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Original Article

Salvage radiotherapy with volumetric modulated arc therapy (VMAT) for recurrent prostate cancer after high-intensity focused ultrasound (HIFU): A large French retrospective series and literature review

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ABSTRACT

Background and purpose: Although not validated as a standard treatment, high-intensity focused ultrasound (HIFU) is increasingly used in the management of localised prostate cancer (PCa). In case of recurrence after HIFU, treatment is currently not standardised. Our aim was to evaluate normofractionated (NFRT) and hypofractionated (HFRT) salvage radiotherapy (RT) using volumetric modulated arc therapy (s-VMAT) with doses used in first-line management of localised PCa.

Material and methods: We identified all patients with local or locoregional recurrence after HIFU treated with s-VMAT in 3 RT centres between 2014 and 2023. We evaluated acute and late toxicity and oncological outcomes.

Results: Fifty-six patients were identified. Median age at recurrence was 75 (70–80) years. Median time between HIFU and s-VMAT was 26.5 months (13.9–47.2). S-VMAT was delivered to the prostate only in 35 (62.5 %) patients and to the prostate and pelvis in 21 (37.5 %) patients. NFRT and HFRT were delivered in 46 (82.1 %) and 10 (17.9 %) patients, respectively. Androgen deprivation therapy (ADT) was given to 27 (48.2 %) patients. Eighteen (32 %) and four (7 %) patients reported an acute grade 2 genitourinary (GU) and gastrointestinal (GI) adverse event (AE), respectively. Two patients presented with a late grade 2 GU AE, and one with a late grade 2 GI AE. No grade 3+ toxicity was reported. With a median follow-up of 19.5 months (12 – 47), no patient had a biochemical, local or distant relapse.

Conclusions: This is the largest series of salvage RT after HIFU using VMAT and escalated doses (78–80 Gy/39-40Fr., or 60 Gy/20Fr.). Acute toxicity was acceptable and late AEs were few. Longer follow-up is required to assess efficacy. Overall, available series suggest that salvage RT could represent a valuable option in the treatment of relapses after HIFU.

Introduction

High-intensity focal ultrasound (HIFU) represents a seducing minimally invasive approach for the treatment of localised prostate cancer (PCa) with the objective of achieving favourable outcomes and limiting treatment-related adverse events (AEs). Despite encouraging oncological results with large prospective series reporting biochemical progression-free survival around 60 % at 10 years [1,2] and acceptable salvage treatment-free survival rates, especially in low-risk patients [3], HIFU remains a subject of debate and is not currently considered a

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standard of care for localised PCa in national [4] and international guidelines [5].

Patients who eventually relapse after HIFU often require a definitive treatment. However, due to the limited data available on the oncological outcomes and toxicity of salvage definitive therapies, there is currently no consensus on the optimal management. Salvage prostatectomy is often proposed as an option, with few retrospective surgical series which have shown acceptable oncological control with low postoperative incontinence [6] but higher erectile dysfunction compared to primary prostatectomy [7].

Salvage radiotherapy (sRT) could represent a potential therapeutic alternative. In the largest available series in the literature, Riviere et al. have reported promising oncological outcomes in patients receiving salvage conformal RT, with a median dose of 72 Gy delivered after HIFU. However, 4.7 % of patients experienced grade 3 genitourinary (GU) toxicity, one had a grade 4 and one had grade 5 [8]. Since, new techniques have been deployed to improve RT, with one of the most important developments in the past decade being intensity-modulated RT (IMRT). IMRT is an advanced RT technique that combines computerised inverse planning and non-uniform intensity of radiation beams resulting in more conformational treatment volumes and significantly less dose delivered to organs at risk, that is to say critical organs in the surrounding of the treatment volume. The most advanced form of IMRT is volumetric modulated arc therapy (VMAT) which involves radiation beams sweeping in arcs around the patient to deliver a targeted dose with minimal dose to the organs at risk [9]. These dosimetric considerations translate into a significantly reduced risk of acute but also late toxicity with IMRT compared to classic 3D RT [10]. Moreover, IMRT enables the delivery of higher doses to the prostate while sparing organs at risk and different randomised trials have demonstrated an improved biochemical control with dose-escalated RT (prescribed dose: 74 – 80 Gy) with acceptable toxicity [11–14]. Hence, dose-escalated IMRT and VMAT (normofractionated or dose-equivalent hypofractionated IMRT) are considered as a gold standard in the treatment of localised PCa [5].

In the setting of salvage therapy following HIFU, dose-escalated IMRT or VMAT could be a valuable option. However, available data in the literature are from a very limited number of series [15–17], making interpretation of the results challenging. The aim of this report is to present, to the best of our knowledge, the toxicity and early oncologic outcomes of the largest series of patients treated with salvage VMAT (s-VMAT) after HIFU for PCa.

Material and methods

This retrospective study was conducted in three French radiotherapy facilities. Inclusion criteria were (1) adults with histologically proven prostate adenocarcinoma treated with HIFU as primary treatment, (2) biochemical relapse after HIFU defined as $PSA_{nadir} + 1.2\ ng.ml^{-1}$ (as this 'Stuttgart definition' of biochemical relapse was found to be the best to predict clinical failure after HIFU) [18], (3) local recurrence on pelvic magnetic resonance imaging (MRI), 18F-choline positron emission tomography – computed tomography (PET-CT) and/or confirmed by a new series of prostate biopsies, (4) absence of distant metastases. Only patients with a minimum follow-up of 1 year were included. Patients with a history of another cancer, chemotherapy or former radiotherapy were not eligible for inclusion.

Treatments

Treatments were decided by a trained multidisciplinary tumor board in consultation with the patients. All patients included in this study underwent one or two sessions of HIFU, preceded or not by a transurethral resection of the prostate (TURP). HIFU was delivered by trained urologists to perform either a whole prostate ablation (whole-gland approach), a hemi-gland ablation or a focal ablation (not whole-gland approaches) using an Ablatherm® or a Focal One® device.

All patients were treated with s-VMAT at relapse. RT was delivered to the prostate +/- the seminal vesicles (SV) +/- the whole pelvis depending on the initial characteristics of the disease and at relapse. Patients were offered either normofractionated (NFRT) or moderate hypofractionated RT (HFRT). Boosts to involved lymph nodes and concurrent androgen deprivation therapy were allowed.

Outcomes

Toxicity after s-VMAT was assessed by physicians using the Common Terminology Criteria for Adverse Events (CTCAE) v4.0 every six months throughout the follow-up period. Acute and late toxicity were defined as toxicity occurring within six months and at one year and later, respectively. Data were retrospectively collected through chart review.

Oncological outcomes included progression-free survival (PFS), biochemical progression-free survival (bPFS), specific survival (SS), and overall survival (OS). PFS was defined as the time from s-VMAT to local, regional, metastatic recurrence or death of any cause, bPFS as the time between s-VMAT and biochemical relapse ($PSA_{nadir} + 2\ ng.ml^{-1}$, Phoenix definition [19]), SS the time between s-VMAT and death by prostate cancer, OS as the time between s-VMAT and death of any cause.

Statistical analyses

Descriptive analyses were performed using median with quartiles (Q1-Q3) for quantitative variables and percentages for qualitative variables. Fisher's exact test was performed in a univariate analysis to identify predictive factors of acute grade 2 + GU AEs. No multivariate analysis was performed because of a low number of events. Analyses were performed using GraphPad Prism version 9.5.0.

The study was conducted in accordance with the Declaration of Helsinki. No patient-identifying information has been released in the present study.

Results

From January 2014 and march 2023, a total of 56 patients underwent s-VMAT for a local or loco-regional recurrence following HIFU. Patient characteristics before HIFU are shown in Table 1. Median age at diagnosis was 72 years (66–75). Most patients initially presented with a low- (48.2 %) or favourable intermediate-risk (35.7 %) PCa. Forty-two (75 %) patients underwent one HIFU session and 14 (25 %) underwent two sessions. The first session consisted in a not whole-gland ablation for most patients (53.6 %) whereas the second session was delivered to the whole gland in 7 (50 %) of concerned patients. A TURP procedure was performed on 37 (66.1 %) patients before or during the HIFU procedure.

Patient characteristics at recurrence are detailed in Table 2. Median age at recurrence was 75 years (70–80). Median time between the last HIFU session and s-VMAT was 26.5 months (13.9–47.2). Twenty-two (39.3 %) patients had a biopsy-proven local recurrence. In all other patients, at least a pelvic MRI or a 18F-choline PET-CT scan was performed to assess the local recurrence. Forty-three (76.8 %) and 13 (23.2 %) had a local and locoregional recurrence, respectively. S-VMAT was delivered to the prostate (+/- SV) only in 35 (62.5 %) patients and to the prostate and pelvis in 21 (37.5 %) patients. NFRT and HFRT were delivered to 46 (82.1 %) and 10 (17.9 %) patients, respectively. The main regimen were 78 Gy to the prostate and 50 Gy to the pelvis with NFRT and 60 Gy to the prostate and 44 Gy to the pelvis with HFRT. Androgen deprivation therapy was administered to 27 (48.2 %) patients, with a median duration of six months (6–24).

There were no reports of grade 3+ acute or late GU or gastrointestinal (GI) toxicity and notably, no cases of recto-urethral fistula were identified. Overall incidences of GU and GI AEs are shown in Table 3.

Eighteen (32 %) patients reported an acute grade 2 GU AE. The most common acute grade 2 AE was urinary urgency. A univariate analysis

Table 1
Patient characteristics before HIFU.

	$n = 56$
Age (years), median (Q1 – Q3)	72 (66–75)
Clinical stage	
T1c	38 (67.8 %)
T2a	14 (25 %)
T2b	2 (3.6 %)
T2c	2 (3.6 %)
T3	0
ISUP classification	
1	31 (55.4 %)
2	22 (39.4 %)
3	2 (3.6 %)
4	1 (1.8 %)
PSA (ng/ml) at diagnosis	
Mean (SD)	7.62 (2.63)
Median (IQR)	7.15 (5.52–9.10)
Risk group	
Low	27 (48.2 %)
Favourable intermediate	20 (35.7 %)
Unfavourable intermediate	8 (14.3 %)
High	1 (1.8 %)
Number of HIFU sessions	
1	42 (75.0 %)
2	14 (25.0 %)
Type of HIFU – first session	
Whole gland	23 (41.1 %)
Hemi-gland or Focal	30 (53.6 %)
NR	3 (5.4 %)
Type of HIFU – second session	
Whole gland	7 (50 %)
Hemi-gland or Focal	5 (35.7 %)
NR	2 (14.3 %)
Nadir PSA (ng/ml) after HIFU	
Mean (SD)	2.74 (2.30)
Median (IQR)	2.20 (0.77–4.40)

HIFU: high-intensity focused ultrasound, Q1 – Q3: quartile 1 – 3, ISUP: International Society of Urological Pathology, PSA: prostate-specific antigen.

Table 2
Patient and treatment characteristics for s-VMAT.

	$n = 56$
Age (years), median (Q1-Q3)	75 (70–80)
Time between HIFU and salvage RT (months), median (IQR)	26.5 (13.9–47.2)
PSA (ng/ml) at recurrence	
Mean (SD)	6.08 (2.75)
Median (IQR)	5.80 (4.18–7.00)
Exams performed at recurrence	
Prostate biopsies	22 (39.3 %)
Prostate MRI	22 (39.3 %)
18F-choline PET/CT	30 (53.6 %)
Bone scintigraphy + CT scan	18 (32.1 %)
Type of recurrence	
Local	43 (76.8 %)
Locoregional	13 (23.2 %)
RT fractionation	
Normofractionation	46 (82.1 %)
Hypofractionation	10 (17.9 %)
RT volumes, overall population / NF / HF	
Prostate (+/- SV) only	35 (62.5 %) / 29 (63 %) / 6 (60 %)
Pelvis	21 (37.5 %) / 17 (36.9 %) / 4 (40 %)
Lymph nodes boost	8 (14.3 %) / 7 (15.2 %) / 1 (10 %)
RT dose to the prostate (NF/HF) (Gy), median (Q1-Q3)	78 (78–80) / 60 (60–60)
RT dose to the pelvis (NF/HF) (Gy), median (Q1-Q3)	50 (46–50) / 44 (44–44)
Androgen deprivation therapy	27 (48.2 %)
Duration (months), median (IQR)	6 (6–24)
Second-generation anti-androgen	1 (1.8 %)
Duration (months)	8

s-VMAT: salvage volumetric modulated arc therapy, Q1 – Q3: quartile 1 – 3, HIFU: high-intensity focused ultrasound, MRI: magnetic resonance imaging, PET/CT: positron emission tomography – computed tomography, RT: radiotherapy, NF: normofractionation, HF: hypofractionation

was performed to identify predictive factors of grade 2 GU AEs. The irradiated volume (pelvis *vs* prostate alone), the fractionation (HFRT *vs* NFRT) and the performance of a TURP procedure before HIFU were not found to be associated with a reduction in GU AEs (Table 4).

Two patients presented with a late grade 2 GU AE: one had grade 2 urinary urgency and one underwent a TURP procedure for a grade 2 urinary retention. One patient experienced incontinence following the HIFU procedure, prior to the commencement of s-VMAT.

Four patients reported an acute grade 2 GI AE, corresponding to diarrhoea that resolved within a few weeks after the end of RT. One patient presented with a grade 2 rectal haemorrhage nine months after s-VMAT, requiring a treatment with plasma argon.

There was no significant difference in acute and late toxicity between patients treated with HFRT and NFRT (supplementary table 1).

Median follow-up was 19.5 months (12 – 47). The median PSA level at recurrence was 5.80 $ng.ml^{-1}$ (4.18 – 7.00) and the PSA_{nadir} after s-VMAT was 0.09 $ng.ml^{-1}$ (0.00 – 0.49). During the follow-up period, no patient had a local or distant relapse and no patient died. Oncologic outcomes are reported in Table 5.

Discussion

Over the past decade, HIFU has been evaluated as a new approach for the treatment of localised prostate cancer. It has been reported that 15 to 35 % of patients with low- or intermediate-risk prostate cancer eventually experience a local or loco-regional relapse following HIFU treatment [1–3]. The HIFI trial was the first to prospectively compare HIFU and radical prostatectomy in men (over 70 years of age in the HIFU arm) with low- or intermediate-risk PCa [20]. In this French multicentre non-randomised non-inferiority study including 3328 patients, the salvage

Table 3
Acute and late adverse events following s-VMAT.

	Grade 1	Grade 2	Grade ≥ 3
Early AEs			
GU	25 (45 %)	18 (32 %)	–
GI	33 (59 %)	4 (7 %)	–
Late AEs			
GU	23 (41 %)	2 (4 %)	–
GI	6 (11 %)	1 (2 %)	–

s-VMAT: salvage volumetric modulated arc therapy, AEs: adverse events, GU: genitourinary, GI: gastrointestinal.
Toxicity after s-VMAT was assessed by physicians through the Common Terminology Criteria for adverse Events (CTCAE) v4.0 every six months during the follow-up period. Acute and late toxicity were defined as toxicity occurring within 6 months and at 1 year and later, respectively.

Table 4
Univariate analysis of risk factors for acute G ≥ 2 genitourinary AEs after s-VMAT.

Risk factor	p-value	OR	95 % CI
HIFU sessions: 2 *vs* 1	0.34	1.88	0.55 – 6.41
RT volume: pelvis *vs* prostate alone	0.55	0.59	0.19 – 2.01
Fractionation: HF *vs* NF	0.14	0.17	0.01 – 1.15
TURP procedure before/during HIFU	0.76	0.74	0.24 – 2.64

P-values were calculated with Fisher's exact test. 95% CI were derived from the Baptista-Pike method.
AE: adverse event, VMAT: volumetric modulated arc therapy, HIFU: high-intensity focused ultrasound, RT: radiotherapy, HF: hypofractionation, NF: normofractionation, OR: odds ratio, CI: confidence interval.

Table 5
Oncologic outcomes.

Median follow-up (months)	19.5 (5.5–47.0)
bPFS	100 %
PFS	100 %
SS	100 %
OS	100 %
median nadir PSA (ng/ml)	0.09 (0.00–0.49)

bPFS: biochemical progression-free survival, PFS: progression-free survival, SS: specific survival, OS: overall survival.

therapy-free survival after HIFU was found to be non-inferior to that reported after RP at the pre-planned 30-month follow-up (89.8 % in the HIFU arm vs 86.2 %; p = 0.008). Additionally, patient-reported functional outcomes such as urinary continence and erectile function were significantly improved with HIFU. Despite the short follow-up period, these promising results may lead to an increase in the number of HIFU procedures in the future. In this context, there is a need to evaluate treatments for recurrence after HIFU.

Along with salvage surgery [7], radiotherapy may represent an option of choice, particularly since the advent of techniques such as IMRT or VMAT which reduce the toxicity of treatment [10]. This report presents the data from the largest series of salvage radiotherapy with VMAT to our knowledge. We also searched for other series of salvage RT post-HIFU in the literature and summed up the data in Table 6.

The acute toxicities described here are within an acceptable range, with grade 2 GU and GI toxicities found in 32 % and 7 % of patients respectively. These findings are consistent with those of previous series [15–17,21,22] examining the use of IMRT or VMAT as salvage treatment after HIFU. These studies, which included a total of 12 to 38 patients, reported grade 2 acute toxicity rates ranging from 0 % [17,21] to 26.6 % [15] for GU toxicity and from 0 % [17] to 20 % [15] for GI toxicity. In addition, the incidence of late toxicity was low in the present report, with only two patients experiencing a grade 2 urinary AE, one patient experiencing a grade 2 GI AE, and no instances of grade 3 + toxicity. Once more, these findings align with the low rates of late toxicity observed in the existing literature on salvage RT series with IMRT or VMAT (see Table 6). It is noteworthy that the incidence of late toxicity was lower in our series than in those with 3D RT [8,23,24]. Indeed, in the largest series published to date, Riviere et al. reported a 23 % incidence of late grade 2 GU AEs and a 6 % incidence of late grade 3 AEs with 3D RT. By optimising dosimetry, IMRT and VMAT may confer advantages in terms of tolerance when compared to 3DRT in patients with post-HIFU recurrence, as in patients receiving RT as first treatment for localised PCa [10].

Furthermore, 10 patients in our study were treated with a hypofractionated regimen. As in the rest of the series, no major acute or late toxicity was reported in these patients, in line with the findings of Rigo et al [21]. In the univariate study of predictive factors for grade 2 GU toxicity, HFRT was not associated with an increase in toxicity and there was no significant difference in acute and late toxicity between patients in the HFRT and NFRT cohorts. HFRT therefore appears to be well tolerated after HIFU, even if data are currently scarce.

It should be noted that tolerance was assessed retrospectively, via chart review. During monitoring consultations, physicians reported the toxicities observed, but did not always use a validated instrument such as the IPSS. This limits the robustness of our results. To ensure the quality of future studies, the use of validated instruments and patient-reported outcomes must be discussed.

Although our series focused on the toxicity of s-VMAT, oncological results were reported. None of the patients had a recurrence. These findings should be examined with caution due to the limited follow-up period (median follow-up of 19.5 months). However, it is noteworthy that the most recent series also reported no biochemical or clinical recurrence before 24 months of follow-up [16,17,22,25]. In contrast, the initial studies conducted by Pasticier et al. [23] and Riviere et al. [8] showed early recurrences. This may be attributed, at least in part, to the heterogeneity of the populations included in all the series that makes them difficult to compare. The prescribed dose may also be responsible for these findings. The mean dose prescribed in the Riviere et al. study was 72 Gy, compared to an escalated dose of 78–80 Gy for NFRT or 60 Gy for HFRT (EQD2 78 Gy with $\alpha/\beta = 1.5$ Gy) in our series. Similar doses to ours were observed in series from Di Lalla et al. and Huang et al. (see Table 6). As in the initial management of localised PCa [13], dose escalation may be an effective strategy for improving post-HIFU local control.

Another potential explanation is the use of ADT in nearly 50 % of our population, as well as the majority of patients in series published between 2021 and 2022 [16,17,22,25], in contrast to the initial series [8,23,26]. The combination of ADT and RT has been proven to be an effective treatment for patients with treatment-naïve localised PCa, based on robust level 1 evidence [27]. To the best of our knowledge, there is currently no data available on the use of ADT in combination with RT following HIFU. Consequently, prescriptions are usually made on an individual basis, taking into account the histological characteristics (ISUP score), the biochemical features (PSA doubling time, initial and/or recurrence PSA level) of the patient, and the clinician's assessment. However, the significance of these factors remains uncertain. In this series, the addition of ADT to s-VMAT was not associated with improved oncological outcomes as no recurrence was observed in the whole population. It is possible that the follow-up period was not sufficiently long to observe differences between the groups. Further studies with longer follow-up periods would provide valuable insight into the optimal dose and the potential benefits of hormone therapy in this context.

It is essential to exercise caution when interpreting data from previous studies, given their limited sample size (ranging from 7 to 38) and retrospective design. Despite the inclusion of a larger population of 56 patients, our study is not immune to the aforementioned weaknesses. This can be attributed to the fact that HIFU is not yet a primary treatment option for localised PCa. Consequently, patients who have experienced recurrence are uncommon, and the treatment provided at recurrence is dependent on the prevailing practices of the centre, the preferences of the clinicians, and the patient's decision. Another limitation is that only 40 % of patients in this series underwent prostate biopsies to diagnose local recurrence. In the remaining cases, the diagnosis of recurrence was based on a combination of radiological data (MRI and/or PET-CT) and an elevation in PSA levels. The diagnostic work-up for suspected local recurrence after a HIFU procedure is not currently standardised, and some teams do not systematically propose biopsies [15,21,26]. While this may increase the heterogeneity of our population, our objective was to present "real-life" results, in which assessments may differ from one patient to another. Finally, it must also be acknowledged that the follow-up period is relatively short and therefore insufficient to provide an accurate assessment of the efficacy and late toxicity of s-VMAT. Nevertheless, we are continuing to monitor the patients and intend to publish new data from this series in the coming years.

Conclusions

The results from this retrospective series indicate that s-VMAT with escalated RT doses is well tolerated, with no early biochemical relapse. In conjunction with other studies in the literature, this research strengthens the case that radiotherapy can be considered a valuable option in patients presenting with a recurrence after HIFU. The choice between salvage treatments such as radical prostatectomy and radiotherapy must be made by a multidisciplinary tumour board in consultation with the patient, taking into account the toxicity profile of the different therapies.

Despite this series representing the largest evaluation of s-VMAT to

Table 6
Review of studies exploring salvage RT after HIFU.

First author, year	Inclusion period	N	Treated volumes	Fractionation, dose	RT technique	ADT use, duration	Median follow-up	Efficacy outcomes	Toxicity
Pasticier, 2008	1995–2004	45*	CTV 1 = Prostate + SV+/- ilio-obturator chains CTV 2 = Prostate	NFRT D = 45 Gy in 25 Fr. D = 68–72 Gy	3D conformal EBRT	No*	37 mo	5-year DFS = 64 % 5-year SS = 100 %	Acute GI: N. R., Late GI: G2 6/45 Acute GU: N. R. Late GU: G2 4/45, G3 1/45
Riviere, 2010	1995–2008	100*	CTV = Prostate	NFRT D_{median} = 72 (68–78) Gy	3D conformal EBRT	No*	33.0 mo	5-year PFS = 72.5 % 10 (12 %) deaths 1 (0.01 %) death from cancer	Acute GI: G2 15 % Late GI: G2 2 % Acute GU: G2 21 %, G3 3.5 % Late GU: G2 23 %, G3 6 %
Ripert, 2012	2004–2008	7	CTV 1 = Prostate + SV CTV 2 = Prostate	NFRT D = 46 Gy in 23 Fr. D = 74 Gy in 37 Fr.	3D conformal EBRT	0/7	36.5 mo	3-year DFS = 83.3 % 3-year OS = 100 %	Acute/late G2 + toxicity: N.R. Late GU: G3 1/6
Munoz, 2013	2004–2011	24	CTV = prostate + SV +/- ilio-obturator chains	NFRT D = 66.6–78 Gy	3D conformal EBRT	7/24 24 or 36 months	40.3 mo	3-year bPFS = 77.8 %	Acute GI: G2 4.2 % Late GI: G3 4.2 % Acute GU: G2 12.5 %, G3 8.3 %, G4 4.2 % Late GU: G3 16.7 %
Alongi, 2014	2005–2011	15	CTV 1 = prostate CTV 2 = prostate + SV CTV 3 = prostate + SV + pelvic lymph nodes (n = 8/15)	HFRT D_{median} = 71.4 Gy in 28 Fr. D_{median} = 65.5 Gy in 28 Fr. D_{median} = 51.8 Gy in 28 Fr.	VMAT, SIB	7/15 2 – 20 mo	12 mo	3/15 (20 %) patients presented a biochemical recurrence	Acute GI: G2 3/15 Late GI: G2 1/15 Acute GU: G2 4/15 Late GU: G2 1/15 No G3 + toxicity reported
Lee J, 2014	2003–2012	10	CTV = prostate + SV	NFRT D_{mean} = 70.4 Gy (70–76) Or EBRT 37.5 Gy + HDR brachytherapy (^{192}Ir) 14 Gy boost (n = 1)	3D conformal EBRT +/-brachytherapy boost	4/10	42.3 mo	5-year bPFS = 100 % 5-year SS = 100 %	GU: G2 + 3/10
Rigo, 2020	N.R.	24	CTV 1 = prostate + SV CTV 2 = prostate CTV 3 = pelvic lymph nodes CTV = prostate	HFRT (n = 16) D = 65.5 Gy in 28 Fr. D = 71.4 – 74.4 Gy in 28 Fr. D = 50.4 – 51.8 Gy in 28 Fr. Or SBRT (n = 8) D = 30 – 35 Gy in 5 Fr.	VMAT, SIB	5/24	31 mo for HFRT 15 mo for SBRT	Complete local control after RT (PET evaluation) = 96 % 7 (29.2 %) biochemical failure during follow-up	Acute GI: G2 3/24 Late GI: N.R. Acute GU: G2 0/24 Late GU: N. R. No G3 + toxicity reported
Von Hardenberg, 2021	2011–2020	13	N.R.	NFRT (n = 12) D = 74 – 80 Gy in 40 Fr. Or HFRT (n = 1), D = 60 Gy in 20 Fr.	N.R.	6 / 13 6 mo or more	34.5 mo	3-year PFS = 100 %	N.R.
Mesci, 2022	2009–2017	14	CTV = prostate	NFRT D = 70–74 Gy in 35–37 Fr.	IMRT or VMAT	7/14	54 mo	5-year bPFS = 100 %	Acute GI: G2 1/14 Late GI: G2 1/14 Acute GU:

(*continued on next page*)

Table 6 (*continued*)

First author, year	Inclusion period	N	Treated volumes	Fractionation, dose	RT technique	ADT use, duration	Median follow-up	Efficacy outcomes	Toxicity
									G2 3/14 Late GU: G2 1/14 No G3 + toxicity reported
Di Lalla, 2022	2013–2018	12	CTV = prostate + proximal 1 cm SV SIB to gross tumor or positive pelvic lymph nodes accepted	NFRT (n = 11) D_{mean} = 76–78 Gy in 38–39 Fr. Or HFRT (n = 1) D_{mean} = 66 Gy in 22 Fr.	IMRT, SIB	9/12	46 mo	5-year bFFS = 83.3 % 5-year MFS = 83.3 % 5-year OS = 100 %	Acute GI: G2 0 % Late GI: G2 0 % (n = 9) Acute GU: G2 0 % Late GU: G2 0 % (n = 9) No G3 + toxicity reported
Huang, 2022	2009–2019	38	CTV 1 = prostate + SV +/- pelvic lymph nodes CTV 2 = prostate + SV CTV 3 = prostate + SV + pelvic lymph nodes (n = 8/15)	NFRT D = 44–50 Gy in 1.8 – 2 Gy/Fr. D_{median} = 65.5 Gy in 28 Fr. D_{median} = 51.8 Gy in 28 Fr.	IMRT	100 %	45.9 mo	5-year bPFS = 73 % 5-year OS = 80.3 %	Acute GI-GU: G2 3/38 Late GI-GU: G2 5/38, G3 3/38
Baude, 2024 (present study)	2014–2023	56	CTV1 = prostate +/- SV CTV2 = pelvic lymph nodes (optional)	NFRT (n = 46) D_{median} = 78 Gy in 39 Fr. D_{median} = 50 Gy in 25 Fr. Or HFRT (n = 10) D_{median} = 60 Gy in 20 Fr. D_{median} = 44 Gy in 20 Fr.	VMAT SIB possible	27/56	19.5 mo	No biochemical, local or distant recurrence	Acute GI: G2 7 % Late GI: G2 2 % Acute GU: G2 32 % Late GU: G2 4 % No G3 + toxicity reported

RT: radiotherapy, ADT: androgen deprivation therapy, CTV: clinical target volume, SV: seminal vesicles, NFRT: normofractionated RT, Fr.: fractions, D: dose, 3D: 3-dimensional, EBRT: external beam RT, mo: months, DFS: disease-free survival, SS: specific survival, GI: gastrointestinal, GU: genitourinary, PFS: progression-free survival, OS: overall survival, bPFS: biochemical progression-free survival, HFRT: moderated hypofractionated RT, VMAT: volumetric modulated arc therapy, SIB: simultaneous integrated boost, HDR: high dose rate, SBRT: stereotactic body RT, PET: positron emission tomography, IMRT: intensity-modulated RT, bFFS: biochemical failure-free survival, MFS: metastasis-free survival, N.R.: not reported.
*N = 45, n = 32 for the evaluation of efficacy outcomes.
*N = 100, n = 83 for the evaluation of efficacy outcomes.

date, several questions remain unanswered. These include the optimal dose of radiotherapy and the combination of ADT with RT, which will require further investigations with longer follow-up.

CRediT authorship contribution statement

Jérémy Baude: Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Charles Teyssier:** Writing – review & editing, Methodology, Investigation, Formal analysis. **Vincent Barbier:** Writing – review & editing, Formal analysis. **Jack-Charles Tremeaux:** Methodology, Conceptualization. **Caroline Azélie:** Writing – review & editing, Investigation. **Alexis Lépinoy:** Writing – review & editing, Investigation, Conceptualization. **Pierre-Charles Henry:** Writing – review & editing, Investigation. **Vincent Bailly:** Writing – review & editing, Formal analysis. **Nicolas Lescut:** Writing – review & editing, Investigation, Conceptualization. **Edouard Lagneau:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization. **Benjamin Schipman:** Writing – review & editing, Validation, Supervision, Methodology, Conceptualization.

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 material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2024.110665.

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