Clinical and Translational Radiation Oncology 44 (2024) 100704

Contents lists available at ScienceDirect

Clinical and Translational Radiation Oncology

journal homepage: www.sciencedirect.com/journal/clinical-and-translational-radiation-oncology

Toxicity profile and Patient-Reported outcomes following salvage Stereotactic Ablative Radiation Therapy to the prostate Bed: The POPART multicentric prospective study

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ARTICLE INFO

Keywords:
Prostate cancer
Postoperative setting
Salvage RT
SBRT

ABSTRACT

Background: While SBRT to the prostate has become a valuable option as a radical treatment, limited data support its use in the postoperative setting. Here, we report the updated results of the multicentric Post-Prostatectomy Ablative Radiation Therapy (POPART) trial, investigating possible predictors of toxicities and patient-reported outcomes.

Methods: Patients with PSA levels between 0.1–2.0 ng/mL after radical prostatectomy received Linac-based SBRT to the prostate bed in five fractions every other day for a total dose of 32.5 Gy ($EQD2_{1.5} = 74.3$ Gy). Late toxicity was assessed using CTCAE v.5 scale, while EPIC-CP, ICIQ-SF, IIEF 5 questionnaires and PSA levels measured quality of life and biochemical control. Pre- and post-treatment scores were compared using a paired *t*-test, with MID established at > 0.5 pooled SD from the baseline. A logistic regression analysis was performed to evaluate potential associations between specific patient/tumor/treatment factors and outcome deterioration.

Results: From April 2021 to April 2023 a total of 50 pts were enrolled and treated. Median follow-up was 12.2 (3–27) months. No late $\geq$ G2 GI or GU toxicity was registered. Late G1 urinary and rectal toxicities occurred in 46 % and 4 % of patients, respectively. Among 47 patients completing all EPIC-CP domains, four (9 %) showed worsened QoL, and eleven (26 %) developed erectile dysfunction correlating with PTV D2% ($P = 0.032$). At Multivariate analysis bladder wall D10cc independently correlated with late G1 GU toxicity ($P = 0.034$). Median post-treatment PSA nadir was 0.04 ng/mL (0.00 – 0.84). At the last follow-up, six patients presented with biochemical failure, including two nodal relapses.

Conclusions: Our findings show that post-prostatectomy SBRT did not result in increased toxicity nor a significant decline in QoL measures, thus showing that it can be safely extended to the postoperative setting. Long-term follow-up and randomized comparisons with different RT schedules are needed to validate this approach.

Introduction

Approximately 20–40 % of patients initially treated with radical prostatectomy (RP) experience recurrence within 10 years [1,2]. Several phase III randomized clinical trials have demonstrated that post-prostatectomy RT improves overall (OS) and progression-free survival

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https://doi.org/10.1016/j.ctro.2023.100704
Received 31 August 2023; Accepted 25 November 2023
Available online 25 November 2023

(PFS), either as adjuvant or early salvage treatment [3–7]. However, these studies have employed conventionally fractionated RT regimens delivered over 6 to 7 weeks. The delivery of a high number of sessions results in an increasing demand for treatment machine time and personnel utilization in RT departments, thus limiting access to care and increasing its total cost. Furthermore, such a long duration of the radiation course can induce distress, especially in patients living far from RT centres, who might often opt for quicker yet nondefinitive treatments such as androgen deprivation therapy (ADT). Since the α/β ratio for prostate cancer has been estimated to be as low as 1.5 Gy [8–10] — significantly lower than the 3 Gy value estimated for late complications [11] — fewer but larger than conventional fractions for a lesser total dose could effectively improve the therapeutic ratio, while maintaining isoeffective tumour doses and shortening overall treatment time. Stereotactic Body Radiation Therapy (SBRT) is at the edge of hypofractionation thus representing a valuable option due to its capacity to deliver fewer RT fractions with high biologically equivalent doses. This approach can decrease equipment utilization, improve care accessibility, and increase patient convenience without losing clinical effectiveness. Although SBRT has demonstrated non-inferiority to normofractionated RT in the treatment of intact prostate [12,13], few data are available to date showing that it can be safely delivered in the postoperative setting [14]. Concerns have risen that too high doses to the anastomosis (where most recurrences occur) may lead to tissue injury, potentially resulting in an increased risk of severe toxicities. We have previously published the early findings of a prospective multicentric trial [15] evaluating the use of SBRT to the prostate bed in patients with biochemical relapse following RP and showed that it did not increase toxicity nor affect Quality of Life (QoL) in the short time. We herein report the updated results with longer follow-up, investigating possible predictors of toxicities and patient-reported outcomes.

Methods

Patients and treatment characteristics

The POPART trial is a multicentric, prospective, observational trial (NCT04831970) aiming at evaluating the feasibility of postoperative SBRT for prostate cancer in terms of toxicity and QoL. The study was approved by the Ethical Committees of the participating centres. All participants provided written informed consent prior to trial enrollment in agreement with the Declaration of Helsinki [16].

Eligibility criteria and treatment procedures have been previously reported in detail [15]. Briefly, patients enrolled in the trial should have had a biochemical relapse following RP (any type) with the prostate-specific antigen (PSA) not exceeding 2.0 ng/mL and no distant metastases on [18F]-PSMA positron emission tomography (PET) within 60 days prior to registration. ADT was allowed, and its prescription was left at the physician's discretion.

All patients were immobilized in the supine position, with empty rectum and bladder filled by drinking 500 mL of still water to assess anatomical reproducibility and mitigate the organ motion. The clinical target volume (CTV) was delineated according to the Groupe Francophone de Radiothérapie Urologique (GFRU) Guideline [17]. The planning target volume (PTV) included CTV with a 5 mm isotropic 3D margin, except for at the rectum interface, where the margin was kept at 3 mm. SBRT was delivered with Volumetric Modulated Arc Therapy (VMAT) consisting of two 6 MV or 10 MV flattening filter free (FFF) arcs on a Linac-platform. Plans were optimized to ensure that the 95 % isodose covered at least 95 % of the PTV, and scheduled in 5 fractions every other day for a total dose of 32.5 Gy ($EQD2_{1.5}$ = 74.3 Gy). Accurate patient setup was obtained using kilovoltage cone-beam CT (CBCT) before each session to check the anatomical reproducibility. Dose–volume constraints were fully described elsewhere [15].

Toxicity and Quality of Life assessment

Toxicity, as defined by the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v.5.0, was assessed at baseline, at the end of treatment and every 3 months thereafter. The International Consultation on Incontinence Questionnaire - Short Form (ICIQ-SF), the International Index of Erectile Function Questionnaire (IIEF 5), and the Expanded Prostate Cancer Index Composite for Clinical Practice (EPIC-CP) [18,19] scores were collected once prior to treatment and thereafter at each time points via questionnaires. Last PSA, patient QoL outcomes, and the maximum treatment-related genitourinary (GU) and gastrointestinal (GI) toxicities from 3 months after treatment to the last follow-up were assessed and compared with the baseline. Paired *t*-test was used to compare pre-treatment and post-treatment questionnaire scores of the patient population. A logistic regression analysis was performed to evaluate potential associations between specific patient-related, tumour-related or treatment-related factors and a worsening of clinical outcomes. Patient-reported outcomes were binarily categorized as worsening or maintenance/improvement of the domain scores compared to the baseline. The minimally important differences (MID) indicating worsening were established as a change in the questionnaire scores of > 0.5 pooled standard deviation (SD) from the baseline [20,21]. Intergroup differences were evaluated using Fischer's exact test for categorical variables and Wilcoxon-Mann-Whitney test for continuous variables, and a ROC analysis was performed to identify significant dose cut-offs. For all tests, a p-value < 0.05 was used for statistically significant differences. All statistical analyses were performed with the software Stata, version 9.0 (StataCorp LLC, Texas, US).

Results

Population characteristics

Between April 2021 and April 2023, 50 patients (median age 70 years; range 52 – 83) were enrolled and treated in the multicentric POPART trial. Table 1 displays their baseline demographic and clinical characteristics, along with treatment details. The median PSA level

Table 1
Patients, disease and treatment characteristics.

Age at RT (year)	**70 (52 – 83)**
Gleason score	
6 (3 + 3)	7 (14 %)
7 (3 + 4)	19 (38 %)
7 (4 + 3)	19 (38 %)
8 (4 + 4)	3 (6 %)
9 (4 + 5)	1 (2 %)
Unknown	1 (2 %)
Pathological T stage	
≤T2c	32 (64 %)
T3a	12 (24 %)
T3b	6 (12 %)
Pathological N stage	
pN0	41 (82 %)
pNx	9 (18 %)
pN1	0 (0 %)
Positive surgical margin	**24 (48 %)**
Fraction dose (Gy)	**6.5**
Total dose (Gy)	**32.5**
Total dose in $EQD2_{1.5}$ (Gy)	**74.3**
Time from RP to SRT (months)	**Median 52 (4 – 156)**
Postoperative PSA (ng/mL)	**Median 0.01 (0.00 – 0.17)**
PSA pre-RT (ng/mL)	**Median 0.3 (0.1 – 1.9)**
ADT use	**5 (10 %)**
ADT duration (months)	**Median 9 (6 – 114)**
Patients with BCR after SRT	**6 (12 %)**

RT: Radiation Therapy; EQD2: Equivalent Dose in 2 Gy Fractions; RP: Radical Prostatectomy; PSA: Prostate Specific Antigen; BCR: BioChemical Recurrence; SRT: Salvage Radiation Therapy; ADT: Androgen Deprivation Therapy.

before RT was 0.3 ng/mL (0.1 – 1.9). Five patients (10 %) received ADT. At baseline, the mean ICIQ-SF and EPIC-CP urinary incontinence scores were 3.5 ± 2.8 and 1.6 ± 1.8, respectively. According to the EPIC-CP and IIEF 5 questionnaire scores, 21 patients already suffered from sexual dysfunction at baseline. Median CTV and PTV volumes were 25.4 cc (4.4 – 149.0) and 62.5 cc (14.8 – 250.2), respectively. A summary of the dosimetric data of the organs at risk is displayed in Table 2.

Treatment outcomes

All patients completed the treatment according to the protocol's schedule. The median follow-up for the study cohort was 12.2 (3.0 – 27.0) months. In the observed timeframe, no late ≥ G2 GI or GU toxicity was registered. Late G1 urinary and bowel toxicity occurred in 23 (46 %) and 2 (4 %) patients, respectively (Table 3). The median post-treatment PSA nadir was 0.04 ng/mL (0.00 – 0.84). At the last follow-up, six patients presented with biochemical failure including two nodal relapses confirmed at PSMA-PET.

Quality-of-Life and patient-reported outcomes

According to EPIC-CP and ICIQ-SF questionnaires, four patients (8 %) had a decline in urinary continence at the last follow-up. In the urinary irritation/obstruction domain of the EPIC-CP, a MID was observed in two (4 %) patients, while zero MID were found in both bowel function and hormonal symptom domains. Moreover, among the 47 and 42 patients who completed the EPIC-CP sexual domain and the IIEF 5 questionnaires, a deterioration was found in six (13 %) and eleven (26 %) patients, respectively. The MID analysis on the overall QoL outcome for the 47 patients who completed all the EPIC-CP domains indicated that a clinical worsening post-treatment occurred in four (9 %). The majority of questionnaire scores remained stable from the baseline, with only minor variations at the last follow-up, as shown in Table 4.

Predictors of clinical and Patient-Reported outcomes

Paired *t*-test comparing pre-treatment and post-treatment questionnaire scores showed no statistically significant differences ($P > 0.05$). Univariate analysis did not identify any factor significantly associated with the worsening of urinary incontinence, urinary irritation/obstruction, bowel and hormonal symptoms, sexual dysfunction or QoL, according to ICIQ-SF and EPIC-CP questionnaires ($P > 0.05$). A significant correlation was observed between the decline in erectile function and the dose received by 2 % of the PTV (OR, 2.560; 95 % CI, 1.186–4.335; $P = 0.032$). Mean ± SD values of maximum PTV dose were 33.2 ± 0.7 Gy for patients who did not report MID and 33.8 ± 0.9 Gy for those reporting MID in the IIEF 5. No factor was found to be significantly related with the five biochemical failure events and the two late G1 GI toxicities. According to the univariate analysis, higher rectum and bladder doses were significant predictors of late G1 GU toxicities: rectum mean dose (OR, 1.391; 95 % CI, 1.048–1.848, $P = 0.022$), rectum wall D50% (OR, 1.322; 95 % CI, 1.049–1.666, $P = 0.018$), bladder mean dose (OR, 1.395; 95 % CI, 1.106–1.759, $P = 0.005$), bladder wall D10cc (OR, 1.181; 95 % CI, 1.057–1.321, $P = 0.003$), bladder wall D25% (OR, 1.161; 95 % CI, 1.037–1.300, $P = 0.009$), and bladder wall D50% (OR, 1.265; 95 % CI, 1.071–1.495, $P = 0.006$). At the multivariate analysis, only bladder wall D10cc (OR,1.250, 95 % CI, 1.017–1.537, $P = 0.034$) showed an independent correlation with the incidence of late G1 GU toxicity. The dose cut-offs associated with significant lower rates of G1 GU toxicity were reported in Table 5.

Table 2
Median, mean and range of the organs at risk dose parameters.

	Median	Mean	Range
Bladder			
Dmean (Gy)	10.8	11.1	1.0 – 24.7
Bladder wall			
D0.035 cc (Gy)	33.6	33.5	31.8 – 34.0
D10cc (Gy)	16.1	14.7	0.7 – 30.9
D25% (Gy)	29.1	22.5	0.7 – 32.5
D50% (Gy)	3.1	6.6	0.3 – 28.1
Rectum			
Dmean (Gy)	8.3	9.2	2.7 – 15.6
Rectum wall			
D0.035 cc (Gy)	32.9	32.9	32.2 – 34.4
D1cc (Gy)	31.6	31.5	27.1 – 32.7
D50% (Gy)	3.6	4.9	0.6 – 13.4

Table 3
Maximum late toxicity after RT.

	Grade 1	Grade 2	Grade ≥ 3
Late GU toxicity	**N (%)**	**N (%)**	**N (%)**
Hematuria	2 (4 %)	–	–
Urinary incontinence	16 (32 %)	–	–
Urinary tract obstruction	1 (2 %)	–	–
Urinary frequency	3 (6 %)	–	–
Non-infectious Cystitis	1 (2 %)	–	–
Total	*23 (46 %)*	–	–
Late GI toxicity	**N (%)**	**N (%)**	**N (%)**
Hematochezia	–	–	–
Tenesmus/Proctitis	1 (2 %)	–	–
Fecal Incontinence	–	–	–
Bowel frequency	1 (2 %)	–	–
Total	*2 (4 %)*	–	–

Table 4
Median and range of patient-reported QoL using EPIC-CP, ICIQ-SF and IIEF 5.

EPIC-CP	**Median (range)**	
	Baseline	**Last follow-up**
Urinary Incontinence	2 (0 – 8)	2 (0 – 8)
Urinary Irritation/Obstruction	1 (0 – 4)	1 (0 – 5)
Bowel Symptoms	0 (0 – 5)	0 (0 – 7)
Sexual Dysfunctions	5 (0 – 12)	5 (0 – 12)
Hormonal Symptoms	0 (0 – 7)	0 (0 – 6)
Quality of Life	9 (0 – 19)	10 (1 – 37)
ICIQ-SF	**Median (range)**	
	Baseline	**Last follow-up**
Urinary Incontinence	4 (0 – 13)	2 (0 – 16)
IIEF 5	**Median (range)**	
	Baseline	**Last follow-up**
Erectile Function	13 (0 – 25)	10 (0 – 25)

EPIC-CP: Expanded Prostate Cancer Index Composite for Clinical Practice; ICIQ-SF: International Consultation on Incontinence Questionnaire Short Form; IIEF 5: International Index of Erectile Function Questionnaire.

Discussion

This study stands out among the few prospective trials that have reported on patients outcomes following salvage SBRT to the prostate bed [22–25]. Nonetheless, the diversity in patient numbers, inclusion

Table 5
Significant dose cut-offs for late G1 GU toxicity.

Organ at risk	Cut-offs	Incidence of toxicity (%)	p-value
Rectum	Dmean < 8.7 Gy	28 % vs 18 %	0.026
Bladder	Dmean < 11.6 Gy	30 % vs 16 %	0.012
Bladder wall	D10cc < 17.1 Gy	34 % vs 8 %	0.001
	D25% < 29.7 Gy	34 % vs 8 %	< 0.001
	D50% < 4.2 Gy	31 % vs 10 %	0.002

criteria, dose fractionation, and follow-up durations has led to heterogeneous results in these studies. Moreover, a systematic review including 11 individual studies has investigated the toxicity and oncological outcome after post-prostatectomy SBRT [14], although the majority of them concentrated solely on treating the macroscopic recurrence.

We recently demonstrated that highly focused radiation in a few fractions to the prostate bed can be safely delivered, with no significant acute $\geq$ G2 side effects nor deterioration in patient-reported QoL measures [15]. The present findings with an extended follow-up validate these initial data, thus adding further evidence that post-operative SBRT has favourable toxicity profiles in the short to medium term. Like others [26], we found a significant correlation between bladder and bladder wall dose-volume parameters and GU toxicity, although they reported significant rates of G2 and G3 events. Noteworthy, our analysis showed that a worse dosimetry to mean and intermediate doses of the rectum and bladder was related to a higher incidence of GU toxicity. However, since most of our patients were already incontinents prior to treatment initiation, we hypothesised that a worse dosimetry might be related to some difficulties in achieving comparable bladder filling relative to others during the simulation CT. The assessment of urinary incontinence and erectile dysfunction is particularly challenging in the post-prostatectomy setting, as a substantial portion of patients, as mentioned earlier, have already developed these side effects prior to irradiation, potentially exacerbating their condition. MID was chosen as a more sensitive measure of change and, overall, patient-reported sexual, urinary, and bowel QoL remained stable at 12 months after SBRT, with only 8 % (4 out of 50) reporting worsening in urinary function. These data compare favourably to a dose escalation study of post-prostatectomy SBRT to the prostate bed, reporting rates of late $\geq$ G3 GU toxicity as high as 15 % at a median follow-up of 60 months [22]. Moreover, these findings align with a similar Phase 1 trial of post-operative extreme hypofractionation showing no acute $\geq$ G3 GU or GI toxicity at any dose levels [23]. Another prospective study of post-prostatectomy SBRT indicated adjusted late $\geq$ G2 GU toxicity (incontinence) of 12.2 % [24]. The Stereotactic Intensity Modulated Radiotherapy After Radical Prostatectomy Trial (SCIMITAR) multicenter phase 2 trial [25] demonstrated that SBRT delivered with CT-guided RT and MRI-guided RT (MRgRT) resulted in acute and late G2 GU toxicity of both 9 % and acute and late G2 GI toxicity of 5 % and 0 %, respectively, with patients treated with MRI-guided RT exhibiting a 30 % reduction in any grade acute GI toxicity and improved bowel QoL likely due to the use of narrower PTV margins. In our series, no late $\geq$ G2 toxicity and a single instance of acute G2 GI toxicity were documented with the adoption of a similar schedule on a Linac platform guided by the CBCT and using an anisotropic expansion for PTV of 5 mm in each direction, except for the rectum interface (3 mm). These findings can be attributed to the short beam-on time achieved by the FFF modality, and the strict bowel and bladder preparation, which ensured target stabilization and anatomical reproducibility while mitigating the risk of intrafraction motion. Furthermore, given the proximity of the bladder trigone and urethra to the target volume, it is unlikely that adopting a more sophisticated treatment technique would substantially reduce GU events. Interestingly, our analysis revealed a significant correlation between the maximum dose to the PTV and a worsening of the IIEF 5 score in comparison to the baseline value. This could be attributed to the inclusion in the treatment volume of the penile bulb, a structure that has been associated with RT-induced erectile dysfunction [27,28]. This soft tissue structure lying immediately below the urogenital diaphragm of the pelvic floor and easily identified on the CT imaging defines the inferior limit of the prostate bed - CTV delineation according to the aforementioned guideline [17], and has been demonstrated to be a surrogate landmark for the prostate apex [29,30] comparable to urethrography [31]. Despite the relatively short follow-up period, the high freedom from biochemical failure (FFBF) rate appears to support the premise that salvage postoperative SBRT can be implemented without compromising treatment efficacy while potentially increasing patients compliance. It is likely that the use of [18F]-PSMA PET before treatment might have helped in excluding distant metastases even at low PSA levels, thus aiding patient selection and accordingly improving oncologic outcomes. These results appear to be encouraging and in agreement with those reported in other prospective [22–26] and retrospective trials [32], yet with the use of a lower total dose. Indeed, a dose-escalated strategy has already been disproved by two randomized controlled studies [33,34] which failed to show a benefit in FFBF, and at the expense of increased $\geq$ G2 toxicity. Our trial was designed prior to the publication of the RTOG 0534 SPPORT trial [35], which showed that the combination of short-term ADT with salvage RT extended to treat the pelvic lymph nodes resulted in meaningful reductions in progression for patients with a detectable or rising PSA after prostatectomy. Notably, however, the highest benefit from this treatment intensification in terms of FFP was observed in patients with entry PSA higher than the minimum and even median value of our cohort.

The primary limitation of this study is the relatively limited follow-up, which cannot exclude late toxicities, namely GU events, which might continue to develop during the time [36]. We believe however that our findings, particularly those on treatment-related incontinence, are reassuring and may contribute to rejecting the belief that post-operative SBRT yields increased toxicity.

Conclusions

In this multicentric prospective study, post-prostatectomy SBRT did not result in increased toxicity nor in a significant decline in QoL measures, thus showing that it can be safely extended to the postoperative setting. Long-term follow-up and a randomized comparison with standard or moderate hypofractionated RT are needed to confirm this approach.

CRediT authorship contribution statement

Federica Ferrario: Data curation, Investigation, Methodology, Resources, Visualization, Writing – original draft. **Ciro Franzese:** Data curation, Investigation, Methodology, Resources, Visualization, Writing – review & editing. **Valeria Faccenda:** Formal analysis, Methodology, Software, Visualization, Writing – original draft. **Suela Vukcaj:** Data curation, Investigation, Resources. **Maria Belmonte:** Data curation, Investigation, Resources. **Raffaella Lucchini:** Data curation, Investigation, Resources. **Davide Baldaccini:** Data curation, Investigation, Resources. **Marco Badalamenti:** Data curation, Investigation, Resources. **Stefano Andreoli:** Methodology, Software. **Denis Panizza:** Formal analysis, Methodology, Software, Visualization, Writing – review & editing. **Alessandro Magli:** Data curation, Investigation, Resources. **Marta Scorsetti:** Data curation, Resources, Supervision, Writing – review & editing. **Stefano Arcangeli:** Conceptualization, Data curation, Investigation, Methodology, Resources, Supervision, Writing – original draft.

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.

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