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The Significance of Ki-67 in Head and Neck Cancers: Review Article.

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ABSTRACT

Widely accepted prognostic factors like lymph node status, tumor size and cell differentiation sometimes are not useful in oral cancer diagnostics and prognosis. Therefore, study of tumor heterogeneity which involves also molecular markers might be useful in order to explain mechanisms of appearance and recurrences of oral squamous cell cancer. The aim of the present study was to search published literature in the last 25 years regarding the role of Ki-67 in the head and neck cancers. Thirty seven articles were included and results showed that Ki-67 is not reliable prognostic marker for oral squamous cell carcinoma because of contradictory results of the available studies.

Keywords: Ki-67, head and neck cancer, molecular marker, prognosis.

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INTRODUCTION

Ki-67 gene is located on the chromosome 10 (10q25). Schluter et al. (1) were the first ones to encode the whole cDNK sequence.Ki-67 location and cell features are dynamic during the cell cycle, being low during the G1 phase and early S-phase, however, it progressively in order to reach its maximum during the mitosis (2).It seems that Ki-67 is an useful biomarker of various phases of the cell growth. Cell proliferation correlates with tumor prognosis (3). Numerous studies have shown that Ki-67 is relevant in breast, lung and prostate cancer prognosis (4-9). Although the significance of Ki-67 in head and neck cancers has been discussed during the past 20 years, no study revealed this controversy in reliable manner.

Numerous studies showed that Ki-67 is a good prognostic marker in the oral squamous cell cancer (10-18), although some researchers suppose otherwise (19, 20). Therefore Xie et al. (21) performed systemic literature search in order to determine prognostic value of Ki-67 expression in patients with oral sqamous cell cancer. Twenty seven published papers on 2146 patients were included. The results showed that systemic treatment, border values of Ki-67 expression, ethnicity and antibody types had significant impact on the results. Statistical analysis of the subgroups suggested that non-systemic treatment and Asian population have increased risk of Ki-67 expression as well as the low cut-off value of Ki-67 expression might influence result identification. The results of the same meta-analysis showed that higher expression of Ki-67 might be negative prognostic marker in patients with oral squamous cell cancer, especially in the Asian population. Furthermore, the same authors (21) concluded that Ki-67 expression influences response to the treatment.

MATERIALS AND METHODS

Pubmed was searched in the last 25 years in order to find out relevant published papers upon role of Ki-67 in head and neck cancers. Thirty seven articles were identified and included in this study.

DISCUSSION

Cell proliferation is thought to be one of the most important mechanisms in the oncogenesis. Gerdes et al. (2) realized that Ki-67 is present in all proliferating cells, however, it is absent in cells which stay still might be potential agent in determining fast ratio of proliferating cells within neoplasm's. Subsequently, large amount of studies have been performed which investigated the role of Ki-67 and correlation with tumors and its potential in prognosis of these tumors (8, 14, 15, 22, and 23). Xie et al. (21) searched all the available data on the internet and have found more than 100 published papers which showed that proliferation index was not relevant to the proliferation rate. Besides, some authors postponed that Ki-67 expression shows radio sensitivity in these cancers (24, 25).

However, most of the conclusion was based on the small sample size and different interventional methods which may lead to the certain controversies. Therefore, Xie et al. (21) performed meta-analysis in order to determine clinical significance of Ki-67 in patients with head and neck cancers. The results have shown that higher expression of Ki-67 correlates with worse prognosis in these patients. Systemic treatment might improve patient prognosis with higher Ki-67 expression, i.e. there is a need that patients with higher Ki-67 expression are systemically treated. Furthermore, the same authors proved that ethnicity influences the prognosis of head and neck cancers. Higher expression of Ki-67 in the Asian population suggest higher risk factor for the development of these cancers, therefore Ki-67 suggest poor prognosis in these patients (21).

Increased expression of Ki-67 correlates with oral cancer with lowered differentiation level, with increased level of dysplasia and worse survival (23, 26, and 27). It seems that Ki67 is a reliable indicator in diagnosis of poorly differentiated and invasive lesions (28). As the cells during the proliferation are more sensitive to the ionizing radiation, Ki67 might be an index of the treatment response to ionizing radiation in patients with oral cancer (29). As prognostic markers for patients with oral cancer are missing, involvement of Ki-67 would support type of therapy given. Cancers with Ki-67 index above median have an average recurrence within period of 42 months, whereas patients with Ki67 index below median have an average recurrence up to 55 months. Therefore, Ki67 might indicate subgroup of surgical treated patients which might benefit from the treatment intensification (30).

Bhuyan et al. (31) determined immunohistochemically expression of Ki-67 antigen on 102 oral cancer patients which were divided into stage I (40 cases), stage II (32 cases), and stage III (30 cases). Nucleus with brown staining was considered positive and the cells have been calculated under the magnification lower than 400×. Proliferative activity was determined and expressed as the percentage of Ki-67 labeling index (Ki-67 LI) for positive sells. Graduate increase of the average Ki-67 value from the stage I to III cancer correlated with histological staging. The study of Bhuyan et al. (31) showed definitive correlation between Ki-67 antigen and Bryne's histological grading. It is assumed that cell proliferation is one of the most important biological mechanisms within oncogenesis and that the cells stained with Ki-67 showed to be efficient in the staging. On the contrary, Brockton et al. (32) reported that Ki-67 did not correlate with poorer survival of the 189 patients with oral squamous cell cancer.

Rezazadeh et al (33) determined the Ki-67 expression in the cytological smears as well as on 48 oral biopsies which included 28 oral cancer tissues as well as 20 samples of the healthy oral mucosa. Out of 28 samples of oral sqamous cell cancer, 22 (78%) cases had Ki-67 positive cells, while the samples of the normal mucosa were negative to Ki-67.

Lopes et al. (34) analyzed samples from 51 patients with oral squamous cell cancer in order to determine immunohistochemical expression of Ki-67. Overall survival for the patients with positive staining to Ki-67 was shorter when compared to the patients who had negative KI-67 staining. Patients with tumors T3 and T4 had significant correlation with Ki-67 immunexpression. Correlation between Ki-67 expression, age, gender, smoking, tumor site, metastases into lymph nodes and disease stage was not significant. The same authors concluded that positive expression of Ki-67 in patients suffering from sqamous cancer might predict survival of these patients (34).

Ki-67 expression on the tumor invasive front (TIF) in correlation with clinical parameters, i.e. TNM classification and prognosis of the oral sqamous cell cancer was determined on the 140 Uruguay patients (35). No significant correlations were determined between Ki-67 immunohistochemical staining and different types of TIF, regional metastases and patient prognosis, although increased Ki-67 expression correlated with poorer clinical stage of the patients. The results of the same authors showed that Ki-67 proliferation marker is not a prognostic marker on the tumor invasive front in patients with oral squamous cell cancer (35).

Gupta et al. (36) determined cytokeratin, Ki-67 and p53 in 15 patients with oral cancer on the healthy and diseased oral mucosa. Primary tumors were positively stained on the cytokeratinn; however there was no Ki-67 and p53 staining. The same authors concluded that cytokeratin might be useful predictor of epithelial differentiation, while Ki-67 and p53 are weak indicators of the malignant progression in the oral tissues.

Almangush et al. (37) searched already published data on the following bases: Scopus, Ovid Medline, Web of Science and Cochrane Library in order to determine prognostic immunochemical markers for the tongue cancer between the years 1985 till 2015. There were 174 studies included and 184 markers regarding tongue cancer were evaluated. The most frequent ones were p53, Ki-67, and p16 which according to the above mentioned authors were not prognostic markers for the tongue cancer.

Expression of p53, cyclin D1, p21 (WAF1) and Ki-67 was determines in oral cancers in order to evaluate whether level of these markers in the invasive tumor front might predict local recurrence. Fifty one patients with T1/T2 tumors were stained for p53, ciklin D1, p21 (WAF1) and Ki-67 and results showed that these might predict the recurrence of oral squamous cell cancer (18).

In conclusion, despite the results of studies which showed a good prognostic value of Ki-67 as a marker for oral squamous cell cancer, there are still a sufficient number of studies which have shown contradictory results. Therefore, new studies with the large sample sizes and standardized immunohistochemistry techniques are recommended.

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