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Letter to the Editor

The time interval between primary surgery and adjuvant therapy determines prognosis of oral squamous cell carcinomas ☆

Introduction

To estimate the prognosis in patients suffering from oral squamous cell carcinoma (OSCC) and to select a therapy concept, staging tests are performed. Patients with similar characteristics are grouped into AJCC stages [1]. For prognosis analysis, the Cox proportional hazard regression (CR) is most widely used [2]. The random forest approach (RFA), as a new statistical method, facilitates an improved estimation of the survival of patients [3–7]. In a retrospective analysis of 106 OSCC patients, we investigated how different clinical and pathological factors affect the overall survival (OS) and the incidence of first local recurrence (LR). We combined RFA, competing risk regression (CRR), and CR to identify major risk factors for a poor clinical outcome.

Patients and methods

Patients

Data of 106 patients with primary OSCCs, treated without neoadjuvant radiation or chemotherapy during 1995–2005, was retrospectively analysed. The average follow-up time was 5.3 ± 4.2 (SD) years. Patients had given written consent to their participation in this study. The study complied with the ethical standards (Declaration of Helsinki) and was approved by the ethical committee of the University of Goettingen (vote No. 07/06/09). Detailed patient characteristics and the examined parameters are given in Table 1.

Statistical analysis

The impact of the parameters on the OS was examined by CR [8]. The incidence of first LR was investigated by CRR to consider death as a competing event [9]. Analyses were first performed in a univariate manner, i.e. separately for each risk factor. Significant risk factors were then combined in a multiple regression model using forward variable selection. Besides the classical CR models, we used the RFA [3,4]. Missing values for the multivariate and the RFA were imputed by 'Multivariate Imputations by Chained Equations' (MICE) [10]. All tests were performed at a significance level of $\alpha = 5\%$, using the statistical software R (Version 3.0.3, www.r-project.org).

Results

Overall survival time

The univariate CR (Table 1) revealed significant correlations between a poor OS and a long time between primary surgery and adjuvant therapy ($p < 0.001$), a combined surgical and adjuvant therapy ($p < 0.001$), an extended plastic reconstruction ($p = 0.005$), an advanced AJCC stage ($p < 0.001$), a high T stage ($p < 0.001$), a positive N stage ($p = 0.005$), a short time to recurrence (TTR; $p < 0.001$), and a short time to first lymph node metastasis (LNM) ($p = 0.047$). A high T stage [$p < 0.001$; HR 4.38; 95% CI (2.15,8.93)] and a short TTR [$p = 0.011$; HR 0.98; 95% CI (0.97,0.99)] significantly correlated with a poor OS in the multivariate analysis. A short TTR revealed the strongest influence on a poor OS by RFA (Fig. 1; detailed RFA ranking is given in supplemental online Table 2).

Incidence of first local recurrence

The univariate CRR (supplemental online Table 3) revealed significant correlations between the incidence of first LR and a high age at primary diagnosis ($p = 0.041$), abuse of less than 46 g of alcohol per day ($p = 0.050$), nicotine abuse of more than 40 pack-year ($p = 0.002$), and an initial high T stage ($p = 0.033$). No factors reached statistical significance in the multivariate analysis. A long time to adjuvant therapy revealed the strongest influence on the incidence of first LR by RFA (Fig. 2; detailed RFA ranking is given in Table 4).

Discussion

In the recent investigation, a short TTR was the main risk factor for poor OS. Biologically aggressive tumours recur rapidly within the first two years, leading to a poor outcome [11–13]. Referring to a group of 515 patients with recurrence after radiotherapy, Stell found that TTR was the most significant factor for OS [13]. The present analysis identified a strong dependence of a worse OS and the incidence of first LR on the period between primary surgery and the onset of adjuvant therapy. This probably caused the findings of Kernohan et al. [14], who reported a significant association between poor OS and a combined treatment approach, possibly due to an advanced initial disease stage, aggressive tumour biology, and limited salvage options.

There are important differences between the extent of tumour infiltration, particularly between different stage T4 tumours.

☆ Author 1 (P. Brockmeyer) and author 2 (B. Hemmerlein) contributed equally to this work.

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Table 1
P values from the univariate Cox proportional hazard regression model for the overall survival time. Descriptive statistics are either absolute (relative) frequencies, or the mean ± standard deviation. Missing values are not included into the calculation of the frequencies. Hazard ratios are presented with 95% confidence intervals. *P* values smaller than 0.001 are reported as <0.001.

Parameter	Level	Desc. stat.	Hazard OR	*P*
Combined surgical and adjuvant therapy	Not performed	56 (53%)		**<0.001**
	Primary OSCC	18 (17%)	7.08 [3.10,16.15]	
	After first LR and/or LNM	32 (30%)	4.26 [2.03, 8.91]	
Age at primary diagnosis (years)		61.40 ± 11.80	1.01 [0.99, 1.04]	0.241
Body Mass Index (BMI)		23.90 ± 4.40	0.93 [0.86, 1.01]	0.090
Alcohol abuse (grams per day)		46.00 ± 41.40	1.00 [0.98, 1.02]	0.996
Histopathological grading	G1	15 (14%)	0.85 [0.46, 1.56]	0.600
	G2	84 (79%)		
	G3	7 (7%)		
Body height (m)		1.70 ± 0.10	0.33 [0.01, 11.78]	0.543
Localisation of primary OSCC	Cheek/lip	9 (8%)	1.20 [0.91, 1.59]	0.186
	Tongue	22 (21%)		
	Alveolar process/jaw	32 (30%)		
	Mouth floor	41 (39%)		
	Palate/oropharynx	2 (2%)		
N stage	Negative	78 (74%)	2.45 [1.34, 4.47]	**0.005**
	Positive	28 (26%)		
Lymphadenectomy (left and/or right side)	Not performed	10 (9%)	3.02 [0.73, 12.55]	0.070
	Performed	96 (91%)		
R status	0	98 (92%)	1.63 [0.58, 4.58]	0.387
	1	8 (8%)		
Reconstruction modality	Local	58 (55%)	2.34 [1.28, 4.30]	**0.005**
	Distant flaps	48 (45%)		
Sex	Male	72 (68%)	1.48 [0.81, 2.72]	0.209
	Female	34 (32%)		
Side of primary OSCC	Left & right	91 (86%)	1.37 [0.61, 3.08]	0.467
	Median	15 (14%)		
Nicotine abuse (pack-year)		37.20 ± 14.60	1.04 [0.98, 1.11]	0.172
AJCC stage	1 & 2	39 (37%)	3.58 [1.67, 7.71]	**<0.001**
	3 & 4	67 (63%)		
T stage	1 & 2	51 (48%)	4.38 [2.15, 8.93]	**<0.001**
	3 & 4	55 (52%)		
Time to adjuvant therapy (days)	Not performed	56 (53%)		**<0.001**
	⩽55 days after primary surgery	9 (8%)	2.21 [0.62, 7.92]	
	Between 56 and 143 days after primary surgery	9 (8%)	45.82 [16.0, 131.31]	
	After first LR and/or LNM (>143 days after primary surgery)	32 (30%)	4.47 [2.13, 9.36]	
Time to first LR (months)		2.92 ± 3.16	0.97 [0.96, 0.99]	**<0.001**
Time to first LNM (months)		1.20 ± 2.80	0.86 [0.71, 1.04]	**0.047**

Significant *p*-values are shown in bold.

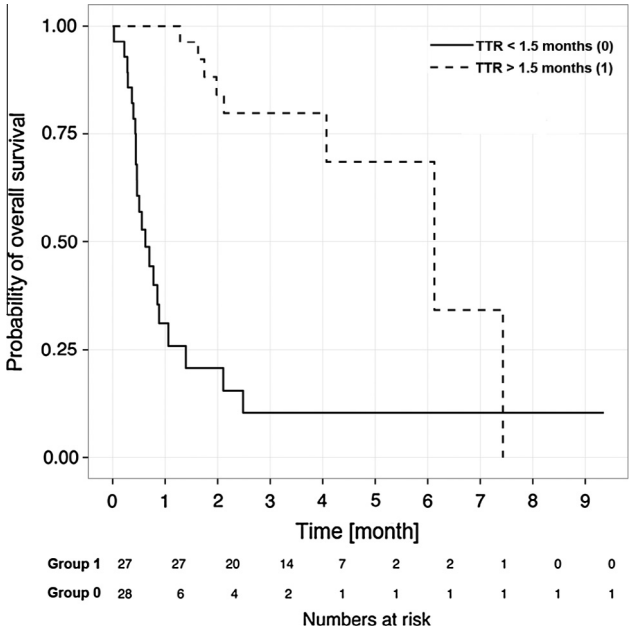

Fig. 1. Probability of overall survival stratified by time to recurrence (TTR). Median of TTR = 1.5 months; TTR above the median (dashed curve); TTR below the median (solid curve).

Depending on localisation, e.g. skull base, different surgical and reconstructive strategies are necessary. In the univariate analysis, patients with extensive plastic reconstruction (extensive tumour infiltration) showed a poor OS compared to those with limited reconstruction (slight tumour extension). Mucke and colleagues [15] reported a better prognosis in patients treated with microvascular flap reconstruction compared to limited reconstruction. However, in those analyses, the time interval between primary surgery and the onset of adjuvant therapy has not been discussed. To date, there is no recommendation as to when an adjuvant therapy should commence. A delay in primary post-surgical adjuvant therapy of more than two months should be avoided to improve the clinical outcome in patients.

We confirmed the impact of the TNM classification system and AJCC criteria on the OS [16–18]. Contrary to others [19,20], we did not find a significant impact of the histopathological grade of differentiation or the anatomical location on prognosis.

In the univariate analysis, a high age at primary diagnosis and the intensity of smoking and alcohol consumption were significantly associated with an increased incidence of first LR, which has been demonstrated earlier [16,18,21]. A long history of intense smoking could explain field cancerization and synchronic or metachronic tumour promotion of smoking-induced oral squamous epithelia at different sites as the genetic background of a metachronic second primary tumour. Low alcohol consumption