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Prognostic Factors for Late Urinary Toxicity Grade 2-3 after Conformal Radiation Therapy on Patients with Prostate Cancer

Ricardo A. Nakamura, Carlos R. Monti, Lisias N. Castilho, Felipe A. Trevisan, Alexandre C. Valim, Jose A. Reinato

Institute Radium of Oncology, Campinas, Sao Paulo, Brazil

ABSTRACT

Objective: Identify prognostic factors associated to late urinary toxicity in patients with prostate cancer submitted to radical conformal radiotherapy (3DCRT).
Materials and Methods: From July 1997 to January 2002, 285 patients with localized prostate cancer were consecutively treated with 3DCRT and retrospectively analyzed. Thirty seven (13%) patients were submitted to transurethral prostate resection previously to 3DCRT. The median dose delivered to the prostate was 7920 cGy (7020-8460). Patient and treatment characteristics were analyzed and correlated to late urinary toxicity grade 2-3, especially whether certain radiation doses applied to certain bladder volumes, when visualized through computerized tomography (CT) planning, correlated with the observed actuarial incidences of late urinary complications, using bladder volume as a continuous variable.
Results: On a median follow-up of 53.6 months (3.6-95.3), the 5-year actuarial free from late urinary toxicity grade 2-3 survival was 91.1%. Seven and fifteen patients presented late urinary toxicity grades 2 and 3, respectively. Prior transurethral resection of prostate and radiation dose over 70 Gy on 30% of initial bladder volume were independent prognostic factors for late urinary toxicity grade 2-3.
Conclusions: This study suggests that restricting radiation doses to 70 Gy or less on 30% of bladder volume, visualized through CT planning, may reduce late urinary complications. It furthermore suggests that patients with prior transurethral resection of prostate may indicate a group of patients with a greater risk for late urinary toxicity grade 2-3 after 3DCRT.

***Key words**: prostatic neoplasms; radiotherapy; bladder; toxicity; prognosis*
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INTRODUCTION

Several studies have reported that higher radiation doses improve the control over prostate cancer (1-4). However, by increasing the radiation dose, the risk of developing complications also increases (1,5). Many studies have observed that the incidence of rectal complications is not exclusively associated to the radiation dose, but also to the volume of organ irradiated (2,6,7). Grade 2 or higher late urinary complications occur in 10-13% of patients treated with radiotherapy, but the relation between radiation dose and irradiated bladder volume (dose-volume relation) has not been well documented (2,3,5,8,9). The pur-

pose of this study is to find out the parameters of this dose-volume relation by means of the initial CT planning, as well as factors inherent to the patients that might reduce the rate of late urinary complications.

MATERIALS AND METHODS

Patients - From July 1997 to January 2002, 285 patients with localized prostate cancer were consecutively treated with 3DCRT on a single institution and they were retrospectively analyzed. All patients were staged according to the 2002 American Joint Committee on Cancer. All patients gave written consent prior to treatment. The median age was 70 years (47-86) and 142 (49.8%) patients had associated diseases. Thirty seven (13%) patients were submitted to prior transurethral resection of prostate due to benign prostatic hypertrophy related symptoms. The median prostate weight estimated by transrectal ultrasound previously to 3DCRT was 35 g (11-123). Urinary symptoms before 3DCRT application were not available on medical records.

Treatment characteristics - Neoadjuvant, concomitant and adjuvant androgen suppression were done by discretion of the urologist or the radiation oncologist. On supine position, patients were submitted to urethrography during three-dimensional simulation and 5 mm tomographic slices were obtained. The images were transferred to workstations and the treatment targets, as well as organs at risk, were delineated. The prostate was delineated in all its volume, including the prostate capsule. Regional lymphatic drainage was considered the external and internal iliac vessels drainage, beginning at the caudal portion of the sacroiliac junction, and the obturatory vessels, excluding the perirectal vessels. For movement margins and setup errors, 10 mm were given in all dimensions, except for the seminal vesicles and prostate, which were given only a 3 mm posterior margin. Organs at risk were delineated as follows: a) bladder: delineation of the whole bladder, including its most external layer, b) rectum: delineation of the whole rectum, including contents from the anal-rectum transition to the rectum-sigmoid transition. Energies of 6 or 15 MeV of photons and 5 fields of radiation were used. The radiotherapy planning was divided into phases: pelvis, seminal vesicles and prostate were irradiated in the first phase; in the second phase, the seminal vesicles and prostate were the target volumes; in the last phase, only the prostate was irradiated. Whenever pelvic irradiation was not done, treatment included only the two latter phases: irradiation of the seminal vesicles and prostate, followed by irradiation of the prostate only. After radiotherapy planning was completed, it was then transferred to the linear accelerator and therapy was done with 180 cGy per day, 5 days per week. The patients have been advised to have a full bladder before treatment planning and the daily treatment. 3DCRT on the pelvis and on the seminal vesicles was performed in 50 (17.5%) and 245 (86%) patients, respectively. Neoadjuvant and concomitant androgen suppression therapy were performed in 123 (43.2%) and 146 (51.2%) patients, respectively.

Follow-up - After 3DCRT, patients were followed up between 3 and 6 months with serial PSA and physical examination. Image studies were done when specific complaints occurred.

Urinary Toxicity - Late urinary toxicity was considered after three months of the end of 3DCRT, and was graded according to Common Terminology Criteria for Adverse Events, version 3 (10), Table-1. Information about patient complaint was obtained by physician interview. Only grade 2 or higher toxicities were considered for analysis. Sexual function was not analyzed. The highest grade of late urinary toxicity was considered for statistical analysis when patients presented more than one type of late urinary toxicity.

Statistical analysis - Patient and treatment characteristics were analyzed and correlated to late urinary toxicity, especially whether certain radiation doses applied to certain bladder volumes, visualized through CT planning, correlated with the observed actuarial incidences of late urinary complications, using volume as a continuous variable. Associations between categorical variables for frequency data in contingency tables were performed through the chi-square test. When at least one expected frequency in 2 x 2 tables resulted in less than 5, Fisher's exact test was adopted. The 5% level of significance was considered for all tests. The free from late urinary toxicity

Table 1 – *Common Terminology Criteria for Adverse Events version 3 (10) modified.*

Complication	Grade	Characteristic
Cystitis	1	Asymptomatic
	2	Frequency with dysuria
	3	Intravenous pain medication; bladder irrigation indicated
	4	Major non-elective intervention indicated
	5	Death
Urinary retention	1	Hesitancy or dribbling, no significant residual urine; retention occurring during the immediate postoperative period.
	2	Hesitancy requiring medication; or operative bladder atony requiring indwelling catheter beyond immediate postoperative period but for < 6 weeks
	3	More than daily catheterization indicated; urological intervention indicated (e.g. transurethral resection of prostate, suprapubic tube, urethrotomy)
	4	Life-threatening consequences; organ failure (e.g. bladder rupture); operative intervention requiring organ resection indicated
	5	Death
Bladder hemorrhage	1	Minimal or microscopic bleeding; intervention not indicated
	2	Gross bleeding, medical intervention, or urinary tract irrigation indicated
	3	Transfusional, interventional radiology, endoscopic or operative intervention indicated
	4	Life-threatening consequences; major urgent intervention indicated
	5	Death
Urinary incontinence	1	Occasional (e.g. with coughing, sneezing, etc). pads not indicated.
	2	Spontaneous, pads indicated.
	3	Interfering with daily living; intervention indicated (e.g. clamp, collagen injections)
	4	Operative intervention indicated (e.g. cystectomy or permanent urinary diversion)
	5	—

grade 2-3 survival was defined as the interval between the date of the beginning of 3DCRT and the date of the first reported urinary complaints or the last information for censored observations. The actuarial free from late urinary toxicity grade 2-3 survival was estimated by the Kaplan-Meier method and the log-rank test was applied to compare survival curves with the confidence interval of 95%. All analyses were performed using the statistical software STATA release 7.0 (StataCorp 2001).

RESULTS

On a median follow-up of 53.6 months (3.6-95.3), the 5-year actuarial free from late urinary tox-

Table 2 – *Time and number of patients with urinary complications after 3DCRT.*

Complication	**Grade**	**Number of Patients**	**Median Time of Event Occurrence in Months** (range)
Cystitis	2	2	18.8 (6.7-83.1)
	3	3	
Urinary retention	2	1	30.1 (10.7-56.9)
	3	8	
Bladder hemorrhage	3	8	22.1 (6.1-83.1)
Urinary incontinence	2	4	45.9 (6.1-53.8)

icity grade 2-3 survival was 91.1%. The number of patients with late urinary toxicities according to their grade and the median time of event occurrence are listed on Table-2. The 5-year actuarial free from late urinary toxicity grade 2-3 survival for patients with and without prior transurethral resection of prostate was 74.3% and 93.9%, respectively (p = 0.0002) (Figure-1). For patients who received more than 70 Gy to 30% of bladder volume (54 patients), visualized through CT planning, the 5-year actuarial free from late urinary toxicity grade 2-3 survival was 86.4%, versus 92% for patients who received 70 Gy or less to 30%

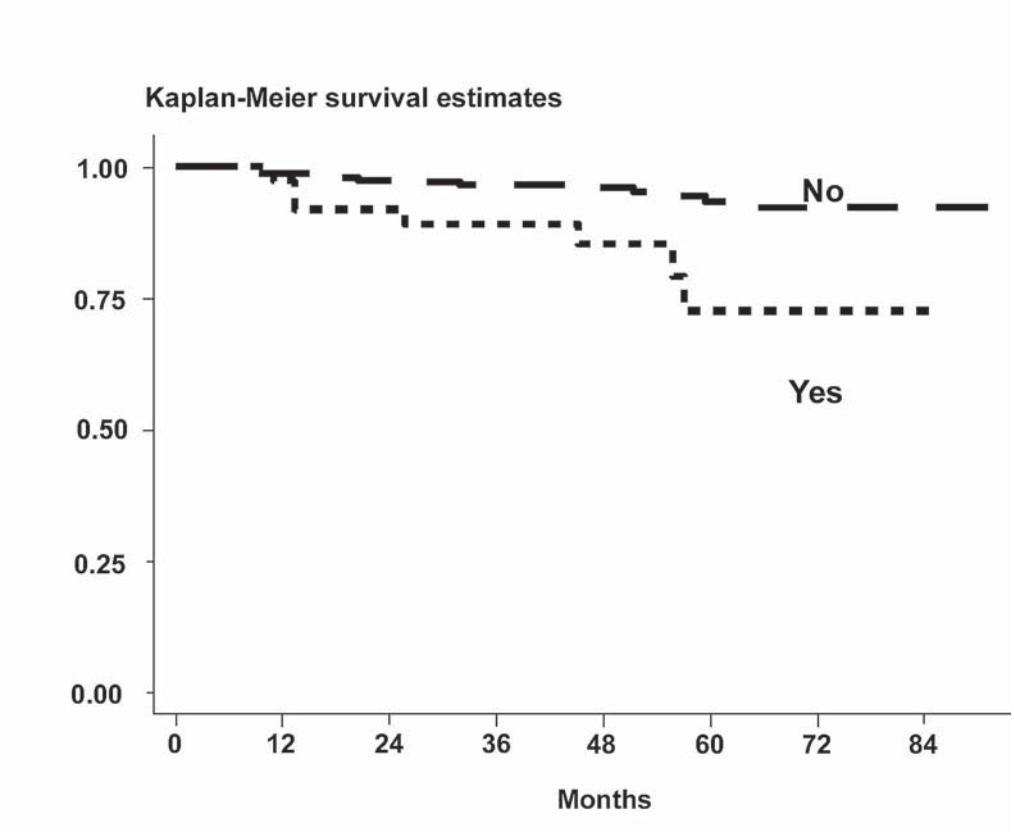

Figure 1 – *Actuarial free from late urinary toxicity grade 2-3 survival according to prior transurethral resection.*

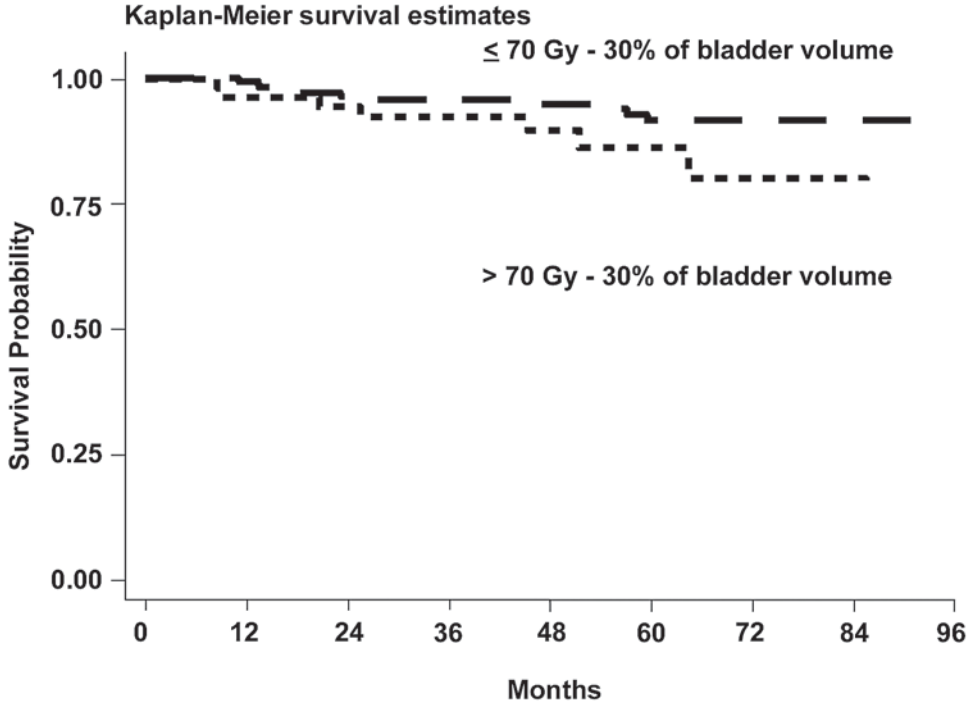

Figure 2 *– Actuarial free from late urinary toxicity grade 2-3 survival according to radiation dose on 30% of initial bladder volume.*

of bladder volume, also visualized through CT planning (p = 0.0264) (Figure-2). Prior transurethral resection of prostate and radiation dose more than 70 Gy to 30% of bladder volume were independent prognostic factors for late urinary toxicity grade 2-3 (Table-3). Analysis of age, ultrasound-estimated prostate weight, associated diseases, Gleason score, initial PSA value, clinical T stage, neoadjuvant, concomitant or adjuvant androgen suppression, irradiation of the pelvis and of the seminal vesicles were not statistically significant for the 5-year actuarial free from late urinary toxicity grade 2-3 survival.

Analyzing each type of late urinary toxicity grade 2-3 (cystitis, bladder hemorrhage, urinary incontinence and urinary retention) with prior transurethral resection and radiation dose more than 70 Gy to

Table 3 – *Independent prognostic factors for late urinary toxicity grade 2-3.*

Variable	**Category**	**Crude Relative Risk** (95% confidence interval)	**Multivariate Relative Risk** (95% confidence interval)
Dose on 30% of bladder volume	> 70 Gy	1.0 (reference)	1.0 (reference)
	≤ 70 Gy	2.7 (1.1 - 6.5)	3.0 (1.2 - 7.7)
Prior transurethral resection	No	1.0 (reference)	1.0 (reference)
	Yes	4.6 (1.9-11.5)	5.7 (2.2-14.5)

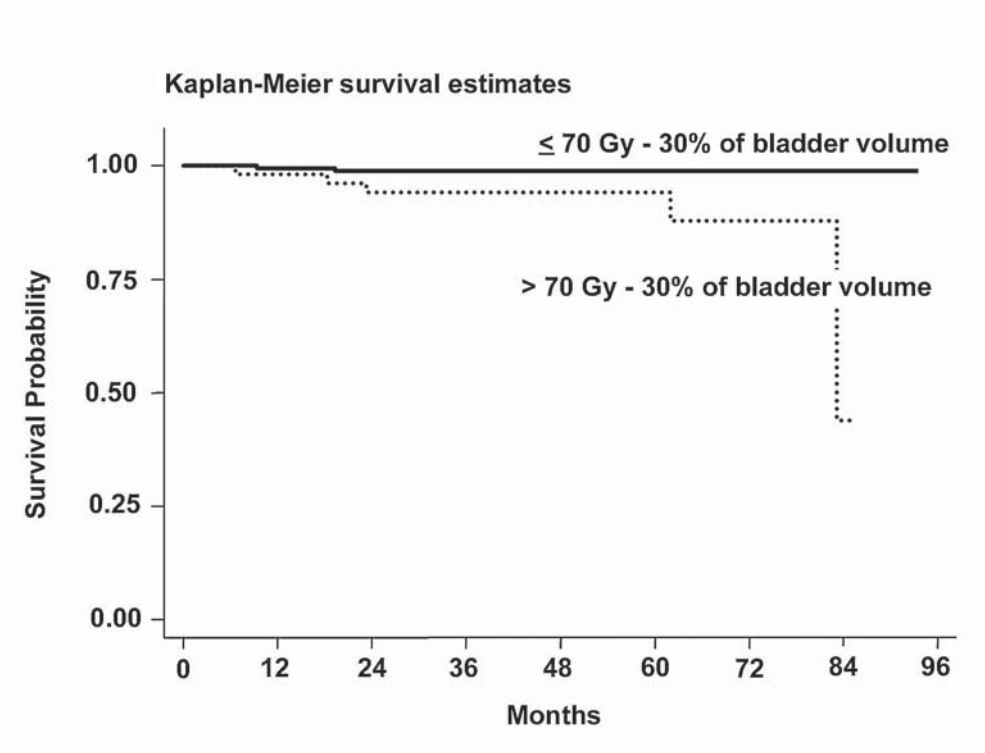

Figure 3 – *Actuarial free from cystitis according to radiation dose on 30% of initial bladder volume.*

30% of bladder volume, only patients with cystitis were associated to radiation dose more than 70 Gy to 30% of bladder volume (p = 0.0008) (Figure-3).

COMMENTS

Various trials did not find any relation between the percentage of bladder volume receiving a certain radiation dose and late urinary toxicity (6,11,12). Kuban et al. (5) postulated that the dose-volume relation is confounded by changes in bladder volume throughout therapy, making it difficult to be evaluated. However, Pinkawa et al. (13) reported that the mean bladder volume can be kept at the same level at the time of the initial treatment planning and during the treatment, if patients are asked to have a full bladder. The M.D. Anderson Cancer Center (6) randomized 189 patients with prostate cancer to receive 70 Gy or 78 Gy. The 5-year Kaplan-Meier risks of Grade 2 or higher late urinary toxicity were 20% and 9% for the 70 Gy and 78 Gy groups, respectively. Late urinary toxicity did not correlate with either the percentage or absolute volume of bladder that received 60 Gy or more, or 70 Gy or more. Koper et al. (11) analyzed 248 patients treated for prostate cancer with radiotherapy in a randomized trial. No association was found between radiation doses applied to certain bladder volumes and late urinary toxicity. However, the total dose of radiation was low (66 Gy on the prostate). Boersma et al. (12) analyzed the radiation dose of certain bladder volumes of 130 patients with prostate cancer treated with 3DCRT in a dose-escalating protocol. The 2-year actuarial incidence of Grade 3 or higher genitourinary complications was 8% and 21% using the RTOG/EORTC and the SOMA/LENT toxicity scales, respectively. They investigated whether the absolute bladder wall volume irradiated by various dose levels of radiation correlated with the actuarial incidence of late bladder complications. Although the crude figures in-

dicated a trend towards higher complication rates with larger irradiated volumes, actuarial analysis did not demonstrate any significant effect. The total radiation dose and the maximum dose applied to the bladder wall did not correlate with the incidence of late bladder complications either. In the first study that found an association between radiation doses applied to certain bladder volumes and low-grade late urinary toxicity, Pinkawa et al. (13) prospectively evaluated the impact of the dose-volume variable in 80 patients with prostate cancer consecutively treated with 3DCRT. The Expanded Prostate Cancer Index Composite (14) was used to grade urinary toxicity. The planned target volume was overlaid by the 90% isodose relative to the ICRU (15) reference point. The total median dose applied to the prostate at the reference point was 70.2 Gy divided into 1.8 Gy daily fractions. It was observed that the initial bladder volume and the percentage of bladder volume receiving 10%-90% of the prescription dose correlated significantly with the urinary function/irritation scales. Bladder volume < 180 mL, planned target volume ≥ 350 mL and area under the dose-volume histogram curve for the bladder ≥ 45% were also prognostic factors for late urinary toxicity. Trying to estimate and to correlate the absolute radiation dose that a percentage of the bladder volume received in this study with low-grade late urinary toxicity, it was found that 25% of bladder volume receiving ≥ 63.2 Gy (90% isodose of 70.2 Gy), 50% of bladder volume receiving ≥ 35.1 Gy (50% isodose of 70.2 Gy) and 65% of bladder volume receiving ≥ 21.1 Gy (30% isodose of 70.2 Gy) resulted in more low-grade late urinary toxicity. The present study used absolute radiation doses applied to a percentage of bladder volume, correlating these variables with late urinary toxicity, because this method is easier to use in clinical practice. It found that more than 70 Gy to 30% of bladder volume, visualized through CT planning, increased the risk of late urinary toxicity grade 2-3 (Figure-2). In medical literature, other factors have been associated to late urinary toxicity after 3DCRT. Peeters et al. (16) analyzed 669 patients with prostate cancer in a randomized trial of dose-escalation therapy. On a median follow-up of 31 months, the 3-year risks of late genitourinary toxicity grade 2 or higher were 28.5% and 30.2% for 68 Gy and 78 Gy, respectively. Androgen suppression therapy, pretreatment genitourinary symptoms and prior transurethral resection of prostate were prognostic factors for late genitourinary grade 2 or higher. Zelefsky et al. (4) analyzed 1100 patients treated with 3DCRT or intensity modulated radiotherapy at Memorial Sloan Kettering Cancer Center and reported a strong relation between radiation dose and late urinary toxicity grade 2. The 5-year actuarial rate of late urinary toxicity grade 2 on patients who received 75.6 Gy or more was 13%, versus 4% on patients who received less than 75.6 Gy ($p < 0.001$). Liu et al. (17) evaluated 1192 patients with prostate cancer treated with radiotherapy and observed that associated genitourinary disease, transurethral resection of prostate previous to radiotherapy and the presence of acute urinary toxicity during treatment were significant prognostic factors for late urinary toxicity grade 3. In the present study, prior transurethral resection of prostate resulted in more late urinary toxicity grade 2-3 (Figure-1). However, data concerning obstructive urinary symptoms before 3DCRT were not available, making it possible that transurethral resection of prostate has selected patients with a higher tendency to urinary toxicity.

CONCLUSIONS

Although bladder volume is not constant during treatment with 3DCRT, restriction of the radiation dose to 70 Gy or less to 30% of bladder volume, visualized through CT planning, seems to be a good measure in order to reduce late urinary toxicity grade 2-3, especially when associated to orientations for the patients to maintain their bladders full during radiotherapy application. Likewise, in spite of the possibility that prior transurethral resection of prostate may have selected patients with a higher propensity for urinary toxicity, the existence of prior transurethral resection of prostate may be an alert to the possibility of late urinary complications.

CONFLICT OF INTEREST

None declared.

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Correspondence address:
Dr. Ricardo Akiyoshi Nakamura
Av. Heitor Penteado, 1780, Taquaral
Campinas, São Paulo, 13075-460, Brazil
Fax: + 55 19 3753-4166
E-mail: ricardonakamura1@gmail.com

EDITORIAL COMMENT

The study focuses on urinary toxicity of 285 patients after conformal radiation therapy for localized prostate cancer after a median follow-up of 54 months. Patient and treatment characteristics were correlated to late urinary toxicity grade 2-3. A dose of > 70Gy to 30% of bladder volume and a prior transurethral prostate resection have been found to predict a greater risk for late urinary toxicity.

Though daily volume variations will occur, the mean bladder volume can be kept at the same level at the time of the initial treatment planning and during the treatment, if the patients are asked to have a full bladder (1,2). With increasing cystitis rates during radiation therapy (greater bladder volume with a higher dose), the mean bladder volume is likely to decrease during the treatment (3). Written bladder filling instructions for patients might be helpful to improve bladder volume consistency (4).

Radiotherapy with an empty bladder has been recommended in the past by several investigators to reduce prostate mobility during a fractionated treatment (5). A recent organ motion study could demonstrate the same prostate mobility with both a full and empty bladder despite an increased variability of bladder filling with a full bladder (1). The dosimetric advantages of a full bladder compared to an empty bladder are a reduced amount of bladder volume in the high-dose region and additionally a reduced dose to bowel loops, that are shifted superiorly (1).

Several studies have dealt with urinary toxicity after radiation therapy for prostate cancer, but most studies did not find a correlation of the dose-volume-load to the bladder and late urinary toxicity. Prospective health-related quality of life analyses of a more homogeneous group of patients in respect to the total dose, treatment volume and post-treatment period support these results, demonstrating the independence of the initial bladder volume, prostate volume and a neoadjuvant hormonal therapy (6,7). These results are crucial for daily radiotherapy treatment planning.

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Dr. Michael Pinkawa
Department of Radiotherapy
RWTH Aachen University
Aachen, Germany
E-mail: mpinkawa@ukaachen.de

EDITORIAL COMMENTS

The purpose of this study was to determine factors that resulted in late urinary toxicity in prostate cancer patients treated with external beam radiation therapy. The authors found that irradiating 30% of the bladder (with a dose of 70 Gy or higher), and previous TURP resulted in an increased risk for at least grade 2, late urinary toxicity. This is an important topic as there is little guidance in the literature regarding specific doses or dosage cut points relating to urinary toxicity.

This is a well-done retrospective study, however it is subject to potential biases inherent to retrospective analysis. It should be pointed out that this a heterogeneous group of prostate cancer patients. Little is known of the patients pre-radiation therapy urinary function.

In the analysis, it was found that irradiating < 30% of the bladder-decreased symptoms by only 5.6% (92% freedom from symptoms vs. 86.4% freedom from symptoms for patients who had < 30% irradiated) though, that was significant. An attempt was made to treat the patients with the bladder full, as a full bladder can minimize the total volume of bladder irradiated, but the actual bladder volumes are not known. Though the patients had been advised to have a full bladder before treatment planning and the daily treatment, it is not known to what extent the patients were able to comply and how this relates to the findings.

The second finding is that patients with previous TURP had a 19.6% higher incidence of urinary toxicity (74.3 vs. 93.9 freedom from symptoms). The authors note that it is possible that patients with previous TURP are a selected group of patients who have a higher propensity for urinary toxicity. I would agree with that conclusion and believe it is related to a select group of patients in whom there has been bladder thickening and irritability due to long standing bladder outlet obstruction that required treatment. It is likely that patients who have had previous TURP already have worse urinary symptoms. It is possible that these patients are more sensitive to irradiation due to physiologic changes (bladder thickening, increased collagen, etc.) associated with bladder outlet obstruction requiring treatment. It is in my opinion there is also a possibility that the effect of bladder irradiation is understated. The investigators used physician interview to determine the side effects and usually patients will underrepresent side effects when talking to the physician as opposed to an anonymous questionnaire.

I believe that this subject is ripe for further study. The authors have opened an important dialogue. I think that in the future it will be important to know specifically how urinary toxicity relates to the bladder's functional status and measurable variables such as bladder capacity, voiding pressures, volume of intravesical prostate, etc.

In summary, I think that this paper addresses very important clinical questions that have the potential to make a difference in every day clinical practice. Clearly more specific information is needed regarding these issues.

Dr. Herbert C. Ruckle
Professor and Chief, Division of Urology
Loma Linda University Medical Center
Loma Linda, California, USA
E-mail: hruckle@ahs.llumc.edu