Original Article

Urethral and bladder dose–effect relations for late genitourinary toxicity following external beam radiotherapy for prostate cancer in the FLAME trial

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ABSTRACT

Purpose or objectives: The FLAME trial (NCT01168479) showed that by adding a focal boost to conventional fractionated EBRT in the treatment of localized prostate cancer, the five-year biochemical disease-free survival increased, without significantly increasing toxicity. The aim of the present study was to investigate the association between radiation dose to the bladder and urethra and genitourinary (GU) toxicity grade ≥ 2 in the entire cohort.

Material and methods: The dose–effect relations of the urethra and bladder dose, separately, and GU toxicity grade ≥ 2 (CTCAE 3.0) up to five years after treatment were assessed. A mixed model analysis for repeated measurements was used, adjusting for age, diabetes mellitus, T-stage, baseline GU toxicity grade ≥ 1 and institute. Additionally, the association between the dose and separate GU toxicity subdomains were investigated.

Results: Dose-effect relations were observed for the dose (Gy) to the bladder D2 cm^3 and urethra D0.1 cm^3, with adjusted odds ratios of 1.14 (95% CI 1.12–1.16, $p < 0.0001$) and 1.12 (95% CI 1.11–1.14, $p < 0.0001$), respectively. Additionally, associations between the dose to the urethra and bladder and the subdomains urinary frequency, urinary retention and urinary incontinence were observed.

Conclusion: Further increasing the dose to the bladder and urethra will result in a significant increase in GU toxicity following EBRT. Focal boost treatment plans should incorporate a urethral dose-constraint. Further treatment optimization to increase the focal boost dose without increasing the dose to the urethra and other organs at risk should be a focus for future research, as we have shown that a focal boost is beneficial in the treatment of prostate cancer.

Whole-gland dose escalation up to 80 Gy to the entire prostate has shown to be effective regarding biochemical disease-free survival (bDFS) in the treatment of prostate cancer [1–5]. However, further increasing the dose to the entire prostate using external beam radiotherapy (EBRT) often results in higher genitourinary (GU) and gastrointestinal (GI) toxicity because of an increased dose to the surrounding organs at risk (OAR) [4,6–9]. Instead of further increasing the dose to the entire prostate, the phase 3 multicenter randomized controlled Focal Lesion Ablative Microboost in ProstatE cancer (FLAME) trial (NCT01168479) compared effectiveness and toxicity of EBRT with and without a simultaneous integrated focal boost up to 95 Gy to the macroscopic tumor(s) in

intermediate- and high-risk localized prostate cancer patients [10]. The addition of a focal boost to conventionally fractionated EBRT significantly increased the five-year bDFS. The differences in cumulative GU toxicity rates were small and not statistically significant between the treatment arms of the FLAME trial [11,12]. The development of GU toxicity is multifactorial and originates from clinical risk factors and irradiated volumes of the bladder and the urethra [13–15]. Dosimetry studies addressing the association between GU toxicity and urethral dose parameters based on large whole-gland dose escalation trials are scarce because of the invisibility of the urethra on computed tomography (CT) scans, which were commonly used for the radiotherapy planning [16]. When MRI is used for contouring of the target volume and OAR, it is possible to delineate the urethra and carry out dose–effect relation analyses for the urethral dose in correlation with GU toxicity.

By adding a focal boost dose to whole-gland EBRT, an inhomogeneous dose to the prostate was given. This inhomogeneous dose allows to differentiate between the dose to the bladder and urethra, Moreover, in the FLAME trial, we did not use a urethral dose-constraint in treatment planning. This resulted in a significant heterogeneity in the dose to the urethra, allowing us to perform a dose–effect analysis with a wide dose range for the urethra. The objective of this study was to perform a dose–effect relation analysis for the urethral and bladder dose parameters and GU toxicity grade ≥2 in patients with localized prostate cancer treated with EBRT in the FLAME trial in the study cohort, irrespective of randomization arm.

Material and methods

Study design and patient population

In the FLAME trial, standard whole-gland EBRT was compared to an additional simultaneous integrated focal boost up to 95 Gy for localized prostate cancer. The University Medical Center Utrecht (UMCU), The Netherlands Cancer Institute (NKI), Radboudumc Nijmegen in The Netherlands and University Hospitals Leuven in Belgium were participating centers.

Patients with intermediate- and high-risk prostate cancer according to the Ash criteria [17] were included. Patients were excluded if they had a WHO performance score >2, IPSS score ≥20, evidence of lymph node involvement or distant metastasis, history of prior pelvic irradiation, prostatectomy or trans urethral resection of the prostate (TURP) within three months prior to radiotherapy. Additionally, patients who could not undergo magnetic resonance imaging (MRI), or patients with an undefinable tumor on MRI were excluded.

Approval was given by the medical ethics committee of the UMCU, The Netherlands (NL26038.041.08) and of the University Hospitals Leuven, Belgium (B322201110225). All included patients gave written informed consent.

Radiotherapy dose and technique

Patients were randomized between the standard arm (77 Gy in 35 fractions of 2.2 Gy to the whole prostate, during seven weeks) and the focal boost arm in a 1:1 ratio, with stratification per center. Patients in the focal boost arm received an additional simultaneous integrated boost to the macroscopic tumor up to 95 Gy, resulting in 35 fractions of 2.7 Gy. In order to reduce positioning errors, gold fiducial markers were implanted. Conventional linear accelerators were used to carry out either intensity-modulated radiotherapy or volumetric modulated arc therapy. For delineation of the target volumes and OAR, CT-scans and multiparametric (mp) MRI-scans with T2-weighted, diffusion-weighted and dynamic contrast-enhanced images were acquired. The boost dose to the gross tumor

volume (GTV) in the focal boost arm varied between patients, as the dose-constraints to the OAR were prioritized over the focal boost dose. The planning target volume (PTV) was prescribed 77 Gy with a margin of 5–8 mm around the clinical target volume (CTV), depending on the participating center. The part of the PTV overlapping the rectum and bladder was prescribed 70 Gy. There was no margin around the GTV.

The entire bladder was contoured, from the bladder neck to the bladder dome. Dose-constraints to the bladder were: V72Gy < 10% and D1 cm^3 < 80 Gy. Bladder filling protocols differed per participating centre, patients were generally advised to have a comfortably filled bladder during planning CT, MRI and treatment. There was no dose-constraint for the urethra used for treatment planning. Therefore, to allow for the present dose–effect relation analysis, the urethra was contoured in all patients using the sagittal and axial images of the T2-weighted turbo spin echo (TSE) sequence. The prostatic urethra was delineated using a circle shape with 6 mm diameter. After delineation of the urethra, cumulative dose-volume histograms (DVHs) were calculated. Absolute dose parameters that represent the near maximum dose (bladder D2 cm^3, urethra D0.1 cm^3) were used, because these are considered to be most susceptible to the focal boost dose.

Toxicity assessment

Patients were reviewed weekly by the physician during treatment. After treatment, follow-up consisted of appointments with the physician at one month, six months, twelve months and yearly thereafter up to ten years. Treatment-related toxicity was scored using the Common Toxicity Criteria for Adverse Events (CTCAE) version 3.0. GU toxicity endpoints were: urinary frequency, retention, bladder spasm, incontinence, hematuria and dysuria. For the CTCAE 3.0, scores ranged from zero to grade five toxicity.

Statistical analysis

In this paper, we investigated the dose to the urethra and bladder, separately, in relation to GU toxicity grade ≥2, irrespective of the treatment arms. Generalized linear mixed effect models were used to assess the association between the dose parameters and GU toxicity over time. The cumulative incidence of toxicity was calculated as the number of patients that experienced any event of grade ≥2 GU toxicity at some point after radiotherapy.

The different rates of acute GU toxicity (up to 90 days after start of treatment) and late GU toxicity (from 90 days after start of treatment up to five years) was accounted for with a separate intercept and a separate effect for time for acute and late toxicity. To account for multiple measurements per patient, we included a random effects intercept and a random effect for time. We accounted for the increasing dose during treatment up to seven weeks (35 fractions), and used the total planned dose thereafter. We adjusted the models for age, baseline GU toxicity grade ≥1, diabetes mellitus, T-stage and institute (fixed effects).

The associations of the dose and urinary frequency, urinary retention and urinary incontinence were assessed without adjusting for potential confounders, because of the low number of toxicity events per subdomain. The endpoints hematuria and dysuria were considered to have too few events per measured time point and were not separately analyzed.

Dose-toxicity curves were created based on the estimated probabilities of late GU toxicity and the planned dose to the bladder D2 cm^3, and the D0.1 cm^3 of the urethra. Probabilities for developing late GU toxicity were calculated based on the average patient. As a range around the average patient curve, we plotted the probability of developing late GU toxicity in an unfavorable risk group in which all potential risk factors for GU toxicity (higher T-stage

(T3b or T4), diabetes mellitus and baseline GU toxicity grade ≥ 1) were present, and a favorable risk group in which none of the aforementioned risk factors were present, with a mean age of 71 years old.

In addition, we analyzed the effect of acute GU toxicity on late GU toxicity in a generalized linear mixed effect model, adjusted for age, baseline GU toxicity grade ≥ 1, diabetes mellitus, T-stage and institute. Additional information on the statistical analyses were presented in the supplementary material Table S1.

All statistical analyses were performed using SPSS version 25.0 (IBM Corp., Armonk, NY, USA) and SAS, version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

At time of the present analysis, all 571 patients had potentially reached five years of follow-up, with a median follow-up of

Table 1
Patient and treatment characteristics of the FLAME trial participants at baseline.

Total number of patients (n)		571	
Age in years (mean, SD)		71	6
iPSA ng/mL (median, IQR)		11.2	7.3–18.5
Risk classification (EAU) (n, %)	Low	6	1%
	Intermediate	85	15%
	High	480	84%
Center (n, %)	UMC Utrecht	320	56%
	UZ Leuven	93	16%
	NKI	109	19%
	Radboudumc	49	9%
T stage (n, %)	Missing	2	0%
	T1c	46	8%
	T2a	58	10%
	T2b	37	7%
	T2c	76	13%
	T3a	237	42%
	T3b	102	18%
	T4	13	2%
N stage (n, %)	Missing	1	0%
	N0	456	80%
	pN < 10 lymph nodes removed	81	14.%
	pN $\geq$10 lymph nodes removed	33	6%
M stage (n, %)	Mx	143	25%
	M0	428	75%
Gleason (n, %)	< 7	103	18%
	7	276	48%
	$\geq$ 8	192	34%
Cardiovascular disease (n, %)	Missing	3	0%
	No	255	45%
	Yes	313	55%
Hormonal therapy (n, %)	Missing	5	1%
	No	190	33%
	Yes	376	66%
Diabetes mellitus (n, %)	Missing	2	0%
	No	504	89%
	Yes	65	11%
Baseline GU toxicity (n, %)	Missing	16	3%
	No	356	62%
	Grade 1	147	26%
	Grade 2	46	8%
	Grade 3	6	1%
	Grade 4	NA	NA
	Grade 5	NA	NA

Abbreviations: SD = standard deviation, iPSA = initial prostate specific antigen, IQR = interquartile range, EAU = European Association of Urology, T stage = T refers to the size and extent of the main tumor, N stage = N refers to the number of nearby lymph nodes that have cancer, M stage = M refers to whether the cancer has metastasized, GU = genitourinary.

72 months (interquartile range (IQR) 58–86). Baseline characteristics are presented in Table 1. The mean age at time of randomization was 71 years (SD 6). For further analysis, 91 patients were excluded. Three patients were excluded because they received a different type of treatment than originally planned: one patient was treated with hormonal treatment alone because of metastatic disease on the planning CT/MRI scans, another patient received additional pelvic radiotherapy because of positive lymph nodes and the third patient underwent a cystoprostatectomy, as he was diagnosed with concomitant bladder carcinoma. Another ten patients without dosimetry data available and 78 patients who underwent a previous TURP were excluded.

For the present study we addressed the GU toxicity up to five years. The cumulative acute and late GU toxicity rates grade ≥ 2 are presented in Table 2. Cumulative acute toxicity grade ≥ 3 was seen in 3% ($n = 18$) of the patients, including urinary frequency ($n = 9$), urinary obstruction ($n = 8$), urinary incontinence ($n = 1$) and dysuria ($n = 1$). Cumulative late toxicity grade ≥ 3 was seen in 5% ($n = 27$) of the patients, including urinary frequency ($n = 5$), urinary obstruction ($n = 11$), urinary incontinence ($n = 7$), bladder spasm ($n = 1$), hematuria ($n = 6$) and dysuria ($n = 2$). Grade 4 GU toxicity occurred in one patient, who required a permanent urinary diversion due to severe incontinence, three years after treatment. Urethral strictures occurred in 18 patients (4%), requiring medical interventions including urethral dilatation, urethrotomy or daily intermittent self-catheterization. Over half of the strictures (13/18) occurred more than two years after treatment. In one patient a cystectomy including a partial prostatectomy was required four years after radiotherapy, because of urethral necrosis following a urethrotomy earlier that year. We did not determine the location of the urethral strictures.

The median planned dose to the D2 cm^3 of the bladder and the D0.1 cm^3 of the urethra were 75 Gy (IQR (74–76) and 80 Gy (IQR 78–87), respectively, see Fig. 1 for the dose distributions per treatment arm. For the bladder D2cm^3 we found a dose–effect relation with an unadjusted odds ratio of 1.15 (95% CI 1.13–1.17, $p < 0.0001$). This means that when the planned dose to the D2cm^3 of the bladder increases with 1 Gy, the odds of developing GU toxicity grade ≥ 2 increases with 1.15. Adjusted for age, T-stage, diabetes mellitus, baseline GU toxicity grade ≥ 1 and institute, the odds ratio was 1.14 (95% CI 1.12–1.16, $p < 0.0001$). The odds ratios for the urethra D0.1 cm^3 for developing GU toxicity grade ≥ 2 were 1.13 (95% CI 1.11–1.15, $p < 0.0001$) and (after adjustment for confounders) 1.12 (95% CI 1.11–1.14, $p < 0.0001$) per increase of 1 Gy (Table 2). These associations were visualized as dose–effect curves for the average patient, and for unfavorable and favorable risk groups based on patient characteristics in Fig. 2. When using a cut-off for the dose to the urethra of 80 Gy, cumulative toxicity rates were 22.3% (58/260) and 26.4% (58/220), respectively.

The dose–effect relations of the GU toxicity subdomains are presented in Table 2. For the endpoints urinary retention and urinary incontinence the random effect for time was excluded, since the corresponding covariance parameter estimates were zero. An additional generalized linear mixed effect model showed that acute GU toxicity was associated with late GU toxicity with an adjusted odds ratio of 5.82 (95% CI 1.65–20.56, $p = 0.006$).

Discussion

Although cumulative toxicity showed no significant difference between treatment arms of the FLAME trial [11], the large dose range to the bladder and urethra in the FLAME focal boost study allowed for the composition of dose–effect relations for the urethra and bladder, separately. By using a longitudinal repeated measures analysis, we found that an increased dose to the bladder and ure-

Table 2

The association between urethra and bladder dose and cumulative GU toxicity: results of generalized linear mixed models with and without adjustment for potential confounding factors for GU toxicity. Results for late cumulative GU toxicity grade ≥2 and late separate GU toxicity grade ≥2 endpoints are shown.

Total *n* = 480	Overall GU toxicity grade ≥2		Urinary frequency grade ≥2	Urinary retention grade ≥2	Urinary Incontinence grade ≥2	Hematuria grade ≥2	Dysuria grade ≥2
Acute* cumulative toxicity	47% (95% CI 42–51%, *n* = 225)		37% (95% CI 33–42%, *n* = 179)	15% (95% CI 12–19%, *n* = 74)	3% (95% CI 2–5%, *n* = 13)	0% (95% CI 0–1%, *n* = 1)	5% (95% CI 3–7%, *n* = 23)
Late* cumulative toxicity	24% (95% CI 21–28%, *n* = 116)		16% (95% CI 13–19%, *n* = 75)	8% (95% CI 6–11%, *n* = 39)	5% (95% CI 4–8%, *n* = 26)	1% (95% CI 1–3%, *n* = 6)	2% (95% CI 1–3%, *n* = 8)
	Unadjusted OR (95% CI)	Adjusted OR (95% CI)	Unadjusted OR (95% CI)				
Bladder D2cm^3	1.15 (1.13 1.17, *p* < 0.0001)	1.14 (1.12 1.16, *p* < 0.0001)	1.17 (1.15 1.20, *p* < 0.0001)	1.17 (1.13 1.22, *p* < 0.0001)	1.12 (1.05 1.20, *p* = 0.001)		
Urethra D0.1 cm^3	1.13 (1.11 1.15, *p* < 0.0001)	1.12 (1.11 1.14, *p* < 0.0001)	1.15 (1.13 1.17, *p* < 0.0001)	1.15 (1.11 1.18, *p* < 0.0001)	1.11 (1.05 1.18, *p* < 0.001)		

The ORs for the dose-parameters mean that when the planned dose to the urethra and bladder increases with 1 Gy, the odds of developing GU toxicity grade ≥2 increase with the corresponding given OR.

*Acute toxicity was defined as toxicity from the start of treatment up to 90 days, late toxicity was defined as from 90 days after start of treatment up to five years after treatment.

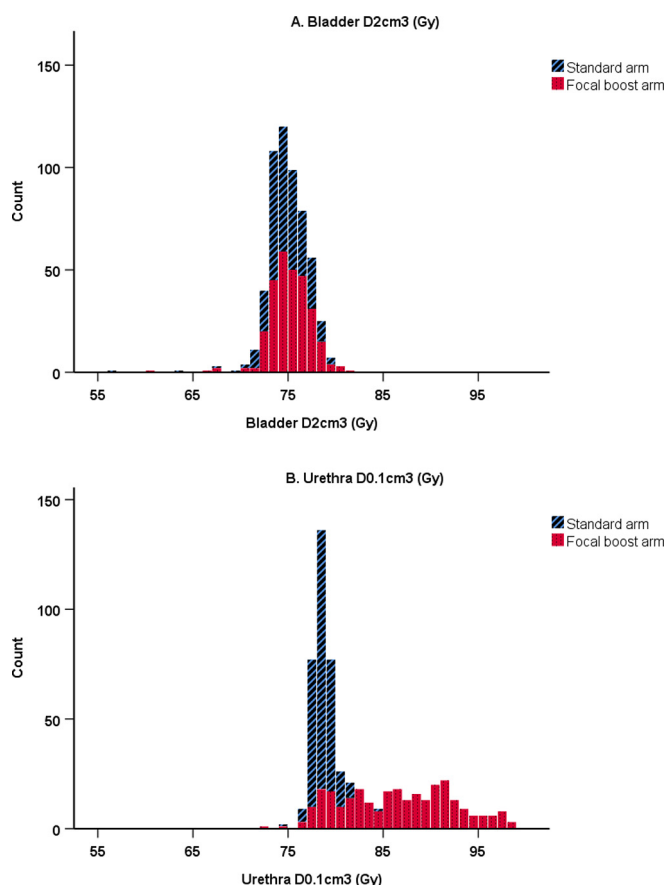Abbreviations: GU = genitourinary, CI = confidence interval, OR = odds ratio.

Fig. 1. Stacked histogram of planned dose (Gy) to the A. bladder D2cm^3 (standard arm and focal boost arm, median 75 Gy (IQR 74–76) and 75 Gy (IQR 74–77), respectively) and B. urethra D0.1 cm^3 (standard arm and focal boost arm, median 78 Gy (IQR 78–79) and 86 Gy (IQR 82–91), respectively) per treatment arm. Abbreviations: IQR = interquartile range.

thra will result in a significant increase in GU toxicity following EBRT. However, no clear threshold dose for the dose to the urethra and GU toxicity grade ≥2 could be observed. As we found a dose–effect relation for the urethra dose, it would be desirable to optimize the radiation plan also taking the urethra dose into account. We, therefore, propose that focal boost treatment plans should incorporate a urethral dose-constraint (pragmatically set at D0.1 cm^3 ≤ 80 Gy as close to conventional whole prostate gland dose) in addition to the pre-existing bladder dose-constraints. A urethral constraint was incorporated in our subsequent hypo-FLAME study [18]. Genitourinary toxicity is multifactorial and depends on other factors than (urethral) dose only. However, when limiting the dose to the bladder and dose to the urethra, we expect to minimize treatment related toxicity.

Whole-gland dose-escalation trials with doses up to 80 Gy, showed higher GU toxicity rates in the dose-escalation arms, showing a dose–effect relation mainly for the high/maximum doses to the bladder and/or urethra [16,19–22]. Frequent GU toxicity complaints are urethral strictures, urinary retention, incontinence and hematuria [13,19,23–25]. Previous studies showed that an increased dose to the bladder region or urethral surrogate structure receiving >75 Gy [25] and >80 Gy [19], respectively, results in an increase in urethral strictures and urinary obstruction. Mylona et al. also identified the dose to the urethra and bladder sub regions as predictors for various urinary symptoms [24]. We found associations for urinary frequency, urinary retention, urinary incontinence and the bladder and urethral dose parameters. A correlation between acute GU toxicity and late GU toxicity was observed. Furthermore, a latency period was present, with GU toxicity occurring years after radiotherapy, including new onset urethral strictures occurring two years, up to seven years, after treatment. This should be taken into consideration and long follow-up is needed to account for (very) late onset genitourinary toxicity.

Strengths of our study are the carefully considered longitudinal analysis that fits our data properly and increases power by using repeated measurements. Another strength is the use of risk groups for presenting the probability of GU toxicity. Notably, these risk groups represent differences in baseline risk of GU toxicity, which is not the same as prognostic modeling and should not be interpreted as such. The unique variation in focal boost dose used and the lack of a urethral dose-constraint in treatment planning, allowed us to carry out a urethral dose–effect relation analysis for a large dose range. Although the differences in cumulative GU
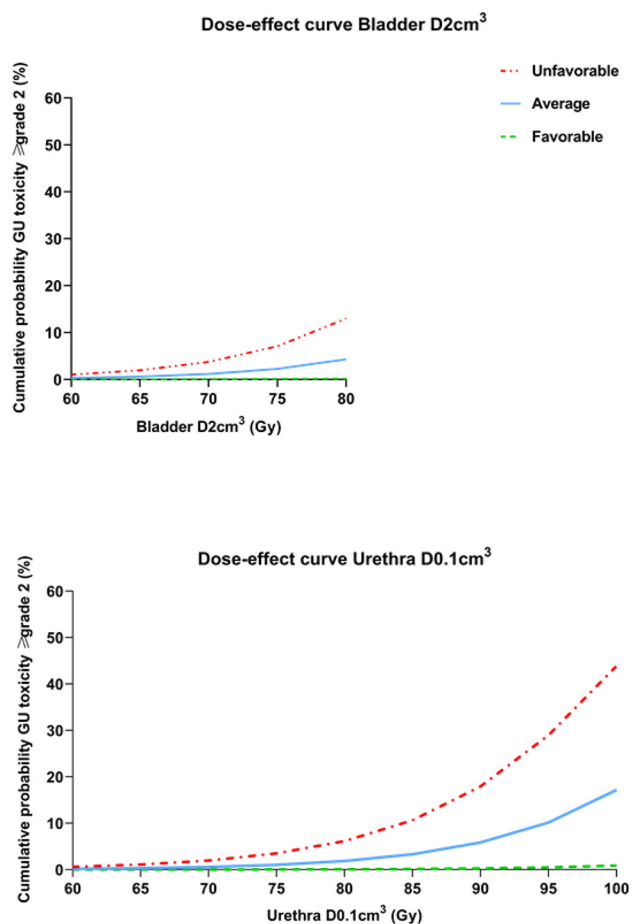
Fig. 2. Dose-toxicity curves of the average and (un)favorable estimated cumulative GU toxicity grade ≥2, related to the planned dose based on the generalized linear mixed effects models adjusted for age, T-stage, diabetes mellitus, baseline GU toxicity grade ≥1. The risk groups are based on baseline patient characteristics potentially correlated with GU toxicity. In the unfavorable risk group, all aforementioned risk factors were present. In the favorable risk group, none of the risk factors were present. A. bladder D2cm^3 (Gy) and B. urethra D0.1 cm^3 (Gy). Abbreviations: GU = genitourinary, T-stage = T refers to the size and extent of the main tumor.

toxicity between the study arms were small and not statistically significant [11], in the present analysis, using the cohort irrespective of randomization, we did observe a dose–effect relation for the bladder and urethra. While this may seem contradictory, this is explained by the observation that in the focal boost arm of the trial, a wide range was found for the dose to the urethra, with some patients receiving a standard dose close to 77 Gy, while others received a much higher dose, depending on the location of the focal boost. The number of patients with a high dose to the urethra in the focal boost arm was too small to observe a significant difference in cumulative GU toxicity. When using cumulative toxicity, the highest toxicity grade at any moment is used to calculate the toxicity rates, not taking into account repeating events of toxicity. Yet, the finding of a significant dose–effect relation for the urethra in the study cohort irrespective of randomization arm, is explained by the longitudinal approach used in the present study. When using repeated measurements, more patients in the focal boost arm had recurring GU toxicity events compared to the standard treatment arm.

Our study has a few limitations. First, the difficulty of delineating the urethra. The urethra was contoured using the T2-weighted sequence of a mpMRI scan [26]. Even though the urethra is visual-

ized better on MRI than CT, the delineation of the urethra even on MRI can be difficult and interobserver variation in contouring may exist [27]. Second, we used center specific bladder filling protocols. As all participating centers aimed for a comfortably filled bladder, we do not expect this to have influenced our findings. Third, the considerable amount of missing toxicity data is a limiting factor. A generalized linear mixed effect model with random effects to determine the dose–effect relations was used to cope with this limitation. In addition to handling both single and recurring toxicity, these models provide unbiased estimations in the presence of missing data under the missing-at-random assumption [28]. Though we have no reason to doubt this assumption, missing-at-random is essentially unverifiable. Fourth, we decided to exclude patients who previously underwent a TURP, as the TURP cavity is not comparable to the anatomical structure of the urethra.

In conclusion, dose–effect relations for both the dose to the bladder and urethra on GU toxicity were observed. For treatment planning of EBRT with a focal boost in the conventional fractionated FLAME scheme, we suggest a dose-constraint for the urethra D0.1 cm^3 of ≤80 Gy, the optimal urethral dose-constraint for hypofractionated schemes is yet to be determined. Further treatment optimization to increase the focal boost without increasing the dose to the urethra, bladder and other OAR should be a focus for future research, as we have shown that a focal boost improves oncological outcomes in the treatment of prostate cancer.

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Conflict of interest statement

All authors declare having no conflict of interest related to the content of this manuscript.

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