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Knowledge Based Planning for Retrospective Quality Study of RTOG 0822 Radiotherapy Plans

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Abstract

Purpose: To create a clinically viable dose-volume histogram (DVH) estimation model using the Varian RapidPlan (Varian Medical Systems, Palo Alto USA) knowledge based planning (KBP) platform. This model aims to evaluate locally advanced rectal cancer with 6X IMRT, and was developed on a plan database taken from the RTOG 0822 national clinical trial. This is the first multi-institutional 6X IMRT dose estimation model designed using RapidPlan. The effectiveness of the model as a dosimetry quality assurance (QA) tool was evaluated.

Methods: Treatment plans submitted to the RTOG 0822 clinical trial were dosimetrically evaluated for plan quality. Plans whose DVH statistics met RTOG 0822 target criteria were identified as high-quality, and were used in the initial training sample for the model. Of the 97 IMRT plans enrolled in the trial, 58 were treated with only 6X photons, and 26 of those were identified as high-quality plans. All 6X enrolled plans were iteratively re-optimized with the model to test clinical effectiveness, evaluate the model as a tool for treatment planning QA, and continuously expand the model's training sample. Re-optimized plans which met target criteria were added to the training sample, resulting in a total of 40 geometries in the training sample.

Results: The rectal IMRT RapidPlan model created in this paper was shown to accurately predict estimated DVH bands for all viable high-quality plans enrolled in the clinical trial. The model was also able improve the DVH statistics for a significant majority of the low-quality plans enrolled in the clinical trial.

Conclusion: The RapidPlan rectal 6X IMRT model created in this study can be used as an effective tool for dosimetry QA and initial plan creation.

Keywords

medical physics, rapidplan, rtog, radiation oncology

Disciplines

Medicine and Health Sciences

License

Knowledge based planning for retrospective quality study of RTOG 0822 radiotherapy plans

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1 Introduction

Colorectal cancer is the third most commonly diagnosed cancer among the worldwide populace, ranking in as the second most common cancer for women and the third most common cancer for men. While the current mortality rate for colorectal cancer is relatively low at 8.5%, studies suggest a rise in rectal cancer mortality due to increasing rates of late-stage discovery of the disease [1,2]. Because rectal cancers are often discovered at these later stages where more extra-rectal tissue is encompassed in the PTV, reducing toxicity to surrounding organs is a primary objective of any rectal radiotherapy plan [3]. Due to these overlapping volumes, IMRT is highly preferred over traditional 3D conformal therapy (3DCRT), and has been shown to provide significant clinical advantages with reduced organ at risk (OAR) dose [4].

While the malleable dose distributions possible with IMRT planning has allowed for more personalized treatment plans as compared to 3DCRT, it has also resulted in greater user-dependency and quality variance across clinics [5,6]. In addition to beam angle and isocenter location, dosimetrists must also account for placement and prioritization of optimization goals, a task which relies heavily on the user's level of experience. More practiced planners can know what DVH they can reasonably achieve from a given patient geometry, whereas others may not reach the most desirable solution within the clinical timeframe. This uncertainty in treatment planning, paired with the lack of QA checks on plan optimality, results in an unnecessary increase of patient risk and normal tissue complications [7]. Thus, there is a need for technologies that can not only reduce plan quality variability, but can also be easily implemented in smaller clinics with potentially less experienced staff.

Varian's solution to this problem is RapidPlan (Varian Medical Systems, Palo Alto, USA), a knowledge based planning (KBP) software that is easily integrated with the Aria record and verify system (RVS) and the Eclipse treatment planning system (TPS). KBP programs are designed to learn what dose distributions are achievable by studying a submitted set of high-quality treatment plans in order to predict an optimized DVH for any given patient with a similar tumor. When a treatment plan is submitted to the KBP as learning material, the KBP correlates the treated gantry angles and patient geometry (input) with the DVH statistics to the segmented organs (output). Principal Component Analysis (PCA) is used to characterize the most salient features of the patient anatomy, and these features are correlated with segmented organ DVH via Support Vector Regression (SVR) [8].

Once these correlations are calculated, the KBP model has effectively learned from its library, and can produce DVH estimations with consistently good optimality [9]. Despite these benefits and ease of use, KBP's such as RapidPlan inextricably need a large library of high-quality plans to produce well-trained models. While this can be a challenge for new or smaller clinics with a limited patient backlog, this need produces renewed opportunities to utilize the data submitted to massive clinical trials, such as the RTOG. Data suggests that compliance with RTOG criteria is associated with increased survival rates, so it is suggested that the library for a given RapidPlan model is created from plans that meet these criteria [10].

RTOG 0822 is a phase II clinical trial that studied the decrease in gastrointestinal toxicity when IMRT is used for preoperative chemoradiotherapy as compared to traditional 3DCRT, as studied in RTOG 0247 [11]. Clinical plans enrolled in this trial treated 45 Gy IMRT to the rectum and draining lymphatics at risk followed by a 5.4 Gy 3DCRT boost at 1.8 Gy daily fractions. The study closed December 2016 with 79 patients accrued with a total 97 therapy plans [12]. It should be noted that only the 6X IMRT plans submitted to this study were used in RapidPlan model created in this paper.

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This paper discusses a rectal 6X IMRT model trained on a library of high-quality plans from RTOG 0822. The model was tested for planning QA and DVH improvement using plans enrolled in the clinical trial.

2 Theory

2.1 Knowledge Based Planning

While the software behind it is moderately complex, KBP is designed to behave very much like a human treatment planner. A collection of plans is submitted to the KBP as learning material, with DVH's the user has defined as optimal and should be replicated. From these high-quality plans, the KBP correlates geometric features with attainable dose distributions, and can predict an optimal dose distribution for a new patient geometry. In this way, the KBP acts as an automatic, easily understood second check on inverse planning optimization, allowing the user to see another optimization route or possibilities for further plan quality improvement. Similarly, KBP can be used as a first step in creating a clinically viable plan or evaluating the differences between gantry angle combinations with little effort needed. Indeed, KBP can be used to great effect in clinics that want or need that extra bit of manpower when it comes to creating or verifying treatment plans.

This study specifically uses the Varian RapidPlan KBP program, available in Eclipse version 13.6.5. RapidPlan utilizes PCA to identify the most important geometric features for quick DVH correlation and estimation.

2.2 Principal Component Analysis

Correlating a patient-gantry geometry with a three-dimensional dose distribution poses a multitude of challenges. These geometries tend to be highly complex, unique to the given patient, and maintain a high voxel resolution, resulting in a large, high-dimensional dataset that cannot be effectively compressed without losing significant data. However, this geometry can be characterized by extracting the most salient features using PCA. This effectively reduces the dimensions of the data, allowing for substantially fewer calculations and correlations to relate patient geometries with dose distributions.

Varian's RapidPlan KBP software creates a dose-to-target histogram (DTH) for each OAR to use alongside PTV and OAR DVH's during PCA calculation. A DTH shows the fractional overlap between an OAR and a virtual volume symmetrically extended out from the PTV by a given distance. A negative distance value indicates OAR/PTV overlap, and this overlap approaches 100% at an increased PTV expansion distance, as seen in Figure 1.
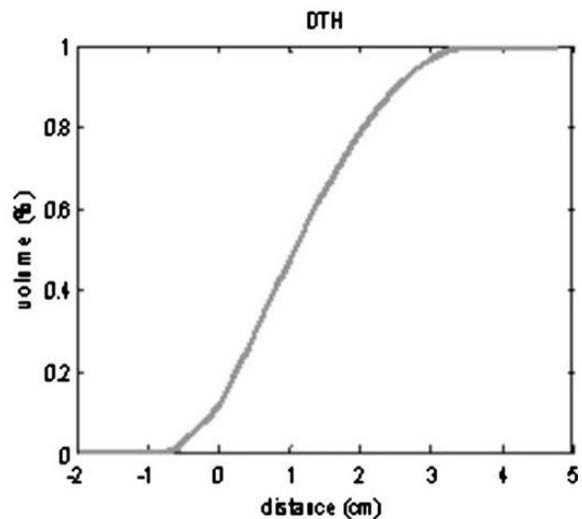
Figure 1: Sample DTH graphic from Zhu et al [8]

For each OAR and the m number of plans within the learning library, the DVH and DTH is sampled m times to creates a m-dimensional component vector known as a feature point. In many studies that aim to develop KBP's, such as Zhu et al [8], an $m = 50$ is used. A component vector for each plan populates an n dimensional feature space specific for each OAR. The coordinate system of the feature space is shifted such that the coordinate origin represents the

average feature value, and points within the space represent deviation from the mean. These feature points are also normalized such that the standard deviation of point distance about the mean equals 1. A m x m covariance matrix of these n points in this new coordinate system is then created, and singular value decomposition is performed to yield m eigenvectors and eigenvalues. These eigenvectors form a PC coordinate system that identifies the principal components (PC's), where the corresponding eigenvalues represent the amount of variation in a given component. Thus, the principal components can be chosen for use in model training based on their variation, where components with larger variations in DVH and DTH yield more significant geometric data. This sophisticated feature selection among the m dimensional data allows for simplified data representation with significant reduction of calculation overhead [13].

Upon identification of the principal components representing the dosimetry and geometric data, SVR is used to map the correlations and allow for DVH estimation. A patient DVH can be predicted by extracting the principal components from an input geometry and applying the inverse rotation and translation to this space to revert back to the original feature space which constructed the correlation map [8].

2.3 RapidPlan

Varian RapidPlan offers a user-friendly KBP platform that consistently estimates high-quality treatment plans. Models created in RapidPlan are modality and site specific, performing best if they have a large library of plans with similar OAR sets. Salient geometric features are extracted for each plan in the library using PCA and correlation with dosimetric features via SVR.

When RapidPlan uses these correlations to predict the dose distributions for a new plan, estimated DVH (EDVH) bands are created for

the segmented and assigned OAR's. The center of the band represents the median EDVH, and the band stretches out one deviation away from this median. For OAR's, a two-dimensional line exists within the bottom half of this band as a continuous optimization line objective. As seen in Figure 2, this provides a useful visual marker for users to understand what OAR sparing they can expect from a given plan before any IMRT optimization takes place.
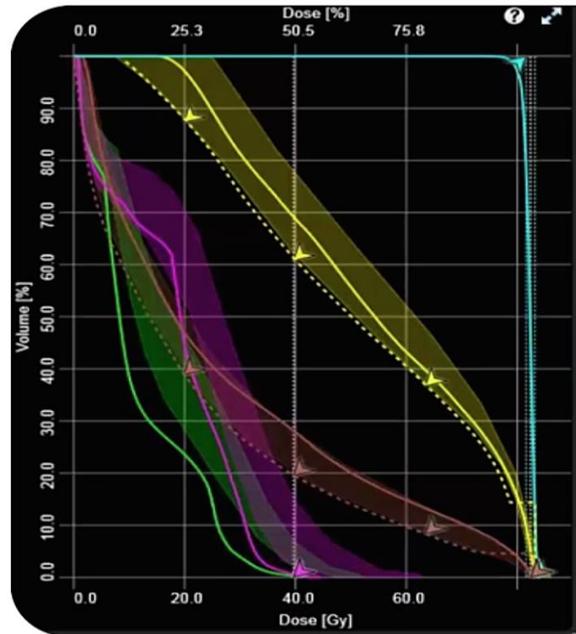
Figure 2: DVH, EDVH, and optimization line for rectal IMRT optimized within RapidPlan during IMRT optimization. The organs shown in this figure are the PTV (**blue**), bladder (**yellow**), small bowel (**brown**), left femoral head (**purple**), and right femoral head (**green**).

Along with showing what the user can expect out of a given plan, visualizing the EDVH's can also alert the user to the limitations of a plan created in RapidPlan. Since the EDVH designates what is expected based on correlations formed from the learning library, the plans and geometries submitted to the library have a lasting effect on the model's effectiveness. If a model's library largely consists of plans with little PTV/OAR overlap, then the model will not explicitly know how to account for geometries with significant PTV/OAR overlap, and will produce an

undesired EDVH. During dose estimation, this is often visualized for the user via warning messages, very thin EDVH bands, or jagged optimization objective lines. Thus, it is important to include a variety of patient geometries within the training library to ensure a wide coverage of patient anatomy and avoid model overtraining for specific geometries.

RapidPlan has a variety of built-in tools to assist users in understanding the statistics and possible limitations of a given model. Within the RapidPlan module built into Aria, users can view a summary of training results with goodness of correlation results and outlier statistics, as well as organ-specific plots of DVH's, geometric statistics, DVH-geometric correlation regressions, and EDVH-DVH residual plots (where linearity indicates good dosimetric estimation and successful model training).

Using these tools, users can readily determine issues with the model as a whole, as well as with a particular submitted plan. If a user finds that the EDVH consistently underperforms for a given DVH region, they can put in a manual point optimization objective, similar to standard IMRT planning. This will be used in the model alongside the EDVH. The user can either manually set the priority of the point objective or allow the model to estimate its priority for a given patient geometry.
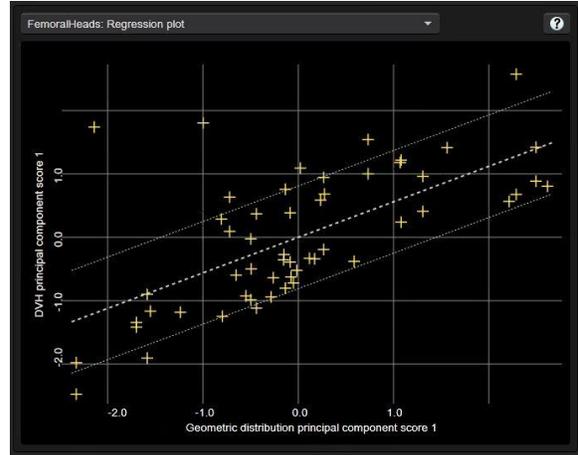
Figure 3: Femoral heads regression plot for RapidPlan model created in this paper

3 Method

3.1 Dosimetric Analysis of RTOG 0822 Plan Library

6X IMRT plans submitted to the RTOG 0822 clinical trial were evaluated for plan quality before being used to create the initial iteration of the model described in this paper. Plan quality was determined by DVH adherence to the target criteria specified in the RTOG protocol. The radiation treatment criteria of a national trial, such as the RTOG, consists of dosimetric target parameters for both the target and relevant OAR's. The RTOG 0822 target criteria specified that the IMRT dose must meet a minimum PTV dose alongside maximum dose constraints for the bladder, femoral heads, small bowel, and PTV. Along with target criteria, acceptable variation criteria is described to allow for slight deviation in parameter compliance and plan quality. These criteria sets are tabulated in Table 1.

Table 1: IMRT DVH target and acceptable variation parameters for the RTOG 0822 clinical trial

Minimum Dose Thresholds			
Structure	Criteria Volume (%)	Target Dose (Gy)	Acceptable Dose (Gy)
PTV	98	41.85	40.5
Maximum Dose Thresholds			
Structure	Criteria Dose (Gy)	Target Volume	Acceptable Volume
PTV	47.25	10%	15%
	49.50	5%	10%
	51.75	0%	N/A
Bladder	40	40%	55%
	45	15%	30%
	50	0%	0%
Femoral Heads	40	45%	65%
	45	25%	40%
	50	0%	0%
Small Bowel	35	180 cc	230 cc
	40	100 cc	130 cc
	45	65 cc	90 cc

Plans enrolled in the clinical trial were anonymously stored on the American College of Radiology (ACR) database and accessed through remote access to the Philadelphia server. From this server, plan DVH's were manually analyzed within the MIM (MIMsoftware Inc, Cleveland, OH 44122) workspace and compared against the RTOG 0822 criteria. These plans were then imported from MIM into ACR's Eclipse platform and planned using the Eclipse CAP – 6X Linac with Dose Dynamic MLC. Dose estimation and IMRT optimization was performed using the AAA_13714 and PO_13714 models, respectively. The planning and dose optimization performed in this study was used with these settings and beam characteristics. Plans which met the RTOG 0822 target criteria were labelled as high-quality and used for initial training of the model described in this paper, since they are more likely to be associated with a positive patient outcome [10].

3.2 RapidPlan Model Construction and Optimization

Of the 97 IMRT plans were enrolled in the RTOG 0822 clinical trial, 39 of them were either not treated with 6X photons or could not be imported into Aria, and thus were not included in the 6X IMRT rectal model created in this paper. Of the remaining 58 treatment plans, 26 met all of the target criteria, and were thus considered high-quality plans. Each of these plans met the protocol's prescribed 45 Gy to the rectal target without the need of scaling or normalization. These 26 plans were used to create the initial iteration of the rectal model described in this paper. While this count met the 20 required plans to create a RapidPlan model and provide a good amount of geometry variance, an effort was made to increase the number of plans in the model's training library while still adhering to the target compliance metric.

Upon every new trained iteration of the model, all of the 6X IMRT plans enrolled in

the clinical trial were reoptimized by the newly trained model. This included both the low-quality plans which did not meet the target criteria as well as the high-quality plans used to initially train the model. Since most of the low-quality plans met the acceptable variation criteria, an additional 12 geometries were able to be re-optimized to reach high-quality, greatly increasing the distribution of geometries in the training library. If a high-quality plan was improved via this cyclical re-optimization, the model-created plan was submitted to the model's training library alongside the initial enrolled IMRT plan. If a subsequent re-optimization resulted in a higher plan quality than the previous re-optimization plan for a given geometry, the lower-quality plan would be replaced in the training pool.

If both the newly iterated and previous DVH's met RTOG target criteria, the significant differences in plan quality between them was evaluated by a net summation of normalized dosimetric differences, as described by Equation 1. Dose differences were calculated at each criteria volume mark and converted to a ratio by diving by the average dose between the two plans and the given volume mark's target dose, as listed in Table 1. As seen, the closer a dose point change is to the target criteria, the more weighted the ratio. These normalized ratios are summed together, to give a simplified evaluation of if plan quality increased in reference to the RTOG criteria, with a positive summation suggesting plan quality increase, and a negative summation suggesting plan quality decrease. PTV dose homogeneity, dose conformity, isodose curves, and normal tissue dose were also qualitatively evaluated to ensure plan quality. If there was no significant plan quality increase, the previous plan was not replaced.

Equation 1: Quantitative difference in plan quality weighted by RTOG criteria proximity

$$Q_{Diff} = \sum_{i=1}^{N_{Org}} \left(\sum_{j=1}^{N_{crit_i}} Z_{ij} \right) + Z_{PTV_{Upper}}$$

$$Z_{ij} = \frac{D_{Prev_{ij}} - D_{New_{ij}}}{\left| \frac{D_{Prev_{ij}} + D_{New_{ij}}}{2} - D_{criteria_{ij}} \right|}$$

$$Z_{PTV_{Upper}} = \frac{D98_{New} - D98_{Prev}}{\left| \frac{D98_{Prev} + D98_{New}}{2} \right| - 45\ Gy}$$

This process was cyclically repeated for every new instance of the model until an equilibrium of re-optimized plan quality was reached.

3.3 Model Inputs

Along with training from the clinical plans submitted to the RTOG clinical trial, the model was also trained and optimized using a set of manual dosimetric optimization goals. This was to focus optimization and plan quality improvements on the RTOG target criteria, increasing the number of geometries used in model training. For OAR dose sparing constraints, optimization goals were set at the target criteria volumes at 5 Gy below the target criteria dose to tend the resulting dose below the target thresholds. Priority for these manual OAR constraints was determined by the model alongside the continuous optimization objective. It should be noted that these OAR point objectives did not impact the result IMRT DVH nearly as significantly as the continuous optimization objectives produced by RapidPlan.

While RapidPlan can also create continuous optimization objectives for the PTV, this was found to produce variable to non-desirable results. To mitigate PTV dose coverage variation, manual optimization objectives with set priorities were

implemented for the PTV. These objectives ensured that plans both met RTOG target criteria and resulted in conformality index values approximately equal to 1. Normal tissue sparing was also manually set to produce consistently good dose falloff from the PTV and eliminate dose hotspots outside of the PTV.

3.4 Model QA Validation

Dosimetric analysis was performed to quantify the effects of re-optimization on plan quality, and thus patient outcome. Plan quality was determined using Equation 1 with the RTOG 0822 target criteria described in Table 1. This was performed for and summed over every OAR and PTV target criteria for a given patient, with a positive value indicating an increase in plan quality and a negative value indicating a decrease. Dose homogeneity, isodose curve geometry, and normal tissue sparing were qualitatively judged alongside this quantitative metric if a plan iteration was of approximately equal quantitative quality as its previous iteration.

4 Results and Discussion

The results of the dosimetric analysis of both the plans enrolled into RTOG 0822 and the plans reoptimized by the model discussed in this paper are listed in Table 3. This shows the number of plans from each set that met the RTOG target criteria, the acceptable variation criteria, and neither criteria (resulting in a failure). As seen, the dose estimation model significantly increased the number of plans which met the target criteria, raising it from 26 of the enrolled plans to 39 of the reoptimized plans. However, it should be noted that model reoptimization also slightly increased the number of plans which failed both the

target and acceptable variation criteria, raising this number from 9 to 10. This suggests that the model was successful in increasing the plan quality of low-quality rectal IMRT plans.

4.1 Model Training

The model was able to be successfully trained and raised to an equilibrium of quality through iterative reoptimization using both enrolled and reoptimized high-quality plans. A total of 40 patient geometries were used in model training. The model was trained to estimate dose for the OAR's specified by RTOG 0822, as well as the individual femoral heads. This was to ensure that one of the femoral heads was not getting a significantly higher dose than the other, a piece of data otherwise lost when evaluated as a single structure. The results of this training are shown in Table 2.

As seen, the training successfully correlated the principle components of all the OAR's used in training. It should be noted that while the bladder was successfully trained, as seen in the very good χ^2 value, a significant PTV/bladder overlap variability among the patient geometries resulting in a lower R^2 value for principal component correlation. While this produced slight EDVH issues towards higher dose regions, as seen in Figure 2, negligible estimated dose errors were observed for the patient geometries evaluated in this study.

Table 2: Model Training Statistics

Organ	Trained	R^2	χ^2
Bladder	Yes	0.517	1.101
Small Bowel	Yes	0.835	1.132
Femoral Heads	Yes	0.701	1.090
Femoral Head [L]	Yes	0.688	1.074
Femoral Head [R]	Yes	0.676	1.069

Figure 4: Geometric plots of the bladders used in model training (upper) and the principal component estimation residual plot (lower)

4.2 Model Optimization and Validation

Results of model reoptimization are shown below in Table 3. As seen, there is a significant increase in the number of plans which met target criteria as compared to the original plans enrolled in RTOG 0822. It should be noted that one of the enrolled 6X IMRT plans could not be reoptimized in RapidPlan due to software issues. While this plan was not included in the statistics for the enrolled plan quality count, reoptimization plan count, and model validation evaluation.

For the reoptimized plans, the performance per organ is listed below in Table 4 and 5. As seen, the RapidPlan model consistently met the RTOG OAR and PTV criteria, raising many of the organs up to either target or acceptable variation criteria. This improvement occurred for all of the OAR's specified in RTOG 0822 except for the femoral heads, which were always within the RTOG target constraints for both the enrolled and reoptimized plans.
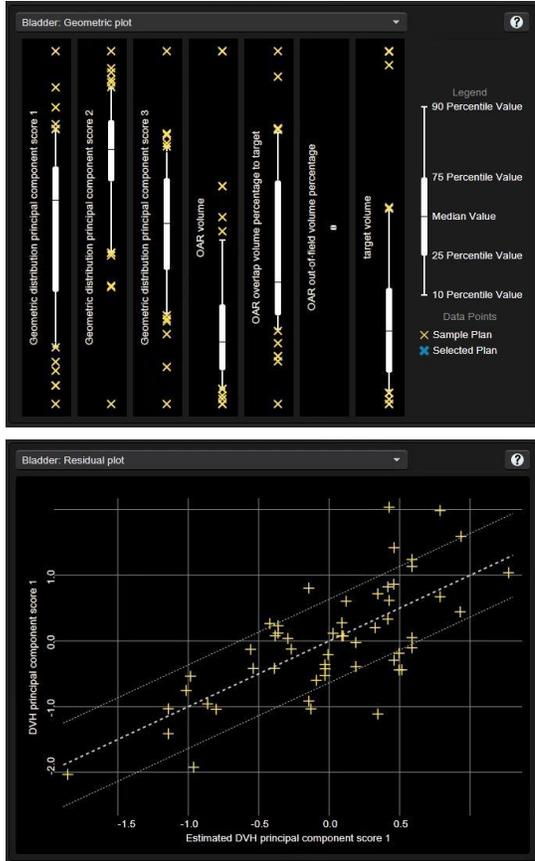
Table 3: Count of plans that met RTOG 0822 criteria

RTOG 0822 Criteria	Enrolled Plans	Reoptimized Plans	Quality Count Diff
Target	26 (44.8%)	39 (67.2%)	+13 (+22.4%)
Acceptable	23 (39.7%)	9 (15.5%)	-14 (-24.1%)
Failed	9 (15.5%)	10 (17.2%)	+1 (+1.7%)

Table 4: Number of reoptimized plans which met quality per organ

Criteria	PTV	Bladder	Femoral Heads	Small Bowel
Target	50 (86.2%)	49 (84.5%)	58 (100%)	53 (91.4%)
Acceptable	0 (0%)	6 (10.3%)	0 (0%)	5 (5.2%)
Fail	8 (14%)	3 (5.2%)	0 (0%)	0 (0%)

Table 5: Organs where model reoptimization caused plan quality changes

Organ	Raised to Target	Raised to Acceptable	Reduced to Acceptable	Reduced to Fail	Net Quality Increase
PTV	7	1	0	7	+1 (+1.7%)
Bladder	11	0	2	2	+7 (+12.1%)
Femoral Heads	0	0	0	0	0 (+0%)
Small Bowel	4	1	0	1	+2 (+3.4%)

For cases where the RTOG constraint on the PTV was broken, this failure was often due to over-exposure in the PTV at 15% and 10% volume in order to maintain a high dose at 98% volume while preserving surrounding organs. This is likely the result of placing manual constraints on the PTV and not allowing the model to directly change these optimization goal priorities. In cases such as these, it is up to the dosimetrist and physician to decide how much they are willing to underdose the PTV or further expose OAR's. In cases where plan quality was reduced due to OAR constraints (either to acceptable variation criteria or failure), this was often due to increased OAR dose to maintain homogenous dose over the PTV. While this is labeled a reduction in plan quality by the metric used in this paper, this risk tradeoff between the PTV and OAR's should be evaluated on a patient-by-patient basis during treatment planning. Below, Figure 5 shows an example of the model improving a low quality DVH to high quality.
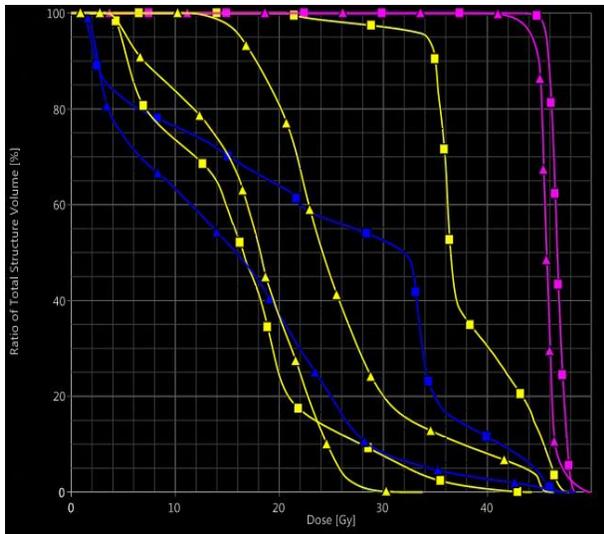

Figure 5: Comparison of original enrolled plan DVH (squares) against the reoptimized plan DVH (triangles). The organs shown in this figure are the PTV (**pink**), bladder (**yellow** [right pair]), small bowel (**blue**), and femoral heads (**yellow** [left pair]).

5 Conclusion

A KBP model was developed using Varian's RapidPlan software platform and designed for dose estimation of locally advanced rectal tumors treated with 6X IMRT. The model described in this paper was initially created using 26 high-quality 6X plans enrolled in the RTOG 0822 clinical trial. Additional plans among the enrolled RTOG plans were raised to high-quality through model-based iterative reoptimization and implementation into the model's training library until an equilibrium of model-produced plan quality was achieved. Through this iterative method, an additional 12 geometries were available for the model to use in EDVH training.

Applying model reoptimization to the plans enrolled in the RTOG exhibited a 22.4% increase in the number of plans that met target criteria. Specifically, the model exhibited significant dose sparing to the bladder and small bowel. However, the model was shown to exhibit overexposure in the PTV in cases of difficult OAR sparing, albeit for a minority of cases. While the ability to produce a high-quality plan can vary from patient to patient, the model introduced in this paper has been shown to consistently produce a plan of equal or greater quality than the RTOG-enrolled plan, and can be used as an effective tool for planning QA of rectal IMRT cases.

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