World Journal of Urology (2023) 41:3333–3344
https://doi.org/10.1007/s00345-023-04605-7

TOPIC PAPER

Stereotactic body radiation therapy after radical prostatectomy: current status and future directions

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Received: 18 July 2023 / Accepted: 28 August 2023 / Published online: 19 September 2023

Abstract

Purpose Around 40% of men with intermediate-risk or high-risk prostate cancer will experience a biochemical recurrence after radical prostatectomy (RP). The aim of this review is to describe both toxicity and oncological outcomes following stereotactic body radiation therapy (SBRT) delivered to the prostate bed (PB).

Method In april 2023, we performed a systematic review of studies published in MEDLINE or ClinicalTrials.gov according to Preferred Reporting Items for Systematic Reviews, using the keywords "stereotactic radiotherapy" AND "postoperative" AND "prostate cancer".

Results A total of 14 studies assessing either adjuvant or salvage SBRT to the whole PB or macroscopic local recurrence (MLR) within the PB, and SBRT on radiorecurrent MLR within the PB were included. Doses delivered to either whole PB or MLR between 30 to 40 Gy are associated with a low rate of late grade ≥ 2 genitourinary (GU) toxicity, ranging from 2.2 to 15.1%. Doses above 40 Gy are associated with increased rate of late GU toxicity, raising up to 38%. Oncological outcomes should be interpreted with caution, due to both short follow-up, heterogeneous populations and androgen deprivation therapy (ADT) use.

Conclusion PB or MLR SBRT delivered at doses up to 40 Gy appears safe with relatively low late severe GU toxicity rates. Caution is needed with dose-escalated RT schedules above 40 Gy. Further prospective trials are eagerly awaited in this disease setting.

Keywords Prostate cancer · Stereotactic body radiation therapy · Postoperative · Macroscopic recurrence · Re-irradiation

Introduction

Biochemical recurrence (BCR) occur in up to 40% of men following radical prostatectomy (RP) [1–4]. Adjuvant radiotherapy (RT) has demonstrated at least a twofold reduction in BCR in four randomized trials [5–8] and a potential benefit in terms of both metastasis-free and overall survival has been shown for patients harboring high-risk pathological features [9]. While adjuvant RT could be still considered for men with adverse pathological features [10, 11], early

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salvage RT represents to date the preferred approach for most men, associated with a 5-year biochemical progression-free survival rates ranging from 85 to 90% [12–15]. In the post-operative setting, the target volume is represented by the prostate bed (PB), encompassing areas deemed at high risk of recurrence (vesicourethral anastomosis, retrovesical region, bladder neck) [16–21]. Yet, up to 8% undergoing either adjuvant or salvage prostate bed radiotherapy (PBRT) will experience further local recurrence [22], highlighting the need for an adequate radiation dose and target volume definition.

Recent advances in imaging techniques with positron emission tomography with computed tomography (PET/CT) using new radiotracers have demonstrated both higher sensitivity and specificity than conventional imaging in detecting recurrence after RP [23]. In the recurrent setting, prostate specific membrane antigen (PSMA) PET/CT recently demonstrated excellent detection rates even at low PSA values (33% for PSA levels $\leq$ 0.2 ng/mL) [24], revealing unsuspected PB recurrence in 27% of the patients [25]. Following salvage prostate bed radiotherapy, radiorecurrent relapses within the prostate bed are scarce (less than 5%) but difficult to manage [26].

Together with the advances in RT techniques and the evidence of a low α/β for prostate cancer [27], an increasing interest has been demonstrated with the use of stereotactic body radiotherapy (SBRT) in several clinical settings. Moderately hypofractionated and extremely hypofractionated RT have become standard of care in the management of patients with localized prostate cancer [10]. In the post-operative setting, moderate hypofractionation demonstrated long-term disease control comparable to conventionally fractionated RT [28]. While several trials first suggested the safety of moderately hypofractionated schedules for PBRT [29–32], the further report of unexpected severe late GU toxicity long discouraged the development of further hypofractionated trials in this clinical setting [33, 34].

This systematic review aims to describe both toxicity and oncological outcomes following SBRT delivered to the PB after RP.

Material and methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines [35]. A systematic search of the literature was performed in April 2023 on Pubmed, using the MeSH terms "stereotactic radiotherapy" AND "postoperative" AND "prostate cancer". Studies were eligible if they reported either oncologic or toxicity outcomes, for patients receiving SBRT (defined as doses > 6 Gy per fraction) on either the whole PB or macroscopic recurrence within the PB. There was no period restriction. This search allowed to retrieve a total of 53 articles. After identification, based on abstract reading, a total of 34 reports was excluded (SBRT for oligometastatic disease, SBRT as primary treatment), leaving a total of 19 articles assessed for eligibility. Studies recruiting both patients with prostate and PB recurrence were excluded. After full-text reading, a total of 14 articles were included in this review. One trial was additionally retrieved from the bibliography of another article. The selection process is resumed in the PRISMA flow-chart (Fig. 1). We also searched ClinicalTrials.gov for ongoing or completed studies assessing SBRT after radical prostatectomy.

A narrative synthesis of the data was performed. The articles have been classified by clinical field, including: adjuvant or salvage SBRT on the whole PB, SBRT on macroscopic local recurrence (MLR) within the PB, SBRT on radiorecurrent MLR within the PB. The primary outcome of this review focused on toxicity after post-operative SBRT. Secondary outcomes included biochemical control, local control and type of recurrences.

Results

Adjuvant or salvage SBRT to the whole PB

Toxicity

There are still scarce data on adjuvant or salvage SBRT to the whole PB (Table 1). Lucchini et al. recently reported the acute toxicity outcomes of 30 men treated within the POP-ART trial [36]. While a MLR within the PB was reported in 26% of the men, the target volume consisted in the whole PB treated at a total dose of 31 or 32.5 Gy, in 5 fractions. No patient reported either acute GU or GI grade $\geq$ 2 toxicity. Ma et al. reported the largest series of men receiving PB SBRT, treated within the SCIMITAR prospective phase II trial [37]. A total dose of 30–34 Gy in 5 fractions was delivered to the whole PB. Pelvic lymph node RT was performed in 27% of men, at a total dose of 25 Gy in 5 fractions. Men diagnosed with MLR received a simultaneous integrated boost at a dose up to 40 Gy in 5 fractions. Satisfactory toxicity outcomes were demonstrated, with a report of 9% and 1% of late grade 2 and grade 3 GU toxicity, respectively. Two further trials were performed to assess the impact of dose-escalation to

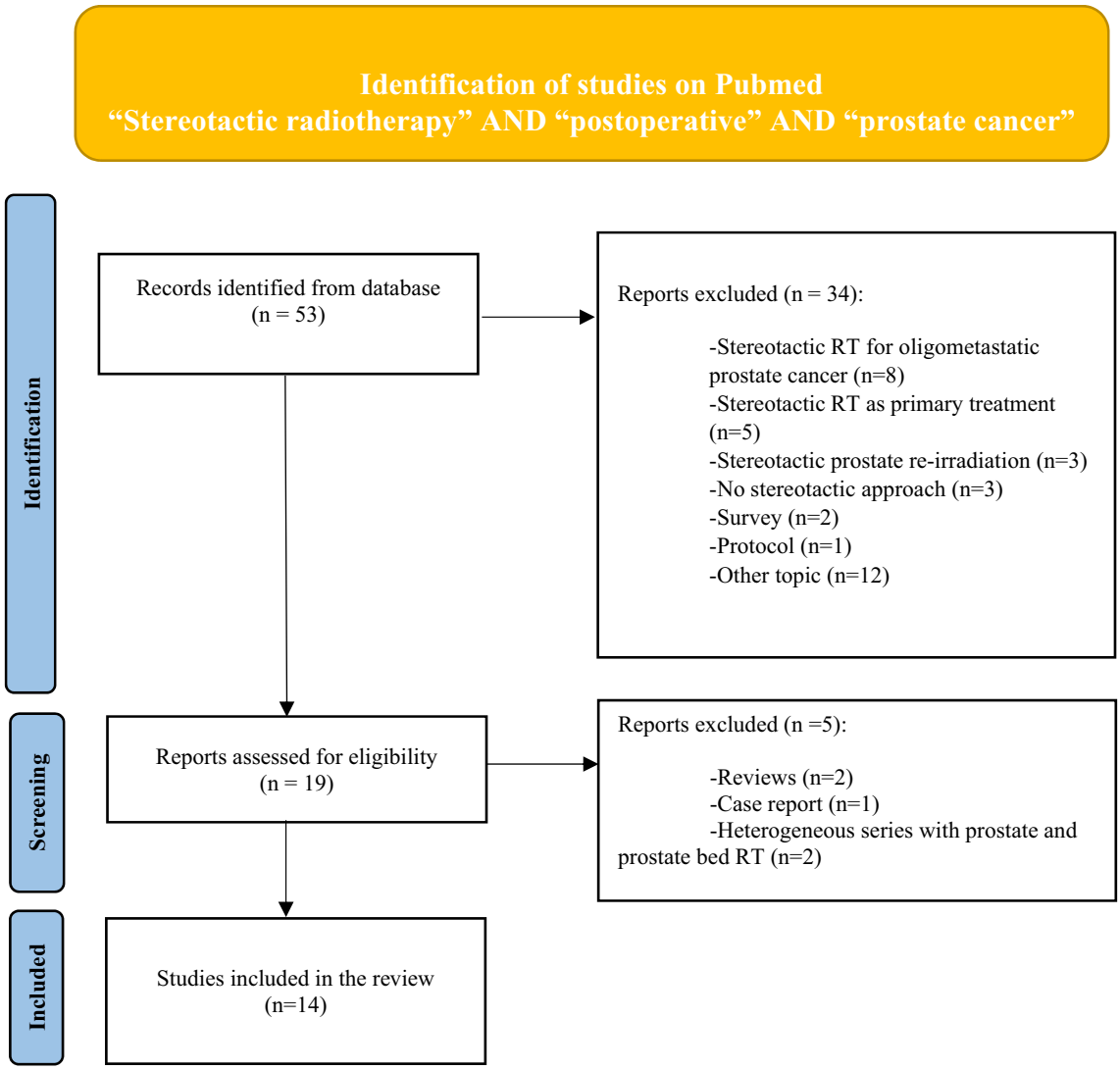

Fig. 1 PRISMA study flow-chart. *RT* radiotherapy

the PB using SBRT. Sampath et al. reported the outcomes of 26 men, receiving either 35 Gy, 40 Gy and 45 Gy, in 5 fractions to the whole PB [38]. An endorectal balloon filled with 70–80 cc of air was placed before treatment. Within a follow-up of 40 months, no dose-limiting toxicity was observed. Late grade ≥ 2 and grade ≥ 3 GI were observed in 11% and 0% of men, respectively. Concerns can be raised with regards to late GU toxicity, as grade ≥ 2 and grade ≥ 3 toxicity occurred in 38% and 15% of men, respectively. Grade 3 GU toxicity consisted of ureteral stenosis requiring the placement of a ureteral stent (7.5%) and incontinence requiring the placement of an artificial sphincter. No difference was observed in late GU toxicity between men treated at the dose of 40 Gy and 45 Gy. Ballas et al. reported the outcomes of another dose-escalation trial, recruiting 24 men requiring either adjuvant or salvage PBRT [39]. Men were allocated to receive either 54 Gy in 15 fractions, 47 Gy in 10 fractions, or 35.5 Gy in 5 fractions, delivered to the whole PB. A high rate of acute grade 2 GI toxicity was reported (either proctitis or rectal hemorrhage), raising up to 50%. Most of these toxicities resolved by 10 weeks, with only 4.2% of men reporting late grade 2 GI toxicity. With regards to GU toxicities, acute and late grade 2 toxicity occurred in 16.6% and 0% of the patients, respectively. Ozyigit et al. reported the outcomes after PB SBRT, in a small retrospective cohort of 66 men [40]. All patients received a total dose of 35 Gy in 5 fractions, either with an adjuvant (41%) or a salvage (59%) intent. Few patients (15%) received pelvic

Table 1 Studies assessing adjuvant or salvage stereotactic radiotherapy on the whole prostate bed

Author	Trial design	Number of patients	Median PSA at recurrence (ng/mL)	Imaging modality	ADT	Target volume	RT technique	RT dose	Median follow-up	Toxicity outcomes	Oncological outcomes
Ma et al., 2022 (SCIMITAR)	Phase II trial	100	0.3 ng/mL	Pelvic MRI Bone scan CT scan PET/CT (76%)	41% of the patients	Whole prostate bed Macroscopic relapse boost (27%) Lymph nodes (27%)	VMAT (69%) MRgRT (31%)	Whole prostate bed: 30-34 Gy/5 fx Macroscopic relapse boost: 35–40 Gy/5 fx Lymph nodes: 25 Gy/5 fx	29.5 months	Late G2 GU: 9% Late G3 GU: 1% Late G2 GI: 0% Late G3 GU: 2%	NS
Lucchini et al., 2022 (POPART)	Prospective	30	0.3 ng/mL	PSMA PET/CT Pelvic MRI	13% of the patients	Whole prostate bed (adjuvant salvage) Macroscopic relapse 26%	VMAT	31–32.5 Gy/5 fx	3 months	Acute G ≥ 2 GU: 0% Acute G ≥ 2 GI: 3%	PSA decrease: 93.3%
Sampath et al.,2020	Phase I dose escalation trial	26	0.4 ng/mL	Bone scan Abdomen and pelvic CT Pelvic MRI	38% of the patients	Whole prostate bed (adjuvant, salvage)	VMAT	35–40–45 Gy/5 fx	40 months	Late G ≥ 2 GU: 38% Late G ≥ 2 GI: 11%	PSA control (≤ 0.2 ng/mL): 42%
Ballas et al., 2019	Phase I dose escalation trial	24	0.06 ng/mL	NS	16.6% of the patients	Whole prostate bed (adjuvant, salvage)	IMRT VMAT	54 Gy/15 fx 47 Gy/10 fx 35.5 fx/5 fx	14.1 months	Acute G2 GU: 16.6% Acute G2 GI: 50% Late G2 GI: 4.2%	NS
Ozyigit et al., 2022	Retrospective	66	0.37 ng/mL	NS	38% of the patients	Whole prostate bed (adjuvant 41%, salvage 59%) Lymph nodes (15%)	VMAT	Whole prostate bed: 35 Gy/5 fx Lymph nodes: 46 Gy/23 fx	24.2 months	Late G2 GU: 15.1% Late ≥ 2 GI: 3%	2-year BFFS: 88.4%

RT radiotherapy, *fx* fraction, *BFFS* biochemical failure free survival, *GU* genitourinary, *GI* gastrointestinal, *G ≥ 2* grade ≥ 2, *NS* non specified, *VMAT* volumetric arc therapy, *PSA* prostate specific antigen, *CT* computed tomography, *MRI* magnetic resonance imaging, *PSMA* prostate specific membrane antigen, *PET/CT* positron emission tomography/computed tomography, *MRgRT* magnetic resonance guided radiotherapy, *IMRT* intensity modulated radiotherapy, *ADT* androgen deprivation therapy, *PFS* progression-free survival

nodal irradiation to a total dose of 46 Gy/23fx due to positive lymph nodes after pelvic lymph node dissection (PLND). Toxicity outcomes were deemed satisfactory, with a report of late grade 2 genitourinary (GU) and gastrointestinal (GI) toxicity in 15% and 3% of men, respectively.

Oncological outcomes

Few data are available with regards to biochemical control after PB SBRT. Lucchini et al. reported encouraging results with a PSA decrease was reported for 93.3% of the patients at 3 months [36]. At a 40 months follow-up, Sampath et al. observed PSA control (< 0.2 ng/mL) in 42% of men. No significant difference in PSA control was demonstrated with dose-escalation up to 45 Gy [38]. Ozyigit et al. observed a 2-year biochemical failure-free survival (BFFS) of 88.4%, after PB SBRT at a total dose of 35 Gy in 5 fractions [40]. Only the pre-PRBT PSA value was predictive of further biochemical failure in multivariate analysis, with a cut-off at 0.2 ng/mL (PSA < 0.2 ng/mL: 2-year BFFS 100%, PSA ≥ 0.2 ng/mL: 2-year BFFS 81%, p = 0.04).

SBRT on MLR within the PB

Toxicity

The occurrence of MLR is associated with poor response to salvage PBRT [41, 42], and to date no standard exists with regards to this clinical situation. While the SPIDER-01 trial suggested the benefit of dose-escalation to the MLR [43], four trials investigated the place of dose-escalated SBRT on MLR within the PB (Table 2). Francolini et al. led the only prospective trial assessing salvage SBRT for MLR within the PB, performed at a total dose of 35 Gy in 5 fractions [44]. No patient received androgen deprivation therapy (ADT). Within 3 months of follow-up, a low rate of acute grade 2 GU and GI toxicity was reported, at 5.3% each. Francolini et al. also retrospectively reported the outcomes of 90 men receiving SBRT for MLR within the PB, at a total dose of 30–40 Gy in 5 fractions [45]. A total of 19% of the patients received concomitant androgen deprivation therapy (ADT), 8.8% of them being castrate-resistant. Excellent results were shown with regards to toxicity, with late grade ≥ 2 GU toxicity reported in only 2.2% of the patients, and no patient report of grade 3 toxicity. In another report, Francolini et al. reported the outcomes of 50 men receiving SBRT on MLR at a dose of 30 Gy in 5 fractions [46]. With an extended follow-up of 40 months, the authors reported acceptable rates of late GU toxicity, with grade 1–2 and 3 raising up to 26% and 2%. Francolini et al. further compared the outcomes of men diagnosed with MLR, treated with either dose-escalated PBRT (66–79 Gy/33–38 fx) or SBRT delivered to the MLR (30–40 Gy/5 fx) [47]. A propensity score analysis was performed after matching the two populations of patients. A lower rate of toxicity was demonstrated in patients undergoing SBRT, late GI and GU events being reported in 0% and 6.7% of patients, respectively (vs 13.3%, p = 0.04 and 22.2%, p = 0.03 with dose-escalated PBRT). Detti et al. also published a report of stereotactic approach using CyberKnife®, MLR prostate cancer after either RP or RP followed by PBRT [48]. Two SBRT schedules were performed: 30 Gy in 5 fractions in previously irradiated men, 35 Gy in 5 fractions in radiotherapy-naïve men. The toxicity outcomes were favorable, with no report of late grade ≥ 2 GU or GI toxicity.

Oncological outcomes

To date, few data are available with regards to long-term outcomes after SBRT to MLR. The early results of the STARR trial showed encouraging results with regards to biochemical control, with biochemical response detected at 3 months in 84.3% of the patients [44]. Detti et al. reported a 43.7% rate of biochemical relapse after SBRT in a population of patients with a median PSA level of 4.1 ng/mL before treatment. While no evidence of local failure was reported, all patients experiencing biochemical relapse were found to have distant metastases. Among a population of patients with a median PSA level of 2.3 ng/mL at the time of SBRT, Francolini et al. demonstrated favorable outcomes with regards to biochemical control (increase in PSA level ≥ 10%) with a median BFFS of 36.4 months. At multivariate analysis, only Gleason score at diagnosis was found to be predictive of biochemical relapse. A total of 25 patients experienced biochemical recurrence, with a report of distant or pelvic recurrences for 11 of them. Francolini et al. also reported a median BFFS of 43 months in men receiving a dose of 30 Gy in 5 fractions to the MLR [46]. Both Gleason score > 7 and concomitant androgen deprivation therapy were shown to be predictive of worst BFFS (respective HR of 2.42, p = 0.02 and 2.83, 95% p = 0.02). Twenty-six percent of the patients showed evidence of metastatic disease, with a 2-year metastasis-free survival (MFS) of 82%. While to date SBRT remains a non-validated approach, Francolini et al. showed that biochemical control tended to be improved with dose-escalated PBRT compared with SBRT (SBRT vs PBRT, HR = 2.15 [0.63–7.25], p = 0.21) [47].

Table 2 Studies assessing stereotactic radiotherapy on macroscopic recurrence within the prostate bed

Author	Trial design	Number of patients	Median PSA at recurrence (ng/mL)	Imaging modality	ADT	Target volume	RT technique	RT dose	Median follow-up	Toxicity outcomes	Oncological outcomes
Francolini et al., 2023 (STARR)	Prospective	19	1.13 ng/mL	PET/CT MRI	0% of the patients	Macroscopic relapse	Cyberknife®	35 Gy/5 fx	3 months	Acute G2 GU: 5.3% Acute G2 GI: 5.3%	PSA response: 58% PSA control (≤0.2 ng/mL): 26.3%
Detti et al., 2015	Retrospective	16	4.1 ng/mL	Pelvic MRI PET/CT	0% of the patients	Macroscopic relapse after RP Macroscopic relapse after RP and PBRT	Cyberknife®	30 Gy/5fx (radiorecurrent) 35 Gy/5 fx	10 months	Acute G2 GU: 6.25% Acute G2 GI: 6.25%	Median BFFS: 9.3 months
Francolini et al., 2020	Retrospective	90	2.3 ng/mL	Pelvic MRI or PET/CT	19% of the patients (8.8% castration-resistant)	Macroscopic relapse	Cyberknife® IMRT	30-40 Gy/5 fx	21.2 months	Late G2 GU: 2.2% No late G ≥ 2 GI toxicity	PSA control (≤0.2 ng/mL): 43.3% Median BFFS: 36.4 months 1-year ADT-free survival: 90%
Francolini et al., 2022	Retrospective	185 (stereotactic: 90 pts, conventional: 95 pts)	Conventional: 1.3 ng/mL Stereotactic: 1.4 ng/mL	Pelvic MRI or PET/CT	38.3% of the patients	Macroscopic relapse	Cyberknife® IMRT	Conventional (66–79 Gy/33–38 fx) Or stereotactic (30–40 Gy/5 fx)	30 months	Conventional: Late G ≥ 2 GU: 8.4% Late G ≥ 2 GI:10.5% Stereotactic: Late G ≥ 2 GU: 2.2% Late G ≥ 2 GI: 0%	No significant difference between matched populations for BFFS and PFS
Francolini et al., 2022	Retrospective	50	NS	Pelvic MRI or PET/CT	22% of the patients	Macroscopic relapse	Cyberknife®	30 Gy/5 fx	48.2 months	Late G1-2GU: 26% Late G1-2: 6% Late G3 GU: 2%	Median BFFS: 43 months 2-year MFS: 82%

RT radiotherapy, *fx* fraction, *BFFS* biochemical failure free survival, *GU* genitourinary, *GI* gastrointestinal, *G ≥ 2* grade ≥ 2, *NS* non specified, *VMAT* volumetric arc therapy, *PSA* prostate specific antigen, *CT* computed tomography, *MRI* magnetic resonance imaging, *PSMA* prostate specific membrane antigen, *PET/CT* positron emission tomography/computed tomography, *IMRT* intensity modulated radiotherapy, *ADT* androgen deprivation therapy, *PFS* progression-free survival, *RP* radical prostatectomy, *PBRT* prostate bed radiotherapy, *MFS* metastasis-free survival

Table 3 Studies assessing stereotactic radiotherapy on radiorecurrent macroscopic relapse within the prostate bed

Author	Trial design	Number of patients	Median PSA at recurrence (ng/mL)	Imaging modality	ADT	Target volume	RT technique	RT dose	Median follow-up	Toxicity outcomes	Oncological outcomes
Caroli et al., 2020	Retrospective	38	1.1 ng/mL	PSMA PET/CT	0% of the patients	Macroscopic relapse	IMRT	18-21 Gy/3 fx	27 months	No G ≥ 2 toxicity	BFFS: 15 months
Olivier et al., 2019	Retrospective	12	1.1 ng/mL	MRI PET/CT	16.6% of the patients	Macroscopic relapse	Cyberknife®	36 Gy/6 fx	34.2 months	Late G2 GU: 16.6% Late G2 GI: 8.3%	PSA decrease: 87% 2-year BFFS: 56%
Archer et al., 2023	Retrospective	117	0.8 ng/mL	PET/CT Pelvic MRI	41% of the patients	Macroscopic relapse	Cyberknife® Vero Other	Median: 35 Gy/6 fx	19.5 months	Cumulative incidence of G ≥ 2 GU: 13% Cumulative incidence of G ≥ 2 GI: 18%	Median PFS: 23.5 months 3-year PFS: 27% 3-year OS: 85%
Perennec et al., 2021	Retrospective	48	2.6 ng/mL	PET/CT MRI	31% of the patients (18.7% castration-resistant)	Macroscopic relapse	Cyberknife® VMAT	36 Gy/6 fx 30 Gy/5 fx	22 months	Late G3 GU: 12.5% Late G3 GI: 0%	Median BFFS: 27 months

RT radiotherapy, *fx* fraction, *BFFS* biochemical failure free survival, *GU* genitourinary, *GI* gastrointestinal, *G ≥ 2* grade ≥ 2, *NS* non specified, *VMAT* volumetric arc therapy, *PSA* prostate specific antigen, *CT* computed tomography, *MRI* magnetic resonance imaging, *PSMA* prostate specific membrane antigen, *PET/CT* positron emission tomography/computed tomography, *IMRT* intensity modulated radiotherapy, *ADT* androgen deprivation therapy, *PFS* progression-free survival

SBRT on radiorecurrent macroscopic relapse within the PB

Toxicity

MLR after RP and PBRT is currently managed with either observation or ADT [10], and the benefit of salvage SBRT remains largely unknown (Table 3). Olivier et al. were the first to report preliminary outcomes after salvage re-irradiation after previous PBRT [49]. Twelve patients treated with SBRT at a median dose of 36 Gy in 6 fractions were included. Within a median 19.5 months of follow-up, the cumulative incidence of grade ≥ 2 GU and GI toxicity was 13% and 18%. Caroli et al. also reported the outcomes of 38 men treated with SBRT for radiorecurrent relapse within the PB [50]. No patient reported any grade ≥ 2 toxicity. Perennec et al. evaluated salvage re-irradiation in 48 patients, receiving SBRT at a dose of either 36 Gy in 6 fractions or 30 Gy in 5 fractions [51]. An excess of GU toxicity was demonstrated within a 22-months of follow-up, with late grade 3 toxicity occurring in 12.5% of the patients, consisting in either cystitis or incontinence. Archer et al. recently published the largest serie of SBRT for MLR within the PB, including a total of 117 men [52]. After a median follow-up of 19.5 months, the cumulative incidence of grade ≥ 2 GU and GI toxicity was respectively 13% and 18%. In multivariate analysis, the site of recurrence (urethrovesical anastomosis) was predictive of the onset of late toxicity of any grade.

Oncological outcomes

Encouraging results were demonstrated with regards to biochemical control, across studies. Olivier et al. observed a PSA decrease in 87% of the patients, together with a median bFFS of 18 months [49]. In a population of patients receiving SBRT alone, Caroli et al. also reported a PSA decrease in 87% of the patients. The median BFFS reached 15 months. At biochemical recurrence, 61.5% and 23.1% of the patients demonstrated respectively nodal and bone metastasis, while only 15.4% of the patients had persistent MLR. Perennec et al. demonstrated a BFFS raising up to 27 months [51], despite a median PSA level higher than the studies of Olivier et al. [49] and Caroli et al. [50]. Off note, 18% of the patients were castrate-resistant at the time of SBRT. The largest series of SBRT on radiorecurrent relapse within the PB demonstrated a 2-year PFS was 48%, dropping at the 3-year evaluation at 27%. In multivariate analysis, a recurrence in contact with the urethrovesical anastomosis was also predictive of poorer PFS (HR = 3.35 [1.38–8.16], p = 0.008), together with the size of the recurrence (> 10cm^3, HR = 1.46 [1.08–1.96], p = 0.01). A significant association between PSA doubling time and risk of further progression was observed in univariate analysis. While no prospective evidence is available in this clinical setting, the REPAIR GETUG-P16 phase 1–2 trial (NCT04536805) is currently enrolling men to receive SBRT on radiorecurrent MLR at doses ranging between 25 and 36 Gy, together with Metformin. Preliminary results of the phase 1 study suggest that acute tolerance is correct at both treatment levels; the phase 2 study is ongoing using a 36 Gy dose [53].

Discussion

Several trials first suggested the safety of moderately hypofractionated schedules for PBRT [29–32], with both no difference in acute and late toxicity and patient-reported outcomes. Yet, further evidence of an excess of late toxicity discouraged is wide implementation in clinical practice. Cozzarini et al. retrospectively analyzed toxicity outcomes after either normofractionated PBRT (70.2 Gy in 39 fractions) or moderately hypofractionated PBRT (65.8–72.8 Gy in 28 fractions or 58 Gy in 20 fractions) [33]. The 5-year rate of late grade 3 GU toxicity raised up to 18.1% in men receiving moderately hypofractionated PBRT. Late grade 3 GU consisted in, either urethral stenosis or bladder neck strictures (59.1%), severe hematuria (26.1%) or incontinence (40.9%). Lewis et al. further reported higher than expected late GU toxicity rates, in patients receiving moderately hypofractionated PBRT at a median total dose of 65 Gy in 28 fractions [34]. Late grade 2 and grade 3 GU toxicity was observed in 39% and 27% of patients respectively, all consisting in severe hematuria. Although not reaching the DLT, the dose-escalated and hypofractionated phase I trial led by Patel et al. showed within the 44.2 Gy in 10 fractions arm together with an ureteral stenosis [54]. SBRT trials also report an increase in late grade ≥ 2 GU toxicity, raising up to 38% in the study led by Sampath et al., together with unexpected ureteral toxicity requiring the placement of ureteral stent [38]. Also, an increase in severe GI toxicity was also reported, represented mostly by rectal hemorrhage requiring either blood transfusion or plasma coagulation. Yet, the increase in severe toxicity may be attributable to dose-escalation more than the use of severe hypofractionation, as trials performing SBRT at doses up to 40 Gy report acceptable rates of late grade ≥ 2 genitourinary (GU) toxicity, ranging from 2.2% [45, 47] to 15.1% [40].

Off note, the recently published SAKK 09/10 trial also demonstrated an excess of late GI toxicity with the use of normofractionated dose-escalated PBRT (70 Gy/ 35fx: late grade ≥ 2 GI toxicity 22.3%, 64 Gy/32fx: late grade ≥ 2 GI toxicity 11.5%, p = 0.009) [55].

Few data are available with regards to biochemical control after PB SBRT. While Ozyigit et al. reported encouraging data on biochemical control (PSA ≤ 0.2 ng/mL), with a 2-year BFFS of 88.4% [40], Sampath et al. reported biochemical control in only 42% at a median follow-up of 40 months [40]. Notably, no benefit in biochemical failure-free survival has been demonstrated with dose-escalation within the SAKK 09/10 trial in the salvage setting [55], leading to unlikely oncological benefit of SBRT dose-escalation trials. Several prospective trials are currently investigating the future place of SBRT delivered to the whole PB, either with (NCT05038332) or without (NCT04848909) dose-escalation.

While Tilki et al. recently demonstrated an impaired overall survival when salvage PBRT is initiated at PSA level above 0.25 ng/mL [56], the current EAU guidelines advocate not to wait till imaging positivity to initiate salvage RT [10]. Both recent standardization of magnetic resonance imaging (MRI) protocols after prostatectomy [57] and the increasing use of PSMA PET/CT at low values of PSA [24] is expected to drive up the number of patients diagnosed with MLR within the PB. While MRI remains the standard of care for the delineation of the target due to higher spatial resolution, the use of PET/CT might lead to higher interobserver agreement [58, 59]. As to date no standard exists with regards to this clinical situation, the SPIDER-01 study recently raised the potential relevance of dose-escalation to the MLR. Indeed, in a population of 310 patients receiving salvage whole PBRT, the prescription of a boost ≥ 72 Gy was associated with a 5-year PFS of 73% (vs 60% in patients with dose-escalation < 72 Gy, p = 0.03) [43]. The MAPS trial (NCT01411345), randomizing PBRT with or without dose-escalation on the MLR is currently recruiting and will provide high-level prospective evidence with this approach. An alternative might be to perform dose-escalation on the MLR while reducing the dose delivered to the whole PB. SBRT on the area of macroscopic recurrence could also represent another approach, with the further benefit to both reduce the target volume and to increase the dose delivered to the macroscopic evidence of disease. Encouraging short-term biochemical results have been demonstrated across trials, with a PSA reduction in up to 84% of the patients [44] and a median BFFS raising up to 36.4 months in a population of patients with mean PSA level at relapse of 2.3 ng/mL [45]. These outcomes compare favorably with historical series, as a 5-year PFS ranging from 20 to 37% has been reported in patients receiving salvage PBRT at PSA values ≥ 2 ng/mL [3, 60]. Furthermore, the rates of local relapse after SBRT ranged from 0% [48] to 2.2% [45], with all progressive patients diagnosed with either pelvic or distant metastases. Despite a short follow-up, these results suggest that SBRT might be sufficient to provide local control in men presenting with macroscopic local recurrence after RP. With regards to toxicity outcomes, the retrospective study led by Francolini et al. demonstrated a lower rate of late grade ≥ 2 toxicity with SBRT than whole PBRT performed with dose-escalation, as late GI and GU events were reported in 0 versus 13.3% ($p = 0.04$) and 6.7 versus 22.2% ($p = 0.03$) of patients, respectively [45]. SBRT on the MLR at a total dose of 35 Gy in 5 fractions is currently being investigated within the single-arm HypoFocal SRT trial (NCT05746806).

Unexpected GU toxicity has been reported in trials performing dose-escalation to the PB. Sampath et al. reported a 7.6% rate of grade 3 ureteral stricture requiring the placement of a ureteral stent, with ultra-hypofractionated PBRT [38]. Similarly, Cozzarini et al. reported a significant rate of late grade 3 GU toxicity, with either urethral stenosis or incontinence, or bladder neck stricture after dose-escalated and moderately hypofractionated PBRT [33]. These findings underline the need to consider and define organs-at-risk that encompass the specificities of the post-operative anatomy (vesicoureteral anastomosis, bladder neck, ureters) when dose-escalation to the PB is considered, and prospectively define the constraints to be placed on it.

The conclusion that can be drawn from the studies included within this systematic review are hampered in several ways. First, heterogeneous populations have been included within trials, including both patients receiving adjuvant or salvage PBRT, macroscopic recurrent and radiorecurrent disease [48] and castration-sensitive and castrate-resistant patients [45, 51]. Second, the use of ADT varied widely across trials, ranging from 0% [48, 50] to 41% of the patients [37, 52], with large variations in duration of prescription. Third, various definitions of biochemical relapses after RT have been reported across trials, either defined as a PSA ≥ 0.2 ng/mL confirmed by a second increasing measure, an increased PSA at two successive measures above the pre-RT level, or an absolute increase in PSA level > 0.2 ng/mL. Last but not least, the small number of patients short follow-up preclude any

definitive conclusion on the long-term safety of SBRT on either whole PB or macroscopic local recurrence.

Conclusion

SBRT to the whole PBRT performed with dose-escalation at doses above 40 Gy in 5 fractions appears to be associated with unacceptable late GU and GI toxicity, warranting caution for the design of further trials. Salvage SBRT to the macroscopic local recurrence appears to be associated with a favorable toxicity profile, together with encouraging oncological outcomes mainly based on retrospective studies. Salvage re-irradiation within the PB is associated with promising oncological results, with a 2-year PFS ranged from 48 to 56% across trials. Prospective trials are eagerly awaited to further explore the future place of SBRT in the post-prostatectomy setting.

Author contributions JLG project development, data collection, data analysis, manuscript writing, editing, NM project development, editing, FC editing, MM editing, MV editing, RDC editing, NB-O editing, PO editing, TN editing, SS editing, PS project development, data analysis, editing.

Declarations

Conflict of interest The authors have no conflict of interest related to this work to disclose.

Research involving human participants and/or animals Not applicable.

Informed consent Not applicable.

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