

Peer Review File

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Reviewer A		
Reviewer comments	Author response and change made	Modifications to paper with italicized changes
<p>Reviewer #1, item #1: Abstract – “Neither report evaluated radiation technique, image guidance, or dosimetric parameters.”</p> <p>This sentence is unclear, as these points have been also summarized in the manuscript.</p>	<p>Thank you for the thoughtful suggestion. We agree that the sentence highlighted could benefit from clarification.</p> <p>The two reports mentioned did not provide specific dosimetric recommendations comparing whole vs partial gland brachytherapy. We have amended the manuscript to clarify this point.</p>	<p>Abstract: Neither report <i>provided a specific comparison of recommendations for dosimetric technique, or normal structure dose constraints.</i></p>
<p>Reviewer #1, item #2: Results – outcomes “higher rates of BFFS” can hardly be concluded from all these studies that were performed in different time periods, different techniques and heterogenous patient groups.</p>	<p>We agree that while the median BFFS was numerically higher, that this conclusion cannot be drawn from a comparison of heterogenous studies.</p> <p>We have made the changes outlined to the right.</p>	<p>Results: The following sentence was deleted: “<i>In general, patients who received whole gland brachytherapy salvage therapy had higher rates of BFFS compared to patients receiving partial gland or focal salvage therapy.</i>”</p> <p>Discussion: The median rate of BFFS was <i>numerically</i> lower (3-year BFFS 58% vs 77%) with partial gland salvage BT; <i>however, given the heterogeneity of the studies included, this finding is hypothesis generating and requires further prospective evaluation.</i></p>

<p>Reviewer #1, item #3: Discussion Several inclusion criteria are recommended. Why did you choose these criteria? If your recommendation is based on your review, you must explain specific inclusion and exclusion criteria based on this review.</p>	<p>We agree that the recommended inclusion criteria would benefit from a more thorough explanation of selection.</p> <p>We have amended the manuscript as described.</p>	<p>Discussion: Based on <i>published clinical guidelines discussed above^{2,28,29}</i> and the analysis of this narrative review, <i>where we found that the most studies utilized pathologic confirmation and staging evaluation</i> for selection of men with locally recurrent prostate cancer for salvage BT, <i>we recommend the following inclusion criteria:</i> pathologic confirmation of local disease, staging evaluation with no evidence of lymph node involvement or distant metastatic disease (preferably with PSMA PET), and $\leq T3b$ disease at the time of relapse. <i>Using a cut-off of $\leq T3b$ disease will allow for full coverage of recurrent disease without excessive toxicity to adjacent organs at risk, while also maximizing patients eligible for this salvage modality.</i></p>
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<p>Reviewer #1, item #4: The same applied to the recommendation of dose prescription and dose constraints. Is it your personal feeling or expert opinion? Is anything based on actual results (dose response or organ tolerance)?</p>	<p>Thank you, this is a valid point and we have amended the manuscript to provide more detail regarding how dose parameter recommendations were selected.</p> <p>Including, a comparison to published clinical guidelines for definitive therapy (while being slightly more conservative) and compiling recommendations from studies described in the review that reported a safe toxicity profile and associated dosimetric parameters utilized.</p>	<p>Discussion: <i>NCCN guidelines for definitive brachytherapy dosing include 145Gy for I-125, 125Gy with Pd-103, and 27Gy/2fx or 38Gy/4fx delivered BID for Ir-192.²</i> Based on the <i>dosing regimens reviewed in the current study and consideration of published definitive dosing regimens</i>, 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 120-145Gy for LDR with I-125, 90-120Gy for LDR with Pd-103, and 24-36Gy in 2-6 fractions for HDR BT, <i>similar, but slightly more conservative, compared to definitive dosing described above.</i> Furthermore, <i>by considering the reported dose constraints and toxicity profiles of included studies</i>, we believe the current review supports the following dose constraints.</p>
<p>Reviewer #1, item #5: If you exclude patients with residual urinary toxicity, you should also comment on patients with residual rectal toxicity.</p>	<p>We have included residual rectal toxicity as a consideration for partial gland therapy as well, given the lower rates of rectal toxicity found in this review, compared to whole gland salvage.</p>	<p>Results: RTOG 0526 excluded patients with significant residual urinary toxicity from their prior radiation treatment.^{16,17} <i>Residual rectal toxicity was not described as an exclusion factor for any of the studies reviewed.</i></p> <p>Discussion: Additionally, based on the results of this analysis, patients with significant residual urinary or rectal toxicity from their <i>initial</i> course of radiation should be considered for</p>

		partial gland BT salvage treatment.
Reviewer #1, item #6: Would you consider other spacers apart from hyaluronic acid – as hydrogel?	The specific language of hyaluronic acid spacer was used, because this was how it was described in the manuscript included. However, hydrogel spacer is appropriate.	We have replaced the use of hyaluronic acid spacer with hydrogel spacer throughout the manuscript.

<p>Reviewer #1, item #7: Abbreviations (in the tables) as “Bx” or “sxs” need to be explained.</p>	<p>Thank you for bringing this to our attention. We have added lists of abbreviations for each table.</p> <p>Additionally, sxs was only used once so the abbreviation was replaced with the full word “symptoms” instead.</p>	<p>Table 2: Abbreviations: 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; NR: not reported; TURP: trans-urethral resection of prostate; G2/3: grade 2 or 3; GI: gastrointestinal; GU: genitourinary; ED: erectile dysfunction; Bx: biopsy; PET/CT: positron emission tomography computed tomography.</p> <p>Table 3: Abbreviations: 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; TURP: trans-urethral resection of prostate; G2/3: grade 2 or 3; GI: gastrointestinal; GU: genitourinary; ED: erectile dysfunction; Bx: biopsy; HRQoL: health-related quality of life; e/o: evidence of; PSMA PET: prostate specific membrane antigen positron emission tomography.</p>
<p>Reviewer B</p>		
<p>Reviewer comments</p>	<p>Author response and change made</p>	<p>Modifications to paper with italicized changes</p>
<p>item #1: Please confirm whether the spelling of Bin S. the is correct.</p>	<p>No, spelling is Bin S. Teh and has been edited.</p>	<p>Authors: Lauren M Andring MD¹; Bin S. <i>Teh</i> MD², Edward Brian Butler MD², Andrew <i>M. Farach</i>, MD²</p>

<p>item #2: Please define BFFS/BT/HIFU/RFS/GU/RP/GI/PE T/CT upon first use in the Abstract.</p>	<p>Abbreviations have been defined upon first use in the abstract.</p>	<p>Abstract: Background/Objective: ...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) <i>positron emission tomography and computerized tomography (PET/CT)</i>. Brachytherapy (<i>BT</i>) represents an excellent option for definitive local salvage treatment. Consensus guidelines for the delivery of salvage <i>BT</i> are heterogenous and limited. Herein, we report the results from a narrative review analyzing whole gland and partial gland <i>BT</i> salvage to help guide treatment recommendations. Key Content and Findings: The median 5-year <i>biochemical failure free survival (BFFS)</i> for men receiving whole gland <i>BT</i> salvage was 52%, which is comparable to 5-year <i>recurrence free survival (RFS)</i> rates for other salvage treatment modalities (<i>radical prostatectomy (RP)</i> 54%, <i>high-intensity focused ultrasound (HIFU)</i> 53%, cryotherapy 50%). However, the median rate of severe <i>genitourinary (GU)</i> toxicity was lower (12%) compared to published rates for other treatment modalities (<i>RP</i> 21%, <i>HIFU</i> 23%, and cryotherapy 15%). Furthermore, patients receiving partial gland salvage <i>BT</i> had even lower median rates of grade 3 or higher <i>GU</i> toxicity (4% vs 12%) and <i>gastrointestinal (GI)</i> toxicity</p>
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		<p>(0% vs 3%), with 3-year BFFS of 58%. Only two studies directly comparing <i>BT</i> whole versus partial gland salvage were identified with comprehensive literature search and neither provided specific comparison regarding prescription dose or dose constraints.</p>
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<p>item #3: Please define LMA/RTOG/PSA/BID upon first use in the Main Text.</p>	<p>Abbreviations have been defined upon first use in the main text.</p>	<p>Materials and Methods: A total of 503 studies were identified in the initial search. Titles and abstracts were reviewed and screened for relevance by <i>author Lauren M. Andring (LMA)</i>.</p> <p>Results: The second prospective study was <i>Radiation Therapy Oncology Group (RTOG) 0526...</i> Furthermore, the two prospective trials^{8,17} required a Gleason score ≤ 7 and <i>prostate specific antigen (PSA) <10ng/mL...</i></p> <p>Discussion: NCCN guidelines for definitive brachytherapy dosing include 145Gy for I-125, 125Gy with Pd-103, and 27Gy/2fx or 38Gy/4fx delivered <i>twice a day (BID)</i> for Ir-192.</p>
<p>item #4: Should PET be replaced with PET/CT in the Introduction of the Main Text to be consistent with the Abstract?</p>	<p>PET/CT is used throughout the manuscript and tables/figures for consistency.</p>	<p>See manuscript edits.</p>
<p>item #5: In the text/table, references should be cited using numbers in round brackets and their baseline should be the same with the other characters. If the references belong to the previous sentences, please identify their correct positions to the front of the punctuation to avoid misunderstandings.</p>	<p>References throughout text and tables have been edited accordingly.</p> <p>See to the right for example and see manuscript for full edits.</p>	<p>Results: In the studies analyzing whole gland salvage brachytherapy, 11 (85%) were retrospective cohort reviews (6, 7, 9-16, 18) and two (15%) were phase II clinical trials (8,17).</p>

<p>item #6: Please provide the full citing information of Ref 27 in the bibliography.</p>	<p>Full citation for Ref 27 has been included.</p>	<p>References: King MT, Yang DD, D’Amico AV, et al. Risk-adaptive paradigm for local versus whole-gland salvage treatment for radiorecurrent prostate cancer. <i>Frontiers Oncol.</i> 2022;12:1-5.</p>
<p>item #7: We suggest replacing the current legend of Table 1, “The narrative review reporting checklist and literature search details” with “The search strategy summary”.</p>	<p>We have made the recommended change to the title of Table 1.</p>	<p>Table 1: The <i>search strategy summary</i></p>
<p>item #8: Table 2</p> <ul style="list-style-type: none"> a. The published year of RTOG 0526 does not correspond with Ref 7 in the bibliography. b. BFFS/NR/PSA/neg should be defined in the explanatory legend. 	<ul style="list-style-type: none"> a. The published year for RTOG 0526 has been edited to 2019, corresponding with reference 17. b. Abbreviations have been defined in the explanatory legend. NR was altered in table to “not reported”. 	<p>Table 2: Abbreviations: ... <i>BFFS: biochemical failure free survival; PSA: prostate specific antigen; neg: negative.</i></p>
<p>item #9: Table 3</p> <ul style="list-style-type: none"> a. BFFS/PSA/ECE/neg should be defined in the explanatory legend. b. TURP can not be identified in the table. Please confirm whether it should be removed. 	<ul style="list-style-type: none"> a. Abbreviations have been defined in the legend – see to the right. b. TURP was removed from legend of Table 3. 	<p>Table 3: ...<i>BFFS: biochemical failure free survival; PSA: prostate specific antigen; ECE: extra-capsular extension; neg: negative.</i></p>