Original Article

Establish a comprehensive plan robustness evaluation platform for intensity modulated proton therapy for bilateral head and neck cancer based on the daily cone-beam computed tomography: a dose accumulation study between the PTV based IMPT (PTV-IMPT) and CTV based robust optimized IMPT (ro-IMPT) planning strategies

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Background: A comprehensive plan evaluation platform was established based on the daily cone-beam computed tomography (CBCT) to assess the treatment robustness quality between planning target volume-based intensity modulated proton therapy (PTV-IMPT) and clinical target volume (CTV)-based robust optimized IMPT (ro-IMPT) planning strategies in bilateral head and neck cancer (HNC) treatment.

Methods: Nine bilateral HNC patients' CT structure sets were used in this study. Daily CBCTs were converted into synthetic-CT (sCT) for dose reconstruction. The accuracy of the proton dose calculation in sCT is cross-validated via the same day's verification-CT sim (vCT) with 3D gamma index comparison. PTV-IMPT and ro-IMPT were generated on the initial planning CT (pCT). CTV high-risk volume (CTV_high) received 70 Gy and CTV low/intermediate-risk (CTV_low) received 60 Gy. For PTV-IMPT, the PTVs were expanded 3 mm from the CTV; for ro-IMPT, robust optimization used a 3 mm setup and 3.5% range uncertainties. Dose accumulations were then calculated on the 35 sets of daily sCT, and the target coverages were compared to the initial plans.

Results: The 3D gamma index dose comparison (3 mm/3%) showed an average pass rate of 98.2%±1.5% comparing the same day's pair of sCT and vCT with both plans (total 38 pairs). Through the dose accumulation of 35 treatment fractions, the PTV-IMPT plan group's mean V100 of CTV_high/CTV_low coverage degraded to 80.70%/85.73% compared to 96.72%/96.13% of the ro-IMPT group ($P<0.002$). One patient did have suboptimal coverage (CTV_low <90%) even with ro-IMPT. Significant weight loss was noted for this patient during the treatment course (>5 lbs).

Conclusions: A comprehensive plan robustness evaluation platform based on the CBCT is established in our clinical workflow and enables dose accumulation and plan robustness evaluation on a daily basis. ro-IMPT demonstrated an optimal planning strategy over PTV-IMPT for bilateral HNC treatment. However, special cautions are needed for patients with significant weight or geometry changes.

Keywords: Intensity modulated proton therapy (IMPT); synthetic-CT (sCT); robustness optimization; head and neck cancer (HNC); dose accumulation

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Introduction

Proton beam therapy (PBT) has been clinically used for several decades. More recently, due to decreasing cost, increasing availability, and improved technology, the adoption of proton therapy has been increasing throughout the world in the last ten years. In addition, with the advent of pencil beam scanning (PBS) technology, intensity modulated proton therapy (IMPT) is now possible and allows for improved conformality around irregular targets.

PBT has been of great interest in head and neck cancer (HNC) treatment which provides better normal tissue sparing such as parotid and oral cavity (OC), compared to photon radiotherapy (1-4). PBT is also commonly used in re-irradiation patients to mitigate the toxicity of the surrounding tissues (5-7). In the upfront definitive setting, multiple studies have demonstrated improved dosimetry and clinical toxicity of IMPT over photon treatments (1-4,8,9).

PBT is inherently sensitive to setup and range uncertainties. This problem is even more pronounced when IMPT is used (10,11). In addition, the weight loss experienced by HNC patients often results in significant dosimetric changes, which cannot be predicted using a standard physics model. Thus, it is important to use adaptive offline replanning to account for the changes (4,12). However, the optimal timing and interval are largely unknown, and it remains a resource-intensive task in a busy clinic due to these additional validation-CTs (vCTs). There is an immediate need to generate a workflow to assess the plan's robustness daily and design a robust treatment planning protocol to ensure the plan quality throughout the treatment course.

Recently, cone-beam computed tomography (CBCT), which was successfully implemented on the proton gantry in the university of Pennsylvania since 2014 (13), has been considered as a new standard of clinical configuration in the new proton therapy center design, preparation, and installation. Besides excellent 3D volumetric image registration and correction, CBCT is able to assess a patient's geometry change or deformation in each treatment fraction. However, due to CBCT technique limitations, the imaging quality in terms of imaging contrasts or inaccuracy CT Hounsfield unit (HU) is not as good as standard CT sim, therefore cannot be used for proton dose calculation directly. However, with the recent advancement in the CBCT imaging correction and synthetic-CT (sCT) generation algorithm (14-16), these corrected CBCT could be used directly for dose calculation to access the dose distribution daily. Such a feature is critical to the PBT for HNC.

Meanwhile, the planning strategy for bilateral HNC using IMPT is evolving from planning target volume (PTV)-based planning to a clinical target volume (CTV)-based robust optimized planning based on understanding the uncertainties and geometry changes (17). However, no study has quantitatively assessed the plan target coverage throughout the treatment course. To our best knowledge, this is the first study to integrate a comprehensive platform to validate the sCT dose calculation accuracy through bi-weekly vCT and quantitatively assess the dose accumulation throughout the treatment course for the two different IMPT planning strategies. We present the following article in accordance with the MDAR reporting checklist (available at https://tro.amegroups.com/article/view/10.21037/tro-21-42/rc).

Methods

IMPT planning strategies

Nine bilateral HNC patients who previously received 35 fractions volumetric modulated arc therapy (VMAT) in our institution were selected in this study which was approved by the institutional review board (#2017-455), and individual consent for this retrospective analysis was waived. Baseline patient characteristics are summarized in *Table 1*. All patients underwent CT simulation for planning and intravenous contrast for contour and concurrent chemotherapy for their definitive treatment. Thermoplastic facemasks were used for immobilization. Prophylactic gastronomy tubes were placed in all patients to prevent

Table 1 Patient characteristics

Patients	Primary	Laterality	T stage	N stage
1	Base of tongue	Right	T2	N2b
2	Unknown	Right	T0	N2b
3	Base of tongue	Right	T4	N2c
4	Base of tongue	Left	T2	N2b
5	Tonsil	Left	T2	N1
6	Base of tongue	Left	T2	N2c
7	Base of tongue	Right	T2	N2b
8	Base of tongue	Left	T1	N2b
9	Base of tongue	Right	T1	N2b

significant weight loss during the course of treatment. All patients had a daily CBCT obtained during their 35 treatments. Daily imaging guided radiation therapy (IGRT) shifts were recorded and used for daily dose calculation as well as to reproduce the daily setup and treatment delivery.

Initial planning was done on the planning CT (pCT). Two planning strategies were used: (I) PTV-based (PTV-IMPT); and (II) CTV based robust optimized IMPT (ro-IMPT). All planning was done in Raystation™ version 5.02 (RaySearch Laboratories, Stockholm, Sweden). A 4-field setup with bilateral anterior and posterior oblique beams was used in both PTV-IMPT and ro-IMPT groups. For PTV-IMPT planning strategy, a PTV margin of 3 mm was used. For ro-IMPT, CTV was used as the optimization target with robust optimization parameter setting as 3 mm setup and 3.5% range uncertainties (total 21 scenarios). All gross tumor volumes (GTVs), CTVs, and organ at risks (OARs) were contoured and verified by a physician. CTV_high was prescribed 7,000 cGy (gross disease) and CTV_low/med was prescribed 6,000 cGy (subclinical disease) in thirty-five fractions. ro-IMPT group was normalized to CTVs V100 >98% on the pCT. In addition, the PTV-IMPT group ensured the PTV coverage received PTV V100 >98%. For the OARs optimization constraints, a maximum brainstem dose of 5,400 and 4,500 cGy for the spinal cord were respected. A maximum mandible dose of 7,000 cGy was used for planning. A mean parotid dose of 2,600 cGy was used for planning, and the mean dose was pushed as low as possible without sacrificing target coverage. Similarly, a mean OC dose of 3,400 cGy, mean larynx dose of 4,400 cGy and mean pharyngeal constrictor (PC) dose of 5,000 cGy was used for planning. Again, those structures were pushed as low as possible without sacrificing CTV coverage or increasing parotid dose.

sCT generation from CBCT

To generate the sCT, a research version of a commercial Deformable Image Registration (DIR) tool (ADMIRE 2.0, Elekta Inc., Stockholm, Sweden) was utilized for the DIR between CT and CBCT. Briefly, the intra-patient algorithm of ADMIRE performs a block-wise non-linear registration to get a robust initial alignment, followed by a dense local-correlation-coefficient (LCC) based deformable registration to get the final deformable vector field (DVF). This tool has been reported and evaluated in several international challenges of head & neck and lung patients DIR with high-ranking results (18-21). Our institution also comprehensively evaluated for HNC patients with expert-delineated contours as ground truth, including seven OARs [brain stem, cord, left and right (L/R) parotids, L/R submandibular gland and mandible] (22). The CT-CT intra-patient propagation achieved Dice similarity coefficient (DICE) greater than 0.85 and mean surface distance (MSD) smaller than 1.2 mm. The DICE and MSD of CT-CBCT propagation were very close to the CT-CT results, decreasing only by 0.03 and 0.2 mm respectively.

sCT validation test

To validate the sCT proton dose calculation accuracy, both vCT and sCT on the same day were used for comparison purpose for both PTV-IMPT and ro-IMPT groups.

Dose Accumulations and plan robustness analysis

In this study, the initial contours were deformed along with the images and manually checked by a physician for accuracy on the sCTs (14-16). Dose accumulation

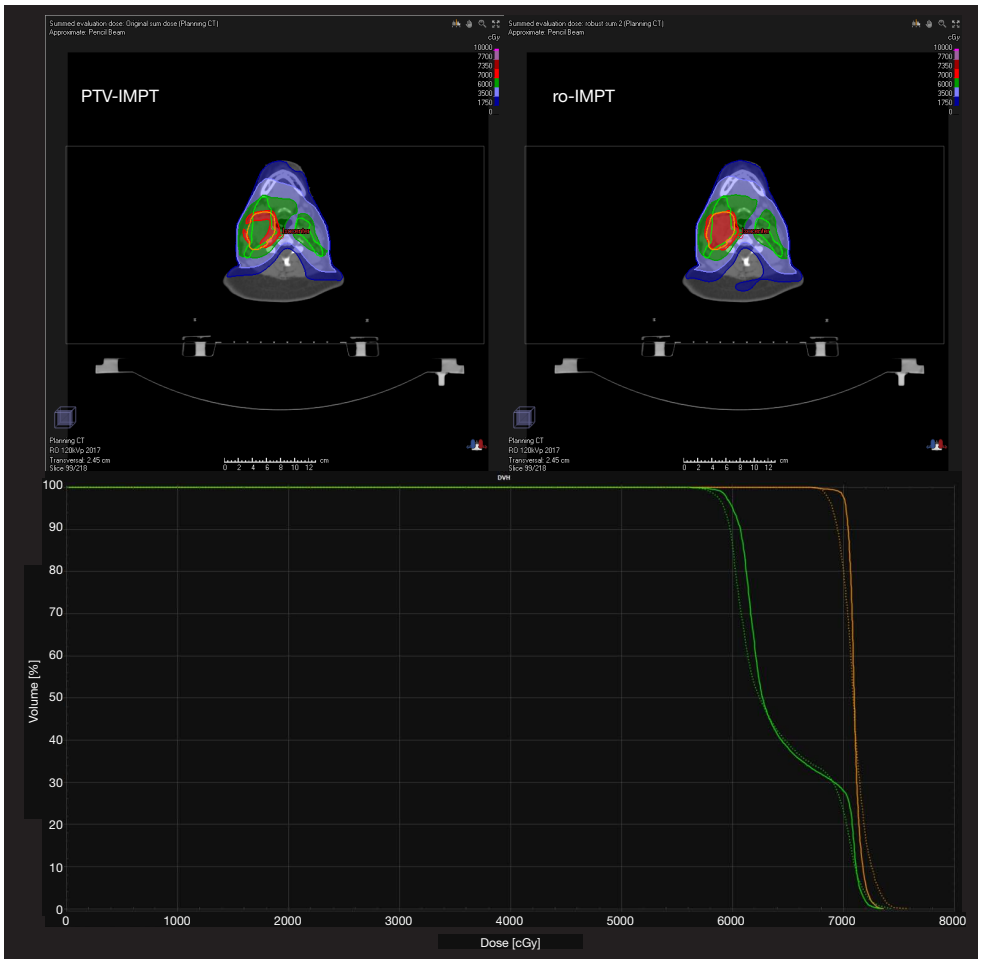

Figure 1 A representative case of sCT and vCT comparisons in proton dose distribution. The 3D gamma index dose comparison (3 mm/3%) showed an average pass rate of 98.2%±1.5% comparing the same day's pair of sCT and vCT. PTV, planning target volume; IMPT, intensity modulated proton therapy; ro-IMPT, robust optimized IMPT; sCT, synthetic-CT; vCT, verification-CT; DVH, dose-volume histogram.

throughout the treatment course for each patient was obtained by summing up the dose recalculated on each daily sCT (total 35 sCTs throughout the treatment courses). Daily CBCT registration shifts from the previous VMAT on the linear accelerators (LINACs) were used to mimic the daily setup uncertainty in the dose recalculation.

Doses to target and normal structure were analyzed among the two planning strategies: PTV-IMPT and ro-IMPT. The difference in "real" dose accumulated (Dose-A) between the two planning groups was compared with the two-sided *t*-test. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board (No. 2017-455) and consent was waived from all individual participants.

Statistics analysis

A two-tailed Wilcoxon Signed Rank test were performed. Hypotheses and determine level of significance: H0 (the median difference is zero) versus H1 (the median difference is not zero α=0.05). With the example size, the critical value of W is 8.

Results

The sCT were compared to two vCTs on the same day with proton dose comparison. Using the 18 pairs of same day's sCT and vCT for both PTV-IMPT and ro-IMPT plans, the average gamma index using 3%/3 mm on the entire volume showed a 98.2%±1.5% pass rate (*Figure 1*).

Table 2 Target volume coverage

Patient	Planning method	CTV1 V100 initial (%)	CTV1 V100 accumulated (%)	CTV2 V100 initial (%)	CTV2 V100 accumulated (%)
1	PTV-IMPT	99.50	66.97	99.44	93.88
	ro-IMPT	98.69	96.84	98.14	98.81
2	PTV-IMPT	100.00	84.88	99.48	88.68
	ro-IMPT	99.17	92.12	98.80	87.79
3	PTV-IMPT	99.51	89.25	99.66	92.96
	ro-IMPT	99.09	99.23	98.69	97.78
4	PTV-IMPT	99.48	84.84	99.86	84.40
	ro-IMPT	98.73	98.93	99.16	96.08
5	PTV-IMPT	98.47	96.72	99.74	92.10
	ro-IMPT	98.60	97.75	98.99	98.68
6	PTV-IMPT	99.03	88.05	99.29	67.80
	ro-IMPT	99.44	95.94	98.38	95.30
7	PTV-IMPT	99.54	72.18	99.19	85.77
	ro-IMPT	99.28	95.31	99.16	97.12
8	PTV-IMPT	100.00	63.24	99.93	79.36
	ro-IMPT	99.83	96.78	99.20	98.49
9	PTV-IMPT	99.78	80.19	99.78	86.61
	ro-IMPT	99.71	97.61	99.97	95.11
Mean	PTV-IMPT	99.48	80.70	99.60	85.73
	ro-IMPT	99.17	96.72	98.94	96.13

CTV, clinical target volume; PTV, planning target volume; IMPT, intensity modulated proton therapy; ro-IMPT, robust optimized IMPT.

The dosimetric results are summarized in *Table 2* (target coverage) and *Table 3* (OARs). An example patient is shown in *Figure 2A,2B*. In the PTV-IMPT plan group, the mean V100 of CTV_high and CTV_low received 99.48% and 99.60% of the prescription dose in (initial dose) Dose-I. However, the Dose-A showed that the mean V100 of CTV_high and CTV_low were degraded to 80.70% and 85.73%, respectively, after 35 treatment fractions. As a comparison, in the ro-IMPT plan group, the mean V100 of CTV_high and CTV_low received 99.17% and 98.94% of the prescription dose in Dose-I. After 35 treatment fractions, the Dose-A showed that the mean V100 of CTV_high and CTV_low were degraded slightly to 96.72% and 96.13%, respectively. The mean accumulated dose difference between the ro-IMPT Dose-A *vs.* PTV-IMPT Dose-A plans for CTV_high/CTV_low was 16.33%/11.06% (we have statistically significant evidence at α=0.05) showed a superior advantage of using ro-IMPT planning strategy for target robustness coverage in bilateral HNC proton treatment.

The mean accumulated dose for ipsilateral and contralateral parotid was 32.7 and 18.1 Gy, respectively. The mean maximum accumulated dose for the brainstem and spinal cord was 20.9 and 25.2 Gy, respectively. Given that no robustness optimization was placed on the OARs, there was no difference in the dose to the OAR with the different planning methods. Based on the final dose accumulation, none of the OARs received unacceptable doses to critical organs (spinal cord, brainstem, and mandible) in either planning group.

We also examined the average daily variation in coverage and compared the two planning strategies throughout these nine HNC patients (*Figure 3*). The PTV-IMPT showed a continued degradation of coverage throughout

Table 3 Organs at risk dosimetry

OAR	Planning method	Initial plan, mean [range]	Accumulated plan, mean [range]
Brainstem max (cGy)	PTV-IMPT	1,939 [703–2,840]	2,093 [1,052–2,714]
	ro-IMPT	1,809 [933–2,406]	1,999 [1,286–2,682]
Spinal cord max (cGy)	PTV-IMPT	2,004 [1,236–3,258]	2,516 [1,283–3,761]
	ro-IMPT	2,204 [1,489–3,349]	2,586 [1,433–3,655]
Ipsilateral parotid mean (cGy)	PTV-IMPT	2,943 [2,104–3,761]	3,272 [2,101–4,276]
	ro-IMPT	2,829 [2,213–3,465]	3,178 [1,903–3,994]
Contralateral parotid mean (cGy)	PTV-IMPT	1,397 [862–1,990]	1,814 [1,167–2,697]
	ro-IMPT	1,362 [983–2,075]	1,802 [1,242–2,979]
Mandible D0.1cc (cGy)	PTV-IMPT	6,964 [6,867–7,007]	6,986 [6,708–7,227]
	ro-IMPT	6,993 [6,865–7,151]	7,014 [6,704–7,132]
Larnx mean (cGy)	PTV-IMPT	4,662 [3,037–6,152]	5,030 [3,327–6,565]
	ro-IMPT	4,674 [3,100–6,245]	4,997 [3,331–6,288]
Oral cavity mean (cGy)	PTV-IMPT	3,391 [2,102–4,335]	3,694 [2,720–4,703]
	ro-IMPT	3,501 [2,630–4,917]	3,749 [2,736–5,407]
Constrictor mean (cGy)	PTV-IMPT	5,854 [5,289–6,266]	6,003 [5,377–6,451]
	ro-IMPT	5,699 [5,152–6,129]	5,869 [5,234–6,385]
Constrictor V70 Gy (%)	PTV-IMPT	23.3 [0–43.2]	23.9 [10.9–36.5]
	ro-IMPT	19.7 [0–39.2]	21.86 [0–40.6]

OAR, organ at risk; PTV, planning target volume; IMPT, intensity modulated proton therapy; ro-IMPT, robust optimized IMPT.

the treatment course. While the ro-IMPT also showed decreasing coverage through the treatment course, its degradation is significantly less than that of the PTV-IMPT method.

There was one patient (#2) with suboptimal coverage (CTV_V100 <95%) with the ro-IMPT planning methods. The patient experienced a 4 kg weight loss over the treatment course that likely contributed to the suboptimal coverage.

Discussion

Clinically, proton therapy remains an attractive option for upfront definitive cases due to the dosimetric advantage and potential to decrease toxicity. Unfortunately, there is a lack of robust data regarding clinical improvement with proton therapy compared to photon therapy. A case-matched analysis from MD Anderson Cancer Center (MDACC) showed a decreased weight loss or G-tube use with IMPT over intensity-modulated radiation therapy (IMRT). Initially, improved G2–3 xerostomia at 3 months did not persist at 1 year (9). In addition, MDACC also published the patient-reported outcomes (PRO) on a similar cohort of the patient population that showed improvement of IMPT with subacute food taste and appetite and chronic appetite over IMRT. Overall though, there was little difference in PRO in the two groups (8). One of the main advantages of proton therapy is the sparing of contralateral parotids compared to photons, and we would anticipate xerostomia to improve with proton therapy. The lack of improvement in xerostomia may be due to their planning method, as it seems there is no significant dose difference in the parotid mean dose based on their prior planning publications (3). Further prospective trials focusing on toxicity are needed to determine the utility of proton therapy. At this time, there is an accruing multi-institutional randomized trial comparing IMRT *vs.* IMPT for HNC with the primary outcome measuring late grade 3–5 toxicity (NCT01893307). To ensure the accurate dose to be delivered to the HNC patients, multiple planning strategies were proposed,

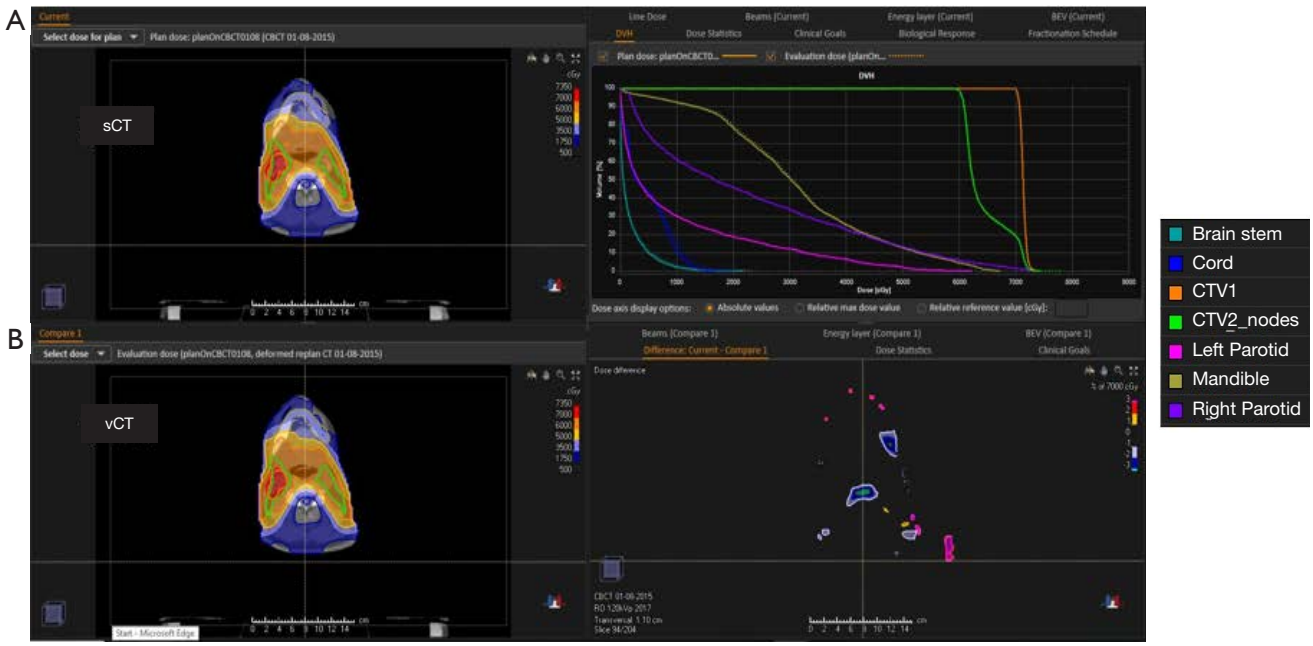

Figure 2 The comparison between the two planning methods. (A) Dose distribution of a representative patient where the image on the left represents the dose accumulated PTV-IMPT planning method and the right represents the dose accumulated ro-IMPT planning method. (B) DVH of the above patient showing coverage of CTV1 (orange) and CTV2 (green). The solid lines represent the dose accumulated ro-IMPT method and the dashed line represents the dose accumulated PTV-IMPT method. sCT, synthetic-CT; vCT, verification-CT; PTV, planning target volume; IMPT, intensity modulated proton therapy; DVH, dose-volume histogram; CTV, clinical target volume; ro-IMPT, robust optimized IMPT.

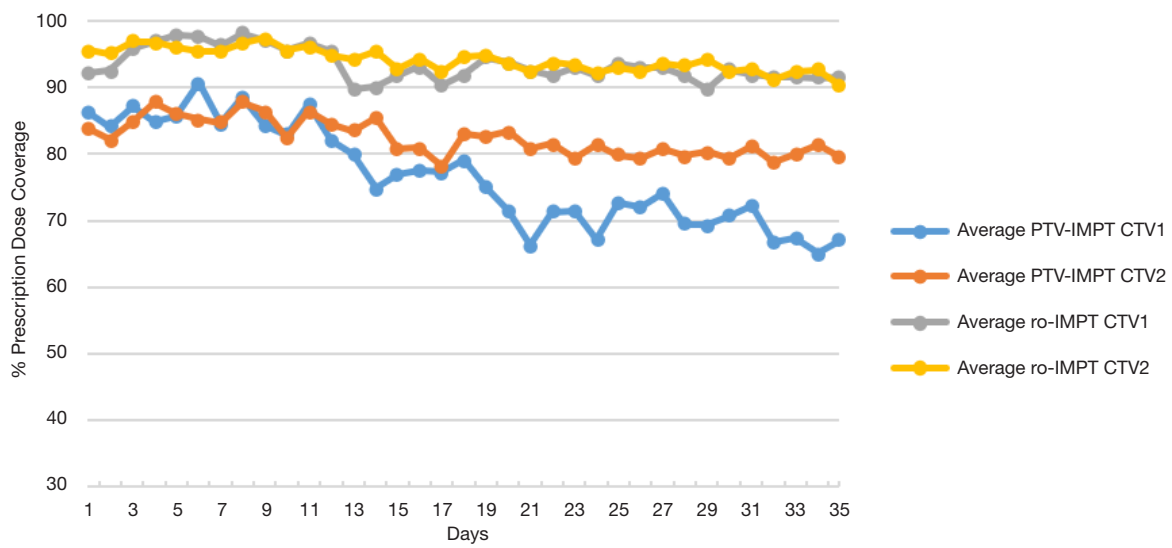

Figure 3 Average daily dose coverage in CTVs for 9 patients comparing between PTV-IMPT *vs.* ro-IMPT planning groups. PTV, planning target volume; IMPT, intensity modulated proton therapy; CTV, clinical target volume; ro-IMPT, robust optimized IMPT.

including robust optimization.

This is the first quantitative and comprehensive clinical study to assess the treatment robustness via these two planning strategies using daily CBCT throughout the whole treatment course. A number of dosimetric studies have demonstrated decreased dose to OAR with IMPT compared to photon IMRT (1-4). However, due to the physical properties of proton therapy, the final dose given to the patient may not be representative based on the initial plan. Proton is inherently more susceptible to motion and uncertainties than photon (23,24). Our results are encouraging and show that ro-IMPT is a valid planning strategy to treat patients with IMPT. On the other hand, PTV-IMPT is a non-robust method, indicating that it may not be the best option for HNC patient treatment in the clinic as the prior study also demonstrates worse coverage with PTV-IMPT (17). Eight out of ten patients had CTV >95% coverage with ro-IMPT.

One patient in this study for which ro-IMPT performed sub-optimally and may be attributed to weight loss during the treatment course. There have been several studies in the past that examine the issue of weight loss in HNC patients and found that critical weight loss during treatment is extremely common (30–50%) (25,26). Multiple patient factors such as pre-treatment body mass index (BMI), age, primary site, dose, chemotherapy, etc. have been shown to predict weight loss. However, for IMPT, it remains critically important to monitor the patient's weight during treatment and have an established protocol for re-imaging and adaptive replanning if the weight loss effects dosimetry. Most importantly, it is critical to perform adaptive replanning at certain time intervals as described by other groups (4,27,28). The optimal time point remains debated. However, this study established a comprehensive platform that gives clinicians data to determine the optimal time point to perform the proton adaptive plans. Based on the data in this study (*Figure 3*), a good starting time point for adaptation maybe every 2–2.5 weeks with weekly evaluation CT to encompass the majority of patients that may have major changes in anatomy.

Conclusions

With this daily proton dose evaluation platform, we established a system for comprehensive robustness evaluation platform into our daily workflow to evaluate the need for replanning taking weight and anatomy changes into account. The study found that the ro-IMPT strategy achieves superior and more robust target coverage than PTV-IMPT in bilateral HNC treatment. Special cautions are needed to take into account the significant weight changes.

Acknowledgments

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Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Therapeutic Radiology and Oncology*, for the series "Pencil Beam Scanning Particle Therapy". The article has undergone external peer review.

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Data Sharing Statement: Available at https://tro.amegroups.com/article/view/10.21037/tro-21-42/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (Available at https://tro.amegroups.com/article/view/10.21037/tro-21-42/coif). The series "Pencil Beam Scanning Particle Therapy" was commissioned by the editorial office without any funding or sponsorship. XD received honorarium fee from IBA speaker Bureau outside the work presented here. The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional review board (No. 2017-455) and consent was waived from all individual participants.

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