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Clinical predictors of severe late urinary toxicity after curative intensity-modulated radiation therapy for localized prostate cancer

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ABSTRACT

Intractable late urinary toxicity is a serious complication after radiotherapy for patients with localized prostate cancer (LPC). We assessed clinical factors correlated with severe late urinary toxicity in LPC treated with curative image-guided intensity-modulated radiation therapy (IMRT). A total of 452 patients with LPC treated with IMRT between 2002 and 2016 were retrospectively analyzed. Among them, 432 patients received androgen deprivation therapy (ADT). The median total irradiated doses were 80 (range, 76–80) Gy. Each daily dose was 2 Gy per fraction. The median follow-up was 83 (range, 4–210) months. Late urinary toxicity was scored according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. Grade 3 late urinary toxicity was observed in 27 patients. No cases with grade $\geq$ 4 late urinary toxicity were observed. The 5-, 10-, and 12.5-year grade 3 late urinary toxicity-free survival rates were 97%, 91.8% and 88.1%, respectively. Age, risk classification, total irradiated dose, ADT duration, antithrombotic therapy (AT), cardiovascular disease, hypertension (HT), diabetes mellitus (DM), dyslipidemia (DL), prior transurethral resection of the prostate (TURP) and prior high-intensity focused ultrasound (HIFU) were investigated for correlations with grade 3 late urinary toxicity. In univariate analysis, AT and prior HIFU and no other studied factors, were correlated with grade 3 late urinary toxicity. AT and prior HIFU appear to be predictive of grade 3 late urinary toxicity. Patients with LPC with these relevant clinical factors should be carefully followed up by sharing detailed information with the urology department.

Keywords: prostate cancer; radiotherapy; late toxicity; urinary toxicity

INTRODUCTION

At present, the advantages of delivering high-dose external beam radiotherapy (EBRT) to achieve optimal tumor-control outcomes have been widely recognized in patients with localized prostate cancer (LPC) [1–4]. The effectiveness of high-dose EBRT for improving overall survival after image-guided intensity-modulated radiation therapy (IMRT) as a nonsurgical treatment for LPC has also been indicated [3–7]. As long-term treatment results improve with the development of the latest technology, maintaining patients' quality of life with reduced adverse events has become more important [8–11]. Intractable late urinary toxicity is a serious complication of EBRT for patients with LPC. Several authors have reported various related factors [12–18]; however, studies regarding clinical factors correlated with serious long-term late urinary toxicity after high-dose EBRT are

limited. Therefore, in this study, we retrospectively assessed clinical factors correlated with severe long-term late urinary toxicity in patients with LPC who underwent image-guided IMRT.

MATERIALS AND METHODS

Patient characteristics

The medical records of 452 consecutive patients with LPC who were treated with image-guided IMRT at our institution between 2002 and 2016 were retrospectively analyzed. The median patient age was 69 (range, 47–85 years). The patients' characteristics are shown in Table 1. The patients were classified as intermediate- (n = 72) or high-risk (n = 380) according to the National Comprehensive Cancer Network (NCCN) guidelines. Of the patients, 432 received androgen deprivation therapy (ADT). The American Joint Committee on Cancer clinical T stage was T1 in 95 patients, T2 in 107, T3 in 245, and T4 in 5. The comorbidities were antithrombotic therapy (AT) in 89 patients, cardiovascular disease in 84, hypertension (HT) in 149, diabetes mellitus (DM) in 66, dyslipidemia (DL) in 21, prior transurethral resection of the prostate (TURP) in seven, and prior high-intensity focused ultrasound (HIFU) treatment in four. All the patients provided written informed consent before the start of the study. This study was approved by the Institutional Research Ethics Committee (approval No. 2011-360).

Table 1. Patient characteristics

	(n = 452)	(%)
Median age (range)(years)	69	(47–85)
NCCN risk group		
Intermediate	72	[16]
High	380	(84)
Clinical T stage		
T1	95	[21]
T2	107	[24]
T3	245	(54)
T4	5	[1]
Use of ADT		
Yes	432	(96)
No	20	[4]
Median of ADT duration (range)(months)	11	(0–107)
Total irradiated dose (Gy)/fractions		
76/38	69	[15]
78/39	13	[3]
80/40	370	(82)
Presence of cardiovascular disease	84	[19]
Presence of hypertension	149	[33]
Presence of diabetes mellitus	66	[15]
Presence of dyslipidemia	21	[5]
Antithrombotic therapy	89	[20]
Prior TURP	7	[2]
Prior HIFU	4	[1]

NCCN, National Comprehensive Cancer Network; ADT, androgen deprivation therapy; TURP, transurethral resection of the prostate; HIFU, high-intensity focused ultrasound

Radiotherapy

The details of the techniques for IMRT treatment planning and delivery were previously reported [6, 19]. Eclipse (release 6.5 or 11.0; Varian Medical Systems, Palo Alto, CA, USA) was used for the dose calculations. All patients were treated with doses prescribed to them in 2-Gy daily fractions. The prescribed dose used to cover 95% of the target volume (D95) was 76 Gy in 69 patients, 78 Gy in 13, and 80 Gy in 370. The maximum dose heterogeneity allowable in the planning target volume (PTV) was 10%. Each treatment plan was optimized to ensure that no more than 65% of the rectal and urinary bladder walls received >35 Gy (V35 ≤ 65%); no more than 45% of the rectal and urinary bladder walls received >55 Gy (V55 ≤ 45%); no more than 25% of the rectal and urinary bladder walls received >75 Gy (V75 ≤ 25%); and the urethral, rectal, and bladder walls received no more than 80 Gy (Table 2). In the overlapping region between the PTV and the critical organs, the constraint was set to 95% of the prescription dose for the rectum and 95% for the urethra. The dose constraint for the urethra has been applied to 419 patients since January 2004. Moreover, since March 2012, 148 patients have shown the following bladder dose constraints: no more than 50% of the bladder received >65 Gy (V65 ≤ 50%); no more than 35% of the bladder received >70 Gy (V70 ≤ 35%); no more than 25% of the bladder received >75 Gy (V75 ≤ 25%); and no more than 15% of the bladder received >80 Gy (V80 ≤ 15%). The rectal dose constraints were added as follows: no more than 50% of the rectum received >50 Gy (V50 < 50%); no more than 35% of the rectum received >60 Gy (V60 < 35%); no more than 25% of the rectum received >65 Gy (V65 < 25%); no more than 20% of the rectum received 70 Gy (V70 < 20%); and no more than 15% of the rectum received 75 Gy (V75 < 15%; Table 2). In addition, before obtaining computed tomography (CT) images during treatment planning and 30 min before the daily IMRT, the patients urinated to ensure that the bladder was in the same state. Moreover, the patients emptied their bowels just before the daily IMRT. For every treatment fraction, the patient was initially prepared using laser marks on the skin and was then repositioned using the Varian On-Board Imager based on the positions of the intra-prostatic fiducial markers. Cone-beam computed tomography (CBCT) images for patient positioning were acquired every three days in all patients.

Follow-up

Post-treatment follow-up evaluations were performed at intervals of three to six months for five years and six to 12 months thereafter. The follow-up period ranged from four to 210 months (median, 83 months).

Toxicity scoring

Late urinary toxicity appeared no earlier than 90 days after IMRT completion and was assessed using the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4.03. In brief, grades 3 and 4 were correlated with severe symptoms requiring hospitalization or urgent intervention and limited self-care activities of daily living. Obstruction, incontinence, and radiation cystitis with gross macroscopic hematuria are the most commonly reported grade 3 symptoms [20].

Table 2. Dose constraints of organs at risk

a. Rectal wall	b. Urinary bladder wall	c. Urinary bladder	d. Rectum
V35 ≤ 65%	V35 ≤ 65%	V65 ≤ 50%	V50 < 50%
V55 ≤ 45%	V55 ≤ 45%	V70 ≤ 35%	V60 < 35%
V75 ≤ 25%	V75 ≤ 25%	V80 ≤ 15%	V65 < 25%
			V70 < 20%
			V75 < 15%

V XX ≤ YY% means that not >YY% of the organ at risk received >XX Gy.
Between 2002 to 2016, a and b dose constraints were set. In addition, since 2012 to 2016, c and d dose constraints were added.

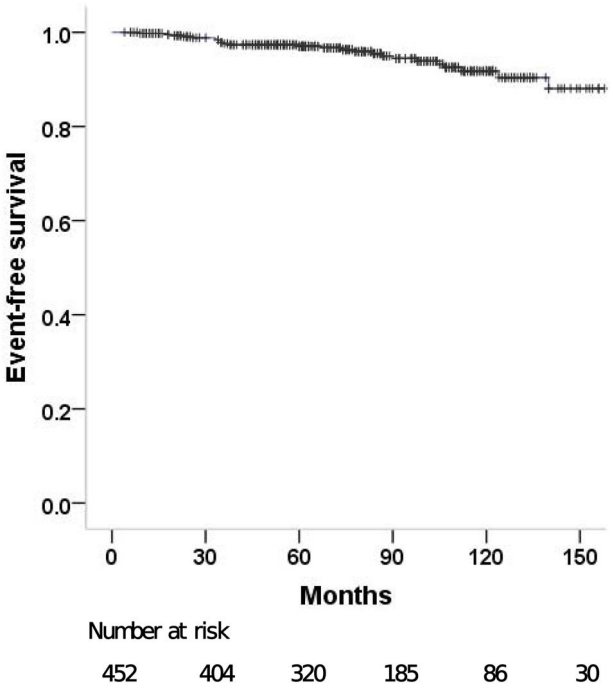

Fig. 1. The grade 3 late urinary toxicity-free survival rates at 5, 10 and 12.5 years were 97%, 91.8% and 88.1%, respectively.

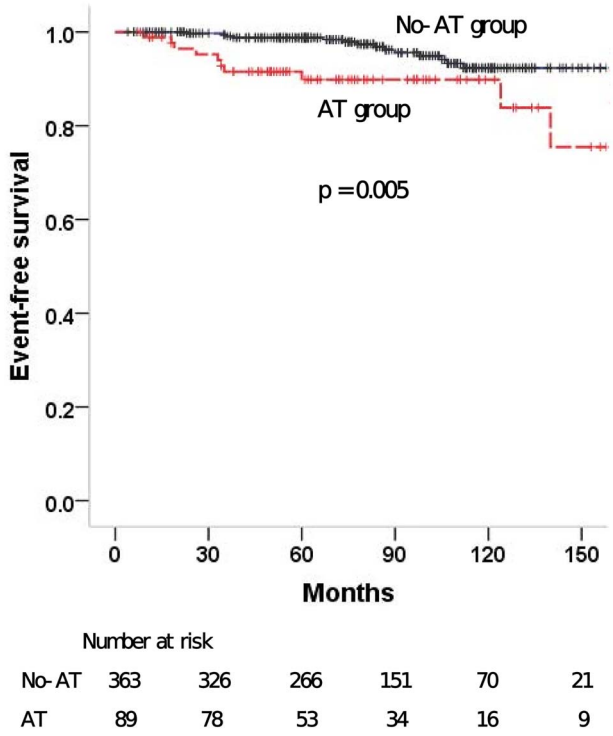

Fig. 2. The grade 3 late urinary toxicity-free survival rates in the AT and no-AT groups at 5, 10 and 12.5 years were as follows: 89.8% and 98.8%, 89.8% and 92.3%, and 75.5% and 92.3%, respectively.

Statistical analysis

The primary end point was grade ≥ 3 late urinary toxicity. Grade ≥ 3 late urinary toxicity-free survival rates were determined using Kaplan–Meier estimates. The time to grade ≥ 3 late urinary toxicity was fit to a univariate proportional hazard regression model to test the clinical continuous variables such as patient age and ADT duration. Other clinical variables such as irradiated total doses, NCCN risk group classification, clinical T stage, presence of cardiovascular disease, HT, DM, DL, AT, prior TURP, and HIFU were tested using log-rank tests. Statistical analyses were performed using SPSS version 21.0 software for Windows. A significance level (two-sided) of $p < 0.05$ was considered for all statistical tests.

RESULTS

The median follow-up period was 83 (range, 4–210) months. Grade 3 late urinary toxicity was observed in 27 patients (median onset time, 74 months; range, 9–192 months). None of the patients had grade ≥ 4 late urinary toxicity. In those with grade 3 late urinary toxicity, radiation cystitis and hemorrhage were observed in 16 patients, urethral stricture was observed in 10, and urethral necrosis was observed in one. All 27 patients were diagnosed clinically with medical examination including cystoscope by urologist. In addition, among these 27 patients, nine patients underwent both urine cytology and diagnostic CT, two patients received urine cytology, and three patients had diagnostic CT. Among these patients, none had urinary hemorrhage due to local failure and five experienced grade 3 late urinary toxicity after >10 years after IMRT. The five-, 10-, and 12.5-year grade 3 late urinary toxicity-free survival rates were 97%, 91.8% and 88.1%, respectively (Fig. 1). Table 3 shows the statistical analysis results for grade 3 late urinary

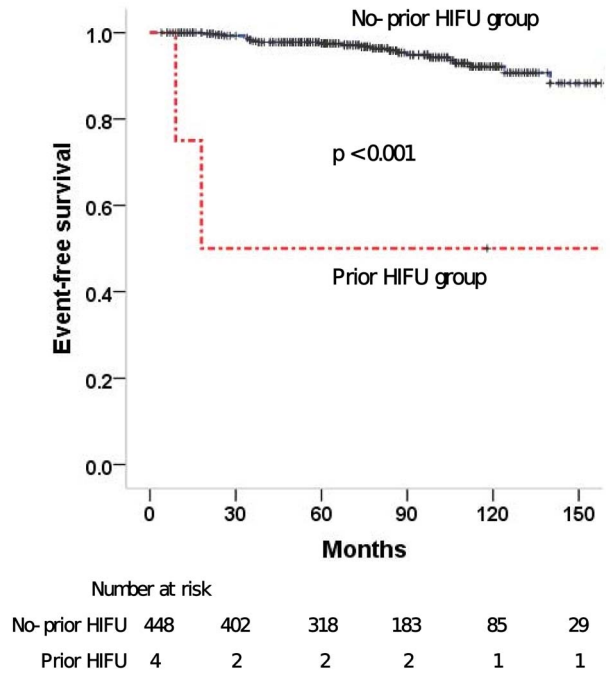

Fig. 3. Grade 3 late urinary toxicity-free survival rates in the prior and no-prior HIFU groups at 5, 10 and 12.5 years were as follows: 50.0% and 97.5%, 50.0% and 92.1% and 50.0% and 88.3%, respectively.

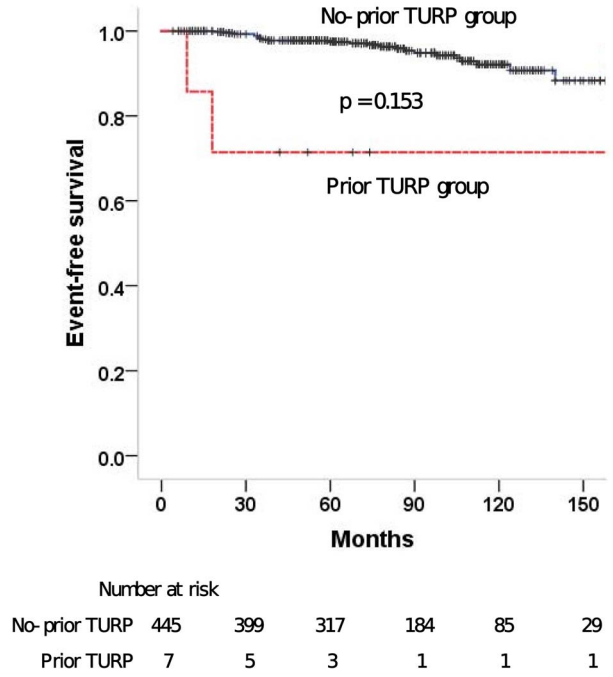

Fig. 4. Grade 3 late urinary toxicity-free survival rates in the prior and no-prior TURP groups at 5, 10 and 12.5 years were as follows: 71.4% and 97.5%, 71.4% and 92.1%, and 71.4% and 88.3%, respectively.

toxicity. In the univariate analysis, only AT ($p = 0.005$) and prior HIFU ($p < 0.001$) significantly correlated with grade 3 late urinary toxicity. The respective five-, 10- and 12.5-year grade 3 late urinary toxicity-free survival rates were as follows: 89.8% and 98.8%, 89.8% and 92.3%, and 75.5% and 92.3% in the AT and no-AT groups (Fig. 2); 50.0% and 97.5%, 50.0% and 92.1%, and 50.0% and 88.3% in the prior and no-prior HIFU groups (Fig. 3); 71.4% and 97.5%, 71.4% and 92.1%, and 71.4% and 88.3% in the prior and no-prior TURP groups (Fig. 4).

DISCUSSION

Our results showed that AT and prior HIFU appear to be predictive of grade 3 late urinary toxicity after curative IMRT for LPC. Mathieu *et al.* also reported the relationship between AT and late urinary toxicity in patients with LPC who were receiving radiotherapy [12]. They mentioned that AT has already been correlated with gross hematuria and could be an independent factor of late urinary toxicity. HIFU is one of the focal therapies and uses transrectally delivered focal ultrasound to the prostate to induce coagulative necrosis [21, 22]. Fomkin *et al.* [23] insisted on the appropriateness of radiotherapy after HIFU ablation; however, the urinary toxicity evaluation period in their study was only one year. Riviere *et al.* [24] reported acceptable toxicity of salvage radiotherapy after HIFU for LPC. However, the total doses with a median of 72 (range, 65–78) Gy were relatively lower than those in our series. Moreover, the median (range) follow-up period was 36.5 (range, 5–164) months; therefore, careful interpretation is mandatory. Although HIFU treatment has led to technical improvements in LPC ablation therapy [25], the long-term follow-up deficit has been limited regarding treatment outcome and patients' quality of life [21, 26–28].

Although other clinical variables reported by other authors [13–18], such as prior TURP, ADT, increased age or DM, were not statistically significant in this study, careful interpretation of this result is necessary.

According to Gardner *et al.* [33] mild late gastrointestinal disorders after high-dose EBRT for LPC often occur; however, the incidence rate is relatively stable and usually does not increase for >5 years. By contrast, severe late genitourinary (GU) morbidities are rare but can occur up to 20 years after RT and most of them are hematuria. Our results showed an increasing incidence of grade 3 late GU toxicity even 10 years after IMRT. In fact, this study included five patients who experienced grade 3 late urinary toxicity >10 years after IMRT. Although long-term follow-up should be considered, regular checkup for all the patients was difficult. Therefore, we propose to closely share patient information particularly about clinical factors, including AT history or prior HIFU, with the institutional urological department on a regular basis to prepare for the onset of late severe adverse events after regular follow-up. Patients with prior TURP should be carefully monitored because several authors also indicated a correlation between prior TURP and late urinary toxicity [13–15].

Further investigation is needed to confirm the relationship between AT and prior HIFU and grade 3 late urinary toxicity. Nevertheless, careful follow-up might be necessary if patients with LPC who have received curative IMRT have had AT or previous HIFU.

Table 3. Statistical analysis results for grade 3 late urinary toxicities

	UA	HR	95% CI
Factors	*P*-value		
Age (years)	0.579	0.983	0.925–1.044
ADT duration (months)	0.409	0.987	0.957–1.018
Total dose 76 vs 78–80 (Gy)	0.563	–	–
76–78 vs 80 (Gy)	0.445	–	–
NCCN risk group		–	–
Intermediate vs High	0.472	–	–
Clinical stage T1 vs T2-4	0.393	–	–
T1-2 vs T3-4	0.647	–	–
T1-3 vs T4	0.456	–	–
cardiovascular disease	0.390	–	–
hypertension	0.257	–	–
diabetes mellitus	0.801	–	–
dyslipidemia	0.696	–	–
Antithrombotic therapy	0.005*	–	–
Prior TURP	0.153	–	–
Prior HIFU	<0.001*	–	–

UA, univariate analysis; HR, hazard risk; CI, confidence interval; ADT, Androgen deprivation therapy; NCCN, National Comprehensive Cancer Network; TURP, transurethral resection of the prostate; HIFU, high-intensity focused ultrasound; *statistically significant

This study has several limitations. First, as mentioned earlier, owing to the retrospective nature of this study, acquiring more detailed information on the symptoms of co-existing underlying diseases from clinical records was difficult for each patient. Second, the accumulated irradiated doses in the local bladder wall throughout the IMRT course were undeniably concerning. Several authors reported that irradiated doses to the bladder trigone were correlated with acute and late urinary toxicities [20, 29–32]. Therefore, evaluating the actual cumulative irradiated doses for the local bladder wall throughout the IMRT course was challenging because the CBCT images for patient positioning in this series were not acquired in every fraction during the IMRT course. Moreover, the quality of the CBCT images were extremely low, which made accurate recognition and delineation of the pelvic organs, including the prostate, rectum, and bladder extremely difficult. Although the regulations of the irradiated doses for at-risk organs, including the whole bladder, complied with the initial IMRT treatment plan for each patient, the definite dose constraint for the local bladder, including the bladder trigone, had not been established in our institution. In addition, owing to uncertain bladder volume changes during IMRT, the planned dose distribution might not have reflected the actual accumulated irradiated doses to the bladder. Third, we could not confirm and analyze dose volume histogram (DVH) data of the urinary bladder and bladder walls of the initial IMRT treatment plan in 94 cases in the early days, so that we could not compare the DVH between the group with and without grade 3 late urinary toxicity. However, as mentioned above, we had ascertained that each patient included in this study had received IMRT based on their compliance of the dose constraints. On the other hands, Mathieu *et al*. insisted that urinary toxicity might be more related to patient risk factors than to dose parameters [12]; therefore, clinical patient factors were assessed in this series.

In conclusion, this study shows that the presence of AT or prior HIFU is significantly correlated with severe late urinary toxicity in patients with LPC after IMRT delivered at curative irradiated doses. We believe that patients with these relevant clinical factors should be carefully followed up by sharing detailed information with the urology department.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

PRESENTATION AT A CONFERENCE

We had presented this study at the American Society for Radiation Oncology (ASTRO) 2020 annual meeting.

REFERENCES

1. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys* 2009;74:1405–18.
2. Hanks GE, Hanlon AL, Epstein B et al. Dose response in prostate cancer with 8-12 years' follow-up. *Int J Radiat Oncol Biol Phys* 2002;54:427–35.
3. Spratt DE, Pei X, Yamada J et al. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85:686–92.
4. Alicikus ZA, Yamada Y, Zhang Z et al. Ten-year outcomes of high-dose, intensity-modulated radiotherapy for localized prostate cancer. *Cancer* 2011;117:1429–37.
5. Kalbasi A, Li J, Berman A et al. Dose-escalated irradiation and overall survival in men with nonmetastatic prostate cancer. *JAMA Oncol* 2015;1:897–906.

6. Takeda K, Takai Y, Narazaki K, et al. Treatment outcome of high-dose image-guided intensity-modulated radiotherapy using intraprostate fiducial markers for localized prostate cancer at a single institute in Japan. *Radiat Oncol* 2012;7:105.
7. Kuban DA, Tucker SL, Dong L et al. Long-term results of the m. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
8. Jacobs BL, Zhang Y, Schroeck FR et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *JAMA* 2013;309:2587–95.
9. Lopez P, Taaffe DR, Newton RU et al. What is the minimal dose for resistance exercise effectiveness in prostate cancer patients? In: *Systematic review and meta-analysis on patient-reported outcomes*. Prostate Cancer Prostatic Dis. 2021;24:465–81.
10. Al-Mamgani A, van Putten WL, van der Wielen GJ et al. Dose escalation and quality of life in patients with localized prostate cancer treated with radiotherapy: long-term results of the dutch randomized dose-escalation trial (ckto 96-10 trial). *Int J Radiat Oncol Biol Phys* 2011;79:1004–12.
11. Yamazaki H, Nakamura S, Nishimura T et al. Transitioning from conventional radiotherapy to intensity-modulated radiotherapy for localized prostate cancer: changing focus from rectal bleeding to detailed quality of life analysis. *J Radiat Res* 2014;55:1033–47.
12. Mathieu R, Arango JD, Beckendorf V et al. Nomograms to predict late urinary toxicity after prostate cancer radiotherapy. *World J Urol* 2014;32:743–51.
13. Peeters ST, Heemsbergen WD, van Putten WL et al. Acute and late complications after radiotherapy for prostate cancer: results of a multicenter randomized trial comparing 68 gy to 78 gy. *Int J Radiat Oncol Biol Phys* 2005;61:1019–34.
14. Ishiyama H, Hirayama T, Jhaveri P et al. Is there an increase in genitourinary toxicity in patients treated with transurethral resection of the prostate and radiotherapy? A systematic review. *Am J Clin Oncol* 2014;37:297–304.
15. Heemsbergen WD, Al-Mamgani A, Witte MG et al. Urinary obstruction in prostate cancer patients from the dutch trial (68 gy vs. 78 gy): relationships with local dose, acute effects, and baseline characteristics. *Int J Radiat Oncol Biol Phys* 2010;78:19–25.
16. Wortel RC, Incrocci L, Pos FJ et al. Late side effects after image guided intensity modulated radiation therapy compared to 3d-conformal radiation therapy for prostate cancer: results from 2 prospective cohorts. *Int J Radiat Oncol Biol Phys* 2016;95:680–9.
17. Yahya N, Ebert MA, Bulsara M et al. Dosimetry, clinical factors and medication intake influencing urinary symptoms after prostate radiotherapy: an analysis of data from the radar prostate radiotherapy trial. *Radiother Oncol* 2015;116:112–8.
18. Kalakota K, Liauw SL. Toxicity after external beam radiotherapy for prostate cancer: an analysis of late morbidity in men with diabetes mellitus. *Urology* 2013;81:1196–201.
19. Takeda K, Ogawa Y, Ariga H, et al. Clinical correlations between treatment with anticoagulants/antiaggregants and late rectal toxicity after radiotherapy for prostate cancer. *Anticancer Res* 2009;29:1831–4.
20. Rancati T, Palorini F, Cozzarini C et al. Understanding urinary toxicity after radiotherapy for prostate cancer: first steps forward. *Tumori* 2017;103:395–404.
21. Ahdoot M, Lebastchi AH, Turkbey B et al. Contemporary treatments in prostate cancer focal therapy. *Curr Opin Oncol* 2019;31:200–6.
22. Lindner U, Trachtenberg J, Lawrentschuk N. Focal therapy in prostate cancer: Modalities, findings and future considerations. *Nat Rev Urol* 2010;7:562–71.
23. Fomkin RN, Popkov VM, Shatylko TV. Salvage external beam radiation therapy for prostate cancer recurrence after high-intensity focused ultrasound ablation. *Urologiia* 2016;50–5.
24. Riviere J, Bernhard JC, Robert G et al. Salvage radiotherapy after high-intensity focussed ultrasound for recurrent localised prostate cancer. *Eur Urol* 2010;58:567–73.
25. Uchida T, Tomonaga T, Kim H et al. Improved outcomes with advancements in high intensity focused ultrasound devices for the treatment of localized prostate cancer. *J Urol* 2015;193:103–10.
26. von Hardenberg J, Westhoff N, Baumunk D et al. Prostate cancer treatment by the latest focal hifu device with mri/trus-fusion control biopsies: a prospective evaluation. *Urol Oncol* 2018;36:401.e1–401.e9.
27. van der Poel HG, van den Bergh RCN, Briers E et al. Focal therapy in primary localised prostate cancer: the European Association of Urology position in 2018. *Eur Urol* 2018;74:84–91.
28. Sanda MG, Cadeddu JA, Kirkby E et al. Clinically localized prostate cancer: aua/astro/suo guideline. Part i: risk stratification, shared decision making, and care options. *J Urol* 2018;199:683–90.
29. Ghadjar P, Zelefsky MJ, Spratt DE et al. Impact of dose to the bladder trigone on long-term urinary function after high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2014;88:339–44.
30. Palorini F, Botti A, Carillo V et al. Bladder dose-surface maps and urinary toxicity: robustness with respect to motion in assessing local dose effects. *Phys Med* 2016;32:506–11.
31. Improta I, Palorini F, Cozzarini C et al. Bladder spatial-dose descriptors correlate with acute urinary toxicity after radiation therapy for prostate cancer. *Phys Med* 2016;32:1681–9.
32. Henderson DR, Murray JR, Gulliford SL et al. An investigation of dosimetric correlates of acute toxicity in prostate stereotactic body radiotherapy: dose to urinary trigone is associated with acute urinary toxicity. *Clin Oncol (R Coll Radiol)* 2018;30:539–47.
33. Gardner BG, Zietman AL, Shipley WU et al. Late normal tissue sequelae in the second decade after high dose radiation therapy with combined photons and conformal protons for locally advanced prostate cancer. *J Urol* 2002;167:123–6.