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Original Research Article

Adaptive radiotherapy for oropharyngeal cancer with daily adapt-to-shape workflow on 1.5 T MRI-linac: Preliminary outcomes and comparison with helical tomotherapy

Andrea Emanuele Guerini [a,*,1], Michela Buglione [a,d,1], Stefania Nici [b], Stefano Riga [b], Ludovica Pegurri [a], Eneida Mataj [a], Davide Farina [c], Marco Ravanelli [c], Paolo Rondi [c], Gianluca Cossali [a], Davide Tomasini [a], Luca Triggiani [a], Giorgio Facheris [a], Luigi Spiazzi [b,d], Stefano Maria Magrini [a,d]

[a] *Department of Radiation Oncology, University of Brescia and Spedali Civili Hospital, Piazzale Spedali Civili 1, 25123 Brescia, Italy*
[b] *Medical Physics Department, ASST Spedali Civili Hospital, Brescia, Italy*
[c] *Radiology Unit, Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Spedali Civili, Piazzale Spedali Civili 1, 25123 Brescia, Italy*
[d] *Centro per lo Studio della Radioterapia guidata dalle Immagini e dai Biomarkers (BIO-RT) – Dipartimento di Specialità Medico-Chirurgiche, Scienze Radiologiche e Sanità Pubblica – University of Brescia, Italy*

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ABSTRACT

Introduction: MR-linac could offer several advantages for radical radiochemotherapy (RCHT) in oropharyngeal squamous cell carcinoma (OPSCC) patients. Currently, only a few case series have been published and no comparison with other techniques have been performed.
Methods: Data of 34 consecutive patients treated from September 2022 to May 2024 at a single Institution with RCHT on Unity® MR-linac for OPSCC with daily adaptive radiotherapy (RT) according to the adapt-to-shape (ATS) workflow were prospectively analyzed. A comparative cohort of 34 patients with similar characteristics treated with helical treatment on Radixact® was retrieved.
Results: Characteristics were well balanced across the two groups. Maximal toxicity grade ≥2 rate was borderline higher at RT end in MRI-linac group (p 0.049), but lower one month after RT (76.5 % vs 91.2 %; p = 0.257). Non-significantly lower rates of grade ≥2 xerostomia and dysgeusia were reported in Unity® group one and three months after RT. Higher rates of hospitalizations were reported in Radixact group at 20 fractions and at RT end (64.1 % vs 35.3 %; p = 0.015). Mean Karnofsky performance status (KPS) was higher in Unity group three months after RT (87.67 vs 83.87; p = 0.038).
After a median follow up of 361.5 days, local complete response was reported for 93.6 % of patients treated with Unity® and 96.8 % of patients treated with Radixact®.
Conclusions: Results of this analysis support the feasibility of an ATS MR-linac workflow for RCHT in OPSCC. Compared with tomotherapy, treatment with Unity® resulted in significantly lower rates of hospitalization and higher KPS three months after RT. Grade 2 xerostomia and dysgeusia rates were non-significantly lower in Unity group. Optimal results in terms of local control were reported for both techniques.

* Corresponding author.
E-mail addresses: andrea.guerini1@unibs.it (A.E. Guerini), stefania.nici@asst-spedalicivili.it (S. Nici), stefano.riga92@gmail.com (S. Riga), ludovicapegurri@libero.it (L. Pegurri), e.mataj@unibs.it (E. Mataj), davide.farina@unibs.it (D. Farina), marco.ravanelli@unibs.it (M. Ravanelli), paolo.rondi@unibs.it (P. Rondi), g.cossali@unibs.it (G. Cossali), tomad88@libero.it (D. Tomasini), luca.triggiani@unibs.it (L. Triggiani), giorgio.facheris@gmail.com (G. Facheris), luigi.spiazzi@unibs.it (L. Spiazzi), stefano.magrini@unibs.it (S.M. Magrini).
[1] Co-first author.

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Introduction

Oropharyngeal squamous cell carcinoma (OPSCC) is among the ten most common cancers worldwide and its incidence is growing due to increased exposure to major risk factors, including human papilloma virus (HPV) infection, smoking and alcohol consumption [1,2]. Etiology and biologic features have a profound impact on clinical outcomes. For instance, HPV-related OPSCC is more radio-chemosensitive and characterized by a better prognosis [3]. Treatment decisions are influenced by the stage and biologic characteristics of the disease, and first line therapeutic options for non-metastatic disease include either definitive radiotherapy (RT) or radio-chemotherapy (RCHT) or surgery, potentially followed by adjuvant RCHT [4,5].

The main challenge of RCHT is to provide the optimal balance between adequate target coverage to achieve disease control and sparing organs at risk (OARs) to limit radiation-induced side effects.

Indeed, RCHT is often burdened by substantial toxicities, that could heavily affect quality of life. Therefore, modern radiotherapy techniques such as Intensity Modulated RT (IMRT) and its evolutions (including volumetric and helical treatments) and Image-Guided RT (IGRT) have been extensively investigated and adopted to deliver more conformal therapy and preserve OARs surrounding target volumes [6–9].

The recent advent of systems integrating a linear accelerator and an on-board MRI-scanner (MRI-linacs) could further improve the safety profile of RCHT for OPSCC. Currently, radiotherapy workflow is mostly based on computed tomography (CT) imaging for treatment planning and delivery verification. Although CT provides valuable anatomical information, its ability to differentiate soft tissues is sub-optimal [10,11]. The advantages of MRI-linacs include superior soft tissue visualization, reducing uncertainties in contouring target volumes and OARs, and the possibility to perform functional studies that aid target definition and help to monitor response to treatment [12]. Moreover, MRI-linacs enable to perform adaptive radiotherapy, as contours of the lesions and OARs can be adjusted on the basis of daily MRI and treatment plan recalculated online for each fraction [13].

On the other hand, switching from a CT-based to an MRI-based workflow requires also to consider several issues that could hinder treatment quality. A synthetic CT must be generated to assign tissue density, that is not directly provided by MRI [14].The presence of a magnetic field induces phenomena such as the electron return effect (ERE) and the electron stream effect (ESE), that could increment superficial dose and dose at air-tissue interfaces in high-field MRI-linacs and potentially result in increased toxicities, while it is nearly negligible in low-field systems [15]. Additionally, patient time on table is relatively longer compared with conventional linacs, remarkably if contours are manually edited and treatment plan fully adapted daily [16]. Currently, the two main commercially available MRI-linacs are the 1.5 Tesla (T) Elekta Unity® (Elekta Unity, Elekta AB, Stockholm, Sweden) and the low-field 0.35 T ViewRay MRIdian® (ViewRay Inc., Oakwood, USA) [17].

Despite the promising capabilities of MRI-Linac technology, there is a noticeable gap in the literature regarding its use for treating head and neck cancers and no comparisons have been made with conventional linacs. In this paper we present our prospective mono-institutional experience in treating OPSCC patients with radical RCHT using a 1.5 T Unity MRI-linac. Additionally, we compared treatment related toxicity and radiologic response of these patients to the outcomes observed in a control cohort of patients that received RCHT for OPSCC with Helical Tomotherapy (HT) performed by Accuray Radixact® system (Accuray, CA, USA).

Methods

Data from the first 34 consecutive patients treated from September 2022 to May 2024 at our Institution with radical RT or RCHT on the Unity® MRI-linac for non-metastatic oropharyngeal cancer. All the patients treated with the MRI-linac were enrolled in a prospective ongoing "basket" observational clinical trial assessing toxicity and clinical outcomes of patients treated with this technology, and part of an interim analysis evaluating biopsy-confirmed non-metastatic OPSCC undergoing radical treatment. Control group was represented by 34 consecutive patients with similar characteristics treated with Radixact® at our Institution. This group included 16 patients prospectively enrolled in the same study as a control group from September 2022 and 18 consecutive patients treated from november 2021 retrospectively included to match the number of patients treated with MRI-linac. Clinical and dosimetric data were collected from medical records. The main outcome assessed in this analysis was the feasibility of a magnetic resonance-guided adaptive radiation therapy (MRgART) in terms of acute and long term treatment induced toxicities, graded using National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0 (CTCAE 5.0) and rates of hospitalization due to treatment-induced toxicity. The secondary outcome was the evaluation of radiologic response after treatment, defined according to Response Evaluation Criteria in Solid Tumors 1.1 (RECIST 1.1) or Positron Emission Tomography Response Criteria in Solid Tumors (PERCIST 1.0). This protocol was approved by the Ethics Committee of our Hospital (number of approval NP 5613).

Treatment planning and delivery workflow

A simulation CT-scan was acquired for each patient using a Big Bore scanner (Brilliance®, Philips NV, Eindhoven, The Netherlands) and a simulation MRI was as well performed for patients undergoing treatment with MRI-linac using a 1.5 T MRI Ingenia® scanner (Philips NV, Eindhoven, The Netherlands) with the same set-up.

The MR simulation protocol consist of standard non-contrast T2-weighted (T2w) 3D MRI sequence and diffusion-weighted imaging (DWI). To improve reproducibility of the set-up, patients were immobilized with an MRI-safe thermoplastic mask. Diagnostic imaging was co-registered with simulation imaging to facilitate the delineation of target volumes.

For patients treated with Unity® OARs, bones, fat and air and external were automaticaly contoured using a threshold system to define the different regions, while relevant organs at risk were contoured by a radiation oncologist on a simulation CT-scan. These contours were then propagated to the T2w 3D MR images with a deformable adaptation, with the mean density as derived by the CT and the HU/CT conversion assigned as bulk- electron density and then manually corrected by a radiation oncologist. The process allows to generate a synthetic-CT.

Clinical target volumes were delineated on simulation CT-scan or simulation MRI (using the standard T2w 3D sequence). Delineation of treatment volumes was based on the consensus guidelines by Gregoire et al [14,18].

Planning target volume (PTV) was obtained through an isotropic geometric expansion of 3 mm for patients treated with MR-linac and through anisotropic expansion (5 mm radial and 6 mm cranio-caudal) for patients treated with helical tomotherapy, and cropped 2 mm from skin. The prescription dose was 56.1 Gy in 33 fractions for precautional volumes, with a simultaneous integrated boost (SIB) of 69.3 Gy on primary tumor and involved lymphnodal laterocervical levels.

Treatment plans were optimized and calculated by medical physicists with the Monaco® TPS (Elekta AB, Stockholm, Sweden) using 17–19 fields step-and-shoot intensity-modulated radiation therapy (IMRT) for patients treated with Unity® and using an elical delivery with the Precision® TPS (iDMs; Accuray Inc.) for patients treated with Radixact®. The same planning dose constraints have been adopted for helical plans and MrgRT: a coverage of 95.

Before each treatment session, an MRI scan is acquired and rigidly registered to the reference planning dataset to detect any anatomical modifications. Subsequently, the OARs and target volumes are deformably transferred onto the daily MRI. If significant anatomical changes

are present, contours can be manually edited. The adapted target volumes and OARs are then used to reoptimize the treatment plan from fluence map. The reoptimization process aims to either reproduce or improve upon the original dose constraints defined in the baseline plan. Monaco treatment planning software provides two workflows for generating daily adapted treatment plans on the daily MRI acquired with Unity®: Adapt-To-Position (ATP) and Adapt-To-Shape (ATS) [19,20]. In ATP, the plan is re-optimized on the reference image simply by shifting the isocenter based on its rigid co-registration with the daily images, therefore retaining the original contours without changing optimization parameters but adjusting beam shapes and weights. In ATS, the plan is calculated and optimized on the daily image and can beextensively adapted to better adapt to the updated patient anatomy. Rather than modifying the original constraints, we focused on maintaining the same clinical goals while adjusting for anatomical changes observed on the day of treatment. This ensures that the delivered plan meets established criteria for both tumor coverage and normal tissue sparing while adapting to the current patient geometry. The reoptimized plan is then reviewed and approved by the clinician before irradiation.

Given their potential variation due to patient positioning and anatomical changes, air cavities contours, that are related to the bulk density of the syntethic CT, were carefully checked and manually corrected during online planning based on the anatomy of the day.

For all patients treated with Elekta Unity® MRI-Linac, a daily 'adapt-to-shape' (ATS) workflow was adopted.Target volumes contours were manually edited daily after rigid or deformable registration. Only contours of the most relevant OARs (parotid glands, oral cavity and larynx) were manually edited daily. Other OARs contours were manually corrected only if results of automatic registration were considered unsatisfactory and/or if dose received was close to the adopted constraints. In patients treated with Radixact daily IGRT based on megavolt CT (MVCT) was performed to partially compensate for inter-fraction movements. A new simulation CT was acquired to re-calculate treatment plan if anatomic variations were deemed excessive by the radiation oncologist assessing daily MVCT scans.

Statistical analysis

The database was formatted through the Microsoft-Excel® software ver.365 and later imported from the IBM-SPSS® software ver. 29.02 (IBM SPSS Inc. Chicago, Illinois); the use of the Stata® software ver. 17.0 (Stata Corporation, College Station, Texas) was also considered.

Normality of the distributions was assessed using the Kolmogorov-Smirnov test.

Continuous variables were presented as means ± SD (in case of a normal distribution), or medians, IQR and min/max (in case of a skewed distribution) and compared with the use of Student's T-test, or the Mann-Whitney; correlations among variables by the Pearson's or Spearman's rank correlation test.

Categorical variables were presented as frequencies or percentages and compared with the use of the Chi-Square test and the Fisher's exact test, as appropriate; associations of the crosstabs were verified using standardized adjusted residuals.

A two-sided alpha level of 0.05 was used for all tests.

Results

Characteristics of the patients are summarized in Table 1. Age, stage, HPV/p16 status and performance status according to Karnofsky scale were well balanced across the two groups, with no significant differences. Patients treated with Unity® received a non-significantly higher cumulative dose of concurrent cisplatin (mean total dose 327,43 mg versus 295,53 mg; p = 0.170).

Treatment volumes are shown in Table 2. Although mean high-dose

Table 1
Characteristics of the patients enrolled in this study, considering the whole cohort and divided by group. HPV/p16+ = Human Papilloma Virus and/or p16 positive tumor; BMI = Body Mass Index; 3w = three-weekly; w = weekly; PS = Performance Status; RT = radiotherapy; std.dev. = standard deviation.

	Whole cohort (n = 68)	Unity (n = 34)	Radixact (n = 34)	p value	
HPV/p16+; n (%)				0.779	
	HPV or p16 + 51 (75 %)	HPV or p16 + 25 (73,53 %)	HPV or p16 + 26 (76,47 %)		
	p16 + 16 (41.2 %)	p16 + 16 (47.1 %)	p16 + 12 (35.3 %)		
	HPV + 2 (10.3 %)	HPV + 2 (5.9 %)	HPV + 5 (14.7 %)		
	p16 + HPV + 7 (23.5 %)	p16 + HPV + 7 (20.6 %)	p16 + HPV + 9 (26.5 %)		
Age at RT start (mean)	65 years (range 39.5–84.3)	65.7 years (range 43.2–84.3)	64.2 years (range 39.5–81.7)	0.508	
Mean BMI pre-RT	25,29 (std.dev. 4.72)	26,4 (std.dev. 4.78)	24,19 (std.dev. 4.46)	0.052	
Subsite of primary tumor	glossoepiglottic area 23 (33.8 %)	glossoepiglottic area 11 (32.4 %)	glossoepiglottic area 12 (35.3 %)	0.520	
	tonsil 41 (60.3 %)	tonsil 22 (64.7 %)	tonsil 19 (55.9 %)		
	posterior wall 2 (2.9 %)	posterior wall 0 (0 %)	posterior wall 2 (5.9 %)		
	superior wall 2 (2.9 %)	superior wall 1 (2.9 %)	superior wall 1 (2.9 %)		
Stage according to TNM	36,76 % stage I	44,12 % stage I	36,76 % stage I	44,12 % stage I	0.100
	19,11 % stage II	14,71 % stage II	19,11 % stage II	14,71 % stage II	
	27,94 % stage III	17,65 % stage III	27,94 % stage III	17,65 % stage III	
	16,17 % stage IV	23,53 % stage IV	16,17 % stage IV	23,53 % stage IV	
	HPV positive	HPV positive	HPV positive	HPV positive	
	49 % stage I	60 % stage I	49 % stage I	60 % stage I	
	19.6 % stage II	16 % stage II	19.6 % stage II	16 % stage II	
	31.4 % stage III	24 % stage III	31.4 % stage III	24 % stage III	
	0 % stage IV	0 % stage IV	0 % stage IV	0 % stage IV	
	HPV negative	HPV negative	HPV negative	HPV negative	
	0 % stage I	0 % stage I	0 % stage I	0 % stage I	
	17.6 % stage II	11.1 % stage II	17.6 % stage II	11.1 % stage II	
	17.6 % stage III	0 % stage III	17.6 % stage III	0 % stage III	
	64.7 % stage IV	88.9 % s	64.7 % stage IV	88.9 % stage IV	
Concurrent cisplatin	No 20.59 %	No 17,65 %	No 23,53 %		0.802
	Weekly 45,59 %	Weekly 50,00 %	Weekly 41,18 %		
	3-weekly 26,47 %	3-weekly 23,53 %	3-weekly 29,41 %		
	From 3w to w 7,35 %	From 3w to w 8,82 %	From 3w to w 5,88 %		
Cisplatin total dose (mean)	312,07 mg (std.dev. 135.23)	327,43 mg (std.dev. 116.84)	295,53 mg (std.dev. 143.04)		0.170
Karnofsky PS at RT start (mean and median)	90,15 and 90,00 (std-dev. 14.46)	90,59 and 90,00 (std-dev. 17.95)	89,71 and 90,00 (std-dev. 10)		0.710

Table 2
Treatment volumes at planning CT or MRI scan divided by group. Std.dev. = standard deviation.

	CTV HD	PTV HD	CTV LD	PTV LD
mean volume MR-linac (ml)	156,3 ml (std.dev. 79.64)	260,6 ml (std.dev. 122.54)	416,2 ml (std.dev. 105.66)	680,4 ml (std.dev. 147.81)
median volume MR-linac (ml)	142,3 ml (std.dev. 79.64)	242,4 ml (std.dev. 122.54)	402,2 ml (std.dev. 105.66)	676,0 ml (std.dev. 147.81)
mean volume tomotherapy (ml)	134,8 ml (std.dev. 78.49)	249,8 ml (std.dev. 139.07)	336,7 ml (std.dev. 137.44)	625,6 ml (std.dev. 178.42)
median volume tomotherapy (ml)	122,1 ml (std.dev. 78.49)	245,4 ml (std.dev. 139.07)	323,9 ml (std.dev. 137.44)	613,1 ml (std.dev. 178.42)
Mean volume p	0.270	0.737	0.010	0.175
mean volume whole cohort (ml)	145,6 ml (std.dev. 79.62)	260,2 ml (std.dev. 131.1)	376,5 ml (std.dev. 129.07)	652,5 ml (std.dev. 165.95)
median volume whole cohort (ml)	132,1 ml (std.dev. 79.62)	242,4 ml (std.dev. 131.1)	370,5 ml (std.dev. 129.07)	649,3 ml (std.dev. 165.95)

CTV was non-significantly larger in patients treated with MRI-linac (+15.9 %), mean high-dose PTV was only 4.3 % larger due to reduced CTV-PTV margins. As for low-dose CTV, mean volume was 23.6 % larger (p 0.010), while mean low-dose PTV was only 8.8 % larger in patients treated with MRI-linac compared with patients treated with helical tomotherapy. Distribution of oropharyngeal sub-site localization of primary tumour, which has a relevant impact on treatment toxicity, was similar across the two groups.

Data regarding main toxicities at 20 RT fractions, at the end of, one month and three months after RT end are reported in Table 3 and illustrated in Fig. 1.

At 20 fractions the rate of maximum grade toxicity ≥2 was equivalent for patients treated with Unity® and Radixact® (88.2 % in both groups). However, the rate of grade 3 toxicity was non-significantly higher for Unity® (20.6 % vs 8.8 %), mainly due to mucositis. Rate of grade ≥2 dermatitis was significantly higher for patients treated with Radixact® at fraction 20 (2.9 % vs 20.6 %; p = 0.021).

At the end of RT, the rate of maximum grade toxicity ≥2 was 100 % for patients treated with Unity® and 94.1 % for patients treated with Radixact® and grade 3 toxicity rate was higher for patients treated with Unity® (58.8 %) compared with patients treated with Radixact (32.4 %) (p 0.049). This difference was mostly due to higher rates of grade 3 dermatitis (20.6 % vs 5.9 %) in patients treated with Unity®, although difference for this single toxicity was not significant (p 0.464). Similar rates of grade 2 xerostomia (73.5 % for Unity® and 79.4 % for Radixact®) and grade 2 dysgeusia (73.5 % for Unity® vs 67.7 % for Radixact®) were robserved.

Necessity of nutritional support through nasogastric tube, gastrostomy tube or parenteral nutrition was reported in 8.8 % of patients treated with Unity® and 5.9 % of patients treated with Radixact® at fraction 20 (p = 0.642), and for 23.5 % and 26.5 % respectively on the last day of radiotherapy (p = 0.779). One month after the conclusion of radiotherapy 2.9 % of patients treated with Unity® and 8.8 % of patients treated with Radixact® still required nutritional support (p = 0.303).

Significantly higher rates of hospitalizations were reported for patients treated with Radixact® at 20 fractions (41.2 % vs 17.7 %; p = 0.033) and at radiotherapy end (64.1 % vs 35.3 %; p = 0.015). All the hospitalization in both groups were due to radiation induced toxicities, represented by mucositis resulting in necessity of invasive nutritional support and/or severe radiodermitis.

One month after the end of radiotherapy, the rate of maximum grade toxicity ≥2 was 76.5 % for patients treated with Unity® and 91.2 % for patients treated with Radixact® (p = 0.257) and grade 3 toxicity rates were respectively 2.9 % for Unity® and 0 % for Radixact®. At the same timepoint, overall rates of dermatitis were 14.7 % for Unity® and 20.6 % for Radixact® (p = 0.495), with no grade > 2 toxicity; grade 2 mucositis was reported for 5.9 % of patients treated with Unity® and 14.7 % of patients treated with Radixact® (p = 0.465). Rates of grade 2 xerostomia and dysgeusia were 61.8 % and 55.9 % for patients treated with Unity® and 76.5 % and 64.7 % for patients treated with Radixact®.

Three months after the end of RT, the rate of maximum grade toxicity ≥2 was 71.0 % for patients treated with Unity® and 74.0 % for patients treated with Radixact® (p = 0.960), with no grade >2 toxicity. Rates of grade 2 xerostomia and dysgeusia were respectively 64.5 % and 29.30 % for patients treated with Unity® and 77.4 % and 48.4 % for patients treated with Radixact® (p = 0.388 for xerostomia and p = 0.266 for dysgeusia). Dermatitis had resolved in all patients, while mucositis was still present in 9.7 % of patients in both groups (all grade 1 in patients treated with Unity® and 3.2 % grade 1 and 6.5 % grade 2 for patients treated with Radixact®).

Mean performance status according to Karnofsky index (KPS) was slightly higher in Unity® group before treatment start (90.59 vs 89.71; p = 0.355). At RT end (83.53 vs 80.59; p = 0.132) and one month after RT (85.00 vs 83.24; p = 0.314) this difference was still not significant, while it became statistically significant three months after RT (87.67 vs 83.87; p = 0.038).

Mean BMI was non significantly higher for patients treated with Unity® before treatment start (26.40 vs 24.19; p = 0.052), while this difference became significant at 20 fractions (25.68 vs 23.23; p = 0.028) and remained significant at RT end (24.86 vs 22.27; p = 0.016), one month after RT (23.89 vs 21.65; p = 0.013) and three months after RT (24.32 vs 21.34; p = 0.032).

Multivariate analysis was performed, but statistical significance was not maintained. This was likely due to several factors, including the relatively limited number of patients and of events (e.g. hospitalizations), the high number of predictive and confounding variables (e.g. cisplatin dose, high and low dose CTV, disease sub-site, KPS and BMI before treatment start), resulting also in small number of patients for each subgroup and the collinearity between those variables.

First radiologic response was assessed for 31 patients treated with Unity® and 32 patients treated with Radixact® after a median of 105.5 days, in 90.5 % of patients with PET-CT and in 9.5 % with MRI. No statistically significant difference in terms of response to treatment were identified across the two groups. Local complete response rate was 83.9 % for Unity® and 75.0 % for Radixact®, partial response rate was respectively 6.5 % and 6.3 % and unclear local response (mainly represented by likely inflammatory uptake, that could still not be ruled out as non-neoplastic) was reported for respectively 9.7 % and 18.8 % of patients. No instances of local progression were reported at first assessment, while one distant progression (3.1 %) and three (9.4 %) unclear out-of-field uptakes were reported at first radiologic follow up, all in patients treated with Radixact®.

After a median follow up of 361.5 days for the whole cohort (246.0 days for patients treated with Unity® and 529.5 days for patients treated with Radixact®) local complete response was reported for 93.6 % of patients treated with Unity® and 96.8 % of patients treated with Radixact® and local progression was reported for respectively 6.5 % and 3.2 % of patients. Distant progression was reported for 3.2 % of patients treated with Unity® and 6.5 % of patients treated with Radixact® and suspect out-of-field progression for another patient (3.2 %) treated with Radixact®. All these differences were statistically non-significant.

Discussion

Radical radio-chemotherapy is an effective treatment option for OPSCC, but it is burdened by relevant side effects, often requiring hospitalization and determining a striking impact on quality of life.The adoption of modern radiotherapy techniques allowed to partially mitigate treatment toxicity. For instance, the introduction of imaging guided

Table 3
Number and rates of toxicity in patients treated with Unity (MR-linac) and Radixact (Tomotherapy) at 20 fractions (20 fr), radiotherapy end (RT end) and one month after RT end (1 mo) and three months after RT end (3 mo).

20 fr		Max grade toxicity	Dermatitis	Mucositis	Xerostomia	Dysgeusia	Nausea/vomit	Fatigue
n %	G0 MR-linac	0 (0 %)	15 (44,1%)	2 (5,9%)	4 (11,8%)	6 (17,7%)	25 (73,5%)	6 (17,7%)
	G1 MR-linac	4 (11,8%)	18 (52,9%)	10 (29,4%)	17 (50,0%)	5 (14,7%)	8 (23,5%)	24 (70,6%)
	G2 MR-linac	23 (67,6%)	1 (2,9%)	18 (52,9%)	11 (32,4%)	23 (67,7%)	0 (0,0%)	4 ()11,8%
	G3 MR-linac	7 (20,6%)	0 (0 %)	4 (11,7%)	2 (5,9%)	0 (0 %)	1 (2,9%)	0 (0 %)
n %	G0 Tomo	0 (0 %)	18 (52,9%)	1 (2,9%)	3 (8,8%)	4 (11,8%)	20 (58,8%)	3 (8,8%)
	G1 Tomo	4 (11,8%)	9 (26,5%)	8 (23,5%)	11 (32,4%)	11 (32,4%)	10 (29,4%)	28 (82,4%)
	G2 Tomo	27 (79,4%)	7 (20,6%)	23 (67,6%)	18 (52,9%)	19 (55,9%)	4 (11,8%)	3 (8,8%)
	G3 Tomo	7 (8,8%)	0 (0 %)	2 (5,9%)	2 (5,9%)	0 (0 %)	0 (0 %)	0 (0 %)
	p	0.383	0.021	0.608	0.374	0.220	0.123	0.484

RT end		Max grade toxicity	Dermatitis	Mucositis	Xerostomia	Dysgeusia	Nausea/vomit	Fatigue
n %	G0 MR-linac	0 (0%)	2 (5,9%)	0 (0,0%)	3 (8,8%)	2 (5,9%)	22 (64,7%)	1 (2,9%)
	G1 MR-linac	0 (0%)	9 (26,5%)	3 (8,8%)	6 (17,7%)	7 (20,6%)	9 (26,5%)	27 (79,4%)
	G2 MR-linac	14 (41,2%)	16 (47,1%)	23 (67,6%)	25 (73,5%)	25 (73,5%)	3 (8,8%)	6 (17,7%)
	G3 MR-linac	20 (58,8%)	7 (20,6%)	8 (23,5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
%	G0 Tomotherapy	0 (0%)	2 (5,9%)	1 (2,9%)	3 (8,8%)	5 (14,7%)	21 (61,8%)	4 (11,8%)
	G1 Tomotherapy	2 (5,9%)	12 (35,3%)	3 (8,8%)	4 (11,8%)	6 (17,7%)	12 (35,3%)	24 (70,6%)
	G2 Tomotherapy	21 (61,8%)	18 (52,9%)	21 (61,8%)	27 (79,4%)	23 (67,7%)	1 (2,9%)	6 (17,7%)
	G3 Tomotherapy	11 (32,4%)	2 (5,9%)	9 (26,5%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	p	0.049	0.344	0.765	0.635	0.485	0.484	0.372

1 m after RT		Max grade toxicity	Dermatitis	Mucositis	Xerostomia	Dysgeusia	Nausea/vomit	Fatigue
n %	G0 MR-linac	1 (2,9%)	29 (85,3%)	22 (64,7%)	3 (8,8%)	4 (11,8%)	32 (94,1%)	16 (47,1%)
	G1 MR-linac	7 (20,6%)	3 (8,8%)	10 (29,4%)	10 (29,4%)	11 (32,4%)	1 (2,9%)	15 (44,1%)
	G2 MR-linac	25 (73,5%)	2 (5,9%)	2 (5,9%)	21 (61,8%)	19 (55,9%)	0 (0,0%)	3 (8,8%)
	G3 MR-linac	1 (2,9%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (2,9%)	0 (0%)
%	G0 Tomotherapy	0 (0%)	27 (79,4%)	21 (61,8%)	2 (5,9%)	3 (8,8%)	31 (91,2%)	20 (58,8%)
	G1 Tomotherapy	3 (8,8%)	6 (17,7%)	8 (23,5%)	6 (17,7%)	9 (26,5%)	1 (2,9%)	12 (35,3%)
	G2 Tomotherapy	31 (91,2%)	1 (2,9%)	5 (14,7%)	26 (76,5%)	22 (64,7%)	2 (5,9%)	2 (5,9%)
	G3 Tomotherapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	p	0.257	0.495	0.465	0.421	0.755	0.389	0.613

3 m after RT		Max grade toxicity	Dermatitis	Mucositis	Xerostomia	Dysgeusia	Nausea/vomit	Fatigue
%	G0 MR-linac	0 (0%)	31 (100%)	28 (90,3%)	1 (3,2%)	7 (22,6%)	30 (96,8%)	24 (77,4%)
	G1 MR-linac	9 (29,0%)	0 (0%)	3 (9,7%)	10 (32,3%)	15 (48,4%)	1 (3,2%)	7 (22,6%)
	G2 MR-linac	22 (71,0%)	0 (0%)	0 (0%)	20 (64,5%)	9 (29,0%)	0 (0%)	0 (0%)
	G3 MR-linac	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
%	G0 Tomotherapy	0 (0%)	31 (100%)	28 (90,3%)	0 (0%)	4 (12,9%)	30 (96,8%)	21 (67,7%)
	G1 Tomotherapy	8 (26,0%)	0 (0%)	1 (3,2%)	7 (22,6%)	12 (38,7%)	1 (3,2%)	9 (29,0%)
	G2 Tomotherapy	23 (74,0%)	0 (0%)	2 (6,5%)	24 (77,42%)	15 (48,4%)	0 (0%)	1 (3,2%)
	G3 Tomotherapy	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
	p	0.960	/	0.223	0.388	0.266	1	0.484

radiotherapy (IGRT) permitted to reduce CTV-PTV margin and thus to limit irradiation of healthy tissues [21]. Development of conformal RT techniques further improved OARs sparing, culminating in the implementation of helical tomotherapy, which, compared with IMRT and Volumetric Modulated Arc Therapy (VMAT) resulted in better preservation of organs function [22,23,25].

The advent of MRI-linacs could represent a further advancement in the effort to improve the therapeutic ratio of RCT for OPSCC. The superior image quality for soft tissue can optimize target and OARs contouring, limiting the inaccuracies secondary to fusion with diagnostic imaging necessary for CT-based RT [24]. Moreover, contours can be edited for each fraction on the pre-treatment daily MRI and plan can be adapted online to take account of anatomic variations. This could further improve the radiation dose actually delivered to targets and OARs [226]. For example, it has been observed that during RT course parotid glands shrink and medialize and this could determine higher exposure of these structures compared to the provisional treatment plan dose [26,27]. Nonetheless, currently only a few reports assessed the potential benefit of the adoption of adaptive radiotherapy with MRI-linac for the treatment of head and neck cancer (HNC). Lim et al retrospectively evaluated cumulative dose of 8 HNC patients treated with 1.5 T MRI-linac: the actual dose delivered to some OARs was significantly higher compared with the original plan, remarkably in structures within the high dose gradient, suggesting a possible advantage of the ATS workflow [27]. Daily adaptation through the adapt-to-shape workflow could also aid to reduce CTV-PTV margins. In our cohort, although low-dose CTV and high-dose CTV were larger in patients treated with Unity, the differences decreased for low and high dose PTVs due to smaller margins. Nonetheless, it should be noted that a large study by Navran et al demonstrated that CTV-PTV margins for

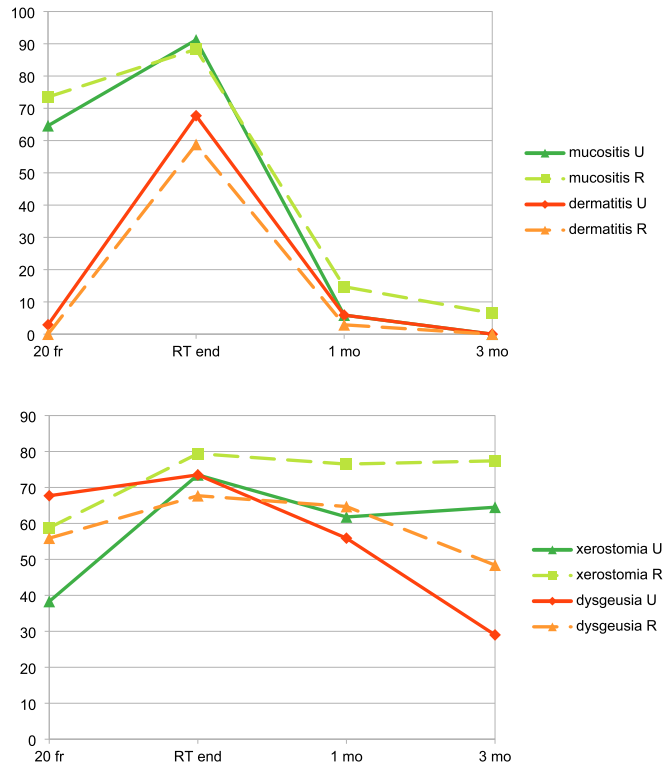

Fig. 1. Rate of grade ≥2 toxicity rates (%) in Unity group (U) and Radixact group (R) at 20 fractions (20 fr), radiotherapy end (RT end) and one month after RT end (1 mo) and three months after RT end (3 mo).

HNC patients can be reduced from 5 to 3 mm using daily CBCT-guided VMAT on a conventional linac without jeopardizing outcome and improving toxicity [28]. Another analysis by van Kranen et al confirmed that margin reduction improves OARs sparing, but at the expense of target coverage in a subgroup of patients that may be identified early during treatment [29]. Daily adaptive radiotherapy with the improved definition provided by MRI could allow to further reduce CTV-PTV margins. Prospective randomized comparisons between MR-linac and conventional linacs assessing margins reduction could help clarify this issue.

However, the transition to an MRI-based workflow poses multiple challenges. This could explain why only a few centers worldwide currently perform RT for head and neck cancers with an MRI-linac and the subsequent lack of literature on this topic. Planning on MRI requires the generation of a synthetic CT and daily re-contouring and re-planning is a time-consuming process that can prolong patient's time on the table. Moreover, the Unity® system currently delivers treatment using a step-and-shoot IMRT technique, which is inherently less conformal than helical tomotherapy.

To partially compensate this limit, a 17–19 field IMRT solution was developed at our Institution to improve treatment conformity and treatment plans in Unity® group. Up to date, only a few clinical studies have been published regarding the use of MRI-linacs for the treatment of Head and Neck Cancers (HNC). In a single prospective series by McDonald et al [30] 10 HNC with heterogeneous characteristics were treated with Unity MRI-linac and limited information was reported regarding treatment effectiveness and toxicity. Patients were treated according to an adapt-to-position protocol, with the possibility to perform an offline revision of the contours and treatment plans. This choice was based on the assumption that a daily ATS workflow would require excessive time. We decide to apply an ATS workflow to entirely exploit the potential of Unity® and provide an actual adaptive treatment for each session. In our experience, ATS treatment for OPSCC was feasible and did not result in excessive patient discomfort. All the patients undergoing MRgART in this study were treated with a full ATS workflow, and no patient required treatment suspension or interruption (even of a single fraction) due to poor tolerability or discomfort. The choice to perform a full daily ATS workflow had the objective to compensate also limited alterations (e.g. rotations, distortions, gradual OARs shift and response of neoplastic lesions) that can occur even within a few fractions. Nonetheless, this process is time consuming and multiple alternative options might be considered. Other studies proposed periodic (e.g. weekly) offline adaptations with an ATS workflow to provide the basis for daily ATP for treatment delivery [31]. Improvement of artificial-intelligence based autocontouring and implementation of faster adaptive workflows such as the ATS-lite [32] could also reduce total time on the table. Another prospective experience by van Timmeren et al [26] reported data and plans of 12 patients treated for HNC with IMRT using a 0.35 T MRI-linac. The workflow included weekly offline adaptations. Evaluation with MRI revealed a volumetric reduction of about 30 % of parotid and submandibular glands and a significant reduction of inter-parotid distance. No data were reported regarding treatment toxicity, except for weight loss. Similarly, Raghavan et al [33] identified significant volume loss and median shift of parotid glands assessing periodic MRI in 6 patients treated with a 0.35 T MRI-linac for HNC. Again, the only reported toxicity was weight loss. The current study represents the largest cohort of patients with HNC, specifically OPSCC, treated with MRI-guided radiotherapy and is the first to compare the outcomes achieved with this technology with those obtained in a control cohort treated with the current gold standard, represented by helical tomotherapy. The groups were well-balanced with respect to performance status at treatment start, disease stage, age and HPV/p16 status, with no significant differences between them. However, in patients treated with Unity® the mean low-dose clinical target volume (CTV) was significantly larger and total dose of administered concurrent cisplatin was non-significantly higher, thus increasing the risk of treatment induced toxicities. Although the sample size was relatively limited, different side effects patterns emerged across the two groups. The higher maximum grade toxicity at RT end in Unity® group was slightly significantly higher ($p = 0.049$), and that was mainly due to higher rates of grade 3 dermatitis. It must be noted, however, that one month after RT end grade ≥2 toxicity rates were non-significantly lower in Unity® group (76.5 % vs 91.2 %, $p = 0.257$) and grade 3 toxicity was reported for 2.9 % patients in Unity® group and no patients in Radixact® group. This could be explained by the recovery from mucositis and dermatitis and by the lower rates of xerostomia and dysgeusia achieved with Unity. Three months post-RT, overall maximum grade toxicity rates between the two groups were substantially equivalent, with no cases of grade 3 or higher toxicity observed. As mentioned above, patients treated with Unity® experienced lower rates of xerostomia and dysgeusia one and three months post-RT compared with those treated with Radixact®, although those benefits did not reach statistical significance. Hospitalization rates were significantly higher for patients treated with Radixact®both at 20 fractions (41.2 % vs 17.7 %; $p = 0.033$) and at the end of RT (64.1 % vs 35.3 %; $p = 0.015$), potentially indicating a higher acute high-grade toxicity burden. Mean KPS was slightly non-significantly higher in Unity® group before treatment start, at RT end and one month after RT, while this difference became statistically significant three months after RT (87.67 vs 83.87; $p = 0.038$). Although KPS is influenced by an interplay of multiple factors, this could suggest a lower impact of treatment induced toxicities on the performance status in this group. Mean BMI was non-significantly higher for patients treated with Unity® before treatment start, while this difference became significant at 20 fractions and remained significant at RT end and one and three months after RT. Coherently, a lower proportion of patients treated with Unity® required invasive nutritional support at RT end and one month post-RT, although this difference was not significant. While the short follow-up period limits any conclusions regarding overall survival (OS) and progression-free survival (PFS), optimal response rates were reported for both groups with no significant

differences.

Although results of this study are promising, several limitations must be acknowledged. This preliminary analysis did not include a dosimetric assessment of target volumes and OARs. We are planning to implement a dosimetric analysis, including the evaluation of cumulative dose to the OARs, that could clarify the benefit of the daily ATS workflow. Other main limitations of this study include the non-randomized nature of the study, the relatively small cohort of patients and the short follow up, remarkably for patients treated with MRI-linac. Moreover, a relevant part of the data in the control group treated with Radixact® was retrospectively collected to achieve the same number of patients of Unity® group. Nonetheless, retrospectively included patients underwent the same clinical and radiologic follow up as prospectively enrolled patients and this is confirmed by the fact that all the analyzed data were retrieved for every of these patients at each timepoint assessed. The study is still ongoing and data from an expanded cohort and with longer follow up will help to clarify the impact on long-term toxicity, detect significant difference in acute and sub-acute side effects and confirm the optimal and equivalent results in terms of disease response and control. Multi-centric studies with larger samples and a randomized design are awaited to confirm these early findings and to assess the potential clinical benefits of MRI-linac in reducing long-term toxicity and improving treatment outcomes. The institution of an international registry such as MOMENTUM (Multi-OutcoMe EvaluatioN of radiation Therapy Using the MR-linac study, MR-linac Consortium) [34] might help to overcome these limits by aggregating data from larger cohorts. Moreover, multiple ongoing studies are assessing the optimal workflow to optimize treatment times and to adapt the treatment not only on daily anatomic variations but also to modulate dose prescription on the basis of radiologic response during treatment (e.g. evaluating functional imaging and/or performing radiomic analyses) [35,36]. The R-IDEAL framework provides a structured method to assess feasibility and safety of the clinical applications of a novel technology, such as MRI-guided radiotherapy. In this context, the present report could be defined as a Stage 2b study, providing proof of early clinical effectiveness and safety of MRgRT for OPC and favoring the development of further clinical programs, such as MRI-guided dose de-escalation for the treatment of OPSCC [37–40].

Conclusions

In this paper the largest cohort of HNC patients treated with MR-linac is presented and outcomes are compared with those obtained in a similar cohort of patients treated with helical tomotherapy. Results of this prospective analysis support the feasibility of an ATS MRI-linac workflow for radical radiotherapy in OPSCC patients. Compared with helical tomotherapy, treatment with Unity® MRI-linac resulted in significantly lower rates of hospitalization and higher KPS three months after RT. Although statistical significance was not reached, due to relatively limited sample size, grade 2 xerostomia and dysgeusia were as well lower in the Unity® group. Substantially equivalent outcomes were reported for other toxicities. Albeit limited by the short follow up, optimal results in terms of local control were reported for both techniques. The adoption of daily adaptive radiotherapy with an ATS workflow for OPSCC is promising, although the limits of this analysis (including the non randomized and partially retrospective nature of the control cohort and the limited sample) must be acknowledged.

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CRediT authorship contribution statement

Andrea Emanuele Guerini: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Michela Buglione:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Stefania Nici:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Stefano Riga:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Ludovica Pegurri:** Data curation, Formal analysis, Methodology, Supervision, Validation, Writing – review & editing. **Eneida Mataj:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Davide Farina:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Marco Ravanelli:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Writing – review & editing. **Paolo Rondi:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Gianluca Cossali:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Davide Tomasini:** Data curation, Formal analysis, Investigation, Writing – review & editing. **Luca Triggiani:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Writing – review & editing. **Giorgio Facheris:** Conceptualization, Data curation, Formal analysis, Writing – review & editing. **Luigi Spiazzi:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Stefano Maria Magrini:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

Data and material are stored according to our Institutional protocols and are available upon request.

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