REVIEW

Lib Oncol. 2016;44(2–3):31–35

# SPECIFICS OF HISTOPATHOLOGICAL ANALYSIS OF HEAD AND NECK CANCER

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**Summary**

Head and neck squamous cell carcinoma is the sixth most common malignancy. High morbidity and mortality, lack of response to radio-and chemotherapy and significant reduction in the quality of life in patients after surgical procedures in the head and neck region stress the need for more effective methods of diagnosis, treatment and prevention of disease recurrence. In the past, pathologist only defined the diagnosis, today pathologist also determines the prognostic and predictive factors that are important in the treatment of patients. This places the pathologist in the core of in a multidisciplinary team for head and neck cancer and decision making.

KEY WORDS: *head and neck, squamous cell carcinoma, pathology*

**SPECIFIČNOSTI PATOHISTOLOŠKE ANALIZE KARCINOMA GLAVE I VRATA**

**Sažetak**

Karcinom pločastih stanica glave i vrata je na šestom mjestu zloćudnih tumora. Karakterizira ga visoka incidencija i visoka smrtnost, također ne pokazuje očekivani odgovor na zračenje i kemoterapiju, a vidljiva je značajno umanjena kvaliteta života u bolesnika nakon kirurškog liječenja. Sve to zahtjeva traženje mnogo učinkovitijih metoda u dijagnosticiu i liječenju kao i prevenciji bolesti. U prošlosti je patolog samo postavio dijagnozu, danas treba odrediti prognostičke i prediktivne čimbenike koji su važni za liječenje bolesnika. Patolog je postao jedna od ključnih osoba u multidisciplinarnom timu karcinoma glave.

KLJUČNE RIJEČI: *glava i vrat, karcinom pločastih stanica, patologija*

Squamous cell cancer of the head and neck is common worldwide. The prognosis for early stage disease is good, but for patients with advanced disease it has chaged very little in the past 20 years. Researches have identified mutations in many genes, and the results of molecular research gives hope to the possibility of better treatment and prognosis of patients. Multidisciplinary teams are essential for optimal management

Head and neck squamous cell carcinoma (HNSCC) develops from the alterations of the surface epithelium include the clinical and pathologic terms known under the common histopathological term - dysplasia. Dysplasia and intraepithelial neoplasia represent a spectrum of abnormal epithelial maturation (dysplasia) and cellular aberations (atypia) that may or may not precede an invasive carcinoma, but the changed epithelium has a high risk of progression to squamous cell cancer. 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.Loss of heterozygosity (LOH) studies indi-

cate that the earliest alterations appear to target specific genes located on chromosome 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,p,8,4q2, and 10q23 (1). There are no individual markers that reliably predict malignant transformation of dysplastic lesions.

Precursor lesions are strongly associated with tobacco smoking and alcohol abuse, and especially a combination of these two. The risk of developing these lesions increases with duration of smoking, the type of tobacco and the practice of deep inhalation. Additional etiological factors are: industrial pollution, specific occupational exposures, nutritional deficiency, and hormonal disturbance. The role of human papillovirus (HPV) infection in precursor lesions may represent an incidental HPV colonization rather than true infection. Finally, identifying an accurate biomarker for the premalignant state would aid in diagnosis and also allow premalignancy rather than carcinoma to be an endpoint in clinical trials (1). Discovery of a biomarker to identify those lesions likely to progress to cancer would represent a considerable advancement in patient care.

The histopathologic interpretation and grading of epithelial dysplastic changes in the upper aerodigestive tract is imprecise and subjective. Various classification have evolved to describe the spectrum of histological changes in relation to their malignant potential and close collaboration between the pathologist and the clinician is essential in each individual case for interpretation of their respective findings and their importance in therapy and prognosis.

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. 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 recurrence and second primary tumors that often occur in patients treated for HNSCC (2).

The clinical or gross appearance of SCC is quite variable and includes ulcerated, flat, exophytic, verrucoid or papillary growths. The histologic appearance of invasive SCC may be as variable as the gross appearance without specific correlation between the gross appearance and the histopathologic findings.

According to the classification of the World Health Organization, SCC of head and neck is divided in some different types: *conventional, verrucous, basaloid, papillary, spindle cell (sarcomatoid), acantholytic, adenosquamous, cuniculatum* (1).

It is known that *conventional type* of SCC express epithelial markers such as cytokeratins. Verrucous carcinoma is a non-metastasizing variant of well-differentiated SCC, but *basaloid SCC* is a high-grade variant of this tumour. It is an aggressive, rapidly growing tumour characterized by an advanced stage at the time of diagnosis (very often cervical lymph node metastases) and a poor prognosis. Neuroendocrine markers and HMB-45 are negative, but this tumour may express neuron specific enolase (NSE) what is considered nonspecific. Variable expression can be seen with vimentin, S-100 protein, and actin.

*Papillary* SCC is a distinct variant with favorable prognosis. Patient with his tumour tend to have a better prognosis compared to those with site-and stage-matched conventional SCC (2).

*Spindle cell carcinoma* is biphasic tumour 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. Synonyms include *sarcomatoid* carcinoma, carcinosarcoma, metaplastic carcinoma, pseudosarcoma and Lane tumour. Spindle cell carcinoma is very aggressive tumour, most frequently occurs in men after the 60 year of age of life. There is mounting molecular evidence that this tumour is a monoclonal epithelial neoplasm with a divergent (mesenchymal) differentiation, rather than a collision tumour, and immunohistochemistry may be of value (3).

*Acantholytic* and *adenosquamous carcinoma* are also aggressive tumors.

*Carcinoma cuniculatum* is a rare variant of oral cancer characterized with proliferation of strati-

fied squamous epithelium in broad process 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 (1).

Treatment of patients with SCC depends on pathohistological prognostic factors. The prognosic parameters are as follows.

**Tumour size**

The overall 5-year survival has been reported to vary in range according to tumour size( T1/T2 as *low-risk umours* and T3/T4 as *high-risk* ). The outcome is greatly influenced by stage of the disease, and prognosis also depends or varies with tumour primary site, nodal involvement, tumour thickness, and status of surgical margins. The tumour size usually affects choice and outcome of treatment. It also affects the surgeon ability to achieve complete resection, especially in deep invading tumors. Increased tumour size has been linked to cervical involvement, high recurrence rate, and poor prognosis (4).

**Tumour volume**

Tumour volume or tumour thickness is closely related to lymph node metastasis, and it is believed that it reflects the aggressiveness of tumour growth. It is believed that the amount and nature of lymph node metastasis are closely related to size and thickness of tumour. It has been found that the size of lymph node involvement is closely related to tumour volume (thickness). Therefore, it is widely accepted that thickness is more accurate predictor of sub-clinical nodal metastasis, local recurrence, and survival than tumour size (5).

**Invasive front**

Tumour growth at the invasive front can show an expansive pattern, an infiltrative pattern or both. Expansive growth pattern is characterised by large tumour islands with well-defined pushing margins and is associated with a better prognosis. Infiltrative growth pattern is characterised by scattered small irregular cords or single tumour cells, with poorly defined infiltrating margins and is associated with a more aggressive course. Some guidelines recommend categorizing tumors into cohesive, and non-cohesive fronts (6).

**Resection margins**

The complete excision of tumour is the most important principle of oncologic surgery. Negative resection margins are generally associated with decreased recurrence and improved survival. Resection margins have not been precisely defined but distances of at least 5 mm or greater are desired (7). The patologist is highly responsible for determining the state of resection margins. Therefore it is necessery to ink the margins before taking a tissue samples.

**Degree of differentiation**

Invasive SCC includes keratinizing and non-keratinizing carcinoma, and according to the degree of keratinisation, cellular and nuclear pleomorphism, and mitotic activity is categorised from well to poorly differentiated. The degree of differentiation is a significant predictor of locoregional failure and tumour recurrence, but grading by differentiation is of limited prognostic value, as compared to pattern of invasion (8).

**Lymph node involvement**

Bad prognosis is expected in patients with ispilateral, contralateral or bilateral nodal involvement. The worst is bilateral then contralateral, then ipsilateral. The size of nodal involvement is a very important determent, and extracapsular invasion was identified as an important predictor of regional recurrence, distant metastasis, and thus, overall survival (4). A pathologist is a key person in determining the involvement of the number of lymph node metastases as determining the extracapsular spread in lymph nodes. Also, must determine the size of the largest metastasis in the lymph node.

**Perineural and endoneural invasion**

Perineural and endoneural invasion is strongly associated with tumour size, histological grading, invasive front and nodal involvement. The perineural spread is affecting overall prognosis and survival, because the perineural and endoneural invasion means spreading of the tumour cells up to base of the skull as the tumour cells spread easily through the nerve and surrounding tissues and compartment (9).

**Lymphovascular invasion**

Lymphovascular invasion is associated with an increased propensity for lymph node and/or distant metastases. It tend to occur in aggressive SCC and is associated with recurrence and poor survival (10).

Molecular biologic studies have been extensively used in patients with head and neck cancers in the evaluation of pathogenesis of disease and as potential determinants in prognosis. Deletion allelic inbalance, or LOH on short arm (p) of chromosome 3 occurs in SCC and have been shown to be associated with aggressive biologic behavior, as well as having prognostic and therapeutic importance (11,12).

Some authors used molecular biologic markers to assess histopathologic negative surgical margin and negative lymph nodes for patients with SCC. They also found p53 mutations in tumour resection margins and lymph nodes that were free of tumour by conventional histologic examination. The presence of p53 mutations in *tumour-free*surgical margins ad lymph nodes carried a substantially higher risk of local recurrent disease than in patients without p53 mutations (13). Today it is very well known that the expression of epidermal growth factor receptor (EGFR) may be a biomarker for an improved response to therapy and a predictive marker as well (14). Elevated levels of EGFR expression have been associated to a poor clinical outcome (15). According to novel data, the PI3K-PTEN-AKT pathway is also frequently activated in SCC of head and neck (16).

Patients with HPV-positive tumors are associated with a more favorable clinical outcome regardless of treatment modalities, and this may be related to immune surveillance to viral antigens (16). The better prognosis associated with HPV status has also been observed in high-grade basaloid SCC of the oropharynx (17). Recent studies indicate that a small population of cancer cells is highly tumorogenic, and that existence of cancer stem cells may be the reason for lack of effectiveness of previous treatment methods. Targeted elimination of these cells is considered to provide a new framework for head and neck cancer treatment (18). The emergence of molecular biology with its new prognostic and ultimately, therapeutic tools represents an enormous opportunity. Unfortunatelly, the biologic markers are very expensive, and laboratory standardization of biologic marker techniques and variability in interpretation of tissue results comprimise the diagnostic significance of these markers.

## CONCLUSION

Early detection of precancer lesions coupled with early interventation could significantly improve patient outcome and reduce mortality. Conventional histopathology is currently unable to predict accurately which individual lesions from oral potentially malignant disorders spectrum will transform to squamous cell carcinoma. Therefore the close collaboration of pathologist and the clinician in everyday treatment decision making is essential.

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