

# Dosimetric and Radiobiological Evaluation of Multiparametric MRI-Guided Dose Painting in Radiotherapy of Prostate Cancer

## Abstract

Radiotherapy is one of the treatment options for locally advanced prostate cancer; however, with standard radiation doses, it is not always very effective. One of the strategies to improve the efficiency of radiotherapy is increasing the dose. In this study, to increase tumor local control rates, a new radiotherapy method, known as dose painting (DP), was investigated. To compare 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) plans with DP for prostate cancer. Twenty-four consecutive patients with locally advanced prostate cancer who underwent an multiparametric-magnetic resonance imaging (MP-MRI) ( $T_2w$ , diffusion weighted image, dynamic contrast enhancement, and MRS) scan before a diagnostic biopsy from September 2015 to April 2016 were invited to take part in this study. The tumor local control probability (TCP) values for 3D-CRT, IMRT, and DP techniques were 45, 56, and 77%, respectively. The DP technique had a 37.5 and 71% higher TCP than IMRT and 3D-CRT, and these differences were statistically significant ( $P = 0.001$ ). The mean normal tissue complication probability (NTCP) values of the organ at risks for 3D-CRT, IMRT, and DP showed that there were statistically significant differences among them in three plans ( $P = 0.01$ ). DP by contours using MP-MRI is technically feasible. This study evaluated biological modeling based on both MP-MRI defined subvolumes and pathologically defined subvolumes. The MP-MRI-guided DP results in better TCP/NTCP than 3D-CRT and IMRT.

**Keywords:** Dose painting, multiparametric MRI, radiobiological evaluation

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## Introduction

Radiotherapy is one of the treatment options for locally advanced prostate cancer. However, with standard radiation doses (64–70 Gy), it is not always as effective as previously believed.<sup>[1]</sup> One of the strategies to improve the efficiency of radiotherapy is increasing the prescribed dose.<sup>[2]</sup> The use of dose escalation of radiation therapy (RT) with doses ranging from 74 to 80 Gy has shown an improvement in the outcome of prostate cancer treatment when it is compared with conventional doses, as reported in a large retrospective study<sup>[3,4]</sup> and in some prospective randomized trials.<sup>[5-10]</sup> A meta-analysis showed that an increase of RT dose from 70 Gy up to 80 Gy in the patients with high-risk prostate cancer resulted in an increase in biochemical prostate-specific antigen (PSA) control rates by 19%.<sup>[11]</sup> An extrapolation of that data suggests that in this population, doses higher than 90 Gy may be necessary to maximize

tumor control rates.<sup>[11]</sup> However, such high doses are impossible to deliver using conventional external beam radiotherapy (EBRT) without an unacceptably high risk of severe toxicity.<sup>[11]</sup> Modulated techniques can reduce toxicity by optimizing radiation conformation.<sup>[12,13]</sup>

The current clinical practice in RT is to deliver a uniform dose to a predefined static planning target volume (PTV) that is believed to accommodate the tumor.<sup>[14]</sup> To increase the tumor local control rates while sparing healthy tissue, new radiotherapy methods are constantly being developed. One example is dose painting (DP), in which the uniform dose is replaced by a highly individualized dose distribution. It is designed to give an additional dose to subvolumes with high radioresistance due to, for example, hypoxia as quantified by functional imaging.<sup>[11]</sup> This is the concept of using functional imaging to identify regions within the conventional target volumes with

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different biology and, thus, may require escalated doses of radiation to achieve proper tumor control.<sup>[15]</sup> If tumor nodules or dominant intraprostatic lesions can be identified with functional magnetic resonance imaging (MRI),<sup>[6]</sup> boosting subvolumes to a higher dose can be an effective strategy to improve local control without increasing complication rates.<sup>[7-12]</sup>

Radiobiological models that estimate tumor local control probability (TCP) and normal tissue complication probability (NTCP) are used to evaluate and compare radiotherapy treatment plans.<sup>[16]</sup> Uzan *et al.* demonstrated that the TCP (Marsden model) increased from 71% for the standard plans to 83.6% (76.6–86.8%) for the DP boost plans. The mean (Lyman–Kutcher–Burman) NTCP for rectal bleeding was 5.2% (range 3.3–6.2%) and 5.2% for fecal incontinence (range 3.6–7.8%). Another study using radiobiological modeling in multiparametric-magnetic resonance imaging (MP-MRI)-guided DP in prostate cancer showed that the TCP had increased from ≈44 to ≈60%, but with absolutely no increase in the average NTCP.<sup>[17]</sup>

In this study, the plans of 24 patients were evaluated with a DP technique using MP-MRI and radiobiological models (Niemierko’s model) in the framework of a feasibility study.

## Materials and Methods

### Study design

This prospective study was approved by the institutional review board, and informed consent was obtained from all patients. Twenty-four patients were invited to take part in a feasibility study. These patients had locally advanced prostate cancer with indication for both surgery and radiotherapy. They underwent an MRI scan before a diagnostic biopsy from September 2015 to April 2016. All patients had biopsy-proven adenocarcinoma of the prostate, and the mean Gleason score was 6.7 (median 7, range 6–9). The inclusion criteria required that radical prostatectomy be performed within 180 days after MRI without any intervening treatment. Exclusion criteria were contraindications to MRI such as cardiac pacemakers, prosthetic valves, and severe claustrophobia.

### Histopathological data

The histopathological data that were used in this study were tumor classification and tumor grading. These data were derived from the records of the pathological examination.

### Data acquisition

A CT simulation study was performed with the patient in a customized immobilization mask and then exported to the radiation treatment planning system (TPS). CT simulation was performed on 64-multidetector computerized tomography, Siemens, Sensation. A functional MRI study was also performed in accordance with CT simulation images (3 mm thickness, Flat table top) but without the mask because of space limitations within the phase array coil. The MRI data sets were obtained from a Siemens Avanto 1.5 Tesla MAGNETOM MRI [Table 1]. The patients received MP-MRI, which consisted of T<sub>2</sub>w MRI, diffusion weighted image (DWI), and dynamic contrast enhancement (DCE)-MRI. For DWI MRI, apparent diffusion coefficient (ADC) maps were generated from a single-shot spin echo-echo (SS-FSE) planar imaging sequence with *b* values 0, 1000 smm<sup>-2</sup>. For DCE-MRI, transfer constant (*K*<sub>trans</sub>) maps were generated by fitting a Tofts<sup>[18]</sup> compartment model of concentration-time data for 200 acquisitions with 2s temporal resolution, acquired using a 3D spoiled gradient echo sequence, with a bolus injection of 0.1 mmol kg<sup>-1</sup> Dotarem (Guerbet Group, Villepinte, France).

The patients were scanned according to the standard diagnostic protocol, and the data were stored in the hospital Picture Archiving and Communications System.

A TPS system with fusion license enables registration and fusion of different DICOM modalities. Fusion software allows manual rotation and movement in all the three spatial directions and enables corrections of a patient position, if it is changed between the two imaging modalities (CT and MR).

### Contouring

The contour of target and organ at risks (OARs) was generated according to Radiation Therapy Oncology Group (RTOG) protocol 0126.<sup>[19]</sup>

**Table 1: MRI conditions and acquisition times**

Sequences	TR (ms)	TE (ms)	FOV	Thickness (mm)	TI (ms)	<i>b</i> -Value
T <sub>1</sub> w-FSE	500	11	380	3	–	–
T <sub>2</sub> w-FSE	4000	80	380	3	–	–
T <sub>2</sub> w-GRE-truefisp	415	2.08	380	3	–	–
STIR	2800	32	380	3	160	–
DWI	5700	103	380	3	–	0, 1000
T <sub>1</sub> W-3D-VIBE	4.8	1.7	260	3	–	–

To define appropriate clinical target volumes (CTV) for the patients with locally advanced prostate cancer undergoing EBRT, the tumor location within the prostate is very important. The whole prostate gland is typically contoured as the target.

### Radiotherapy treatment planning

The PTV will provide a margin around the CTV to compensate for the variability of treatment setup and internal organ motion. Three PTVs were determined for each patient: (a) PTV1, as the prostate and the seminal vesicles with 5 mm uniform margins, (b) PTV2, as the prostate with 5 mm margins uniform, and (c) PTV3, as the area with ADC <1 mm<sup>2</sup>/s in DWI,  $K_{trans}$  amount equal to the 0.2–1 min<sup>-1</sup> in DCE-MRI and between 0.5 and 1 to MRS, with a margin of 5 mm uniform and 5 mm avoids the rectum and the bladder. An inconsiderable difference ( $P < 0.05$ ) was observed for inconsistency between different imaging modalities [Figure 1]. It should be noted that this issue was considered in contouring and treatment planning.

Seven-field 3-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT) (Inverse planning mode, Step and shoot technique, 18MV, Multiple segments) techniques were used for treatment planning. All PTVs received the dose 60 Gy that had been prescribed for PTV1. For each patient, dose 78 Gy to PTV2 and dose 90 Gy to PTV3 were prescribed. Prescribed doses for each PTV were the average dose defined in the volume D50. In addition, D98 within the PTV should exceed 95% of the prescribed dose and D2; the higher dose within the PTV should not exceed 107%. The RTOG-126 was used for the dose constraints of OAR and normal tissue [Table 2].

### Dosimetric evaluation

The TIGRT TPS was used for performing dose calculation in this study. 3D-CRT and IMRT planning techniques were compared with DP technique. The plans were evaluated based on isodose distributions and dose

volume histograms (DVHs) for the target and the critical structures. On the basis of the DVHs and according to dose constraint in Table 1, doses were reported for PTVs and OARs volumes.

### Biological modeling

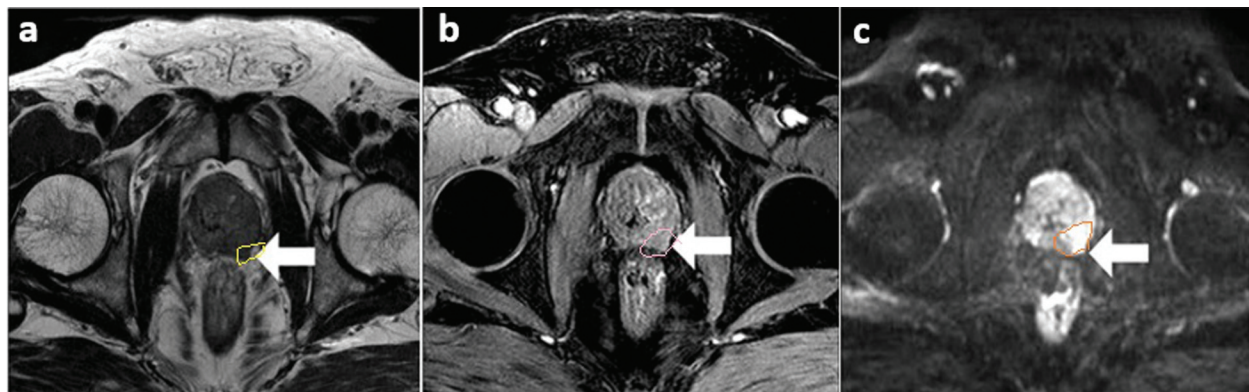
As equivalent uniform dose (EUD) or TCP/NTCP was used to optimize the treatment plan, it could also be used for biologically based plan evaluation. For the evaluation of radiobiological model response, calculated DVHs from the TIGRT (TPS) were used. According to Niemierko's model, the EUD is defined as:<sup>[20]</sup>

$$EUD = \left[ \frac{\sum (V_i D_i)^a}{1} \right]^{1/a} \quad (1)$$

**Table 2: Dose constraints for OAR**

Critical structure	Dose-volume parameter
Penile bulb <sup>a</sup>	D95 <sup>c</sup> < 50 Gy
	D70 < 70 Gy
	No hot spots
Bladder <sup>a</sup>	V80 <sup>d</sup> < 15%
	V75 < 25%
	V70 < 35%
	V65 < 50%
	V50 < 50%
Rectum <sup>a</sup>	V60 < 35%
	V65 < 25%
	V70 < 20%
	V75 < 15%
	V50 < 5%
Femoral heads <sup>b</sup>	V3 < 50%
Testis <sup>b</sup>	V3 < 50%

<sup>a</sup>QUANTEC recommendations. <sup>b</sup>RTOG recommendations. <sup>c</sup>The received dose by 95% of the Penile bulb should be <50 Gy. <sup>d</sup>The 80% of volume of the bladder should be receiving <15% of the prescribed doses.



**Figure 1: Inconsistency between different imaging modalities. (A) T<sub>2</sub>w, (B) DCE-MRI, and (C) DWI. The arrows and contours illustrate lesion in the left periphery of the prostate**

where  $a$  is a unitless model parameter that is specific to the normal tissue or tumor and describes the volume effect.  $V_i$  is the unitless quantity and represents the  $i$ th partial volume receiving dose  $D_i$  in Gy.<sup>[14]</sup> Given that the total volume of the structure is equal to 1, the sum of all  $V_i$  will be equal to 1. It can be used for both tumors and normal tissues.

To calculate the NTCP-based EUD, Niemierko proposed the parameterization of the dose response characteristics using the logistic function as follows:

$$NTCP = \frac{1}{1 + (TD_{50}/EUD)^{4\gamma_{50}}} \quad (2)$$

The  $TD_{50}$  is the tolerance dose for a 50% complication rate at a specific time interval (e.g., 5 years) in the Li *et al.*<sup>[20]</sup> normal tissue tolerance data when it homogeneously irradiated. The  $\gamma_{50}$  is a unitless model parameter that is specific to the normal structure or tumor of interest and describes the slope of the dose response curve. Parameters  $a$  and  $\gamma_{50}$  should be obtained by fitting the clinical dose response data to the EUD-based NTCP or EUD-based TCP model.

Similarly, to calculate the tumor control probability (TCP), the EUD is substituted in the following equation:

$$TCP = \frac{1}{(TCD_{50} + EUD)^{4\gamma_{50}}} \quad (3)$$

The  $TCD_{50}$  is the tumor dose to control 50% of the tumor cells when it is homogeneously irradiated.<sup>[20]</sup> The values should then be adjusted to achieve a better fit with the available clinical data.

### Evaluation and analysis

The MATLAB program (Faculty, staff, and students; version R2016a; The MathWorks, Inc., Arizona) was used for radiobiological modeling analysis. The data of TPS were manually imported into the MATLAB program, and TCP/NTCP and EUD were calculated using the appropriate formula.

### Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences version 20.0 software (SPSS Inc., Chicago, IL, United States). Quantitative data were expressed using range, mean, standard deviation, and median. The agreement of different predictive with outcome was used and expressed in sensitivity, specificity, positive predictive value, and negative predictive value.  $P$ -value of  $<0.05$  was considered as statistically significant.

## Results

### Patients' characteristics

Patients' characteristics and statistical parameter are summarized in Table 3.

Twenty-four consecutive patients with locally advanced prostate cancer took part in this study.

### Dosimetric analysis

Treatment plans were generated for 24 patients. Overall, 24 RT plans were generated, and the target volume objectives as well as the OAR dose constraints were applied. The results of these plans are given in Table 4.

The difference of dose values of PTVs and OARs among 3D-CRT, IMRT, and DP was significant [Figure 2]. The dose distribution is represented by various colors, with red representing the high doses (105% of the prescribed doses), blue representing the low doses (10% of the prescribed doses), and the other colors representing the doses between them.

**Table 3: Patient characteristics and statistical parameter**

Parameters	Mean	SD	Minimum	Maximum
Age (years)	59	7	52	66
PSA (ng/ml)	7.81	5.73	6	9
Gleason scores	7	1.5	6	9

**Table 4: Comparison of OARs dose in three techniques**

		3D-CRT <sup>a</sup>		IMRT <sup>b</sup>		DP <sup>c</sup>	
		Mean (cGy)	SD	Mean (cGy)	SD	Mean (cGy)	SD
Bladder	V80 <sup>d</sup>	4935.6	12.9	2386.7	10.1	2783.3	610.4
	V75	4755.3	12.7	2273.9	10.6	498.5	12.2
	V70	4509.8	12.5	2217.9	33.5	2373.4	10.4
	V65	4119.7	432.9	2046.9	18.4	2114.7	11.7
Penis bulb	V95	2240.6	11.3	1088.1	11.3	1121.7	10.6
	V70	2133.1	12.3	1051.2	11.9	1055.2	12.5
Rectum	V50	4845.2	13	2280.8	614.1	2174.8	10.9
	V60	4465.5	12.1	1890.5	11.1	1902.4	11.5
	V65	4193.2	11.4	1835.3	12.6	1830.5	10.5
	V70	4102	10.8	1778.4	11.2	1482	12.1
Femoral heads	V75	3811.2	11.3	1717.9	10.5	1724	11.3
	V50	1844.5	11.5	2254.3	12.2	2254.2	12.2
Testis	V3	102.6	11.6	51.8	13.9	51.5	14.2

<sup>a</sup>The prescription dose equal to 70 Gy in 35 fractions. <sup>b</sup>78 Gy in 39 fractions. <sup>c</sup>90 Gy in 45 fractions. <sup>d</sup>80% of the bladder received 4935.6 cGy of the prescribed dose (70 Gy).

Their comparison was made according to DVH as well as biological outcome (TCP and NTCP). For the prostate, the EUD and TCP values were calculated using the alpha–beta ratio of 1.2. Similarly, the EUD and NTCP values were calculated for the OARs. The alpha–beta ratio for the rectum, the bladder, and the femoral heads used in this study was 3.9, 8.0, and 0.85, respectively [Table 5].

The results of calculation of EUD and TCP/NTCP for the prostate and OARs are given in Table 6.

The TCP values for 3D-CRT, IMRT, and DP techniques were 45, 56, and 77%, respectively. The DP technique had a 37.5 and 71% higher TCP than IMRT and 3D-CRT, and these differences were statistically significant ( $P=0.001$ ).

The IMRT technique had a 24.4% higher TCP than 3D-CRT, and this difference was statistically significant ( $P=0.002$ ).

The mean NTCP values of the OARs for 3D-CRT, IMRT, and DP are provided in Table 6. There were statistically significant differences among them in three plans ( $P=0.01$ ) [Figure 3].

### Discussion

This study demonstrates the technical feasibility of DP and radiobiological impact of 3D-CRT and IMRT techniques with DP for locally advanced prostate cancer. The use of radiobiological models to evaluate treatment plans is well established. When biological modeling forms part of the inverse-optimization process, in combination with dose volume constraints, it is possible to limit normal tissue toxicity while achieving higher local control compared with standard “one-dose-fits-all” planning.

In this study, DP approach was compared with 3D-CRT and IMRT techniques, and it was found that DP was achievable while staying within published dose

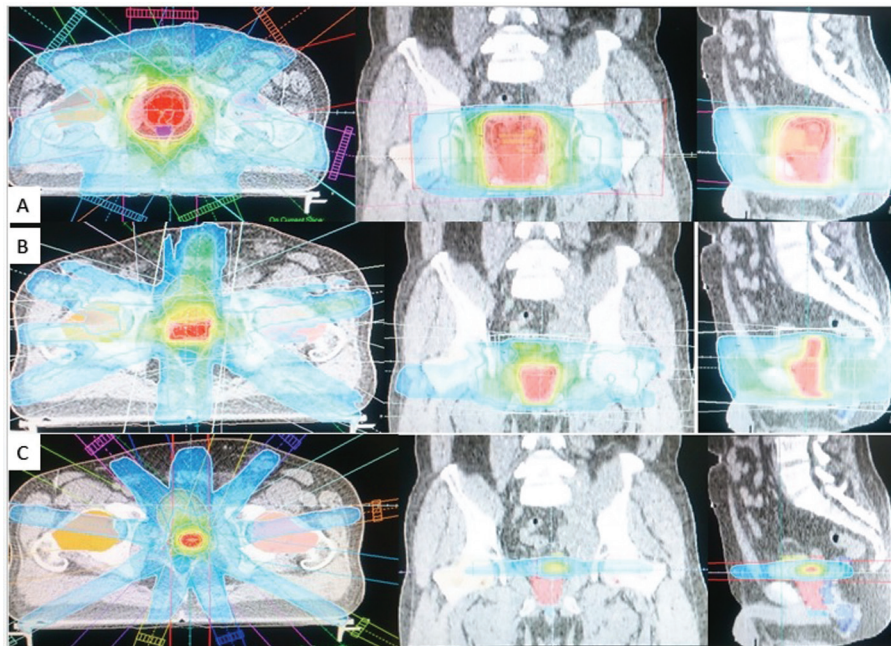


Figure 2: Colorwash representations of the dose distribution of the different plans. Three RT plans are illustrated: (A) 3D-CRT, (B) IMRT, and (C) DP. The dose distribution is represented by various colors, with red representing the high doses (105% of the prescribed doses), blue representing the low doses (10% of the prescribed doses), and the other colors representing the doses between them

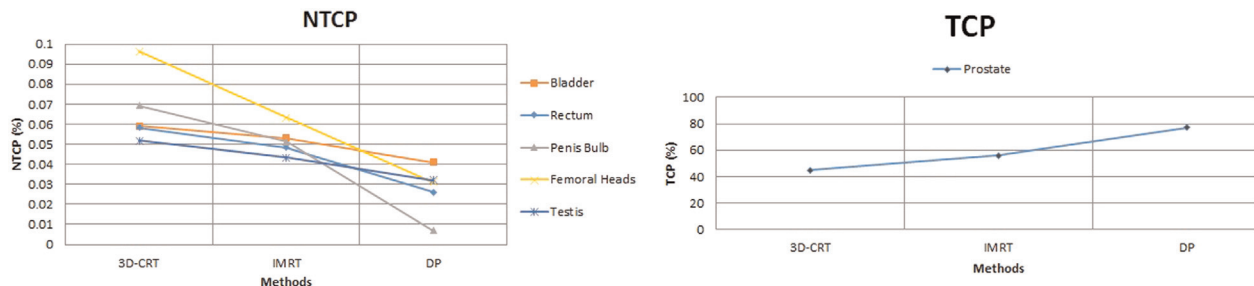


Figure 3: The TCP/NTCP value differences in the prostate and OARs

**Table 5: The parameters needed for the calculation of TCP and NTCP indices**

Tissue	<i>a</i>	$\alpha_{50}$	TD <sub>50</sub> (Gy)	TCD <sub>50</sub> (Gy)	$\alpha/\beta$ (Gy)
Prostate	-10	1	-	28.34	1.2
Bladder	2	4	80	-	8
Rectum	8.33	4	80	-	3.9
Femoral head	4	4	65	-	0.85

constraints. The DP approaches had TCPs superior to standard RT while not having significantly different NTCPs. While MP-MRI had excellent overall accuracy for defining subvolumes in the entire patient cohort, in some individual patients, the extent of the disease may not have been accurately defined. Therefore, in a patient in whom MP-MRI does not accurately define the entire subvolume, a large proportion of the subvolumes may be underdosed, leading to a lower TCP.

The strategy of dose escalation to the imaging-defined targets and dose de-escalation to the rest of the prostate has been advocated by a number of previous studies. Van Lin *et al.*<sup>[21]</sup> performed an RT planning study of five patients who had target defined using DCE-MRI and MRS. Two plans were generated for each patient: a standard whole-prostate RT plan with 78 Gy and DP plan with target dose escalation to 90 Gy and the remainder of the prostate dose de-escalation to 70 Gy. The two plans had similar TCPs; however, the experimental plan (90 Gy) had lower NTCPs. The authors concluded that the experimental plan had a higher treatment efficiency and, therefore, might be preferable. In another study, Nahum and Uzan<sup>[16]</sup> showed that the TCP (Marsden model) increased from 71% for the standard plans to 83.6% for the DP boost plans, and the mean (Lyman–Kutcher–Burman) NTCP for rectal bleeding was 5.2% for fecal incontinence.

All studies calculated TCPs according to the way we calculated TCP, that is, they calculated the TCP based on imaging (MP-MRI) data alone. For the purposes of calculating TCP, those studies assumed that imaging had 100% sensitivity for defining the subvolume, with no overestimation. As such, they assumed that their dose escalation volumes contained the subvolumes in their entirety and that their dose de-escalation volumes did not contain any portions of the subvolumes.<sup>[21]</sup> It was, therefore, a historical conclusion that dose de-escalation to volumes containing no subvolumes would not degrade the overall TCPs according to this method (Niemierko’s model) of calculation.<sup>[22]</sup> In fact, that is found with “our TCPMP-MRI calculation” with our approach. There are higher TCPs for every patient, even for 90 Gy dose, which contains a dose de-escalation volume, which resulted in higher TCPs for every patient. The reason that the previous studies calculated their TCPs based on imaging data alone is that they did not have histopathological data available for comparison.<sup>[22]</sup>

**Table 6: The results of the calculation of EUD and TCP/NTCP for the prostate and OARs**

		3D-CRT	IMRT	DP
Prostate	EUD (Gy)	53	74.2	86.7
	TCP (%)	45	56	77
Bladder	EUD (Gy)	51	40.12	36.93
	NTCP (%)	0.059	0.053	0.041
Rectum	EUD (Gy)	59	48	45
	NTCP (%)	0.0582	0.0483	0.0261
Penis bulb	EUD (Gy)	38	29	21
	NTCP (%)	0.0692	0.0512	0.007
Femoral heads	EUD (Gy)	42	31	26
	NTCP (%)	0.0962	0.0632	0.031
Testis	EUD (Gy)	33	21	14
	NTCP (%)	0.0518	0.0435	0.032

In our study, all patients underwent radical prostatectomy; therefore, one could use histopathological sections to better correlate with imaging data for calculating TCP. The hypothesis of our study was that the higher RT doses delivered to the tumor would result in higher local control rates. Higher local control rates might then lead to decreased metastatic dissemination. The ultimate aim of this study was to evaluate the techniques that could improve survival in the patients with prostate cancer. This is most likely not achievable with dose escalation alone, due to factors such as the high prevalence of micrometastatic disease already present at the time of treatment.<sup>[23]</sup> Systemic therapies such as androgen deprivation and other emerging therapies will probably need to be used in conjunction with dose escalation to lead to meaningful improvements in outcomes.<sup>[20]</sup>

This study has limitations, and several factors would have to be addressed before adopting this strategy clinically. First, the optimal method for defining subvolumes was debated. MP-MRI was used in this study, in-keeping with guidelines based on histopathological correlation with prostatectomy specimens, T<sub>2</sub>w sequences combined with DWI sequences, or DWI combined with DCE sequences, have sensitivities and specificities of 70–87%.<sup>[24]</sup> Other imaging modalities such as <sup>11</sup>C-choline PET scan have already been successfully used to guide prostate DP in clinical trials.<sup>[15]</sup> Secondly, accurate image coregistration is essential. A soft-tissue auto-match with manual correction as necessary was adopted here. Deformable registration might prove superior, because this could deal with change in the prostate shape and discrepancies in the prostate size between imaging modalities more adequately than was possible using rigid registration. However, this technique has not been validated in the setting of subvolumes. The optimal method of registration might well include models that add additional subvolume margins to specifically consider registration errors, although techniques requiring

additional margins may be difficult to implement without unacceptable increases in NTCP.

Uncertainties resulting from subvolume definition and registration will reduce the actual TCP benefit achieved from subvolume boosting to less than that calculated here. Third, a robust image guidance together with appropriate PTV margins is essential. For the PTV1 (prostate only) and PTV2 (prostate + margins), 5–10 mm margins were used, compatible with daily online fiducial-based image guidance (without intrafraction tracking). There is evidence that intrafraction motion becomes more problematic with increasing daily treatment time, particularly beyond 8 min.<sup>[25]</sup> The plans in this study had average estimated delivery times of 5 min (maximum 5.9 min). Intrafraction motion, therefore, may not be a major concern.

Adequately addressing the above issues is more important in the context of DP, where the TCP and NTCP consequences of inaccurate dose delivery are greater.

## Conclusion

It was illustrated that DP for locally advanced prostate cancer using MP-MRI is technically feasible. This study evaluated biological modeling based on both MP-MRI defined subvolumes and pathologically defined subvolumes. The MP-MRI-guided DP results in better TCP/NTCP than 3D-CRT and IMRT. As such, MP-MRI-guided DP has higher therapeutic ratios.

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Nil.

## Conflicts of interest

There are no conflicts of interest.

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