Radiobiological model comparison of 3D conformal radiotherapy and IMRT plans for the treatment of prostate cancer*

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Abstract

The main aim of radiotherapy is to deliver a dose of radiation that is high enough to destroy the tumour cells while at the same time minimising the damage to normal healthy tissues. Clinically, this has been achieved by assigning a prescription dose to the tumour volume and a set of dose constraints on critical structures. Once an optimal treatment plan has been achieved the dosimetry is assessed using the physical parameters of dose and volume. There has been an interest in using radiobiological parameters to evaluate and predict the outcome of a treatment plan in terms of both a tumour control probability (TCP) and a normal tissue complication probability (NTCP). In this study, simple radiobiological models that are available in a commercial treatment planning system were used to compare three dimensional conformal radiotherapy treatments (3D-CRT) and intensity modulated radiotherapy (IMRT) treatments of the prostate. Initially both 3D-CRT and IMRT were planned for 2 Gy/fraction to a total dose of 60 Gy to the prostate. The sensitivity of the TCP and the NTCP to both conventional dose escalation and hypo-fractionation was investigated. The biological responses were calculated using the Källman S-model. The complication free tumour control probability (P+) is generated from the combined NTCP and TCP response values. It has been suggested that the α/β ratio for prostate carcinoma cells may be lower than for most other tumour cell types. The effect of this on the modelled biological response for the different fractionation schedules was also investigated.

Key words 3D-CRT, IMRT, radiobiology, TCP, NTCP

Introduction

Prostate cancer is potentially curable if detected and treated in the early stages. There are several treatment options available for prostate cancer[1]. These treatment options vary according to the stage of the cancer and other medical conditions. Radiotherapy and surgery are the two main options used to eliminate the primary tumour[2]. Radiotherapy is one of the most effective methods for cancer treatment. It is currently in the process of rapid change. This movement has mainly been driven by rapid achievements in computer technology which led to the development of new treatment planning and delivery systems[3]. 3D-Conformal Radiation Therapy (3D-CRT) and Intensity Modulated Radiation Therapy (IMRT) have being used for both the palliative and curative treatments of cancer. The main goal of curative radiation therapy is to deliver a dose of radiation high enough to control the tumour while at the same time minimizing the radiation dose to the surrounding normal tissues. In many cases there is clinical evidence that increasing the tumour dose results in improved tumour control. This is particularly the case for prostate cancer[4,5]. The major challenges in achieving this goal are the uncertainties of tumour volume delineation, minimising the effects of patient set-up errors and the limitations of the dose delivery system[6]. This limits the tumour dose that can be safely prescribed and delivered to the patient.

Currently, the treatment planning process is defined and evaluated only in terms of physical dose and physical volume. Radiobiological models attempt to describe the dose response of tumour and normal tissues on irradiation and also the dependence on the fractionation schedule. These mathematical models can be used to calculate the tumour control probability (TCP) and normal tissue complication probability (NTCP)[7-11] for a given dose distribution. Ultimately, it would be desirable to use radiobiological models directly in the treatment planning optimisation process[12].

The ratio α/β is a measure of a tissue's sensitivity to fractionation, that is, the size of dose given in each

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treatment[13]. There is an increasing body of evidence that prostate cancer cells behave as a late reacting tissue and therefore the α/β value for prostate cancer cells could have a value as low as 1 to as high as 5[14-20]. This is in sharp contrast to the accepted value of 10 for most tumours. The rectum and bladder have a α/β value of 3 or 4 so if the α/β value for prostate cancer is indeed lower than this then it suggests that the tumour cells would be more sensitive to changes in the dose per fraction than the normal tissue cells and that this could be exploited through hypo-fractionation[21]. Clinical experience would appear to support this hypothesis however the relative failure of small radiation doses per fraction (< 2 Gy/fraction) in controlling prostate cancer might be complicated further by hypoxia[22].

In this study we investigate the hypothesis that IMRT can improve the clinical outcome for prostate radiotherapy using radiobiological models that are available in the Pinnacle (Philips Medical Systems) treatment planning system. The work also investigates the use of these radiobiological models to evaluate some of the dose escalation schedules, both conventional and hypo-fractionation that have been used in the radiotherapy treatment of prostate cancer patients. Finally, the rationale for hypo-fractionation in the treatment of prostate cancer is investigated by varying the α/β parameter for the prostate in the radiobiological models.

Theory

Advanced treatment optimization is possible using quantitative radiobiological dose response models[23]. Radiobiological models can quantify the response of heterogeneous tumours and organized normal tissues to non-uniform dose delivery. These responses can be used to find the right balance between cure and complications either including them directly in the optimization or by using them as an evaluation tool for the clinical outcome of a treatment. With such models it is possible to find the intensity-modulated dose delivery that maximizes the complication-free cure and at the same time minimizes the risk of severe normal tissue side effects. The predictive power of the models is assessed through analysis of complications or control data before they can be considered reliable for clinical treatment planning. However, limited validation of these models has been performed using clinical data[20].

Although there are several sophisticated models for TCP[24-26] and NTCP[27] that have been published, the radiotherapy treatment planning software Pinnacle v7.6c has been used to calculate the biological responses in this study for simplicity. The responses are calculated in Pinnacle using the Kallman S-model[28,29].

TCP calculations

TCP is the probability that the tumour is completely eradicated. A radiation therapy plan represents a volumetric distribution of radiation dose. The TCP value for a given tumour volume is calculated in Pinnacle using equation

$$P_i^j = e^{-\exp(e\gamma^j - \alpha^j d_i - (\beta^j d_i^2)/n)} \quad (1)$$

where P_i^j is the probability to achieve tumour control in voxel *i* for tumour volume *j*.

γ is the normalized slope of the dose response curve.

d_i is the dose / fraction at the voxel *i*.

n is the number of fractions.

α/β is the survival curve shape parameter.

α is generated using equation

$$\alpha^j = \frac{e\gamma^j - (\ln\ln 2)\frac{D_{50}^j}{nd}}{(1+(\bar{d}/(\alpha/\beta)^j))D_{50}^j} \quad (2)$$

β is generated using equation

$$\beta^j = \frac{e\gamma^j - (\ln\ln 2)\frac{D_{50}^j}{nd}}{(\bar{d}+(\alpha/\beta)^j)D_{50}^j} \quad (3)$$

where D_{50} is the dose level to achieve a 50 % probability of tumour control.

The composite value for all TCP responses is calculated using equation

$$P_B = \prod_j P_B^j \quad (4)$$

where P_B is the overall probability for benefit of the treatment by destroying all *j* tumours.

NTCP calculations

The NTCP value for a given organ is calculated using equation

$$P_I^j = \left(1 - \prod_{i \in V^j} [1 - (P_i^j)^{s^j}]^{\Delta v_i^j}\right)^{1/s^j} \quad (5)$$

Where, P_I^j is the probability of causing normal tissue complication for organ *j*.

s^j is the relative seriality of the organ *j*.

P_i^j is calculated using equation (1)

V^j is the index set for the voxels covered by organ *j*.

Δv_i^j is the relative volume calculated using equation

$$\Delta v_i^j = \frac{v_i^j}{\sum_{i \in V^j} v_i^j} \quad (6)$$

The composite value for all NTCP responses is calculated using equation

$$P_I = 1 - \prod_{j \in I_0} (1 - P_I^j) \quad (7)$$

where P_I is the overall probability of injury to normal tissue.

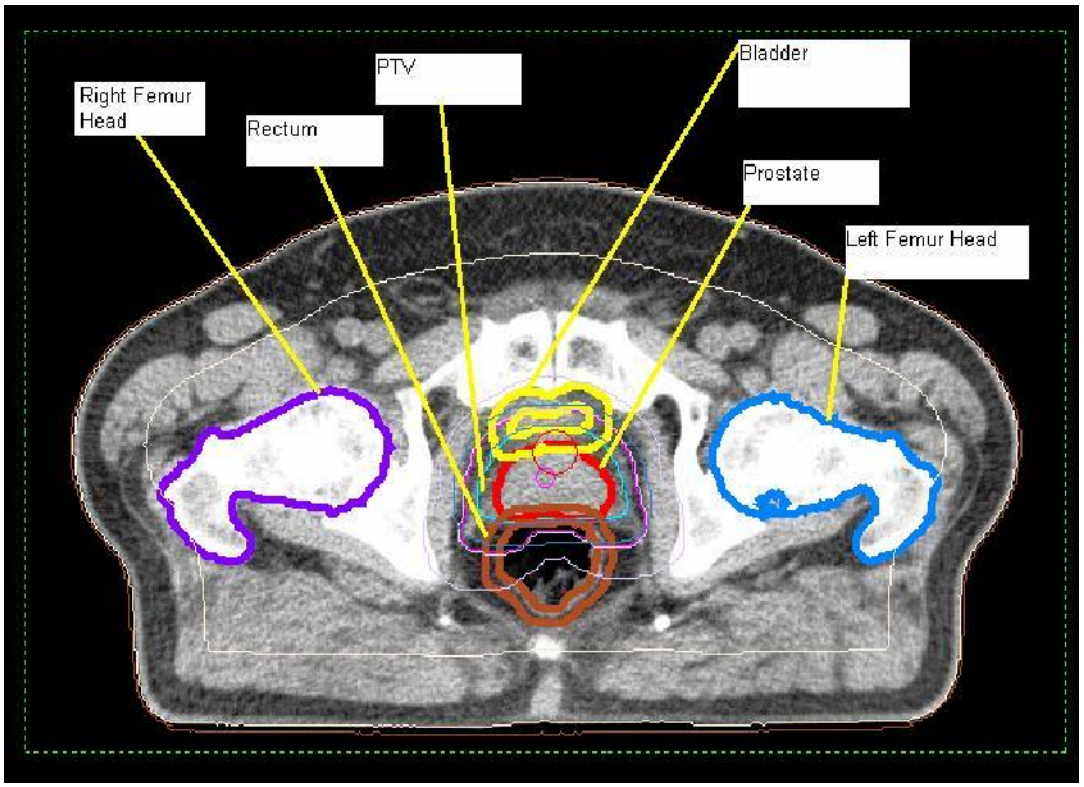

Figure 1. *The contoured patient volumes used in this study, PTV, rectal wall, bladder wall and femoral heads.*

Table 1. *Parameters used in the radiobiological models for calculation of TCP and NTCP. The values listed here are part of a radiobiological database in the Pinnacle treatment planning system that is based on published data.*

Organ	D_{50}	γ	α/β	Relative seriality
Prostate (PTV)	52.57	4.2	1-10	-
Bladder	80	3	3.0	0.18
Rectum	80	2.2	3.0	1.5
Femoral heads	65	2.7	3.0	1.0

Complication free tumour control probability (P+) calculations

P+, the composite response value is generated from the combined NTCP and TCP response value[30]. The P+ value is calculated using equation

$$P_{+} = P_B - P_I \tag{8}$$

where, P_B and P_I are the composite values for all TCP and NTCP given by equations (4) and (7) respectively.

Methods

A prostate patient was planned using two different 3D-CRT techniques and an IMRT technique. The different plans were evaluated using radiobiological models that are available in the Pinnacle Planning system. The visible tumour, critical structures and other relevant landmarks were outlined slice-by-slice on the patient CT dataset. The prostate and the surrounding organs at risk (rectum, bladder, left and right femur heads) were outlined according to International Commission on Radiation Units and Measurements (ICRU) Reports 50 and 62[31, 32]. The volumes of these organs are shown in figure 1. For all plans in this study the same volumes were used.

To simplify the IMRT optimization process the beam angles are fixed. Beam angle selection is important however and may have an impact on the final optimized IMRT plan. Five photon beams were used for the IMRT plans (36°, 100°, 180°, 260° and 324°). For the 3D-CRT plans, two different sets of beam angles were designed. Four photon beams were used in one plan (0°, 90°, 180° and 270°) and in the second plan five photon beams (0°, 90°, 120°, 240° and 270°) were used.

The effect of different dose escalation strategies was investigated and assessed for the three different treatment plans using the Pinnacle radiobiological evaluation module. The parameters used in the radiobiological models for calculation of TCP and NTCP are listed in table 1. Conventional dose escalation where the dose/fraction was

Table 2. *Dose prescriptions for treatment trials in 3D-CRT 4 field, 3D-CRT 5 field and IMRT plans. BED_2 is the biologically equivalent 2 Gy per fraction dose for α/β=1.5 and α/β=10.*

Dose (Gy)	No. of fractions	Fraction size (Gy)	BED_2 (α/β=1.5) (Gy)	BED_2 (α/β=10) (Gy)
60	30	2.000	60.0	60.0
61	30	2.033	61.6	61.1
62	30	2.066	63.2	62.3
63	30	2.100	64.8	63.5
64	30	2.133	66.4	64.7
65	30	2.166	68.1	65.6
66	30	2.200	69.8	67.1
67	30	2.233	71.5	68.3
68	30	2.266	73.2	69.5
70	30	2.333	76.6	71.9
62	31	2.000	-	-
64	32	2.000	-	-
66	33	2.000	-	-
68	34	2.000	-	-
70	35	2.000	-	-

Table 3. *Published prostate hypo-fractionation trials that were investigated in this study. The BED_2 was calculated for α/β = 1.5 and α/β =10.0.*

Fractionation schedule	Biologically equivalent 2 Gy dose [α/β =1.5]	Biologically equivalent 2 Gy dose [α/β =10.0]	Trial reference
60 Gy (20 x 3 Gy)	77.1 Gy	65.0	PMH, Toronto[37]
70 Gy (28 x 2.5 Gy)	80.0 Gy	72.9	Cleveland Clinic, OH[38]
50 Gy (16 x 3.125 Gy)	66.1 Gy	54.7	Christie Hospital[39]
55 Gy (20 x 2.75 Gy)	66.8 Gy	58.4	Adelaide Hospital[40]

fixed at 2 Gy and the number of fractions increased was investigated. The dose, number of fractions, and the dose per fraction investigated for the three different treatment plans are listed in table 2. The effect of fixing or reducing the number of fractions and increasing the dose per fraction was also investigated using some published hypo-fractionation schedules for prostate patients. These are listed in table 3. The sensitivity of the TCP to variations in α/β over the range of 1–10 was investigated for the different fractionation schedules and the three planning techniques.

Results and discussion

Sensitivity of the radiobiological evaluation to the fractionation schedule

TCP

Figure 2 shows the TCPs as a function of prescription dose planned in 30 fractions (I) and in 2 Gy per fraction (II) for α/β = 1, 1.5, 2, 2.5, 3, 4, 5 and 10 in three treatment plans. The results are shown for two conformal plans and one IMRT plan.

In all cases, the TCPs obtained for the fixed dose/fraction are smaller by about 1 % than those for increased dose/fractions. Despite the difference due to dose/fraction in all cases IMRT gives the highest TCPs. The difference due to dose/fraction increased as prescription dose increased between 62 and 66 Gy. This difference gradually decreases when the prescription dose increases as TCPs tend to 100 %. TCPs are not so sensitive to α/β values when the dose/fraction is fixed compared to when when the dose/fraction is changed. If α/β is in fact lower than previously accepted, then changing the fraction size has an effect on the calculated TCP. If α/β is high then total prescription dose is the important parameter, not dose/fraction.

NTCP

The treatment plans are evaluated for normal tissue complications by calculating their corresponding NTCPs. A lower NTCP means a higher probability of normal tissue sparing. NTCPs were calculated for the rectum, bladder and

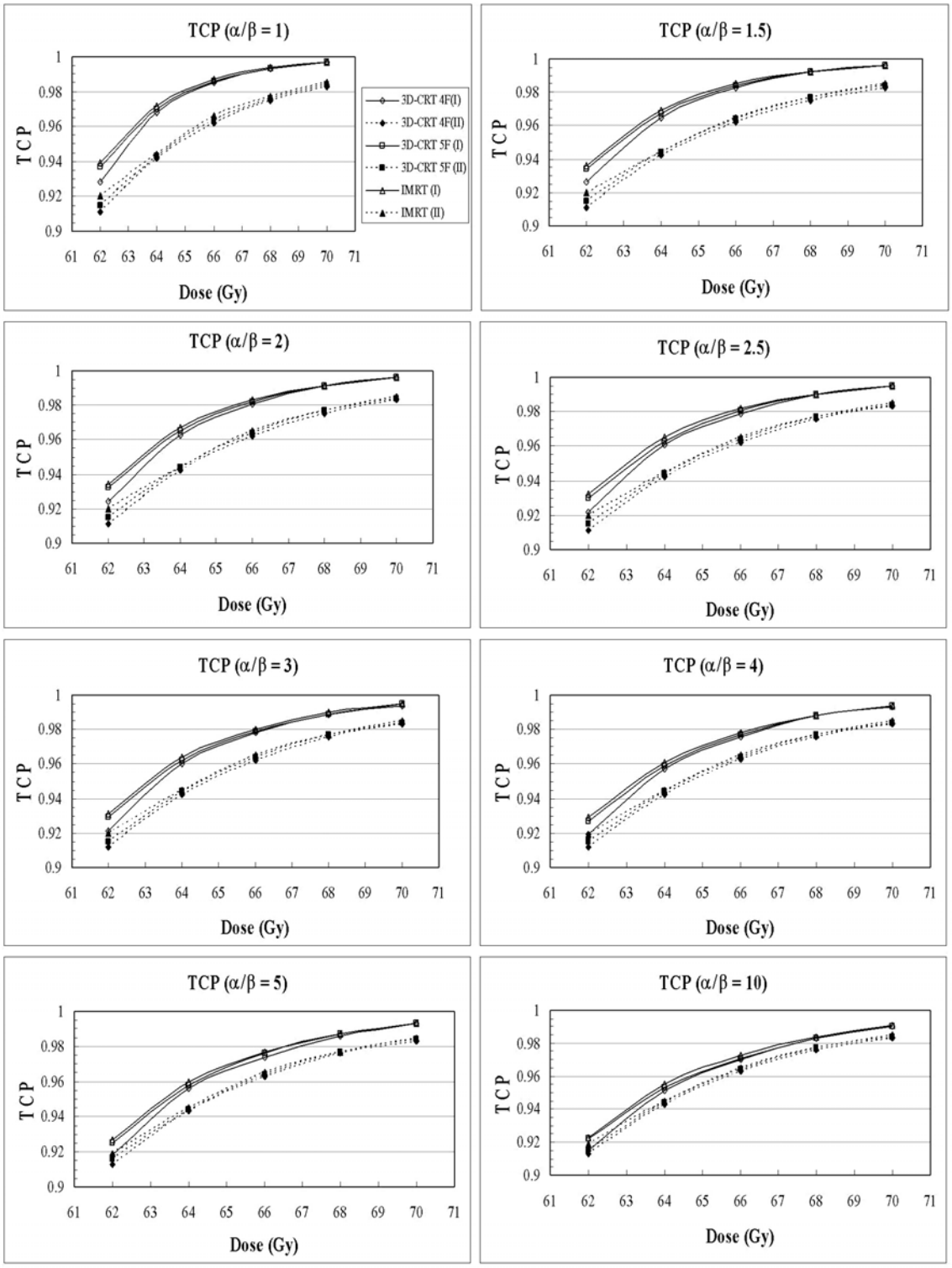

Figure 2. *TCPs as a function of prescription dose planned (I) in 30 fractions (solid line) and (II) in 2 Gy per fraction (dotted line) in 3D-CRT 4fields (diamond), 3D-CRT 5 fields (square), and IMRT (triangle) plans for α/β = 1, 1.5, 2, 2.5, 3, 4, 5, and 10 Gy.*

femoral heads for the three different treatment plans and for the two different fractionation schedules listed in table 2. These NTCP values are compared in Figure 3 for investigating the effects of the dose/fraction on NTCP.

Figure 3 shows the NTCPs calculated for the prescription dose planned in 30 fractions, and the NTCPs calculated for the prescription dose planned in 2 Gy per fraction for each of the three treatment plans.

NTCPs for the rectum are plotted in the top left panel of figure 3. It can be seen that the NTCPs are higher for a fixed 30 fractions than when the dose is planned for a fixed 2 Gy dose/fraction. So for dose escalation, higher

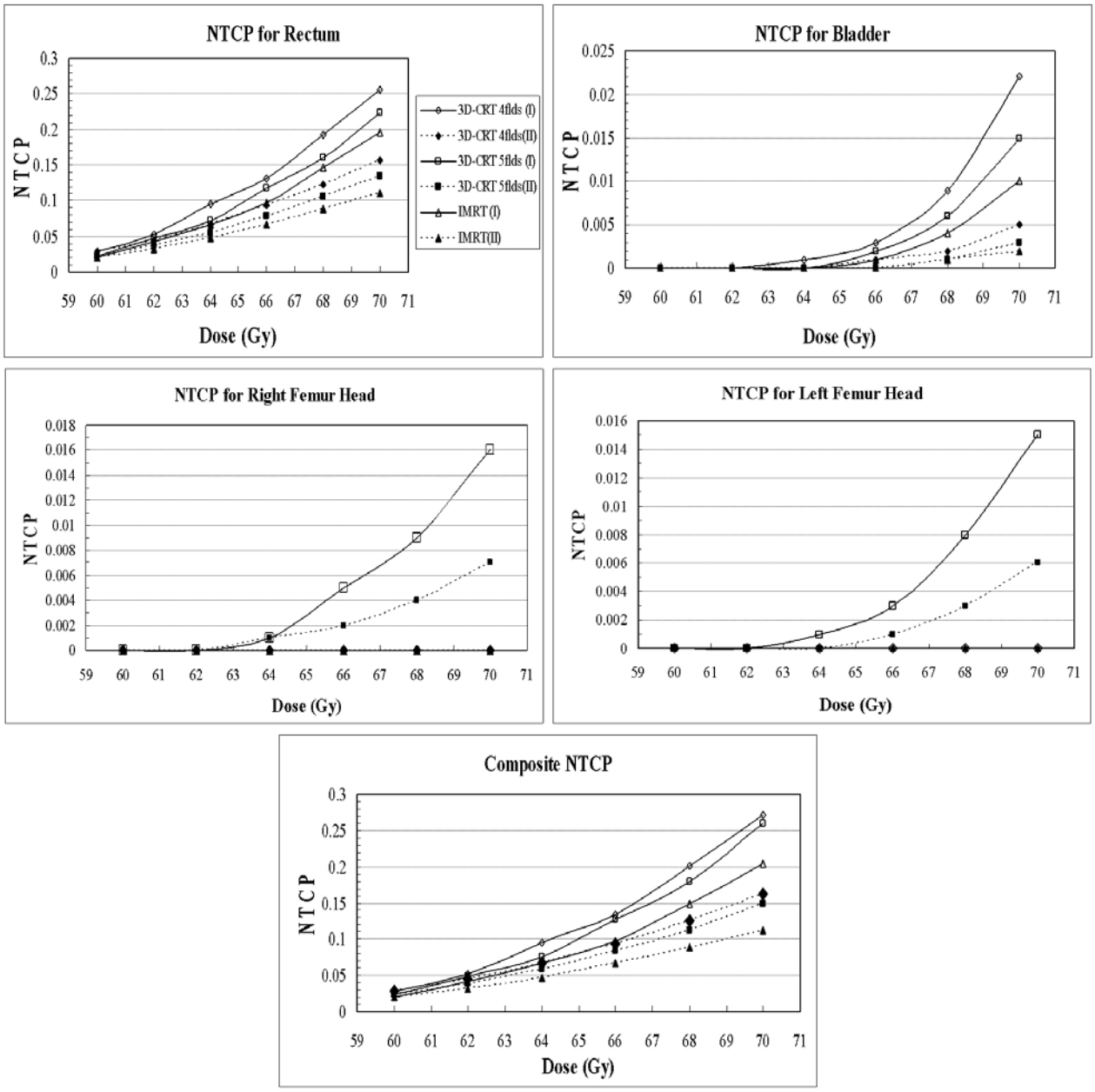

Figure 3. *NTCPs for rectum, bladder, femur heads, and composite NTCPs as a function of prescription dose for a fixed 30 fractions and a variable dose/fraction (solid line) and also for a fixed 2 Gy per fraction but variable number of fractions (dotted line). Calculations for the three different treatment planning techniques are shown for comparison.*

dose/fraction increases complications. IMRT plans show the minimum NTCPs in both fractionation schedules. The NTCPs for bladder and femoral heads were calculated for both fractionation schedules and are shown in figure 3.

Figure 3 shows the composite NTCPs for the three treatment plans and for the dose planned using the different fractionation schedules. Higher dose/fraction is seen to increase the probability of normal tissue complications. IMRT is shown to reduce the normal tissue complications compared to the 3D-CRT plans.

Complication free tumour control probability (P+)

The aim of a radiotherapy treatment is to not only have a high tumour control probability, but also to have low normal tissue complications probability. This can be evaluated in simple terms through use of the P+ described in equation (8).

The dose/fraction is shown to have a significant effect on P+. Since high dose/fraction increases the NTCP more than the increase in TCP, a lower P+ is observed. The results for two different schedules of dose/fraction for the same prescription dose are shown in figure 4. The P+ for different plans is also shown. At lower doses, the dose/fraction difference is very small, so the differences of P+ are also small at that dose range. But for high prescription dose, the dose/fraction difference is large,

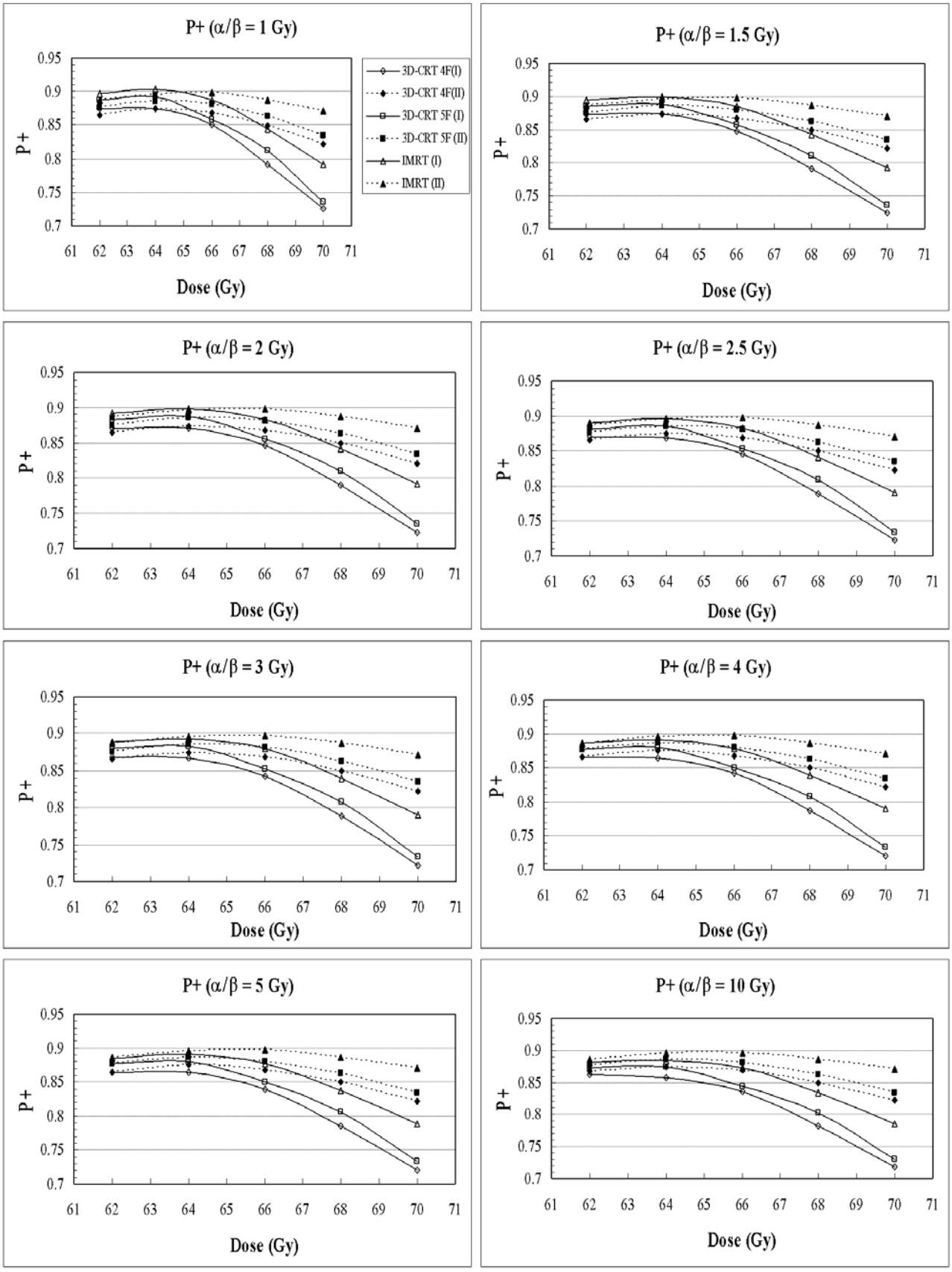

Figure 4. *Complication free tumour control probability (P+) as a function of prescription dose planned in (I) a fixed 30 fractions and (II) a fixed 2 Gy/fraction in different treatment plans for α/β value = 1, 1.5, 2, 2.5, 3, 4, 5 and 10 Gy.*

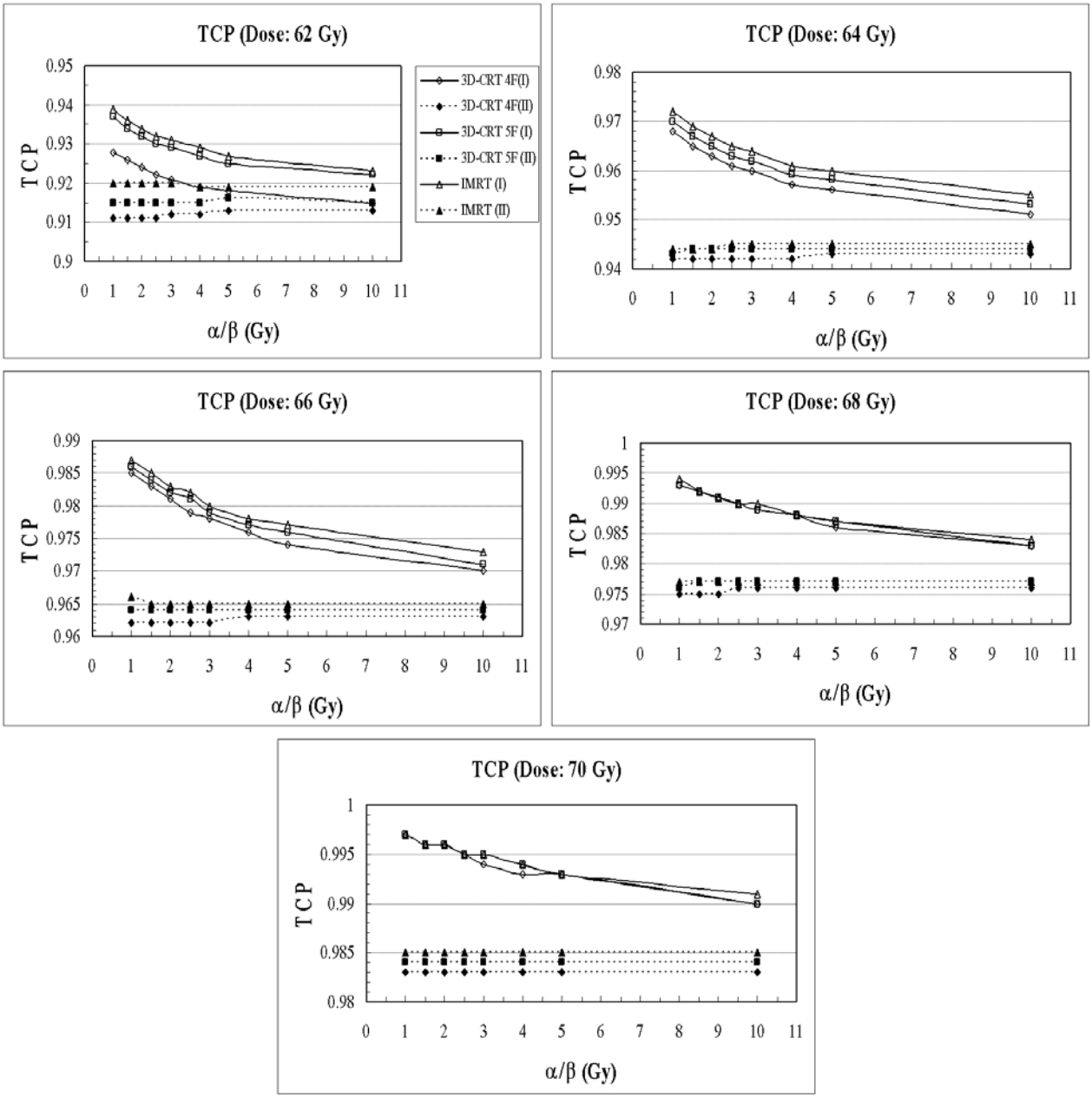

Figure 5. *TCPs as a function of α/β value for the prescription dose of 62, 64, 66, 68 and 70 Gy planned (I) in 30 fractions (solid line) and (II) in 2 Gy/fraction (dotted line) in 3D-CRT 4 field (diamond), 3D-CRT 5 field (square), and IMRT (triangle) plans.*

0.33 Gy for the case of 70 Gy, which cause a large NTCP. As a result P+ decreases. IMRT treatment plans show the highest P+ for all cases. The plots all show a maximum at around 64-66 Gy with higher doses resulting a reduction in the uncomplicated control P+. The fall off in P+ is more significant for the fractionation schedules where the dose/fraction is increased compared to the conventional dose escalation with increasing number of fractions. These are calculations for single phase treatments. Most dose escalation trials for prostate cancer are two phases with phase one being a treatment of the whole PTV to around 64 Gy and phase two involving a boost dose to a reduced PTV. The results here validate this schedule for dose escalation; increasing the dose beyond 64-66 Gy to the whole PTV is seen to result in a reduction in P+ due to an increase in the NTCP.

Sensitivity of the radiobiological evaluation to the α/β parameter

Sensitivity of the TCP and P+ to the different values of α/β ratio were investigated for various prescription doses planned to be delivered in either a fixed number of fractions (I) or in a fixed dose per fraction (II).

TCP as a function of α/β

TCPs as a function of α/β are shown in figure 5. These

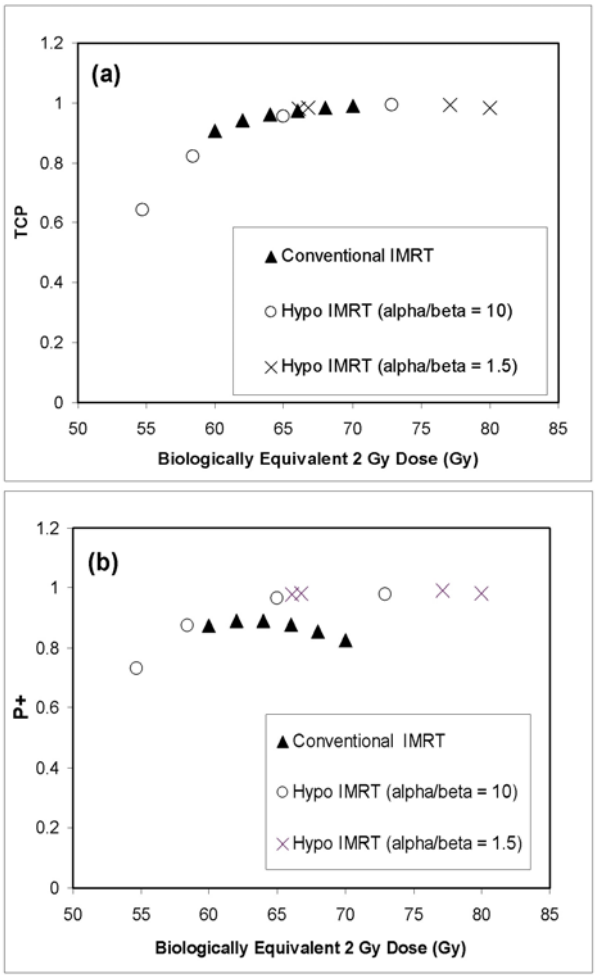

Figure 6. Plots of calculated (a) TCP and (b) P+ values for conventional and hypo-fractionated IMRT as a function of the biologically equivalent 2 Gy dose.

were obtained for different prescription doses planned as either fixed number of 30 fractions and increasing the dose/fraction (I) or as a fixed 2 Gy/fraction and increasing the number of fractions (II). This was performed for each of the 3 different treatment plans.

For all of the cases, lower α/β values give the higher tumour control probabilities when prescription doses are planned in 30 fractions. In those cases, the dose/fraction increased with prescription dose. TCPs are not significantly sensitive to the α/β values when prescription dose are planned in 2 Gy/fraction. This agrees with previous work that if indeed the α/β is lower than previously thought then increasing the dose/fraction would be radiobiologically advantageous[20]. It confirms that if α/β is really lower than expected, better tumour control should be achieved by fewer fractions but a larger dose/fraction[14, 16, 33]. To test this further four different published hypo-fractionation trials (listed in table 3) for prostate cancer were investigated. Figure 6 shows the calculated (a) TCP and (b) P+ values for the conventional fractionation and published hypo-fractionated IMRT schedules as a function of the biologically equivalent 2 Gy/fraction dose. This shows that significantly higher TCP and uncomplicated control, P+ can be expected for only two of the hypo-fractionation schedules, 60 Gy (20 x 3 Gy) and 70 Gy (28 x 2.5 Gy) if the α/β closer to the previously assumed value of around 10. The two hypo-fraction schedules 50 Gy (16 x 3.125 Gy) and 55 Gy (20 x 2.75 Gy) rely on α/β being lower than 10 to obtain the required gains in TCP and P+. The results of P+ in figure 6 compared to those in figure 4 show that if the dose / fraction are increased the number of fractions should also be decreased to preferentially spare the organs at risk by minimising the NTCP.

The models used in the Pinnacle treatment planning system are relatively simplistic. They take no account of cell repopulation effects between treatment fractions and also cell oxygenation levels that may vary spatially and temporally within a tumour. Hypoxic cells are known to be more radio-resistant than oxic cells[22]. The models used in this study do not account for variations in dose rate; IMRT treatment times can be significantly longer than for a 3D conformal treatment[34] and this has shown to affect the tumour dose-response. Also due to the method of delivery the dose rate can vary spatially across the tumour volume[35]. Further, the radiobiological parameters used in the models to characterise the dose response curves, the D_{50}, γ, seriality and α/β are subject to significant uncertainty. This limits the use of the simple models in calculating an absolute measure of tumour control probability and normal tissue complication probability; however, we suggest that they can be used as a valuable tool in comparing and evaluating different treatment techniques and protocols.

Conclusions

This study has investigated the use of radiobiological models that have recently become available in a commercial treatment planning system (Pinnacle v.7.6) to determine a more clinically meaningful evaluation of the different methods for delivering radiotherapy treatments to prostate patients. Tumour control probability (TCP) and normal tissue complication probability (NTCP) were evaluated and compared for two different 3D conformal treatment plans and an intensity modulated radiotherapy treatment plan. The IMRT plan was found to significantly reduce the NTCP for the rectum while achieving a small gain in TCP. The effect of different fractionation schedules for dose escalation was also investigated. The effect of these different fractionation schedules was found to be strongly dependent on the α/β of the prostate. If the α/β is indeed lower than previously assumed (around 1.5) then increasing the dose/fraction was shown to significantly improve the TCP for all four of the published hypo-fractionation schedules, 60 Gy (20 x 3 Gy), 70 Gy (28 x 2.5 Gy), 50 Gy (16 x 3.125 Gy) and 55 Gy (20 x 2.75 Gy). If the α/β is closer to the previously assumed value (around 10.0) then improvements in TCP were observed for only the 60 Gy (20 x 3 Gy) and 70 Gy (28 x 2.5 Gy) hypo-fractionation schedules. This study showed that radiobiological parameters can be effectively used to

determine a more clinically meaningful evaluation of a radiotherapy treatment plan than just dose and volume. The dependence of TCP on the α/β parameter for the prostate highlights the need for more clinical studies such as the CHHiP (Conventional or Hypofractionated High Dose Intensity Modulated Radiotherapy for Prostate Cancer) trial[36] and assessment of patient follow up data to validate and refine the use of these radiobiological models and the parameters used in them. This will be the first step in achieving the holy grail of radiotherapy, patient specific biologically optimised radiotherapy treatments.

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