Treatment: Outcome and Toxicity of Volumetric Modulated Arc Therapy in Oropharyngeal Carcinoma

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Abstract. *Background/Aim: Radiotherapy is a common approach for treating squamous cell carcinoma (SCC) of the oropharynx. We aimed to analyze toxicity and outcome of patients affected by oropharyngeal SCC treated with volumetric modulated arc therapy (VMAT). Patients and Methods: Fifty-four patients presenting advanced orophayngeal carcinoma who were treated with radical radiotherapy were analyzed. All patients were treated with VMAT-RapidArc, with simultaneous integrated boost in 33 fractions for a dose of 69.96 Gy to the high-risk, and of 54.45 Gy to the low-risk volume. Results: Median follow-up was 23 months. In eight cases, locoregional relapse was observed (median time to relapse=10.7 months). Four among eight local recurrences appeared in the high-dose target volume. The 1- and 2-year actuarial disease-free survival rates were 88% and 80%, respectively. The 1- and 2-year actuarial overall survival rates were 94% and 87%, respectively. Conclusion: VMAT for oropharyngeal SCC treatment is effective and safe, with interesting rates of control of disease and survival.*

Radiotherapy (RT) is currently a common approach for treating squamous cell carcinoma (SCC) of the oropharynx, due to evidence of survival rates similar to those after surgery (1). The combination of chemotherapy (CHT) to RT improved survival compared to RT alone but with an increase in toxicity rates (2-4). Oropharyngeal carcinoma, compared to other head and neck tumors, is characterized by high cure rates; for this reason, the quality of life of patients and the side-effects of treatments are of great importance.

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The introduction of intensity-modulated radiotherapy (IMRT) for head and neck tumours led to delivery of RT treatments characterized by highly conformed doses. Different dosimetric studies demonstrated a reduction of doses to the organs at risk (OARs) and better coverage of targets with IMRT compared to 3D conformal RT (3DCRT) (5-10). Recently, a phase III trial demonstrated a reduction of xerostomia in patients with head and neck tumours treated with parotid-sparing technique (11). On this basis, the use of IMRT as definitive treatment for oropharynx cancer has increased exponentially in the past decade, becoming the standard-of-care in many centres across the world. As a further evolution of IMRT, volumetric modulated arc therapy (VMAT) has been introduced. VMAT can be considered an appealing approach for treating oropharyngeal carcinoma because of the presence of several OARs and the frequent concave shape of the target. This technique has been studied for dosimetric benefit in head and neck cancer (12-14), but few studies have explored its possible clinical benefits (15-17). In particular, there is a lack of publications evaluating the toxicity profile and outcome using the VMAT approach.

We have implemented the VMAT technique for all head and neck tumors since 2009, associated with simultaneous integrated boost (SIB), delivering the whole treatment in 33 fractions. In this study, we aimed to analyze the toxicity and outcome of patients affected by oropharyngeal carcinoma treated only with VMAT technique and SIB.

Patients and Methods

Patient selection. The records of 54 patients affected by oropharyngeal SCC treated with VMAT from 2009 to 2015 at Humanitas Hospital were analyzed. All patients were treated in agreement with the Helsinki declaration. Informed consent was obtained from all individual participants included in this study, according to the procedure established by the Humanitas Cancer Center Ethical Committee for retrospective data analysis (included in the informed consent protocol). Patients were staged according to the American Joint Committee on Cancer (AJCC)

staging system (18). Clinical and disease characteristics of the patients are shown in Table I. Before treatment, patients underwent staging work-up, including history taking, physical examination, head and neck examination with laryngoscopy, and computed tomography (CT) and magnetic resonance imaging (MRI) of the head and neck region.

Radiotherapy. A contrast-enhanced simulation CT with 3 mm slices was obtained for treatment planning; if necessary, a contrast-enhanced MRI or a ^{18}Fluorodeoxyglucose positron-emission tomography (PET) were acquired and registered with CT to define the target. The gross tumor volume (GTV) was delineated. The high-risk clinical target volume (CTV) encompassed the GTV with an additional 1 cm margin, correcting for anatomical boundaries. The low-risk CTV included the elective nodes according to internationally accepted guidelines (18). An isotropic 5 mm margin was then added to CTVs to obtain the planning target volumes (PTV). PTVs were cropped 4 mm inside the body contour. Normal structures, including the parotid glands, oral cavity, mandible, optic nerves and chiasm, brainstem, larynx, pharynx, oral cavity, thyroid, and spinal cord, were also contoured on the CT scans. All patients were treated with VMAT in its RapidArc form, with SIB in 33 fractions of 2.12 Gy to the high-risk volume, and of 1.65 Gy to the low-risk volume, for a total dose of 69.96 Gy and 54.45 Gy, respectively.

RapidArc treatments used 6 MV beams from either TrueBeam, Clinac DHX, or Unique linear accelerator (Varian Medical Systems). All treatment units were equipped with a multileaf collimator Millennium 120-MLC (Varian Medical Systems, Palo Alto, CA, USA). Treatment plans were optimized for two to four full arcs with different collimator angles according to the patient anatomy. The progressive resolution optimizer (PRO) engine was used for inverse planning and doses were estimated with anisotropic analytical algorithm (AAA) dose calculation algorithm on the Varian Eclipse treatment planning system (versions 8.5 to 11; Varian Medical Systems).

Dose planning objectives and dose evaluation. Dose planning objectives for PTVs were: 95% of the prescribed dose to cover 95% of the PTV ($V_{95\%}$>95%); near-to-maximum dose to high-risk PTV ($D_{2\%}$) below 105% of its prescription dose; near-to-maximum dose minimized for the low-risk PTV.

Concerning OARs, the mean dose to the parotids was to be <26 Gy to the full gland, near-to-maximum dose ($D_{0.1\ cm^3}$) to the spinal cord and brainstem below 45 Gy and 54 Gy, respectively. The volume of the oral cavity receiving medium-high doses was analysed. Constrictor muscles and larynx were not included in the optimization process, while keeping their dose as low as possible. Mean dysphagia threshold doses to constrictors were considered to be 51, 48 and 32 Gy to the superior, middle and inferior constrictors, respectively, for late toxicity. A mean laryngeal dose of 43.5 Gy was considered as predictive for laryngeal oedema.

Many quantitative dose–volume histogram (DVH) parameters were analysed for all patients.

Chemotherapy. In 43 cases (79.6%) concurrent systemic treatment was added to RT. Thirty-five patients (64.8%) received cisplatinum-based CHT and eight (14.8%) patients received cetuximab for medical contraindication to cisplatinum. Induction CHT was administered to 24 patients. The most common schedule for induction CHT included docetaxel, cisplatin and 5-fluorouracil; only one patient was treated with the combination of carboplatin and 5-fluorouracil.

Table I. *Patients' characteristics*.

Total number of patients		54 (%)
Age, years	Median	66
	Range	31-86
Gender, n (%)	Male	37 (68.5%)
	Female	17 (31.5%)
Performance status, n (%)	0	36 (66.6%)
	1	15 (27.7%)
	2	3 (5.7%)
Sub-site, n (%)	Base of tongue	17 (31.4%)
	Left tonsil	17 (31.4%)
	Right tonsil	16 (29.6%)
	Soft palate	2 (3.7%)
	Posterior wall	2 (3.7%)
T-Stage, n (%)	1	10 (1.8%)
	2	20 (37%)
	3	11 (20.3%)
	4a	8 (14.8%)
	4b	5 (9.2%)
N-Stage, n (%)	0	10 (18.5%)
	1	4 (7.4%)
	2a	3 (5.5%)
	2b	20 (37%)
	2c	15 (27.7%)
	3	2 (3.7%)
TNM Stage, n (%)	I	1 (1.8%)
	II	5 (9.2%)
	III	4 (7.4%)
	IVa	37 (68.5%)
	IVb	7 (12.9%)
Induction CHT, n (%)	TPF	22 (40.7%)
	CBCDA+5FU	1 (1.8%)
	No	31 (57.5%)
Concomitant CHT, n (%)	Cisplatinum, every week	31 (57.4%)
	Cisplatinum, every 3 weeks	4 (7.4%)
	Cetuximab	8 (14.8%)
	No	11 (20.4%)
OTT, months	Median	49
	Range	43-69
Local response, n (%)	CR	46 (85.2%)
	PR	6 (11.1%)
	Unknown	2 (3.7%)
Recurrence, n (%)	No	43 (79.6%)
	Yes	11 (20.4%)
Local recurrence, n (%)	Yes	8 (14.8%)
Distant recurrence, n (%)	Yes	4 (7.4%)
Follow-up, months	Median	23
	Range	4-63

CHT: Chemotherapy; TPF: docetaxel, cisplatin and fluorouracil; CBCDA+5FU: carboplatin+5-fluorouracil; OTT: overall treatment time; CR: complete remission; PR: partial remission.

Toxicity assessment and follow-up. Toxicity was recorded and graded according to the Common Toxicity Criteria CTCAE version

4 (20). It was defined as acute when occurring during radiotherapy and in the first 3 months after, and late when occurring at between 6 and 12 months after the end of RT.

All patients had at least weekly clinical evaluation during treatment, and at 1 month after treatment. Patient follow-up continued according to the schedule of every 3 months for the first 3 years, every 6 months for fourth and fifth years, and then yearly. Post-treatment imaging study was obtained at the first follow-up visit and then as clinically indicated. Response to the treatment was evaluated with CT/MRI according to RECIST criteria v. 1.2 (21), with PET for metabolic activity and clinical assessment.

Survival endpoints were measured from the end of the RT treatment to the last follow-up date. Kaplan–Meier curve analysis method was used; a log-rank test was executed to compare groups. A *p*-value of less than or equal to 0.05 was considered statistically significant.

Results

The median follow-up, as calculated from the start of RT, was 23 months (range=4-63 months) and at the time of analysis, 48 patients were alive. All patients completed the planned treatment and the median overall treatment time (OTT) was 49 days. At evaluation of response, complete remission was confirmed in 46 cases and partial response in six. Among all patients treated, locoregional relapse was observed in eight with a median time to relapse of 10.7 months (range=7.1-44.9 months). Four among eight local recurrences appeared in the high-dose PTV, while one appeared at the junction between the high- and low-dose PTVs. Distant metastases developed in four patients in a median time of 4.4 months (range=4.1-27.7 months).

The 1- and 2-year disease-free survival (DFS) rates were 88.0% and 80.0%, respectively. The 1- and 2-year overall survival (OS) rates were 93.6% and 87.2%, respectively. On univariate analysis, age, gender, TNM stage and OTT had no significant impact on DFS or OS, nevertheless the use of induction CHT seemed to have a positive effect on DFS (p=0.004) but not OS (p=0.06) (Figure 1). Concomitant CHT (cisplatinum or cetuximab) did not affect survival in our analysis.

Regarding the pattern of toxicity, the most common acute side-effects concerned the skin and mucosa, as shown in detail in Table II. Grade 1-2 skin toxicity was observed in 76% of patients, and grade 1-2 mucosal toxicity in 78%. Grade 3 toxicity of skin and mucosa was observed in 7% and 13%, respectively. Acute dysphagia was reported as grade 3 in 4%, and acute xerostomia as maximum grade 1-2 in 28%. No patient required a feeding tube.

In the early late setting summarized in Table II, grade 3 dysphagia was reported by one patient. Late xerostomia was more frequent, being described in 39% of the population as grade 1-2, and in 7% as grade 3. No case of grade 4 toxicity was observed in the acute nor late settings. In one case, trismus appeared during follow-up after RT.

Dose parameters for OARs were evaluated to check for possible correlations with the toxicity profile; data for most important OARs are reported in Table III. At ANOVA univariate analysis, a significant correlation was found for the mean dose to the oral cavity affecting acute mucositis (p=0.04). No other dosimetric parameter was found to significantly affect acute toxicity in OARs. Regarding late toxicity, parotid volume was found to positively correlate with xerostomia (p=0.03), while a borderline significance was found for median dose (p=0.05) and $D_{33\%}$ (p=0.07). No correlation was found of dysphagia with constrictor muscles dosimetric parameters in acute and late settings. For the one patient who presented trismus after RT, we found the mean dose to the temporo-mandibular joint was 52.1 Gy (for 6.4 cm^3) and the volumes receiving more than 50, 60 and 70 Gy were 3.9, 2.8, and 0.7 cm^3, respectively.

Discussion

The use of VMAT has raised interest for patients with head and neck cancer since its introduction in 2008. Several trials have investigated the benefit of IMRT in head and neck cancer. Recently a randomized trial demonstrated that IMRT allows parotid sparing, significantly reducing the incidence of xerostomia (11). Moreover, the use of SIB reduces the OTT (22). Many dosimetric comparisons of VMAT with other RT techniques (3DCRT, IMRT) have been published (12, 13, 23-27), showing in general better PTV dose homogeneity and coverage, together with better sparing of OARs. On the other hand, few trials investigated the clinical aspects of VMAT for definitive treatment of head and neck cancer.

In the current study, we analyzed the outcome and toxicity of 54 patients affected by oropharyngeal SCC and treated with exclusive RT or concomitant CHT-RT both with radical intent. To our knowledge, this is the only study in the literature investigating the role of VMAT technique in a group of patients affected by oropharyngeal carcinoma. Large analyses have been reported about the role of IMRT for this site. Huang *et al*. evaluated IMRT in a cohort of 71 patients affected by Stage III-IV SCC of the oropharynx. Patients were treated with three dose levels, 70 Gy in 2.12 Gy per fraction for GTV, 59.4 Gy in 1.80 Gy per fraction for high-risk CTV, and 54 Gy in 1.64 Gy per fraction for low-risk CTV. They found 3-year actuarial rates of locoregional control (LRC) and OS of 90% and 83%, respectively (28). With a similar group of patients, Chao *et al*. reported 4-year LRC and OS of 87% and 87%, respectively, at a median follow-up of 33 months after treating all patients with 70 Gy, 63 Gy and 56 Gy in 35 fractions to high-, intermediate- and low-risk volumes, respectively (29). Furthermore, a group of Stanford University analysed 107 patients affected by oropharyngeal SCC, mostly at locally advanced stage (stage

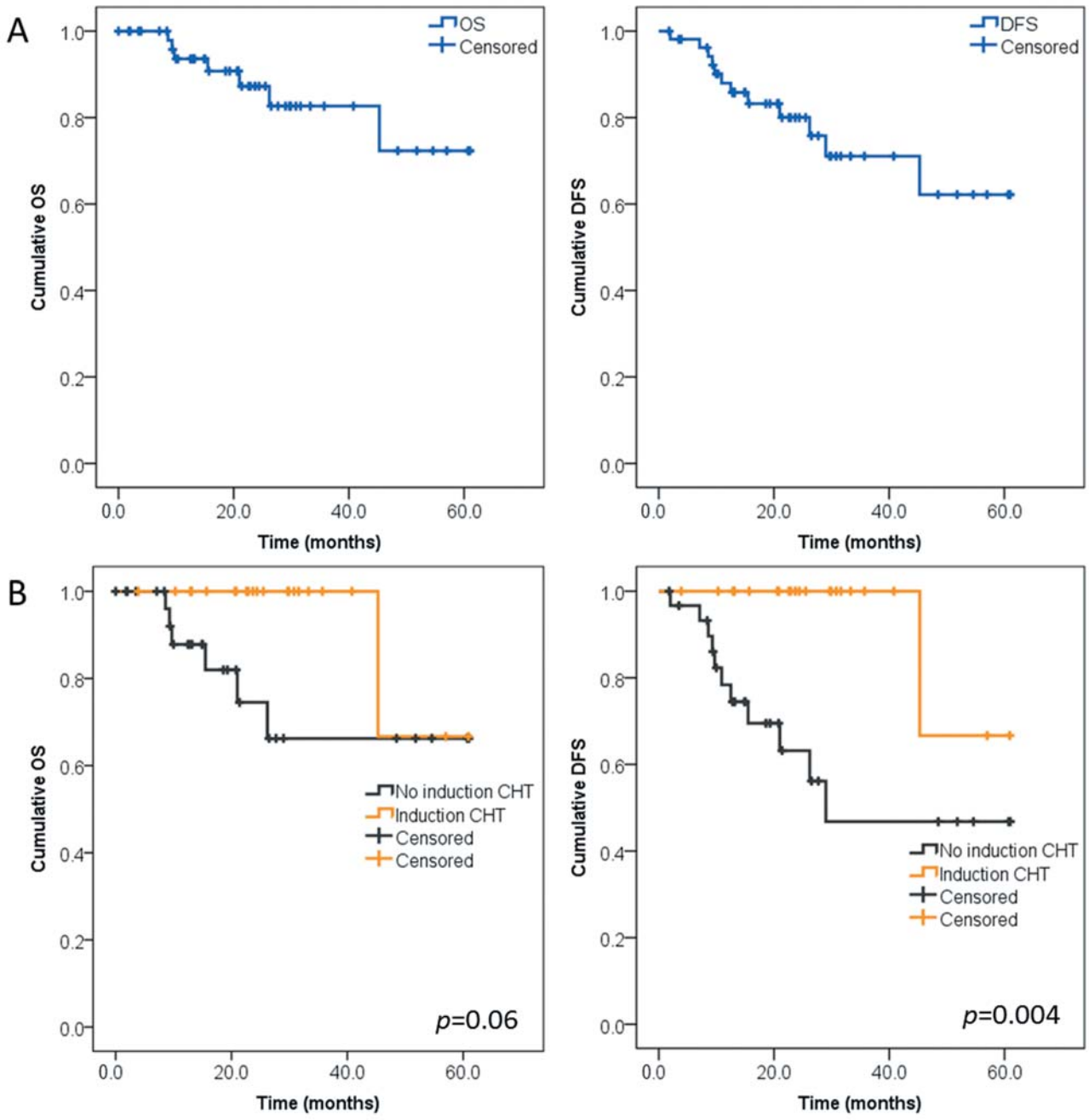

Figure 1. *Overall (OS; left) and disease-free (DFS; right) survival for the whole patient cohort (A) and stratified for induction chemotherapy (CHT) (B).*

III/IV in 96% of the cohort). Three dose levels were used even in this study: 66 Gy at 2.2 Gy per fraction to the high-risk PTV, 54 Gy at 1.8 Gy per fraction to the standard-risk PTV, and 50-52 Gy at 1.67-1.73 Gy per fraction to the low-risk PTV. They demonstrated 3-year LRC, freedom from distant metastasis, OS, and DFS rates of 92%, 92%, 83%, and 81%, respectively (30).

In our analysis, we found 2-year DFS and OS rates of 80.0% and 87.2%, which can be considered in line with the results of previous studies on IMRT. We have to take into account that in our population sample, 81% of patients presented stage IV disease. So far, only Smet *et al*. have compared IMRT with VMAT in patients affected by head neck cancer. Their study included different subsites, mainly

Table II. *Acute and late toxicity experienced by patients after volumetric modulated arc therapy for oropharyngeal carcinoma.*

Toxicity	Grade	Acute toxicity, n (%)	Late toxicity, n (%)
Skin	0	9 (17%)	54 (100%)
	1	22 (41%)	0 (0%)
	2	19 (35%)	0 (0%)
	3	4 7%)	0 (0%)
	4	0 (0%)	0 (0%)
Mucosal	0	6 (11%)	52 (96%)
	1	17 (31%)	1 (2%)
	2	25 (46%)	1 (2%)
	3	7 (13%)	0 (0%)
	4	0 (0%)	0 (0%)
Dysphagia	0	28 (52%)	50 (93%)
	1	9 (17%)	3 (6%)
	2	15 (28%)	0 (0%)
	3	2 (4%)	1 (2%)
	4	0 (0%)	0 (0%)
Salivary	0	39 (72%)	29 (54%)
	1	12 (22%)	11 (20%)
	2	3 (6%)	10 (19%)
	3	0 (0%)	4 (7%)
	4	0 (0%)	0 (0%)
Taste	0	31 (57%)	39 (72%)
	1	16 (30%)	9 (17%)
	2	7 (13%)	6 (11%)
	3	0 (0%)	0 (0%)
	4	0 (0%)	0 (0%)
Other	No	54 (100%)	51 (94%)
	Yes	0 (0%)	3 (6%)

Table III. *Dosimetric data for volumetric modulated arc therapy for oropharyngeal carcinoma.*

Organ at risk	Parameter	Mean±SD (SE)
Oral cavity	Volume (cm^3)	126.0±23.5 (0.5)
	Mean (Gy)	50.3±6.6 (0.1)
	V_{60Gy} (%)	38.8±16.1 (0.3)
Parotids	Volume (cm^3)	23.2±9.2 (0.1)
	Mean (Gy)	27.3±8.4 (0.1)
	$D_{1/3V}$ (Gy)	32.7±10.5 (0.1)
	Median (Gy)	22.9±10.3 (0.1)
Submandibulars	Volume (cm^3)	8.6±2.5 (0.1)
	Mean (Gy)	63.0±8.9 (0.1)
Constrictors, inferior	Volume (cm^3)	4.6±1.5 (0.1)
	Mean (Gy)	43.7±8.6 (0.2)
Constrictors, middle	Volume (cm^3)	2.6±1.1 (0.1)
	Mean (Gy)	58.2±9.1 (0.2)
Constrictors, superior	Volume (cm^3)	11.2±2.6 (0.1)
	Mean (Gy)	66.5±4.5 (0.1)

SD: Standard deviation; SE: standard error of the mean.

oropharynx (41% in IMRT *vs*. 44% in VMAT group), and almost all patients were classified as having stage III-IV disease. No significant differences were observed in 3-year OS (70.8 *vs*. 57.3%, p=0.219) or LRC (84.9 *vs*. 72.7%, p=0.118) between the two groups but a significantly better DFS in favour of VMAT was seen (64.4 *vs*. 56.5%, p=0.016) (17). We found eight locoregional recurrences; four were located in the high-risk volume, three in the low-risk volume and one at the junction between the two volumes. In the literature, data exist regarding marginal failure in patients treated with IMRT for head and neck cancer. An incidence rate of 3% was reported by Schoenfeld *et al*. (31) and Eisbruch *et al*. (32). Sanguineti *et al*. analysed the local recurrence in a group of patients affected by oropharyngeal carcinoma and found on retrospective observation that failures were associated with involved lymph nodes included in the low-dose target (33).

Regarding the treatment-related toxicity, our results appear quite favourable since there was an absence of grade 4 or more events in the acute and early late settings. Considering that IMRT represents the standard of care for head and neck tumours, due to the possibility to reduce OAR morbidity, 3DCRT should not be take into account as a comparison. In the work of Daly *et al*. about 107 patients treated with IMRT for oropharyngeal carcinoma (definitive or adjuvant), the majority of patients experienced grade 2 (42%) or grade 3 (56%) acute mucosal or skin toxicity, with no grade 4 toxicity reported (30). In our analysis of patients all treated with radical intent and VMAT technique, acute grade 3 toxicity was uncommon, representing 7% for skin and 13% for mucosa. No higher than grade 3 toxicity appeared in our patients, while one of grade 5 occurred in analysis of Daly *et al*. Some contribution to these lower rates of toxicity could come from our fractionation, already described in our previous study on locally advanced head and neck SCC (34). Smet *et al*. evaluated clinical results by comparing two groups of 78 and 79 patients treated with IMRT or VMAT technique, respectively (17). The fractionation was 20 fractions of 2 Gy followed by four fractions of 1.6 Gy twice a day to the elective volume, followed by 16 fractions of 1.6 Gy twice a day to the boost volume (no SIB), for a total treatment time of 6 weeks (30 days). Grade 3 acute mucositis was reported in 49% of the patients, grade 3 dysphagia in 63%, and there was one case of grade 4 dysphagia. This toxicity profile is worse than what we report here, the main difference between the two studies being the fractionation scheme. The different fractionations and toxicity scores reported in literature led to difficulty in comparing data in a systematic way. The use of altered fractionation RT is commonly associated with a borderline significant increase in the incidence of grade 3-4 acute mucositis compared to conventional fractionation, as seen in a recent review. Altered fractionation was also associated with a significantly reduction of the risk of late xerostomia; in fact the odds ratio

of grade 3 or worse xerostomia was 0.59 in favour of altered compared with conventional fractionation (35). A complete analysis of the long-term late toxicity was not possible for our group given the median follow-up of 23 months.

There are some limitations to the current work: the short follow-up, together with the retrospective nature of the analysis, and the rather limited number of patients. The work will however continue, by collecting data for longer follow-up, as well as including a larger number or patients.

In conclusion, our results confirm the effectiveness and safety of VMAT for the treatment of oropharyngeal SCC, with interesting toxicity profiles, DFS and OS. Due to existing heterogeneity the in literature, prospective trials are still necessary to identify the doses and fractionations that provide the best balance between survival and toxicity.

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