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DEPTH OF TUMOR INVASION AS INDICATOR OF MALIGNANT PROGRESSION IN PATIENTS WITH LOWER LIP SQUAMOUS CELL CARCINOMA WITH AND WITHOUT NECK LYMPH NODE METASTASIS

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Abstract

Squamous cell carcinoma (SCC) of the lower lip is a relatively rare carcinoma, but it is the most common carcinoma in the oral cavity and accounts for approximately 25%-30% of all oral malignant tumors. Prognosis of patients with lower lip SCC is predominantly dependent on stage of the disease, but recent research suggest that neoplasm morphological characteristics can have a significant influence on its progression and consequently on patient's outcome.

The aim of this study was to determine the role of depth of neoplasm invasion in the process of tumor progression, that is, in the onset of neck metastases in patients with lower lip squamous cell carcinoma and to correlate it with the neoplasm grade.

The study comprised 60 tumor tissue specimens obtained from patients with lower lip SCC. The examined group consisted of 45 specimens from patients without metastasis and 15 specimens from patients with metastasis in the regional lymph nodes. Histopathological sections were made with paraffin technique and stained with H.E. method. Depth of invasion was measured with the software for histomorphological morhometry.

There was a difference in the depth of stromal invasion in lower lip SCC, which was registered in the neoplasms of different histological differentiation and it was statistically significant ($p=0.00001$) according to the Kruskal-Wallis test.

The difference in the depth of stromal invasion in lower lip SCC registered in neoplasms of patients without metastases and in patients with metastases was statistically significant ($p=0.000083$).

Depth of neoplasm invasion is a parameter that can be used as an indicator for neoplasm progression, that is, as an indicator for neck metastases in patients with squamous cell carcinoma of the lower lip.

Keywords: squamous cell carcinoma SCC, lower lip, depth of stromal invasion, neoplasm differentiation, metastasis

Introduction

Squamous cell carcinoma (SCC) of the lower lip is a relatively rare carcinoma, with incidence between 1% and 2%, but it is the most common carcinoma in the oral cavity accounting for approximately 25-30% of all malignant oral tumors. Carcinoma of the lower lip appears in patients at the age of 60-70 years, mainly in white populations and is far more common in males than in females [1,2].

The neck lymph nodes metastases from squamous cell carcinoma of the lower lip develop in approximately 20% of patients and they are more frequent in patients with poor carcinoma differentiation. Depth of invasion is also a parameter that might be used as a morphological characteristic indicating neoplasm progression. This was the subject of our investigation.

Although new surgical techniques and radio-chemotherapeutic modalities have improved the survival in patients with squamous cell carcinoma of the lower lip, still the total 5-year survival rate in these patients is about 60%. Therefore, intensive search for new parameters that would point out to neoplasm progression, such as depth of invasion, might contribute to development of new therapeutic modalities in these patients.

Aim

The aim of this study was to determine the depth of neoplasm invasion in tumor progression, that is, in onset of neck metastases in patients with lower lip squamous cell carcinoma, as well as to correlate it with the tumor differentiation grade.

Material and methods

For the purposes of this study the archival material from the Institute of Pathology was retrieved, and paraffin blocks, histopathological slides and histopathological reports were used.

A total of 60 specimens of lower lip squamous cell carcinoma were analyzed, of which

- 45 specimens of SCC of patients without metastases in regional lymph nodes
- 15 specimens of SCC of patients with metastases in regional lymph nodes

The neoplasm differentiation was taken from the pathological reports, and, in addition, the depth of stromal tumor invasion at the neoplasm invasive front was analyzed.

The depth of invasion in each separate case was measured with computer software for histomorphologic morphometry using Olimpus BX-41 microscope at a magnification of 10 x 40. The distance from the basal membrane of intact epidermis to the deepest nest of the invasive front (malignant cells deep in the dermis) was measured. The obtained values were absolute numbers presented in micrometers (μm).

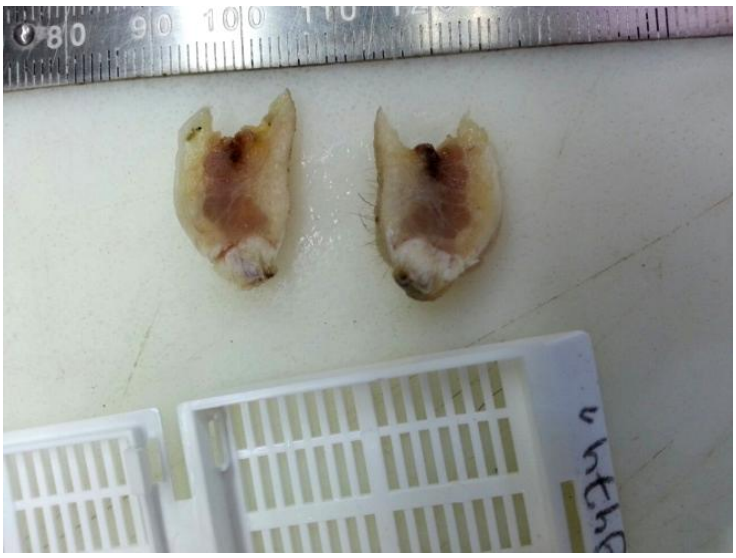


Figure1. Squamous cell carcinoma (SCC) of lower lip. Triangle-shape excision with relatively clear defined, grayish-white stained tumor tissue, which infiltrates to the lower lip musculature.

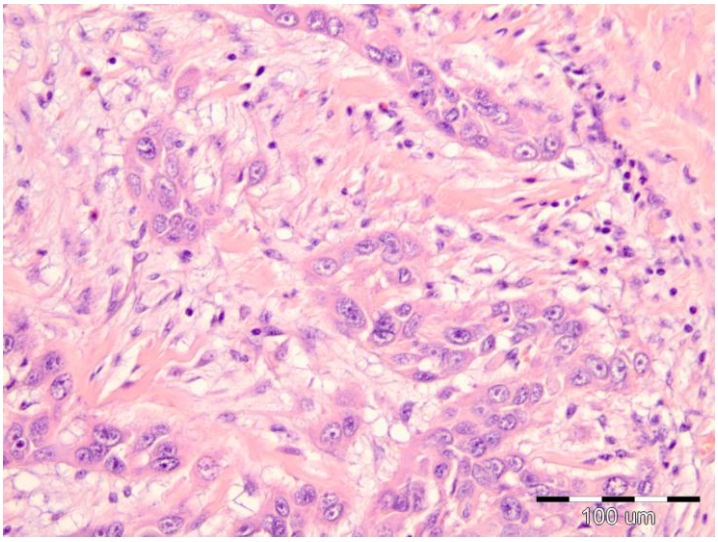
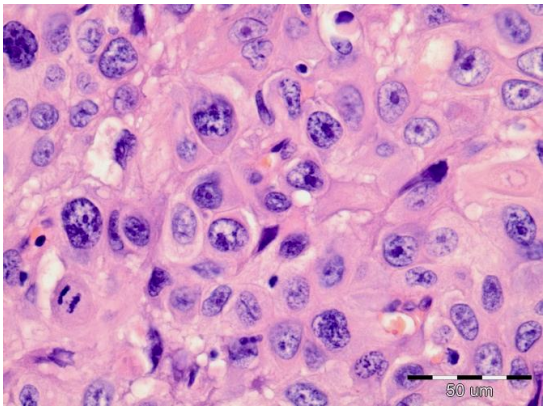


Figure2. Intensive tumor invasion into the stroma of SCC presented as small nests, strips and separate cells (HE 10 x 4)

a)



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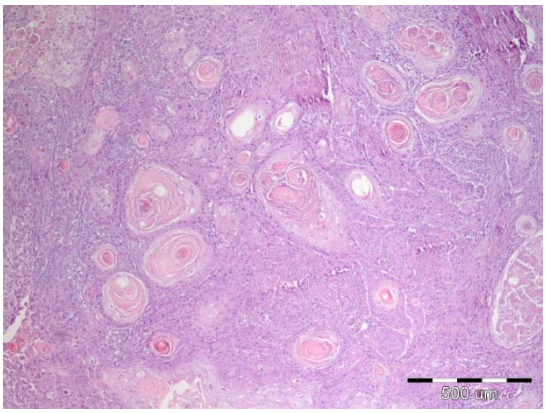

Figure 3.a) Squamous cell carcinoma G3 (HE 10 x 100) **b)** Squamous cell carcinoma G1 (HE 10 x 40)

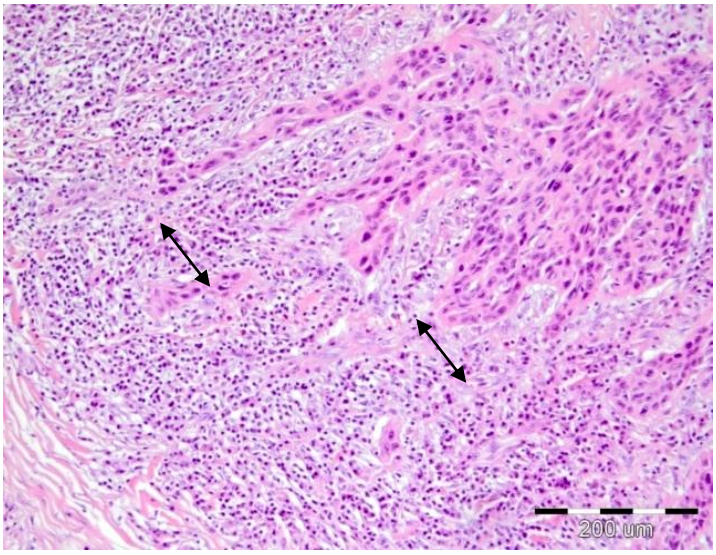

Figure 4. Invasive front and spreading of malignant cells, stripe-shaped, into the stroma of lower lip SCC (HE 10 x 20)

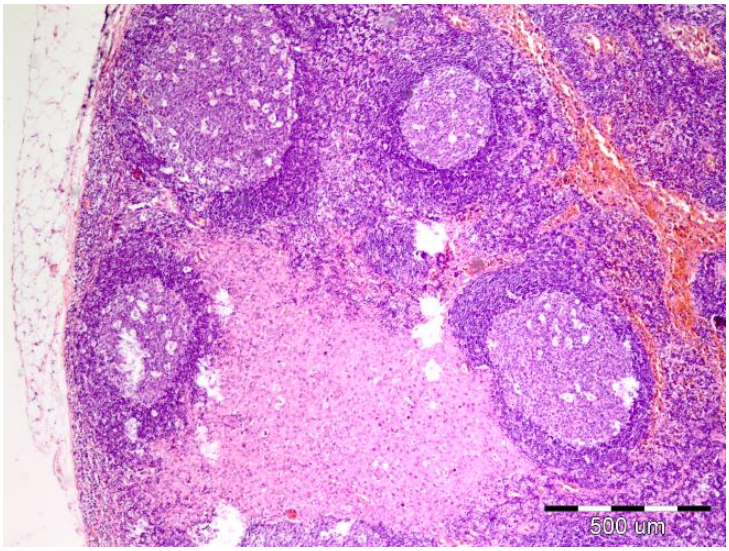

Figure 5. Neck lymph node with present metastatic deposit from a patient with moderately differentiated squamous cell carcinoma of lower lip (HE 10 x 4)

Results

Of the total number of 60 analyzed specimens, 13 (21.7%) were from female patients, aged 65-75 years, with a mean age of 70.2±2.9 years, and 47 (78.3%) were from male patients, aged 41-78 years, with a mean age of 66.4 ±8.5 years (Figure6).

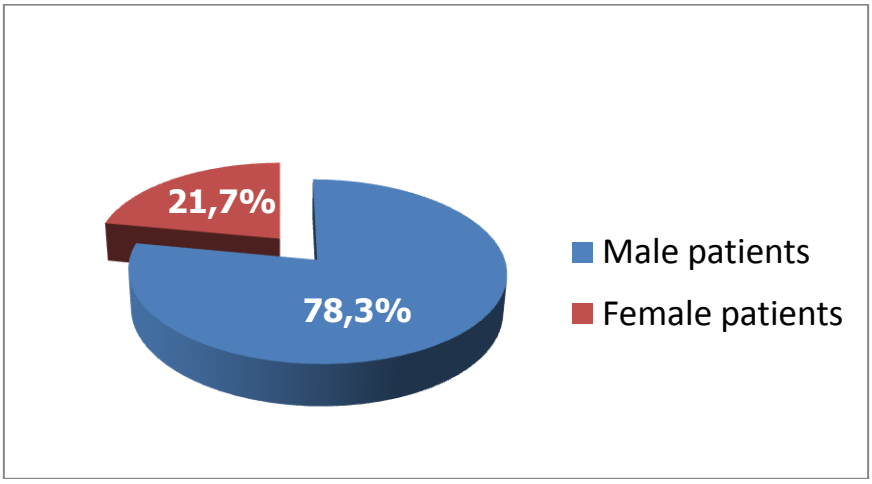

Figure 6. Distribution of patients by gender

Figures 7 and 8 present distribution of analyzed cases according to tumor differentiation and according to presence of positive neck lymph node metastases in patients with SCC.

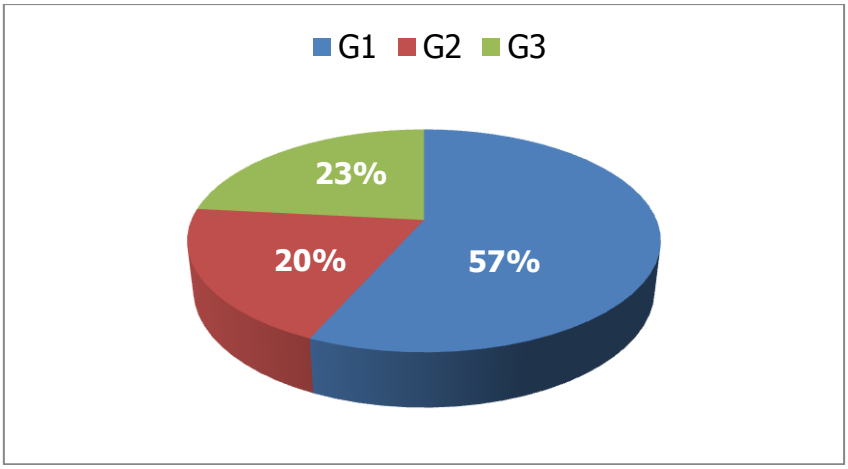

Figure 7. Distribution of specimens of patients with lower lip SCC according to neoplasm differentiation grade
Legend: (G1) – well-differentiated carcinoma, (G2) – moderately differentiated carcinoma, (G3) – poorly differentiated carcinoma

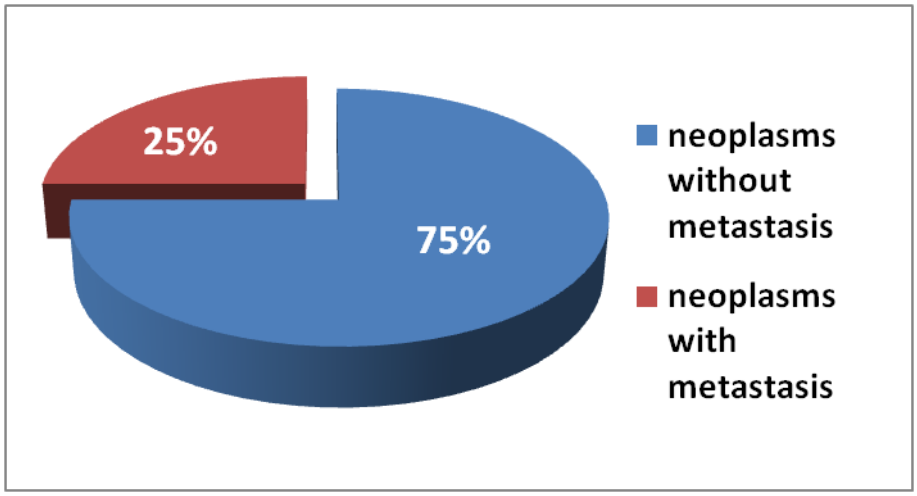

Figure 8. Distribution of specimens from patients with lower lip SCC without and with metastases

The results obtained from the performed measurements in correlation with the tumor grade in patients without neck metastases are presented in Table 1.

Table 1. Values of depth of tumor invasion into the stroma at invasion front in lower lip SCC without **neck metastases**, classified according to neoplasm differentiation grade

Parameter	Number of cases	Mean value	Standard deviation	Minimal value	Maximal value
Depth of tumor invasion (μm)					
G1	33	2650.82	± 959.59	1341.33	5713.78
G2	9	4388.33	± 2156.34	2197.75	7953.62
G3	3	8802.65	± 1026.62	7734.18	9781.56

The deepest neoplasm invasion at the invasive tumor front was found in poorly differentiated neoplasms compared to moderately and well-differentiated neoplasms ($p<0.00001$).

Table 2 shows the values of performed measurements in correlation with the tumor grade in patients with neck metastases.

Table 2. Results of depth of tumor invasion in the stroma at invasive front in lower lip SCC in patients **with neck metastases**, classified according to neoplasm differentiation grade

Parameter	Number of cases	Mean value	Standard deviation	Minimal value	Maximal value
Depth of tumor invasion (μm)					
G1	1	1817.22	/	1817.22	1817.22
G2	3	4945.84	± 3149.92	1718.89	8012.62
G3	11	9669.69	± 2660.16	4192.47	14105.62

The depth of tumor invasion was larger in neoplasms with G3 than with G2 and G1 in patients with neck metastases. This difference was also statistically significant ($p<0.000083$).

The difference in the depth of tumor invasion in patients with and without neck metastases was statistically significant (Mann-Whitney U тест, $p=0.000083$) (Figure 9).

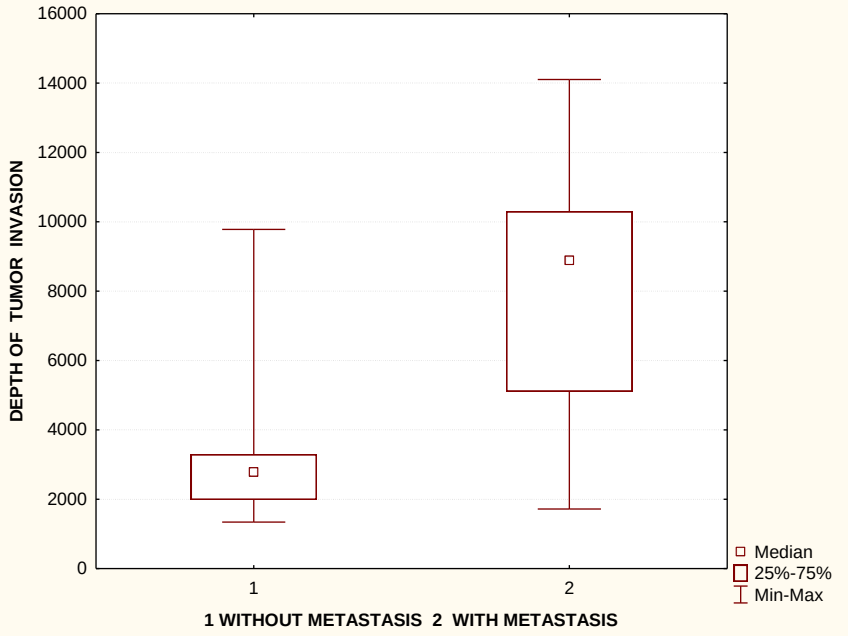

Figure 9. Comparison of depth of tumor invasion in lower lip SCC between neoplasms with and without metastases analyzed with the statistical method of Mann-Whitney U test.

Discussion

According to the definition of the World Health Organization squamous cell carcinoma is a malignant neoplasm of epidermal keratinocytes and mucous membranes characterized by variable keratinocyte cell differentiation [3]. Keratinocyte neoplasms are a significant health problem in spite of the low mortality rate.

Oral squamous cell carcinoma accounts for 95% of all forms of carcinomas that appear in the area of the head and neck. Squamous cell carcinoma is the most common oral carcinoma, and the lower lip carcinoma is the most common one in the oral cavity [4]. Squamous cell carcinoma of the lip very often develops as a result of pre-existing precancerous lesions such as: radiodermatitis, chronic cheilitis, and xeroderma pigmentosum. Risk factors include exposure to ultraviolet radiation, tobacco and alcohol abuse, exposure to some chemical factors as well as infections with human

papilloma virus, herpes simplex virus 1 and 2, which have been detected in about 25% of head and neck malignant neoplasms [5,6].

Prognosis of lower lip squamous cell carcinoma depends on several factors including: exposure to the above-mentioned risk factors and their combinations [5], stage of the disease [7], size of the tumor [8], regional lymph nodes metastasis, different histological variables such as tumor grade, maximal thickness, perineural invasion and protein expression [9], and other factors from the domain of surgical variables associated with surgical interventions [5].

Onset of metastatic deposits in regional lymph nodes is a predictive and prognostic parameter in patients with lower lip squamous cell carcinoma [10]. Metastases are rare in patients with well-differentiated tumors (about 5%) compared to those with undifferentiated carcinoma (20%). Early detection of this carcinoma is of particular importance for achieving good esthetic and functional postoperative results and favorable prognosis for patients [11].

Many authors have examined the depth of invasion of malignant neoplasms as a factor that has influence on tumor progression, recurrence, metastases and survival of patients with different types of malignant neoplasms and in different organs, such as skin malignant melanoma [12], anal carcinoma [13], stomach carcinoma [14], colon carcinoma [15], endometrial carcinoma [16], tongue carcinoma [17], uterine carcinoma [18] and others.

In the 90's of the last century Bruninger et al. made microstaging of squamous cell carcinoma by analyzing skin carcinomas (on the head, auricle, trunk and extremities) and lower lip, using parameters such as clinical size, that is, the largest lesion diameter, depth of invasion, tumor thickness and course of the disease monitored in a 5-year period. In their study, in addition to tumor thickness, as one of the important parameters that influenced on the onset of metastases in squamous cell carcinoma, was depth of invasion beyond the subcutis (perichondrium, periosteum, musculature) [19].

Regarding the oral squamous cell carcinoma, metastases are more often and hence, the assessment of risks for their appearance is of particular importance along with the influence of certain clinical and pathological parameters on patients' survival [9,10]. In the study "How does depth of invasion influence the decision to do a neck dissection in clinically N0 oral cavity cancer?" the authors demonstrated that depth of invasion of the primary tumor should be considered as a predictor of early metastasis in patients with early-stage squamous cell carcinoma in the oral cavity [20]. The same conclusion was brought by Shariat-Madar B and Lui JC in their study, but they also emphasized the fact that depth of invasion of the primary tumor had clinical significance in treatment of patients with oral squamous cell carcinoma [21].

Having in mind that factors which point out to tumor progression are of substantial importance, in this study the depth of invasion was measured in exact numbers and was correlated with the tumor grade as one of the indicators of progression supported by the presence of neck metastases as another parameter for tumor progression.

Depth of tumor invasion into the stroma was significantly larger in poorly differentiated carcinomas in comparison with moderately and well-differentiated carcinomas.

Regarding lower lip carcinomas, a significantly deeper invasion into the stroma of squamous cell carcinoma was found in patients with metastatic deposits in neck lymph nodes when compared to those without neck lymph nodes metastases.

Therefore, the depth of invasion of the primary neoplasm can be used as a predictive parameter for onset of neck lymph node metastasis in patients with squamous cell carcinoma of the lower lip. This finding is also in agreement with many studies in the literature [18-21].

Conclusion

The depth of invasion into the stroma of squamous cell carcinoma increases with the decrease of neoplasm differentiation, and the depth of tumor invasion in lower lip SCC can be a predictive factor for the onset of neck metastasis.

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