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REVIEW

Anatomical locations in the oral cavity where surgical resections of oral squamous cell carcinomas are associated with a close or positive margin—a retrospective study

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Abstract

Objectives This study aimed to identify anatomical areas where resections of oral squamous cell carcinomas (OSCC) are significantly associated with close or positive margins.

Materials and methods This retrospective study included 330 patients with a primary OSCC from 2010 to 2015. Patient and tumour data were categorised into three groups by R-status (R0 [clear], ≥ 5 mm, 185 patients [56.06%]; R1 [positive], < 1 mm, 24 patients [7.27%]; and R0 [close], 1–5 mm, 121 patients [36.67%]).

Results Areas where resections were significantly associated with close or positive margins were the hard palate ($p < 0.001$), buccal mucosa ($p = 0.03$), floor of the mouth ($p = 0.004$), lower alveolar ridge ($p = 0.01$), retromolar triangle ($p = 0.005$), and dorsal tongue ($p = 0.02$).

Conclusions Anatomical areas were identified in the oral cavity where it is challenging to resect OSCCs with an adequate safety margin.

Clinical relevance These results may enable surgeons to achieve a postulated safe distance during tumour resection, leading to a survival benefit for patients.

Keywords Oral squamous cell carcinoma · Resection margin · R-status · Anatomical areas · Safety distance

Introduction

Oral squamous cell carcinoma (OSCC) is the most common malignant tumour of the head and neck and its incidence has increased over the past years [1, 2]. The primary treatment for OSCC is usually surgical resection [3]. The aim of surgery is a complete resection of the tumour with a defined safety distance in order to reduce long-term risk of recurrence [4]. A tumour-free resection margin with a safety distance is the most important prognostic factor for a patient with an OSCC [5, 6]. Positive or close margins significantly increase the risk of recurrence of the tumour after surgery [7, 8].

Regarding OSCCs, there is no uniform consensus definition of a “safe” margin [9]. The usual consensus for the surgeon is to achieve a macroscopic tumour-free margin of at least 1 cm around the tumour in three dimensions, depending on the invasive patterns of the tumour [10].

Pathologists have defined a final negative margin of at least 5 mm of normal tissue, without carcinoma or carcinoma in situ, between the edge of the tumour and the resection margin because of tissue shrinkage through formalin fixation and slide preparation [10–13]. The resection status not only influences long-term survival, but is also decisive for selecting the right adjuvant therapy for patients with tumours [14–16]. Despite a paucity of consistent evidence about the relationship between safety distance and local recurrence, close or positive margins are one of the key determinants of the need for adjuvant therapy [17].

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Negative margins are achieved in only 50 to 80% of patients with head and neck tumours treated at cancer centres due to the anatomical complexity and close relationship to vitally important structures in the head and neck region [18, 19]. Furthermore, an overview of the oral cavity is limited, making a surgical approach and resection of the tumour difficult. However, there is no consensus regarding the best intraoperative method for assessing margins [20].

This retrospective study was performed to identify anatomical localisations in the oral cavity where surgical resections of OSCC are associated with a close or positive tumour margin. These results may provide surgeons with an intraoperative guidance to reach a better safety distance, resulting in a survival benefit for the patient.

Materials and methods

This retrospective study included 330 patients with a primary OSCC treated at the Department of Oral and Maxillofacial Surgery, University of Erlangen-Nürnberg, between 2010 and 2015. All patients underwent primary resection of the OSCC. Patient and tumour data were collected (gender, age, anatomical location, TNM category, tumour grade, number, and location of margin tissue samples). Data were generated from the Comprehensive Cancer Centre of the University of Erlangen-Nürnberg, Germany.

The 330 patients were treated via a conventional surgical approach.

All of the operations were carried out by five consultant surgeons at the Department of Oral and Maxillofacial Surgery, University of Erlangen-Nürnberg.

Patients with tumour types other than OSCC, treatment for tumour relapse, carcinoma in situ without an invasive tumour component, patients for whom therapy was considered non curative, and those without consistent follow-up data were excluded from this study.

All histopathological types of OSCC were included [21].

For the description of the tissue margins of the OSCC, we used the definition of the United Kingdom Royal College of Pathologists [22]. It categorises a safety distance of 1–5 mm as close, and > 5 mm as clear. A margin with tumour cells is defined as positive (R1). We sorted all patients with positive or close margins into one group to identify critical anatomical areas of the oral cavity for tumour resection. This group was compared with patients who had a clear margin (Table 1). Additionally, the influence of the T category, tumour grade, lymph node status, and gender was evaluated (Table 2).

Areas of the oral cavity were categorised as defined by the American Joint Committee on Cancer: buccal mucosa, floor of the mouth, hard palate, lip, upper alveolar ridge, lower alveolar ridge, retromolar triangle, anterior two thirds of the tongue, and rest of the tongue [23]. Additionally, we investigated the pillars. This location belongs to the oropharynx, but was rated as interesting for the results.

Table 1 Distribution of the resection margin status in relation to the anatomical region

Localisation	R0 (%)	Close (%)	Positive (R1) (%)
Upper alveolar ridge	13 (3.94)	1 (0.30)	0
Buccal mucosa	19 (5.75)	10 (3.03)	0
FOM	49 (14.84)	44 (13.33)	4 (1.21)
Hard palate	1 (0.30)	5 (1.51)	5 (1.51)
Lip	14 (4.24)	4 (1.21)	1 (0.30)
Lower alveolar ridge	26 (7.87)	21 (6.36)	5 (1.51)
Pillars	8 (2.42)	2 (0.60)	0
RMT	14 (4.24)	9 (2.72)	7 (2.12)
Tongue	41 (12.42)	25 (7.57)	2 (0.60)

FOM floor of the mouth, *RMT* retromolar triangle

Statistical analysis was performed using the statistical programming language R. The relationship between clinicopathologic factors for OSCC and positive resection margins was examined with a penalised logistic regression model. $P < 0.05$ [*] was considered statistically significant.

Results

The patient collective consisted of 212 male and 118 female patients with an average age of 62.18 years. Most of the patients had a tumour ≤ 2 cm (T1) (135 patients [40.91%]), 104 patients had a T2 tumour (31.52%), 23 patients had a T3 tumour (6.97%), and 68 patients had a T4 tumour (20.61%) (Table 3). The majority of patients had a tumour with a G2 grade (208 patients [63.03%]), 49 patients had a G1 grade (14.85%), and 73 patients had a G3 grade (22.12%). A total of 212 patients (64.25%) had a negative lymph node status (pN0) and 118 patients (35.75%) had a positive lymph node status (pN+).

Table 2 Distribution of the T category, lymph node status, and tumour grade of the patients

	Patients, *n* (%)
T stage	
T1	135 (40.91)
T2	104 (31.52)
T3	23 (6.97)
T4	68 (20.61)
Lymph nodes	
pN+	118 (35.76)
pN0	212 (64.24)
Tumour grade	
G1	49 (14.85)
G2	208 (63.03)
G3	73 (22.12)

Table 3 Distribution of T category and gender

T stage	Males (%)	Females (%)
T1	77 (23.33)	58 (17.57)
T2	70 (21.21)	34 (10.30)
T3	19 (5.75)	4 (1.21)
T4	46 (13.93)	22 (6.67)

An average of 9.57 intraoperative specimens per patient was taken by the surgeons and submitted as frozen sections.

We sorted all patients with positive or close margins into one group. A total of 145 patients (43.94%) had a close or positive margin, and 155 patients (56.06%) had a clear margin.

The reference in the regression model was the upper alveolar ridge since this location showed the best results for a clear margin after tumour resection. That means, this region showed the lowest risk and a comparison with this reference allowed us to examine the significance of the potentially higher risks at all other locations.

The small frequency of observations with specific localisations due to the small number of patients resulted in rather wide confidence intervals, even when odds ratios (ORs) were significantly larger than 1 ($p < 0.05$). Therefore, an interpretation of the ORs for localisations is questionable and was omitted (Table 4). The localisations that significantly increased the risk compared to those of the upper alveolar ridge were the buccal mucosa ($p = 0.0341$), floor of the mouth ($p = 0.0038$), lower alveolar ridge ($p = 0.01$), retromolar triangle ($p = 0.0051$), and rest of the tongue ($p = 0.0185$).

Table 4 Results of gender, T category, tumour grade, and tumour localisation. Significant results are marked (*$p < 0.05$)

	Odds ratio (95% CI)	*p*
Intercept	0.033 (0.003–0.177)	< 0.0001*
Gender (reference: males)		
Women	0.610 (0.363–1.018)	0.0584
Tumour (reference: T1)		
T2	2.307 (1.324–4.060)	0.0031*
T3	2.808 (1.116–7.341)	0.0282*
T4	2.699 (1.356–5.469)	0.0046*
Tumour grade (reference: G1)		
G2	2.466 (1.142–5.665)	0.021*
G3	2.656 (1.110–6.671)	0.028*
Subsite (reference: upper alveolar ridge)		
Buccal mucosa	6.334 (1.135–67.251)	0.0341*
FOM	8.582 (1.858–83.088)	0.0038*
Hard palate	95.999 (10.468–1843.323)	< 0.001*
Lip	6.429 (0.990–73.038)	0.0513
Lower alveolar ridge	7.364 (1.538–72.296)	0.01*
Pillars	2.599 (0.278–33.638)	0.3989
RMT	9.514 (1.853–96.849)	0.0051*
Tongue anterior	5.467 (0.316–102.370)	0.2271
Rest of the tongue	6.398 (1.322–63.481)	0.0185*

CI, confidence interval; *FOM*, floor of the mouth; *RMT*, retromolar triangle

The hard palate was also statistically significant for having a positive or close resection margin after tumour resection, with an OR significantly larger than 1 ($p < 0.001$). However, the low frequency of R0 patients with hard palate tumours resulted in a very unstable estimation of the regression coefficient, leading to a very wide confidence interval and a hardly interpretable OR.

The lip ($p = 0.0513$), pillars ($p = 0.3989$), and anterior tongue ($p = 0.2271$) showed no statistically significant results (Table 4).

A higher T category was significantly associated with a higher risk of a positive or close margins. T1 was the reference category in the logistic regression model; all other categories were significantly associated with an increased risk of a positive or close margin: T2 (OR = 2.31, $p = 0.0031$*), T3 (OR = 2.81, $p = 0.0282$), and T4 (OR = 2.70, $p = 0.0046$). A higher grade of the tumour had a negative effect on achieving a clear safety distance; G2 (OR = 2.47, $p = 0.021$) and G3 (OR = 2.66, $p = 0.028$) were significantly associated with an increased risk compared to G1.

Gender had no significant influence on achieving a clear safety margin ($p = 0.0584$). Chi-square test showed that T categories did not differ significantly between women and men ($p = 0.07$).

Discussion

A tumour-free margin is the most important prognostic factor in patients with OSCC. Thus, we investigated if there are regions of the oral cavity that are more at risk for having a positive or close resection margin after surgical resection.

The hard palate was significantly associated with a positive or close resection margin after tumour resection. This localisation had, on average, the most positive margins of all localisations after tumour resection. A possible explanation is an early invasion of the tumour cells into local bone due to the thin thickness of the soft tissue. Histopathological assessment of the resection margins in specimens that include bone is complex and frozen sections are not possible. Hence, when bone resection is required, the frozen section analysis is determined by analysing the mucosa of the soft tissue overlying the bone. The delay associated with the demineralisation and the consequent deterioration in the quality of the soft tissue elements are disadvantages of this approach.

Our data show that there is a significant risk of a positive margin in the retromolar triangular site during tumour resection. It is suggested that limitations in access and visibility during resection make it difficult to achieve a full overview during surgery [24].

A higher risk for not achieving a tumour-free resection margin in the buccal mucosa was statistically significant. This is an interesting finding because of the limited anatomical restriction of vitally important anatomical structures and good visibility in this area. A further possible explanation includes the desire to preserve the facial skin unless frozen sections reveal positive margins or macroscopic infiltration into the dermis is visible. Furthermore, the natural laxity of a split-thickness cheek resection, which leads to excessive tissue shrinkage following delivery of the resection specimen from the patient prior to and during fixation, may play a crucial role. The amount of shrinkage has been reported to depend on the site, and shrinkage can reduce the width of the surgical margin by as much as 46% [24–28].

The floor of the mouth also showed significant results for having a positive (R1) or close resection margin. There are anatomical characteristics that can promote vertical tumour growth. Alveolar tissue, the sublingual gland, or muscle provides little anatomical resistance to tumour growth [24, 29]. Furthermore, the hypoglossal and lingual nerves are usually preserved unless there is a neural invasion of the tumour. Excision of the tongue and floor of the mouth may further endanger the lingual nerve, making resection of the tumour surgically more challenging and increasing the risk for a positive margin [29, 30].

The rest of the tongue (excluding the anterior tongue) was significantly associated with a positive or close margin compared with the anterior region of the tongue (anterior tongue, $p = 0.227$). One factor contributing to this poor survival might be the difficulty in examining this region. As a result, many lesions are not discovered until they have reached an advanced stage [31].

Resection of this tumour site is associated with functional problems, so it seems logical to prevent damage to important structures and to accept a close resection [32]. Other authors also had similar results from an investigation of resection margins around tumours of the posterior tongue. The tongue base has a large volume margin, with a propensity for occult tumour extension [33].

Close or positive margins were more likely to be posterior than anterior and lateral than medial. Furthermore, close or positive mucosal margins are rare in contrast to the deep soft tissue margins. Anatomical restraints are more likely to affect the deep margins since it is difficult to “visualise” particular growth patterns and other features of the deep advancing tumour front, both pre- and intraoperatively, since those characteristics are only evident with microscopy [24].

Wider resection margins in the early stages are recommended because of the poor survival and recurrence rate at this tumour site [34, 35]. Furthermore, anatomical characteristics and preservation by the surgeon of important structures involved in swallowing, breathing, or speech or that affect physical appearance could also be a prognostic factor of the resection. An aggressive treatment is effective, but can significantly impact the patient’s health-related quality of life [36].

The degree of differentiation showed a significant association between the T category (T2, T3, T4), tumour grade (G2, G3), and positive margins. This is not surprising because a larger tumour with more degenerated tissue, which has an invasive pattern and islands of tumour cells, may invade outside of the main tumour mass.The resection of advanced stage OSCC is markedly difficult because of the potential and considerable limitations in function and aesthetics of the outcome. If the tumour has spread to the paravertebral muscles, invaded the skull base, or encased or invaded the carotid artery, a negative surgical margin may be difficult or impossible to achieve [32].

DiNardo and colleagues found that use of intraoperative controlled frozen section specimens was more reliable in patients with a lower T stage than in patients with T3 and T4 tumours [26, 33]. Frozen section results have high specificity (100%), but only moderate sensitivity (60%). Therefore, a negative frozen section margin does not ensure a tumour-free margin in the final specimen, but a positive frozen section margin uniformly reflects a positive permanent margin [33].

Better control of the resection margin was investigated in a study using Mohs total frozen section margins. Compared to conventional frozen section techniques, they showed a decrease in loco-regional recurrences by analysing nearly 100% of the margins. Positive margins were often situated on the deeper side, which might be specific for Mohs margins; however, like conventional frozen sections, it is not possible to perform a bone margin control [37].

Gender had no significant effect on positive margin results. We analysed if there was a difference in the T category of female and male patients in our collective. However, the Fischer test showed no significant Chi-Quadrat value for differences in classification of T categories. These findings are supported by other studies showing that gender is not a prognostic factor, and that there is no difference between early and late tumour stages in women compared to men. [38, 39]

A problem with the resection of tumours is the determination of the resection margins, since the extension of the tumour tissue during the resection cannot be clinically identified. Intraoperative fluorescence imaging with cetuximab conjugated to IRDye 800 successfully showed good contrast between tumour and normal tissue. This study was a first-in-human, phase I study showing promising results [40]. Still, this method must be optimised for the oral cavity, which is limited by its anatomy, complex topography, and varied geography when imaged; hence, the fluorescent signal varies as a function of distance [41].

Transoral robotic surgery is another interesting possibility for improving tumour-free resection margins in limited spaces, giving the surgeon deeper access.

Especially in the anatomical subsites of the oropharynx, like the soft palate or the base of the tongue, TORS is of particular interest for the ability to treat OSCC [42].

The technique is minimally invasive and has less functional compromise, but it is technically challenging, and surgeons reported a loss of tactile sensation [43].

This study identified localisations with a higher risk of a close or positive margin after surgical treatment, which may improve surgeons' ability to achieve a higher rate of clear margins in those restricted areas. Because of the complexity of factors influencing the surgical procedure in the oral cavity, surgeons should be sensitive to these localisations. Although there is a need to preserve important structures, each millimetre of additional margin improves the survival benefit of patients with an OSCC [9, 44].

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent For this type of study, formal consent is not required.

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