Analyzing the impact of close margins and extra-resection margins on failure rates in postoperative oral cavity cancers

Analýza vlivu těsných a dodatečných resekčních okrajů na míru selhání léčby karcinomu ústní dutiny po operaci

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Summary

Background: Postoperative oral cancers with close margins belong to medium- to high-risk category for local failure. During re-surgery for close margins, there is sufficient doubt as to whether the re-excised tissue is from the same region as the close margin. Therefore, we planned a retrospective review of these cases of close margins that were re-excised with extra-resection margins (ERMs). ***Material and methods:*** Details of 2011 oral cavity patients resected at our hospital were retrieved. Cases with close margins were segregated and the status of ERMs was noted. The postoperative histopathological details, radiotherapy details, and failure patterns in all these cases were documented. The primary objective of the study was to assess the overall survival (OS) and disease-free survival (DFS) in cases with ERMs. The secondary objective was to assess the local and regional control rates and variation with the number and status of close and ERMs. OS, DFS, and local failure rates were defined from the date of registration. Statistical analysis was performed with the SPSS statistical software package. All survival analyses were performed using the Kaplan-Meier method. Log-rank test was used to test the statistical significance. A P-value of 0.05 was considered statistically significant. ***Results:*** Sixty-four cases with a median age of 47 years (range: 29–76) were considered for the final analysis. The median follow-up was 40 months (range: 9.5–56.5). The 2-year OS and DFS rates were 91.5% and 88.5%, respectively. The crude local and regional failure rates were 10.9% and 3.1%, respectively. The 3-year locoregional control rate was 90.2%. The 2-year locoregional control rate for one close margin was significantly better as compared to more than one close margin (P = 0.049). No difference in survival and failure rates was found between the number of ERMs resected (one vs. two) and ≤ vs. > 3 mm close margin status. Two patients developed bone metastases. ***Conclusion:*** The survival rates and locoregional control rates did not differ much between the groups that had one or more ERMs. However, the locoregional control rates were better in cases with one close margin as compared to those with more than one close margin. A larger study with longer follow-up is needed to detect statistically significant differences in outcomes and identify the factors that portend poor prognosis in these cases with close margins and ERMs.

Key words

close margin – extra-resection margin – postoperative oral cancer – re-excised – locoregional control rate

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Souhrn

Východiska: Karcinomy dutiny ústní s těsnými okraji pooperačně patří do středně až vysoce rizikové kategorie z hlediska selhání léčby. Při reexcizi kvůli těsnému okraji je značná pochybnost o tom, zda reexcidovaná tkáň patří do stejné oblasti jako původní těsný okraj. Proto jsme provedli retrospektivní analýzu případů s těsnými okraji, které byly reexcidovány s následným posouzením dodatečných resekčních okrajů (extra-resection margins – ERM). ***Materiál a metody:*** Byly získány podrobné údaje o pacientech po resekcích dutiny ústní provedených v naší nemocnici v roce 2011. Byly vyčleněny případy s těsnými okraji a zaznamenán stav ERM. U všech těchto případů byly zdokumentovány pooperační histopatologické údaje, údaje o radioterapii a byla posouzena míra selhání léčby. Primárním cílem studie bylo zhodnotit celkové přežití (overall survival – OS) a přežití bez známek onemocnění (disease-free survival – DFS) u případů s ERM. Sekundárním cílem bylo zhodnotit míru lokální a regionální kontroly a změny v závislosti na počtu a velikosti těsných okrajů a ERM. OS, DFS a míra selhání lokální léčby se počítaly od data registrace pacientů. Statistická analýza byla provedena pomocí statistického softwaru SPSS. Všechny analýzy přežití byly provedeny pomocí Kaplanovy-Meierovy metody. K testování statistické významnosti byl použit log-rank test. Hodnota p = 0,05 byla považována za statisticky významnou. ***Výsledky:*** Do konečné analýzy bylo zařazeno 64 případů s mediánem věku 47 let (rozmezí 29–76 let). Medián doby sledování byl 40 měsíců (rozmezí 9,5–56,5 měsíce). Dvouleté OS a DFS činily 91,5 a 88,5 %. Přibližná míra selhání lokální a regionální léčby byla 10,9 a 3,1 %. Tříletá lokoregionální kontrola byla 90,2 %. Dvouletá lokoregionální kontrola při jednom těsném okraji byla významně lepší než při počtu těsných okrajů > 1 (p = 0,049). V přežití a míře selhání léčby nebyl zjištěn žádný rozdíl z hlediska počtu ERM (jeden vs. dva) nebo velikosti těsných okrajů (≤ 3 mm vs. > 3 mm). U dvou pacientů se vyvinuly kostní metastázy. ***Závěr:*** Míra přežití a lokoregionální kontroly se mezi skupinami, které měly jeden nebo více ERM okrajů, příliš nelišily. Míra lokoregionální kontroly však byla lepší v případech s jedním těsným okrajem ve srovnání s případy s více těsnými okraji. Pro zjištění statisticky významných rozdílů ve výsledcích a pro určení faktorů, které předznamenávají špatnou prognózu v případech s těsnými okraji a ERM, jsou zapotřebí rozsáhlejší studie s delším trváním.

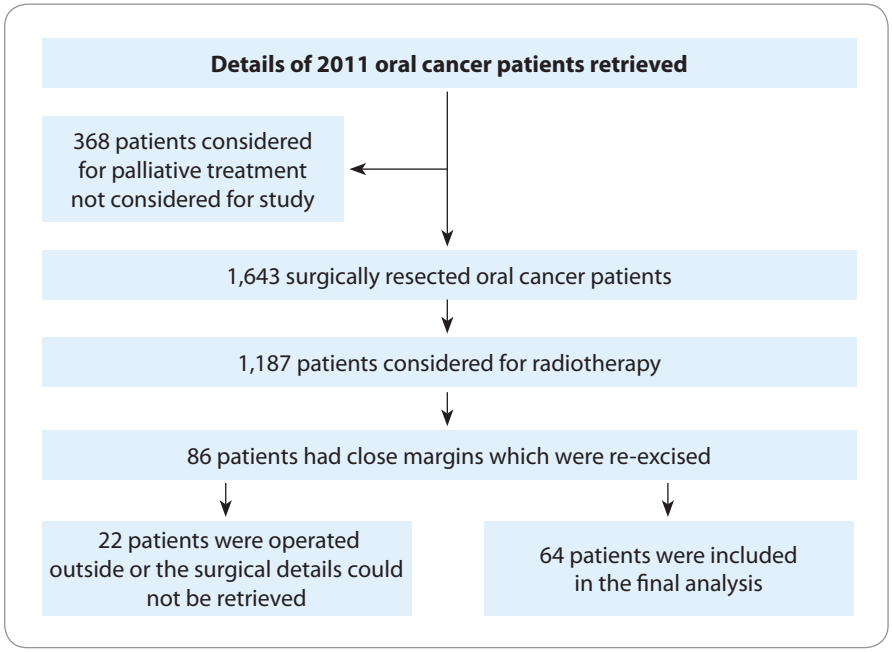
Klíčová slova

těsný resekční okraj – dodatečný resekční okraj – karcinom dutiny ústní pooperačně – reexcize – míra lokoregionální kontroly

Introduction

Oral cavity cancers account for one third of all cancers in Southeast Asia [1]. The majority of oral cancers are squamous cell carcinomas [2]. Surgery is the primary treatment modality [3].

Adjuvant radiotherapy after surgery is indicated in cases with pathological tumor size of pT3 or more, pathological node positivity, close margins, lymphovascular invasion positive and perineural invasion positive. The cases with positive margins, extranodal extension positivity, or multiple positive nodes require chemoradiotherapy or high doses up to 66 Gy [4]. Patients with close margins represent a medium- to high-risk category of patients, depending on the total number of risk factors present [5]. Often, during resection, if the margin is close or involved in frozen section, surgeons excise additional tissue (extra-resection margins – ERMs). There is sufficient doubt as to whether the re-excised tissue or specimen is from the same region as the close or positive margin and there is some uncertainty as to whether to consider it a clear margin when re-excised. So, it's prudent to assess whether these cases of close margins who are re-excised can be categorized in the moderate risk category or if they need higher radiotherapy (RT) doses. Thus, we planned a retrospective review of the cases of oral cancers that had close margins during surgery and were re-excised with ERMs, and the outcomes were assessed. The aim of the study was to evaluate the survival and failure outcomes in oral cavity cancer patients with one or multiple resected surgical margins after the initial close margin in frozen section report.



Scheme 1. Consort diagram.

Material and methods

This was a retrospective single-arm observational analysis conducted at a tertiary cancer centre in India.

Data on oral cavity patients surgically resected in the oncology department of the tertiary cancer centre was retrieved. Data from around 2011 surgically resected oral cavity cancer patients

were retrieved. Of these, all the patients who had received RT were evaluated. These patients were then studied in detail to find out which cases had one or more close margins and were re-excised with ERMs. These cases were included in the retrospective analysis. The consort diagram representing the actual number of patient data retrieved has been depicted in Scheme 1. The treatment records of all these patients were thoroughly reviewed. The demographic details (age and gender), surgical details (primary tumour resection and the type of neck dissection), postoperative histopathology (pathologic factors like pathological tumour stage, pathological nodal stage, lymphovascular invasion, perineural invasion, depth of invasion, number of positive lymph nodes, extracapsular extension, margin status-close or positive), the radiotherapy doses, the failure patterns (local, regional, distant, and second primary), and the treatment received in terms of salvage and/or palliation were reviewed. After reviewing all the treatment records, the follow-ups details were assembled. The patients whose complete follow-up details could not be found in the files were telephonically interviewed for a proper assessment of their current condition.

Information regarding the close margins and ERMs was studied in detail. In addition to the determination of the margin status of the original specimen, pathology records were reviewed to identify cases where intraoperative frozen sections or tumour bed margins were sent. The extent and a number of close margins were reviewed. The ERMs for the respective close margins were noted, and their number and extent were studied. The final margin status was considered clear if the sum of the minimum dimension of the resection margin and the ERM was more than 0.5 cm (as per standardized departmental protocol).

Radiotherapy was delivered to a dose of 60–66 Gy using 6-MV photons, using a standard 2-Gy dose per fraction, one fraction per day, 5 days a week, by using linear accelerator (Elekta Compact and Synergy; Elekta, Crawley, UK) with a collimator leaf width of 1 cm at the isocenter. The patients were treated with either two-dimensional or three-dimensional conformal radiotherapy using either anterior-lateral fields in a single phase to a dose of 60–66 Gy respecting the spinal cord tolerance or using anterior and lateral fields or parallel opposed fields in two phases, in which 46 Gy was delivered in the first phase and a coned-down boost of 14–20 Gy was delivered in the second phase. The median dose of radiotherapy was 60 Gy (range 58–66 Gy). All patients were followed up on a regular basis: monthly once for first 6 months, every 2 months for the next year, every 3 months for the third and fourth years, and then every 6 months to annually thereafter.

The primary objective of the study was to assess the overall survival (OS) and disease-free survival (DFS) in cases with ERMs. The secondary objective was to assess the local and regional control rates and their variation with the number of close margins, the number of ERMs, and the close margin status.

All the time intervals were calculated from the date of registration in the oncology department to the date of event of interest. OS was measured from the date of registration to the date of death from any cause. DFS was defined as the time from the day of registration to the date of failure (either locoregional, distant, or both) or death. Locoregional failure was defined as the appearance of a tumour in the postoperative bed, cervical node metastasis, or both. Distant metastasis-free survival (DMFS) was defined as the time interval until the development of distant metastasis. Statistical analysis was performed with the SPSS statistical software package for Mac (version 23.0; IBM, Armonk, NY, USA). All survival analyses were performed using the Kaplan-Meier method. The log-rank test was used to test the statistical significance of differences in the survival and control rates. The value of $p < 0.05$ was considered statistically significant. All potential prognostic factors were analyzed.

Results

Patient Characteristics

Sixty-four patients were included in the final analysis. The median age was 47 years (range 29–76), with a male : female ratio of 4 : 1. All the patients had squamous cell carcinoma of the oral cavity. All the patients underwent ipsilateral neck dissection except one, who underwent ipsilateral modified neck dissection and contralateral supraomohyoid neck dissection. The demographic, clinical, and histopathological features of the cohort are presented in Tab. 1.

Survival rates

The median follow-up was 40 months (range 9.5–56.5). The 2-year OS and DFS were 91.5 and 88.5%, respectively (Graph 1). The crude OS and DFS rates were 89.1 and 82.9%, respectively. There were no statistically significant differences between survival outcomes for the number of ERMs (Tab. 2).

Local control rates

The crude local and regional failure rates were 10.9% and 3.1%, respectively. The 3-year locoregional control rate was 90.2%. The estimated 4-year local and locoregional control rates were 79.6% and 78.3%, respectively (Graph 2). The 2-year locoregional control rate for one close margin was significantly better as compared to more than one close margin ($P = 0.049$) (Graph 3). The local control rate was slightly better for one close margin compared with more than one close margin, albeit statistically insignificant ($P = 0.304$). No difference in local control and locoregional control rates was found between the number of ERMs resected (1 vs. 2) and ≤ vs. > 3 mm margin status.

Margin status

Three patients had positive margins. The ERMs were clear in all the cases with close margins which were re-excised. One ERM had a foci of tumor present. Nine patients had two ERMs with rest all having one ERM. Close margin status (< 3 vs. > 3 mm) had no significant influence on survival outcomes or failure rates (Tab. 2). Of the margins that were re-excised, twenty cases had < 3 mm margins, while the rest of the cases had > 3 mm margins. Most of the patients had one ERM, while only 11 cases had more than one resection margin.

Tab. 1. Patient demographics.

Characteristics		N = 64	%
gender	male	48	75
	female	16	25
site	tongue	12	18.8
	buccal mucosa	30	46.9
	GBM/RMT	14	21.9
	alveolar complex	8	12.5
pathological T stage	T1	11	17.2
	T2	23	35.9
	T3	7	10.9
	T4	23	35.9
pathological N stage	N0	33	51.6
	N1	11	17.2
	N2	16	25
	N3	4	6.3
AJCC 8th stage	I	5	7.8
	II	12	18.8
	III	11	17.2
	IV	36	56.3
nodal dissection	ipsilateral	63	98.4
	bilateral	1	1.6
neck dissection type	SOND	16	25
	MND	48	75
perineural invasion	present	12	18.8
	absent	52	81.2
lymphovascular invasion	present	7	10.9
	absent	52	81.2
number of close margins	1	39	60.9
	2	20	31.3
	3	3	4.7
	4	1	1.6
	5	1	1.6
number of extra-resection margins	1	53	82.8
	2	11	17.2
margins (≤ 3mm, > 3mm)	≤ 3mm	20	31.3
	> 3mm	44	68.8

AJCC – American Joint Committee on Cancer, GBS – gingivo-buccal sulcus, MND – modified neck dissection, N – lymph node, RMT – retromolar triangle, SOND – supraomohyoid neck dissection, T – tumor

Distant metastasis

Two patients developed bone metastases. Both patients received palliative RT as well as palliative chemotherapy (CHT). The distant metastasis rates were not statistically different for the number of close margins, number of ERMs or > vs. ≤ 3 mm margin status.

Recurrence and secondary malignancy

One patient developed flap recurrence at local site and was cured after surgery (pT1) and didn't require further treatment and was alive without any morbidity at the last follow up cut-off date. One patient developed breast cancer as a second malignancy, and was cured after surgery, CHT and RT.

Discussion

Adequate surgical resection is an important component of the multimodal treatment approach for oral cancers [6,7]. The adequacy of the surgical resection depends upon the margin status achieved during the procedure (8]. The histologic status of surgical margins is an independent prognostic factor for deciding local control and survival outcomes [8]. The rate of involved margins in oral cancers is estimated to be < 10% [9]. However, there continues to be controversy regarding the independent effects of margin status on failure rates and outcomes [10]. One of the main possible reasons for the discrepancy is likely due to the variable definition of margin status used in different studies [11].

A recent meta-analysis on the effect of clearance of positive margins reported that surgical revision of positive margins to clear margins based on frozen section guidance is not equivalent to initial negative margin in terms of local control rates [12]. Several other studies [13–15] also suggested that positive margins cleared to negative had poor locoregional control rates compared to initially negative margins. Scholl et al. reported that those patients with initially positive margins that were rendered negative at the completion of the procedure and treated with surgery only had a significantly increased local recurrence rate and reduced survival compared with patients similarly treated with initially negative margins [16].

Clear surgical margins can be difficult to achieve, depending on the anatomical location and size of the tumour. The National Comprehensive Cancer Network defines 5 mm as the mar-

Tab. 2. Variation of survival outcomes with number of extra-resection margins, margin status and number of close margins.

	No. of extra-resection margins		Margin status		No. of close margins	
	1	2	≤ 3 mm	> 3mm	1	> 1
OS	88.8	85.7	95	85.7	89.7	94.4
	P = 0.067		P = 0.910		P = 2.690	
DFS	90	81.8	81.4	71.7	86.4	92
	P = 0.673		P = 0.757		P = 0.314	
LRC	83.4	81.8	85.7	81.6	94.7	92
	P = 2.157		P = 1.144		P = 0.049	
LC	98.1	81.8	85.7	92.6	97.4	92
	P = 3.067		P = 0.787		P = 0.304	
RC	98	100	100	97.6	97.2	100
	P = 0.394		P = 0.873		P = 1.493	
DM	96.2	100	95	97	94.7	100
	P = 0.427		P = 0.33		P =1.334	

DFS – disease-free survival, DM – distant metastasis, LC – local control, LRC – locoregional control, OS – overall survival RC – regional control

gin status to define it as a clear margin for head and neck squamous cell carcinoma without any generalization of subsites [17]. The Royal College of Pathology defines margins as follows: < 1 mm is considered to be involved, 1–5 mm is considered close, and > 5 mm is considered as a clear margin [18].

Several authors have evaluated the ideal margin status for oral cancers. A wide range of cut-off margins have been described, ranging from 1 to 7 mm. Zanoni et al. advocated that a 3 mm margin may be sufficient in an evaluation of 381 cases [19]. They reported that the optimal margin associated with locoregional failure-free survival (LRFS) was 2.2 mm. Patients with a margin of 2.3–5 mm have similar LRFS as those with > 5 mm (hazard ratio (HR 1.31), where HR for a 0.1–2.2 mm margin was 2.83. However, the use of adjuvant treatments like RT and CHT may have acted as a confounding factor. Nason et al. reported equal survival and recurrence rates among the patients with 3–4 mm margins compared to ≥ 5 mm margins [20]. However, another study by Barrya et al. did not find any difference between 3–4.9 mm and > 5 mm margins in terms of recurrences between pT1/2N0 and pT1/2N+ cases [21].

Brinkman et al. studied 244 cases of patients who underwent surgery and postoperative radiotherapy (PORT) retrospectively. Sixty-five patients had involved margins, whereas 119 cases had close margins. Both the 2 mm and 3 mm close margin cut-offs were significantly associated with local failure rates (P = 0.02 and 0.01, respectively) and OS (P = 0.03 and 0.005, respectively). On multivariate analysis, a 3 mm margin was found to be predictive for OS [11]. Another study of 398 oral cancer cases using 5 mm as the standard for clear margins reported locoregional recurrences and 5-year OS rates of 30% and 52% vs. 18% and 60% for patients with inadequate compared to adequate margins, respectively [22]. A report of 827 cases by Liao et al. reviewed the impact of different resection margins from 3 mm to 11 mm. They concluded that resection margins of less than 7 mm were significantly associated with decreased local control [23].

A recent retrospective study of 432 oral cavity cancer cases by Tasche et al. analyzed local failure rates in relation to each millimeter of invasive cancer from the inked tumour specimen margin. The locoregional recurrence rates for microscopic positive margins (< 1 mm, 1 mm, 2 mm, 3 mm, 4 mm, and > 5 mm margins) were 44%, 28%, 17%, 13%, 13%, 14%, and 11%, respectively. The authors concluded that resection of additional tissue beyond a 1 mm margin doesn't improve local control rates [24]. Another study by Wong et al. proposed that surgical margins of 2 mm may be considered the cut-off for a recommendation for PORT [25]. Ching et al. suggested that patients with close margins as the only risk factor for PORT also had acceptable local control without PORT [26]. Another report by Scholl et al. concluded that initially positive margins cleared to negative by re-excision benefited from adjuvant PORT, and the locoregional control rates were similar to those of margin negative [16].

The current study did not find any significant differences in survival outcomes between close margins of one and more than one. Margin status of > vs. ≤ 3 mm also did not yield any significant differences in survival outcomes. The number of ERMs also did not have any statistically significant differences in the survival outcomes. The possible reasons could be the small sample size, which results in a limited

number of events, although the follow-up is 40 months, which is adequate for head and neck cancers, as most of the failures and recurrences in these cancers generally occur within a 24-month period [27].

Although the debate around margin status continues to rage, one more issue that remains is that different head and neck sites require different margins [9]. Therefore, although a precise microscopic 5 mm margin is usually considered adequate, this may not be the best case for all sites in the head and neck region. Individualized studies targeting different surgical resection margins with larger patient cohorts from specific sites are needed to validate the question of exact and adequate margin status.

Advantages

The strengths of the study include the nature of the evaluation. This is one of the first studies evaluating the role of ERMs in treatment failures. The follow-up duration of around forty months seems adequate.

Limitations

The limitations of our paper include its retrospective nature. Also, it was a single-arm study. A match-paired analysis with a larger cohort of patients might better discern the differences in outcome and whether dose escalation is needed in cases with ERMs. Also, the data may be confounded by a number of other risk factors other than margin status. The sample size is relatively small to detect a significant difference between survival and failure outcomes.

It is difficult to perform a study where we can compare these cases with ERM who have received PORT with those cases who have not received PORT, as the treatment in the second case will be unethical as there are multiple other risk factors that mandate the use of PORT. So, a number of other confounding factors will be present, and it will be difficult to isolate patients with only ERM as a risk factor for PORT. Therefore, only single-arm studies that are retrospective in nature can help evaluate the outcomes.

Conclusion

The survival rates and locoregional control rates did not differ much between the groups which had one or more ERMs. However, the locoregional control rates were better in cases with one close margin as compared to those with more than one close margin. A larger study with a longer duration is needed to detect statistically significant differences in outcomes and identify the factors that portend poor prognosis in these cases with close margins and ERMs.

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