Intensity-Modulated Proton Therapy Adaptive Planning for Patients with Oropharyngeal Cancer

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Abstract

Purpose: The authors aimed to illustrate the potential dose differences to clinical target volumes (CTVs) and organs-at-risk (OARs) volumes after proton adaptive treatment planning was used.

Patients and Methods: The records of 10 patients with oropharyngeal cancer were retrospectively reviewed. Each patient’s treatment plan was generated by using the Eclipse treatment planning system. Verification computed tomography (CT) scan was performed during the fourth week of treatment. Deformable image registrations were performed between the 2 CT image sets, and the CTVs and major OARs were transferred to the verification CT images to generate the adaptive plan. We compared the accumulated doses to CTVs and OARs between the original and adaptive plans, as well as between the adaptive and verification plans to simulate doses that would have been delivered if the adaptive plans were not used.

Results: Body contours were different on planning and week-4 verification CTs. Mean volumes of all CTVs were reduced by 4% to 8% (P < .04), and the volumes of left and right parotid glands also decreased (by 11% to 12%, P < .004). Brainstem and oral cavity volumes did not significantly differ (all P > .14). All mean doses to the CTV were decreased for up to 7% (P < .04), whereas mean doses to the right parotid and oral cavity increased from a range of 5% to 8% (P < .03), respectively.

Conclusion: Verification and adaptive planning should be recommended during the course of proton therapy for patients with head and neck cancer to ensure adequate dose deliveries to the planned CTVs, while safe doses to OARs can be respected.

Keywords: deformable image registration; intensity-modulated proton therapy; oropharyngeal cancer; adaptive planning; dose uncertainty
Introduction

There has been substantial growth in the use of proton therapy in the treatment of cancer in the past decade [1]. Owing to its ability to create sharp distal falloff of proton beams within tissue, this technologically advanced form of particle therapy has substantial advantages over conventional photon therapy by reducing unnecessary radiation doses to organs at risk (OARs) and also other healthy tissues. Numerous reports have documented the theoretical advantages of proton therapy over photon therapy for head and neck malignancies [2, 3], and clinical results achieved with proton beams have been promising [4]. The fundamental tenet of radiation therapy (RT) is the delivery of a high radiation dose to the tumor, while limiting the unnecessary radiation dose to the surrounding normal tissues [5]. However, because changes in patient anatomy (such as weight loss) may occur during treatment, the planned radiation doses to clinical target volumes (CTVs) and also OARs can change significantly, as protons have a very defined and finite range for targeting and RT dose deposition.

Nonrigid, deformable imaging registration (DIR) has gained popularity in recent years; it is emerging as an essential tool in both adaptive and image-guided radiation therapies to account for tissue changes during the treatment course [6]. Using DIR, the authors evaluated the dose precisely throughout the entire treatment and, if needed, generated an adaptive treatment plan to correct dose differences and ensured that OAR dose limits were met and appropriate. Numerous studies have been performed by using deformable dose accumulation methods on prostate and head and neck cancer treatments with photon-based intensity-modulated RT planning [7, 8] and adaptive strategies [6, 9], respectively. However, there have been no studies quantifying the degree of dose variations for patients undergoing treatment with intensity-modulated proton therapy (IMPT). Because of the inherent sharp falloff in the distal range of a Bragg peak, small changes in anatomy can cause a large dosimetric deviation in target coverage and/or OARs.

In this retrospective study, the authors evaluated the contribution of repeated computed tomography (CT) verification scans and the impact of adaptive IMPT planning in assessing anatomically based volumetric and dosimetric changes during the patient course of IMPT treatments.

Patients and Methods

Patient Selection, Treatment Planning, and Delivery

Between November 2013 and December 2014, ten patients with pathologically confirmed oropharyngeal carcinoma were retrospectively selected for clinical review. Institutional review board-approval was obtained and informed consent was waived due to the nature of this project as a retrospective study. These patients were all treated by concurrent chemotherapy along with IMPT. All patients received radiation to the bilateral neck volumes, and had their verification CT plan before treatment and at 4 weeks (±1 business day) after RT began. Based on a previous internal study [10], owing to weight loss the patient body contours began to deviate more significantly at about 4 weeks after RT started. In the authors’ practice, almost 100% of patients had verification plan and more than 90% of patients had adaptive plans; some patients were done earlier than 4 weeks mostly owing to poor initial setup. The patients (<10%) who did not require adaptive planning (as determined by radiation oncologist) were not included. The criterion to implement an adaptive plan for patient treatment was to maintain the CTV1 D95% ≥ 100% (ie, dose to 95% of CTV1 volume ≥ 100% prescription dose), and also OAR dosages were respected according to the Radiation Therapy Oncology Group’s guidelines. This group of 10 patients represented the authors’ early experience for adaptive planning and the workflow at their institution while IMPT was being implemented. These patients were treated with definitive chemoradiation using IMPT to primary disease site, the gross tumor volume (GTV) with a dose of 70 Gy (RBE) (relative biological equivalence), typically in 33 fractions overall with 2.12 Gy (RBE)/fraction. The clinical target volumes (CTV1, CTV2, and CTV3) were designed accordingly to the clinical evaluation of the anatomic areas that were at risk (to various levels) for gross and/or microscopic involvement of the cancer, including nodal regions; the average volumes were 176, 204, and 241 cm³ for CTV1, CTV2, and CTV3, respectively. Computed tomography scans and volumes were obtained in a GE CT simulator (General Electric Company Inc, Fairfield, Connecticut) and transferred electronically to the Eclipse Treatment Planning System (TPS) (Varian Medical Systems, Palo Alto, California). Verification CT scans were acquired before the first treatment, and then weekly depending on the disease characteristics and physician’s preference, and most commonly, and definitely for the series of patients reported here, during the fourth week. To compare, the verification CT images were registered with the original planning CT images by using the Eclipse rigid registration tool simulating the daily patient treatment alignment process. All plans were calculated by using the TPS for delivery of proton therapy with discrete spot beam scanning [11]. The delivery of the actual IMPT plan was accomplished by the use of a synchrotron and the Hitachi PROBEAT proton beam therapy system (Hitachi Ltd, Tokyo, Japan). A standard 3-field...
beam arrangement was used, with right anterior oblique, left anterior oblique, and posterior to anterior direction beams, which were noncoplanar, with robustness consideration (Figure 1) [12, 13]. Varian Eclipse proton-based IMPT inverse planning techniques were used with overall target margin of 0 cm distally and proximally, and 1 cm laterally, respectively. The amounts of spot spacing(s) were determined by the TPS according to maximum energy for each individual field \( s = \alpha \times \text{FWHM} \) [full width at half maximum], \( \alpha \leq 0.65 \) [14]. The planning goals for all CTVs were V100% > 95% (ie, at least 95% of prescription doses cover 100% of the corresponding CTV volumes), V95% > 99%, V105% < 10%, and D\(_{\text{max}}\) < 120%. The maximum energy of the proton beams per field varied between 102 and 203 MeV, depending on the case and the incident beam angle. An energy absorber (6.7-cm water equivalent thickness) was mounted onto the treatment snout, to ensure dose coverage in the shallow area of the head and neck regions near the skin.

**Evaluation**

Deformable imaging registrations were performed between the 2 CT image sets by using commercial deformable registration software (Velocity Medical, Varian Medical Systems). The accuracy of the DIR algorithms has previously been evaluated by Kirby et al [15] and Schreibmann et al [16]. The authors’ systems were also additionally validated according to Mohamed et al [17]. The treatment targets had 3 CTVs (CTV1, CTV2, and CTV3) corresponding to intended dose levels of 70, 63, and 57 Gy (RBE), respectively. Major OARs were parotids, oral cavity, spinal cord, and brainstem. Both CTVs and OARs were deformed and transferred from the original CT images to the verification CT image data set. All deformed contours were reviewed by a staff radiation oncologist before the adaptive plan would be generated. The beam configuration and intensity distribution profile from the original treatment plan was then copied to the verification CT image set to create a verification plan, for the calculation of the updated radiation dose levels reflecting the most recent anatomic changes. From the dosimetric results, the radiation oncologist would then evaluate, compare, and determine whether the adaptive treatment plans should be created. These plans were highly individualized and depended on multiple other clinical characteristics. The authors then compared the
accumulated dose to CTVs and OARs between the original and adaptive plans, and looked at the difference between the adaptive verification plans, to simulate the doses that would have been delivered if the adaptive plans were not used. The last 9 fractions of RT dose were used for this comparison. For being consistent with the authors’ analyses, those patients who had more than 10 or fewer than 8 fractions (9 ± 1 treatments) of treatments left at the time of adaptive planning on the fourth week of treatment were excluded.

Statistical Considerations

All dosimetric data were extracted by using the Eclipse Application Programming Interface (API) tool, which was developed in-house, to access the Eclipse dosimetric database. This API tool facilitated the efficient and accurate extraction of multiple dosimetric data from the Eclipse treatment planning database, compared with the manual methods. All CTVs and OAR volumes were compared between the original and verification CT scans with paired sample analyses; these analyzed OARs included brainstem, parotid glands, and oral cavity, with their own calculated dose-volume histograms along with the CTVs. Wilcoxon matched pairs nonparametric tests [18] were used to evaluate the effect of adaptive versus verification planning, based on volume and dosimetric changes. A probability value of $P \leq .05$ was considered to be statistically significant; all statistical analyses were calculated with R Programming (R Foundation for Statistical Computing, Vienna, Austria).

Results

Volume Comparisons

Body contours changed significantly, usually at about 3 to 4 weeks into the treatment course (Figure 1). Clinical target volume and OAR locations inside the patient’s contours also changed, which ultimately could impact the actual dose distribution physically (Figure 2); the CTV coverages were shown to change between the original and verification CT scans. Table 1 compares the volumes of CTVs and OARs under these circumstances, for both the original and verification CT scans. Between the original and verification (week 4) CT scans, the mean volumes of the 3 different CTVs were all reduced, respectively ($P \leq .04$), along with decreased parotid gland volumes bilaterally ($P \leq .004$). There were no significant differences in the volumes of the brainstem and oral cavity between the original and verification CT scans ($P > .14$ for both). Volumes of the other OARs examined (brainstem, spinal cord, and oral cavity) remained not significantly modified.

| Table 1. Volumetric comparisons of the various OAR and CTV indices that were compared between the CT original and verification-week 4 plans. |
| Mean volume (cc) recorded for planning | Original CT | Verification CT | Mean % changes | $P$ value |
|----------------------------------------|-------------|----------------|---------------|-----------|
| CTV1 (70 Gy)                           | 176.7       | 162.5          | −8%           | .04       |
| CTV2 (63 Gy)                           | 213.1       | 204.4          | −4%           | .02       |
| CTV3 (57 Gy)                           | 258.6       | 241            | −6.8%         | .02       |
| Right parotid                          | 32.2        | 28.3           | −12%          | .004      |
| Left parotid                           | 33.5        | 29.6           | −11%          | .002      |
| Brainstem                              | 26.2        | 26.1           | −0.4%         | .36       |
| Oral cavity                            | 212.8       | 193.5          | −9.3%         | .14       |
| Spinal cord                            | 26.6        | 24.3           | −8.7%         | .08       |

Abbreviations: OAR, organ-at-risk; CTV, clinical target volume; CT, computed tomography.

Dosimetric Comparisons

There were no significant dosimetric differences between the original and adaptive plans (Figure 3). This was expected, as the re-planning process should mimic and reproduce the same planning goals that were originally set with the specified dose constraints, for as closely as possible based on the verification CT. However, there existed significant dosimetric differences between the adaptive and verification plans. In Table 2, the mean doses (D99 and D95) of CTV1, CTV2, and CTV3 were all decreased ($P \leq .04$) on the verification scanning, whereas the mean doses (D$_{mean}$) of the right parotid and oral cavity were increased ($P = .03$; more right-sided tumors in the patient series). There were no differences regarding the mean maximum dose (D$_{max}$) increases to the brainstem ($P > .12$).
Figure 3 shows an example of a patient’s dose-volume histogram for both CTVs and OARs, derived from the adaptive (triangles) and verification (squares) plans, respectively. On the verification dose-volume histogram plan, 95% of the CTV1 volume was covered by the prescription dose (70 Gy [RBE]); however, the dose homogeneity and conformity were degraded. The decrease in both dose homogeneity and conformity became more significant for CTV2 and CTV3. Doses to the right parotid and oral cavity increased. Comparing the adaptive versus verification plans, values for V26 Gy (ie, the percentage volume that received 26 Gy or more) for the right parotid were 33% and 54%, respectively; for the oral cavity, the V30 Gy values were 6% and 10%, respectively.

Discussion
This retrospective study demonstrated the importance of performing verification CT imaging and the need to develop a systematic workflow for adaptive planning during the course of IMPT for patients with head and neck cancer who are
undergoing radiotherapeutic treatments. Wang et al [19] found that patients with head and neck cancer could have anatomic structure changes during the course of RT owing to the shrinkage of the tumor or lymph nodes or to body weight loss; it was also found that GTVs can be reduced by as much as 70% [20]. Therefore, it is important during the proton treatment to evaluate the dosimetric effect over the duration of the complete treatment course. The authors’ results were consistent with what was stated in previous studies [19, 20], for which multiple authors concluded that CTV and parotid volumes consistently decreased after radiation treatment (in their case, after 3 weeks). The dosimetry outcomes reported in this study are consistent with those findings [21, 22], but they did not use DIR, which has played an important role in generating adaptive treatment planning in this modern series. Deformable imaging registration can reduce the workload of physicians in recontouring all structures in the new CT image data set, which can be time-consuming during a busy clinical practice in both academic and community settings; however, it certainly represents a very important step for ensuring the basis and accuracy of the adaptive treatment plan design and evaluation.

There were no significant volume changes for the brainstem, spinal cord, or oral cavity, which are expected. The radiation doses to these organs are typically lower. It is also worth noting that many commercial and in-house DIR systems have been developed in recent years. These systems use a variety of approaches, and the accuracy of contour deformation needs to be further evaluated and used with caution [15]. As a result, the new contours review or modification process on the new CT data set cannot be completely eliminated and replaced with DIR [17]; this is a subject of ongoing research at the authors’ facility.

Figure 3. (A) The generated DVHs were used for clinical target volume comparisons (all shown in 33 fractions), which were derived from the original (square lines) and adaptive (triangles) plans. (B) These DVHs were generated for CTV and organs-at-risk comparisons based on the verification (square lines) and adaptive (triangle lines) plans. In this case, there were no significant differences for CTV coverage. However, a significant difference between the verification and adaptive plans was seen. (C) In this DVH, D95 was noted to be less than prescription dose, for CTV1. As a result, an adaptive plan was required even though other organs at risk had no significant changes. Abbreviations: CTV, clinical target volume; DVH, dose-volume histogram.; D95, dose that was received by 95% of the target volume.
The results here of parotid dose changes are consistent with the finding from Hansen et al [21]. The right parotid mean dose was increased on verification compared with adaptive plan ($P = .03$), whereas the left parotid dose had insignificant changes in the present series ($P = .40$). Among the 10 patients, 4 patients had GTV on the right side and 6 on the left side. Further study revealed that the average size of CTV1 for the 4 patients who had GTV on the right side was much less than that for the patient with GTV on the left side (138 versus 180 cm$^3$). This result suggests patient anatomic change may have higher impact on a patient who has smaller primary tumor size, as compared to those having larger tumor size. Further studies will be needed to evaluate the geometric relationship of deformed CTVs and parotids to proton dosing and OAR protections. Future investigation can also be extended to a large number of patient cases being treated, which have used DIR for calculating accumulated doses from multiple plans and to correlate treatment outcomes. More studies should also be done to investigate change in CTVs and different degrees of shrinkage in OARs (especially parotids) between photon and proton modalities. Owing to variable proton RBE phenomena, which can happen in a variety of tissue types, the use of DIR has become increasingly important in estimating uncertainties related to IMPT treatment for patients with head and neck cancers. Finally, there are increased workloads and costs for physicians, physicists, and dosimetrists to perform re-planning. The Eclipse API may automate this process in a seamless fashion and thus reduce the burden on all involved personnel and staff.

The present study had a number of limitations. First, this study represents only a small number of initial cases from the authors' institutional experience, and further prospective evaluation efforts and improvement will be needed from both the clinical and physics departments. This study used only about 9 fractions for adaptive planning, and in contrast, the verification plan used 33 fractions for the plan initial evaluation in deciding whether an adaptive plan would be needed. This may exaggerate the need for adaptive planning, since the accurate dose changes daily depending on patient setup and/or tumor changes in relation to the established CTVs. A more sophisticated plan evaluation process will need to be studied in the future, to see if the current verification and adaptive plan reviewing procedures represent the best clinical solution and workflow. The other potential verification plan options can be the following: (1) sum dose from the original and verification plans, including undelivered fraction; and (2) sum dose from original and adaptive plans, that is, to be delivered for the remaining fractions. The generation of adaptive plan and the quality assurance process in association with it must also be completed in a timely fashion. The efficacy and feasibility of such a program is outside the scope of this project; a substantial additional staff resource will need to be allocated for this. Monte Carlo methods are usually believed to be most accurate as a technique for calculation of dose distributions. However, owing to lengthy calculation time requirement, they are difficult to use and be adapted in the usual clinical environment/practice, or for large retrospective study use. Patients' plan showing borderline results for OARs should be considered for Monte Carlo calculation to confirm if dose uncertainty exists, on a case-by-case basis. Research has been

| Dosimetric parameters | Adaptive plan (9 fractions) | Verification plan (9 fractions) | Mean % changes | $P$ value |
|-----------------------|-----------------------------|-------------------------------|----------------|---------|
| CTV1                  |                             |                               |                |         |
| $D_{99}$              | 1893 cGy                    | 1882 cGy                      | 1%             | .014    |
| $D_{95}$              | 1930 cGy                    | 1913 cGy                      | 1%             | .05     |
| CTV2                  |                             |                               |                |         |
| $D_{95}$              | 1794 cGy                    | 1769 cGy                      | 1%             | .04     |
| CTV3                  |                             |                               |                |         |
| $D_{95}$              | 1669 cGy                    | 1563 cGy                      | 7%             | .03     |
| Right parotid         |                             |                               |                |         |
| $D_{\text{mean}}$    | 726 cGy                     | 764 cGy                       | −5%            | .03     |
| Left parotid          |                             |                               |                |         |
| $D_{\text{mean}}$    | 875 cGy                     | 873 cGy                       | 0%             | .40     |
| Oral cavity           |                             |                               |                |         |
| $D_{\text{mean}}$    | 535 cGy                     | 582 cGy                       | −8%            | .03     |
| Brainstem             |                             |                               |                |         |
| $D_{\text{max}}$     | 980 cGy                     | 1015 cGy                      | −3%            | .28     |
| Spinal cord           |                             |                               |                |         |
| $D_{\text{max}}$     | 1058 cGy                    | 1095 cGy                      | −3%            | .12     |

Abbreviations: CTV, clinical target volume; $D_{99}$, dose to 99% of the volume; $D_{95}$, dose to 95% of the volume; $D_{\text{mean}}$, mean dose; $D_{\text{max}}$, maximum dose.
conducted on fast dose calculator, which could reduce dose calculation time to less than 5 minutes per patient in the future [23]. Finally, the adaptive planning should consider the dose deficiency from the original and verification plan review, and the new adaptive plan should account for the changes accordingly, even if it may not appear best optimized. As a result, a criterion for triggering the evaluation and needs for a re-planning can be based on the amount of volume loss in target volumes, which will require future research effort for validation. Robust optimization research in IMPT to account for anatomy changes in head and neck cancer is also needed in these areas [24].

Conclusion

Verification CT imaging and adaptive planning are highly recommended during the course of IMPT for patients with head and neck cancer to identify anatomic and dosimetric changes and to ensure adequate doses to target volumes and safe doses to normal tissues. These results indicate that DIR is an essential tool for such evaluation for IMPT planning and accurate dose delivery.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of Interest: Drs Radhe Mohan and Steven J. Frank are members of the International Journal of Particle Therapy’s editorial board. All others authors have no conflicts of interest to disclose.

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