Multi-Case Knowledge-Based IMRT Treatment Planning in Head and Neck Cancer

by

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Thesis submitted in partial fulfillment of
the requirements for the degree of Master of Science in the
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ABSTRACT

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Abstract

Head and neck cancer (HNC) IMRT treatment planning is a challenging process that relies heavily on the planner's experience. Previously, we used the single, best match from a library of manually planned cases to semi-automatically generate IMRT plans for a new patient. The current multi-case Knowledge Based Radiation Therapy (MC-KBRT) study utilized different matching cases for each of six individual organs-at-risk (OARs), then combined those six cases to create the new treatment plan.

From a database of 103 patient plans created by experienced planners, MC-KBRT plans were created for 40 (17 unilateral and 23 bilateral) HNC "query" patients. For each case, 2D beam's-eye-view images were used to find similar geometric "match" patients separately for each of 6 OARs. Dose distributions for each OAR from the 6 matching cases were combined and then warped to suit the query case's geometry. The dose-volume constraints were used to create the new query treatment plan without the need for human decision-making throughout the IMRT optimization. The optimized MC-KBRT plans were compared against the clinically approved plans and Version 1 (previous KBRT using only one matching case with dose warping) using the dose metrics: mean, median, and maximum (brainstem and cord+5mm) doses.

Compared to Version 1, MC-KBRT had no significant reduction of the dose to any of the OARs in either unilateral or bilateral cases. Compared to the manually planned unilateral cases, there was significant reduction of the oral cavity mean/median dose (>2Gy) at the expense of the contralateral parotid. Compared to the manually planned bilateral cases, reduction of dose was significant in the ipsilateral parotid, larynx, and oral cavity (>3Gy mean/median) while maintaining PTV coverage.

MC-KBRT planning in head and neck cancer generates IMRT plans with better dose sparing than manually created plans. MC-KBRT using multiple case matches does not show significant dose reduction compared to using a single match case with dose warping.

Dedication

I dedicate my thesis to my family who has always supported me in all my endeavors.

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Acknowledgements

I would like to thank Dr. Das and Dr. Lo in their support and guidance throughout this project. I am also thankful for Vorakarn Chanyavanich, Matthew Freeman, Deon Dick, David Good, and Christopher Busselberg for starting the KBRT process. I have been honored to work with Matthew Schmidt and Carly Lutzky on different aspects of the head and neck KBRT project.

1. Introduction

1.1 Clinical Relevance

Head and neck cancer (HNC) incorporates between 3-5% of all cancers diagnosed in the United States. As defined by the National Cancer Institute, head and neck cancers include cancer in the nasal cavity, sinuses, nose, lips, mouth, salivary glands, throat, or larynx and excludes tumors in the brain, eyes, thyroid gland, skin, muscles, and bones [1]. In 2013, according to the American Cancer Society, 55,070 individuals will be diagnosed with head and neck cancer. In addition, over 20% of these individuals will die from this type of cancer annually. Early stage diagnosis of head and neck cancer has a high cure rate; however, approximately 2/3 of the cases are diagnosed in later stages of tumor growth, making treatment difficult. Treatment of patients with this disease includes surgery and radiation therapy. Occasionally in more advanced stages of this cancer, adjuvant chemotherapy is used in order to use all efforts to reduce the effects of cancer [2].

1.2 Head and Neck IMRT Optimization

Intensity modulated radiation therapy (IMRT) is the preferred external beam radiation therapy (EBRT) option for head and neck cancer. IMRT is intended to target the tumor precisely, while sparing the normal tissue including the organs at risk (OARs) [3-8]. The target defined in IMRT is the planning target volume (PTV). The PTV is an expansion of the clinical target volume (CTV), which includes the gross tumor volume in

addition to a margin for sub-clinical disease spread and an additional margin allowing for uncertainties in the treatment delivery or planning [9].

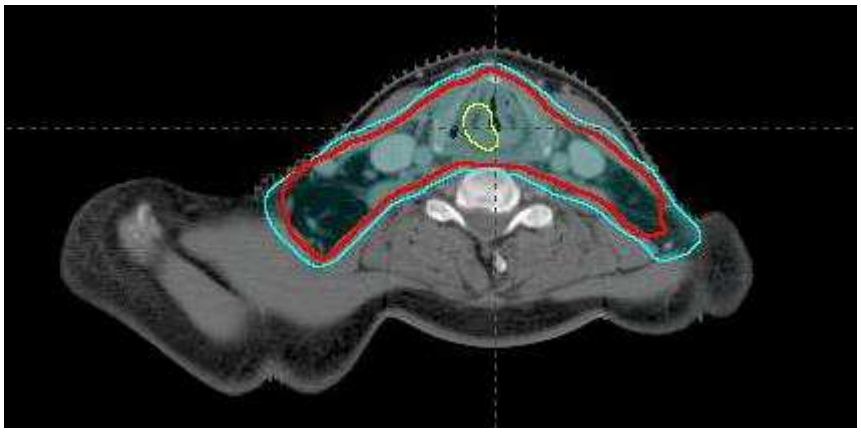

Figure 1: Example of GTV (yellow), CTV (red), and PTV (blue) expansion on an axial CT slice for a case of glottis cancer.

The PTV defined by the physician should ideally receive a uniform 100% of the prescribed dose with preferably no area receiving greater than 115% of the prescription dose.

In addition to delivering the prescription dose to the PTV, dose to the normal tissue and OARs must be minimized. The OARs that are prevalent in head and neck cancer include the larynx, left and right parotids, spinal cord, brainstem, and oral cavity.

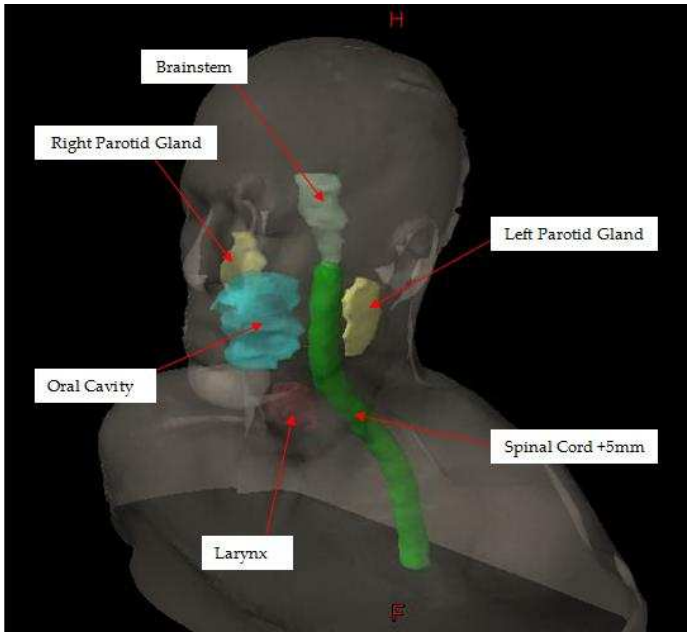

Figure 2: OARs spared in HNC treatment plans. Generated with Eclipse treatment planning software

At Duke University, a standard margin of 5mm is added to the spinal cord to create a planning risk volume that incorporates possible errors in motion and patient positioning. Mandible is not included in the study due to its recent incorporation in the planning process. Radiation damage to any of these OARs could have life-impairing effects on the patient including sensory disturbances, motor function anomalies, cognitive impairments, regulatory problems, xerostomia, mucositis, sleepiness, etc. HNC is considered to be the most challenging disease site in radiation therapy due to the complex juxtaposition and overlap between PTV and OARs. With an IMRT plan, the dose to the OARs is ideally zero, but since that is not practically possible, instead the goal is to keep doses below certain limits. For this research, limits are reflected by the

standards used in the Duke clinic. For the parotid glands and larynx, an upper limit of 24 Gy median dose is desirable, the oral cavity has a limit of 30 Gy median dose, the brainstem has an upper limit of 20 Gy maximum dose, and the spinal cord+5mm has a limit of 45 Gy maximum dose. Patient responses to radiation are variable, so these limits are guidelines to create a quality plan [10].

The IMRT optimization process involves the minimization of an objective function. The total objective function includes meeting the constraints and priorities specified by the dosimetrist for both the PTV and all of the OARs. Once this objective function is minimized, the fluence intensity map within each beam is altered throughout the treatment.

When compared to 3D conformal treatment planning, IMRT shows superior sparing of the OARs and reduced risk of complications, but may not cover the target as homogeneously [11, 12]. A study was performed to analyze the stimulated parotid saliva (SPS) flow at 12 months after radiation therapy compared to before treatment. These patients' SPS flow returned to at least 25% of its initial function in 83.3% of patients receiving IMRT compared to only 9.5% of patients receiving conventional radiation therapy. Patients receiving IMRT had notably better parotid sparing and improved quality of life [13].

1.3 KBRT Treatment Planning Background

IMRT plans are usually created by optimizing the doses in a trial-and-error fashion. In the clinic, head-and-neck cancer (HNC) IMRT treatment planning relies heavily on the planner's experience in achieving the best dose sparing to OARs and generally takes a considerable amount of time [14, 15]. More experienced planners have been shown to produce superior IMRT plans [16].

Research has been done toward creating high quality IMRT treatment plans for a new "query" patient by adapting the parameters from previously planned "match" patients who are anatomically similar to the new patient. Prior work has been done from other groups in data-driven IMRT treatment planning including one study that used an overlap volume histogram instead of looking at the geometric overlap [17]. Looking particularly at other research in prostate treatment planning, "machine learning" was applied to develop new plans using the organ volumes and a distance-to-target histogram [18]. Another study of pancreatic adenocarcinoma used a shape-based treatment planning method to predict the dose received based on the OAR orientation and distance to the PTV [19].

Within our group, a prostate study was performed using the same mutual information technique that is still currently used. Unlike with HNC where dose warping is used, optimization parameters were simply taken from the match case [15]. The overlap of the PTV with OARs can be measured by the closeness of the beams-eye-

view (BEV) projection images of the target volume and the OARs. This gives a similarity metric between the "query" and "match cases" [15, 20]. In previous knowledge-based work, it was assumed that the manually planned patients most geometrically similar to a new patient will have treatment plans that can be easily adapted to the new "query" patient. Within our group, similar dose-volume histograms (DVHs) for a new patient were achieved by using the OAR dose-volume constraints extracted from the DVH of previously planned similar cases to guide the IMRT planning optimization process for both prostate and HNC cases [15, 21]. The premise behind this knowledge-based method is to produce high quality plans at a fraction of the time when creating *de novo* plans.

Head-and-neck treatment plans show larger deviations from the prescribed doses compared to brain and prostate cancer plans [22]. The PTVs of HNC patients vary significantly from one another in both size and shape between patients. Due to irregular shapes of the targets and suboptimal HNC plans in the database, the methodology that our group used to generate prostate plans needed to be revised. The revised methodology for knowledge-based radiation therapy (KBRT) IMRT treatment planning for HNC has been performed by warping the dose distribution from the single most similar patient to suit the PTV/OAR geometry of the new patient. This warped dose distribution was used to generate dose-volume constraints for the new patient, and this previous approach will be referred to as Version 1 (V1) [21].

This work aims to semi-automatically generate IMRT treatment plans, based on the individual OARs, that are of the same quality as plans produced by both experienced human planners and prior automated work. Most importantly, this is the first study that incorporates data from multiple matching plans, each of which represents the best overlap of the PTV with individual OARs. This multi-case KBRT approach is compared against not only the original, clinically treated plan, but also the V1 approach that is based on only the single, best matching case.

2. Methods and Materials

2.1 Knowledge Database

The knowledge database used in this research included clinical IMRT treatment plans from 103 head and neck cancer patients treated at Duke University Health System between 2009 and 2012. The clinical cases chosen included the primary and boost plans, which consisted of between 6 and 9 coplanar 6 MV beams. Beam angles were either distributed equally for bilateral cases or focused around the target side for unilateral cases. The OARs considered for this dose-sparing study included the larynx, parotid glands, oral cavity, brainstem, and spinal cord +5 mm expansion.

The clinical plans were optimized manually to meet the planning constraints set by the radiation oncologist. In general, these clinical constraints were set at < 24 Gy median dose for the parotid glands, oral cavity, and larynx, < 25 Gy for the maximum dose to the brainstem, and < 45 Gy maximum dose to the spinal cord +5 mm. In particularly difficult individual cases, the constraints were either relaxed or tightened depending on the overlap of the OARs and the target [10].

Twenty-three bilateral and seventeen unilateral patients were chosen randomly as query patients for whom new multi-case knowledge-based IMRT (MC-KBRT) treatment plans were to be created. The unilateral cases were comprised of 1 left parotid gland cancer, 1 right parotid gland cancer, 1 oral tongue cancer, 1 recurring sinus cancer, 1 lymph node cancer, 1 bone marrow cancer, 5 left tonsil cancers, and 6 right tonsil

cancer cases (See Appendix for prescription doses); bilateral cases were comprised of 1 glottis cancer, 1 supraglottis cancer, 1 lip cancer, 1 oropharyngeal cancer, 1 right tonsil cancer, 1 left tonsil cancer, 2 nasopharyngeal cancers, 6 lymph node cancers, and 9 base of tongue cancers (See Appendix for prescription doses). Prescription doses for all of these patients varied from 60 to 70 Gy. For each query case in question, the remaining 102 cases in the knowledge base served as potential match cases. These potential match cases were used to guide the query MC-KBRT plan. The MC-KBRT plans generated were compared dosimetrically to both the original clinical plans used to treat the patients and Version 1.

2.2 Match Case Selection

The query patient's anatomical structures were converted into 2D Beam's Eye View (BEV) projections of the standard 9 angles. These query BEV's were compared to the database using a summation of the mutual information (MI) values at each angle to find the closest anatomical/geometric "match" for each OAR. For each query OAR, IMRT optimization constraints were adapted from the closest match case. These constraints were imported into the Eclipse Treatment Planning System (version 10.0.28, Varian Medical Systems, Palo Alto, CA) for optimization and then analyzed and compared to previous research and the originally planned case. Details of these steps follow.

From Eclipse, anatomical structure data were exported in DICOM files. These files were read in Computational Environment for Radiotherapy Research (CERR) via MATLAB (Mathworks, Natick, MA) to generate 3-dimensional images of the head and neck structures [23]. The CERR code has been adjusted to provide a constant cm-to-pixel ratio of the 3D images. Since the query plan cases will be generated from the match cases, 2D images of the BEV projection images at each of the 9 beam angles are acceptable for the match comparison.

Each query case was compared to the remaining 102 database cases to determine the best matching cases. In order to ensure a similar match PTV based on size, shape, and location, a mean squared error (SE) calculation was performed between the query patient and the match database's 2D BEVs (180 and 260 degrees) to find the top 10 geometrically matched PTVs. The match BEVs for these angles were translated along the query image using a gradient descent of the least squared error measurement (Equation 1) in order to properly align the two images.

$$SE = \sum_{i,j} \left(I_{i,j}^{\text{moving}} - I_{\text{i,j}}^{\text{target}} \right)^2 \quad (1)$$

In the above equation, the query is the target and each match is the moving image. The *I* values represented here are the binary pixel intensities (1 in PTV and 0 outside). Figure 3 shows the BEV images before and after the shift is applied. The shift

allows for the match PTV to be properly aligned with the query for an optimal similarity metric.

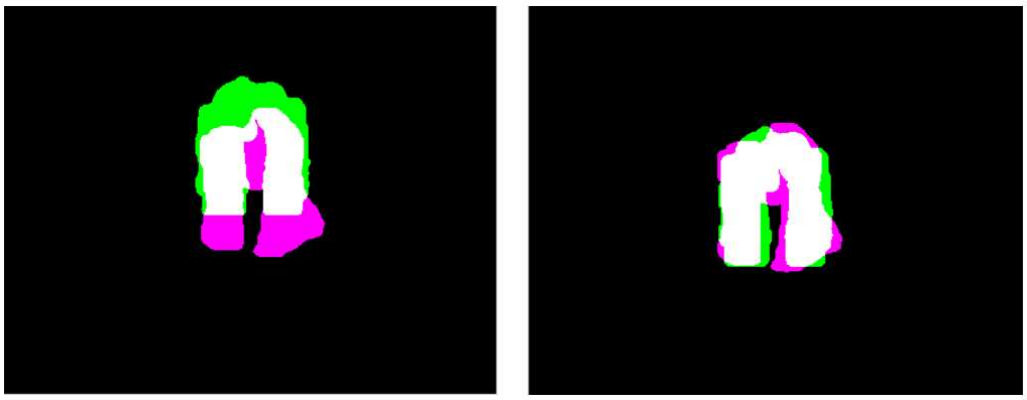

Figure 3: An unregistered query (green) BEV image at 180 degrees with the top PTV match (pink) on the left. The shifted BEVs are now ready for the mutual information calculation (right).

This initial alignment step reduced the amount of time and memory used later when computing mutual information. For each of the paired angles, squared error was calculated and the sum computed. The case with the minimum summed squared error value corresponded to the case that has a PTV that is most similarly matched.

To compute mutual information, two-dimensional BEV projection masks were created for each OAR. The masks were images that assigned pixel values using the following numbering scheme such that each structure or PTV with its overlap had a unique number: 1 within the OAR, 2 within the PTV, 3 within the PTV/OAR overlap, 0 elsewhere.

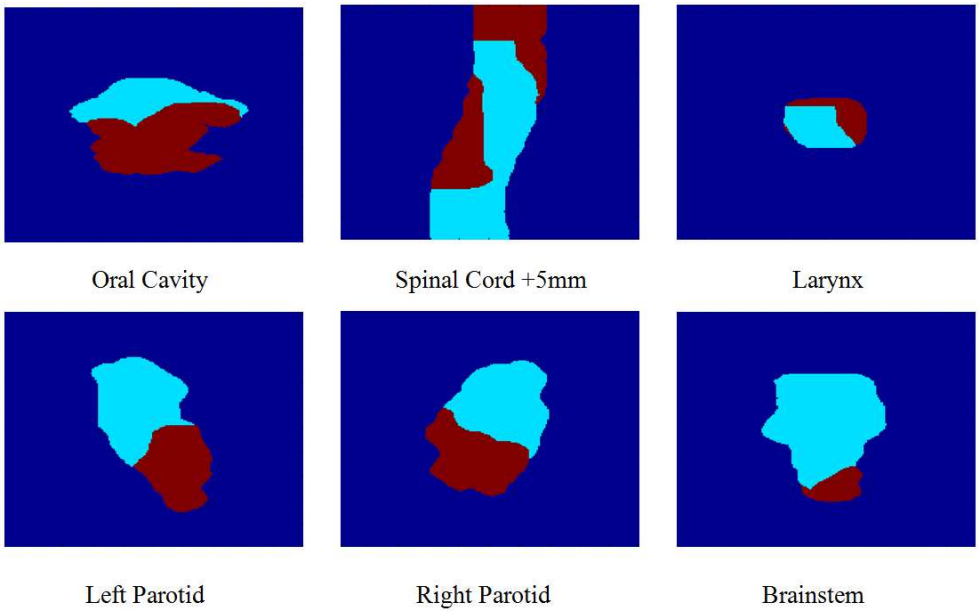

Figure 4: Example of BEV projection of overlap PTV with each OAR (light blue = OAR, red = OAR overlap with PTV, dark blue = outside of OAR)

From the top 10 potential PTV matches, a mutual information similarity with the query and "match" for each OAR can begin. The metric used for this was the summed mutual information of the overlap between the potential match and the query for each of the 9 projection angles. This mutual information between the query and each potential match was calculated by the following equation.

$$MI(A,B) = \sum_{i_a, i_b} p_{AB}(i_a, i_b) \log_2 \left(\frac{p_{AB}(i_a, i_b)}{p_A(i_a) p_B(i_b)} \right) \quad (2)$$

In the above equation, A is the query and B is the match, i_A is the intensity level of image A and i_B is the intensity level of image B, and P_A and P_B are probabilities of i_A and i_B occurring in images A and B respectively. P_{AB} shows the joint probability that the

intensity of A, i_A, will be present in the same pixel in B as i_B. Mutual information was calculated and the potential match shifted over the query image along a gradient of steepest descent until the mutual information value is maximized. This assured that the two images were aligned in the best way possible. Of the 10 potential match cases, the case with the highest summed mutual information metric over all beam angles was designated to have the most geometrical similarity for a specific OAR of the query patient. This process was performed for each OAR, generating 6 top match cases, one for each OAR. The hypothesis was that finding a top match for each individual OAR would provide more accurate matches with better-fitting dose distributions for each OAR in question.

2.3 Constraint Calculation and Priority/ Beam Angle Generation

Prior KBRT work in prostate cases imported deformed beam fluences from the match case (deformed to suit the PTV/OAR geometry of the query case) in addition to the dose-volume constraints from the single top match to optimize the dose distribution in the query case [15, 24]. Since HNC cases are extremely variable in size and location, this method could not be used to optimize the query case.

To generate better-suited constraints for the query case, the match case dose distribution for each OAR and target was warped to conform to the corresponding shapes of the OAR in the query case [21]. This dose warping was performed by mapping doses in concentric shells of equal thickness surrounding the match target

volume onto the concentric shells surrounding the query target volume. The figure below represents the shell method of warping the dose.

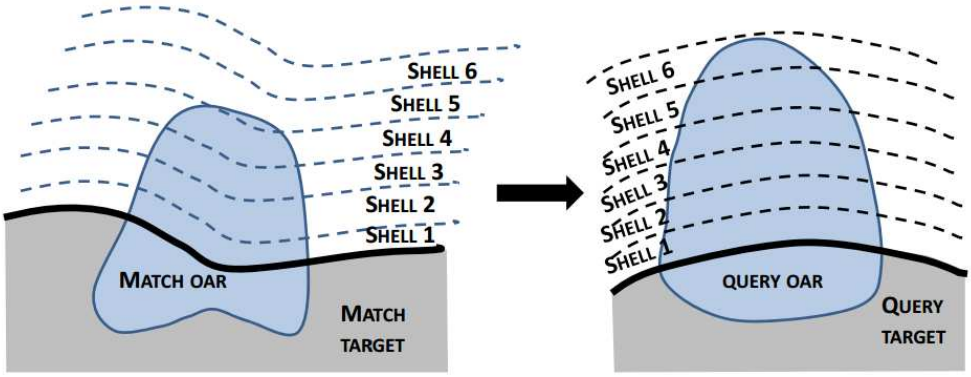

Figure 5: Doses in concentric shells of equal thickness surrounding the match target mapped onto concentric shells surrounding the query target volume

Figure 5 shows the scenario in which the query OAR extends farther away from the target than the match case. In the opposite situation of the match OAR extending farther away from the target than the query OAR, the match shells were scaled down to create smaller query shells. The shells were scaled in proportion to the maximum extension of the query OAR from the target surface to the maximum extension of the match OAR from the target surface. This was done to cause a steeper OAR dose falloff, eventually generating tighter constraints.

Unlike prior HNC KBRT work where a single match using a composite of all OARs and the PTV to generate the dose-volume constraints (Version 1), the constraints were generated for each OAR based on its individual top match. In order to produce

optimal query dose-volume constraints with optimal OAR sparing, the query dose-volume constraints were set to the minimum from either: (a) the warped component plan dose distribution or (b) the warped total plan dose distribution (primary and boost) scaled in proportion to the ratio of the component plan to the total prescription dose.

With the query dose distribution generated for each OAR, a hypothetical Dose-Volume Histogram (DVH) plot was created in MATLAB. For the larynx, oral cavity, left and right parotids, the absolute dose in cGy was extracted for the doses at 40% and 60% volume. For both the brainstem and spinal cord +5mm, the max dose was extracted at 1% volume. These values correspond to the dose-volume constraints put into the IMRT optimization process.

Since this method combines the different matches from each of the OARs, a single, overall context must be used in order to produce a plan that is consistent for the anatomy of the single query patient. Both the priorities weightings for each constraint and the beam angles were extracted from the top match of the ipsilateral parotid (i.e., the parotid on the side where the tumor is primarily located). This allows for consistent context instead of having 6 match cases mixed together. Due to increased OAR plan quality, a PTV priority of 120 was selected to achieve better homogeneity of the PTV.

2.4 Treatment Plan Generation and Optimization

Using the query beam angles, dose-volume constraints, and priorities, a query treatment plan optimization was run in Eclipse until the objective function reached an

asymptote. There was no user intervention of manually modifying the constraints during the optimization process.

This research assumes contoured CT data has already been provided by the physician. With the appropriate PTV target selected (primary or boost), a static plan was created on a Varian 21EX Linear accelerator with an energy of 6MV.

Figure 6: Duke's Varian 21EX Clinac

Using the beam angles generated, new fields were created at the designated angles. For each field, the collimator is fit to the structure with a 1 cm margin added. For all angles entering the patient posteriorly, the jaws were physically adjusted such that the beam did not penetrate the shoulders and impart extra dose through lung and healthy tissue.

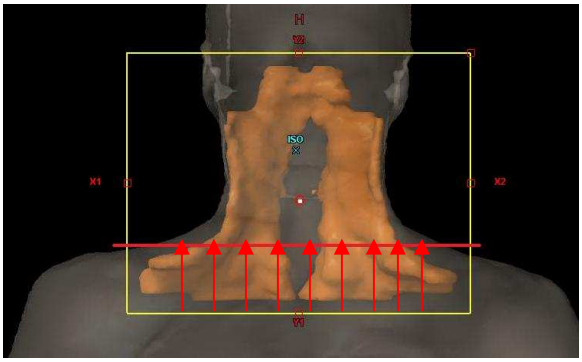

Figure 7: Adjusting collimator jaws for posterior angles

Once the beams and prescription dose were set, the optimization setup was begun. Anisotropic Analytical Algorithm (AAA) is a pencil beam superposition convolution method used in Eclipse for dose calculations. The jaws were fixed for posterior and lateral entry beams to reduce dose to the lungs and shoulders. The dose-volume constraints and priorities generated in MATLAB were entered into the optimization window. We then allowed this optimization to run for 100 iterations or until the objective function reached an asymptote in order to ensure consistency and allow the minimization of the total objective function to be complete.

Once the optimization was complete, a fluence map was generated for each field. The MU's were calculated for each beam and then multi-leaf collimator (MLC) leaf motion was calculated for each field using the standard sliding window technique. The dose-volume was then calculated and normalized such that 100% of the dose covered 95% of the volume.

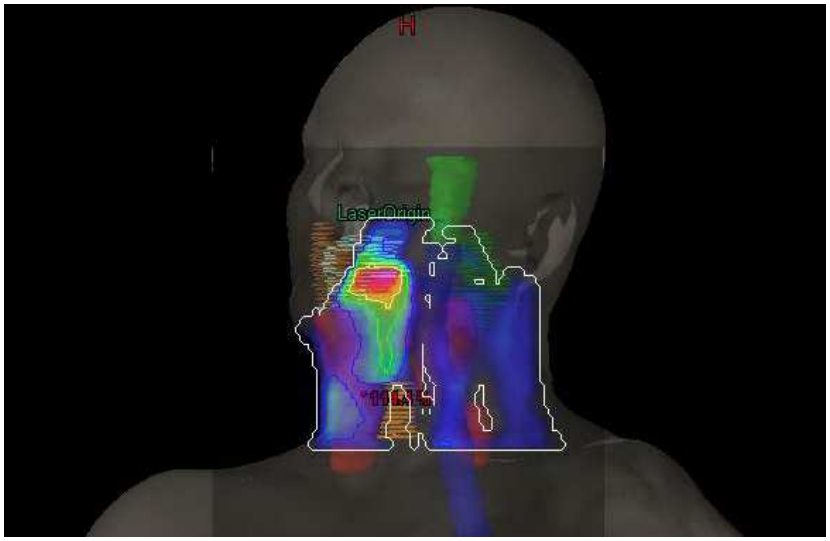

Figure 8: Patient with modulated fluence from beam at 140 degrees. The collimator jaws have been fixed above the shoulders

For any additional boost plans, this process was repeated. Dose-volume histograms were created in Eclipse for each plan. For each plan (primary or boost), the PTV was selected for analysis of the homogeneity index (HI) and sigma index (SI). In order to analyze the total dose delivered to each OAR in a composite DVH, a plan sum was created from the primary and any additional boost plans.

2.5 Plan Evaluation and Analysis

In order to provide an accurate comparison of MC-KBRT to each of the other methods (originally planned method and Version 1), they were compared side by side. The cases were separated into unilateral and bilateral cases in order to give an accurate comparison. The contralateral parotid glands in unilateral cases were significantly spared compared to bilateral cases and this would skew the results. Values for the OAR mean and median doses (larynx, oral cavity, parotids) or maximum doses (cord+5mm or

stem) were analyzed. The parotid glands were characterized as either ipsilateral or contralateral.

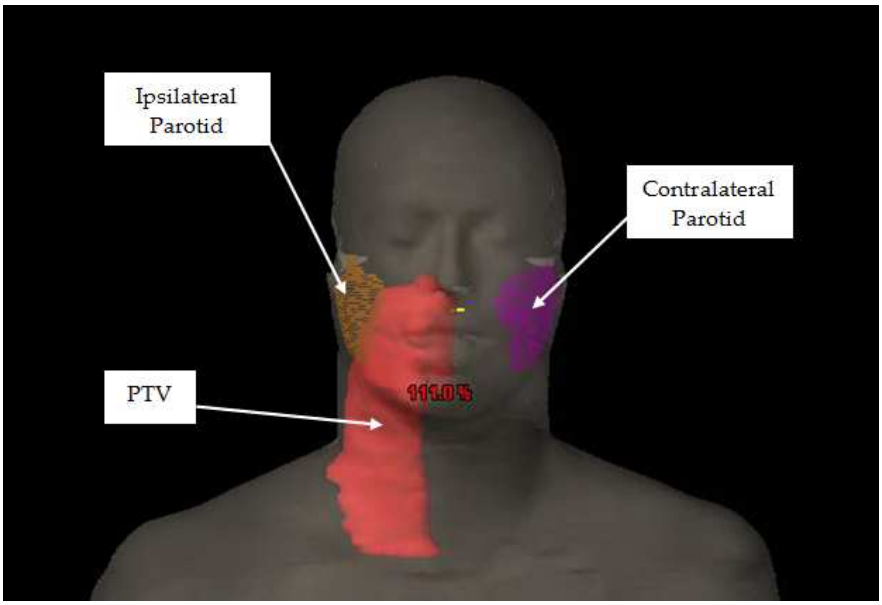

Figure 9: Ipsilateral Right Unilateral Parotid.

Finally, the PTV was analyzed based on its maximum dose percentage, Homogeneity Index (HI), and Sigma Index (S-Index). For both the OARs and the PTV, the maximum dose was defined as the dose to the highest 1% volume.

The coverage of the PTV is the most significant criterion when first looking at HNC cases and then OAR sparing comes into play. The PTV of the manually planned case, Version 1, and MC-KBRT were compared by evaluating the Homogeneity Index and the Sigma Index for each plan. HI measures the steepness of the slope of the PTV DVH while the S-Index measures the deviation from the mean PTV dose [25].

$$HI = \frac{D_2 - D_{98}}{D_p} * 100\% \quad (3)$$

In the HI equation, D_2 and D_{98} represent doses to the highest 2% and 98% PTV volume, respectively, and D_p is the prescription dose

$$S_{index} = \sqrt{\sum (D_i - D_{mean})^2 * \frac{v_i}{V_{total}}} \quad (4)$$

In the S-Index equation, D_i is the dose within the volume v_i, D_{mean} is the average dose in the PTV, and V_{total} is the total volume of the PTV. HI and S-Index values were obtained for each plan PTV (primary/boost).

Values for the median dose, mean dose, maximum dose, HI and S-Index were averaged for each method. An HI value below 15 was clinically acceptable along with a PTV maximum dose below 115% for both the primary and boost plans. The PTV metrics were compared based on the individual plans (primary or boost) and the OAR metrics were compared based on the sum of the primary and boost plans (15/17 unilateral cases had both primary and boost plans; all bilateral cases had both primary and boost plans). The non-parametric Wilcoxon signed rank test was performed to determine statistical significance in the OAR and PTV dose difference between: (a) Original and Version 1; (b) Original and MC-KBRT; and (c) Version 1 and MC-KBRT [26].

3. Results

3.1 PTV and OAR Analysis

Tables 1 and 2 contain the average max dose percentage, HI, and S-Index along with the p-values for both the primary and boost cases of the 17 unilateral and 23 bilateral cases, respectively. For pair-wise comparisons (rightmost 3 columns), gray shading indicates the 1st listed method is better. Bold facing indicates a p-value below 0.05. Gray shading indicates better PTV coverage in boost plans from MC-KBRT (MC) when compared to both the original (Orig) plan and Version 1 (V1) in columns 6 and 7, respectively. Although the values for the primary max dose percentage, HI, and S-Index are significantly worse in MC-KBRT compared to the original plan for both unilateral and bilateral, the percent difference is clinically small. The boost PTV for unilateral cases using MC-KBRT showed significant improvement over the originally planned cases, but still did not show a clinically significant difference.

Table 1: Max Dose Percent, Homogeneity Index, and S-Index averages and p-values of 17 unilateral cases

Unilateral Cases				P-values		
OAR Metric	**Original**	**Version 1**	**MC-KBRT**	**V1 - Orig**	**MC - Orig**	**MC - V1**
Primary Max Dose %	107.91 ± 2.40	109.95 ± 2.94	109.14 ± 1.19	**0.04**	**0.02**	0.27
Boost Max Dose %	109.51 ± 2.07	107.78 ± 1.66	107.23 ± 1.20	0.06	**<0.01**	0.05
Primary HI	9.65 ± 2.62	12.47 ± 7.45	9.95 ± 1.32	0.08	0.33	0.07
Boost HI	11.05 ± 2.63	8.44 ± 1.59	7.65 ± 2.30	**<0.01**	**<0.01**	0.32
Primary S-Index	1.05 ± 0.02	1.07 ± 0.03	1.06 ± 0.01	0.06	0.19	0.15
Boost S-Index	1.01 ± 0.05	0.99 ± 0.05	0.99 ± 0.05	**<0.01**	**<0.01**	0.56

Table 2: Max Dose Percent, Homogeneity Index, and S-Index averages and p-values of 23 bilateral cases

Bilateral Cases				P-values		
OAR Metric	**Original**	**Version 1**	**MC-KBRT**	**V1 - Orig**	**MC - Orig**	**MC - V1**
Primary Max Dose %	109.48 ± 1.54	113.22 ± 3.98	113.07 ± 2.34	**<0.01**	**<0.01**	0.57
Boost Max Dose %	108.65 ± 2.26	108.48 ± 1.77	108.04 ± 1.73	0.68	0.26	0.08
Primary HI	10.71 ± 2.05	14.11 ± 3.75	13.99 ± 2.51	**<0.01**	**<0.01**	0.83
Boost HI	10.00 ± 2.97	9.46 ± 2.06	9.37 ± 3.06	0.41	0.16	0.24
Primary S-Index	1.07 ± 0.02	1.10 ± 0.04	1.09 ± 0.02	**<0.01**	**<0.01**	0.79
Boost S-Index	1.04 ± 0.03	1.04 ± 0.02	1.03 ± 0.02	0.42	0.06	0.10

The OARs were analyzed in a similar fashion of comparing the absolute dose in gray and computing p-values based on the dose differences for unilateral and bilateral cases. Tables 3 and 4 contain the average dose values and the p-values for the dose differences for the 17 unilateral cases and the 23 bilateral cases, respectively. Gray shading indicates better dose sparing in MC-KBRT (MC) when compared to either the original plan (Orig) or version 1 (V1) in columns 6 and 7, respectively. Compared to the original, clinically approved treatment plan, gray shading in columns 5 and 6 ("Orig-V1" and "Orig-MC") indicates that both version 1 and the latest MC KBRT plans provided better dose sparing, albeit at the cost of increased dose for contralateral parotid that was not clinically significant.

In unilateral cases, MC-KBRT had reduced dose compared to the original for all OARs with the exception of the contralateral parotid. The contralateral parotid gland dose increased (2.98 ± 0.97 Gy to 4.12 ± 1.43 Gy median dose) and was below the 5 Gy threshold for all unilateral cases. The oral cavity dose was significantly reduced in MC-KBRT plans compared to the originals (22.82 ± 7.61 Gy to 19.69 ± 8.27 Gy median dose). Of the 17 unilateral cases, this dose reduction is clinically significant in preventing toxicity (Below the 25-30 Gy median dose threshold) in 3/17 cases. Median doses of these plans are 32.55 Gy to 28.06 Gy, 30.46 Gy to 21.53 Gy, and 30.96 Gy to 26.09 Gy. Non-significant dose reduction to the ipsilateral parotid gland (mean and median), larynx (mean and median), brainstem (maximum), and cord+5mm (maximum) was

achieved in MC-KBRT compared to the original. Doses to the contralateral parotid gland (mean and median) and brainstem (maximum) were reduced compared to Version 1, but were not significant.

In bilateral cases, MC-KBRT had reduced dose to all of the OARs with the exception of the contralateral parotid when looking at the original plans. The contralateral parotid gland median dose increased from 14.34 ± 3.38 Gy to 18.36 ± 7.32 Gy which is below the 24 Gy clinically acceptable threshold. The ipsilateral parotid gland median dose was significantly reduced from an average of 32.60 ± 15.5 to 21.71 ± 7.32 Gy. This proved to be clinically significant (Lowering the dose below the threshold of 24 Gy) in 8/23 cases. Of these cases, the median dose values were reduced from 31.50 Gy to 17.26 Gy, 39.59 Gy to 15.09 Gy, 24.66 Gy to 21.78 Gy, 45.15 Gy to 17.41 Gy, 39.86 Gy to 23.52 Gy, 40.79 Gy to 13.91 Gy, 41.88 Gy to 18.02 Gy, and 41.87 Gy to 20.29 Gy. Lowering the median parotid gland dose reduces the chance of xerostomia. MC-KBRT was also able to significantly reduce the median dose of the larynx from 25.81 ± 11.37 Gy to 22.85 ± 8.85 Gy. This is clinically significant in 4/23 cases in which the threshold is reduced below the 24 Gy threshold. Of these cases, the larynx median dose is reduced from 25.93 Gy to 22.95 Gy, 30.68 Gy to 21.97 Gy, 27.73 Gy to 23.36 Gy, and 26.28 Gy to 16.38 Gy. In addition to the ipsilateral parotid gland and larynx median doses being lowered, the MC-KBRT method also significantly improved the dose sparing to the oral cavity compared to the original plans, reducing the median dose from 30.76 ± Gy to

25.53 ± Gy. In 4/23 cases, the median dose was reduced to below the 24 Gy threshold. These cases had reduction from 30.64 Gy to 22.19 Gy, 25.14 Gy to 22.82 Gy, 32.44 Gy to 19.42 Gy, 36.21 Gy to 24.08 Gy, and 25.57 Gy to 22.76 Gy. Compared to the original, dose reduction was also achieved in the brainstem and spinal cord but did not show clinical significance. When MC-KBRT was compared to Version 1, non-significant dose reduction to all OARs except the contralateral parotid was achieved.

Table 3: Absolute dose averages and p-values of 17 unilateral cases

Unilateral Cases	Absolute Dose (Gy)			P-values		
OAR Metric	**Original**	**Version 1**	**MC-KBRT**	**V1 - Orig**	**MC - Orig**	**MC – V1**
Ipsilateral Parotid Mean	35.40 ± 10.40	33.43 ± 7.05	33.60 ± 8.52	0.52	0.23	1.00
Ipsilateral Parotid Median	31.29 ± 15.97	26.71 ± 11.04	27.49 ± 11.83	0.25	0.21	0.85
Contralateral Parotid Mean	3.34 ± 1.41	6.15 ± 2.60	5.45 ± 1.99	**<0.01**	**<0.01**	0.16
Contralateral Parotid Median	2.98 ± 0.97	4.53 ± 1.86	4.12 ± 1.44	**<0.01**	**<0.01**	0.27
Larynx Mean	18.31 ± 6.77	17.21 ± 5.70	17.32 ± 9.88	0.23	0.08	0.23
Larynx Median	14.27 ± 5.54	13.57 ± 4.91	13.81 ± 10.01	0.50	0.10	0.26
Oral Cavity Mean	26.81 ± 8.28	22.87 ± 8.23	24.89 ± 9.44	**0.03**	**0.03**	0.06
Oral Cavity Median	22.82 ± 7.61	17.27 ± 7.57	19.69 ± 8.27	**0.02**	**0.01**	0.06
Brainstem Maximum	16.95 ± 11.77	15.73 ± 11.60	15.51 ± 11.93	0.33	0.33	0.98
Cord+5mm Maximum	31.48 ± 7.46	28.55 ± 6.06	28.93 ± 6.03	0.06	0.14	0.65

Table 4: Absolute dose averages and p-values for 23 bilateral cases

Bilateral Cases	Absolute Dose (Gy)			P-values		
OAR Metric	**Original**	**Version 1**	**MC-KBRT**	**V1 - Orig**	**MC - Orig**	**MC – V1**
Ipsilateral Parotid Mean	34.55 ± 12.43	32.32 ± 7.11	29.86 ± 8.36	0.09	**0.01**	0.21
Ipsilateral Parotid Median	32.60 ± 15.49	24.40 ± 8.63	21.71 ± 9.53	**<0.01**	**<0.01**	0.26
Contralateral Parotid Mean	20.56 ± 4.60	23.81 ± 6.43	24.81 ± 6.62	**0.01**	**<0.01**	0.16
Contralateral Parotid Median	14.34 ± 3.38	16.70 ± 6.21	18.36 ± 7.32	0.14	**<0.01**	0.09
Larynx Mean	28.29 ± 10.45	28.93 ± 9.55	26.11 ± 8.16	0.72	**0.03**	0.18
Larynx Median	25.81 ± 11.37	25.04 ± 9.75	22.85 ± 8.85	0.31	**<0.01**	0.48
Oral Cavity Mean	34.72 ± 10.51	34.10 ± 8.88	31.15 ± 10.29	**0.04**	**<0.01**	0.14
Oral Cavity Median	30.76 ± 12.31	28.23 ± 10.16	25.53 ± 10.29	**0.03**	**<0.01**	0.50
Brainstem Maximum	18.84 ± 10.21	17.89 ± 8.09	16.18 ± 6.86	0.41	0.06	0.07
Cord+5mm Maximum	35.28 ± 5.49	33.27 ± 5.71	33.00 ± 5.07	0.10	0.11	0.95

3.2 Case-wise Analysis

When analyzing HNC cases, it is helpful to evaluate all of the cases and investigate how many OARs perform better or worse than the original and Version 1 plans. Tables 5 and 6 compare the OARs for the 17 unilateral and 23 bilateral cases respectively, grouped according to the number of OARs (out of 6) for which the plans were either better (lower dose than the original plan by more than 5%) or comparable (the percent difference from the original plan is within +/- 5%). Table 5 shows the MC-KBRT plan was comparable or better to the original plan in 11/17 cases for ≥ 4OARs and in 15/17 cases for at least half of the OARs in the unilateral cases. For bilateral cases in Table 6, 14/23 cases for ≥ 4 OARs and 20/23 cases for more than half of the OARs in MC-KBRT were better or comparable to the original. When compared to Version 1, 9/17 unilateral cases and 13/23 bilateral cases were better or comparable for ≥ 4OARs with 12/17 unilateral cases and 20/23 bilateral cases being better or comparable for more than half of the OARs.

Table 5: Number of unilateral cases (% of cases) for which OARs were better spared in the MC-KBRT plan compared to both the original plan and Version 1

Number of OARs that were better or comparable (out of 6 OARs)	Original - Version 1	Original - MC-KBRT	Version 1 - MC-KBRT
6 OARs	0 (0%)	0 (0%)	0 (0%)
≥ 5 OARs	0 (0%)	3 (18%)	2 (12%)
≥ 4 OARs	9 (53%)	11 (65%)	9 (53%)
≥ 3 OARs	14 (82%)	15 (88%)	12 (71%)
< 3 OARs	3 (18%)	2 (12%)	5 (29%)

Table 6: Number of bilateral cases (% of cases) for which OARs were better spared in the MC-KBRT plan compared to both the original plan and Version 1

Number of OARs that were better or comparable (out of 6 OARs)	Original - Version 1	Original - MC-KBRT	Version 1 - MC-KBRT
6 OARs	3 (13%)	1 (6%)	1 (6%)
≥ 5 OARs	6 (26%)	5 (22%)	7 (30%)
≥ 4 OARs	13 (57%)	14 (61%)	13 (57%)
≥ 3 OARs	20 (87%)	20 (87%)	20 (87%)
< 3 OARs	3 (13%)	3 (13%)	3 (13%)

In addition to analyzing the total number of OARs that have better dose sparing in each method, we compiled the number of specific OARs and PTVs. With the exception of the contralateral parotid gland, all of the OARs had better dose sparing in at least half of the cases (>7 unilateral and >11 bilateral) when the MC-KBRT plan was compared to the original plan as seen in Tables 7 and 8. Dose sparing in more than half of the OARs were achieved when MC-KBRT was compared to Version 1 for both unilateral and bilateral cases with the exception from the unilateral oral cavity. The multi-case KBRT method can achieve better OAR dose reduction in more than half of the cases when compared to Version 1.

Tables 7 and 8 also show an analysis of the PTVs of both the primary and boost cases. When the MC-KBRT was compared to the original plan (Orig), worse primary PTV coverage was seen (Only 7/17 unilateral and 3/23 bilateral PTVs were better) although the boost PTV coverage was better in more than half of the cases. When unilateral cases of MC-KBRT (MC) were compared to Version 1 (V1) in column 4 of Tables 7, more than half of the unilateral primary PTVs and 12/15 boost PTVs were

better. MC-KBRT was able to achieve better PTV coverage than Version 1 in unilateral cases; however the dosimetric difference is small. Doses to the contralateral parotid gland (median and mean) and brainstem (maximum) were reduced compared to Version 1 but were not significant. In the bilateral cases in Table 8, primary PTV coverage was evenly split between MC-KBRT and Version 1. Boost PTV coverage was slightly better in MC-KBRT than Version 1, showing 16/23 cases with improved PTVs.

Table 7: OAR/PTV – specific comparison for 17 unilateral cases between Version 1, MC-KBRT, and the original plan (Values represent the number of cases in the 2nd method that have lower doses than the 1st method)

Structure	Orig – V1	Orig - MC	V1 – MC
Ipsilateral Parotid Gland (out of 15)	9 (60%)	10 (67%)	9 (60%)
Contralateral Parotid Gland	2 (12%)	3 (18%)	10 (59%)
Larynx (out of 16)	9 (56%)	12 (75%)	14 (88%)
Oral Cavity	13 (76%)	14 (82%)	6 (35%)
Spinal Cord	13 (76%)	13 (76%)	10 (59%)
Brainstem	10 (59%)	11 (65%)	9 (53%)
Primary PTV	5 (29%)	7 (41%)	12 (71%)
Boost PTV (out of 15)	13 (87%)	12 (80%)	12 (80%)

Table 8: OAR/PTV – specific comparison for 23 bilateral cases between Version 1, MC-KBRT, and the original plan (Values represent the number of cases in the 2nd method that have lower doses than the 1st method)

Structure	Orig - V1	Orig - MC	V1 – MC
Ipsilateral Parotid Gland	19 (83%)	16 (70%)	14 (61%)
Contralateral Parotid Gland	7 (30%)	4 (17%)	11 (48%)
Larynx (out of 21)	13 (62%)	20 (95%)	14 (67%)
Oral Cavity	16 (70%)	19 (83%)	14 (61%)
Spinal Cord	17 (74%)	16 (80%)	15 (65%)
Brainstem (out of 22)	12 (55%)	14 (64%)	18 (82%)
Primary PTV	2 (9%)	3 (13%)	13 (57%)
Boost PTV	14 (61%)	17 (74%)	16 (80%)

Figure 10 shows the DVHs of an ipsilateral left bilateral case (Case 4). When MC-KBRT is compared to both the original and Version 1, 5 OARs are comparable. Only the contralateral parotid is failing in both cases. When the PTVs are compared, MC-KBRT's primary PTV performs worse than the original and Version 1, but the HI is still below 15. The boost PTV was better in MC-KBRT compared to both methods.

Bilateral Case 4

Original Plan (__) vs. MC-KBRT (….) Version 1 (__) vs. MC-KBRT (….)

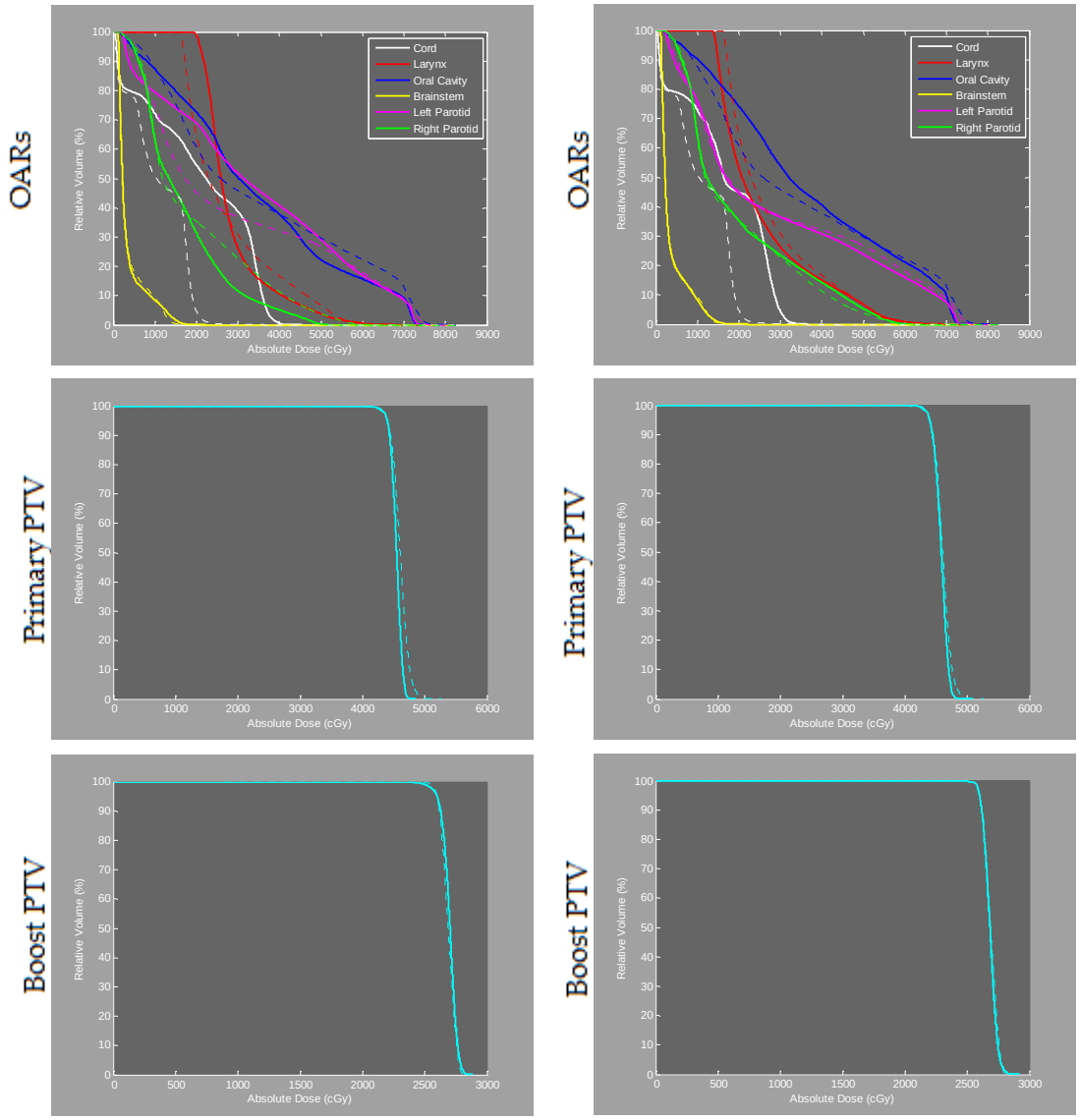

Figure 10: DVH of case 4 for OAR (first row), Primary PTV (middle row), and Boost PTV (bottom row) for MC-KBRT compared to both the Original plan (left column) and Version 1 (right column).

Figure 11 shows the DVHs for an ipsilateral right unilateral case (Case 89). When MC-KBRT is compared to the Original, 4 OARs are comparable. Only the contralateral left parotid gland and brainstem are worse than the original plan. Similar PTV coverage is achieved. When MC-KBRT is compared to Version 1, 5 OARs are worse. Only the ipsilateral parotid is better in MC-KBRT. As is visible in the primary PTV, having good PTV coverage can make OARs harder to spare. This is a case in which MC-KBRT was better than the original, but Version 1 outperformed MC-KBRT.

Unilateral Case 89

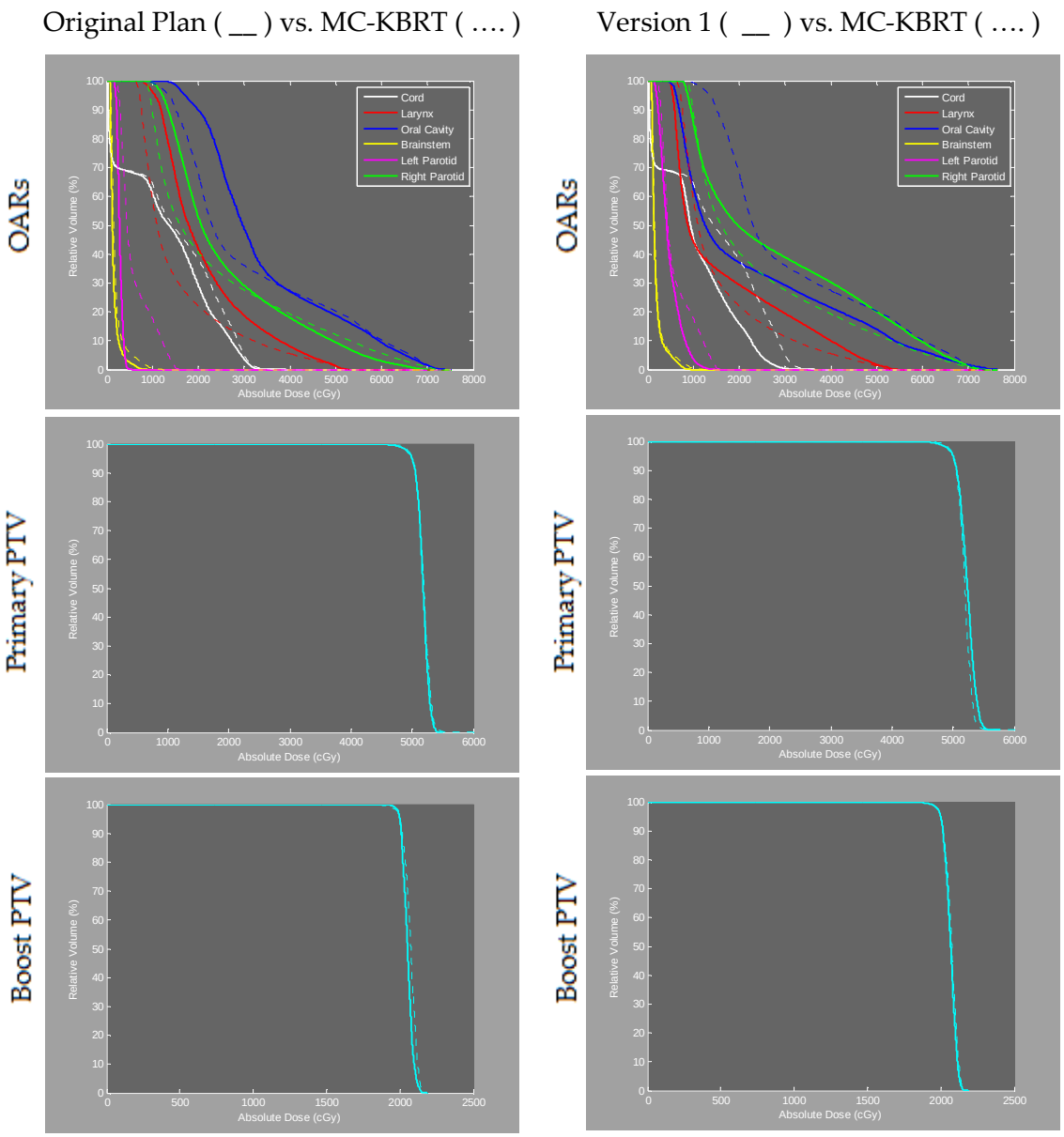

Figure 11: DVH of case 89 for OAR (first row), Primary PTV (middle row), and Boost PTV (bottom row) for MC-KBRT compared to both the Original plan (left column) and Version 1 (right column).

Figure 12 shows case 58 which is an ipsilateral left bilateral case (Case 58). When MC-KBRT is compared to the original plan, of the 6 OARs only the spinal cord and the contralateral parotid were better. From the DVHs, it is apparent that the dose differences are small but MC-KBRT did not spare the OARs as much. Comparing MC-KBRT to Version 1, all OARs except the ipsilateral parotid were better. This is a case in which both MC-KBRT and Version 1 did not outperform the Original case, but MC-KBRT was able to show superior quality to Version 1.

Bilateral Case 58

Original Plan (__) vs. MC-KBRT (….) Version 1 (__) vs. MC-KBRT (….)

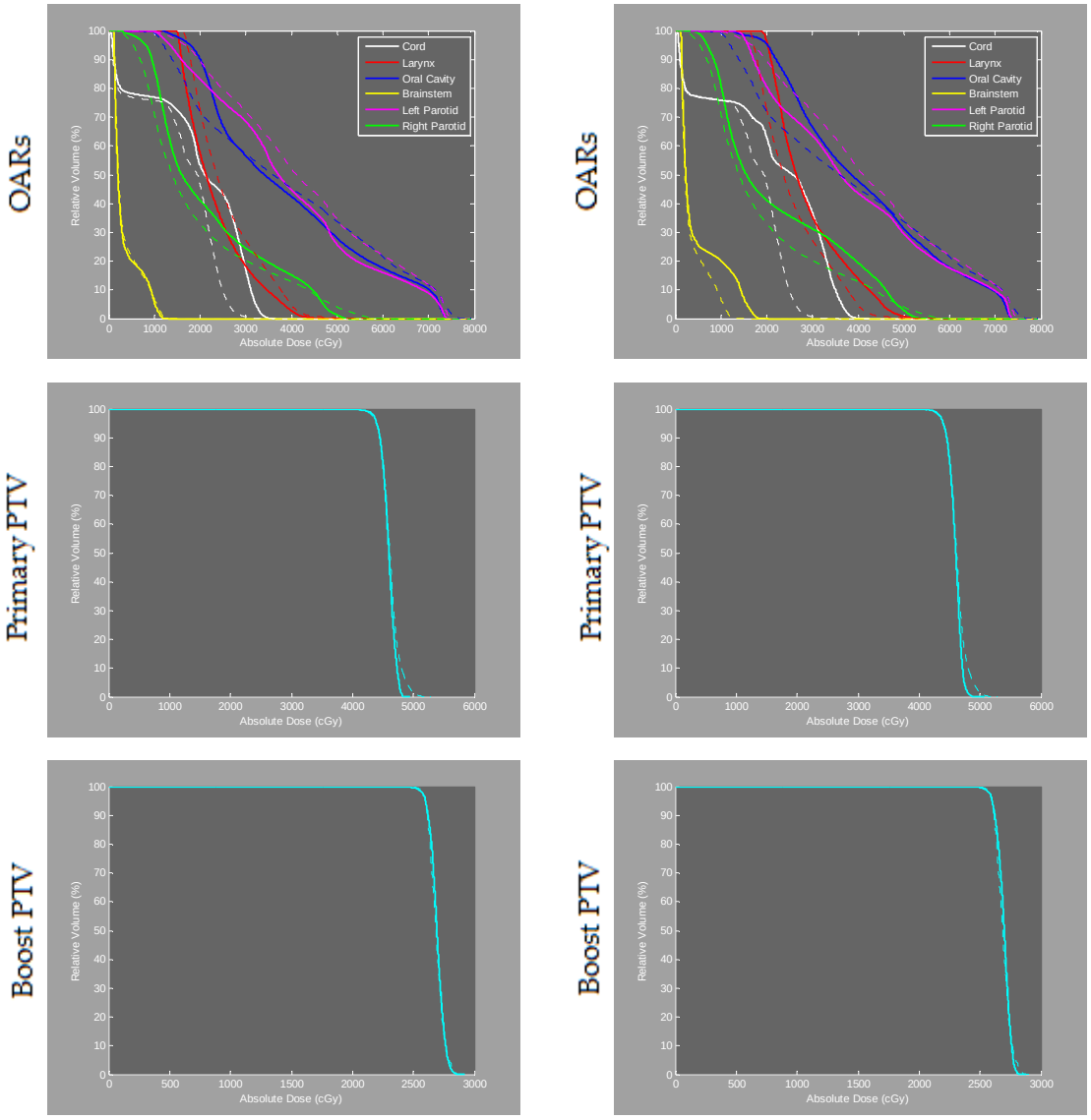

Figure 12: DVH of case 58 for OAR (top row), Primary PTV (middle row), and Boost PTV (bottom row) for MC-KBRT compared to both the original plan (left column) and Version 1 (right column).

4. Conclusion and Future Work

4.1 Discussion

Knowledge-based IMRT treatment planning is intended to generate consistent quality plans more quickly than manual planning while simultaneously removing the number of decisions to be made by the planner. Other knowledge-based studies simply use the treatment parameters from the match case[15, 17, 18, 19]. This study uses dose warping to generate the constraints. Current single-match knowledge-based treatment planning methods semi-automatically allow the user to create comparable plans. The purpose of multi-case KBRT is to improve upon already existing KBRT methods. By finding top geometric "matches" for individual OARs, better organ sparing should be achievable without deteriorating the target coverage. The results of this study show that the MC-KBRT method generates quality HNC plans that are dosimetrically similar to both Version 1 and the original plans.

In unilateral cases, MC- KBRT had reduced dose compared to the original for all OARs with the exception of the contralateral parotid gland. Only the oral cavity was significantly spared in the MC-KBRT version. It is more difficult to improve upon unilateral plans since the PTV is generally smaller and OARs are farther from the target.

In bilateral cases, MC-KBRT showed greater OAR dose reduction than in the unilateral cases. Due to the intricate geometry of bilateral cases, the plans are harder to create in an automated fashion. The dose warping sets constraints that can spare the

OARs much more significantly. When MC-KBRT was compared to Version 1, non-significant dose reduction to all OARs except the contralateral parotid was achieved. Although there is some dosimetric improvement made by MC-KBRT compared to Version 1, the dose difference is small it is not clinically significant. Analyzing more cases may make the dose difference significant for bilateral OARs but it still will not be clinically significant.

In both the unilateral and bilateral cases, MC-KBRT did not outperform Version 1 significantly. This suggests there may be better ways to merge together disparate data from multiple cases in order to fully realize the potential of the improved overlap of PTV with individual OARs. This is likely because the dose-warping strategy diminishes the disadvantages of picking from a single case, i.e., there is no significant advantage to selecting from multiple cases. The dose warping appears to adequately adjust the dose to individual OARs, so choosing multiple match cases is not as important. If MC-KBRT were compared to earlier attempts of Version 1 in which the treatment parameters were taken directly from a single match case, it is likely that the current method of multiple match cases would have performed better.

Manually planning a HNC IMRT case generally takes between 2-6 hours. The single match KBRT method (Version 1) reduces this time to about 35 minutes per plan (primary or boost). The new MC-KBRT method takes about 45 minutes per plan (primary or boost). Since both Version 1 and MC-KBRT generate comparable plans

(both equally improved when compared to the original), it would seem there is no significant improvement in MC-KBRT since it is more time-consuming.

4.2 Future Work

This multi-case KBRT method utilizes 6 "match" OAR cases to generate a new query plan. In order to have quality plans, an optimized database is required. Current work is being performed to manually optimize the cases already in the knowledge database. Some suboptimal plans in HNC cases are unavoidable in the clinic due to the complexity and close proximity of the OARs to the target. With better match dose distributions, tighter query constraints can be calculated, producing better plans.

In addition to optimizing the already existing database, increasing the size of the database to more than 103 patients would be helpful. Since HNC target geometry is quite variable, having more potential match cases would allow for a better geometric match for each OAR.

MC-KBRT IMRT treatment planning does not weight the constraints and priorities generated for individual OARs. Since certain OARs such as the brainstem and contralateral parotid glands are more sensitive, investigation into weighting these warped constraints/priorities is in progress. More uniform OAR sparing with better target coverage may be achievable.

4.3 Conclusions

The results of 17 unilateral HNC plans show general dose reduction in most of the OARs while maintaining PTV coverage when compared to clinical manually planned cases. The 23 bilateral HNC plans show significant improvement in all OARs but the contralateral parotid gland. It is easier to improve the bilateral cases because the dose warping method imposes lower constraints to push down the OAR doses.

When compared to single match KBRT (Version 1), there is no significant improvement. Since the results are very similar but not significantly improved, the original KBRT method seems to be more efficient in both time saving and dose sparing.

Appendix

Unilateral Patient Information

# of cases	Type of Cancer	Primary Dose (Gy)	Boost Dose (Gy)
1	Left Parotid gland cancer	54	6
1	Right Parotid Gland cancer	64	0
1	Oral tongue cancer	50	20
1	Recurring ethmoidal sinus cancer	60	6
1	Bone and bone marrow cancer	44	16
1	Lymph node cancer	50	10
5	Left Tonsil cancer	50	20
		50	10
		50	10
		44	26
		44	16
6	Right Tonsil cancer	60	0
		46	24
		44	26
		44	26
		44	26
		44	26

Bilateral Patient Information

# of cases	Type of Cancer	Primary Dose (Gy)	Boost Dose (Gy)
1	Glottis cancer	50	20
1	Supraglottis cancer	44	26
1	Lip cancer (vermillion border)	44	16
1	Oropharyngeal cancer	44	26
1	Right tonsil cancer	44	26
1	Left tonsil cancer	46	24
2	Nasopharyngeal cancer	44	26
		44	26
6	Lymph node cancer	50	20
		44	26
		44	26
		44	26
		44	26
		44	26
9	Base of tongue cancer	50	20
		50	20
		44	26
		44	26
		44	26
		44	26
		44	26
		44	26
		44	22

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