Oral squamous cell carcinomas developing from oral lichen planus: Do they differ in recurrence and metastatic potential?

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Abstract

Background:

Due to the low proportion of squamous cell carcinomas of the oral cavity (OSCC) developing from oral lichen planus (OLP-OSCC) there is only little data regarding the frequency of lymph node metastasis and clinical characteristics such as relapse and outcome in this sub-entity. Therefore, a retrospective analysis of OLP- OSCC was performed.

Methods:

In a retrospective monocenter analysis, all consecutive patients with an OSCC treated in the time period 2000 to 2016 were composed. All patients with an OSCC developing from OLP/ OLLs were identified and analyzed for epidemiological data, risk profile, location of primary tumor, pTNM classification, lymph node metastasis, primary therapy, recurrence, and outcome.

Results:

A total of 103 patients (45%♂/ 55%♀) with an average age of 62 ± 14 y were included in this study. At the time of initial diagnosis, 17% (n = 18) of patients had cervical metastases (CM) whereas only 11% (11 patients) displayed advanced tumor sizes (T > 2). T-status (p = 0.003) and histopathological grading (p = 0.001) had an impact on the incidence of CM. 39.6% of the patients developed a relapse after an average of 24 months with a mean of two recurrences per patient. Advanced tumor size had a significant impact on the 5-year overall survival and was associated with disease free survival of the patients (p < 0.001, respectively p = 0.004).

Conclusion:

Even if initial lymph node metastases were not found more frequent, more aggressive recurrence patterns compared to OSCC could be demonstrated for OLP-OSCC. Therefore, a modified recall for these patients might be necessary.

Introduction:

Oral cancer is one of the most common malignoma worldwide with an annual incident rate of 4.0 per 100,000 and a worldwide mortality rate of 2.7 per 100,000 [1]. Apart from the classic risk factors like smoking and alcohol, potentially malignant disorders are the most important prerequisites for the development of oral squamous cell carcinoma (OSCC). Oral lichen planus (OLP), according to the World Health Organization defined as “a chronic inflammatory disease of the skin and the oral mucosa of unknown etiology”, is considered to be one of the most common and therefore most relevant

premalignant conditions for the development of OSCC with inconsistent described transformation rates of up to 1–3% [2–4].

Although the exact etiopathogenesis of the OLP has not been disclosed, the immunological system is believed to play a leading role for this chronic inflammatory disease of the skin and mucous membrane that frequently involves the oral mucosa [5, 6]. Typical clinical characteristics of OLP are of higher prevalence in women, commonly developing on the buccal mucosa followed by the tongue and the reticular lesion type being the most recognizable clinical form [5, 6].

The latest molecular studies on the OLP support the hypothesis of OLP as a preneoplastic inflammatory model with an inflammatory cytokine-rich microenvironment favoring tumor promotion [6, 7]. Especially from the erythematous and erosive form, the development of OSCC is a feared complication [6]. At the beginning of the 20th century, the first case of malignant transformation of an OLP was described, being followed by a large number of case report [5]. Since then several reviews focused on existing follow-up studies. Due to the low proportion of OSCC developing from OLP (OLP-OSCC) of the oral cavity, there is little isolated data regarding the frequency of lymph node metastasis and clinical characteristics such as relapse and outcome [8–10].

Therefore, OLP is discussed controversially as an independent risk factor for the development of OSCC in literature [5, 6]. Further reasons for this are the lack of generally accepted diagnostic criteria and the fact of heterogeneous follow-up studies based only on clinical diagnostic criteria or the combination of clinical and histological criteria [6]. Furthermore the histologic diagnosis of OLP is challenging with moderate inter- and intraobserver variability [11] as well as difficult to discriminate from other oral lichenoid lesions (OLL) [12]. Treatment of OLP-OSCC remains challenging: chronic inflammation of the oral mucosa lead to cervical lymphadenitis that complicates CM diagnostic. Next, high recurrence rates hamper first line therapy options and worsen patient outcomes.

The aim of this retrospective study was therefore to analyze the subgroup OLP-OSCC with special regard on recurrence patterns and cervical metastasis.

Patients And Methods:

In this retrospective monocenter analysis all consecutive patients with OLP-OSCC being treated between 2000–2016 in the Department of Oral and Maxillofacial Surgery – Plastic Surgery of the University Medical Center Mainz, Germany, were analyzed.

For inclusion criteria, medical records of all OSCC patients with a histopathologically confirmed OLP prior to tumor development were reviewed.

The type of treatment for OLP was symptomatically only and included dietary adaptions (abstaining from hot, spicy and acidic dishes, alcohol and carbonated beverages), mouth rinse with lidocaine additive or retinoid derivate (Retinoral 0,01%) or application of topical steroids such as triamcinolone (Volon A

unguent 0,1%). No systemically treatment with steroids or other immunosuppressive agents was documented. Every patient was informed about their underlying disease with a potentially high risk for OSCC development and was monitored with a close recall system. Here, intervals ranging from two to six months, depending on the manifestation of the disease (e.g. erosive lesions were re-visited every two months). Therefore, the patients were not treated in a special lichen clinic, but included in the above mentioned regularly outpatient consultation specifically for mucosal disorders.

Patients with distant metastasis at the time of primary presentation, OSCC without OLP, as well as malignancies that were not treatment-naïve were excluded. The data inquiry was accomplished using conventional and electronic patient records. Epidemiological data, risk profile for nicotine and alcohol, location of primary tumor, pTNM, lymph node metastasis, primary therapy, recurrence and outcome were analyzed. The 7th version of the TNM-classification by the Union for International Cancer Control (UICC) was applied due to the retrospective manner of this study. All patients were treated surgically in accordance to current guideline recommendations after interdisciplinary tumor board advice. A safe resection margin was histologically defined > 5 mm (R0). Recurrence was defined as either local carcinoma recurrence at the same anatomic site within 5 years after primary treatment or regional recurrence meaning lymph node metastases within 5 years after primary treatment. A tumor recurrence after 5 years was defined as a second cancer.

The study was conducted within the Helsinki Declaration of Human Rights and in accordance to the guidelines of the local ethics committee (Ethikkommission Ärztekammer Rheinland-Pfalz, Mainz, Germany).

SPSS 23.0 for Windows (IBM Deutschland GmbH, Ehningen, Germany) was used for statistical analysis. For multivariate analysis, ANOVA testing was performed to detect possible risk factors for tumor relapse and overall survival. For graphic display, Kaplan–Meier plots in combination with log-rank Mantel-Cox regression were used. Due to the multiple testing, a Bonferoni correction was applied and a p -value ≤ 0.0025 was defined as statistical significant.

Results:

Epidemiological data:

A total of 103 patients with a mean age of 62 ± 14 y were included in the study (Table 1). 55% ($n = 57$, 64 ± 14 y) were female and 45% ($n = 46$, 59 ± 14 y) male. 65% of the patients consumed alcohol and/ or cigarettes regularly and 71% had one or more underlying diseases apart from OSCC. In average, woman had more underlying diseases (3 ± 2) than men (2 ± 1). The most frequent conditions were cardiovascular diseases and diabetes mellitus

Table 1
Epidemiological data and TNM classification of the patients with OLP-
OSCC at the point of initial diagnosis.

	Female	Male	All patients
Gender	55% (n = 57)	45% (n = 46)	(n = 103)
Risk profile			
Positive	61% (n = 35)	70% (n = 32)	65% (n = 67)
Negative	39% (n = 22)	30% (n = 14)	35% (n = 36)
Underlying diseases			
Yes	70% (n = 40)	72% (n = 33)	71% (n = 73)
No	30% (n = 17)	28% (n = 13)	30% (n = 30)
Age (years $\pm$ SD)	64 $\pm$ 14	59 $\pm$ 14	62 $\pm$ 14
T-Stage			
T1	60% (n = 34)	61% (n = 28)	60% (n = 62)
T2	31% (n = 18)	26% (n = 12)	29% (n = 30)
T3	2% (n = 1)	% (n = 0)	1% (n = 1)
T4	7% (n = 4)	13% (n = 6)	10% (n = 10)
N-Stage			
N0	84% (n = 48)	80% (n = 37)	83% (n = 85)
N+	16% (n = 9)	20% (n = 9)	17% (n = 18)
G-Stage			
G1	51% (n = 29)	37% (n = 17)	45% (n = 46)
G2	49% (n = 28)	57% (n = 26)	52% (n = 54)
G3	0% (n = 0)	6% (n = 3)	3% (n = 3)
Tumor-Stage			
I	60% (n = 34)	59% (n = 27)	59% (n = 61)
II	23% (n = 13)	15% (n = 7)	19% (n = 20)
III	2% (n = 1)	9% (n = 4)	5% (n = 5)
IV	16% (n = 9)	17% (n = 8)	17% (n = 17)

Localization and pTNM-Classification:

Most often the cancer was localized at the margin of the tongue (28%), followed by the buccal mucosa (25%) and the lower jaw (22%). Rare localizations were the upper jaw (14%) and the floor of the mouth (11%). In majority, 89% (n = 92) of the tumors were detected at an early stage (T1 or T2), eleven patients showed larger tumor sizes T3 or T4 (11%). 79% (n = 81) were summarized as an I/II stadium, 21% of the cases (n = 22) were staged as III/IV in accordance with the 7th UICC version (Table 1). Histopathologically, 56% (n = 57) of the resected specimen displayed moderate to poor differentiated grading. For the majority of the patients (88%, n = 93) a sufficient adequate safety margin (R = 0) could be achieved by primary surgical therapy (Table 1). Eighteen patients (17%) had developed a CM at the time of initial diagnosis what was significantly associated with an advanced tumor size (T3-4; p = 0.003). Furthermore, high grading showed an influence on occurrence of CM (G2-3; p = 0.001), but not gender, age, risk factors, underlying diseases, nor anatomic site of tumor manifestation (Table 2). An estimation of the percentage of occult metastases was not possible since 96% (n = 102) of patients had preoperatively an abnormal cervical lymph node status in CT and sonography.

Table 2
Presence of CM according to different clinical parameters at the point of initial diagnosis.

	N0		N+	Portion of N+ to the respective factor		
T1	n = 62	n = 61	n = 1	2%	p = 0.003*	
T3	n = 30	n = 19	n = 11	37%		
T3	n = 1	n = 0	n = 1	100%		
T4	n = 10	n = 5	n = 5	50%		
G1	n = 46	n = 45	n = 1	2%	p = 0.001	
G2	n = 54	n = 38	n = 16	30%		
G3	n = 3	n = 2	n = 1	33%		
Male	n = 46	n = 37	n = 9	19%	p = 0.729	
Female	n = 57	n = 50	n = 7	15%		
Positive RF	n = 67	n = 56	n = 11	16%	p = 0.544	
Negative RF	n = 36	n = 29	n = 7	19%		
Positive UD	n = 73	n = 62	n = 11	15%	p = 0.456	
Negative UD	n = 30	n = 23	n = 7	23%		
Upper jaw	n = 15	12	3	20%		p = 0.527
Buccal mucosa	n = 25	24	4%			
Tongue	n = 28	25	3	10%		
Lower jaw	n = 23	13	10	44%		
Mouth floor	n = 12	11	1	8%		
Age ≤ 50y	n = 22	21	1	5%	p = 0.073	
Age > 50y	n = 81	67	14	17%		

Primary Therapy:

For primary therapy, all patients were treated surgically in accordance to current guideline recommendations after interdisciplinary tumor board advice. For reconstruction of the defect, in 46% (n = 49) primary wound closure was sufficient, 40% (n = 42) were reconstructed with a local and 13% (n = 14) with a microvascular anastomosed flap. 24.5% of the patients (n = 26) needed adjuvant radiation. Thirteen of the previous cases needed adjuvant radiation in addition to cisplatin chemotherapy as a radiosensitizer, because of extended T-status and multiple lymph node metastases with or without extracapsular spread.

Follow up and patient's outcome:

In total, 40% (n = 42) of the patients developed a relapse (median follow-up interval: 62.3 ± 44.2 months). Second cancer (n = 21, 20%) and local recurrence (n = 18, 17%) were detected most often as a primary recurrence type. Regional relapse occurred rare: isolated in a single case, another two cases also experienced local recurrence (n = 2, 2%). In average, first recurrence took place after 34.4 ± 33.6 months. Whereas 26 patients (24.5%) showed one singular relapse, sixteen patients (15.1%) developed two or more recurrences; 2% (n = 2) even showed up to six recurrences. Until second and third relapse in average 19.8 ± 23.2 months, respectively 17.9 ± 19.9 months passed. A noteworthy influence of advanced T-status T3/T4 on presence of tumor relapse in the follow-up could be found (p = 0.004, Fig. 1). No influence could be found for presence of lymph node metastasis (p = 0.154), grading (n = 0.251), or resection margin (p = 0.137).

In multivariate analysis, there was no epidemiological factor associated with tumor recurrence (gender, age, tumor localization, positive risk factors, all: p > 0.05) of the analyzed cohort (Table 3).

Table 3

Presence of Relapse according to different clinical parameters at the point of initial diagnosis.

		No Relapse	Relapse	Portion of Relapse to the respective factor	
T1	n = 62	n = 40	n = 22	35%	p = 0.734
T2	n = 30	n = 17	n = 13	43%	
T3	n = 1	n = 0	n = 1	100%	
T4	n = 10	n = 5	n = 5	50%	
G1	n = 46	n = 30	n = 16	35%	p = 0.444
G2	n = 54	n = 31	N = 23	43%	
G3	n = 3	n = 1	n = 2	67%	
N0	n = 85	56	32	36%	p = 0.187
N+	n = 18	8	10	56%	
Male	n = 46	29	17	38%	p = 0.094
Female	n = 57	33	24	41%	
Positive RF	n = 67	41	26	41%	p = 0.715
Negative RF	n = 36	22	14	38%	
Positive UD	n = 73	41	32	45%	p = 0.075
Negative UD	n = 30	23	7	26%	
Upper jaw	n = 15	7	8	53%	p = 0.338
Buccal mucosa	n = 26	17	9	35%	
Tongue	n = 30	19	11	37%	

		No Relapse	Relapse	Portion of Relapse to the respective factor	
Lower jaw	n = 23	10	13	57%	
Mouth floor	n = 12	11	1	8%	
Age ≤ 50y	n = 22	17	5	23%	p = 0.175
Age > 50y	n = 84	47	37	44%	

For the overall survival, within the median follow-up interval of $62,3 \pm 44,2$ months, fourteen patients (13%) died. There was a significant influence on impaired overall survival for larger tumor size T3/T4 vs. T1/T2 ($p < 0.001$, Fig. 2), and a noteworthy influence of presence or absence of CM ($p = 0.047$) and presence or absence of relapse ($p = 0.036$) in the respective Kaplan–Meier plots and log-rank Mantel-Cox regression. In multivariate analysis, no influence was seen for the tested epidemiological data (gender, age, underlying diseases, tumor localization) or for insufficient resection status (all $p > 0.05$), tumor relapse ($p = 0.186$), and presence of cervical metastasis ($p = 0.061$).

Discussion:

Within this retrospective study, a total of 103 patients with OLP-OSCC were re-examined. As a major result, moderate rates of initial lymph node metastases as well as an aggressive recurrence pattern compared to OSCC could be found.

Apart from classical life-style risk factors like tobacco and alcohol, [13, 14] the group of OPMDs belongs to the most important risk factors responsible for OSCC (3). OLP having a global prevalence of 2% and a malignant transformation rate of 1% is one of the most relevant disorders within OPMDs [2, 9, 15].

The demographic data collected from our pool of patients with OLP-OSCC differ from the literature when compared to OSCC patients. Even though the average age (62 ± 14) and a higher average age within female patients in this study are in accordance with the literature, the overall higher rate of affected females is different. Particularly with over 50% of the affected patients being female there is a deviation from the typical 1:3 ratio between male and female described in literature regarding OSCC patients [16]. In accordance with literature we also observed higher rates for men concerning risk factors like parallel consumption of alcohol and tobacco [17]. However, this is an epidemiological distribution often found in patients with OLP [5].

Regarding the anatomic location of OSCC the provided data in literature is not consistent but depends on the geographical region where the study was performed [16]. Specifically in Asian studies, the OSCC preferably occurred on buccal mucosa whereas in German-speaking regions the tongue and the floor of

the mouth were the most affected site[18]. In the present study, the location of the primary tumor was in most cases (> 50%) the tongue and cheek. Notably the floor of the mouth was affected less frequently. This aberration within the distribution pattern of OLP-OSCC could be attributed to the predilection sites of OLP which specifically manifest symmetrically at the buccal mucosa and tongue [19]. In addition to both these sites, there is a high occurrence of OLP in the gingiva of the maxilla and mandibular which could contribute to the high rate (35.9%) of OLP-OSCC in these anatomic regions in comparison to OSCC.

The diagnosis was made for most of our patients (~ 90%) at an early stage with a small tumor size (T1-2). These findings significantly differ from the numbers stated in corresponding literature dealing with the classical form of OSCC which describe smaller fractions (~ 1/3 of patients) with T1-2 at the time of diagnosis [20]. The higher rates of early stage tumors at the time of diagnosis within the presented patient pool can probably be accounted for by the characteristics of OLP as the underlying disease, which in most cases lead to a close check-up and therefore to a higher probability of an early tumor detection.

At the time of diagnosis, only a minority of the patients (17%) had a positive N-status. This number seems even higher (29%) in the literature for comparable groups of patients with T1-2 tumor size of OSCC [21]. This reflects the importance of a close follow up of these patients. In the present analysis the risk of developing CM could clearly be correlated to an increased tumor size and dedifferentiation. This distinct correlation between the rate of metastatic disease and both tumor size and cell dedifferentiation is also reported in existing literature for OSCC [21, 22]. Due to this early stage at the time of diagnosis, 99% of the patients could receive a curative surgical treatment. As a result of the accordingly low numbers of patients with an advanced tumor stage (III-IV) adjuvant therapy (radio and/ or radio-chemotherapy) had to be conducted exclusively for 24.5% of the patients.

Within the follow-up period, 40% of the examined patients developed a recurrence, half of them within the first 24 months. In addition, the presented results found evidence that the first recurrence for OLP-OSCC occurred within a wider time corridor than in OSCC [18, 21, 23–25]. Furthermore, almost half of the patients with recurrence had sequential recurrences. On average, 2.3 recurrences occurred. Here the time intervals until the next recurrence in general became shorter with increasing number of recurrences for a patient. Second to increasing number and type of recurrence also shifted from being a regional to a local recurrence.

Regarding the location of recurrence according to tumor presentation at the point of initial diagnosis, the lower jaw was affected the most whereas the floor of the mouth was the least affected site. Interestingly, when the maxilla was primarily affected a high proportion of relapses were demonstrated. One may hypothesize that, similarly to primary tumor presentation; this may be associated with the initial affected anatomical localizations of OLP. This may partly explain the high rate of recurrences in the maxilla that are normally sparse in OSCC. Again, in contrast to OSCC, the tumor size as well as G- and N-status did not significantly influence the risk of developing recurrences [23, 25, 26]. Interestingly, relapse within the first 5 years led only to a 10% decrease of survival rate whereas in corresponding literature of OSCC relapses had a strong influence on survival in patients with OSCC [21, 24].

In spite of various therapeutic methods available today for treating OSCC, the mortality rates for oral carcinoma in the first 5 years is still high (50%) [16]. However, looking at the analyzed study group, the 5-year survival rate was 93%. It seems that subgroup of OLP-OSCC may show a better overall survival in comparison to OSCC, but tumor recurrence could occur more often and during a longer follow-up period. Mignogna *et al.* found similar outcomes of patients with OLP-OSCC 5-year survival rate of 96.7% [27]. In further agreement with existing literature [20], there is no distinct difference between male and female regarding 5-year survival. Also the existence of further risk factors had no significant influence on 5-year survival. The evaluation of the cumulative survival showed that an increasing tumor size (T3-4) and positive N-status correlates with poor prognosis, the former being the most significant factor. These observations are identical to those in the literature on clinical factors for OSCC overall survival [20, 21, 28]. Histological grade of dedifferentiation in contrast had no statistically significant effect on cumulative survival. Therefore, the much better survival rates may be attributed to the high rate of identified tumors in an early stage (T1-2) as well as to the strict call-recall-system established for patients with OLP-OSCC.

Because of its retrospective manner, this study has some major limitations. Above all, data acquisition depends highly on the accuracy of the clinical records and these may not be sufficient: No information about the time period between first diagnoses of lichen (including different types of lichen) and the date of malignant transformation could be obtained. Furthermore, no conclusion of a possible impact of the type of treatment, the follow-up period and the outcome could be drawn due to lack of specific data.

Conclusion:

The obtained data on OLP-OSCC showed differentiations in epidemiological features, especially gender distribution, in comparison to OSCC. Also, anatomical sites of primary tumor presentation differed to distribution pattern of classical OSCC. Whereas lymphogenic metastasis was not seen more frequent, drastically higher recurrence rates of 40% reflect the aggressive potential of OLP-OSCC in comparison to OSCC. Notably with increasing incidence rate of recurrence the time interval between two incidences decreased.

In summary, it seems that OLP-OSCC differs significantly in biological behavior in comparison to OSCC. Although the overall prognosis for OLP-OSCC was better than for OSCC in general, a close check-up for OLP patient is an essential requirement for detection and treatment of a malignant transformation in an early stage.

Declarations

Funding: The study was not sponsored.

Conflict of Interest/Competing interests: The authors declare that they have no conflict of interest/no competing interest.

Ethics approval and consent to participate: This retrospective chart review study involving human participants was in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. According to the hospital law of Rhineland-Palatine, Germany (*Krankenhauslandesgesetz*), no approval by the local ethics committee is necessary.

Consent to participate: For this type of study, formal consent is not required.

Consent for publication: For this type of study, formal consent is not required.

Availability of data and material: All obtained data is analyzed in the study, there is no additional data.

Code availability: not applicable

Authors' contributions: All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by Sebastian Blatt, Keyvan Sagheb, Roman-Kia-Rahimi-Nedjat and Christian Walter. Kawe Sagheb and Abdullatif Lingawi performed statistical analysis. The first draft of the manuscript was written by Sebastian Blatt and Keyvan Sagheb and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

References

1. Chi AC, Day TA, Neville BW (2015) Oral cavity and oropharyngeal squamous cell carcinoma—an update. *CA: a cancer journal for clinicians* 65 (5):401-421. doi:10.3322/caac.21293
2. Warnakulasuriya S, Johnson NW, van der Waal I (2007) Nomenclature and classification of potentially malignant disorders of the oral mucosa. *J Oral Pathol Med* 36 (10):575-580. doi:10.1111/j.1600-0714.2007.00582.x
3. Speight PM, Khurram SA, Kujan O (2017) Oral potentially malignant disorders: risk of progression to malignancy. *Oral Surg Oral Med Oral Pathol Oral Radiol*. doi:10.1016/j.oooo.2017.12.011
4. Humans IWGotEoCRt (2004) Betel-quid and areca-nut chewing and some areca-nut derived nitrosamines. *IARC Monogr Eval Carcinog Risks Hum* 85:1-334
5. Xue JL, Fan MW, Wang SZ, Chen XM, Li Y, Wang L (2005) A clinical study of 674 patients with oral lichen planus in China. *J Oral Pathol Med* 34 (8):467-472. doi:10.1111/j.1600-0714.2005.00341.x
6. Eisen D (2002) The clinical features, malignant potential, and systemic associations of oral lichen planus: a study of 723 patients. *J Am Acad Dermatol* 46 (2):207-214
7. Georgakopoulou EA, Achtari MD, Achtaris M, Foukas PG, Kotsinas A (2012) Oral lichen planus as a preneoplastic inflammatory model. *J Biomed Biotechnol* 2012:759626. doi:10.1155/2012/759626
8. Gonzalez-Moles MA, Scully C, Gil-Montoya JA (2008) Oral lichen planus: controversies surrounding malignant transformation. *Oral Dis* 14 (3):229-243. doi:10.1111/j.1601-0825.2008.01441.x

9. Fitzpatrick SG, Hirsch SA, Gordon SC (2014) The malignant transformation of oral lichen planus and oral lichenoid lesions: a systematic review. *J Am Dent Assoc* 145 (1):45-56.
doi:10.14219/jada.2013.10
10. van der Meij EH, Schepman KP, Smeele LE, van der Wal JE, Bezemer PD, van der Waal I (1999) A review of the recent literature regarding malignant transformation of oral lichen planus. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 88 (3):307-310
11. van der Meij EH, Reibel J, Slootweg PJ, van der Wal JE, de Jong WF, van der Waal I (1999) Interobserver and intraobserver variability in the histologic assessment of oral lichen planus. *J Oral Pathol Med* 28 (6):274-277
12. Kamath VV, Setlur K, Yerlagudda K (2015) Oral lichenoid lesions - a review and update. *Indian J Dermatol* 60 (1):102. doi:10.4103/0019-5154.147830
13. Petti S (2009) Lifestyle risk factors for oral cancer. *Oral oncology* 45 (4-5):340-350.
doi:10.1016/j.oraloncology.2008.05.018
14. Hashibe M, Brennan P, Benhamou S, Castellsague X, Chen C, Curado MP, Dal Maso L, Daudt AW, Fabianova E, Fernandez L, Wunsch-Filho V, Franceschi S, Hayes RB, Herrero R, Koifman S, La Vecchia C, Lazarus P, Levi F, Mates D, Matos E, Menezes A, Muscat J, Eluf-Neto J, Olshan AF, Rudnai P, Schwartz SM, Smith E, Sturgis EM, Szeszenia-Dabrowska N, Talamini R, Wei Q, Winn DM, Zaridze D, Zatonski W, Zhang ZF, Berthiller J, Boffetta P (2007) Alcohol drinking in never users of tobacco, cigarette smoking in never drinkers, and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. *Journal of the National Cancer Institute* 99 (10):777-789. doi:10.1093/jnci/djk179
15. Aghbari SMH, Abushouk AI, Attia A, Elmaraezy A, Menshawy A, Ahmed MS, Elsaadany BA, Ahmed EM (2017) Malignant transformation of oral lichen planus and oral lichenoid lesions: A meta-analysis of 20095 patient data. *Oral oncology* 68:92-102. doi:10.1016/j.oraloncology.2017.03.012
16. Warnakulasuriya S (2009) Global epidemiology of oral and oropharyngeal cancer. *Oral oncology* 45 (4-5):309-316. doi:10.1016/j.oraloncology.2008.06.002
17. Scully C, Bagan J (2009) Oral squamous cell carcinoma: overview of current understanding of aetiopathogenesis and clinical implications. *Oral Dis* 15 (6):388-399. doi:10.1111/j.1601-0825.2009.01563.x
18. Wolff KD FM, Nast A (2012) The diagnosis and treatment of oral cavity cancer. *Deutsches Arzteblatt international* (109):829-835
19. van der Waal I (2009) Oral lichen planus and oral lichenoid lesions; a critical appraisal with emphasis on the diagnostic aspects. *Med Oral Patol Oral Cir Bucal* 14 (7):E310-314
20. Lambert R, Sauvaget C, de Camargo Cancela M, Sankaranarayanan R (2011) Epidemiology of cancer from the oral cavity and oropharynx. *Eur J Gastroenterol Hepatol* 23 (8):633-641.
doi:10.1097/MEG.0b013e3283484795
21. Sagheb K, Blatt S, Rahimi-Nedjat RK, Eigenbrodt S, Al-Nawas B, Walter C (2016) Cervical metastases behavior of T1-2 squamous cell cancer of the oral mucosa. *Clin Oral Investig*. doi:10.1007/s00784-

22. Sagheb K KV, Rahimi-Nedjat R, Dollhausen M, Ziebart T, Al-Nawas B, Walter W (2016) Cervical metastases behavior of T1-2 squamous cell carcinoma of the tongue. *J Maxillofac Oral Surg*. doi:10.1007/s12663-016-0936-0
23. Noguti J, De Moura CF, De Jesus GP, Da Silva VH, Hossaka TA, Oshima CT, Ribeiro DA (2012) Metastasis from oral cancer: an overview. *Cancer Genomics Proteomics* 9 (5):329-335
24. Safi AF, Kauke M, Grandoch A, Nickenig HJ, Zoller JE, Kreppel M (2017) Analysis of clinicopathological risk factors for locoregional recurrence of oral squamous cell carcinoma - Retrospective analysis of 517 patients. *J Craniomaxillofac Surg* 45 (10):1749-1753. doi:10.1016/j.jcms.2017.07.012
25. Brands MT, Brennan PA, Verbeek ALM, Merks MAW, Geurts SME (2018) Follow-up after curative treatment for oral squamous cell carcinoma. A critical appraisal of the guidelines and a review of the literature. *Eur J Surg Oncol* 44 (5):559-565. doi:10.1016/j.ejso.2018.01.004
26. Hartmann S SM, Maurus K, Bhole E, Brands A, Kübler C, Müller-Richter A (2018) Head and Neck squamous cell carcinoma. From pathology to treatment. *MKG-Chirurg* 11 (1):30-37
27. Mignogna MD, Fedele S, Lo Russo L (2006) Dysplasia/neoplasia surveillance in oral lichen planus patients: a description of clinical criteria adopted at a single centre and their impact on prognosis. *Oral oncology* 42 (8):819-824. doi:10.1016/j.oraloncology.2005.11.022
28. Murthy V, Agarwal JP, Laskar SG, Gupta T, Budrukhar A, Pai P, Chaturvedi P, Chaukar D, D'Cruz A (2010) Analysis of prognostic factors in 1180 patients with oral cavity primary cancer treated with definitive or adjuvant radiotherapy. *J Cancer Res Ther* 6 (3):282-289. doi:10.4103/0973-1482.73360

Figures

Figure 1

Overall survival based on the tumor size ($p < 0.001$ for T4).

Figure 2

Disease free survival based on the tumor size ($p=0.004$ for T4).