The Need for Adaptive Intensity Modulated Radiotherapy Replanning in Head-and-Neck Patients with Anatomical Changes During Treatment

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of
Master of Science in the Graduate Program in
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2013

<u>ABSTRACT</u>

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Abstract

Purpose: The aim of this study is to quantify the effectiveness of adaptive radiation therapy (ART) when anatomical changes to the tumor and/or the organs are observed for head and neck patients during the course of intensity modulated radiation therapy (IMRT).

Methods and Materials: In this study, ART was retrospectively studied in 10 head and neck cancer treated patients after examining the 2nd CT, obtained after the first several fractions of radiotherapy, to see if anatomical changes had taken place. The adaptive treatment plan (ATP) was generated on the 2nd CT to mimic the relative dose-volume histograms of the spinal cord, brainstem, parotid glands, larynx, and oral cavity from the original treatment plan. The total ATP was generated as the sum of the original treatment plan delivered to the initial CT for the first several fractions and the ATP delivered to the 2nd CT for the remaining fractions. The delivered treatment plan (DTP) was generated as the sum of the original treatment plan delivered to the initial CT for the first several fractions and the original treatment plan delivered to the 2nd CT for the remaining fractions. For quantification of the effectiveness of ART, planning target volume (PTV) coverage and homogeneity, maximum dose to the brainstem and spinal cord, and median, mean doses, and $D_{1\%}$ (highest dose to 1% volume) for the parotid glands, the oral cavity, and the larynx were compared between the adaptive treatment plan (ATP) and delivered treatment plan (DTP) using the Wilcoxon signed-rank test, a non-parametric comparison test. For a total of 15 comparisons, significance was set at $p = 0.0033$ accounting for Bonferroni correction.

Results: For ATP compared to DTP, PTV44/70 homogeneity was improved by 10.38% ($p = 0.0234$) and 7.96% ($p = 0.04922$) respectively. PTV44/70 coverage (%volume covered by prescription dose) were improved by 7.27% ($p = 0.0078$) and 12.00% ($p = 0.0020$) respectively. Maximum dose to the spinal cord and brainstem were reduced by 6.47% ($p = 0.0195$) and 8.24% ($p = 0.0098$), respectively. Median and mean doses for the parotid glands were reduced by 6.01% ($p = 0.0029$) and 4.14% ($p = 0.0043$) respectively whereas $D_{1\%}$ remained approximately the same with a reduction of 0.78% ($p = 0.8789$). Median dose to oral cavity was reduced by 0.20%, but mean dose and $D_{1\%}$ increased by 0.43% and 2.12%, respectively; however all oral cavity changes were insignificant ($p = 0.9102$, $p = 0.7344$, and $p = 0.2031$ respectively). Similarly, larynx mean dose was reduced by 3.54%, median dose was reduced by 2.15%, and $D_{1\%}$ was reduced by 7.11%, but all reductions were statistically insignificant ($p = 0.5625$, $p = 0.6875$, and $p = 0.8789$ respectively).

Conclusions: In cases where anatomical changes are observed during therapy, ART can be applied to significantly reduce median parotid glands dose and improve target coverage. However, these changes are small and may not be clinically significant, implying that adaptive radiotherapy may not provide benefit for head-and-neck cases, on average.

Dedication

Special thanks to my family, friends, professors, and my supervisor Dr. Das.

Also, really appreciate your support, J.

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1. Introduction

1.1 Background

The term "head and neck cancer" represents squamous cell carcinomas in head and neck region which includes pharynx, larynx, oral cavity, and salivary glands. Although head and neck cancers account for only about 3 percent of all the cancers in the United States, the five-year relative survival rate for all stages is only 61% which is lower than the average survival rate of all cancer types in the nation, 67% [1].

Two major methods of treatment for head and neck cancer are surgery and radiation therapy. However, physical removal of the tumor often results in compromised functioning of important organs such as salivary glands and thus diminishes patient's quality of life. Furthermore, due to the complex shape of the cancer and its proximity to several important organs (larynx, parotid glands, oral cavity, spinal cord, brainstem), radiation therapy is preferred because it can selectively irradiate the tumor with minimal irradiation of critical organs.

1.2 Radiation Therapy Techniques

3D conformal therapy and Intensity Modulated Radiation therapy (IMRT) are the major radiation therapy methods to treat head and neck cancer. The advantage of 3D conformal therapy is that more homogeneous Planning Target Volume (PTV) coverage can be achieved. On the other hand, IMRT treatment is more likely to spare dose to

Organs at Risk (OAR) and increase PTV conformality while minimally compromising PTV coverage and homogeneity.

In head and neck cancer tumors located near or including significant organs relating to speech and digestion that are highly correlated with the Quality of Life (QoL) of the patients. Tribius et al. [2] observed that patients treated with IMRT were able to have better QoL than those treated with 3D conformal therapy. In that study, QoL was scored by the seriousness of the side effects caused by radiation therapy such as xerostomia, incapability of smell and taste, and fatigue [2]. Moreover, IMRT is capable of reducing salivary gland toxicity without compromising tumor control [3][4]. Consequently, many head and neck patients nowadays are treated with IMRT in most institutions including the Duke Radiation Oncology Clinic.

1.3 IMRT optimization

To understand IMRT optimization process, the manner in which dose constraints for the PTV and OARs operate together to arrive at an optimal solution requires explanation. Also, the clinical rationale behind the constraints should be understood. These concepts are explained below.

1.3.1 Objective Function

For 3D planning, the doses to the organs and PTV are manually modified by adjusting the weighting of the individual beams, until a suitable dose distribution is achieved. On the other hand, for IMRT planning, each unit fluence (size of a few square millimeters) within a beam has a different weighting factor, resulting in many thousands of fluence weights that need to be adjusted. Therefore, automated optimization is achieved by continuous modification of the fluence weighting factors until the constraints are satisfied. In order to find the optimal solution, objective functions that reflect the desire to achieve PTV coverage and reduce dose to the critical structures are formulated. Minimizing the sum of the objective functions results in the optimal solution. The objective function for PTV is formulated as

$$\Omega^{target} = w_{max}^{target} \times \frac{\sum_{i \in target} \max\left(d_i^{target} - d_{max}^{target}, 0\right)^2}{N_{target}} + w_{min}^{target} \times \frac{\sum_{i \in target} \max\left(d_{min}^{target} - d_i^{target}, 0\right)^2}{N_{target}} \qquad \text{Eq}(1)$$

where Ω^{target} is the objective function of PTV, w is weight of the maximum and minimum constraints for PTV, d_i^{target} is the dose of an i^{th} voxel in PTV in CT scan, $d_{max,min}^{target}$ are the maximum and minimum dose constraints for PTV, and N_{target} is the number of voxels in the target that is governed by the constraints. In other words, from the first part in equation (3), when a voxel dose is higher than the maximum constraint dose, the voxel dose is subtracted from the maximum constraint dose then squared (if a voxel dose is smaller, d_i^{target} - $d_{max,min}^{target}$ is less than 0 so 0 is chosen by the function "max"). This is repeated for every voxel, summed and weighted. The minimum constraints work in the same way.

The objective function for organs at risk (OARs) works similarly to the objective function for PTV except that there are no minimum constraints for OAR. When the whole volume of the OAR is governed by a constraint, the objective function would be the equation (2). Whereas, if only the partial volume is restricted to receive the certain dose, the objective function would be the equation (3) where N is the number of the pixels in the volume that is governed by the constraint.

$$\Omega^{OAR} = w_{max}^{OAR} \times \frac{\sum_{i \in OAR} \max\left(d_i^{OAR} - d_{max}^{OAR}, 0\right)^2}{N_{OAR}} \text{ (max)} \qquad \text{Eq(2)}$$

$$\Omega^{OAR} = w_{max}^{OAR} \times \frac{\sum_{i \in OAR} \max\left(d_i^{OAR} - d_{max}^{OAR}, 0\right)^2}{N_{OAR}^{\text{pixels under constraint}}} \text{ (general)} \qquad \text{Eq(3)}$$

The total objective function, the sum of individual objective functions, then becomes

$$\Omega = \Omega^{target} + \sum \Omega^{OAR} \qquad \text{Eq(4)}$$

The objective function indicates how well the constraints are achieved, i.e. a lower objective function implies that the constraints are closer to being satisfied. The optimization starts with equal fluences and then iteratively adjusts the fluences to minimize the objective function. The procedure for iteratively adjusting the fluences usually employs some variation of the gradient descent algorithm.

1.3.2 Dose and Volume Constraints

PTV constraints are typically set to be within approximately ±2% of the prescription dose to ensure homogeneous coverage. The actual optimized dose distribution, however, almost never achieves these constrains because of competing constraints from OARs. The optimized dose distribution is normalized to cover 95% of the PTV with 100% of the prescription dose. This implies that about 5% of the PTV is allowed to be below the prescription dose.

For organs at risk, the QUANTEC (Quantitative Analysis of Normal Tissue Effects in the Clinic) report recommends dose-volume constrains based on consensus in the literature. According to QUANTEC, a mean dose of less than 20 Gy for one parotid gland or 25 Gy for both glands is recommended to avoid severe xerostomia [6]. The maximum spinal cord dose and brainstem dose are limited to 54 Gy to have less than 1% estimated risk of myelopathy and limited risk of neuropathy respectively [7-8]. A mean dose for larynx is recommended to be less than 40-45 Gy and a maximum dose for larynx is limited to 63-66 Gy if the tumor extent allows these constraints [9]. No recommendation for oral cavity constraints are given in QUANTEC, but according to

RTOG (Radiation Therapy Oncology Group), the mean oral cavity dose for non-oral cavity cancers is recommended to be below 30 Gy, with a maximum dose below 50 Gy [10]. In the Duke clinic, the organ at risk constraints are individualized to each patient, based on the organ proximity to the PTV. An organ far away from PTV is usually given a constraint that is below tolerance to maximize sparing. As far as possible, the following constraints are applied: median dose of 20 - 24 Gy for larynx and parotid glands, maximum dose to cord + 5mm expansion of 45 Gy, maximum dose to brainstem of 20 - 25 Gy, median dose of 30 Gy to oral cavity.

1.4 Offline Adaptive Radiation Therapy

Fractionated treatment is employed in radiotherapy to minimize normal tissue injury by using the faster recovery property of normal cells than cancerous cells when the delivered dose is low. Consequently, patients treated with radiation therapy usually undergo numerous fractions of treatments. In the treatment of head and neck cancers, a patient receives around 30 to 35 fractionated treatments in general. However, because the total treatment takes about 6 - 7 weeks in total, the tumor and/or other organs could possibly shrink or enlarge during this period due to patient weight loss, radiation-induced changes, or tumor growth. Tumor shrinkage of head and neck cancer is routinely observed and thought to be a possibly significant factor in degrading the effectiveness of the treatment plan. One solution to overcoming this problem is to adapt the treatment plan(Adaptive Radiation Therapy (ART)) whenever changes that are likely to affect the dose distribution are detected. Offline ART is performed between fractions as opposed to online ART which requires a fast automatic technique to adapt plans at a particular treatment based on imaging done immediately prior to treatment.

1.5 Aim

Changes in the tumor during therapy (size, location) lead to changes in the outer body shape and the relative position of OARs with respect to the tumor. As a result, the original treatment plan may no longer be suitable, requiring a new adaptive plan. The overall objective of this work is to evaluate whether adaptive planning results in significantly better PTV coverage and OAR sparing, compared to using the original non-adaptive treatment plan for the entire course of treatment. The specific goals of the study are to: (a) evaluate PTV coverage for the adaptive and non-adaptive plans, and (b) evaluate OAR dose changes between two plans.

2. Methods and Materials

2.1 Patient Selection

All patients in this retrospective study were treated with radiation therapy at Duke Hospital between 2008 and 2012 for head and neck cancer, which includes oral cavity cancer, pharyngeal cancer, laryngeal cancer, and parotid gland cancer.

In order to perform the adaptive treatment plan, patients who have had either CT or cone beam computed tomography (CBCT) at some point during therapy were selected. Furthermore, because volume changes in tumor may not occur in the first few fractions, patients with a 2nd CT/CBCT acquired after at least 6 fractions were chosen for this study. For 7 out of 10 patients, CT/CBCT were taken at the 9th through 12th fractions (Table 1). For 3 out of 10 patients, CT/CBCT were taken at the 6^{th}, 14^{th} and 18^{th} fractions.

Except for patient #2, the OTP (original treatment plan) consist of the primary plan with 22 - 23 fractions and the boost plan with 12 - 13 fractions with 2 Gy per fraction. In total, 70 Gy from 35 fractions is delivered to a patient.

Table 1. Information about type and time of CT used for ART of each patient.

Patient #	CT type	Second CT taken fraction	Total number of treatment fractions
1	CT	11	35
2	CBCT	12	30
3	CT	18	35
4	CT	11	35
5	CT	9	35
6	CT	6	35
7	CBCT	14	35
8	CBCT	10	35
9	CT	9	35
10	CT	11	35

2.2 Adaptive Treatment Plan (ATP) generation

The OTP does not take into account changes in size and position of PTV and OARs during the course of radiotherapy. The ATP (adaptive treatment plan), which accounts for these changes, is compared to the DTP (delivered treatment plan), which is the dose distribution that actually results from delivering the OTP to the changing patient anatomy. This comparison allows us to quantify the effectiveness of the ATP.

In brief, deformable image registration is performed to map the structures (OARs, PTV) from CT_plan (the original CT used to plan the OTP) to CT_intra (the CT/CBCT acquired during therapy, used for ATP and DTP). The ATP plan is generated by optimizing on CT_intra with the intention of mimicking the relative DVHs of the OTP. The total ATP doses are generated by summing the doses from OTP on CT_plan for the first several fractions up to CT_intra being acquired and the ATP plan doses on CT_intra for the remaining fractions. The DTP doses are generated by summing the doses from the OTP on CT_plan with the doses from the DTP on CT_intra, again accounting for the number of fractions delivered to each CT set.

2.2.1 Image Registration

The two images are manually superimposed and then automatic rigid and deformable registrations are executed. If the images do not seem to match after the automatic processes, manual rigid registration is adjusted and automatic registration is repeated, until the alignment is satisfactory. Not only are the discrepancies in the bony structures checked, but the discrepancies in the soft tissues are also needed to be checked carefully to ensure that PTV and OARs are appropriately deformed.

Once the image registration is complete, target and OAR structures from CT_plan are copied to CT_intra. The deformable image registration between the CT_plan and CT_intra is used to appropriately deform the structures, to reflect any anatomical changes during treatment.

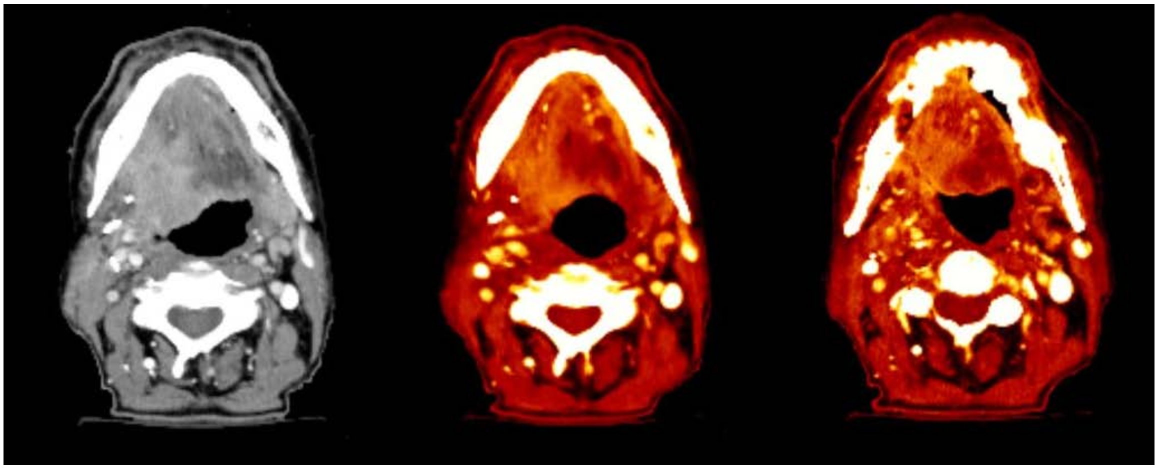

Figure 1: The left is a slice from CT_plan, the middle is from CT_intra after deformation, and the right is from CT_intra before deformation.

Although the PTV and OARs that are deformably transformed into the coordinate system of the CT_intra should be accurate, some structures lie on the edge of the body or even slightly outside of it due to small errors in the image registration. All the structures are cropped so as to be at least 3 mm inside the body as the original structures are cropped in the same way.

2.2.2 Setup Field Adjustment

Both ATP and DTP use the beam orientations of the OTP. The DTP is assumed to be treated with the original plan despite anatomical changes. To create the DTP on CT_intra, the isocenter of the original beams is placed in CT_intra to match the setup fields in AP and lateral radiographs with those from the OTP, to the best extent possible.

Once the adjustments are made, the digitally reconstructed radiographs (DRRs) and setup fields for the two CTs look almost identical as shown in Figure 1.

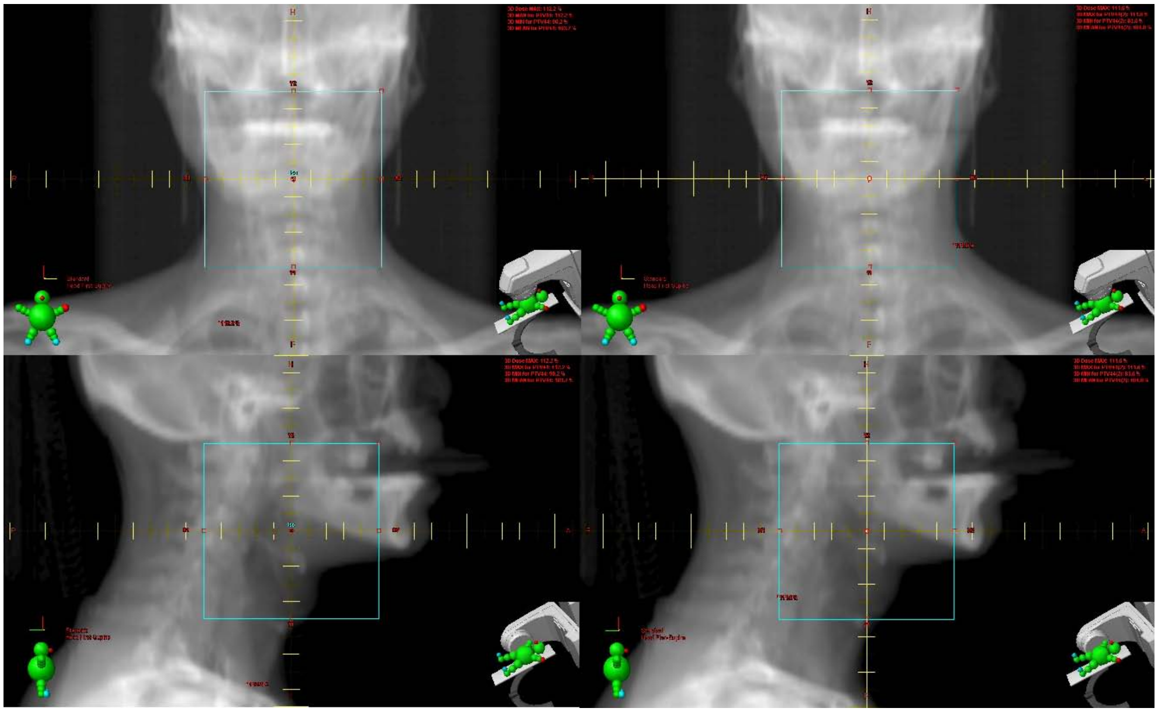

Figure 2: AP and Rt LAT DRR and their setup field (sky blue square rim) with graticules for the CT scans. The images on the left are from CT_plan and the images on the right are from CT_intra.

2.2.3 IMRT Optimization

ATP IMRT optimization on CT_intra was performed to mimic the dose-volume histograms from the OTP. The constraints and the weighting factors of the OARs and PTV initially used those from the OTP optimization and were iteratively adjusted to ensure that the ATP and OTP DVHs were equivalent.

2.2.4 Dose Summation

Figure 3 illustrates the flow chart for dose summation. Once optimization for ATP primary and boost plans on CT_intra are accomplished and DTP primary and boost plans are calculated on CT_intra, they are all deformed to CT_plan, the primary CT scan. To generate the ATP doses for the entire treatment, OTP doses for the first several fractions on CT_plan (e.g. 11 fractions for patient 1 from Table 1) are summed to the deformed ATP primary and boost doses for the remaining fractions. Similarly, to generate the DTP doses for the entire treatment, OTP doses for the first several fractions on CT_plan (e.g. 11 fractions for patient 1 from Table 1) are summed to the deformed DTP primary and boost doses for the remaining fractions.

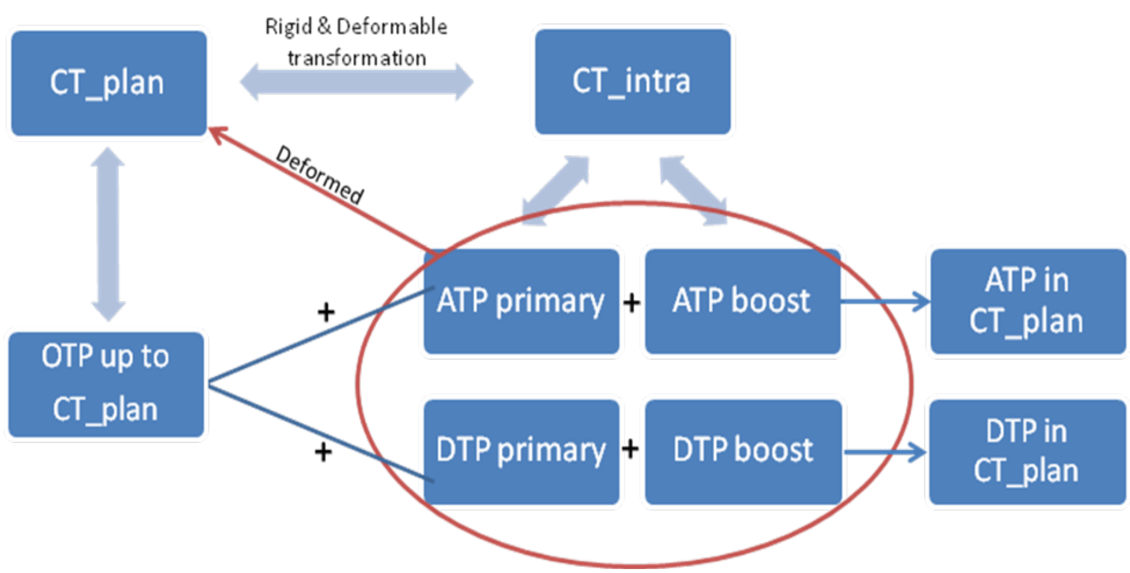

Figure 3: Flow chart for dose summation of ATP and DTP. The plus sign represents the summation of dose.

2.3 Plan Comparison

OARs doses and PTV coverage of ATP and DTP were compared to evaluate the effectiveness of ATP. The ATP was normalized in the same manner as the OTP, i.e., 95% of the target volume receives 100% of the prescription dose.

The planning target volumes are composed of PTV44 (or PTV46) for the primary plan and PTV70 for the boost plan and they are analyzed separately (the number next to PTV indicates the prescription dose to the PTV in Gy). The homogeneity of PTV dose distribution is defined to be the dose difference between $D_{98\%}$ and $D_{2\%}$, where $D_{x\%}$ refers to the dose to x% of the PTV volume. Also, PTV coverage, defined to be the % volume above prescription dose, is compared between ATP and DTP.

Maximum doses between ATP and DTP are compared for brainstem and cord + 5mm. Mean and median doses are compared for parotids, larynx, and oral cavity. The maximum doses to the organs, measured as $D_{1\%}$ are also compared to see if there are excessive hot spots.

The number of patients in this study is limited to a small number (10 patients) and thus the assumption that the dose differences between ATP and DTP is normally distributed may not be valid. The two-tailed Wilcoxon signed-rank test, a non-parametric test, is used to compare the statistical significance of dose differences. Furthermore, 15 comparisons are made in total so the Bonferroni correction is used to arrive at a statistically significant p value of 0.0033 (= 0.05/15).

3. Results

3.1 PTV Homogeneity and Coverage

PTV70 homogeneity was worse for DTP compared to ATP by 7.96%, but difference was not statistically significant (p = 0.4922). Two patients did not have a boost plan so only 8 patients contributed to PTV44 results. PTV44 homogeneity was improved by 10.38% for ATP but the result was not statistically significant (p = 0.0234).

PTV70 coverage was higher for ATP compared to DTP by 12.00% and the difference was statistically significant (p = 0.0020). PTV44 coverage was higher for ATP by 7.27% but the difference was not statistically significant (p = 0.0078).

Table 2. PTV70 Homogeneity

Patient #	PTV70 homogeneity		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	405.3	591.9	31.52
2*	994.2	1040.1	4.42
3	548.9	621.1	11.63
4	685.5	737.5	7.04
5	1141.2	962.5	-18.57
6	614.8	1627.7	62.23
7	634.7	858.8	26.09
8	1121.1	935.5	-19.8
9	630.2	556.4	-13.26
10	488.8	437.7	-11.67
Average	726.5	838.9	7.96
p-value			0.4922

*PTV60.

Table 3. PTV44 Homogeneity

Patient #	PTV44 homogeneity		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	394.6	429.1	8.03
2*	NA	NA	NA
3	498.7	534.0	6.61
4	450.4	535.8	15.94
5	454.8	431.7	-5.34
6	570.7	837.4	31.85
7**	NA	NA	NA
8***	889.8	1027.6	13.41
9	480.8	495.5	2.97
10	357.7	395.5	9.55
Average	512.2	585.8	10.38
p-value			0.0234

* no boost plan. **more than 2 PTV44. ***PTV46, not PTV44.

Table 4. PTV70 Coverage

Patient #	PTV70 coverage		
	Adaptive Tx Plan (%)	Delivered Tx Plan (%)	Adaptive-Delivered (% Change)
1	99.1	89.7	9.47
2	94.4	52.0	44.88
3	98.9	89.8	9.23
4	98.3	92.9	5.48
5	94.5	91.2	3.53
6	99.0	80.5	18.72
7	94.0	83.2	11.55
8	94.9	88.6	6.65
9	98.4	96.5	1.97
10	97.4	89.1	8.54
Average	96.9	85.3	12.00
p-value			0.0020

Table 5. PTV44 Coverage

Patient #	PTV4 coverage		
	Adaptive Tx Plan (%)	Delivered Tx Plan (%)	Adaptive-Delivered (% Change)
1	96.7	93.5	3.36
2*	NA	NA	NA
3	95.9	92.6	3.46
4	97.4	92.0	5.57
5	95.2	86.9	8.66
6	97.2	83.0	14.55
7**	NA	NA	NA
8***	91.9	84.0	8.64
9	97.3	93.3	4.18
10	96.5	87.1	9.75
Average	96.0	89.0	7.27
p-value			0.0078

* no boost plan. **more than 2 PTV44. ***PTV46, not PTV44.

3.2 OAR

3.3.1 Spinal Cord

9 out of 10 patients received less maximum dose to the spinal cord + 5mm with the Adaptive Treatment plan. The average percent change was 6.47% but statistically not significant, as shown in Table 6. One patient in the adaptive and delivered plans received doses exceeding the limit of 45 Gy (the adaptive plan dose could not be reduced further without compromising PTV coverage normalization, i.e., 95% of PTV covered by the prescription dose). One other patient in the DTP exceeded the 45 Gy limit.

Table 6. Maximum Spinal Cord + 5mm Dose

Patient #	**Maximum Spinal Cord + 5mm Dose**		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	4328.5	4344.9	0.38
2	1137.3	1270.6	10.49
3	4204.6	4355.1	3.46
4	3986.7	4228	5.71
5	4161	3984.9	-4.42
6	3774.6	4251.6	11.22
7	5985.7	6232.1	3.95
8	3323.4	4228.7	21.41
9	4032.8	4137.5	2.53
10	4270.3	4740.6	9.92
Average	3920.5	4177.4	6.47
p-value			0.0195

3.3.2 Brainstem

8 out of 10 patients received less maximum dose to brainstem with the ATP than DTP. The average percent change was 8.24% but not statistically significant. The percentage change was 15.94% for the most improved case.

Table 7. Maximum Brainstem Dose

Patient #	**Maximum Brainstem Dose**		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	1536.2	1716.6	10.51
2	1847.5	2335.2	20.88
3	1711.7	1844.4	7.19
4	1469.3	1676.3	12.35
5	2018.7	2311.2	12.66
6	1339.4	1593.3	15.94
7	5061.2	5010.3	-1.02

8	1532.9	1501.6	-2.08
9	2296.2	2378.6	3.46
10	3328.2	3415.3	2.55
Average	2214.1	2378.3	8.24
p-value			0.0098

3.3.3 Parotid Glands

Either one or two parotid glands are considered to be OARs (in cases where one parotid gland had substantial overlap with PTV, the physician placed no constraint on this gland) without any distinction by their positions (left or right). 14 out of 18 parotid glands received less median dose with the adaptive plan with an average percent change of 6.01% and the change is statistically significant ($p = 0.0029$). 16 out of 18 parotid glands received less mean dose with the adaptive plan with an average percent change of 4.14% but the change is not statistically significant ($p = 0.0043$).

10 out of 18 parotid glands received less $D_{1\%}$ with the adaptive plan, with an average improvement of 0.78% and the change is not statistically significant ($p = 0.8789$).

Table 8. Median Parotid Glands Dose

Patient #	**Median Parotid Glands Dose**		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	1186.3	1229.8	3.54
	1302.1	1281.8	-1.58
2	329.4	387.5	14.99
3	938	959	2.19
	1038.3	1046	0.74
4	1541.2	1750.2	11.94
	1430.6	1923.1	25.61
5	279.9	271.4	-3.13

	4192.1	4515.4	7.16
6	3452.4	3462	0.28
	1683.8	1711.2	1.6
7	3208.2	3623.9	11.47
8	2729.7	2758.6	1.05
	2086.4	2874.1	27.41
9	1274.1	1271.3	-0.22
	3215.1	3355.1	4.17
10	1536.1	1508	-1.86
	4061.1	4176.5	2.76
Average	1971.4	2116.9	6.01
p-value			0.0029

Table 9. Mean Parotid Glands Dose

Patient #	Mean Parotid Glands Dose		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	1831.3	1928.4	5.04
	1650.3	1776.8	7.12
2	453.5	559.3	18.92
3	1378.6	1395.8	1.23
	1419.5	1426.9	0.52
4	1939.7	2089.5	7.17
	2542.3	2788.8	8.84
5	294	278.7	-5.49
	4046.6	4305.7	6.02
6	3953.7	3686.4	-7.25
	2221.9	2349.2	5.42
7	3954.5	4066	2.74
8	3261.5	3405.8	4.24
	2792.6	3131.1	10.81
9	2433.2	2441.2	0.33
	3552.9	3592.7	1.11
10	2095.8	2215.3	5.39
	4249.3	4354.5	2.42
Average	2448.4	2544.0	4.14
p-value			0.0043

Table 10. Parotid Glands $D_{1\%}$

Patient #	Parotid Glands $D_{1\%}$		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	5053	5383.8	6.14
	4372	4528.9	3.46
2	1222	1571.6	22.25
3	4085	4123.6	0.94
	4264	4247.5	-0.39
4	4736	4786	1.04
	7369.4	7235.8	-1.85
5	480	429	-11.89
	6760	6946.4	2.68
6	7389	7306.5	-1.13
	4921	5109.1	3.68
7	7481	7425.5	-0.75
8	7456	7281	-2.40
	6078	5882.5	-3.32
9	7498	7257.9	-3.31
	7418	7147.5	-3.78
10	6807	6916.5	1.58
	6779	6852	1.07
Average	5564.9	5579.5	0.78
p-value			0.8789

3.3.4 Oral Cavity

9 out of 10 patients had dose constraints for oral cavity. Less than 1% changes were observed in median and mean oral cavity doses (0.2% and -0.43% respectively) and the results were statistically insignificant ($p = 0.9102$, $p=0.7344$) as shown in Table 11 and 12. D1% for ATP is worse by 2.12% compared to DTP, but the result is statistically insignificant ($p = 0.2031$).

Table 11. Median Oral Cavity Dose

Patient #	Median Oral Cavity Dose		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	2105.3	2158.9	2.48
2	1945.3	1967.1	1.11
3	2139.8	2102.5	-1.77
4	1695.2	1798.5	5.74
5	2347.7	2444.5	3.96
6	3069.1	2724.1	-12.66
7	6663.1	6628.9	-0.52
8	NA	NA	NA
9	3009.2	3186.8	5.57
10	6705.3	6568.4	-2.08
Average	3297.8	3286.6	0.20
p-value			0.9102

Table 12. Mean Oral Cavity Dose

Patient #	Mean Oral Cavity Dose		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	2414.9	2498	3.33
2	2335.1	2276.2	-2.59
3	2205.3	2238.4	1.48
4	1967.3	2165.4	9.15
5	3093.9	3131.5	1.20
6	3713.7	3302.4	-12.45
7	6124.2	6007.2	-1.95
8	NA	NA	NA
9	3345.7	3358.5	0.38
10	6266.4	6115.9	-2.46
Average	3496.3	3454.8	-0.43
p-value			0.7344

Table 13. Oral Cavity $D_{1\%}$

Patient #	Oral Cavity $D_{1\%}$ Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	5950	5973.8	0.40
2	4880	4564.7	-6.91
3	4659	4850.85	3.95
4	7435	7246.28	-2.60
5	6351	6469.62	1.83
6	7333	7066.32	-3.77
7	7586	7414.63	-2.31
8	NA	NA	NA
9	7369	7263.7	-1.45
10	7413	7282.7	-8.19
Average	6552.9	6459.2	-2.12
p-value			0.2031

3.3.5 Larynx

Because laryngeal cancer is one of the most common head and neck cancer types, larynx often is a part of the PTV. In this study, only 6 out of 10 patients had dose constraints for larynx. Although there were some improvements in percentage change for mean, median dose, and $D_{1\%}$, all the results were statistically insignificant ($p = 0.5625$, $p = 0.6875$. $p = 0.8789$ respectively).

Table 14. Mean Larynx Dose

Patient #	Mean Larynx Dose Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	NA	NA	NA
2	NA	NA	NA
3	NA	NA	NA
4	NA	NA	NA
5	2182.4	2147.5	-1.63
6	2412.5	2558.2	5.70
7	4573.5	4418.6	-3.51
8	2813.4	3215.8	12.51
9	2765.3	2727.8	-1.37
10	2920.2	3229	9.56
Average	2944.6	3049.5	3.54
p-value			0.5625

Table 15. Median Larynx Dose

Patient #	Median Larynx Dose Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	NA	NA	NA
2	NA	NA	NA
3	NA	NA	NA
4	NA	NA	NA
5	1704.8	1698.3	-0.38
6	2259.4	2333.4	3.17
7	4367.5	4203.4	-3.9
8	2571.2	2842.5	9.54
9	2468.4	2466.8	-0.06
10	2623.2	2747.7	4.53
Average	2665.8	2715.4	2.15
p-value			0.6875

Table 16. Larynx $D_{1\%}$

Patient #	Larynx $D_{1\%}$		
	Adaptive Tx Plan (cGy)	Delivered Tx Plan (cGy)	Delivered-Adaptive (% Change)
1	NA	NA	NA
2	NA	NA	NA
3	NA	NA	NA
4	NA	NA	NA
5	5005	4875.3	-2.66
6	4232	4858.5	12.89
7	7323	7003	-4.57
8	5400	5989.05	9.84
9	4786	4962.05	3.55
10	5013	6559.6	23.58
Average	5293.2	5707.9	7.11
p-value			0.8789

3.3 Dose Volume Histogram (DVH) Comparison

DVHs may also be used to examine the dose differences between ATP and DTP, and to evaluate each plan. For patient 8, whose CBCT was used for CT_intra, the brainstem, the parotid glands, and the larynx received lower doses for ATP than DTP, with better PTV70 coverage as shown in Figure 4.

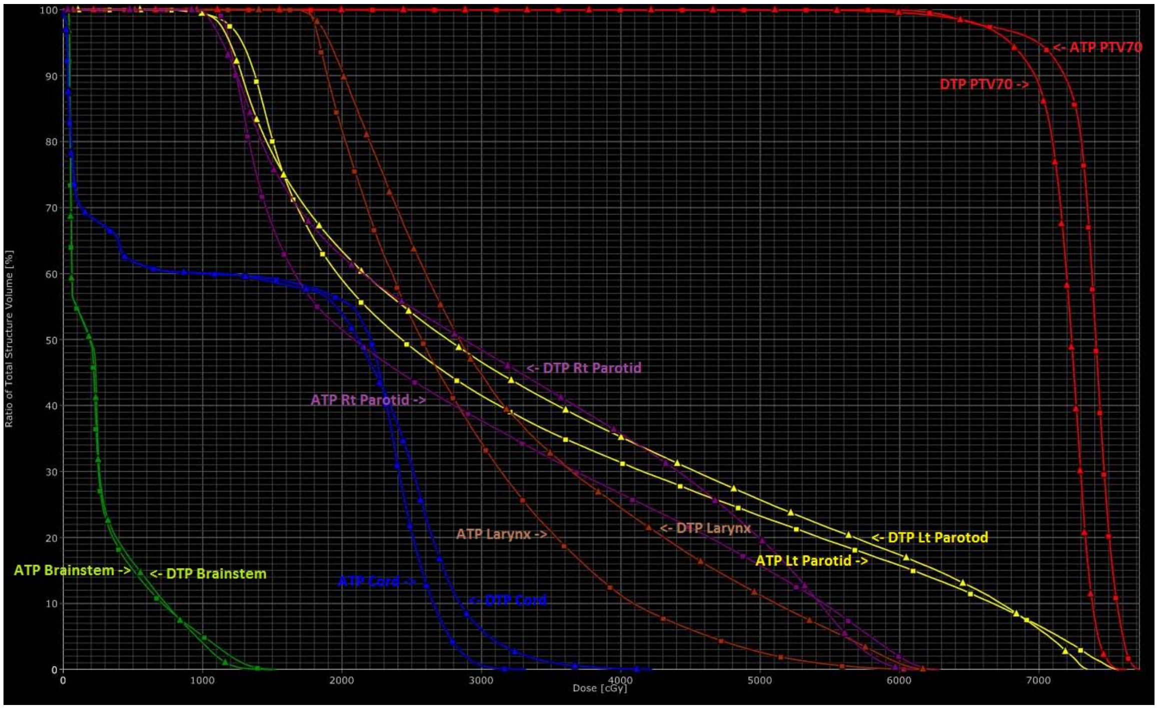

Figure 4: Comparison between ATP (square) and DTP (triangle) for patient 8 with the PTV70 in red, the brainstem in green, the Cord + 5mm in blue, the left parotid in yellow, the right parotid in violet, and the larynx in brown.

For patient 4, 9, and 10, regular CT scans are used for CT_intra. All OAR doses were reduced for patient 4 as shown in Figure 5, with improved PTV70 coverage.

Figure 6 shows the case where almost no change to OARs was made by ATP, but PTV70 coverage improved. Figure 7 represents the average case where there were improvements to OARs and also improved PTV coverage.

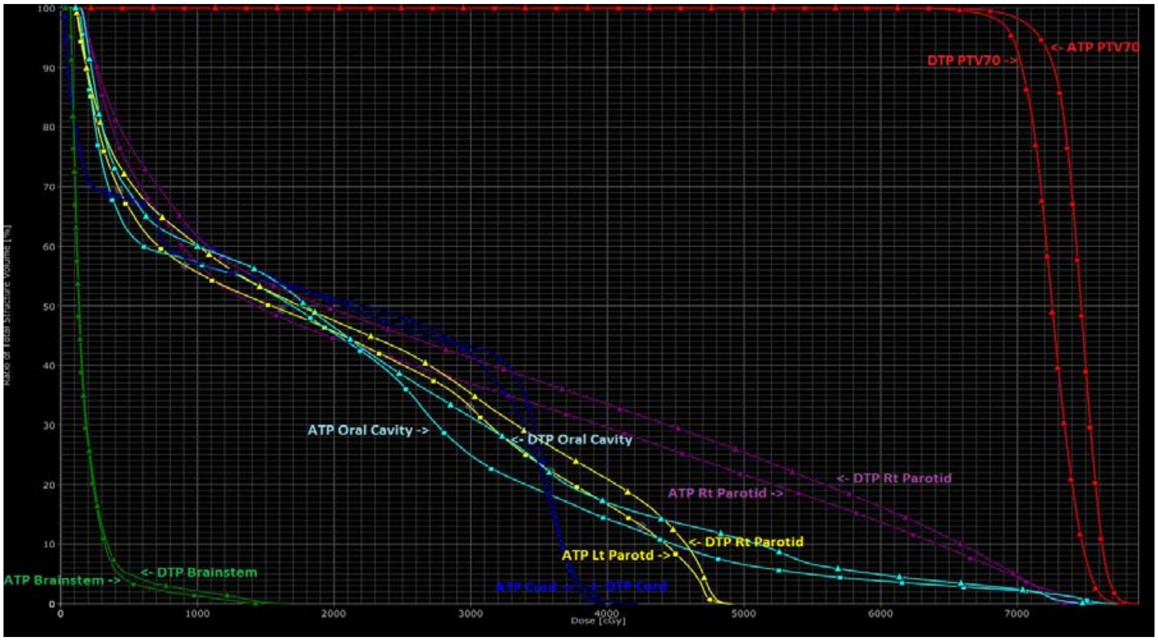

Figure 5: Comparison between ATP (square) and DTP (triangle) for patient 4 with the PTV70 in red, the brainstem in green, the Cord + 5mm in blue, the left parotid in yellow, the right parotid in violet, and the oral cavity in sky blue.

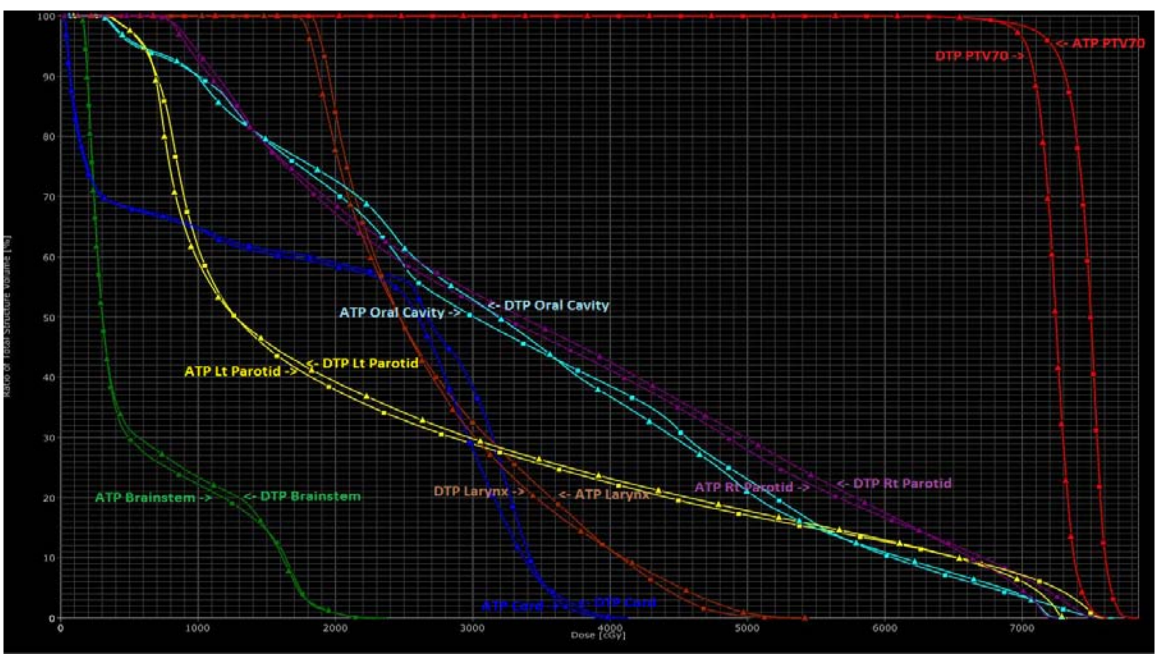

Figure 6: Comparison between ATP (square) and DTP (triangle) for patient 9 with the PTV70 in red, the brainstem in green, the Cord + 5mm in blue, the left parotid in yellow, the right parotid in violet, the larynx in brown, and the oral cavity in sky blue.

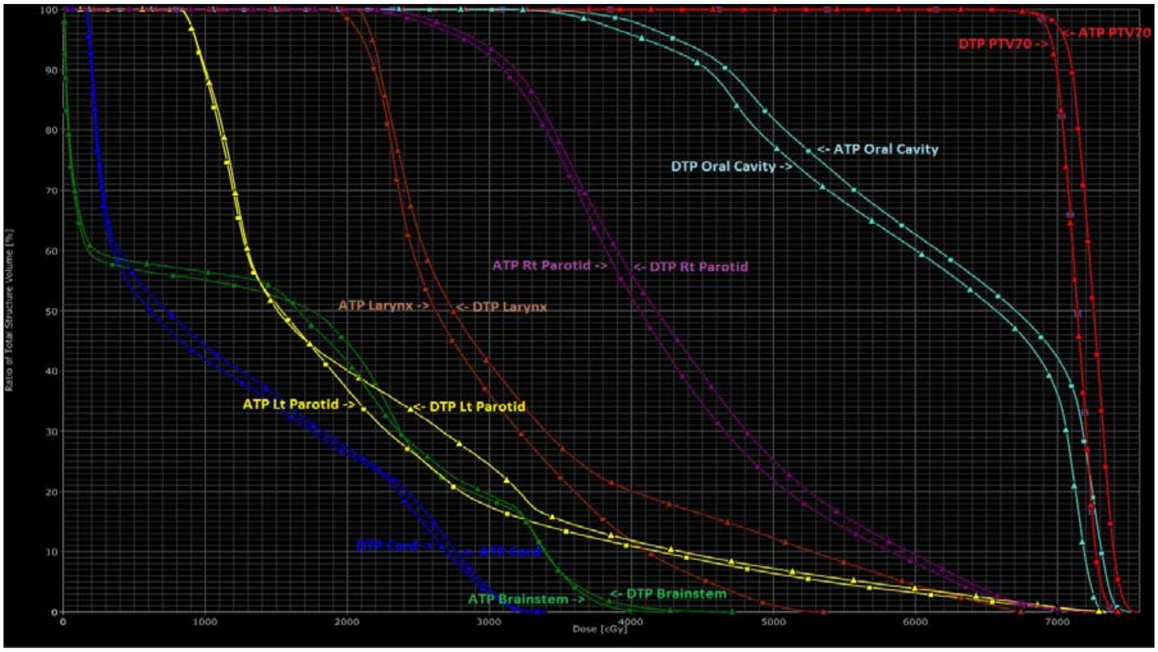

Figure 7: Comparison between ATP (square) and DTP (triangle) for patient 10 with the PTV70 in red, the brainstem in green, the Cord + 5mm in blue, the left parotid in yellow, the right parotid in violet, the larynx in brown, and the oral cavity in sky blue.

4. Discussion

The aims for this study were to quantify the effectiveness of ATP. Most of the results with CBCT have noticeable changes in positive and negative ways. This might be due to the poor resolution of CBCT causing the inaccuracy in image registration process and in dose calculation. Therefore, ATP with CBCT requires extra caution to be used in the clinical situations.

4.1 PTV

PTV70 and PTV44 homogeneities were more uniform for ATP as shown in Table 2 and 3. PTV70 and PTV44 coverages were higher for ATP as shown in Table 4 and 5. Therefore, PTV dose for ATP is said to be more uniform and more conformal.

4.2 Spinal Cord

ATP can reduce the spinal cord dose up to about 20% and an average of 6.47% as shown in Table 6. This is about a 3 Gy reduction for a constraint dose of 45 Gy. Thus, for a patient with the original maximum dose for the spinal cord being around 45 Gy, ATP can be effective. Correlation between percentage change in PTV volumes and percentage decrease in maximum spinal cord dose was calculated and stronger correlation was shown with PTV44 volume change ($r = 0.79$) than with PTV70 ($r = 0.52$) in Figure 8. The correlation seems to be reasonable as PTV44 volume is initially bigger and likely to be closer to spinal cord and thus the change in PTV44 volume affects decrease in cord dose more significantly.

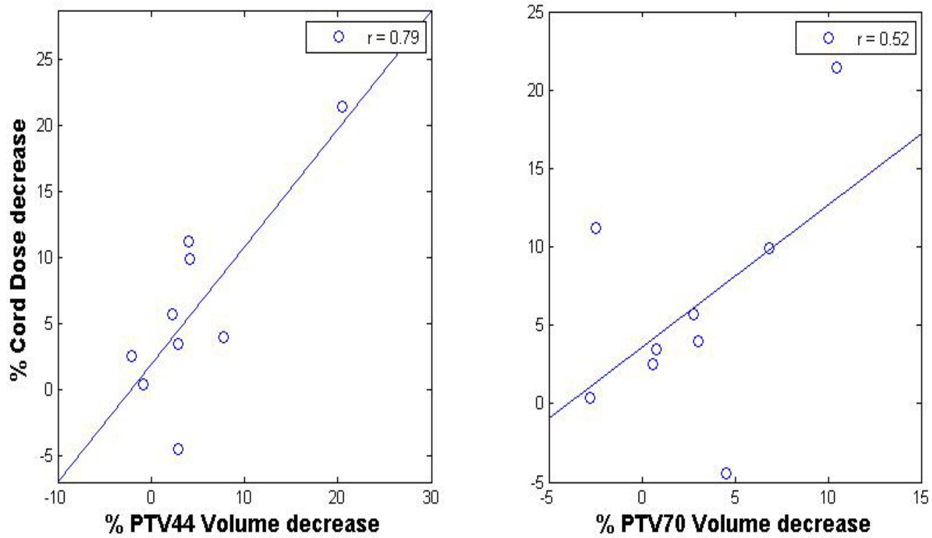

Figure 8: Correlation between percentage change in PTV44 volume and percentage decrease in maximum cord dose (left) and correlation between percentage change in PTV70 volume and percentage decrease in maximum cord dose (right).

4.3 Brainstem

The maximum brainstem dose can be reduced by an average of 8.24%. Except for the ATP with CBCT, the reduction in dose can vary between 2.55% and 12.94%. The reasoning for the variation might come from the location of brainstem and PTV. For example, when comparing the best sparing case, patient 6, with the least sparing case, patient 10, the brainstem of patient 6 is distant from PTV and is rarely on the same transverse axis with PTV, whereas the brainstem of patient 10 is close to PTV and almost half of the volume is on the same transverse plane as the PTV.

In many cases, the maximum brainstem dose exceeded the Duke recommended limit (20 - 25 Gy), so the certain dose reduction by ATP can help reduce the risk of patient nausea.

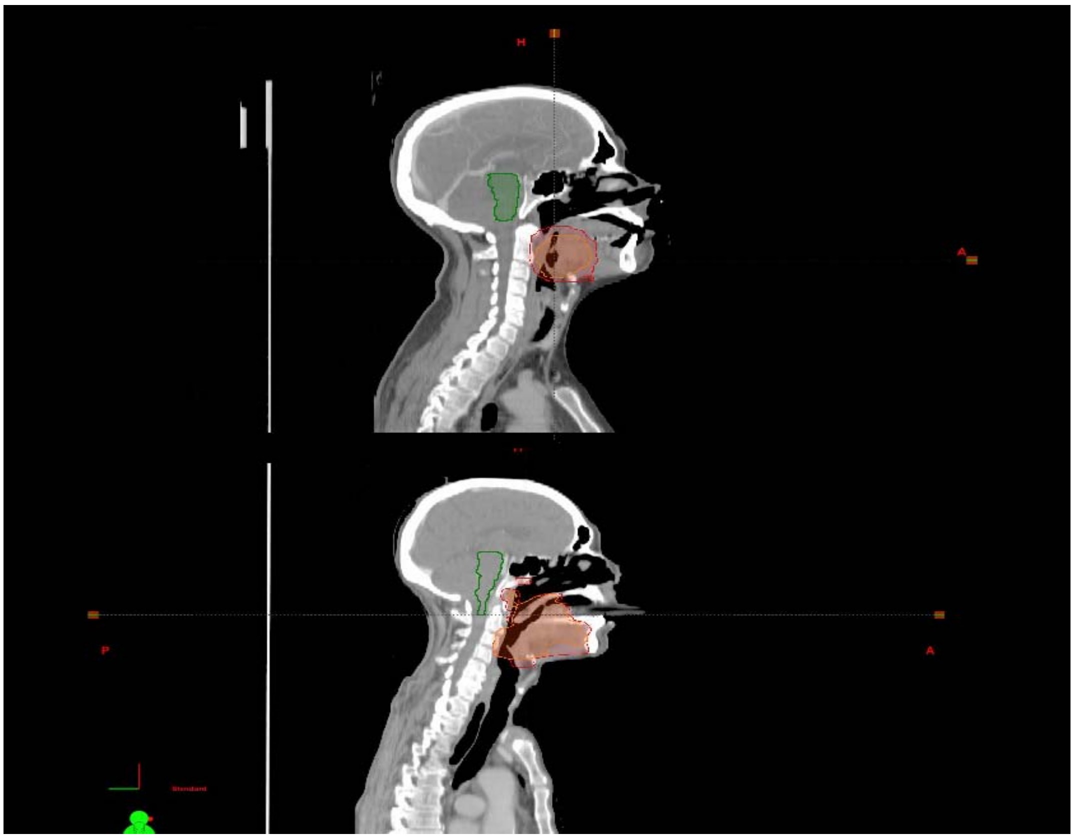

Figure 9: Sagittal view for CT scan to see how close the brainstem is to the PTV. The upper image is patient 6 whose maximum brainstem dose is reduced by 12.9% for ATP and the lower image is patient 10 whose maximum brainstem dose is reduced by 2.6%. The brainstem in green, PTV44 in red, and PTV70 in orange.

4.4 Parotid Glands

On average, median and mean doses for parotid glands are reduced by 6.01% and 4.14% respectively. The range of the change in median dose is from -3.13% to 27.41%, and change in mean dose is from -7.25% to 18.92%. Correlation between median and mean right parotid dose decrease and decrease in PTV volume are shown in Figure 10 and 11 respectively. The correlation coefficients for median right parotid dose are approximately the same for both percentage PTV44 volume change and PTV70 volume change ($r = 0.66$, $r = 0.65$ respectively). The correlation coefficients for mean right parotid dose are bigger for PTV44 volume change than PTV70 volume change ($r = 0.52$, $r = 0.32$ respectively). On the other hand, the correlation coefficients for mean and median left parotid doses did not show any strong correlations ($r = 0.13$, $r = 0.32$ for mean dose with PTV44 and PTV70 respectively and $r = -0.098$ and -0.19 for median dose with PTV44 and PTV70 respectively) so the correlation between change in mean and median right parotid doses with the PTV volumes reduction might be due to coincidence.

The variations are extensive as the parotid glands usually overlaps with PTV. Therefore, improvement in mean and median doses by adapting ATP depend substantially on the volume of PTV and the parotid gland overlap as shown in Figure 12.

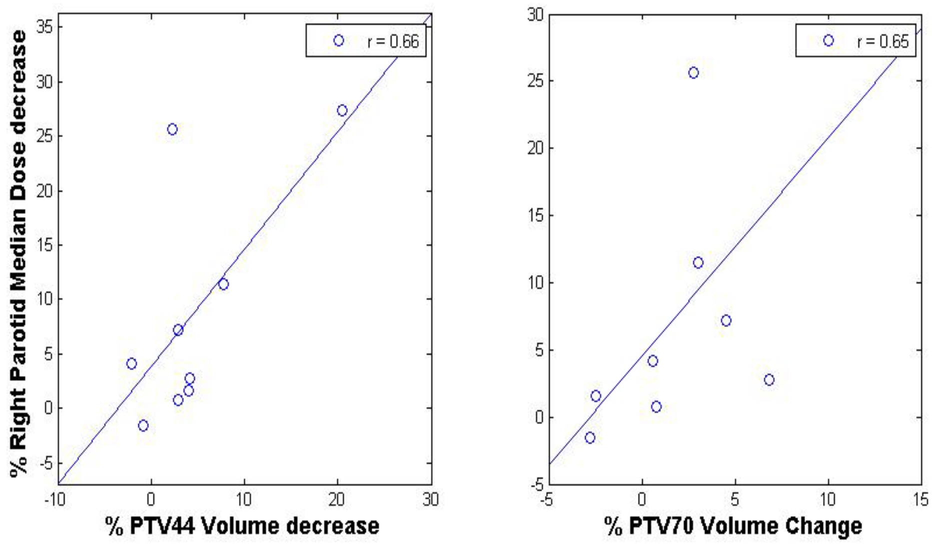

Figure 10: Correlation between percentage change in PTV44 volume and percentage decrease in median right parotid dose (left) and correlation between percentage change in PTV70 volume and percentage decrease in median right parotid dose (right).

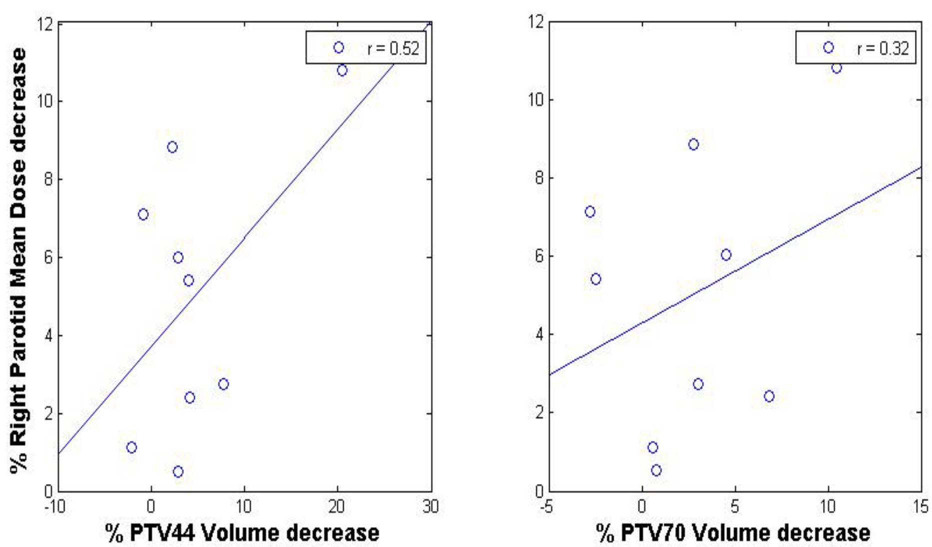

Figure 11: Correlation between percentage change in PTV44 volume and percentage decrease in mean right parotid dose (left) and correlation between percentage change in PTV70 volume and percentage decrease in mean right parotid dose (right).

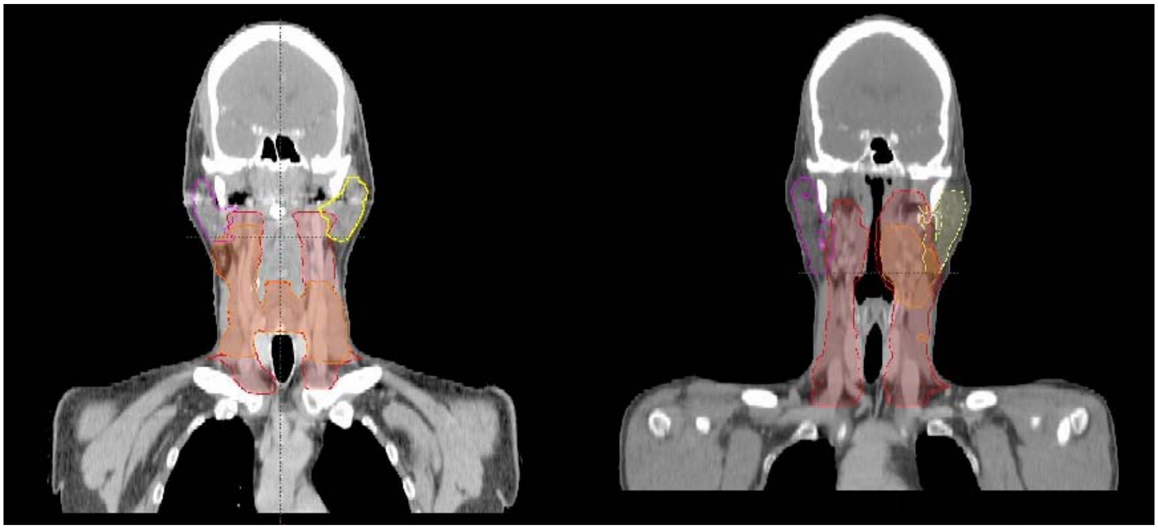

Figure 12: Coronal view for CT scan to see the overlap of the parotid glands with PTV. The left hand side image is patient 4 whose median and mean doses for the right parotid glands are reduced by 25.61% and 8.84% for ATP compared to DTP. The right hand side image is patient 6 whose median dose of the left parotid is reduced by 0.28% but mean dose is increased by -7.25%. The right parotid in violet, the left parotid gland in yellow, PTV44 in red, and PTV70 in orange.

4.5 Oral Cavity and Larynx

Both oral cavity and the larynx doses are not significantly different with ATP. However, the sample size of patients with healthy larynx was too small to confirm, so further study will be required.

5. Conclusions

The dose reductions from adaptive planning was significant for median parotid glands doses (6.01%). Additionally, PTV70 coverage in the adaptive plans was also significantly better by 12.00%. The extent of correlation between PTV44 volume change and dose reduction was strongest for maximum spinal cord dose (r = 0.79) and less so for median right parotid dose (r = 0.66) and mean right parotid dose (r = 0.52). The correlation between PTV70 volume change and dose reduction was strongest for median right parotid dose (r = 0.65) and less so for maximum spinal cord dose (r = 0.52) and mean right parotid dose (r = 0.32).

The dose changes to median parotids dose and PTV70 coverage, while significant, are small and hence may not be clinically significant. This suggests that adaptive planning may not be necessary in head-and-neck cases on average. However, individual cases with large volume changes could warrant adaptive therapy.

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