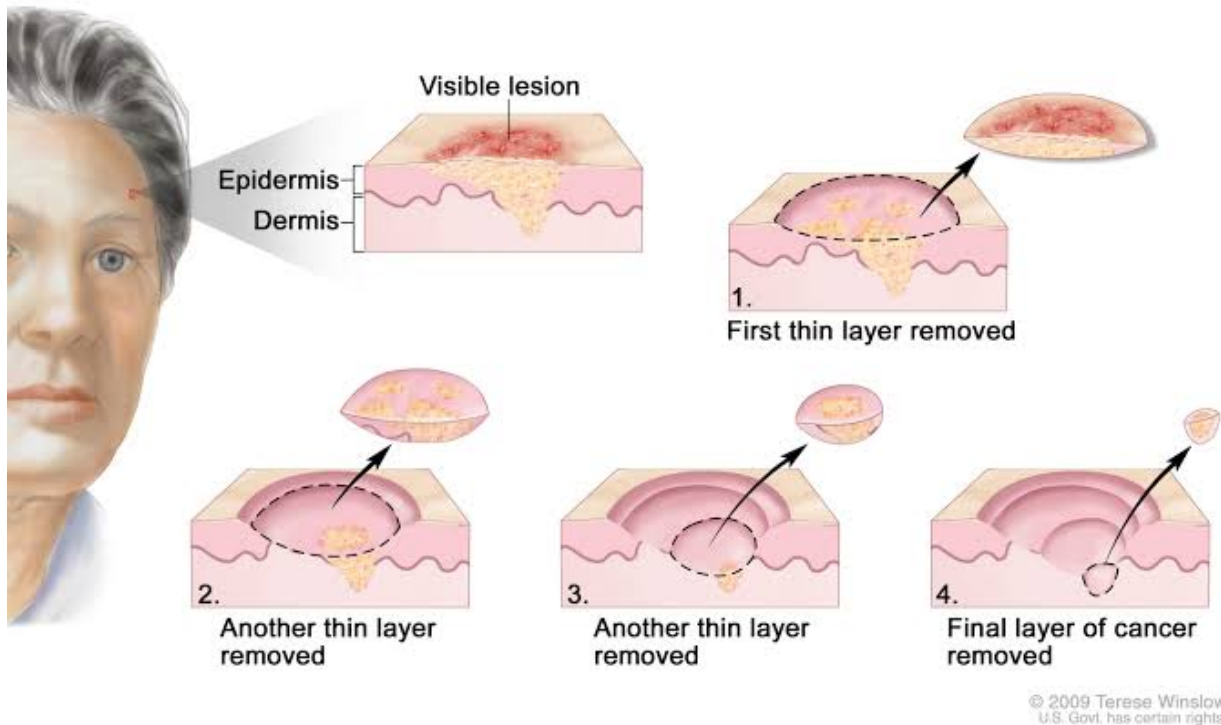
Radiation therapy uses X-rays or other types of radiation to destroy cancer cells. Most radiation is delivered from a machine outside your body that is targeted directly at the cancer cells. This may be an option for treating deeper tumors, those that have a risk of returning after surgery and tumors in people who can't undergo surgery.

C) Chemotherapy

- Chemotherapy uses drugs to stop the growth of cancer cells, either by destroying the cells or by stopping the cells from dividing. Chemotherapy for squamous cell carcinoma and actinic keratosis usually is applied to the skin as a cream or lotion, which is called topical chemotherapy. Medicated creams or lotions. For very superficial cancers, you may apply creams or lotions containing anti-cancer medications directly to your skin.

Chemotherapy may be used for squamous cell carcinoma that is metastatic (has spread to other organs) or when the skin cancer cannot be treated with local therapy but only in specific circumstances.

Mohs Surgery



D) Photodynamic Therapy

Photodynamic therapy uses a drug and a laser light to destroy cancer cells. The drug is injected in a vein and only becomes active when the laser light shines on the skin.

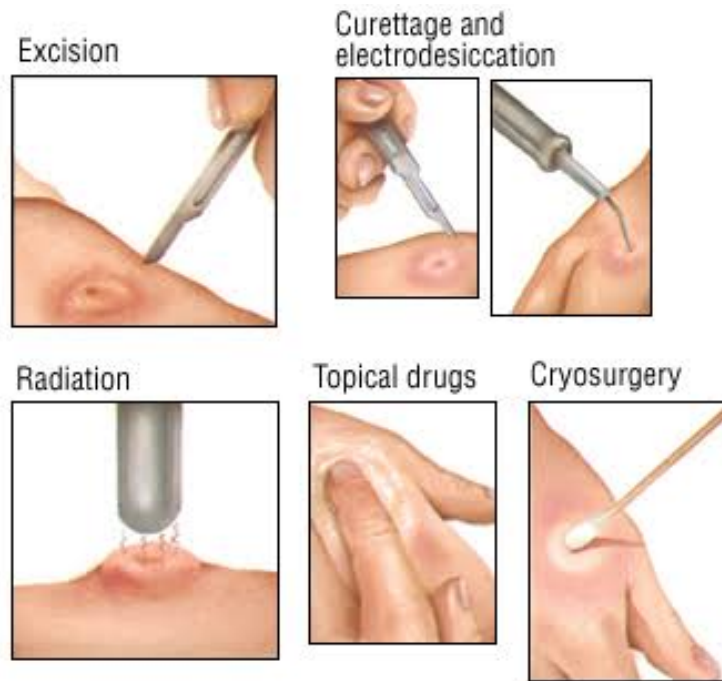
E) Immunotherapy

Immunotherapy, also called biologic therapy, helps boost a patient's immune system to fight cancer. Interferon may be injected to help treat squamous cell carcinoma by slowing the growth of cancer cells.

Immunotherapy may be used for squamous cell carcinoma that is metastatic (has spread to other organs) or when the skin cancer cannot be treated with local therapy.

F) Electrodesiccation and curettage

ED and C treatment involves removing the surface of the skin cancer with a scraping instrument (curet) and then searing the base of the cancer with an electric needle. This treatment is often used for very small squamous cell cancers of the skin.



G) Curettage and cryotherapy

Similar to the ED and C procedure, after the tumor removal and curettage, the base and edges of the biopsy site are treated with liquid nitrogen.

H) Laser therapy

An intense beam of light vaporizes growths, usually with little damage to surrounding tissue and with a reduced risk of bleeding, swelling and scarring. Laser treatment may be an option for very superficial skin lesions.

I) Freezing



Figure 8: Cryosurgery

This treatment involves freezing cancer cells with liquid nitrogen (cryosurgery). It may be an option for treating superficial skin lesions.

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