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| 原文題目(出處)： | **Histopathologic risk factors in oral and oropharyngeal squamous cell carcinoma variants: An update with special reference to HPV-related carcinomas(***Journal section: Oral Medicine and Pathology* **)** |
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內文：

**Abstract**

Accurate identification of the microscopic risk factors of oral and oropharyngeal (OP) squamous cell carcinomas (SCC) and their morphologic variants is of at most importance, as these generally determine treatment modalities, prognosis and overall patient outcome. The great majority of oral and oropharyngeal squamous cell carcinomas are microscopically described as kerartinizing squamous cell carcinoma (KSCC). Tobacco habits and excessive consumption of alcoholic beverages have been considered to be the main etiologic agents in these carcinomas. The tumors occurred in older patients more commonly affected the oral tongue and floor of the mouth with well established morphologic risk factors including tumor grade, pattern of invasion and peri-neural involvement.

Within the last 30 years however, the advent and expanding prevalence of high risk human papillomavirus (HPV) as an important etiologic agent for head and neck squamous cell carcinoma, particularly in the OP, has resulted in a significant change in the established morphologic criteria for risk assessment. The majority of HPV relate carcinomas of the OP are non-keratinizing squamous cell carcinoma (NKSCC). Examples of HPV-related squamous cell carcinoma variants that will be addressed here are: basaloid squamous cell carcinoma (BSCC), undifferentiated carcinoma (UCa), papillary squamous carcinoma (PSCC) and small cell carcinoma.

## Keratinizing squamous cell carcinoma (KSCC); morphologic risk factors

Traditionally KSCCs have been graded according to their state of differentiation and resemblance to normal squamous epithelium into well, moderate and poorly differentiated variants. However, because the morphologic features can vary considerably from area to area within the same tumor, the Broder grading system was found to lack significant prognostic value. Several authors suggested that more useful prognostic information may be deduced from the invasive fronts of the tumors where the deepest and presumably more aggressive cells reside. The scores for all the variant are summed to provide a total malignancy score for a particular tumor. The parameters used are: degree of keratinization, nuclear pleomorphism, number of mitosis per high power field (HPF), pattern of invasion and inflammatory lymphoplasmacytic host response.

A newer risk model was developed by Brandwein- Gensler and associates as an extension and modification of prior multivariable histologic systems analyzing the advancing tumor front. In this model a risk category is assigned by examining the resection specimen of the primary tumor and quantifying 3 significant histologic variables; 1- Pattern of invasion at the advancing tumor edge (PI). The different types of patterns are described as; pushing border, finger like growth, large islands, small islands or distant satellites. 2- Perineural invasion (PNI) involving either small nerves or large ones (>1mm). 3- Lymphocytic host response at the advancing tumor edge described as strong, intermediate or weak. The model was significantly predictive of loco-regional recurrence and disease specific survival. Based on these observations it was suggested that some low stage oral SCC that would traditionally be treated surgically may benefit from adjuvant radiotherapy if classified in the high risk group.

## HPV-Related squamous cell carcinoma

During the last 30 years accumulating epidemiologic and clinical evidence has shown that high risk human papillomavirus (HPV) is a major etiologic factor in a subset of head and neck squamous cell carcinomas. These tumors have distinct clinical, microscopic and molecular features. They are characterized by younger age at onset weak or no association with alcohol and tobacco use but strong association with sexual behavior, particularly oral sex. Despite a characteristic early lymph node metastasis, HPV-related oropharyngeal squamous cell carcinomas are associated with significantly better treatment outcome and patient survival.

Microscopically, HPV-related squamous cell carcinoma of the OP are distinguished by a nonkeratnizing morphology The tumors are characterized by relatively monomorphic, ovoid and spindle-shaped basaloid cells with indistinct cell border (Fig. 1). The cells form sheets, nests and cords with sharply defined borders. These carcinomas also show a distinct immune-histo-chemical profile namely, a strong and diffuse p16 reactivity, very high Ki-67 labeling scores (Fig. 1) and negative or week staining with p53.

p16 over expression is now considered a surrogate marker for HPV-related NKSCC of the OP. p16 is a cell cycle protein associated with tumor suppression by the retinoblastoma pathway. HPV E7 oncoprotein interacts with pRb active form resulting in its functional inactivation. The paradoxical overexpression of an inhibitory protein in actively replicating neoplastic cells is thought to result from feed-back control secondary to pRb deregulation

The nonkeratinizing morphology is significantly more likely to be HPV and p16positive than KSCC, and to have better overall survival (OS) and disease specific survival (DSS) with a p value of<0.001 and 0.01 respectively. It was also shown that p16overexpression in oropharyngeal SCC is associated with HPV positivity and has significantly better patient outcome.

Detection p16overexpression by immunohistochemistry is the most commonly used technique for this purpose. Another common detection method is in situ hybridization (ISH) for HPV DNA. While highly specific it is not very sensitive. On the other hand, PCR analysis for HPV DNA is highly sensitive but not necessarily specific.

E6/E7 mRNA expression is considered the "gold standard" for identification of clinically significant HPV infection in tumor specimens. Reverse transcriptase polymerase chain reaction (RT-qPCR) are the main methods used for detection and quantitation of E6/E7 mRNA. ISH for E6/E7 mRNA is a slide-based chromogenic assay that has been developed under the name RNA scope. Results from HPV E6/E7 mRNA ISH were found to be highly concordant with p16immunohistochemistry and RT-qPCR.

The exact causal mechanisms involved in poor clinical outcome and patient survival in a minority of HPV positive SCC of the oropharynx are not clear. However, certain relevant molecular profiles have been proposed. These include over-expression of Bcl2, EGFR, and BclxL,. EGFR is a transmembrane tyrosine kinase, its function affects cell cycle progression, apoptosis, angiogenesis, tumor cell mobility and metastasis. Similarly over-expression of the antiapoptotic proteins Bcl2 and BclxL was shown to be associated with poor OS and DFS as well as DSS in HPV + OPSCC these proteins are known to confer resistance to chemotherapy and radiation therapy of head and neck SCC. It has also been documented that patients who continue to smoke after treatment have a significantly worse DSS than those who were past or never smokers

### HPV Related squamous cell carcinoma of the oral cavity

Unlike the OP, the oral cavity proper is a rare site for HPV related SCC. However, considerable variations in the prevalence of HPV in oral SCC have been reported in the literature. Prevalence may also vary by geographic distribution of the studied cases. A range of between 0%-11% has been reported. HPV+ oral SCC, unlike those in the OP, do not exhibit nonkeratinizing morphology. The significance of HPV in oral SCC and its relationship to treatment outcome and patient's survival is currently not known.

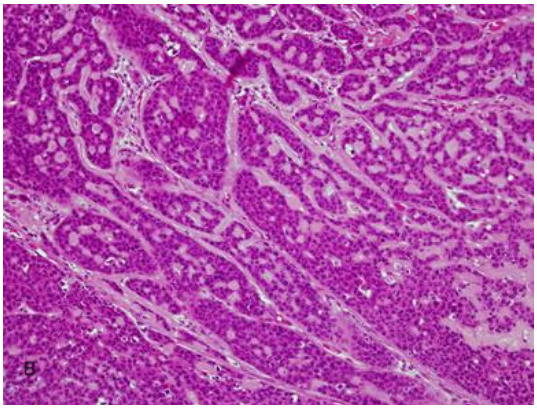
### HPV-Related SCC variants

The great majority of HPV relate SCC of the OP is non-keratinizing as described above. However, more recently increasing numbers of variants of squamous cell carcinoma, that are HPV-positive, are reported in the oropharynx as well as in other head and neck sites. Examples of HPV-related squamous cell carcinoma variants that will be addressed here include: basaloid squamous cell carcinoma, undifferentiated carcinoma, papillary squamous carcinoma, small cell carcinoma and keratinizing squamous cell carcinoma.

### Basaloid squamous carcinoma (BSCC)

In the upper aerodigestive tract, BSCC is rare variant of conventional SCC. It occurs more commonly in the hypopharynx and larynx and less frequently in the oropharynx. Like SCC the tumor is typically associated with traditional risk factors like tobacco smoking and alcohol abuse. It is generally considered a high grade malignant neoplasm with poor prognosis.

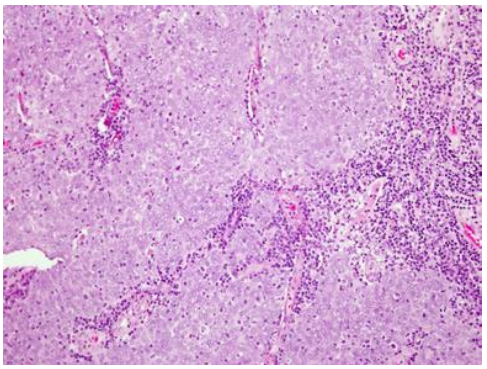
The basaloid cells are small, crowded with hyperchromatic round nuclei and scant cytoplasm. They form sheets and lobules that produce a "jigsaw puzzle" growth pattern with cystic spaces containing PAS –positive myxoid material.



A causal relationship between HPV and some cases BSCC has been documented in the upper aerodigestive tract. Chernock *et al*, using ISH for HPV DNA and p16 immunohistochemistry found that 75% of orophryngeal BSCC are HPV related while none (0%) of 16 laryngeal/hypopharyngeal tumors were positive. Using PCR for HPV 16DNA as well as p16immunostaining, Begum and Westra documented HPV in 76% of oropharyngeal BSCC and in 6% of tumors in non-oropharyngeal sites.

## Undifferentiated carcinoma (lymphoepithelial, nasopharyngeal type)

In the head and neck undifferentiated carcinoma (UDCa) is best recognized in the nasopharynx. While undifferentiated carcinoma of the nasopharynx has a strong etiologic relationship to Epstein-Barr virus (EBV), undifferentiated carcinoma of the oropharynx has recently been shown to be predominantly HPV and not EBV-related.



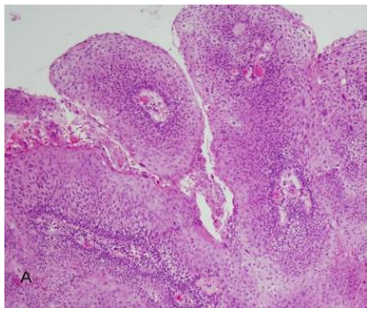
The tumors are composed of solid sheets, trabeculae, nests and single neoplastic epithelial cells intimately intermingled with lymphocytes and plasma cells. The epithelial tumor cells are large with indistinct cell borders forming a syncytium (Fig. 4).

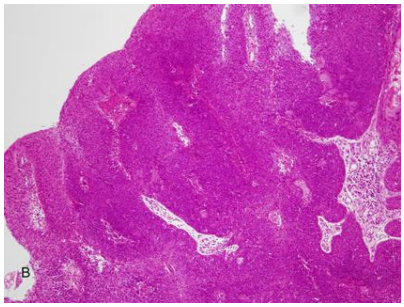
The 3 year OS was found to be 55%, while the DSS was 100%. No tumor recurrence was observed during a median follow up period of 23 months. The patient's outcome in HPV positive undifferentiated carcinoma of the OP is generally favorable and comparable to that of the nonkeratinizing HPV-related squamous cell carcinoma.

## Papillary squamous cell carcinoma

Papillary squamous cell carcinoma (PSCC) is a poorly understood variant of SCC of the upper aerodigestive tract that is often confused with other exophytic mucosal malignancies such as verrucous carcinoma and squamous cell carcinoma with verrucous features. As defined by the WHO, PSCC is characterized by a predominant papillary growth pattern with thin fibrovascular cores covered by immature basaloid cells or dysplastic cells with minimal or no keratinization. PSSC is generally believed to have a better prognosis than conventional squamous cell carcinoma.

Jo *et al*. found that 15 of 31 cases of PSCC of the head and neck were both p16 and HPV ISH positive. The majority of those (11 cases) were oropharyngeal. Two morphologic types were identified: (1) a keratinizing type (K) in which the dysplastic epithelium showed maturation trend with minimal surface parakeratin, and a (2)nonkeratinizing (NK) type in which the papillae were covered with immature basaloid cells (Fig. 5). The majorities of these were found in younger patients, occurred more commonly in the OP, had NK morphology and were less likely to be p53 positive. The 5 years DSS for p16positive and p16negative cases was 80% and 70 % respectively.



### Small cell (neuroendocrine) carcinoma

Bishop and Westra found that 5 of 9 cases of oropharyngeal small cell carcinoma were HPV-related. All cases showed a characteristic neuroendocrineimmunophenotype,. Three of the 5 patients died within 15 month of diagnosis with widely disseminated disease. Disease recurrence occurred in 5 of 6 patients with available clinical follow-up, with 3 developing metastasis to bone, lung, pleura, adrenal gland and pancreas.

HPV-related small cell carcinoma of the oropharynx shares common features with small cell neuroendocrine carcinoma of the uterine cervix. Both are associated with high risk HPV, commonly coexist with non-small. cell squamous cell carcinoma and share the same aggressive clinical behavior with early distant metastasis and poor overall survival

### HPV-Related keratinizing squamous cell carcinoma of the oropharynx

Classical KSCC of the OP is becoming much less frequently encountered in some parts of the world .A very small minority of these are HPV related. In a recent study we have found that only 7 of 54 (13%) KSCC of the OP overexpressed p16. HPV E6/E7 RNA ISH was positive in 5 tested cases. The OS and DSS was significantly better in the p16 positive than the p16 negative KSCC cases ($p$=0.01 and 0.04) respectively (47).

### Discussion

Within the last few decades an HPV related nonkeratinizing variant of SCC was identified. The majority of which occurred in the oropharynx. The exact molecular mechanisms underlying the ex-pression of this specific histopathologic phenotype are not clear. It is possible that interactions between HPV oncoproteins and cell cycle mediators may play a role. It is known that high risk HPV oncoproteins, particularly E6and E7, interfere with Rb and p53 functions leading to cell cycle progression, cell immortalization, suppression of apoptosis and essentially uncoupling of proliferation and maturation.

As the numbers of reported HPV positive head and neck squamous cell carcinoma variants are increasing, particularly in the oropharynx, it is of importance to establish the status of the virus in the tumors cells. Currently, the number of cases of SCC variants with established HPV causal relationship is still limited. Based on these studies, there is some evidence to suggest that variants such as BSCC, undifferentiated carcinoma and PSCC may have favorable prognosis similar to that of conventional NKSCC and better than their HPV negative counterparts. On the other hand, HPV related small cell carcinoma has been shown to be associated with early distant metastasis and poor overall survival. It is thus too early to reach a definite conclusion regarding the biologic behavior of HPV-related SCC morphologic variants.

| 題號 | 題目 |
|---|---|
| 1 | 1. HPV-related oropharyngeal squamous cell carcinomas are associated with significantly better treatment outcome and patient survival. Which one is not including in ?<br>(A) **Small cell (neuroendocrine) carcinoma**<br>(B) **Papillary squamous cell carcinoma**<br>(C) **Undifferentiated carcinoma**<br>(D) **Basaloid squamous carcinoma** |
| 答案<br>(A ) | 出處：oral pathology third eddition |
| 題號 | 題目 |
| 2 | **Which statement is not corresct about squamous undifferentiated carcinoma?**<br>(A) Common in nasal cavity<br>(B) Most founded in older people<br>(C) Have better prognosis than coventional squamous cell carcinom<br>(D) High recurrence rate |
| 答案<br>( D) | 出處：oral pathology third edition p427 |