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Multiple-CT optimization: an adaptive optimization method to account for anatomical changes in intensity-modulated proton therapy for head and neck cancers

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Abstract

Purpose: We aimed to determine whether multiple-CT (MCT) optimization of intensity-modulated proton therapy (IMPT) could improve plan robustness to anatomical changes and therefore reduce the additional need for adaptive planning.

Methods and Materials: Ten patients with head and neck cancer who underwent IMPT were included in this retrospective study. Each patient had primary planning CT (PCT), a first adaptive planning CT (ACT1), and a second adaptive planning CT (ACT2). Selective robust IMPT plans were generated using each CT data set (PCT, ACT1, and ACT2). Moreover, a MCT optimized plan was generated using the PCT and ACT1 data sets together. Dose distributions optimized using each of the four plans (PCT, ACT1, ACT2, and MCT plans) were re-calculated on ACT2 data. The doses to the target and to organs at risk were compared between optimization strategies.

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Results: MCT plans for all patients met all target dose and organs-at-risk criteria for all three CT data sets. Target dose and organs-at-risk dose for PCT and ACT1 plans re-calculated on ACT2 data set were compromised, indicating the need for adaptive planning on ACT2 if PCT or ACT1 plans were used. The $D_{98\%}$ of CTV1 and CTV3 of MCT plan re-calculated on ACT2 were both above the coverage criteria. The CTV2 coverage of the MCT plan re-calculated on ACT2 was worse than ACT2 plan. The MCT plan re-calculated on ACT2 data set had lower chiasm, esophagus, and larynx doses than did PCT, ACT1, or ACT2 plans re-calculated on ACT2 data set.

Conclusions: MCT optimization can improve plan robustness toward anatomical change and may reduce the number of plan adaptation for head and neck cancers.

Keywords

Multiple CT optimization; adaptive planning; head and neck cancer; intensity-modulated proton therapy

Introduction

Intensity-modulated proton therapy (IMPT), by exploiting the sharp distal fall-off of proton Bragg peaks, offers similar target conformity to that of intensity-modulated photon therapy (IMRT) as well as lower doses to adjacent normal tissues than those of IMRT [1-5]. IMPT therefore is particularly suitable for head and neck cancers, e.g., nasopharyngeal cancer, because of the amount and proximity of critical structures encountered in these cancers. However, the characteristics of IMPT also make it highly vulnerable to range and setup uncertainties and anatomical changes [6, 7]. These uncertainties may cause under-dosage of tumor volumes and/or over-dosage of critical normal structures.

The inclusion of robustness in plan optimization has been proposed in recent years to account for some of these uncertainties. Robust optimization explicitly accounts for range and setup uncertainties using the worst-case [8, 9], minimax [10, 11], or probability optimization [12] methods. An IMPT plan optimized using the robust optimization method is significantly less sensitive to range and setup uncertainties than a conventional plan is [13]. However, anatomical changes, which are not considered in traditional robust optimization, can still lead to substantial changes in dose distribution for IMPT during the actual course of treatment [14-17].

Anatomical changes during radiotherapy can be roughly classified as inter-fractional (e.g., anatomical variation over the course of radiation therapy) and intra-fractional (e.g., variations due to swallowing) [5, 18]. Patients with head and neck cancer in particular are known to have severe inter-fractional anatomical changes throughout the treatment course, including shrinking primary tumors or nodal masses, resolving postoperative changes/edema, changes in nasal cavity filling, and weight loss [14, 19, 20]. Anatomical changes seen over the course of treatment of head and neck cancer have a unique behavior. For example, weight loss and tumor shrinkage are often observed during the treatment. However, the trend of the tumor shrinkage or nasal cavity filling is highly unpredictable [5, 19, 20]. In addition, the final dose distribution for an IMPT plan is obtained by combining all individually inhomogeneous proton fields (typically 3-4 fields). Head and neck IMPT

plans are often heavily modulated in each of the fields, featuring steep dose gradients and inhomogeneous fluence within fields, thus potentially further increasing the sensitivity of head and neck IMPT plans to these anatomical changes [3, 5]. In clinical practice, repeated imaging and adaptive planning are used to account for anatomical changes during the treatment course [1, 5]. Currently, there is no standard solution for patients who have continuous and major anatomical changes; these patients may need two or more plan adaptations over the course of treatment. At our institution, about 40% of head and neck patients who undergo IMPT require adaptive planning after re-evaluation of the original IMPT plans on verification CTs during treatment, and about 10% of head and neck patients require more than one plan adaptation.

However, the adaptive planning process itself (e.g., image registration and dose accumulation) introduces uncertainties in the actual dose delivered to the patient that are difficult to quantify. The adaptive planning process also increases the workload for physicians and physicists and increases the economic burden for patients. Given the need for retaining the plan robustness and the possibility of reducing these burdens, the reduction of adaptive planning is an urgent challenge for IMPT for head and neck cancers.

The purpose of this study was to investigate a technique to reduce the adaptive planning of IMPT for head and neck cancer patients. To that end, we hypothesized that the robustness of a plan to inter-fractional anatomical changes can be improved using both primary and first adaptive CT data to generate a treatment plan that meets dose criteria of both CTs. We evaluated this multi-CT (MCT) plan using a second adaptive CT data, which was not available at the time of the first adaptation, to determine whether the MCT plan also met the dose criteria of the second adaptive CT. The field range and spread-out Bragg peak (SOBP) also were analyzed to quantify the relationships between the anatomical changes and dose deviations.

Methods and Materials

Patient Data

Ten patients with head and neck cancer treated under an institutional review board–approved protocol who received IMPT and underwent at least two adaptive plans at our center from March 2012 to September 2014 were selected for this retrospective study. A total of around 110 head and neck cancer patients received IMPT at our center in that time frame. Table 1 summarizes the characteristics (e.g., age, stage, and weight) of these patients. During treatment, patients were scanned with verification CT scans. The original treatment plan was then recalculated on repeated CTs, and contours were deformed from the planning CT to repeated CT. Then the treating physician reviewed the new contours and the dose calculated on the repeated CT to determine if an adaptive planning was needed [22]. If an adaptive plan was deemed necessary, the plan would be developed using same optimization criteria as the original plan, and underwent the same patient-specific quality assurance process before the adaptive plans were used for patient treatment.

The time intervals between primary planning CT (PCT) and the first adaptive planning CT (ACT1) scan as well as the second adaptive planning CT (ACT2) scan are also reported in

Table 1 for each patient. All CT data sets were acquired using a GE LightSpeed 16-slice CT scanner (GE Healthcare, Waukesha, WI) with a slice thickness of 2.5 mm. The CT scan timeline is also shown in Table 1.

The targets and organs at risk (OARs) were delineated as follows: Clinical target volume (CTV) and OARs were all contoured on the PCT. The planning target volume (PTV) was defined by adding 3 mm to the CTVs. Before the process of delineation on ACTs, the ACTs were registered with the PCT using rigid registration of the bony anatomy on an Eclipse treatment planning system (Varian Medical Systems, Palo Alto, CA). The registration results and structures of the PCT were copied to the ACTs and then modified and confirmed by the same physician as the one who contoured them on the PCT.

The external volumes (at three individual slices) at the levels of the C2 and C5 vertebral bodies and at the base of the skull were contoured; the external volumes of these landmarks have been reported to be correlated with weight loss in head and neck cancer patients during radiotherapy [19]. The SOBP length calculated by the Eclipse system is the distance between the most distal target depth and the most proximal target depth (equivalent to water) of the field. The range and SOBP deviations between primary and adaptive CTs for each field are sometimes an indication for adaptive planning [21]; therefore, deviations in field range and SOBP between the primary and the adaptive plans were calculated as $100\% \times (R_{\text{ACT}} - R_{\text{PCT}})/R_{\text{PCT}}$, where R is the field range or SOBP calculated using the Eclipse treatment planning system.

Plan Optimization

To reduce variation in the processes of treatment planning and adaptive planning, the clinical plans were not used. Instead, the treatment plans were re-optimized by a single planner using the following target objectives: the prescribed dose to CTV1 (defined as the gross extent of the tumor shown by imaging studies and physical examination plus a 1-cm margin) was 70 Gy relative biological effectiveness (RBE) in 33 fractions; to CTV2 (encompassing the high-risk nodal volume adjacent to gross disease, includes the entire nasopharynx, retropharyngeal lymph nodal regions, clivus, skull base, pterygoid fossae, parapharyngeal space, inferior sphenoid sinus and posterior third of the nasal cavity and maxillary sinuses) 63 Gy (RBE) in 33 fractions; and to CTV3 (encompassing an addition margin beyond CTV2 for patients with pharyngeal tumors and uninvolved nodes in the neck considered at risk of harboring subclinical disease) 57 Gy (RBE) in 33 fractions [1]. Two optimization methods were compared: selective robust optimization and MCT optimization. Selective robust optimization used anatomical information from only one CT data set (PCT, ACT1, or ACT2), whereas MCT optimization combined anatomical information from the PCT and the ACT1 data sets. Both optimization methods used multi-field optimization. In selective robust optimization which is implemented in Eclipse version 13.7, as detailed in our previous research [3, 23], the objective function of the PTV was computed in the nominal situation, and the objective function of the CTV was computed in the worst-case situations, including range uncertainties of $\pm 3.5\%$ and setup uncertainties of ± 3 mm. To investigate if an IMPT plan that satisfies all target coverage and OAR dose requirements could be created using PCT only, additional plans with different compromise on target and OAR dose, along with

different assumed setup uncertainties up to ± 5 mm and range uncertainties up to $\pm 4\%$ were also created using Eclipse and evaluated on ACT1 and ACT2. For MCT optimization, both PCT and ACT1 data sets were used, and the primary structures of PCT and adaptive structures of ACT1 were both include in optimization. We used a standard quadratic objective function, and each iteration of the objective function of MCT was obtained by adding the PCT's objective function and the ACT1's objective function together. The dose distribution was optimized in only the nominal scenario, excluding the influence of range and setup uncertainties, for CTV and OARs. To facilitate MCT optimization, ACT1 images were first rigidly registered to the PCT images, and then the plan isocenter on ACT1 was calculated according to the registration results. After registration, the CT image data sets as well as the structures and plan information from the PCT and ACT1 data sets were exported to our in-house-developed treatment planning system [8]. All MCT and selective robust optimizations were performed with a dose grid resolution of 2.0 mm. The framework and definition of the MCT optimization were detailed in our previous study [21]. The optimization objective for all selective robust and MCT plans was to achieve 100% of the prescribed dose to the CTV first and then to minimize the dose to OARs. The robustness optimization criterion was that 98% of the target volume received at least 98% of the prescribed dose in the worst case scenario. After optimization, all plans were normalized to facilitate dose comparisons. The normalization point was a CTV1 $D_{99\%}$ of 70 Gy, where $D_{x\%}$ was defined as the lowest dose covering x% of the volume. All plans for all ten patients had the same three gantry angles (180° , 300° , and 60° , as shown in Fig. S2) to facilitate the evaluation of correlations between external volumes and SOBP or range [1].

Plan Evaluation

For each patient, we generated four plans: three selective robust optimization plans using the PCT (PCT plan) and the two adaptive CTs (ACT1 and ACT2 plans) and a MCT optimized plan (MCT plan) based on the primary CT and the first adaptive CT. Using these plans, we re-calculated the dose using the second adaptive CT. We thus generated eight sets of dose distributions for each patient: a selective robust optimization plan using a primary CT calculated on PCT data set (P-PCT), a PCT plan re-calculated on ACT2 data set (P-ACT2), a selective robust optimization plan using a first adaptive CT calculated on ACT1 data set (A1-ACT1), an ACT1 plan re-calculated on ACT2 data set (A1-ACT2), a selective robust optimization plan using a second adaptive CT calculated on ACT2 data set (A2-ACT2), a MCT plan calculated on PCT data set (M-PCT), a MCT plan calculated on ACT1 data set (M-ACT1), and a MCT plan re-calculated on ACT2 data set (M-ACT2). Abbreviations for all plans and dose data sets are shown in Table S1.

We also calculated the accumulated dose for the two plan optimization methods. We evaluated three adaptive strategies of plans: 1. M-PCT, M-ACT1 and M-ACT2 were accumulated with number of respective fractions calculated according to the timing of ACT1 and ACT2, representing the accumulated dose of treatment completed with MCT plan and no adaptive planning; 2. P-PCT, A1-ACT1 and A1-ACT2 were accumulated with corresponding fractions, representing the accumulated dose with one adaptive planning; 3. P-PCT, A1-ACT1 and A2-ACT2 were accumulated with corresponding fractions, representing the accumulated dose with two adaptive planning.

To quantify the differences between dose distributions, dose-volume histograms were used to assess the dose coverage and conformity of the CTV and the protection of OARs. The CTV evaluation parameters were $D_{98\%}$ (CTV coverage), $D_{2\%}$, conformity index (CI), and homogeneity index (HI). The criteria for target coverage of CTVs were defined as at $D_{98\%}$ 98% prescribed dose. The CI, defined as $100\% \times (TV_{PI})^2 / (PI_{100} \times TV)$, describes the conformity of the prescribed dose around the target volume [24]; TV is the target volume, TV_{PI} is the volume of the target covered by the prescribed isodose, and PI_{100} is the volume receiving 100% of the prescribed isodose; conformity improves as the CI approaches 100%. The HI, defined as $100\% \times (D_{2\%} - D_{98\%}) / D_{50\%}$, was used to document dose homogeneity within each target volume; plans that are more homogenous have HI values closer to 0% [25]. Mean doses to parallel OARs (e.g., both parotids) were compared. For serial OARs such as the spinal cord, brain stem, optic chiasm and esophagus, the $D_{2\%}$ were compared.

Robustness evaluation was also performed for all plans using worst-case scenario analysis, assuming range uncertainties of $\pm 3.5\%$ and setup uncertainties of ± 3 mm [3, 23].

Statistical Analysis

SPSS 24.0 software (IBM, Armonk, NY) was used for statistical analyses of all dosimetric indices. We conducted a paired, two-tailed Wilcoxon signed-rank test to compare the dose distributions between

1. the A2-ACT2 and the M-ACT2,
2. the P-ACT2 and the M-ACT2, and
3. the A1-ACT2 and the M-ACT2.

Comparison 1 allowed us to determine whether a MCT plan that met the dose criteria of ACT1 and PCT data sets could be robust to the anatomical changes of ACT2 and to evaluate the dosimetric advantages of each plan. Comparisons 2 and 3 assessed the MCT plan's robustness to anatomical changes compared with that of the primary plan (PCT plan) and the adaptive plan (ACT1plan).

The accumulated dose of three adaptive strategies of plans were also analyzed with a paired, two-tailed Wilcoxon signed-rank test between

1. accumulated dose of MCT plan with accumulated dose of PCT and ACT1 plans,
2. accumulated dose of MCT plan with accumulated dose of PCT, ACT1 and ACT2 plans
3. accumulated dose of PCT and ACT1 plans with accumulated dose of PCT, ACT1 and ACT2 plans.

We also conducted a two-tailed Spearman correlation test to evaluate the relationships between the external volumes of the landmarks and the field range or the SOBP.

P values of less than 0.05 were considered statistically significant.

Results

To illustrate the differences in dose distribution between plans, we present patient 1 (changes in nasal cavity filling), patient 5 (weight loss), and patient 6 (tumor shrinkage) as representative cases; their anatomical changes are shown in Fig. S2. Fig. 1 compares the dose distributions of the different plans recalculated on the ACT2—namely, the P-ACT2, A1-ACT2, A2-ACT2 and M-ACT2 plans—for these three patients. M-ACT2 and A2-ACT2 did not markedly differ. However, because of anatomical changes between PCT and ACT2 and between ACT1 and ACT2, P-ACT2 had significant cold spots in patients 1, 5, and 6, and A1-ACT2 had significant cold spots in patient 5.

Dose-volume histograms for patient 5 are compared between plans in Fig. 2. Fig. 2a shows the differences between the P-ACT2 plan (triangle line), the A1-ACT2 plan (circle line), and the M-ACT2 plan (square line). The M-ACT2 plan had better CTV dose coverage, as well as lower dose to the brain stem and spinal cord, than did the P-ACT2 and A1-ACT2 plans. The degraded CTV coverage by P-ACT2 and A1-ACT2 indicates the need for adaptive planning. The differences between the M-ACT2 plan and the A2-ACT2 plan are shown in Fig. 2b. The M-ACT2 plan had a slightly lower but still acceptable CTV dose coverage and a higher maximum dose to the CTVs (indicating worse HI), but lower doses to the brain stem and spinal cord, than did the A2-ACT2 plan.

Table 2 shows the CTV $D_{98\%}$, $D_{2\%}$, CI, and HI for the different plans. For all patients, the $D_{98\%}$ values of CTV1 and CTV3 did not significantly differ between the M-ACT2 and A2-ACT2 plans, and the M-ACT2 plan had significantly better $D_{98\%}$ for CTV3 than did the P-ACT2 ($p = 0.013$) and A1-ACT2 ($p = 0.007$) plans, better $D_{98\%}$ for CTV1 than did the P-ACT2 plan ($p = 0.028$), and better $D_{98\%}$ for CTV2 than did the P-ACT2 plan ($p = 0.017$). The M-ACT2 plan had higher $D_{2\%}$, higher HI, and lower CI than did the A2-ACT2 plan.

OAR dose are compared between plans in Table 3. Compared with the A2-ACT2 plans, the M-ACT2 plans showed a decrease in some OARs adjacent to CTV, such as those to the optic chiasm ($p = 0.006$), esophagus ($p = 0.027$), and larynx ($p = 0.007$). M-ACT2 plans also spared the optic chiasm, esophagus, and larynx better than did the A1-ACT2 and P-ACT2 plans.

The comparisons between accumulated dose data using different plans are shown in the Table S3 and S4. Table S3 shows the comparison of accumulated dose for target coverage. The MCT plan was able to maintain coverage on all target volumes without adaptive planning, where if the selective robust optimized plan with only one adaptive plan was used (PCT+ACT1), the target coverage was deteriorated for CTV2. The target dose was recovered with an additional adaptive planning on ACT2 (PCT+ACT1+ACT2), as expected. There were statistical significant difference between dose with two adaptive plans and dose with one adaptive plan for CTV2 and CTV3 $D_{98\%}$, and no statistical significant difference between dose with MCT plan and dose with one or two adaptive plan for all three target volumes. Table S4 shows the comparison of accumulated dose for normal tissue sparing. Dose with MCT plan shows superior optic chiasm, larynx and esophagus sparing compared to dose with both selective robust optimization and one or two adaptive planning.

There was no uniform trend among the cases in volume changes in the external skin contours at the level of the C2, the C5, and the base of the skull as treatment days elapsed, as shown in Fig. S1, in the Supplementary Material. Fig. 3 showed that the range and SOBP for each field varied between PCT and ACT1 data sets and between PCT and ATC2 data sets. The Spearman correlation test showed that the field range and SOBP were each highly correlated with external skin volumes (Table S2).

Robustness evaluation results for the PCT and MCT plans on PCT data set using worst-case scenario analyses with range uncertainties of $\pm 3.5\%$ and setup uncertainties of ± 3 mm, and the results for patient 5 are shown in Fig. S3. When evaluating $D_{98\%}$ under the worst case scenario for target volumes, no statistical difference between the two plans were found.

Discussion

Our results show that for a selected group of 10 head and neck patients representing large anatomical changes, a MCT plan leads to significantly more robust prescription dose coverage for the unpredictable anatomical changes of the ACT2 than do the PCT and ACT1 plans using selective robust optimization. In other words, improving the robustness of an IMPT plan to anatomical changes using MCT optimization is feasible, and therefore the number of adaptive plans may be reduced.

Contrary to the possible assumption that anatomical changes remain monotonic throughout the course of radiotherapy, some studies have shown that these anatomical changes sometimes fluctuate [5, 19]. In the current study, we also found that the patient skin volume fluctuated considerably (Fig. S1), likely owing to the varying thickness of fat layers (e.g., due to weight loss or weight gain), or shrinking primary tumors or nodal masses [14, 19]. No trend was found in skin volume change as a function of the treatment time, suggesting that the adaptation plan strategy is not enough to maintain acceptable target coverage through the entire treatment, especially for patients with drastic anatomical changes. If a patient undergoes continuous and unpredictable anatomical changes throughout the treatment, there could be a risk that the dose is not delivered as planned even though adaptation planning is performed. However, our strategy of MCT optimization could provide a more robust plan to overcome the anatomical changes compared with a normal adaptive plan. As shown in Fig. S2 and as indicated by the changes in field ranges and SOBP (Fig. 3), MCT optimization can account for changes in the thickness of fat layers or changes in target volumes by optimizing the weights of spots to make the plan more generalizable to the anatomical change-induced field-range and SOBP variations (as shown in Fig. 1 and Fig. S3). As shown in Fig. S2, even the nasal cavity filling is unpredictable and introduces large field-range and SOBP changes; if one of the two optimized CTs has the nasal cavity filling situation similar to that of the third one, the MCT optimization could reduce the impact of nasal cavity filling on the target coverage. Therefore, the MCT optimization could improve the robustness of the first adaptive plan to adapting to anatomical change without knowing the trends of future anatomical changes—for example, whether a patient gains or loses weight.

The MCT optimization process is a tradeoff between conformity of targets and plan robustness to anatomical change. For example, the robust optimization may compromise

some doses to OARs, in order to make the CTVs more robust to setup and range uncertainties [26]. Although the MCT optimization sacrifices some extent of conformity of targets to cover the CTVs on both CTs, it might reduce the margins in the directions which OARs were adjunct comparing to the robust optimization, as illustrated in Figure S4. Hence the dose overflowing onto OARs might be reduced. This is the reason for the better sparing of some OAR with the MCT optimization than the robust optimization (Table 3, S4).

Proton therapy in general and IMPT in particular are highly sensitive to anatomical changes. Owing to the different physical characteristics of photons and protons, the classical PTV [27, 28] of IMRT does not necessarily improve the robustness of IMPT against range and setup uncertainties [3, 17, 29]. The robustness of the IMPT plan is thus a major concern for clinical practice. In our study, the MCT planning technique we used did not explicitly include setup and range uncertainties in the optimization process. As shown in Fig. 3, the range and SOBP variations between the PCT and ACT1 are about 1.5%-3%, which is on the same order as the range uncertainties usually prescribed for robust optimization. We also evaluated the robustness of the setup and range uncertainties for MCT plan and the selective robust plan for all patients in this study, and the result for patient #5 is shown in Fig. S3. The robustness of the setup and range uncertainties for MCT plan was similar to that of the selective robust plan according to the dose-volume histogram band evaluation method using 3mm setup/3.5% range uncertainties, when evaluating using $D_{98\%}$ under the worst case scenario for target volumes, no statistical difference between the two plans were found [3, 30]. (Fig. S3). However, the robustness evaluation results did not predict the change in actual dose distribution during the treatment course, as shown in Fig. 1e and 1f. The M-ACT2 plan maintained target coverage, whereas the P-ACT2 plan did not. Except for the range and SOBP deviations between PCT and ACT1 (Fig. 3), the setup errors between the PCT and ACT1 (e.g. shoulder positioning or small rotations) may also be included in the MCT optimization. The MCT optimization saved some room for both the anatomical and setup uncertainties between PCT and ACT1 data set, so that the PCT plan would be mechanically less robust than the MCT plan. Therefore, the robustness evaluation techniques which were developed for evaluating the setup and range uncertainties are not effective for the anatomical changes, which can lead to substantial changes in dose distribution.

In our previous study, the use of multi-CT optimization has shown the potential to increase the robustness of the plans against anatomical changes for lung tumors [21]. In the recent studies, Van de Water *et al.* [20] and Cubillos-Mesías *et al.* [31] both evaluated the possibility of adding additional CT data into robustness optimization to improve the robustness of head and neck IMPT plans. Van de Water *et al.* included the synthetic CTs with different nasal cavity filling overwrites into the robust optimization. The result shows adequate target coverage in a repeated CT, but they did not evaluate the influence of the other anatomical changes to the target coverage. Cubillos-Mesías *et al.* included the primary CT and first two weekly CTs (usually from the first two weeks of treatment) into the robust optimization. The result shows that the robustness of the plan against anatomical changes during treatment was superior to the classical robust optimization. However, the first two weekly CTs may not be able to fully quantify the patient anatomical variation, and changes such as the body shrinkage, tumor shrinkage may not be adequately included. The lack of longitudinal anatomical change information could contribute to their result that

one of the patient could not maintain target coverage even with their propose technique to include anatomical variation. In our current study, we focused on the extreme cases where at least two adaptive planning were required throughout the proton treatment, which could indicate large anatomical variation over time, and account for ~10% of the H&N patients received proton therapy at our center. We demonstrated that after including anatomical change information in the treatment planning process, all such patients could maintain target coverage throughout the course of treatment without adaptive planning.

A considerable amount of work remains to further improve the MCT optimization. Since both the primary and first adaptive CTs were needed in the MCT optimization proceeding, the MCT optimization could only help to improve the plan robustness for the first adaptive plan. Because the daily setup and anatomical uncertainties were unavoidable, the multi-CT optimization could cover these small and unpredictable uncertainties and retain the target coverage. Recently, the If MCT optimization is using in clinical practice, the verification CT or cone-beam CT was still needed to observe the significant anatomical changes, but the possibility of the second plan adaption may be reduced. Our research will continue using daily cone-beam CT, CT-on-rails, or other simulation images to complete the MCT optimization conveniently. As indicated by Table S2, using the changes in skin volume in daily cone-beam CT may also be a direct predictor and indicator to quantify the necessary level for the plan adaptation. Knowledge-based models could also be built to predict patient anatomical changes (such as weight loss and tumor shrinkage) and facilitate MCT optimization with only the planning CT, which would make the method more practical and applicable to more patients [32]. The plan robustness of MCT plan is also needed to be quantitative evaluated with the other methods and different robust optimization settings in future studies.

In conclusion, compared with selective optimization, MCT optimization can increase treatment plan robustness to anatomical change that cannot be overcome by the primary plan or even the first adaptive plan. Implementing MCT optimization into IMPT planning for use in clinical practice could help to improve the robustness of IMPT for treating head and neck cancers. In follow up studies the patients that will benefit from this approach and the method to select them need to be further addressed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Abbreviations: M-ACT2 = MCT plan re-calculated on ACT2 data; A2-ACT2 = ACT2 plan calculated on ACT2 data; P-ACT2 = PCT plan re-calculated on ACT2 data; A1-ACT2 = ACT1 plan re-calculated on ACT2 data. Comparison of dose distributions in the transverse plane for three representative cases (P1, P5, and P6): P-ACT2 (a, e, and i); A1-ACT2 (b, f, and j); A2-ACT2 (c, g, and k); M-ACT2 (d, h, and l). The red arrows indicate the cold spots of CTV1 (pink contour) in (a), CTV1 (red contours) in (e and f) and CTV1 (red contours) in (i) which is supposed being covered by 70Gy (blue lines).

Figure 2:

- (a) Comparison of dose distribution histograms of the P-ACT2 plan (triangle line), the A1-ACT2 plan (circle line), and the M-ACT2 plan (square line) for representative case 5.
- (b) Comparison of dose distribution histograms of the M-ACT2 plan (square line) and the A2-ACT2 plan (triangle line) for representative case 5.

Figure 3:

Abbreviations: ACT1 = First adaptive CT; ACT2 = Second adaptive CT. The percentage deviation of field range (a) and SOBP (b) between PCT and ACT1 and between PCT and ACT2 for each field. The beam angles are shown in the following order for each patient: 180°, 300°, and 60°.

Table 1.

Patient and target characteristics

Patient number	Types	Age (years)	Disease Stage	PCT					ACT2					Weight (kg)	Fractions after ACT2			
				CTV1 (cm³)	CTV2 (cm³)	CTV3 (cm³)	Weight (kg)	Fractions between PCT and ACT1	CTV1 (cm³)	CTV2 (cm³)	CTV3 (cm³)	Weight (kg)	Fractions between ACT1 and ACT2					
1	nasopharynx	44	T2N2	166.4	318.5	109.1	50	13	166.1	317.7	110.4	49	12	164.8	319.9	110.8	47	8
2	nasopharynx	51	T4N1	161.4	296.6	121.4	59	8	163.4	322.9	125.4	59	17	164.1	312.1	117.9	54	8
3	nasopharynx	59	T4N1	148.5	214.0	53.8	62.5	11	148.5	206.4	54.7	60	14	141.5	216.2	47.2	59.5	8
4	nasopharynx	32	T4N1	172.5	147.5	69.8	61	13	176.5	140.1	72.3	59	12	172.6	146.1	69.9	57	8
5	oropharynx	19	T2N2	203.6	324.5	97.8	56	13	201.0	325.6	98.4	52.3	12	199.0	322.0	93.7	53	8
6	oropharynx	55	T4N2	306.2	523.2	216.4	121	12	318.6	535.7	206.7	118	13	270.9	484.5	205.9	113.4	8
7	oropharynx	18	T2N1	142.3	119.8	222.1	81.6	14	141.0	121.8	234.8	81	11	137.8	107.8	215.0	77.3	8
8	oropharynx	53	T1N2	257.7	483.2	244.9	114.5	11	250.1	465.9	254.4	113.3	14	259.3	484.3	239.0	115.5	8
9	nasopharynx	43	T4N1	260.5	570.8	298.5	115.5	11	264.4	571.1	310.8	113.7	14	259.8	552.9	311.9	110.3	8
10	nasopharynx	50	T4N2	170.4	385.9	256.9	84.2	12	171.1	387.5	260.5	85	13	173.5	387.2	252.6	82.4	8

Abbreviations: PCT = primary planning CT; CTV1 = clinical target volume 1; CTV2 = clinical target volume 2; CTV3 = clinical target volume 3; ACT1 = first adaptive planning CT; ACT2 = second adaptive planning CT.

Table 2.

Summary of analysis of target coverage and conformity index

Parameter	M-ACT2	A2-ACT2	P^b	P-ACT2	P^c	A1-ACT2	P^d
CTV1 ^a (prescribed dose 70Gy)							
D _{98%} (Gy)	70.21 (0.47)	70.45 (0.24)	0.386	69.16 (1.16)	0.028 [*]	69.80 (0.89)	0.241
D _{2%} (Gy)	77.35 (1.85)	75.68 (0.72)	0.009 [*]	76.40 (1.18)	0.139	76.24 (1.28)	0.114
HI (%)	9.54 (2.51)	7.03 (1.06)	0.007 [*]	9.86 (1.83)	0.721	8.75 (1.27)	0.285
CI (%)	63.92 (5.63)	72.22 (8.29)	0.005 [*]	68.07 (5.48)	0.028 [*]	68.34 (6.44)	0.037 [*]
CTV2 ^a (prescribed dose 63Gy)							
D _{98%} (Gy)	62.49 (1.07)	63.30 (1.03)	0.022 [*]	60.38 (2.24) [#]	0.017 [*]	61.49 (1.41) [#]	0.093
D _{2%} (Gy)	76.50 (2.21)	75.11 (0.97)	0.028 [*]	75.64 (1.47)	0.203	75.64 (1.66)	0.203
HI (%)	19.51 (2.48)	16.89 (1.25)	0.010 [*]	21.75 (3.85)	0.169	20.24 (2.50)	0.799
CI (%)	62.29 (7.54)	72.42 (3.96)	0.009 [*]	66.93 (5.19)	0.007 [*]	67.48 (4.33)	0.022 [*]
CTV3 ^a (prescribed dose 57Gy)							
D _{98%} (Gy)	57.11 (1.18)	57.37 (0.41)	0.575	53.47 (3.34) [#]	0.013 [*]	55.94 (1.02)	0.007 [*]
D _{2%} (Gy)	65.20 (2.72)	62.52 (1.54)	0.005 [*]	63.85 (2.46)	0.074	63.41 (1.98)	0.022 [*]
HI (%)	12.89 (4.04)	8.68 (2.45)	0.005 [*]	17.16 (8.35)	0.110	12.36 (4.09)	0.528
CI (%)	48.58 (9.28)	59.27 (8.88)	0.007 [*]	53.02 (8.63)	0.022 [*]	55.09 (7.35)	0.019 [*]

Abbreviations: M-ACT2 = MCT plan re-calculated on ACT2 data; A2-ACT2 = ACT2 plan calculated on ACT2 data; P-ACT2 = PCT plan re-calculated on ACT2 data; A1-ACT2 = ACT1 plan re-calculated on ACT2 data; D_x = dose delivered to x% of volume; HI = homogeneity index; CI = conformity index.

^aShown as mean (standard deviation)

^bComparison of A2-ACT2 plan with M-ACT2 plan

^cComparison of P-ACT2 plan with M-ACT2 plan

^dComparison of A1-ACT2 plan with M-ACT2 plan

[#]Target coverage is not satisfied

^{*}P < 0.05

Table 3.

Summary of analysis of dose to organs at risk

Parameter	M-ACT2	A2-ACT2	p^b	P-ACT2	p^c	A1-ACT2	p^d
Spinal cord, $D_{2\%}$ (Gy) ^a	37.97 (5.40)	35.44 (3.72)	0.130	36.79 (5.58)	0.798	35.84 (4.30)	0.201
Brain stem, $D_{2\%}$ (Gy) ^a	43.75 (7.78)	45.17 (7.11)	0.385	45.36 (7.80)	0.381	44.17 (8.34)	0.641
Optic chiasm, $D_{2\%}$ (Gy) ^a	13.84 (7.78)	24.26 (13.10)	0.007 [*]	24.56 (14.10)	0.010 [*]	26.67 (14.05)	0.005 [*]
Mandible, D_{mean} (Gy) ^a	31.94 (3.58)	32.91 (4.22)	0.074	32.66 (3.28)	0.139	33.21 (3.92)	0.074
Left parotid ^e , D_{mean} (Gy) ^a	30.41 (2.82)	31.50 (8.86)	0.758	32.82 (5.81)	0.200	34.03 (5.19)	0.136
Right parotid ^e , D_{mean} (Gy) ^a	33.54 (4.44)	32.59 (9.53)	0.681	36.05 (9.04)	0.284	33.86 (6.81)	0.791
Larynx, D_{mean} (Gy) ^a	35.19 (3.62)	41.11 (4.16)	0.007 [*]	43.70 (4.39)	0.005 [*]	41.09 (4.15)	0.017 [*]
Esophagus, $D_{2\%}$ (Gy) ^a	48.69 (7.09)	51.05 (4.79)	0.027 [*]	53.29 (6.90)	0.029 [*]	52.95 (7.40)	0.040 [*]

Abbreviations: M-ACT2 = MCT plan re-calculated on ACT2 data; A2-ACT2 = ACT2 plan calculated on ACT2 data; P-ACT2 = PCT plan re-calculated on ACT2 data; A1-ACT2 = ACT1 plan re-calculated on ACT2 data.

^aShown as mean (standard deviation)

^bComparison of A2-ACT2 plan with M-ACT2 plan

^cComparison of P-ACT2 plan with M-ACT2 plan

^dComparison of A1-ACT2 plan with M-ACT2 plan

^eThe parotids were evaluated with the volume of total parotids minus the volume of CTVs

^{*} $P < 0.05$