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Original Research Article

Oral Cavity Squamous Cell Carcinoma: Impact of Clear Margin Distance on Locoregional Control in Patients Undergoing Postoperative Radiotherapy

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Abstract

Introduction: Postoperative radiotherapy can improve locoregional control (LC) in oral cavity squamous cell carcinoma (OCSCC) patients with positive resection margins. The present study aimed to evaluate the impact of surgical margin size on LC in this patient population. **Methods:** This retrospective study involved 162 patients with OCSCC who underwent postoperative radiotherapy between 2000 and 2020 at the Department of Radiation Oncology, University Hospital Heidelberg and the German Cancer Research Center. The study aimed to determine the impact of different resection margins on LC, as well as overall survival (OS), progression-free survival (PFS), and treatment-related toxicity (CTCAE 4.03). **Results:** Seventy-seven patients (47.5%) had involved (<1 mm) margins, 22 patients (13.6%) close (≤5 mm) margins, and 63 patients (38.9%) clear (>5 mm) margins. A surgical margin ≤ 5 mm was a significant predictor for worse LC (HR 2.6, 95% CI 1.2, 6.1), but not for OS (HR 1.2, CI 0.7, 1.9) or PFS (HR 1.2, 0.7, 2.0). **Conclusion:** Patients who have narrow resection margins (1-5 mm) experience poor local control and should receive postoperative radiotherapy. It is necessary to conduct further prospective studies to determine whether a narrower margin window could be achieved to better determine the appropriate indication for adjuvant radiotherapy.

Keywords

oral cancer, radiotherapy, postoperative, prognostic factors, toxicity, margin

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Introduction

Oral cancer affects various parts of the mouth, including the oral tongue, floor of the mouth, and buccal mucosa. It is the eighth most common cancer globally,[1] with an incidence of four cases per 100,000 people in 2018.[2] Treatment for oral cavity squamous cell carcinoma (OCSCC) requires an interdisciplinary team, and surgery is the recommended approach. Radiotherapy is frequently used to assess postoperative cases and in situations where there are risk factors such as positive resection margins, extracapsular spread (ECS), or lymph node involvement. This helps to enhance locoregional control (LC), overall survival (OS), and progression-free survival (PFS).[3] The EORTC #22931 and RTOC #9501 trials have shown that patients with head and neck tumors (including OCSCC) who have positive

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margins and/or ENE will benefit from chemoradiotherapy instead of radiotherapy alone.[4]

Several studies have demonstrated that close margin resection (<5 mm) and advanced tumor stages without clear margins result in worse LC rates.[5-7]

There is a lack of information and interpretation of close margin status and its implication for prognostic significance. Specific values are missing to differentiate clear, close, and involved margins.[8-11] The Royal College of Pathologists has issued guidelines for the histological diagnosis of resection margins.[10,11] According to these guidelines, surgical margins less than 1 mm are considered "involved," 1 to 5 mm are considered "close," and greater than 5 mm are considered "clear." However, the definition of a close margin has not been widely accepted as an indicator for postoperative radiotherapy.[12-15] We conducted a retrospective analysis to examine the clinical significance of postoperative radiotherapy in patients with clear margins. The analysis examined the impact of margin distance on LC.

Materials and Methods

Patient Selection

This retrospective study identified all consecutive patients who received postoperative radiotherapy for OCSCC at the Department of Radiation Oncology at the University Hospital Heidelberg between 2000 and 2020. The ethical review board approved the analysis (S-421/2015), and the institutional review board waived the requirement for written informed consent from each individual. The study collected medical and radiotherapy data and patient information. The reporting of this study adheres to STROBE guidelines. Inclusion criteria for our analysis included: patients who underwent surgery at our institution, patients who underwent radiotherapy maximum time 12 weeks after surgery, any T stage, any N stage (local neck lymph nodes), any gender or age, with curative intention. Exclusion criteria included patients who had metastatic disease (includes systemic lymphatic spread which refers to spread beyond the cervical lymph nodes), patients with previous or simultaneous malignancies or patients with incomplete data. The final patient cohort for analysis comprised 162 patients.

There were 80.9% male and 19.1% female patients with a median age at diagnosis of 60 years. Detailed patient characteristics are shown in Table 1.

Table 1. Patient Characteristics

Characteristic	Number of patients (percentage)
Gender	
Male	131 (80.9%)
Female	31 (19.1%)
Age, years	
Median (range)	60 years (32-84 years)
T-stage	
T1	43 (26.5%)
T2	86 (53.1%)
T3	17 (10.5%)
T4	16 (9.9%)
N-stage	
N0	48 (29.6%)
N+	114 (70.4%)
Grading	
1	4 (2.5%)
2	98 (59.9%)
3	60 (37.1%)
ECS	
Positive	37 (22.8%)
Negative	125(77.2%)
Lymphatic invasion	
Positive	26 (16.0%)
Negative	136 (84.0%)
Vascular invasion	
Positive	31 (19.2%)
Negative	131 (80.8%)
Perineural invasion	
Positive	11 (6.8%)
Negative	151 (93.2%)
Resection margin	
<1 mm	77 (47.5%)
1-5 mm	22 (13.6%)
>5 mm	63 (38.9%)
RT technique	
3D-CRT	56 (34.6%)
IMRT	106 (65.4%)
RT-dose	
<60 Gy	22 (13.6%)
≥60 Gy	140 (86.4%)

Treatment, Follow-Up, and Toxicity

Surgery was done in the whole patient collective. Pathologic margin evaluation was done from pathological institute Heidelberg after surgery or from external pathological institute where the patients surgery was. The examination of the entire specimen was done grossly and microscopically to comment whether the tumor is completely resected or not. Of 162 patients, 77 patients (47.5%) had involved (<1 mm) margins, 22 patients (13.6%) close (1-5 mm) margins, and 63 patients (38.9%) clear (>5 mm) margins (see Table 1).

Radiation was performed with photons either as 3D-planned, image-guided IMRT (TomoTherapy®, Accuray, Sunnyvale, CA, USA) or VMAT (Elekta, Sweden). Furthermore, the therapy was fractionated over 5 days a week, consisting of a main plan and a boost plan. The median total dose of the main schedule was 54 Gy (single dose 2 Gy) and the median total dose of 12 Gy (single dose 2 Gy) for the boost schedule, resulting in a median cumulative dose of 66 Gy. Information to deep of invasion could not be collected in medical reports in this collective. For follow-up care, patients received a CT scan and clinical examinations by an ENT specialist every 3 months during the first year. Check-ups were then carried out every six months and annually in the following years. Toxicity was classified according to the Common Terminology Criteria for

Adverse Events v4.03 (CTCAE). All patients in this group received chemotherapy with cisplatin.

Statistical analysis and outcome evaluation

OS, PFS, and LC were calculated using Kaplan–Meier analysis. OS, PFS, and LC were calculated from the start of radiotherapy (RT) until death or the date of last follow-up, tumor progression, or death, or the date of last follow-up, whichever occurred first, or until locoregional tumor progression at the primary tumor site. Patients who were lost to follow-up were censored. IBM SPSS software version 24 was used to calculate Kaplan–Meier estimates. The log-rank test was used to compare subgroups. Statistical significance was considered for p-values of 0.05 or less. Odds ratios were presented with 95% confidence intervals. The study received ethical approval from the local ethics committee at University Hospital Heidelberg (S-421/2015). We followed relevant Equator guidelines in this study.

Results

Treatment Outcome

Follow-up time was 59 months (range, 14-227 months). There were 89 patients (54.9%) still alive, 73 patients (45.1%) had died: 14 (8.6%) patients died due to pulmonary infection, cardiac disease or carcinoma not associated with OCSCC, and the remaining 59 patients (36.3%) died due to disease progression.

Tumor progression was observed in 70 patients (43.2%), locoregional recurrence in 34 patients (21.0%), and distant metastases in 24 patients (14.8%). Out of the total number of patients, only 12 (7.4%) experienced both locoregional tumor progression and distant metastases.

The median PFS was 44.5 months (range, 13.9-227.7 months), median LC was 59.4 months (range, 13.2-227.7 months) and median OS since RT was 58.6 months (range, 14.4-227.7 months). The 5- and 10-year Kaplan–Meier estimates for OS (standard error 8.3, 95% CI 113.2-145.9), PFS (standard error 8.6, 95% CI 104.1-137.7), and LC (standard error 8.4, 95% CI 155.1-188.1) were 69.2%, 70.8%, and 84,5%, and 50.3%, 49,7%, and 73,6% respectively. Distant metastases developed after a median time of 75.9 months (range: 13-230 months). Patients with resection margins >5 mm had a 5-year OS rate of 59.7%, compared to 59.9% for those with margins <5 mm (HR 1.2, 95% CI 0.7-1.9, $p = 0.13$). The 5-year local control rate was 79.9% for patients with margins >5 mm and 76.7% for those with margins <5 mm (HR 2.6, 95% CI 1.2-6.1, $p = 0.04$) (Figure 1).

Univariate analysis was performed using the following variables: margin status (with cutoffs of (<1 mm) margins, 1-5 mm margins, >5 mm margins), T-stage, N-stage, ECS, age, gender, RT-dose.

A resection margin of <5 mm was found to be a predictor of poor LC, with a more than 2-fold increase in the risk of recurrence ($p = 0.022$, HR 2.6, 95% CI 1.2, 6.1). People aged younger than 60 years, female gender, total dose >60Gy, ECS +, T3/4-stage and N+ (local lymph nodes) did not show any correlation with LC, PFS, or OS. A surgical margin of <5 mm was a significant predictor of worse local control (HR 2.6, 95% CI 1.2, 6.1) (Figure 1), but not for OS (HR 1.2, CI 0.7, 1.9) or PFS (HR 1.2, 0.7, 2.0). Table 2 shows that there was no significant difference in terms of OS, PFS, or local control among the margin cut-offs using 1 mm intervals. After performing multivariate analyses with all variables of Table 2 for LC there was a margin of <5 mm (HR 2.3, 95% CI 1.1, 5.9, $p = 0.031$) associated as an risk factor for worse LC.

Treatment Toxicity

The most common acute complications related to radiotherapy were oral mucositis (85.8%), dermatitis (72.2%), dysphagia (72.3%), xerostomia (39.5%), and ageusia (66.0%). No deaths were caused by the treatment. Late complications related to radiotherapy included xerostomia (64.2%), trismus (26.5%), and osteoradionecrosis (9.3%). Seventy patients (43.2%) required supportive nutrition via a percutaneous gastric tube (PEG) during radiotherapy.

Discussion

Radiotherapy has an established role as adjuvant treatment of patients with incompletely resected cancer of the oral cavity. The primary purpose of the present study was to examine the clinical significance of postoperative radiotherapy in patients with clear margins and identify a margin cut-off in patients with OCSCC where postoperative radiotherapy is required or not. The risk of worse LC in patients with uninvolved, but close surgical margins has been recognized. Clear margins refer to invasive carcinoma more than 5 mm away, close margins if within 1 to 5 mm from invasive disease, and involved margins if <1 mm from invasive disease.[7] There are numerous studies demonstrating an improved outcome with margins >5 mm, but there is a paucity of evidence using resection margin cutoffs of 4, 3, 2, and 1 mm.[10,16,17]

Zelefsky et al reported about overall control rates with close margins between 71% and 79%, respectively. However, there was no significant difference in patients with incomplete versus complete resection margins in LC rates.[7] Gokavarapu et al detected no significant difference in locoregional recurrence ($p = 0.8$) depending on margin status.[18]

Postoperative radiotherapy (RT) efficacy for patients with close margins compared to surgery alone is not well-documented. Common guidelines recommend safety margins of more than 5 mm from the tumor in the anterior region. Tasche et al conducted a retrospective study that showed invasive tumors within 1 mm of the permanent specimen margin are associated with a significantly higher locoregional recurrence rate and the need for additional treatment.[19]

The rationale for postoperative radiotherapy is shown in several studies who showed locoregional failure rates of

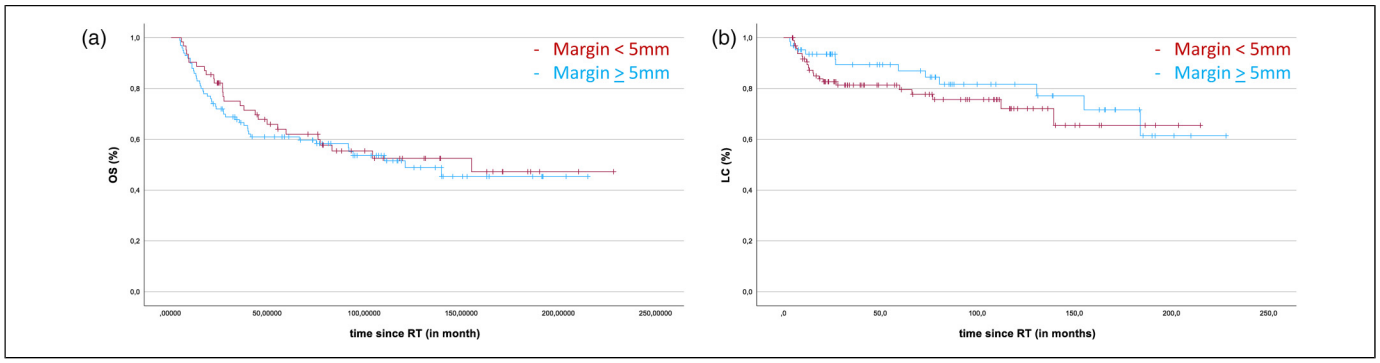


Figure 1. (a) 5-Year OS rate for patients with resection margins > 5 mm was 59.7% (red) and 59.9% for patients with margins ≤ 5 mm (HR 1.2, 95% CI 0.7-1.9, $p = 0.1$) (blue). (b) 5-Year LC rate for patients with resection margins > 5 mm was 79.9% (red) and 76.7% for patients with margins ≤ 5 mm (HR 2.6, 95% CI 1.2-6.1, $p = 0.04$) (blue). (Abbreviations: OS: overall survival, HR: hazard ratio, CI: confidence interval, LC: locoregional control.)

Table 2. Univariable Cox Regression Analysis for OS, PFS and Local Control

Parameter	OS		PFS		LC	
	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value	HR (95% CI)	*p*-Value
Age	0.8(0.4-1.7)	0.594	0.9 (0.5-1.4)	0.596	0.6 (0.3-1.2)	0.145
Sex Male versus female	1.2 (0.7-2.3)	0.544	1.7 (0.8-3.3)	0.149	1.8 (0.6-5.1)	0.268
T stage T1/2 vs T3/4	1.3 (0.8-2.3)	0.319	1.1 (0.6-2.1)	0.672	0.8 (0.3-2.0)	0.574
N stage N0 vs N+	1.1 (0.7-1.9)	0.626	0.8 (0.5-1.3)	0.318	0.7 (0.4-1.4)	0.332
Grading	1.2 (0.7-1.6)	0.521	0.9 (0.4-1.1)	0.378	0.8 (0.3-1.4)	0.432
ECS Negative vs positive	0.9 (0.5-1.4)	0.535	0.9 (0.5-1.5)	0.723	0.8 (0.4-1.7)	0.544
Lymphatic invasion Negative vs positive	1.1 (0.7-1.8)	0.245	0.7 (0.3-1.2)	0.443	0.5 (0.3-1.3)	0.114
Vascular invasion Negative vs positive	1.3 (0.8-1.9)	0.676	1.1 (0.8-1.5)	0.823	0.9 (0.6-1.9)	0.447
Perineural invasion Negative vs positive	0.8 (0.3-1.4)	0.535	0.8 (0.4-1.5)	0.823	0.7 (0.4-1.7)	0.234
RT technique IMRT vs 3D-CRT	0.6 (0.4-1.1)	**0.08**	1.0 (0.5-1.7)	0.849	0.7 (0.3-1.6)	0.458
RT dose >60 Gy	1.4 (0.8-2.5)	0.231	1.4 (0.8-2.5)	0.210	1.4 (0.6-3.1)	0.450
Resection margin <1 mm vs ≥1 mm	0.9 (0.6-1.4)	0.682	0.9 (0.6.1.4)	0.590	1.2 (0.6-2.3)	0.657
Resection margin <2 mm vs ≥2 mm	1.0 (0.7-1.6)	0.913	1.0 (0.6-1.5)	0.837	1.3 (0.6-2.5)	0.487
Resection margin <3 mm vs ≥3 mm	1.1 (0.7-1.8)	0.697	1.0 (0.6-1.6)	0.913	1.5 (0.7-3.0)	0.274
Resection margin <4 mm vs ≥4 mm	1.1 (0.7-1.8)	0.634	1.0 (0.6-1.6)	0.993	1.4 (0.7-2.9)	0.321
Resection margin ≤5 mm vs >5 mm	1.2 (0.7-1.9)	0.495	1.2 (0.7-2.0)	0.432	**2.6 (1.2-6.1)**	**0.022**

about 80% in patient with positive resection margins and surgery alone.[8] Johnson et al compared patients who underwent surgery and postoperative RT to those who had surgery alone. The combination group showed statistically significant LC rates compared to the surgery-only group with positive margins.[20] The results in Table 2 show in the univariate analyzes that there was no difference with regard to the lymph nodes (N0 vs N+). It should be noted here that we only looked at the local neck lymph nodes in our collective and used them for the evaluation. This goes in line with current literature. Looking at different resection margin cutoffs (1 mm, 1-3 mm, and 4-5 mm), we found significantly worse LC rates in patients

with resection margins ≤ 5 mm (HR 2.6, 95% CI 1.2, 6.1), as a consequence, it was precisely that these group had to undergo significantly more salvage surgery.

One finding of the present study is that patients with resection margins > 5 mm had significantly better LC rates than patients with margins ≤ 5 mm. Compared to other studies with main specimen margins ≤ 3 mm in literature, no significantly smaller cutoff could be determined by our study. Our study indicates that the specification of resection margins should be pursued by surgeons and pathologists. The present study reported about 5-year LC rate was 79.9% for patients with resection margins >5 mm and 76.7% for patients with margins ≤ 5 mm. This supports observations of Johnsen[20] and Nason et al[11] who utilize a cutoff of 5 mm to classify patients as having close margins and need postoperative treatment with radiotherapy. Previous reports identified 3 mm but not 5 mm to be significant for locoregional recurrence and survival, but none of these patients underwent adjuvant radiation treatment.[21] Our data as well as other studies confirm that positive surgical margins are associated with shorter time to tumor recurrence.[22]

The current study is limited by its retrospective design. There are differences between our cohort and others: the fact that it represents only patients with OCSCC who underwent combined treatment with radiotherapy, we include only patients treated in combination with surgery and postoperative radiotherapy. Therefore, comparison with literature is more difficult. Only 38.9% of patients had resection margins >5 mm, making it difficult to achieve a statistically significant difference for this group; however, this more accurately reflects other published series, where >5 mm margin clearance is only achieved in a minority of patients.[16,19,23] Furthermore, in this retrospective analysis for risk factors listed in NCCN 8th Edition depth of invasion (DOI) was not applicable because many patients in this collective were treated with 7th NCCN classification. Another limitation of the study is that there was no power calculation done. A new prospective study it is currently working based on this data. Our data suggests that patients with OCSCC who have resection margins ≤ 5 mm should consider adjuvant treatment. However, prospective studies are required to determine if a redefinition of close and clear margins is necessary.

Conclusions

It is common known that there is an improved outcome in patients with resection margins > 5 mm but a paucity of evidence using resection margin cutoffs 5, 4, 3, 2, and 1 mm. Postoperative radiotherapy has an established role in patients with incomplete resected cancer in oral cavity. Our data suggested that patients with resection margins ≤ 5 mm needed postoperative radiotherapy to achieve better LC rates. Using divided subclassifications of resection margins could not identify risk factors for LC, therefore further prospective studies with special patient selection criteria are needed.

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Authors Contribution

K.L. and S.A. did conceptualization and methodology. K.L. performed formal analysis and writing—original draft preparation. T.H., C.F., K.Z., B.F., J.H., P.P. J.D., J.D., and S.A. performed writing—review and editing. J.D. and S.A. did supervision.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

The study was approved by the ethics committee of the University of Heidelberg, Germany (S-421/2015). Individual written informed consent from all subjects involved in the study was not necessary to obtain according to the local ethics committee approval.

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