

Oral squamous cell carcinoma

Identity

Note An invasive epithelial neoplasm with varying degrees of squamous differentiation that arises from the following anatomic sites: the oral cavity, particularly oral soft tissues including the gingival and alveolar mucosa, floor of the mouth, tongue, soft and hard palates, tonsils and oropharynx. Oral squamous cell carcinomas (SCC) have a propensity to early and extensive lymph node metastases.

Clinics and Pathology

Epidemiology Oral cancer consistently ranks as one of the top ten cancers worldwide, with broad differences in geographic distribution. They represent approximately 5% of cancers in men and 2% in women. Oral SCC often develops after the age of 50, with a highest peak in the sixth decade of life. The major risk factor for these neoplasms is chronic exposure of oral mucosa to tobacco and alcohol. Apart from these, human papilloma virus (HPV) infection, especially HPV 16 and 18, are found in a variable but small proportion of oral, and up to 50% of tonsillar and oropharyngeal SCC. It has been realized for a long time that patients with oral SCC are at risk of second tumors in the upper aerodigestive tract, reported to occur in 10-35% of case.

Clinics More than 90-95% of oral cancers are SCC or one of its variants. SCC typically presents as a persistent mass, nodule, or indurate ulcer. The three most common sites of involvement are tongue, lip and floor of the mouth. They can develop from precancerous lesions, such as leukoplakia and erythroplakia, or apparently normal epithelium. Histopathologically, they can be categorized into three degrees of differentiation:
Well differentiated disease shows greater than 75% keratinization.
Moderately differentiated disease contributes to the bulk of SCC and is characterized by 25% to 75% keratinization.
Poorly differentiated disease demonstrates less than 25% keratinization.
The degree of differentiation may vary from one part of the tumor to another. Tumor stage is according to TNM classification.

Prognosis Histological grade correlates poorly with patient outcome and thus has limited value for prognostication. Tumor size and nodal status are the most significant prognostic factors. At the time of diagnosis, the majority of patients with SCC present advanced disease (stage III-IV), and approximately one third of them show lymph node metastasis. After curative treatment, about 50% of the patients suffer recurrences; 80% within 2 years and the remaining within 4 years. The major cause of death is loco-regional failure.

Cytogenetics

Note **Classical cytogenetics**
Clonal chromosome abnormalities have been described in about 250 oral SCC (115 of oral cavity, 81 of tongue, and 53 of oro- or hypopharynx). The great majority of these neoplasms are characterized by complex karyotypes with a clearly nonrandom pattern of losses and gains of chromosome segments. This is in line with the notion that oral SCC, like most of other epithelial malignancies, develop by the accumulation of multiple genetic aberrations.
The most frequent imbalances were loss of 3p, 8p, 11q, 15p, 13p, 14p, 4p, 10p, 6q, 2q33-qter, and chromosomes Y, 21, 22, and 18, and gain of chromosomes 20 and 7, 8a and 11a13. The most common structural aberrations were i(8a). homoaneously

staining region (hsr), i(3q), i(5p), i(1q), del(16)(q22), i(13q), i(14q), del(2)(q33), and del(3)(p11). Another striking feature is that close to half of all structural rearrangements involve breakpoints in the centromeric or juxtacentromeric bands, particularly in chromosomes 8, 1, 3, 5, 13, 14 and 15.

Molecular consequences of chromosomal aberrations revealed by fluorescence in situ hybridization (FISH)

A number of fluorescence in situ hybridization (FISH), including multicolor FISH, studies have been undertaken in cytogenetically characterized oral SCC and SCC from other sites of head and neck region, in order to define the molecular consequence of chromosomal regions commonly involved in structural rearrangements, such as centromeric and pericentromeric rearrangements, homogeneously staining regions in chromosomal band 11q13 and other chromosome loci. From these studies, it could be concluded that the essential outcome of near-centromeric or centromeric rearrangements is genomic imbalances, i.e., loss or gain of cancer-associated genes. For instance, target regions for deletions in 1p and 8p have been identified. Characterization of hsr, a cytogenetic sign of gene amplification, has shown that hsr in these neoplasms almost always derives from 11q13 DNA sequences, that such amplicons always include the [CCND1](#) gene, and that the amplification is often concomitant with loss of the distal part of 11q and with the overrepresentation of distal 3q.

Frequent finding of comparative genomic hybridization (CGH) and allelic imbalance studies

Molecular genetic studies of oral SCC have been focused on the identification of tumor suppressor gene loci and amplified oncogenes. Earlier LOH studies focused on specific chromosome segments have pointed out the frequent loss of alleles from 3p, 8p, 9p, chromosome 13 and 17p in [head and neck SCC](#), including oral SCC. A number of recent studies using allelotyping and comparative genomic hybridization (CGH) indicate that head and neck SCCs display massive and widespread genomic imbalances and that certain chromosome segment are lost more often than others. These studies confirmed the frequent deletion and LOH from 3p, 9p, [13q](#), and 17p, detected in more than 50% of the cases. Furthermore, deletions in 3q, 4p, 4q, 5q, 6p, 6q, 8p, 8q, 11q, 14q, 17q, 18q, and 20p have been shown in significant subsets.

Cytogenetics
Molecular

Candidate tumor suppressor genes (TSG) in frequently deleted chromosome region

Chromosomal arm 3p: Loss of 3p material, in particular 3p13-p21, p21-23, and p25, is a common genetic change shared by several types of carcinomas. Several tumor suppressor genes have been mapped to these regions. Among them, two genes, i.e., [FHIT](#) in 3p14.2 and [VHL](#) in 3p25-26, were studied for the presence of inactivation mutations in oral SCC. The finding of alterations of FHIT in oral precancerous lesions and SCC supports the pathogenetic role of FHIT in oral SCC carcinogenesis. However, very little evidence for the involvement of VHL in oral SCC could be observed.

Chromosome arms 4p and 4q: No TSG in these chromosomal arms has been identified in oral SCC so far.

Chromosome arm 5q: [APC](#) located at 5q21 is a TSG important for [familial colon cancer](#) and [sporadic colon cancer](#). Some studies support the involvement of APC in oral SCC, whereas others do not.

Chromosome arms 6p and 6q: No TSG in these chromosomal arms has been identified in oral SCC so far.

Chromosome arm 8p: 8p12 and 8p22 are frequently deleted in oral SCC. A recent study using RT-PCR showed reduced expression of FEZ1/LZTS1, a candidate tumor suppressor gene mapped to 8p22, which may contribute to the development of oral SCC. No other genes in these regions have been investigated.

Chromosome arm 9p: [CDKN2A](#) (a.k.a. p16), a cell cycle regulatory gene, located at 9p21, is frequently down regulated through homozygous deletion or hypermethylation in oral SCC.

Chromosome arms 11p and 11q: 11p14 and 11q14qter were reported to be lost in a

fraction of oral SCC. However, no TSG has been identified yet.

Chromosome arm 13q: Some studies showed LOH of [RB1](#), mapped to 13q14, in a fraction of oral SCC. Furthermore, lack of expression of RB1 in about half of cases has been reported in one immunohistochemistry study.

Chromosome arm 17p: Loss of 17p is not very common at the cytogenetic level. However, such deletions are frequent at LOH studies. The prevalence of [TP53](#) mutation and expression of a mutated protein has been reported in 40-60% of oral SCC. Expression of mutated TP53 in oral premalignant lesions may indicate malignant transformation. Especially, expression above the basal cell layer has been highly predictive of malignant development. A number of studies have shown that TP53 mutation is associated with increased risk of locoregional recurrence and poor outcome.

Chromosome arm 18q: No target gene important for oral SCC has been reported for this chromosome arm.

Frequent amplification of oncogenes in homogeneously staining regions and amplified chromosome segments

Hsr in 11q13 and CCND1 amplification: The second most common structural rearrangement identified in oral SCC is hsr, a cytogenetic sign of gene amplification, found in about 25% of cytogenetically aberrant tumors. Approximately one half of the hrs were found in chromosomal band 11q13. FISH studies have demonstrated that hsr in 11q13, as well as at other chromosomal loci, almost always originates from 11q13 DNA sequences and that the amplification then always includes CCND1. These findings are in agreement with extensive molecular investigations by various techniques, indicating that CCND1 is the prime target in the amplification process and important for oral SCC development. A recent study has shown that Cyclin D1 overexpression alone can induce extension of the replicate life span of normal keratinocytes, and the combination of cyclin D1 overexpression and TP53 inactivation led to their immortalization. Furthermore, several molecular studies have shown that CCND1 amplification and/or overexpression is a prognostic marker for disease free survival.

Chromosome arm 3q: A number of oncogenes, such as [LAZ3/BCL6](#), PIK3CA, DCUN1D1/SCCRO, telomerase RNA and AIS gene, map to 3q26-28, a frequently gained chromosomal segment shown by cytogenetic and CGH studies. Among them, SCCRO and PIK3CA may play a role in the pathogenesis of oral SCC through amplification at 3q26, and SCCRO appears to be a significant predictor of regional metastasis and may be a marker for tumor aggressiveness and clinical outcome.

Chromosome arm 7p: Gain of part of or the entire chromosome 7 has been a common finding in oral SCC. Epidermal growth factor receptor EGFR and the insulin like growth factors IGFB1 and IGFB2 are three potentially interesting genes located in 7p13-22. EGFR has been extensively investigated in oral SCC, particularly with respect to therapeutic targeting of these neoplasms. The results of these studies suggest that amplification of the EGFR gene occurs at a relatively early stage of the development of oral SCC and a high level of EGFR gene expression probably plays an important role in the progression to invasive cancer.

Chromosome arm 8q: Gain of 8q material through the formation of isochromosome i(8q) and unbalanced structural rearrangements are the most common structural change in oral SCC. Several genes of interest, such as [MYC](#) and PTK2, are localized at 8q23-24. However, as yet, no evidence for the involvement of these genes has been reported in oral SCC.

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