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Surgery vs. primary radiotherapy in early-stage oropharyngeal cancer

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ABSTRACT

Background: Early-stage oropharyngeal squamous cell carcinoma (OPSCC) can currently be treated by surgical resection or definitive radiotherapy (RT). The aim of this study is to review the outcomes of early-stage OPSCC submitted to surgery or primary RT. Preliminary results have shown similar overall survival (OS) and locoregional recurrence-free survival (LRFS).
Material/Methods: Retrospective study of patients with cT1-T2 cN0-N1 OPSCC, diagnosed between January 2009 and December 2014, treated with surgery or primary RT.
Results: 61 patients with cT1-T2 cN0-N1 OPSCC were included. Forty-two (69%) were submitted to surgical resection, of which 37 (88%) had adjuvant treatment (24 received RT and 13 chemoradiotherapy). Nineteen (31%) were treated with primary RT, and 3 of them had concurrent chemotherapy. RT was given with intensity-modulated radiation therapy (IMRT) (71%) or three-dimensional conformal radiation therapy (3D-CRT) (29%). At a median follow-up of 5.4 years, there were 3 tumor persistences, 5 local failures, 2 regional failures and no distant metastasis. The 3-year and 5-year OS were 77% and 71% in the RT group vs. 71% and 59% in the surgery group, respectively (HR 0.60, 95% CI 0.22–1.61; $p = 0.30$). The 3-year and 5-year LRFS were 71% and 64% in the RT group vs. 66% and 50% in the surgery group, respectively (HR 0.59, 95% CI 0.24–1.45; $p = 0.24$). Up to 34% had acute grade 3 toxicity and 11% had grade 4 osteoradionecrosis of the jaw.
Conclusions: Longer follow-up still does not show a significant difference in OS and LRFS between both treatments. Because most patients submitted to surgery required adjuvant RT and since its side-effects were not negligible, further studies are warranted to better suit the first treatment for each patient and to prevent the need for adjuvant treatment and the risk of toxicity.

Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is a relatively rare disease. In the United States, each year, there is approximately 49,670 new cases, which represents about 2.9% of all new cancer cases, and about 9,700 deaths [1]. Tobacco and alcohol are two of the main risk factors, affecting older patients who also have high risk of second head and neck or aerodigestive cancer due to field cancerization [2]. While prevention campaigns against smoking have led to a decrease in these tumors [3], there has been a significant increase in OPSCC related to human papillomavirus (HPV), which currently represents approximately 39% of OPSCC in Europe and 56% in North America [4]. It presents mostly in younger patients without smoking or alcohol habits [3] and is associated with improved local control rate, progression-free survival and overall survival [5,6].

The management of patients with OPSCC remains controversial. In the past, it was usually treated with open surgery, which was associated with severe complications, poor function, bad cosmetic results and did not avoid adjuvant therapy in many cases. Then attention was turned to organ preservation approaches with radiotherapy (RT) as primary treatment [6].

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Current guidelines for early stage OPSCC (T1-2 N0-1), such as National Comprehensive Cancer Network (NCCN 2.2017), recommend definite RT, primary surgery or, in case of T2N1, chemoradiotherapy (CRT). After RT, persistent or progressive disease can be treated with resection of residual primary or neck dissection. And after primary surgery, if there is extracapsular spread or a positive margin (high-risk features), the patient should receive adjuvant CRT. When other adverse features are present (pT3-4 primary, N2-3 nodal disease, nodal disease in levels IV or V, perineural invasion or vascular embolism), adjuvant RT should be given and concomitant systemic therapy can also be considered.

Even though surgery and primary RT seem to be equally effective in terms of local control and overall survival [7,8], no randomized trial comparing both options in early-stage OPSCC has been published yet and most data come from retrospective trials. Two randomized controlled trials are currently ongoing (EORTC 1420 and ORATOR), but early results are expected in 2021 [9].

The purpose of this study is to present a retrospective, nonrandomized analysis of the outcomes of OPSCC submitted to primary surgery or primary RT in a single tertiary center.

Material and methods

Patients

Retrospective study with the following inclusion criteria: (1) patients diagnosed with histologically confirmed OPSCC between January 2009 and December 2014; (2) clinical stage T1 or T2 N0/N1 M0; (3) primary treatment with surgery or RT.

Evaluation

All patients were initially evaluated by a multidisciplinary tumor board. Diagnosis was established by biopsy. The extent of the disease was evaluated with a detailed physical examination of the head and neck region, flexible fiberoptic endoscopic examination, computed tomography or magnetic resonance imaging of head and neck region with contrast enhancement, chest X-ray, complete blood counts, liver function tests and basic metabolic panel. Dental evaluation and preventive measures or necessary tooth extractions were performed before any treatment. The disease was staged according to the 7th edition of Tumor Node Metastasis (TNM) system of American Joint Committee on Cancer (AJCC, 2010).

Treatment

Patients were submitted either to primary surgery or primary RT. Resectable tumors were selected to surgery at the description of the treating physician. When clinically indicated, according to NCCN guidelines, adjuvant RT was delivered. If one high risk factor or more than one adverse feature were present, RT was given concomitantly with chemotherapy (CT). Tumors where surgery would have been too mutilating, were treated with primary RT. Patients with nodal disease also received concomitant CT, unless they had more than 70 years-old or co-morbidities that increased the risk of toxicity.

Surgical approach was chosen according to the location of the primary tumor (partial pharyngectomy, partial tonsillectomy, hemiglossectomy) and always included unilateral or bilateral lymph node dissection.

RT was administered as intensity-modulated radiation therapy (IMRT) using simultaneous integrated boost (SIB) or three-dimensional conformal radiation therapy (3D-CRT). The prescribed dose was 66–70 Gy to the high-risk planning target volume (PTV) and 50–54 Gy to the low/intermediate-risk PTV.

High-dose cisplatin was used as systemic therapy (intravenous administration of 100 mg/m^2 at D_1, D_{22}, D_{43}).

We analyzed patient charts, multidisciplinary clinical evaluation, imaging and clinical data regarding the tumor, primary and adjuvant therapies, treatment-related morbidity and tumor response.

Acute toxicity (any adverse event occurring within 90 days of RT), was graded according to Common Terminology Criteria for Adverse Events (v4.0). Late toxicity was scored according to Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer criteria.

Follow-up

Patients were typically evaluated 1–2 months after the end of treatment and then every 3 months during 3 years, every 6 months during the following 2 years and then annually. Post-treatment baseline imaging of the head and neck region was carried out within 2 months of treatment and then every 6 months. Chest X-ray and laboratory evaluation were performed every 6 months. A positron emission tomography was also obtained when clinically indicated. Any suspicious lesion was biopsied.

Statistical analysis

Comparison of clinical and demographic variables between surgical and RT primary treatment groups was done using two-sample t-test for age, Fisher's exact test for sex, clinical T and N classifications and Pearson's Chi-squared test with computed *p*-values by Monte Carlo simulation (based on 2000 replicates) for smoking and drinking status and clinical AJCC stage. Toxicities between the two groups were compared using Fisher's exact test.

Overall survival (OS) and locoregional recurrence-free survival (LRFS) were analyzed using the Kaplan–Meier method and log-rank test for group comparison. Hazard ratios (HR) were estimated using proportional hazards Cox regression model. We estimated the crude HR and the adjusted HR controlling for the clinical and demographic variables with different distribution between treatment groups. LRFS was defined as the time from the first day of treatment to loco-regional relapse or death from any cause. Cases of persistent local disease after treatment, defined as presence of viable tumor cells within 6 months of treatment (surgery or definitive/adjuvant RT), were considered events for LRFS endpoint at the time of evaluation. OS was defined as time elapsed from the first day of treatment to death from any cause.

Results

Sixty-one patients were initially identified with cT1-T2 cN0-N1 M0 OPSCC. They were treated with surgical resection or primary RT. Seven were surgically upstaged to pT1 pN2(2), pT2 pN2 (3) or pT3 pN0 (2). Fifty-two (85%) were male and 9 female (15%), with a median age of 57 years-old (range 36–86). Forty-nine (80%) were current moderate to heavy-smokers (more than 10 pack-years) and 37 (61%) were current moderate to heavy-drinkers (more than 14 units of alcohol per week).

The primary site included tonsil in 34 patients (56%), soft palate in 15 (24%) and base of tongue in 12 (20%). The tumor was clinically classified as T1 in 17 patients (28%) and T2 in 44 (72%). Forty-two were node-negative (69%) and 19 node-positive (31%). The disease was in stage I in 13 patients (21%), stage II in 29 (48%) and stage III in 19 (31%). Patient demographics and tumor-

related characteristics are listed in Table 1. Fig. 1 shows the study design algorithm.

Forty-two patients received primary surgery (69%). Thirty-seven required adjuvant treatment (88%) with RT (24) or CRT (13), due to positive surgical margins (12), close margins (24) and/or other features, including lymphovascular invasion (6), pN2 (5),extracapsular nodal spread (4), perineural invasion (4) and/or pT3 (2).

Nineteen were treated with primary RT (31%) and 3 of them received concomitant CT.

Overall, 56 patients (92%) were submitted with primary (19) or adjuvant RT (37). Thirty-three were treated with IMRT-SIB (71%) and thirteen (29%) with 3D-CRT.

The median follow-up for the surviving patients was 5.4 years (range 0.3–7.9 years).

Three patients had tumor persistence (5%), 5 had local failure (8%) and 2 regional failure (3%). Of these 10 patients, 4 had been treated with primary RT, 1 with primary surgery and 5 with surgery and adjuvant RT for close margins.

Overall, 3-year and 5-year OS were 73% and 63%, and 3-year and 5-year LRFS were 68% and 54%, respectively. The Kaplan–Meier OS and DFS curves are shown in Figs. 2 and 3. Median OS was 6.5 years in the surgery group and was not reached in the RT group or when considering the whole cohort. Median LRFS was 6.5 years in the whole cohort, 6.1 years in the surgery group but not reached in the RT group.

The 3-year and 5-year OS were 77% and 71% in the RT group vs. 71% and 59% in the surgery group, respectively (p = 0.30). The 3-year and 5-year LRFS were 71% and 64% in the RT group vs. 66% and 50% in the surgery group, respectively (p = 0.24). The crude hazard ratios for the comparison of OS and LRFS between primary RT vs. primary surgery were 0.60 (95% CI 0.22–1.61) and 0.59 (95% CI 0.24–1.45), respectively. When adjusting for age and location, the HRs for OS and LRFS both decreased to 0.51 (95% CI 0.17–1.54) and 0.52 (95% CI 0.19–1.44), respectively, without statistical significance in both cases.

Twenty-three patients died, 5 due to local progression, and the remaining due to non-oropharyngeal cancer causes: second tumor (5), infection (4), suicide (1), undetermined (8). No one developed distant metastasis.

Acute grade 3 toxicity was reported by 19 patients (34% of the patients treated with RT). The most common were mucositis (29%), dysphagia (18%), dermatitis (11%) and xerostomia (2%). They were just as common in the adjuvant setting as they were in the primary one (32% vs. 37%; odds ratio [OR] = 1.21; 95% CI 0.32–4.44; p = 0.77). Most of these patients (17) were treated with IMRT and half of them (9) received concomitant CRT. The odds of acute grade 3 toxicity was higher in concomitant CRT compared to isolated RT (56% vs. 25%; OR = 3.75, 95% CI 0.96–15.56; p = 0.03) and also in IMRT compared to 3D-CRT (43% vs. 13%; OR = 5.04; 95% CI 0.95–51.57; p = 0.059), but the latter was not statistically significant. There was no grade 4 acute side effects.

Severe late toxicity was reported by 6 patients (11%), all of whom had grade 4 osteoradionecrosis (ORN) of the jaw (half required hyperbaric oxygen therapy). There was no grade 3 late side effects. Three of the patients who had mandibular ORN received primary RT and the other 3 adjuvant RT. Four were treated with 3D-CRT and 2 were given concomitant CT. The odds of ORN was higher in 3D-CRT-treated patients than IMRT (25% vs. 5%; OR = 6.08, 95% CI 0.76–74.97, p = 0.049). No statistically significant association could be demonstrated between ORN and primary or adjuvant RT (16% vs. 8%; OR = 2.09, 95% CI 0.25–17.44, p = 0.40) or concomitant CRT (13% vs. 10% isolated RT; OR = 1.28, 95% CI 0.10–10.15, p = 1.00).

Discussion

The management of OPSCC should be performed by specialized teams in a multidisciplinary tumor board setting. The choice of the right treatment is complex and should take into consideration multiple factors related to the patient (such as performance status,

Table 1
Patient demographics and tumor-related characteristics.

	All patients (n = 61)	Primary surgery (n = 42)	Primary radiotherapy (n = 19)	p
Age, years				
Mean (±SD)	59 (±11)	57 (±11)	63 (±10)	0.041
Median (IQR)	57 (51–65)	55 (50–63)	63 (55–70)	
Range	36–86	36–86	47–80	
Sex, n (%)				
Male	52 (85)	36 (86)	16 (84)	1.000
Female	9 (15)	6 (14)	3 (16)	
Smoking status, n (%)				
Current moderate/heavy smoker	49 (80)	34 (81)	15 (79)	0.757
Former smoker	4 (7)	2 (5)	2 (10.5)	
Lifelong non-smoker	8 (13)	6 (14)	2 (10.5)	
Drinking status, n (%)				
Current moderate/heavy drinker	37 (61)	24 (57)	13 (68)	0.818
Former drinker	4 (7)	3 (7)	1 (5)	
Lifelong non-drinker	20 (33)	15 (36)	5 (26)	
Subsite, n(%)				
Tonsil	34 (56)	30 (71)	4 (21)	0.002
Soft palate	15 (24)	7 (17)	8 (42)	
Base of tongue	12 (20)	5 (12)	7 (37)	
Clinical T stage, n (%)				
T1	17 (28)	12 (29)	5 (26)	1.000
T2	44 (72)	30 (71)	14 (74)	
Clinical N stage, n (%)				
N0	42 (69)	29 (69)	13 (68)	1.000
N1	19 (61)	13 (31)	6 (32)	
Clinical AJCC stage, n (%)				
I	13 (21)	9 (21)	4 (21)	1.000
II	29 (48)	20 (48)	9 (47)	
III	19 (31)	13 (31)	6 (32)	

AJCC, American Joint Committee on Cancer; SD, standard deviation; IQR, Interquartile range.

comorbidities, compliance, previous RT), the tumor (location, TNM stage, HPV status) and the physician's expertise.

Early-stage OPSCC is currently treated with primary surgery or primary RT, based on previous retrospectives series that have shown similar control and survival rates [8]. On top of survival, at the moment, the discussion between the two options is also about toxicities and quality of life, since the epidemiological shift toward HPV-related cancer has meant that we are now treating

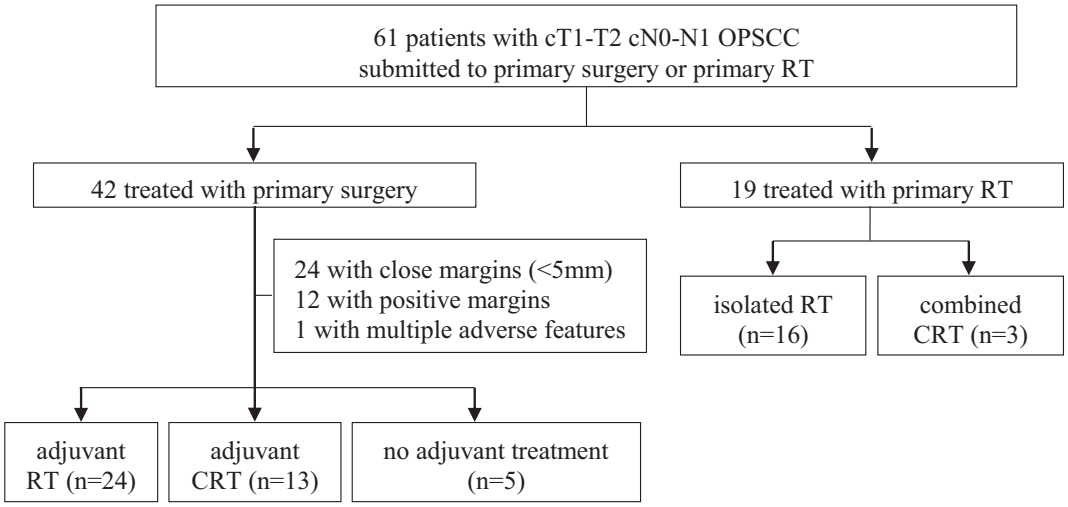

Fig. 1. Study design algorithm. OPSCC, oropharyngeal squamous cell carcinoma. RT, radiotherapy. CRT, chemoradiotherapy.

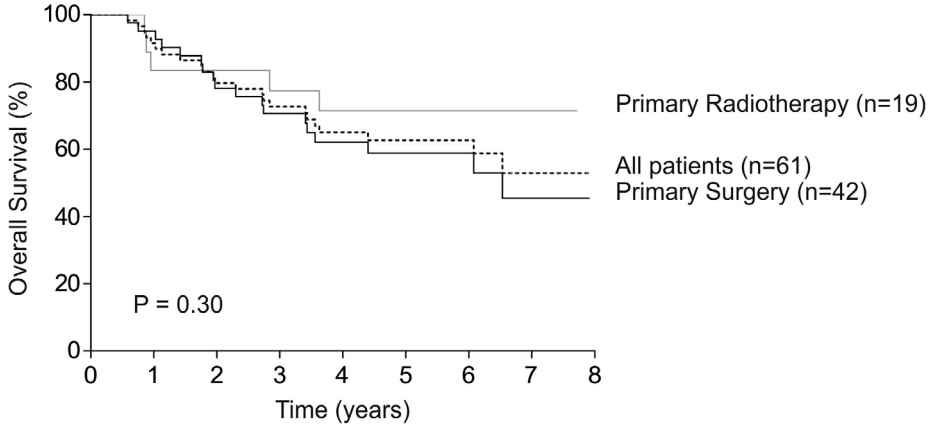

Fig. 2. Estimate of overall survival for patients with cT1-T2 cN0-1 oropharyngeal squamous cell carcinoma by upfront treatment.

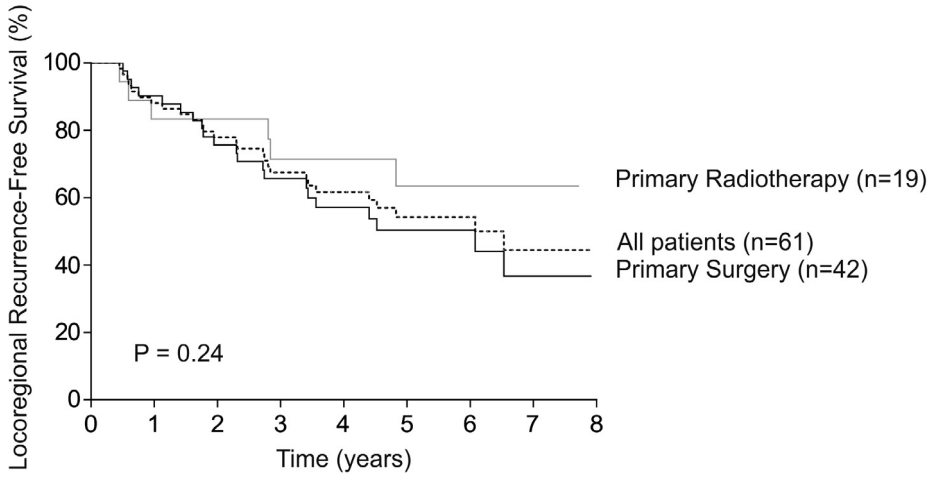

Fig. 3. Estimate of locoregional recurrence-free survival for patients with cT1-T2 cN0-1 oropharyngeal squamous cell carcinoma by upfront treatment.

younger patients with good prognosis that are more likely to survive and suffer the long-term side-effects. Given the fact that both modalities are associated with complications [8], focus has turned to minimally invasive techniques (such as transoral robotic surgery, TORS) or de-escalation strategies (reduction of radiation dose or sensitizer modification in HPV-positive disease) [10]. However, until randomized trials clarify the benefit of TORS or reduced-dose radiation over conventional treatments and because robotic surgery is not readily available in most hospitals, the discussion between surgery vs. RT in early-stage OPSCC is still open. To our knowledge, published studies directly comparing the two modalities, specifically in early-stage disease, are limited and therefore, that is the purpose of this report.

Before comparing the two groups, it is important to note that despite the curative intent of surgery, 88% of these patients received multimodal treatment. In most cases, adjuvant therapy was required due to close (57%) or positive (29%) margins. Therefore, surgery as sole treatment was unlike in the majority of patients, since only 12% (n = 5) did not receive adjuvant therapy.

Nevertheless, when we consider the primary approach, as expected, there was no significant difference in 3-year and 5-year OS and LRFS between the two treatments. Our 5-year OS (63%) was slightly lower than average rates reported in literature, which is usually over 80% [3].

In terms of toxicity, our results are consistent with previous studies that have shown similar rates of grade 3 acute side-effects: mucositis in 14–25% of patients, dysphagia in 10–15% and dermatitis in 6–18% [11–13]. The late toxicity rate was lower than other series, who report up to 35% severe late side-effects [14]. Our rate of ORN, however, was higher than the 5–7% described in the literature [3], but previous reports of our center have already documented poor oral healthcare among our patients [15].

The main limitation of this report is the retrospective nature of this analysis and the small sample size. Another drawback is that outcomes were not stratified by HPV status (our center did not routinely test for HPV during the time period analyzed in this study). Due to its strong prognostic value, this could possibly have shown some differences between the two treatments. However, comparing the two groups (surgery and RT), both had 80% of moderate/ heavy smokers and that could override the HPV impact. In addition, knowing that function and quality of life are currently main endpoints when comparing both treatments, the absence of their thorough evaluation also impairs the comparison between surgery and RT.

Our preliminary results have already been presented [16]. As our data matured, results consistently show no difference in outcomes regardless the primary treatment.

To conclude, despite the limitations mentioned above, our results are consistent with the literature. Until randomized trials are published, this report contributes to the growing knowledge and experience in OPSCC, through a direct comparison between surgery and primary RT in early-stage disease.

Conclusions

This analysis confirms there is not a significant difference in OS and LRFS between surgery and primary RT. However, it highlights the fact that most patients submitted to upfront surgical resection required adjuvant treatment. RT was associated with significant acute side effects, both in the adjuvant and the primary setting, but the overall late toxicity rate was low. Further studies should help clarify the best first approach for each patient, in order to prevent the need for unnecessary treatments and the risk of toxicity.

Prior presentation

Preliminary results were presented in e-poster form at ESTRO 36, Vienna, May 2017.

Conflict of interest

The authors declare that they have no conflict of interest.

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