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Original Article

Non-operative management for oral cavity carcinoma: Definitive radiation therapy as a potential alternative treatment approach

Ali Hosni [a,*], Kevin Chiu [a], Shao Hui Huang [a], Wei Xu [b], Jingyue Huang [b], Andrew Bayley [a], Scott V. Bratman [a], John Cho [a], Meredith Giuliani [a], John Kim [a], Brian O'Sullivan [a], Jolie Ringash [a], John Waldron [a], Anna Spreafico [c], John R. de Almeida [d], Eric Monteiro [d], Ian Witterick [d], Douglas B. Chepeha [d], R.W. Gilbert [d], Jonathan C. Irish [d], David P. Goldstein [d], Andrew Hope [a,*]

[a] Department of Radiation Oncology; [b] Department of Biostatistics; [c] Department of Medical Oncology; and [d] Department of Otolaryngology-Head & Neck Surgery/Surgical Oncology, Princess Margaret Cancer Centre, University of Toronto, Canada

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ABSTRACT

Purpose: To determine the outcomes of oral cavity squamous cell cancer (OSCC) patients treated with non-surgical approach i.e. definitive intensity-modulated radiation therapy (IMRT).
Methods: All OSCC patients treated radically with IMRT (without primary surgery) between 2005–2014 were reviewed in a prospectively collected database. OSCC patients treated with definitive RT received concurrent chemotherapy except for early stage patients or those who declined or were unfit for chemotherapy. The 5-year local, and regional, distant control rates, disease-free, overall, and cancer-specific survival, and late toxicity were analyzed.
Results: Among 1316 OSCC patients treated with curative-intent; 108 patients (8%) received non-operative management due to: medical inoperability (n = 14, 13%), surgical unresectability (n = 8, 7%), patient declined surgery (n = 15, 14%), attempted preservation of oral structure/function in view of required extensive surgery (n = 53, 49%) or extensive oropharyngeal involvement (n = 18, 17%). Sixty-eight (63%) were cT3-4, 38 (35%) were cN2-3, and 38 (35%) received concurrent chemotherapy. With a median follow-up of 52 months, the 5-year local, regional, distant control rate, disease-free, overall, and cancer-specific survival were 78%, 92%, 90%, 42%, 50%, and 76% respectively. Patients with cN2-3 had higher rate of 5-year distant metastasis (24% vs 3%, p = 0.001), with detrimental impact on DFS (p = 0.03) and OS (p < 0.02) on multivariable analysis. Grade $\geq$ 3 late toxicity was reported in 9% of patients (most common: grade 3 osteoradionecrosis in 6%).
Conclusions: Non-operative management of OSCC resulted in a meaningful rate of locoregional control, and could be an alternative curative approach when primary surgery would be declined, unsuitable or unacceptably delayed.
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The majority of mucosal head and neck squamous cell carcinoma (HNSCC) patients are treated with definitive radiation therapy (RT) or concurrent chemoradiation (CRT). However, oral cavity squamous cell carcinoma (OSCC) represents a unique entity in terms of its management and treatment outcomes. Surgery is the main treatment modality for OSCC while postoperative radiation therapy (PORT) is indicated mainly for patients with advanced disease (e.g. pT3-4, pN2-3) or adverse pathologic/treatment features (e.g. close resection margin), and concurrent chemotherapy with PORT for patients with high risk features (positive microscopic resection margin[s] and/or pathologic extranodal extension) [1–5]. In addition, OSCC has been shown to have inferior outcomes compared to other mucosal HNSCC despite the aggressive multimodality approach for higher risk patients [1–6].

In a substantial proportion of OSCC patients, primary surgical management may not be possible in view of patient-related factors (e.g. patients refuse surgery or with medical comorbidities that preclude safe surgical interventions), tumor-related factors (e.g. unrescetable tumor, or complex primary tumor location/extension where surgery will result in unacceptable local morbidity), or healthcare system-related factors (e.g. type of insurance or available healthcare facilities and resources) [7–11].

There has been a general perception of inferior outcomes with definitive RT/CRT as the primary treatment for OSCC [12]. The pur-

* Corresponding authors at: Princess Margaret Cancer Centre, 610 University Ave., Toronto, Ontario M5G 2M9, Canada.
E-mail addresses: Ali.Hosni@rmp.uhn.on.ca (A. Hosni), Andrew.Hope@rmp.uhn.on.ca (A. Hope).

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pose of this study was to determine the outcomes of OSCC patients treated definitively with primary RT/CRT using intensity-modulated radiation therapy (IMRT).

Methods

Study design

This is a retrospective review that was initiated following institutional research ethics board approval. Our institution maintains a prospective quality assurance system updated at point-of-care, which provided data for this analysis [13].

Inclusion and exclusion criteria

Between January 2005 and December 2014, all newly diagnosed primary OSCC patients cT1-4, N0-3, M0 (UICC/AJCC 7th edition) treated at our institution with upfront definitive RT/CRT were included. Patients with gross disease following diagnostic-intent excisional biopsy for the primary OSCC were included, while patients with prior curative-intent surgery for the primary OSCC or previous RT to HNSCC were excluded. Those with primary oropharyngeal cancer with extension to oral cavity were also excluded.

Definitive RT

Upfront curative-intent surgery is the routine standard treatment for OSCC at our institution. Definitive RT is used for OSCC patients who decline or are medically unfit for surgery, have unresectable disease or extensive oropharyngeal involvement, or as an attempt to preserve organ function where the surgery required would be unacceptably extensive. All decisions about non-operative management of OSCC were made following multidisciplinary assessment to provide consensus on treatment decision and after a comprehensive discussion with the patient to ensure their preference for non-operative management based on the principle of individualized patient-centered care.

All patients were treated with IMRT with daily cone beam CT for image guidance. The details of primary (CTVp) and nodal (CTVn) clinical target volume are described in Table 1. A 5 mm geometric expansion of the CTVs was used to create corresponding planning target volumes (PTVs).

Concurrent chemoradiation (CRT)

Patients with early stage OSCC with limited or no nodal involvement were treated with definitive RT (conventional fractionation), while advanced stage OSCC patients received CRT, unless the patient declined chemotherapy or was unsuitable/unfit. The conventional RT schedule with concurrent chemotherapy consisted of 70 Gy/35fractions (2 Gy/fraction) over 7 weeks, with a planned cisplatin dose of 100 mg/m^2 every 3 weeks (or 40 mg/m^2 weekly). Other targeted therapy (e.g. cetuximab or panitumumab) was occasionally used as part of clinical trials during the study period.

Accelerated fractionation RT

In patients who did not receive CRT, three distinct accelerated fractionation RT protocols were applied: (1) accelerated conventional fractionation RT (70 Gy/35fractions [2 Gy/fraction, 6 fractions/week] over 6 weeks), (2) accelerated hypofractionated RT (60 Gy/25fractions [2.4 Gy/fraction] over 5 weeks), and (3) accelerated hyperfractionated RT (64 Gy/40fractions [1.6 Gy/fraction twice daily, at least 6hours apart] over 4 weeks [10 fractions/week]). The choice of accelerated fractionation RT schedule was based on physician/patient preference and patient/tumor characteristics.

Salvage surgery

Patients with biopsy-proven local and/or regional failure following definitive RT/CRT were managed with surgical resection of the recurrence (primary tumor resection and/or neck dissection) where feasible. Salvage surgery was not undertaken in medically unfit patients, those with unresectable recurrence, or synchronous distant metastases.

Evaluation and follow up

The standard pre-treatment workup included clinical history, physical examination, and staging investigation with MRI and/or CT scan of the head and neck, chest X-ray or CT chest. PET-CT scan was not routinely employed during the study period due to regulatory approval in our jurisdiction. Histological confirmation of malignancy was required before treatment. CT and/or MRI head and neck was arranged typically 10–12 weeks post-RT, and upon suspicion of recurrence. Patients were seen in multidisciplinary head and neck clinic every 3 months in the initial 2 years, every 4–6 months during the 3rd–5th year, and then every 12 months afterwards, when comprehensive clinical examination (including endoscopic evaluation) was performed.

Table 1
Radiation target volume and dose for oral cavity cancer.

	Volume description	Radiation schedule with dose to corresponding PTV			
		Conventional Fx 35 Fr/7 wk	Accelerated conventional Fx 35 Fr/6 w	Accelerated hypo-Fx 25 Fr/5 w	Accelerated hyper-Fx 40 Fr/4 w BID
CTVp_High dose	GTVp + 3–5 mm isotropic margin expansion	70 Gy	70 Gy	60 Gy	64 Gy
CTVp_Elective dose	GTVp + 10 mm isotropic margin expansion	56 Gy	56 Gy	25 Gy	46 Gy
CTVn_High dose	GTVn + 5 mm isotropic margin expansion	70 Gy	70 Gy	60 Gy	64 Gy
CTVn_Intermediate dose	Borderline LN + 3–5 mm isotropic margin expansion	63 Gy	63 Gy	55 Gy	56 Gy
CTVn_Elective dose	1) GTVn + 10 mm isotropic margin expansion, and 2) Nodal levels deemed at risk of microscopic tumor involvement in: • Ispliateral neck • Contralateral neck based on primary tumor location and/or proximity to the midline, and gross nodal involvement in contralateral neck	56 Gy	56 Gy	25 Gy	44 Gy

CTVp, primary clinical target volume; CTVn, nodal clinical target volume; GTV, gross tumor volume; PTV, planning target volume, Fx, fractionation; Fr, fractions.

Data collection and statistical consideration

The clinical information and outcomes (including grade $\geq$ 3 late RT toxicities according to Common Terminology Criteria for Adverse Events) in this database were prospectively collected at the point of care [13]. The reason for delivering definitive RT instead of primary surgery was collected from the electronic medical record. The outcome measures were local failure, regional failure, distant metastases (evaluated by cumulative incidence method with competing risk analysis), disease free survival (DFS), and overall survival (OS) (analyzed by Kaplan–Meier method), and cancer specific survival (CSS) (by competing risk analysis). Outcome were measured from the last day of RT. Univariable followed by multivariable analyses were applied using the cox-proportional hazard regression method to identify factors associated with DFS and OS. Clinical variables that were evaluated in the multivariable analysis included: cT- and N-categories, age, ECOG performance status, histological grade, primary tumor subsite, and use of concurrent chemotherapy. The model selection procedure was based on backward selection algorithm with a significance level less than 0.1 to enter the model and less than 0.05 to stay in the model.

Results

A total of 1316 OSCC patients were treated with curative-intent at our institution during the 10-year study period, of whom 672 (51%) treated with surgery only, 536 (41%) with primary surgery and PORT+/− concurrent chemotherapy, while 108 patients (8%) received non-operative management with definitive RT/CRT. The reason for non-operative management was: medical contraindication (n = 14, 13%), surgical unresectability (n = 8, 7%), patient declined surgery (n = 15, 14%), attempt to preserve of oral structures/function in view of the extensive surgery that would be required for adequate tumor ablation (n = 53, 49%), or extensive involvement of the oropharynx from primary OSCC (n = 18, 17%). The median follow-up period for our study cohort was 52 months

Table 2
Summary of patient demographics and tumor characteristics.

Variable	Whole cohort n = 108	Conventional fractionation RT		Accelerated fractionation RT		
		Alone n = 18	with chemo n = 38	conventional Fx n = 10	hypo-Fx n = 37	hyper-Fx n = 5
Sex						
Male	67 (62%)	9 (50%)	25 (66%)	8 (80%)	22 (60%)	3 (60%)
Female	41 (38%)	9 (50%)	13 (34%)	2 (20%)	15 (40%)	2 (40%)
Age (years): median (range)	66 (37–89)	70 (50–85)	59 (37–80)	75 (61–86)	78 (43–89)	61 (59–75)
Alcohol use at time of diagnosis						
None	41 (38%)	7 (39%)	16 (42%)	4 (40%)	14 (38%)	0
Light, <2 drinks/day	8 (7%)	2 (11%)	3 (8%)	0	2 (5.5%)	1 (20%)
Moderate, 3 drinks/day	15 (14%)	3 (16.5%)	3 (8%)	3 (30%)	5 (14%)	1 (20%)
Heavy, >3 drinks/day	28 (26%)	5 (3%)	10 (26%)	3 (30%)	8 (21%)	2 (40%)
Ex-drinker	11 (10%)	0	4 (11%)	0	6 (16%)	1 (20%)
Not reported	5 (5%)	1 (5.5%)	2 (5%)	0	2 (5.5%)	0
Tobacco use at time of diagnosis						
Current smoker	43 (40%)	6 (33.3%)	14 (37%)	7 (70%)	13 (35%)	3 (60%)
Ex-smoker	38 (35%)	6 (33.3%)	14 (37%)	1 (10%)	15 (40.5%)	2 (40%)
Non-smoker	26 (24%)	6 (33.3%)	10 (26%)	2 (20%)	8 (21.5%)	0
Missing Data	1 (1%)	0	0	0	1 (3%)	
ECOG performance status						
0	60 (55.5%)	11 (61%)	18 (47%)	9 (90%)	19 (51%)	3 (60%)
1	31 (28.5%)	2 (11%)	16 (42%)	1 (10%)	11 (30%)	1 (20%)
2	12 (11%)	4 (22%)	4 (11%)	0	3 (8%)	1 (20%)
3	2 (2%)	1 (6%)	0	0	1 (3%)	0
Not reported	3 (3%)	0	0	0	3 (8%)	0
cT category						
T1–2	40 (37%)	8 (44%)	5 (13%)	4 (40%)	21 (57%)	2 (40%)
T3–4	68 (63%)	10 (56%)	33 (87%)	6 (60%)	16 (43%)	3 (60%)
cN category						
N0	56 (52%)	11 (61%)	8 (21%)	6 (60%)	28 (76%)	3 (60%)
N1	14 (13%)	2 (11%)	5 (13%)	2 (20%)	3 (8%)	2 (40%)
N2	37 (34%)	5 (28%)	24 (63%)	2 (20%)	6 (16%)	0
N3	1 (1%)	0	1 (3%)	0	0	0
Clinical overall stage (UICC/AJCC 7th edition)						
I	7 (6.5%)	1 (5.6%)	0	0	6 (16%)	0
II	22 (20.5%)	5 (27.7%)	0	3 (30%)	13 (35%)	1 (20%)
III	21 (19%)	3 (16.7%)	5 (13%)	3 (30%)	8 (22%)	2 (40%)
IVA–B	58 (54%)	9 (50%)	33 (87%)	4 (40%)	10 (27%)	2 (40%)
Primary tumor subsite						
Retromolar trigone	36 (33.3%)	4 (22%)	9 (23.5%)	3 (30%)	15 (40.5%)	5 (100%)
Oral tongue	22 (20.3%)	3 (16.7%)	14 (37%)	2 (20%)	3 (8%)	0
Buccal mucosa	13 (12%)	3 (16.7%)	4 (10.5%)	2 (20%)	4 (11%)	0
Floor of mouth	13 (12%)	1 (6%)	6 (16%)	1 (10%)	5 (13.5%)	0
Alveolus/gingiva	11 (10%)	3 (16.7%)	2 (5%)	1 (10%)	5 (13.5%)	0
Hard palate	9 (8.3%)	2 (11%)	2 (5%)	1 (10%)	4 (11%)	0
Lip	4 (4%)	2 (11%)	1 (3%)	0	1 (2.5%)	0

Chemo, chemotherapy; Fx, fractionation.

(range: 3–136 months). Among 108 eligible cases, 68 patients (63%) were cT3–4 and 38 (35%) were cN2–3. The most common primary tumor subsites were retromolar trigone (n = 36, 33%) and oral tongue (n = 22). Patient and tumor characteristics were summarized in Table 2.

Approximately half of the OSCC patients (52/108, 48%) were treated with accelerated fractionation RT including accelerated conventional RT (10/108, 9%), accelerated hypofractionated RT (37/108, 34%) and accelerated hyperfractionated RT (5/108, 5%). The remaining 56 patients received conventional fractionation RT alone (18/108, 17%) in early stage disease with limited or no nodal involvement, or CRT (38/108, 35%) in view of advanced disease in patients suitable to receive chemotherapy. Among the 38 patients who received CRT, 19/38 (50%) patients received 3 cycles of Q3-week high dose cisplatin, 10 (26%) received 2 cycles, another 3 patients (8%) received weekly cisplatin, while the remaining 6 patients (16%) received targeted therapy as part of clinical trials.

The 5-year local failure rate was 22% (95%CI: 20–25%). There were 26 local failures, including 7 patients with persistent local disease following RT, and 3 patients with late recurrences beyond 5 years. The median time to local recurrence was 9 months (range: 0–90 months). The rate of 5-year local failure for cT1, T2, T3, T4a and T4b categories were 13% (95%CI: 7–26%), 21% (95%CI: 16–27%), 22% (95%CI: 17–29%), 28% (95%CI: 23–33%), and 14% (95% CI: 7–28%) respectively (p = 0.9). Of the 26 patients who experienced local failure, seventeen (65%) underwent subsequent salvage surgery. The median interval from completion of RT to salvage surgery was 9 months (range 3–90 months). Following salvage surgery, 10/17 (59%) achieved cancer control until last follow up, 6 (35%) had a subsequent locoregional failure, and 1 patient developed subsequent distant-only failure.

Only 8 patients had regional failure; with pre-treatment cN-categories as following: cN0 (n = 3), cN2a (n = 1), cN2b (n = 3), cN2c (n = 1). The median time to regional failure was 5 months (range: 3–43 months). The 5-year rate of regional recurrence for the entire cohort, cN0 and cN+ patients was 8% (95%CI: 6–10%), 7% (95%CI: 4–10%), and 10% (95%CI: 7–13%) respectively (p = 0.4). Salvage neck dissection was performed in 6 (75%) out of 8 patients with regional recurrence. Following salvage neck dissection, 4 patients (67%) achieved tumor control until last follow up, while 1 had a subsequent regional failure, and 1 patient developed subsequent distant-only failure.

Eleven patients had distant failure, 3 subsequent to locoregional failure and 8 with distant-only failure. The 5-year distant metastasis rate was 10% (95%CI: 9–13%). The median time to distant failure was 5 months (range: 1–18 months). The 5-year distant metastasis rate for cN0–1 patients was 3% (95%CI: 2–5%) vs 24% (95%CI: 19–29%) for cN2-3 patients (p = 0.001). Fig. 1 shows the outcomes in stage I–II vs stage III–IV.

The 5-year DFS, OS and CSS were 42% (95%CI: 33–53%), 50% (95%CI: 41–62%), and 76% (95%CI: 73–79%) respectively. A total of 60 patients died with a median OS of 5.5 years. Causes of death included: OSCC (n = 26), other cancer (n = 12), comorbidities (n = 17), while 5 patients died of unknown cause. On multivariable analysis, cN2–3 was the only predictor of poor DFS (HR = 1.73 [95% CI: 1.06–2.83], p = 0.03) and OS (HR = 1.83 (95%CI: 1.08–3.1), p = 0.02), Table 3.

No grade 4–5 RT-related late toxicity was reported. Ten patients (9%) were found to have grade 3 late toxicities including: osteoradionecrosis of the jaw (n = 6, 6%), oral cavity fistula (n = 1, 1%), trismus (n = 1, 1%), and severe dysphagia (n = 2, 2%).

Discussion

Several studies evaluating definitive RT for OSCC reported a local control rate ranging from 27% to 75% (Supplementary Table 1) [9,14–21]. Direct comparison between these studies cannot be made due to varying tumor characteristics (e.g. site and stage) and treatment methods (e.g. use of IMRT technique and concurrent chemotherapy). Considering the previous factors, the local control of our study cohort is favorable [9,14–20]. In addition to IMRT [6], daily image guidance, standardized quality assurance of RT at our institution, and/or more optimal selection of OSCC patients for non-operative management may be contributing factors for relatively-higher tumor control in our study cohort. Some authors advocate the importance of interstitial brachytherapy in the radiotherapy management of OSCC [22–24]. However, there are risks of severe late toxicity associated with this technique [22,25–31].

The 5-year local and regional control of the current study cohort (78% and 92% respectively) are reasonable compared to our previously reported our institutional experience in treating 300 OSCC patients with surgery and PORT (using IMRT) between 2005 and 2012 (5-year local control: 85% and 5-year regional control: 82%) [32]. However, the discrepancy between clinical and pathologic

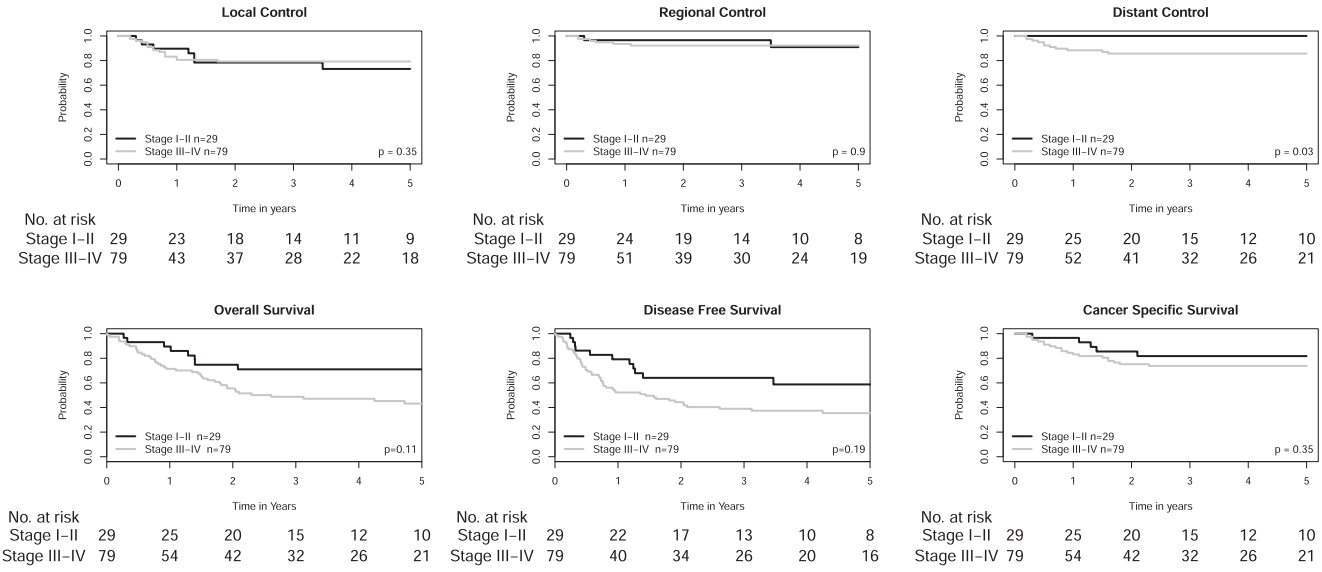

Fig. 1. Outcomes of stage I–II versus stage III–IV oral cavity squamous cell carcinoma patients following non-operative management.

Table 3
Univariable and multivariable analysis to identify factors associated with disease free survival and overall survival.

Covariate	Disease free survival				Overall survival			
	Univariable		Multivariable		Univariable		Multivariable	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value	HR (95% CI)	*p* value
cT category								
T1–2	Reference		–	–	Reference		–	–
T3–4	1.51 (0.91–2.53)	0.11			1.56 (0.9,2.69)	0.11		
cN category								
N0–1	Reference				Reference			
N2–3	1.85 (1.14–2.98)	**0.01**	1.73 (1.06–2.83)	**0.03**	2.13 (1.28–3.54)	**<0.01**	1.83 (1.08–3.1)	**0.02**
Age	1.01(0.99–1.03)	0.48	–	–	1.01 (0.99–1.03)	0.27	–	–
ECOG performance								
0–1	Reference		–	–	Reference		–	–
2–3	1.16 (0.58–2.28)	0.68			1.6 (0.8,3.17)	0.18		
Smoking								
Non-smoker	Reference				Reference		–	–
Current/ex-smoker	1.24 (0.66–2.33)	0.52	–	–	1.59 (0.76,3.33)	0.13		
Histological grade								
Grade 1	Reference		–	–	Reference		–	–
Grade 2–3	0.98 (0.51–1.9)	0.95			1.4 (0.65,2.98)	0.39		
Primary tumor subsite								
All except tongue	Reference		–	–	Reference		–	–
Oral tongue	1.01 (0.56–1.82)	0.97			1.15 (0.62,2.13)	0.66		
Concurrent chemotherapy								
No	Reference		–	–	Reference		–	–
Yes	0.91 (0.55,1.5)	0.7			0.91 (0.53,1.55)	0.73		

staging represents an obstacle to perform a direct comparison between these 2 series that were treated at the same institution during the same time period. Previous studies showed stage migration from clinical to pathologic staging in a substantial proportion of OSCC patients, likely due to uncertainty in the physical examination judgement, limited accuracy of radiologic evaluation, occasional resection of the tumor in fragments, shrinkage of the tumor after the fixation process, or presence of occult single or multiple lymph nodes [33,34].

Primary surgery with PORT has become the standard treatment sequence for advanced OSCC since the results of the RTOG-7303 phase III randomized controlled trial (RCT) (n = 227, 14% were OSCC) which showed better locoregional control with PORT compared to preoperative RT (p = 0.04) [35,36]. However in a subgroup analysis of 129 patients with advanced resectable OSCC/oropharyngeal carcinoma who were randomly assigned to either preoperative RT, PORT, or definitive RT, there were no statistically significant differences in locoregional control (43% preoperative, 52% postoperative, 38% definitive RT, p = 0.4), or in OS (30% preoperative, 36% postoperative, 33% definitive RT, p = 0.8). Another RCT compared primary surgery with PORT vs definitive CRT (with cisplatin/5-Fu) for stage III/IV HNSCC (n = 119, 27% were OSCC). There were no statistically significant difference in 3-year DFS (54% for PORT vs 43% definitive CRT, p = 0.4) and 3-year OS (50% for PORT versus 40% for definitive CRT, p = 0.6) [37]. Despite the relatively small number of OSCC patients in these RCT, their results suggest the potential value of definitive RT/CRT (with surgery reserved for salvage if residual/recurrent disease) or preoperative RT (with planned delayed surgery) as an alternative treatment approach for OSCC in settings when upfront primary surgery may not be possible.

Concurrent chemotherapy has been shown to improve locoregional control and OS in HNSCC [38]. The rate of chemotherapy usage in our study (35%) was lower than several published series (Supplementary Table 1). This is likely explained by the subgroup of patients in our cohort with early stage disease with no or limited nodal involvement (18/108, 17%) who did not require concurrent chemotherapy, and approximately half of the study cohort (52/108, 48%) were medically unfit to receive chemotherapy and underwent altered-fractionation RT instead. A meta-analysis of 33 trials showed survival benefit with altered-fractionation RT over conventional fractionation RT in definitive treatment for HNSCC. The benefit was found to be higher with hyperfractionated RT [39]. There is currently no RCT comparing CRT with altered-fractionation RT in OSCC.

Data on salvage surgery after definitive RT/CRT in OSCC is limited [40]. Lin et al reported on 11 OSCC patients who were initially treated with definitive RT. Six out of their 11 patients (55%) were salvaged and achieved locoregional control [16], which was comparable to the 10 out of 17 (59%) salvage success in the current study.

Despite the reasonable tumor control in our cohort, the 5-year OS was 50%. Although, comparable to reported literature of non-operative management in OSCC (Table 4), but lower than our previously reported institutional experience in treating OSCC patients with surgery and PORT (5-year OS: 69%) [32]. A disparity in OS between surgical and non-surgical populations has been well described in multiple disease sites due to at least in part to patient selection. In the current study, the cause of death in 17 (28%) out of 60 patients who died was medical comorbidity, which could contribute to the relatively lower survival in the current study cohort.

An important limitation of our study is the retrospective nature of treatment assignment. Although the oncologic outcomes data were prospectively collected, there was heterogeneity in patient selection and treatment, which could lead to bias. Acceptable tumor control with non-operative management remains an interesting finding, while also recognizing that surgical patients may be healthier, with consequent more favorable survival outcomes. The retrospective collection of reasons that patients received definitive RT/CRT instead of primary surgery, could be limited by documentation inadequacies. Furthermore, the comparison of treatment approaches and the side effects and toxicity of each of the approaches is a critical comparison and difficult to measure in a retrospective study. Patients with cN-3 had more frequent distant metastases with a detrimental impact on DFS and OS, which

merits prospective evaluation of further systemic treatment intensification in this subgroup.

To establish the true trade-offs of substituting definitive RT for primary surgery in certain OSCC patients, it would be critical to determine equivalent locoregional control in patients who opt for non-surgical treatment on a prospective study (possibly with modification of fractionation or systemic therapy delivery). However, our results suggest that definitive RT/CRT likely represents the most realistic alternative to treatment of OSCC when surgical management is not favorable as determined by multidisciplinary discussion and patient preference.

In conclusion, we observed an acceptable rate of locoregional control with definitive RT/CRT for OSCC, suggesting that this strategy could be a reasonable substitute for primary surgery when it is not feasible. Patients with cN2-3 had more frequent distant metastases with a detrimental impact on DFS and OS, which merits prospective evaluation of further systemic treatment intensification in this subgroup.

Conflict of interest notification

None declared.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.08.013.

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