

Squamous Cell Carcinoma

Oral Pathology Department, Fall 2018

Lecture C

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

It is estimated that there are about 5 million new skin cancer cases each year in the United States.

Squamous cell carcinoma (SCC) is the second most common form of skin cancer. More than 1 million cases of SCC are diagnosed in the U.S. each year, resulting in more than 15,000 deaths.

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 it is not treated.

Etiology

- Neoplastic tissue 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 is hard to specify a certain dose or quantity at which the neoplastic tissue generates. 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.

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.
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.
 - People with an inherited condition known as xeroderma pigmentosum have an extreme sensitivity to sunlight are also very susceptible to cellular damage caused by UVA and UVB rays.

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.

Oncogenes and Tumor suppressor genes

Mutation, deactivation and disregulated expression of oncogenes and tumour-suppressor genes may be involved in the pathogenesis of oral squamous cell carcinoma (SCC). Deactivation of the p53 tumour-suppressor gene

allows cell proliferation and blocks apoptosis of malignant oral keratinocytes. Mutation in the ras oncogene results in persistent mitogenic signalling. Upregulated c-Myc expression, in the presence of growth factors, provides an additional proliferative signal. Loss of retinoblastoma tumour-suppressor gene (Rb) function may contribute to oral keratinocyte hyperproliferation and recent evidence suggests that simultaneous deactivation of both p53 and Rb is required for tumourigenesis. Enhanced Bcl-2 and reduced Fas expression inhibit tumour cell apoptosis and may convey resistance to cytotoxic drugs and T cell-mediated cytotoxicity, respectively. Exogenous mutagens such as tobacco, alcohol and viral oncogenes may cause altered expression of oncogenes and tumour-suppressor genes in some cases of oral SCC. The impact of these mechanisms on future therapies for oral SCC is highlighted.

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 phototherapy (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 vermillion 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:

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

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.

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:

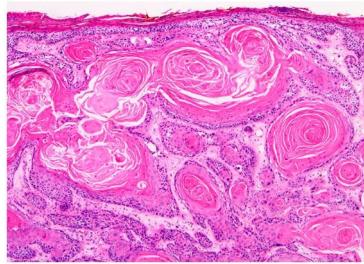
- Smoking habit
- Exposure to UV either by sunlight or artificially
- Precancerous lesion

Types of squamous cell carcinoma:

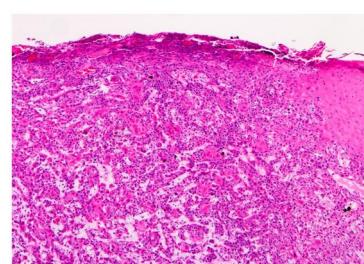
- Verrucous squamous-cell carcinoma
- Clear Cell SCC
- Spindle cell squamous cell carcinoma
- Adenoid/pseudoglandular squamous cell carcinoma
- Intraepidermal squamous cell carcinoma
- Large cell keratinizing squamous cell carcinoma
- Large cell non-keratinizing squamous cell carcinoma
- Lymphoepithelial 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 prickle 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.



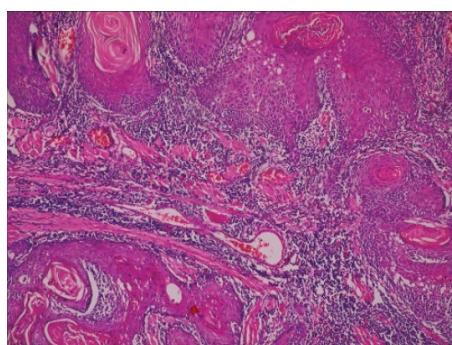
(a) Well-differentiated lesions show prominent keratinization and may form “pearl-like” structures where dermal nests of keratinocytes attempt to mature in a layered fashion (40x).



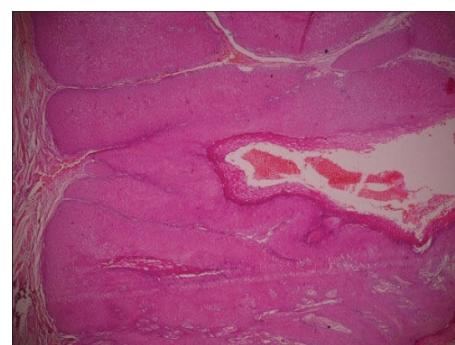
(b) Moderately differentiated lesions of SCC show much less organization and maturation with significantly less keratin formation (40x).

Variants

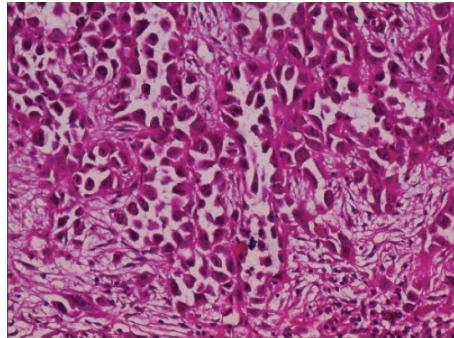
Conventional SCC and variants of SCC frequently arise within the oral cavity. Precise histopathological diagnosis can help the clinician to plan accurate treatment, as the prognosis of each of them differs considerably.



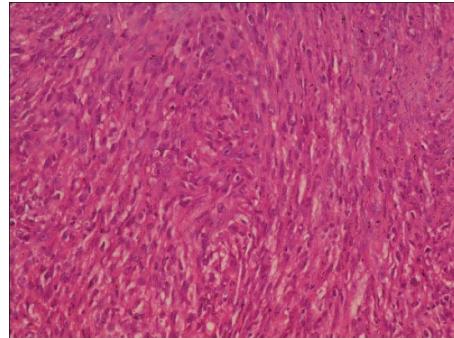
1. **Conventional Squamous Cell Carcinoma:** Conventional oral squamous cell carcinoma-malignant epithelial islands showing keratin pearl formation.



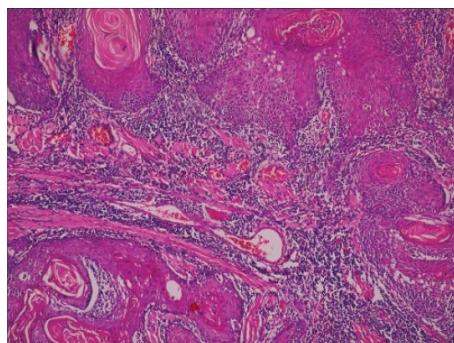
2. **Verrucous Carcinoma:** Verrucous carcinoma—broad bulbous pushing rete ridges with parakeratotic plugging.



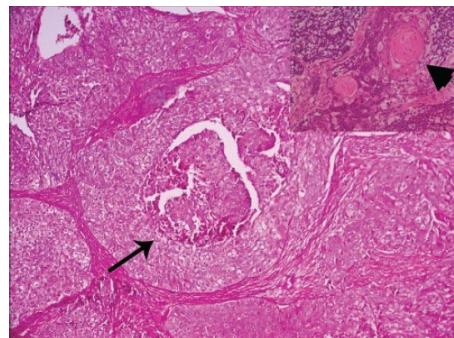
3. **Adenoid squamous cell carcinoma:** Adenoid squamous cell carcinoma -pseudoglandular pattern with acantholytic tumor cells.



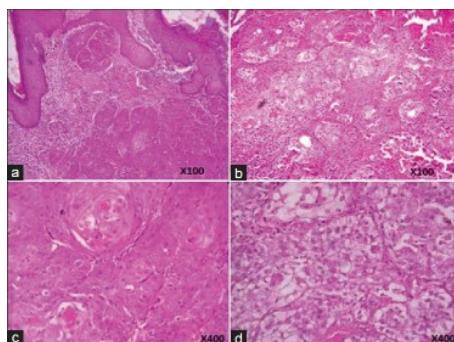
4. **Spindle cell carcinoma:** Spindle cell carcinoma-malignant epithelial cells showing spindling/sarcomatoid appearance.



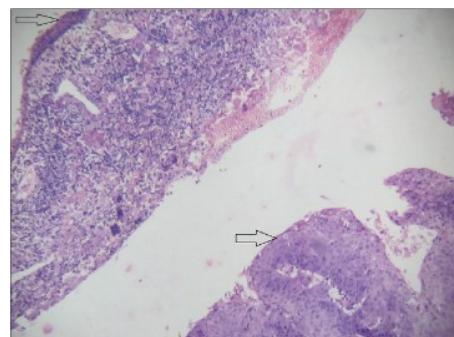
5. **Adenosquamous carcinoma:** Adenosquamous carcinoma-biphasic tumor showing true glandular differentiation (arrowhead) along with squamous differentiation (arrow) (H&E stain, $\times 100$). Inset depicts alcian bluepositive mucin secretion ($\times 400$). Characterized histopathologically by a combination 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 arrows).

Tumor Grading

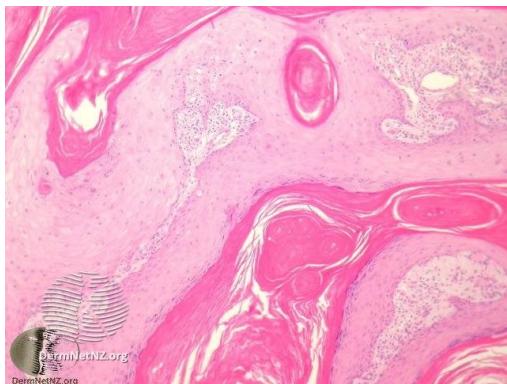
Tumor grading can be used to predict the prognosis of the lesion and its aggressiveness and further assess the treatment plan.

Histopathological Grading Systems for Oral Squamous Cell Carcinoma:

1. Broder's System (1927)
2. Pindborg's System (1997)
3. Anneroth et al (1987)
4. Bryne's invasive front grading (1989, 1992)
5. Jakobbson et al (1973)
6. Fisher (1975)
7. Lund et al (1975)
8. Willen et al (1975)
9. Crissman et al (1980)

1. Broder's System (1927)

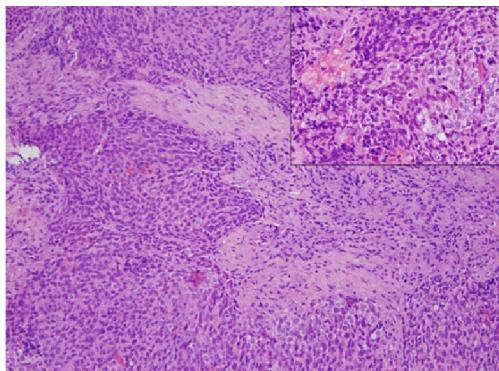
Accordingly, tumors were graded on the basis of degree of differentiation and keratinization of tumor cells into:



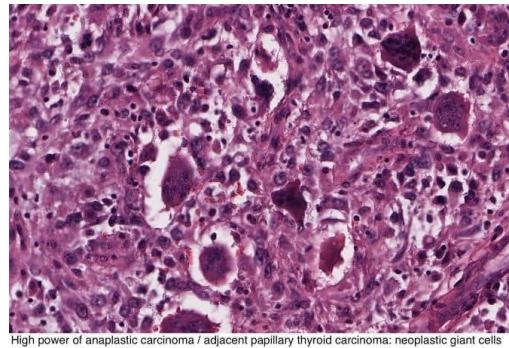
(a) **Grade I:** Well differentiated tumors – 75-100% of cells are differentiated



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



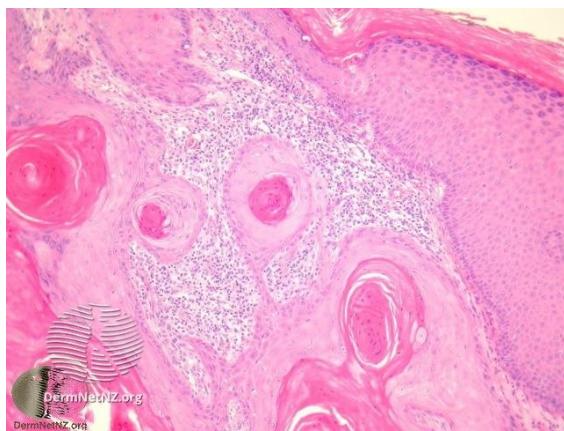
(c) **Grade III:** Poorly differentiated tumors – 25-50% of cells are differentiated



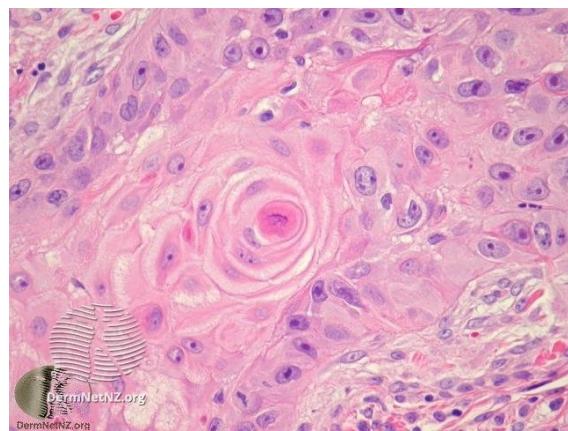
(d) **Grade IV:** Anaplastic tumor – 0-25% of cells are differentiated

2. Pindborg's System (1997)

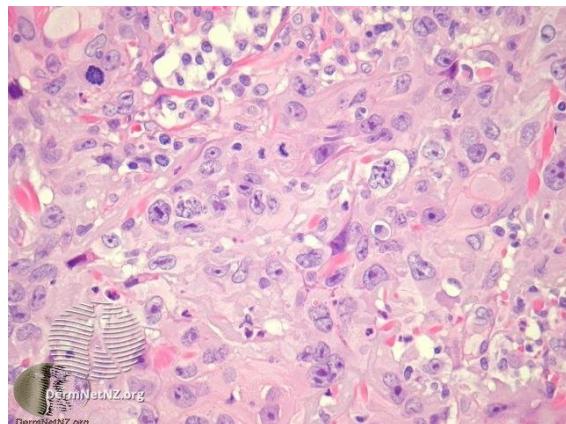
This grading is generally based on the method originally described by Broders, which takes into account a subjective assessment of the degree of keratinization, cellular and nuclear pleomorphism and mitotic activity.



(a) **Grade I:** (Well differentiated) Histological and cytological features closely resemble those of the squamous epithelial lining of the oral mucosa



(b) **Grade II:** (Moderately differentiated) This is a neoplasm with features intermediate between well differentiated and poorly differentiated.



(c) **Grade III:** (Poorly differentiated) Histologically and cytologically there is only a slight resemblance to the normal stratified squamous epithelium of the oral mucosa.

3. Anneroth's et al (1987) - Multifactorial grading system:

According to this system, three parameters reflecting tumor cell features including

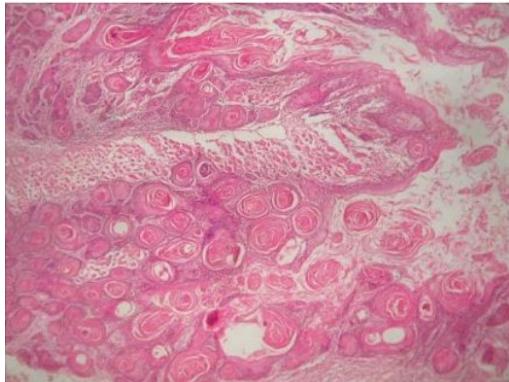
1. Keratinization
2. Nuclear pleomorphism
3. Mitoses

They're evaluated in the whole thickness of the tumor and each scored from 1-4.

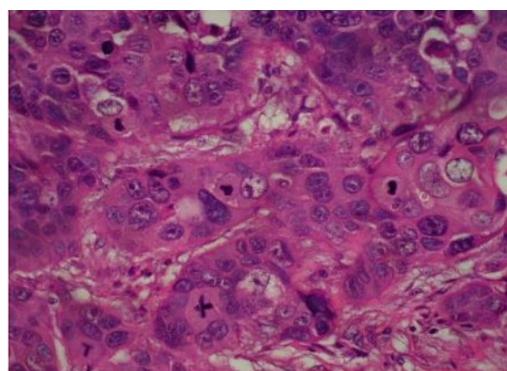
Also

1. Pattern of invasion
2. Stage of invasion
3. Lymphoplasmacytic infiltration representing tumor-host relationship are graded in the most invasive margins and scored from 1-4.

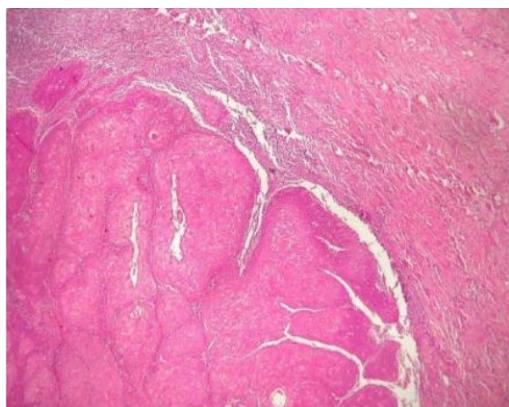
Then the sum of scores is grouped as follows: 6-12 grade I, 13-18 grade II, 19-24 grade III, and the results were compared in the metastasizing and non-metastasizing groups.



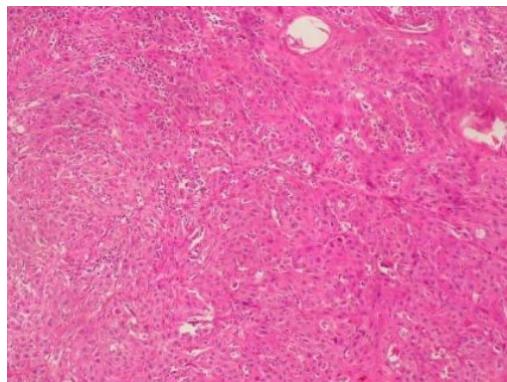
Degree of keratinization, Score 1 (Highly Keratinized)



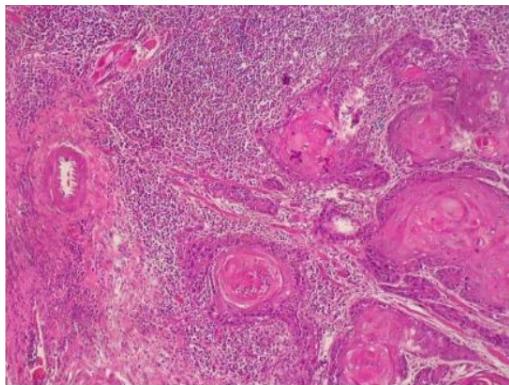
Nuclear Pleomorphism, Score 4 (Extreme)



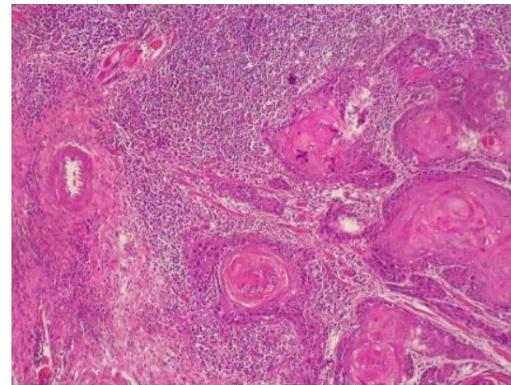
Pattern of invasion, Score 1 (pushing borders)



Pattern of invasion, Score 4 (Marked and widespread cellular dissemination).



Pattern of invasion, Score 3 (Small groups and cords of infiltrating cells.)



Lymphoplasmacytic infiltration, Score 1 (Marked)

Anneroth's et al (1987) multifactorial grading system for oral SCC's

Morphologic parameter	POINTS			
	1	2	3	4
Degree of keratinization	>50% cells keratinized	20-50% cells keratinized	5-20% cells keratinized	0-5% cells keratinized
Nuclear pleomorphism	Little nuclear pleomorphism	Moderately abundant nuclear pleomorphism	Abundant nuclear pleomorphism	Extreme nuclear pleomorphism
Number of mitosis/hpf	0-1	2-3	4-5	>5
Pattern of invasion	Pushing, well-delineated infiltrating borders	Infiltrating, solid cords, bands and/or strands	Small groups or cords of infiltrating cells	Marked and widespread cellular dissemination in small groups and/or in single cells
Stage of invasion	Carcinoma-in-situ and/or questionable invasion	Distinct invasion, but involving lamina propria only	Invasion below lamina propria adjacent to muscles, salivary gland tissues, and periosteum	Extensive and deep invasion replacing most of the stromal tissue and infiltrating jaw bone
Lymphoplasmacytic infiltration	Marked	Moderate	Slight	None

4. Bryne's et al (1992) deep invasive cell grading system

According to this system,

1. Number of mitosis and stage of invasion was omitted from the Anneroth's grading system,
2. The rest of the 4 parameters (Keratinization , nuclear pleomorphism , pattern of Invasion and lymphocytic Infiltration) are measured in the deepest invasive margins, and not in the whole thickness of the tumor, and graded similarly.

The sum of scores are grouped as follows:

- 4-8 grade I
- 9-12 grade II
- 13-16 grade III

A summary table of data showing tumors in the study as graded by Bryne's deep invasive cell grading system

Bryne's deep invasive cell grading system	Metastatic group No. (%)	Non- metastatic group No. (%)	Total No. (%)
Grade-I	10 (32.3)	23 (88.5)	33 (57.9)
Grade-II	16 (51.6)	03 (11.5)	19 (33.3)
Grade-III	05 (16.1)	00 (00.0)	05 (08.8)
Total	31 (100.0)	26 (100.0)	57 (100.0)

5. JAKOBSSON ET AL. (1973)

This system includes

1. The morphologic parameters structure - tendency to keratinization - nuclear aberrations - number of mitosis
2. Evaluation of tumor-host relationship as estimated by parameters such as Mode - stage of invasion - vascular invasion - degree of lymphoplasmocytic infiltration

Histological malignancy grading system developed by Jakobsson et al.

Histological grading of malignancy based on tumor cell population				
Tumor cell Population	1	2	Points 3	4
Structure	Papillary and solid Strands		Small cords and groups of cells	Marked cellular Dissociation
Differentiation	Highly: keratinization	Moderately: Some Keratinisation	Poorly: Minimum keratinization	Poorly: No-keratinization
Nuclear polymorphism	Few enlarged nuclei	Moderate number of enlarged nuclei	Numerous irregular enlarged nuclei	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous
Histologic grading of malignancy based on tumor-host relationship				
Tumor -host Relationship	points			
	1	2	3	4
Mode of invasion	Well-defined borderline	Cords less marked borderline	Groups of cells, no distinct borderline	Diffuse growth
Stage of invasion	Possibly	Micro-carcinoma (few cords)	Nodular into connective tissue	Massive
Vascular invasion	None	Possibly	Few	Numerous
Cellular response (plasma-lymphocytic Infiltration	Marked	Moderate	Slight	None

6. FISHER (1975)

They modified slightly the grading system developed by Jakobsson et al.

- indicated the malignancy grade of biopsy tissue tended to be lower than the grade of definitive section obtained from surgical specimen.

Histologic Malignancy Grading System Developed By FISHER

	Tumor score			
	1	2	3	4
Differentiation	Much keratin	Some keratin	Squamous	Anaplastic
Nuclear polymorphism	Few aniso	Moderate aniso	Many aniso	Bizarre
Mitoses	Occasional	Few	Moderate	Many
Stroma	Abundant	Dense	Delicate	None
Mode	Pushing	Bands	Cords	Diffuse
Stage	No invasion	Micro-invasion	In connective tissue	Deep
Vascular	None	Possible	Few	Many
Inflammatory response	Marked	Moderate	Slight	None

7. LUND et al (1975)

They also modified, grading system of Jakobsson et al.

by:

- Presenting a more exact definition of each parameter and grade.
- Introducing a histologic score, defined a total sum of points divided by the number of parameters evaluated.
 - statistically significant correlation between microscopic score and
 - Death rate
 - Frequency of local recurrence
 - Regional lymph node metastases

Histologic malignancy grading system developed by LUND:

Microscopic grading				
POINTS				
	1	2	3	4
Appearance	Exophytic papillomatous	Inverted papillomatous	Small cords and group of cells	Marked cellular dissociation
Cytoplasmic differentiation (keratinization)	High > 50% keratinized	Moderate 20-50% keratinized	Poor 5-20% keratinized	None 0-5%
Nuclear differentiation (Broder's)	High more than 75% mature	Moderate 50-75% mature	Poor 25-50% mature	None 0-25% mature
Mitosis*	Single 0-1	Moderate number 0-3	Great number 0-5	Numerous more than 5
Mode of invasion (modus)	Well defined borderline	Cords, less marked borderline	Group of cells. No distinct borderline	Diffuse growth
Stage of invasion (depth) †	Possible invasion	Micro-invasion (few cords)	Nodular into Sub mucosa	Invasion deeper than sub mucosa
Vascular invasion	None	possible	Lymph, vessels	Blood vessels
Cellular response (plasma lymphocytic)	Marked (continuous rim)	Moderate (many large patches)	Slight (a few small patches)	None

*Minimum evaluation of five fields x 250, † No invasion may constitute preinvasive lesion.

8. WILLEN et al (1975)

They also used modified system of Jakobsson et al.

1. Deletion of two morphological parameter structure and vascular invasion.
- The results showed no definitive correlation between the clinical stage and histologic grading of malignancy.
- In the group with no metastases the neoplasm were highly differentiated and mitotic rates were low, but nuclear polymorphism was sometime prominent.
- In the group with metastases the neoplasm were less differentiated and advanced nuclear aberrations with increase mitotic rates.

Histologic malignancy grading system developed by Willen et al.

Histologic grading of malignancy				
1.Tumor cell population				
	1	2	3	4
Differentiation	Highly keratinized	Moderately, some keratinization	Poorly, minimal keratinization	Poorly, no keratinization
Nuclear Polymorphism	Few enlarged nuclei	Moderate number of enlarged nuclei	Numerous irregular enlarged nuclei	Anaplastic immature enlarged nuclei
Mitoses	Single	Moderate number	Great number	Numerous
Histologic grading of malignancy				
2.Tumor-host relationship				
	1	2	3	4
Mode of invasion	Well-defined borderline	Cords, less marked borderline	Groups of cells, no distinct borderline	Diffuse invasion
Stage of invasion	Suspicious	Micro-carcinoma few cords	Nodular invasion in connective tissue	Massive invasion
Cellular response	Marked	moderate	slight	None

9. CRISSMAN et al

They modified the criteria outlined by Jakobsson et al. in two steps.

1. They included a different point scale for vascular invasion and structure and mode of invasion into a single parameter **pattern of invasion**.
2. The new parameter was considered to reflect the capacity of the **tumor cells cohesiveness**.
 - “Differentiated” cohesive neoplasm infiltrated with well delineated pushing margins
 - “Less differentiated” non-cohesive neoplasm infiltrated as small, irregular neoplastic cell aggregates or single cells.

Histologic malignancy grading system developed by Crissman et al.

HISTOLOGIC CRITERIA		TUMOUR SCORE		
		1	2	3
Tumor cytology				
Cytoplasmic Keratinization	High degree (> 50% of cell), Well-formed keratin pearls	Moderate degree (20%-50% of cells), attempts at pearl formation	Low degree (5%-20% of cells)	None identified
Nuclear differentiation	Few enlarged nuclei, 75% mature	Moderate number enlarged, variable sized nuclei 50-70% mature	Numerous enlarged pleomorphic nuclei, 25-50% mature	Anaplastic nuclei, 0-25% mature
Frequency of mitosis*	0-1	2-3	4-5	>5
Stroma Of Tumour –Host Interface				
Inflammatory Cells Response Tumour Growth Pattern	Marked continuous rim	Moderate, patchy	Slight, few small patches	None
Stage Of Invasion	CIS, [†] probable invasion	early or micro invasion	nodular infiltration into sub mucosa	invasion through sub mucosa
Pattern Of Invasion	Verrucous or Exophytic pushing border	Exophytic with infiltrating cords	Sessile with infiltrating cords	Infiltrating in small groups and dissociated cells
Vascular Invasion	Not identified			Identified

*HPF=high power field (average count/HPF, as many microscopic fields counted as possible), † CIS = carcinoma in situ.

CONCLUSION

- A significant percentage of patients with early stages of SCC have a poor prognosis despite the small size of the tumor.
- TNM staging system used in clinical practice does not provide information on the biological characteristic and aggressive clinical behavior of oral SCC.
- The first and most widely practiced grading system for oral SCC was developed by AC Broder.
- However, the grading systems developed by Bryne et al (1992), which analyses four factors of the carcinoma in its invasive front is most reproducible but less popularly used.
- We found a significant positive trend between Bryne's deep invasive cell grading system with lymph node metastasis; while all the other grading systems, especially the most popularly used Broder's classification failed to show any statistical significance to lymph node metastasis.
- In conclusion, we believe that Bryne's grading of the invasive parts of oral SCC could be taken as a valuable predictive factor in lymph node metastasis.
- Immunohistochemical markers like expression of vascular endothelial growth factor-C (VEGF-C) and Ki-67 that take into account the biological behavior of the tumor.

Tumor Markers

Tissue Markers

1. Epithelial markers
 - Cell surface markers – Histocompatibility
 - Intracellular markers – Cytokeratins
 - Basement membrane markers – Type 4 collagen
 - Matrix markers – Tenascin
 - Membrane antigen – Blood group antigens.
2. Connective tissue markers
 - Intermediate filament proteins – Desmin
 - Other filament proteins – Laminin
 - Cellular enzymes – Amylase, lysozyme
 - Cytoplasmic non-filamentous non-enzymatic proteins – Myoglobin, S100 protein
 - Membrane antigen – Leukocyte specific antigen.

Salivary Markers (Most Recent)

Most recently, detection of four proteins in the saliva of cancer patients has been found to be the useful markers of oral cancer with 90% sensitivity and 83% specificity for oral squamous cell carcinoma. These proteins include

1. Calcium-bindingprotein MRP14 implicated in several types of cancer;
2. CD59 overexpressed on tumor cells that enables them to escape from complement-dependent and antibody-mediated immune responses;
3. Profilin 1,a protein involved in several signaling pathways with cytoplasmic and nuclear ligands, generally secreted into tumor micro environments during the early progressive stage of tumorigenesis;
4. Catalase,a member of the enzymatic antioxidative system,whose level is elevated in many human tumors and involved in carcinogenesis and tumor progression.However, long-term studies employing large number of oral cancer patients as well as subjects at high risk of developing oral cancer are needed to validate these potential biomarkers

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.

Prognosis

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

According to differentiation (**Grade**):

- Well differentiated -> Good prognosis
- Moderately differentiated -> Moderate prognosis
- Poorly differentiated -> Worse prognosis

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