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# High Dose 3D Conformal Radiotherapy of Prostate Cancer Using Spaceoar Gel

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**Abstract**
The aim of this study was to investigate the applicability of high dose radiation therapy following the administration of SpaceOar Hydrogel to decrease rectal toxicity in patients with prostate cancer who had received definitive three-dimensional conformal radiation therapy. Seven patients with a diagnosis of prostate cancer received, under general anesthesia, 10 ml of prostate SpaceOar hydrogel injections transperineally into the space between the prostate and the rectal front wall under the guidance of

transrectal ultrasonography. Abdominal tomography and magnetic resonance images of the patients were taken before and after the application of hydrogel. Using both imaging sets and similar algorithms, 3D conformal radiotherapy plans were made that aided in making the calculations. The radiation dose to be applied was calculated from the dose-volume histograms of the target and at risk organs of the patients with tailor-made plans. In the treatment of prostate cancer patients with and without hydrogel plans, there was a statistically significant difference between the rectal V70 and V50 doses, which were 20% ± 14.9 vs 11% ± 2.2 ( p:0.002), and 34 ± 7.9 vs 28.2 ± 11 (p: 0.048), respectively. The D95 and D5 values were similar in all patients with and without hydrogel plans. Rectal toxicity decreased in patients with a distance of >15 mm (p=0.053). Consequently 3D conformal radiotherapy can be successfully and safely applied at high dose with low toxicity to prostate cancer patients after placing hydrogel between the rectum and prostate.

**Keywords:** Prostate cancer, radiotherapy, spaceoar hydrogel, rectal toxicity

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## Introduction

The incidence of prostate cancer (PC) ranks first in the developed world according to 2010 data. It is an important life-long health concern for males. Surgery is one of the treatment options for early stage PC(Jemal et al., 2011). However, serious complications are the norm for surgical therapies. Among these are incontinence (67 %), rectal injury (15%), and narrowing of the bladder neck (29%)(Garzotto & Wajsman, 1998; Stephenson et al., 2004) . For this reason, radiotherapy (RT) is considered to constitute a good alternative to surgery (Bucci, Bevan, & Roach, 2005). In addition, occurrence of impotence and incontinence is less frequent in RT than surgery(Robinson, Moritz, & Fung, 2002). It has been established that dose escalation in RT improves the biochemical parameters (Viani, Stefano, & Afonso, 2009). However, the dose escalation is limited because of rectal toxicity (Brenner, 2004). Methods for decreasing rectal toxicity have been developed. These include advanced RT techniques like intensity modulated radiotherapy (IMRT) and image guided radiotherapy (IGRT). There are other applications that have been developed to protect the rectum by increasing the distance between the prostate and rectum in order to decrease the effect of radiation (Nguyen et al., 2013; Pinkawa et al., 2011; Pinkawa et al., 2013; Pinkawa, Schubert, Escobar-Corral, Holy, & Eble, 2015; Prada et al., 2007; Prada et al., 2009; Susil, McNutt, DeWeese, & Song, 2010; Uhl et al., 2013). One such application is the injection of Prostate Spacer Hydrogel (SpaceOAR™ System, Augmenix Inc., Waltham, MA) between rectum and prostate.
In this study, we investigated the protection that hydrogel proveided against rectal toxicicty induced by high dose 3D conformal radiotherapy (3D-CRT) in prostate cancer patients.

## Methods and Materials

### Patients

In this study, to reduce the rectal toxicity of high dose RT, hydrogel was injected between the prostate and rectum. Using abdominal tomography (CT) imaging before and after the injection of hydrogel, 3D-CRT plans of patients were made and compared dosimetrically. In addition, rectal radiotoxicity levels were evaluated in patients receiving hydrogel in accordance with the plans. This method was applied to 7 patients admitted to the Oncology Department between April 2014 and April 2015. The patients had pathologically confirmed prostate cancer with T1 and T2, N0 and M0. This type of therapy used to be a routine procedure sanctioned by the Ministry of Health. However, after the initiation of the study, the provision of hydrogel for this type of treatment has been discontinued by the state because of cost concerns. Therefore, we were unable to recruit more patients. However, the results proved to be beneficial for the patients, encouraging submission for publication.

### Placement of Hydrogel

Prostate spacer hydrogel is polyethylene glycol that polymerises in 10 seconds. The gel is injected by using an 18G needle into the perineal region between the prostate and rectum under the guidance of transrectal ultrasonography. To establish sufficient space between the retroprostatic fascia and the rectal front plane for the hydrogel, 25 ml of isotonic solution is injected prior to the injection of the gel. The injected hydrogel solidifies within 10 seconds in the perirectal adipose tissue and thereby separates the prostate and rectum. Thus, the space increases by about 14-15 mm after the injection of the hydrogel. This can be confirmed by magnetic resonance imaging (MRI). The injection process takes about 5 minutes. The 7 patients who received the hydrogel were transferred to operation theatres to provide a sterile environment. The procedure was performed under general anesthesia to avoid pain sensation, to

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provide psychologic comfort and to allow easy application. The patients were followed for two hours in the postoperative care room before discharging to the ward. It is important that the space created by the injection of the hydrogel is retained for three months for the duration of RT. The hydrogel is resorbed within 6 months of its application and discharged by the kidneys (Pinkawa et al., 2015). Axial T2 weighted pelvic MRI images of a patient immediately after the injection of the hydrogel and 9 months after the application are shown in figure 1, which show that the hydrogel has disappeared completely within this period.

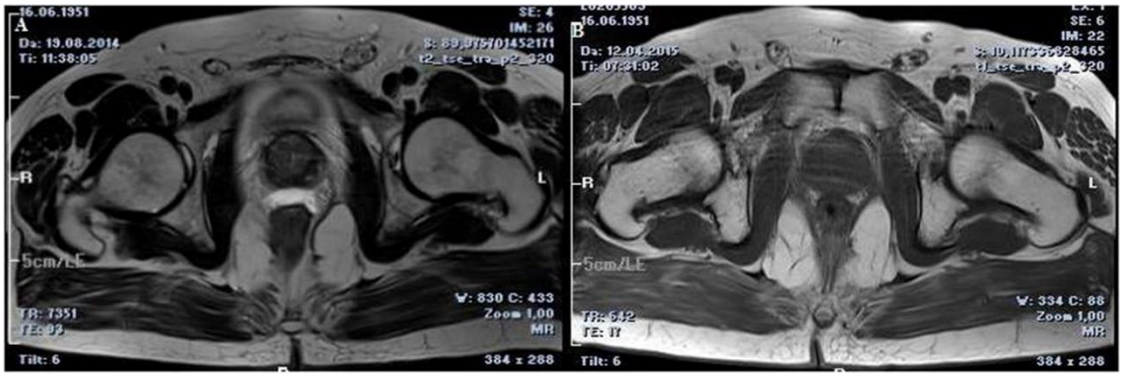


**Figure 1.** Illustration of hydrogel absorption in a patient by lower abdominal T2w MRI. Axial images (A) post hydrogel/pre 3D CRT, and (B) 9 months post hydrogel from the same patient.

**Treatment Planning and Therapy**

Abdominal CT scanning of patients for planning were performed on full bladder achieved by water consumption at a rate of 0.5 L/30 min. Patients presented with enlarged recti on scanning were asked to discharge intestinal contents by natural means. Scans were set at 3 mm sections and taken in supine position before (CT1) and after (CT2) application of hydrogel using LB Toshiba simulator CT. Furthermore, T2 weighted MRI images were taken to allow post-injection image fusion. The volumes were contoured by the same radiation oncologist in order to avoid operator dependent variations. The prostate, seminal vesicles, rectum, bladder and the other normal tissues were identified and drawn. The rectum contoured from the anal canal to the rectosigmoid junction (Pinkawa et al., 2006). Gross tumor volume was identified by the prostate tissue as imaged by CT. The clinical target volume was assessed on the basis of the state of the patient. PTV were set to include prostate only in low risk patients (T1, 2a and Gleason score ≤ 6 or PSA< 10ng/mL), the prostate and proximal seminal vesicles in medium risk patients (T2b, T2c or Gleason score of 7 or PSA 10-20 ng/mL), and the prostate, seminal vesicles and periprostatic lymph nodes in high risk patients (T3, T4 or Gleason Score of 8-10 or PSA > 20ng/mL). In planning RT, a margin of 5 mm in the posterior is recommended for PTV (Nederveen et al., 2002; Teh et al., 2003), which was the case in this study, too. Simultaneous cone beam CT (CBCT) scan imaging was used to confirm compliance with the plans during treatment.

Treatment plans were drawn using 3D-CRT with and without hydrogel plans under the area technique[11] with portal angles of 30, 90, 150, 270, and 330 degrees (CMS XIO, release 5.00.01 treatment planning system, with 18 MV photon). CT images from both plans and isodose distributions of patients are shown in Figure 2. It is apparent that the rectum is protected in the hydrogel plan. The ICRU reference point was defined within PTV and the planning was escalated in 39 fractions from 2 Gy to 78 Gy per day. More than 99% of the PTV was to receive at least 95% of the dose and the maximum dose was adjusted to be less than 107% of the defined value. Based on the recommendations of RTOG (Nederveen et al., 2002; Teh et al., 2003) , plans of V50 < 50% and V70 < 20% for the rectum were made and dose volume histograms (DVH) were drawn. Both plans were dosimetrically compared. For the sample patient, DVH of both rectal plans are shown in Figure 3. The rectal dose was significantly less with the hydrogel plan than with the one without.

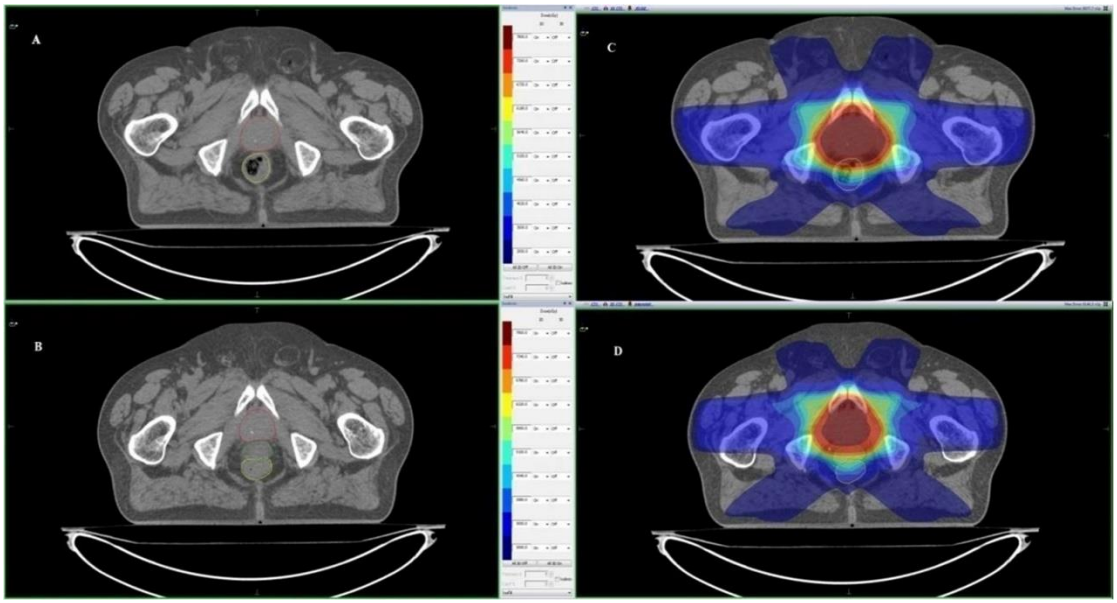


**Figure 2.** Axial plane abdominal CT images before (A) and after (B) hydrogel, and images of hydrogel planned by the conformal techniques before (C) and after (D) isodose distributions.

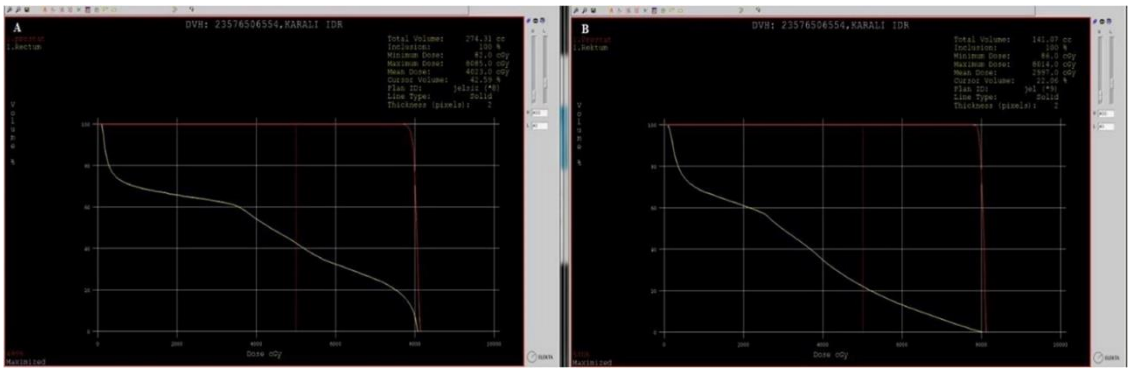


**Figure 3.** Rectal DVHs with and without hydrogel.

**Statistical Analysis**

DVH were used in the comparison of the target volume and at-risk organ doses in all of the treatment plans. The Mann-Whitney U-test for non-parametric-interval data and the $chi^2$-test for ordinal/nominal data were used to compare the groups. All statistical tests were two-sided, with a threshold for statistical significance of $p<0.05$. Statistical analysis was carried out utilizing SPSS version 13.

**RESULTS**

Patient and tumor characteristics are given in Table 1. In the treatment of patients with hydrogel plans, there was a statistically significant difference between the rectal V70 and V50 doses. There was no significant difference between the two plans for other parameters. The dosimetric results are summarized in Table 2.

Posterior displacements have been analyzed at three different representative levels in the mid-sagittal plane: the superior prostate/ seminal vesicle (point P1), the level of the bladder neck (point P2), and the inferior prostate (point P3). The definitions of the base, middle and apex, as well as points P1, P2 and P3, are demonstrated in Figure 4. The P1-3 measurements of the patients are shown in table 1. While the highest values correspond to P1, the lowest match with P3. The average distance between the prostate and rectum of the patients was 14.2 (range 10.5-25.2) mm from the centre of the rectum. This distance has no significant correlation with rectal toxicity and tenesmus ($p=0.07$). However, there was a drop in rectal toxicity in patients with a distance of >15 mm between the rectum and prostate ($p=0.053$).

There was no complication pertaining to the hydrogel application except for one patient had more than ten tenesmuses a day, which resisted symptomatic treatment. Patient's compalints gradually subsided as

therapy progressed. Symptoms of radiation proctitis were assessed via the Radiation Therapy Oncology Group/ European Organization for Research and Treatment of Cancer (RTOG/EORTC) gastrointestinal (GI ) and genitourinary (GU) toxicity score (acute and late) (Cox, Stetz, & Pajak, 1995). Weekly and at the completion of RT, patients were evaluated for acute GU and GI toxicity. During follow-up toxicity assessments were performed 3, 6, 9, 12 and 30 months after the end of radiation therapy (RTOG/ EORTC). The patients had no GU syptoms including polyuria, nocturia, or hematuria. One patient experienced grade 2 acute GI toxicity, requiring analgesics and medication, including rectal discomfort and tenesmus. No patient experienced grade 3 or 4 toxicities. No patient experienced grade 3 or 4 toxicities. While there was no rectal toxicity in patients with a hydrogel distance of ≥12.5 mm (n=3), rectal toxicity was observed in one patient whose hydrogel distance was 10.5 mm.

**Table 1.** Characteristics of patients and tumors

| **Patient no** | **Age** | **PSA** | **T** | **GS** | **N** | **M** | **Distance between prostate and rectum distant (mm)** | | | **Tenesmus Frequency (grade)** | **Rectal Toxicity (grade)** |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | P1 | P2 | P3 | | |
| **1** | 62 | 16 | T2c | 6 | 0 | 0 | 19.1 | 25.2 | 18.4 | 3 | 0 |
| **2** | 73 | 8 | T2c | 7 | 0 | 0 | 14.8 | 11.2 | 8.3 | 1 | 1 |
| **3** | 63 | 10.5 | T2c | 6 | 0 | 0 | 12.5 | 11.1 | 9.4 | 1 | 1 |
| **4** | 76 | 134 | T1c | 8 | 0 | 0 | 15.5 | 12.1 | 10.5 | 1 | 1 |
| **5** | 64 | 9.6 | T2c | 6 | 0 | 0 | 15.7 | 12.5 | 9.5 | 1 | 0 |
| **6** | 57 | 3.35 | T1c | 6 | 0 | 0 | 15.8 | 10.5 | 6.5 | 0 | 2 |
| **7** | 61 | 4.04 | T1c | 6 | 0 | 0 | 25.1 | 17.2 | 11.5 | 0 | 0 |

Abbreviations: GS: Gleson scor,T: tumor, N: Nodal metastasis, M: Distal Metastasis

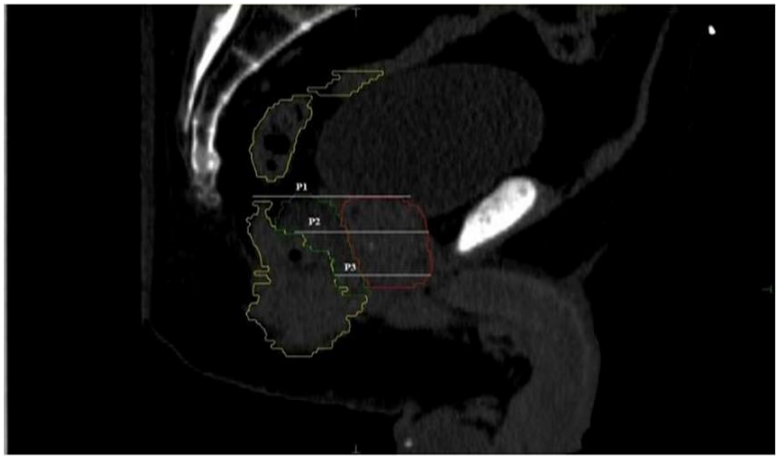


**Figure 4.** Sagittal CT reconstruction demonstrating the definition of the levels of the bases P1, P2 and P3.

 

**Table 2:** Dosimetric comparison of both plans

| | Non-Hydrogel Plan | Hydrogel Plan | p value |
|---|---|---|---|
| **PTV78-D95 (Gy)** | 75.9±0.3 | 76.3±0.6 | 0.09 |
| **PTV78-D5 (Gy)** | 80.7±0.7 | 81.1±0.6 | 0.08 |
| **Rectum-V70 (%)** | 20±14.9 | 11±2.2 | 0.002 |
| **Rectum-V50 (%)** | 34±7.9 | 28.2±11 | 0.048 |
| **Rectum-V35 (%)** | 53.6±9.4 | 51±14.6 | 0.55 |
| **Bladder-V70 (%)** | 31.9±16.2 | 21.5±9.9 | 0.33 |
| **Bladder-V50 (%)** | 46.3±20.5 | 37.6±16 | 0.33 |
| **Bladder-V35 (%)** | 55.7±24 | 48.7±21 | 0.74 |
| **Penile bulb mean** | 61.8±7.7 | 61±6.6 | 0.94 |
| **Penile bulb V40** | 85.6±11.6 | 84±12.2 | 0.98 |
| **Penile bulb V14** | 97.9±4 | 98.3±2.8 | 1.0 |
| **Right femur max (Gy)** | 47.6±6.5 | 50.6±3.7 | 0.44 |
| **Left femur max (Gy)** | 47.6±6.1 | 49.1±2.7 | 0.52 |

## DISCUSSION

Results of RT for treatment of PC are dose dependent. Medium risk patients treated with 78 Gy versus 70 Gy did better in a study conducted in the MD Anderson Centre, confirming the benefit of dose escalation however, it has been reported that dose escalation also results in increase in grade 2 rectal toxicity (25% vs 46%, respectively) (Kuban et al., 2008). Reduction of rectal toxicity while maintaining high dose therapy has been possible by advanced technologies like IMRT and IGRT (Peeters et al., 2006; Zelefsky et al., 2006). While applying these methods for the treatment of local PC, reduction of rectal toxicity has gained prominence (Bohrer et al., 2008; Kuban et al., 2008; Viani et al., 2009; Zelefsky et al., 2006). Because of therapeutic complications, including rectal bleeding, proctitis, pain, and incontinence, which reduce life quality (Maeda, Høyer, Lundby, & Norton, 2011; Pinkawa et al., 2010; Rancati et al., 2011). For this reason, various methods have been evaluated to reduce rectal toxicity. These include rectal balloon application (Patel, Orton, Tomé, Chappell, & Ritter, 2003; Smeenk, Teh, Butler, van Lin, & Kaanders, 2010; van Lin, Hoffmann, van Kollenburg, Leer, & Visser, 2005; van Lin et al., 2007) and use of hyaluronic acid or collagen(Noyes, Hosford, & Schultz, 2012; Prada et al., 2007; Wilder et al., 2010) with limited success. Recently, a new approach has been developed that involves injection of hydrogel between the prostate and rectum to allow rectal toxicity reduction (Pinkawa et al., 2011; Pinkawa et al., 2013; Pinkawa et al., 2015; Susil et al., 2010). Since the rectum is segregated from the target tissues by about 15 mm, its exposure to damaging radiation is drastically reduced. In these patients, ratios of early and late toxicity are very low. In

planning for PC RT, limiting dose prescriptions were designed to lower severe proctitis, necrosis or rectal fistula. The rectal doses of V50 and V70 should be <50% and 20%, respectively, and the maximum dose must be below 76 Gy. IMRT is better suited for these doses than the 3D-CRT. In our study, in which hydrogel was used in patients for 3D-CRT, we achieved this outcome by remaining way below these doses. Rectal V50 and V70 values were 28.2% ± 11 and 11% ± 2.2, which are statistically significant (p=0,048 and p=0.002). When the distance between the prostate and rectum is considered in relation to toxicity, patients with a gap of over 15 mm show a decrease in toxicity near to statistically significant levels (p=0.053). No toxicity was observed in patients in whom this distance was over 12.5 mm. Lack of statistical significance is likely related to the low number of cases. For this reason, a distance of 12.5-15 mm seems sufficient.

Reporting of data pertaining to the use of hydrogel is increasing. In a recent study in which hydrogel was used during therapy, 3D-CRT and IMRT plans were compared dosimetrically (Pinkawa et al., 2011). It was found that the probability of dose related rectal toxicity decreased in both plans regardless of dose alterations of PTV and bladder. In a multicenter study, Uhl et al (Uhl et al., 2013) found that application of hydrogel during IMRT reduced rectal toxicity. In this study, in which 78 Gy RT was employed, no toxicity rating 3 or 4 was observed. The results of this study are similar to ours. Data for hydrogel use is also available for brachytherapy. Salvage brachytherapy was applied to a patient with recurrence following RT after hydrogel injection (Pinkawa et al., 2015). The risk of rectal fistula after surgical treatment is reported to be 3.4% (Nguyen et al., 2013), but this approach limits rectal radiation exposure. In this way, it was shown that patients with recurrence post-RT can be treated by brachytherapy following hydrogel injection. Total RT dose cannot exceed 60-64 Gy because of rectal toxicity in patients with postoperative RT indication (Bolla et al., 2012; Thompson et al., 2009). However, by employing hydrogel, high dose RT (76 Gy) was successfully used to treat post-operative recurrence (Pinkawa et al., 2011). Hyrogel use is also well placed for the treatment of cervical cancer because of the anatomical location, requirement of high RT and radiation-induced rectal damage.

Hydrogel injection-induced hydrodisection facilitates linear and homogenous distribution (Nguyen et al., 2013). We utilized this method in our applications. In addition, intraoperative ultrasonography was used to monitor and ensure desired hydrogel placement. Non-homogenous distribution of hydrogel may result from the intensity of tenesmus after application. In one of our patients with >10 tenesmuses per day, the hydrogel space was 25 mm corresponding to the middle of the prostate. This results in pressure on the rectum that leads to tenesmuses. The complaints of the patient progressively decreased during therapy and disappeared before completion. This complication may adversely affect the wellbeing and adaptation to the therapy of the patient.

The gap created by hydrogel injection remains stable through RT and, depending on the resorption rate; it begins to shrink by about 6 months and disappears by 9 months (Uhl et al., 2013). In our cases, the hydrogel gap disappeared by 9 months which was verified by MRI (Figure 1).

## CONCLUSION

3D-CRT can be successfully and safely applied at high intensity with low toxicity to prostate cancer patients after placing hydrogel between the rectum and prostate. We achieved important rectal protection by using hydrogel plans without expending on

therapeutic dosages on PTV and bladder. This approach may bear importance for the treatment of cervical cancer patients, too. However, there is a requirement for studies analyzing the biochemical response and long term toxicity in larger patient groups, which may affect patient survival.

**Conflicts of Interest: The** authors declare no conflicts of interest.
**Ethics Approval and Consent to Participate:** Ethical consent was obtained from Recep Tayyip Erdogan Universitiy Local Ethics Committee. Decision no: 2017/45. Date: 17.03.2017.
**Authors' Contributions**: All authors participated in patient treatment and were involved in the preparation of the manuscript. All authors reviewed and approved the final manuscript.
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