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Squamous cell carcinoma of the mandible – Patterns of metastasis and disease recurrence in dependence of localization and therapy☆

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ABSTRACT

Introduction: Oral squamous cell carcinomas exhibit distinct patterns of disease progression, depending on their localisation. This study aimed to evaluate clinicopathological data in patients with tumors of the mandibular alveolar process, to facilitate risk assessment and therapy planning.
Materials and methods: A retrospective cohort study was designed including patients with squamous cell carcinoma of the mandibular gingiva. Clinical and pathological data were collected to determine the rate of cervical metastases and clinical outcomes depending on tumor stage, localization (anterior, intermediate and posterior) and the extent of tumor resection.
Results: 120 patients were included in the analysis. Rate of metastases was 42.6%. Tumors of the anterior part of the mandible exhibited significantly higher rates of bilateral metastases (anterior: 85.7%, intermediate: 15.8%, posterior: 4%, $p < 0.001$) and local recurrence (anterior: 25%, intermediate: 16.3%, posterior: 5.5%, $p = 0.03$) compared to posterior malignancies.
Conclusion: Tumors of the anterior segment of the mandible are characterized by high rates of metastases and local recurrence. Therefore, we propose radical segmental resection and bilateral neck dissection in those patients.

1. Introduction

Squamous cell carcinomas of the oral cavity (OSCC) form a major part within the group of head and neck squamous cell carcinomas (HNSCC) (Ferlay et al., 2010). Ranging among the eight most common malignant diseases worldwide, this entity is characterized by molecular and clinical heterogeneity (Alsahafi et al., 2019). The development of local disease recurrence and cervical and distant metastases has been shown to be the main prognostic factors in OSCC (Cooper et al., 2004; Akhtar et al., 2007; Pignon et al., 2009; D'Cruz et al., 2015). Surgical therapy is the established first-line standard of care and is combined with adjuvant radio- or radiochemotherapy depending on tumor size and occurrence of metastases (Forastiere et al., 2001; Pignon et al., 2009; D'Cruz et al., 2015).

While in the past, OSCC were generally treated alike independent of their anatomic localization, lately evidence has grown showing that each subsite of the oral cavity exhibits distinct patterns of metastasis, disease recurrence and survival (Berger et al., 2015; Moratin et al., 2018, 2019, 2020).

Although several epidemiological studies presented clinical features of their investigated cohort, only a few have investigated the existence of site-specific relations between primary tumors, lymph node metastases and regional disease recurrence. Surgical tumor ablation in combination with elective neck dissection (ND) is regarded as the established first-line modality for the treatment of

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resectable OSCC. Nevertheless, radicalness and extent of the surgical procedures are a constant matter of debate. This applies especially for tumors located on or near the mandible. Here, surgical treatment options include either radical segmental resection or marginal resection. The surgeon often has to balance optimal oncological outcome and postoperative functionality and quality-of-life. Furthermore, there is no consistent standard in terms of uni- or bilateral neck dissection for patients with cN0 status. This may potentially lead to undertreatment in terms of insufficient primary and adjuvant therapy as e.g. postoperative radiation in most cases is being planned according to the pathological report. Even in pathologically confirmed cases of metastasis-free necks, bilateral ND improves adjuvant therapy as it is possible to reduce toxicity in these cases (Perkins et al., 2012; Spencer et al., 2014).

To avoid overtreatment with exaggerated surgical procedures and simultaneously achieve a maximum of oncological safety, there is an urgent need for preoperative risk assessment. This includes a rigorous validation of patients' risk for the development of cervical metastases which has been shown to be influenced by the stage and localization of the primary tumor (Moratin et al., 2019, 2020).

OSCCs located near the alveolar process of the mandible display an elevated risk of early bone infiltration. The specific rates of uni- or bilateral cervical metastases in dependence of T stage and sagittal localization of the primary tumor are crucial for therapy planning and the assessment of a patient's prognosis. Tumor removal including partial or segmental resection of the mandible is the established treatment (Brown et al., 2002; Rogers et al., 2004; Shaw et al., 2004; Mucke et al., 2011). Apart from achieving an optimal clinical outcome, preserving the patient's quality-of-life is a major goal in oncological therapy and mutilating surgical procedures should be limited to a minimum if possible. There are publications on clinical outcome depending on the extent of resection in patients with SCC located on the mandible (Brown et al., 2002; Wolff et al., 2004; Mucke et al., 2011). Nevertheless, the reported results and given recommendations are partly contradictory and there has not yet been a validation of different localizations within the mandible and their influence on metastasis and disease recurrence.

Therefore, the goal of this study was to investigate the incidence of regional metastases and patterns of disease recurrence in a cohort of patients with OSCC of the mandibular alveolar process in dependence of the sagittal tumor localization. Moreover, the prognostic impact of the extent of surgical therapy on clinical outcome was evaluated.

2. Material and methods

2.1. Data collection

The study was planned as a retrospective cohort study including patients with surgically treated squamous cell carcinoma of the mandible and was conducted in full accordance with ethical principles, including the World Medical Association Declaration of Helsinki (version 2002). Moreover, the protocol has been approved by the Ethics Committee of the Medical Faculty of the University of Heidelberg (Ethic vote: S-183/2015) and written informed consent was obtained from all patients. Inclusion criteria were the diagnosis of a squamous cell carcinoma of the mandibular gingiva with and without preoperative signs of osseous infiltration and primary surgical treatment in the Department of Oral and Cranio-Maxillofacial Surgery of Heidelberg University Hospital between the years 2010 and 2017. Adjuvant radiotherapy or additional platinum-based chemotherapy was administered in cases of advanced tumor stage, incomplete tumor resection, the existence of neck node metastases, or histopathological risk factors like lymphatic, perineural or vascular infiltration. Clinical and therapeutic follow-up were assessed retrospectively via SAP patient management research (SAP, Walldorf, Germany). Demographic, clinical and pathological data was collected including the sagittal localization of the primary tumor and patterns of cervical metastases with a special regard to the affected side. Patients were grouped according to sagittal tumor localization on the mandible. The intercanine part of the mandibula was defined as anterior, the region of the premolar teeth and the first molar was defined as intermediate and the retromolar region was defined as posterior (Fig. 1).

Survival data was collected and overall and progression-free survival was assessed in dependence of the factors mentioned before. Overall survival was defined as the period of time from initial surgical therapy until the date of death or the last follow-up (censored data). Progression-free survival was defined as the period of time from initial surgical therapy to local, regional or distant disease progression or last follow-up (censored data).

2.2. Statistical analysis

Microsoft Excel 2013 (Microsoft, Redmond, WA, USA) and SPSS Statistics® 18 (IBM, Armonk, NY, USA) were used for statistical analysis. Survival analysis was carried out using the Kaplan–Meier method and log-rank testing was used to estimate differences between the groups. Multivariate Cox regression analysis was used to evaluate the impact of relevant clinical and pathological features on overall and progression-free survival. A p-value of 0.05 or less was considered to indicate statistical significance.

3. Results

3.1. Patient cohort and therapy

120 patients met the inclusion criteria. 54 patients were female and 66 were male with a mean age of 67.6 ± 10.1 years. All patients received primary surgical treatment via tumor ablation including partial (n = 26, 21.7%) or complete segmental resection (94, 78.3%) of the mandible and uni- (n = 52, 43.3%) or bilateral (n = 68, 56.7%)

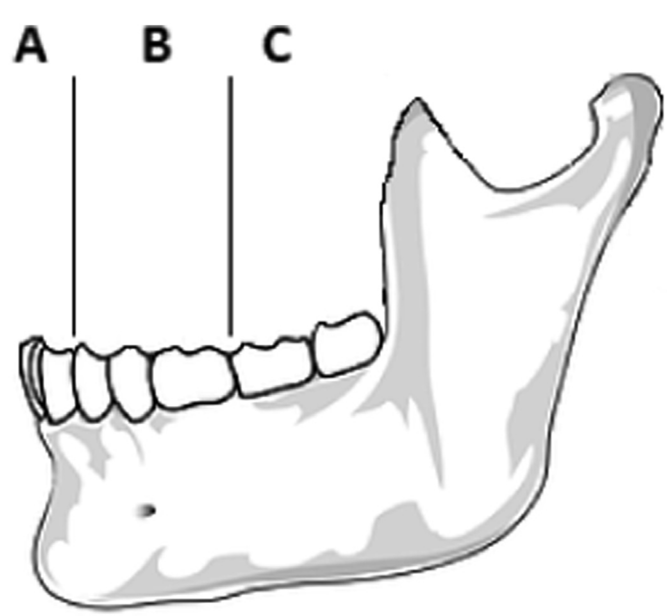

Fig. 1. Classification of sagittal localization within the mandible (A – anterior; B – intermediate; C – posterior).

neck dissection. 6 patients (5%) received a primary wound closure and 114 patients (95%) received a free flap reconstruction including 32 radial forearm flaps (28.1%), 38 antero-lateral thigh flaps (33.3%), 10 scapula flaps (8.8%), 4 DCIA flaps (3.5%) and 30 fibula flaps (26.3%).

18 patients (15%) received adjuvant radio-chemotherapy and 40 patients (33.3%) received postoperative radiotherapy alone. Table 1 provides an overview over demographic, clinical and pathological data of the investigated cohort.

3.2. Tumor localization and stadium

The majority of tumors in the investigated cohort were located in the intermediate (n = 49, 40.8%) or posterior (n = 55, 45.8%) parts of the mandible. 20 patients (16.7%) had T1 tumors, 25 patients (20.8%) had T2, 4 patients (3.3%) had T3 and 71 patients (59.2%) had T4 tumors. Fig. 2 displays the distribution of T stages in dependence of the sagittal tumor localization. A comparison of preoperative staging via CT scan and postoperative T stadium is depicted in Table 2. A relevant number of tumors showed pathological T4 stadium although preoperative imaging had not revealed infiltration of the mandible.

3.3. Incidence of regional metastases

The incidence of primary cervical metastases was 42.6%. Table 3 and Fig. 3 display incidence and distribution of primary cervical metastases in relation to sagittal tumor localization. While there was no significant difference in overall incidence of metastases in relation to tumor localization, there was a significant accumulation of contra-/bilateral metastases in tumors of the anterior part of the mandibula ($p < 0.001$). While there was an accumulation of T4

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

Parameter	Number of cases (%)
Gender	
Female	54 (45)
Male	66 (55)
Age	
<65 years	46 (38.3)
>65 years	74 (61.7)
T Stage	
T1	20 (16.7)
T2	25 (20.8)
T3	4 (3.3)
T4	71 (59.2)
Sagittal position	
Anterior (inter-canine)	16 (13.3)
Intermediate (canine to first molar)	49 (40.8)
Posterior (first molar to jaw angle)	55 (45.8)
N Stage	
0	69 (57.4)
1	17 (14.2)
2a	2 (1.7)
2b	20 (16.7)
2c	10 (8.3)
3	2 (1.7)
M Stage	
0	120 (100)
1	0
UICC Stadium	
1	14 (11.7)
2	17 (14.2)
3	9 (7.5)
4	80 (66.6)
Differentiation Grade	
1	6 (5)
2	87 (72.5)
3	21 (17.5)
Missing	6 (5)
R	
0	110 (91.7)
1	9 (7.5)
x	1 (0.8)
Risk Factors	
Tobacco Consumption	
Yes	56 (46.7)
No	64 (53.3)
Alcohol Consumption	
Yes	39 (32.5)
No	81 (67.5)
Disease Recurrence	
Local recurrence	15 (12.5)
Regional metastases	10 (8.3)
Distant metastases	6 (5)

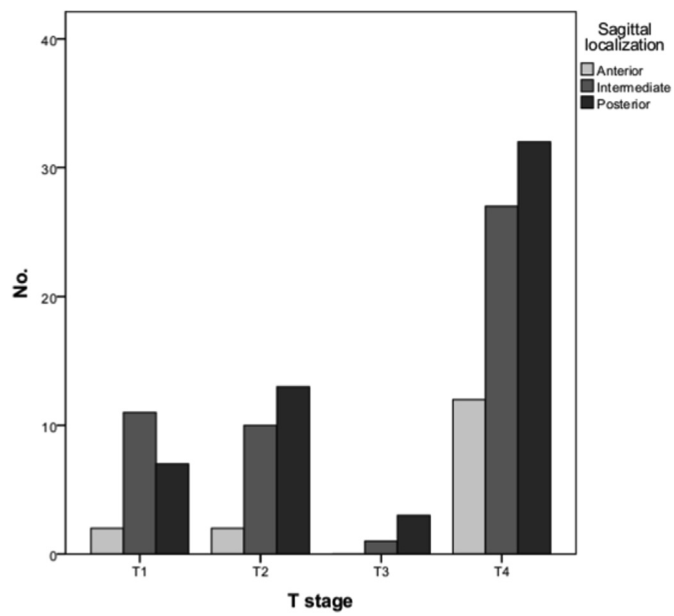

Fig. 2. Distribution of T stages in dependence of the sagittal localization of the primary tumors.

Table 2
Comparison of preoperative T stadium (cT) according to CT scan and pathological T stadium (pT).

	pT1	pT2	T3	T4
No tumor detectable	2 (33.3%)	0	1 (16.7%)	3 (50%)
cT1	6 (60%)	4 (40%)	0	0
cT2	9 (13.4%)	18 (26.9%)	3 (4.5%)	37 (55.2%)
cT3	1 (14.3%)	1 (14.3%)	0	5 (71.4%)
cT4	2 (6.7%)	2 (6.7%)	0	26 (86.6%)

Table 3
Incidence and localization of cervical metastases in relation to primary tumor position.

Tumor localization	N0	N+	p-Value
Anterior	9 (56.3%)	7 (43.8%)	
Intermediate	30 (61.2%)	19 (38.8%)	>0.05
posterior	31 (56.4%)	24 (43.6%)	
	N + uni-/ipsilateral	N + contra-/bilateral	p-Value
Anterior	1 (14.3%)	6 (85.7%)	
Intermediate	16 (84.2%)	3 (15.8%)	<0.001
posterior	24 (96%)	1 (4%)	

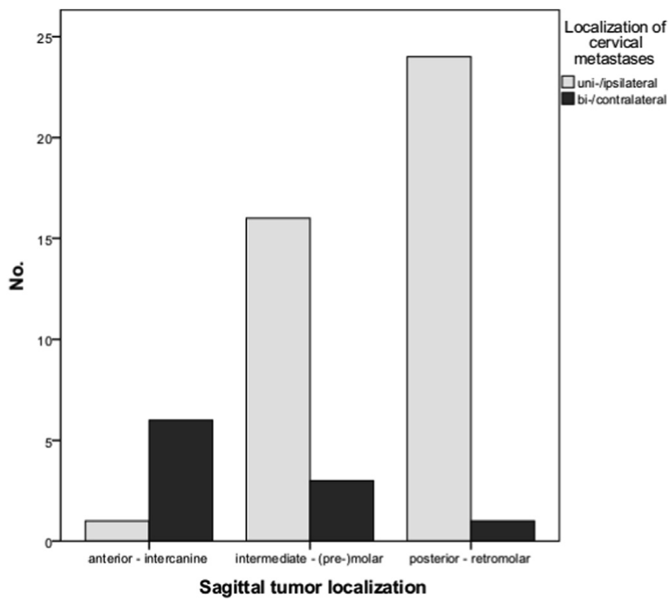

Fig. 3. Incidence of uni- or contra-/bilateral metastases in dependence of the sagittal localization of the primary tumor.

Table 4
Local disease recurrence in dependence of sagittal tumor localization.

	No recurrence (%)	Recurrence (%)	p-Value
Anterior	12 (75)	4 (25)	
Intermediate	41 (83.7)	8 (16.3)	p = 0.03
Posterior	52 (94.5)	3 (5.5)	

tumors in the anterior part of the mandible (75% of anterior tumors), we did not find a significant correlation of T stage and the development of neck node metastases ($r = 0.15$, $p = 0.11$).

3.4. Disease recurrence rates

Local disease recurrence was observed in 15 patients (12.5%). There was a significant accumulation of cases of disease recurrence in patients with tumors of the anterior or intermediate part of the mandible ($p = 0.03$). Table 4 gives an overview on cases of local disease recurrence in dependence of the sagittal tumor localization. There were no significant differences in local recurrence rates in dependence of applied adjuvant therapy ($p = 0.27$) or pathological T stage ($p = 0.62$).

There was an accumulation of cases of local disease recurrence in patients who only received partial resection of the mandible, although differences were not statistically significant ($p = 0.096$).

We included the safety margins in our analysis to determine potential correlations of margins with events of disease recurrence (see Table 1). The rate of local recurrences was higher in patients with R1 (3/9 patients; 33.3%) or close margin resection (2/15 patients; 13.3%) compared to patients with clear R0 resection (11/96 patients; 11.5%), but the differences were not statistically significant (chi-squared testing; p-Value: 0.18). Moreover the safety margins did not differ significantly between the sagittal tumor localizations (chi-squared testing; $p = 0.28$).

3.5. Survival analysis

Survival rates were analysed with regard to the sagittal localization of the primary tumor. While there was no significant impact of tumor localization on overall survival, progression-free survival was significantly lower in patients with tumors of the anterior and intermediate parts of the mandible compared to the posterior part ($p = 0.03$) Fig. 4 displays the survival plots for overall and progression-free survival in dependence of the sagittal tumor localization. Multivariate analysis confirmed the anterior position of the primary tumor as an independent prognostic factor for adverse clinical outcome regarding progression-free survival, while there was no significant impact on overall survival (Table 5).

There was no significant impact of tumor stage on overall or progression-free survival in the uni- or multivariate survival analysis. The existence of cervical metastases was significantly associated with worse overall and progression-free survival in uni- and multivariate survival analysis ($p < 0.001$).

4. Discussion

The purpose of this study was to evaluate different clinical and pathological factors affecting outcome in a cohort of patients with OSCCs located on the alveolar process of the mandible. Therefore, rates of metastases and disease recurrence in dependence of the localization of the primary tumors were investigated to facilitate therapy planning with regard to different strategies of surgical

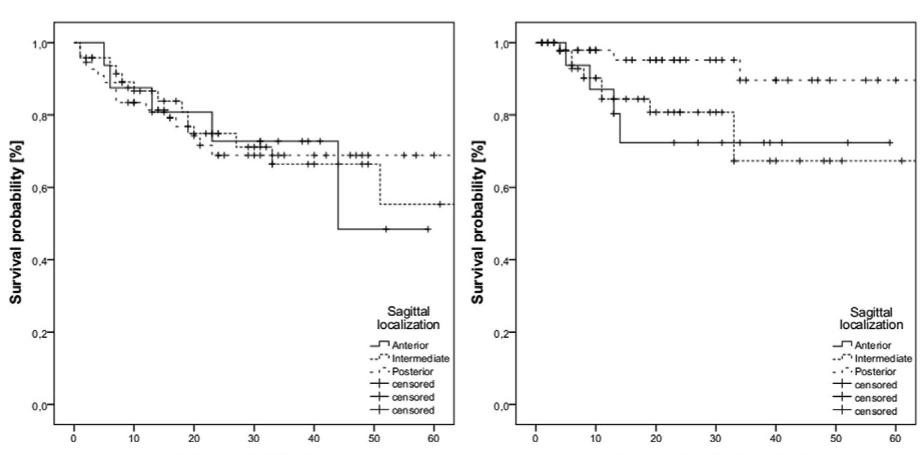

Fig. 4. Kaplan–Meier plots depicting overall survival (log-rank: $p = 0.75$) and progression-free survival ($p = 0.03$) in dependence of the sagittal localization of the primary tumor (anterior, intermediate, posterior).

Table 5
Multivariate analysis of overall and progression-free survival in dependence of sagittal tumor localization and relevant covariates.

Overall survival			Progression-free survival		
Characteristics	HR (95% CI)	p-Value	Characteristics	HR (95% CI)	p-Value
T stage	0.99 (0.7–1.3)	0.9	T stage	1.19 (0.9–1.6)	0.27
N+	4.05 (1.8–9.1)	<0.001	N+	3.76 (1.7–8.3)	<0.001
Sagittal localization	1.01 (0.7–1.4)	0.89	Sagittal localization	0.69 (0.5–1.0)	0.048
Partial vs. radical resection	1.64 (0.6–4.7)	0.36	Partial vs. radical resection	0.62 (0.3–1.6)	0.31
Adjuvant therapy	0.63 (0.3–1.4)	0.27	Adjuvant therapy	0.66 (0.3–1.5)	0.29

Table 6
Selection of publications on the surgical management of squamous cell carcinoma of the mandible.

Authors [Year]	No. of Patients	Conclusions
(Brown et al., 2002)	100	• Marginal mandibular resection possible in many cases without compromising clinical outcome • Involved margins mostly associated with soft tissue resection
(Wolff et al., 2004)	136	• No significant difference regarding recurrence and survival rates between segmental and marginal resection in mandibular SCC
(Mucke et al., 2011)	334	• No significant association of bone invasion with patients' survival • Significant association of extent of mandibular resection with survival ($p = 0.038$)
(Becker et al., 2012)	111	• Extent of surgical resection significantly impacts postoperative quality-of-life in patients with mandibular resection due to oral cancer • Quality-of-life is significantly worse in segmental resection compared to marginal resection
(Sproll et al., 2020)	259	• No significant survival differences between marginal and segmental resection in oral cancer • Bone invasion in 47% of patients after segmental resection and in 14% of patients after marginal resection

tumor resection and neck management. While surgical tumor removal whenever possible is the major treatment option for OSCC, the extent of the resection in terms of marginal or segmental mandibular resection and the extent of the neck dissection, especially in patients with early-stage tumors and clinically negative neck nodes, remains controversial. Advanced tumor size, existence of ipsilateral metastases and tumors crossing the midline are generally regarded as indications for a contralateral neck dissection (Kowalski et al., 1999; Koo et al., 2006).

While the tumor stage generally is used as a guideline to estimate patients' prognosis and the risk for the development of cervical metastases, the anatomical conditions of the alveolar process aggravate this strategy due to the proximity of any tumor to the mandibular bone. The fraction of T4 tumors was high in our cohort (59.2% of all tumors), while other subsites of the oral cavity, e.g. the tongue, display considerably lower rates of T4 tumors (Moratin et al., 2019, 2020). A high rate of bone infiltration may explain both high rates of primary metastases and a tendency to develop local disease recurrences (Jones et al., 1997). Li et al. described the negative impact of medullary mandibular infiltration in contrast to cortical infiltration for overall and disease-specific survival in OSCC (Li et al., 2017). As the differentiation between those patterns of invasion is hardly feasible preoperatively, a radical approach seems to be the safer way with regard to oncological outcome in cases where medullary involvement cannot securely be ruled out. In our analysis, a high discrepancy between preoperative imaging and pathological tumor stadium was revealed (see Table 2). This fact may partly be explained by cases of treatment delay between staging and surgical therapy that may have facilitated tumor growth. Nevertheless, preoperative imaging seems to be susceptible to inaccuracy, especially in the mandible where artefacts caused by dental metal aggravate the appraisal.

There is an ongoing discussion about the extent of mandibular resection (marginal or segmental) and its influence on postoperative quality-of-life and clinical outcome in terms of oncological safety with various authors advocating either radical or more conservative approaches (Table 6) (Brown et al., 2002; Rogers et al., 2004; Wolff et al., 2004; Mucke et al., 2011; Becker et al., 2012; Sproll et al., 2020). Our data indicates a higher risk of local tumor recurrence in case of marginal resection of the mandible, although the results were not significant. This may possibly be explained by the small fraction of patients receiving marginal resection of the mandible in our cohort ($n = 26$, 21.7%). Yet, Qiu et al. report similar results from a cohort of 82 patients with SCC of the mandible (Qiu et al., 2018). In our analysis, there was a tendency towards a higher risk for local recurrences in patients with close margin resections compared to clear R0 ($\geq$5 mm) resection, but the difference was not statistically significant. Again, as intraoperative assessment of bone margins is not yet possible in a standardized manner, a wider resection may result in better oncological outcome in many cases. Still, as already mentioned, SCC of the mandible requires a special balancing of oncological safety and postoperative quality-of-life. While the initial cut-down on patients' quality-of-life after segmental mandibular resection may be severe compared to a less radical approach, the elevated risk of disease recurrence seems to be an inadequate trade-off, particularly regarding the possibility of primary mandibular reconstruction (Rogers et al., 2004; Sproll et al., 2020).

In the investigated cohort, the overall rate of primary cervical metastases was 41.7% which is high in comparison to other subsites of the oral cavity (Berger et al., 2015; Moratin et al., 2019, 2020). Similar rates of metastases have been reported in other studies on mandibular SCC (Mucke et al., 2011; Safi et al., 2018). While there was no significant difference in the rates of metastases in relation to sagittal tumor localization, metastases of SCC of the anterior part of the mandible were bilateral in 86% of the cases, whereas they were contra-/bilateral in 15.8% in tumors of the intermediate part and 4% in tumors of the posterior part of the mandible. This significant accumulation of bilateral metastases illustrates the urgent need for bilateral neck dissection in anterior tumors. While elective neck dissection in general often is regarded as diagnostic intervention, studies of patients with early-stage OSCC located on the tongue have shown relevant rates of contralateral metastases and subsequently contralateral regional recurrence (Ganly et al. 2012, 2013).

As infiltration of the alveolar bone in many cases cannot securely be ruled out preoperatively and is excluded solely by histopathological examination, this recommendation applies for all tumors irrespective of clinical staging. In our analysis, 7 tumors (9.9%) classified as T4 in histopathological examination were either classified as "no cancer detectable" or "not assessable" in preoperative CT imaging. Tumors of the intermediate part of the mandible exhibited a considerably lower, yet relevant risk of contra-/bilateral metastases (15.8%). In these cases, the authors recommend bilateral neck dissection as the removal of metastases and a well-founded adjuvant therapy counterbalance the risks and additional surgery time of a bilateral neck dissection. Only one patient (4%) with a T4 tumor located in the posterior part of the mandible exhibited contralateral metastases in our observation. While contralateral metastases still may occur in posteriorly localized cancers, incidence rates seem very low and unilateral neck dissection seems to be appropriate in patients with clinically negative neck status.

5. Conclusion

SCCs of the mandibular alveolar process display high rates of osseous infiltration and cervical metastases. The rate of contralateral cervical metastases is highest in tumors localized in the anterior part of the mandible and unlikely in tumors of the posterior part. Therefore, we recommend elective bilateral neck dissection in patients with OSCC of the anterior and intermediate part of the mandible irrespective of clinical tumor staging to allow for adequate risk assessment, planning of adjuvant therapy and subsequently to achieve an optimal clinical outcome for affected patients.

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Declaration of Competing Interest

All authors declare that they have no conflict of interest.

Author Contributions

Julius Moratin: Conceptualization, Methodology, Data curation, Writing- Original draft preparation, Dominik Horn: Data curation, Writing- Reviewing and Editing, Karl Metzger: Software, Validation, Visualization, Investigation, Oliver Ristow: Methodology, Writing- Reviewing and Editing, Michael Engel: Methodology, Investigation, Writing- Reviewing and Editing, Jürgen Hoffmann: Supervision, Writing- Reviewing and Editing, Kolja Freier: Conceptualization, Methodology, Writing- Reviewing and Editing, Christian Freudlsperger: Conceptualization, Supervision, Writing-Reviewing and Editing.

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