Int. J. Radiation Oncology Biol. Phys., Vol. 78, No. 1, pp. 19–25, 2010

0360-3016/$–see front matter

ELSEVIER

doi:10.1016/j.ijrobp.2009.07.1680

ASTRO Online CME

CLINICAL INVESTIGATION Prostate

URINARY OBSTRUCTION IN PROSTATE CANCER PATIENTS FROM THE DUTCH TRIAL (68 GY VS. 78 GY): RELATIONSHIPS WITH LOCAL DOSE, ACUTE EFFECTS, AND BASELINE CHARACTERISTICS

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Purpose: To investigate the relationship between late urinary obstruction and the details of the dose distribution of irradiated prostate cancer patients, taking into account their baseline symptoms and acute complaints.

Patients and Methods: We selected patients from the Dutch multicenter trial randomized between 68 Gy and 78 Gy, for whom toxicity data and dose data were available (n = 557). The absolute dose surface parameters of the delineated bladder were calculated. Next, we constructed three-dimensional dose maps of the area around the prostate, providing an approximate identification of the corresponding anatomic locations. The dose difference maps were constructed by subtracting the mean dose maps of the patients with and without late urinary obstruction. Selected local dose points were analyzed using Cox regression analysis.

Results: Urinary obstruction was scored for 40 patients, including 19 of 296 patients who received 68–72 Gy and 21 of 261 patients who received 76–78 Gy. A total of 19 events occurred within 2 years after irradiation and 21 events after 2 years. The bladder surface receiving ≥80 Gy predicted (p <.01) the occurrence of obstruction within 2 years. The dose difference map indicated highly significant differences in the bladder neck situated in the trigonal region (p < .001) that were especially predictive of obstruction after 2 years and of the diagnosis of bladder neck obstruction. Baseline complaints and transurethral resection of the prostate and acute complaints were mainly predictive for obstruction within 2 years.

Conclusion: Relatively early events of urinary obstruction were associated with urinary problems existing before RT, acute toxicity, previous transurethral resection of the prostate, and hotspots in the bladder. Events after 2 years were associated with the local dose in the trigonal area.

Prostate cancer, urinary obstruction, dose maps, dose–effect relationship.

INTRODUCTION

External radiotherapy (RT) for prostate cancer is the main treatment option when considerable risk of tumor invasion of the prostatic capsule and/or SVs is present. Conformal RT with dose levels of 74–80 Gy has become clinical practice since several studies reported improved freedom from failure compared with RT dose levels of 64–70 Gy (1). The side effects of RT mainly concern the rectum and bladder. A severe complication can be urinary retention. This symptom is, in most cases, the result of a severe outflow obstruction (stricture) in the bladder neck or urethra, which can be divided in the proximal part close to the bladder neck, the prostatic urethra, and the distal urethra near the external sphincter. Other possible causes of obstruction include ureter obstruction and an enlarged prostate.

In a recent study (2) of prostate cancer patients (n = 6,597), the estimated cumulative incidence of treated urethral stricture at 4 years was 5% for external RT, 11% for brachytherapy, and 11% for radical prostatectomy. In their study, they noted that prostatectomy and brachytherapy led to relatively early obstruction (within 24 months) and the onset of obstruction was delayed after RT. Harsolia *et al*. (3) studied a trial population of 332 patients with a median follow-up of 1.6 years who had received high doses (median, 79 Gy). The cumulative incidence of treated urinary retention at 3 years was 5% in their population. In our Dutch trial, the

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Supported by the Dutch Cancer Society (NKB Grants NKI 98-1830, NKI 2007-3895, and CKTO 96-10).

Conflict of interest: none.

Acknowledgments—We thank Prof. Dr. H. Bartelink and Prof. Dr. M. Verheij for critically reviewing the manuscript, and we acknowledge Josien de Bois for her efforts spent on the dose map validation.

Received April 27, 2009, and in revised form July 3, 2009. Accepted for publication July 19, 2009.

cumulative incidence at 3 years was similar: 6% in the 78-Gy arm and 4% in the 68-Gy arm (4). At 7 years, the incidence in the 78-Gy arm and 68-Gy arm had increased to 11% and 8%, respectively (1).

Data on the hypothesized radiation dose–effect relationships concerning urinary toxicity have not been conclusive. The elderly patient population is also subject to the development of complaints because of aging, which obscures the toxicity scoring. Another aspect is that a number of these patients had been visiting a urologist because of pre-existing urinary problems at the time their prostate cancer was diagnosed. Apart from determining the most relevant toxicity, the measurement of relevant dose parameters is also not trivial. The studied dose parameters have usually been derived from the total delineated bladder without evaluating local structures (such as the bladder neck) separately. Owing to variable filling and stretching of the bladder during treatment, the position of the bladder on the planning computed tomography (CT) scan is probably of limited value that can obscure the dose–effect relationships.

A number of reported baseline parameters associated with genitourinary (GU) toxicity include prostate volume, hormonal therapy, diabetes, and transurethral resection of the prostate (TURP) (3–5). A consequential relationship between acute and late GU toxicity has also been reported (3, 6, 7).

In the present study, we investigated the relationship between the dose parameters and incidence of late urinary obstruction, accounting for baseline problems and specific acute complaints. We analyzed the absolute dose surface data and the dose maps representing the dose in the total ''bladder region'' around the prostate. We hypothesized that such dose maps could be useful to identify more local dose–effect relationships for late GU toxicity.

PATIENTS AND METHODS

Patient group

In the Dutch trial, 664 patients were randomized to 68 Gy or 78 Gy. The patient population and treatment have been extensively described elsewhere (1, 4). We selected patients for whom acute and late toxicity was scored using checklists, which was the case for most of the patients treated at two hospitals ($n = 566$). For 5 patients, no late toxicity data were available because of limited follow-up, and, for 4 patients, not all dose data were available, leaving 557 patients for the present analysis.

Treatment

Treatment plans were constructed using CT data. The clinical target volume (CTV) was defined as the prostate or prostate plus seminal vesicles (SVs), depending on the estimated risk of SV invasion. Delineations were done on the transversal CT slides; however, at that time, the software did not allow one to check the delineations in the sagittal view, which caused typical deformations such as the CTV shape in Fig. 1. Magnetic resonance imaging was not available to establish the border between the prostate and the bladder neck; therefore, a part of the bladder neck was included in the CTV for a number of patients. A 1-cm margin was applied to the CTV for construction of the planning target volume (PTV) for the first 68 Gy (2 Gy/fraction). A 5-mm margin (0 mm toward the rectum) was applied for the 10-Gy boost. The bladder and rectum were delineated. For the bladder, no dose constraints were included in the trial protocol.

Toxicity scoring

Acute (28–120 days after the start of RT) and late (>120 days) toxicity were scored by the trial data managers, using the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer and late effects normal tissue/subjective, objective, management, analytic toxicity scales (4). Patients reported complaints on a checklist, before, during, and after RT. This checklist included high urinary frequency during the day and/or night, pain/cramps when passing urine, urinary incontinence (leakage), and a weak urinary stream. We grouped patients as having urinary obstruction when they were treated for symptoms of complete urinary retention, with a score of Grade 2 or greater for catheterization, transurethral resection, and/or dilation. We also analyzed the events by defining relatively early events and events after a lag period. The cutoff was 2 years of follow-up. Because of the delay in reporting events (follow-up visits were scheduled every 3–6 months), we included events reported $\leq$26 months after the start of RT as events occurring within 2 years.

Dose–surface histogram parameters

We used a volumetric database that had direct access to the CT images, dose distributions, and delineations. For each patient, the outer bladder wall was delineated on the planning CT scan, and the two-dimensional contours were triangulated to a three-dimensional surface. We calculated the absolute surface receiving $\geq$5 Gy to $\geq$80 Gy, with dose steps of 5 Gy. As described by Hoogeman *et al.* (8), absolute dose–surface data are the best choice, because they vary less with bladder filling changes than do relative data or dose–volume data.

Dose map construction

Dose maps offer a method to compare or combine the treatment planning dose distributions of different patients in three dimensions. We visualized the dose in the bladder region using dose maps, without considering the delineated bladder contours. Within 6 cm outside the prostate surface of each patient, the dose was calculated for the same set of dose points, defined by their radius from the surface and their direction relative to the center of mass (given by two angles). We started with the coordinates of the dose grid voxels of a first patient (the template patient). For all other patients, the dose values for the same sets of radius–angle values were calculated, by trilinear interpolation of the nearest dose points of the individual dose grid. Thus, the obtained dose maps of all patients were comparable and could be averaged by averaging the dose in the dose points with an identical radius and angle. The mean dose maps of the patients without and with obstruction were created and subtracted to form a dose difference map. This map visualized the local areas in which patients with obstruction received a greater dose than had patients without obstruction. For each point in the dose difference maps, we also calculated the p value for the local dose difference (based on t-distributions) to roughly determine the regions of interest. The mapped dose distributions were visualized using the anatomy of the template patient. This patient had had a prostate volume of 52 cm^3, a rectal volume of 41 cm^3, and a bladder volume of 389 cm^3.

Dose point selection

From our dose difference maps, we selected two dose points for additional evaluation. First, we selected a dose point (referred to

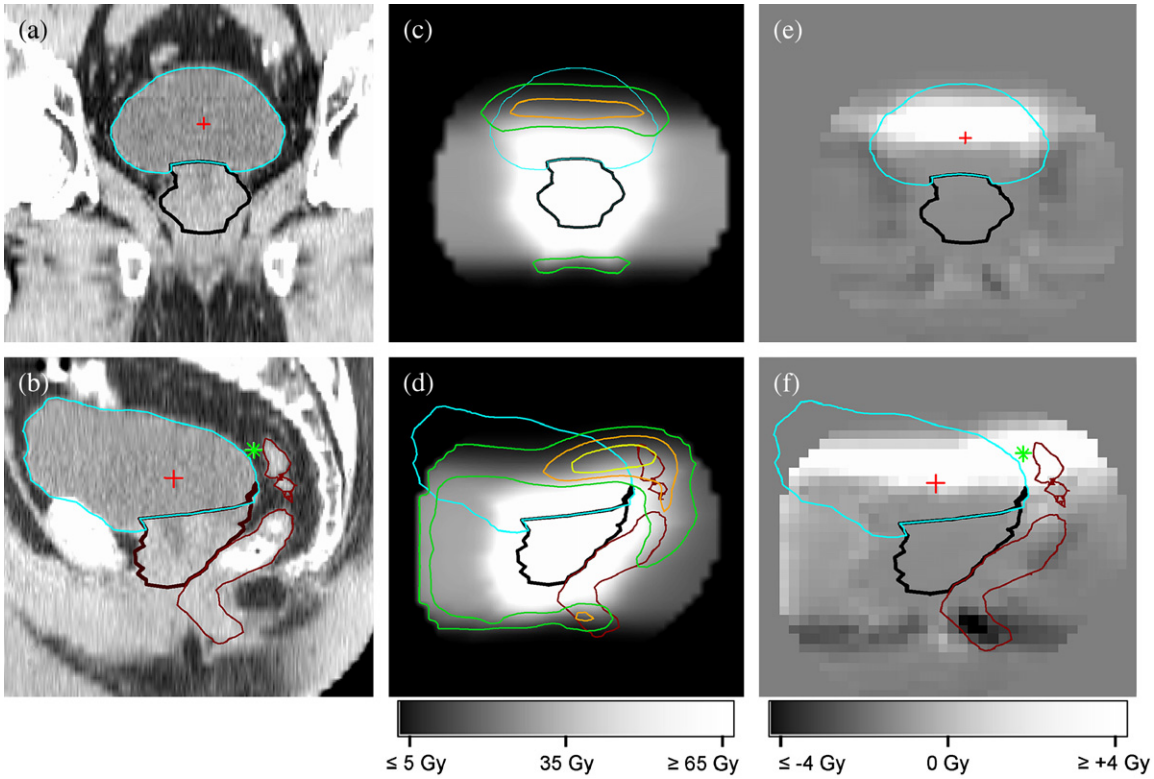

Fig. 1. (a, b) Coronal and sagittal views of computed tomography scan in prostate/bladder region for template patient (blue, bladder; black, prostate; dark red, rectum). Cross indicates trigone point 2 cm above starting point of prostatic urethra in coronal slice with urethra visible. Asterisk in Fig. b indicates region in which largest dose differences were found (see Fig. 1e, f). (c, d) Average planned dose for all patients in corresponding coronal and sagittal views. Apart from delineated organs, contours of standard deviations included to indicate roughly area of largest dose variations (green, 10-Gy contour; orange, 15 Gy; yellow, 20 Gy). (e, f) Dose difference maps (coronal and sagittal views). Mean dose map of patients without urinary obstruction subtracted from mean dose map of patients with obstruction. White region indicates significant ($p < .02$) dose differences (range 4–12 Gy). Asterisk in Fig. f indicates region with largest dose differences.

as the trigone point) in the trigonal area of our template patient. The trigonal area was defined as the triangle-shaped area in which the bladder neck is situated, the urethra starts, and the ureters end in the bladder. For this purpose, we studied the coronal CT slice in which the prostatic urethra was visible (Fig. 1a), and we visually followed the urethra to the prostate edge at which the urethra started. Next, we marked a point in the trigone area 2 cm above the starting point of the prostatic urethra. It was not expected to find dose–effect relationships for dose points closer to the prostate contour and bladder neck, because this part would mainly be situated in the PTV, receiving about the same dose as the targeted prostate. We also chose a second dose point in the dose difference map at which the dose differences were most significant (referred to as the maximal point).

Validation of dose maps

We picked the trigone point in our template patient, assuming that this point was also situated in the trigone area for all other patients. To validate this assumption, we manually checked this for 69 patients. For this purpose, we determined individually the corresponding point using the same method that we had used for the template patient.

The local dose and anatomic position (dose map coordinates) of this manual trigone point were then compared with those of the trigone point from the mapping procedure. For this procedure, we selected 23 patients with a determined bladder neck obstruction and/or obstruction that had occurred later than 2 years, and we randomly picked another 46 patients by selecting the study number above and below the patients with obstruction. Patients with hotspots were excluded.

The dose in the trigone point according the manual procedure correlated highly with the dose in the trigone point according the automated dose mapping procedure (Pearson correlation coefficient, 0.92). The mean dose in the selected obstruction group (n = 23) was 57.3 Gy according to the dose mapping procedure and 58.0 Gy according to the manual procedure. For the group without obstruction (n=46), the corresponding doses were 47.2 Gy and 47.5 Gy. The mean distance between the two points was 0.07 ± 0.2 cm, 0.08 ± 0.2 cm, and 0.05 ± 0.5 cm for the left–right, craniocaudal, and anteroposterior direction, respectively.

Statistical analysis

We determined on univariate analysis which parameters were significantly associated with late urinary obstruction, and we evaluated which factors remained significant using a multivariate model (Cox regression analysis). We also determined the prognostic value of the relevant parameters separately for events <2 years and >2 years after treatment and for diagnosed bladder neck obstruction. The interval to an event was calculated from the start of RT. The Statistical Package for Social Sciences, for Windows, release 15.0, software was used for the analyses (SPSS, Chicago, IL).

RESULTS

General statistics

The median follow-up was 71 months for living patients. Table 1 lists the distribution of the patients with regard to

T stage, dose, and pretreatment characteristics. The 296 patients receiving 68–72 Gy consisted of 278 patients randomized to 68 Gy and 18 patients randomized to 78 Gy, but who received a lower dose mainly because of dose-limiting constraints. Table 2 summarizes the calculated dose parameters and bladder characteristics. The cumulative incidence of urinary obstruction was 9.7% at 7 years of follow-up for all patients, 8.4% for patients receiving 68–72 Gy, and 11.2% for patients receiving 76–78 Gy (p = .4).

Urinary obstruction

Urinary obstruction was observed in 40 patients and was mainly scored as Grade 3 toxicity. The earliest event was noted 7 months after RT and the latest 8.5 years after RT. Of the 40 events, 19 occurred within 2 years and 21 occurred >2 years after RT. We studied the patient files to determine the location of the obstruction. It was located in or close to the bladder neck in 16 patients (of whom 1 patient was known to have obstruction of both ureters). For 14 patients, the location was indicated as the ''urethra'' or ''prostatic urethra'': it could not be excluded that it was also close to the bladder neck. For 3 patients, the obstruction was located in the distal urethra, and for 2 patients, the obstruction was probably caused by an enlarged prostate. The location remained unknown for 5 patients.

Baseline and acute variables

A previous TURP was strongly associated with obstruction (Table 3 and Fig. 2). Figure 2 shows that the effect of TURP was present during the first 2 years, as well as in the following years, for which the Kaplan-Meier curves were still separating. The corresponding estimated hazard ratios (HRs) were 3.6 and 2.8 (Table 3). No relationships were found for diabetes, prostate volume, hormonal therapy, smoking, or age. The predictive GU baseline complaints were (Table 3): urinary leakage (incidence, 12%) and nocturia ≥3 (27%). Furthermore, these factors were stronger predictors for events <2 years compared with >2 years.

The predictive acute complaints (maximal score) were pain when passing urine (64%) and urinary leakage (28%). The correlation of obstruction with acute toxicity only seemed to be present for events within <2 years, for which the HRs were very significant ($p \leq .001$).

Dose–surface histogram

In Fig. 3, the dose–surface histograms (DSHs) have been plotted for patients with and without urinary obstruction. The DSHs were close to each other with large standard deviations. The total bladder surface (and volume) was, on average, slightly larger for the patients with obstruction (p = .2). Hotspots, defined as areas >0.5 cm^2, were significantly associated with obstruction (HR, 3.2 for an area >0.5 vs. <0.5 cm^2; Table 3 and Fig. 4a). The HR was 6.0 for diagnosed bladder neck obstructions. Hotspots were mainly associated with events <2 years after RT (HR, 5.9) and not with events >2 years after RT (HR, 1.0). However, the subgroup of patients with hotspots was small; only 39 patients with a surface ≥0.5 cm^2 received ≥80 Gy.

Table 1. Patient characteristics (n = 557)

Variable	Total group
Tumor stage	
T1-T2a	239 (43)
T2b-T3a	236 (42)
T3b-T4	82 (15)
Radiation dose to SV (Gy)	
0	99 (18)
48–50	102 (18)
66–78	356 (64)
Radiation dose to prostate (Gy)	
68	293 (53)
70–72	3 (1)
76–78	261 (47)
Hormonal therapy	134 (24)
TURP	65 (12)
Diabetes	33 (6)
Mean age ± SD (y)	68 ± 6.4

Abbreviation: TURP = transurethral resection of prostate.
Data in parentheses are percentages.

Dose map

In Fig. 1, the results of the mapping procedure are shown for a coronal and sagittal slice. In Fig. 1a,b, the anatomy of the CT scan of our template patient is illustrated, including the delineated prostate, rectum, and bladder. Figure 1c, d shows the mean dose maps of the total group with the contours of the standard deviations. The dose difference map revealed large significant dose differences of ≤12 Gy (p <.01) superior to the PTV (*i.e.,* in the bladder area; Fig. 1e, f). The maximal point, indicating the area with the most significant dose difference, was situated about 4 cm dorsally and 2 cm cranially from the trigone point (indicated with a cross). The corresponding mean doses at these points were 47 Gy and 31 Gy (Table 2). For 515 patients with no obstruction, the mean dose at the trigone point was 46.7 ± 14 Gy. It was 52.1 ± 12 Gy for patients with obstruction. For established bladder neck obstruction, the mean dose was 52.3 ±

Table 2. Bladder and dose characteristics (n = 557)

Variable	Total group
Bladder surface (cm^2)	241 ± 92
Bladder volume (cm^3)	292 ± 181
Dose–surface histogram (cm^2)	
Surface ≥20 Gy	161 ± 39
Surface ≥40 Gy	127 ± 34
Surface ≥60 Gy	75 ± 23
Surface ≥80 Gy (n)	
0 cm^2	515 (92)
0–0.49 cm^2	8 (1)
0.5–14.7 cm^2	34 (6)
Dose map (Gy)	
Dose trigone point	47 ± 14
Dose maximal point	31 ± 23

Data presented as mean ± standard deviation, unless otherwise noted; data in parentheses are percentages.

Table 3. Results of Cox regression for endpoints urinary obstruction, established bladder neck obstruction, and events within and after 2 y

	Univariate								Multivariate	
	Urinary obstruction (40 events)		Bladder neck obstruction (16 events)		Obstruction <2 y (19 events)		Obstruction >2 y (21 events)		Urinary obstruction (40 events)	
Parameter/endpoint	HR	*p*	HR	*p*	HR	*p*	HR	*p*	HR	*p*
Baseline										
TURP (yes vs. no)	3.2	.001	2.8	.07	3.6	.009	2.8	.04	3.6	.001
Urinary leakage (yes vs. no)	2.9	.003	1.7	.4	3.3	.02	2.5	.07	2.7	.007
Nocturia ≥3 times	2.7	.004	2.4	.1	5.6	.002	1.5	.4	—	
Acute toxicity										
Pain passing urine*	3.1	<.001	3.2	.02	4.3	.003	2.4	.05	3.4	<.001
Urinary leakage (yes vs. no)	2.5	.006	2.9	.04	5.9	.001	1.2	.6	—	
Dose parameter										
Surface >80 Gy (<0.5 vs. >2 cm^2)	3.2	.01	6.0	.002	5.9	.001	1.0	1.0	3.5	.006
Trigone point (<47 vs. >47 Gy)	2.7	.01	5.4	.03	1.7	.3	4.5	.02	2.6	.02
Max point (<31 vs. >31 Gy)	2.6	.005	5.4	.009	1.8	.2	3.9	.008	—	
Prostate dose (/10 Gy)	1.3	.4	1.9	.2	1.6	.3	1.0	.9	—	
SV dose (/10 Gy)	1.2	.03	1.4	.09	1.2	.2	1.2	.2	—	

Abbreviations: TURP = transurethral resection of prostate; SV=seminal vesicle.
* Moderate/severe vs. no/little.

10 Gy. Patients with previous TURP received, on average, a significantly greater dose to the trigone dose point (52.1 Gy vs. 46.4 Gy, p = .002). The dose to the trigone point and the maximal point correlated highly and both were significant predictors for obstruction, especially for bladder neck obstruction and events >2 years after RT (Table 3). Figure 4b shows the Kaplan-Meier curves above and below the mean dose to the trigone point.

Dose to prostate and SVs

As indicated in Table 3, the dose to the prostate was not a significant predictor for any endpoint. In contrast, the dose to the SVs was a significant predictor for urinary obstruction. Additional explorative analyses revealed that the craniocaudal extent of the delineated SVs (calculated as the extent of the prostate plus the SVs minus the extent of the prostate) was also significantly associated with urinary obstruction (p = .03) and that the bladder volume on the planning CT scan was significantly associated with the craniocaudal extent of the SV (p = .001). The bladder volume on the CT scan itself (volume >500 vs. <500 cm^3) was associated with obstruction (HR, 2.0; p = .07) for patients irradiated to the SVs. These correlations strongly suggested that when the bladder fills, the SVs move. As a result, a patient with a full bladder on the CT scan will have a larger craniocaudal extent of the RT field to cover the stretched SVs. Thus, more dose will have been planned to the bladder neck area, increasing the risk of bladder toxicity.

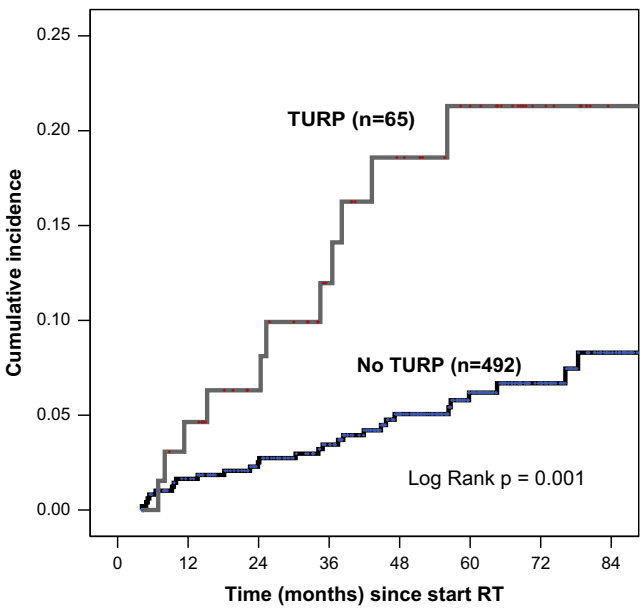

Fig. 2. Kaplan-Meier curve showing greater incidence (p = .001) of late urinary obstruction for patients with previous transurethral resection of prostate compared with those without previous transurethral resection of prostate.

Multivariate analysis

When we tested the factors on multivariate analysis with urinary obstruction as the endpoint (Table 3), urinary leakage in the acute phase, which correlated with leakage at baseline, was not more significant. There seemed to be only a consequential effect (acute complaints predicting for late) for "pain with passing urine." The dose to the maximal point and the dose to the SVs were not entered in this model because they correlated highly with the dose to the trigone point; thus, replacing the trigone point with the maximal point or the SV dose gave similar results.

DISCUSSION

We found the baseline and acute factors to be significantly associated with urinary obstruction, in agreement with the findings of other studies (3, 5–7). In the DSH analyses, we found that high-dose regions (≥80 Gy) contributed to the development of urinary obstruction, which was also recently

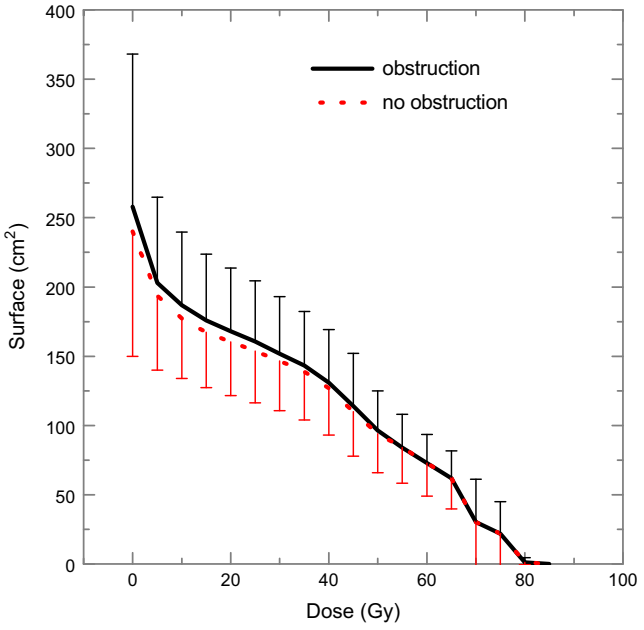

Fig. 3. Absolute dose–surface histograms for patients with and without urinary obstruction.

reported by others (3, 9). The incidence of hotspots was, however, only 13% for our high-dose group. In our study, the effect of hotspots was most apparent for diagnosed bladder neck obstructions, which would be expected because bladder hotspots are usually found in the bladder neck area close to the CTV. Furthermore, hotspots were mainly associated with urinary retention within 2 years.

By constructing dose maps, we found strong indications for a local dose–effect relationship in the trigonal area that was the greatest for patients with diagnosed bladder neck obstruction and for events >2 years after RT. The mean local dose to the trigone point was 47 Gy. Validation of the dose map procedure showed good correspondence of the dose and anatomic location of the trigone point from the automated mapping procedure compared with the trigone point of the manual procedure. The results from the dose mapping should be interpreted with care because local areas of clinical interest were indicated rather than local points. It is likely that bladder DSH analysis could find the local dose effect for late obstruction if the relevant area has been delineated, providing more conclusive evidence of a dose–effect relationship.

In our study, 40 of 557 patients had urinary obstruction at a median follow-up of 71 months, which seemed rather high. We found a greater incidence of Grade 2-3 or greater GU toxicity in our trial than in other similar dose-escalation trials (10–12), which we attributed to our detailed and frequent follow-up procedures. Most other dose-escalation trials have not reported detailed information on urinary obstruction. The MRC RT01 study reported that 20 of 422 patients receiving 74 Gy had urethral strictures (median follow-up, 63 months).

Transurethral resection of prostate

We found that previous TURP was associated with a greater post-RT risk of GU complications, in this case, urinary retention. As hypothesized by others, this can be explained by the local damage caused by the TURP, the relative devascularization, and the decreased repair capacity of the mucosa (5). TURP was, on average, associated with a greater dose in the trigone area, which probably also contributed to the observed increased toxicity rate. This phenomenon can be explained by the anatomy of the prostate that has undergone TURP: the base is usually broadened; therefore, the CTV is broadened at the bladder site, leading to inclusion of a larger part of the bladder neck in the PTV.

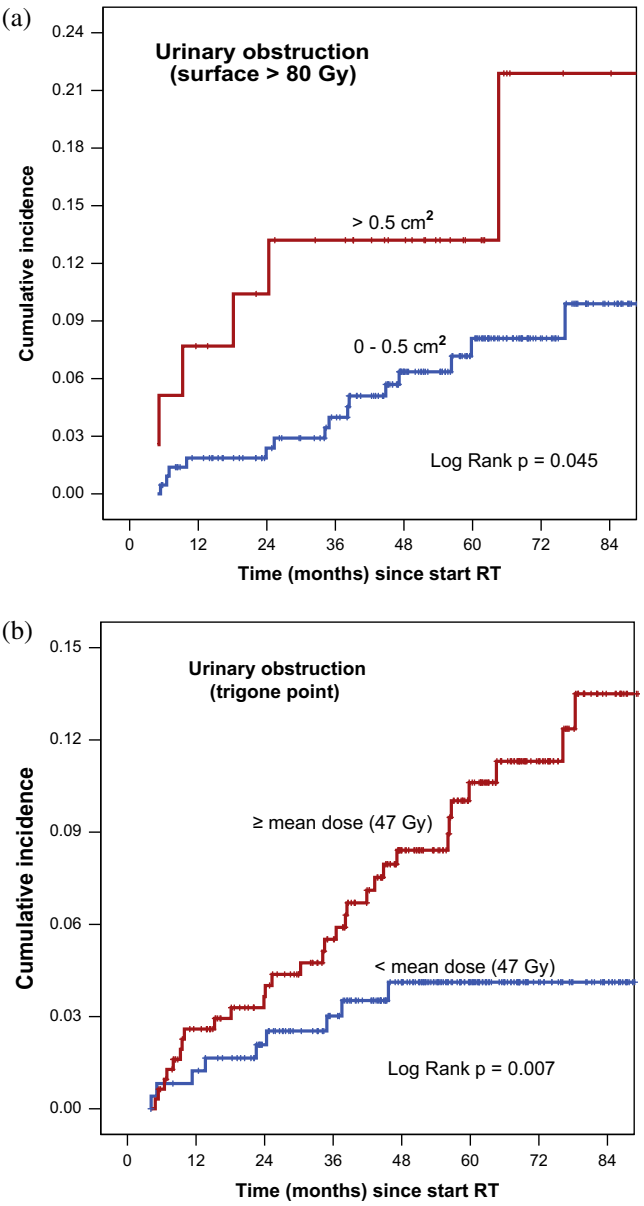

Fig. 4. Kaplan-Meier estimates for obstruction. (a) Cumulative incidence for subgroups receiving dose greater than and less than mean dose to trigone point. (b) Cumulative incidence for patients with and without hotspots (surface <0.5 or >0.5 cm^2 received >80 Gy) for subgroup receiving radiation dose >76 Gy (total n = 256, n = 39 with surface >0.5 cm^2).

Bladder neck obstruction

For 16 patients, obstruction in the bladder neck region was confirmed and was significantly associated with the dose to the trigone point. However, in the dose-difference map, the largest dose differences occurred cranially from the bladder neck, which seemed counterintuitive. It could be that the dose in this area correlated from one point to another, with the largest (and most significant) dose differences usually appearing in the penumbra. Therefore, a greater or lower dose in the bladder neck area will be associated with an even more pronounced dose difference in the penumbra at a certain distance from the point of interest. Second, the dose next to the bladder neck area could also be relevant, because the bladder neck will probably move in and out of this area during treatment. Furthermore, the dose just cranial from the prostate is probably predictive for bladder neck obstruction; however, only limited dose variation will occur in this area because it has been included in the PTV and will mainly have received 68 Gy or 78 Gy. The cumulative incidence of confirmed bladder neck obstruction at 7 years was 2.6% and 6.1% for the 68–72-Gy and 76–78-Gy dose groups, respectively ($p = .2$).

The presented data suggest highly that bladder neck obstruction is a result of the dose delivered to the trigonal area. Limiting the dose to this area is often not an aim in dose planning. Omitting hotspots in the bladder neck and restricting the dose to the lower part of the bladder (wall) would lower the risk of this severe adverse event and could therefore be a very relevant aim during treatment optimization.

Obstruction within and after 2 years

By defining the events before and after 2 years of follow-up, we were able to discriminate between factors predicting for early events, late events after a lag period, and for both in this explorative analysis. Persisting and aggravating baseline complaints, as well as TURP, acute complaints, and high hotspots, were mainly predictive for events within 2 years. The local dose to the trigone point was especially predictive for obstruction after 2 years. It is plausible that factors causing mechanical damage, such as TURP and hotspots, induce tissue damage and subsequent clinical problems after a shorter period than would be expected from radiation damage. In contrast, radiation effects are to be expected after a lag period. It is likely that radiation-induced obstruction will be found after longer periods of follow-up than included in the present study. For this purpose, it would be interesting to update the trial toxicity data for $\leq$10–15 years of follow-up.

Other GU endpoints

In our explorative analysis, we also produced dose maps for other endpoints, including the presence/absence of hematuria, incontinence, nocturia of $\geq$4 times, and daytime frequency of $\geq$16 times. For some endpoints, dose differences were noticed further from the prostate where the dose maps are less reliable with respect to the correspondence between patients of anatomic locations, making it difficult to interpret the results unambiguously. For the endpoint hematuria, we found clear dose differences in the bladder wall of the lower bladder that were most pronounced at the posterior side. We will study these dose map results further in future analyses.

CONCLUSION

The results of the present study have shown that urinary obstruction within 2 years after RT is s associated with urinary problems existing before RT, acute toxicity, previous TURP, and hotspots in the bladder. Events after a period of 2–7 years are associated with the local dose in the trigonal area and other correlated dose points in this bladder area. Limiting the dose to the bladder neck area is often not an aim in treatment optimization. Because of the serious nature of urinary obstruction, sparing the bladder neck area is advised to prevent the patient from unnecessary risk.

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