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# Solid Tumour Section

**Review**

# Head and Neck: Squamous cell carcinoma: an overview

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## Identity

**Note**

Head and neck squamous cell carcinoma (HNSCC) develops from the mucosal linings of the upper aerodigestive tract, comprising 1) the nasal cavity and paranasal sinuses, 2) the nasopharynx, 3) the hypopharynx, larynx, and trachea, and 4) the oral cavity and oropharynx. Squamous cell carcinoma (SCC) is the most frequent malignant tumor of the head and neck region. HNSCC is the sixth leading cancer by incidence worldwide. There are 500000 new cases a year worldwide. Two thirds occur in industrialized nations. HNSCC usually develops in males in the $6^{th}$ and $7^{th}$ decade. It is caused by tobacco and alcohol consumption and infection with high-risk types of human papillomavirus (HPV). SCC often develops from preexisting dysplastic lesions. The five-year survival rate of patients with HNSCC is about 40-50%.

## Classification

SCC can occur either in 1) the nasal cavity and paranasal sinuses, 2) the nasopharynx, 3) the hypopharynx, larynx, and trachea, or 4) the oral cavity and oropharynx. The 2005 World Health Organization (WHO) classification of Head and Neck Tumors (Barnes et al., 2005) distinguishes different types of SCC:

- Conventional
- Verrucous
- Basaloid
- Papillary
- Spindle cell (sarcomatoid)
- Acantholytic
- Adenosquamous
- Cuniculatum

Each variant can arise in any one of the 4 above mentioned head and neck regions, except for the cuniculatum type which only develops from the oral mucosa.

SCC can be well-, moderately- or poorly-differentiated, and either keratinizing or non-keratinizing. Most cases are moderately to poorly-differentiated.

Precursor lesions (dysplasia) can be (arbitrarily) separated into mild, moderate, or severe (carcinoma in situ) (see below).

## Clinics and pathology

### *Etiology*

The most important risk factors for developing HNSCC are tobacco smoking and alcohol consumption, which have a synergistic effect. Smoking habits that increase the risk of developing HNSCC are smoking black tobacco (compared to blond tobacco), smoking at a young age, long duration, high number of cigarettes per day, and deep smoke inhalation (Benhamou et al., 1992). Avoiding cigarettes and alcohol could prevent about 90% of HNSCCs, especially laryngeal and hypopharyngeal tumors. Tobacco chewing is a major cause of oral and oropharyngeal SCC in the Indian subcontinent, parts of South-East Asia, China and Taiwan, especially when consumed in betel quids containing areca nut (Znaor et al., 2003). In India, chewing accounts for nearly 50% of oral and oropharyngeal tumors in men and over 90% in women (Barnes et al., 2005). Significant risk increases of developing HNSCC have also been reported among non-drinking smokers and, to a lesser extent, non-

smoking heavy drinkers. Heavy consumption of all types of alcoholic beverages (wine, beer, hard liquors) confers an increased risk (La Vecchia et al., 1999). Conversely, protective effects of diets rich in fresh fruits and vegetables have been described (Pelucchi et al., 2003).
Some occupational exposures may be associated with a higher risk of developing HNSCC, especially of the larynx: polycyclic aromatic hydrocarbons, metal dust, cement dust, varnish, lacquer, etc... Significant associations were also found with ionizing radiation, diesel exhausts, sulphuric acid mists, and mustard gas (Barnes et al., 2005).
The incidence of HNSCC in specific sites has been slowly declining during the past decade, due to a decrease in the prevalence of the more traditional risk factors, most notably smoking. However, in the Western World, HNSCCs, notably of the oral cavity and oropharynx, are becoming more prevalent, which may be related to an increase in oral and oropharyngeal HPV infections (Leeman et al., 2011). Indeed, recent studies have shown that infection with high-risk types of HPV (e.g. HPV-16 and -18) is responsible for a subgroup of HNSCCs. HPV-positive tumors represent a different clinicopathological and molecular entity compared to HPV-negative cases (see below). HPV infection is now recognized as one of the primary causes of oropharyngeal SCC (especially SCC of the tonsils and the base of the tongue). In the USA, about 40-80% of oropharyngeal cancers are caused by HPV, whereas in Europe the proportion varies from around 90% in Sweden to less than 20% in communities with the highest tobacco use (Marur et al., 2010). Patients tend to be younger, with no prior history of tobacco and/or heavy alcohol consumption. There is evidence that HPV-positive HNSCC is a sexually transmitted disease. A strong association between sexual behavior (oral sex) and risk of oropharyngeal cancer as well as HPV-16-positive HNSCC has been demonstrated (Smith et al., 2004; Gillison et al., 2008).
Finally, certain inherited disorders, such as Fanconi anemia or Bloom syndrome, predispose to HNSCC (Kutler et al., 2003; Barnes et al., 2005).

## Epidemiology

SCC is the most frequent malignant tumor of the head and neck region. HNSCC represents the sixth leading cancer by incidence and there are 500000 new cases a year worldwide (Kamangar et al., 2006). Two thirds occur in industrialized nations. Most HNSCCs arise in the hypopharynx, larynx, and trachea, and in the oral cavity and oropharynx. The majority of laryngeal SCCs originate from the supraglottic and glottic regions. Tracheal SCCs are rare compared to laryngeal ones. The most common oropharyngeal site of involvement is the base of the tongue. Within the oral cavity, most tumors arise from the floor of the mouth, the ventrolateral tongue or the soft palate complex.
HNSCCs occur most frequently in the sixth and seventh decades. They typically develop in men though women are more and more affected because of increased prevalence of smoking over the last two decades (Barnes et al., 2005). For laryngeal, hypopharyngeal and tracheal SCCs, the incidence in men is high in Southern and Central Europe, some parts of South America, and among Blacks in the United States. The lowest rates are recorded in South-East Asia and Central Africa. The disease is slightly more common in urban than in rural areas. For oral and oropharyngeal SCCs, the disease usually affects adults in the $5^{th}$ and $6^{th}$ decades of life. Extremely elevated rates are observed in France, parts of Switzerland, Northern Italy, Central and Eastern Europe, and parts of Latin America. Rates are high among both men and women throughout South Asia. In the US, incidence rates are two-fold higher in Blacks compared to Whites (Barnes et al., 2005).

## Clinics

Clinical features of HNSCC depend on the localization of the tumor.

**Nasal and paranasal sinuses**

Patients with SCC arising in the nasal or paranasal sinuses may complain of nasal fullness, stuffiness, or obstruction, but also of epistaxis, rhinorrhea, pain, paraesthesia, swelling of the nose and cheek or of a palatal bulge. Some may present with a persistent or non-healing nasal sore or ulcer, a nasal mass, or in advanced cases, proptosis, diplopia, or lacrimation (Barnes et al., 2005; Thompson, 2006).

**Nasopharynx**

Most patients with nasopharyngeal carcinoma present with painless enlargement of upper cervical lymph nodes. Nasal symptoms, particularly blood-stained post-nasal drip are reported in half the cases. Serous otitis media following Eustachian tube obstruction is also common. Headaches and cranial nerve involvement indicate more advanced disease. However, 10% of the patients are asymptomatic (Barnes et al., 2005; Thompson, 2006).

**Hypopharynx, larynx, and trachea**

Hypopharyngeal and supraglottic tumors may be responsible of dysphagia, change in quality of voice, foreign body sensation in the throat, haemoptysis, and odynophagia. Glottic SCC most commonly presents with hoarseness (**Fig. 1**). In case of subglottic tumor, dyspnea and stridor are frequent clinical features. SCC arising in the trachea may cause dyspnea, wheezing or stridor, acute respiratory failure, cough, haemoptysis, and hoarseness (Barnes et al., 2005; Thompson, 2006).

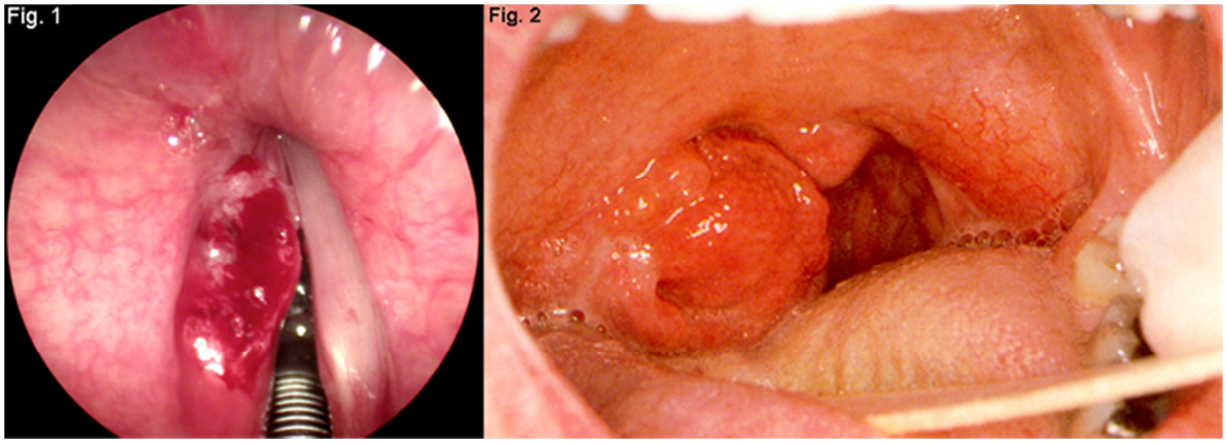


**Figure 1:** Endoscopy. Exophytic and ulcerative SCC of the left vocal cord. **Figure 2:** Large exophytic and ulcerative SCC of the left amygdala. Fig. 1-2 were kindly provided by Dr S. Hans (Georges Pompidou European Hospital, Paris, France).

**Oral cavity and oropharynx**

Most patients display at the time of diagnosis signs and symptoms of locally advanced disease. Clinical features vary according to the exact site of the lesion. The most common presenting features are ulceration, pain, referred pain to the ear, difficulty with speaking, opening the mouth or chewing, difficulty and pain with swallowing, bleeding, weight loss, and neck swelling (**Fig. 2**). Cancer of the buccal mucosa may present as an ulcer with indurated raised margins or as an exophytic growth. SCC of the floor of the mouth may arise as a red or ulcerated lesion or as a papillary growth. Cancer of the gingiva usually presents as an ulceroproliferative growth. Cancer of the tongue may appear as an ulcer infiltrating deeply and reducing the mobility of the tongue. SCC of the base of the tongue usually presents at a locally advanced stage as an ulcerated, painful, indurated growth. Cancer of the hard palate often presents as a papillary or exophytic growth rather than a flat or ulcerated lesion. Cancer of soft palate and uvula often appears as an ulcerative lesion with raised margins or as a fungating mass. Occasionally, patients harbor enlarged cervical lymph nodes with no identifiable oral or oropharyngeal lesion. In very advanced disease, patients may present an ulceroproliferative lesion with areas of necrosis and extension to surrounding structures, such bone, muscle and skin (Barnes et al., 2005; Thompson, 2006).

## Pathology

**Precursor lesions**

The 2005 WHO classification of precursor lesions (Barnes et al., 2005) is as follows:

- Squamous cell hyperplasia

Hyperplasia describes increased cell numbers. This may be in the spinous layer (acanthosis) and/or in the basal/parabasal cell layers (progenitor compartment), termed basal cell hyperplasia. The architecture shows regular stratification without cellular atypia.

- Mild dysplasia (Squamous Intraepithelial Neoplasia (SIN) 1)
- Moderate dysplasia (SIN 2)
- Severe dysplasia (SIN 3)
- Carcinoma in situ (SIN 3)

The Ljubljana classification of squamous intraepithelial lesions has also been proposed (see below) (Barnes et al., 2005).

| **2005 WHO Classification** | **Squamous Intraepithelial Neoplasia (SIN)** | **Ljubljana Classification Squamous Intraepithelial Lesions (SIL)** |
|---|---|---|
| Squamous cell hyperplasia | | Squamous cell (simple) hyperplasia |
| Mild dysplasia | SIN 1 | Basal/Parabasal cell hyperplasia |
| Moderate dysplasia | SIN 2 | Atypical hyperplasia |
| Severe dysplasia | SIN 3 | Atypical hyperplasia |
| Carcinoma *in situ* | SIN 3 | Carcinoma *in situ* |

Invasive HNSCCs arise in most cases from preneoplastic lesions grouped under the term "dysplasia". Dysplastic lesions present with an increased likelihood of progressing to SCC. The altered epithelium displays architectural and cytological changes that range from mild to severe (see below). Precursor lesions are mostly seen in the adult population and affect men more often than women. They are strongly associated with tobacco smoking and alcohol consumption, and especially a combination of the two. The duration of smoking, the type of tobacco and the practice of deep inhalation play a role in the development of precursor lesions. Other etiological factors have been reported such as industrial pollution, specific occupational exposures, and nutritional deficiency. Mean age of patients with first diagnosis of precursor lesions is 48-56.5 years. Rarely, malignant

transformation may develop from morphologically normal epithelium (Barnes et al., 2005; Thompson, 2006).

The clinical picture of precursor lesions depends on the location and severity of the disease. In case of dysplastic lesions of the hypopharynx, larynx or trachea, patients may present with fluctuating hoarseness, sore throat, and/or chronic cough of a few months' duration. However, some individuals may be asymptomatic.

Endoscopically, the lesions may be discrete or diffuse, smooth or irregular, flat or exophytic. Precursor lesions may present as a small flat patch or as a large warty plaque. The surface may be brown to red (erythroplakia) or present with circumscribed whitish plaques (leukoplakia). White patches may be ulcerated. Leukoplakia, in contrast to erythroplakia, tends to be well demarcated and seems to have a lower risk of malignant transformation. The lesions are commonly diffuse, with a thickened appearance. However, in a minority of cases, patchy atrophy may be present. In the larynx, the precursor lesions appear mainly along the anterior true vocal cords. Two thirds of vocal cord lesions are bilateral. Occasionally, precursor lesions may present macroscopically as normal mucosa (Barnes et al., 2005; Thompson, 2006).

Microscopically, dysplasia is defined as architectural and cytological changes of the epithelium, without evidence of invasion. The diagnostic features of dysplasia are not uniformly accepted or interpreted. In dysplastic lesions, the epithelium presents with irregular stratification, loss of polarity of basal cells, drop-shaped rete ridges, increased number of mitotic figures, abnormal superficial mitoses, premature keratinization in single cells (dyskeratosis) and keratin pearls within rete pegs. Cytological changes include abnormal variation in nuclear or cell size and shape, increased nuclear to cytoplasmic ratio, increased nuclear size, atypical mitotic figures, increased number and size of nucleoli, and hyperchromasia. The spectrum of dysplasia is divided for practical reasons into mild, moderate and severe. In mild dysplasia, architectural disturbances and cytological atypia are limited to the lower third of the epithelium. In moderate dysplasia, architectural and cytological changes extend into the middle third of the epithelium. Up-grading from moderate to severe dysplasia may be considered when there is marked cytological atypia. Severe dysplasia displays greater than two thirds altered epithelium. Carcinoma in situ presents with full thickness or almost full thickness architectural abnormalities accompanied by cytological atypia (**Fig.3**). Superficial and atypical mitotic figures are commonly seen. By definition, invasion has not yet occurred. Differential diagnosis of dysplastic lesions includes reactive or regenerative squamous epithelium (Barnes et al., 2005; Thompson, 2006).

**Conventional type squamous cell carcinoma**

SCC is characterized by squamous differentiation (often seen as keratinization, sometimes with keratin pearl formation) and invasive growth with disruption of the basement membrane. Extension into the underlying tissue is often accompanied by a desmoplastic stromal reaction and a dense inflammatory infiltrate, mainly comprised of lymphocytes and plasma cells. Angiolymphatic and perineural invasion may be seen. SCC is graded into well-, moderately-, and poorly-differentiated. Well-differentiated SCC closely resembles normal squamous mucosa whereas moderately-differentiated SCC displays nuclear pleomorphism, mitoses (including atypical forms), and usually less keratinization (**Fig. 4-6**). In poorly-differentiated SCC, immature cells predominate, with numerous typical and atypical mitoses, minimal keratinization, and sometimes necrosis. Most SCCs are moderately-differentiated (Barnes et al., 2005; Thompson, 2006).

HNSCCs express epithelial markers such as cytokeratins. In well-differentiated tumors, no additional stains are usually needed. In poorly-differentiated lesions, immunohistochemistry may be useful. HNSCCs are immunopositive for cytokeratin cocktails, AE1/AE3 and pancytokeratin. CK5/CK6 and p63 are also excellent markers to detect squamous differentiation (Dabbs, 2006).

**Verrucous carcinoma**

Verrucous carcinoma (VC) is a non-metastasizing variant of well-differentiated SCC characterized by an exophytic, warty, slowly-growing tumor with pushing rather than infiltrative margins (Barnes et al., 2005). The larynx is the second most common site of VC in the head and neck region after the oral cavity. The gross appearance is of a broad-based, exophytic, warty, firm to hard, white mass. Microscopically, the thickened, club-shaped, projections are lined by well-differentiated squamous epithelium devoid of the malignant features commonly seen in SCC. Mitotic figures are rare and not atypical. The advancing margins are usually broad with a pushing appearance. A dense inflammatory response is often present in the underlying tissue. There is abundant surface keratosis ("church-spire" keratosis) (**Fig. 7**). Differential diagnosis includes verrucous hyperplasia and very well-differentiated SCC. Distinguishing these entities from verrucous carcinoma can be delicate. Analysis of a sample of sufficient size which has been accurately oriented is necessary before rendering a definitive diagnosis. The separation of verrucous hyperplasia from verrucous carcinoma is often difficult, requiring clinical-pathological confrontation. Pure VC does not metastasize and has an excellent prognosis. However, hybrid VC (displaying a conventional SCC component) has the potential to metastasize and should be managed as similarly staged SCC (Barnes et al., 2005; Thompson, 2006).

**Basaloid squamous cell carcinoma**

Basaloid squamous cell carcinoma is a high-grade variant of SCC composed of both basaloid and squamous components (Barnes et al., 2005). It is an aggressive, rapidly growing tumor characterized by an advanced stage at the time of diagnosis (cervical lymph node metastases) and a poor prognosis. The basaloid component is comprised of small packed cells displaying hyperchromatic nuclei without nucleoli, and scant cytoplasm. The tumor grows in a solid pattern with a lobular configuration, and sometimes a prominent peripheral palisading. Comedo-type necrosis is frequently seen (**Fig. 8**). Small cystic spaces containing PAS- and Alcian Blue-positive material and stromal hyalinization may be noticed. BSCC is always associated with a SCC component, usually located superficially. The SCC component may also present as focal squamous differentiation within the basaloid lobules. The junction between the two components may be abrupt. The differential diagnosis includes neuroendocrine carcinoma, adenoid cystic carcinoma, and adenosquamous carcinoma. BSCC requires aggressive multimodality treatment, including radical surgery (including neck dissection), radiotherapy, and chemotherapy (especially for metastatic disease). Survival rate is only 40% (Thompson, 2006).

**Papillary squamous cell carcinoma**

Papillary squamous cell carcinoma (PSCC) is a distinct variant of SCC characterized by an exophytic, papillary growth, and a favorable prognosis. PSCC presents as a soft, friable, polypoid, exophytic, papillary tumor. It frequently arises from a thin stalk, but broad-based lesions have also been described. The tumor is characterized by a predominant papillary growth pattern. By definition, the lesion must demonstrate a dominant (> 70%) exophytic or papillary architectural growth pattern with unequivocal cytological evidence of malignancy. The papillary pattern consists of multiple, thin, delicate, finger-like papillary projections. These papillae have thin fibrovascular cores covered by neoplastic, immature basaloid cells or more pleomorphic cells. Commonly, there is minimal keratosis. Foci of necrosis and hemorrhage are common. Invasion may be difficult to define, especially in superficial biopsies. Stroma invasion consists of a single or multiple nests of tumor cells with dense lymphoplasmacytic inflammation at the tumor-stroma interface. Differential diagnosis includes squamous papilloma, verrucous carcinoma, and exophytic SCC. Though squamous papilloma and verrucous carcinoma share similar architectural features with PSCC, the latter is easily recognized by atypia of the squamous epithelium. Patients with PSCC tend to have a better prognosis compared to those with site- and stage-matched conventional SCC. This is probably related to limited invasion in PSCC. Approximately, one third of patients develop recurrence, frequently more than once (Barnes et al., 2005; Thompson, 2006).

**Spindle cell carcinoma**

Spindle cell carcinoma is a biphasic tumor composed of a squamous cell carcinoma, either in situ and/or invasive, and a malignant spindle cell component with a mesenchymal appearance, but of epithelial origin (Barnes et al., 2005). Spindle cell carcinoma most often occurs in males. It usually exhibits a polypoid appearance with a mean size of 2 cm. The surface is frequently ulcerated. The spindle cell component usually forms the bulk of the tumor. It can be arranged in a diverse array of appearances, including storiform, interlacing bundles or fascicles, and herringbone. The two components can abut directly against one another with areas of blending and continuity between them. Hypocellular areas with dense collagen deposition can be seen. Pleomorphism is often mild to moderate, without a severe degree of anaplasia. The tumor cells are plump fusiform cells, although they can be rounded and epithelioid. Rarely, metaplastic or frankly neoplastic cartilage or bone can be seen. Resemblance to fibrosarcoma or malignant fibrous histiocytoma is most common. Evidence for squamous epithelial derivation can be seen as either in situ carcinoma or as invasive SCC. The SCC component is usually minor to inconspicuous with the sarcomatoid part dominating. Carcinoma in situ can be obscured by extensive ulceration. Infiltrating SCC may be focal, requiring multiple sections for demonstration. Sometimes, only spindle cells are present; in such cases, SPCC can be mistaken for a true sarcoma. Metastases usually contain SCC alone or both SCC and the spindle cell component, and rarely, only the spindle cell component. SPCC can also be confused with reactive or benign spindle cell proliferation (such as nodular fasciitis), inflammatory myofibroblastic sarcoma, low-grade myofibroblastic sarcoma, and myoepithelial carcinoma. There is mounting molecular evidence that SPCC is a monoclonal epithelial neoplasm with a divergent (mesenchymal) differentiation, rather than a collision tumor. This is the one SCC variant in which immunohistochemistry may be of value. The individual neoplastic spindle cells react variably with keratin (AE1/AE3), EMA, and CK18, even though only 70% of cases will yield any epithelial immunoreactivity. A nonreactive or negative result should not dissuade the pathologist from the diagnosis, especially in the right setting. Spindle cell carcinoma metastasizes to the regional lymph nodes in up to 25% of cases, but distant dissemination is less common (5-15%). The reported 5-year survival rate is between 65% and 95% (Barnes et al., 2005; Thompson, 2006).

**Acantholytic squamous cell carcinoma**

This is an uncommon histopathologic variant of squamous cell carcinoma, characterized by acantholysis of the tumor cells, creating pseudolumina and false appearance of glandular differentiation. No special etiologic factor has been discovered for the mucosal acantholytic SCC. It is most frequent in sun-exposed

areas of the head and neck. The tumor is composed of SCC, but with foci of acantholysis in tumor nests, creating the appearance of glandular differentiation. The pseudolumina usually contain acantholytic and dyskeratotic cells, or cellular debris, but they may be empty. They are more frequent in the deeper portions of the tumor. There is no evidence of true glandular differentiation or mucin production. The SCC component predominates, and is usually moderately-differentiated. The stroma is usually desmoplastic, with a lymphoplasmacytic response. The acantholysis may also form anastomosing spaces and channels mimicking angiosarcoma. Acantholytic SCC must be differentiated from adenosquamous carcinoma, adenoid cystic carcinoma, and mucoepidermoid carcinoma. Prognosis is similar to that of SCC. However, some reports suggest a more aggressive behavior (Barnes et al., 2005; Thompson, 2006).

**Adenosquamous carcinoma**

This rare aggressive neoplasm originates from the surface epithelium and is characterized by both squamous cell carcinoma and true adenocarcinoma. The larynx is the most frequent site of occurrence. Most patients (65%) present with lymph node metastases. Adenosquamous carcinoma occurs throughout the upper aerodigestive tract, often as an indurated submucosal nodule usually less than 1 cm in diameter. It can present as an exophytic or polypoid mass, or as poorly defined mucosal induration, frequently with ulceration. The main feature is both true adenocarcinoma and SCC. The two components occur in close proximity, but they tend to be distinct and separate, not intermingled as in mucoepidermoid carcinoma. The SCC component can present either as in situ or as an invasive SCC. The adenocarcinomatous component tends to occur in the deeper parts of the tumor. It consists of tubular structures that give rise to "glands within glands". The adenocarcinoma component can be tubular, alveolar, and glandular, although mucus-cell differentiation is not essential for the diagnosis. Mucin production is typically present, either intraluminal or intracellular, and can appear as signet ring cells. There is typically a sparse inflammatory cell infiltrate at the tumor-stroma interface. Differential diagnosis includes mucoepidermoid carcinoma, acantholytic SCC, and SCC invading seromucinous glands, and necrotizing sialometaplasia. The most important differential diagnosis is from mucoepidermoid carcinoma as adenosquamous carcinoma has a poorer prognosis. Aggressive surgery with neck dissection yields an approximately 55% 2-year survival rate (Barnes et al., 2005; Thompson, 2006).

**Carcinoma cuniculatum** is a rare variant of oral cancer displaying similarities with lesions more commonly described in the foot in which the tumor infiltrates deeply into the bone. There is proliferation of stratified squamous epithelium in broad processes with keratin cores and keratin-filled crypts which seem to burrow into bone tissue, but lack obvious cytological features of malignancy. Clinical-pathological correlation is often needed to make the diagnosis (Barnes et al., 2005).

**Nasopharyngeal carcinoma** and **lymphoepithelial carcinoma** are rare entities distinct from conventional squamous cell carcinomas. Lymphoepithelial carcinoma (LEC) may develop in the nasal cavity and paranasal sinuses, the hypopharynx, larynx and trachea, and in the oral cavity and oropharynx. It is a poorly differentiated squamous cell carcinoma or histologically undifferentiated carcinoma accompanied by a prominent reactive lymphoplasmacytic infiltrate, morphologically similar to nasopharyngeal carcinoma. Most sinonasal LECs are associated with Epstein-Barr virus (EBV) infection (Barnes et al., 2005).

Nasopharyngeal carcinoma (NPC) is a carcinoma arising in the nasopharynx that shows light microscopic or ultrastructural evidence of squamous differentiation. It encompasses squamous cell carcinoma, non-keratinizing carcinoma (differentiated or undifferentiated), and basaloid squamous cell carcinoma. Keratinizing squamous cell carcinoma of the nasopharynx is morphologically similar to keratinizing squamous cell carcinomas occurring in other head and neck sites. NPC incidence is considerably higher in Chinese, Southeast Asians, North Africans, and native people from the Arctic region. There is a near constant association of NPC with EBV, suggesting an oncogenic role of the virus. NPC harbors a highly malignant behavior with extensive loco-regional infiltration, early lymphatic spread, and hematogenous dissemination (Barnes et al., 2005).

**Histogenesis**

SCC originates from the squamous mucosa or from ciliated respiratory epithelium that has undergone squamous metaplasia (Barnes et al., 2005).

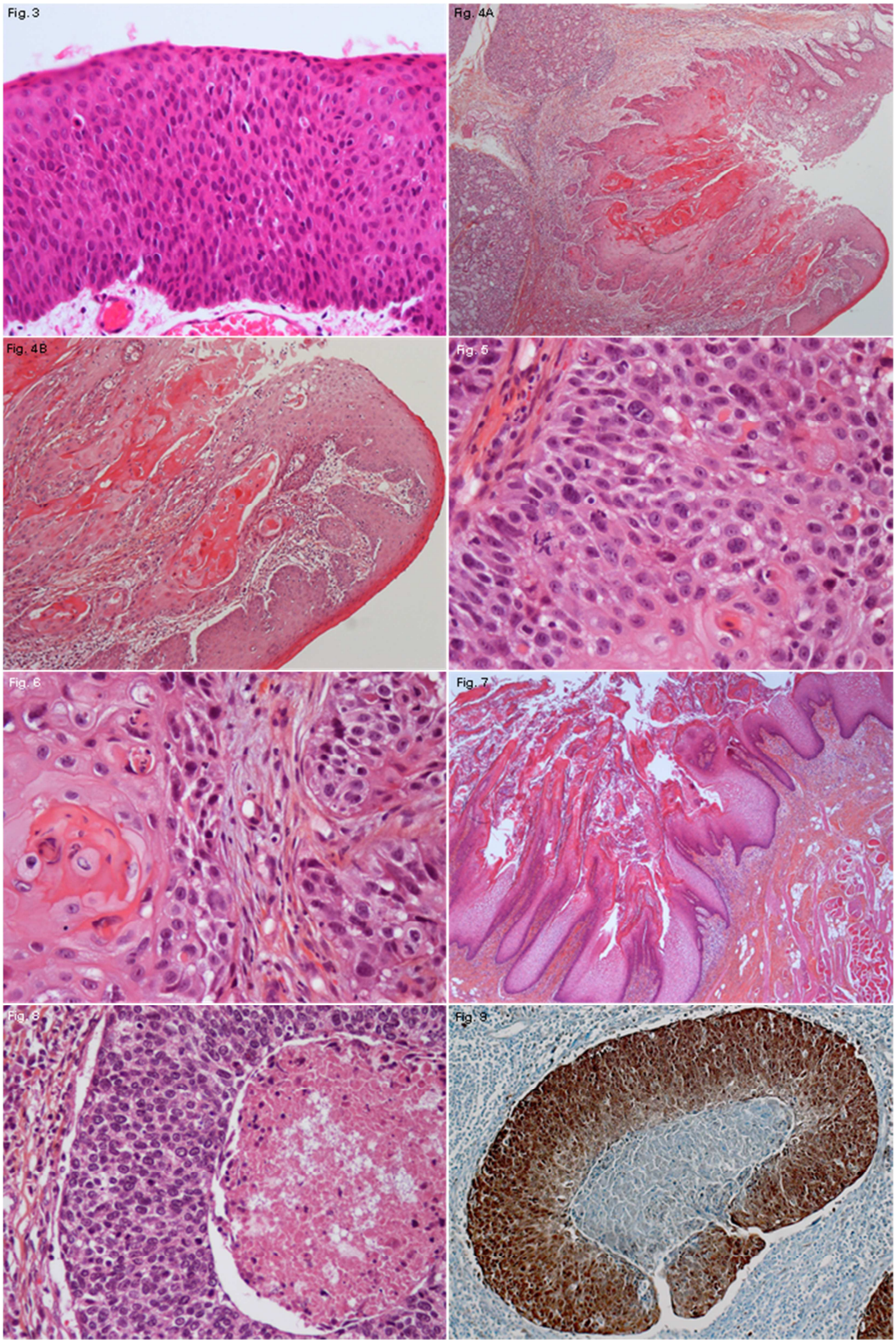


**Figure 3:** Carcinoma in situ. Full thickness architectural abnormalities and cytological atypia Hematoxylin and eosin staining (original magnification x200). **Figure 4:** Invasive SCC. Invasive growth with disruption of the basement membrane and extension into the underlying tissue. Hematoxylin and eosin staining (original magnification Fig. 4A: x20, Fig. 4B: x100). **Figure 5:** Invasive SCC. Mitoses (at 9 o' clock) and nuclear atypia. Hematoxylin and eosin staining (original magnification x400). **Figure 6:** Invasive SCC. Focal keratinization (left hand side). Hematoxylin and eosin staining (original magnification x400). **Figure 7:** Verrucous carcinoma. Thickened, club-shaped, projections of well-differentiated squamous epithelium and abundant surface keratosis ("church-spire" keratosis). Hematoxylin and eosin staining (original magnification x20). **Figure 8:** Basaloid SCC. Solid pattern of growth and central comedo-type necrosis. Hematoxylin and eosin staining (original magnification x100). **Figure 9:** p16 immunostaining in basaloid SCC (original magnification x200).

## Cytogenetics

**Precursor lesions**

Malignant transformation of the mucosal lining is a genetic process resulting from accumulation of multiple genetic alterations that dictates the frequency and pace of progression to invasive carcinoma. LOH studies indicate that the earliest alterations appear to target specific genes located on chromosomes 3p, 9p21 (CDKN2A), and 17p13 (TP53). Alterations that tend to occur in association with higher grades of dysplasia and SCC include cyclin D1 amplification, PTEN inactivation, and LOH at 13q21, 14q32, 6p, 8, 4q27, and 10q23 (Barnes et al., 2005).

There are no individual markers that reliably predict malignant transformation of dysplastic lesions. Ploidy studies of dysplastic leukoplakias showed that the great majority of aneuploid lesions developed SCC in the follow-up period, by contrast with 60% of tetraploid lesions and only about 3% of diploid lesions (Sudbo et al., 2001). Similar studies on erythroplakias confirmed the higher predictive potential of aneuploidy in identifying cases which progressed to SCC (Sudbo et al., 2002).

**Invasive squamous cell carcinoma**

HNSCC is a heterogeneous disease, comprising at least two distinct genetic subclasses: tumors that are caused by infection with high-risk types of HPV, and those that do not contain HPV. Approximately 20% of HNSCCs contain transcriptionally active HPV whereas 60% harbor a TP53 mutation. In the remaining 20%, other genes encoding proteins in the p53 pathway may be targeted or these tumors may undergo p53-independent malignant progression.

**- HPV-negative squamous cell carcinoma**

Tobacco and alcohol-induced HNSCCs are characterized by TP53 mutation. The excess of G to T transversions and the codons more frequently affected were attributed to the carcinogenic effect of tobacco smoking (Barnes et al., 2005). Other genes are involved in the pathogenesis of HPV-negative tumors. CCND1, which encodes cyclin D1, is amplified or gained in more than 80% of HPV-negative HNSCCs. CDKN2A (encoding p16) can be inactivated by mutation, homozygous deletion, or promoter hypermethylation (Barnes et al., 2005).

EGFR (Epidermal Growth Factor Receptor) is overexpressed in most HNSCCs (Hama et al., 2009). The EGFR is a receptor tyrosine kinase belonging to the erbB family of cell surface receptors. Once phosphorylated, it can signal through MAPK, Akt, ERK, and Jak/STAT pathways. These pathways are related to cellular proliferation, apoptosis, invasion, angiogenesis, and metastasis. Dysfunction of the receptor and its associated pathways occurs in 80-90% of HNSCCs (Kalyankrishna et al., 2006). Mutations and amplifications of EGFR have been reported, albeit at relatively low frequencies. EGFR amplification has been detected in 10-30% of cases (Temam et al., 2007; Sheu et al., 2009). Even though few activating mutations have been found, the mutant form EGFRvIII has been detected in 42% of HNSCCs (Sok et al., 2006). Interestingly, it has been shown that microscopically normal mucosa adjacent to invasive SCC displayed a high degree of overexpression and that the upregulation of EGFR occurs in the transition from dysplasia to cancer (Grandis et al., 1993; Shin et al., 1994). Elevated levels of EGFR expression have been associated to a poor clinical outcome (Chung et al., 2004; Temam et al., 2007). High copy number amplification has also been shown to portend a dismal prognosis in HNSCCs (Chung et al., 2006). However, overexpression of EGFR may be a biomarker for an improved response to therapy and could serve as a predictive marker (Bentzen et al., 2005). The EGFR pathway can be targeted through the use of specific tyrosine kinase inhibitors (TKIs), monoclonal antibodies blocking receptor dimerization, and anti-sense oligodeoxynucleotides or siRNA blocking mRNA expression (Glazer et al., 2009).

Both mutations and gene amplifications of MET have been described in HNSCCs. MET, the receptor for Hepatocyte Growth Factor (HGF) is a tyrosine kinase encoded by MET on chromosome 7q31. It activates the AKT and Ras pathways and influences growth, motility and angiogenesis in HNSCCs (Leeman et al., 2011).

Finally, the PI3K-PTEN-AKT pathway is frequently activated in HNSCCs (Leeman et al., 2011).

**- HPV-induced squamous cell carcinoma**

HPVs are DNA viruses that show a tropism for squamous epithelium. HPV is a strictly epitheliotropic, circular double-stranded DNA virus. There are more than 100 subtypes of HPV, some of which are involved in cervical carcinogenesis and have been designated as high-risk HPVs (e.g. HPV-16 and -18) (zur Hausen, 2002; Moody et al., 2010). HPV-positive HNSCCs present with distinct molecular profiles compared to HPV-negative tumors whereas they harbor similarities with HPV-positive cervical SCCs. Most HPV-induced HNSCCs are caused by one subtype, HPV-16. HPV infection is an early, and probably initiating, oncogenic event in HNSCCs. High-risk oncogenic HPV subtypes have been shown to be capable of transforming oral epithelial cells through the viral oncoproteins E6 and E7. The E6 protein induces degradation of p53 through ubiquitin-mediated proteolysis, leading to substantial loss of p53 activity. The usual function of p53 is to arrest cells in G1 or induce apoptosis to allow host DNA to be repaired. E6-expressing cells are not capable of this p53-mediated response to DNA damage and, hence, are susceptible to genomic instability. The E7 protein binds and inactivates the retinoblastoma tumor suppressor gene product pRB, causing the cell to enter S-phase, leading to cell cycle disruption. This functional inactivation of pRB also results in a reciprocal overexpression of p16 protein. By

immunohistochemistry, most HPV-positive HNSCCs show p16 overexpression (Marur et al., 2010) (**Fig. 9**). The combination of low EGFR and high p16 expression has been shown to highly correlate with better clinical outcome compared with high EGFR expression and low HPV titer or high EGFR and low p16 expression (Kumar et al., 2008). P16 expression in oropharyngeal SCCs has also been associated with longer survival times regardless of HPV status (Lewis et al., 2010).

The best method for HPV detection is still controversial. PCR-based detection of HPV E6 oncogene expression in frozen samples is generally regarded as the gold standard but in situ hybridization is also commonly used. P16 immunohistochemistry could serve as a potential surrogate marker (Marur et al., 2010).

As mentioned above, HPV-positive HNSCCs are typically TP53 wild-type. There also seems to be an inverse relationship between EGFR expression and HPV status.

## Prognosis

### Precursor lesions

Some precursor lesions are self-limiting and reversible (particularly if apparent etiologic factors are removed), others persist and some progress to SCC. The likelihood of malignant change directly relates to the severity of dysplasia. However, it is clear that malignancy can develop from any grade of dysplasia or even from morphologically normal epithelium. Dysplastic lesions classified as moderate to severe have an 11% rate of malignant transformation. Diagnosis of precursor lesions implies a need for close follow-up and complete excision. Patients with carcinoma in situ require more extensive management (Thompson, 2006).

Dysplastic lesions are frequently found in the surgical margins of invasive SCC, meaning such lesions can remain in the patient. These unresected fields act as an important source of local recurrences and second primary tumors that often occur in patients treated for HNSCC.

### Invasive squamous cell carcinoma

The prognosis for patients with HNSCC is determined by the stage at presentation, established based on the extent of the tumor, as well as the presence of lymph-node metastases and distant metastases. About one third of patients presents with early-stage disease, whereas two thirds present with advanced cancer with lymph node metastases (Jemal et al., 2007). Early-stage tumors are treated with surgery or radiotherapy and have a favorable prognosis. The standard of care for advanced tumors is surgery combined with adjuvant radiation therapy and/or chemotherapy. Survival outcomes are poor (40-50% five-year survival rates) and the treatment is uniformly morbid. Organ-preservation protocols, with combined chemotherapy/radiation therapy and surgery for salvage, are increasingly performed. These protocols are particularly effective for young patients with a good performance status presenting with moderately-advanced laryngeal or pharyngeal SCC. Several characteristics of patients with HNSCC have been linked to favorable prognosis, including non-smoker, minimum exposure to alcohol, good performance status, and absence of co-morbid disorders (Marur et al., 2010). Thirty-five to 55% of patients with advanced-stage HNSCC remain disease-free 3 years after standard treatment. However, locoregional recurrence develops in 30% to 40% of patients and distant metastases occur in 20% to 30% of HNSCCs (Forastiere et al., 2003). Locoregional recurrences often require a combination of surgery, radiation therapy, and/or chemotherapy, and metastatic disease is treated with chemotherapy.

Recently, the use of targeted drugs has entered the field. Cetuximab is one of the most well studied monoclonal antibodies directed against EGFR. Binding of the antibody to EGFR prevents activation of the receptor by endogenous ligands. An overall survival benefit and an increased duration of locoregional control have been observed in advanced HNSCCs treated with a combination of radiation therapy and cetuximab, compared to radiation therapy alone (Bonner et al., 2006).

It has been demonstrated that the presence and type of TP53 mutation is also of prognostic relevance. Several studies have shown a correlation between p53 mutation and lower response rates to chemotherapy and shorter overall survival times (Erber et al., 1998; Cabelguenne et al., 2000; Temam et al., 2000; Poeta et al., 2007).

On the whole, survival has not markedly improved in recent decades because patients still frequently develop locoregional recurrences, distant metastases, and second primary tumors. Primary prevention could be achieved by cessation of smoking and reduction of alcohol consumption.

Patients with HPV-positive HNSCC tend to be younger and have a lower tobacco and alcohol consumption. They often present at a late stage with large metastatic cervical lymph nodes. Histopathologically, the tumor is often moderately to poorly-differentiated with basaloid features (Gillison et al., 2000). However, HPV-positive HNSCCs are associated with a more favorable clinical outcome regardless of treatment modalities, and this may be related to immune surveillance to viral antigens (Leemans et al., 2011). Prognosis is better not only for patients treated with radiation therapy or concomitant chemotherapy/radiation therapy but also for patients treated with surgery alone (Lassen et al., 2009; Fischer et al., 2010). In patients with oropharyngeal SCC treated with surgery, the 5-year survival rates for p16-negative and p16-positive patients were 26.8% and 57.1%, respectively (Lassen et al., 2009). In another study, patients with HPV-positive oropharyngeal SCC had a 58% reduction in the risk of death (Ang et al., 2010). The better prognosis associated with HPV-status

has also been observed in high-grade basaloid SCCs of the oropharynx (Thariat et al., 2010). Most studies confirm that HPV is one of the most important independent prognostic factors in HNSCC. However, only the rate of locoregional recurrence, but not that of distant disease, is diminished in patients with HPV-positive SCC. Increased sensitivity to chemotherapy and radiotherapy in HPV-positive oropharyngeal cancer may be related to absence of exposure to tobacco and presence of functional p53 protein. Increased survival of patients with HPV-positive SCC may be in part attributable to absence of dysplastic fields related to tobacco and alcohol exposure. So, HPV-status of HNSCC is a prognostic factor for progression-free and overall survival and might also be a predictive factor. Use of HPV vaccines against infection and therapeutic vaccines in the adjuvant setting for locoregional recurrence and distant disease should be assessed in this form of HNSCC.

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