Does Intravesical Prostatic Protrusion Affect Oncological Outcomes and Toxicity in Prostate Cancer Patients Receiving Definitive Radiotherapy?

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ABSTRACT

Intravesical prostatic protrusion (IPP) is associated with increased urinary toxicities after radical prostatectomy. The aim of the current study is to investigate the effect of IPP on treatment outcomes and toxicity in prostate cancer patients who underwent definitive radiotherapy (RT). Medical records of 130 patients who received RT between April 2007 and October 2017 were retrospectively evaluated. All patients received conventionally-fractionated intensity-modulated RT to a total dose of 70-78Gy. We found a very strong positive correlation with MRI and CT thus IPP grades for the whole cohort were evaluated using CT scans. Acute toxicities were evaluated using CTCAE version4.0 and late toxicities were evaluated using RTOG/EORTC guidelines. Mann-Whitney U, chi-square and student-t tests were used for statistical analyses in SPSS version15.0. Forty-two patients did not have IPP, 19 patients had grade I, 47 patients had grade II and 22 patients had grade III IPP. There was no difference in age, PSA level and GS but prostate volume was higher in the IPP group (p= 0.013). With a median follow-up of 53.4 months, biochemical recurrences were observed in 10 patients in the IPP group and 2 patients in the non-IPP group (p= 0.334). There was no significant difference in treatment outcomes. RT was well tolerated however grade ≥ 2 acute genitourinary (GU) toxicity was higher in the IPP group (p= 0.024). CT scan is strongly correlated with MRI in terms of grading IPP. IPP does not affect RT outcomes however it seems to be a risk factor for acute GU toxicity.

Keywords: Intravesical prostatic protrusion, Radiotherapy, Prostate cancer

INTRODUCTION

Prostate cancer (PCa) is the most common type of cancer among men with an estimated 174,650 new cases in 2019.[1] External beam radiation therapy (EBRT) with or without androgen deprivation therapy (ADT) is one of the treatment options for clinically localized PCa.[2,3] Although, new radiotherapy (RT) techniques like intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) reduced gastrointestinal (GI) toxicities, significant reductions of urinary-related toxicities after high-dose RT have not been observed yet.[4,5] Frequency of ≥ grade 2 acute and late genitourinary (GU) related toxicities (including erectile impotence, urinary frequency/urgency and urinary incontinence) in PCa patients who underwent definitive IMRT is approximately 11% and 69% respectively.[5] In the literature, a few studies reported increased radiation dose to the lower bladder and bladder trigone seemed to be associated with increased GU toxicity.[6,7] Previously, the presence of diabetes mellitus, receiving anticoagulant treatment, increased RT dose were found to be associated with increased late GU toxicity.[8]

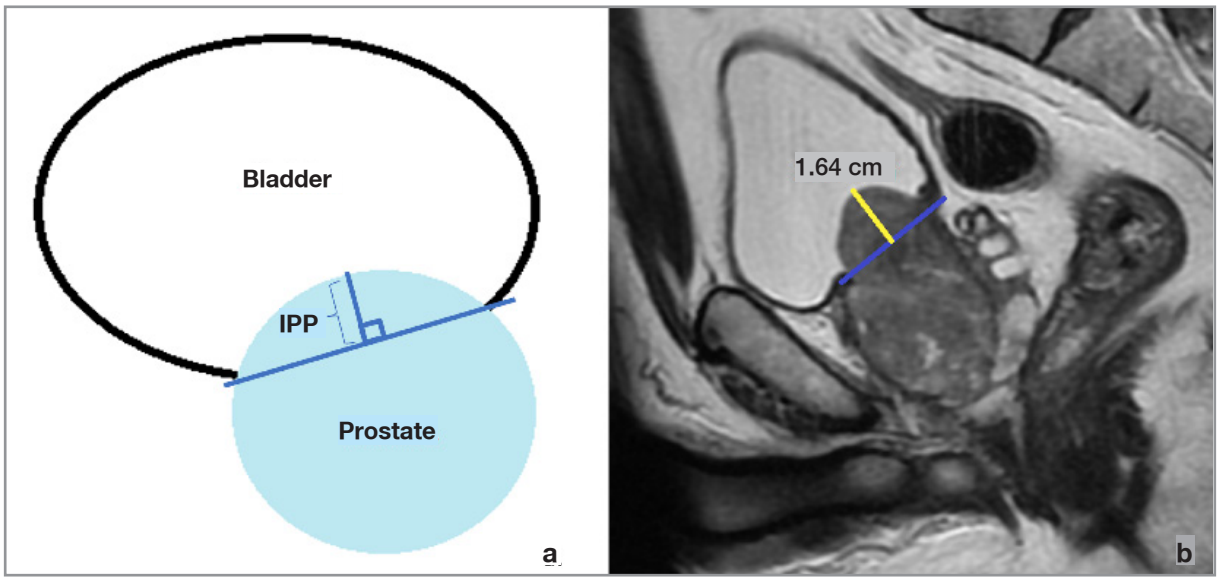

Figure 1. Measurement of the intravesical prostatic protrusion (IPP). **(a)** Schematic estimation of IPP: The vertical distance from the tip of the protruding prostate to the base of the bladder. **(b)** Sagittal view of magnetic resonance imaging (MRI) and protruding prostate

Intravesical prostatic protrusion (IPP) was found to be correlated with bladder outlet obstruction and decreased International Prostate Symptom Score (IPSS) after transurethral resection of the prostate (TURP) for benign prostatic hyperplasia.[9,10] Although IPP was previously found to be associated with increased urinary incontinence rates and prolonged duration of postoperative urinary incontinence after radical prostatectomy[11], there is no evidence that IPP affects oncological outcomes and early or late GU toxicity in patients who underwent definitive radiotherapy. Previously, IPP was evaluated by using ultrasonography or magnetic resonance imaging (MRI), there is no evidence that IPP can be evaluated by computed tomography (CT). Therefore, the present study aimed to evaluate the correlation of IPP grades between MRI and CT scans and the effect of IPP on oncological outcomes and early or late toxicity after radiotherapy.

PATIENTS AND METHODS

Medical records of 130 patients who underwent definitive RT for localized PCa between April 2007 and October 2017 were retrospectively evaluated. All patients received conventionally fractionated IMRT to a total dose of 70-78 Gy using the Brainlab® Novalis system. Radiotherapy planning CT scans were obtained when the bladder was filled with 500 ml of saline solution. All of the evaluations were made using planning CT. Since the patients with lymph node involvement were not included in the present study, lymphatic irradiation was not performed in any of the patients. The clinical target volume (CTV) was defined as the whole prostate gland with or without bilateral SV. The extent of the delineation of SVs depended on the D'Amico risk group stratification system.[12] In intermediate-risk disease, proximal SVs were countered, whereas in high-risk disease whole SVs were countered. CTV was enlarged with a 0.5 cm margin in anterior, left and right directions and 0.3 cm in the posterior direction to constitute planning target volume (PTV). Bladder volume that receives 70 Gy (V70) and 40 Gy (V40) was allowed to be < 35% and < 40% of all bladder volume and rectum volume that receives 65 Gy (V65) and 40 Gy (V40) was allowed to be 35% and 40% of all rectum volume in treatment planning.[13]

IPP was retrospectively evaluated by two experienced radiologists using diagnostic multiparametric MRI and CT scans. Since not all patients had diagnostic multiparametric MRI, firstly the correlation of IPP between MRI and CT images were evaluated in 49 patients who had both MRI and CT scans. According to Gravas et al IPP was defined as the vertical distance from the tip of the protrusion

Table 1. IPP grades in CT and MRI scans showed a very strong positive correlation (r= 0.758, p< 0.001)

		MRI			
		No IPP (n)	**Grade I IPP (n)**	**Grade II IPP (n)**	**Grade III IPP (n)**
CT	No IPP (n)	12	5	5	0
	Grade I IPP (n)	1	2	5	0
	Grade II IPP (n)	0	2	8	1
	Grade III IPP (n)	0	0	1	7

Abbreviations: CT= Computed tomography; MRI= Magnetic Resonance Imaging; IPP= Intravesical prostatic protrusion

to the base of the bladder in the sagittal plane and graded as grade I if the distance was < 5 mm, grade II if the distance was 5-10 mm and grade III if the distance was > 10 mm (Figure 1).[14]

We divided 130 patients into two groups according to the presence of IPP in CT scans. Acute side effects were evaluated using CTCAE version 4.0 and late side effects were evaluated using RTOG/EORTC guidelines. Patients had a PSA test every 3 months in the first 2 years following RT and every 6 months thereafter. Biochemical recurrence was defined as PSA nadir + 2 ng/mL based on the Phoenix definition.[15]

Statistical analysis was performed with SPSS version 20 (SPSS Inc., Chicago, IL, USA) and statistical significance was defined as a p value of < 0.05. The variables were investigated using visual (histograms, probability plots) and analytical methods (Kolmogorov-Simirnov/Shapiro-Wilk's test) to determine whether or not they are normally distributed. While investigating the associations between non-normally distributed and/or ordinal variables, the correlation coefficients and their significance were calculated using the Spearman test. The Mann-Whitney U test was used to compare non-normally distributed and ordinal variables between the groups. Student's t-test was used to compare normally distributed variables between the groups. This retrospective study was conducted in compliance with the principles of Helsinki declaration and informed consent was obtained from each patient.

Ethical approval for this retrospective study was obtained from the Institutional Review Board of Hacettepe University (IRB Decision number: 2020/04-24).

RESULTS

The median age of the patients was 71.5 years (range= 45-86 years), median GS was 7.5 (range= 6-10), median PSA level at diagnosis was 28 ng/mL (range= 2-374 ng/mL) and median prostate volume was 46.25 mL (range= 11-166 mL). There were 10 patients (7.7%) in the low-risk, 22 patients (16.9%) in the intermediate-risk and 98 patients (75.4%) in the high-risk group according to D'Amico risk group stratification system. After RT, 118 patients received ADT of median 12 months (range= 3-84 months). Since not all patients had diagnostic multiparametric MRI, we first evaluated the correlation of IPP between pretreatment MRI and CT images in 49 patients that have both MRI and CT scans. MRI and CT showed a very strong positive correlation for IPP grades (r= 0.758, p< 0.001) and the IPP grades were given in detail for both MRI and CT scans in Table 1.

Thus IPP grades for the whole cohort were evaluated in CT scans by the same radiologists; 42 patients (32.3%) did not have IPP, 19 patients (14.6%) had grade I, 47 patients (36.2%) had grade II and 22 patients (16.9%) had grade III IPP. There was no significant difference in age, PSA level, GS, duration of hormonal therapy and the volume of SVs in RT field between IPP and non-IPP groups but prostate volume was found significantly higher in the IPP group (p= 0.013) (Table 2).

Median follow-up time was 53.4 months (8.5-148.9 months). Median survival was not achieved during the follow-up period. Biochemical recurrences (BCR) were observed in 10 patients (11.9%) in the IPP group and 2 patients (4.8%) in the non-IPP group (p= 0.334). There was no significant dif-

Table 2. Comparison of patient characteristics between IPP and non-IPP groups

Median (IQR)	IPP group (n= 42)	Non-IPP group (n= 88)	P value
Age	72 (66-76)	70 (66-75)	0.275
PSA level (ng/ml)	31 (18-98)	24.5 (12.25-79.75)	0.464
Gleason Score	8 (7-9)	7 (7-9)	0.730
Duration of hormonal therapy (months)	12 (10-24)	12 (9-24)	0.656
Prostate volume (mL)	48.65 (34.55-63.93)	34.25 (22.30-56.65)	0.013*

* Mann-Withney U test; statistical significance was defined as p< 0.005

ference in 5-year overall survival (OS) (78.4% vs 91%; p= 0.559) and biochemical recurrence-free survival (bRFS) rates (83.3% vs 90.6%; p= 0.183) between IPP group and non-IPP group (Figure 2).

The treatment was well tolerated and no acute or late grade 3-4 toxicity was observed in this study. Frequency in 24 patients, dysuria in 31 patients, transient urinary incontinence in 3 patients and urgency in 1 patient were observed as acute GU toxicities. Proctitis was observed in 5 patients as acute GI toxicity. Urinary incontinence was observed in 2 patients as both acute and late GU toxicity. Dysuria in 3 patients, frequency in 16 patients, erectile dysfunction in 2 patients, hematuria in 1 patient, urinary incontinence in 5 patients and urgency in 2 patients were observed as late GU toxicities. Acute GI toxicity, late GI toxicity, and late GU toxicity rates were similar between the IPP and non-IPP groups. However grade ≥ 2 acute GU toxicity was significantly higher in the IPP group than the non-IPP group (p= 0.024). For the whole cohort median V70 and V40 for bladder was 7% (0-33%) and 28% (4%-63%) respectively. Median V65 and V40 for rectum was 9% (2%-24%) and 33% (13%-55%) respectively. No significant difference was observed in V70 or V40 for bladder (p= 0.137, p= 0.267 respectively) and V65 or V40 for rectum (p= 0.090, p= 0.088 respectively) between IPP and non-IPP groups.

DISCUSSION

IPP occurs as the prostate gland enlarges into the bladder with median lobe hypertrophy. Ultrasonography and MRI are useful and non-invasive methods for measurement of IPP.[10,16] In this study, since not all patients had MRI, the correlation of IPP grades between pretreatment diagnostic MRI and planning CT was performed initially and CT was found to be well correlated with MRI in terms of evaluating IPP grades. Subsequently IPP grades of all patients were evaluated using pre-treatment CT scans and it was found that IPP was associated with higher acute grade ≥ 2 GU toxicity without interfering oncological outcomes.

Acute or late GU toxicity is one of the most common side effects after definitive RT in PCa patients that affects the quality of life.[5] Presence of diabetes mellitus, receiving anticoagulant treatment, hypofractionation, older age, hormonal therapy, concurrent chemotherapy, increased RT dose to the lower bladder and bladder trigone was previously found to be associated with GU toxicity after definitive RT.[6,8,17-19] The current study showed that IPP was associated with high rates of grade ≥ 2 acute GU toxicity in PCa patients who underwent definitive RT. The patients' characteristics such as age, duration of hormonal therapy were similar between groups. None of the patients had hypo-fractionated RT or concurrent chemotherapy in the current study. The difference in GU toxicities seems to be caused by the presence of IPP. Although prostate volume is higher in the IPP group that might affect the volume of bladder in the RT field we couldn't find a difference in bladder dose-volume parameters in two groups. However there might be currently unknown different parameters that should be used to estimate the difference that leads to acute GU toxicities. To the best of our knowledge, this is the first evidence about the association between the presence of IPP and GU toxicity in PCa patients who underwent definitive RT.

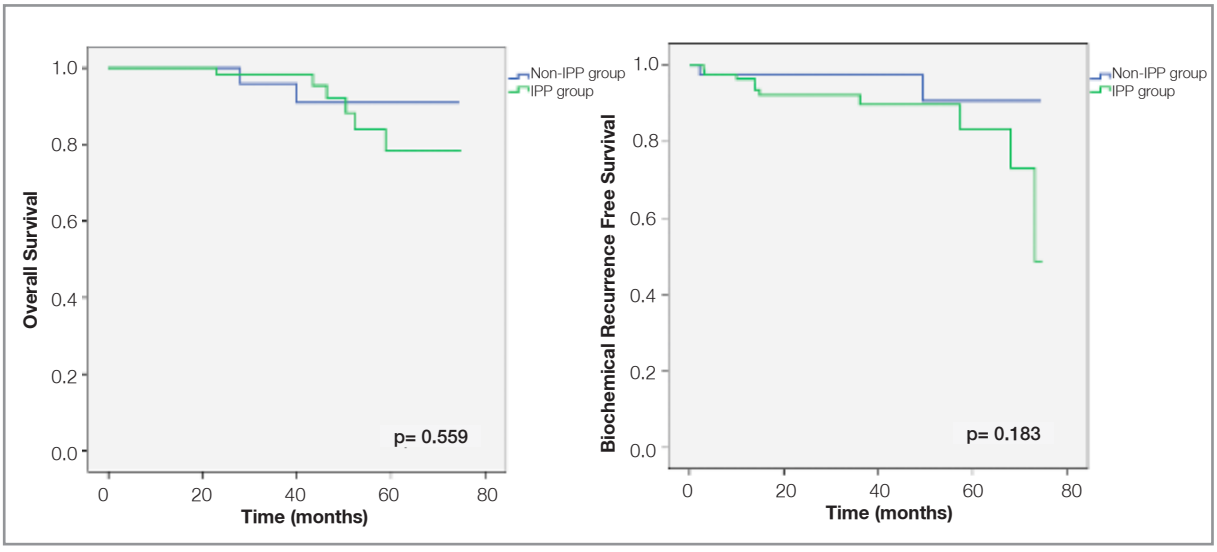

Figure 2. Comparison of 5-year overall survival and biochemical recurrence-free survival between the IPP group and non-IPP group.

Although a few studies are supporting that IPP was associated with bladder outlet obstruction in benign prostatic hyperplasia, there are controversial reports about the association of IPP and recovery of urinary incontinence after robot-assisted radical prostatectomy.[20-22] Lee et al. showed that although IPP was associated with higher rates of urinary incontinence after laparoscopic radical prostatectomy, it was also found as a predictor of early urinary continence recovery.[11] Jo et al, also reported that the presence and grade of IPP were related to low postoperative continence rates after robot-assisted laparoscopic radical prostatectomy.[22] Hamidi et al. reported the presence of IPP did not affect oncological outcomes but was a disadvantage in gaining early urinary continence after robot-assisted radical prostatectomy.[21]

The current study showed no difference in 5-year OS and bRFS between the groups that are similar to literature for patients treated with surgery. However it should be kept in mind that IPP might be correlated with positive surgical margins at the base during robot-assisted laparoscopic radical prostatectomy.[21,23]

To the best of our knowledge current study is the first study to find a correlation of MRI and CT in the evaluation of IPP grades. Strong correlation in between helps to use planning CT in IPP grading in the routine practice. Additionally the effect of IPP on GU toxicity after surgery has been reported before however this is the first study to show the association of IPP and GU toxicity after definitive RT in the IMRT era.

The current study has some limitations. Firstly, the data was collected retrospectively. The information about predicting factors for GU toxicity such as the presence of diabetes mellitus, receiving anticoagulant treatment could not be reached from the patient records. The second limitation of this study is evaluating urinary symptoms without using objective methods such as IPSS or the number of pads per day. Patient-reported medical records were used for evaluation of urinary incontinence status.

In conclusion CT scan was found to be strongly correlated with MRI in terms of grading IPP. In future studies, planning CT scans can be used for the measurement of IPP in PCa patients. The presence of IPP does not affect the treatment outcomes however it seems to be a risk factor for GU toxicity. Thus reduction in the prostate volume before radiotherapy might be a good option to avoid acute GU toxicity.

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