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The occurrence of cervical metastases in squamous cell carcinoma of the tongue: Is there a rationale for bilateral neck dissection in early-stage tumors?

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ABSTRACT

Introduction: The aim of this retrospective study was to evaluate the incidence of regional metastases in squamous cell carcinoma (SCC) of the tongue, in order to validate different neck management regime recommendations.
Materials and methods: A cohort of 97 patients suffering from primary SCC of the tongue was analyzed in regard to the development of primary and late neck node metastases, considering tumor stage and affected side. Survival analysis was performed to determine the impact of different relevant clinical and pathological factors on overall and progression-free survival.
Results: Regional metastases occurred in 29 patients (29.9%). In early-stage tumors (T1 and T2), the rates of primary metastases were 28.6% and 22.4%, respectively. Bilateral cervical metastases are rare but were detected in early-stage cancer in several cases (T1: 2.1%; T2: 11.8%).
Conclusion: The development of regional metastases in the ipsilateral and contralateral neck, even in early-stage SCC of the tongue, illustrates the importance of elective bilateral neck dissection in the treatment of affected patients.

1. Introduction

Squamous cell carcinoma of the head and neck (HNSCC) is the sixth most common malignancy worldwide, with around 600,000 new cases annually. Most cases arises in the oral cavity (Ferlay et al., 2010). Locoregional disease recurrence and the development of cervical as well as distant metastases have been identified as the main prognostic factors. While new treatment regimens and multidisciplinary approaches have been established, overall survival associated with HNSCC has improved only marginally within recent decades (Cooper et al., 2004; Akhtar et al., 2007; Pignon et al., 2009; D'Cruz et al., 2015).

Various risk factors have been suggested for estimating the probability of locoregional recurrence in order to help decide on adjuvant therapy or how to adjust the clinical and radiological follow-up. These factors include advanced tumor stages, incomplete tumor resection, lymphatic/vascular/perineural tumor invasion, presence of cervical lymph node metastases (LNM), and lymph node ratio (LNR) (D'Cruz et al., 2015; Baumeister et al., 2018). LNR is calculated as the ratio of positive lymph nodes to dissected nodes, and has been identified by various authors as an independent prognostic factor in patients with oral squamous cell carcinoma (Sayed et al., 2013; de Ridder et al., 2016; Hosni et al., 2017).

While there is general agreement about the need for elective neck dissection in patients suffering from oral squamous cell carcinoma (OSCC), the recommendations regarding the extent of treatment differ. A number of publications suggest an ipsilateral neck dissection only for early-stage tumors, especially for squamous cell carcinoma of the tongue (Lim et al., 2006; Abu-Ghanem et al., 2016). Furthermore, there is a strong tendency towards deintensification of adjuvant radiotherapy in patients without cervical metastases after radiological assessment (Perkins et al., 2012; Spencer et al., 2014). This, however, requires a high

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certainty of the diagnostic tool used to predict a negative lymph node status, to ensure a successful long-term oncological outcome for the affected patient.

Many epidemiological studies have presented the relevant clinical features of the investigated cohort, including the localization of primary tumors and the lymph node status. However, only a few have focused on the existence of site-specific relations between primary tumors, lymph node metastases by therapy onset, and the development of late metastases.

The goal of this study was to investigate the incidence of primary and late regional metastases in a cohort of patients with SCC of the tongue. Furthermore, it validated the prognostic significance of regional metastases and affected neck side for the survival of patients.

2. Materials and methods

2.1. Data collection

The study included patients with squamous cell carcinoma of anterior two-thirds of the tongue, who underwent surgical treatment in the Department of Oral and Cranio-Maxillofacial Surgery, Heidelberg University Hospital, between 2010 and 2017. Patients with squamous cell carcinoma of the tongue base were not included. Patients with advanced tumor size (T4), positive resection margins, lymph node metastases, or histopathological risk factors received adjuvant radiation only, or in combination with platinum-based systemic therapy. Written informed consent was obtained from each patient. The study was approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (ethic vote: S-183/2015). Clinical and therapeutic follow-up was assessed retrospectively using SAP patient management research (SAP, Walldorf, Germany).

2.2. Statistical analysis

Statistical analysis was performed using Microsoft Excel 2013 (Microsoft, Redmond, WA, USA) and SPSS Statistics® 18 (IBM, Armonk, NY, USA). Demographic and clinical data were summarized using descriptive statistics. Survival rates were calculated, using the Kaplan–Meier method, from the date of diagnosis until death or the end of data collection. Log-rank testing was implemented to estimate differences in survival. Multivariate Cox proportional hazard models were applied to determine the impact on overall and progression-free survival. Pearson's correlation coefficient was used to investigate the correlation between clinical and pathological parameters. A p-value of 0.05 or less was deployed to demonstrate statistical significance.

3. Results

3.1. Patient cohort

Overall, 97 patients were included in the analysis. 38 (39.2%) were female and 59 (60.8%) were male, with a median age of 61 ± 14.3 years (range: 18–86 years). All patients presented SCC of the anterior two-thirds of the tongue, and received primary surgical treatment in the Department of Oral and Cranio-Maxillofacial Surgery of the University of Heidelberg between 2010 and 2017. 83 patients (85.6%) presented early-stage tumors and 14 patients (14.4%) locally advanced tumors. Table 1 provides an overview on relevant clinical and pathological data for the investigated cohort.

All patients were submitted to neck dissection of levels I–III, irrespective of their clinical neck node status. 10 patients (10.3%) underwent a unilateral and 87 patients (89.7%) a bilateral neck dissection.

Table 1
Descriptive data regarding demographic and clinical features of the investigated cohort.

Parameter	Number of cases (%)
Gender	
Female	38 (39.2)
Male	59 (60.2)
Age	
<65 years	53 (54.6)
≥65 years	44 (45.4)
T stage	
T1	49 (50.5)
T2	34 (35.1)
T3	11 (11.3)
T4	3 (3.1)
Side affected	
Right side	45 (46.4)
Left side	52 (53.6)
N stage	
0	70 (72.2)
1	6 (6.2)
2a	1 (1.0)
2b	11 (11.3)
2c	6 (6.2)
3	3 (3.1)
M stage	
0	97 (100)
1	0 (0)
UICC	
1	47 (48.5)
2	18 (18.6)
3	9 (9.3)
4	23 (23.6)
Differentiation grade	
1	7 (7.2)
2	70 (72.2)
3	17 (17.5)
Missing	3 (3.1)
Resection status	
0	94 (96.9)
1	1 (1)
X	2 (2.1)
Sagittal localization	
Anterior	8 (8.2)
Intermediate	46 (47.4)
Distal	43 (44.4)
Risk factors	
Tobacco consumption	
Yes	34 (35.1)
No	63 (64.9)
Alcohol consumption	
Yes	28 (28.9)
No	69 (71.1)
Disease recurrence	
Local recurrence	8 (8.2)
Regional metastases	11 (11.3)
Distant metastases	4 (4.1)

3.2. Incidence of regional metastases

The incidence of lymph node metastases under histopathological examination by the time of primary surgery was 29.9% (29 cases). Table 2 shows the distribution of cervical metastases in relation to primary tumor stage. In 24.1% (seven cases) of primary regional metastasis, the contralateral side was involved (Table 3).

Table 2
Tumor stage and primary neck node metastases in 97 cases of SCC of the tongue.

Tumor stage	n	No. of events	%
T1	49	3	6.1
T2	34	16	47.1
T3	11	8	72.7
T4	3	2	66.7

Table 3
Neck side affected by regional metastases in relation to extent and side of primary tumor.

Tumor stage	Side affected by lymph node metastases		Total
	Ipsilateral	Contralateral	
T1	2	1	3
T2	12	4	16
T3	7	1	8
T4	1	1	2

3.3. Disease recurrence rates

During follow-up, a recurrence rate of 23.6% was revealed, including eight cases of local disease recurrence (8.2%), 11 cases of regional recurrence (11.3%), and four cases of distant metastases (4.1%). The majority of late regional metastases developed in patients with primary N+ stages (pN0 group: 3, pN + group: 8, $p < 0.01$, Table 4). The majority of cervical metastases developed ipsilaterally, although there were also several cases of contralateral metastasis (27.3%) (Table 5).

3.4. Survival analysis

Upon conclusion of data collection, 13 patients had died (13.4%) and 84 (86.6%) were alive. 21 patients (21.6%) experienced locoregional disease recurrence. The mean time to death was 16.2 months; the mean time to disease recurrence was 11.7 months.

The study also showed a significant trend towards worse progression-free survival in patients with higher tumor stages ($p < 0.05$). However, there was no significant impact of T stage on overall survival (Fig. 1A, B).

Fig. 2A, B depict the survival rates for patients with primary N0 and N+ necks respectively. Furthermore, there was a significant tendency for worse overall and progression-free survival in patients with lymph node metastases ($p < 0.01$). Multivariate survival analysis confirmed the presence of neck node metastases as independent prognostic factor for overall survival together with locoregional disease recurrence and the presence of pathological risk factors (Table 6).

4. Discussion

The main purpose of this study was to determine the incidence rates of cervical metastases in general, with a particular focus on the contralateral neck in squamous cell carcinoma of the tongue. There is an ongoing discussion on either implementing a wait-and-see strategy or an unilateral neck dissection in early-stage tumors of the oral cavity and especially in SCC of the tongue. Similar investigations have been performed for other subsites such as the floor of the mouth or the maxilla, where most authors tend to recommend elective neck dissection in early-stage tumors. The tongue, however, still seems to be regarded as a locus of minor risk when it comes to the development of regional metastases (Berger et al., 2015; Joosten et al., 2017; Ding et al., 2019; Moratin et al., 2018). Up to now, there is a lack of investigations reporting on the site-specific rate of metastasis and relevant therapeutic implications for squamous cell carcinoma of the tongue. The treatment recommendations for early-stage tumors tend to be more restrictive compared to advanced diseases in order to avoid overtreatment and to preserve postoperative quality of life for the patient. However, accurate evaluation is needed even for small tumors. In this respect, our analysis revealed that early-stage carcinomas show a distinct tendency to develop ipsilateral and, more importantly, contralateral cervical metastases.

Our survival analysis also demonstrated that the tumor size has no significant impact on overall survival, whereas the presence of neck node metastases led to significantly worse overall and progression-free survival. In our multivariate Cox Regression analysis, we were able to confirm the N+ status to be an independent prognostic factor regarding overall survival, together with local or regional disease recurrence; this is in line with a plethora of existing investigations and confirms the validity of our data (Kligerman et al., 1994; Akhtar et al., 2007; D'Cruz et al., 2015).

The presented patient collective displayed an incidence rate of cervical metastases of 29.9 %. This was mainly due to the small percentage of metastatic events in the relatively large portion of T1 tumors. In T2 tumors, however, the rate of primary cervical metastases was 47.1%, with increasing rates for T3 and T4 tumors (Table 2). This data indicates that the tongue presents a similar risk of developing cervical metastases as other subsites of the oral cavity. Hence, the same treatment recommendations should be applied regarding tumor resection and management of the clinically negative neck (Morice et al., 2016; Niu et al., 2017; Zirk et al., 2018).

In our cohort, we observed several occurrences of bilateral metastases in T1 and T2 tumors that primarily had been staged as N0 in clinical and radiological examination. Although sensitivity and specificity of computed tomography scans for the detection of cervical metastases were described as high in the past, there is a significant tendency towards under-staging of necks in our cohort, particularly in cases of early-stage tumors with clinically negative necks. While most literature shows optimism about the aptitude of CT scans in tumor staging, various publications reported on the low accuracy of CT scans regarding the detection of extracapsular spread (Chai et al., 2013; Carlton et al., 2017). This underscores the need of an accurate histopathological evaluation of the dissected

Table 4
Incidence of late lymph node metastases in relation to primary neck status and affected neck side.

Primary neck status	*n*	Incidence of late lymph node metastases	
N0	67	3	$p < 0.01$
N+	19	8	
Primary N+	Side affected by late lymph node metastases		
	Ipsilateral	Contra-/bilateral	
	4	4	

Table 5
Incidence of late lymph node metastases in relation to primary tumor stage.

Tumor stage	*n*	Ipsilateral	Contra-/bilateral	Total No. (%)
T1	49	3	0	3 (6.1)
T2	34	1	5	6 (17.6)
T3	11	1	0	1 (9.1)
T4	3	1	0	1 (33.3)

Table 6
Multivariate analysis of overall survival regarding neck node status and relevant covariates.

Characteristics	HR	95% CI	*p*-value
T1–2/T3–4	0.28	0.45–1.749	0.17
N0/N+	16.264	2.285–115.77	<0.01*
Grading	1.17	0.301–4.56	0.82
Age >65	0.56	0.153–2.24	0.43
Late lymph node metastasis	22.78	4.72–109.881	<0.01*
Local disease recurrence	19.81	2.35–166.84	<0.01*
Pathological risk factors	2.33	1.13–4.84	0.02

*p-values < 0.01.

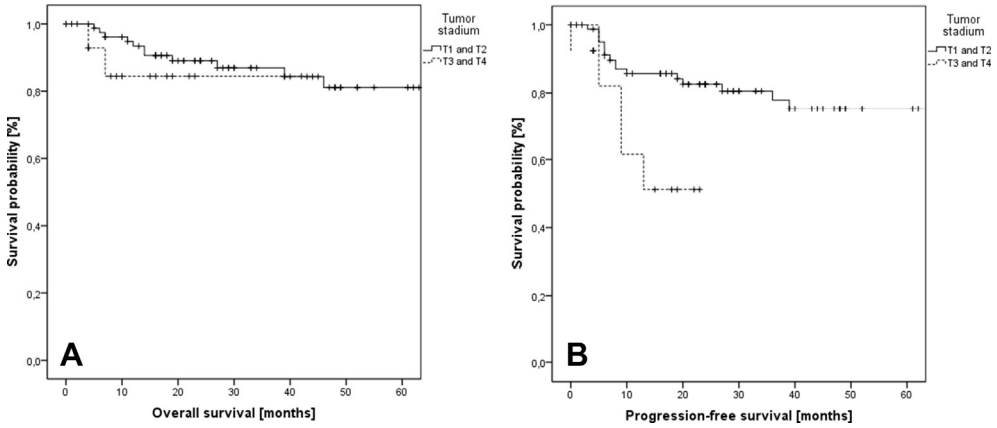

Fig. 1. A: Overall survival for patients with SCC of the tongue in relation to tumor stage (T1/T2 and T3/T4, log-rank: $p = 0.4$). B: Progression-free survival for patients with SCC of the tongue in relation to tumor stage (T1/T2 and T3/T4, log-rank: $p < 0.05$).

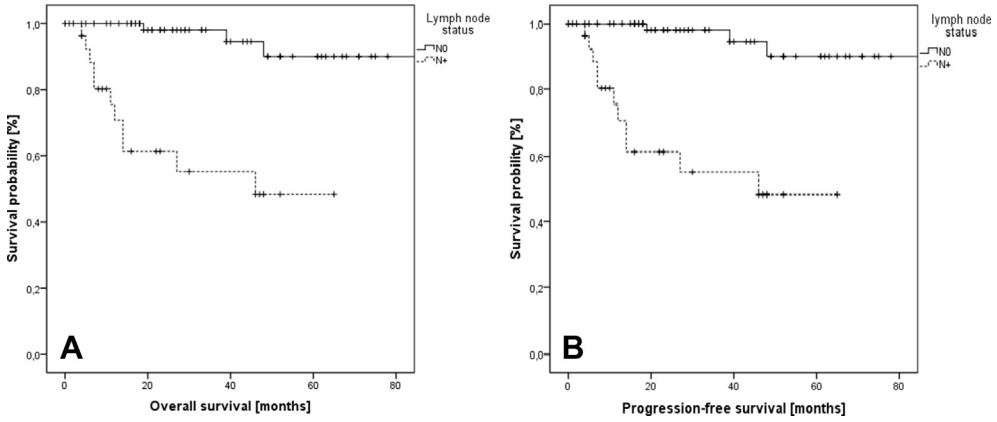

Fig. 2. A: Overall survival for patients with SCC of the tongue in relation to primary neck status (log-rank: $p < 0.01$). B: Progression-free survival for patients with SCC of the tongue in relation to primary neck status (log-rank: $p < 0.01$).

nodes. In the end, a positive event of extracapsular spread is an important prognostic factor of adverse clinical outcome and potentially requires intensified and combined adjuvant therapy (Bernier et al., 2004, 2005).

Furthermore, the ongoing struggle to reduce toxicity in radiotherapy by cutting down the radiation dose and, more importantly, sparing of the clinically negative contralateral neck may lead to under-treatment. It also may have a negative impact on patient's outcome if cervical metastases are not being detected and removed via bilateral neck dissection (Eisbruch et al., 2004; Perkins et al., 2012; Spencer et al., 2014). The aforementioned tendency to reduce radicalness of therapy is an evident fact in the administration of adjuvant radiotherapy. Torrecillas et al. recently reported on the considerably smaller probability to receive adjuvant therapy in T1N1 OSCC compared to T2N1 tumors, while the same investigation demonstrated a better survival for patients with adjuvant therapy (Torrecillas et al., 2018).

Our analysis showed that the majority of regional disease recurrences developed in formerly metastatic necks. Contralateral involvement occurred in 5 cases (45.5%). All cases of late contralateral metastases occurred in patients with primary T2 tumors (Table 5). Overall, the rate of regional disease recurrence in terms of late cervical metastases was 11.3% and as reported earlier. The affected patients presented significantly worse overall and progression-free survival rates compared to non-recurrent patients ($p < 0.01$). While a bilateral elective neck dissection of the levels I-III may not be a method to guarantee the prevention of late metastases, it still increases the chance of either removing micrometastases in time or at least to fortify the indication for adjuvant therapy and accordingly improve clinical outcome (Ganly et al., 2012, 2013; Abu-Ghanem et al., 2016).

5. Conclusion

Our data indicates that the incidence of cervical metastases in early-stage cancer of the tongue is smaller compared to more advanced cases. Nevertheless, several T1 and T2 tumors developed contralateral cervical metastases although they were initially staged as N0. This demonstrates the urgent need for elective bilateral neck dissection in squamous cell carcinoma of the tongue, irrespective of the tumor stage. Apart from removing potentially existing micro-metastases, this facilitates an exact risk assessment and the adequate administration of adjuvant therapy.

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Conflicts of interest

All authors declare that they have no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jcms.2019.03.003.

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