



## Definitive (chemo)radiotherapy is a curative alternative for standard of care in advanced stage squamous cell carcinoma of the oral cavity

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### ABSTRACT

**Objective:** To compare outcome after definitive (chemo)radiotherapy (CRT group) with standard of care (surgery group) for advanced stage oral cavity carcinoma (OCC). Although definitive (chemo)radiotherapy is assumed to be inferior to surgery with regard to disease control, data on outcome of this approach are scarce.

**Methods:** Retrospective analysis by chart review (2000–2013). Endpoints were locoregional control (LRC), disease-free survival (DFS), disease specific survival (DSS) and overall survival (OS).

**Results:** Between the CRT-group (n = 100) and Surgery-group (n = 109), baseline characteristics were equally distributed except stage and local tumor diameter (all  $p \leq .001$ ). In the CRT group, at 5 years the LRC rate was 49%, DFS 22%, DSS 39% and OS 22%. In the surgery group, at 5 years the LRC rate was 77%, DFS 45%, DSS 64% and OS 45%. The survival curves of the two groups significantly differed for LRC ( $p < .001$ ), DFS and DSS ( $p = .001$ ) and OS ( $p = .002$ ). After adjusting for confounders and prognostic factors, we found a significant difference between the treatment groups in LRC (adjusted HR = 2.88, 95%CI 1.35–6.16,  $p = .006$ ). Within 100 days, 5 patients (5%) died from treatment-related toxicity in CRT group and 1 patient after surgery ( $p = .21$ ).

**Conclusions:** Although surgery with adjuvant radiotherapy for advanced stage OCC results in favorable locoregional control, definitive (chemo)radiotherapy is a curative alternative in patients often considered beyond cure and should be considered when surgery is not feasible.

### Introduction

Head and neck squamous cell carcinoma is the 7th most common cancer in men and the 9th most common cancer in women in The Netherlands. Per year, 900 out of 2900 head and neck cancer patients are diagnosed with oral cavity carcinoma (OCC) [1]. Although there has been a shift towards organ preservation treatment in other head and neck cancer subsites [2], the standard of care for advanced oral cavity cancer is surgery with adjuvant (chemo)radiotherapy (CRT). However, especially in patients with locally advanced disease, this surgery may lead to extensive mutilation and results in a disappointing 5-year overall survival of 65% in stage III and 37% in stage IV disease [3].

Therefore, definitive CRT may be a possible curative alternative when surgery is not feasible or may lead to unacceptable loss of functionality. As reported by Heukelom et al., CRT for inoperable head and neck carcinoma resulted in 40% 5-year overall survival, when all different tumor subsites were combined [4]. However, this treatment modality is known to yield inferior results in OCC compared to other subsites. As a consequence, patients who are not candidate for curative surgery are often considered beyond cure. However, there is a lack of solid evidence to support this, as most of the data are available from few and small retrospective studies and not from randomized trials [5–11]. Consequently, it remains to be determined whether definitive CRT serves as a curative alternative when organ preservation is not possible in

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**Table 1**  
Patient and tumor characteristics at baseline.

Variable	CRT group (n = 100)		Surgery group (n = 109)		p-value
	N	%	N	%	
Age, mean (SD)	62 (14)		61 (12)		p = .59
Sex, male	66	66	71	65	p = .90
ASA score					p = .13
1–2	79	79	100	92	
> 2	14	14	9	8	
Unknown	7	7	0	0	
Alcohol abuse					p = .59
No	35	35	50	46	
Yes	43	43	45	41	
Former	9	9	12	11	
Unknown	13	13	3	3	
Smoking status					p = .36
No	20	20	23	21	
Yes	53	53	59	54	
Former	13	13	25	23	
Unknown	14	14	2	2	
Previous treatment					p = .24
Surgery	8 <sup>a</sup>	8	5	5	
Laser + PDT	2	2	0	0	
Radiotherapy	0	0	1	1	
None	90	90	103	94	
Tumor site					p = .31
Mobile tongue	40	40	29	27	
Floor of mouth	29	29	39	36	
Retromolar trigone	12	12	13	12	
Alveolar process/ gingiva	14	14		20	
Other <sup>b</sup>	5	5	6	6	
T stage					p < .001
1–2	10	10	43	39	
3–4	90	90	66	61	
N stage					p = .001
0–1	44	44	73	67	
2–3	56	56	36	33	
Stage					p < .001
III	17	17	36	33	
IVA	72	72	72	66	
IVB	11	11	1	1	
Local tumor diameter, in cm					p < .001
Median (range)	4.1 (1.0–8.1)		3.0 (0.3–9.0)		
Unknown	8		4		

PDT = photodynamic therapy.

<sup>a</sup> All patients received (C)RT as primary treatment, not postoperative.

<sup>b</sup> < 5 cases; cheek and hard palate.

NB: Not all percentages sum up exactly to 100% due to rounding errors.

advanced stage OCC. For this purpose, we retrospectively analyzed all patients with advanced stage OCC treated between 2000 and 2013 in our institute. We addressed the following research question: what is the locoregional control (LRC), disease free survival (DFS), disease specific survival (DSS) and overall survival (OS) after definitive (chemo)radiotherapy? For guidance in clinical decision-making, we compared this group of patients with patients who were treated with surgery followed by adjuvant (chemo)radiotherapy.

**Patients and methods**

*Patients*

We retrospectively analyzed all patients with advanced stage squamous cell carcinoma of the oral cavity (OCC) between 2000 and 2013 in the Netherlands Cancer Institute - Antoni van Leeuwenhoek (NKI-AVL), treated with definitive (chemo)radiotherapy (further referred to as CRT group) or with standard of care, i.e. surgery and

**Table 2**  
Treatment characteristics.

Variable	CRT group (n = 100)		Surgery group (n = 109)	
	N	%	N	%
<i>Reason for Radiotherapy</i>				
Functional inoperable	89	89	NA	
Comorbidity	3	3	NA	
Patients preference	8	8	NA	
<i>Concurrent systemic treatment</i>				
None	17	17	85	78
Platinum <sup>a</sup>	83	83	24	22
<i>Surgery</i>				
Transoral resection	NA		32	14
Composite resection	NA		77	86
<i>Neck dissection</i>				
Unilateral	NA		78	72
Bilateral	NA		27	25
None	NA		4	4
<i>Neck dissection</i>				
Selective	NA		19	17
Modified	NA		68	62
Selective + Modified	NA		18	17
None	NA		4	4
<i>Reconstruction, flap</i>				
Fibula	NA		18	17
Free radial forearm	NA		27	25
Pectoralis major	NA		19	17
Lateral upper arm	NA		5	5
Rest	NA		8	7
None	NA		32	29

NA = not applicable.

<sup>a</sup> Cisplatin dose in the CRT group: daily 6 mg/m<sup>2</sup> (n = 28), low dose 40 mg/m<sup>2</sup> (n = 2), high dose 100 mg/m<sup>2</sup> i.v. (n = 31) and 150 mg/m<sup>2</sup> i.a. (n = 19), unknown (n = 3). In the Surgery group: daily 6 mg/m<sup>2</sup> (n = 5) and high dose (100 mg/m<sup>2</sup>) (n = 19).

NB: Not all percentages sum up exactly to 100% due to rounding errors.

adjuvant (chemo)radiotherapy (surgery group). In total, 100 and 109 patients were identified, respectively. See Table 1 for a detailed overview of baseline characteristics. All patients were staged according to the American Joint Committee on Cancer (AJCC) staging manual 7th edition [12] based on clinical examination, ultrasonography and MRI. A contrast-enhanced CT-scan was performed in patients not eligible for MRI. Workup further included a chest X-ray to exclude distant metastases. After 2007, FDG-PET was gradually introduced. Tumor size was assessed by the largest tumor diameter.

*Treatment, CRT group*

Criteria for (functional) irresectability were (1) no functional reconstruction possible after removal of the tumor, mostly due to extensive tumor growth, or (2) tumors requiring (sub)total glossectomy. Treatment characteristics are described in Table 2.

All patients were considered for platinum-based concurrent chemoradiotherapy. Multiple dose regimens have been administered both intravenous and intra-arterial, e.g. daily cisplatin (6 mg/m<sup>2</sup>), low dose (40 mg/m<sup>2</sup> weekly), high dose cisplatin i.v. (100 mg/m<sup>2</sup> on day 1, 21 and 43) and 150 mg/m<sup>2</sup> i.a. weekly in the first 4 weeks of treatment. Patients received daily cisplatin mainly due to age; they were on average older than in the high dose cisplatin group (mean 68 versus 55 years, respectively; p < .001). In the daily cisplatin group, tumors were smaller than in the high dose group (median 3.5 cm versus 5 cm, p = .03) and patients were more often treated for different HNSCC before (p = .01). Four out of eighty-three patients (5%) only received one dose of 100 mg/m<sup>2</sup> cisplatin due to nephrotoxicity. Three of these patients further received carboplatin.

Approximately 50% of patients was treated with 3D conformal radiotherapy between 2000 and 2005. Intensity modulated

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