

Original Article

Inclusion of radiobiological factors in prostate brachytherapy treatment planning

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Abstract

Purpose: Comparison of prostate seed implant treatment plans is currently based on evaluation of dose-volume histograms and doses to the tumour and normal structures. However, these do not account for effects of varying dose-rate, tumour repopulation and other biological effects. In this work, incorporation of the radiobiological response is used to obtain a more inclusive and clinically relevant treatment plan evaluation tool.

Materials and Methods: Ten patients were evaluated. For each patient, six different treatment plans were created on the Prowess system. Plans with iodine-125 used a prescription dose of 145 Gy while plans with palladium-103 used 115 Gy. The biologically effective dose was used together with the tumour control probability and the normal tissue complication probabilities of urethra, bladder, rectum and surrounding tissue to evaluate the effectiveness of each treatment plan. Results from the radiobiological evaluation were compared to standard dose quantifiers.

Results: The use of response probabilities is seen to provide a simpler means of treatment evaluation compared to standard dose quantifiers. This allows for different treatment plans to be quickly compared. Additionally, the use of radiobiologically-based plan evaluation allows for optimisation of seed type and initial seed strengths to find the ideal balance of TCP and NTCP.

Conclusion: The goal of this work was to incorporate the biological response to obtain a more complete and clinically relevant treatment plan evaluation tool. This resulted in a simpler means of plan evaluation that may be used to compare and optimise prostate seed implant treatment plans.

Keywords

treatment planning; brachytherapy; radiobiology; prostate

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INTRODUCTION

Low dose-rate brachytherapy (LDR) is a popular radiation therapy modality used in the

treatment of prostate adenocarcinoma. For low-grade disease, LDR offers several advantages compared to external beam radiotherapy including shorter course of treatment and lower normal tissue toxicity. Presently, treatment planning goals for LDR of the prostate are based on dose-volume histograms (DVH), isodose distributions and dose objectives to the target volume and organs at risk (OAR), as recommended in the American Association of Physicists in Medicine Task Group 137 report (TG-137).¹

These quantifiers presume that the only quantity of importance is the delivered dose. However, the amount of biological damage attained with a certain dose is dependent on many factors, such as the dose rate, photon energy, tissue sensitivity, tissue seriality and sub-lethal damage repair during irradiation. These additional parameters vary greatly among the different radioisotopes used in prostate seed implants. Under some circumstances, plans with similar dose distributions have been shown to have different estimated radiobiological outcomes.²

We, hypothesise that, with the addition of radiobiological indices to the TG-137 criteria, a more clinically relevant, treatment planning analysis may be obtained. In this work, a radiobiologically-based treatment planning tool was produced to improve plan comparison through the addition of a small number of evaluation criteria. The aim of this work was to show that the recommended radiobiological indices are useful to differentiate patient treatment plans and that the calculated response estimates are realistic.

MATERIALS AND METHODS

This study is a retrospective analysis of ten patients receiving prostate seed implants as monotherapy. All the patients were treated with ¹²⁵I seeds (BARD, BrachySource model, Covington, GA, USA) and prescribed 145 Gy for their clinical implant. For each patient, five additional treatment plans were created

with different dose distributions. One of these additional plans used ¹⁰³Pd seeds (Theragenics, model 200, Buford, GA, USA) and a prescription of 125 Gy. Each plan was created with a different goal in mind, given in Table 1, and therefore each had a unique dose distribution. However, while the isodose distributions for each plan were different, the plans had similar dosimetric characteristics. The goal of using these additional treatment plans was to simulate a realistic clinical situation where one must choose the best plan for a patient. Observations about calculated response accuracy were based on the follow-up data for the clinically used plan and responses reported in literature at similar dose levels.

Dose quantifiers and DVH distribution for these treatment plans are given in Table 3 and Figure 2. Pre-implant prostate volume studies were performed using transrectal ultrasound (TRUS). These ultrasound images were used for treatment planning on the Prowess Panther 3D Brachy Pro (Prowess, Concord, California, USA) system. Volumes for the prostate, urethra, rectum and bladder were drawn by a physician.

The physical dose was calculated with the in-house software using the TG-43 formalism, which used the seed strengths and coordinates from Prowess.³ The dose calculation was validated by comparing point doses and isodose distributions for a single source and a simple distribution of five seeds. All point doses agreed with Prowess within one percent. Then, the

Table 1. Description of goals for each treatment plan.

Plan #	Treatment plan description
1	Original plan, 0.369 mCi I-125
2	Avoid Urethra, 0.369 mCi I-125
3	Uniform PTV coverage, disregard urethra, 0.369 mCi I-125
4	Increase seed activity 0.369 -> 0.5 mCi I-125, avoid urethra
5	Seed activity 0.250 mCi I-125
6	2.2 U Pd-103 seeds

organ contours for each ultrasound image slice was exported from Prowess. Based on the physical dose and type of tissue present in each voxel, the tumour control probability (TCP) was calculated.²

The value of TCP is based on a calculation of biologically effective dose (BED), which is calculated for the tumour and normal tissues using equations 1a and 1b, respectively.^{19–21}

$$BED_{tum} = D_{eff} \left\{ RBE + \left[\frac{R_0}{(\mu + \lambda)(\alpha/\beta)_{tum}} \right] * A * (B - C) \right\} + \frac{K}{\lambda} \ln \left(\frac{K}{RBE * R_0} \right) \quad (1a)$$

$$BED_{NT} = D_{eff} \left\{ RBE + \frac{R_0}{(\mu + \lambda) * (\alpha/\beta)_{NT}} \right\} \quad (1b)$$

where,

$$A = \frac{1}{1 - e^{-\lambda T_{eff}}}$$

$$B = \frac{1 - e^{-2\lambda T_{eff}}}{2\lambda}$$

$$C = \frac{1 - e^{-T_{eff}(\mu + \lambda)}}{\mu + \lambda}$$

In equations 1a and 1b, R_0 is the initial dose rate and λ is the decay constant (for ^{125}I $\lambda = 0.01166 \text{ day}^{-1}$, for ^{103}Pd $\lambda = 0.04079 \text{ day}^{-1}$). The sublethal damage repair constant (μ) was calculated using equation 2.

$$\mu = \frac{\ln(2)}{T_{1/2}} \quad (2)$$

This factor accounts for the decrease in cell kill as the cell repairs damage. Here, a general repair half-life of 15 minutes was assumed for both tumour and normal tissues, making $\mu = 2.8 \text{ hour}^{-1}$.^{22,23} The tumour repopulation factor (K) accounts for the growth of new tumour cells during treatment and is calculated from equation 3. A potential doubling time (T_{pot}) of 42 days was used in this analysis

resulting in a repopulation factor of $0.11 \text{ Gy} * \text{day}^{-1}$.^{22,24}

$$K = \frac{\ln(2)}{\alpha T_{pot}} \quad (3)$$

The effective dose (D_{eff}) was calculated using equation 4. The effective treatment time (T_{eff}) was determined from equation 5. The endpoint for brachytherapy has been defined as the point where the rate of cell kill is equal to the tumour repopulation factor.²⁵ For normal tissues it is assumed that $T_{eff} = \infty$, hence the effective dose is taken to be equal to the total physical dose accumulated over the lifetime of the seeds.

$$D_{eff} = D(1 - e^{-\lambda T_{eff}}) \quad (4)$$

$$T_{eff} = -\frac{1}{\lambda} \ln \left(\frac{K}{R_0 * RBE} \right) \quad (5)$$

The relative biological effectiveness (RBE) for ^{125}I and ^{103}Pd has been reported to be between 1.4 – 1.5 and 1.6–1.9.^{25–27} For this study

Table 2. Dose-response parameters for each tissue evaluated.

Tissue Type	γ	α/β	D_{50}	s	End Point
PTV	4	2	50	1.0	Control
Bladder	3	3	80	0.3	Symptomatic Contracture
Urethra	3	3	190	0.5	RTOG Grade 2
Rectum	2.2	3	80	0.7	Proctitis, Fistula, Stenosis
Other	4	3	80	0.5	Necrosis

values of $RBE= 1.45$ and $RBE= 1.75$ were used for ^{125}I and ^{103}Pd , respectively. The specific radiobiological parameters α/β , D_{50} and γ used for each tissue are given in Table 2. D_{50} is the dose which gives a 50% response and γ is the maximum normalised dose-response gradient. The D_{50} and γ parameters are derived from clinical materials and describe the shape of the dose-response curve.²⁸ These parameters and the radiobiological model used are similar to those recommended in TG-137.²⁹ Voxel response probability (P) was then determined using equation 6, where BED becomes BED_{Tum} or BED_{NT} depending on whether the given voxel belongs to the tumour or an OAR.^{30–32} The overall response probability for the tumour and normal tissues is calculated using equations 7a and 7b, respectively.

$$P = \exp(-\exp(\exp(1) * \gamma - \alpha * BED)) \quad (6)$$

$$P_{Tum}(D, V) = \prod_{i=1}^N TCP(D_i)^{\Delta v_i} \quad (7a)$$

$$P_{NT}(D, V) = \left[1 - \prod_{i=1}^N (1 - TCP(D_i, V_i)^s)^{\Delta v_i} \right]^{1/s} \quad (7b)$$

where N is the total number of voxels in the organ, s is the tissue-specific relative seriality parameter and Δv_i is the fractional subvolume

of the organ irradiated. The overall probability of tumour control (P_B), the overall probability of injury to the involved normal tissues (P_I) and the complication-free tumour control probability (P_+) for the treatment were calculated using equations 8, 9 and 10, respectively. The biologically effective uniform dose (\bar{D}) which is the uniform dose that causes the same tumour control as the actual dose distribution for a given treatment, was calculated from equation 11.

$$P_B = \prod_{j=1}^{N_{tumors}} P_{Tum}^j \quad (8)$$

$$P_I = 1 - \prod_{j=1}^{N_{organs}} (1 - P_{NT}^j) \quad (9)$$

$$P_+ = P_B - P_I \quad (10)$$

$$P(\vec{D}) \equiv P(\bar{D}) \quad (11)$$

The biologically effective uniform dose (\bar{D}) calculates the uniform dose that would provide the same clinical outcome as the inhomogeneous dose distribution. It is a function of physical dose and tissue specific radiobiological parameters. The general expression of \bar{D} is derived numerically from the first part of the following equation, where for a

tissue of uniform radiosensitivity, \bar{D} is given from the analytical formula of the second part of equation 12.

$$P(\vec{D}) \equiv P(\bar{D}) \Rightarrow \bar{D} = \frac{e\gamma - (\ln(-\ln P(\vec{D})))}{e\gamma - \ln(\ln 2)} \quad (12)$$

where \vec{D} denotes the 3-dimensional dose distribution delivered to the tissue and $P(\vec{D})$ is the response probability of the tissue. The second part of the equation has been derived using the Poisson model.

RESULTS

The results from the dosimetric analysis for common dosimetric qualifiers are presented in Table 3.^{4–8} The results for the radiobiological analysis are presented for each organ of interest in Table 4. Comparing Tables 3 and 4, the PTV D_{90} were well above the prescription level, indicating adequate dose to the tumour. Although the PTV V_{150} was considerably dif-

ferent, the radiobiological response for all plans was very high. Considering the rectum, the average dose for all the plans 1–5 was similar, while the maximum dose varied considerably among plans. Plan 1 had a substantially larger rectal D_{max} than any of the other plans and also yielded the highest complication probability. Plans 2–4 have similar dosimetry and complication ratios. Plan 6, which used ¹⁰³Pd seeds, had rectal doses lower than the other plans and also a complication response that was much lower than plans 2–4. The urethra V_{100} was similar for each plan. The urethra V_{150} varied significantly, perhaps explaining the differences in urethral response among plans.

Table 4 shows the complication-free tumour control probability ($P+$) for each treatment. The number of seeds used for each plan, given in Table 3, is consistent with goals of each plan. Plan 4 uses fewer seeds due to the increased seed strength and plan 5 uses more seeds due to the decreased seed strength. Plan 5 has the highest $P+$ value, and in a clinical situation would be the preferred treatment plan. However, since P_B is very high and P_I

Table 3. Dosimetric data for each treatment plan. Given as average ± standard deviation.

Plan	PTV D90 (Gy)	PTV V150 (%)	Rectum Dmax (Gy)	Rectum Avg (Gy)	Urethra V100 (%)	Urethra V150 (%)	Seed Count
1	192 ± 7.4	74 ± 5.7	195 ± 92.7	57 ± 7.9	74 ± 8.5	29 ± 17.1	82 ± 13.9
2	190 ± 7.0	73 ± 7.3	141 ± 24.6	56 ± 5.7	68 ± 8.2	0.4 ± 1.3	81 ± 11.7
3	201 ± 10.3	78 ± 8.4	136 ± 24.7	55 ± 6.2	76 ± 7.8	32 ± 17.0	80 ± 8.4
4	194 ± 8.2	76 ± 8.6	144 ± 23.2	56 ± 7.2	76 ± 8.7	16 ± 15.5	60 ± 9.0
5	188 ± 7.5	68 ± 7.8	138 ± 20.8	52 ± 6.2	71 ± 7.5	5.5 ± 6.8	105 ± 16.2
6	172 ± 14.2	87 ± 6.5	126 ± 27.9	34 ± 6.4	77 ± 6.8	36 ± 22.2	89 ± 16.2

Table 4. Radiobiological response data for each treatment plan. Given as average ± standard deviation.

Plan	P Benefit	PI Bladder	PI Other	PI Rectum	PI Urethra G2	P+
1	99.9 ± 0	2.9 ± 7.7	2.9 ± 0.9	23.7 ± 17.7	40.5 ± 18.2	48.2 ± 21.8
2	99.9 ± 0	2.8 ± 6.2	2.9 ± 0.8	17.1 ± 10.5	39.6 ± 17.0	38.7 ± 22.4
3	99.9 ± 0	4.3 ± 11.9	2.6 ± 0.5	15.5 ± 11.1	74.4 ± 12.8	13.0 ± 15.3
4	99.9 ± 0	8.0 ± 20.9	2.8 ± 1.0	16.6 ± 12.1	22.2 ± 15.7	61.8 ± 17.9
5	99.9 ± 0	2.4 ± 6.5	1.9 ± 0.7	11.4 ± 8.3	13.5 ± 12.3	77.3 ± 11.8
6	99.9 ± 0	4.8 ± 16.8	2.2 ± 0.7	8.6 ± 7.5	44.4 ± 21.9	50.1 ± 20.7

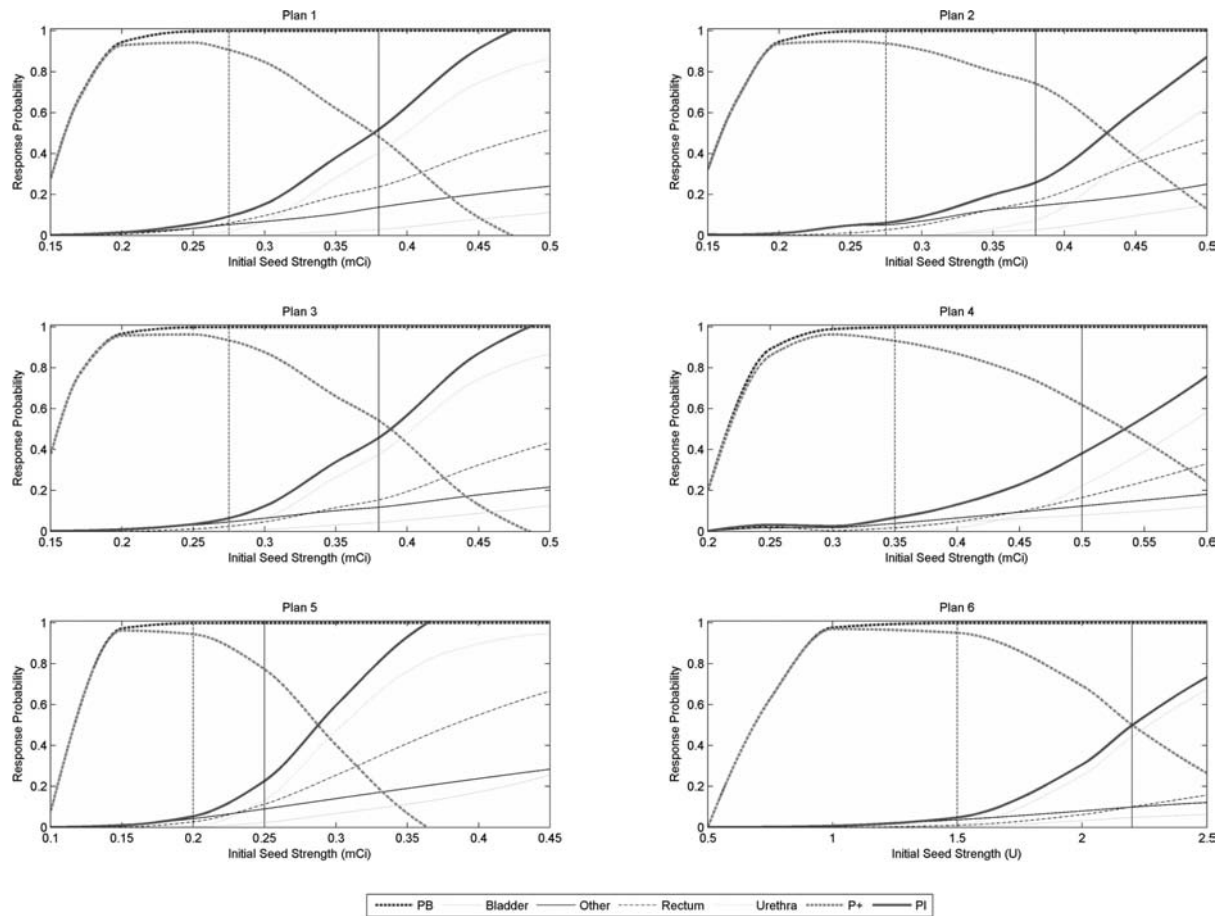


Figure 1. For each treatment plan the response probabilities of each organ, P_+ and P_I are shown versus initial seed strength. The solid vertical line indicates the initial seed strength used clinically. The dashed vertical line indicates the optimal initial seed strength.

is significant, it appears that simple refinement of the seed strengths may improve the treatment plans. Figure 1 shows the response probabilities as a function of initial seed strength for each treatment plan, as an average of all patients.

Figure 1 shows that for each plan the relationship between the response curves is different. The P_+ curve indicates that for each plan the clinical initial seed strength is above optimal. This is seen to increase normal tissue complication probabilities (NTCP) while providing no additional tumour control. Using the initial seed strength that maximises P_+ , a simplistic plan optimisation was performed and compared to the original treatment plans. It is

important to note that this simple optimisation is meant only to produce better plans for comparison in this work. A true treatment plan optimisation would include the spatial position of the seeds in addition to their strengths and is beyond the scope of this report. Figure 2 shows the DVHs of each plan, as an average of all patients. Tables 5 and 6 give dosimetric information and response probabilities for the optimised dose prescription.

Figure 2 and Table 5 show that all of the dose quantifiers are significantly reduced from the original treatment plans. All but plan 4 meet the criteria $D_{90} \geq 100\%$ for a successful plan. Table 6 shows that TCP is virtually unchanged while the NTCP is dramatically reduced. The

optimised plans have $P+$ nearly 40 % greater than the original plans.

DISCUSSION

Presently, the appropriateness of a treatment plan is determined by evaluating DVH distributions and dose quantifiers for the tumour and OAR. This can prove challenging when different indices give contradictory results. The aim of this project was to create a criterion whereby a diverse group of plans maybe compared in a simple and intuitive manner. Using a radiobiological model, the suitability of a plan may be determined by evaluating a few response probabilities for the tumour and OAR. These probabilities may be further combined to yield a single criterion, $P+$. A limited patient cohort was evaluated in this study. However, these patients show the utility of the recommended evaluation tool. Evaluation of additional patients would likely further reinforce this result.

In Figure 1 the response probabilities for each plan was evaluated for a range of initial seed strengths. Using $P+$ to determine the ideal balance of TCP and NTCP, it was clear that each plan used seeds strengths that were higher than ideal; resulting in increased NTCP with no added TCP. Using the optimal seed strengths for each plan, new treatment plans were created and evaluated for each patient. The DVH distribution of the optimised plans is shown in Figure 2, with the dosimetric and radiobiological response data given in Tables 5 and 6, respectively. Figure 2 shows that for each plan the doses to the tumour and OAR are reduced, with plan 3 showing the most dramatic reduction in OAR doses, particularly the urethra.

Table 5 indicates that plan 4 has dose levels slightly below what is commonly considered acceptable. A possible explanation for the lower dose yet high TCP may be related to the smaller number of seeds that were used. The DVH drops more rapidly in the mid-dose region, lowering D_{90} , while the high-dose tail extends

Table 5. Dosimetric data for each treatment plan. Given as average/percent decrease from original plan.

Plan	PTV D90 (Gy/%)	PTV V150 (%/%)	Rectum Dmax (Gy/%)	Rectum Avg (Gy/%)	Urethra V100 (%/%)	Urethra V150 (%/%)
1	149/6.3	43/13.2	195/0.0	50/3.3	59/5.6	2.1/43.2
2	147/6.4	43/12.9	139/0.4	47/4.4	29/20.1	0.0/50.0
3	152/6.9	42/15.0	125/0.2	46/4.5	62/5.1	1.9/44.4
4	140/8.1	33/19.7	131/3.5	43/6.6	38/16.7	0.1/49.4
5	153/5.1	40/12.7	131/1.3	46/3.2	54/6.9	0.2/46.2
6	123/8.3	50/13.3	103/4.9	25/7.7	45/13.2	2.0/44.8

Table 6. Radiobiological response data for each treatment plan. Given as average/percent difference from original plan.

Plan	P Benefit (%/%)	PI Bladder (%/%)	PI Other (%/%)	PI Rectum (%/%)	PI Urethra G2 (%/%)	$P+$ (%/%)
1	99.8/0.1	0.0/2.9	1.1/1.8	6.1/17.6	2.1/3.3	90.6/7.1
2	99.8/0.1	0.1/2.7	1.1/1.8	2.7/14.4	0.0/0.0	93.8/2.4
3	99.9/0.0	0.3/4.0	1.0/1.6	2.5/13.0	1.8/2.3	93.4/1.7
4	99.0/0.9	2.5/5.5	0.8/2.0	1.7/14.9	0.1/0.1	93.2/6.9
5	99.9/0.0	0.2/2.2	0.9/1.0	2.8/8.6	0.4/0.1	94.5/2.5
6	99.9/0.0	0.4/4.4	0.8/1.4	1.0/7.6	1.5/2.6	95.2/2.1

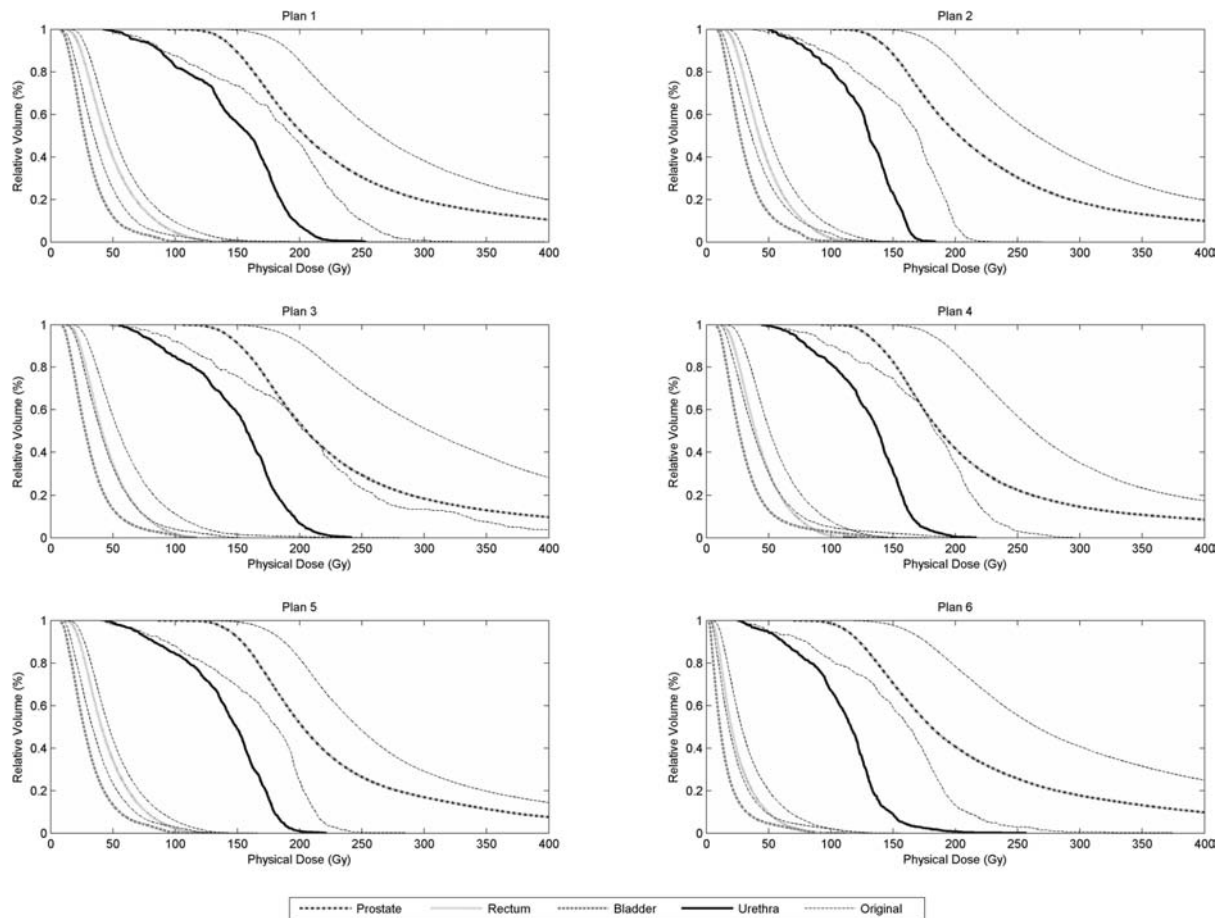


Figure 2. DVH distributions for optimised plans are shown in solid lines, with the DVH distributions of the initial plans shown as dashed lines.

further. In short, plan 4 is a more inhomogeneous dose distribution than the other plans. Table 6 shows that while the tumour dose was decreased, the TCP was nearly unchanged and NTCP was greatly reduced. By using the optimal initial seed strength for each plan $P+$ is improved by about 40%.

Prostate seed implants are unique among radiotherapy modalities in that the delivered dose distribution is largely dependent on the skill of the implanting physician and subsequent prostate edema. The predicted TCP for each plan is very high, 99.8%. Other investigators have reported lower relapse-free survival of 89–94% among similar patient populations.^{9,10} This discrepancy is likely due to the slight differences between the planned and the delivered

dose distribution from edema and inexact seed placement. The effects of prostate edema would likely be small for iodine-125 implants since the isotope half-life is much longer than the edema half-life.^{11,12} The effect of edema on palladium-103 implants, however, may be more significant.

Concerning the calculated rectal response, the optimised plans are significantly lower than the original plans. Authors have reported rectal complication rates of 8–18% for plans with similar dose distribution as the original plans.^{13,14} Our results are consistent with these response probabilities. The optimised plans have reduced rectal doses, as is seen in Figure 2, and the response probability is correspondingly less.

For both the original and optimised plans the bladder response was negligible. This is consistent with our clinical experience that the bladder is located relatively far from the prostate and receives limited dose. Concerning the urethra, reported complication rates vary widely. This is likely due to the variability of urethral doses that may occur. Thomas et al. has reported a urethra grade 2 complication rate of 36% for plans with dosimetry similar to those used here in the original plans, which is consistent with our results.¹⁵ Others have reported higher complication rates, 85–92%, for plans with dosimetry much higher than the original plans presented here.^{16,17} However, these rates are consistent with those determined for plans with high initial seed strengths, seen in Figure 1. The urethral response for the optimised plans is significantly lower than those of the original plans. This is due to a similarly significant drop in urethral doses in the optimised plans.

The response probabilities determined for the original plans are consistent with patient follow-up data. None of the patients required additional treatment for their prostate cancer. Some patients reported minor rectal complications, such as temporary diarrhea or bloody stool. The most common complaints were of urinary symptoms such as dysuria and increased nocturia. Patients that had the most severe symptoms also had the highest calculated response probabilities.

The main advantage of this treatment planning tool is that it uses the response calculated for each voxel to predict the clinical outcome. This allows for simpler plan comparison based on a few criteria, such as response probabilities and $P+$.¹⁸ It also allows for optimisation of the seed strengths in order to better balance increased TCP with increased NTCP.

CONCLUSION

The goal of this work was to apply and produce a radiobiologically-based treatment planning evaluation tool to improve and simplify plan comparison through the use of a small number of evaluation criteria. By analysing several treat-

ment plans for each patient we have shown that a radiobiologically-based treatment plan evaluation is more intuitive than dose quantifiers and offers opportunities to optimise treatment plans.

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