INTERNATIONAL JOURNAL OF
RADIATION ONCOLOGY • BIOLOGY • PHYSICS
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CLINICAL INVESTIGATION

# Urethra-Sparing Prostate Cancer Stereotactic Body Radiation Therapy: Sexual Function and Radiation Dose to the Penile Bulb, the Crura, and the Internal Pudendal Arteries From a Randomized Phase 2 Trial

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Received Oct 17, 2023; Accepted for publication Dec 23, 2023

**Purpose:** Erectile dysfunction (ED) is a common side effect after prostate cancer stereotactic body radiation therapy (SBRT). We aimed to assess the correlation between the dose to the penile bulb (PB), internal pudendal arteries (IPA), and crura with the development of ED after ultrahypofractionation as part of a phase 2 clinical trial of urethra-sparing prostate SBRT.

**Methods and Materials:** Among the 170 patients with localized prostate cancer from 9 centers included in the trial, 90 men with Common Terminology Criteria for Adverse Events version 4.03 grade 0 to 1 ED (ED−) at baseline treated with 36.25 Gy in 5 fractions were selected for the present analysis. Doses delivered to the PB, crura, and IPA were analyzed and correlated with grade 2 to 3 ED (ED+) development. The effect on quality of life, assessed by the European Organisation for Research and Treatment of Cancer (EORTC QLQ-PR25) questionnaire, was reported.

**Results:** After a median follow-up of 6.5 years, 43% (n = 39) of the patients developed ED+, and 57% (n = 51) remained ED−. The dose delivered to the crura was significantly higher in ED+ patients than in ED− patients (7.7 vs 3.6 Gy [$P$ = .014] for the $D_{mean}$ and 18.5 vs 7.2 Gy [$P$ = .015] for the $D_{2\%}$, respectively). No statistically significant difference between ED+ and ED−

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Vérane Achard and Thomas Zilli made equal contributions to this study.

Disclosures: The authors declare no conflicts of interest. This study was funded by a grant from Fundació Privada Cellex and Brainlab. The granting bodies were not involved in data collection or analysis.

Data Sharing Statement: Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijrobp.2023.12.037.

*Acknowledgments*—The authors acknowledge Laurence Zulianello, PhD, Isabelle Semac, PhD, Michel Rouzaud, MSc, Angele Marzin, MSc, Maud Jaccard, MSc, Geneva University Hospital, Geneva, Switzerland.



https://doi.org/10.1016/j.ijrobp.2023.12.037

patients was observed for the dose delivered to the PB and IPA. The median ED+-free survival was worse in patients receiving a crura $D_{mean} \geq 4.7$ versus $< 4.7$ Gy (51.5% vs 71.7%, $P = .005$) and a crura $D_{2\%} > 12$ versus $\leq 12$ Gy (54.9% vs 68.9%, $P = .015$). No ED+-free survival differences were observed for doses delivered to the PB and IPA. Decline in EORTC QLQ-PR25 sexual functioning was significantly more pronounced in patients with higher doses to the crura.

**Conclusions:** By keeping a $D_{mean}$ and $D_{2\%}$ to crura below 4.7 and 12 Gy, respectively, the risk of developing ED+ after prostate SBRT may be significantly reduced. 

## Introduction

Patients with localized prostate cancer at low- or intermediate-risk have an overall good prognosis, whether they underwent a radical treatment or active surveillance, with 15 years cancer-specific survival being above 95%.[1] However radical treatments, unlike active surveillance, can be associated with treatment-related long-term side effects that may affect patients' quality of life (QoL).[2] To guide patients' treatment decisions, knowledge of treatment-related toxicity is essential.

Erectile dysfunction (ED) is commonly reported after radiation therapy (RT), with occurrence rates in randomized trials varying from 30% to 40%.[3] It directly affects patients' satisfaction with their treatment,[4,5] and sexual dysfunction is a factor highly associated with regret after prostate cancer treatment.[6] Sparing of critical erectile structures is thought to play a role in maintenance of functional erections despite contradictory results in studies investigating the correlation between the radiation dose delivered to these structures and the occurrence of ED after curative RT.[7]

The last decade has been characterized by a shift toward use of ultrahypofractionation and stereotactic body RT (SBRT) for patients with localized prostate cancer after the results of several landmark studies. The HYPO-RT-PC, a phase 3 randomized controlled trial (RCT) comparing ultrahypofractionation versus conventional fractionation, demonstrated the noninferiority of a 7-fraction schedule over an 8-week treatment at the price of a transiently higher acute urinary toxicity.[8] This toxicity increase was not shown in the PACE B trial, the second phase 3 RCT comparing standard fractionation to a 5-fraction SBRT, with no significant differences between the 2 arms in terms of acute and occurrence of grade $\geq 2$ gastrointestinal, genitourinary, and sexual toxicity at 24 months.[9,10] Last but not least, a large meta-analysis of 38 prospective studies and more than 6,000 patients revealed favorable oncological outcomes, toxicity profiles, and patient-reported outcomes (PRO) after curative SBRT.[11] Following these results, SBRT has been implemented more and more in clinical routine to treat patients with localized intermediate-risk prostate cancer, and knowledge of its side effects, notably its sexual-related toxicity, is therefore crucial.

We recently reported the 5-year results of a randomized phase 2 trial (the Novalis Circle trial, NCT01764646) investigating the effect of overall treatment time and urethra-sparing in patients with localized prostate cancer treated with a 5-fraction SBRT schedule.[12] The long-term results and outcome of our SBRT schedule with a 10% dose reduction to the urethra were similar between patients treated every other day and patients treated once a week, with a minimal effect on long-term toxicity and QoL. Nevertheless, further optimization of SBRT treatments is in continuous development, and a better understanding of the effect of SBRT treatments on erectile function is becoming increasingly important. Using the data set of patients randomized in the prospective Novalis Circle trial of urethra-sparing SBRT we analyzed in the present study the relationship between the delivered doses to the penile base structures and the occurrence of ED, with the goal to define specific SBRT dose constraints to be used for erectile function sparing.

## Methods and Materials

Among the 170 patients with prostate cancer with a histologically confirmed adenocarcinoma of the prostate of Gleason score $\leq 7$, tumor stage cT1c-3a N0 M0 on conventional imaging, and an estimated risk of nodal involvement $\leq 20\%$[13] who were included in the multicenter Novalis Circle randomized phase 2 trial from August 2012 to December 2015, 90 patients without ED (ED−) at baseline (absence of ED or decrease in frequency or rigidity of erections with no indication for erectile intervention; National Cancer Institute Common Terminology Criteria for Adverse Events [CTCAE] version 4.03 scale grade 0-1) were included in the present analysis.

Patients were randomized (1:1) to receive a 5-fraction SBRT treatment delivered every other day (arm A; n = 44, 48.9%) or once a week (arm B; n = 49, 51.1%). The prostate with or without inclusion of the seminal vesicles[14] with an isotropic expansion of 5 mm (3-mm posteriorly) received a dose of 36.25 Gy in 5 fractions of 7.25 Gy with a dose reduction to the urethra planning-risk volume to 32.5 Gy in 5 fractions of 6.5 Gy. All patients were implanted with fiducial markers, and in 7 out of the 9 centers an endorectal balloon was used to limit intrafractional motion (QLRAD). SBRT was delivered with either an intensity modulated RT (n = 46) or volumetric modulated arc therapy (n = 44) technique using a Novalis linear accelerator (LINAC) (BrainLab AG and Varian Medical System) integrating a 6-degrees-of-freedom couch and an ExacTrac repositioning system.[15] Mandatory organs at risk were the rectum, the urinary

bladder, the urethra, and the femoral heads. No specific dose-volume objectives were applied to the erectile structures. Treatment planning dose-volume constraints have been previously reported.[16] Androgen deprivation therapy (ADT) with 6 months of luteinizing hormone-releasing hormone agonists (2 months neoadjuvant and 4 months concomitant and adjuvant) was administered in 20 patients (22.2%) presenting with 2 or more unfavorable clinical or histopathologic characteristics. The study was approved by the local ethical committee of every center (NCT01764646), and all patients provided written informed consent according to Internal Council for Harmonisation/Good Clinical Practice regulations.

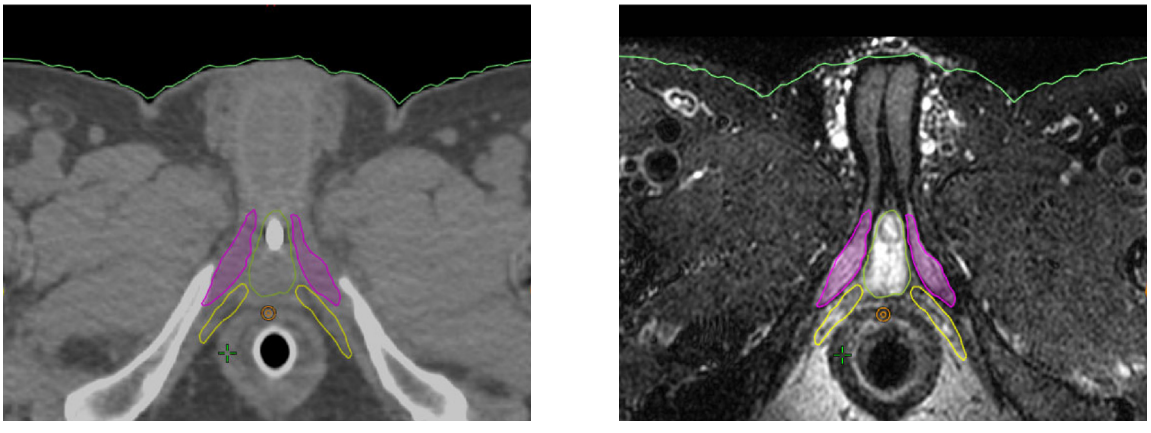
Follow-up (FU) consisted of weekly controls during SBRT, at week 12 since the start of SBRT, at months 6, 12, and 18 since randomization, and yearly thereafter (FU at years 2.5, 3.5, 4.5, 5.5, etc). The CTCAE version 4.03 scale was used by a physician to grade toxicity, with acute toxicity considered as any adverse event occurring during the first 3 months. QoL was evaluated at the same endpoints using the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 and QLQ-PR25 questionnaires.[17] Erectile dysfunction (ED+) was defined as the occurrence of CTCAE version 4.03 grade 2 to 3 (decrease in erectile function with intervention indicated or not helpful). For the present analysis, we focused on sexual activity and sexual functioning EORTC QLQ-PR25 subscales.[18]

For the study proposal, for all 90 patients, penile base structures (proximal crura and internal pudendal arteries [IPA]) were retrospectively delineated by 2 experienced radiation oncologists (G.L. and M.B.) on the treatment planning computed tomography (CT) scans with the help of multiparametric magnetic resonance imaging (MRI; 71%) using the treatment planning system (Eclipse 13.6; Varian; Fig. 1). As per protocol, the penile bulb (PB) was previously delineated by each center using a dedicated MRI as a critical structure for treatment plan optimization. The PB was defined according to Radiation Therapy Oncology Group recommendations as the bulbous portion of the corpus spongiosum near the divergence of the corpora cavernosa.[19] Proximal crura were defined as the divergent proximal portions of the corpora cavernosa, originating under the ischiopubic rami as 2 separate structures and merging under the pubic arch.[19,20] The IPA were defined according to Mc Laughlin et al.[21,22] Mean dose ($D_{mean}$) and near maximum dose ($D_{2\%}$) were analyzed for each penile base structure.

Mean, SD, median, and IQR for quantitative and percentages for qualitative variables including QoL scores were performed for data description. A minimally clinically meaningful change in QoL scores was defined using the Osoba et al[23] definition (ie, mean changes in scores ≈5-10, ≈10-20, and >20, for little, moderate, and significant changes between the baseline and the last FU, respectively). The Kaplan-Meier method was used to determine toxicity-free survival rates and medians, using the log-rank test for comparisons. Cox proportional hazard regression models were used for univariate and multivariate analyses to assess the effect of different variables on ED development. Dosimetric threshold predictors of ED were defined as the median value of each penile base structure's dose-volume descriptors. The Student or Wilcoxon Mann-Whitney test was used to compare variables depending on the normality of the distribution for quantitative parameters, with $\chi^2$ or Fisher tests for quantitative parameters. All statistical analyses were performed with the statistical package SAS 9.4.

## Results

In the analyzed patient population, the median age was 69 years (range, 51-81). Ninety-one percent (n = 82) of the patients presented with a World Health Organization performance status of 0, and the remaining 8 patients were graded as 1. Patients mostly had intermediate-risk prostate cancer (n = 56, 62%), and low-risk and high-risk disease were found in 27 and 7 patients, respectively. The median



(a) (b)

**Fig. 1.** Penile bulb (green), internal pudendal arteries (yellow), and crura (purple) visualization on planification contouring computed tomography scanner (a) and associated magnetic resonance imaging (b).

prostate-specific antigen level at diagnosis was 6.7 ng/mL (range, 2.5-20).

The average $D_{mean}$ and $D_{2\%}$ for PB were 9.8 ± 7.9 Gy and 21.5 ± 13.6 Gy, respectively. The corresponding doses were 13.9 ± 3.9 Gy and 24.1 ± 7.8 Gy for IPA and 8.0 ± 7.1 Gy and 15.7 ± 12.4 Gy for the crura. As illustrated in Figure 2, there was a strong correlation between doses delivered to the crura and the onset of ED, with $D_{mean}$ and $D_{2\%}$ of crura being 6.3 versus 10.3 Gy ($P$ = .014) and 12.6 versus 19.7 Gy ($P$ = .015) for ED− versus ED+ patients, respectively. On the other hand, there was no correlation between the dose delivered to the IPA and PB and the development of ED. $D_{mean}$ and $D_{2\%}$ of IPA were 13.7 versus 14.3 Gy ($P$ = .423) and 23.6 versus 24.8 Gy ($P$ = .536) for ED− versus ED+ patients, respectively, and $D_{mean}$ and $D_{2\%}$ of PB were 9.1 versus 10.7 Gy ($P$ = .213) and 20.4 versus 23 Gy ($P$ = .395) for ED− versus ED+ patients, respectively.

After a median FU of 6.5 years, 43.3% (n = 39) of patients developed ED+, and 56.7% (n = 51) of patients remained with a grade 0 to 1 ED (ED−). The median ED+-free

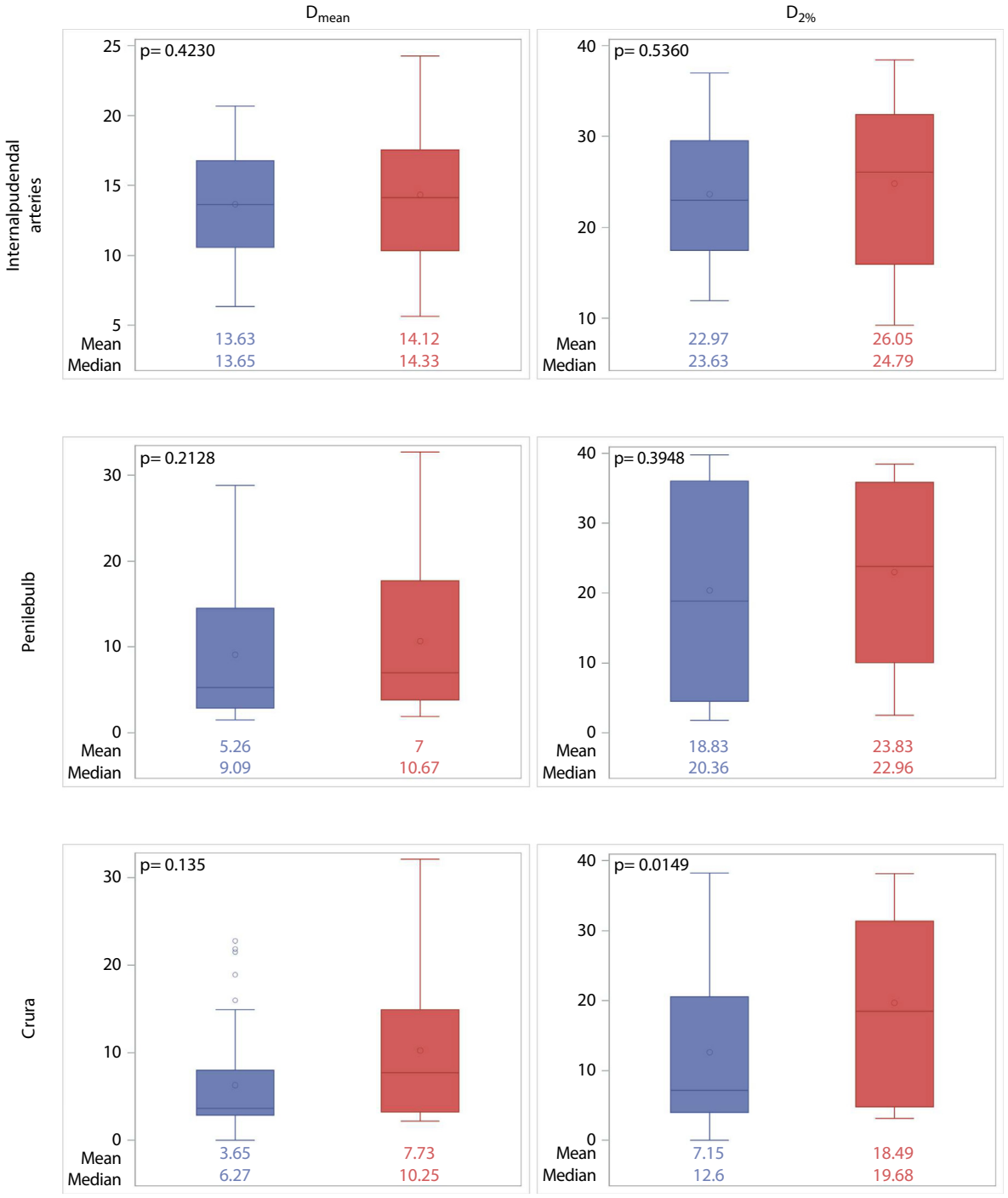



**Fig. 2.** Boxplots summarizing the effect of penile structure dosimetry on deterioration of erectile function, ED- in blue and ED+ in red.

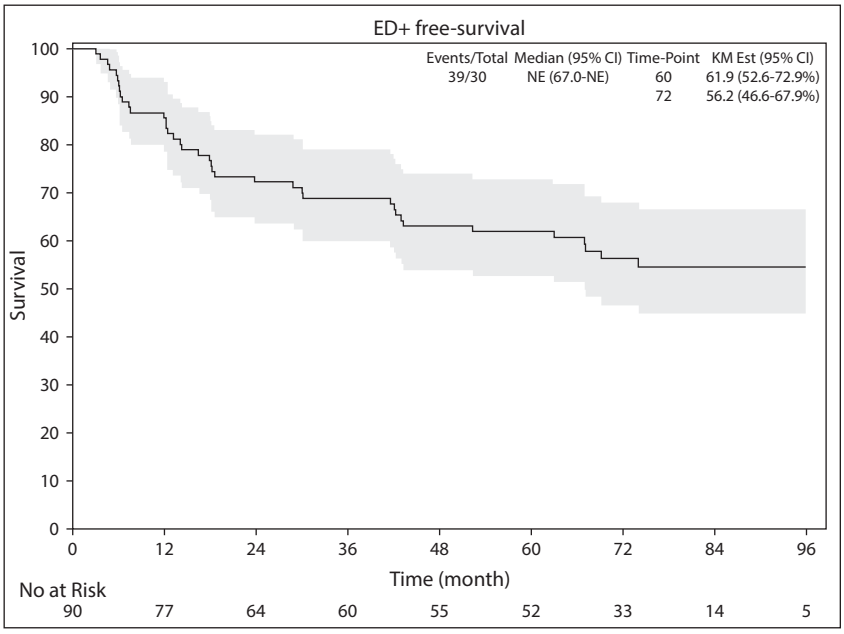



**Fig. 3.** Time to deterioration of erectile function.

survival was not reached (Fig. 3), with an estimated ED +-free survival at 6 years of 56.2% (95% CI, 46.6%-67.9%). On univariate analysis, crura $D_{mean}$ and $D_{2\%}$ were the only statistically significant predictors for development of ED+ (Table 1), and age, SBRT treatment technique, and use of ADT were not. As illustrated in Figure 4, the median ED +-free survival was worse in patients receiving a crura $D_{mean}$ > 4.7 versus ≤ 4.7 Gy (51.5% vs 71.7%, $P$ = .0058) and a crura $D_{2\%}$ > 12 versus ≤ 12 Gy (54.9% vs 68.9%, $P$ = .0156). On the other hand, no differences in ED+-free survival rates were observed for doses delivered to the PB and IPA. This predictive value for ED+ development was confirmed in the multivariate Cox model after adjusting for age, use of ADT, and SBRT technique (Table 1).

**Table 1 Factors affecting erectile function over time (univariate and multivariate Cox regressions)**

| | Variable | Reference | HR | 95% CI | *P* value |
|---|---|---|---|---|---|
| Univariate Cox regression | Age (y) | >69.5 vs ≤69.5 | 1.14 | [0.61-2.13] | .689 |
| | ADT | Yes vs no | 1.37 | [0.65-2.88] | .412 |
| | RT technique | VMAT vs IMRT | 0.75 | [0.39-1.41] | .367 |
| | Pudendal $D_{mean}$ (median, Gy) | >13.9 vs ≤13.9 | 1.11 | [0.59-2.08] | .75 |
| | Pudendal $D_{2\%}$ (median, Gy) | >23.4 vs ≤23.4 | 1.09 | [0.58-2.05] | .783 |
| | Penile bulb $D_{mean}$ (median, Gy) | >6.6 vs ≤6.6 | 1.18 | [0.63-2.21] | .614 |
| | Penile bulb $D_{2\%}$ (median, Gy) | >21.4 vs ≤21.4 | 1.35 | [0.72-2.54] | .355 |
| | Crura $D_{mean}$ (median, Gy) | >4.7 vs ≤4.7 | 2.45 | [1.27-4.72] | .008 |
| | Crura $D_{2\%}$ (median, Gy) | >12 vs ≤12 | 2.2 | [1.14-4.24] | .018 |
| Multivariate Cox regression model 1 | Age | >69.5 vs ≤69.5 | 1.31 | [0.68-2.52] | .420 |
| | ADT | Yes vs no | 1.54 | [0.72-3.27] | .263 |
| | RT technique | VMAT vs IMRT | 0.80 | [0.41-1.58] | .520 |
| | Crura $D_{mean}$ (median, Gy) | >4.7 vs ≤4.7 | 2.50 | [1.27-4.93] | .008 |
| Multivariate Cox regression model 2 | Age (y) | >69.5 vs ≤69.5 | 1.28 | [0.67-2.46] | .455 |
| | ADT | Yes vs no | 1.56 | [0.73-3.32] | .250 |
| | RT technique | VMAT vs IMRT | 0.82 | [0.42-1.64] | .582 |
| | Crura $D_{2\%}$ (median, Gy) | >12 vs ≤12 | 2.26 | [1.13-4.5] | .020 |

*Abbreviations:* ADT = androgen deprivation therapy; $D_{2\%}$ = dose to 2% of the volume; $D_{mean}$ = mean dose; HR = hazard ratio; IMRT = intensity modulated RT; RT = radiation therapy; VMAT = volumetric modulated arc therapy.

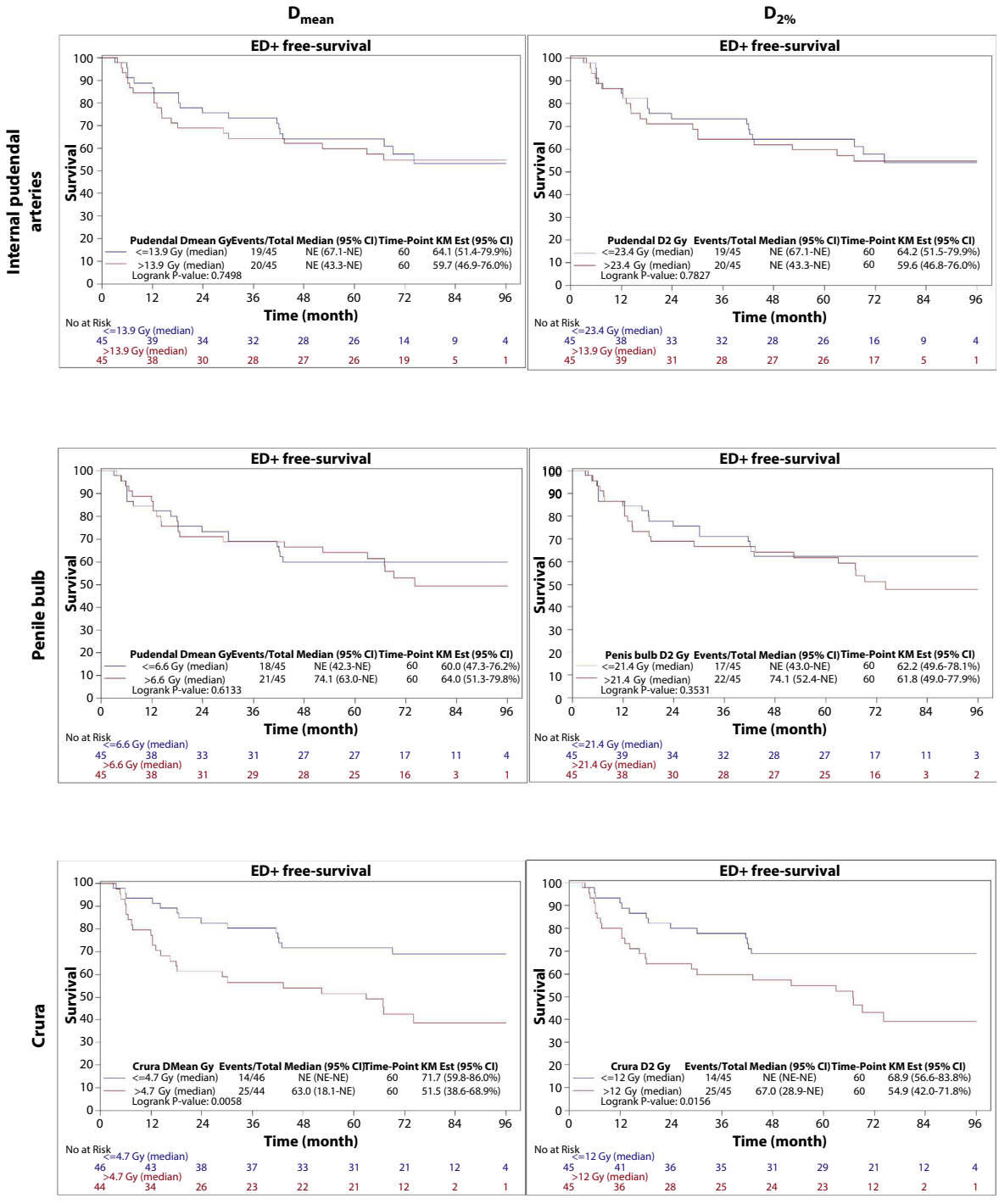



**Fig. 4.** Effect of the dose received by the penile base structures on the time to deterioration of erectile function.

As far as health-related QoL domains are concerned, the percentage of patients completing the EORTC QLQ-PR25 questionnaire was 93% (n = 84) at 2.5 years and 74% (n = 67) at 5.5 years. No correlation between the doses received by penile base structures and the minimally clinically important change difference was observed in terms of sexual activity as evaluated by the EORTC QLQ-PR25 questionnaires. On the other hand, changes in sexual functioning scores were significantly correlated with the dose delivered to the crura (Table 2). Sexual functioning as measured by EORTC QLQ-PR25 was worse over FU time in patients with higher $D_{mean}$ and $D_{2\%}$ to penile base structures, with the exception of IPA (Fig. E1). No dose-volume descriptor was a predictor of a decline in sexual activity over time (Fig. E2).

## Discussion

In a recent systematic review evaluating the incidence of radiation-induced ED with modern techniques including

**Table 2 Relation between doses (Gy) delivered to the penile base structures and minimally clinically important changes for sexual activity and sexual functioning**

| | Variable | No change ≤5 | Little change 5-10 | Moderate change 10-20 | Significant change >20 | *P* value |
|---|---|---|---|---|---|---|
| Sexual activity | Pudendal $D_{mean}$ | | | | | .6596 |
| | ≤13.9 (median, Gy) | 3 (6.7%) | 5 (11.1%) | 31 (68.9%) | 6 (13.3%) | |
| | >13.9 (median, Gy) | 6 (13.3%) | 3 (6.7%) | 29 (64.4%) | 7 (15.6%) | |
| | Pudendal $D_{2\%}$ | | | | | .7162 |
| | ≤23.4 (median, Gy) | 4 (8.9%) | 5 (11.1%) | 31 (68.9%) | 5 (11.1%) | |
| | >23.4 (median, Gy) | 5 (11.1%) | 3 (6.7%) | 29 (64.4%) | 8 (17.8%) | |
| | Penile bulb $D_{mean}$ | | | | | .9322 |
| | ≤6.6 (median, Gy) | 4 (8.9%) | 5 (11.1%) | 30 (66.7%) | 6 (13.3%) | |
| | >6.6 (median, Gy) | 5 (11.1%) | 3 (6.7%) | 30 (66.7%) | 7 (15.6%) | |
| | Penis bulb $D_{2\%}$ | | | | | .757 |
| | ≤21.4 (median, Gy) | 4 (8.9%) | 3 (6.7%) | 30 (66.7%) | 8 (17.8%) | |
| | >21.4 (median, Gy) | 5 (11.1%) | 5 (11.1%) | 30 (66.7%) | 5 (11.1%) | |
| | Crura $D_{mean}$ | | | | | 1 |
| | ≤4.7 (median, Gy) | 5 (10.9%) | 4 (8.7%) | 30 (65.2%) | 7 (15.2%) | |
| | >4.7 (median, Gy) | 4 (9.1%) | 4 (9.1%) | 30 (68.2%) | 6 (13.6%) | |
| | Crura $D_{2\%}$ | | | | | .9322 |
| | ≤12 (median, Gy) | 5 (11.1%) | 3 (6.7%) | 30 (66.7%) | 7 (15.6%) | |
| | >12 (median, Gy) | 4 (8.9%) | 5 (11.1%) | 30 (66.7%) | 6 (13.3%) | |
| Sexual functioning | Pudendal $D_{mean}$ | | | | | .2166 |
| | ≤13.9 (median, Gy) | 7 (17.1%) | 10 (24.4%) | 20 (48.8%) | 4 (9.8%) | |
| | >13.9 (median, Gy) | 3 (7.7%) | 8 (20.5%) | 18 (46.2%) | 10 (25.6%) | |
| | Pudendal $D_{2\%}$ | | | | | .0897 |
| | ≤23.4 (median, Gy) | 8 (20.0%) | 8 (20.0%) | 20 (50.0%) | 4 (10.0%) | |
| | >23.4 (median, Gy) | 2 (5.0%) | 10 (25.0%) | 18 (45.0%) | 10 (25.0%) | |
| | Penile bulb $D_{mean}$ | | | | | .5907 |
| | ≤6.6 (median, Gy) | 7 (16.7%) | 10 (23.8%) | 19 (45.2%) | 6 (14.3%) | |
| | >6.6 (median, Gy) | 3 (7.9%) | 8 (21.1%) | 19 (50.0%) | 8 (21.1%) | |
| | Penis bulb $D_{2\%}$ | | | | | .3961 |
| | ≤21.4 (median, Gy) | 7 (16.7%) | 9 (21.4%) | 21 (50.0%) | 5 (11.9%) | |
| | >21.4 (median, Gy) | 3 (7.9%) | 9 (23.7%) | 17 (44.7%) | 9 (23.7%) | |
| | Crura $D_{mean}$ | | | | | .0201 |
| | ≤4.7 (median, Gy) | 8 (18.2%) | 6 (13.6%) | 25 (56.8%) | 5 (11.4%) | |
| | >4.7 (median, Gy) | 2 (5.6%) | 12 (33.3%) | 13 (36.1%) | 9 (25.0%) | |
| | Crura $D_{2\%}$ | | | | | .0085 |
| | ≤12 (median, Gy) | 8 (18.6%) | 5 (11.6%) | 25 (58.1%) | 5 (11.6%) | |
| | >12 (median, Gy) | 2 (5.4%) | 13 (35.1%) | 13 (35.1%) | 9 (24.3%) | |

*Abbreviations:* $D_{2\%}$ = dose to 2% of the volume; $D_{mean}$ = mean dose.

SBRT, a direct correlation between the incidence of ED and increasing radiation dose to the prostate was found.[24] This speaks for the existence of critical prostate-adjacent structures responsible for erection and sensitive to radiation dose. In the present work, using a unique data set of patients with localized prostate cancer treated with curative SBRT in a multicenter phase 2 trial, we have been able to show for the first time, to the best of our knowledge, a relationship

between the dose delivered to the crura and the occurrence of sexual dysfunction with external beam RT. This dose-effect relationship was observed both in terms of clinician-reported outcomes and PROs.

Two recent publications investigated in a post hoc analysis of 2 phase 3 RCTs the relationship between the doses delivered to the PB and the occurrence of ED in patients treated with different hypofractionated regimens. Murray et al[25] published a study on 233 patients without severe ED at baseline treated within the CHHiP trial with moderate hypofractionated RT. They showed that PB dose appears predictive of post-RT ED with a calculated threshold mean dose of 20 Gy (equivalent dose in 2-Gy/fractionwith $\alpha/\beta = 3$ Gy ($EQD2_3$)). In line with this finding, Rasmusson et al[26] proposed a PB $D_{mean} < 20$ Gy and $D_{2\%} < 50$ Gy ($EQD2_3$) to increase potency preservation after demonstrating the existence of a relationship between delivered dose to PB and ED in initially potent patients treated within the HYPO-RT-PC trial. In our study, the median $D_{mean}$ and $D_{2\%}$ delivered to PB were 6.6 and 21.4 Gy ($EQD2_3$ 31.2 Gy), respectively. The fact that the mean and near maximum doses are way below the 20 and 50 Gy threshold doses proposed by the previous studies may explain why we failed in our series to demonstrate a correlation between PB dose and ED. In line with our findings, Wiegner and King[27] reported on a prospective phase 2 trial including 32 patients with low-risk prostate cancer treated with 36.25 Gy in 5 fractions using a robotic-based LINAC. They observed that the dose to the PB was not associated with ED after a median FU of 35.5 months. In this trial, the median dose to the PB was 13.06 Gy (±3.4 Gy), corresponding to a median $EQD2_3$ of 17.02 Gy (±8.07 Gy), below the recommended 20 Gy threshold.

More recently, vessel-sparing RT techniques, in analogy with nerve-sparing radical prostatectomy, have been proposed to improve erectile function preservation. Spratt et al[28] studied the erectile function preservation outcome when limiting the dose to IPA to 36 Gy in a single-arm phase 2 trial enrolling 135 patients with prostate cancer treated with conventional fractionated RT ± low-dose rate brachytherapy boost. For 93% of patients, the treatment plans were able to meet this dose constraint with a median $D_{90\%}$ and $D_{10\%}$ for the IPA of 13 and 37 Gy, respectively. At 5 years, almost 67% of the 135 men enrolled in the study remained without ED (International Index of Erectile Function 5 score ≥16). In our study, the median $D_{2\%}$ to IPA was 23.4 Gy, corresponding to 36 Gy in $EQD2_3$, and the ED +-free survival at 5 years was 61.9%, very close to the 67% observed in the study by Spratt et al. Despite all the inherent limitations associated with this kind of comparison, it is interesting to observe comparable outcome results when using similar dose thresholds for the IPA. In our study, the median $D_{2\%}$ was comparable to the median $D_{10\%}$ observed in the Spratt et al study, indicating that even without specifying any dose constraints to the IPA, we were able to considerably limit the doses delivered to the IPA. Use of high conformational RT techniques may explain these findings, together with the use of an endorectal balloon in 7 out of 9 participating centers. Indeed, as previously demonstrated, the use of an endorectal balloon significantly reduced the dose on IPA by increasing the median distance between the IPA and the prostate target volume.[29] For the moment, to our knowledge, there is no published dose constraint threshold for IPA in the setting of SBRT.[25,26] From our findings combined with Spratt et al data, it may be assumed that if such a threshold exists, it is a near-maximum dose below 36 Gy in $EQD2_3$ (or 24 Gy for a 5 fraction SBRT schedule).

Although we were unable to find a correlation between the dose delivered to PB or IPA and the development of sexual dysfunction, we have been able to show the existence of a strong correlation with the dose delivered to the crura and the development of sexual dysfunction, whether it is patient- or physician-assessed. The crura are formed by the posterior one-fourth of the corpora cavernosa, 2 expandable erectile tissues responsible for erection. If in their anterior three-fourths the 2 corpora cavernosa lie in intimate apposition with one another, in the posterior part they are diverging to constitute the crura.[30] Few studies of RT (brachytherapy or 3-dimensional conformal normofractionated external beam RT) have investigated the correlation between the dose to the crura and ED, with overall negative results.[31-35] Only 1 study of brachytherapy reported a correlation between the dose to the crura and the development of ED. In this study, Merrick et al used a patient-administered validated QoL questionnaire to investigate the onset of ED in a population of 128 sexually potent patients treated with curative brachytherapy.[32] The 3-year actuarial rate of potency preservation was 50.5%, and in multivariate analysis, the preimplant International Index of Erectile Function score and the dose to proximal crura were strong predictors of brachytherapy-related ED. The $D_{95\%}$ to the crura was 22.1 versus 14.6 Gy in patients with or without ED, respectively. The much higher dose to the crura delivered in other studies can explain the negative correlation results observed.

The fact that dose to crura was a predictor of RT-induced ED deserves some consideration. Indeed, most studies have focused attention on the potential link between dose to PB and ED. However, it has been suggested by Mulhall et al[36,37] that radiation doses to the crura may be more important than those to the PB because the corpora cavernosa are true erectile tissues whereas the corpus spongiosum is believed to play little role in the maintenance of erectile rigidity. PB being a structure easily recognized on axial CT—contrary to the crura, which is more difficult to delineate because of an ambiguity in defining the borders of the crura from the rest of the corpora cavernosa[32,34]—may explain why correlation between PB and ED has been more extensively studied. Moreover, the PB could serve as a surrogate for other structures immediately lateral and inferior to it, such as the crura. By differentiating the PB and the crura and by keeping the dose to the PB and the IPAs very low, the crura could be identified as a fairly radiosensitive structure that may play an important role in the onset of ED. Besides, it is worth mentioning that in their study of vessel-sparing RT, Spratt et al also used dose constraints on the proximal corpora

cavernosa (ie, the crura). The median $D_{90\%}$ and $D_{10\%}$ on this structure were 5 and 20 Gy, respectively, which can also account for the high rate of sexual preservation witnessed in this study, in addition to the IPA-sparing technique.

Two prospective trials are ongoing to evaluate the role of neurovascular-sparing SBRT. The first study, POTEN-C (NCT03525262), is a phase 2 trial in which 120 potent patients with low- to intermediate-risk prostate cancer eligible for SBRT without ADT were randomized between standard SBRT to 40 to 45 Gy/5 fractions or neurovascular-sparing SBRT (sparing of neurovascular bundles + IPA + PB + crura).[38] These critical organs at risk are delineated on mpMRI with patients treated on a conventional LINAC. The primary endpoint is 2-year patient-reported potency, measured by the Expanded Prostate Cancer Index Composite questionnaire. The second study, ERECT (NCT04861194), is a single-arm phase 2 trial using magnetic resonance−guided online adaptative RT (MRgRT) to assess the effect of neurovascular-sparing SBRT. In this trial, 70 potent patients will receive neurovascular-sparing MRgRT in 5 fractions of 7.25 Gy, with the primary endpoint being erectile function at 3 years after treatment. In an attempt to assess the planning feasibility of neurovascular-sparing MRgRT for localized prostate cancer, the group behind the ERECT trial published a preliminary study in which they compared for 20 patients 2 treatment plans, a neurovascular-sparing plan and a standard clinical pretreatment plan.[39] They found that dose to the neurovascular bundles, the IPA, and corpora cavernosa was significantly lower in the neurovascular-sparing plans than in the standard plans with no statistically different dose for the PB. Interestingly, in the neurovascular-sparing plans, they obtained a median dose of 11.9 Gy for the IPA, 4.7 Gy for the crura, and 7.9 Gy for the PB. These numbers are very close to the median dose obtained in our study for the corresponding structures: 13.9 Gy for the IPA, 4.7 Gy for the crura, and 6.6 Gy for the PB. This speaks in favor of a sufficient and safe sparing of neurovascular structures without adaptative MR guidance, at least for the structures assessed in this study, which are the IPA, the crura, and the PB (we chose not to delineate neurovascular bundles because of paucity of data on the subject and subsequent lack of evidence on the clinical effect of sparing neurovascular bundles during RT treatment planning).

Finally, on multivariate analysis, we were unable to find any statistically significant correlation between the occurrence of ED and age at baseline or ADT use, which might seem surprising at first. Considering the use of short-term ADT and a median estimated time to testosterone recovery of 1.5 years,[40] it is possible that the effect of ADT on ED was mitigated in our study by the median FU of 6.5 years, which is longer than the period of androgen suppression. As for age, it is a well-known factor associated with ED.[41] However, the small number of persons in our cohort may explain why we failed to demonstrate an association between age and ED.

There are some limitations to our study. First, this is a post hoc analysis of a randomized clinical trial of SBRT, with all the inherent limitations of such type of analysis. Second, in our trial, comorbidities at baseline were not recorded and neither was the use of phosphodiesterase inhibitors, although the toxicity scores intrinsically integrate this information. Third, in 29% of the cases, the pudendal arteries and the crura were delineated on the planning CT without the fusion with an MRI, which may have led to under/overestimation of the actual delivered dose to these penile base structures. However, the prospective nature of this trial, the long FU, the multiple assessments, and measurement of ED integrating QoL evaluations reinforce our conclusions.

## Conclusion

With modern RT techniques and without specifying any dose constraints to penile base structures, the dose delivered to these structures with prostate SBRT was very low. Dose to the crura ($D_{mean}$ and $D_{2\%}$) was correlated with the development of ED and sexual dysfunction as assessed by both physician-reported outcomes and PROs. A $D_{mean}$ to the crura below 4.7 Gy and a $D_{2\%}$ below 12 Gy can be recommended as new dose constraints to optimize SBRT treatments in an attempt to further reduce the risk of ED in patients with localized prostate cancer.

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