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Moderately hypofractionated salvage radiotherapy in patients with biochemical recurrence of prostate cancer after prostatectomy: long-term results and comparative analysis of two schedules

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Hypofractionation in salvage radiotherapy (HSRT) for biochemical recurrence of prostatic cancer after prostatectomy is a debated issue and at present, it should be considered purely investigational because of the lack of evidence supporting its use. In this study, we report the outcomes of patients presenting with biochemical recurrence after radical prostatectomy who received HSRT. The additional aim of this study is to compare two moderately HSRT schedules. Patients treated to prostate bed with daily Image Guided-VMAT and a total dose of 65 Gy/26 fractions (Group A) or 66 Gy/30 fractions (Group B) were included in the study. Inclusion criteria were: pN0/pNx, pre-HSRT PSA ≥0.2 ng/ml and ≤1 ng/ml, no evidence of pelvic/extrapelvic disease at restaging, no pelvic irradiation or dose boost on macroscopic local recurrence, no neoadjuvant/concomitant Androgen Deprivation Therapy (ADT), follow-up ≥36 months, and available pre/post HSRT data. Genitourinary (GU) and gastrointestinal (GI) toxicities, early and late, were assessed using CTCAE Vers. 5.0. One hundred patients were retrospectively identified to 50 in each group. Median follow-up was 59 months. All patients completed the prescribed HSRT. 5-year biochemical failure-free survival, local control, distant relapse-free survival, and ADT- free survival were 52.1%, 85.9%, 63.7%, and 73.2%, respectively. No significant differences in these outcomes were found between the two groups. On multivariate analysis, a hypofractionation schedule was not associated with any outcome, but ISUP score ≥ 4 and pre-HSRT PSA were associated with worse biochemical failure-free survival while only ISUP score ≥ 4 was associated with worse distant relapse-free survival. No Grade 3 GU/GI acute event was reported; 6 (6%) and 2 (2%) patients experienced late Grade ≥ 2 GU and GI events, respectively. No difference was found between the two groups neither in acute nor in late GU/GI toxicities. Our findings demonstrate that HSRT is feasible, effective, and safe. Our analysis did not show any significant difference between the two hypofractionated schedules. Further studies and randomized controlled trials are required in order to confirm these results and to identify the optimal hypofractionated schedule in the salvage setting.

Key words: prostate cancer, salvage radiotherapy, biochemical recurrence, hypofractionation

Biochemical recurrence (BCR) after radical prostatectomy (RP) occurs in 30–35% of patients [1, 2], and this rate increases in patients with one or more unfavorable pathological features (such as extracapsular disease, infiltration of seminal vesicles, Gleason score ≥8 or positive surgical margins) [3–8]. When a patient experiences BCR, defined as a confirmed increase in prostate-specific antigen (PSA) ≥0.2 ng/ml [9, 10], the only potentially curative treatment option currently available is salvage radiotherapy (SRT) [11, 12], which is conventionally delivered in 1.8–2 Gy fractions to a total dose of 64–72 Gy in 7–8 weeks [13].

However, conventional protracted regimens, despite their benefits, are often associated with an increased inconvenience, which may also lead to deferring the radiation treatment. In addition, they are frequently associated with poor patient compliance due to logistical reasons as well as with an increased burden on radiotherapy services.

Many studies have reported a low α/β ratio for prostate cancer (PCa) cells, which indicates a high sensitivity to dose per fraction [14]. The reported PCa α/β ratio of 1.5 Gy, which is far below the α/β ratio of bowel and bladder (4–5 Gy), has led to the concept of hypofractionation [15]. This means

that a higher biologically effective dose (BED) can be given to the tumor volume without increasing the total dose to surrounding tissues and, as a result, without worsening radiation-induced side effects [16–18].

In addition to the delivery of a higher BED, the advantages of hypofractionated schemes over conventional fractionation also involve the reduction of overall treatment time, the number of hospital trips, and of use of linear accelerators, thus benefitting patients as well as the radiotherapy department. This is particularly advantageous for radiotherapy centers with limited resources, long waiting lists, and/or a geographically-dispersed population in which many patients live far from the center.

In the definitive treatment setting, there is robust evidence of the superiority of hypofractionation over standard fractionation in the improvement of disease control [19, 20], whereas in the postoperative setting hypofractionation remains a debated issue [21].

In the postoperative salvage setting, data on hypofractionation are sparsely reported and only a few non-randomized and retrospective reports on hypofractionated salvage radiation therapy (HSRT) are currently available. However, most of these studies include relatively small patient numbers, employ a variety of dose fractions, total doses and target volumes, use different inclusion criteria, and have a limited follow-up time, which affects the comparability between studies.

Many clinical trials are currently underway to assess the long-term efficacy and toxicity of HSRT. Nevertheless, to date, this treatment approach in the salvage setting must be considered solely investigational [21].

The aim of our study was to assess the clinical outcomes of patients presenting with biochemical recurrence after radical prostatectomy who received HSRT. Our additional aim was to compare two moderately HSRT schedules.

Patients and methods

Patients' selection. We retrospectively reviewed the medical records of 397 consecutive patients treated with HSRT between January 2014 and May 2019 for BCR of prostate cancer at the Centro di Riferimento Oncologico di Aviano (CRO) IRCCS, Aviano, Italy. For all patients, BCR defined as a PSA level of 0.2 ng/ml or greater (followed by another increased measurement at the same level or higher) was recorded. Patients were included in our analysis if they met the following criteria: 1/ no pathologically involved pelvic lymph nodes (pN0) or pelvic nodal dissection not performed (pNx) during prostatectomy; 2/ pre-HSRT PSA ≥0.2 ng/ml and ≤1 ng/ml; 3/ no evidence of pelvic/extrapelvic disease at restaging investigation (when indicated); 4/ treatment delivered with daily Image Guided-Volumetric Modulated Arc Therapy (IG-VMAT) technique; 5/ no pelvic lymph node irradiation; 6/ no dose boost on macroscopic local recurrence (if present); 7/ no use of neoadjuvant/concomitant Androgen Deprivation Therapy (ADT); 8/ follow-up ≥36 months; 9/ available pre/post HSRT data.

The final cohort for this analysis consisted of 100 patients who received prostate bed HSRT. All patients included in this study had been evaluated at the time of recurrence by a multidisciplinary tumor board and had signed a written informed consent for HSRT and for the use of the anonymized data for research or educational purpose. The study was approved and retrospectively registered by the Ethics Committee (Comitato Etico Unico Regionale www.egas.sanita.fvg.it) on 25th February 2022 (study registration number: CRO 2021-92).

HSRT protocol. HSRT was delivered by Linac-based external beam radiation. Patients received one of the two treatment schedules in force at the Aviano Cancer Centre at the time patients were treated: 1/ a total dose of 65 Gy in 25 daily fractions of 2.5 Gy, five fractions/week, which translates into a biologically effective dose (BED) of 173.3 Gy (for α/β 1.5 Gy) (defined as Group A); 2/ a total dose of 66 Gy in 30 daily fractions of 2.2 Gy, five fractions/week, which translates into a biologically effective dose (BED) of 162.8 Gy (for α/β 1.5 Gy) (defined as Group B).

The schedule was selected by a radiation oncologist on his/her experience, not guided by clinical-pathological cancer features.

Patients underwent a non-contrast-enhanced multi-slice CT scan with a 2 mm slice thickness. Patient immobilization during CT acquisition and treatment was obtained by knee-fix® and feet-fix® (CIVCO Medical Solutions, Kalona, IA, USA). All patients were asked to empty the bowel (oral and written instructions for diet and enema were given) and to have a full urinary bladder for computed tomography (CT) planning and during all treatment fractions (patients were educated to drink a half-liter of water 30 min before the procedure). Clinical target volume (CTV) consisted of a prostate bed plus extension to cover remnants of seminal vesicles according to RTOG postoperative radiotherapy for prostate cancer guidelines with a planning target volume (PTV) margin of 0.5 cm around CTV (0.3 cm posteriorly) [22]. On each slice, contouring of organs at risk was also performed: rectum, bladder, penile bulb, and femoral heads. The planning objectives for the target were the following: at least 98% of the CTV to be covered by 98% of the prescribed dose (V98% >98%) and at least 99% of the PTV to be covered by 95% of the dose (V95% >99%). Hot spots >107% were accepted only if inside the CTV. Patients were treated with Linac Volumetric Modulated Arc Therapy (VMAT) technique (RapidArc®, Varian Medical Systems, Palo Alto, CA) with 2 arcs. In particular, in this study all treatment plans were optimized and delivered on a Trilogy® or a TrueBeam® Linac (Varian Medical Systems, Palo Alto, CA, USA), with 18-MV flattening-filter photon beams; the maximum dose rate available was 600 MU/min. The treatment planning system in use was Eclipse version 13.6 with Anisotropic Analytical Algorithm version 13.6.23 (Varian Medical System, Palo

Alto, CA, USA) with a grid resolution of 2.5 mm or less. Avoidance sectors were planned in the case of metal implants in the femoral heads of patients. Dose-volume objectives applied during plan optimization for organs at risk (OARs) were as follows: for rectum and anal canal, V10 Gy <80%, V30 Gy <35%, V50 Gy <15%; for bladder, V30 Gy <50%, V50 Gy <25%; for femoral heads, V35 <1%; for penile bulb, Dmean <44 Gy. Image guidance was performed before each fraction. In particular, before each fraction, a cone beam CT (CBCT) was performed to verify the correct position as well as full bladder and empty rectum. Set-up corrections were performed after the hautomatic matching of CBCT images to reference planning CT (using the integrated algorithm on the Varian on-board imager console) followed by manual adjustments with an action level of 1 mm. When set-up corrections were greater than 5 mm, or bladder and rectum preparation was not correct, the patient was repositioned and re-verified. The entire process, starting from the CBCT acquisition to the end of radiation delivery, required <15 min.

Pre-HSRT staging investigations (bone scan, computerized tomography, whole-body MRI, or choline/PSMA PET-CT) were mostly performed in case of PSA Doubling Time <3 months or PSA at BCR >0.8 ng/ml [23].

Follow-up after HSRT. After HSRT, the PSA level dosage was recorded at 3 months after treatment, every 3 months for the following 2 years, every 6 months until the fifth year, and then annually. Acute (<3 months) and late (>3 months) toxicities were retrospectively assessed through the patient's chart review by two investigators (FM, AD) using Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0. Sexual dysfunction was not analyzed due to a lack of baseline evaluation. Post-HSRT biochemical failure was defined as a rise in PSA of 0.2 ng/ml above the post-radiotherapy nadir followed by a second higher value or any PSA value.

Patients with post-HSRT biochemical failure underwent imaging studies to define the relapse pattern using any available imaging modality (bone scan, computerized tomography, whole-body MRI, or choline/PSMA PET-CT).

Typically, in the event of oligorecurrent disease [24], Stereotactic Body Radiation Therapy (SBRT) of the involved sites on imaging studies, was delivered instead of ADT [25].

Conversely, ADT was prescribed both for polymetastatic relapse and for new oligorecurrent progression occurring less than 6 months after the previous SBRT course and associated with PSA doubling time <6 months [26].

The disease was considered castration-resistant metastatic prostate cancer (mCRPC) when there was evidence of radiological progression associated with PSA ≥2 ng/ml+nadir and testosterone level was <50 ng/dl [27].

Vital status, date, and underlying cause of death (i.e., the condition that led to death) were ascertained up to May 31st, 2022.

Statistical analysis. For each patient, the time at risk was computed as the time elapsed from the end of HSRT to the occurrence of any event of interest which were: PSA increase (defined as above) for biochemical failure-free survival (bFFS); radiological detection of local or distant disease for clinical relapse-free survival (CRFS); radiological diagnosis of prostatic bed recurrence for local control (LC); radiological diagnosis of regional or metastatic disease for distant relapse-free survival (DRFS); toxicity for GU and GI toxicity.

The median follow-up of the entire patient population was 59 months, 72 months in Group A and 52 months in Group B, respectively ($p<0.001$). To account for differences in median follow-up in the 2 groups, analyses were truncated to 60 months.

Survival probabilities for different oncological outcomes were estimated through the Kaplan-Meier method and differences between strata were tested through the log-rank test. The risk of unfavorable oncological outcome was evaluated using the Cox proportional hazards model; multivariable hazard ratios (HR), and corresponding 95% confidence intervals (CI), were calculated by adjusting potential confounders. To account for competing risks, cumulative incidences of late toxicity were calculated and differences by strata were tested using Gray's test [28]. Statistical significance was claimed for $p<0.05$ (two-tailed).

Results

Patient and tumor characteristics. Table 1 reports the characteristics of the patients included in our analysis. Both Group A and Group B consisted of 50 patients each.

No significant differences were observed between the two groups in pathological characteristics (ISUP grade group, pT/pN stage, R status), restaging procedures before HSRT, radiological evidence of local macroscopic recurrence, time to recurrence, PSA at BCR, or pre-treatment PSA.

Tumor outcome. All patients completed the planned treatment. The median PSA after HSRT was 0.10 ng/ml and the median PSA nadir was 0.03 ng/ml. No statistical difference was found between the 2 groups.

Biochemical failure was observed in 44 (44%) patients with a median time to relapse of 21 months (12–32 months). Clinical failure was observed in 36 (36%) patients. In all cases, clinical relapse was preceded by a biochemical failure.

Table 2 summarizes the 1-3-5-year bFFS, LC, DRFS, ADT-FS. No significant differences in these outcomes were found between the two groups (Table 2, Figures 1A–1D).

Table 3 summarizes the patterns of relapse recorded in the entire population and in each group. For both groups, loco-regional lymph nodes were the most frequent site of recurrence. Among patients with a loco-regional or distant failure, 25 (66%) patients had oligorecurrent relapse, 17 patients (68%) in Group A and 8 (32%) in Group B; 6 patients had polymetastatic relapse, 4 patients (67%) in Group A and 2 (33%) in Group B, respectively.

Within 5 years from the end of radiotherapy, 2 (10%) patients developed mCRPC, both in Group B. At the 5-year

follow-up, 98 (98%) patients were alive and 55 (55%) showed no evidence of disease. Two (2%) patients died, both in Group B, 1 patient of disease-related illness and 1 for other causes.

On multivariate analysis, the hypofractionation schedule was not associated with any outcome, but the ISUP grade group ≥4 and pre-HSRT PSA were associated with worse bFFS while only the ISUP grade group ≥4 was associated with worse DRFS (Table 4).

Toxicity. Table 5 summarizes acute and late toxicities. Overall, 22 (22%) patients reported GU or GI acute toxicity, 3 of these patients experienced both GU and GI toxicities. Considering the maximum grade of toxicity observed up to 3 months after HSRT, 78 (78%) patients had no acute toxicities; the maximum grade of acute toxicity was grade 2, reported by 4 (4%) patients for GU and 1 (1%) patient for GI toxicity.

There were no significant differences between the two groups regarding the cumulative incidence of acute toxicities.

Table 1. Sociodemographic and clinical characteristics in patients receiving salvage radiotherapy, according to the radiotherapy scheme.

	All patients (n=100)		HSRT				p-value
			65 Gy/26 (n=50)		66 Gy/30 (n=50)		
	n	%	n	%	n	%	
Age at HSRT (years)							
Median (IQR)	70	66–73	70	66–73	69	65–72	p=0.166
ISUP grade group							
1	20	20	8	16	12	24	p=0.195
2	32	32	18	36	14	28	
3	22	22	11	22	11	22	
4	19	19	12	24	7	14	
5	7	7	1	2	6	12	
T stage							
T2a	8	8	4	8	4	8	p=0.713
T2b	9	9	5	10	4	8	
T2c	49	49	22	44	27	54	
T3a	24	24	12	24	12	24	
T3c	10	10	7	14	3	6	
N stage							
pN0	68	68	34	68	34	68	p=1.000
pNx	32	32	16	32	16	32	
Surgical margins							
R–	60	60	28	56	32	64	p=0.541
R+	39	39	21	42	18	36	
Unknown	1	1	1	2	0	0	
Pre-HSRT restaging							
No	79	79	40	80	39	78	p=1.000
Yes	21	21	10	20	11	22	
MLR at pre-HSRT restaging investigation							
No	11	52	6	60	5	45	p=0.670
Yes	10	48	4	40	6	55	
Time between RP and BCR (months)							
Median (IQR)	34	12–62	32	10–56	36	14–69	p=0.328
PSA value at BCR (ng/ml)							
Median (IQR)	0.23	0.20–0.29	0.23	0.20–0.28	0.23	0.20–0.30	p=0.590
PSA before HSRT (ng/ml)							
Median (IQR)	0.30	0.24–0.44	0.31	0.24–0.43	0.30	0.23–0.44	p=0.981
PSA after HSRT (ng/ml)							
Median (IQR)	0.10	0.05–0.20	0.12	0.07–0.20	0.10	0.03–0.17	p=0.135
Nadir PSA (ng/ml)							
Median (IQR)	0.03	0.01–0.15	0.05	0.01–0.18	0.02	0.01–0.10	p=0.442

Abbreviations: HSRT-hypofractionated salvage radiotherapy; IQR-interquartile range; ISUP-International Society of Urological Pathology; MLR-macroscopic local recurrence; RP-radical prostatectomy; BCR-biochemical recurrence

Six (6%) and 2 (2%) patients experienced late Grade ≥2 GU and GI events, respectively. One (1%) patient experienced a late grade 3 GU event consisting of frequent macroscopic hematuria requiring hospitalization, blood transfusions, and hyaluronic acid bladder instillations. Two (2%) patients experienced a late grade 2 GI event consisting of rectal hemorrhage treated with Argon Plasma Coagulation. At the last follow-up, no patient exhibited grade 3 GU toxicity or grade 2 GI toxicity.

Considering the cumulative incidence of late events, no difference emerges between the two groups in terms of late toxicity (Figure 2).

Discussion

SRT is the only therapeutic option, which may offer a curative prospect in patients with BCR of prostate cancer after RP.

Traditionally, SRT has been delivered using conventional protracted regimens. We assumed that the use of hypofractionation in the salvage setting would increase both the efficacy and safety of treatment with several advantages to both the patient and the radiotherapy facility.

Compared to the radical setting, the role of hypofractionation in SRT is still extensively debated. In addition, because of the lack of phase 3 trials to support the use of hypofractionation in the salvage setting, the use of hypofractionated schemes is currently to be considered only as investigational.

In this retrospective study, we focused on HSRT with the aim of evaluating its efficacy, feasibility, and toxicity profile. In addition, our analysis focused on evaluating possible differences between two different HSRT schemes with the aim of thoroughly exploring the potential contribution of hypofractionation in the salvage setting.

Several studies investigating the efficacy of HSRT have been recently published. However, because of the lack of randomized trials, the data on the efficacy of hypofractionated schemes currently stem almost exclusively from the retrospective analysis.

One main issue, in our analysis, concerns the comparability of data between these studies, due to the different selection criteria employed by the authors in each study.

Most of these studies include patient populations, which are extremely heterogeneous, especially with regard to patient characteristics and they make no distinction between adjuvant and salvage treatments. In addition, these studies employ a heterogeneity of techniques and treatment schemes and there is in many cases the concomitant use of pelvic irradiation and ADT.

Furthermore, these studies employ different definitions for disease progression (rising PSA ≥0.2 ng/ml, PSA ≥0.4 ng/ml, PSA ≥2 ng/ml+nadir), which sometimes make the reported outcomes poorly comparable [29].

In our retrospective cohort, we included only patients with selected pathological and clinical characteristics who underwent prostate bed only HSRT delivered with daily IG-VMAT using two distinct hypofractionated schemes and received no ADT.

Our results for bFFS, with a 3- and 5-year cumulative incidence of 65.9% and 52.1%, respectively, are broadly in line with those reported in other published papers. However, it must be emphasized that our data are not influenced by the use of ADT.

In addition, the toxicity profile recorded in our population is characterized by the absence of grade 3 events in the acute setting and by the low percentage of G2-3 events in the late setting (6% and 2% respectively for GU and GI events).

With a patient population similar in size to our study (108 patients), Kruser et al. [30] reported data of salvage RT using

Table 2. 5-year survivals of selected oncological outcomes.

	Events	Survival probability, %			Log-rank test
		1 year	3 years	5 years	
bFFS					
Overall	47	89.0	65.9	52.1	
65 Gy/26	29	88.0	61.9	43.7	p=0.199
66 Gy/30	18	90.0	69.8	62.7	
LC					
Overall	8	98.9	95.1	85.9	
65 Gy/26	5	97.9	92.9	85.6	p=0.471
66 Gy/30	3	100.0	97.4	90.8	
DRFS					
Overall	33	91.0	73.6	63.7	
65 Gy/26	21	89.9	70.3	54.9	p=0.188
66 Gy/30	12	92.0	76.9	74.1	
ADT-FS					
Overall	33	95.0	89.0	73.2	
65 Gy/26	19	98.0	84.0	76.7	p=0.461
66 Gy/30	14	92.0	79.8	70.1	

Abbreviations: bFFS-biochemical failure-free survival; LC-local control; DRFS-distant relapse-free survival; ADT-FS-androgen deprivation therapy-free survival

Table 3. Description of 44 relapses within 5 years from end of radiotherapy in prostate cancer patients undergoing HSRT.

Outcome	All patients		65 Gy/26		66 Gy/30	
	n	%	n	%	n	%
Biochemical relapse only	8	8	5	10	3	6
Clinical recurrence	36	36	21	21	15	30
Local only	5	5	2	4	3	6
Local and locoregional nodes	2	2	2	4	0	0
Local and metastatic site	0	0	0	0	0	0
Locoregional nodes only	16	16	10	20	6	12
Locoregional nodes and metastatic sites	8	8	4	8	4	8
Metastatic sites only	4	4	2	4	2	4
Local and locoregional nodes and metastatic sites	1	1	1	2	0	0
Total	44		26		18	

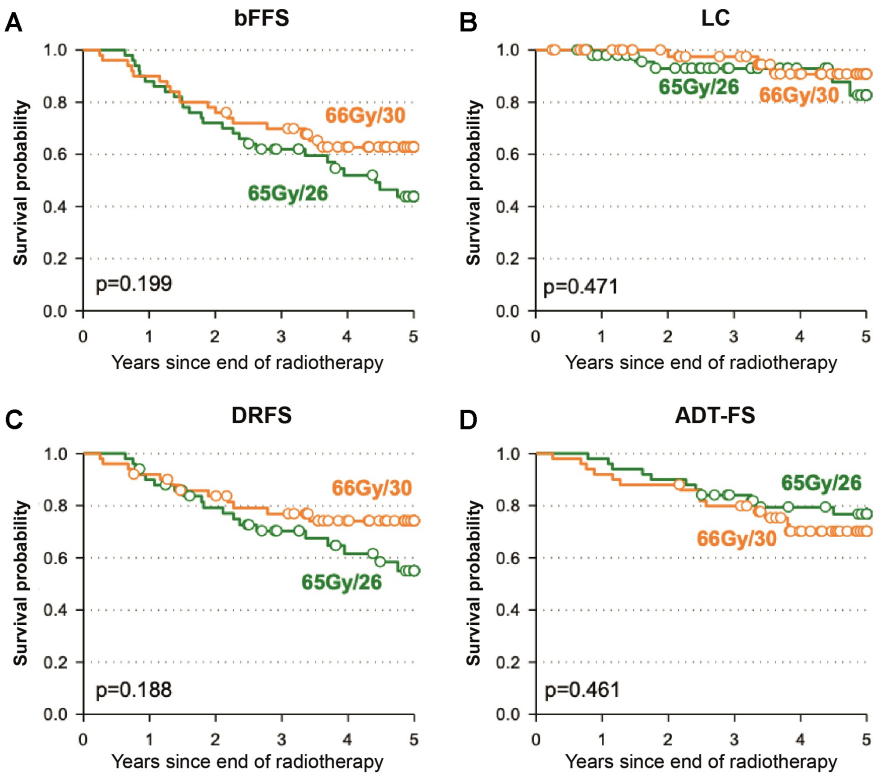

Figure 1. Kaplan-Meier estimates according to the treatment. A) bFFS-biochemical failure-free survival; B) LC-local control; C) DRFS-distant relapse-free survival; D) ADT-FS-androgen deprivation therapy free survival

Table 4. Multivariable hazard ratios (HR) and corresponding confidence intervals (CI)[a] according to clinical characteristics.

	Outcome		
	bFFS	**LC**	**DRFS**
All patients			
Age ≥70 years	1.16 (0.59–2.29)	1.31 (0.27–6.50)	1.26 (0.57–2.78)
ISUP grade group ≥4	2.18 (1.12–4.24)	2.15 (0.41–11.36)	2.68 (1.26–5.71)
Time to BCR <24 months	1.69 (0.84–3.39)	1.12 (0.20–6.23)	1.99 (0.89–4.48)
Restaging pre-HSRT	0.88 (0.31–2.53)	1.25 (0.12–12.78)	0.78 (0.21–2.97)
MLR at staging investigation	0.55 (0.13–2.35)	1.77 (0.12–26.95)	0.57 (0.09–3.46)
Pre-treatment PSA	4.81 (1.08–24.46)	1.94 (0.06–64.51)	3.06 (0.49–19.00)
66 Gy/30 vs. 65 Gy/26	0.81 (0.43–1.52)	0.70 (0.15–3.20)	0.72 (0.34–1.51)

Note: [a]Estimated from Cox proportional hazards model, including all term in the table. Abbreviations: bFFS-biochemical failure-free survival; LC-local control; DRFS-distant relapse-free survival; ISUP-International Society of Urological Pathology; BCR-biochemical recurrence; MLR-macroscopic local recurrence

one of the fractionations we employed in our study (total dose of 65 Gy in 26 fractions) delivered with either IMRT or tomotherapy; although 17% of patients received ADT, at a median follow up of 32 months the reported bFFS was 67%. Similarly, to our findings, higher Gleason scores were associated with biochemical failure thus confirming the first level prognostic role played by the degree of tumor differentiation. Unlike our study, however, a worse acute toxicity profile is reported, characterized in particular by a 14% rate of acute gastrointestinal toxicity.

Comparable to our study for the median pre-treatment PSA value (0.32 ng/ml) and for the hypofractionation scheme used (65 Gy in 26 fractions) is the paper by Lewis et al. [31] who reported the outcomes of 56 patients undergoing either adjuvant or salvage treatment. The 4-year bFFS rate was 75% (but with 18% of patients undergoing neoadjuvant/concomitant ADT treatment), whereas the late toxicity profile was characterized by 28% of patients who developed grade 3 GU toxicity (hematuria) approximately 2 yr after treatment. The authors suggested that the high GU toxicity rate was attribut-

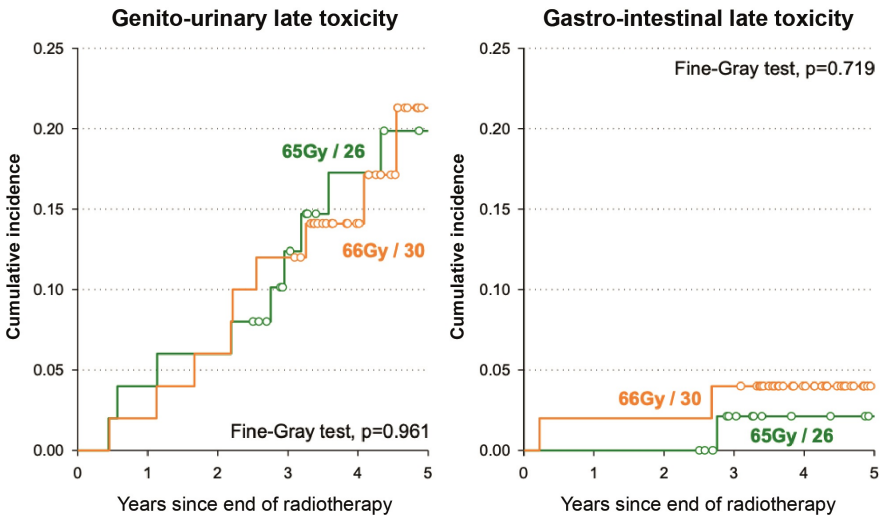

Figure 2. Cumulative incidence of late toxicity according to treatment.

able to the large treatment volume and the high proportion of patients on anticoagulants.

Ferrera et al. [32] reported the results of a retrospective study in a group of 129 patients treated with a very moderate hypofractionation scheme (2.12–2.25 Gy for 29 fractions) similar to one of the schemes we considered (2.2 Gy for 30 fractions). In this study, only 36% of treatments were in the context of salvage therapy, ADT was administered to 50% of patients and a non-negligible percentage of patients received also prophylactic pelvic irradiation. Although there are considerable limitations in comparability with our study, the 4-year bFFS was reported to be 79%. It should be noted that in Ferrera study, no acute G3 toxicity was reported and that late GU G3 toxicity was 1.5%.

Remarkably different are the toxicity data reported by Cozzarini et al. [33]. In his study, 247 patients were treated with RT using several hypofractionated regimens with 18.1% grade 3 GU late toxicities. At multivariate analysis, the dose per fraction (2.35–2.9 Gy/fraction) was an independent predictor of GU toxicity. Other reported causes of such high toxicity rates were the generous margins in the planning of the radiotherapy treatments and the non-negligible percentage of patients undergoing pelvic RT.

In a panorama of studies largely of the retrospective design, Leite et al. [34] carried out a prospective phase II trial to evaluate the safety and feasibility of postoperative HSRT (51 Gy in 15 fractions) delivered to the prostate bed using intensity modulated and image guided radiation therapy techniques. In 61 patients after a median follow-up of 16 months, the bFFS was 95.1%, while acute and late toxicities were significantly high with acute, grade ≥2 GU and GI toxicity rates of 11.5% and 13.1%, and late grade ≥2 GU and GI toxicity 8.2% and 11.5%, respectively.

Table 5. Toxicities in 100 prostate cancer patients undergoing HSRT.

	All patients		65 Gy/26		66 Gy/30		Fisher's exact test
	n	%	n	%	n	%	
Acute genitourinary							
G0	82	82	43	86	39	78	p=0.551
G1	14	14	5	10	9	18	
G2	4	4	2	4	2	4	
Acute gastrointestinal							
G0	93	93	47	94	46	92	p=1.000
G1	6	6	3	6	3	6	
G2	1	1	0	0	1	2	
Late genitourinary							
G0	82	82	41	82	41	82	p=1.000
G1	12	12	6	12	6	12	
G2	5	5	2	4	3	6	
G3	1	1	1	2	0	0	
Late gastrointestinal							
G0	97	97	49	98	48	96	p=1.000
G1	1	1	0	0	1	2	
G2	2	2	1	2	1	2	
G3	0	0	0	0	0	0	

In a larger population sample compared to our study, Viani et al. [35] carried out a cohort study followed by a meta-analysis of 5 retrospective studies. A total of 412 patients were treated with three different hypofractionation schemes (2.5 Gy/fraction for 20 or 25 fractions or 2.63 Gy/fraction for 20 fractions). The reported results are closely similar to those reported in our study with a 73% 3-year bFFS and a 6% and 3% rate of grade ≥2 late GU and GI toxicity, respectively; no grade 3–5 toxicities were reported. Also, consistent with our and Krauser et al. experiences [30], a Gleason score ≥8

was significantly associated with biochemical progression. It is worth noting that according to the authors, the late GU toxicity was associated with EQD2 Gy1.5 ≥70 Gy.

A larger series of patients was evaluated by Mahase et al. [36] in a review of ten retrospective studies. In this review, the emphasis is placed on the extreme heterogeneity of inclusion criteria across the studies and on the different doses and treatment techniques employed. With a median follow-up ranging from 36 to 120 months and bFFS ranging from 51% to 86%, the authors concluded that these studies were similar in the low rate of G3 toxicity.

Advanced radiotherapy techniques such as IMRT and especially VMAT in combination with image-guided radiotherapy (IGRT) offer a significant contribution in reducing the risk of toxicity associated with moderate hypofractionation to the target volume. Therefore, we included in our study only patients undergoing HSRT delivered with daily IG-VMAT in order to evaluate results obtained with the most modern techniques. It should be noted that our toxicity data differ considerably from hypofractionation treatments delivered with less refined treatment techniques.

In a study of moderate hypofractionation with 3D-Conformal Radiation Technique (3D-CRT) by Tramacere et al. [37], 69 patients underwent radiotherapy on the prostatic bed to a total dose of 62.5 Gy in 25 fractions. The data on late toxicity reported 1 grade 4 GU toxicity (urinary fistula), 3 grade 3 GU toxicities (urethral stricture), and 3 patients with grade 2 or greater late GI toxicity (rectal bleeding).

The 3D-CRT technique with a hypofractionation regimen (60 Gy in 20 fractions, three times a week) in the salvage setting was employed also by Ishikawa et al. [38] on 38 patients. With a median follow-up of 62 months, late grade 2 GU morbidities were observed in 13% of patients.

A comparison between techniques was proposed by Alongi et al. [39] who evaluated 172 patients undergoing postoperative moderately hypofractionated RT with either 3D-CRT or tomotherapy/IMRT to the prostate bed. The acute GI toxicity profile was significantly better in the latter group. The authors concluded that the risk of acute GI toxicity after postoperative RT delivered with IMRT was significantly lower than with conventional radiotherapy, mainly due to better bowel sparing.

Three HSRT studies performed with the VMAT technique allow for better comparability with our toxicity data. The study by Fersino et al. [40], in which 125 patients treated with a total dose of 65.5–71.4 Gy, 2.2–2.4 Gy/fr, did not show any G >2 late toxicities. The study by Franzese et al. [41], in which out of 181 patients treated with salvage therapy with the 70 Gy scheme in 25/28 fractions, reported only 5 (2.7%) and 3 (1.6%) patients with grade 3 GU and GI toxicities, respectively. In the study by Valero et al. [42], in which in a population of 113 patients treated with salvage RT hypofractionated by either IMRT or VMAT integrated with Image Guided, the greatest late GU toxicity was G3 in 1% of patients and the greatest late GI toxicity was G2 in 2% of patients.

These studies, in accordance with our experience, suggest a substantial benefit in improving the toxicity profile of HSRT when performed with modern technology.

A distinctive feature of our study is the comparative analysis between the two hypofractionated schemes employed.

Although the peculiar radiobiology of PCa suggests that dose escalation is a key aspect of the improvement of the oncological outcome, our analysis did not show any significant differences in efficacy and toxicity between the two treatment schemes employed, characterized by a different equivalent biological dose.

Our result is consistent with Tandberg et al. [43] who, by comparing the outcomes in 294 patients receiving conventional radiotherapy (66 Gy in 1.8–2 Gy fractions) to the prostatic bed and the outcomes in 167 patients receiving hypofractionated radiotherapy (65 Gy in 2.5 Gy fractions) to the same volume, did not find any significant differences in bFFS. However, hypofractionation seems to be associated with greater acute G2 and late G3 GU toxicity.

The superiority of a normofractionated regimen (66 Gy in 33 fractions) over a hypofractionated scheme (52.5 Gy in 20 fractions) in the biochemical control of disease is reported by Murgic et al. [44]. According to the authors, the superiority of the normofractionated regimen is a result of the lower biological dose of the hypofractionated schedule compared to the normofractionated. Other major limitations reported by the authors are the baseline imbalance in ADT use, ADT duration, and ISUP grade group distribution between the two radiotherapy cohorts.

The non-contribution of an intensified dose of 72 Gy versus a standard dose of 66 Gy to bFFS improvement is also demonstrated by Qi et al. [45] in a group of 144 patients, although in this experience the patients with a higher Gleason score and treated with 72 Gy had a statistically significant improvement in bFFS compared with the 66 Gy cohort.

This finding is consistent with evidence from TCP (Tumor Control Probability) models, which suggests a benefit in biochemical control of disease from an increase of the radiation dose, especially in patients with high PSA or Gleason scores [46].

It should be noted that in the experience by Qi et al. [45] dose escalation was not associated with greater acute or late GU/GI toxicities and that dose escalation did not increase urinary incontinence rates.

Largely consistent with these findings are the data from 3 phase III trials. The SAKK 09/10 [47] trial showed no significant differences in bFFS, clinical PFS, time to ADT, and OS between salvage treatment with conventional dose (64 Gy) versus intensified dose SRT (70 Gy), whereas the trial reported a significant increase in late grade 2 and 3 GI toxicity with the dose intensification scheme. The early NRG-GU003 [48] results reported similar findings. At a median follow-up of 2.1 years, the two treatment regimens, the conventional of 66.6 Gy in 37 fractions and the hypofrac-

tionated of 62.5 in 25 fractions, did not differ in bFFS, nor in the EPIC scores reported at 6–12 and 24 months, respectively. Finally, the final results of the RADICALS-RT [49] trial are expected, which will provide comparison data between two fractionation schemes (66 Gy in 33 fractions and 52.5 Gy in 20 fractions).

A peculiar feature of our study is the exclusion of patients undergoing neoadjuvant/concomitant ADT; this criterion is consistent with our choice to analyze patients with pre-RT PSA less than 1 ng/ml.

In the SRT setting, two randomized controlled studies have explored the addition of ADT. Both the GETUG-AFU-16 [50] and RTOG 9601 [51] demonstrated a benefit on bFFS in this patient setting. Both studies underlined the pivotal role of pre-treatment PSA and agreed on the non-significant impact on metastatic progression and overall survival of ADT for low PSA values. The use and the optimal ADT duration are therefore still debated when associated with salvage RT. Additional findings are awaited from the RADICALS-HD trial (NCT00541047) as well as from the LOBSTER trial (NCT04242017).

An additional distinctive feature of our analysis is the exclusion of patients undergoing simultaneous pelvic irradiation. In most published papers to date on hypofractionated salvage radiotherapy, a significantly variable percentage of patients have undergone pelvic radiotherapy on the basis of a number of risk factors. Therefore, no firm conclusion can be drawn regarding the possible benefits of pelvic irradiation combined with hypofractionated salvage radiotherapy.

Although the available data are difficult to interpret, from a theoretical point of view pelvic irradiation in patients with pN0/pNx BCR after prostatectomy appears to offer a potential benefit mainly for high Gleason scores and/or high pre-treatment PSA values [46]. However, when considering pelvic irradiation, the impact on the toxicity profile must be evaluated [52].

Macchia et al. [53] reported data about 124 patients undergoing either adjuvant or salvage hypofractionated treatment to the prostatic bed and normofractionated to the pelvis; at a median follow-up of 30 months, the authors reported Grade 2 acute GI and GU toxicity in 24.2% and 17.7% of patients, respectively.

The newly published SPPORT trial [54] has contributed to the evaluation of ADT and pelvic irradiation in this patient setting. The comparison between the three treatment groups evaluated in the study at a median follow-up of 8.2 years shows that extending salvage radiotherapy to treat the pelvic lymph nodes in combination with short-term ADT results in a significant reduction in disease progression. Late side effects were similar among the different groups evaluated but for hematological toxicity, which was significantly related to pelvic irradiation with or without ADT. There is evidence both in the SPPORT, the GETUG-AFU-16 and the RTOG 9601 trials of the fundamental prognostic and therapy-driven role of pre-treatment PSA.

In conclusion, high-level evidence for the implementation of HSRT is currently lacking and the next step is to perform RCTs investigating the role of hypofractionation in SRT.

Ongoing phase III RCTs, such as the PERYTON trial (ClinicalTrials.gov Identifier: NCT04642027), the RG GU003 trial (NCT03274687), the SHARE trial (NCT03920033), and the PAROS trial (Deutsches Register klinischer Studien: DRKS00015231) can help to assess the definitive role of hypofractionation in the salvage setting. Of note, among these studies, the 3-arm PAROS trial comprises one arm of hypofractionated treatment delivered with protons.

Our study differs from most prior studies on hypofractionation in the salvage setting in the strict selection criteria employed with the aim of reducing the impact of potential confounding factor, such as ADT, pelvic irradiation, and focal boost. In addition, one of the selection criteria was to include in the analysis only treatments performed with modern technology to evaluate its potential benefits.

Our study offers a comparative analysis between the two hypofractionated schemes in two highly homogeneous groups of patients, compared with other published studies.

On the other hand, we acknowledge some limitations of our study, such as the retrospective design, the small patient sample size, and the follow-up time which, although longer compared with other studies, is potentially inadequate to fully assess the late toxicity and other oncological outcomes.

Overall, despite these limitations, our study shows that HSRT is a feasible and well-tolerated approach with a promising tumor control rate.

These results may contribute to the growing evidence of HSRT as a valid option in the context of salvage therapies for the biochemical recurrence of prostate cancer after prostatectomy.

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