Oral Oncology 80 (2018) 74–81

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Multi-criteria optimization achieves superior normal tissue sparing in intensity-modulated radiation therapy for oropharyngeal cancer patients

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ARTICLE INFO

Keywords:
Head and neck cancer
Oropharyngeal cancer
Intensity-modulated radiation therapy
Radiotherapy planning
Multi-criteria optimization
Normal tissue sparing

ABSTRACT

Objectives: To evaluate the benefit of intensity-modulated radiation therapy (IMRT) with multi-criteria optimization (MCO) in patients with oropharyngeal cancer (OPC) and compare the dose difference between the MCO plans navigated by physicians and dosimetrists.

Materials and methods: The conventional IMRT plans (nonMCO) and MCO IMRT plans navigated by physicians and dosimetrists (MCOp and MCOd) were created for 30patients with OPC. All the plans were reviewed, and the planning time and dose-volume parameters were compared.

Results: The difference of D_{95} among three kinds of plans was not significant ($p > 0.05$). The maximum dose and D_2 of spinal cord, brain stem, the mean dose of bilateral parotids, cochlea, oral cavity and glottic larynx were lower in MCO plans than those in nonMCO plans ($p < 0.017$). Furthermore, MCOp showed better bilateral parotids, oral cavity and glottic larynx sparing compared to MCOd ($p < 0.017$), in which the magnitude was related to the overlapping volume of the corresponding organ at risk (OAR) and targets. The active planning time was reduced by a median of 94.3 min (MCOd *vs.* nonMCO) or 91.6 min (MCOp *vs.* nonMCO).

Conclusion: MCO IMRT plans significantly reduced the dose of OARs and the active planning time, without compromising the target coverage in OPC patients; navigations by physicians could be beneficial to the dose sparing of the OARs with high complication rate and those overlapping with targets; the constraints could be the predominant factor affecting the results of optimization in the MCO IMRT planning.

Introduction

Combined concomitant chemoradiotherapy is the standard treatment for non-resectable patients with oropharyngeal cancer (OPC), and is also preferable for resectable patients whose anticipated functional outcome with surgical treatment is poor [1]. Particularly, OPC with human papilloma viruses more sensitive to radiotherapy and chemotherapy [2–4]. Studies demonstrated that intensity-modulated radiation therapy (IMRT) is associated with better locoregional control, survival rates, quality of life and less complication of radiotherapy for OPC [5–12]. Even so, complication including xerostomia [13], osteoradionecrosis [14], trismus [15], dental caries, dysphagia [15–17], voice quality worsening and speech impairment [18], taste impairment [19], after chemo-IMRT for OPC have been frequently reported, the morbidity of which is associated with higher radiation dose of organs at risk (OARs) [8,13–16,18–22]. Therefore, it is of great importance to reduce the radiation dose of OARs for the patients with OPC.

However, IMRT planning needs to balance the dose requirements between targets and OARs. In clinical practices, these processes are usually performed by dosimetrists through manually adjusting the parameters of the different objectives. Therefore, the quality of IMRT plans is often related to the experience of the dosimetrists [23,24]. Moreover, IMRT planning is time consuming for dosimetrists. Multi-criteria optimization (MCO) is a novel approach for IMRT optimization

Abbreviations: BS, brainstem; GL, glottic larynx; LC and RC, left and right cochleae; LM and RM, left and right mandible; LPG and RPG, left and right parotid glands; MCOp and MCOd, the multi-criteria optimization plans navigated by physicians and dosimetrists; OC, oral cavity; SC, spinal cord

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https://doi.org/10.1016/j.oraloncology.2018.03.020
Received 3 January 2018; Received in revised form 28 March 2018; Accepted 30 March 2018
Available online 04 April 2018

generating a set of Pareto optimal plans through automatically emphasizing different objectives (a treatment plan is Pareto optimal if it cannot be improved in any one objective without worsening another). The user can reach a satisfactory dose distribution interactively by real time navigation across the Pareto surface which is a continuous surface approximated by forming convex combinations of these base plans. The previous reports indicated that the MCO IMRT plan reduces active planning time and the dose of OARs for tumors such as glioblastoma [25], pancreatic cancer [25], prostate cancer [26,27], non-small cell lung carcinoma [28], and other anatomical sites [29–33], while the target coverage is equal or better. Furthermore, the MCO IMRT planning provides an efficient way for physicians to be their own decision makers in treatment planning [25].

However, in MCO IMRT planning, a deliverable plan cannot be directly created by navigation as it only affects the navigation dose. A new optimization must be implemented to match the reference dose and generate a deliverable plan, which can lead to a difference between the navigation dose and final dose [34]. On the other hand, physicians have adapted the conventional IMRT process in which physicians approve the final plan completed by dosimetrists. Consequently, some physicians request dosimetrists to provide a recommended dose distribution through careful navigation across the Pareto surface, while other physicians tend to navigate it by themselves. This phenomenon was reflected by previous reports, in which some MCO plans are driven by dosimetrists [26,31], others by physicians [25]. To our knowledge, the dose difference of the MCO IMRT plan navigated by physicians and dosimetrists has not been reported. Furthermore, the advantage of the MCO IMRT plan in OPC has not yet been elucidated. Here, we evaluated the benefit of MCO IMRT plans in OPC and compared the dose difference between those plans navigated by physicians and dosimetrists.

Materials and methods

Patient selection

A total of 30 histologically confirmed OPC patients were enrolled, who were treated with IMRT at West China Hospital between April 2011 and March 2017. Postoperative patients without primary gross tumor volume and nodal gross tumor volume were excluded. The characters of the patients are shown in Table 1.

Table 1
Patients characters.

Characteristic		N (%)
Age	Median (Range)	61(34,88)
Gender	Male	18(60.0%)
	Female	12(40.0%)
Site	Tonsil	7(23.3%)
	Base of tongue	13(43.3%)
	Pharyngeal wall	9(30.0%)
	Soft palate	1(3.3%)
T stage	T1	6(20.0%)
	T2	9(30.0%)
	T3	4(13.3%)
	T4	11(36.7%)
N stage	N0	6(20.0%)
	N1	9(30.0%)
	N2	14(46.7%)
	N3	1(3.3%)
AJCC stage	I	1(3.3%)
	II	7(23.3%)
	III	10(33.3%)
	IV	12(40.0%)
Concurrent chemotherapy	Yes	25(83.3%)
	No	5(16.7%)
Neck dissection	Yes	13(43.3%)
	No	17(56.7%)

Volumes definitions and dose specifications

Each patient was immobilized with a thermoplastic mask in the supine position, then a contrast enhanced treatment-planning CT with 3-mm slice thickness covering the total head and neck volume from the vertex to about 3 cm below the head of the clavicle was obtained (SOMATOM Definition AS+, SIEMENS).

The guidelines for target volumes delineation were discussed in the literature [35]. The prescription dose for the planning target volume (PTV) was: PTV1, 69.96 Gy in 2.12 Gy per fraction; PTV2, 59.4 Gy in 1.8 Gy per fraction; and PTV3, 54.12 Gy in 1.64 Gy per fraction. The requirements of targets dose were: D_{95} (D_V is the absorbed dose in V% of the volume) ≥ the prescription dose or D_{99} ≥ 93% of the prescription dose, while no more than 1 cc of unspecified tissue outside the targets to exceed 77 Gy. Brainstem (BS), spinal cord (SC), left and right mandibles (LM and RM, the mandible was divided into LM and RM by the center line of the body), left and right parotid glands (LPG and RPG), oral cavity (OC, excluding planning target volume); glottic larynx (GL), left and right cochleae (LC and RC) were delineated as OARs. The BS planning organ at risk volume (PRV) and SC PRV were defined as BS and SC plus a three-dimensional margin of 2 and 5 mm, respectively. The constraints of OARs included:BS PRV, the maximum dose (D_{max}) ≤ 54 Gy or V_{60} (V_D is the percentage of the OAR volume receiving ≥ D Gy) ≤ 1%; SC PRV, D_{max} ≤ 45 Gy or no more than 1% to exceed 50 Gy; LPG and RPG, the mean dose (D_{mean}) < 26 Gy or V_{30} < 50% for either gland; LM and RM, D_{max} ≤ 70 Gy or no more than 1 cc to exceed 75 Gy; LC and RC, V_{55} ≤ 5%; OC, D_{mean} < 40 Gy; GL, D_{mean} < 45 Gy or V_{50} < 67%.

Treatment planning

All static IMRT plans were generated in the RayStation (RaySearch Laboratories, *v*4.7) treatment planning system (TPS) and customized to the accelerator (Elekta Synergy, Elekta Oncology, UK) with a 6-MV photon beam by two experienced dosimetrists. Every dosimetrist was responsible for 15 conventional IMRT plans (nonMCO) and 15 MCO IMRT plans randomly. They were uninformed of the patients and uninformed of each other. Nine coplanar beams at 40° intervals (started from 0°) and no more than 70 segments were used for nonMCO and MCO plans. All plans used the collapsed cone algorithm to compute the final dose.

For the nonMCO plan, the direct machine parameter optimization was utilized. The plan was selected after multiple iterations and no further improvement of the parameters in the optimization. For the MCO plan, the optimization parameters differ from those in conventional IMRT planning. For the objectives, the minimum and maximum dose with the dose level at the prescription were used for all targets, while the maximum effective uniform dose (Max EUD = 0, a = 1 or 2) was used for all OARs. For the constraints, D_{95} and D_{99} of targets were set as 100% and 95% of prescription dose respectively, while the Max Dose of the body was set as 75 or 76 Gy; the Max EUD for parallel OARs and Max Dose for serial OARs were used. In order to find an optimal solution in which the doses of OARs were as low as possible, we properly adjusted the constraints of OARs based on the distance between the targets and OARs for every patient. In MCO plans, segment-based Pareto plan mode was used. Although less than 50 Pareto plans were used in previous report [36], in our study, the number was arbitrarily set as 60 due to the complexity of targets and the surrounding anatomical structures.

After completing the Pareto optimization, the plans were replicated. Two radiation oncologists and two dosimetrists explored the trade-off plans based on their experience across the Pareto surface. They were uninformed of the patients and uninformed of each other. Then the plans were optimized and the deliverable plans were generated. All plans can be explored repeatedly until the satisfactory results were obtained.