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Physics Contribution

Knowledge-Based Assessment of Focal Dose Escalation Treatment Plans in Prostate Cancer

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Purpose: In a randomized focal dose escalation radiation therapy trial for prostate cancer (FLAME), up to 95 Gy was prescribed to the tumor in the dose-escalated arm, with 77 Gy to the entire prostate in both arms. As dose constraints to organs at risk had priority over dose escalation and suboptimal planning could occur, we investigated how well the dose to the tumor was boosted. We developed an anatomy-based prediction model to identify plans with suboptimal tumor dose and performed replanning to validate our model.

Methods and Materials: We derived dose-volume parameters from planned dose distributions of 539 FLAME trial patients in 4 institutions and compared them between both arms. In the dose-escalated arm, we determined overlap volume histograms and derived features representing patient anatomy. We predicted tumor D98% with a linear regression on anatomic features and performed replanning on 21 plans.

Results: In the dose-escalated arm, the median tumor D50% and D98% were 93.0 and 84.7 Gy, and 99% of the tumors had a dose escalation greater than 82.4 Gy (107% of 77 Gy). In both arms organs at risk constraints were met. Five out of 73 anatomic features were found to be predictive for tumor D98%. Median predicted tumor D98% was 4.4 Gy higher than planned D98%. Upon replanning, median tumor D98% increased by 3.0 Gy. A strong correlation between predicted increase in D98% and realized increase upon replanning was found ($\rho = 0.86$).

Conclusions: Focal dose escalation in prostate cancer was feasible with a dose escalation to 99% of the tumors. Replanning resulted in an increased tumor dose that correlated well with the prediction model. The model was able to identify tumors on

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which a higher boost dose could be planned. The model has potential as a quality assessment tool in focal dose escalated treatment plans.

Introduction

Focal dose escalation to the tumor in prostate cancer radiation therapy has been hypothesized to improve patient outcome without increasing acute and late toxicities.[1] In the multicenter randomized Focal Lesion Ablative Microboost in prostatE cancer (FLAME) trial, patients in the dose-escalated arm received an escalated dose up to 95 Gy to the visible tumor. The aim of the trial was to increase the 5-year biochemical recurrence-free survival rate by 10%. To prevent increased toxicity compared with the standard arm, strict dose-volume constraints were imposed on the organs at risk (OARs). During treatment planning, these OAR constraints had priority over dose escalation. Indeed, no significant increase in toxicity was found up to 2 years after treatment.[2] Because of the OAR constraints being prioritized, however, the planned dose escalation to the tumor was limited by the spatial separation between the tumor and the OARs. This raises the question as to how much dose escalation to the gross tumor volume (GTV) was really achieved in the dose-escalated arm of the trial. For this reason, we investigated in the first part of this study to what extent a dose escalation to the visible tumor was realized via comparison of dose-volume parameters between both arms of the trial.

Besides patient anatomy, the degree of dose escalation to the tumor can also be affected by decisions made during optimization of the treatment plan. In clinical practice, it is difficult for a planner or radiation oncologist to assess if a treatment plan can be considered optimal. Over the past years knowledge based planning (KBP) techniques have been introduced to enable automated plan quality assessment (QA) in radiation therapy.[3-13] These studies use a database of previously treated patients to guide treatment planning of a new patient, based on similarities of the patient's anatomy with existing ones in the database. For standard prostate treatment planning, several KBP techniques were used to predict OAR dose from the patient anatomy.[6,14,15] However, to date no KBP methods have been published to predict achievable focal dose escalation in prostate cancer. In the second part of the study we therefore developed an anatomy-based prediction model using our own database to predict the achievable dose in the tumor. We compared the predicted achievable tumor dose with the tumor dose realized in the clinical plans. We tested the validity of our model and the potential for a QA tool with a replanning of a subset of treatment plans based on our model's predictions.

In this work we present how much of the intended dose was actually planned, how much dose escalation could have been achieved, and how much of the predicted dose escalation could be realized upon replanning. Focal dose escalation is a promising strategy in prostate cancer. By combining dosimetric evaluation with knowledge-based planning predictions, this study gives a comprehensive overview of the current feasibility and limitations of this dose escalation strategy for prostate cancer, in addition to an indication of potential improvements that could be realized upon future clinical implementation.

Methods and Materials

Patient characteristics

Data from 571 patients with prostate cancer who participated in the randomized FLAME trial (clinicaltrials.gov NCT01168479) were used. All patients had biopsy-proven, clinically localized, intermediate or high-risk prostate cancer.[16] Patients were excluded from the trial if they received previous pelvic radiation or underwent prostatectomy, if they had a World Health Organization score > 2, an International Prostate Symptom Score ≥ 20, a transurethral resection of the prostate less than 3 months before treatment, contraindications for magnetic resonance imaging (MRI), or if they could not discontinue anticoagulate usage, which was required for implanting gold fiducial markers. We obtained approval from the institutional review board and written informed consent from all participating patients.

Patients were treated at 4 institutions: 320 patients at the University Medical Center Utrecht (UMCU), 93 at the University Hospitals in Leuven (UZL), 109 at the Netherlands Cancer Institute in Amsterdam (NKI), and 49 at the Radboud University Medical Center in Nijmegen (Radboudumc). At each institution, patients were assigned randomly and in a 1:1 ratio to the standard or dose-escalated treatment arm. Treating physicians were not blinded for the randomization to evaluate and approve the treatment plans.

The primary endpoint of the trial was to achieve an increase in 5-year biochemical recurrence free survival rate of 10% among patients in the dose-escalated arm of the trial compared with the standard arm patients. To identify biochemical recurrence, the prostate specific antigen (PSA) level in the blood was measured twice per year, and biochemical recurrence was defined as a PSA rise of 2 n/mL above nadir PSA level, according to the Phoenix definition.[17] Treatment-related acute and late toxicity, measures by the Common Toxicity Criteria for adverse

events version 3.0,[18] as well as quality of life and disease-specific survival were secondary endpoints of the trial.

For this study we considered patients who were included in the per-protocol analyses of the trial.[2] Patients who did not receive the assigned treatment or decided to discontinue the treatment due to anxiety for increased toxicity in the dose-escalated arm were not included in the per-protocol analyses. From the patients eligible for the per-protocol analyses, we excluded 3 patients who were assigned to the standard treatment arm for which no bladder was delineated. In total, 274 patients in the standard arm and 265 patients in the dose-escalated arm were available for analysis.

Treatment planning and delivery

All patients received a planning computed tomography (CT) scan and a pretreatment multiparametric-MRI examination, including a T2-weighted, diffusion-weighted imaging and dynamic contrast-enhanced sequence. The prostate gland was delineated on the T2-weighted MRI by a radiation oncologist. The clinical target volume (CTV) consisted of the prostate gland and, depending on the risk of tumor involvement, the seminal vesicles. For patients who were randomized to the dose-escalated treatment arm, any tumor tissue in the CTV that was visible on the multiparametric-MRI was contoured and defined as GTV. After registration of MRI to CT, target volumes and OARs were defined and delineated. The planning target volume (PTV) was defined as the CTV with a margin of 5 to 8 mm, according to institutional practice. Based on negligible dosimetric effect of PTV margins around intraprostatic GTVs, in this trial no margins were applied to the GTV.[19,20]

The study protocol prescribed a radiation dose of 77 Gy to the PTV in 35 fractions, with an integrated boost up to 95 Gy to the identified tumors of patients in the dose-escalated arm. Depending on institutional practice, 55 to 77 Gy was prescribed to the seminal vesicles whenever it was included in the CTV. Dose constraints to the OARs followed institutional practice and applied to both arms of the trial. In addition, dose constraints of 77 Gy to 1 cc of the rectum and 80 Gy to 1 cc of the bladder were included. One institution applied an endorectal balloon to further reduce dose to the rectal wall (Radboudumc).

Among the participating institutions, different treatment planning systems and delivery techniques were used. The UMCU used PLATO (Nucletron, Veenendaal, The Netherlands) and Monaco (Elekta, Stockholm, Sweden) to generate 7-beam intensity modulated radiation therapy treatment plans, respectively, for 126 and 183 patients. The UZL generated 2-arc volumetric-modulated arc therapy treatment plans with Eclipse (Varian, Palo Alto, CA). The NKI and Radboudumc used Pinnacle TPS (Philips Radiation Oncology Systems, Fitchburg, WI) to generate 1- or 2-arc volumetric-modulated arc therapy plans.

Dose evaluation

A prescription dose map was constructed using the CTV and GTV masks with corresponding prescription dose levels. All dose distributions were resampled to a 1 mm isotropic voxel grid. From the dose distributions we derived dose-volume parameters within the PTV, all GTVs in the prostate, the CTV minus GTV, the bladder, and the rectum.

In both study arms we determined the near-maximum dose D2% and high-dose volume V107% in the CTV minus GTV. The V107% was calculated as the volume percentage with a dose escalation greater than 107% of the prescribed 77 Gy (82.4 Gy). We chose to evaluate the GTV coverage in terms of CTV prescription dose, because the trial prioritized OAR sparing over achieving GTV coverage, and therefore GTV coverage was not explicitly required. Furthermore, we derived the V95% in the PTV and the near-maximum doses D1cc and D2cc in the bladder and the rectum. For plans in the dose-escalated arm, we evaluated to what extent we reached the prescribed dose escalation of 95 Gy. We determined the number of plans with a GTV D50% and D98% greater than 82.4 Gy. Statistically significant differences between both arms were examined with 1-way analysis of variance tests. Because we applied several tests, Bonferroni correction for multiple testing was used to correct the significance level.

At 1 institution (Radboudumc), an endorectal balloon was applied to reduce rectal wall dose and decrease inter- and intrafraction motion. For this relatively small patient group we merged rectal wall and balloon contours to represent the rectum, on which we report dose-volume parameters to be in accordance with literature. We compared GTV and rectum dose-volume parameters between patients with and without endorectal balloon in situ to decide if both patient cohorts could be combined for development of a prediction model.

Another 25 patients from UMCU and NKI received adaptive treatment. For these patients a rigid registration of planning and adaptive CT scan was performed and a weighted sum was applied to the coregistered planned dose distributions. The weights corresponded to the number of treatment fractions that each dose distribution was delivered in. Three patients had a replanning CT. In addition to the rigid registration of CT scans, we extracted binary masks of prostate, bladder, and rectum and pairwise deformably registered the masks between the first and second planning sessions. The deformable registration involved an implementation of the b-spline deformation algorithm described by Ruekert et al.[21] The normalized cross-correlation similarity measure was used for optimization, and registrations were visually assessed. Replanned dose distributions were mapped accordingly, resulting in locally deformed dose distributions for prostate, bladder, and rectum. Planed dose distributions were weighted separately for prostate, bladder, and rectum to allow for dose-volume parameter derivation. In the second part of the

study we only considered the initial treatment plans to develop a prediction model.

Prediction model

We developed a prediction model that calculated the highest achievable D98% in the GTV based on the anatomy of all patients. We chose to predict the near-minimum dose, as this was regarded to be most sensitive to trade-offs between OAR dose and tumor coverage.

We derived overlap volume histograms (OVHs) of delineated PTV, GTV, bladder, and rectum to encode the patient's anatomy.[3,6] We defined 10 structure pairs (PTV → bladder, PTV → rectum, GTV → bladder, GTV → rectum, PTV → GTV, and vice versa) and derived the OVH of each structure pair on a 1 mm resolution. In case of multiple GTVs per patient, we performed our analysis per GTV to allow for a dose prediction per GTV. Per structure pair we combined the OVHs of all patients and performed principal component analysis to reduce dimensionality.[6] We determined the set of principal components (PCs) that described 90% of the variance in OVHs. We reconstructed the OVHs using the derived PCs and defined the obtained patient-specific coefficients as PC scores. In addition, we added radii r5%, r50%, and r95% corresponding with 5%, 50%, and 95% fractional overlap between 2 structures. In contrast to the PC scores these radii were only dependent on the patient's individual OVHs.

The model we developed combined automatic feature selection with a modified linear regression algorithm to predict the D98% in the GTV. Given the complexity of a dose escalated treatment plan, it is difficult to manually assess if a treatment plan was made optimal in terms of highest GTV D98% for a given set of anatomic constraints. Because of the large size of the study, we expected the plans in our data set to range between not optimal and close to optimal planned dose distributions. Therefore, we modified the regression algorithm such that for treatment plans with similar anatomy, a larger weighting was applied to tumors with higher planned D98%.

Depending on the anatomy, values for planned D98% are expected to lie in the range of 77 to 95 Gy. In some cases a GTV with a low D98% may be optimal given the anatomy. To account for a nonuniform distribution of D98% values over the dose range, we also applied a weighting of the planned D98% that compensated for the sparsity of data points at lower dose. Details on the model's training and validation scheme can be found in Appendix E1.

To verify inclusion of patients with endorectal balloon in situ did not bias the performance of the model, we retrained the model after exclusion of patients with balloon and compared the pairwise difference between the predicted GTV D98% by the 2 models.

Evaluation of the model

We determined the dose difference between predicted and planned D98% for all GTVs in the dose-escalated arm. We ranked the GTVs according to predicted dose difference to select treatment plans for replanning. We selected 5 treatment plans with the largest predicted dose difference and another 16 random plans: 8 with a GTV with at least 10 Gy predicted dose difference and 8 without. Among the largest predicted dose differences, no bias toward any of the institutions was observed. Replanning was performed by planning specialists (D.E., P.R., and R.R.) with 10, 9, and 3 years of experience in treatment planning. The planning specialists were blinded for the predicted dose difference by the model, and instructed to plan the highest achievable dose to the GTVs while adhering to the existing target objectives and OAR constraints. New treatment plans were generated in the original treatment planning system, based on original delineations and according to the FLAME study treatment protocol. Because of decommissioning, 7 treatment plans originally planned with the PLATO treatment planning system were replanned using Pinnacle. We compared our predicted tumor D98% with the D98% obtained upon replanning to evaluate our model. All analyses were performed in MATLAB (MathWorks, Natick, MA).

Results

Dose evaluation

The observed dose-volume parameters for the PTV, GTV, CTV minus GTV, bladder, and rectum are described in Table 1. The median D50% to the GTV was 93.0 Gy, and the median D98% was 84.7 Gy. The percentage of GTVs that received a D50% greater 82.4 Gy (107% of 77 Gy) was 98.7%, and 70.4% received a D98% greater than that level. Histograms of the distribution of GTV D50% and D98% in the dose-escalated arm are shown in Figure 1.

The median V95% in the PTV was 98% in both study arms. The median near-maximum dose D2% and high-dose volume V107% in the CTV minus GTV were, respectively, 79.3 Gy and 0.7% in the standard arm and 91.2 Gy and 25.9% in the dose-escalated arm and differed significantly between both arms. The difference is explained by dose gradients surrounding the GTVs in the dose-escalated arm. The median D1cc in the bladder and rectum were 75.5 and 74.1 Gy in the standard arm and 76.2 and 74.9 Gy in the dose-escalated arm, respectively. The median bladder and rectum D2cc were 74.6 and 73.3 Gy in the standard arm and 75.2 and 73.5 Gy in the dose-escalated arm, respectively.

Between patients treated with and without an endorectal balloon in situ we observed minor differences in GTV

Table 1 Comparison of dose-volume parameters in both arms of the FLAME trial

Structure	Dose-volume parameters	Standard arm (n = 274)*	Dose-escalated arm (n = 265)*	*P* value†
PTV	$V_{95\%}$ (%)	98.3 (95.5–98.8)	98.1 (95.3–98.7)	.127
CTV − GTV	$D_{2\%}$ (Gy)	79.3 (78.8–79.8)	91.2 (88.6–92.7)	**<.001**
	$V_{107\%}$ (%)	0.7 (0.0–2.7)	25.9 (17.3–39.2)	**<.001**
GTV	$D_{50\%}$ (Gy)		93.0 (90.3–94.5)	
	$D_{98\%}$ (Gy)		84.7 (81.3–88.4)	
	$V_{95\%}$ (%)		77.6 (50.6–92.0)	
Bladder	D_{1cc} (Gy)	75.5 (74.4–76.7)	76.2 (75.0–77.6)	**<.001**
	D_{2cc} (Gy)	74.6 (73.7–76.0)	75.2 (74.0–76.6)	**.009**
Rectum	D_{1cc} (Gy)	74.1 (73.5–74.8)	74.9 (73.7–75.9)	**<.001**
	D_{2cc} (Gy)	73.3 (72.5–74.0)	73.5 (72.4–74.4)	.037

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; PTV = planning target volume.
Statistically significant *P*-values are presented in bold.
* Median + interquartile range (IQR) reported.
† Differences were tested with a 1-way analysis of variance (ANOVA) test. A posthoc Bonferroni method was applied to correct the significance level for multiple testing.

D50% and D98% that were nonsignificant, and small differences in rectum D1cc and D2cc that were significant but not exceeding clinical dose constraints. The results of this comparison are presented in Table E2.

Prediction model

The model was trained on 382 GTVs. After principal component analysis, 4 to 5 PCs were extracted from each OVH. The trained model consisted of 5 features, listed with corresponding coefficients in Table E1. The predicted GTV D98% is plotted against the planned D98% in Figure 2. The influence of the larger contribution of plans with a higher planned GTV D98% is reflected by the small fraction of data points above the identity line. Planned GTV D98% values are observed up to 95 Gy, which reflects the aim of the trial. Predicted GTV D98% in some cases, however, exceeded the 95 Gy, suggesting that according to the model the anatomy of these patients would allow for further dose escalation. In 1 extreme case, a GTV D98% of 104.6 Gy was predicted, which appeared to be a small tumor at a relatively large distance from the rectum.

The median dose difference between predicted and planned D98% was 4.4 Gy, and dose differences ranged between −2.8 Gy and 16.7 Gy. In 135 of 265 patients who received a focal dose escalation, at least for 1 GTV an achievable increase of 5 Gy was predicted.

Between the prediction models trained with and without inclusion of patients treated with endorectal balloon in situ, we observed a median pairwise difference of 0.0 Gy (95% confidence interval, −0.4 to 0.1 Gy), which justified the inclusion of patients with balloon in our presented prediction model. The difference between predicted and planned D98% of both models can be found in Appendix E1, as well as a scatter plot of the pairwise difference in predicted D98% between the 2 models (Fig. E2).

Evaluation of the model

The 21 treatment plans selected for replanning involved 43 GTVs. We plotted the predicted GTV D98% from our model versus the planned D98% and the replanned D98% in Figure 3. Before replanning we observed a median dose difference between predicted and planned GTV D98% of

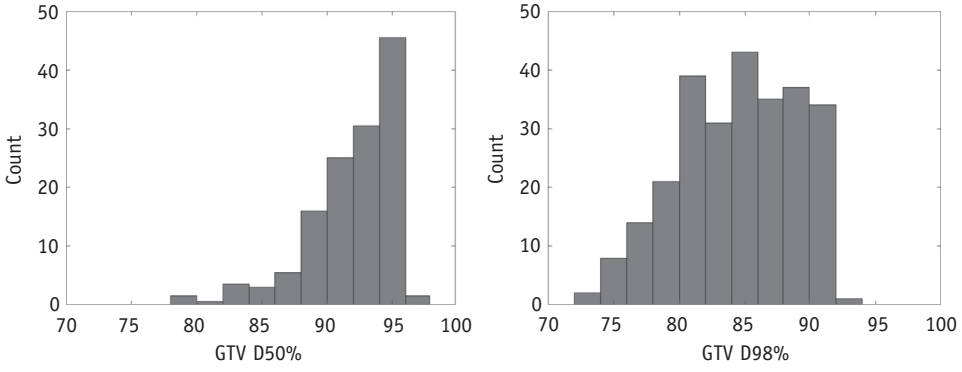

Fig. 1. Histograms of planned $D_{50\%}$ (left) and $D_{98\%}$ (right) of 265 patients in the dose-escalated arm.

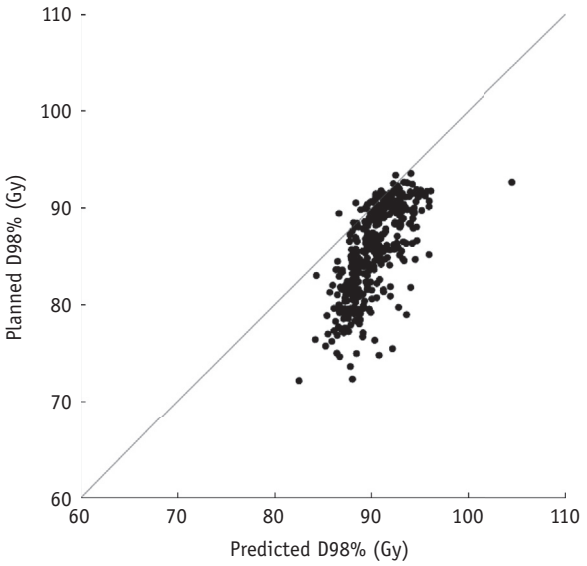

Fig. 2. Scatterplot of predicted $D_{98\%}$ versus planned $D_{98\%}$ in the gross tumor volume (GTV) after training of the modified linear regression model. The majority of data points can be observed below the identity line as a result of the asymmetrical cost function.

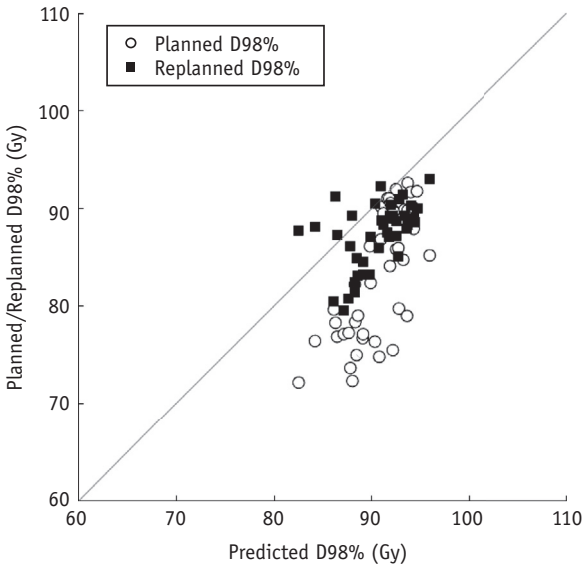

Fig. 3. Scatterplot of the predicted $D_{98\%}$ in the gross tumor volume (GTV) versus the planned and replanned $D_{98\%}$. Upon replanning, an increase in GTV $D_{98\%}$ can be observed that correlates with the predicted increase in $D_{98\%}$.

7.5 Gy (0.5−16.7 Gy). After replanning, the median dose difference between predicted and replanned GTV D98% was 3.8 Gy (-5.2−7.7 Gy). A strong correlation ($\rho = 0.86$) was observed between the predicted increase in D98% and realized increase in D98% after replanning.

A median increase from planned to replanned GTV D98% of 3.0 Gy (−4.0 to 16.9 Gy) was found. For GTVs with a planned D98% less than 80 Gy we observed a median increase of 10.4 Gy. GTVs with a planned D98% between 80 and 85 Gy had a median increase of 4.9 Gy, between 85 and 90 Gy a decrease of 0.7 Gy, and greater than 90 Gy a decrease of 1.7 Gy. Less than 85.9 Gy, all GTV's D98% increased upon replanning. In 16 out of 43 GTVs, we observed a decreased D98% after replanning, with a median decrease of 1.4 Gy (range, 0.2−4.1 Gy). These GTVs had a relatively high median D98% of 90.1 Gy, which reduced the likelihood of improved tumor dose after replanning. For the 5 treatment plans that were selected based on largest predicted dose difference, the median difference between planned and replanned GTV D98% was 9.0 Gy. For the 16 randomly selected treatment plans this was 1.7 Gy.

We observed comparable median PTV V95% of 97.1% before and 97.9% after replanning. Median bladder D1cc and D2cc were, respectively, 77.0 and 75.8 Gy before and 76.8 and 75.4 Gy after replanning, whereas median rectum D1cc and D2cc were, respectively, 74.3 and 73.3 Gy before and 75.8 and 74.4 Gy after replanning. The small increase in dose to the rectum was expected to correlate with an increased dose to the GTV. Maximum bladder and rectum dose were still in accordance with clinical constraints.

Discussion

We showed that integrated focal dose escalation in the prostate is feasible with a median dose greater than 107% of the standard dose of 77 Gy achieved in 99% of patients. Observed dose-volume parameters show a median GTV D50% of 93.0 Gy, which was close to the intended 95 Gy, and a median D98% of 84.7 Gy.

We also developed a prediction model based on OVHs and planned D98% to identify GTVs for which a higher escalated dose was regarded as feasible. After replanning of a subset of treatment plans, we observed a considerable increase in planned D98%, which strongly correlated with the predicted increase by the model.

A recent trial on dose painting in prostate cancer (the Hypofractionated External Beam Image-Guided Highly Targeted Radiotherapy [HEIGHT] trial) with up to 89.3 Gy in 38 fractions found a GTV V95% (greater than 84.8 Gy) between 95.2% and 99.8%.[22] Because of the different fractionation scheme and level of dose escalation, a comparison with our results could not be made.

D2% and V107% in the CTV minus GTV and D1cc in the bladder and the rectum showed a significant increase of dose in the dose-escalated arm, but D2cc in the bladder and the rectum did not. These findings can partially be explained by the study protocol that allowed for dose escalation in the healthy prostate, provided that dose-volume constraints to OARs were not violated.

In the dose-escalated arm there were 382 GTVs in 265 plans, which on average was 1.4 GTVs per plan. This is in agreement with findings by Van Schie et al.[23] A higher

average of 2.0 GTVs per plan was observed in the replanning selection of 21 plans. The higher average in the replanning selection can partly be explained with statistics because a plan with multiple GTVs had an a priori higher chance of inclusion in the replanning selection. We also observed an overestimation of the achievable D98% compared with the planned dose upon replanning. One explanation is the design of the trial, in which we aimed for an escalated dose up to 95 Gy. Our model, however, was not restricted by this dose constraint and, based on patient anatomy, could in principle predict a higher achievable escalated dose than 95 Gy. Although both observations can partly be assigned to statistics and trial design, we do believe they are to some extent also explained by the limitation of our prediction model that did not consider the effect of multiple GTVs per prostate. The model determined the achievable GTV D98% for each GTV individually, which could lead to violation of OAR dose constraints in case of multiple GTVs within the prostate. During replanning, this likely has resulted in a reduced GTV D98%, because OAR dose constraints were prioritized.

We demonstrated that focal dose escalation was achieved in almost all patients in the dose-escalated arm of the trial. Although several trials have hypothesized clinical benefits of focal dose escalation, no KBP methods exist to predict the highest achievable integrated boost dose to the tumor. Here, we demonstrated a novel methodology that, using anatomic features and based on a heterogeneous data set, could predict the highest achievable dose in the GTV and allowed for identification of GTVs for which the escalated dose could be improved. A limitation of existing KBP methods is that the predicted dose range reflects the range of clinical plans. In our model we introduced an upward bias to predict the highest achievable dose by putting extra weight on the better optimized plans in the database. Because it was trained on data from multiple institutions, the model is robust to different treatment planning systems. We recognize that our model does not allow for a precise estimation of the achievable tumor dose. We do, however, believe that our model can assist as a QA tool to identify GTVs that could be planned with a higher escalated dose.

Focal dose escalation is a promising dose escalation strategy in prostate cancer. By combining dosimetric evaluation with KBP predictions we were able to demonstrate the feasibility of focal dose escalation up to 95 Gy in the prostate, and present a methodology to potentially improve on focal dose escalation treatment plans in a clinical setting. Although developed for a novel dose escalation strategy in prostate cancer, we believe our methodology can be of general applicability to other treatment sites and radiation strategies as well.

Conclusions

Focal dose escalation in prostate cancer was feasible in almost all GTVs, with an escalated dose much higher than the standard prescribed dose. We developed a prediction model to identify GTVs for which a higher escalated dose was considered feasible. Using this model to select plans for replanning, a considerable increase in D98% was found achievable, specifically for lower planned D98%. Our prediction model has potential as a QA tool and identify suboptimal GTV doses to be optimized via replanning.

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