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Associations of dose to the urethra and long-term patient-reported outcomes after radiotherapy with EBRT and HDR brachytherapy boost for prostate cancer

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ABSTRACT

Purpose: Implications of radiation dose exposure to the urethra on urinary morbidity after prostate radiotherapy are poorly understood, especially by long-term patient-reported outcomes (PRO). Therefore, our primary objective was to investigate associations of urethral dose and long-term patient-reported urinary morbidity after external beam radiotherapy and high-dose rate brachytherapy boost for prostate cancer.

Materials and methods: We conducted a pre-registered (https://doi.org/10.17605/OSF.IO/A6DC3) cross-sectional study at a tertiary academic center including a consecutive sample of patients being at least two years after treatment. Primary outcome measurements included urinary domains of the EPIC-26 questionnaire. Their associations with predefined urethral dose levels were assessed by univariable analyses (Pearson's correlation) and by predefined multivariable analyses (multiple regression). Sample size calculation was based on a predefined multivariable model. A p-value < 0.05 was considered statistically significant.

Results: Among 277 screened patients, 113 patients were alive, eligible, consented, and provided PRO. The median time passed since radiotherapy was 4 years. Per univariable analysis, a higher near maximum point dose of the urethra ($D_U0.1cc$) was associated with worse urinary incontinence ($r = -0.32$; CI = −0.48 − -0.13; $p < 0.001$) and worse overall urinary function ($r = -0.21$; CI = −0.38 − -0.03; $p = 0.02$) of the respective EPIC-26 domains. Per predefined multivariable analysis, $D_U0.1cc$ and urinary incontinence remained significantly associated ($B = -0.005$; CI = −0.008 − -0.002; $p = 0.003$). These associations were only present, when very high $D_U0.1$ cc above 137 Gy were kept in the analysis.

Conclusions: Very high urethral near point doses appear to be associated with worse long-term patient-reported urinary morbidity after radiotherapy for prostate cancer. Urethral dose should be considered in practice and future trials to potentially minimize long-term urinary morbidity.

Trial registration: The study protocol was pre-registered prior to patient accrual on the Open Science Framework (https://doi.org/10.17605/OSF.IO/A6DC3).

1. Introduction

Patients with localized prostate cancer often show long-term survival and low disease related mortality [1]. Any treatment should therefore minimize long-term treatment related morbidity [2]. To estimate morbidity, physician-rated toxicity is commonly used despite frequent

Abbreviations: ADT, Androgen deprivation therapy; DRS, Decisional Regret Scale; EBRT, external beam radiotherapy; EQD2, equivalent doses in 2 Gy per fraction; HDR-BT, High Dose-Rate Brachytherapy; IPSS, International Prostate Symptom Score; OAR, organs at risk; PSCC, Patient Satisfaction with Cancer-related Care; SBRT, stereotactic body radiotherapy; SCQ, Self-Administered Comorbidity Questionnaire; TURP, transurethral resection of the prostate.

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underreporting of symptoms compared to standardized patient-reported outcomes of health-related Quality of Life [3–5].

Among a variety of treatment options, radiotherapy is established, effective, and well tolerated [1]. To limit acute and long-term morbidity, radiotherapy planning aims to minimize radiation exposure to healthy organs (organs at risk (OAR)). Higher radiation exposure to larger volumes of the bladder or rectum, for example, relate to increased urinary or rectal side effects [6]. Concerning the urethra, an association of radiation dose exposure and the degree of long-term morbidity, especially patient-reported, is hypothesized yet not well understood [4,7]. This association has not yet been studied in depth, potentially because standard external beam radiotherapy (EBRT) delivers a homogenous dose to the whole prostate and urethra without significant variations in urethral dose exposure. Furthermore, it is difficult to visualize the urethra on standard planning CT scans [8,9]. However, a better understanding of potential associations of urethral dose and long-term urinary morbidity is desirable. This could be used to improve radiotherapy planning and to potentially inform future studies of, for example, stereotactic body radiotherapy (SBRT) delivering an inhomogeneous dose to the prostate or for studies aiming to increase the dose to a dominant intraprostatic lesion in proximity of the urethra [10–13].

At our institution, we commonly use the "Kiel Concept" of High Dose-Rate brachytherapy (HDR-BT) as a two-fraction boost modality in combination with EBRT [14]. This HDR-BT concept deliberately delivers an inhomogeneous and U-shaped dose distribution: the whole prostate receives a lower dose (8 Gy per fraction) as compared to its peripheral zone (15 Gy per fraction) resulting in significant variations of urethral dose exposure depending on the patient's anatomy (Supplementary Fig. 1) [15]. Furthermore, the urethra is well visualized during HDR-BT using transrectal ultrasound and a foley catheter [16]. Given the variability of urethral dose exposure in this concept and the possibility to visualize the urethra during HDR-BT, prostate cancer patients treated with the "Kiel Concept" of HDR-BT boost could be ideal candidates to study the role of urethral dose exposure on long-term patient-reported morbidity [17].

Therefore, the primary aim of our protocol-based study was to investigate associations of radiation dose exposure to the urethra and long-term urinary morbidity per patient-reported outcomes. Secondary aims were to assess such associations for further organs at risk including the neck of the bladder and rectum concerning patient-reported urinary and gastrointestinal morbidity, respectively.

2. Materials and methods

2.1. Study design

We conducted a protocol-based cross-sectional study at an academic tertiary cancer center in Germany. Ethical approval was obtained from the local committee and the study protocol was pre-registered on the Open Science Framework prior to enrolment of the first patient (https://doi.org/10.17605/OSF.IO/A6DC3). Patients were eligible if they (i) had histologically confirmed prostate cancer, (ii) had EBRT + HDR-BT boost ("Kiel Concept") as primary treatment and were at least two years after radiotherapy, (iii) had no evidence of disease per Phoenix-criteria (PSA > 2 ng/ml above nadir), (iv) had no foley catheter at the time of the survey, (v) had no surgical intervention to the genitourinary tract after radiation, (vi) were able to understand and self-report questionnaires, (vii) were older than 18 years, and (viii) gave written informed consent. These eligibility criteria were chosen *a priori* in order to study our primary objective to investigate associations of radiotherapy dose to the urethra and long-term patient-reported urinary outcomes. This followed the assumption that, for example, a biochemical relapse and subsequent treatment or genitourinary surgery could confound potential associations of urethral dose and long-term patient-reported outcomes at the time of the cross-sectional evaluation.

Potentially eligible patients were contacted consecutively starting with patients being at least two years after treatment in a cross-sectional fashion up until sample size requirements were met. Recruitment ran from September 2023 until December 2023 including patients treated from September 2021 until September 2016. Participating patients provided patient-reported outcomes via post The STROBE guideline was respected for reporting the study as applicable [18].

2.2. Treatment

All patients were treated with EBRT and HDR-BT boost as primary treatment for prostate cancer. EBRT was delivered to the prostate, seminal vesicles and typically to lymph nodes in the small pelvis in 2 Gy per fraction up to a total dose of 40 to 50 Gy in 20 to 25 fractions in 5 weekly fractions. The ultrasound image-guided HDR-BT boost was delivered as one fraction at week two and one fraction at week four during the EBRT course. Per HDR-BT fraction, 8 Gy were delivered to the whole prostate gland and 15 Gy to the peripheral zone of the prostate (Supplementary Fig. 1). Of note, this unique and U-shaped HDR-BT dosing regimen results in varying doses delivered to the urethra thereby potentially allowing for dose–response analyses of dose to the urethra and long-term patient-reported outcomes as planned in this study. Androgen deprivation therapy (ADT) was administered at the discretion of the physician and patient.

2.3. Outcomes and variables

Patient-reported outcomes were collected explicitly for the purpose of this study in a cross-sectional fashion from consenting patients. Patient-reported outcome measures (PROM) included following validated questionnaires: EPIC-26, EORTC QLQ-C30, Patient Satisfaction with Cancer-related Care (PSCC), Decisional Regret Scale (DRS), and Self-Administered Comorbidity Questionnaire (SCQ) [19–23]. The EPIC-26 was the main PROM for analyses presented here. It includes five health-related Quality of Life domain summary scores relevant to patients with prostate cancer: urinary incontinence, urinary irritative/obstructive, bowel ("overall gastrointestinal function"), sexual, and hormonal. Further, it includes a single question on overall urinary function and five single-item questions on specific bowel functions (e.g. bloody stools). Higher standardized values indicate higher functioning in the respective domain or item.

Clinical and dosimetric data were extracted retrospectively from medical charts of participating patients. Predefined dose levels to organs at risk (OAR) included D_U0.1cc (dose of the most exposed absolute volume 0.1cc of the respective structure), D_U10% (dose of the most relative volume 10% of the respective structure), and D_U30% to the intraprostatic urethra (surface of the foley catheter), and D_R0.1cc, D_R1cc, and D_R2cc to the rectum. Dose to the neck of the bladder was approximated by using D_{BN}max. D_{BN}max was the maximum point dose to the surface of the most proximal intraprostatic urethral slice as defined by the surface of the foley catheter on intraoperative ultrasound at each HDR-BT fraction. Anatomical contouring of the bladder neck was judged infeasible based on available transrectal ultrasound images. These dose levels were chosen *a priori* based on published guidelines for dose constraints as well as based on results of published studies [5,24–28]. All doses to OAR were cumulative doses from the EBRT and HDR-BT boost plans combined. For the EBRT plans, we calculated OAR exposure based on the prescribed dose to the PTV given that we evaluated high dose exposures to small OAR volumes. This means that for an EBRT plan prescribed with 46 Gy in 23 fractions, we assumed a urethral or rectal EBRT dose of 46 Gy as it was infeasible to contour the urethra on planning CT scans. For HDR-BT boost plans, the urethral contour was defined as surface of the foley catheter as visualized on intraoperative endorectal ultrasound. If patients had a previous TURP and a resection cavity was evidenced on ultrasound, the resection cavity was defined as urethral contour. Urethrograms were not performed. The rectal contour was defined as rectal wall as visualized on ultrasound. The respective

OAR dose exposures were extracted from the brachytherapy planning program for each fraction. We used an Alpha/Beta-Ratio of 1.5 for the urethra and bladder neck and of 2.5 for the rectum to calculate equivalent doses in 2 Gy per fraction (EQD2) [29,30].

2.4. Statistical analysis and sample size calculation

We used descriptive statistics to display the study cohort. Univariable associations of OAR dose levels and the respective EPIC-26 domains were performed using Pearson's correlation. Furthermore, we predefined a set of covariables based on previously available data and assumed clinical relevance for a multivariable logistic regression model on the association of urethral dose levels and urinary EPIC-26 domains [4]. These covariables included d'Amico risk group, age at radiotherapy, time since radiotherapy, use of ADT at time of the survey, prostate volume at radiotherapy, history of surgery for benign prostate conditions (e.g. transurethral resection of the prostate (TURP)) prior to radiotherapy, history of smoking, history of diabetes, and use of antiobstructive prostate medication [4]. Baseline International Prostate Symptom Score (IPSS) values were planned to be included in the model but were judged infeasible due to lack of reporting prior to treatment. Assumptions of linear regression models were checked using Durbin-Watson values, variance inflation factors, actual residual vs. predicted residual plots and Q-Q plots. Sample size calculation was based on the predefined multivariable model requiring at least ten patients per variable resulting in at least 110 patients [31]. Kruskal-Wallis tests were used to compare medians of groups without normal distribution or with outliers. A two-sided p-value of < 0.05 was considered statistically significant. All analyses were performed with JASP v0.17.2.1 (JASP Team [2022], Amsterdam, the Netherlands).

3. Results

3.1. Characteristics of the study cohort

Among 277 potentially eligible patients, 31 were ineligible due the biochemical relapse, 4 due to genitourinary surgery after radiotherapy and 1 due to a foley catheter in place (Fig. 1). Eventually, 125 patients met eligibility criteria and consented to participate. Of these, 113 patients returned questionnaires and were included in analyses. Table 1 displays patient and treatment characteristics. The median age was 73 years (IQR: 8) at treatment and 79 years (IQR: 8) at the survey. The median time since radiotherapy was 4 years (IQR: 2). Eleven percent of the patients (12/113) had a history of TURP prior to radiotherapy. Concerning patient-reported outcomes, 95 % of included patients completed the urinary EPIC domains (107/113) and the gastrointestinal EPIC domains (108/113), respectively. EPIC results are shown in Supplementary Fig. 2. In brief, the mean EPIC urinary incontinence score was 86 (SD: 21). Patients reported a mean EPIC overall urinary function score of 81 (SD: 25). The mean EPIC bowel score was 93 (SD: 15). The mean EPIC sexual functioning was reported at 31 (SD: 23). Cumulative radiation dose exposures to the urethra and rectum are shown in Fig. 2. The median D0.1cc of the urethra (D_U0.1cc) amounted to 112 Gy (IQR: 13). There were two outliers with very high D_U0.1cc values (216 Gy and 147 Gy) both of whom had a history of TURP (Fig. 2). *Post hoc* interaction tests of previous TURP and D_U0.1cc did not show a statistically significant difference of median D_U0.1cc in patients who had a TURP (median: 113 Gy; IQR: 23) versus patients without TURP (median: 112 Gy; IQR: 13) as shown by a Kruskal-Wallis test ($p = 0.376$). Similarly, there was no significant difference of D_U0.1cc of included study patients ($n = 113$; median: 112 Gy; IQR: 13) versus patients who were excluded as per eligibility criteria due to lower genitourinary tract surgery after radiotherapy or a foley catheter in place at the time of the survey ($n = 5$; median: 118 Gy; IQR: 8) as per Kruskal-Wallis test ($p = 0.434$). The median maximum dose to the bladder neck was 70 Gy (IQR: 10). Next, we assessed associations of EPIC domains and radiation dose to OAR.

Table 1
Patient characteristics (n = 113). Absolute numbers are given in brackets. Numbers may not add up to 100 % due to rounding error or missing values. Comorbidity score: Higher score indicates higher number of comorbidities. Global health status/QoL: higher score indicates better health-related quality of life. Abbreviations: cc, cubic centimeter; EBRT, external beam radiation therapy; HDR-BT, high dose rate brachytherapy; QoL, quality of life; IMRT, intensity modulated radiation therapy; IQR, interquartile range; PSA, prostate specific antigen; SCQ, Self-Administered Comorbidity Questionnaire; SD, standard deviation; TURP, transurethral resection of the prostate; VMAT, volume modulated arc therapy; 3D-CRT, 3D conformal radiation therapy.

Total number of patients		100 % (113)
Patient characteristics		
Age at radiotherapy [years]		Median: 73; IQR: 8
Age at survey [years]		Median: 79; IQR: 8
Time passed since radiotherapy [years]		Median: 4; IQR: 2
Performance status	ECOG 0	90 % (102)
	ECOG 1	10 % (11)
Prostate volume at radiotherapy	cc	Median: 32.8; IQR: 14.2
D'Amico risk group	Low risk	5 % (6)
	Intermediate risk	57 % (64)
	High risk	38 % (43)
Initial PSA value [ng/mL]		Median: 9.7; IQR: 7.5
History of TURP prior to radiotherapy [yes]		11 % (12)
History of smoking [yes]		62 % (70)
Use of antiobstructive medication at survey [yes]		36 % (41)
Comorbidity score [SCQ; 0–100]		Median: 10.3, IQR: 12.8
Presence of diabetes [yes]		17 % (19)
Global health status/ QoL [EORTC QLQ-C30; 0–100]		Median: 75; IQR: 16.7
Treatment characteristics		
EBRT technique	3D-CRT	70 % (79)
	IMRT/VMAT	30 % (34)
Number of needles for HDR-BT		Median: 14; IQR: 3
History of hormone therapy [yes]		40 % (45)
Hormone therapy at survey [yes]		5 % (6)

3.2. Associations of long-term patient-reported urinary outcomes and urethral dose

To assess our primary objective, we investigated associations of long-term urinary EPIC domains (incontinence; overall urinary function; obstruction/irritation) and dose exposure to the urethra (D_U0.1cc; D_U10%; D_U30%). As per univariable Pearson's correlations shown in Fig. 3, we observed a statistically significant correlation of high near point doses to the urethra (D_U0.1cc) and worse urinary incontinence ($r = -0.32$ [95 % CI, $-0.48 - -0.13$]; $p < 0.001$) as well as worse overall urinary function ($r = -0.21$ [95 % CI, $-0.38 - -0.02$]; $p = 0.02$). Neither further dose levels of the urethra (D_U10%; D_U30%) nor obstruction/irritation showed statistically significant correlations (Fig. 3). Controlling for covariables as per predefined multivariable linear regression, the association of high near point doses to the urethra (D_U0.1cc) and worse urinary EPIC domains remained statistically significant for urinary incontinence (standardized $\beta = -0.317$ [95 % CI, $-0.008 - -0.002$]; $p = 0.003$) but not for overall urinary function (standardized $\beta = -0.153$ [95 % CI, $-0.007 - 0.001$]; $p = 0.153$) (Table 2 and Supplementary Table 1). Of note, a history of TURP prior to radiotherapy was not a statistically significant covariable in the multivariable linear regression model of D_U0.1cc and urinary incontinence (unstandardized $\beta = -0.114$ [95 % CI, $-0.248 - 0.021$]; $p = 0.097$) (Table 2). Nevertheless, we conducted a *post hoc* secondary analysis excluding both described outliers of D_U0.1cc, both of whom had a TURP, to study the impact of very high point doses to the urethra. Excluding these outliers, the statistically significant associations of D_U0.1cc and urinary EPIC domains persisted neither in the univariable analysis nor in the

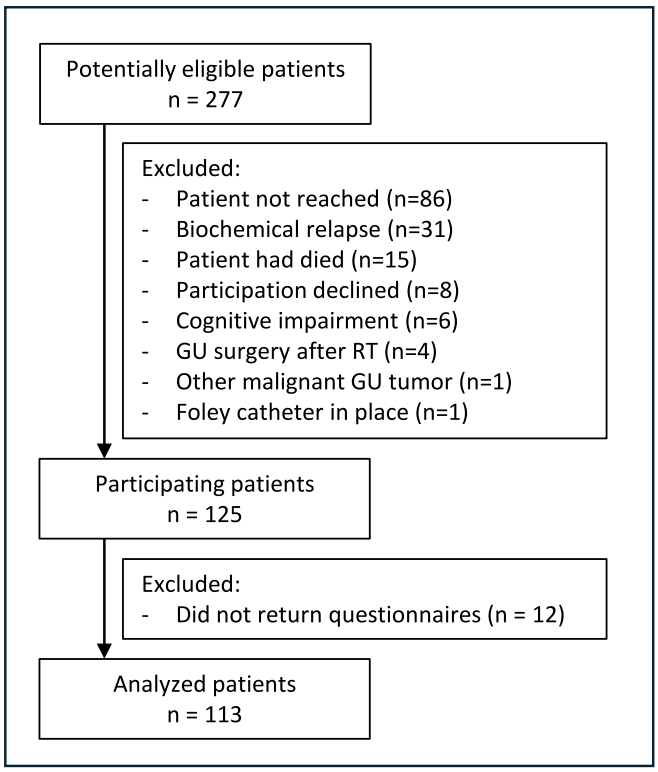

Fig. 1. Flow chart of patient enrolment. Abbreviations: GU, genitourinary; RT radiation therapy.

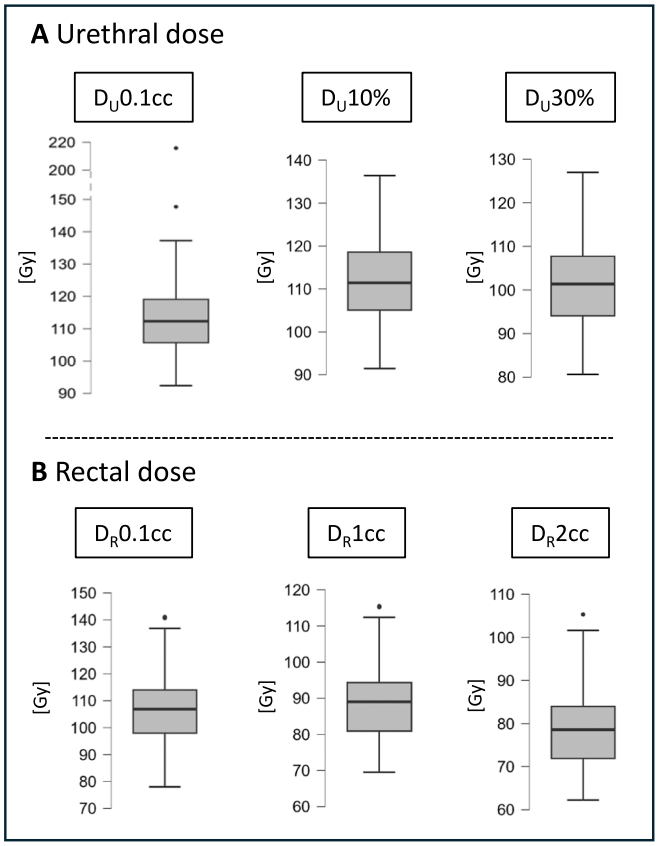

Fig. 2. Box-and-whisker-plot of **(A)** urethral dose levels (D_U 0.1 cc, D_U 10%, D_U 30%) and **(B)** rectal dose levels (D_R 0.1 cc, D_R 1cc, D_R 2cc).

multivariable analysis (Supplementary Fig. 3 and Supplementary Table 2). The maximum D_U0.1cc was 137 Gy in this *post hoc* analysis.

3.3. Associations of long-term patient-reported outcomes and dose to the bladder neck or rectum

To assess our secondary objective, we investigated associations of long-term EPIC domains and dose exposure to further OAR including the neck of the bladder and rectum. We did not observe statistically significant correlations of maximum point dose to the bladder neck (D_{BN}max) and urinary EPIC domains (Supplementary Fig. 4). Similarly, there were neither statistically significant associations of predefined dose levels to the rectum (D_R0.1cc, D_R1cc, and D_R2cc) and the "overall gastrointestinal function" domain of the EPIC questionnaire (Supplementary Fig. 5) nor of rectal dose levels and EPIC gastrointestinal subdomains (e.g. bloody stools) (Supplementary Table 3).

4. Discussion

We evaluated associations of radiation dose to OAR and patient-reported long-term morbidity at least two years after radiotherapy for prostate cancer in this predefined cross-sectional study. Overall, patients reported favorable urinary and gastrointestinal functioning. Concerning our primary objective, we found a significant correlation of very high near point doses to the urethra and patient-reported urinary incontinence. Concerning our secondary objectives, we did not find associations of radiation dose to the bladder neck or rectum for urinary or gastrointestinal patient-reported outcomes, respectively.

The result of our primary objective, the association of higher urethral dose and worse urinary incontinence, needs to be interpreted in the context of this analysis and further studies. It could be pointed out that the association of urethral dose and urinary incontinence was only present, when two outliers were kept in the analysis which might limit the generalizability of our data [32]. However, these outliers represented two patients that had a TURP prior to radiotherapy. TURP was a predefined covariable in the multiple regression model and in our view, it is therefore legitimate to assume that there is an association of very high urethral dose exposure and long-term patient-reported urinary incontinence. This assumption is in line with previous studies. First, a number of studies have reported higher grades of urinary toxicity after higher dose exposure to the urethra [26,27,33,34]. Groen and colleagues, for example, reported a subanalysis of the FLAME study which assessed the addition of a simultaneous EBRT boost to the intraprostatic dominant tumor lesion. This subanalysis found that higher near maximum point doses to the urethra (Du0.1cc) were associated with higher urinary toxicity [26]. However, these studies only relied on physician-reported toxicity instead of patient-reported outcomes as in our study despite known differences [3,5,35]. Second and most importantly, Pinkawa and colleagues have also reported on a significant association of very high doses to the urethra and patient-reported urinary incontinence outcomes after HDR-BT boost yet at shorter follow-up (median 3 years) and in a non-predefined statistical model [6,36]. Furthermore, associations of urethral dose and patient-reported urinary morbidity have been reported by other studies albeit again mostly at shorter follow-up as compared to our cohort with a median time since therapy of 4 years [5,28,37]. Morton and colleagues, for example, reported that patient-reported urinary morbidity corelated with urethral dose at a median follow-up of 2 years after hypofractionated EBRT and single fraction HDR-BT boost [5]. An open question remains the optimal threshold for urethral doses without compromising oncological outcomes. A recent review on urethra-sparing techniques in SBRT trials, for example, identified a urethral dose threshold of $D_{max} < 90$ Gy EQD2 (Alpha/Beta-Ratio 3) above which acute and late urinary physician-reported toxicity increased [38]. This appears to be a lower threshold than what we have observed in our data. However, the review authors used an Alpha/Beta-Ratio of 3 whereas we used an Alpha/Beta-Ratio of

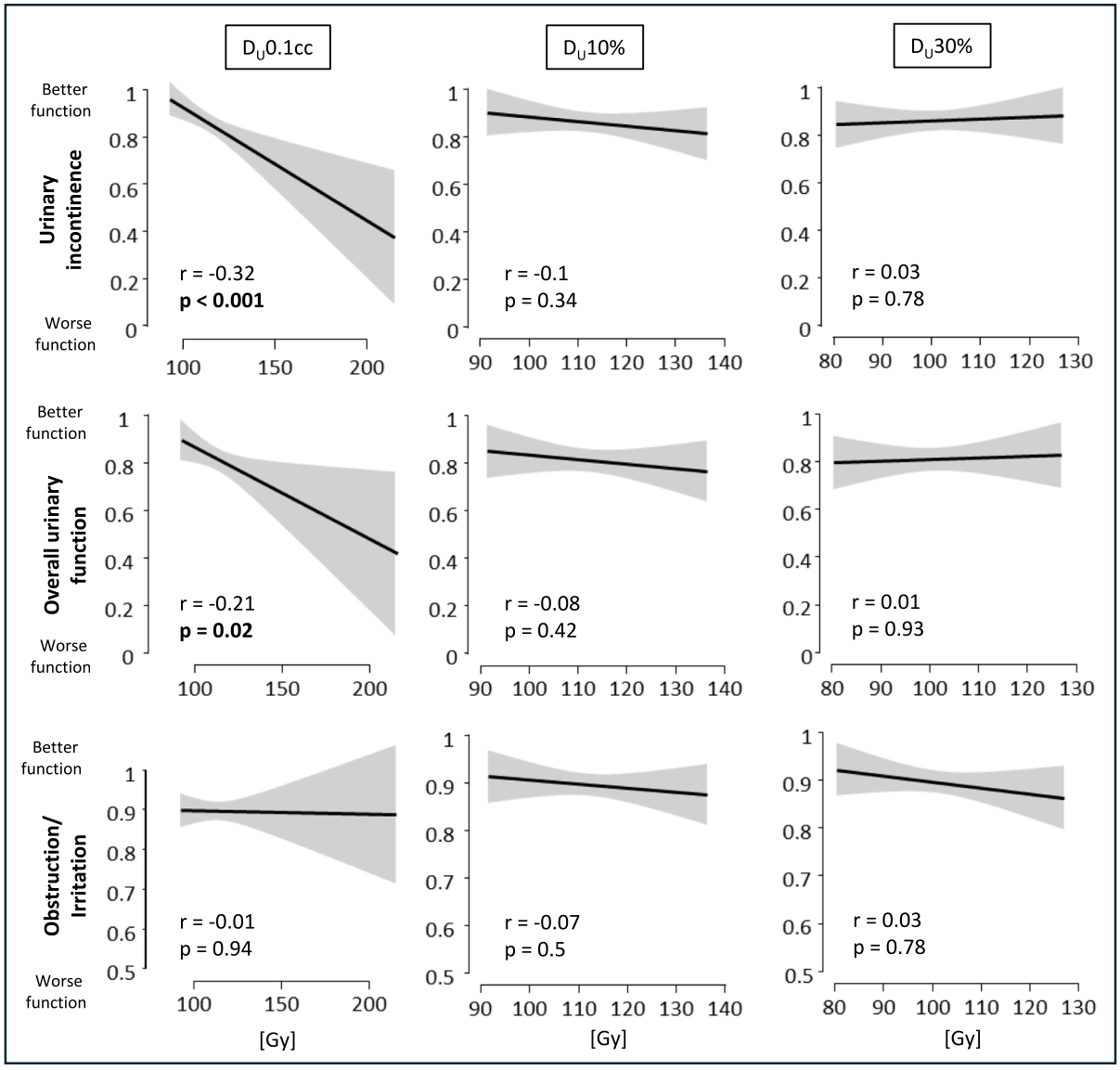

Fig. 3. Pearson correlation analyses of patient reported EPIC urinary incontinence, obstruction/ irritation and overall genitourinary function and urethral dose levels (D_U 0.1 cc, D_U 10%, D_U 30%). Higher values in the EPIC domains indicate better function. P-values $\leq$ 0.05 are displayed in bold font.

Table 2
Multivariable linear regression of patient reported EPIC urinary incontinence and the impact of urethral dose (n = 107). Statistically significant p-values < 0.05 are displayed in bold font. Abbreviations: ADT, androgen deprivation therapy; CI, confidence interval; D_U 0.1 cc, dose of the most exposed absolute volume 0.1 cc of the urethra; PSA, prostate specific antigen; RT, radiation therapy; TURP, transurethral resection of the prostate.

Dependent Variable: EPIC urinary incontinence						
Independent Variables	**Unstandardized B**	**Standardized[a] β**	**t**	**p**	**Lower 95 % CI**	**Upper 95 % CI**
D_U0.1cc	**−0.005**	**−0.317**	−3.031	**0.003**	−0.008	−0.002
Prostate volume	0	0.017	0.166	0.869	−0.004	0.005
History of TURP	−0.114		−1.677	0.097	−0.248	0.021
D'Amico risk group	0.036	0.099	0.962	0.338	−0.039	0.111
Age at RT	−0.005	−0.142	−1.471	0.145	−0.011	0.002
Time passed since RT	0	−0.034	−0.336	0.738	−0.003	0.002
ADT at survey	−0.022		−0.244	0.808	−0.2	0.156
History of smoking	−0.029		−0.702	0.484	−0.112	0.054
Antiobstructive medication	−0.029		−0.661	0.510	−0.115	0.058
Presence of diabetes	−0.097		−1.706	0.091	−0.210	0.016

[a]Standardized coefficients can only be computed for continuous predictors.

1.5 to calculate cumulative doses [30]. Based on a typical 5 fraction SBRT course, the urethral dose threshold reported in the review of $D_{max} < 90$ Gy EQD2 for an Alpha/Beta-Ratio 3 would amount to a $D_{max} < 111$ Gy EQD2 for an Alpha/Beta-Ratio of 1.5 approaching our data. Moreover, the review focused on physician-reported outcomes whereas our data rely on patient-reported outcomes. Taken together, we assume an association of very high urethral dose exposure and worse long-term urinary function such as urinary incontinence based on our data and supporting literature. In the near future, recent developments including Artificial Intelligence-based autosegmentation of OAR and automated radiotherapy planning may allow to better respect urethral dose in radiotherapy planning across radiotherapy modalities [2,9,39,40].

Although dose exposure to the neck of the bladder has been discussed as a potential contributor to urinary morbidity after radiotherapy, we were unable to detect such associations in our cohort [4]. A reason for this could have been difficulties in delineating the bladder neck in our cohort which is why we used the most proximal slice of the urethra as surrogate for the bladder neck. Other studies of HDR-BT, however, share our negative finding concerning dose to the bladder neck and urinary morbidity [41,42].

Another interesting finding of our study was that patients reported modest outcomes for sexual functioning with a mean EPIC sexual functioning score of 31. In comparison, the recently published PACE-A trial of SBRT versus surgery reported a median score of 63 two years after SBRT and 18 after surgery [43]. Potential reasons for this discrepancy of our cohort compared to the SBRT cohort are the older population (median age at survey 79 years in our study vs. 65 years at randomization in the PACE-A trial) and a significant proportion of patients had a history of hormone therapy (40 % vs. 0 %).

Limitations of our study include, first, various time points of cross-sectional patient-reported outcome measurement after a minimum cut-off of two years post treatment. This was accounted for by including the variable “time since treatment” in the predefined multivariable model. Second, we had no baseline patient-reported outcomes available. Third, we excluded patients that potentially had major radiation associated morbidity after radiotherapy by reporting a history of genitourinary surgery or a present foley catheter. Yet only five patients fell into this category (Fig. 1) and patient selection was predefined in the protocol to best study our primary objective. Fourth, direct OAR dose accumulation might result in “worst case scenarios” as near maximum doses do not necessarily fall into the same anatomical region at each HDR-BT fraction. Although initial approaches of deformable dose accumulation have been reported, they may again introduce uncertainties and direct addition of doses appears reasonable as reported in gynecological brachytherapy [44]. Finally, albeit the “Kiel Concept” of EBRT and HDR-BT allowed for an investigation of our primary objective due to the inherent inhomogeneity of urethral dose, our results should be replicated for other radiation modalities such as EBRT alone or SBRT.

5. Conclusions

In conclusion, our predefined cross-sectional study showed an association of high radiation doses to the urethra and worse long-term patient-reported outcomes after EBRT and HDR-BT boost for prostate cancer. This association was driven by very high point doses to the urethra and was not present when the maximum urethral near point dose was limited to 137 Gy (EQD2; Alpha/Beta-Ratio 1.5). Very high urethral radiation doses should be avoided during radiotherapy planning to potentially limit long-term urinary morbidity.

Declarations

Ethics approval: Ethical approval was obtained from the local committee at the Medical Faculty of the Kiel University prior to enrolment of the first patient (D 505/23).

Funding: There was no external funding for this study.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: AF has received honoraria from Merck Sharp &Dohme.

DK has received honoraria from Astra Zeneca, best practice onkologie, ESO, ESMO, Gilead, med update, Merck Sharp & Dohme, Novartis, onkowissen, and Pfizer, as well as research funding from Stiftung Deutsche Krebshilfe and Merck KGaA.

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OW received honoraria and travel grants from Brainlab AG and novocure AG.

SR has received honoraria from BMS, Merck, MSD and Novartis and has equity interest in Rocketlane Medical Ventures GmbH.

All other authors declare no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctro.2025.100918.

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