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Time to recurrence and patient survival in recurrent oral squamous cell carcinoma

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ABSTRACT

Objectives: Tumour relapse remains one of the major problems in managing oral squamous cell carcinoma (OSCC) with mortality rates of up to 92%. Early recurrences have a worse prognosis than late relapses. However, few has been written about the influence of clinicopathological parameters on the timing of recurrence and the patient survival.

Materials and methods: Retrospective chart review of 159 patients with an OSCC recurrent disease. Exclusion criteria were neoadjuvant chemoradiotherapy, follow-up < 6 weeks, perioperative death, second primaries and inadequate information on clinicopathological parameters. Statistical analysis was performed using univariate and multivariate analysis.

Results: A significant correlation was found in the $\chi 2$-analysis between the timing of recurrence and the margin status ($p = 0.020$), lymph node ratio ($p = 0.030$) and grading ($p = 0.003$) of the primary tumour. In the multivariate survival analysis, the timing of recurrence ($p < 0.001$), margin status of the primary tumour ($p = 0.023$), presence of extracapsular spread in the primary tumour ($p = 0.003$) and performance of a salvage treatment ($p < 0.001$) were shown to be independent risk factors for overall survival.

Conclusion: For patients with a recurrent OSCC, the time to recurrence, margin status, extracapsular spread and the performance of a salvage treatment are independent prognostic factors for overall survival. Furthermore, a significant association exists between the moment of recurrence and the lymph node ratio, the margin status and grading of the primary tumour. This knowledge can allow for the development of individualised surveillance programs and like this, an earlier diagnosis and better second treatment chance in the case of a recurrence.

Introduction

Head and neck squamous cell carcinoma is the sixth most common malignancy in the world [1,2]. The oral cavity is the most common subsite and accounts for about 3% of all cancer cases worldwide [3,4]. Oral squamous cell carcinoma (OSCC) have a poor prognosis [5–9]. Moreover, the patient's prognosis decreases dramatically in case of relapse with mortality rates of up to 92% [5,7,10]. After curative intended surgery of the primary tumour, recurrence rates in the range of 7 – 47.4% have been reported [2,3,5,11–14]. Since the recurrence rate and its associated mortality rate have not substantially changed although significant improvements in diagnostics and treatment modalities were made, tumour relapse remains one of the major problems in managing OSCC [3,15,16]. Up to 86% of all recurrent tumours recur in the first 2 years after treatment [6,7,16–18]. These early recurrences have been described to have a worse prognosis than late relapses [11,18,19]. However, few has been written about the influence of clinicopathological parameters on the timing of recurrence and patient survival. Therefore, this retrospective study investigated these parameters and survival rates within a group of 159 patients with an OSCC recurrent disease. The identification of the clinicopathological factors that influence the timing of relapse and patient survival can lead to an adjusted, patient-specific follow-up program based on risk stratification rather than a general surveillance program.

Materials and methods

Patient and data collection

Our retrospective study followed the guidelines of the Helsinki

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Declaration. The files of 691 patients, diagnosed and treated between October 2002 and December 2015 for oral squamous cell carcinoma at our Department of Oral and Craniomaxillofacial Plastic Surgery were collected and retrospectively reviewed. Out of this total of 691 patients, 159 patients (23%) with recurrent disease were included in this study. Inclusion criteria were patients with a first recurrence of an oral squamous cell carcinoma and primarily curative intended surgery with negative resection margins. Exclusion criteria were neoadjuvant chemoradiotherapy, follow-up < 6 weeks, perioperative death, second primaries and inadequate information on clinicopathological parameters.

Relapse was defined as a tumour of similar histology appearing minimally 6 weeks after primary treatment [5,7,15,20]. The moment of recurrence was defined as the date of the pathological confirmation of the recurrence. Hence, the time to recurrence was defined as the time from the first surgery to pathologically confirmed recurrence. The period of record ended on the 31st of December 2015. Patients, who did not die by this date, were evaluated based on their last examination in our clinic.

Clinicopathological parameters were carefully retrieved from the medical records and pathology reports. Parameters included gender, age, date of diagnosis, date of primary operation, last follow-up date, death, date and cause of death, tumour site, type of neck dissection, type of adjuvant treatment, pathologic T-classification, pathologic N-classification, clinical M-classification, UICC-stage, grading, number of positive lymph nodes, number of removed lymph nodes, lymph node ratio (LNR), margin status, perineural invasion, lymph vessel invasion, blood vessel invasion, extracapsular spread, date of recurrence, type of recurrence. The histopathological staging of all cases was performed according to l' Union Internationale Contre le Cancer (UICC) tumour, node, metastasis (TNM) classification, 8th edition. Older data were retrospectively updated to the 8th edition by using the pathological reports.

Overall survival (OS) was calculated as the period of time from the beginning of the primary therapy to death, independent of the cause of death, in months. Patients, who had not passed away at the end of the investigated period, or patients in whom it was unclear if they had passed away, were censored.

Statistical analysis

Contingency tables and the χ^2-test were used to detect associations between the clinicopathological parameters of the primary tumour and the moment of recurrence. The timing of recurrence of the primary tumour was considered as the dependent variable and the clinicopathological features as the independent variable. The Kaplan-Meier analysis was used to estimate overall survival, and to estimate the relevant clinicopathological parameters for overall survival. Differences were determined by performing the log-rank test.

The Cox proportional hazard model was performed in the multivariate analysis to estimate the impact of significant clinicopathological parameters from the univariate analysis, on the overall survival. The significance level chosen for all tests was $p < 0.05$. Statistical analyses were performed using SPSS Statistics 24.0 (IBM Corporation, Armonk, NY, USA).

Results

Patient characteristics and clinicopathologic data

At the time of diagnosis of the primary tumour the mean age of patients was 63.11 years (standard deviation 11.64 years) and the median age was 62 years. There were 87 men and 72 women involved, resulting in a male-to-female range of 1.2–1. The mean follow-up time was 60.7 months (standard deviation 60.4 months, range 3–408 months) and the median was 43 months. Overall, 36% of recurrences occurred in the first year after primary treatment, 60% occurred in the first 2 years after primary treatment. In 40% the recurrence occurred after 2 years. 91% of patients received a salvage treatment after locoregional recurrence. The remaining 15 patients (9%) had an inoperable recurrence without sufficient remaining radiation dose, had incurable distant metastasis or refused further treatment. The mortality rate was 42% (66/159). Patient's and tumour characteristics are summarised in Tables 1 and 2.

Table 1
Patient's characteristics and univariate survival analysis in 159 patients with a recurrent oral squamous cell carcinoma (OS = Overall Survival).

Patient's characteristics	Number of patients (%)	5-year OS (%)	10-year OS (%)	p-value
Gender				0.173
Male	87 (55)	57	43	
Female	72 (45)	69	52	
Treatment regime of the primary tumour				**< 0.001**
Surgery	70 (44)	75	70	
Surgery + adjuvant radiotherapy	31 (20)	65	48	
Surgery + adjuvant radiochemotherapy	58 (37)	45	20	
Extend of Neck Dissection				**< 0.001**
SND ipsilateral	67 (42)	81	75	
MRND ipsilateral	30 (19)	59	36	
RND ipsilateral	6 (4)	60	30	
SND bilateral	19 (12)	60	41	
MRND ipsilateral + SND contralateral	24 (15)	43	13	
MRND bilateral	11 (7)	12	12	
RND ipsilateral + SND contralateral	2 (1)	0	0	
Recurrence				**0.027**
Local/Locoregional	128 (81)	65	50	
Regional	25 (16)	52	52	
Distant	6 (4)	40	0	
Timing of Recurrence				**< 0.001**
1–4 months	11 (7)	0	0	
5–8 months	32 (20)	40	40	
9–12 months	15 (9)	52	52	
13–24 months	37 (23)	49	49	
25–60 months	64 (40)	87	59	
Salvage Treatment				**0.003**
Yes	144 (91)			
Salvage Surgery	137 (86)	66	56	
Definitive Radio(chemo) therapy	7 (4)	40	40	
No curative intent	15 (9)			
Palliative Radiotherapy	6 (4)	50	0	
Palliative Chemotherapy	5 (3)	0	0	
Supportive therapy	4 (3)	25	0	

Clinicopathological data in association with the timing of recurrence

A significant correlation was found in the χ^2-analysis between the timing of recurrence and the margin status ($p = 0.020$), the lymph node ratio (LNR) ($p = 0.030$) and the histopathological grading ($p = 0.003$) of the primary tumour.

Survival analysis

Using Kaplan Meier analysis, we computed that the 5-year survival rate of our patient population was 62%, the 10-year overall survival rate was 47% (Fig. 1). The moment of recurrence had a significant influence ($p < 0.001$) on the overall survival, with earlier recurrences having a lower survival rate then later recurrences (Fig. 2). Furthermore, we found a significant correlation in this univariate analysis between the overall survival and the presence of extracapsular spread ($p < 0.001$; Fig. 3), the R-status ($p < 0.001$; Fig. 4), the T-

Table 2
Tumour characteristics and univariate survival analysis in 159 patients with a recurrent oral squamous cell carcinoma (OS = Overall Survival).

Tumour characteristics	Number of patients (%)	5-year OS (%)	10-year OS (%)	p-value
Tumour site				0.863
Floor of mouth	55 (35)	57	51	
Tongue	29 (18)	83	35	
Lower jaw	38 (24)	62	42	
Upper jaw and hard palate	13 (8)	73	73	
Soft palate	8 (5)	60	45	
Cheek	16 (10)	46	46	
pT-classification				**0.001**
T1	39 (25)	81	73	
T2	48 (30)	71	47	
T3	20 (13)	54	27	
T4a	44 (28)	45	26	
T4b	10 (6)	17	17	
pN-classification				**< 0.001**
N0	96 (60)	73	62	
N1	21 (13)	64	16	
N2a	12 (8)	65	65	
N2b	9 (6)	56	21	
N2c	5 (3)	0	0	
N3a	0 (0)	–	–	
N3b	16 (10)	15	15	
UICC stage grouping				**< 0.001**
Stage 1	36 (23)	85	80	
Stage 2	32 (20)	68	52	
Stage 3	18 (11)	71	0	
Stage 4a	49 (31)	57	34	
Stage 4b	24 (15)	0	0	
Grading				**< 0.001**
G1	9 (6)	100	100	
G2	122 (77)	62	43	
G3	27 (17)	52	46	
G4	1 (0.6)	0	0	
Lymphovascular invasion				**< 0.001**
L0	126 (79)	68	53	
L1	33 (21)	40	27	
Blood vessel invasion				**< 0.001**
V0	138 (87)	67	50	
V1	21 (13)	26	26	
Perineural invasion				0.213
Pn0	130 (81)	63	48	
Pn1	29 (18)	59	40	
Extracapsular spread				**< 0.001**
No	138 (87)	67	51	
Yes	21 (13)	26	18	
Margins				**< 0.001**
R0 (free margin)	121 (76)	67	51	
R1 (close margin < 5 mm)	38 (24)	45	33	
Lymph Node Ratio (LNR)				**< 0.001**
< 0.07	130 (82)	69	52	
≥ 0.07	29 (18)	28	24	

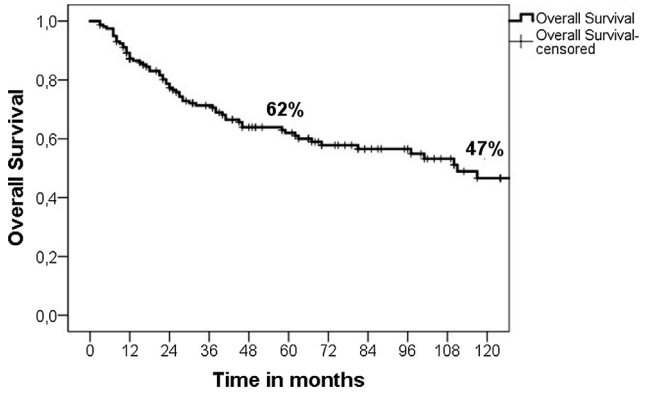

Fig. 1. Overall survival of the total patient population.

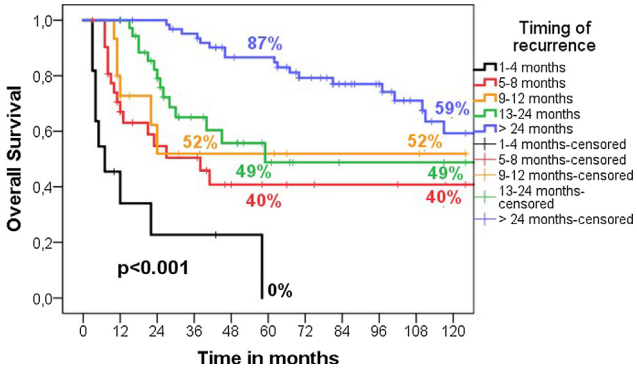

Fig. 2. Overall survival in relation to the timing of the recurrence.

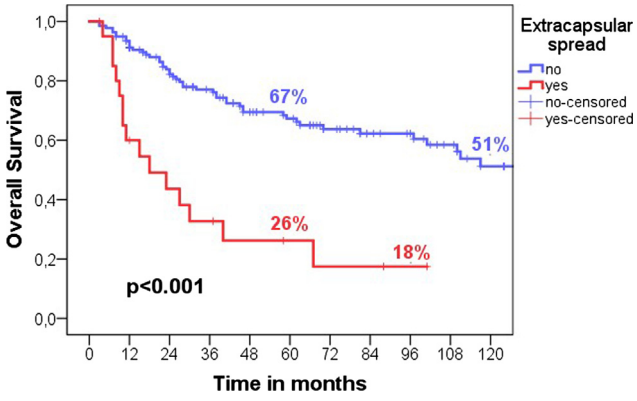

Fig. 3. Overall survival in relation to the presence of extracapsular spread in the primary tumour.

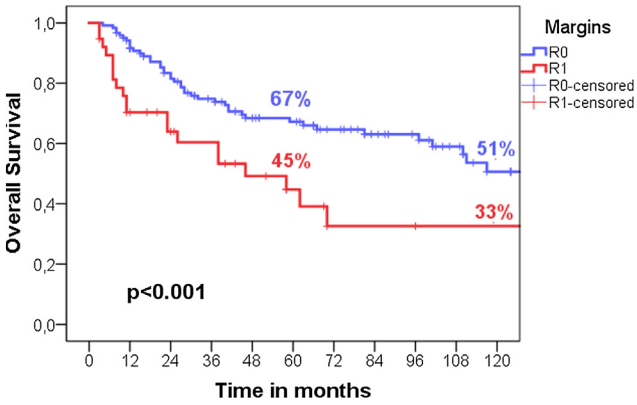

Fig. 4. Overall survival in relation to the margin status of the primary tumour.

classification of the primary tumour (p = 0.001), the N-classification (p < 0.001), the UICC stage grouping (p < 0.001), the degree of differentiation (p < 0.001), lymphovascular invasion (p < 0.001), blood vessel invasion (p < 0.001), lymph node ratio (p < 0.001), the treatment modality (p < 0.001), the extent of neck dissection (p < 0.001) and the performance of a salvage treatment (p = 0.003).

The site of the primary tumour (p = 0.863) and the presence of perineural infiltration in the primary tumour (p = 0.213) did not significantly influence the overall survival in the survival analysis. The 5- and 10-year survival rates, as well as the p-values of the univariate factors for overall survival, are summarised in Tables 1 and 2.

Multivariate Cox regression analysis for overall survival

In multivariate analysis, the timing of recurrence (p < 0.001), the

Table 3
Multivariate analysis of prognostic factors for overall survival (CI = Confidence Interval, HR = Hazard Ratio).

Parameter	HR (95% CI)	P-value
Timing of recurrence		**< 0.001**
5–8 vs. 1–4 months	0.233 (0.094–0.574)	0.002
9–12 vs 1–4 months	0.244 (0.079–0.751)	0.014
13–24 vs. 1–4 months	0.144 (0.057–0.364)	< 0.001
> 24 vs. 1–4 months	0.056 (0.022–0.144)	< 0.001
Extracapsular spread (no vs. yes)	0.352 (0.177–0.699)	**0.003**
Margin status (R0 vs. R1)	0.498 (0.274–0.907)	**0.023**
T-classification (T1T2 vs. T3T4)	0.600 (0.320–1.124)	0.111
N-classification (N0 vs. N +)	0.718 (0.376–1.371)	0.315
Grading (G1G2 vs. G3G4)	0.752 (0.381–1.486)	0.412
Treatment (OP vs. OP + RT/RCT)	1.073 (0.512–2.249)	0.852
Salvage treatment (yes vs. no)	0.226 (0.114–0.447)	**< 0.001**

margin status of the primary tumour (p = 0.023), the presence of extracapsular spread in the primary tumour (p = 0.003) and the performance of a salvage treatment (p < 0.001) were shown to be independent risk factors for overall survival in patients with recurrent disease (Table 3).

Discussion

Tumour recurrence is associated with a dramatic worsening of the patient's prognosis and therefore remains one of the major problems in managing OSCC [2,3,12,16]. The mortality rate in our population was 41.5%, while other authors even describe mortality rates in patients with recurrent disease from 79.2% to 92% [5,7,10]. Early recurrences have been shown to have a worse prognosis than late relapse [11,19]. However, literature on the influence of clinicopathological parameters on the timing of recurrence is scarce.

Clinicopathological data in association with the timing of recurrence

Although abundant evidence exists for a significant association between the occurrence of relapse and histopathological grading of the primary tumour [5,7,21] or lymph node ratio [20,22], this study is - to our best knowledge – the first to show a significant association between these clinicopathological parameters and the time to recurrence. Recently, a relationship between margin status and timing of recurrence was described by Hosni et al. [23] in a multivariate analysis, with patients with microscopic positive resection margins having a higher risk of an early recurrence. Our data confirm this association between the time to recurrence and the margin status.

The primary tumour site, T-classification, N-classification, UICC staging, lymph vessel infiltration, blood vessel infiltration, perineural infiltration, the treatment modality and the extent and the type of neck dissection did not have an influence on the moment of recurrence in our patient population. We could only find two studies [23,24] that reported an effect of one of these factors on the timing of recurrence. In a multivariate analysis, Hosni et al. [23] identified a significant association between an oral tongue subsite of the tumour and the development of an early recurrence. DeConde et al. [24] described that the performance of a neck dissection demonstrates a decreased risk of an early recurrence, but no significance could be achieved.

Survival analysis

The 5-year overall survival rate of our patient population was 62%. This value is clearly higher as most survival rates described by other authors, who have reported a 5-year overall survival rate of 24.5–50% for patients with recurrent disease [1–3,11,12,16,25]. Several explanations for this poor prognosis of recurrent disease have been described, such as depletion of therapeutic modalities, the health impact of the primary tumour treatment and aggressive biology of the primary tumour [12].

Within our univariate survival analysis, we found a strong statistical correlation between the moment of recurrence and overall survival (p < 0.001). Multivariate survival analysis confirmed the moment of recurrence to be an independent prognostic factor for overall survival, with earlier recurrences having a significantly lower overall survival rate then later recurrences. Mücke et al. [11] also described the time interval from initial treatment to recurrence as an independent prognostic factor for OSCC. They set a cut-off at 18 months and reported that patients suffering from recurrent disease within the first 18 months after initial treatment had a significantly higher probability of death than those having a recurrence after 18 months. Also, Chang et al. [19] identified a recurrence-free interval of less than 1 year as an independent prognostic factor for overall survival in a large study with 4839 patients with an OSCC recurrence. Furthermore, Guo et al. [18] found that a longer time to recurrence was independently associated with a survival greater than 24 months for both HPV+ and HPV- patients. Recently, Haque et al. [2] reported that patients undergoing salvage surgery have significantly worse outcomes if the time to recurrence is less than 6 months. This worse prognosis for earlier recurrences could be explained by the fact that biologically more aggressive tumours will recur more quickly and therefore have a poorer outcome. On the other hand, Blanchard et al. [26] report about a subset of young patients (< 40 years) who develop early and aggressive relapses despite presenting favourable clinical and pathological features and suggest the need for an individualised follow-up program.

Furthermore, the presence of extracapsular spread in the primary tumour was a strong prognostic factor for overall survival in the univariate (p < 0.001) and multivariate (p = 0.003) survival analysis. Patients without extracapsular spread in their primary tumour had a 0.35-fold lower risk of death in case of recurrent disease, regardless of their T-classification, N-classification, tumour grading, margin status, therapy regime, the moment of recurrence and the performance of salvage treatment. The poor prognosis for patients with extracapsular spread was confirmed by other investigators [6,27–32] and can be explained by the fact that extracapsular spread is a very strong predictor for regional and systemic spread [7,28]. Interestingly, Suton et al. [28] report that extracapsular spread is not only a frequent feature in locally advanced OSCC but is also detected in a significant proportion of patients with a clinically negative neck and may be more common in smaller lymph nodes than is generally assumed. This suggests that extracapsular spread may occur at an early stage of the metastatic process.

Margin status is not only an important predictor for the moment of recurrence but also for the overall survival in patients with recurring disease. Both in the univariate (p < 0.001) as in the multivariate (p = 0.023) survival analysis, margin status was shown to be a significant prognosticator for overall survival. Patients with negative resection margins had a 0.50-fold lower risk of death in case of recurrence, independent of their T-stadium, N-stadium, tumour grading, presence of extracapsular spread, therapy regime, the moment of recurrence and the performance of salvage treatment. Several authors [29,31] confirmed margin status to be an independent prognostic factor for overall survival by multivariate analysis.

Also, the performance of a salvage treatment was detected to be a prognostic factor for overall survival in univariate (p = 0.003) and multivariate (p < 0.001) survival analysis. Patients who underwent a salvage treatment for their relapse had a 0.23-fold lower risk of death, independent of their T-stadium, N-stadium, tumour grading, presence of extracapsular spread, margin status, therapy regime and moment of recurrence. This finding is probably biased since a treatment without curative intent was only performed in patients with an inoperable recurrence without sufficient remaining radiation dose, in patients with incurable distant metastasis or in patients who refused further (operative) treatment. All others underwent salvage treatment.

Within our univariate survival analysis, we also found a strong

association between overall survival and pN-classification ($p < 0.001$), as was confirmed by other researchers [6,27–29,32–34]. However, a multivariate association between a pathologically positive neck and overall survival, as described by Chen et al. [29] and Wong et al. [27], could not be detected in our cohort. In patients with positive cervical lymph nodes, LNR is proven to be a more accurate way to predict survival than conventional TNM lymph node staging [20,22]. LNR had a strong significant influence on the overall survival in our population ($p < 0.001$) but, in contrary to the finding of Gil et al. [22], LNR was not an independent influencer of overall survival in the multivariate analysis. Furthermore, a strong significance between the presence of lymph or blood vessel invasion ($p < 0.001$ for both parameters) and overall survival was detected. Tumours with aggressive biological activity and therefore poorer prognosis are significantly more associated with vascular invasion. Lymph vessel invasion has been reported to be an important prognosticator for cervical lymph node metastasis and like this for poor locoregional control and reduced overall survival [20,21,27,29,35]. Also, histopathological grading of the primary tumour has a strong significant influence on the overall survival rate in patient with recurrent disease ($p < 0.001$). Although grading may be subjective, and the inter- and intraobserver validation may be debatable, our data, as well as the evidence provided by many other researchers, confirm the influence of tumour grading on the patient prognosis [3,5,6,21,29,36]. The treatment modality has a significant impact on the overall survival ($p < 0.001$) with patients who underwent surgery only for their primary tumour having a significantly better prognosis than patients who underwent an adjuvant therapy. Other authors confirm poorer outcome for patients whose disease fails maximal combination therapy [12,16]. This finding could be explained by a combination of more advanced disease at initial presentation, a more violent initial tumour biology, limited remaining salvage options and maybe radiation-induced DNA damage after adjuvant therapy. Finally, the extent of the neck dissection was significantly associated with overall survival rates, with patients who underwent a less extended neck dissection having a better prognosis in case of relapse. An explanation for this finding might be selection bias, as more extended neck dissections are performed on patients with a higher N-classification and more advanced-stage disease.

Various studies pointed out a significant association between the site of the primary tumour and overall survival [7,16,21,37]. They explain this by a difference in lymphatic drainage [37] or by a compromise at the surgical margins of the tumour at some sites [38]. Kernohan et al. [16] even described the site of failure to be an independent prognostic factor for patients with lyplymph a first OSCC recurrence. However, we could not detect any significance in our cohort. Similarly, various studies showed an association between perineural invasion and poor survival [6,27,29,39], although others denied this correlation [21]. As for tumour site, we could not detect a significant effect of perineural invasion on the overall survival. This could be due to the relatively small patient group, as a result of the retrospective nature and the single-centre data of this study.

Conclusion

For patients with a recurrent OSCC, the time to recurrence, the margin status, the presence of extracapsular spread and the performance of a salvage treatment are independent prognostic factors for overall survival. They have an independent influence on overall survival in patients with recurrence and the absence or presence of these factors can predict a significantly better or worse survival accordingly. Furthermore, the moment of recurrence is significantly influenced by the lymph node ratio, the histopathological grading and margin status of the primary tumour. Since early diagnosis of an OSCC relapse is important to offer the patient a realistic second treatment chance, an adequate identification of patients at higher risk can allow for the development of individualised surveillance programs and earlier diagnosis in the case of recurrence. This prognostic information may also be helpful when planning the treatment of the relapse and in the counselling of patients with recurrent disease.

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Declaration of Competing Interest

None declared.

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