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Original Article

ONE SHOT - single shot radiotherapy for localized prostate cancer: 18-month results of a single arm, multicenter phase I/II trial

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ABSTRACT

Purpose: To assess in a prospective, multicenter, single-arm phase I/II study the early safety and efficacy profile of single fraction urethra-sparing stereotactic body radiotherapy (SBRT) for men with localized prostate cancer.
Material and methods: Patients with low- and intermediate-risk localized prostate cancer without significant tumor in the transitional zone were recruited. A single-fraction of 19 Gy was delivered to the prostate, with 17 Gy dose-reduction to the urethra. Intrafraction motion was monitored using intraprostatic electromagnetic transponders with intra-fraction correction of displacements exceeding 3 mm. Genitourinary (GU), gastrointestinal (GI), and sexual toxicity during the first 18 months were evaluated using the CTCAE v4.0 grading scale. Quality of life was assessed using the International Prostate Symptom Score, the Expanded Prostate Cancer Index composite 26 score, and the International Index of Erectile Function score.
Results: Among the 45 patients recruited in 5 centers between 2017 and 2022, 43 received the single fraction without protocol deviations, and 34 had a minimal follow-up of 18 months. The worst GU toxicity was observed at day-5 after SBRT (42.5 % and 20 % with grade 1 and 2, respectively), returning to baseline at week-12 and month-6 (<3% with grade 2), with a 12 % grade 2 flare at month 18. Gl toxicity was mild in the acute phase, with no grade $\geq$ 2 events (12 % grade 1 at month 6). Grade-3 proctitis was observed in one patient at month 12, with $<$ 3 % grade 2 toxicity at month 18. Mean GU and GI bother scores showed a decline at day 5, a complete recovery at month 6, and a flare between month 12 and 18. Mean PSA dropped from 6.2 ng/ml to 1.2 ng/ml at month 18 and 0.7 ng/ml at month 24. After a median follow-up time of 26 months, 3 biochemical failures (7 %) were observed at month 17, 21 and 30.
Conclusions: In this multicenter phase I/II trial, we demonstrated that a 19 Gy single-fraction urethra-sparing SBRT is feasible and associated with an acceptable toxicity rate, mostly returning to the baseline at week-12 and with a symptoms flare between months 12 and 18. Longer follow-up is needed to assess the potential long-term adverse effects and the disease control efficacy.

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Introduction

Total dose and dose per fraction play an important role in optimizing the curative treatment of prostate cancer with external beam radiotherapy (EBRT). In the last decade, based on radiobiological modeling showing a low α/β ratio (i.e., ~ 1.5 Gy) for prostate cancer cells [1], moderate hypofractionated EBRT (i.e., dose per fraction 2.5 Gy to 4 Gy) has largely been adopted in the clinical practice with the attempt to potentially increase the tumor cell killing effect with relatively less toxicity on the surrounding late responding normal tissues. Several authors have reported their experience with moderate hypofractionation for prostate cancer confirming the equivalence in terms of disease control and tolerance compared to standard fractionated treatments [2,3].

Biomathematical models using large patient data sets have focused mainly on RT schedules using less than 4 Gy per fraction [1,4]. It deserves to be acknowledged that the linear quadratic (LQ) model may not be accurate of cell survival and isoeffects with doses per fraction above 4 Gy. Indeed, the predictions of the LQ model at very high dose/fraction (extreme hypofractionation) may be somehow "ambivalent", either overestimated (less reoxygenation and less repair of sublethal damage thus, a lower value for "β") or underestimated (increased indirect cell-death secondary to intravascular endothelial damage) [5,6]. With these considerations in mind, clinical research on extreme hypofractionation started some 20 years ago when stereotactic body radiotherapy (SBRT) technology appeared as a treatment option against localized prostate cancer competing with high-dose rate brachytherapy (HDR-BT) [7]. Indeed, results on extreme hypofractionation with SBRT have been reported during the last few years mainly for low- and intermediate-risk patients. Most frequently, 5 fractions of 7—8 Gy have been delivered for a total equivalent dose to the tumor of approximately 90 Gy in 2 Gy/fraction (LQ model) and a success rate of > 95 %, 5-year biochemical relapse-free survival (bRFS) rates [8–11].

Investigating the role of a single high-dose SBRT fraction for treating prostate cancer is undoubtfully an interesting research question, already explored with promising results in other disease sites like bone metastases, lung cancer, and renal cell carcinoma. Such type of effort has already been attempted with HDR-BT with somehow disappointing results in terms of long-term disease control [7,12,13]. To address the role of single fraction SBRT in prostate cancer, a phase I/II prospective, multicenter, single-arm study, the ONE-SHOT trial, was designed more than 5 years ago to evaluate the efficacy and safety of a monotherapy treatment with 19 Gy to the whole gland with urethra sparing (17 Gy) and real-time electromagnetic image guided RT (IGRT) tracking for localized prostate cancer [14].

In a previous report we demonstrated promising results in terms of acute toxicity on the first 6 patients included in the phase I segment of the trial [15]. In addition, we showed that the dosimetric impact of intrafraction prostate motion was minimal regarding target coverage using real-time electromagnetic tracking combined with beam gating [16]. In the present report, we present the preliminary results on the whole patient population after 18-months follow-up.

Materials and methods

This multicenter study was approved by the Ethics committee of the Geneva University Hospital (2017–01236) and was registered on clinicaltrials.gov (NCT03294889). Three Swiss, two Italian, and one US radiation oncology departments participated in the study. The protocol details of the present study (*i.e.*, endpoints, patient eligibility, exclusion criteria, dose prescription, dose constraints, and quality assurance) were reported exhaustively in 2018 [14]. Briefly, disease characteristics were as follows: low- or intermediate-risk localized prostate cancer (cT1c-2c N0 M0; ISUP grade group 1–2; PSA 15 ng/ml; multiparametric (mp) MRI-based prostate volume up to 70 cc; absence of significance tumor in the transitional zone and no extracapsular extension on mpMRI. Additional inclusion criteria were age between 18 and 85 years, WHO performance status 0–1, and International Prostate Symptoms Score (IPSS) < 10 (alpha blocker allowed). Exclusion criteria included prior pelvic RT, previous surgery for prostate cancer, previous or ongoing androgen deprivation therapy, hip prosthesis, and/or transurethral resection < 12 weeks before registration.

All participating centers shared the same SBRT delivery technique (i.e., volumetric modulated arc therapy, VMAT) with megavoltage 6–10 MV beams using a flattening filter-free (FFF) modality from a *TrueBeam*® (*Varian Medical Systems, Palo Alto, CA*). In addition, all participating centers used *Calypso*® (*Varian Medical Systems, Palo Alto, CA*) electromagnetic transponders (beacons) implanted into the prostate at least one week before simulation and treatment planning for real-time IGRT. The *Calypso*® system aimed to locate and continuously track target location. In addition, image verification was done with Linac-embarked CBCT before, in the middle, and at the end of every treatment. The proposed treatment verification schedule used a threshold limit for Calypso® of ± 3 mm with geometric check limits set to 2 mm (geometrical residual) and rotations of 10° (default values). The availability of VMAT and of *Calypso*® were both major conditions for radiation oncology departments to be eligible to take part in the study.

The definition of volumes and the dose reporting were in accordance with the *ICRU* (*International Commission on Radiation Units and Measurements*) *report 83*. The Clinical Tumor Volume (CTV) was delineated through co-registration with multiparametric MRI as the prostate +/− the proximal 2/3 of the seminal vesicles (SV) based on the risk of SV involvement as determined by the Roach score using a cutoff threshold of 15 %. The planning target volume (PTV) was defined as the CTV plus 5 mm margins in all directions except for a 3 mm margin posteriorly towards the rectal wall. The urethra PRV was defined on CT images by contouring a 12 French Foley catheter with a 2 mm isotropic rim expansion. All organs at risk (OARs) were contoured according to RTOG guidelines [17] and included the bladder and the rectal walls (both defined as a 5-mm internal margin created from the external surface), the penile bulb, and the proximal femurs. The dose variation in the planning target volume (PTV) was assessed by the near-minimum dose (D98%) and near-maximum dose (D2%).

Centralized radiation therapy quality assurance (RTQA) was an important asset of this multicenter trial. Target and OARs volumes, as well as treatment plans were submitted electronically for pretreatment assessment. Patients were treated only after validation and approval. The urinary catheter was inserted before irradiation for urethra-sparing purposes and to help to ensure a consistent and reproducible bladder volume.

The main objective of the phase I trial was to determine if a single fraction SBRT, with a dose of 19 Gy, is safe and well tolerated by assessing the incidence of Grade ≥ 3 acute adverse events (AE) during the first 3 months in a "3 + 3" cohort-base. The main objective of the phase II trial was to determine if the single 19 Gy fraction is an effective treatment option by assessing bRFS (from time of inclusion until biochemical progression according to the *Phoenix* consensus recommendation) at 3 years in 39 additional patients (45 patients total). Primary and secondary endpoints to be addressed were progression-free survival, prostate-cancer specific survival, acute and late toxicity (CTCAEv4.03, GU and GI), and quality of life (QoL): Expanded Prostate Cancer Index Composite (EPIC-26), the IPSS, and the International Index of Erectile Function (IIEF-5). Patients were seen at day-5 after SBRT, at weeks 6 and 12, every 6 months for 2 years post treatment, and yearly up to 5 years of follow-up. Clinical updates and physical exams were conducted recording any acute and/or late adverse event (AE) and sequential PSA measurements. IPSS, IIEF-5, and QoL (EPIC-26 questionnaire) assessments were also performed. Data description was performed using the mean, standard deviation, median, and interquartile range (IQR) for quantitative variables and percentages for qualitative ones. A minimally clinically meaningful change in QoL scores was defined using the definition by Osoba *et al.* [18] (*i.e.*, mean changes in scores %5–10, %10–20, and > 20, for "little," "moderate," and

"significant" changes between the baseline and the last follow-up, respectively). Radiological investigations including MRI, bone scan, choline-PET, and/or PSMA-PET were recommended in case of disease progression, either biochemical or clinical.

Sample size was determined assuming a 3-yrs bRFS of 96 % based on the 5 fx SBRT series (equivalent dose similar to the single shot 19 Gy schedule) [8] and one series of 19 Gy HDR-BT monotherapy [19]. Assuming these hypotheses and an expected drop-out rate of 10 %, 45 patients (including the 6 included in the phase I study) are needed in the phase II, to evaluate the 3-yrs bRFS with a lower one-sided confidence interval of 97.5 % and a width of the interval of 0.06 (upper bound = 90 %). Efficacy analyses have been performed on an intention to treat basis (i.e., involving those patients following the major inclusion criteria and repeated one per protocol set).

Median survival time and its 95 % bilateral confidence intervals were determined using the *Kaplan Meier* method. Survival rates were assessed at 1, 2, 3, and 5 years. Univariate and multivariate *Cox* regression models were fit to assess the effect of relevant baseline clinical and pathologic features on outcome. Hazard ratios (HR) with their 95 % confidence intervals were calculated. Median follow-up was estimated using the reverse *Kaplan Meier* method. QoL scores (EPIC, IPSS, IIEF-5) were described at each clinical surveillance follow-up time by the mean, standard deviation, median, and range. Domain scores were calculated in accordance with the relevant scoring manual. Mixt models were used to characterize changes in QoL across time and considered for confounding clinical and pathologic factors. All statistical analysis were performed with *SAS 9.4*.

Results

Forty-five patients with localized prostate cancer were recruited and included in the study between August 2017 and February 2022 in four of the five recruiting centers. Table 1 provides a summary of patients' and disease characteristics. Among the 45 patients included in the trial, 43 were retained for the present analysis and 34 had a minimal follow-up of 18 months. The 43 analyzed patients received the planned treatment, though two stepped down (one refused on treatment planning day; the second dropout happened after the beacons' implant). Most of the patients presented with intermediate-risk favorable or unfavorable disease (41 % and 33 %, respectively), while 26 % presented with low-risk disease. All treatment plans fulfilled the dose objectives as per protocol after a prospective RTQA assessment (Suppl. Table 1).

Table 1
Patient and tumors characteristics ($n = 43$).

Characteristics	(n = 43)
Age (years)	
Median (range)	72 (60–82)
WHO performance status	
0	41 (95 %)
1	2 (5 %)
PSA at diagnosis (ng/mL)	
Median (range)	6.2 (2–11.9)
cT-stage ($n = 42$)	
T1c	25 (60 %)
T2a	11 (26 %)
T2b	3 (7 %)
T2c	3 (7 %)
Biopsy ISUP group	
1	14 (33 %)
2	29 (67 %)
NCCN risk classes ($n = 42$)	
Low	11 (26 %)
Intermediate-favorable	17 (41 %)
Intermediate-unfavorable	14 (33 %)
TURP ($n = 41$)	
Yes	5 (12 %)
No	36 (88 %)
Alfa-lytic use	
Yes	9 (20 %)
No	33 (80 %)
Prostate CTV, median in cc (range)	61.0 (26.2—112.4)
Prostate PTV, median in cc (range)	113.5 (55.9—186.7)
Urethral PRV, median in cc (range)	4.7 (2.2—33.7)

Abbreviations: PSA = prostate-specific antigen; ISUP = International Society of Urological Pathology; NCCN = National Comprehensive Cancer Network; TURP = transurethral resection of the prostate; CTV = clinical target volume; PTV = planning target volume; PRV = planning risk volume.

The worst GU toxicity was observed at day-5 after SBRT (42.5 % and 20 % of grade 1 and 2, respectively) returning to baseline at week-12 and month-6 (<3% grade 2) but there was a 12 % grade 2 flare at month 18. Cystitis, urgency and pollakiuria (grades 1 and 2) were the most observed side effects. Gl toxicity was mild in the acute phase (i.e., 12 % grade 1 at month 6) with no grade ≥ 2 events. Late grade 2 toxicity was observed at month 18 in < 3 % of the cases. Grade-3 proctitis with rectal bleeding was observed at month 12 in only one patient but subsided by month 18. Grade 2 or higher erectile dysfunction increased from 21.4 % at baseline to 38.2 % at month 18 (Fig. 1 and Suppl. Table 2).

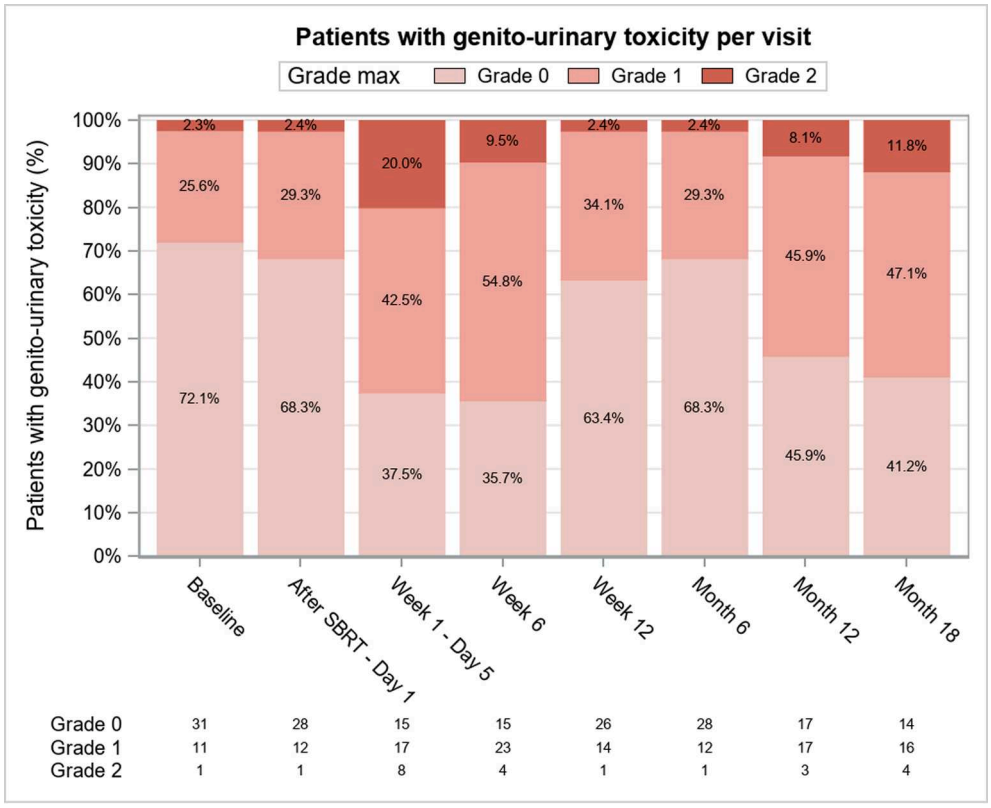
Quality of life bother scores were overall well aligned with the physician-reported outcomes. The median IPSS score increased from 6 at baseline to 12 at day 5 after SBRT, including a 17.1 % of patients with severe symptoms (20–35 score) at this first timepoint. After returning to baseline at week 12 and month 6, a new flare was observed at month 18 (median score 10, with 64.5 % of the patients presenting moderate and severe symptoms) (Suppl. Fig. 1). Mean GU and GI EPIC-26 bother scores showed a decline at day-5, a complete recovery at month-6, and a new flare between month 12 and 18, while a constant decline was observed for the sexual domains (Fig. 2 and Suppl. Fig. 2). IIEF-5 scores showed an increase in the rate of patients with severe erectile function (ED) from 10.8 % at baseline to 28.6 % at month 18, while the corresponding rates of patients with normal erectile function or moderate ED declined from 32.4 % at baseline to 17.8 % at month 18 (Suppl. Fig. 3). Overall, a significant minimally clinically important changes in EPIC GU and sexual scores was observed in less than 20 % of the patients. The impact in GI bother scores was minimal (Fig. 3).

Mean PSA values dropped from 6.8 ng/ml to 1.2 ng/ml at month 18 and 0.7 ng/ml at month 24 after SBRT. A transitory rise of the mean PSA value up to 12.8 ng/ml at day-5 after SBRT completion was observed (Fig. 4). After a median follow-up time of 26 months (24–36 months, 95 % CI), 3 biochemical failures (7 %) were observed at month 17, 21, and 30 in 3 patients, all with intermediate-risk disease (2 intermediate favorable and 1 unfavorable). One patient died at month 16 from a stroke.

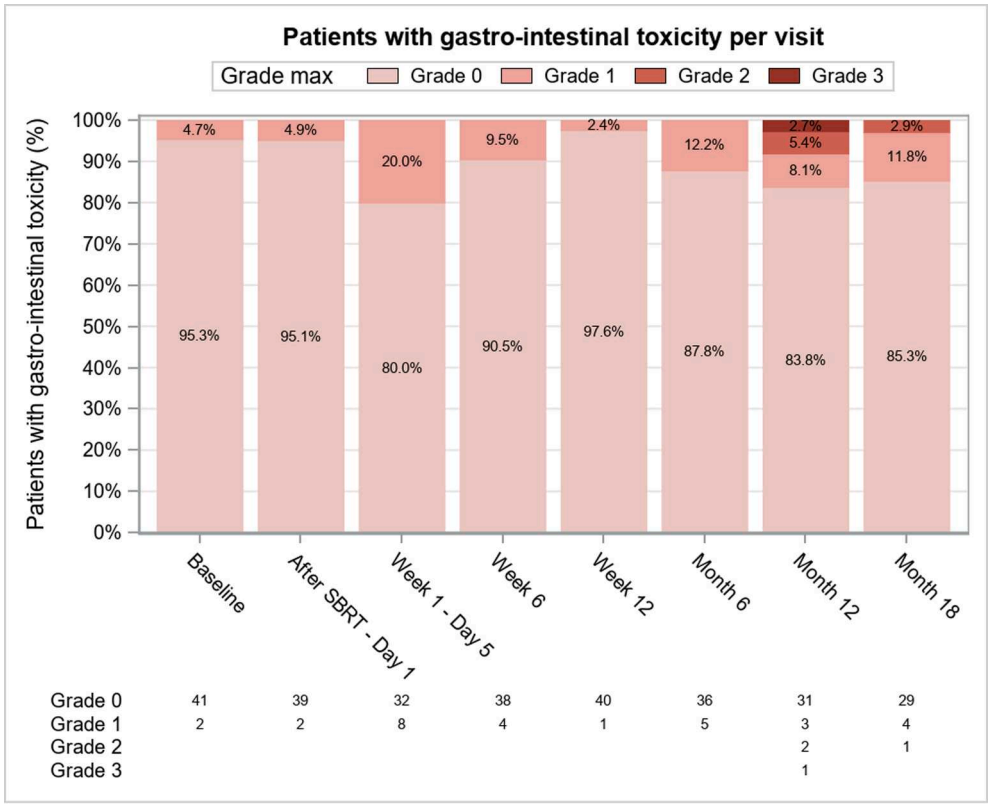
Discussion

After a median follow-up period of 26 months, we have been able to assess in patients with localized prostate cancer treated with a single fraction SBRT the tolerance and patient's self-reported QoL (IPSS, EPIC-26, and IIEF-5 questionnaires) timeline from baseline to day 5, week 6, week 12, month 6, month 12, and month 18 after treatment. The most striking observation has been the two-phase GU toxicity flare, a first one during the first week and a second one between month 12 and 18 post-treatment, mostly consisting of a mild grade 1 or 2 GU and GI toxicity.

Single fraction experience with EBRT techniques is scant. Indeed, one of the few existing reports on this matter is the 2021 publication of Greco *et al.*, [20]. They presented the outcome of a group of 15 patients treated with a single fraction of 24 Gy as part of a two-arm phase-II trial with the second arm deemed to deliver a dose of 45 Gy in 5 fractions also in 15 patients. The 15 patients treated with the single shot were planned with the goal to reduce the dose to the urethra by a 20 % (i.e., 20 Gy) using an endorectal ballon to reduce intrafraction motion. After a median interval of 48 months follow-up, they observed, as we did, a similar two-phase flare of GU toxicity (*i.e.*, days/week and 12–18 months after irradiation), though, unlike our experience, the higher dose to the

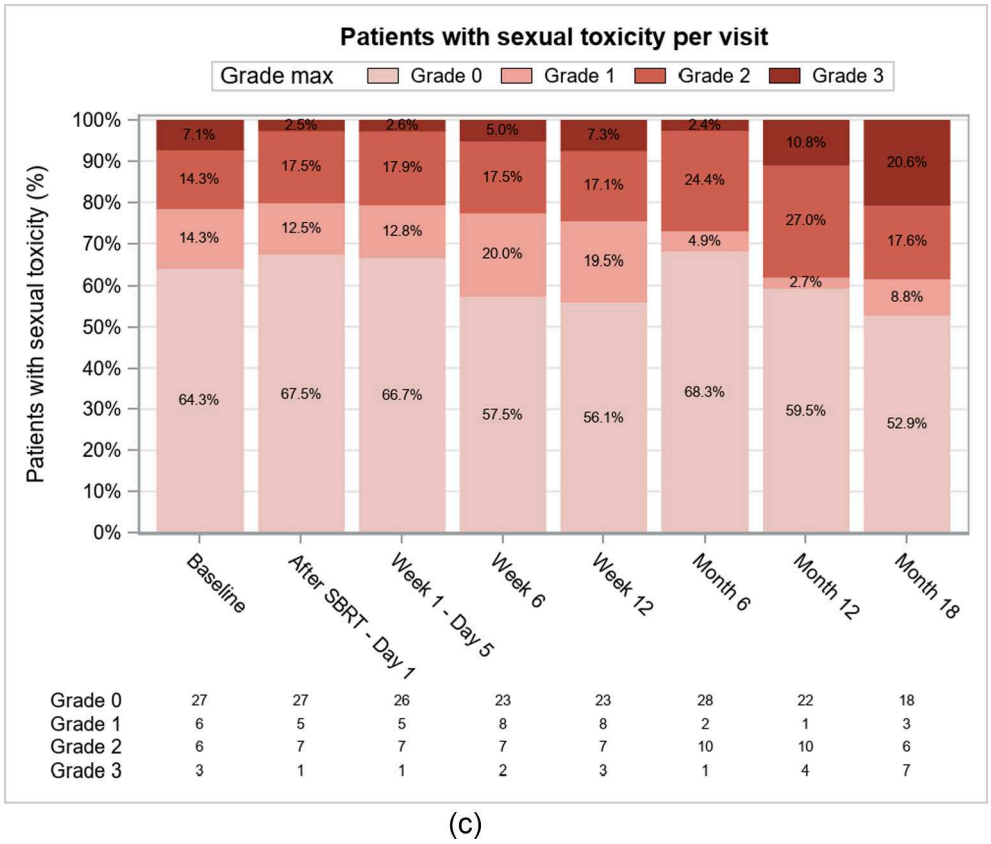


(a)



(b)

Fig. 1. Worst-grade National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAEv4.03) genitourinary (A), gastrointestinal (B), and sexual (C) toxicities between baseline and 18 months after radiotherapy.



(c)

Fig. 1. (*continued*).

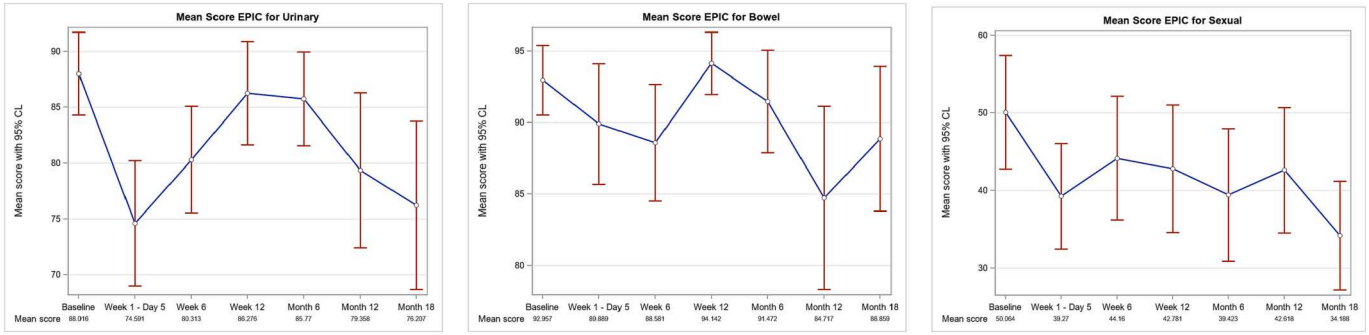


Fig. 2. Mean values for Expanded Prostate Cancer Index Composite (EPIC-26) scores for urinary, bowel, and sexual treatment-related symptoms between baseline and 18 months after radiotherapy.

urethra prescribed by Greco *et al.,* [20] (i.e., 20 Gy theirs *vs.* 17 Gy ours) may explain, at least in part, the differences in GU minimally clinically important differences (MCID) at 18 months of 47 % of theirs and < 20 % of ours.

Several authors have published in the last few years their respective experiences with HDR-BT delivered in one single fraction of 19–20.5 Gy (in some cases with a focal boost up to 23 Gy) [12,19,21–24]. Unlike the experience reported from SBRT single-shot trials, most HDR-BT single-dose reports have described less GU toxicity events both acute and late. Indeed, most authors have described a low-risk of grade-2 GU toxicity among their patients treated with a single HDR-BT implant [12,19,21,25]. GU events, especially the acute ones, may be strongly correlated with prostate volume and/or with bladder wall dose, specifically the bladder trigone, in addition to the dose to the urethra [26]. Single fraction HDR-BT reports describe, though acute GU events, mostly obstructive and needing occasionally (in 5–6 % of patients) transient urinary catheterization [12,19,25]. Even if in our study we took care of lowering the dose to the urethra we observed a 22.6 % of severe obstructive symptoms (IPSS score > 19) at 18 months follow-up (none at baseline) among 31 eligible patients at this time-point. Unlike us, Hoskin *et al.*, reported a much lower rate of IPSS scores > 19, 9.5 % (compared to 8 % at baseline) through a 22–26 month follow-up in a group of 42 patients treated with 19 Gy or 20 Gy with HDR-BT [19]. This is not an isolated observation as it also joins the conclusions reached by Morton *et al.*, regarding a two-arm phase-II trial with 87 and 83 patients receiving either single 19 Gy fraction or two 13.5 Gy fractions, respectively [25]. In this trial, none of the patients in the single fraction arm reported any severe GU obstructive symptoms after month 9 and trough month 24 (20 months, median follow-up) even though grade-2 GU events were described in 10 patients (14.7 %).

When we first conceived the study in 2016, we used biomathematical modelling to estimate rectal normal tissue complications probabilities

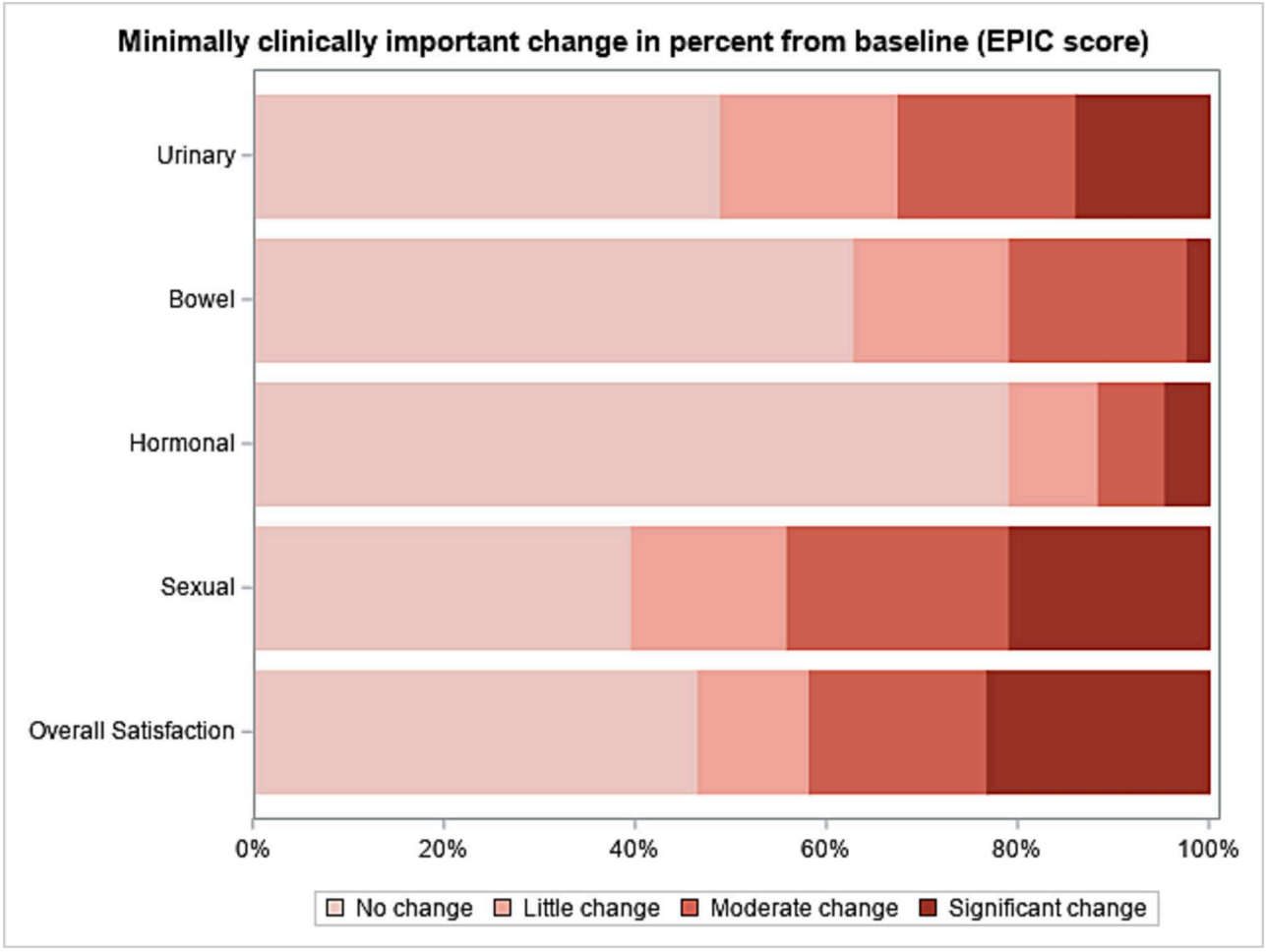


Fig. 3. Minimally clinically important changes in percentage from baseline on different Expanded Prostate Cancer Index Composite (EPIC-26) domains.

(NTCPs) to help us to choose a safe enough prescription dose to keep the risk for grade-2 rectal bleeding or grade-3 late toxicity below 10 % [27,28]. We assessed different target dose prescription scenarios from 19 Gy up to 24 Gy. Unfortunately, without the use of a recto-prostatic spacer, all treatment plans aiming to deliver higher than 19 Gy to the prostate (*e.g.*, a simultaneous boost up to 24 Gy to the intraprostatic dominant lesion) predicted a severe toxicity ranging from 10 % up to 25 % for the least and the most robust plans, respectively. In the other hand, the 19 Gy prescription dose without spacer predicted < 5 % risk of severe toxicity, safe enough to make 19 Gy to the whole prostate our final choice for the present trial. Indeed, as expected, the late grade ≥ 2 GI toxicity has been of < 3 % at 18-month follow-up with minimal impact on GI bothers according to the almost no different EPIC-26 scores compared to baseline. If one compares this good GI toxicity profile with those reported from the single dose HDR-BT literature, one can conclude on an almost optimal late GI tolerance from the latter, too. Indeed, grade ≥ 2 GI toxicity was reported as none by Prada *et al.* [4], and by Hoskin *et al.* [19], to 3 % by Morton *et al.* [25], and to 5.9 % by Siddiqui *et al.* [13].

In our study, grade-$\geq$2 erectile dysfunction increased almost twice from baseline (21.4 %) to 18 months post-treatment (38.2 %), from an EPIC-26 mean score of 50 dropping to 34.2 from baseline to the 18 months follow-up assessment, though MCID for sexual scores was less than 20 %. This contrasts with the reported 33 % MCID score drop in the study by Greco *et al.,* [20]. Both Morton et *al.*, and Siddiqui *et al.,* reported on sexual tolerance in their series of patients treated with a single fraction HDR-BT [13,25]. In both cases the sexual function was acceptably preserved in most patients. Siddiqui *et al.*, reported on a grade ≥ 2 incidence of 14.7 % after a median follow-up of 3.9 years, while Morton *et al.*, reported on a 12 % risk after a median follow-up of 20 month, a MCID score drop by 11.1 points after the first year of follow-up [13,25].

Although, the short follow-up in our study does not allow us to release reliable results regarding outcome we already faced three biochemical failures. This rejoins a similar observation made by Greco *et al.*, with three biochemical failures among their 15 patients in their single shot treatment arm though with a follow-up time almost twice than ours. Nonetheless, all three failures reported by Greco *et al.*, happened among the unfavorable intermediate-risk patients but none among the low- or favorable intermediate-risk ones [20]. Single dose HDR-BT data published so far concerning disease outcome are poorly consistent. Prada *et al.*, reported a 6-year biochemical control rate of only 66 % [12], which induced them to escalate the dose from 19 to 20.5 Gy to overcome the failure problem. By doing so, they improved their biochemical control rate at 6 years to 82 % among 60 consecutive patients treated with no difference between risk groups and no significant GU and GI toxicity [21]. Siddiqui *et al.*, reported a 77.2 % 5-year bRFS with a single 19 Gy HDR-BT implant [13]. Finally, Hoskin *et al.*, reported the higher disease control so far, with 94 % 4-year biochemical control [19]. Recently presented at ASTRO 2023, long-term results up to 10 years of this study confirmed the good outcome of 19–20 Gy single dose HDR-BT, comparable to those observed with 2 or 3 fractions HDR-BT regimens. It may be important to remind that these differences in outcome among authors may be related to patients' selection according to risk groups as it was observed by Greco *et al.* for their SBRT [20]. This seemed to be the case for Hoskin *et al.* [19], but not for Prada *et al.* or

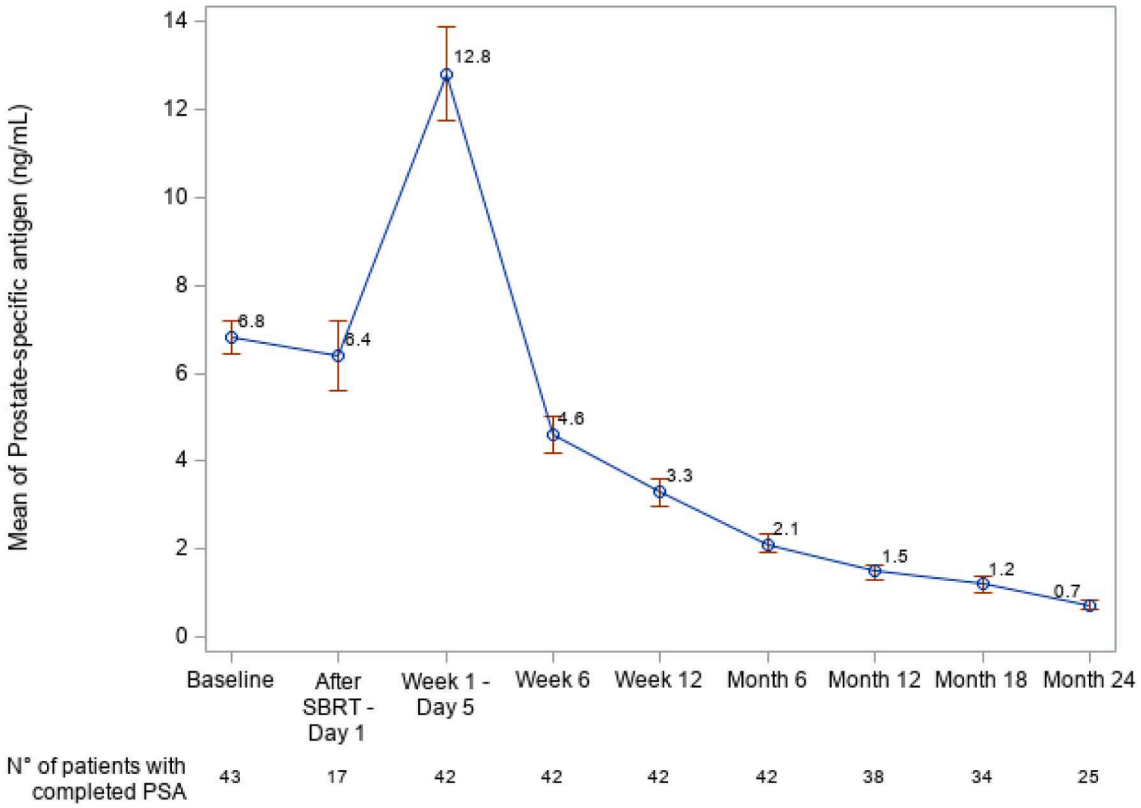


Fig. 4. Mean prostate specific antigen (PSA) values between baseline and 24 months after radiotherapy.

Siddiqui *et al.* [13,21].

In summary, in this multicenter phase I/II trial we demonstrated that a 19 Gy single-fraction urethra-sparing SBRT is feasible and associated with an acceptable toxicity rate, mostly returning to the baseline at week-12 and with a delayed GU flare between months 12 and 18. Longer follow-up is needed to assess the disease control efficacy of this SBRT fractionation.

CRediT authorship contribution statement

Thomas Zilli: Conceptualization, Funding acquisition, Data curation, Writing – original draft, Investigation, Formal analysis, Supervision. **Ciro Franzese:** Writing – review & editing, Investigation, Validation. **Matthias Guckenberger:** Writing – review & editing, Investigation, Validation. **Niccolò giaj-levra:** Writing – review & editing, Investigation, Validation. **Nicolas Mach:** Writing – review & editing, Investigation, Validation. **Nikolaos Koutsouvelis:** Writing – review & editing, Investigation, Validation. **Verane Achard:** Writing – review & editing, Investigation, Validation. **Andrew Mcdonald:** Writing – review & editing, Investigation, Validation. **Filippo Alongi:** Writing – review & editing, Investigation, Validation. **Marta Scorsetti:** Writing – review & editing, Investigation, Validation. **Guillaume Constantin:** Data curation, Formal analysis, Methodology, Project administration and Software, Writing – original draft, Writing – review & editing. **Aurelie Bertaut:** Formal analysis, Methodology, Project administration and Software, Writing – review & editing. **Raymond Miralbell:** Conceptualization, Funding acquisition, Writing – original draft, Writing – review & editing, Investigation, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110181.

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