

Research Article

Outcome in Irradiated Oral Cavity Carcinoma: An Update

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Abstract

Background: In contrast to pharyngo-laryngeal cancer, definitive radiation-chemotherapy of advanced oral cavity cancer (OCC) results in inferior disease control rates. Surgery in combination with radiation +/- concomitant chemotherapy is therefore the treatment of choice for squamous cell OCC stages \geq pT1-2pN0-1. Modern intensity modulated radiation techniques (IMRT) allow more conformal dose distribution to the tumor area with consecutively less dose to surrounding normal tissues. Aim was to give a recent overview about outcome data in OCC treated in the modern IMRT era (i.e. time period since ~2000) including presentation of the own single institution results.

Methods: our OCC IMRT cohort was evaluated with respect to disease control and radio-osteonecrosis (RON) as most serious late term effect following radiation.

Results: 202 OCC patients treated between 10/2002-10/2013 with a follow up of mean 30months (3-124) were assessed. 5-year overall and distant metastasis free survival, local and nodal control rates for postoperatively (n=147 (73%), 60-66Gy tumor dose) vs definitively (n=55 (27%), 70Gy) irradiated patients was 70 vs 36% (p<0.0001) and 84%vs84% (p=0.2), 70% vs 40% (p<0.0001) and 83% vs 70% (p=0.006), respectively. The incidence of RONgrade 1-2 was 3% (:12/147 (9%) in postoperative, 1/55 (2%) in definitive IMRT); 1 grade 3 RON was observed after post IMRT dental implants. In all grade 1-2 RON, restitutio ad integrum was achieved after conservative treatment or limited surgery (debridement/decortication/sequestrectomy).

Conclusion: Disease control and survival following combined postoperative MRT are significantly higher than after definitive IMRT(-chemotherapy). The RON incidence revealed being higher in the operated subgroup.

ABBREVIATIONS

OCC: Oral Cavity Cancer; RON: Radio-Osteonecrosis

INTRODUCTION

Oral Cavity Cancer (OCC) is an aggressive disease with high risk for loco-regional treatment failure in intermediate and advanced stage disease. While interstitial brachytherapy achieves excellent results in early stage T1, 2 tumors of the mobile tongue or floor of the mouth, definitive radiation-chemotherapy (i.e. IMRT without surgery but as potential salvage treatment) of advanced OCC results in inferior disease control rates compared to results following postoperative radiation- in contrast to pharyngo-laryngeal cancer. Surgery in combination with radiation +/- concomitant chemotherapy (i.e. postoperative IMRT) is therefore the treatment of choice for most advanced squamous cell oral cavity cancer (OCC) stages \geq pT1-2p N0-1. Modern modulated radiation therapy techniques (MRT)

allow more conformal dose distribution to the tumor area with consecutively less dose to surrounding normal tissues. This was shown to translate into substantially reduced rates of severe (grade 3) radio-osteonecrosis (RON) as compared to former three-dimensional non-modulated radiation techniques [1,2].

Aim of this work was to give a recent overview about outcome data in OCC treated in the modern IMRT era (i.e. time period since ~2000).

MATERIALS AND METHODS

The own single center OCC cohort was retrospectively evaluated with respect to disease control and treatment late term tolerance following IMRT (including intensity modulated radiation therapy (IMRT) as well as volumetric modulated arc therapy (VMAT)). In 73% of our patients, MRT was combined with concomitant cisplatin chemotherapy or with the monoclonal EGFR antibody cetuximab. Reasons not to combine with systemic

therapy were age, comorbidity, early stage disease, or patient refusal. The percentage of patients treated with no systemic therapy was comparable in the postoperative versus definitive IMRT subgroups (76 % and 72%, NS). Mean age was 62.3 years (range 21-93), male : female ratio was 2:1 in the postopIMRT, 1.5:1 in the definitive IMRT subgroup. T1/2/3/4 and recurrence stage distribution was the following: 12%, 34%, 11%, 31% and 12%; the corresponding percentage for N0/1/2/3 and nodal recurrences were 33%, 16%, 45%, 1% and 5%, respectively.

The data collection was prospectively performed since 2002 (when IMRT was clinically implemented in the own department). In order to minimize avoidable oral damage due to radiation, all patients underwent prophylactic and/or therapeutic dental care procedures prior to, during and after IMRT, respectively, according to our in-house routine dental care program. This less invasive 'risk adapted' dental care procedure was reactively adjusted to the IMRT-related option of improved normal tissue sparing [3].

RON rates were assessed using the grading system according to Glanzmann and Graetz [4], Table 1.

Parts of the presented data on our OCC cohort have been presented in former publications [1,3,5].

Published IMRT literature in English language with focus on OCC available in PubMed was considered for comparison purposes.

Statistical calculations (survival analysis, Kaplan-Meier curves) were performed using StatView® Version 4.5. P-values <0.05 were considered as statistically significant.

RESULTS AND DISCUSSION

Disease control

202 OCC patients treated at the Department of Radiation Oncology University Hospital Zurich between 10/2002 and 10/2013 with a follow up of mean 30 months (3-124) were assessed.

At the time of analysis (December 2013), 72% of the postoperative MRT patients (n=147, 73% of the entire OCC cohort) were alive with no evidence of disease when last time seen; 7% were alive with disease, 3% had died from other reasons, and 17% had died from disease, respectively.

The corresponding rates for the definitively irradiated subgroup (n=55, 27%) were 29%, 10%, 10%, and 51%.

Table 1: Grading system for RON.

Grading of radio-osteonecrosis (RON), according to Glanzmann & Graetz 1995 [4]
Grade 1: exposed bone without signs of infection for at least 3 months
Grade 2: exposed bone with signs of infection or sequester, but not grades 3-5
Grade 3: osteonecrosis, treated with mandible resection, with satisfactory result
Grade 4: osteonecrosis with persistent problems despite of mandible resection
Grade 5: death due to RON

5-year overall and distant metastasis free survival, local and nodal control rates for postoperatively (n=147, 60-66Gy tumor dose) vs definitively (n=55, 70Gy tumor dose) irradiated patients was 70% vs 36% (p<0.0001) and 84% vs 84% (p=0.2), 70% vs 40% (p<0.0001) and 83% vs 70% (p=0.006), respectively.

In sum, treatment regimens of OCC including surgery in order to eliminate macroscopic disease significantly increases loco-regional disease control as well as overall survival in OCC patients. No difference was found in the probability for distant metastases. These results are in concordance with several other reports on OCC cohorts treated by MRT (+/- systemic therapy) with and without surgery, Table 2 [6-17], i.e. postoperative radiation translates into higher loco-regional disease control as well as higher overall survival rates, while surgery seems not to have any impact on the distant metastasis rate. The comparison definitively and postoperatively irradiated cohorts as well as between the listed reports is somewhat limited by the fact of retrospectively analyzed series with different TN stages or stage grouping (I-IV), and a substantially larger number of postoperative IMRT patients (which is due to the known poor outcome of OCC patients undergoing definitive radiation). The impact of additional systemic therapy to postoperative radiation in advanced stages head neck cancer has been proven back in 2004 by two independent prospective randomized trials (RTOG 9501 and EORTC 22931 [18,19]: level I evidence). The impact of additional radiation on the outcome of operated high risk OCC patients is not quantified based on prospective trials, however many cohort reports confirm satisfying disease control in advanced disease stages treated with postoperative irradiation [20]. While MRT not seems to obviously change disease control in OCC as compared to previous radiation techniques, the substantially improved late term profile following MRT is proven [1,2,21] and nowadays MRT considered the standard technique for head neck cancer radiation.

RON

The incidence of RON grade 1-2 (Table 1) in the own cohort was 7%: 12/147 (9%) after postoperative, 1/55 (2%) after definitive IMRT; 1 grade 3 RON after postMRT dental implant was observed. In all RON grade 1-2 restitutio ad integrum was achieved after limited surgery (debridement/decortication/sequestrectomy). In 4 of the 14 cases, RON occurred following manipulations in the high dose area (boost): n=3 following postMRT implants, n=1 following tooth extraction in the boost area immediately prior to MRI start, n=1 following soft tissue plastic reconstruction postIMRT that was complicated by osteomyelitis (counted as 'RON' in this analysis). In sum, 4/14 RON developed following invasive manipulation in the high dose area (>60-72Gy), i.e. 10 cases remaining as 'real' RON grade 1 - 2-3 events (5%). Interestingly, the higher incidence of RON was observed in postoperative MRT (13/147): in the postoperative setting lower radiation doses are needed and therefore lower RON rates expected. This finding may indicate the impact of surgical manipulations on soft or bony tissues on the RON risk, likely via impaired local trophic conditions.

Another relevant late term effect is grade 3-4 xerostomia. Due to improved salivary gland sparing achieved by IMR and by consequent dental care, the incidence of severe xerostomia

Table 2: selected published series on outcome in OCC patients treated with IMRT.

Author [ref]	Center	year	interval	N	postop IMRT	CT	T3/4	N>/=2	III / IV	LRC		DMFS		OAS	
										postop	definitive	postop	definitive	postop	definitive
Eisbruch et al. [6]	U of MI	2004	1997-2002	27	most postop	na	na	na	na	59% (3y)	na	na	na	na	na
Yao et al. [7]	U of Iowa	2007	2001-2005	55	49 (89%)	11%	56%	36%	91%	85% (3y)	na	89% (3y)	na	68% (3y)	na
Studer et al. [8]	UH of Zurich	2007	2002-2007	58	28 (48%)	78%	69%	28%	62%	91% (2y)	43% (2y)	95% (2y)	85% (2y)	83% (2y)	30% (2y), n=30
Gomez et al. [9]	MSKCC	2009	2000-2006	35	35 (100%)	29%	40%	38%	80%	77% (3y)	none	85% (3y)	na	74% (3y)	none
Chen et al. [10]	Chiayi, Taiwan	2009	2002-2005	22	22 (100%)	na	na	7(32%)	100%	64% (3y)	none	na	na	67% (3y)	none
Collan et al. [11]	U of Helsinki	2011	2001-2007	40	40 (100%)	38%	na	na	na	na	none	na	na	75% (3y)	none
Sher et al. [12]	DFCI	2011	2004-2009	42	30 (71%)	~76%	45%	30%	64%	91% (2y)	64% (2y)	94% (2y)	83% (2y)	85% (2y)	63% (2y), n=12
Daly et al. [13]	Stanford UMC	2011	2002-2009	37	30 (81%)	68%	54%	46%	57%	53% (3y)	60% (3y)	81% (3y)	71% (3y)	60% (3y)	57% (3y), n=7
Geretschlager et al. [14]	UH Berne (CH)	2012	2006-2010	53	53 (100%)	55%	38%	43%	100%	79% (3y)	none	90% (3y)	none	73% (3y)	none
Zhang et al. ** [15]	U of Alberta	2013	1998-2010	222	183 (82%)	24%	68%	44%	100%	na	na	~80% (5y)	~75% (5y)	~50% (5y)	10% (5y), n=38
Chan et al. [16]	PMH Toronto	2013	2005-2010	180	180 (100%)	26%	na	na	81%	78% (2y)	none	83% (2y)	none	65% (20)	none
George et al.° [17]	U of California	2014	2102-2012	53	53 (100%)	81%	41%	38%	43%	na	none	na	none	72% (5y)	none
own cohort	UH of Zurich	2014	2002-2013	202	147 (73%)	73%	56%	56%	69%	66% (5y)	38% (5y)	84% (5y)	84% (5y)	70% (5y)	36% (5y), n=55
TOTAL	N=12	2004-'14	14y	1079	~873 (~81%)	11-81%	40-69%	28-56%	43-100%	53-91% (2-5y) n ~ 873	38-60% (2-5y) n = 142	80-95% (2-5y) n ~ 873	71-85% (2-5y) n = 142	50-85% (2-5y) n ~ 873	30-63% (2-5y) n = 142

Abbreviations:

U: University; UH: University Hospital; Y: Year; LRC: Locoregional Control; DMFS: Distant Metastasis; Free Survival; OAS: Overall Survival

*data in part included in reference [1] and [5]

** multi-institutional trial, Alberta Cancer Registry

° selection of matched pairs treated at the academic center

grade 3-4 and its oral complications could be reduced as well. In the own entire MRT cohort this was below 1% (affected were patients with nasopharyngeal carcinoma, [21]).

CONCLUSION

Disease control and survival of OCC patients is significantly higher following combined postoperative IMRT (-chemotherapy) than after definitive IMRT (-chemotherapy). The higher RON rate in the operated subgroup may indicate surgery being a relevant co-risk factor for RON.

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