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Experience Based Quality Control in IMRT Treatment Planning of High Risk Post-Prostatectomy Prostate Cancer with RapidPlan

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Abstract

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Methods: An initial dosimetric analysis was carried out to identify high quality plans from clinical trial RTOG 0621. Treatment plans for patients enrolled in the trial were scored according to the system used by the Imaging and Radiation Oncology Core (IROC) of the National Clinical Trials Network (NCTN) of the NCI to assess adherence to the trial protocol. Of the 80 plans enrolled in the trial 39 were chosen for the training sample. Another subset of 8 plans, orthogonal to the training sample, was chosen for the validation sample to ensure that the model accurately predicts dose volume histograms (DVHs) for all critical structures. The validation plans were then re-optimized with the model in order to test its effectiveness as a tool for planning QA. DVHs of the re-optimized plans were compared with those of the original clinical plans. Normal tissue complication probabilities and tumor control probabilities were calculated with the Lyman-Kutcher-Burman (LKB) model before and after re-optimization to determine the effect on patient outcome.

Results: The RapidPlan prostate model was shown to accurately predict estimated DVH bands for all plans in the validation sample that matched the geometry of the training sample. Three treatment plans in the validation sample were geometric outliers with respect to the training sample leading to inaccuracies in the model predictions for the cone down phase of these treatment plans. All of the re-optimized plans showed increased dose sparring to the bladder and rectum respectively without lose of target coverage. The average reduction in NTCP was 0.34 ± 0.21 % for the bladder and 0.11 ± 0.25 % for the rectum with corresponding p-values of 0.116 and 0.668. The average TCP for the prostate bed decreased slightly from 97.05 % to 96.54 % with a p-value of 0.149. Due to limited statistics the changes reported in these numbers are not statistically significant as indicated by the p-values. Although the average values are inconclusive the model was effectively used to identify sub-optimal treatment plans which were improved through re-optimization with the model. For treatment plan 0621c0027 the NTCP decreased from 0.35 % to 0.06 % for the bladder and from 0.10 % to 0.06 % for the rectum while the TCP increased from 96.78 % to 96.87 %.

Conclusions: The RapidPlan prostate model developed in this study is an effective tool for monitoring the quality of IMRT treatment plans for high-risk post prostatectomy prostate cancer.

Keywords

RapidPlan, knowledge based planning, KBP, IMRT, prostate cancer, radiation therapy, RTOG 0621, 0621

Disciplines

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1 Introduction

Worldwide prostate cancer is the second most common cancer among men and the fifth most common overall [1]. Radical prostatectomy has become the standard of care in the treatment of prostate cancer with an estimated 20 % of patients receiving adjuvant radiation therapy (RT) for pT3 disease (extracapsular extension and/or seminal vesicle invasion) and 16 % receiving salvage RT for positive surgical margins. [2] Post-prostatectomy RT for either pT3 disease or positive surgical margins has been shown to reduce the risk of recurrence in three randomized trials: Southwest Oncology Group (SWOG), European Organization for Research and Treatment of Cancer (EORTC) and Auckland Radiation Oncology (ARO). [3, 4, 5]. Furthermore studies have shown that compared with 3D Conformal Radiation Therapy (3DCRT) Intensity Modulated Radiation Therapy (IMRT) can achieve better target conformity leading to increased sparing of nearby organs-at-risk (OARs) such as the bladder, rectum and femoral head as well as reduced GI/GU toxicity. [6, 7, 8]

RTOG 0621 is a phase II clinical trial that aimed to assess whether the addition of androgen suppression therapy (AST) and docetaxel to adjuvant 3DCRT/IMRT radiation therapy in the treatment of high-risk post-prostatectomy prostate cancer improves freedom from progression (FFP) defined as a prostate specific antigen (PSA) < 0.4 ng/mL and no clinical failure (loco-regional or distant failure) in three years. The trial stipulates a prescription dose of 66.6 Gy ($\pm$1.8 Gy) to the prostate bed and 50.4 Gy to the pelvic lymph nodes in 1.8 Gy fractions. It opened in April 2008 with a target accrual of 76 patients and closed in September 2010 having accrued 80 patients.

Although IMRT offers clear clinical benefits to 3DCRT one disadvantage is that there is significant variation in the quality of treatment plans across the field [9, 10]. This is particularly evident when comparing treatment plans produced at University hospitals and large research centers with those produced at smaller community hospitals [11]. Plan quality depends heavily on the knowledge and experience of planners as well as the institutional resources available to them. The inverse planning process used in IMRT planning can make it difficult for inexperienced planners to know whether a plan is fully optimized or whether it can be improved further by devoting more time and effort to it. Combined with the need to minimize planning time per patient, given limited resources, this leads to significant differences in plan quality across institutions. Studies have shown that suboptimal IMRT plans are associated with increased normal tissue complication risks [12]. A concerted effort must be made to reduce the variability in treatment plans and to improve their overall quality.

Knowledge based planning (KBP) techniques have been developed to predict dose volume histograms and optimal dosimetric objectives for IMRT treatment planning [13]. These techniques study the correlations between patient anatomy, in particular the position of OARs relative to the target, and dose distribution and use these correlations to predict the optimal dose distribution for a patient given their target-OAR geometry. Principal Component Analysis (PCA) is used to characterize the salient features of the patient anatomy and dose distribution and Support Vector Regression (SVR) is used to model their correlation. These mathematical tools are described in detail in the context of adaptive IMRT planning of prostate cancer in [14].

RapidPlan (Varian Medical Systems, Palo Alto, USA) is a commercially available KBP tool that allows users to build predictive models for particular treatment sites and pathologies by training them on a collection of high quality plans from previously treated patients. These models can then provide a guideline for treatment planners to better understand the plan quality that is achievable on a case by case basis.

There is good evidence that adherence to trial compliance criteria is a strong indicator of high plan quality which is associated with increased survival in patients enrolled in national clinical trials [15]. This suggests that treatment plans from patients enrolled in national clinical trials, that adhere well with compliance criteria, are a natural place to look for high quality plans from which to train a RapidPlan model.

This paper presents the results of a prostate model built with RapidPlan and trained on a collection of high quality cases from RTOG 0621. The model was validated and tested as a tool for planning QA on an orthogonal set of plans from the same trial.

2 Theory

2.1 Knowledge Based Planning

The aim of KBP is to use a database of high quality treatment plans to predict the optimal dose distribution for a given patient anatomy. These predictions then provide a guideline for planners that indicate the degree of OAR sparing that is achievable. The main benefit of KBP is that it allows planners to more easily distinguish plans that can be improved further from those that are already fully optimized, which

allows them to better manage their time. By incorporating KBP tools into routine treatment planning radiation oncology departments can make the best use of resources to treat more patients without sacrificing plan quality.

This study makes use of a KBP tool, known as RapidPlan, available in Eclipse treatment planning system (TPS) version 13.6.5. RapidPlan is based on the work of Zhu *et al* [14] which uses PCA to build KBP models by identifying the most important features of patient anatomy and dose distribution and studying their correlations.

2.2 Principal Component Analysis

PCA is used to characterize high dimensional data in reduced dimensions by extracting the most salient features. This is particularly useful when studying the correlation between two high dimensional data sets. Despite the high dimensions of the data sets their correlation is often dominated by a limited number of important features. Thus the problem can be simplified considerably by identifying these features through PCA and describing their correlation. In the context of IMRT treatment planning the two data sets are the dose distribution and the target/OAR geometry for a collection of treatment plans. The dose distribution data consists of the DVHs for each OAR. The target/OAR geometry data consists of the target and OAR volumes and the distance-to-target histograms (DTH) for each OAR. The DTH shows the fractional volume of an OAR within a certain distance of the PTV surface. For voxels inside the PTV the distance is negative, indicating overlap. An example DTH for a rectum is shown in Fig. 1 [14]

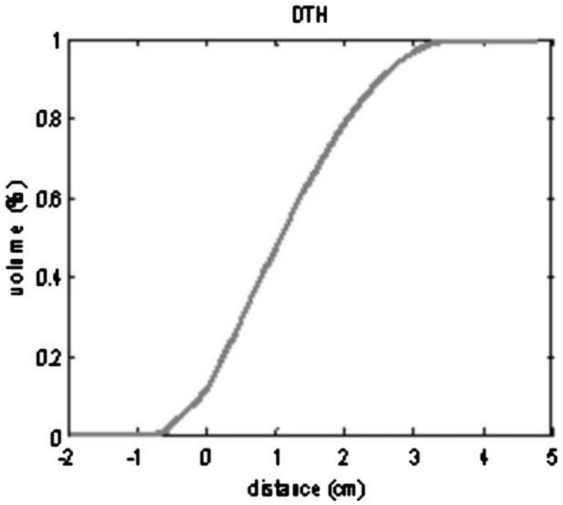

Figure 1: Example distance-to-target histogram for the rectum in a prostate cancer patient [14]. Approximately 10 % of the rectum overlaps with the target.

Each DVH and DTH is sampled m times (m = 50 in the original work by Zhu *et al* [14]) producing an m component vector called a feature point. These feature points populate an n dimensional feature space for each OAR where n is the number of treatment plans in the data set. The feature point corresponding to the average curve (DVH or DTH) is identified and the origin of the coordinate system is shifted there such that the components of each feature point now represent deviations from their average value. The feature points are then normalized such that the standard deviation of each component about 0 is 1.

The m×m covariance matrix of the n feature points in this shifted coordinate system is formed and diagonalized to find the m eigenvectors and eigenvalues. The eigenvectors now define a new coordinate system which is a rotation of the shifted coordinate system. The components of the feature points in this rotated system no longer represent the m sampled points of the curve but some distinct features of the data which are some combination of the sampled points. The eigenvalues give the average deviation of these components from their average. A subset of these components with the largest deviations are identified as the principle components (PCs) and their values are the principle component scores (PCSs). PCSs are specified for each PC (1st PC, 2nd PC, etc...) of the geometric and dosimetric data of each OAR in each treatment plan.

Once the PCs are identified for the dosimetric and geometric data SVR is used to map their correlations. The map can then be used to determine the dosimetric PCSs from the geometric PCSs that are derived from the geometric input which include the target and OAR volumes and DTHs for each OAR. The DVH for the patient can then be predicted from the dosimetric PCSs by simply applying the inverse rotation and translation to revert back to the original feature space in which the components correspond to the m sample points of the DVH.

2.3 RapidPlan

RapidPlan allows users to build KBP models for specific disease sites by training from a database of high quality plans. It applies PCA and SVR to the training sample to develop a mapping between geometric and dosimetric features which can be used to produce estimated DVH (EDVH) bands for patients with similar geometry. The bands represent

one standard deviation variation around the model predicted average DVH. Planners can then proceed to optimize the treatment plan for the patient as in conventional inverse planning but also making use of the EDVH bands to understand the degree of OAR sparing that can be expected.

RapidPlan includes a number of tools to visualize the training results of a model. These include overlay plots of the clinical DVHs and EDVH bands, residual plots that show the actual PCS values against the model predicted values and regression plots showing the correlation between the leading dosimetric PCS and the most important geometric regression parameter which may be the leading geometric PCS, another feature such as a the target or OAR volume or some combination of these. It also displays the goodness of fit parameters R^2 and χ^2.

It is important to ensure that the training sample includes enough treatment plans for the full range of geometries the model is intended for. If there are geometric outliers in the training sample the model will be overtrained for that specific geometry and predict narrow EDVH bands based on the DVH for that particular plan. Outliers should either be removed from the training sample or more plans of that geometry should be added so that the model is no longer overtrained. RapidPlan calculates a range of outlier statistics for each OAR in each plan in the training sample to help the user identify potential outliers. These include the crook's distance, modified z score, studentized residual and areal difference in estimate. If any of these statistics exceed a specific threshold value they are highlighted for further investigation. It also displays geometric box plots showing the distribution of various geometric features of the training data including the geometric PCSs.

3 Methods and Materials

3.1 Dosimetric Analysis of Clinical Treatment Plans in RTOG 0621

The treatment plans submitted to RTOG 0621 were analyzed to determine how well each plan adheres to the compliance criteria specified in the trial protocol. The Imaging and Radiation Oncology Core (IROC) of the National Clinical Trials Network (NCTN) of the NCI implements a scoring scheme to assess the compliance of each plan in a trial. Under the scheme a plan receives a score from 1 to 3 with 1 indicating the most compliant plans, 2 indicating plans that are less compliant but still acceptable and 3 indicating plans that are a protocol violation. The RT compliance criteria of a national clinical trial consist of a set of constraints on dosimetric parameters for the target and all relevant critical structures. Score 1 plans meet all constraints while score 2 plans show a variation of one or more parameters with respect to the constraint value within a range that is deemed acceptable. Score 3 plans show a variation outside of this acceptable range. The compliance criteria for RTOG 0621 are shown in Table 1. Target 1 includes the prostate bed and the pelvic lymph nodes (LNs) and is taken to 50.4 Gy. Target 2 is the prostate bed alone and is taken to 66.6 ± 1.8 Gy. The criteria include constraints on $V_{100\%}$ and dose heterogeneity $D_{het} = (D_{2\%}\text{-}D_{98\%})/D_{Rx}$ for each target to ensure coverage and homogeneity and upper limits on V_{50Gy} and $V_{66.6Gy}$ for the Bladder and Rectum.

All plans submitted to RTOG 0621 were analyzed by exporting the Dose Volume Histograms (DVHs) from MIM (MIMsoftware Inc, Cleveland, OH 44122) in the IROC analysis environment of the IROC/ACR cloud and processing them with a MatLab [16] tool which extracts dose-volume statistics. These statistics were then compared with the constraints outlined in the trial protocol to assign a score to each plan. A summary of the results of this analysis including the percentages of plans that pass each criteria are shown in Table 3. These scores were then used to help select plans for the knowledge database used to train the model. Score 1 and 2 plans were selected for the initial training sample since evidence suggests a strong correlation between overall survival and compliance with the trial protocol [15].

3.2 Model Building and Validation

Of the 80 patients submitted to the trial 22 were either 3DCRT plans or could not be used for other reasons such as incomplete treatment or missing data. Of the remaining 58 patients 47 have been used in this study. The DICOM data (CT, RTStruct, RTPlan and RTDose files) for these 47 treatment plans were imported to Eclipse treatment planning system (TPS) version 13.6.15. 39 score 1 and 2 plans were chosen for the training sample and the remaining 8 were used for validation and testing the model. The plans were submitted to the trial by various institutions and so were planned for different machines and with different TPSs. The trial protocol specifies a prescription dose of $D_{Rx} = 66.6/1.8 \pm 1.8$ Gy. Of the 47 treatment plans used in the study 27 have a prescription dose of 66.6 Gy, 9 have 64.8 Gy and 11 have 68.4 Gy. The protocol requires a

3DCRT	Dose Goal (Prescription, Gy) (Dp)	PTV Volume Receiving Goal Dose	PTV Dose Heterogeneity (D2-D98)/Dp		Minimum CTV Dose (Gy)
			No Variation	Minor Variation	
Target Volume 1	66.6±1.8	≥95%	≤7%	8-12%	45 / 50.4
Target Volume 2	45 / 50.4	≥95%	≤7%	8-12%	45 / 50.4

IMRT	Dose Goal (Prescription, Gy) (Dp)	PTV Volume Receiving Goal Dose		PTV Dose Heterogeneity (D2-D98)/Dp		Minimum CTV Dose (Gy)
		No Variation	Minor Variation	No Variation	Minor Variation	
Target Volume 1	66.6±1.8	≥95%	90-94%	≤15%	16-25%	45 / 50.4
Target Volume 2	45 / 50.4	≥95%	90-94%	≤15%	16-25%	45 / 50.4

IMRT	Volume Receiving ≥66.6 Gy		Volume Receiving ≥50 Gy	
Normal Organ Limit	No Variation	Minor Variation	No Variation	Minor Variation
Bladder	≤40%	41-47.5%	≤60%	61-67.5%
Rectum	≤25%	26-32.5%	≤50%	51-57.5%

Assessment	Per Protocol	Variation, Acceptable	Deviation, Unacceptable
Fractionation	Within 0.05 Gy of specified 1.8 Gy daily fraction size	> 0.05 Gy to 0.10 Gy of 1.8 Gy	> 0.10 Gy of 1.8 Gy
Elapsed Days During Radiotherapy	1 to 7 break days	8 to 14 days	> 14 days

Table 1: Compliance criteria for RTOG 0621 national clinical trial. The criteria include constraints on the targets and two organs-at-risk (OARs): the bladder minus the prostate bed and the rectum. Target volume 1 includes the prostate bed and pelvic lymph nodes and target volume 2 includes only the prostate bed.

target coverage of $V_{100\%} \geq 95\%$ with an allowed variation of 5% for a minimum of $V_{100\%} \geq 90\%$. All plans included in the model had target coverage at or above 95%. Before adding them to the model they were renormalized to 95% for consistency and easy comparison. Scaling plans in this way has been shown not to effect the quality of the model [17].

All patients in the trial were treated in two phases. The initial phase covers target 1 with 45 Gy or 50.4 Gy (if PTV1 includes the remnants of the seminal vesicles) and the cone down (CD) phase covers target 2 to 66.6 ± 1.8 Gy. These are referred to as PTV1 and PTV2 in the following. Since the treatment plans were separated in this way separate RapidPlan models were built for the initial and CD phases. The models were trained and validated separately.

The models were initially trained on 39 score 1 and 2 clinical plans submitted to the trial. These plans were then re-optimized in order to try to achieve better sparing of the bladder-CTV2 and rectum while maintaining target coverage at 95% and minimizing D_{het} within the target as much as possible. This re-optimization was done using the model as a guideline. The model was applied to each plan to generate estimated DVH bands and line objectives to aid in the re-optimization process. Plans for which dose sparing of these OARs was increased without violating the criteria on target coverage and dose heterogeneity described in Table 1 were judged to be an improvement. The re-optimized plans were then added to the model in place of the original clinical plans and the model was re-trained. The new refined model was then used to re-optimize plans in the training sample further and the process was repeated until the plans were optimized as much as possible. All plans were re-optimized using Eclipse (13.6.15) with a Clinac 23EX beam model and 400 MU/min dose rate.

3.3 Quality Assurance and Plan Optimization

To test the results each model is applied separately to the initial and boost phases of all the plans in the validation/testing sample. A plan sum is then made from the re-optimized initial and boost plans and compared to the original plan sum. The clinical and re-optimized treatment plans were studied to determine whether re-optimization with RapidPlan improved the quality of treatment in these cases.

3.3.1 Biological Analysis of Optimized Plans

A biological analysis was carried out in order to quantify the effect of re-optimization in terms of patient outcome. First the values of V_{50Gy} and $V_{66.6Gy}$ were compared before and after re-optimization. Constraints are placed on these dose volume parameters for both the bladder-CTV2 and rectum in the compliance criteria for this trial, shown in Table 1. They also coincide with the range of parameters found to be correlated with biological outcome for these OARs by Emammi and Burman [18]. They found that the probability of grade 2-3 late rectal and bladder toxicity is constrained by placing upper limits on V_{50Gy}-V_{75Gy} and V_{65Gy}-V_{80Gy} for the rectum and bladder respectively.

In addition to studying the effect of re-optimization on these dose volume parameters the equivalent uniform dose (EUD), normal tissue complication probability (NTCP) and tumor control probability (TCP) were calculated using the Lyman-Kutcher-Burman (LKB) model. The EUD is defined as the uniform dose which produces the same probability of a particular biological endpoint as a given inhomogeneous dose distribution. In this study it is calculated with the following equation

$$EUD = \left(\Sigma v_i D_i^a\right)^{1/a} \tag{1}$$

due to Niemierko [19], where a is a dimensionless model parameter that depends on the tissue irradiated. In the LKB model NTCP is defined in terms of the error function as

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-t^2/2} dx \tag{2}$$

$$t = \frac{EUD - TD_{50}(v)}{m \times TD_{50}}$$

$$TD_{50}(v) = TD_{50}(1)/v^n$$

v = V/V_{ref} where V is the volume irradiated and V_{ref} is a reference volume. When V_{ref} is the total volume v is the fraction of the structure irradiated. Equ. 2 yields the characteristic sigmoid shape that describes the biological response of tissue to radiation.

This model contains four parameters which must be determined from a fit to clinical data. They include V_{ref}, TD_{50}, m and n. TD_{50} is the tolerance dose for a 50 % complication rate at 5 years after treatment. m determines the slope of the sigmoid. n

describes the volume dependence of TD_{50} and is the reciprocal of the parameter a in equation 1. In this work the NTCP is calculated with

$$NTCP = \frac{1}{1 + \left(\frac{TD_{50}}{EUD}\right)^{4\gamma_{50}}} \quad (3)$$

This is an approximation of the integral definition given in Equ. 2 which does not have a closed form solution. γ_{50} is not another independent model parameter but rather a combination of the others. TCP for the prostate bed is calculated with an equation similar to Equ. 3 with TD_{50} replaced with TCD_{50} defined as the uniform dose to achieve 50 % local control after 5 years. The values of the model parameters used in this study to calculate EUD, TCP and NTCP are taken from a fit to the Emami data [20, 21] and are summarized in Table 2. The biological endpoints are symptomatic contraction and volume loss for the bladder and severe proctitis/necrosis, stenosis/fistula for the rectum.

In order to calculate EUD for a given dose distribution from these parameters the DVHs must be converted to the biological equivalent dose (BED) of the source data from which the parameters were determined. This is done on a voxel-by-voxel basis by first converting the cumulative DVH to the differential DVH and then calculating BED for each dose bin. The fractionation for each bin is the dose divided by the total number of fractions. The fractionation for the Emami source data is 1.8 Gy/Fx. This BED calculation requires the α/β parameters for each structure which are also given in Table 2

Structure	a	γ_{50}	TD_{50}	TCD_{50}	α/β
Prostate	-10	1	-	28.34	1.20
Rectum	8.33	4	80	-	3.90
Bladder	2	4	80	-	8.00

Table 2: LKB model parameters used to calculate EUD, TCP and NTCP in this study. [20, 21]

4 Results and Discussion

The results of the initial dosimetric analysis of the treatment plans in RTOG 0621 are shown in table 3. The table shows the number of treatment plans that receive a score of 1, 2 and 3 in the IROC scoring scheme described in section 3.1 for each of the compliance criteria stipulated in the trial protocol. Table 4 gives a summary of these results. It shows the number of plans that score 1, 2 and 3 for all constraints on targets (CTV1, CTV2, PTV1 and PTV2) and organs at risk (bladder-CTV2 and rectum). Each plan is given an overall score for targets and OARs equal to the lowest score (highest number) for any of the target and OAR constraints. 43 of the 47 training plans used in this study receive scores of 1 or 2 for all structures meaning that they satisfy all compliance criteria according to the protocol requirement 'per protocol' or they vary within an acceptable range of the protocol requirement 'variation acceptable'. The remaining 5 plans violate at least one of the compliance criteria. 39 of the 43 score 1 and 2 plans were chosen for the training sample from which to build the RapidPlan model.

It was assumed that score 1 and 2 plans would provide the best starting point to build a sample of high quality plans from which to build the model. However there is not a one-to-one correspondence between the IROC score and the quality of a treatment plan. Plan quality depends on the patient anatomy and in particular the target and OAR geometry. Treatment plans that receive an IROC score of 3 may violate the compliance criteria despite being high quality plans because the geometry makes planning particularly difficult. It may be that these plans achieve the best OAR sparing possible given the challenging geometry. Similarly a score 1 or 2 plan may not be a high quality plan if the geometry makes it particularly easy to meet the compliance criteria. Therefore the plans chosen for the training sample must be further optimized in order to ensure the strength of the model. Starting with score 1 and 2 plans was merely the most practical and efficient way of building the training sample.

score	Targets	OARs	Total
1	36 (76.6 %)	34 (72.3 %)	25 (53.2 %)
2	7 (14.9 %)	8 (17.0 %)	14 (29.8 %)
3	4 (8.5 %)	5 (10.6 %)	8 (17.0 %)

Table 4: Summary of the results of the preliminary dosimetric analysis of the treatment plans in RTOG 0621 used in this study. A total of 47 treatment plans from the trial were used in the study.

4.1 Model Optimization

Fig 2 shows an example DVH comparing one of the original clinical treatment plans submitted to the trial to the model re-optimized plan. This treatment plan is included in the training sample and was re-optimized in order to improve the quality of the model. After re-optimization the clinical treatment plan was replaced in the training sample by the re-optimized plan and the model was retrained. This process was repeated in a number of iterations in

	CTV1	CTV2	PTV1		PTV2		Rectum		Bladder	
score	D_{min}	D_{min}	$V_{100\%}$	D_{hetero}	$V_{100\%}$	D_{hetero}	V_{50Gy}	$V_{66.6Gy}$	V_{50Gy}	$V_{66.6Gy}$
1	48	48	46	43	39	45	42	48	38	46
2	0	0	2	3	6	2	6	0	2	5
3	0	0	0	2	3	1	0	0	5	0

Table 3: Results of the preliminary dosimetric analysis of the treatment plans in RTOG 0621 used in this study. The table shows the number of plans that score 1, 2 and 3 for each of the trial compliance criteria shown in table 1. A total of 47 treatment plans from the trial were used in the study.

order to achieve the highest quality possible for the treatment plans in the training sample. The full set of DVHs for all re-optimized plans in the training sample are shown in appendix A.

The plots show a significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage. In general the re-optimized plans do have increased dose heterogeneity within the target with respect to the original clinical plans submitted to the trial. This can lead to a degradation in plan quality as it may reduce TCP of the prostate bed. Clinically this must be weighed against the benefit of the increase in dose sparing to the bladder-CTV2 and rectum which will reduce NTCP for these OARs. Ultimately the decision of which treatment plan is of higher overall quality and therefore should be delivered to the patient is made by a physician on the basis of their clinical experience and a range of considerations specific to the patient. For the purposes of this study a moderate increase in dose heterogeneity within the target was accepted if it lead to significant increase in dose sparing to the OARs.

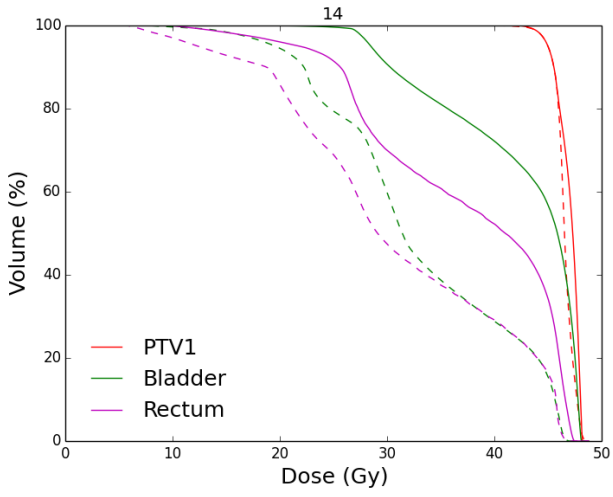

Figure 2: Dose volume histogram (DVHs) showing a comparison of the initial clinical treatment plan with the treatment plan re-optimized with the model for a patient in the training sample (0621c0014). The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan.

4.2 Validation and Plan Optimization

After the model was trained it was validated and tested as a tool for improving plan quality on a sample of 8 treatment plans selected from outside the training sample. The EDVH bands and model generated optimization objectives were used to attempt to reduce dose to the OARs while maintaining target coverage and minimizing dose heterogeneity within the target as much as possible.

Validation was carried out to ensure that the model accurately predicts EDVH bands for all geometries included in its training sample. To do this re-optimized DVHs were compared with the EDVH bands for all plans in the validation/testing sample. Fig 3 shows an example validation plot for patient 0621c0032 demonstrating that the DVHs for the bladder-CTV2 and rectum fall within the EDVH bands as expected. Validation plots for the full validation/testing sample are shown in appendix B.

In the initial phase of treatment for all patients in the validation sample the DVHs for the bladder-CTV2 and rectum fall within the EDVH bands over most of the dose range. In a few cases the DVHs fall within the EDVH bands for most of the range and just beyond the bands for part of the range. This can be expected given that the bands represent a one standard deviation variation from the average DVH predicted by the model. The model for the initial phase is well validated.

For the CD phase there are some discrepancies between the DVHs and EDVH bands arising from patients in the validation sample that are geometric outliers with respect to the training sample. The most dramatic example of this is for patient

0621c0031 for which both the target volume and target/rectum overlap are significantly larger than the mean values in the training sample. This causes the model to make an unrealistic prediction for the rectum DVH. Patient 0621c0016 also shows a significant discrepancy between the DVH and the EDVH band for the bladder-CTV2. For patients 0621c0016 and 0621c0032 the EDVHs for the bladder-CTV2 become quit narrow in the high dose range showing a sharp kink near the full prescription dose of the CD phase. These patients were identified by RapidPlan as outliers of the model. For 0621c0016 the target of the CD phase (PTV2) is too large with respect to the patients in the training sample for the model to make an accurate prediction. Similarly for 0621c0032 the overlap region between the bladder-CTV2 and PTV2 is too large. These outlier geometric features account for the narrow EDVH bands for these patients. There are few patients corresponding to their geometry in the training sample and so the model is overtrained for those geometries. In the case of patient 0621c0016 this leads to a significant discrepancy between the DVH and EDVH band near the kink. With these exceptions the model for the CD phase is well validated by the remaining patients in the validation/testing sample.

In addition to validation the model was tested as a planning QA tool by comparing the re-optimized treatment plans to the original clinical treatment plans submitted to the trial. A comparison of DVHs before and after re-optimization with the model is shown in Fig 4 for patient 0621c0039. The plot shows a significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage. For the bladder-CTV2 V_{50Gy} is reduced from 47.17 % to 32.82 % and $V_{66.6Gy}$ is reduced from 14.20 % to 6.32 %. For the rectum V_{50Gy} is reduced from 23.64 % to 13.09 % and $V_{66.6Gy}$ is reduced from % 3.38 to 0.49 %. Dose heterogeneity within the target (D_{het}) is increased from 6.61 % to 15.47 %. Of the 8 patients in the validation/testing sample 5 were able to be re-optimized with the model to achieve greater OAR sparing without excessive degradation of D_{het}. For the remaining 3 patients the treatment plans were not able to be optimized beyond the clinical plans submitted to the trial.

Similar comparison plots for these re-optimized plans are shown in appendix C. Table 6 in appendix D gives the values of V_{50Gy}, $V_{66.6Gy}$ and D_{het} for these patients before and after re-optimization with the model. The integral dose to the bladder-CTV2 and rectum as well as V_{50Gy} and $V_{66.6Gy}$ for the bladder-CTV2 and V_{50Gy} for the rectum are reduced for all 5 plans. $V_{66.6Gy}$ for the rectum is reduced in 2 plans and increased in 3 plans.

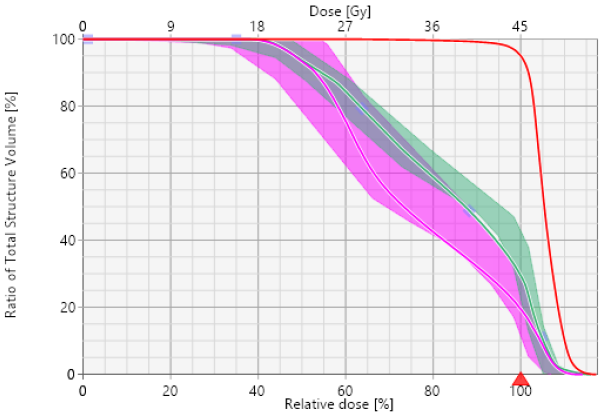

Figure 3: Plot showing overlay of DVHs with estimated DVH bands predicted by the RapidPlan model for the bladder-CTV2 (green), rectum (magenta) and PTV1 (red). The plot shown is for patient 0621c0032 in the validation/testing sample

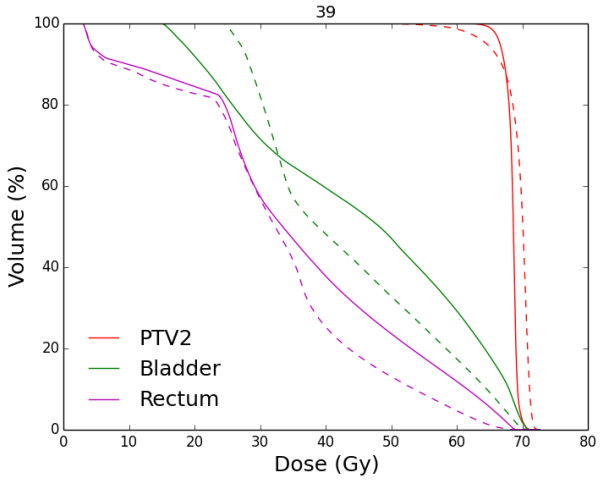

Figure 4: Dose volume histogram (DVHs) showing a comparison of the clinical treatment plan with the treatment plan re-optimized with the model for patient 0621c0032 in the validation/testing sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. DVH Comparison plots for the full validation/testing sample are shown in appendix C.

4.2.1 Biological Effect of Optimization

A summary of the results of the radiobiological analysis described in section 3.3.1 is shown in table 5. The table shows average values of a number of important radiobiological parameters for the treatment plans in the validation/testing sample before and

after re-optimization with the model. These include V_{50Gy}, $V_{66.6Gy}$, EUD, NTCP for the rectum and bladder-CTV2 and TCP for the prostate bed. The average reduction in V_{50Gy} and $V_{66.6Gy}$ for the bladder-CTV2 was 14.29 ± 9.14 % and 6.68 ± 6.94 %. The average reduction in V_{50Gy} for the rectum was 9.89 ± 7.62 % while $V_{66.6Gy}$ actually increased by 0.5 ± 4.76 %. The average reduction in NTCP was 0.34 ± 0.21 % for the bladder-CTV2 and 0.11 ± 0.25 % for the rectum with corresponding p-values of 0.116 and 0.668. The average TCP for the prostate bed decreased slightly from 97.05 % to 96.54 % with a p-value of 0.149. Due to limited statistics in the validation/testing sample the changes reported in these numbers are not statistically significant. The error bars overlap significantly and the p-values are too large to reject the null hypothesis that re-optimization with the model has no effect on overall plan quality on average.

However, although the average values are inconclusive the model was effectively used to identify individual treatment plans that were sub-optimal and improve their quality through re-optimization. The results of the radiobiological analysis for each of the 5 re-optimized plans are shown in appendix D. For patient 0621c0027 the NTCP decreased from 0.35 % to 0.06 % for the bladder-CTV2 and from 0.10 % to 0.06 % for the rectum while the TCP increased from 96.78 % to 96.87 %.

	Clinical	Model	p-value
PTV2			
D_{het} (%)	9.58 ± 1.98	15.80 ± 1.99	0.027
EUD (Gy)	68.02 ± 1.12	65.42 ± 1.32	0.134
TCP (%)	97.05 ± 0.18	96.54 ± 0.30	0.149
Bladder			
V_{50Gy} (%)	60.41 ± 7.51	46.12 ± 5.21	0.118
$V_{66.6Gy}$ (%)	24.07 ± 5.92	17.39 ± 3.62	0.336
EUD (Gy)	54.13 ± 2.64	49.80 ± 2.02	0.193
NTCP (%)	0.43 ± 0.21	0.09 ± 0.04	0.116
Rectum			
V_{50Gy} (%)	38.56 ± 6.40	25.67 ± 4.14	0.091
$V_{66.6Gy}$ (%)	5.70 ± 3.33	6.21 ± 3.40	0.915
EUD (Gy)	55.10 ± 1.62	52.20 ± 2.35	0.310
NTCP (%)	0.38 ± 0.17	0.27 ± 0.19	0.668

Table 5: Summary of mean and standard deviation for dose volume parameters, equivalent uniform dose (EUD), tumor control probabilities (TCP) for the PTV and normal tissue complication probabilities (NTCP) for the bladder-CTV2 and rectum before and after re-optimization. The values are given for each individual treatment plan in the appendix D

5 Conclusion

A KBP model was developed with RapidPlan for the treatment of high risk post-prostatectomy prostate cancer with IMRT. The model was trained on a sample of 39 treatment plans submitted to the national clinical trial RTOG 0621 with IROC scores of 1 or 2 indicating good adherence to the trial compliance criteria. The model was optimized through an iterative process of re-optimizing plans in the training sample and retraining. It was then validated and tested on a sample of 8 treatment plans selected from outside the training sample. The model was shown to accurately predict estimated DVH bands for all plans in the validation sample excluding geometric outliers. The model was tested as a planning QA tool by using it to re-optimize plans outside the training sample and doing a radiobiological comparison of the re-optimized plans and the clinical plans submitted to the trial.

Five treatment plans were re-optimized with the model showing significant increase in dose sparing for the bladder-CTV2 and rectum with some increase in dose heterogeneity within the target. The determination of whether overall plan quality was improved in these cases ultimately depends on patient specific details as well as the experience and judgement of the treating physician. On average the NTCP for the bladder-CTV2 and rectum decreased for both OARs while the TCP for the prostate bed increased slightly, however these changes were not statistically significant given the limited statistics in the study. Nonetheless the model was successfully used to identify sub-optimal plans and improve their quality suggesting that it may be an effective tool for planning QA for the treatment of prostate cancer with IMRT.

Appendicies

A Re-optimization of Treatment Plans in Training Sample

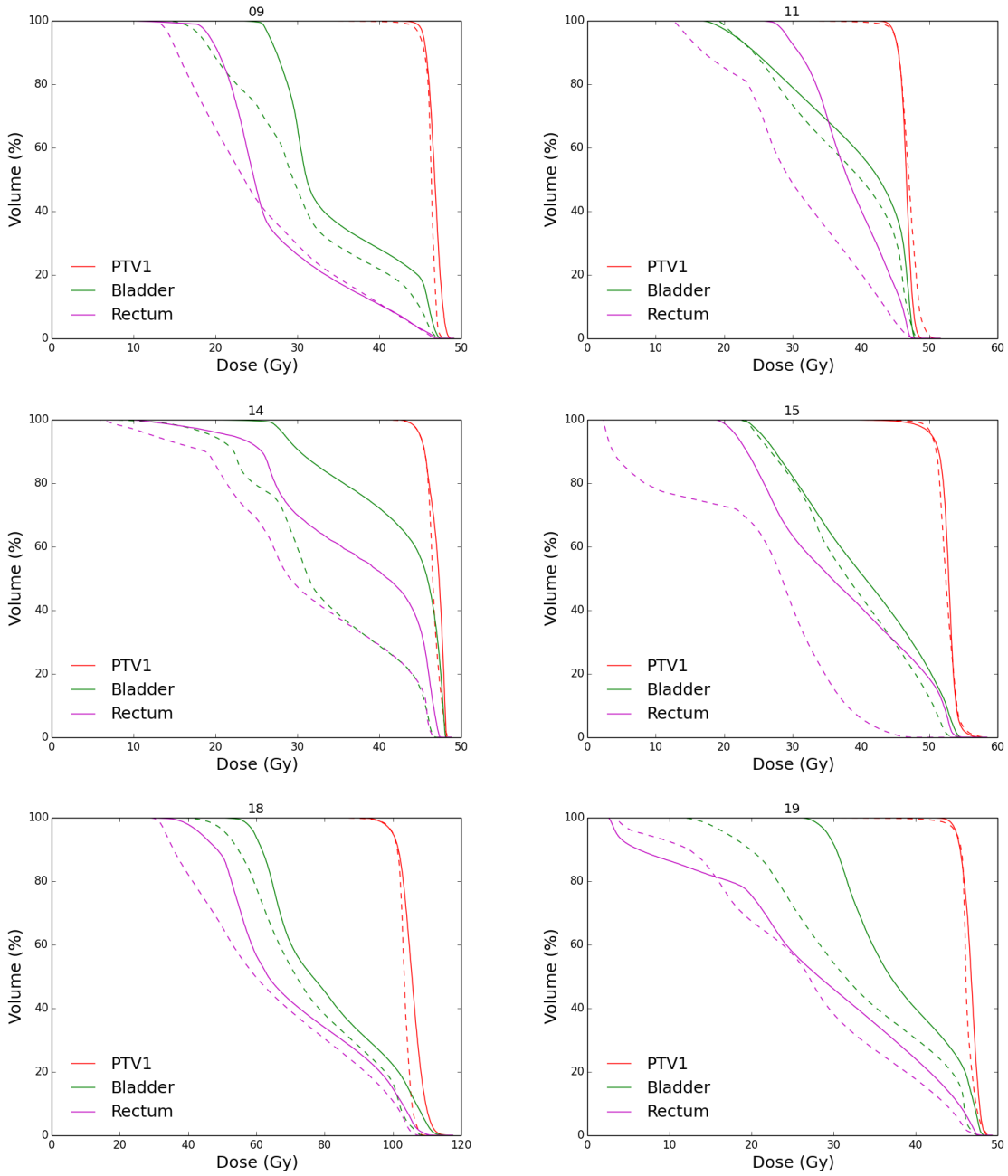

Figure 5: Dose volume histogram (DVHs) showing a comparison of the initial phase of the clinical and re-optimized treatment plans for patients 09, 11, 14, 15, 18 and 19 in the training sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage. The clinical plans were replaced in the training sample by these re-optimized plans to improve the quality of the model.

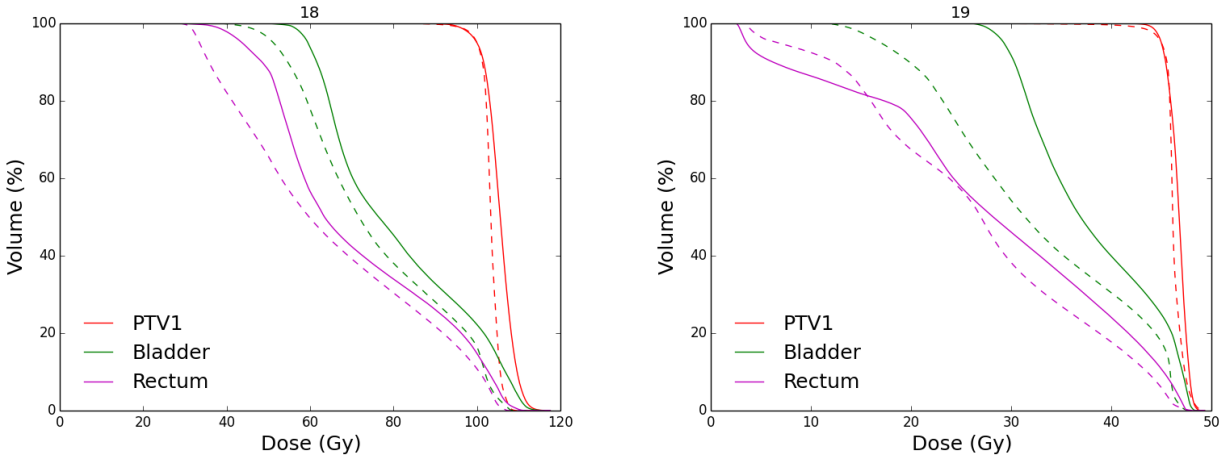

Figure 6: Dose volume histogram (DVHs) showing a comparison of the initial phase of the clinical and re-optimized treatment plans for patients 09, 11, 14, 15, 18 and 19 in the training sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage. The clinical plans were replaced in the training sample by these re-optimized plans to improve the quality of the model.

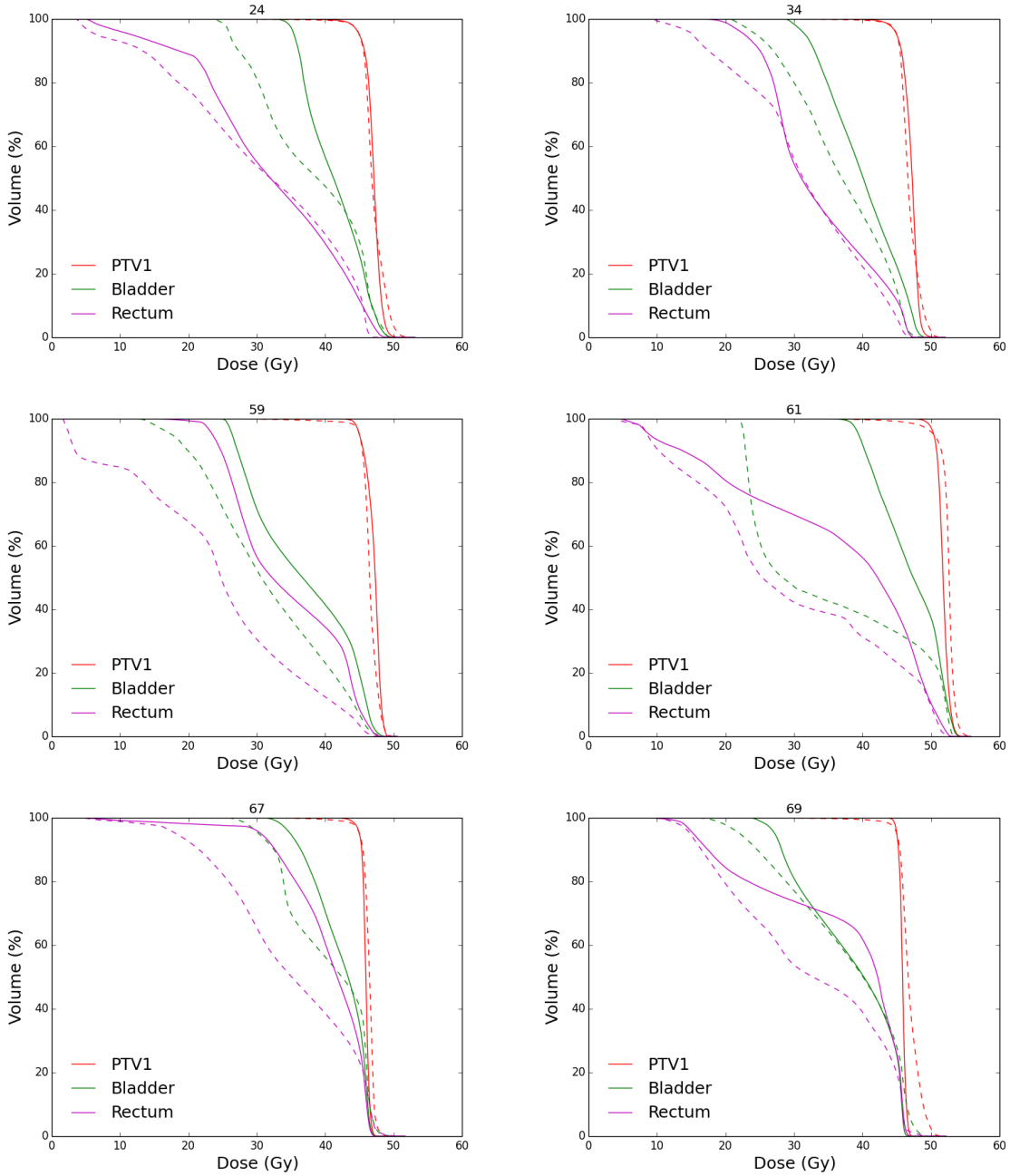

Figure 7: Dose volume histogram (DVHs) showing a comparison of the initial phase of the clinical and re-optimized treatment plan for patients in the training sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage. The clinical plans were replaced in the training sample by these re-optimized plans to improve the quality of the model.

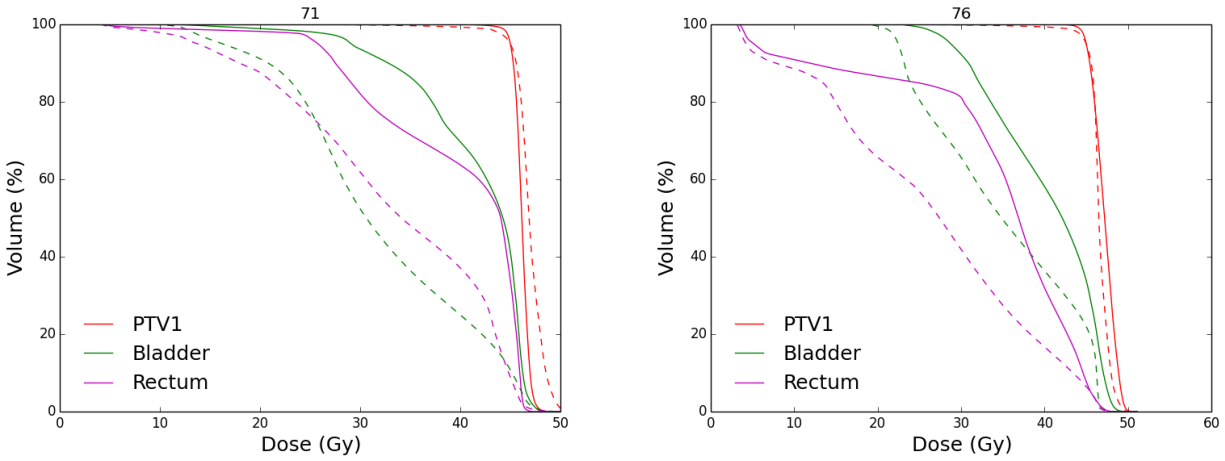

Figure 8: Dose volume histogram (DVHs) showing a comparison of the initial phase of the clinical treatment plan with the treatment plan re-optimized with the model for patients 71 and 76 in the training sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage.

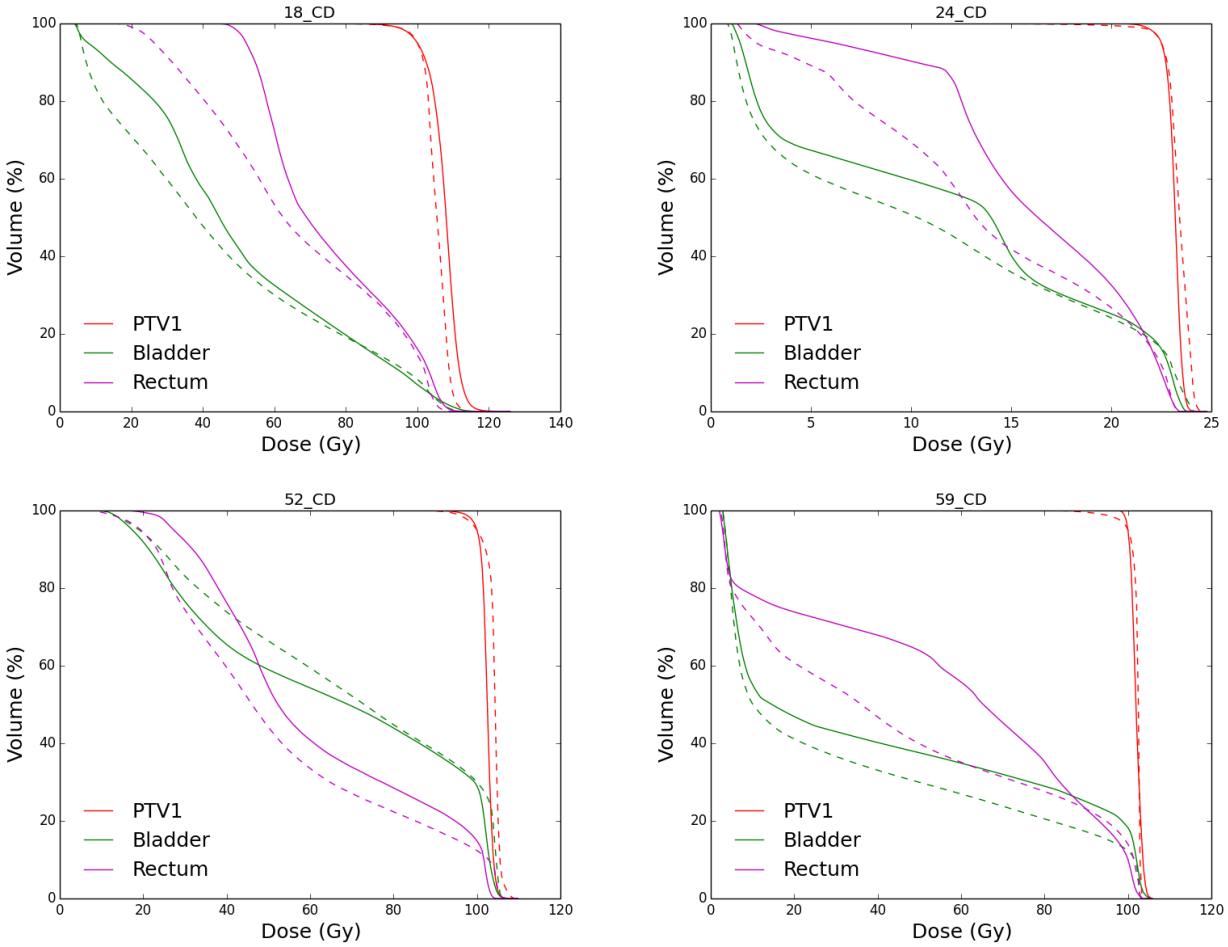

Figure 9: Dose volume histogram (DVHs) showing a comparison of the CD phase of the clinical and re-optimized treatment plan for patients 18, 24, 52 and 59 in the training sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage.

B Model Validation

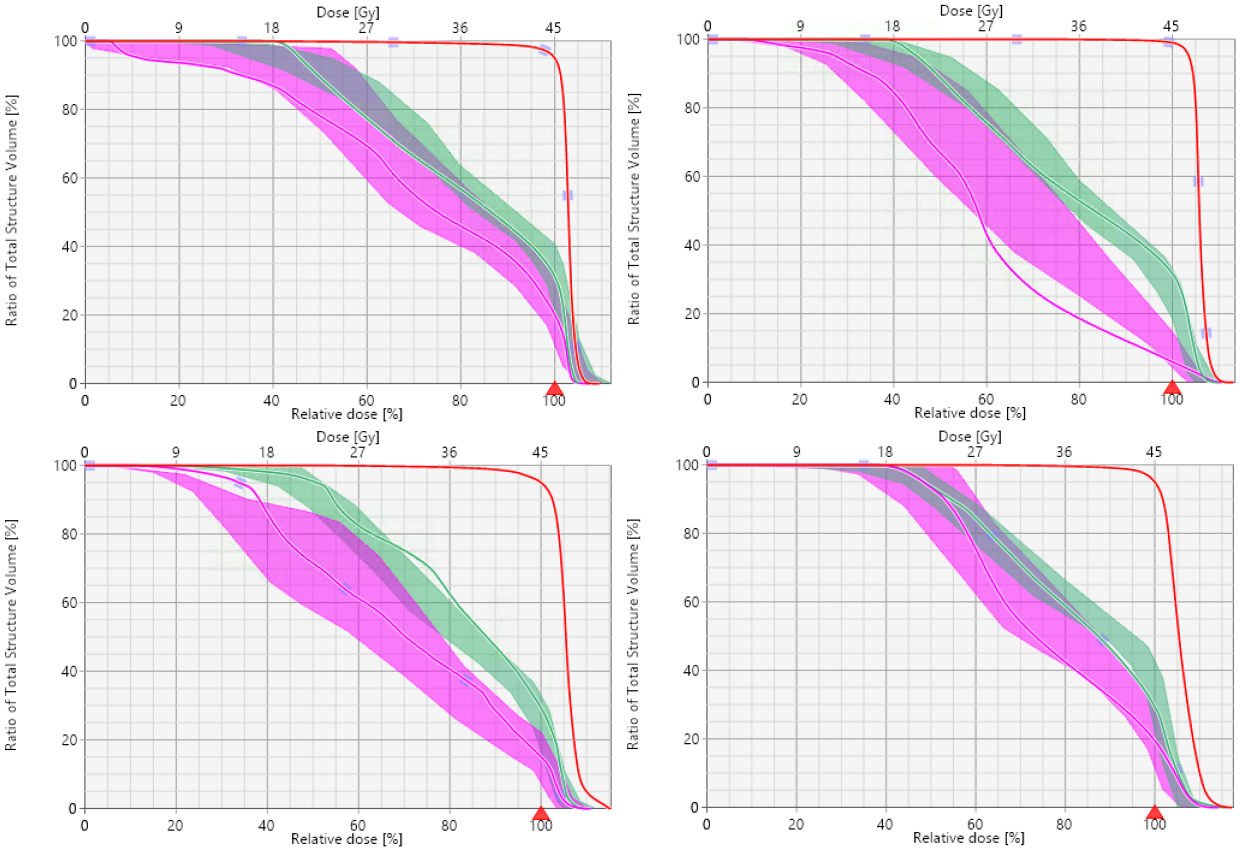

Figure 10: Plots showing overlay of DVHs with estimated DVH bands predicted by the RapidPlan model for the bladder-CTV2 (green) and Rectum (magenta) and PTV1 (red) in the initial phase of treatment. The plots shown are for the treatment plans in the validation/testing sample which includes patients 16, 27, 31 and 32 (reading left to right from top left to bottom right).

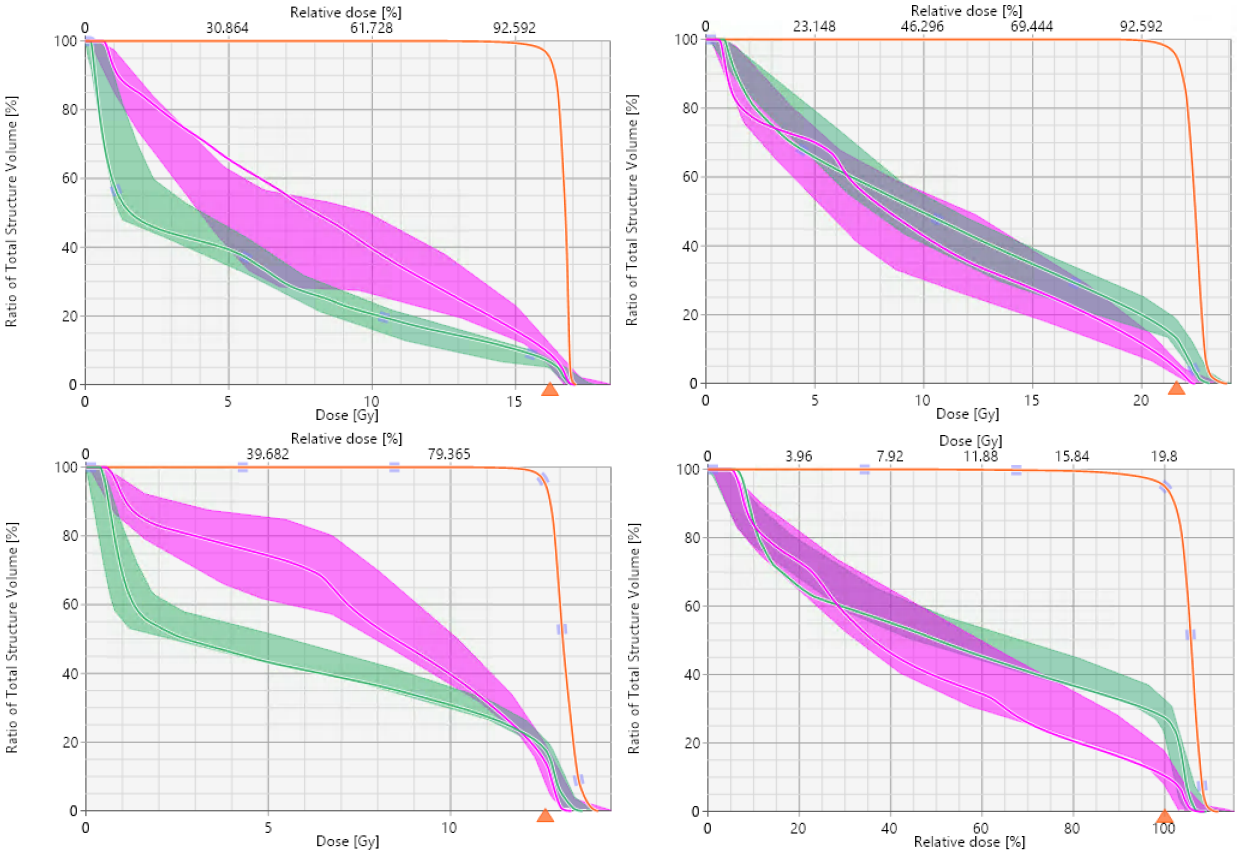

Figure 11: Plots showing overlay of DVHs with estimated DVH bands predicted by the RapidPlan model for the bladder-CTV2 (green) and rectum (magenta) and PTV2 (orange) in the CD phase of treatment. The plots shown are for patients 33, 39, 43 and 80 (reading left to right from top left to bottom right)

C Re-optimization of Treatment Plans in Validation/Testing sample

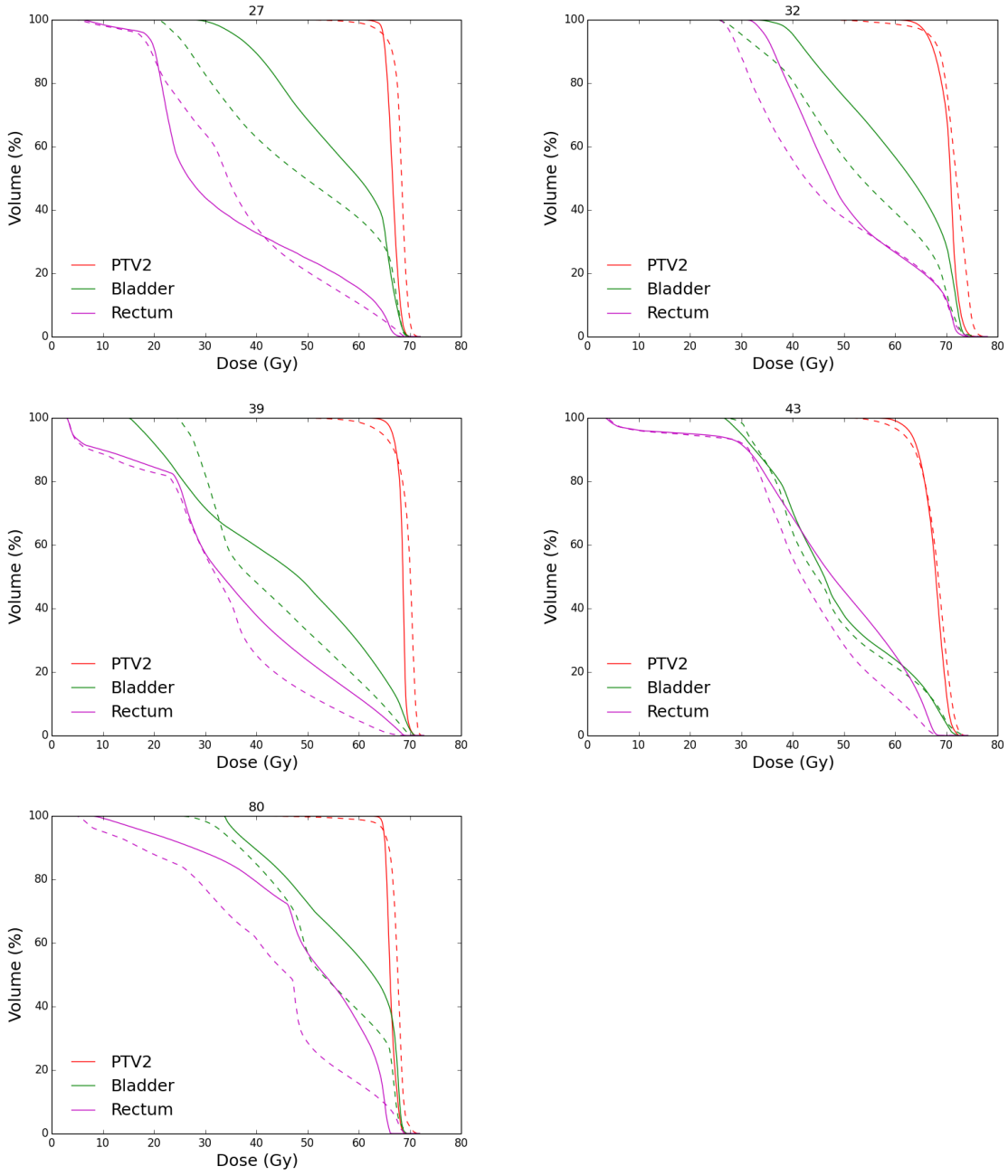

Figure 12: Dose volume histogram (DVHs) showing a comparison of the clinical treatment plan with the treatment plan re-optimized with the model for patients 27, 32, 39, 43 and 80 in the validation/testing sample. The solid curve represents the clinical treatment plan and the dashed curve represents the re-optimized treatment plan. The plots show significant improvement of OAR sparing for both the rectum and bladder-CTV2 without sacrificing target coverage.

D Results of Radiobiological Analysis

Case	Structure	Plan	V_{50} (%)	$V_{66.6}$ (%)	D_{het} (%)	EUD (Gy)	(N)TCP (%)
27	bladder	clinical	68.45	16.57	-	56.22	0.35
		model	49.49	20.57	-	50.14	0.06
	rectum	clinical	24.52	1.54	-	51.90	0.10
		model	20.49	3.13	-	50.50	0.06
	PTV2	clinical	-	-	7.06	66.33	96.78
		model	-	-	12.16	66.83	96.87
32	bladder	clinical	75.79	41.11	-	60.64	1.17
		model	56.55	27.53	-	54.34	0.21
	rectum	clinical	42.15	18.61	-	60.00	0.99
		model	37.54	19.11	-	60.10	1.02
	PTV2	clinical	-	-	13.51	71.79	97.63
		model	-	-	19.52	67.41	96.97
39	bladder	clinical	47.17	14.20	-	47.49	0.02
		model	32.82	6.32	-	43.44	0.01
	rectum	clinical	23.64	3.38	-	51.23	0.08
		model	13.09	0.49	-	45.70	0.01
	PTV2	clinical	-	-	6.61	69.37	97.29
		model	-	-	15.47	67.50	96.99
43	bladder	clinical	38.02	12.91	-	48.32	0.03
		model	34.80	12.77	-	47.45	0.02
	rectum	clinical	45.58	4.96	-	55.57	0.29
		model	28.52	1.55	-	51.13	0.08
	PTV2	clinical	-	-	15.17	66.71	96.85
		model	-	-	21.02	64.87	96.49
80	bladder	clinical	72.61	35.57	-	57.99	0.58
		model	56.96	19.78	-	53.64	0.17
	rectum	clinical	56.90	0.00	-	56.79	0.41
		model	28.70	6.76	-	53.59	0.16
	PTV2	clinical	-	-	5.56	65.87	96.69
		model	-	-	10.81	60.50	95.41

Table 6: Summary of dose volume parameters, tumor control probabilities (TCP) for the prostate bed and normal tissue complication probabilities (NTCP) for the bladder-CTV2 and rectum before and after re-optimization for each plan in the validation/testing sample. In most cases V_{50Gy}, $V_{66.6Gy}$, EUD and NTCP for the bladder-CTV2 and rectum are reduced by re-optimization.

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