The Impact of Anatomic Change on Pencil Beam Scanning in the Treatment of Oropharynx Cancer

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Abstract

**Purpose:** To investigate the potential impact of anatomic change in the treatment of locally advanced oropharyngeal cancer with proton pencil beam scanning.

**Materials and Methods:** Ten patients with locally advanced oropharyngeal cancer who previously received intensity-modulated radiation therapy (IMRT) and synchronous chemotherapy underwent replanning by using RapidArc IMRT and proton pencil beam scanning. Deformable image registration deformed the planning computed tomography (CT), target volumes, and organs at risk (OARs) contours onto each weekly cone-beam CT scan. Target and OARs volumes were reviewed and modified. Treatment plans were forward calculated onto each corrected cone-beam CT scan and dose-volume histograms produced for targets and OARs volumes.

**Results:** Proton pencil beam scanning compared with RapidArc IMRT achieved lower mean doses to the contralateral parotid gland (14.8 Gy versus 20.6 Gy, \(P < .05\)) and oral cavity (31.5 Gy versus 43.0 Gy, \(P < .001\)). For proton pencil beam scanning, mean delivered doses to several OARs significantly increased from week 3 or 4 of treatment; this was not observed in RapidArc plans. The respective overall increases in mean delivered doses (average weeks 1 to 7, compared with week 1) to the pharyngeal constrictor muscles, larynx, and oral cavity were 1.0 Gy (SD, ±1.3), 3.3 Gy (SD, ±3.3), and 1.7 Gy (SD, ±1.9).

**Conclusions:** Although proton therapy provided dosimetric advantages on initial planning, it was more sensitive to interfraction anatomic changes, resulting in clinically significant increases in delivered doses to several OARs. We would therefore advocate for clinical implementation of methods to measure, account for, and adapt to these changes during the course of treatment in order to fully realize the potential benefits of proton therapy in this setting.

Keywords: proton therapy; pencil beam scanning; oropharynx cancer; adaptive replanning

Introduction

Locally advanced oropharyngeal cancer may be treated by an organ- and function-preservation approach with intensity-modulated radiation therapy (IMRT) and synchro-
nous chemotherapy [1]. Improvements in local regional control and survival outcomes have focused attention on reducing late treatment effects [2, 3]. The increased incidence of human papilloma virus–associated disease [4, 5], which is associated with younger age at diagnosis and excellent cure rates [6, 7], has made this a pressing objective. The use of advanced technologies and function-sparing IMRT reduces late treatment–related toxicities, but these remain of concern and adversely impact quality of life [8, 9]. An alternative strategy is to use proton therapy, whereby dosimetric data for head and neck cancer demonstrate improved treatment conformity and normal tissue sparing [10, 11]. Preliminary clinical data suggest it is also well tolerated with encouraging outcomes [12].

Proton pencil beam scanning (PBS) uses single-field uniform dose (SFUD) and/or multifield optimization (MFO), also termed intensity-modulated proton therapy [13]. Compared to photons, the nature of the rapid dose falloff with proton therapy causes it to be more sensitive to setup errors or changes in anatomy. The effect of per-treatment changes in aeration of the nasal cavity/sinuses on proton dose distribution was reported in a retrospective study of 20 patients treated for sinonasal disease, using a passive scatter technique [14]. The effect of the proton beam passing through air rather than tumor or fluid resulted in more distal dose deposition and clinically relevant increases in delivered doses to critical structures.

The effect of per-treatment anatomic changes is also of concern for the primary treatment of locally advanced oropharyngeal cancer, where tumor shrinkage is commonly observed [15, 16]. In a planning study of intensity-modulated proton therapy for oropharyngeal cancer, the combined effects of simulated anatomic, range, and setup uncertainties resulted in compromise to target volume coverage, which was improved by adaptive replanning [17]. The implementation of on-line adaptive treatment with correction for setup variations and anatomic changes remains challenging, and for proton therapy there is currently very limited access to cone-beam computed tomography (CBCT) verification imaging.

This study compares proton PBS and rotational arc IMRT (RapidArc) for definitive treatment of locally advanced oropharyngeal cancer.

**Materials and Methods**

**Patient Selection**

This study comprised 10 patients with locally advanced oropharyngeal cancer who previously received definitive IMRT and concurrent cisplatin or cetuximab, with at least weekly kilovoltage CBCT verification imaging and an adequate field of view (extending superiorly from the pterygoid plates and inferiorly through the cricoid cartilage).

**Treatment Volumes, Organs at Risk, and Dose Prescription**

Planning CT scans were acquired at 2-mm-slice intervals from the vertex of skull to the carina. Target volume contours for the initial CT scans were adjusted to the craniocaudal field of view for the CBCT scans and included gross tumor volume (GTV); clinical target volume 1 (CTV1), GTV without additional margin; CTV2, CTV1 with a 5-mm isotropic margin (edited for natural barriers to disease spread such as bone, air, fascia), involved and ipsilateral nodal levels II-III, VIIb (retrostyloid nodal level); and CTV3, ipsilateral nodal levels Ib, Va, Vlla (retropharyngeal nodal level) and contralateral nodal levels II-III. Nodal level IV was not included, as the CBCT images did not adequately encompass this region. The planning target volumes (PTVs) for RapidArc IMRT and proton PBS were defined by respective isotropic expansions of 3 mm and 5 mm (for proton PBS, the additional margin represents standard departmental policy and accounts for range uncertainty, approximated to 3.5% nominal beam range plus 1 mm), both edited for skin. Defined organs at risk (OARs) dose constraints were as follows: spinal cord, maximum dose (1 cm³) < 45 Gy; contralateral parotid gland, mean dose < 26 Gy; ipsilateral parotid gland, mean dose as low as reasonably achievable; contralateral submandibular gland, mean dose < 39 Gy; oral cavity [18], mean dose < 40 Gy; pharyngeal constrictor muscles [19], mean dose < 50 Gy; and supraglottic and glottic larynx [20], mean dose < 40 Gy. For quality assurance, the target and OARs volumes were reviewed by a second radiation oncologist.

Prescribed doses to PTV1, PTV2, and PTV3 were 70, 63, and 59.5 Gy (cobalt Gray equivalent using a relative biological effectiveness of 1.1 for proton therapy), over 35 respective daily fractions of 2.0, 1.8, and 1.7 Gy, using a simultaneous integrated boost technique.

**Treatment Planning, Optimization, and Cone-Beam Computed Tomography Scan Dose Recalculation**

The planning objectives (in order of priority) were as follows: (1) dose constraint to spinal cord; (2) PTV coverage; and (3) dose constraints for remaining OARs. Goal PTV coverage was 95% and 99% of each PTV to receive 100% and 93% of the
prescription dose, respectively. A proton PBS plan was generated for each patient for purposes of comparison to the treated IMRT plan. For proton plans, SFUD and MFO were used to maximize dose homogeneity and treatment conformity (SFUD/MFO, relative contributions for 6 patients was 80%/20% and for 4 patients, 50%/50%). The ratio of SFUD to MFO used was implemented with priority on using SFUD as much as possible (given less uncertainty with SFUD versus MFO), but incorporating MFO to the extent needed to be able to meet planning constraints, consistent with current clinical practice at our center. The Eclipse treatment planning system v.11.0 (Varian Medical Systems, Palo Alto, California) was used for both modalities.

A 2-field, posterior oblique arrangement was used, so that beam could be delivered through a 7.3-cm water-equivalent high-density table that serves as a range shifter, as required given the spot sizes needed to treat shallow targets associated with the head and neck region, and consistent with the current clinical practice unique to our center. The minimum and maximum energies were 100 MeV and 230 MeV (approximate range, 7.5-32 cm in water), controlled by an upstream energy selection system. The spot size varied with energy and depth; the full-width half maximum for the maximal energy spot measured at the isocenter in air was 8 mm.

To facilitate dose recalculation and target volume delineation on the 7 weekly CBCT scans, SmartAdapt v.11.0 deformable image registration software (Varian Medical Systems), based on the validated “demons” algorithm, was used to deform the planning CT onto each of the CBCTs [21] for CBCT image intensity correction. In this way, the deformed planning CTs contained the geometric features (head positioning, body, soft tissue, and bony anatomy outlines) of CBCTs but with Hounsfield units similar to the planning CT that were calibrated for photon or proton dose calculation, and with image quality equal to planning CT for purposes of target volume delineation on the CBCT. Deformable registration was also used to transfer the target volumes and OAR contours to each of the corrected CBCTs. The target and OAR volumes were then reviewed and modified, if needed, by a radiation oncologist. CTV1/PTV1 was not adjusted (keeping with standard practice not to reduce the gross tumor volume owing to tumor response); CTV2/PTV2, CTV3/PTV3, and OAR contours were amended to account for anatomic and positional alterations (ie, redefined to conform to anatomic definitions/boundaries) [22]. The GTV was redefined on each corrected CBCT only to allow later correlation of change in volume with variations in dosimetric parameters. To reduce the potential for introduction of bias, the redefined GTVs were independently assessed by a second radiation oncologist. The initial RapidArc IMRT and PBS plans were forward calculated onto each corrected CBCT.

Evaluation Criteria and Statistics

For each treatment plan, dose-volume histograms were produced for targets and OARs. On the initial planning CT, dosimetric comparisons were made between RapidArc IMRT and PBS for mean doses to OARs and PTV coverage: V95%, V99%, V107% (volume receiving 95%, 99%, and 107% of the prescribed dose, respectively); mean dose to PTV; PTV coverage conformity index: PTV covered by 95% isodose divided by PTV volume; and, for normal tissues sparing, the healthy tissues conformity index: PTV covered by 95% isodose divided by volume of 95% isodose [23]; homogeneity index: dose received by 2% of PTV minus dose received by 98% of PTV divided by mean dose to PTV. Mean doses to OARs were compared by using 2-tailed paired Student t test.

PTV1 and PTV2 coverage (mean V95%, conformity and homogeneity indices) and mean doses to OARs were evaluated on the forward calculated RapidArc IMRT and PBS plans on the corrected CBCTs. For 2 patients, data from 1 CBCT were not evaluable and for purposes of data analysis values imputed from the previous scan. Comparisons from weeks 1 to 7 were made by repeated-measures one-way analysis of variance. Where significant differences were observed, the Dunnett post hoc test was used to compare the means at week 1 with each subsequent time point (weeks 2 to 7). Significant per-treatment weekly changes in dose were investigated by multivariate regression analyses: patient, week of treatment (time), change in GTV volume, and change in weight were independent variables. Analyses were performed by using GraphPad Prism 6 (GraphPad Software, La Jolla, CA) and R version 3.1.0. Differences were considered statistically significant at \( P < .05 \).

Results

Baseline patient, tumor, and treatment factors are shown in Table 1.

Dosimetric Comparison of Intensity-Modulated Radiation Therapy versus Pencil Beam Scanning on Baseline Plans

All baseline plans (IMRT and PBS) met planning objectives with respect to OAR sparing and PTV coverage (Tables 2 and 3). The PBS plan (when compared to IMRT) significantly reduced mean doses to the oral cavity and contralateral parotid gland.
Table 2, but with higher doses to centrally located structures such as the spinal cord, larynx, and pharyngeal constrictors (without violation of planning goals/constraints; Table 2).

**Per-Treatment Changes in Doses to Organs at Risk and Coverage of Planned Target Volumes for RapidArc Intensity-Modulated Radiation Therapy and Proton Pencil Beam Scanning**

There were no statistically significant changes in mean doses to OARs from weeks 1 to 7 with IMRT (Table 4). However, for PBS, statistically significant increases in mean doses to the pharyngeal constrictors, larynx, and oral cavity occurred over time (Table 4), with the greatest increase in doses observed between weeks 3 and 5 (Figure 1). For both modalities, the coverage of PTVs was maintained during treatment (Table 5). There were decreases in the healthy tissues conformity index for normal tissue sparing from weeks 1 to 7 for both IMRT and PBS, suggesting increased volume of normal tissue encompassed by the respective 95% treatment isodose lines.

**Correlation of Proton Pencil Beam Scanning Changes in Doses to Organs at Risk with Gross Tumor Volume and Patient Weight**

From the initiation to the completion of treatment, GTV volume decreased an average of 75% (34.6 cm$^3$ to 8.8 cm$^3$), and patient body weight decreased by an average of 5.8% (77.7 kg to 73.2 kg).

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**Table 1.** Patient, tumor, and treatment factors.

| Patient | Gender | Age, y | Smoking status | Oropharynx tumor subsite | Tumor SCC differentiation | p16 status | TNM stage | Synchronous systemic therapy |
|---------|--------|--------|----------------|--------------------------|--------------------------|------------|-----------|----------------------------|
| 1       | Female | 45     | Former         | Base of tongue           | Poor                     | Positive   | T4aN2c    | Cisplatin every 3 weeks ($\times$2); cetuximab weekly ($\times$3) |
| 2       | Male   | 58     | Never          | Base of tongue           | Moderate                 | Positive   | T4aN2c    | Cisplatin weekly             |
| 3       | Male   | 63     | Former         | Soft palate              | Moderate                 | Positive   | T4aN2c    | Cetuximab weekly             |
| 4       | Male   | 71     | Former         | Base of tongue           | Poor                     | Positive   | T3N2b     | Cetuximab weekly             |
| 5       | Female | 85     | Never          | Base of tongue           | Poor                     | Positive   | T4aN2b    | Cetuximab weekly             |
| 6       | Male   | 58     | Current        | Base of tongue           | Poor                     | Positive   | T4aN2b    | Cisplatin weekly             |
| 7       | Male   | 55     | Former         | Tonsil                   | Moderate                 | Positive   | T4aN0     | Cisplatin weekly             |
| 8       | Male   | 56     | Former         | Tonsil                   | Moderate                 | Positive   | T2N2b     | Cisplatin every 3 weeks ($\times$ 2); carboplatin every 3 weeks ($\times$ 1) |
| 9       | Male   | 64     | Former         | Base of tongue           | Moderate                 | Positive   | T4aN2b    | Cisplatin weekly             |
| 10      | Male   | 67     | Current        | Tonsil                   | Well                     | Negative   | T3N2b     | Cisplatin weekly             |

Abbreviation: SCC, squamous cell carcinoma.

**Table 2.** Mean doses to organs at risk for RapidArc IMRT and proton pencil beam scanning on the planning CT scan.

| Organs at risk                          | RapidArc IMRT mean dose (SD), Gy (n = 10) | Proton PBS mean dose (SD), Gy (n = 10) | P value |
|-----------------------------------------|-------------------------------------------|----------------------------------------|---------|
| Spinal cord, 1 cm$^3$                   | 30.0 (6.2)                                | 36.6 (3.6)                             | .007    |
| Pharyngeal constrictor muscles, mean    | 46.3 (4.9)                                | 50.5 (4.3)                             | <.001   |
| Larynx, mean                           | 31.8 (3.5)                                | 36.5 (5.5)                             | .004    |
| Oral cavity, mean                      | 43.0 (4.3)                                | 31.5 (8.2)                             | <.001   |
| Parotid gland (ipsilateral), mean      | 30.2 (2.5)                                | 32.4 (6.4)                             | .25     |
| Parotid gland (contralateral), mean    | 20.6 (3.1)                                | 14.8 (9.0)                             | <.05    |
| Submandibular gland (contralateral), mean | 41.8 (10.6)                             | 41.6 (9.4)                             | .88     |

Abbreviations: IMRT, intensity-modulated radiation therapy; CT, computed tomography; SD, standard deviation of the mean; n, number of patients; PBS, pencil beam scanning.

Note: Statistical comparisons use 2-tailed Student paired t test.
Table 3. Dosimetric data and coverage of planning target volumes (A) PTV1, (B) PTV2, and (C) PTV3, for RapidArc IMRT and proton pencil beam scanning on the planning computed tomography scan.

| (A) PTV1 (prescription dose, 70 Gy) | RapidArc IMRT, mean (SD), n = 10 | Proton PBS, mean (SD), n = 10 |
|-------------------------------|---------------------------------|-------------------------------|
| Volume (cm³)                  | 76.7 (28.2)                     | 76.7 (28.2)                   |
| PTV coverage conformity index | 1.0 (0.0)                       | 1.0 (0.0)                     |
| % Volume receiving 95% prescribed dose, V95% (6650 cGy) | 99.3 (1.5)                      | 99.9 (0.0)                    |
| % Volume receiving 99% prescribed dose, V99% (6930 cGy) | 98.3 (0.6)                      | 99.4 (0.5)                    |
| % Volume receiving 107% prescribed dose, V107% (7490 cGy) | 8.5 (3.9)                       | 2.0 (2.2)                     |
| Mean dose to volume (Gy)      | 73.2 (0.2)                      | 72.8 (0.2)                    |
| Homogeneity index             | 0.1 (0.0)                       | 0.1 (0.0)                     |

| (B) PTV2 (prescription dose, 63 Gy) | RapidArc IMRT, mean (SD), n = 10 | Proton PBS, mean (SD), n = 10 |
|-------------------------------|---------------------------------|-------------------------------|
| Volume (cm³)                  | 247.7 (113.9)                   | 247.8 (113.9)                 |
| PTV coverage conformity index | 1.0 (0.0)                       | 1.0 (0.0)                     |
| Healthy tissues conformity index (normal tissue sparing) | 0.5 (0.1)                       | 0.4 (0.1)                     |
| % Volume receiving 95% prescribed dose, V95% (5985 cGy) | 97.2 (0.7)                      | 98.6 (0.6)                    |
| % Volume receiving 99% prescribed dose, V99% (6237 cGy) | 99.2 (0.3)                      | 99.7 (0.3)                    |
| Mean dose to volume (Gy)      | 69.4 (0.7)                      | 69.6 (0.7)                    |
| Homogeneity index             | 0.2 (0.0)                       | 0.2 (0.0)                     |

| (C) PTV3 (prescription dose, 59.5 Gy) | RapidArc IMRT, mean (SD), n = 10 | Proton PBS, mean (SD), n = 10 |
|-------------------------------|---------------------------------|-------------------------------|
| Volume (cm³)                  | 145.0 (57.5)                    | 145.0 (57.5)                  |
| % Volume receiving 95% prescribed dose, V95% (5653 cGy) | 99.4 (0.1)                      | 99.8 (0.2)                    |
| % Volume receiving 99% prescribed dose, V99% (5891 cGy) | 97.2 (0.5)                      | 98.9 (0.6)                    |
| Mean dose to volume (Gy)      | 64.2 (0.6)                      | 64.3 (0.9)                    |
| Homogeneity index             | 0.2 (0.0)                       | 0.2 (0.0)                     |

Abbreviations: PTV, planning target volume; IMRT, intensity-modulated radiation therapy; SD, standard deviation of the mean; n, number of patients; PBS, pencil beam scanning; CI, conformity index.

Notes: PTV coverage conformity index, CI = PTV covered by 95% isodose/PTV volume; healthy tissues conformity index (normal tissue sparing), CI = PTV covered by 95% isodose/volume of 95% isodose; homogeneity index, HI = dose received by 2% of PTV – dose received by 98% of PTV/mean dose to PTV. Dose in Gy.

Table 4. Mean radiation doses to organs at risk recalculated on cone-beam computed tomography scans from weeks 1 to 7 for (A) RapidArc IMRT and (B) proton pencil beam scanning plans.

| (A) Organs at risk                      | Week 1   | Week 2   | Week 3   | Week 4   | Week 5   | Week 6   | Week 7   | P value |
|----------------------------------------|----------|----------|----------|----------|----------|----------|----------|---------|
| Spinal cord, 1 cm³                      | 29.8 (5.9) | 30.0 (6.2) | 29.9 (6.3) | 30.3 (6.6) | 30.2 (6.3) | 30.2 (6.4) | 30.3 (6.7) | .23     |
| Pharyngeal constrictor muscles, mean   | 46.0 (5.1) | 45.6 (5.1) | 46.1 (4.6) | 46.4 (3.8) | 46.9 (5.3) | 47.0 (5.5) | 47.0 (4.8) | .10     |
| Larynx, mean                           | 32.1 (3.0) | 33.0 (3.2) | 33.5 (3.6) | 34.1 (3.2) | 34.3 (2.8) | 34.0 (3.1) | 33.3 (3.0) | .08     |
| Oral cavity, mean                      | 43.2 (5.4) | 42.8 (4.8) | 43.0 (4.6) | 42.9 (5.1) | 42.7 (4.6) | 42.7 (4.8) | 43.4 (5.0) | .38     |
| Parotid gland (ipsilateral), mean      | 31.1 (3.6) | 31.7 (4.3) | 32.6 (5.4) | 32.2 (5.0) | 32.6 (7.1) | 33.5 (5.5) | 34.2 (5.5) | .12     |
| Parotid gland (contralateral), mean    | 20.9 (3.7) | 20.7 (4.1) | 20.3 (3.6) | 20.0 (4.0) | 20.9 (4.7) | 20.9 (4.5) | 20.4 (5.0) | .62     |
| Submandibular gland (contralateral), mean | 43.3 (9.1) | 42.7 (10.2) | 43.7 (9.3) | 42.8 (11.0) | 42.4 (11.0) | 42.4 (10.6) | 42.2 (10.6) | .69     |

| (B) Organs at risk                      | Week 1   | Week 2   | Week 3   | Week 4   | Week 5   | Week 6   | Week 7   | P value |
|----------------------------------------|----------|----------|----------|----------|----------|----------|----------|---------|
| Spinal cord, 1 cm³                      | 35.8 (3.7) | 36.2 (4.3) | 36.2 (3.9) | 36.1 (4.2) | 36.2 (4.1) | 35.9 (4.0) | 35.9 (4.1) | .56     |
| Pharyngeal constrictor muscles, mean   | 51.3 (4.8) | 51.1 (4.7) | 51.0 (3.3) | 52.8 (4.4) | 53.6 (5.8) | 53.0 (5.2) | 53.4 (5.2) | .002    |
| Larynx, mean                           | 39.7 (5.8) | 40.6 (4.9) | 40.9 (4.0) | 45.2 (6.8) | 47.2 (8.1) | 43.4 (4.8) | 43.7 (5.8) | .011    |
| Oral cavity, mean                      | 30.9 (9.2) | 30.9 (7.9) | 33.2 (8.5) | 33.2 (7.9) | 32.8 (6.4) | 33.0 (8.3) | 34.2 (9.1) | < .05   |
| Parotid gland (ipsilateral), mean      | 32.0 (7.7) | 32.5 (8.2) | 33.9 (7.9) | 33.5 (8.4) | 35.0 (7.2) | 35.2 (7.6) | 37.1 (8.0) | .05     |
| Parotid gland (contralateral), mean    | 15.0 (9.5) | 14.7 (9.6) | 15.5 (9.3) | 14.9 (9.7) | 14.5 (9.4) | 16.1 (9.4) | 16.1 (10.3) | .35     |
| Submandibular gland (contralateral), mean | 43.4 (9.3) | 43.2 (12.9) | 46.1 (7.3) | 47.3 (7.3) | 48.2 (7.5) | 46.8 (9.1) | 47.3 (7.7) | .33     |

Abbreviation: IMRT, intensity-modulated radiation therapy.

Note: Data shown as mean (standard deviation of mean) radiation doses for 10 patients from weeks 1 to 7. Statistical comparisons use repeated-measures one-way analysis of variance from weeks 1 to 7. Dose in Gy.

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Multivariate regression analysis confirmed a significant relationship between increase in delivered dose to OARs and week of treatment (time), with neither change in GTV volume nor weight loss providing additional predictive information, despite GTV volume decrease showing significant correlation with increase in dose to OARs on univariate analysis.

Discussion

With the evolving demographics of head and neck cancer to a larger proportion of patients being diagnosed with HPV-associated cancers, and fewer with tobacco-induced, HPV-negative cancers [4], many patients now will have the expectation

![Figure 1](https://example.com/figure1.png)

**Table 5.** Dosimetric coverage of PTVs (PTV1, PTV2) on cone-beam computed tomography scans from weeks 1 to 7 for (A) RapidArc IMRT and (B) proton pencil beam scanning plans.

|                  | Week 1 | Week 2 | Week 3 | Week 4 | Week 5 | Week 6 | Week 7 | P value |
|------------------|--------|--------|--------|--------|--------|--------|--------|---------|
| **(A) PTV1 (prescription dose, 70 Gy)** |        |        |        |        |        |        |        |         |
| % Volume receiving 95% prescribed dose, V95% (66.5 Gy) | 99.4 (0.5) | 99.8 (0.3) | 99.6 (0.3) | 99.7 (0.2) | 99.7 (0.3) | 99.7 (0.3) | 99.8 (0.2) | -       |
| PTV coverage conformity index | 0.99 (0.0) | 1.0 (0.0) | 0.99 (0.0) | 1.0 (0.0) | 1.0 (0.0) | 0.99 (0.0) | 1.0 (0.0) | -       |
| Homogeneity index | 0.09 (0.0) | 0.09 (0.0) | 0.09 (0.0) | 0.09 (0.0) | 0.09 (0.0) | 0.09 (0.0) | 0.09 (0.0) | -       |
| **PTV2 (prescription dose, 63 Gy)** |        |        |        |        |        |        |        |         |
| % Volume receiving 95% prescribed dose, V95% (59.9 Gy) | 98.3 (0.7) | 98.2 (0.8) | 98.3 (0.7) | 98.2 (0.8) | 98.5 (1.1) | 98.1 (1.2) | 98.2 (1.0) | -       |
| PTV coverage conformity index | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | -       |
| Homogeneity index | 0.50 (0.1) | 0.49 (0.1) | 0.49 (0.1) | 0.47 (0.1) | 0.47 (0.1) | 0.48 (0.1) | 0.48 (0.1) | .008    |
| **(B) PTV1 (prescription dose, 70 Gy)** |        |        |        |        |        |        |        |         |
| % Volume receiving 95% prescribed dose, V95% (66.5 Gy) | 99.8 (2.0) | 97.9 (2.7) | 98.1 (2.5) | 98.2 (2.2) | 98.2 (2.1) | 99.0 (1.4) | 98.6 (2.4) | -       |
| PTV coverage conformity index | 0.99 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.98 (0.0) | 0.99 (0.0) | 0.98 (0.0) | -       |
| Homogeneity index | 0.10 (0.0) | 0.13 (0.1) | 0.12 (0.0) | 0.14 (0.0) | 0.14 (0.0) | 0.14 (0.1) | 0.14 (0.1) | .15     |
| **PTV2 (prescription dose, 63 Gy)** |        |        |        |        |        |        |        |         |
| % Volume receiving 95% prescribed dose, V95% (59.9 Gy) | 97.9 (1.8) | 96.8 (2.6) | 97.5 (2.8) | 97.5 (1.9) | 97.5 (2.5) | 97.9 (1.6) | 98.2 (1.1) | -       |
| PTV coverage conformity index | 0.99 (0.0) | 0.97 (0.0) | 0.97 (0.0) | 0.97 (0.0) | 0.97 (0.0) | 0.99 (0.0) | 0.98 (0.0) | -       |
| Healthy Tissues conformity index (normal tissue sparing) | 0.43 (0.1) | 0.42 (0.1) | 0.40 (0.1) | 0.40 (0.1) | 0.40 (0.1) | 0.40 (0.1) | 0.40 (0.1) | .002    |
| Homogeneity index | 0.22 (0.1) | 0.26 (0.1) | 0.23 (0.1) | 0.25 (0.1) | 0.24 (0.1) | 0.24 (0.1) | 0.23 (0.1) | .49     |

**Abbreviations:** PTV, planning target volume; IMRT, intensity-modulated radiation therapy; CI, conformity index.

Note: Data shown as mean (standard deviation of mean) for 10 patients from weeks 1 to 7. PTV coverage conformity index, CI = PTV covered by 95% isodose/PTV volume; healthy tissues conformity index (normal tissue sparing), CI = PTV covered by 95% isodose/volume of 95% isodose; homogeneity index, HI = dose received by 2% of PTV – dose received by 98% of PTV/mean dose to PTV. Statistical comparisons use repeated-measures one-way analysis of variance from weeks 1 to 7.
of excellent, long-term disease outcomes [6]. However, even with the most advanced techniques of radiation delivery, many patients will need to live and cope with the long-term effects of their treatment on their daily quality of life [8, 9]. Promising methods to diminish treatment toxicity, such as with proton therapy, are therefore critical in the evolution of the multimodality approach to treating head and neck cancer. Current technologies, such as on-board soft tissue imaging and adaptive replanning, shown to be helpful in maximizing the therapeutic benefit in patients receiving IMRT [16], are not yet commonly available for patients receiving PBS. To our knowledge, this is the first article to report per-treatment weekly changes in proton PBS target coverage and doses to OARs for oropharyngeal cancer, and to highlight the importance and potential clinical implications of integrating adaptive replanning in the treatment of locally advanced oropharynx cancer with pencil beam scanning proton therapy.

Our study shows that PBS is superior to IMRT in sparing several critical structures, such as the parotid gland and oral cavity. Sparing of such structures has the potential to reduce late effects such as xerostomia [19, 24], dysphagia [25], and dysgeusia. The physical characteristics of a proton beam that make such improvements possible, however, also make PBS more susceptible to changes in anatomy, such as that seen from a bulky head and neck cancer that responds briskly during the course of therapy. We found that not performing PBS adaptation for a responding tumor, while not compromising target coverage, does lead to significant increases in doses delivered to several critical OARs. While we found that increases in mean doses over the course of treatment were on average only several units of Gray, there were individual patients for whom non-adaptation of the RT plan in response to anatomic changes from disease response and/or weight loss led to very large increases in OAR dose to structures such as the oral cavity (Figure 2) and larynx (Figure 3). For patients such as these, failure to perform adaptive planning could possibly subject them to a significantly higher risk of treatment-related morbidity, both short and long term.

There are several limitations to our study that warrant mention. First, ours was a dosimetric-based study of 10 patients and does not report clinical patient outcomes. Although all patients had similar tumors (large, bulky, unresectable squamous cell carcinoma of the oropharynx), and were treated in a similar fashion (concurrent chemoradiation), it is possible that our findings may not be applicable to other types of head and neck cancers (of different histology or location). We chose the 2-field, posterior oblique approach (used clinically for PBS treatment of patients with head and neck cancer at our institution) based on its ability to cover targets unique to oropharynx cancer and sparing structures such as the salivary glands and especially anterior structures such as the oral cavity; however, we acknowledge that other approaches that are in clinical use [12], which
Conclusion

In summary, we find that for PBS-based treatment of bulky, oropharyngeal squamous cell carcinoma, treatment adaptation in response to anatomic changes from disease response is required to fully realize the potential benefits of PBS proton therapy for head and neck cancers. We believe that this is most relevant for patients with large, baseline tumors, located close to or abutting critical OARs, for which clinical response during the course of treatment is brisk and early, and without adaptation, would lead to unintended increase in doses to OARs, with an expected resultant increase in risk of toxicity. We therefore advocate for the continued development and clinical implementation of methods to reliably and efficiently image for anatomic changes (such as with on-board CBCT) and assess the potential consequences of such changes (real-time dose calculation), and of methods to perform adaptive replanning in response to these changes. This is the subject of current and future work at our institutions, and we expect that through these efforts, the questions regarding the important issues of plan robustness and optimal timing will be answered. It is only through this, and reporting on patient outcomes, that the full potential of PBS for treatment of head and neck cancer will be realized.

ADDITIONAL INFORMATION AND DECLARATIONS

Conflicts of interest: The authors have no conflicts to disclose.

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