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Original Article

Radiobiological comparison of single and dual-isotope prostate seed implants

Courtney Knaup[1], Panayiotis Mavroidis[1,2], Carlos Esquivel[1], Sotirios Stathakis[1], Gregory Swanson[1], Dimos Baltas[3,4], Nikos Papanikolaou[1]

[1]*Department of Radiation Oncology, University of Texas Health Science Centre at San Antonio, San Antonio, TX, USA,* [2]*Department of Medical Radiation Physics, Karalinska Institutet & Stockholm University, Stockholm, Sweden,* [3]*Dept. of Medical Physics and Eng., Offenbach Clinic, Offenbach, Germany,* [4]*Nuclear and Particle Physics Section, Physics Department, University of Athens, Greece*

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Abstract

Purpose: Several isotopes are available for low dose-rate prostate brachytherapy. Currently most implants use a single isotope. However, the use of dual-isotope implants may yield an advantageous combination of characteristics such as half-life and relative biological effectiveness. However, the use of dual-isotope implants complicates treatment planning and quality assurance. Do the benefits of dual-isotope implants outweigh the added difficulty? The goal of this work was to use a linear-quadratic model to compare single and dual-isotope implants.

Materials & Methods: Ten patients were evaluated. For each patient, six treatment plans were created with single or dual-isotope combinations of ^{125}I, ^{103}Pd and ^{131}Cs. For each plan the prostate, urethra, rectum and bladder were contoured by a physician. The biologically effective dose was used to determine the tumor control probability and normal tissue complication probabilities for each plan. Each plan was evaluated using favorable, intermediate and unfavorable radiobiological parameters. The results of the radiobiological analysis were used to compare the single and dual-isotope treatment plans.

Results: Iodine-125 only implants were seen to be most affected by changes in tumor parameters. Significant differences in organ response probabilities were seen at common dose levels. However, after adjusting the initial seed strength the differences between isotope combinations were minimal.

Conclusions: The objective of this work was to perform a radiobiologically based comparison of single and dual-isotope prostate seed implant plans. For all isotope combinations, the plans were improved by varying the initial seed strength. For the optimized treatment plans, no substantial differences in predicted treatment outcomes were seen among the different isotope combinations.

Keywords

Prostate; Brachytherapy; Radiobiological Modeling; Treatment Planning

Correspondence to: Niko Papanikolaou, PhD, Cancer Therapy & Research Center, University of Texas Health Science Center at San Antonio, 7979Wurzbach Rd, San Antonio, TX 78229, USA, phone: +1 210-450-5664, e-mail: papanikolaou@uthscsa.edu

INTRODUCTION

Low dose-rate (LDR) brachytherapy is a common radiotherapy technique used in the treat-

ment of prostate cancer. Three isotopes are commonly used: Iodine-125 which has a half-life of 59.4 days and emits a 28 keV gamma ray, Palladium-103 which has a 17 day half-life and emits a 21 keV gamma ray and Cesium-131 which has a 9.7 day half-life and emits a 30 keV gamma ray. The choice of isotope is typically made based on cancer grade, patient geometry and physician preference. Some have considered the possibility of using dual-isotope implants. Currently however, most commercially available treatment planning systems do not allow the use of dual-isotope plans. Additionally, the dosimetric planning goals would vary depending on what isotopes are used, as well as the fraction of total dose delivered by each isotope. With the added complexity of dual-isotope implants, one wonders if they provide disease control superior to mono-isotope implants.

In this work, a 3D treatment plan evaluation tool, based on the radiobiological response of each voxel is used to compare single and dual-isotope plans. For each treatment plan the probability of injury to the tumour and organs at risk (OAR) was calculated for three prostate cancer risk groups.

MATERIALS AND METHODS

Ten patients were used in this study. Treatment plans were created using ^{125}I seeds (BARD, BrachySource model, Covington, GA, USA) to a D_{100} of 145 Gy; ^{103}Pd seeds (Theragenics, model 200, Buford, GA, USA) to a D_{100} of 125 Gy; and ^{131}Cs seeds (IsoRay, CS-1 Rev2, Richland, WA, USA) to a D_{100} of 115 Gy.[1, 2] For each patient six treatment plans were created for the following configuration of isotopes: ^{125}I only, ^{103}Pd only, ^{131}Cs only, ^{125}I and ^{103}Pd, ^{125}I and ^{131}Cs, ^{103}Pd and ^{131}Cs. 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 contoured by the same physician for all plans. A single physician was used for consistent contouring. Prowess does not allow treatment plans using multiple isotopes, so for the dual-isotope implants, two plans were created and combined using our in-house software. For the dual-isotope plans, the prescription dose for the constituent single-isotope plans was one-half of that used in mono-isotope plans. When combining the plans, the seed locations were examined to ensure seeds were not overlapping and there were no more than three consecutive seeds.

The radiobiological response of the treatment was calculated using the linear-quadratic model. The physical dose was calculated from the American Association of Physicists in Medicine Task-Group 43 formalism, using the seed strengths and coordinates from Prowess.[3] The in-house software dose calculation was validated by comparing point-doses and isodose distributions with Prowess, for a single-source geometry and a simple distribution of five seeds. The differences in the calculated doses between the in-house software and Prowess were less than one percent. Then, the organ contours for each ultrasound image slice was exported from Prowess to the in-house software. Based on the physical dose and type of tissue present in each voxel, the tumour control probability (TCP) was calculated.[4]

RESULTS

The calculated response probabilities for the prostate and OARs for the treatment plans using the standard prescriptions are shown in Table 1. Table 1 shows the tumour response determined using the *favourable* parameters, which were identical to the *intermediate* and *unfavourable* parameters at the standard prescription level.

The tumour control probability was determined using equation 8. The OAR responses were calculated using equation 9 with appropriate biological parameters. Table 1 shows that TCP is high, but so are many of the OAR responses. The P_+ values also vary greatly among the plans. This seemed to indicate that for the single-isotope implants a reduction in dose may be advantageous. For the dual-isotope implants this also indicates that a reduction in dose may

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Table 1. Response probabilities using original initial seed strengths and favorable tumour parameters reported as an average of all patients.

Plan	Strength	TCP (%)	Rectum (%)	Bladder (%)	Urethra (%)	Other (%)	P_+ (%)
I-125	0.37 mCi	99.9±0.0	23.2±17.7	2.8±7.5	38.4±18.9	26.9±6.9	35.6±19.1
Pd-103	2.2 U	99.9±0.0	11.6±9.6	5.2±15.6	51.8±19.4	23.0±5.7	31.3±15.9
Cs-131	2.0 U	99.9±0.0	6.1±3.9	1.3±4.2	2.8±3.9	14.6±4.7	76.8±7.7
I & Pd	0.37 & 2.2	99.9±0.0	24.7±13.8	7.6±17.1	64.1±20.1	32.4±8.4	15.4±8.2
I & Cs	0.37 & 2.0	99.9±0.0	21.1±15.3	4.9±11.1	32.0±22.1	28.7±7.8	36.9±17.4
Pd & Cs	2.2 & 2.0	99.9±0.0	11.9±10.6	5.3±15.3	25.3±21.0	23.8±5.4	47.7±17.2

be advantageous, but also a different weighting of the seed strengths may yield better plans. For each plan the initial seed strength was varied to determine the maximum P_+, and therefore the optimal initial seed strength. Figure 1 shows the response of the tumour and OARs as a function of initial seed strength for the single-isotope plans. Figure 2 shows P_+ for the dual-isotope plans as a function of the initial seed strengths.

Figure 2 shows that for all combinations, the shape of the curve is very similar. The large, mostly flat topped shoulder indicates that there is no *best* combination of seed strengths. Rather, there is simply a trade-off of the two seed strengths that yield similar results. Close inspection of the shoulder region shows that the apex is not flat, rather it slopes slightly. This tilt shows that P_+ is slightly higher when the short-lived isotope delivers the majority of the dose. Hence the ^{125}I and ^{131}Cs graph was tilted the most and the ^{103}Pd and ^{131}Cs was tilted the least. From the initial seed strength analysis, the optimal strengths were determined and the response probabilities for these treatments are shown in Table 2. Since the optimal seed strengths are lower than those planned, the *intermediate* and *unfavourable* tumour parameters were also used to determine if the lower dose would compromise treatment effectiveness for a more resistant disease.

DISCUSSION

Table 1 shows that for the common prescription levels used here, the effectiveness of different isotopes varies considerably. The response probabilities of the tumour and OARs are consistent with those commonly observed in the clinic. The differences between P^+ values were thought to arise primarily from high prescription dose levels rather than from inherent isotope differences. To further explore this, different initial seed combinations were evaluated to determine the optimal seed strengths, and therefore the best treatment that the particular isotope could provide. By comparing the optimal plans, the different isotopes may be compared on a more even level.

Figure 1 shows that differences in TCP at a given dose level, for different tumour types, varies significantly for ^{125}I, and minimally for ^{103}Pd and ^{131}Cs implants. This is consistent with the practice of using short-lived isotopes to maintain high TCP in high-grade tumours.[5,6,1] Figures 1 and 2 indicate that for *favourable, intermediate* and *unfavourable* tumours, there is a wide therapeutic window between the tumour and OAR responses. This suggests the possibility that reducing dose levels may significantly reduce OAR toxicity without adversely affecting TCP. Indeed, many investigators have similarly concluded that a reduction of dose prescriptions may be warranted.[7,8] Table 2 shows the response probabilities for the plans using the optimal initial seed strengths. These show that the toxicity to the OARs may be significantly reduced with no discernible reduction in TCP.

The major limitation of this analysis stems from the use of specific radiobiological parameters, which are known to vary somewhat between patients and even within the same organ. Thus, the probabilities calculated should only be considered as estimates of the response for a *typical* patient. However, this limitation is also shared by all the common radiobiological and dosimetric quantifiers, because the degree of radiation induced effect for a specified dose level is also variable within a patient population.

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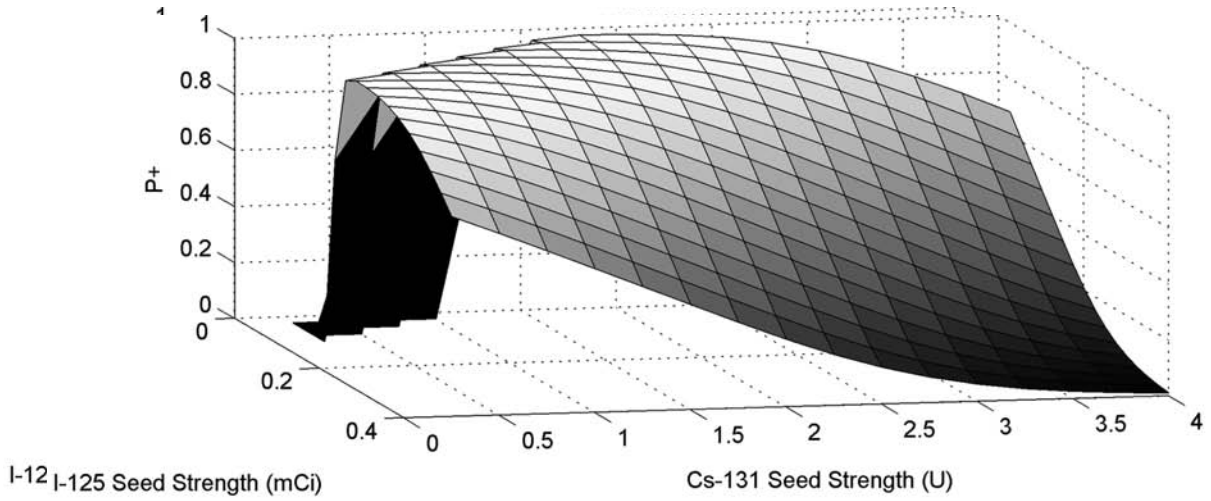

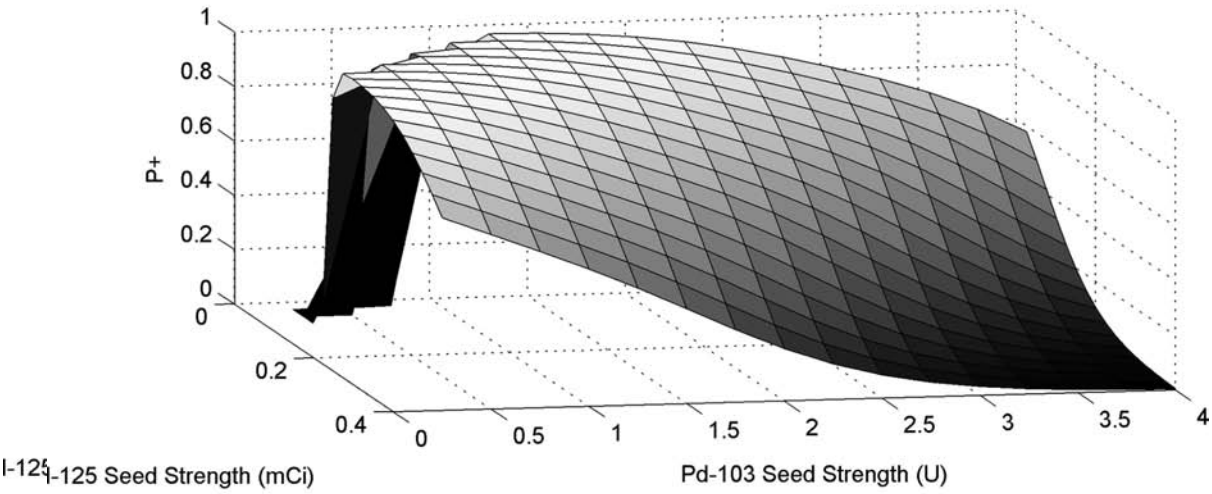

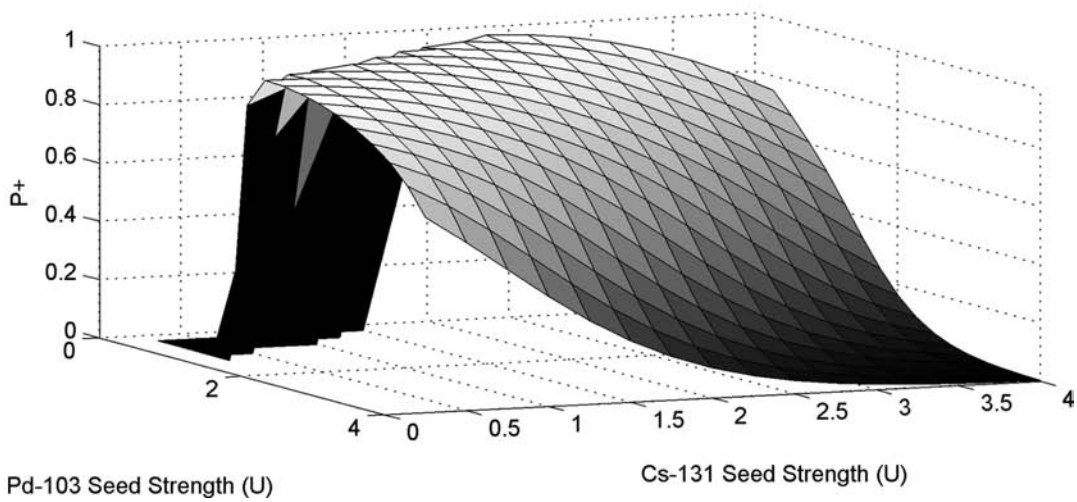

Figure 1. Response curves as a function of initial seed strength for single-isotope plans.

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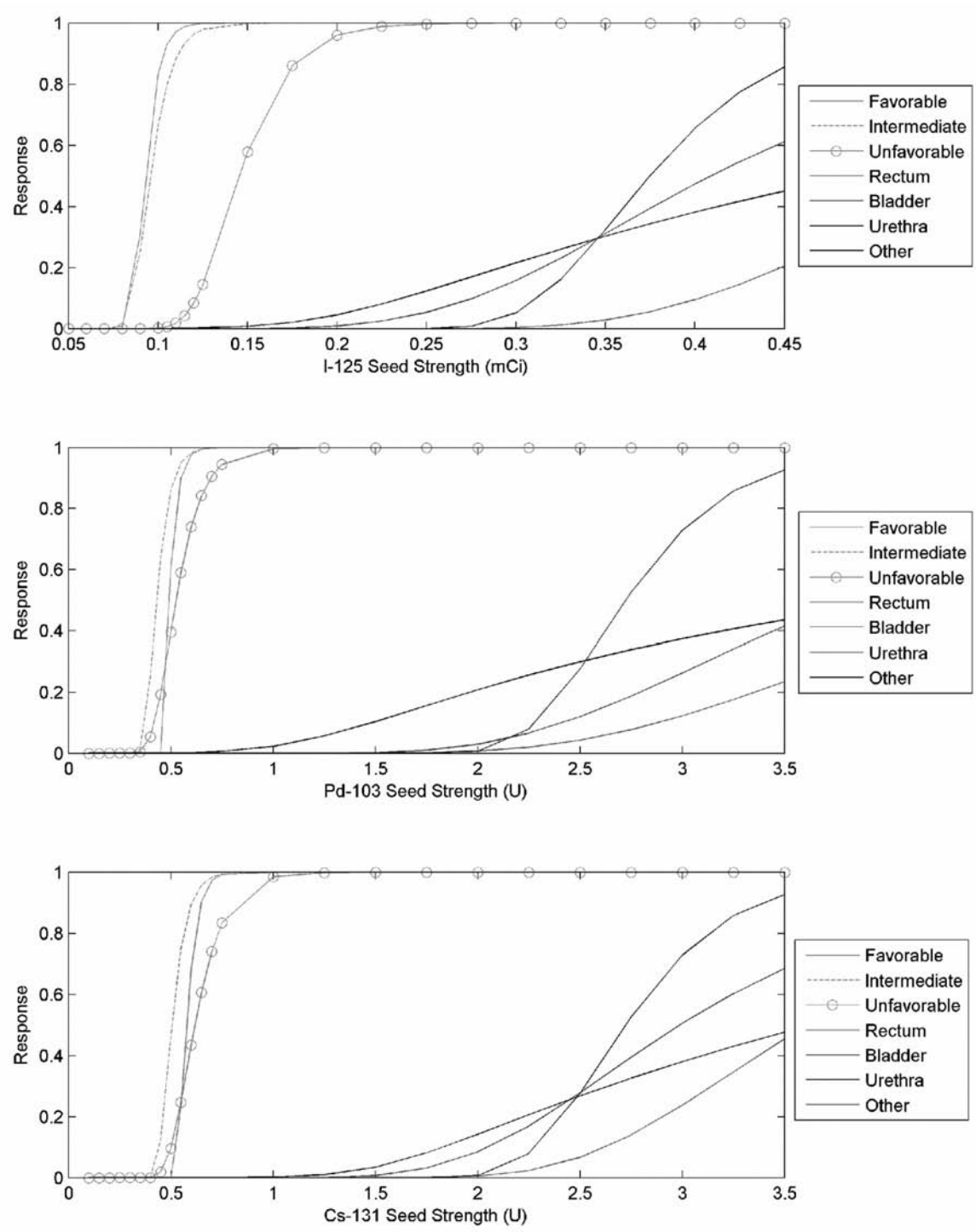

Figure 2. P_+ as a function of initial seed strength for the dual-isotope combinations.

Additional factors not considered in this work may also contribute to the radiobiological response. Hypoxic cells, for example, have been shown to dominate the response of the tumour. However, in practice the imaging information of the location of those hypoxic

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Table 2. Response probabilities using optimal initial seed reported as an average of all patients.

Plan	Strength	Favourable (%)	Intermediate (%)	Unfavourable (%)	Rectum (%)	Bladder (%)	Urethra (%)	Other (%)	P_+ (%)
I-125	0.21 mCi	99.9±0.0	99.9±0.0	95.8±2.6	0.7±1.2	0.0±0.0	0.0±0.0	3.6±1.2	95.7±2.0
Pd-103	1.13 U	99.9±0.0	99.9±0.0	99.9±0.1	0.1±0.2	0.0±0.0	0.0±0.1	3.0±1.5	96.8±1.7
Cs-131	1.45 U	99.9±0.0	99.9±0.0	99.9±0.1	0.5±0.5	0.0±0.0	0.0±0.0	3.1±1.1	96.4±1.3
I & Pd	0.13 & 1.13	99.9±0.0	99.9±0.0	99.1±0.4	0.0±0.1	0.0±0.0	0.0±0.0	2.5±0.8	97.5±0.1
I & Cs	0.13 & 1.43	99.9±0.0	99.8±0.1	97.8±1.1	0.1±0.3	0.0±0.0	0.0±0.0	1.6±0.4	98.2±0.5
Pd & Cs	1.10 & 1.23	99.9±0.0	99.9±0.0	99.3±0.5	0.1±0.2	0.0±0.0	0.0±0.2	2.9±0.6	97.0±0.6

Table 3. Radiobiological parameters for the tumour.

Tissue type	γ	α/β	D^{50}	s	End point
Favourable	6.5	3	35	1.0	Control
Intermediate	3.7	7	40	1.0	Control
Unfavourable	2.0	10	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

cells is not available and the whole tumour is considered to have a homogeneous radiosensitivity. In this way, the effective radiobiological values representing the radiosensitivity of the whole tumour are determined. The use of such parameters may be acceptable for evaluating similar treatment plans, but may be insufficient for performing a full scale plan optimization.[9] While the specific parameters may vary, Table 2 shows for cancer grades that vary substantially, the calculated responses are comparable. Furthermore, the wide plateau seen in figures 1 and 2 indicate that modest changes in the radiobiological parameter would have little effect on the calculated response.

Comparing the responses in Table 2 for the different seed combinations, one sees that there is little difference. P_+ for the ^{125}I implants was the lowest of all the combinations evaluated. P_+ for the dual-isotope combination of ^{125}I and ^{131}Cs was the highest. While the results of this work suggest that use of short-lived isotopes are preferred in treating high-grade tumours, the benefits of dual-isotope implants were not seen. A difference may be seen if significant prostate edema is present. However, edema is difficult to model and varies considerably between patients. Considering the energies of the isotopes, ^{103}Pd may be slightly more susceptible to volume changes due to edema. Therefore, one might expect the addition of ^{125}I and ^{131}Cs to ^{103}Pd implants to reduce the effects of edema. More research is needed before models of prostate edema can be included in treatment planning.[10,11] It is also important to note that this work treated the tumour as homogeneous in risk. Using dual-isotopes to boost disease foci may yield more effect than single-isotope implants.[8]

CONCLUSION

The rationale for the use of dual-isotope prostate seed implants is to combine the *favourable* characteristics of different isotopes to obtain a better clinical outcome for the patient. The goal of this work was to perform a radiobiologically-based comparison of single and dual-isotope prostate seed implants. The results of this work indicate that there is room for optimisation within a

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given plan. However, comparison of different isotope combinations showed that all were nearly equivalent, even when considering *favourable, intermediate* and *unfavourable* cancer risk groups.

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APPENDIX

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.[12,13]

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

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

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 λ = 0.01166 day^{-1}, ^{103}Pd λ = 0.04079 day^{-1}, ^{131}Cs λ = 0.07144 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 μ = 2.8 hour^{-1}.[14,15] The tumour repopulation factor (K) accounts for the growth of new tumour cells during treatment and is calculated from equation 3.[6,14]Prostate cancer is considered to be a slow growing cancer. The potential doubling time (T_{pot}) reported in the literature for *favourable* tumours and used in this report was 42 days. Resulting in a repopulation factor of 0.11 Gy/day, which is consistent with a slow growing disease. Models of repopulation often assume a ''kick-off'' time for repopulation to occur.[16] Equation 1a, which is widely used, does not assume any kick-off time. However, even in the case of such a biological mechanism, the effective value of the potential doubling time would incorporate its effects, since T_{pot} is determined from retrospective clinical data. Especially in the case of seed implants, where the treatment follows a certain treatment time pattern, this issue plays no role.

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

The effective dose (D_{eff}) was calculated using equation 4. The effective treatment time (T_{eff}) was determined from equation 5. The end-point for brachytherapy has been defined as the point where the rate of cell kill is equal to the tumour repopulation factor.[17] 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.

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

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

The relative biological effectiveness (RBE) for ^{125}I, ^{103}Pd and ^{131}Cs used in this study were 1.45, 1.75 and 1.45, respectively.[17, 18]. The RBE for ^{131}Cs has been assumed to be the same as for ^{125}I, based on their similar decay energy. The specific radiobiological parameters α/β, D_{50} and γ used for each tissue are given in Table 3. D_{50} is the dose which gives a 50% response and γ is the maximum normalised dose-response gradient. In this study, three sets

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of parameters were evaluated for each plan representing *favourable*, *intermediate* and *unfavourable* cancer risk groups, indicating increasing radioresistance, as suggested by King et al.[19] The α/β indicates the proportion of the process of cell kill that are related to the α and β parameters. However, the level of this ratio is determined by the value of the α parameter, which expresses the cell radiosensitivity. So as it can be seen in Table 3, although *favourable* tumours have α/β similar to that of dose-limiting normal tissues, which indicates a similar dependence on dose-rate, their α value indicates that they are radiosenesitive. Both α and β parameters are intrinsic for each tumour and they are determined from clinical trials. The use of a high α/β for *favourable* group and a low α/β for the *unfavourable* group could possibly play some role on the results of this study, but since this is not indicated by the clinical studies that determined those parameters, the authors did not examine this scenario.

Voxel response probability (P) was 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.[20,21,22] The overall response probability for the tumour and normal tissues is calculated using equations 7a and 7b, respectively.

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

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

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

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 ($\bar{\bar{D}}$) 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.

$$P_B = \prod_{j=1}^{N_{tumors}} P^j_{Tum} \qquad (8)$$

$$P_I = 1 - \prod_{j=1}^{N_{organs}} (1 - P^j_{NT}) \qquad (9)$$

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

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

The biologically effective uniform dose ($\bar{\bar{D}}$) 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 $\bar{\bar{D}}$ is derived numerically from the first part of the following equation, where for a tissue of uniform radiosensitivity, $\bar{\bar{D}}$ is given from the analytical formula of the second part of equation 12.

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

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 (4).

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