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# Improving prostate brachytherapy outcomes through MRI-Assisted dominant lesion dose painting

Faranak Rahmani[1], Mohammad Javad Tahmasebi Birgani[1], Fatemeh Mohammadian[2], Maryam Feli[2] and Seyed Masoud Rezaeijo[1,3*]

## Abstract

**Background** The aim of this study was to assess the feasibility of using magnetic resonance (MR) images to implement a dose painting (DP) approach in prostate high-dose-rate brachytherapy.

**Methods** The study included 45 patients with prostate tumors of varying grades, with the tumors (DILs) manually segmented with a 0.5 cm margin on T2W MR Images. The bladder, rectum, and urethra were considered as organs at risk (OARs) and treated using LLA300-KB plastic needles and the HDRplus treatment planning system. The patients received an external dose of 45 Gy and a boost dose based on the tumor's malignancy, with the dosimetric evaluations and radiobiological analysis performed according to the RTOG protocol and using the equivalent dose in 2 Gy fractions (EQD2).

**Results** Our study found no statistically significant differences in dose values for the rectum between the DP methods and conventional treatment planning for tumor grades 2 to 5 ($p > 0.05$). However, two patients with grade 5 tumors showed rectal V75cc values exceeding the limit with the DP method and a 43 Gy boost dose, although the average V75 remained below 1 cc. The analysis revealed no significant differences in bladder dose values between conventional treatment planning and DP methods for tumor grades 2 to 4 ($p > 0.05$). However, the mean V75cc of the bladder in grade 5 patients with a 43 Gy boost dose exceeded the permissible limit at 1.09. There was no significant difference in urethral V125cc values for patients with tumor grades 2 and 3 between both DP methods and conventional planning ($p > 0.05$). However, a significant difference was observed for patients with tumor grades 4 and 5. The average V125% and V150% of the whole prostate remained within the standard range of 50–65% and 20–35% respectively for all tumor grades, and both DP methods and conventional treatment planning were within acceptable limits. However, the average V125 and V150 DILs for all tumor grades exceeded the standard limits and showed a significant difference from conventional treatment planning ($p < 0.05$). Our results showed a significant difference in EQD2 values for the whole prostate and DIL in the DP method for all tumor grades ($P < 0.05$).

**Conclusion** The DP approach offers individualized doses but may be limited by the proximity of DILs to OARs.

**Keywords** MRI, Dose painting, Prostate, High dose rate brachytherapy

*Correspondence:
Seyed Masoud Rezaeijo
rezaei-sm@ajums.ac.ir
[1]Department of Medical Physics, Faculty of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2]Interventional Radiotherapy Ward, Department of Radiation Oncology, Golestan Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3]Cancer Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

## Introduction

Today, prostate cancer (PCa) ranks second among other cancers and is a significant health concern for men [1, 2]. One in every six men will be diagnosed with prostate cancer during their lifetime, making it important for researchers and medical professionals to continue to study and improve treatment options [3, 4]. The highest percentage of prostate cancer is related to the peripheral area of the prostate, but it may also spread to other parts such as the bone and lymph nodes [5]. Prostate cancer treatment methods include surgery, hormone therapy, chemotherapy, and radiation therapy. The choice of each of these methods is different depending on the patient's specific case and the Gleason score, a system used to grade the aggressiveness of prostate cancer [6, 7]. However, due to the significant heterogeneity of biological characteristics in tumors, when using a uniform dose of radiation for heterogeneous tumors, local recurrence occurs after radiation therapy. Therefore, local control can be improved by performing a complementary radiation for biological volumes relatively sensitive to treatment [8]. Recent research has shown that in prostate cancer, tumor recurrence occurs in DILs (dominant intra-prostatic lesions), and by increasing the dose in these areas, tumor recurrence can be prevented [9]. This highlights the importance of personalized treatment approaches and targeting specific areas of the prostate that are more likely to experience recurrence. In conclusion, it is crucial for ongoing research to continue in order to develop more effective and targeted treatment options for prostate cancer patients.

The main goal of radiation therapy is to deliver and prescribe doses to the tumor target volume that create a sufficient balance between tumor control probability (TCP) and normal tissue complication probability (NTCP) [10]. However, this can be challenging as high doses to the tumor can also damage surrounding healthy tissue. To overcome this problem, the DP (dose painting) method was proposed. This method allows for a nonuniform dose distribution, where highly suspicious disease sites or close margins can be treated with higher doses while the dose in distant areas can be reduced. To achieve this, one or more target volumes based on biology (BTV) can be selected within the gross tumor volume (GTV) and treated with higher doses using intensity-modulated radiation therapy (IMRT) or brachytherapy strategy. Brachytherapy, a form of internal radiation therapy, has been widely used in the treatment of prostate cancer. However, the ability to deliver high doses to the tumor while minimizing the dose to surrounding normal tissue remains a challenge [11–15]. To overcome this limitation, the DP method has been proposed. Previous studies have demonstrated the potential of the DP method in improving the treatment outcome in prostate cancer patients when combined with brachytherapy. A study by Rezaeijo et al. [16] used multiparametric MRI (mpMRI) to acquire functional and anatomical images of the prostate and found that the combination of mpMRI and DP method improved the accuracy of the treatment planning. Previous studies have shown that the presence of DILs inside the prostate is the main factor for tumor recurrence after treatment. Therefore, additional dose therapy is a method for preventing the recurrence of these residues. If this dose is not given to the patient, the patient will relapse after a few years [17]. Therefore, despite the major advantages of the DP method compared to conventional treatment methods in external prostate radiation therapy and brachytherapy, studies in this field are limited. Therefore, the goal of this study is to investigate the DP method in brachytherapy for patients with different grades of prostate tumors. In this study, the levels of dose that are based on which, in addition to covering the full volume of BTV or DILs, will be held at an appropriate level of emergency tissue will be investigated. Also, the parameters and limiting factors of the DP method for different tumor grades will be examined based on the damage to the organ at risk (OARs) such as the bladder, urethra and rectum. Therefore, we aim to further investigate the potential of the DP method in combination with brachytherapy using T2W images, with careful reference to mpMRI guidance in improving the treatment outcome in prostate cancer patients. Finally, we aimed to compare the effectiveness of the conventional treatment method and the DP method in prostate cancer patients. To do this, we designed two treatment plans for each patient, one using the conventional method and the other using the DP method. The plans were then evaluated based on dosimetric and radiobiological analyses. By comparing the results of the two treatment plans, we were able to determine the advantages and limitations of the DP method in comparison to the conventional method.

## Materials and methods

### Dataset

In this study, we used the PROSTATEx-2 dataset, which was previously used as the training dataset for the PROSTATEx-2 2017 challenge. The dataset was reviewed by a radiologist who identified suspicious lesions in each magnetic resonance imaging (MRI) and assigned a PI-RADS score. Lesions with a PI-RADS score greater than 3 were subsequently examined using magnetic resonance-guided biopsy and graded by a pathologist. These outcomes were used as the ground truth for the study. The dataset includes T2W, high B-Value DWI (HBVAL), and Apparent diffusion coefficient (ADC) images, however, for this study, we only used T2W images. The decision to use T2W images stems from their superior anatomical detail, which is essential for precise localization and

**Table 1** MRI parameters

| Sequence | TR/TE (ms) | Slice Thickness (mm) | Matrix Size | Voxel Size (mm) |
|---|---|---|---|---|
| **T2W-axial** | 5660/104 | 3 | 384*384*19 | 0.5 × 0.5 × 3 |
| **T2W-sagittal** | 5590/101 | 3 | 320*320*19 | 0.56 × 0.56 × 3.6 |
| **DW-MRI** | 2500/64 | 3 | 84*128*19 | 2 × 2 × 4.5 |
| **DCE-MRI** | 2700/63 | 3 | 84*128*19 | 2 × 2 × 4.5 |

**TR/TE**: Repetition Time/Echo Time; FOV: Field of View

delineation of the prostate and its substructures. While other sequences (such as DWI and ADC) provide functional insights, T2W images were selected as the primary modality for contouring due to their effectiveness in distinguishing prostate boundaries and focal lesions for treatment planning.

. In this study, we included a total of 45 patients, distributed among the following tumor grades: 15 patients with grade 1 tumors, 14 patients with grade 2 tumors, 3 patients with grade 3 tumors, 7 patients with grade 4 tumors, and 6 patients with grade 5 tumors. The MR imaging parameters are summarized in Table 1.

### Contouring and treatment planning procedure

The DILs were manually segmented with a margin of 0.5 cm on T2W images, in accordance with the provided reference location and the RTOG (Radiation Therapy Oncology Group) protocol. The OARs considered in this study were the bladder, rectum, and urethra. The urethra was hypothetically reconstructed on the images, and the clinical target volume (CTV) was drawn with a margin of 3–5 mm, meeting necessary standards. In this study, the placement of applicators was from the anterior (front) to the posterior (back) of the prostate to ensure comprehensive coverage of the clinical target volume (CTV). The applicators used were LLA300-KB plastic needles, which were inserted through the entire prostate and extended slightly beyond it to provide proper stabilization and optimal dose distribution. This explanation aligns with the 3D rendering provided in the manuscript, which accurately illustrates the path and positioning of the applicators and clarifies the extent of the implant geometry [18]. For treating prostate cancer, LLA300-KB plastic needles with a diameter of 1.65 mm and a length of 300 mm were used. Based on the volume of the prostate, between 14 and 16 catheters were placed in the prostate, as shown in Fig. 1. The HDRplus treatment planning system was used to plan the treatments, with all patients receiving an external dose of 45 Gy. A boost dose was considered for DILs of grades 2–5, based on their malignancy, with the total prostate dose set as a single fraction HDRBR and equal to 15 Gy for grade 1 patients. The boost doses for DILs with grade 2, 3, 4, and 5 patients were 22 Gy, 29 Gy, 36 Gy, and 43 Gy, respectively. In the treatment planning using the DP method, the dose of each tumor grade was increased by 7 Gy relative to the previous grade. Both a conventional treatment plan and one plan using the DP method were performed for each patient, and the results were compared based on dosimetric and radiobiological analyses.

### Dosimetric and radiobiologic evaluation

The dosimetric evaluations of the CTV and OARs were performed according to the RTOG protocol and as

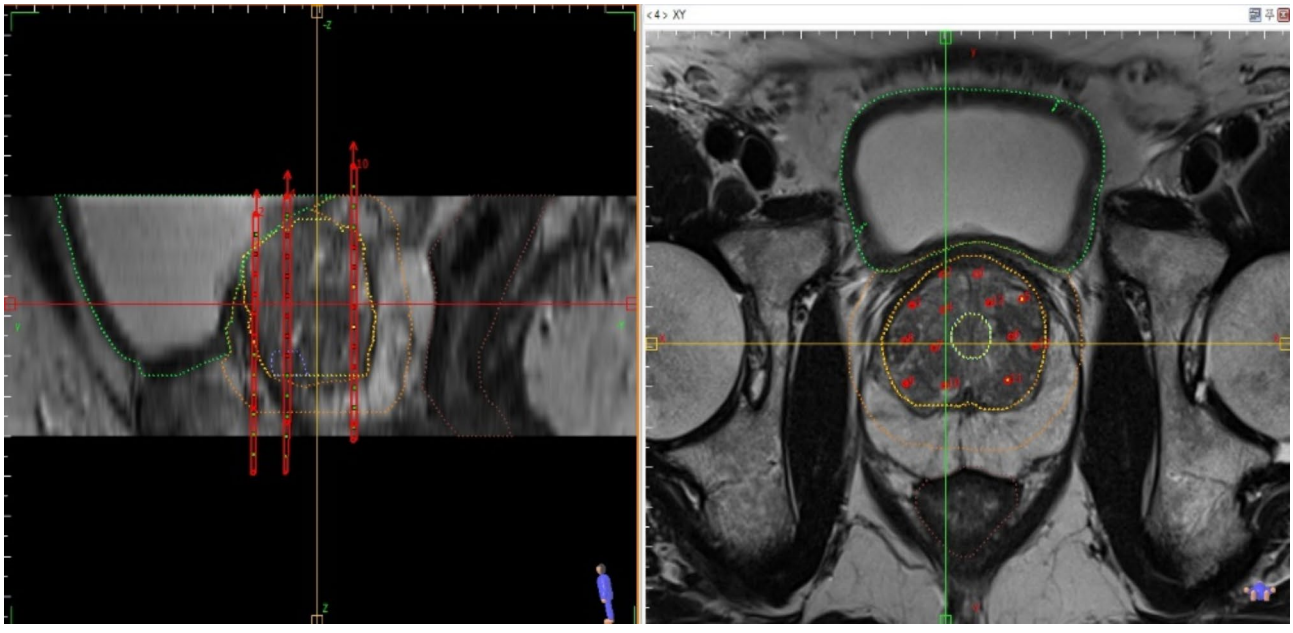


**Fig. 1** The catheter positions

**Table 2** Dosimetric parameters for CTV and oars

| organs | | Dosimetric parameters |
|---|---|---|
| CTV | | V100 ≥ 90%<br>V125 = 50-65%<br>V150 ≈ 20-35% |
| Urethra | | V150 = 0%<br>V125 ≤ 1 cc |
| Bladder | V75 ≤ 1 cc | |
| Rectum | V75 ≤ 1 cc | |

indicated in Table 2. For radiobiological analysis, the equivalent dose in 2 Gy fractions (EQD2) was used. Alpha/beta (α/β) ratio is defined in radiobiology as a measure of intrinsic radiosensitivity of a specific tissue, measured in Gy. In the linear quadratic model, a widely accepted model to describe radiation-induced cell death, α and β are constants representing two different processes of cell death caused by radiation. In this study, the α/β ratio for OARs was set at 3 Gy, while the α/β ratio for the prostate was determined to be 1.5 Gy. These values were selected based on established findings from past radiobiological studies that indicate the radiosensitivity profiles of these tissues, ensuring consistency with widely accepted literature.

The dose (d) delivered in each fraction (n) to the target organ was calculated as D90, while for critical organs it was calculated as the minimum dose to a defined volume (D2cc).

$$\mathrm{BED} = \mathrm{nd}\left(1+\frac{\mathrm{d}}{\mathrm{a/b}}\right) \tag{1}$$

$$\mathrm{EQD2} = \frac{\mathrm{BED}}{1+\frac{2}{\mathrm{a/b}}} \tag{2}$$

### Data analysis

In this study, data analysis was performed using GraphPad software (GraphPad, USA). The normality of the data was initially assessed using the Kolmogorov-Smirnov (KS) test. If the data were found to have a normal distribution, parametric statistical tests were employed; otherwise, nonparametric tests were utilized. To compare dosimetric and radiobiological parameters between the conventional technique and the DP method, the t-test statistical method was used when data were normally distributed, and the Mann–Whitney test was applied when the data were not normally distributed. A p-value less than 0.05 was considered statistically significant, and results with a p-value less than this threshold were interpreted as such.

**Table 3** Comparison of V75 dosimetric parameter for rectum in DP and conventional methods

| Organ | Tumor grade | Dosimetric parameter | Conventional | DP | P-value |
|---|---|---|---|---|---|
| | | | mean ± standard deviation | mean ± standard deviation | |
| Rectum | 1 | V75 cc | 0.84 ± 0.31 | 0.84 ± 0.31 | --- |
| | 2 | | 0.76 ± 0.29 | 0.41 ± 0.95 | 0.06 |
| | 3 | | 0.44 ± 0.47 | 0.64 ± 0.43 | 0.54 |
| | 4 | | 0.69 ± 0.25 | 0.74 ± 0.22 | 0.66 |
| | 5 | | 0.59 ± 0.43 | 0.78 ± 0.48 | 0.26 |

## Results

### Dosimetric analysis

Table 3 shows that there was no significant difference in dose values between the DP methods and conventional treatment planning for the rectum in tumor grades 2 to 5 ($p > 0.05$). The DP method for rectum in grade 2 patients had a higher average compared to other grades despite receiving a lower boost dose (22 Gy). This was due to the close proximity of DILs in grade 2 patients to the rectum. However, it was not possible to perform the DP method in 5 out of 14 grade 2 patients. Two Grade 5 patients show rectum V75cc value exceeding limit in DP method with 43 Gy boost dose, but average V75 remains below 1 cc. Figure 2 displays the average values of the dosimetric parameter normalized to 100 for the rectum across all grades.

Our analysis revealed that there was no statistically significant difference in dose values for the bladder between conventional treatment planning and DP methods for tumor grades 2 to 4 ($p > 0.05$), as depicted in Table 4. However, a significant difference was observed in patients with tumor grade 5. In the DP method with a 43 Gy boost dose to the tumor area, the mean V75cc of the bladder in grade 5 patients was 1.09, exceeding its permissible limit. In comparison, the mean V75cc of the bladder in grade 4 patients with a 36 Gy boost dose was 0.81. Unfortunately, the implementation of the DP method was not possible for two grade 4 patients and four grade 5 patients due to the proximity of the bladder to the DIL. As shown in Fig. 3, the average values of the dosimetric parameters normalized to 100 for the bladder across all grades are presented.

The results showed no significant difference in urethral V125cc values between patients with tumor grades 2 and 3 for both DP methods and conventional planning ($p > 0.05$). However, a significant difference was observed for patients with tumor grades 4 and 5, as shown in Table 5. The mean V125cc for patients with tumor grade 5 receiving a 43 Gy boost dose in DP methods was beyond the standard limit (V125 ≤ 1 cc). According to RTOG protocols, the permissible value of urethral

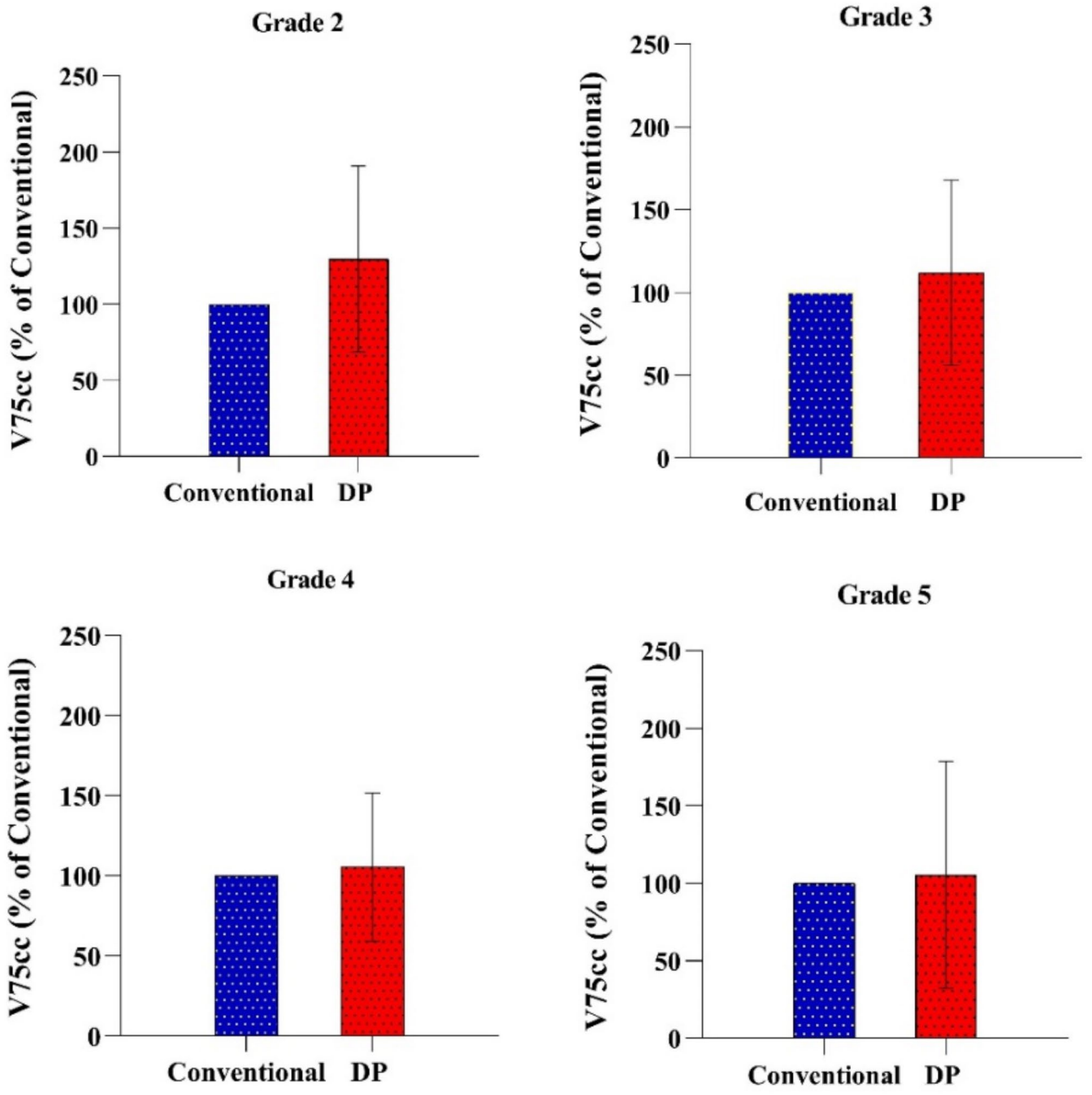


**Fig. 2** A comparison of the normalized rectum dosimetric parameter V75 between the DP and conventional methods

V150 is V150 = 0%. For patients with tumor grades 2 and 3, both DP methods and conventional treatment planning resulted in average V150% values between 0% and 0.03%, which are within acceptable limits. However, for DP planning in patients with tumor grades 4 and 5, the average urethral V150% exceeded the permissible limit, with a value of 0.56. Figure 4 presents the average values of dosimetric parameters normalized to 100 urethra for all grades.

In this study, the results showed no significant differences in dose values between the DP methods and conventional treatment planning for V100, V125, and V150 of the prostate in patients with tumor grades 2 to 5 ($p > 0.05$), as shown in Table 6. The acceptable limit for prostate V100 was set at V100 ≥ 90%, and the average V100% of the entire prostate was within the acceptable range for all tumor grades in both DP plans and conventional treatment planning. The average V125% of the whole prostate was within the standard range of 50–65% for all tumor grades. The average V150% of the whole prostate for all grades was between 20% and 35% and within the acceptable limit for both DP methods and

**Table 4** Comparison of V75 dosimetric parameter for bladder in DP and conventional methods

| Organ | Tumor grade | Dosimetric parameter | Conventional | DP | P-value |
|---|---|---|---|---|---|
| | | | Mean ± standard deviation | Mean ± standard deviation | |
| Bladder | 1 | V75cc | 0.90 ± 0.18 | 0.90 ± 0.18 | --- |
| | 2 | | 0.85 ± 0.27 | 0.93 ± 0.05 | 0.28 |
| | 3 | | 0.73 ± 0.19 | 0.78 ± 0.01 | 0.69 |
| | 4 | | 0.68 ± 0.33 | 0.81 ± 0.39 | 0.21 |
| | 5 | | 0.68 ± 0.29 | 1.09 ± 0.43 | *0.01 |

*Significant difference

conventional treatment planning. However, the average V125 and V150 DILs for all tumor grades exceeded their standard limits, and there was a significant difference from the conventional treatment planning ($p < 0.05$). The average V100 DILs for all tumor grades was equal to 100, and its difference from the conventional treatment planning was significant for all tumor grades except grade 3 ($p < 0.05$). Figure 5 displays the average values of the dosimetric parameters, normalized to 100, for the whole prostate and DILs in all grades. Figure 6 presents the cumulative dose-volume histograms (DVH) for the prostate and OARs in the DP and conventional treatment planning methods. As depicted, the DP method leads to improved dosimetric parameters for the OARs when compared to the conventional method.

### Radiobiological analysis

The comparison of EQD2 values between DP methods and conventional treatment planning for the rectum, bladder, and urethra showed no significant difference ($p > 0.05$) as demonstrated in Table 7; Fig. 7. The mean EQD2 values for DP methods displayed minimal deviation from conventional treatment planning methods. Figure 8 depicts the average values of normalized EQD2 (to 100) for OARs across all grades.

The results of the study revealed a significant difference in EQD2 values for whole prostate and DIL in the DP method across all tumor grades ($P < 0.05$), as demonstrated in Table 8. It should be noted that the conventional dose values are exactly the same as the DP method for the whole prostate.

The average DIL EQD2 for grades 1 to 5 was 113.1 Gy, 190 Gy, 295.3 Gy, 428.1 Gy, and 589 Gy, respectively. As depicted in Fig. 8, the average EQD2 values normalized to 100 for both prostate and DIL are illustrated for all grades.

## Discussion

Prostate cancer is a disease that can occur in multiple locations within the prostate [19, 20]. Despite this, a uniform dose is typically prescribed for the entire prostate. However, increasing the dose to the entire prostate has limitations due to the close proximity of OARs. There is evidence suggesting that recurrence after radiation therapy mainly occurs at the site of DILs [18]. In a study conducted by Cellini et al. [7], 18 prostate cancer patients were exposed to radiation doses ranging from 65 to 70 Gy. The study found that all 12 observed recurrences in the prostate were located at the DILs, suggesting that delivering a higher dose to these areas can reduce the risk of metastasis. This conclusion was confirmed by PUCAR et al. [21], who demonstrated that recurrence after external beam radiation therapy occurs at the site of DILs using pathology specimens after prostatectomy. Dose escalation can be achieved through a combination of HDR brachytherapy and external beam radiation therapy, with many studies suggesting that patients experience better biochemical control when both are combined [22]. However, the reliability of imaging techniques to identify intraprostatic lesions is a crucial issue for dose escalation to DILs. The technique used in the present study has demonstrated high sensitivity in previous studies [23–25]. Crook et al. [26] examined the feasibility of the DP method in 26 prostate cancer patients with intraprostatic lesions. The treatment included HDR brachytherapy for the entire prostate, a 12.5 Gy boost dose to the DIL, and 46 Gy of external radiation therapy. The study showed that HDR brachytherapy based on the DP method, with a boost dose of up to 125% of the prescribed dose to the DILs, is possible. In the present study, the boost dose was increased up to 43 Gy for patients with tumor grade 5, but this resulted in excessive doses to the bladder and urethra. The boost dose was reduced to 36–38 Gy for grade 5 patients to prevent exceeding the standard limit for OARs. In more than half of the patients with tumor grade 5, the reason for increasing the dose was the close proximity of the DILs to the bladder and urethra. In a study by Blake et al. [27], a dose of 74 Gy was given to the prostate and 86 Gy to the DILs, and the CTV was increased to 86 Gy in 7 patients and limited to 80 Gy in 5 patients due to the proximity of the DIL to the urethra. This highlights the fact that the proximity of the DIL to OARs is a limiting factor for the prescribed dose. In the present study, 5 out of 14 patients with tumor grade 2 were unable to receive the DP method due to the close proximity of the lesion to the rectum, which would result in excessive doses to this OAR. A study conducted by

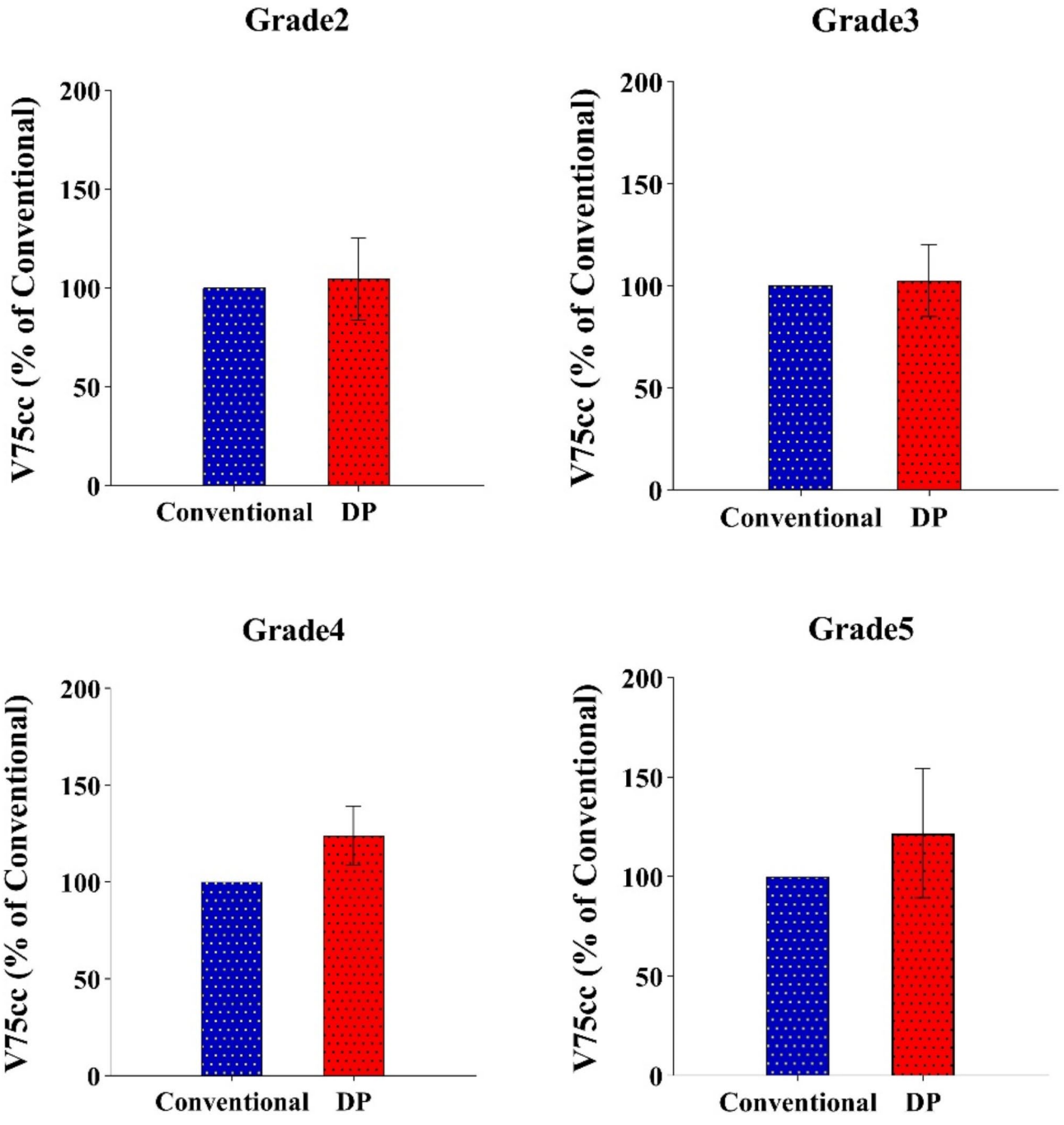


**Fig. 3** A comparison of the normalized bladder dosimetric parameter V75 between the DP and conventional methods

Skjøtskift et al. [28] compared the DP method using PET images with conventional treatment plans. The CTV received a prescription dose of 60 Gy and a boost dose ranging from 65 to 73 Gy. The study showed that the DP method improved tumor control without increasing side effects compared to conventional radiation therapy.

In a study, Ghobadi et al. [29] confirmed the possibility of dose escalation to DILs with higher Gleason scores, this is what we used in the present study and determine the values of dose boost compared to the malignancy of DILs with higher Gleason scores. In order to achieve the best result of radiation therapy, it is necessary to perform

**Table 5** Comparison of urethral dosimetric parameters (V125 and V150) in DP and conventional methods

| Organ | Tumor grade | Dosimetric parameter | Conventional | DP | P-value |
|---|---|---|---|---|---|
| | | | mean ± standard deviation | mean ± standard deviation | |
| Urethra | 1 | V125cc | 0.26 ± 0.14 | 0.26 ± 0.14 | --- |
| | | V150% | 0.04 ± 0.08 | 0.04 ± 0.08 | --- |
| | 2 | V125 cc | 0.51 ± 0.33 | 0.57 ± 0.52 | 0.31 |
| | | V150% | 0.03 ± 0.13 | 0.03 ± 0.09 | 0.98 |
| | 3 | V125 cc | 0.02 ± 0.02 | 0.03 ± 0.02 | 0.67 |
| | | V150% | 0.0 ± 0.0 | 0.01 ± 0.000 | 0.42 |
| | 4 | V125 cc | 0.14 ± 0.30 | 0.26 ± 0.27 | *0.03 |
| | | V150% | 0.0 ± 0.0 | 0.11 ± 0.20 | 0.18 |
| | 5 | V125 cc | 0.42 ± 0.19 | 1.08 ± 0.33 | *0.02 |
| | | V150% | 0.08 ± 0.20 | 0.56 ± 0.62 | 0.12 |

*Significant difference

radiobiological evaluation along with dosimetric evaluation. In fact, radiobiological evaluation is required for individual treatment, Also, in this study, the radiobiological parameters were also evaluated. Many studies have investigated the DP method based on the radiobiological assumptions can balance between the TCP and the NTCP. Also all our goals in radiotherapy are to reach an optimal state between TCP and NTCP.

UZAN et al. [30]conducted a study with the aim of investigating prostate radiation therapy with the DP method. Based on the results of their study, the TCP increased from 71% for standard plans to 83.6% for DP plans. Also, Grönlund et al. [10] in another study proved that with the DP method, the increase in TCP is greater for patients who have a lower expected TCP for administrating a homogeneous dose, and the increase in TCP with DP is also associated with an increase in the Gleason score and a larger prostate volume. In our study, radiobiological evaluation was performed by calculating EQD2. By calculating the EQD2 values of the patients, all EQD2 values of target organs and critical organs were kept within standard range. It was possible to increase the boost dose of brachytherapy up to 43 Gy for single fraction HDRB and EQD2 ≥ 90 Gy for the DIL. DIL has significant difference in the comparison between DP and conventional techniques and it was possible to increase the dose of the DIL without increasing critical organ toxicity and the whole prostate. Radiobiological evaluations of DIL showed a significant difference in the comparison between DP and conventional techniques. The average EQD2 of the OARs and the whole prostate in the DP

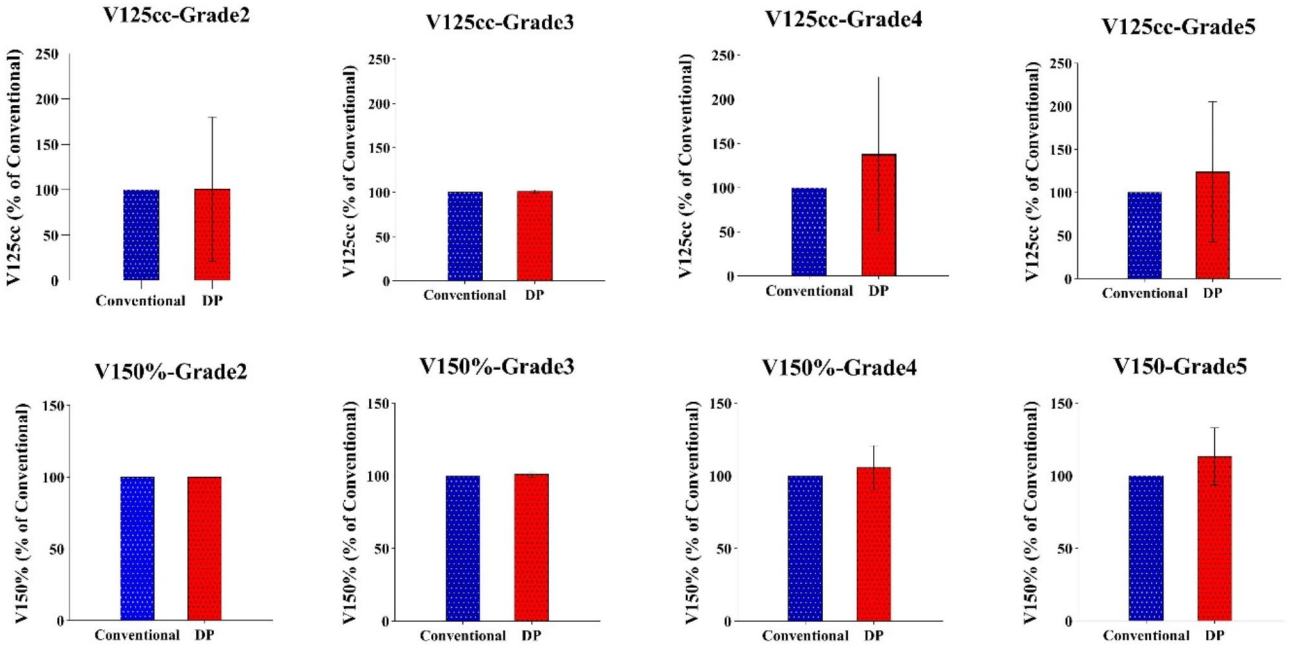


**Fig. 4** A comparison of the normalized urethra dosimetric parameters (V125 and V150) between the DP and conventional methods

**Table 6** Comparison of prostate dosimetric parameters (V100, V125, and V150) in DP and conventional methods

| Organ | Tumor grade | Dosimetric parameter | Conventional | DP | | *P*-value | |
|---|---|---|---|---|---|---|---|
| | | | mean ± standard deviation | mean ± standard deviation | | | |
| | | | | Whole prostate | DIL | DP-Whole prostate vs. Conventional | DP-DIL vs. Conventional |
| **Prostate** | 1 | V100% | 90.15 ± 15.26 | 90.15 ± 15.26 | 90.15 ± 15.26 | --- | --- |
| | | V125% | 62.24 ± 2.04 | 62.24 ± 2.04 | 62.24 ± 2.04 | --- | --- |
| | | V150% | 31.87 ± 3.44 | 31.87 ± 3.44 | 31.87 ± 3.44 | --- | --- |
| | 2 | V100% | 89.85 ± 1.80 | 90.48 ± 1.05 | 99.84 ± 0.37 | 0.32 | *0.0001 |
| | | V125% | 61.91 ± 2.33 | 62.44 ± 3.31 | 99.89 ± 0.21 | 0.59 | *0.0001 |
| | | V150% | 30.36 ± 9.54 | 33.83 ± 9.58 | 91.88 ± 4.09 | 0.33 | *< 0.0001 |
| | 3 | V100% | 99.10 ± 0.10 | 100 ± 0.11 | 100 | 0.42 | < 0.999 |
| | | V125% | 53.23 ± 1.05 | 56.31 ± 3.78 | 100 | 0.35 | *< 0.0001 |
| | | V150% | 21.80 ± 0.72 | 24.53 ± 2.26 | 91.53 ± 5.14 | 0.08 | *0.001 |
| | 4 | V100% | 90.57 ± 5.49 | 91.53 ± 8.97 | 100 | 0.74 | *0.004 |
| | | V125% | 2.69 ± 52.33 | 57.63 ± 2.63 | 100 | 0.77 | *0.015 |
| | | V150% | 27.41 ± 3.74 | 30.01 ± 9.42 | 100 | 0.62 | *0.015 |
| | 5 | V100% | 89.95 ± 1.80 | 90.38 ± 1.48 | 100 | 0.051 | *0.0001 |
| | | V125% | 59.28 ± 3.64 | 60.33 ± 6.37 | 100 | 0.92 | *0.015 |
| | | V150% | 28.85 ± 4.60 | 30.52 ± 6.73 | 100 | 0.56 | *0.031 |

*Significant difference

method were kept within their standard range, so that the average EQD2 of the bladder and rectum was less than 75 Gy and the average EQD2 of the urethra and prostate was less than 125 Gy, while the EQD2 was up to 528 Gy increased for grade 5 patients, indicating that increasing the dose of DIL improves local tumor control without increasing critical organ toxicity.

The radiobiological evaluation in this study was performed by calculating the equivalent dose in 2 Gy (EQD2) values. The EQD2 values of the target and critical organs were kept within standard range, allowing for an increase in boost dose up to 43 Gy for single fraction Brachytherapy and EQD2 ≥ 90 Gy for DIL. A significant difference was observed in the comparison between the DP and conventional techniques, with the DP method allowing for an increase in DIL dose without increasing critical organ toxicity and the whole prostate. The average EQD2 of the OARs and the whole prostate were within standard range, with the average EQD2 of the bladder and rectum less than 75 Gy, and the average EQD2 of the urethra and prostate less than 125 Gy. The EQD2 was up to 528 Gy increased for grade 5 patients, indicating improved local tumor control without increasing critical organ toxicity.

The present study has several limitations. Firstly, the study is based on the PROSTATEx-2 dataset, which was previously used as the training dataset for the PROSTATEx-2 2017 challenge. This dataset was reviewed by a radiologist and includes T2W images only, and the results may not be generalizable to other datasets. Secondly, the study only included a limited number of patients, distributed among different tumor grades. This may limit the generalizability of the results to the general population.

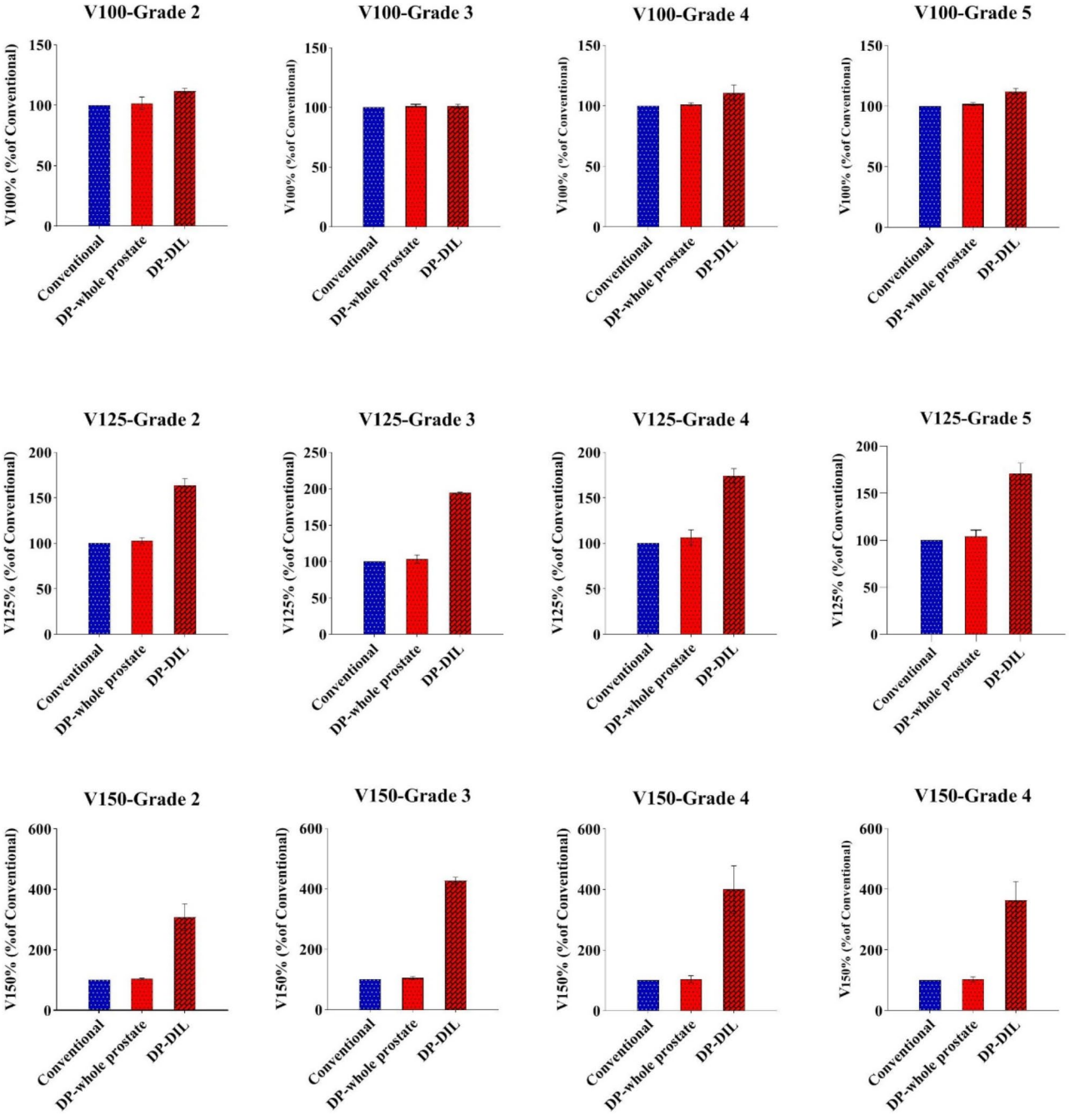


**Fig. 5** A comparison of whole prostate and DILs dosimetric parameters (V100, V125, and V150) between the DP and conventional methods

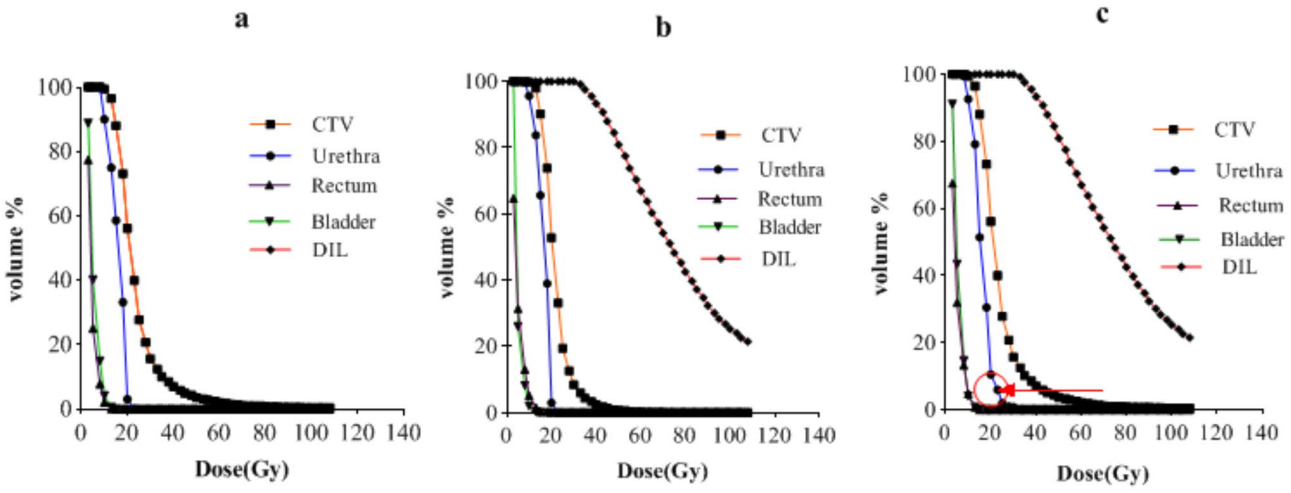


**Fig. 6** (**a**) DVH for conventional treatment planning (**b**) DVH for DP method with a boost dose of 43 Gy (**c**) DVH for DP method with a boost dose of 43 Gy and urethra toxicity (V150% ≥ 0%)

**Table 7** Comparison of radiobiologic parameter EQD2 for oars in DP and conventional methods

| Organ | Radiobiologic parameter | Conventional | DP | P-value |
|---|---|---|---|---|
| | | mean ± standard deviation | mean ± standard deviation | |
| **Bladder** | EQD2-Gy | 66.35 ± 1.87 | 69.65 ± 2.34 | 0.10 |
| **Rectum** | | 65.90 ± 3.06 | 67.16 ± 2.40 | 0.76 |
| **Urethra** | | 94.71 ± 8.82 | 99.51 ± 10.39 | 0.71 |

Thirdly, the survival of patients treated with the DP technique is not known and more studies and multi-year follow-ups are needed to assess the long-term efficacy and safety of the DP method. These follow-up studies should also record the survival of these patients for several years to validate the results of the present study. In conclusion, the findings of the present study should be interpreted with caution and further studies with larger sample sizes

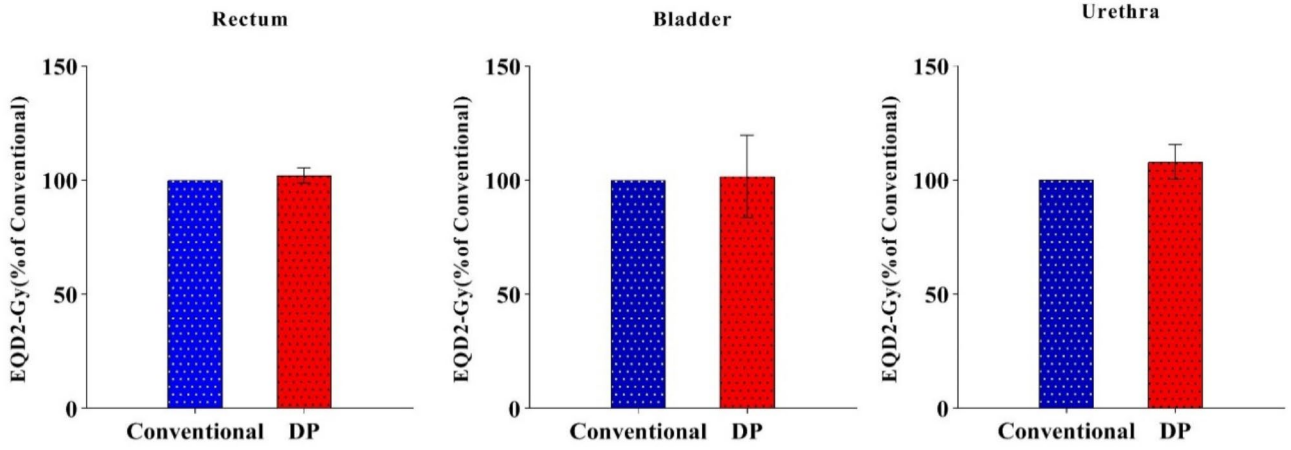


**Fig. 7** Comparison of radiobiologic parameter EQD2 for OARs between the DP and conventional methods

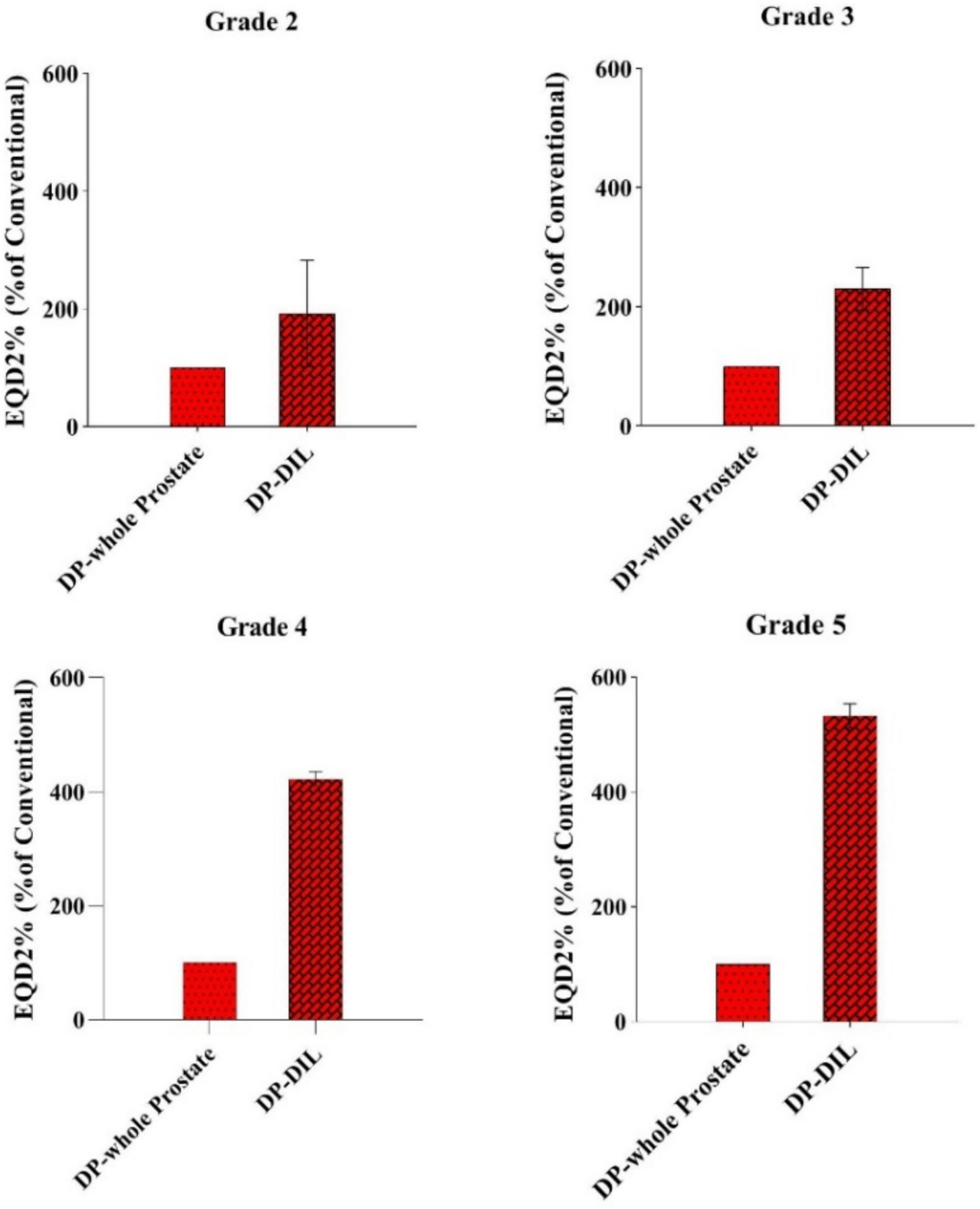


**Fig. 8** Comparison of radiobiologic parameter EQD2 for whole prostate and DIL between the DP and conventional methods

**Table 8** Comparison of radiobiologic parameter EQD2 for whole prostate and DIL in DP

| Tumor grade | Radiobiologic parameter | DP | | P-value |
|---|---|---|---|---|
| | | mean ± standard deviation | | |
| | | Whole prostate | DIL | |
| 1 | EQD2-Gy | 113.1 ± 0.23 | 113.1 ± 0.23 | --- |
| 2 | | 114.25 ± 0.26 | 190 ± 3.32 | *0.03 |
| 3 | | 114.36 ± 0.31 | 295.3 ± 3.85 | *0.02 |
| 4 | | 114.52 ± 0.21 | 428.1 ± 5.81 | *0 < 0.0001 |
| 5 | | 114.88 ± 0.41 | 589 ± 9.165 | *0 < 0.0001 |

*Significant difference

and longer follow-up periods are needed to fully evaluate the clinical utility of the DP technique.

## Conclusion

The results of the dosimetric and radiobiological evaluations of the DP method demonstrate its potential as a promising technique for increasing the dose to DILs. The DP approach is unique in that it allows for individualized dose delivery tailored to each patient's anatomy and the toxicity thresholds of OARs and CTV. However, the statistical analysis revealed that the differences in OAR dose values between the DP and conventional techniques were not significant, highlighting a limitation in the ability of the DP method to achieve superior sparing of OARs compared to conventional methods. Additionally, the close proximity of DILs to critical organs such as the rectum, bladder, or urethra restricts the amount of boost dose that can be safely administered.

Despite these limitations, our study supports the potential of the DP method as an effective treatment planning strategy that can enhance dose delivery to DILs while maintaining acceptable levels of toxicity. Future research with larger sample sizes and extended follow-up periods is essential to fully understand the clinical benefits and to confirm whether the DP approach can consistently offer superior outcomes over conventional treatment in prostate cancer therapy.

### Abbreviations

| | |
|---|---|
| PCa | Prostate cancer |
| DILs | Dominant intra-prostatic lesions |
| TCP | Tumor control probability |
| NTCP | Normal tissue complication probability |
| DP | Dose painting |
| BTV | Target volumes based on biology |
| GTV | Gross tumor volume |
| IMRT | Intensity-modulated radiation therapy |
| mpMRI | Multiparametric MRI |
| OARs | Organ at risk |
| MRI | Magnetic resonance imaging |
| HBVAL | High B-Value DWI |
| ADC | Apparent diffusion coefficient |
| RTOG | Radiation Therapy Oncology Group |
| CTV | Clinical target volume |
| EQD2 | Equivalent dose in 2 Gy fractions |
| KS | Kolmogorov-Smirnov |
| DVH | Dose-volume histograms |

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### Author contributions

Seyed Masoud Rezaeijo and Mohammad Javad Tahmasebi Birgani are responsible for the study conception, design, data acquisition and analysis, drafting, and finalizing the manuscript. Faranak Rahmani, Fatemeh Mohammadian, Maryam Feli contributed in the data acquisition and analysis and also the drafting and approval of final manuscript. All the authors read and approved the final manuscript.

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### Data availability

No datasets were generated or analysed during the current study.

## Declarations

### Consent for publication

Not applicable.

### Competing interests

The authors declare no competing interests.

### Ethics approval and patients' consent to participate

This study was approved by ethics committee (IR.AJUMS.MEDICINE.REC.1401.018). All the patients gave written informed consent for their treatment. All experiments were performed in accordance with the guideline approved by the ethics committee.

### Clinical trial number

Not applicable.

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