MULTIPLE PATHOHISTOLOGICAL PARAMETERS INFLUENCING PROGNOSIS AND SURVIVAL OF ORAL CANCER PATIENTS

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Abstract
The aim of this study is to determine the prognostic value of available clinical and histological parameters to predict subclinical nodal metastases and survival. For that purpose we used a modification of the Jakobsson [9] grading system proposed by Richard W. Nason [12] and applied it to a series of patients with oral carcinoma. Correlation between histological parameters and cervical lymph node metastasis were made and the chi-square test showed a strong significant association between mode of invasion, depth of tumor invasion, vascular invasion and cervical metastases. Analysis of overall survival showed that overall survival strongly correlates with cervical node metastases (p = 0.0004). We found that overall survival correlates with vascular invasion (p = 0.005) and also overall survival correlates with tumour depth (p = 0.001). There is a strong relationship between malignancy score and survival (p = 0.00001) and a high malignancy score is associated with poor prognoses. Patients: a total 32 with over 14 points of malignancy score, 25 (78.1%) died and 7 (21.9%) are alive.

Analysis of the risk factors for subclinical cervical metastases in patients with oral cancer is important for predicting prognosis and achieving a high survival rate.

Key words: oral cancer, malignancy grading score, survival rate, neck metastases.

Introduction
Many factors can influence survival in patients with oral squamous cell cancer, the most significant is lymph node metastasis. Advance tumour stage together with adverse histological features further reduce survival. Jakobsson (1973) first reported the application of a multifactorial malignnancy grading system using eight features of the tumour, including tumour cell structure, differentiation, nuclear polymorphism, mitotic count, mode of invasion and inflammatory cellular response in the prognostic evaluation of OSCC of the larynx.


Haksever M, et al. [7], have found an association between nodal involvement and depth of muscle invasion, and histological differentiation. Camisasca DR, et al. [4] found that risk factors for recurrence include an infiltrating pattern of tumour growth, diffuse histological invasion and tumour within 5 mm of the resection mar-
gin. Tumour thickness has been found to be an independent prognostic marker for subclinical nodal metastasis and survival by many authors such as Woolgar, et al. [17], Huang S, et al. (2009), Kane SV, et al. (2006). These authors suggest that investigators should look for information of predictive significance from a small biopsy specimen of the primary tumour to aid the clinician in surgical treatment planning.

The aim in this study is to determine the prognostic value of available clinical and histological parameters to predict subclinical nodal metastases and survival.

For that purpose we used a modification of the Jakobsson grading system proposed by Richard W. Nason and applied it to a series of patients with oral carcinoma.

**Material and methods**

A total of 75 patients with oral squamous cell cancer were included in this study, all of whom were hospitalized at the clinic for maxillofacial surgery in Skopje in a five-year period. This study was limited to patients with II, III and IV clinical stage oral carcinoma.

After the clinical staging of the patients through manual palpation, US. KT and MRI, a resection of the primary oral carcinoma was performed and simultaneous neck dissection. (Image 1)

![Image 1 – Surgical specimen](Image 1)

Fifty-seven patients met the criteria for the histopathological analysis

The operative material of the primary tumour was analysed and the degree of malignancy was determined for every patient. Grading of the degree of malignancy was made according to the system suggested by Nason Richards. We analyzed eight histological parameters: cytoplasmatic differentiation, nuclear pleomorphism, vascular invasion, depth of tumour invasion, mitotic count, mode of invasion, desmoplasia and inflammatory response. (Table 1, Image 2) Every histological parameter was presented with three modalities rated with 1, 2, or 3 points. For every patient we calculated the tumour malignancy score as the sum of all points from presented histological parameters. (Table 2) We correlated every histologic parameter with neck metastases and we also correlated the overall malignancy score with neck metastases and survival.

<table>
<thead>
<tr>
<th>Grade of malignancy evaluated from the primary tumor</th>
<th>1 point</th>
<th>2 points</th>
<th>3 points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytoplasmic differentiation</td>
<td>Abundant keratinization</td>
<td>Some keratinization</td>
<td>None to focal keratinization</td>
</tr>
<tr>
<td>Nuclear pleomorphism</td>
<td>None to mild</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Mitotic count</td>
<td>0-10/10 high power field</td>
<td>10-19/10 high power field</td>
<td>&gt; 19/10 high power field</td>
</tr>
<tr>
<td>Mode of invasion</td>
<td>Pushing border</td>
<td>Defined border and infiltrating cords</td>
<td>Irregular infiltrating cords</td>
</tr>
<tr>
<td>Inflammatory cellular reaction</td>
<td>Marked</td>
<td>Moderate</td>
<td>None</td>
</tr>
<tr>
<td>Desmoplasia</td>
<td>None to mild</td>
<td>Moderate</td>
<td>Marked</td>
</tr>
<tr>
<td>Vascular-lymphatic invasion</td>
<td>Absent</td>
<td>Probable</td>
<td>Positive</td>
</tr>
<tr>
<td>Level of invasion</td>
<td>Submucosa</td>
<td>Superficial muscle</td>
<td>Deep muscle</td>
</tr>
</tbody>
</table>

![Image 2 – PH findings; abundant keratinization, mode of invasion irregular, vascular invasion, moderate desmoplasia](Image 2)
Statistical Analysis
The chi square test was used to evaluate the risk of cervical node metastasis associated with histologic parameters and the histological grade of malignancy. The correlation between histologic parameters and overall survival was analyzed with the log rank test. Survival curves were plotted using the Kaplan-Meier method.

Results
Correlations between histological parameters and cervical lymph node metastasis were made and the chi-square test showed a strong significant association between the mode of invasion, depth of tumour invasion, vascular invasion and late cervical metastases ($p = 0.0084$, $p = 0.0004$, $p = 0.00006$). (Graphs 1, 2, 3) Patients with irregular-infiltrative mode of invasion of the primary tumour, deep invasion of the primary tumour in the muscular layer and also patients with positive vascular invasion of the tumour are at highest risk of early neck metastases.

Graphic 1 – Correlation between mode of invasion and lymph node metastases

The malignancy score was measured for each patient and the patients were divided into three groups: the first group patients with less than 14 points of malignancy score, the second with points ranged from 14 to 17 and the third group of patients with more than 17 points of malignancy score. We found a significant association between malignancy score and nodal metastases, 21 patients out of 29 with histologically proven nodal metastases had more than 17 points of malignancy score. (Graph 4)

Graphic 2 – Correlation between depth of invasion and late nodal metastasis

Analysis of overall survival showed that overall survival strongly correlates with cervical node metastases ($p = 0.0004$). (Graph 5) We found that overall survival correlates with vascular invasion ($p = 0.005$) and also overall survival correlates with tumour depth ($p = 0.001$). (Graphs 6, 7) Positive neck nodes found in dissection specimen significantly reduce the survival of patients.
There is a strong relationship between malignancy score and survival ($p = 0.00001$), a high malignancy score is associated with poor prognoses. A total of 32 patients with over 14 points of malignancy score, 25 (78.1%) died and 7 (21.9%) are alive. (Graph 8)

**Discussion**

In everyday practice we meet patients with early oral carcinoma but with aggressive behavior of the tumour and a poor prognosis. It seems clear that tumour stage alone is not reliable for predicting which patients with oral carcinoma are at greatest risk of cervical node metastases.

Therefore, an analysis of the risk factors for subclinical cervical metastases in patients with oral cancer is important for predicting prognosis and achieving a high survival rate. In our study tumour depth and vascular invasion of the tumour are superior to other prognostic parameters in prediction nodal metastases and survival.

Haksever M, et al. [7], Kane SV, et al. [10] Woolgar, et al. [17], Arduino PG, et al. [2] and others concluded that tumour depth is of major importance for predicting nodal metastases. We found that the critical tumour depth is when the tumour is invading the musculature and that is highly associated with subclinical nodal metastases. An irregular mode of invasion of the primary tumour is also highly associated with neck metastases and bed survival.

Martinez-Gimeno, et al. [11] designed a scoring system. In his study patients with scores ranging from 7–12, 13–16, 17–20 and 21–30 points showed metastasis in 0%, 20%,
63.6% and 86.7% of cases. Richard Nason, et al. [12] applied a malignancy score system to patients with stages I and II oral carcinoma. He defined 3 groups of patients: 1 with 14, 2 with 14–16 and 3 with more than 16 points, and he found the incidence of cervical metastasis of 12.8%, 35% and 90%. Sklenicka S, et al. [15] reported that multifactorial analysis and malignancy grading of the oral cancer patients is valid in predicting occult metastases and survival.

Pereira MC, et al. [14] found that survival is influenced by stage at presentation, nodal status, and histologic grade. Camisasca DR, et al. [4] concluded that the tumour site, tobacco use, and pathological features were involved in the recurrence of OSCC and should be taken into account for OSCC treatment and follow-up. In our study we found that a high malignancy score was strongly associated with nodal metastases and poor prognosis.

Conclusion

In conclusion, tumour depth, vascular invasion and mode of invasion are the most reliable predictive factors for subclinical nodal metastases. A malignancy grading system based on significant histological parameters is useful in everyday practice for selecting the patients with high risk of occult metastasis and predicting aggressive behavior of the tumour.

REFERENCES

Резиме

ВЛИЈАНИЕТО НА МУЛТИПНИ ПАТОХИСТОЛОШКИ ПАРАМЕТРИ ВРЗ ПРОГНОЗАТА И ПРЕЖИВУВАЊЕТО НА ПАЦИЕНТИТЕ СО ОРАЛЕН КАНЦЕР

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Вовед: Многу фактори влијаат на времето на преживување на пациентите со орален карцином, најзначајен фактор е присуството на метастатски лимфни јазли. Но напреднат клинички стадиум на болеста заедно со неповолните патохистолошки фактори, дополнително го редуцира времето на преживување.

Цел: Целта на овој труд е да ја детерминира прогностичката вредност на одредени патохистолошки параметри, т.е. да утврди кои патохистолошки фактори влијаат на појавата на вратни метастази и на времето на преживување кaj пациентите со орален планоцелуларен карцином.

Материал и методи: Вкупно 75 пациенти со орален карцином беа оперативно третирани на Клиниката за максилофацијална хирургија и вклучени во ова испитување. На Институтот за патохистологија направена е анализа на примарниот тумор, беа анализирани 8 патохистолошки параметри и секој параметар е класифициран во три градации кои беа бодувани. Беа анализирани следниве патохистолошки параметри: хистолошка депресија, дезмоопласија, број на митотски делби, дробочина на инвазија, тип на инвазија, инфламаторна реакција, васкуларна инвазија и нуклеарен плечоморфизам.

Резултати: Дробочината на инвазијата на туморот во ткивата (туморната дебелина) е силен прогностиčки фактор за постојење на вратни метастази. Најдозволен фактор за повисока претстапност на малигнитет и вратните метастази. Статистичката анализа покажа силна асоцијашост помеѓу степенот на малигнитет и вратните метастази (p = 0,0004), васкуларната инвазија на туморот (p = 0,005) и туморната дробочина-дебелина (p = 0,001).

Заклучок: Туморната дробочина, васкуларната инвазија на туморот и типот на инвазија се најважни фактори за предвидување на агресивното однесување на туморот и лошата прогноза на пациентот.

Системот за бодување, т.е. градуирање на степенот на малигнитет на примарниот тумор во секојдневната практика е корисен за селектирање на пациентите кои се со висок риск од окултни метастази и пациенти кај кои ќе очекуваме агресивен тек на болеста.

Ключни зборови: орален планоцелуларен карцином, хистолошко градуирање на малигнитетот, вратни метастази, време на преживување.