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ORIGINAL ARTICLE

A novel histopathological scoring system for patients with oral squamous cell carcinoma

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Abstract

Objectives Tumor invasion into blood and/or lymphatic vessels, perineural invasion, and histopathological grading are evaluated to assess the biological aggressiveness of oral squamous cell carcinoma (OSCC). We aim to assess the prognostic impact of a novel scoring system, based upon the aforementioned histological parameters.

Materials and methods Retrospective chart review of 334 patients with treatment-naive squamous cell carcinoma of the oral cavity. Statistical analysis was performed using univariate and multivariate analysis. Histological grade G1 or G2 were assigned 0 points and G3 or G4 1 point. Invasion of the lymphatic vessels, blood vessels, or perineural space was given 1 point. Zero points were given, when invasion was not detectable. The final score was conducted through addition of each parameter. Therefore, our scoring system ranged between 0 and 4 points.

Results T-classification ($p < 0.001$), N-classification ($p < 0.001$), UICC stage ($p < 0.001$), extracapsular spread ($p < 0.001$), locoregional recurrence ($p < 0.001$), and overall survival ($p < 0.001$) were significantly associated with the OSCC-Histoscore. In multivariate analysis, T-classification ($p = 0.001$), N-classification ($p = 0.039$), resection margins ($p = 0.038$), and OSCC-Histoscore ($p < 0.001$) were independent prognostic markers for overall survival rate.

Conclusion Our presented OSCC-Histoscore serves as a strong independent prognostic parameter for 5-year overall survival (OS) and predicts OS better than T-classification, N-classification, and resection margins.

Clinical relevance Our presented histoscore improves prediction of the overall survival of patients with OSCC.

Keywords Prognosis · Oral cancer · Histological · Survival · Recurrence · Score

Introduction

Head and neck cancer is the sixth most common cancer worldwide with an annual incidence of more than 500,000 [1, 2]. Approximately 50% originate from the oral cavity with 90% of these being squamous cell carcinoma (OSCC) [3]. Albeit there have been significant advances in diagnostic and therapeutic techniques, the 5-year overall survival rate has not improved within the last three decades and still remains below 50% [4–10]. One of the main reasons for this is the lack of suitable markers that enable appropriate prognostic differentiation and thus improve therapeutic decision-making [11, 12]. In daily clinical routine, the TNM Classification is primarily used for these purposes [4–8, 13]. However, since the TNM classification does not take into account the biologic characteristics of OSCC, there is wide consensus to consider additional parameters, such as perineural invasion, lymph vessel invasion, blood vessel invasion, and histopathological grading [14, 15]. Their significant prognostic and therapeutic importance for OSCC has led many authors to demand their implementation into the TNM system [14, 15]. However, a major drawback of this requirement is that a significantly higher number of TNM subgroups would arise. This would, on the

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one hand, hinder comparison and comprehensibility of the TNM system and on the other lead to a more complex and less representative classification [14, 15]. Hence, to address this conceptual shortcoming, we created an easily applicable scoring system, consisting of tumor invasion into lymphatic and/or blood vessels, perineural invasion, and histopathological grading, and examined whether this might serve as a prognostic tool for patients with OSCC.

Material and methods

Patients and data collection

The retrospective study included 334 patients, who were diagnosed with a treatment-naive squamous cell carcinoma of the oral cavity between 2001 and 2009.

All cases were staged histopathologically according to l'Union Internationale Contre le Cancer (UICC) tumor, node, metastasis (TNM) classification, 7th edition. Staging was updated retrospectively to the 7th edition by using the histopathological reports. Clinicopathological data were obtained from medical charts as well as pathological and surgical reports. The pathological parameters were carefully reviewed in all cases and included age, sex, T-classification, N-classification, resection margins, UICC stage, extracapsular spread, histologic grade (G), treatment, lymphangiosis, hemangiosis, perineural invasion, and survival data. The clinical characteristics of the patients are listed in Table 1. The mean patient follow-up time for all patients was 46.1 months. Median follow-up for all patients was 39 months with standard deviation of 38 months.

Treatment strategies

Treatment included radical surgery and neck dissection depending on the tumor stage. Patients, who were clinically classified as cN0 received selective neck dissection at least of the level I-III/IV. Patients with clinically positive cervical lymph node status (cN+) or histopathologically proven lymph node metastasis (pN+) were treated with a modified radical neck dissection of levels I–V. Whenever bilateral cervical lymph node metastasis was present, we performed a bilateral neck dissection. Surgery in combination with postoperative radiotherapy was chosen for locally advanced disease. Radiotherapy included daily doses of 1.8–2.0 Gy 5 days per week for a total dose of 60–65 Gy, as chemotherapy regimen carboplatin was administered in weeks 1 and 5. In cases with limited disease, only surgery was performed.

Table 1 Patient characteristics and univariate analysis of prognostic factors

Parameter	*N* (%)	5-year OS (%)	*p* value
Age			
Younger half of median	167 (50)	72.7	0.399
Older half of median	167 (50)	72.0	
Sex			0.553
Male	210 (62.9)	71.1	
Female	124 (37.1)	73.8	
T-classification			*< 0.001*
T1	98 (29.3)	97.0	
T2	114 (34.1)	74.1	
T3	31 (9.3)	44.4	
T4a	68 (20.4)	56.6	
T4b	23 (6.9)	22.8	
N-classification			*< 0.001*
N0	218 (65.3)	84.9	
N1	44 (13.2)	66.2	
N2a	19 (5.7)	58.9	
N2b	33 (9.9)	46.9	
N2c	17 (5.1)	0	
N3	3 (0.9)	33.3	
Resection margins			*< 0.001*
R0	269 (80.5)	81.9	
R1/R2	65 (19.5)	37.3	
UICC stage			*< 0.001*
Stadium I	93 (27.8)	96.9	
Stadium II	73 (21.9)	75.5	
Stadium III	44 (13.2)	73.2	
Stadium IVa	98 (29.3)	59.1	
Stadium IVb	26 (7.8)	20.5	
Extracapsular spread			*< 0.001*
No	280 (83.8)	76.9	
Yes	48 (14.4)	41.5	
Failing	6 (1.8)		
Histological grading			*< 0.001*
G1	23 (6.9)	84.8	
G2	262 (78.4)	74.5	
G3	49 (14.7)	54.6	
G4	0	–	
Treatment			0.071
Surgical treatment	118 (35.3)	46	
Surgical treatment + RT/RCT	216 (64.7)	37	
Lymphangiosis			*< 0.001*
No	269 (80.5)	77.6	
Yes	65 (19.5)	38.2	
Hemangiosis			*< 0.001*
No	93 (27.8)	77.9	
Yes	73 (21.9)	44	
Perineural invasion			*< 0.001*
No	280 (83.8)	78.3	
Yes	48 (14.4)	40.2	
OSCC-Histoscore			*< 0.001*
0	178 (53.3)	89.4	
1	108 (32.3)	62.5	
2	34 (10.2)	46.5	
3	14 (4.2)	7.1	

Tissue samples

Histopathological analysis of lymph nodes was performed at the Institute of Pathology, University of Cologne. After fixation of the lymph nodes in 5% formaldehyde, they were embedded in paraffin. Longitudinal bisection and further

sectioning were obtained if the thickness was larger than 2 mm. From each paraffin block, two-step sections were cut at 50 μm levels. Afterward, staining was performed with hematoxylin and eosin, as well as periodic acid-Shiff, to histologically examine the presence or absence of metastatic disease. All specimens were evaluated by two independent, experienced pathologists.

Statistical analysis

Survival data were calculated by using the Kaplan-Meier method. Prognostic factors were identified in univariate analysis through the log-rank test. Clinicopathological parameters were explored in multivariate analysis through the Cox proportional hazard regression model. The significance level was set at $p < 0.05$. All statistical analyses were performed using SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA).

Scoring system

Histological grade G1 or G2 were assigned 0 points and G3 or G4 1 point. Invasion of the lymphatic vessels, blood vessels, or perineural space was given 1 point. Zero points were given, when invasion was not detectable. The final score was conducted through addition of each parameter. Therefore, our scoring system ranged between 0 and 4 points.

Results

Patient characteristics

At the time of diagnosis, patients had a mean age of 61.46 years (standard deviation 11.5). Median age was 61.50 years.

Parameters predicting overall survival and disease-free survival in patients with OSCC

Table 2 displays the results from the univariate analysis of associations between the OSCC-Histoscore and clinicopathologic parameters. T-classification ($p < 0.001$), N-classification ($p < 0.001$), cervical lymph node metastasis ($p < 0.001$), UICC stage ($p < 0.001$), extracapsular spread ($p < 0.001$), and locoregional recurrence ($p < 0.001$) correlated significantly with the OSCC-Histoscore. None of the pathological specimens were classified as G4 (see Table 1).

Five-year OS was associated significantly with hemangiosis carcinomatosa ($p < 0.001$), lymphangiosis carcinomatosa ($p < 0.001$), perineural invasion ($p < 0.001$), and histological grade ($p < 0.001$). Also, OSCC-Histoscore was significantly associated with OS ($p < 0.001$). The higher the score, the poorer the prognosis. As shown in Fig. 1, overall survival noticeably decreased for patients with an OSCC-Histoscore more than 1. Patients with 4 points even had a 5-year OS rate of 0%. As shown in Fig. 2, the higher the score, the higher the risk of locoregional recurrence in the next 5 years. For patients with 3 or 4 points, locoregional control over the next 5 years was 0%. For patients with an OSCC-Histoscore of 1 point or more, we observed that a surgical therapy combined with radiochemotherapy was associated with a higher overall survival rate (45%) than surgery with radiotherapy (28%) alone. For patients classified with an OSCC-Histoscore of 0 points, surgery alone was associated with the highest 5-year OS compared to surgery combined with radiotherapy or radiochemotherapy.

In multivariate analysis, as shown in Table 3, T-classification ($p = 0.001$), N-classification ($p = 0.039$), and resection margins ($p = 0.038$) were independent prognostic factors for overall survival rate. The most significant independent prognostic factor was OSCC-Histoscore ($p < 0.001$). Especially, an OSCC-Histoscore of 0 vs. 1 showed the most significant difference.

Table 2 Associations between OSCC-Histoscore and clinicopathological parameters

Parameter	*p* value
Age	0.912
Sex	0.074
T-classification	*< 0.001*
N-classification	*< 0.001*
Extracapsular spread	*< 0.001*
Locoregional control	*< 0.001*

Discussion

Tumor invasion into lymphatic and/or blood vessels, perineural invasion, and grading are frequently determined for histological evaluation of tumor progression and prognosis of oral squamous cell carcinoma (OSCC) [16–19]. A large number of studies demonstrated the significant importance of these parameters for assessment of tumor aggressiveness and therefore demanded their implementation into TNM classification [16–19]. However, the notable increase in the number of subgroups would lead to a more difficult and less representative staging system. Hence, an easily applicable scoring system, considering the histopathological characteristics of OSCC, would be of high prognostic and therapeutic value. Therefore, we investigated statistically, whether a combination of perineural invasion, blood vessel invasion, lymph vessel invasion and grading, into a novel scoring system (OSCC-Histoscore), might be helpful to overcome this issue. Uni- and multivariate analysis determined the OSCC-Histoscore as a strong independent prognostic parameter. Interestingly, multivariate analysis revealed a prognostic superiority of the OSCC-Histoscore compared to the T- and N-

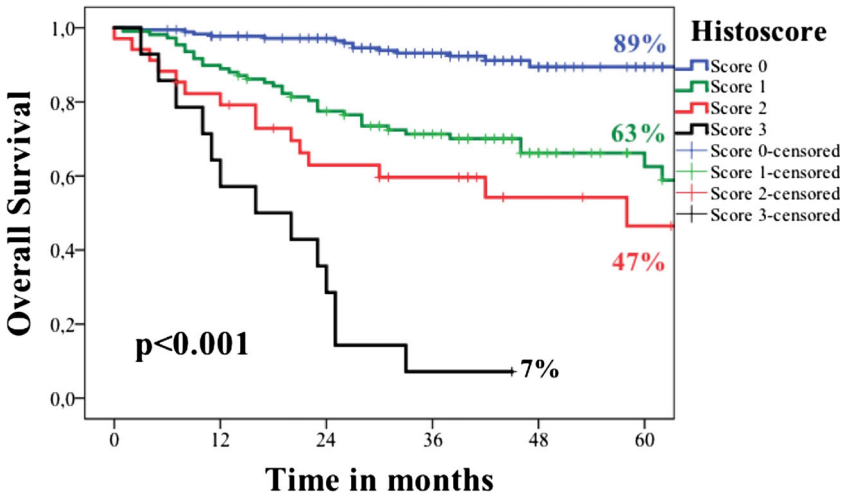

Fig. 1 Kaplan-Meier curve on the influence of the OSCC-Histoscore on overall survival

classification, showing the significant importance of the biological characteristics of OSCC (see Table 3).

Within the scoring system, we found that the higher the score, the worse the prognosis. For example, patients, assigned with 0 points had a 5-year overall survival rate of 89%, whereas none (0%) of the patients with 3 points had a 5-year overall survival (see Fig. 1).

Furthermore, we discovered a strong significant correlation between the OSCC-Histoscore and the occurrence of cervical lymph node metastasis (N-classification) and extracapsular spread. This reflects the fact that especially invasion into lymph vessels and blood vessels shows the metastasizing potential of OSCC [20, 21].

Invasion of lymphatic and/or blood vessels is defined as the presence of neoplastic epithelium within an endothelial-lined channel [22]. Approximately 50% of head and neck squamous cell carcinoma shows vascular invasion ([19]. Tumors with aggressive biological activity and therefore poor prognosis are significantly associated with vascular invasion [19]. In particular, lymphatic vessel invasion represents an independent prognostic factor for cervical lymph node metastasis [23]. A shortcoming of our study, which includes patients with OSCC from 2002 to 2009, is the technique of staining, as this plays a significant role for identification of blood vessel and lymph vessel invasion [24]. Due to our H&E staining technique, it might be that more specific methods, such as D2-40

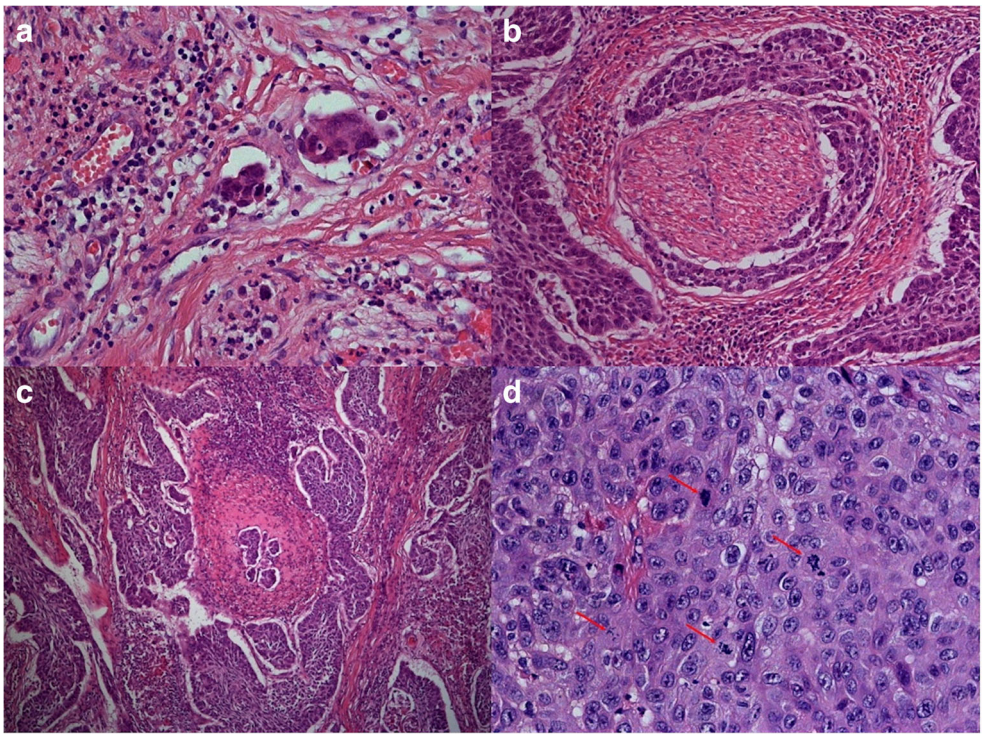

Fig. 2 Composite figure showing **a** OSCC with lymph vessel invasion at × 200, **b** OSCC with perineural invasion at × 200, **c** OSCC with blood vessel invasion at × 200, **d** OSCC graded as G3 at × 200

Table 3 Multivariate analysis of prognostic factors for overall survival

Parameter	Relative risk (95% CI)	*p* value
T-classification (T1 and T2 vs. T3 and T4)	0.42 (0.25–0.71)	*0.001*
N-classification (N0 vs. N+)	0.577 (0.34–0.97)	*0.039*
Age (younger half vs. older half)	1.376 (0.88–2.16)	0.168
Sex (male vs. female)	0.878 (0.54–1.44)	0.605
Treatment (surgery vs. surgery + RT/RCT)	0.43 (0.17–1.07)	0.072
Resection margins (R0 vs. R1)	0.596 (0.37–0.97)	*0.038*
Histoscore		*< 0.001*
Score 0 vs. score 1	0.090 (0.039–0.21)	*< 0.001*
Score 0 vs. score 2	0.304 (0.15–0.61)	*0.001*
Score 0 vs. score 3	0.339 (0.16–0.73)	*0.006*

would have been a better choice to differentiate such pathological alterations [24]. Van den Eyden et al. indicated that D2-40 and podoplanin are the most sensitive and specific antibodies for the detection of lymphatic endothelium [24]. Hence, it would be advisable in future studies to use more specific and more sensitive staining techniques.

In addition, the OSCC-Histoscore was significantly associated with T-classification. This might be explained by the finding that the histopathological parameters considered in the OSCC-Histoscore commonly occur in advanced stage diseases [16–21].

Furthermore, our multivariate analysis indicated that the OSCC-Histoscore is a better prognostic marker than the status of the resection margins (see Table 3). We assume that this might be associated with the fact that the OSCC-Histoscore is a combination of independent prognostic parameters, which significantly increase the prognostic power, thus leading to an even higher prognostic impact than the resection margins. On the other hand, this finding might be associated with the relatively small patient groups included into our subgroup analyses, as a result of the retrospective nature and single-center data of our study.

The first published biological scoring system for malignancies was published by Broders et al. in 1920 [15]. Their classification system was based upon the biological activity of tumors, graded as poorly, moderately, or highly differentiated [15]. They pointed out that poorly differentiated tumors, in particular, were associated with lower survival rates, due to their significant association with cervical lymph node metastasis [15]. Multiple subsequent studies confirmed these results, so that implementation of histological grading into the assessment of malignancies became diagnostic standard [14, 19, 25]. In accordance with Frierson et al. and Brandwein-Gensler et al., we differentiated between G1/G2 and G3, because patients with G3 have a significantly higher risk to develop cervical lymph node metastasis [26–28]. Furthermore Giacomarra et al. found out that prognosis for patients with a high grade OSCC is significantly worse than patients with G1 or G2 tumors [29].

In 1973, Jacobsson et al. propagated a new scoring system, which mainly focused on tumor cell population and tumor host relation [30]. They included the following eight histological features: tumor cell structure, differentiation, nuclear polymorphism, mitosis, mode of invasion, stage of invasion, vascular invasion, and cellular response [30]. In accordance with the malignancy grade of the tumor, they assigned for each feature 0 to 4 points [30]. Although this classification system allows a very detailed and informative description of the tumor biology, the main disadvantage is the unprecise definition of the included tumor parameters [14, 19]. Therefore, standardization and comparison of the gathered data have a high risk of being biased [14, 19]. In 1997, Bryne et al. developed a modification of the system of Jacobsson et al. and focused on the invasive front of the tumor (IFG) [31]. They assessed the degree of keratinization, nuclear polymorphism, pattern of invasion, and host inflammatory response [31]. IFG was highlighted and confirmed by multiple subsequent studies as an independent prognostic parameter for patients with OSCC [14, [19, 25]. Further modifications of the system of Jacobsson et al. were made by Lund et al., Willen et al., Anneroth et al., Crissman et al., or Martinez-Gimeno et al. [32–36]. However, their implementation into clinical practice has not been established yet [14, 19, 25]. Compared with these grading systems, the main advantages of our presented OSCC-Histoscore are, on the one hand, that the included parameters are determined routinely in daily clinical practice and, on the other hand, that it is easily applicable.

Conclusions

For patients with oral squamous cell carcinoma (OSCC), our presented OSCC-Histoscore serves an independent prognostic parameter for 5-year overall survival (OS) and predicts OS better than T-classification, N-classification, and resection margins. However, further studies, especially conducted on larger cohorts, are necessary to evaluate our findings and to improve understanding of the biological behavior of OSCC.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

Ethical approval Due to the retrospective nature of this study, it was granted an exemption in writing by the University Hospital of Cologne IRB. Our investigation followed the guidelines of the Helsinki Declaration. This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent For this type of study, formal consent is not required.

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