research article

Definitive radiotherapy for squamous cell carcinoma of the oral cavity: a single-institution experience

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Background. Surgery is standard of care for oral cavity cancer (OCC). We provide a single-institution experience using definitive radiotherapy (RT) with or without concurrent systemic therapy for primary unresectable OCC.

Patients and methods. We retrospectively examined 49 patients with non-metastatic primary unresectable OCC treated with definitive RT between 2000 and 2019. The majority of patients (63.3%) were treated with definitive chemo-radiotherapy while 26.5% were given single-agent cetuximab weekly simultaneous to definitive RT. Five patients were treated with definitive RT alone because of limited disease and no nodal involvement.

Results. Median follow-up was 73 months (range, 6–236 months), median progression free survival (PFS) was 42 months (range, 2–157 months), median local disease-free survival (LDFS) was 44 months (range, 2–157 months) and median overall survival (OS) from the time of RT initiation was 52 months (range, 5–236 months). There were 65.3% locoregional failures, 84.4% local and 15.6% distant metastasis. The majority of patients with local failure presented with American Joint Committee on Cancer (AJCC) Stage III–IV disease (59.2%). The 5-year Kaplan-Meier estimates for OS (III–IV *vs.* I–II) was 22.8% *vs.* 54.2 % (p = 0.03, HR 2.090, 1.1–4.2). Patients who were treated with systemic therapy had a significant better 5-year overall survival compared to those with RT alone (43.9% *vs.* 23.1%, p = 0.05, 1.0–4.1). RT with doses less than 70 Gy (p = 0.046, HR 2.1 (1.0–4.5) was associated with worse overall survival. Mucositis was the most common ≥ grade 3 acute toxicity and occurred in 19 patients (39%). Incidences of chronic toxicities were loss of taste, trismus, osteoradionecrosis and xerostomia.

Conclusions. Definitive RT with or without concurrent systemic agents in patients with unresectable OCC resulted in an eloquent rate of locoregional control and good overall survival rates and is currently the best available treatment option in this patient collective.

Key words: oral cancer; systemic therapy; definitive radiotherapy; local failure

Introduction

Oral cancer includes cancers of all subsites of the oral cavity (oral tongue, floor of mouth, buccal mucosa, upper lip, lower lip, upper gum, lower gum, palate, and retromolar area) and is the eighth most common cancer worldwide.[1,2] Worldwide incidence of oral cancer in 2018 was four cases per 100,000 people.[3] Most related risk factors for oral cancer belong to tobacco and alcohol use.[4]

Treatment of oral cavity cancer (OCC) includes single modality surgery, radiotherapy (RT) or various combinations of these modalities with or without systemic agents. The selection of treatment is based on disease stage, considerations of disease control, anticipated functional and cosmetic outcomes and expertise. Standard treatment option for OCC is surgery.[5] Primary RT with or without systemic therapy is not used routinely. There are less prospective trials available which directly compared primary surgery *vs*. primary RT in oral squamous cell carcinoma (OSCC) specifically.[5-8] In literature 5-year overall survival rate since first diagnosis in patients treated with RT alone was 15%.[6,9] To improve local control and overall survival rates intensified treatment with concurrent chemotherapy to RT is necessary instead of RT alone.[9,10] Stenson *et al.* reported in a retrospective series overall survival rates with 66.9% in locally advanced oral cancer patients (stage III–IV) undergoing concurrent chemoradiotherapy (CCRT).[10] In a meta-analysis from Pignon *et al*. of individual patient data from clinical trials comparing RT *vs*. CCRT (MACH-NC) in locally advanced head and neck cancers, OCC comprised 21% of cases. Results showed an improvement of survival in OCC with CCRT compared to RT alone.[9-11]

To examine the clinical significance and outcome in patients who do not underwent surgery we retrospectively reviewed our experience in treating OCC with primary RT with or without concurrent systemic therapies.

Patients and methods

This study was performed following institutional guidelines and the Declaration of Helsinki of 1975 in its most recent version. Ethical approval for the study was given from the local ethics committee at University Hospital Heidelberg (S421-2015).

Clinical, operative, and hospital course records were reviewed. We analyzed data from Nationales Centrum für Tumorerkrankungen (NCT) Cancer Registry in Heidelberg and imported data into our HIRO Research Database.[12] All patients underwent systemic workup including cross-sectional imaging with referring providers prior to commencing RT. Afterwards, the patients underwent CT simulation with a standard immobilization 5-point mask. Target volume definition was based on CT and MRI scans with contrast agents, included the primary tumor region as well as nodal involvement according to the International Commission on Radiation Units and Measurements (ICRU) definition.[11-16] Patients underwent regular follow-up, including CT examinations every three months in the first two years after definitive treatment, in year three and four every 6 months and year five and six once a year as well as regularly clinical examinations at the Department of Oral and Maxillofacial Surgery. All follow-up CT-scans were reviewed by an experienced radiologist by the institutions own diagnostics. We excluded all patients with a metastatic disease (M1) at initial diagnosis.

Treatment toxicity

Acute toxicity was evaluated during and at the end of RT. Late toxicity was evaluated minimum 90 days after completion of RT and was described according to the Common Terminology Criteria for Adverse Events (CTCAE) criteria (version 4.03, U.S. Department of Health and Human Services, Washington, DC, USA).

Statistical analysis and outcome evaluation

Overall survival (OS), progression free survival (PFS) and local disease-free survival (LDFS) were calculated using Kaplan-Meier analysis. OS was calculated from the time of RT initiation until death or the date of last follow-up. PFS was calculated as the time from RT initiation to tumor progression or death/ date of last follow-up, whichever occurred first. LRFS was defined as the time from RT initiation until local tumor progression at the primary tumor site. Patients still alive at the time of analysis, without tumor progression, or patients lost to follow-up were censored. Kaplan-Meier estimates were calculated using IBM SPSS software version 24. Subgroups were compared using the log-rank test. p-values of 0.05 or less were considered statistically significant. For comparison between groups, the Chi-squared test was performed in categorical and continuous variables. Kaplan-Meier estimates of potential prognostic factors were compared us-

ing the log-rank test for univariate analysis and the cox-regression model for multivariate analysis.

Results

Patient characteristics

There were 49 patients treated either with definitive RT alone or in combination with chemotherapy/immunotherapy at the Department of Radiation Oncology, University Hospital of Heidelberg. Only patients with cancer of the oral tongue (23 patients), floor of mouth (21 patients) and buccal mucosa (4 patients) were included (ICD-O-3 topography codes C02-C06).

Information regarding a risk factor history was available for all patients, there were 19 patients current and former smokers, 10 patients with alcohol consumption and 61 patients had a smoking and drinking history. Detailed patient characteristics are shown in Table 1.

Treatment characteristics

RT was carried out using photon irradiation with either 3D-planned (17 patients, 34.7%), IMRT (32 patients, 65.3%) (TomoTherapy®, Accuray, Sunnyvale, CA, USA) or volume-modulated RT (VMAT) (Elekta, Sweden), with treatment delivered one fraction per day with 5 fractions per week. The main RT treatment features are listed in Table 2.

There were 5 patients (10.2%) treated with RT alone because of limited disease or no nodal involvement. The majority of patients (31 patients, 63.3%) were treated with single-agent cisplatin 40 mg/m^2 chemotherapy weekly and 13 patients (26.5%) were given single-agent cetuximab 400 mg/m^2 one week prior to start of treatment followed by 250 mg/m^2 weekly as an alternative to chemotherapy.

Treatment results for the whole cohort

After a median follow-up of 73 months (range, 6–236 months), 11 patients (22.4%) were still alive, while 38 patients (77.6%) had died: 31 (81.6%) due to disease progression and 7 (18.4%) due to pulmonary infection, cardiac disease, secondary carcinoma or other comorbidities. There were 32 patients (65.3%) with locoregional failures in this cohort, 27 patients (84.4%) of which were local failures alone and 5 patients (15.6%) were distant. The majority of patients who failed locally presented with American Joint

TABLE 1. Patient characteristics

Characteristic	Number of patients (percentage)
Gender	
Male	30 (61.2%)
Female	19 (38.8%)
Age, years	
Median (range)	61 years (17–85 years)
T-stage	
T1	8 (16.3%)
T2	12 (24.5%)
T3	7 (14.3%)
T4	22 (44.9%)
N-stage	
N0	20 (40.8%)
N+	29 (59.2%)
Grading	
1	5 (10.2%)
2	10 (20.4%)
3	34 (69.4%)
Risk factors	
Smoking history	29 (59.2%)
Alcohol consumption	6 (12.2%)
none	14 (28.6%)

TABLE 2. RT treatment characteristics

Technique	
3D-CRT	17 (34.7%)
IMRT	32 (65.3%)
RT-Dose	
Median total dose base plan (without boost)	57.5 Gy (range: 50.0–65.9 Gy)
Median single dose base plan (without boost)	1.9 Gy (range: 1.7–2.1 Gy)
Boost	
Yes	45 (91.8%)
SIB	38 (84.4%)
Sequential	7 (15.6%)
no	4 (8.2%)
Median total dose boost plan	12.0 Gy (range: 8.0–20.0 Gy)
Median single dose boost plan	2.2 Gy (range: 2.0–2.2 Gy)
Cumulative total dose (base + boost plan)	70.0 Gy (range: 60.0–72.0 Gy)
RT-Volume	
CTV dimension base plan	829.6 ccm (range: 61.7–1554.4 ccm)
CTV dimension boost plan	178.5 ccm (range: 31.4–535.8 ccm)

CTV = clinical target volume; Gy = gray; IMRT = intensity modulated radiotherapy, RT = radiotherapy, SIB = simultaneous integrated boost; 3D-CRT = three dimensional-conformal radiotherapy

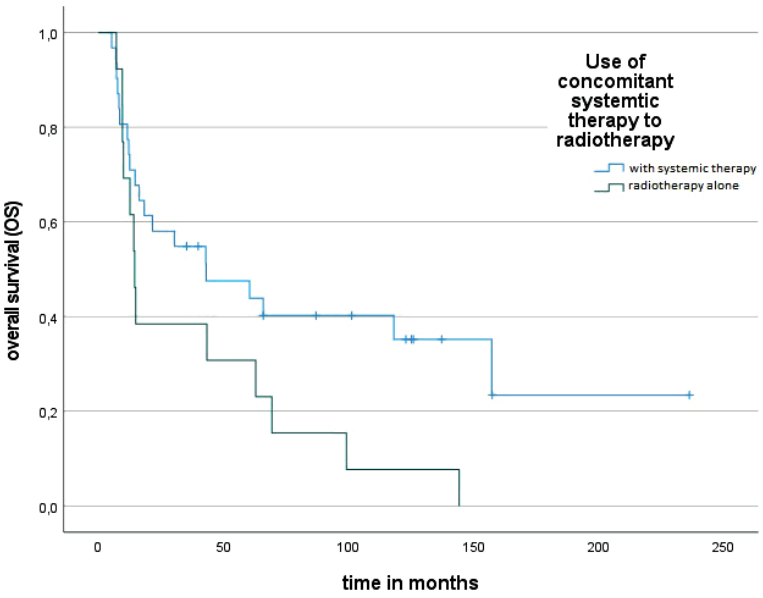

FIGURE 1. The 5-year Kaplan-Meier estimates for overall survival (OS) with systemic treatment (blue) was 43.9% vs. 23.1% with radiotherapy alone (green) (p = 0.05, HR 2.1, 1.1–4.2).

Committee on Cancer (AJCC) Stage III–IV disease (n = 29, 59.2%), while there were 20 patients (40.8%) that occurred in patients with early (Stage I–II) disease. The 5- and 10-year Kaplan-Meier estimates for OS, PFS, and LDFS were 37.9%, 35.9%, and 44.9%, and 23.0%, 28.6%, and 36.0% respectively. The median time to development of distant metastases was 66 months (range, 3.0–236 months).

The 5-year Kaplan Meier estimates for OS using systemic treatment versus RT alone was 43.9% *vs.* 23.1% (p = 0.05, Figure 1, HR 2.1, 1.1–4.2), there was no significant difference for PFS and LDFS.

Results of univariate analysis

The 5-year Kaplan-Meier estimates for OS (III–IV *vs.* I–II) was 22.8% *vs.* 54.2 % (p = 0.03, HR 2.090, 1.1–4.2).

On univariate analysis, treatment with RT alone (p = 0.005), RT doses < 70Gy (p = 0.05) and nodal positive stage (p = 0.036) were associated with a greater risk of death (Table 3). For LDFS and PFS only positive nodal stage (p = 0.026 and 0.027) was associated with a significantly worse outcome.

Results of multivariate analysis

Multivariate analysis was performed using the following variables: type of treatment, RT concept and nodal tumor stage. RT with doses less than 70Gy (p = 0.046, HR 2.1 (1.0–4.5) was associated with worse overall survival. Table 3 summarizes univariable cox Regression analysis for OS, PFS, LDFS and metastasis free survival (MFS).

TABLE 3. Overview about univariable cox regression analysis for overall survival (OS), progression free survival (PFS), local disease-free survival (LDFS), and metastasis free survival (MFS) in patients with oral squamous cell carcinoma (OSCC) undergoing definitive radiotherapy

Parameter	OS		PFS		LDFS		MFS	
	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*	HR (95% CI)	*p-value*
Age (< 60 years)	1.2 (0.6–2.2)	0.637	0.9 (0.4–1.7)	0.647	0.6 (0.3–1.3)	0.224	3.4 (0.7–16.8)	0.120
Sex male *vs.* female	1.2 (0.6–2.4)	0.570	0.9 (0.5–2.0)	0.950	1.1 (0.5–2.4)	0.881	1.3 (0.3–5.1)	0.741
T stage T1/2 *vs.* T3/4	**2.1 (1.1–4.2)**	**0.036**	1.3 (1.0–1.8)	0.077	1.4 (0.9–2.0)	0.072	2.1 (0.9–4.5)	0.071
N stage N0 *vs.* N+	**2.1 (1.1–4.2)**	**0.036**	**2.4 (1.1–5.3)**	**0.026**	**2.7 (1.1–6.3)**	**0.027**	2.8 (0.8–5.4)	0.071
RT dose < 70.0 Gy *vs.* >/= 67.0 Gy	**1.9 (1.0–3.8)**	**0.05**	1.5 (0.7–3.1)	0.267	1.4 (0.6–3.1)	0.393	1.7 (0.4–7.0)	0.428
Concomitant therapies	**2.1 (1.0–4.1)**	**0.05**	1.2 (0.9–1.5)	0.227	1.5 (0.7–3.5)	0.294	0.4 (0.1–3.3)	0.409
Concomitant therapies CHT *vs.* IT	1.2 (0.9–1.5)	0.216	1.5 (0.7–3.3)	0.296	1.2 (0.6–2.7)	0.586	0.7 (0.2–2.7)	0.580
RT technique IMRT *vs.* 3D	0.6 (0.4–1.2)	0.183	0.7 (0.3–1.3)	0.258	0.7 (0.3–1.4)	0.282	1.2 (0.3–5.0)	0.765
Risk factor history	1.1 (0.8–1.4)	0.536	0.9 (0.7–1.3)	0.690	0.9 (0.6–1.1)	0.328	1.5 (0.7–3.0)	0.295

CHT = chemotherapy; CTV = clinical target volume; Gy = gray; IMRT = intensity modulated radiotherapy, IT = immunotherapy; LDFS = local disease-free survival; RT = radiotherapy, SIB = simultaneous integrated boost; 3D = three dimensional-conformal radiotherapy

Toxicity

Mucositis was the most common grade > 3 acute toxicity present in 19 patients (39.0%) followed by dysphagia grade 3 in 12 patients (24.0%). Other significant acute toxicities grade 1/2 included dermatitis (56.3%) and xerostomia (39.7%). There were no treatment-related deaths. Late RT-related complications (grade 3) included xerostomia (64.4%), loss of taste (60.3%), trismus (26.0%) and osteoradionecrosis (9.6%). A total of 27 (56.0%) patients received a percutaneous endoscopic gastrostomy (PEG) tube: 5 (19.2%) prophylactically (reflecting the prior institutional practice of routine PEG placement prior to treatment), 22 acutely during treatment (80.8%). Toxicities are summarized in Table 4.

TABLE 4. Early and late toxicity after radiotherapy

Early treatment toxicity (< 90 days)	No of patients n (%)	Late treatment toxicity (> 90 days)	No of patients n (%)
CTCAE grade		**CTCAE grade**	
Mucositis			
1	6 (13.0)		
2	19 (39.7)		
3	17 (35.6)		
4	2 (3.4)		
Dermatitis			
1	12 (24.7)		
2	15 (31.5)		
3	5 (11.0)		
Xerostomia			
1	15 (30.8)	1	19 (39.7)
2	4 (8.9)	2	17 (35.6)
3	1 (2.1)	3	1 (2.1)
Dysphagia			
1	9 (19.2)	1	15 (30.8)
2	17 (34.9)	2	5 (11.0)
3	12 (24.0)	3	4 (8.9)
Loss of taste (late toxicity)			
29 (60.0)			
Trismus (late toxicity)			
13 (26.0)			
Osteoradionecrosis (late toxicity)			
4 (8.9)			

CTCAE = Common Terminology Criteria for Adverse Events

Discussion

The primary purpose of the present study was to evaluate the outcome and prognostic factors for patients with unresectable OCC who underwent definitive RT. Several studies reported local control rates and 5-year OS for definitive RT in OCC ranging between 27% to 70%[9,11,13] and 37–67%[14], which goes in line with our results.

In our study 59.2% of patients had advanced-stage disease III–IV with significant OS in stage I–II. Over the last decades the role of concomitant systemic therapy has become clearer. Pignon *et al*. reported in MACH-NC about better outcome and locoregional control rates when using concurrent chemotherapy and RT with a better absolute benefit of 4.5% at 5 years.[9,16] In our study there were 10.2% patients treated with RT alone due to either comorbidities, worse performance status or because of denied surgery. Patients who were treated with systemic treatment had a significantly better 5-year OS compared to those without (43.9% *vs*.

TABLE 5. Summary of the most important studies for definitive radiotherapy in patients with oral cavity cancer as an overview radiotherapy

	Study Period	Radiotherapy	No. of patients	CHT/IT	LDFS	PFS	OS
Lin *et al*.[18]	1995–2007	42% IMRT	115	48% CHT	27% (3yr)	n/a	15% (3yr)
Foster *et al*.[17]	1994–2014	54% IMRT	140	100% CHT	79% (5yr)	59% (5yr)	63% (5yr)
Studer *et al*.[8]	2002–2011	100% IMRT	54	68% CHT/IT	n/a	37% (4yr)	37% (4yr)
Pederson *et al*.[9]	2001–2004	100% IMRT	21	100% CHT	76% (5yr)	71% (5yr)	76% (5yr)
Hosny *et al*.[19]	2005–2014	100% IMRT	21	35% CHT	42% (5yr)	78% (5yr)	50% (5yr)
Present Study	2000–2019	74% IMRT	119	86.5% CHT/IT	61.9% (5yr)	52.1% (5yr)	47.2% (5yr)

CHT = chemotherapy; IMRT = intensity modulated radiotherapy; IT = immunotherapy; LDFS = local disease-free survival; n/a = not applicable; OS = overall survival; PFS = progression free survival; yr = years

23.1%) (p = 0.05, HR 2.1, 1.1–4.2) but no significant difference for PFS and LDFS.

While other studies found T-stage, age, grading and gender to be prognostic factors for PFS and LC [14-20], the present study did not find these to have a significant effect in uni- or multivariate analysis. In our collective treatment with RT alone, cumulative total RT doses < 70 Gy and positive nodal stage were associated with a greater risk of death and worse local control. For LDFS and PFS only positive nodal stage was associated with a significant worse outcome.

Cumulative total doses of less than 70 Gy is standard in patients who underwent postoperative treatment and not suggested as definitive RT treatment concept which goes in line with literature.[15]

Early and late toxicity from definitive RT to the oral cavity of our collective is comparable to data from other published series.[7,9,19,21,22,23] Most common acute RT-related complications (CTCAE grade > 3) in our study were oral mucositis (39.0%) and dysphagia (24.0%). Other significant acute toxicities grade 1/2 included dermatitis (56.2%) and xerostomia (39.7%). Late RT-related complications included xerostomia (64.4%), loss of taste (60.3%), trismus (26.0%), edema (47.3%). These late complications appear similar in other series.[7,9,16,19,22] The rate of osteoradionecrosis in the present study was 9.6%, which falls in line with other studies – ranging from 1% to 56%[23-28] in which both conventional and IMRT were utilized. Reuther *et al*. reported that a total dose above 60 Gy was a significant parameter for osteoradionecrosis (ORN).[29] This is similar with our study, all patients with ORN had a cumulative total dose of more than 66 Gy.

The limitations of this study include its retrospective nature, which led to a shortage of necessary data on some single cases. However, we were able to retrieve follow-up data covering a lengthy time period for all patients at a large department with a lot of experience in field of oral tumor diseases.

The power of this study is that we were able to show in a dedicated collective of patients with OCC undergoing definitive RT and an extended follow up of 73 months good control and overall survival rates with moderate toxicity.

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