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The impact of benign prostatic hyperplasia on bladder volume in radiotherapy of prostate cancer

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► ***Original article***

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ABSTRACT

Background: Benign prostatic hyperplasia (BPH) is a common disease among older men and many patients with prostate cancer (PC) also have BPH. External beam radiation therapy (EBRT) is one of the important treatments for PC, nevertheless, few studies have analyzed the effect of BPH on EBRT. We tried to know the risk of bladder toxicity by analyzing the bladder volume variability in patients with BPH. ***Materials and Methods***: Changes in prostate location with respect to the presence of BPH and bladder volume by bladder zone were analyzed. Dosimetric parameters of prostate and bladder were analyzed using planning computed tomography (CT) scans in 20 patients with PC. Three planning CTs were performed on each patient during RT. Maximum bladder volume variations were calculated using the three planning CT scans and volumes of upper and lower zones were compared. ***Results:*** Mean upper and lower bladder volume ratio was 0.85 and 0.15, and mean maximum differences in bladder volumes for the three CTs were 97.33 cc and 10.36 cc for upper and lower bladders, respectively ($p < 0.001$). Prostate size and location with respect to prostate upper margin showed a moderate linear correlation ($r = 0.567$, $p = 0.009$). Prostate superior margins of patients with or without BPH were located at mean distances of 3 mm above and 4.8 mm below the superior border of pubic bones, respectively ($p = 0.019$). ***Conclusion:*** The prostates of patients with BPH were more likely to be located in the upper bladder zone, which exhibited greater bladder volume variability. This implies that the clinical target volume of EBRT is located in an unstable bladder zone, which would decrease treatment accuracy and increase treatment-related bladder toxicity. The further clinical study is required to analyze the relation between BPH and the severity of RT-induced bladder toxicity.

Keywords: *prostate cancer, benign prostatic hyperplasia, radiotherapy, bladder toxicity.*

INTRODUCTION

Prostate cancer (PC) is the most common cancer among males in the western world, and it is expected that its incidence will substantially increase in coming decades due to population aging, and thus, PC is set to become a huge health care problem [1, 2]. Radiation therapy (RT), surgery, and hormone therapy are the principal treatment modalities for PC [3]. And RT is usually administered by external beam RT (EBRT) or by brachytherapy. Recently, hypofractionated schedules have been actively attempted thanks to advancements in radiation delivery techniques and stereotactic devices [4]. However, the conventional RT schedule for PC is five times a week for two months, and maintaining patient posture is important for ensuring treatment

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accuracy. Furthermore, this maintenance includes accounting for movements of internal organs as well as body posture. In particular, the bladder requires considerable attention, because its volume is highly variable and these changes are likely to affect the accuracy of RT and RT-related toxicity [5].

The bladder is located behind the pubic bone, and the upper bladder may be more flexible than the lower bladder, which is supported by pubic bone. Furthermore, because the bladder is filled toward the upper part of the pubic bone, bladder volume variability is expected to be greater above the pubic bone. A constant bladder volume is important for improving the accuracy of RT treatment [6], but the majority of PC patients are elderly, and urination is not easily controlled in this population [7, 8]. In addition, urinary control may be difficult prior to RT due to benign prostatic hyperplasia (BPH), or because of radiation cystitis caused by RT, which is a common side effect of RT of the lower abdomen [9]. Radiation cystitis is a term used to describe the side effect of inflammation and subsequent destruction of the normal anatomy of the urinary bladder at the cellular level following RT for pelvic cancers. RT can also be used to treat primary bladder cancer and to treat tumors in many organs surrounding the bladder, such as, the colon, rectum, ovaries, uterus, and prostate. Thus, unintentional exposure of healthy bladder tissue is an important consideration [10].

BPH is common in older men, and thus, is present in many PC patients [11, 12]. The prostate is located in the postero-inferior area of pubic bone and has a volume of ~20 cc. However, in patients with BPH, the prostate is enlarged to > 30 cc and may extend above pubic bone [13]. Thus, in the presence of BPH, the prostate is located near the upper bladder, which exhibits considerable size variations. These occurrences imply high level risks of therapeutic uncertainty and side effects.

BPH can dosimetrically affect the irradiation of pelvic area. Considering the anatomical location, BPH is likely to increase radiation cystitis. There are several dosimetric studies on the correlation between prostate size and brachytherapy. However, studies on EBRT are rare. Unlike brachytherapy, interfractional variability is important in EBRT and is directly affected by bladder volume. Therefore, it is thought that bladder volume variability has a significant impact on bladder toxicity in EBRT. In the present study, we tried to analyze the bladder volume deviation according to bladder region and the relationship with prostate size was examined. Ultimately, we want to know the impact of BPH on the interfractional bladder volume variability in EBRT.

MATERIALS AND METHODS

Patients and treatment

Twenty male PC patients that received definitive RT and enrolled at one institution from January 2016 to December 2017 constituted the study cohort. All patients were Korean. Patients with a tumor longest diameter of size > 1.5 cm were excluded to determine the impact of BPH alone. All patients underwent planning computed tomography (CT) using a Toshiba Asteion helical CT scanner (Toshiba Medical Systems, Tokyo, Japan) prior to RT. Second and third CT scans were performed at 1 and 4 weeks after the first RT treatment session. All patients drank 300 cc water after urination and 30 minutes later, planning CT and RT were conducted. Defecation was performed in a regular pattern every morning. RT was delivered using a 21 EX (Varian Medical Systems, Palo Alto, CA) using a 10-MV X-ray beam. Clinical target volumes were contoured according to Radiation Therapy Oncology Group guidelines, and planned target volumes exceeded clinical target volumes by 3 mm [14, 15]. This study was approved by our institutional review board (110757-201802-HR-05-02) and was conducted in accordance with the principles of the Declaration of Helsinki.

Prostate location analysis

Planning CT was performed in the supine position using a 3 mm slice thickness. To determine prostate locations, MRI images were

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fused to all planning CT images using the Eclipse™ treatment planning system (TPS; Varian Medical Systems, Palo Alto, CA). The MRI for staging work-up was performed within one month before planning CT. Prostate margins were delineated using fused images, prostate volumes were measured and superior margin locations were evaluated. The distance between the superior border of pubic bone and the superior margin of prostate was measured. Prostate locations patients with or without BPH were compared. BPH was defined as a prostate size > 30 cc [13].

Bladder volume evaluation and dosimetric parameters

All patients underwent 3 planning CT scans during RT, and bladders were delineated using the Eclipse™ treatment planning system. The superior border of pubic bone was used to delineate upper and lower bladder, and volumes of upper and lower bladder regions were measured (figure 1). Maximum differences in total, upper and lower bladder volumes were calculated using the 3 planning CT scans for each patient and compared. In addition, we calculated upper and lower to total bladder ratios.

Statistically analysis

The Mann Whitney U-test was used to compare mean values, and Spearman's correlation analysis was used to analyze the relationship between prostate location and size. The statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL), and *p*-values of <0.05 were considered statistically significant.

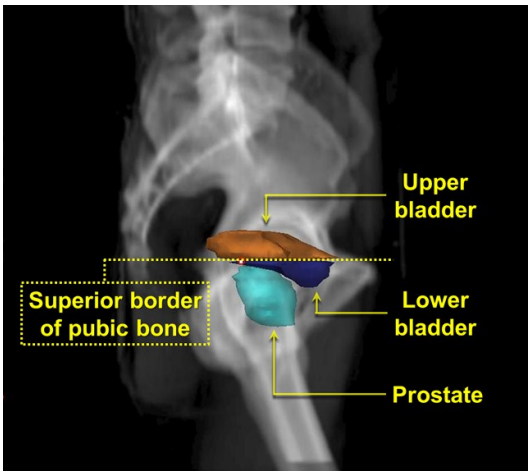


Figure 1. Bladder zones. The upper bladder and lower bladder were defined about the superior border of pubic bone.

RESULTS

The mean age of the 20 study subjects was 75 years and all were of National Comprehensive Cancer Network risk groups above intermediate risk. Fifteen patients underwent elective RT with 44 Gy in the pelvic lymph node chain. Five patients were treated only on prostate and seminal vesicles without elective regional lymph node RT. The median total dose was 78 Gy and intensity modulated radiation therapy was performed with a fraction dose of 2 Gy. Detailed patient information is provided in table 1.

Mean prostate volume of the 20 patients, was 30.39 cc, and tumor volume exceeded 3 cc in all. Patients were dichotomized using a prostate volume of 30 cc, and 10 patients had and 10 did not have BPH. Mean prostate volumes of patients with or without BPH were 43.43 and 17.35 cc, respectively. In order to analyze prostate locations, distances to the superior margins of prostates were measured from the superior borders of pubic bones; mean distance was 0.9 mm in the inferior direction. Prostate superior margins in patients with or without BPH were located at mean distances of 3 mm

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above and 4.8 mm below superior borders of pubic bones, respectively, and this difference was significant (table 2).

Spearman's correlation analysis was performed to investigate the relation between prostate sizes and locations of prostate superior margins. The analysis showed a moderate correlation between the two (r=0.567, p=0.009). Only one of the 10 patients without BPH had a prostate above the superior border of pubic bone, whereas 6 of the 10 patients with BPH had a prostate above the superior border. Results of this analysis are presented in figure 2.

Planning CT was performed three times in all patients, and bladder volumes and volume variabilities were measured. For all study subjects, mean bladder volumes were 157.35, 164.91 and 143.06 cc in 1st, 2nd, and 3rd CT images, respectively, and upper bladder zone to total bladder volumes ratios were 0.88, 0.83 and 0.84, respectively. In addition, mean upper and lower bladder volumes and ratios were significantly different. Results are presented in Table 3. Mean maximum differences between upper and lower bladder volumes in the three CTs were 97.33 and 10.36 cc, respectively (figure 3).

Table 1. Patients characteristics.

Characteristics	No.
Age (yr), median (range) <70 / 70-80 / >80	75 (68-81) 3 / 16 / 1
ECOG performance status	
0 / 1	15 / 5
T stage	
1 / 2 / 3	7 / 7 /6
N stage	
0 / 1	17 / 3
Gleason score	
6 / 7 / 8-10	1 / 9 / 10
Initial PSA (ng/ml)	
<10 / 10-20 / >20	12 / 3 / 5
NCCN risk group	
intermediate / high and very high	6 / 14
RT dose (Gy), median (range)	78 (66-78)
RT fraction, median (range)	39 (33-39)

ECOG=Eastern Cooperative Oncology Group, PSA=prostate specific antigen, NCCN=National Comprehensive Cancer Network, RT=radiation therapy.

Table 2. Prostate volumes and upper margin locations.

Variable	Total (n=20)	With BPH (n=10)	Without BPH (n=10)	p-value[a]
Prostate volume (cc)				
Mean	30.39±15.35	43.43±9.56	17.35±5.33	
Maximum	68.76	68.76	27.62	
Minimum	8.68	38.42	8.68	
Location of upper margin [b] (mm)				
Mean	-0.9±7.79	3±7.87	-4.8±5.69	0.019
Maximum	15	15	3	
Minimum	-15	-12	-15	

BPH = benign prostatic hyperplasia.
Mean values are presented as mean ± standard deviation.
a Comparison of patients with and without BPH.
b Distance to superior margin of prostate from the superior border of pubic bone.

Table 3. Bladder volumes according to upper and lower bladder regions.

Variable	Initial CT	CT (2nd)	CT (3rd)	Mean	p-value[a]
Bladder volume (cc)					
Total	157.35±99.90	164.91±166.85	143.06±111.80	155.10±117.80	
Upper bladder	141.98±98.38	147.54±165.12	124.61±112.64	138.04±117.91	<0.001
Maximum	433.80	752.49	543.84	576.71	
Minimum	42.26	21.48	37.32	46.12	
Lower bladder	15.37±13.29	17.37±15.03	18.45±16.25	17.06±13.71	
Maximum	52.07	61.84	37.15	47.99	
Minimum	0.66	1.33	2.73	2.83	
Ratio					
Upper / total	0.88±0.11	0.83±0.18	0.84±0.14	0.85±0.13	<0.001
Lower / total	0.11±0.11	0.17±0.18	0.16±0.14	0.15±0.13	

Mean values are presented as mean ± standard deviation.
a For comparisons between mean upper and lower bladder values.

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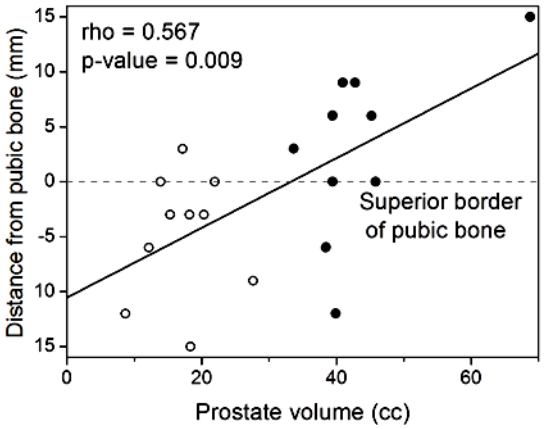


Figure 2. Spearman correlation analysis of the relation between prostate size and location. White and black dots indicate patients without and with BPH, respectively. The dotted line indicates the superior border of pubic bone.

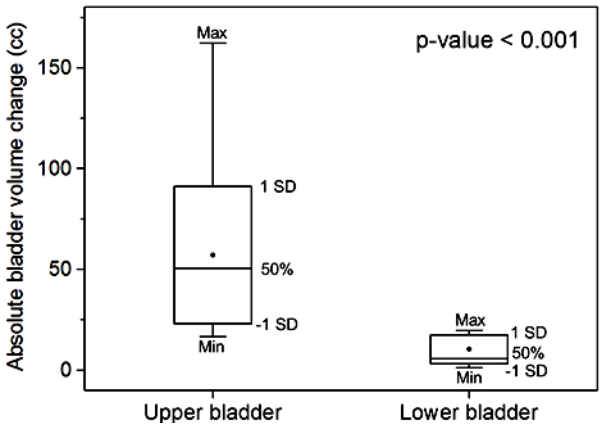


Figure 3. Absolute bladder volume changes of upper and lower bladder regions.

DISCUSSION

The purpose of the present study was to determine location changes of prostate caused by BPH and to nature of these changes with respect to the bladder, and thus, to assess the increased risk of radiation cystitis associated with the presence of BPH. PC is predominantly a disease that affects older men and BPH is also common in this population. Nevertheless, despite the large number of patients with both diseases, relatively few studies have addressed the impact of BPH on RT for PC. A small number of reports have concluded an enlarged prostate increases the risk of RT-induced toxicities and that use of androgen deprivation therapy (ADT) to reduce prostate size can reduce these adverse effects of RT [16-19]. However, most of these studies were conducted in the context of brachytherapy and studies on EBRT are rare. In the present study, we investigated the topic in the context of EBRT. In patients with BPH, RT target volume was located in the upper bladder region and bladder volume variability was high. This can be a major source of uncertainty in EBRT and increase the risk of radiation cystitis.

***Conflicts of interest*:** *Declared none.*

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