Review Article

Focal versus whole gland salvage brachytherapy for recurrent prostate cancer in the prostate specific membrane antigen PET era: a narrative review

Lauren M. Andring[1], Bin S. Teh[2], Edward Brian Butler[2], Andrew M. Farach[2]^

[1]Department of Radiation Oncology, MD Anderson Cancer Center, Houston, TX, USA; [2]Department of Radiation Oncology, Houston Methodist Hospital, Houston, TX, USA

Contributions: (I) Conception and design: LM Andring, AM Farach; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: LM Andring; (V) Data analysis and interpretation: LM Andring, AM Farach; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Andrew M. Farach, MD. Associate Professor, Director of Brachytherapy, Department of Radiation Oncology, Houston Methodist Hospital, 6565 Fannin St, DB1-077, Houston, TX, USA. Email: amfarach@houstonmethdodist.org.

Background and Objective: Prostate cancer is the second most common cause of cancer in men worldwide. A significant proportion of patients will develop biochemical failure after definitive radiotherapy and an increasing number of local failures are now identifiable with prostate specific membrane antigen (PSMA) positron emission tomography and computerized tomography (PET/CT). Brachytherapy (BT) represents an excellent option for definitive local salvage treatment. Consensus guidelines for the delivery of salvage BT are heterogenous and limited. Herein, we report the results from a narrative review analyzing whole gland and partial gland BT salvage to help guide treatment recommendations.

Methods: The PubMed and MEDLINE databases were searched in October 2022 to identify studies analyzing BT salvage in patients with recurrent prostate cancer after definitive external beam radiation therapy (EBRT). 503 initial studies met search criteria. After title and abstract screening, 25 studies met inclusion criteria and full-text review was performed. Twenty studies were included for analysis. Reports included whole gland (n=13) and partial gland or focal (n=7) salvage BT.

Key Content and Findings: The median 5-year biochemical failure free survival (BFFS) for men receiving whole gland BT salvage was 52%, which is comparable to 5-year recurrence-free survival (RFS) rates for other salvage treatment modalities (radical prostatectomy (RP) 54%, high-intensity focused ultrasound (HIFU) 53%, cryotherapy 50%). However, the median rate of severe genitourinary (GU) toxicity was lower (12%) compared to published rates for other treatment modalities (RP 21%, HIFU 23%, and cryotherapy 15%). Furthermore, patients receiving partial gland salvage BT had even lower median rates of grade 3 or higher GU toxicity (4% *vs.* 12%) and gastrointestinal (GI) toxicity (0% *vs.* 3%), with 3-year BFFS of 58%. Only two studies directly comparing BT whole versus partial gland salvage were identified with comprehensive literature search and neither provided specific comparison regarding prescription dose or dose constraints.

Conclusions: This narrative review identified only two studies that directly compared whole versus partial gland BT salvage treatment. Neither report provided a specific comparison of recommendations for dosimetric technique or normal structure dose constraints. Therefore, this review highlights a significant gap in the existing literature and provides an important framework to guide radiation treatment (RT) recommendations for both whole gland and partial gland salvage BT in patients with recurrent prostate cancer.

^ ORCID: 0000-0002-9982-4557.

Keywords: Prostate cancer; salvage; recurrence; brachytherapy (BT); focal; whole gland

Submitted Jan 31, 2023. Accepted for publication Jun 16, 2023. Published online Jun 27, 2023.
doi: 10.21037/cco-23-4
View this article at: https://dx.doi.org/10.21037/cco-23-4

Introduction

Aside from non-melanomatous skin cancer, prostate cancer is the most common cancer in men worldwide and is the fourth most common cancer overall (1). Depending on the prostate cancer risk-grouping, the National Comprehensive Cancer Network (NCCN) guidelines recommend treating definitively with external beam radiation therapy (EBRT), brachytherapy (BT), EBRT with BT boost, or with prostatectomy and pelvic lymph node dissection (2). However, studies have shown that up to 30% of patients who receive definitive radiation treatment (RT) for prostate cancer will develop a biochemical recurrence (3).

In the era of advanced imaging technology and prostate specific membrane antigen (PSMA) positron emission tomography (PET/CT), the site of prostate cancer recurrence is more accurately identified as compared to older imaging techniques. A large meta-analysis by Perera *et al.* found that more than half of biochemical recurrences were attributable to local disease failure identified by PSMA PET/CT (4). As improved sensitivity of available imaging modalities results in the detection of more local prostate recurrences, there will be an increased need for salvage local treatment options.

For patients who develop local prostate recurrence after definitive RT, there are different salvage treatment options that exist, including surgical resection, BT, stereotactic body radiation therapy (SBRT), high-intensity focused ultrasound (HIFU), cryoablation, or palliative treatment with androgen deprivation therapy (ADT). A recent meta-analysis by Valle *et al.* demonstrated that non-surgical approaches were associated with less toxicity when compared with radical prostatectomy (5). BT is a promising treatment option in the setting of re-irradiation and offers a dosimetric advantage through internal implantation of the radiation source, which allows for dose escalation to the target while safely protecting nearby organs at risk (OARs). The NCCN guidelines list salvage BT as a treatment option for local disease recurrence; however, recommendations regarding BT modality, dose, target, and technique are limited. Thus, there is a need for improved and consistent guidelines to help guide BT planning and delivery for salvage treatment of prostate cancer recurrence. We present this article in accordance with the Narrative Review reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-4/rc) (*Table 1*), to describe existing literature and to help guide treatment practices regarding salvage BT for local prostate recurrence after previous radiotherapy.

Methods

A comprehensive literature search of the PubMed and MEDLINE databases was completed in October 2022 to identify published articles that studied salvage BT for recurrent prostate cancer in patients who were initially treated with definitive EBRT. We used the following search terms: prostate cancer, recurrence, salvage, BT, whole gland, focal salvage, and partial gland. Study eligibility included (I) prior definitive RT and (II) salvage radiation using BT (*Table 1*). Studies were excluded (n=5) if the patient population included salvage treatment options other than BT, such as SBRT, HIFU, or cryoablation. A separate search was performed using the search terms listed above to identify articles directly comparing salvage BT to the entire prostate versus focal salvage BT.

A total of 503 studies were identified in the initial search. Titles and abstracts were reviewed and screened for relevance by author Lauren M. Andring (LMA). 25 studies were selected for full manuscript review. After full-text review, 20 studies met inclusion criteria and were analyzed (*Figure 1*). From each study, we obtained the following data for descriptive analysis: year of publication, study design (retrospective cohort, prospective registry, clinic trial), study inclusion criteria, population size, volume of gland treated, BT technique, prescription dose, dose constraints, image guidance used for treatment planning [MRI, trans-rectal ultrasound (TRUS), fluoroscopic], biochemical failure free survival (BFFS), and toxicity. One original article and one review article directly compared focal to whole gland salvage BT for recurrent prostate cancer and were also included for analysis. Example plans for whole gland and partial gland salvage are shown (*Figure 2*).

Table 1 The search strategy summary

Items	Specification
Date of search	October 6th, 2022
Databases and other sources searched	PubMed and MEDLINE
Search terms used	Prostate cancer, recurrence, salvage, brachytherapy, whole gland, focal salvage, and partial gland
Timeframe	1995 to present
Inclusion and exclusion criteria	Inclusion: (I) prior definitive RT and (II) salvage radiation using brachytherapy
	Exclusion: (I) study population/analysis included salvage treatment modalities other than brachytherapy (i.e., SBRT, HIFU, cryoablation)
Selection process	Author LMA reviewed/screened titles and abstracts for relevance. 25 studies selected for full manuscript review. 20 studies included in analysis
Additional considerations	A separate search was performed using terms listed above to identify articles directly comparing salvage brachytherapy to the whole versus partial gland

SBRT, stereotactic body radiation therapy; HIFU, high-intensity focused ultrasound.

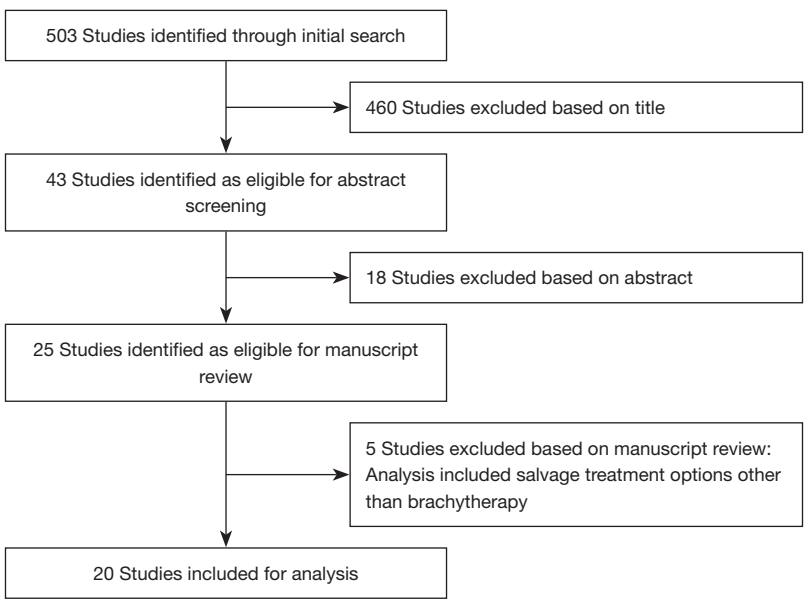

Figure 1 Study inclusion flowchart.

Results

Study characteristics and inclusion criteria

Twenty studies were included for analysis, of which 13 (65%) evaluated the role of whole gland salvage BT (*Table 2*) and 7 (35%) reported on partial gland salvage therapy (*Table 3*) (6-25). In the studies analyzing whole gland salvage BT, 11 (85%) were retrospective cohort reviews (6,7,9-16,18) and 2 (15%) were phase II clinical trials (8,17). The first prospective study by Nguyen *et al.* included 25 men with local recurrence after definitive EBRT (n=13) or BT (n=12) with primary end points of late genitourinary (GU) and gastrointestinal (GI) toxicity and BFFS (8). The second prospective study was Radiation Therapy Oncology Group (RTOG) 0526, which included 92 men with intraprostatic recurrence after EBRT and had primary study end points evaluating rates of late grade 3 or higher GU or GI toxicity (17). Biopsy proven local recurrence was part of the inclusion criteria for all of these

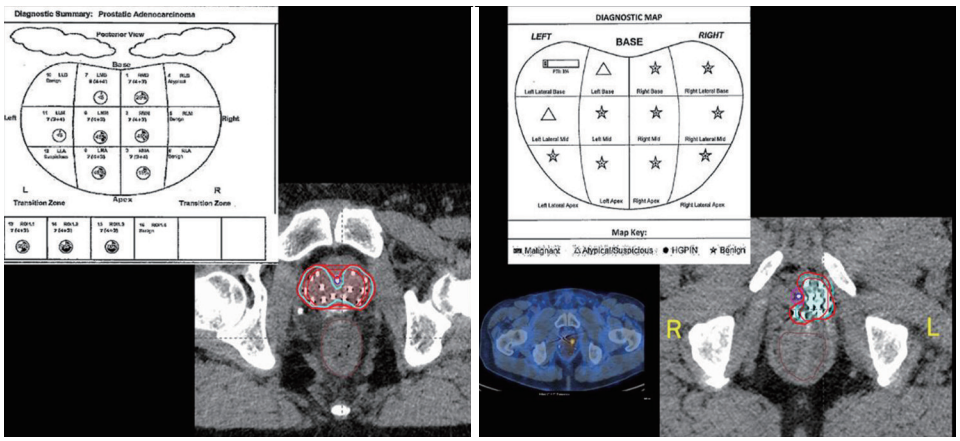

Figure 2 Example of whole (left) *vs.* partial gland (right) high dose rate brachytherapy salvage plans.

studies, with the exception of Kissel *et al.*'s study. Additionally, most studies (n=10) required a negative metastatic staging work-up including pelvic imaging and either a bone scan or PET/CT (8-11,13-18). Furthermore, the two prospective trials (8,17) required a Gleason score ≤ 7 and prostate-specific antigen (PSA) <10 ng/mL as part of their inclusion criteria, and reports by Henríquez López *et al.* and RTOG 0526 excluded patients with significant residual urinary toxicity from their prior RT (16,17). Residual rectal toxicity was not described as an exclusion factor for any of the studies reviewed. The year of publication ranged from 1999 to 2022 and the number of patients analyzed varied from 17 to 119 per study (*Table 2*).

Of the seven studies evaluating focal salvage BT, 4 (57%) were retrospective cohort studies (19-22), 2 (29%) were phase II clinical trials (23,25), and 1 (14%) was a prospectively maintained patient registry (24). The first prospective phase II trial evaluated 50 patients treated with focal high-dose rate (HDR) salvage BT with primary outcomes of BFFS and late toxicity (23). The prospective registry cohort study by van Son *et al.* analyzed 150 patients undergoing HDR partial gland salvage therapy and primary outcomes focused solely on toxicity, including late GU/GI toxicity and rates of erectile dysfunction (ED) (24). The final prospective phase II trial by Corkum *et al.* included 30 patients, also treated with HDR focal salvage therapy, with primary outcome of acute GU/GI toxicity and secondary outcomes of late GU/GI toxicity, health-related quality of life (HRQoL), and BFFS (25). All studies required biopsy proven local recurrence; however, the study by van Son *et al.* did not require biopsy of local disease after 2018 after the advent of PSMA PET/CT. Furthermore, all studies required negative metastatic staging work-up with either negative pelvic imaging and bone scan or negative PET/CT (19-25). The retrospective report by Peters *et al.* (20) also utilized a PSA <20 ng/mL and no evidence of extracapsular extension (ECE) as inclusion criteria. Maenhout *et al.*'s (21) retrospective study required a PSA <10 ng/mL for inclusion. The years of study publication were from 2013 to 2022 and the number of men evaluated ranged from 15 to 150 per study (*Table 3*).

Radiation technique, dose, and constraints

Whole gland

Of the studies evaluating whole gland salvage BT, 9 (69%) utilized low-dose rate (LDR) BT with either Iodine-125 (I-125) or Palladium-103 (Pd-103) (6-12,14,17), 3 (23%) studies used HDR with an Iridium-192 (Ir-192) source (13,15,18), and one study allowed for either LDR with I-125 or HDR with Ir-192 (16). The total dose varied by study, the type of BT modality used, and radiation source employed. For LDR with I-125, the total dose ranged from 108 to 160 Gy with median of 142 Gy. LDR delivered with a Pd-103 source used doses ranging from 90 to 144 Gy with median of 112.5 Gy. Aaronson *et al.* reported on a hybrid technique, where the entire gland was prescribed to 108 Gy and the area of gross recurrence was treated to 144 Gy (10). For patients receiving whole gland salvage therapy with HDR, the dose delivered ranged 24–36 Gy in 2–6 fractions.

Similarly, planning dose constraints for OARs varied with each study and based on treatment modality. Of note, there were six studies published before 2010, of which none utilized specific dose constraints for BT planning (6-10,12).

Table 2 Comparison of treatment strategy and outcomes in prior studies of patients with recurrent prostate cancer treated with whole gland brachytherapy salvage treatment

Study	Year	Study type	N	Modality	Dose	Dose constraints	Image guidance	BFFS	Toxicity	Inclusion criteria
Grado *et al.* (6)	1999	RR	49	LDR, I-125 Pd-103	I-125 160 Gy, Pd-103 120 Gy	None	Fluoroscopic & TRUS	3 y 48%; 5 y 34%	Graded toxicity not reported; 14% TURP for obstruction; 4% rectal ulcers; 2% colostomy	Bx confirmed
Wong *et al.* (7)	2006	RR	17	LDR, I-125 Pd-103	I-125 120 Gy, Pd-103 112.5 Gy	None	TRUS	4 y 75%	G2 GU 41%; G3+ GU 47%; G2 GI 29%; G3+ GI 6%	Bx confirmed
Nguyen *et al.* (8)	2007	Ph 2	25	LDR, I-125	Min 137 Gy	None	MRI	4 y 70%	G3+ GU/GI 30%; 4 y urostomy or colostomy 13%	Bx confirmed, neg pelvic imaging and bone scan, Gleason ≤7, PSA <10
Lee *et al.* (9)	2008	RR	21	LDR, Pd-103	90 Gy	None	Fluoroscopic & TRUS	3 y 94%; 5 y 38%	G2 GU 19%; G3+ GU 0%; G2 GI 5%; G3+ GI 0%	Bx confirmed, neg pelvic imaging and bone scan
Aaronson *et al.* (10)	2009	RR	24	LDR, I-125 Pd-103	108 Gy whole prostate; 144 Gy focal	None	TRUS	3 y 90%	G2 GU 29%; G3+ 0%; G2 GI 0%; G3+ GI 4%	Bx confirmed, neg pelvic imaging and bone scan
Moman *et al.* (11)	2010	RR	31	LDR, I-125	145 Gy	V150 <67%; V200 <33%; rectum <100%; urethra <200%	TRUS	5 y 20%	G2 GU 39%; G3+ GU 19%; G2 GI 3%; G3+ GI 6%	Bx confirmed, neg pelvic imaging and bone scan
Burri *et al.* (12)	2010	RR	37	LDR, I-125, Pd-103	I-125 135 Gy, Pd-103 110 Gy	None	TRUS	5 y 65%	G2+ GU/GI 46%; G3+ GU/GI 11%	Bx confirmed
Chen *et al.* (13)	2013	RR	52	HDR, Ir-192	36 Gy/6 fx	Rectum V75 <1 cc; bladder V75 <1 cc; urethra V125 <1cc	TRUS	5 y 51%	G2 GU 54%; G3+ GU 2%; G2 GI 4%; G3+ GI 0%; G2-3 ED 35%	Bx confirmed, neg systemic work-up
Vargas *et al.* (14)	2014	RR	69	LDR, Pd-103	D90 100 Gy	Rectum V100 <1 cc; urethra V150 <0.5 cc	TRUS	5 y 55%	G2 GU 4%; G3+ GU 9%; G2 GI 6%; G3+ GI 0%	Bx confirmed, neg pelvic imaging and bone scan
Wojcieszek *et al.* (15)	2016	RR	83	HDR, Ir-192	30 Gy/3 fx	Rectum D10% <70%; bladder D10% <70%; urethra D10% <120%	TRUS	5 y 67%	G2 GU 39%; G3+ GU 13%; G2+ GI 0%	Bx confirmed, neg pelvic i maging and bone scan
Henríquez López *et al.* (16)	2019	RR	119	LDR, I-125 or HDR Ir-192	145 Gy or 30–36 Gy in 2–4 fx	V150 <45%; V200 <10%; rectum D2cc <100%; urethra D10% <150%	TRUS	5 y 71%	G2 GU 19%; G3+ GU 24%; G2+ GI 0%	Bx confirmed, neg pelvic imaging and bone scan. Exclusion: Significant urinary symptoms
RTOG-0526 (17)	2019	Ph 2	92	LDR, I-125 or Pd-103	Min 140 Gy or 120 Gy	^{125}I, V150 <45%, V200 <10%; ^{103}Pd V150 <55%, V200 <15%; no rectal or urethral constraints	TRUS	5 y 68%	G3+ GI/GU 14%; Fistula 1%	Bx confirmed, neg pelvic imaging and bone scan, PSA <10, no residual G2+ GI/GU toxicity
Kissel *et al.* (18)	2022	RR	64	HDR, Ir-192	24–26 Gy/2 fx	V150 <40%; rectal Dmax <75%; urethra Dmax <115%	TRUS	2 y 58%	G2 GU 18.5%; G3+ GU 1.5%; G2 GI 1.5%; G3+ GI 1.5%	Neg pelvic imaging and bone scan or PET/CT

BFFS, biochemical failure free survival; RR, retrospective review; Ph2, Phase II trial; LDR, low-dose rate; HDR, high-dose rate; Gy, gray; fx, fraction; V100, volume of tissue receiving 100% of the prescribed dose (etc.); Dmax, maximal point dose; D90, dose to 90% of organ (etc.); TRUS, trans-rectal ultrasound; MRI, magnetic resonance imaging; y, year;; TURP, trans-urethral resection of prostate; G2/3, grade 2 or 3; GI, gastrointestinal; GU, genitourinary; ED, erectile dysfunction; Bx, biopsy; neg, negative; PSA, prostate specific antigen; PET/CT, positron emission tomography computed tomography.

Table 3 Comparison of treatment strategy and outcomes in prior studies of patients with recurrent prostate cancer treated with partial gland brachytherapy salvage treatment

Study	Year	Study type	N	Modality	Dose	Dose constraints	Image guidance	BFFS	Toxicity	Inclusion criteria
Hsu *et al.* (19)	2013	RR	15	LDR, I-125, Pd-103	I-125 144 Gy; Pd-103 125 Gy	Rectum mean V100 <0.5% (0.07 cc); urethra mean V100 <12%	MRI	3 y 71%	G2 GU 33%; G3+ GU 0%; G2+ GI 0%; 13% ED	Bx confirmed, no e/o metastatic disease
Peters *et al.* (20)	2014	RR	20	LDR, I-125	144 Gy	Rectum D2cc <100%; urethra D10% <150%	MRI	3 y 71%	G2 GU 20%; G3+ GU 5%; no change in GI or ED toxicity	Bx confirmed, neg pelvic imaging and bone scan, PSA <20, no ECE
Maenhout *et al.* (21)	2017	RR	17	HDR, Ir-192	19 Gy/1 fx	Rectum D1cc <12 Gy; bladder D1cc <12 Gy; urethra D10 <17.7 Gy	MRI	1 y 92%	G2 GU 24%; G3+ GU 6%; G2+ GI 0%; worsening ED 29%	Bx confirmed, neg PET/CT or PSMA, PSA <10
Slevin *et al.* (22)	2020	RR	43	HDR, Ir-192	19 Gy/1 fx	Rectum D2cc <65% (~12 Gy); urethra D10 <110%	TRUS (MRI cf)	3 y 42%	G2 GU 42%; G3+ GU 2%; G2+ GI 0%	Bx confirmed, neg PET/CT, MRI visible
Chitmanee *et al.* (23)	2020	Ph 2	50	HDR, Ir-192	19 Gy/1 fx	Rectum D2cc <15 Gy; urethra D10 <22 Gy	MRI	3 y 46%	G2 GU 46%; G3+ GU 10%; G2 GI 8%; G3+ GI 0%; G2/3 ED 28%	Bx confirmed, neg pelvic imaging and bone scan
van Son *et al.* (24)	2021	Prospective cohort	150	HDR, Ir-192	19 Gy/1 fx	Rectum D1cc <12 Gy; bladder D1cc <12 Gy; urethra D10% <17.7 Gy	TRUS (MRI cf)	NR	G2 GU 41%; G3+ GU 3%; G2 GI 5%; G3+ GI 0%; G2 ED 22%; G3 ED 15%	Bx confirmed before 2018, neg PSMA PET/CT
Corkum *et al.* (25)	2022	Ph 2	30	HDR, Ir-192	27 Gy/2 fx	Rectum V80 <0.5 cc; urethra D10 <<115%	TRUS (MRI cf)	3 y 62%	G2 GU 36.7%; G3+ GU 3%; G2 GI 7.7%; G3+ GI 0%; HRQoL no change in bowel, bladder function, sexual domain decreased over study	Bx confirmed, no e/o metastatic disease

BFFS, biochemical failure free survival; RR, retrospective review; Ph 2, phase II trial; LDR, low-dose rate; HDR, high-dose rate; Gy, gray; fx, fraction; V100, volume of tissue receiving 100% of the prescribed dose (etc.); D10, dose to 10% of organ (etc.); TRUS, trans-rectal ultrasound; MRI, magnetic resonance imaging; cf, confirmatory; y, year; NR, not reported; G2/3, grade 2 or 3; GI, gastrointestinal; GU, genitourinary; ED, erectile dysfunction; HRQoL, health-related quality of life; Bx, biopsy; neg, negative; PSA, prostate specific antigen; ECE, extra-capsular extension; e/o, evidence of; PSMA PET/CT, prostate-specific membrane antigen positron emission tomography and computerized tomography.

For LDR treatment planning, the dose constraints for the rectum differed but ranged from no part of the rectum receiving 100% of the prescribed dose (11) to less than 2 cc receiving 100% of the prescribed dose (16). For cases planned with HDR, the dose constraints for the rectum were more conservative, one study used a cutoff of less than 1 cc receiving 75% of the dose (13), another study limited the dose going to 10% of the rectum to 70% of the prescribed dose (15), and, lastly, Kissel *et al.* (18) used a maximum dose cutoff of less than 75% of the total dose. The LDR plans did not include a bladder dose constraint; however, some of the studies evaluating HDR planning did include a constraint for the bladder, which mirrored the constraints utilized for the rectum listed above (13,15). Urethral dose constraints for LDR included a maximum point dose of less than 200% of the total dose (11) and less than 0.5 cc receiving 150% of the prescription dose (14). For patients receiving HDR, the urethral constraints included less than 1 cc receiving 125% of the prescribed dose in one study (13), less than 10% receiving 120% in another (15), and a dose maximum of 115% (18).

All studied utilized image guidance for implant insertion and treatment planning. Of these, 10 studies (77%) used TRUS guidance (7,10-18), two studies employed combined TRUS and fluoroscopic guidance (6,9), and one study used MRI (8).

Partial gland

For patients receiving focal salvage therapy, two studies (19,20) (29%) utilized LDR with either I-125 or Pd-103 and five studies (21-25) (71%) employed HDR with Ir-192. The prescribed dose for LDR salvage therapy with I-125 was 144 and 125 Gy for patients treated with Pd-103. For HDR salvage, the prescribed dose was either 19 Gy in one fraction or 27 Gy in two fractions.

All of the studies evaluating partial gland salvage BT used dose constraints during the treatment planning process. The dose constraints differed based on the study and the treatment technique. For LDR treatment, the rectal dose constraints included a volume receiving 100% of the prescribed dose as less than 2 cc in one study (20) and less than 0.07 cc in the other (19). The rectal dose constraints for HDR salvage therapy included a maximum dose going to 1cc of the rectum as less than 12 Gy (21,24), less than 12–15 Gy going to 2 cc (22,23), and less than 0.5 cc receiving 80% of the prescribed dose (25). Only two studies included dose constraints for the bladder, both evaluated patients receiving HDR BT and both included a cutoff of 12 Gy going to 1 cc (21,24). The two studies evaluating LDR salvage therapy also included the following urethral dose constraints: less than 10% of the urethra receiving 150% of the prescribed dose (20) and less than 12% receiving 100% of the prescribed dose (19). Finally, for HDR focal salvage therapy, the cutoff for the maximum dose going to 10% of the urethra ranged between 17.7–22 Gy or 93–115% of the dose prescribed (21-25).

For treatment planning, four studies (19-21,23) (57%) utilized MRI for image guidance and the other three (22,24,25) (43%) employed TRUS guidance with MRI confirmation of the treatment area.

Outcomes (BFFS)

For patients receiving whole gland therapy, the rates of BFFS reported ranged from 3 to 5 years and differed by study and treatment timeframe. The 3-year BFFS ranged between 48–94% (median, 77.3%), 4-year BFFS 70–75% (median, 72.5%), and 5-year BFFS 20–71% (median, 52%) (*Table 2*). In men receiving focal salvage BT, one study reported a 1-year BFFS of 92% and the 3-year BFFS ranged between 42–71% (median, 58%) (*Table 3*).

Treatment toxicities

All studies reported on patient GI and GU toxicity. A minority reported on long-term ED. Rates of toxicity were graded on a scale from 1 to 5, based on the Common Terminology Criteria for Adverse Events (CTCAE).

Among studies analyzing whole gland salvage therapy, varying rates of late GI and GU toxicity were described. In the 1999 study by Grado *et al.*, which evaluated whole gland salvage treatment, graded toxicity, using CTCAE was not reported; however, 14% of patients required a transurethral resection of the prostate (TURP) for obstructive symptoms, 4% developed rectal ulcers, and 2% required a colostomy after whole gland salvage therapy (6). The other studies evaluating whole gland salvage therapy prior to the standardization of using OAR dose constraints reported relatively high rates of grade 3 or higher toxicity. Wong *et al.* reported grade 3 or higher GU toxicity in 47% and GI toxicity in 6% of patients (7). Nguyen *et al.* described grade 3–4 toxicity, which could include GU or GI, in 30% of the study population and a 13% 4-year rate of urostomy or colostomy (8). Aaronson *et al.* used a hybrid technique, which delivered a lower dose to the whole gland and incorporated a boost to the area of gross disease, this

technique was associated with lower rates of grade 3 or higher toxicity (0% GU, 4% GI) (10). For studies evaluating whole gland salvage therapy with the use of planning dose constraints, the median rate of grade 3 or higher GU toxicity was 12% (range, 1.5–24%) and the median rate of GI toxicity was 3% (range, 0–14%) (11,13-18). The study by Chen *et al.* reported on long-term erectile function and described a 35% rate of grade 2–3 chronic ED (13). Further toxicity information is available in *Table 2*.

Studies evaluating focal gland salvage generally reported lower rates of toxicity compared to studies assessing whole gland salvage therapy. For patients undergoing partial gland salvage therapy (19-25), the median rate of grade 3 or higher GU toxicity was 4% (range, 0–10%), which compares favorably to the median rate (12%) for whole gland treatment. Furthermore, in the focal salvage cohort (19-25), the rate of grade 3 or higher GI toxicity was 0% in all studies, again demonstrating superior toxicity outcomes compared to rates for whole gland salvage therapy. Long-term erectile function was more commonly reported in studies evaluating partial gland treatment. Hsu *et al.* reported a 13% rate of ED refractory to medical management (19). Three studies (21,23,24) reported worsening ED with rates ranging from 28–37% (median, 31%) and the report by Peters *et al.* (20). described no change in sexual function. Corkum *et al.* also described the impact of therapy on HRQOL and findings showed no change in bowel or bladder function, but a decrease in the sexual domain over the study period (25).

Direct comparison of whole gland vs. partial gland salvage therapy

After completing a comprehensive literature review, only two articles directly comparing whole gland to partial gland salvage BT were identified (26,27). The first study was published in 2016 by Guimas *et al.* and compared 10 patients treated with LDR whole gland salvage to 8 patients who received partial gland salvage therapy. Of note, 8 patients (7 whole glands, 1 partial gland) from the entire study population also underwent hydrogel placement for rectal sparing. Authors of this study concluded that the median cumulative biological equivalent dose to the rectum was lower in patients treated with focal salvage radiation (172.6 *vs.* 258.1 Gy, P<0.01) and patients who received hydrogel had significantly lower median rectal maximum dose (63.3 *vs.* 83.9 Gy, P=0.04) (26). The second study comparing whole gland to partial gland salvage BT was an opinion article by King *et al.* This study evaluated several whole gland and focal gland studies, including RTOG 0526, to create a risk-adaptive paradigm to guide treatment recommendations. The authors conclude that by using a risk-adaptive strategy, patients at high-risk for urinary toxicity can be identified and treated with focal salvage to better preserve urinary quality of life. This article did not include discussion regarding dose, target, technique, or normal structure dose constraints (27).

Discussion

Different salvage options exist for men with recurrent localized prostate cancer after prior definitive RT. In this narrative review we further explore salvage BT, comparing whole gland to partial gland treatment, with a specific focus on RT technique, dose, and normal tissue constraints. The median 5-year BFFS for men in this review receiving whole gland BT salvage was 52%, which is comparable to published 5-year RFS rates for other salvage treatment modalities (prostatectomy 54%, HIFU 53%, cryotherapy 50%) (5). However, the median rate of severe GU toxicity was lower in men receiving whole gland BT salvage (12%) compared to published rates for other treatment modalities; Valle *et al.* report median rates of severe GU toxicity after RP (21%), HIFU (23%), and cryotherapy (15%). The median rate of severe GI toxicity in this analysis was similar to rates for other treatment options, as described in the existing literature (5). Additionally, our findings show lower median rate of grade 3 or higher GU toxicity (4% *vs.* 12%) and GI toxicity (0% *vs.* 3%) for patients receiving partial gland salvage BT compared to whole gland. The median rate of BFFS was numerically lower (3-year BFFS 58% *vs.* 77%) with partial gland salvage BT; however, given the heterogeneity of the studies included, this finding is hypothesis generating and requires further prospective evaluation. RTOG-0526, which evaluated patients receiving whole gland BT salvage, showed that the only factor predictive of late adverse events was the percent of prostate encompassed in the 100% isodose line (V100), suggesting that partial gland salvage therapy may have an improved toxicity profile, further corroborating our results (17).

Current guidelines for salvage BT patient selection for locally recurrent prostate cancer after prior RT are heterogenous. The NCCN recommends salvage BT with either LDR or HDR for patients with pathologically confirmed local recurrence and no evidence of nodal or distant metastatic disease on staging evaluation (2). The

European Association of Urology (EUA) has more stringent guidelines for inclusion; recommendations include a life expectancy of at least 10 years, initial clinical staging of T1 or T2, a pre-salvage PSA <10 ng/mL, no lymph node involvement or evidence of distant metastatic disease, and few co-morbidities (28). Furthermore, the Delphi consensus group includes ECOG 0-1, pathologically confirmed local recurrence using 12–24 core needle biopsies, negative metastatic staging evaluation, ≤ T3b disease at both primary and time of relapse, and an International Prostate Score Symptom (IPSS) from 8 to 15 (29).

Based on published clinical guidelines discussed above (2,28,29) and the analysis of this narrative review, where we found that the most studies utilized pathologic confirmation and staging evaluation for selection of patients with locally recurrent prostate cancer for salvage BT, we recommend the following inclusion criteria: pathologic confirmation of local disease, staging evaluation with no evidence of lymph node involvement or distant metastatic disease (preferably with PSMA PET/CT), and ≤ T3b disease at the time of relapse. Using a cut-off of ≤ T3b disease will allow for full coverage of recurrent disease without excessive toxicity to adjacent OARs, while also maximizing patients eligible for this salvage modality. The studies included for analysis had a range of Gleason score and total PSA at the time of salvage therapy and only a few studies included specific cut-off values for Gleason score, PSA, or existing urinary symptoms; therefore, we believe recommendations regarding these criteria should be further studied prospectively prior to inclusion in patient selection. Additionally, based on the results of this analysis, patients with significant residual urinary or rectal toxicity from their initial course of radiation should be considered for partial gland BT salvage treatment to limit worsening long-term function and decreased quality of life.

An important aspect of this review includes the in-depth evaluation and comparison of RT dose, target, technique, and dose constraints between whole gland and partial gland salvage BT. NCCN guidelines for definitive BT dosing include 145 Gy for I-125, 125 Gy with Pd-103, and 27 Gy/2 fx or 38 Gy/4 fx delivered twice a day (BID) for Ir-192 (2). Based on the dosing regimens reviewed in the current study and consideration of published definitive dosing regimens, we propose recommendations for dose and dose constraints for whole gland (LDR *vs.* HDR) and partial gland (LDR *vs.* HDR) salvage treatment. For whole gland salvage therapy, we recommend treating to a dose of 120–145 Gy for LDR with I-125, 90–120 Gy for LDR with Pd-103, and 24–36 Gy in 2–6 fractions for HDR BT, similar, but slightly more conservative, compared to definitive dosing described above. Furthermore, by considering the reported dose constraints and toxicity profiles of included studies, we believe the current review supports the following dose constraints. For LDR therapy to the entire prostate: the rectal V100 should be less than 2 cc, with a goal of maximum dose (Dmax) <100%, the urethral Dmax should be <200% and volume receiving 150% of the prescribed dose (V150%) <0.5 cc. For HDR whole gland salvage therapy the rectum and bladder should have V75% <1 cc, with a goal of a Dmax <75% and the urethral V125% should be <1 cc, with goal of a Dmax <115%. For partial gland salvage therapy the site of recurrence should be treated to 144 Gy using I-125 LDR therapy, 125 Gy for Pd-103 LDR, and 27 Gy in 2 fractions if utilizing HDR BT. Dose constraints for partial gland salvage therapy using LDR should include a rectal V100% <2 cc, with goal of a Dmax <100%, and urethral dose going to 10% (D10%) <150% of the prescribed dose. For HDR treatment, we recommend a rectal/bladder dose constraint of 12 Gy going to 1cc (V12 <1 cc), and urethral D10 <115% with goal of D10 <93%. In all cases, hydrogel placement for rectal sparing should be considered if technically feasible.

After a comprehensive literature search, we found only two studies that directly compared BT salvage with whole gland versus partial gland treatment. To the best of our knowledge, this narrative review is the first to provide a direct comparison, solely focusing on whole versus partial gland BT salvage, to compare and provide recommendations regarding treatment modality, technique, dose, and dose constraints. Current clinical guidelines for patient selection are heterogenous and recommendations for treatment planning and technique are limited. Therefore, this analysis provides a significant addition to the current body of knowledge and should help to guide treatment decision making and treatment planning. Improved treatment guidelines are especially important in the era of PSMA PET/CT and increased need for definitive local salvage therapy options.

A few limitations of this review exist and should be discussed. The following study is a narrative review, which by definition is limited in scope and does not include all existing published data. The studies included for analysis are heterogenous in design, treatment era, radiation technique, and type of image guidance. Additionally, whole gland salvage BT has been utilized over a longer period of time and early studies did not include specific normal tissue dose constraints, whereas partial gland salvage therapy has

been utilized more in the modern era of treatment. Despite these limitations, this review is the first to exclusively compare whole versus partial gland salvage BT with an emphasis on treatment planning technique and dose constraints and therefore, provides a significant addition to the existing body of literature. The conclusions from this study are pending prospective evaluation. Loyola University is currently enrolling on a phase I/II trial (F-SHARP) evaluating focal salvage HDR BT; however, future prospective randomized studies comparing partial gland to whole gland salvage are needed.

Conclusions

This narrative review identified only two studies that directly compared whole versus partial gland BT salvage treatment. Neither report provided a specific comparison of recommendations for dosimetric technique, or normal structure dose constraints. Therefore, this review highlights a significant gap in the existing literature and provides an important framework to help guide RT recommendations for both whole gland and partial gland salvage BT in patients with recurrent prostate cancer, an increasingly prevalent problem encountered in the PSMA era.

Acknowledgments

Funding: None.

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-4/rc

Peer Review File: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-4/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-4/coif). BST serves as an unpaid editorial board member of *Chinese Clinical Oncology* from July 2020 to June 2024. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Prostate Cancer Statistics: World Cancer Research Fund International. WCRF International. Apr. 2022; Available online: https://www.wcrf.org/cancer-trends/prostate-cancer-statistics/
2. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology. Prostate Cancer (version 1.2023). Available online: https://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf, October 21, 2022.
3. Zapatero A, Guerrero A, Maldonado X, et al. High-dose radiotherapy and risk-adapted androgen deprivation in localised prostate cancer (DART 01/05): 10-year results of a phase 3 randomised, controlled trial. Lancet Oncol 2022;23:671-81.
4. Perera M, Papa N, Roberts M, et al. Gallium-68 Prostate-specific Membrane Antigen Positron Emission Tomography in Advanced Prostate Cancer-Updated Diagnostic Utility, Sensitivity, Specificity, and Distribution of Prostate-specific Membrane Antigen-avid Lesions: A Systematic Review and Meta-analysis. Eur Urol 2020;77:403-17.
5. Valle LF, Lehrer EJ, Markovic D, et al. A Systematic Review and Meta-analysis of Local Salvage Therapies After Radiotherapy for Prostate Cancer (MASTER). Eur Urol 2021;80:280-92.
6. Grado GL, Collins JM, Kriegshauser JS, et al. Salvage brachytherapy for localized prostate cancer after radiotherapy failure. Urology 1999;53:2-10.
7. Wong WW, Buskirk SJ, Schild SE, et al. Combined prostate brachytherapy and short-term androgen deprivation therapy as salvage therapy for locally recurrent prostate cancer after external beam irradiation. J Urol

2006;176:2020-4.
8. Nguyen PL, Chen MH, D'Amico AV, et al. Magnetic resonance image-guided salvage brachytherapy after radiation in select men who initially presented with favorable-risk prostate cancer: a prospective phase 2 study. Cancer 2007;110:1485-92.
9. Lee HK, Adams MT, Motta J. Salvage prostate brachytherapy for localized prostate cancer failure after external beam radiation therapy. Brachytherapy 2008;7:17-21.
10. Aaronson DS, Yamasaki I, Gottschalk A, et al. Salvage permanent perineal radioactive-seed implantation for treating recurrence of localized prostate adenocarcinoma after external beam radiotherapy. BJU Int 2009;104:600-4.
11. Moman MR, van der Poel HG, Battermann JJ, et al. Treatment outcome and toxicity after salvage 125-I implantation for prostate cancer recurrences after primary 125-I implantation and external beam radiotherapy. Brachytherapy 2010;9:119-25.
12. Burri RJ, Stone NN, Unger P, et al. Long-term outcome and toxicity of salvage brachytherapy for local failure after initial radiotherapy for prostate cancer. Int J Radiat Oncol Biol Phys 2010;77:1338-44.
13. Chen CP, Weinberg V, Shinohara K, et al. Salvage HDR brachytherapy for recurrent prostate cancer after previous definitive radiation therapy: 5-year outcomes. Int J Radiat Oncol Biol Phys 2013;86:324-9.
14. Vargas C, Swartz D, Vashi A, et al. Salvage brachytherapy for recurrent prostate cancer. Brachytherapy 2014;13:53-8.
15. Wojcieszek P, Szlag M, Głowacki G, et al. Salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after primary radiotherapy failure. Radiother Oncol 2016;119:405-10.
16. Henríquez López I, González-San Segundo C, Vegas JO, et al. Salvage brachytherapy for locally-recurrent prostate cancer after radiation therapy: A comparison of efficacy and toxicity outcomes with high-dose rate and low-dose rate brachytherapy. Radiother Oncol 2019;141:156-63.
17. Crook JM, Zhang P, Pisansky TM, et al. A Prospective Phase 2 Trial of Transperineal Ultrasound-Guided Brachytherapy for Locally Recurrent Prostate Cancer After External Beam Radiation Therapy (NRG Oncology/RTOG-0526). Int J Radiat Oncol Biol Phys 2019;103:335-43.
18. Kissel M, Pounou A, Ka K, et al. Efficacy and toxicity following salvage high-dose-rate brachytherapy for locally recurrent prostate cancer after radiotherapy. Brachytherapy 2022;21:424-34.
19. Hsu CC, Hsu H, Pickett B, et al. Feasibility of MR imaging/MR spectroscopy-planned focal partial salvage permanent prostate implant (PPI) for localized recurrence after initial PPI for prostate cancer. Int J Radiat Oncol Biol Phys 2013;85:370-7.
20. Peters M, Maenhout M, van der Voort van Zyp JR, et al. Focal salvage iodine-125 brachytherapy for prostate cancer recurrences after primary radiotherapy: a retrospective study regarding toxicity, biochemical outcome and quality of life. Radiother Oncol 2014;112:77-82.
21. Maenhout M, Peters M, van Vulpen M, et al. Focal MRI-Guided Salvage High-Dose-Rate Brachytherapy in Patients With Radiorecurrent Prostate Cancer. Technol Cancer Res Treat 2017;16:1194-201.
22. Slevin F, Hodgson S, Rodda SL, et al. Efficacy and toxicity outcomes for patients treated with focal salvage high dose rate brachytherapy for locally recurrent prostate cancer. Clin Transl Radiat Oncol 2020;23:20-6.
23. Chitmanee P, Tsang Y, Tharmalingam H, et al. Single-Dose Focal Salvage High Dose Rate Brachytherapy for Locally Recurrent Prostate Cancer. Clin Oncol (R Coll Radiol) 2020;32:259-65.
24. van Son M, Peters M, Moerland M, et al. Determining the safety of ultrafocal salvage high-dose-rate brachytherapy for radiorecurrent prostate cancer: A toxicity assessment of 150 patients. Clin Transl Radiat Oncol 2020;27:1-7.
25. Corkum MT, Morton G, Loblaw DA, et al. A Prospective Study of Magnetic Resonance Imaging-guided Focal Salvage High-dose-Rate Brachytherapy for Radiorecurrent Prostate Cancer: Updated Results of 30 Patients. Pract Radiat Oncol 2022;12:e531-7.
26. Guimas V, Quivrin M, Bertaut A, et al. Focal or whole-gland salvage prostate brachytherapy with iodine seeds with or without a rectal spacer for postradiotherapy local failure: How best to spare the rectum? Brachytherapy 2016;15:406-11.
27. King MT, Yang DD, D'Amico AV, et al. Risk-adaptive paradigm for focal versus whole-gland salvage treatment for radio-recurrent prostate cancer. Front Oncol 2022;12:998390.
28. Mottet N, Bellmunt J, Briers E, et al. European association of urology (EAU) prostate cancer guideline. Available online: https://d56bochluxqnz.cloudfront.net/documents/full-guideline/EAU-EANM-ESTRO-ESUR-ISUP_

SIOG-Guidelines-on-Prostate-Cancer-2022.pdf, updated 2022, accessed 22 Oct 2022.
29. Kaljouw E, Pieters BR, Kovács G, et al. A Delphi consensus study on salvage brachytherapy for prostate cancer relapse after radiotherapy, a Uro-GEC study. Radiother Oncol 2016;118:122-30.

Cite this article as: Andring LM, Teh BS, Butler EB, Farach AM. Focal versus whole gland salvage brachytherapy for recurrent prostate cancer in the prostate specific membrane antigen PET era: a narrative review Chin Clin Oncol 2023;12(3):26. doi: 10.21037/cco-23-4