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Salvage High-Dose-Rate Brachytherapy for Recurrent Prostate Cancer After Definitive Radiation

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Salvage high dose rate brachytherapy for recurrent prostate cancer after definitive radiation

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Abstract:	Purpose: Salvage high-dose-rate brachytherapy (sHDRBT) for locally recurrent prostate cancer after definitive radiation is associated with biochemical control in approximately half of patients at 3-5 years. Given potential toxicity, patient selection is critical. We present our institutional experience with sHDRBT and validate a recursive partitioning machines model for biochemical control. Materials and Methods: We performed a retrospective analysis of 129 patients who underwent whole-gland sHDRBT between 1998-2016. We evaluated clinical factors associated with biochemical control as well as toxicity. Results: At diagnosis the median PSA was 7.77 ng/mL. Majority of patients had T1-2 (73%) and Gleason 6-7 (82%) disease. 71% received external beam RT alone, while 22% received permanent prostate implants. The median DFI was 56 months, and median pre-salvage PSA was 4.95ng/mL. At sHDRBT, 46% had T3 disease and 51% had Gleason 8-10 disease. At a median of 68 months following sHDRBT, 3 and 5-year disease free survival were 87% (95% CI 80-93%) and 69% (95% CI 60-78%), respectively. Median PSA nadir was 0.18 ng/mL, achieved a median of 10 months after sHDRBT. Patients with ≥35%+ cores and a DFI <4.1 years had worse biochemical control (19% vs. 50%, p = 0.02). 14 patients (11%) developed acute urinary obstruction requiring Foley placement while and 19 patients (15%) developed strictures requiring dilation. Conclusions: sHDRBT is a reasonable option for patients with locally recurrent prostate cancer following definitive RT. Those with <35%+ cores or an initial DFI of ≥4.1 years may be more likely to achieve long-term disease control following sHDRBT.

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Anthony Zietman, MD, FASTRO
Editor-in-Chief

Dear Dr. Zietman,

Thank you for considering our manuscript, titled "*Salvage high dose rate brachytherapy for recurrent prostate cancer after definitive radiation*".

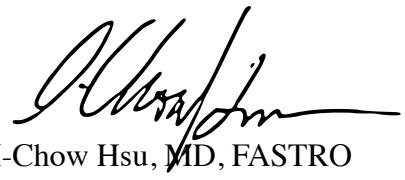
This manuscript describes our institutional experience with salvage high-dose-rate brachytherapy for prostate cancer after definitive radiation from November 1998-December 2016.

We believe this represents the largest series of salvage high-dose-rate brachytherapy to date and identifies potential clinical criteria that can be used to improve patient selection. It adds to the literature regarding acute and late side effects following salvage brachytherapy for prostate cancer, given the recent toxicity data published from RTOG 0526[1], and offers data on biochemical control while we await those oncologic outcomes.

All authors contributed equally to this work, and have approved the manuscript for submission. This work has not been published previously. There are no financial or other conflicts of interest that may influence the content of this manuscript.

We feel this paper is well suited for *IJROBP* and thank you for your consideration.

Sincerely,



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Salvage high dose rate brachytherapy for recurrent prostate cancer after definitive radiation

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Abbreviations:
ADT: androgen deprivation therapy
CTCAE: Common Terminology Criteria for Adverse Events
DFI: Disease free interval
DFS: disease free survival
EBRT: external beam radiotherapy
FDG: Fluorodeoxyglucose
GI: gastrointestinal
GU: genitourinary
HDRBT: high-dose-rate brachytherapy
IQR: interquartile range
NED: no [without] evidence of disease
OS: overall survival
PNI: perineural invasion
PPI: permanent prostate implants
PSA: prostate specific antigen
PSMA: Prostate specific membrane antigen
RT: radiation
SBRT: stereotactic body radiotherapy
sHDRBT: salvage high-dose-rate brachytherapy
TRUS: trans-rectal ultrasound

Abstract

Purpose:

Salvage high-dose-rate brachytherapy (sHDRBT) for locally recurrent prostate cancer after definitive radiation is associated with biochemical control in approximately half of patients at 3-5 years. Given potential toxicity, patient selection is critical. We present our institutional experience with sHDRBT and validate a recursive partitioning machines model for biochemical control.

Materials and Methods:

We performed a retrospective analysis of 129 patients who underwent whole-gland sHDRBT between 1998-2016. We evaluated clinical factors associated with biochemical control as well as toxicity.

Results:

At diagnosis the median PSA was 7.77 ng/mL. Majority of patients had T1-2 (73%) and Gleason 6-7 (82%) disease. 71% received external beam RT alone, while 22% received permanent prostate implants. The median DFI was 56 months, and median pre-salvage PSA was 4.95ng/mL. At sHDRBT, 46% had T3 disease and 51% had Gleason 8-10 disease.

At a median of 68 months following sHDRBT, 3 and 5-year disease free survival were 87% (95% CI 80-93%) and 69% (95% CI 60-78%), respectively. Median PSA nadir was 0.18 ng/mL, achieved a median of 10 months after sHDRBT. Patients with ≥35%+ cores and a DFI <4.1 years had worse biochemical control (19% vs. 50%, p = 0.02). 14 patients (11%) developed acute urinary obstruction requiring Foley placement while and 19 patients (15%) developed strictures requiring dilation.

Conclusions:

sHDRBT is a reasonable option for patients with locally recurrent prostate cancer following definitive RT. Those with <35%+ cores or an initial DFI of ≥4.1 years may be more likely to achieve long-term disease control following sHDRBT.

Keywords: Salvage brachytherapy, recurrent prostate cancer

Introduction

Biochemical failure following definitive radiation in the treatment of prostate cancer occurs in up to 30% of patients with intermediate to high risk disease, even in the era of dose escalated radiation with brachytherapy(1).

Between 50-70% of patients with biochemical failure will have isolated local failure (2, 3). For these patients, potential salvage treatment options that offer the possibility of long-term disease control include radical salvage prostatectomy, brachytherapy, stereotactic body radiotherapy (SBRT), and cryotherapy. However, the majority of patients do not receive potentially curative treatment, with rates ranging from 2% (5/257) (4) to 16% (97/609) (5). Up to half of patients are not offered any treatment, and rather are managed with observation (4). Zumsteg et al. found that following biochemical failure, the median time to clinically detected distant metastases was 5.4 years, and the median time to prostate cancer-specific mortality was 10.5 years (5). Though the impact of specific local salvage therapies on prostate cancer specific mortality is not clear, there is data to suggest that local failure is associated with the development of distant metastases(6).

Prior series examining the role of salvage HDR brachytherapy (sHDRBT) have demonstrated 2-year biochemical control approaching 90% (7) and 5-year biochemical control of approximately 50% in appropriately selected patients (8, 9). sHDRBT offers dosimetric advantages that help limit dose to the rectum, bladder, and urethra(10), with predominantly grade 2 genitourinary toxicity that compares favorable to other salvage options such as radical prostatectomy (9, 11-13).

Here we update our institutional experience with sHDRBT and validate a previously developed recursive partitioning machines model for biochemical control.

Materials and Methods:

We performed a single institution retrospective review of 153 patients treated with sHDRBT between November 1998 and December 2016. We excluded patients who received pelvic radiotherapy at the time of sHDRBT (n= 11), had partial prostate implants (n= 3), or did not have follow-up PSA measurements available (n=10); our final analysis includes 129 patients. Outcomes for 84 patients have not previously been published, while 45 patients were previously described with shorter follow-up (XXX). Biochemical failure following initial RT and after sHDRBT was defined using the Phoenix criteria (15). Patients were required to have biopsy proven locally recurrent prostate cancer and no evidence of metastatic disease on systemic imaging, which could include CT/MRI and ^{99}Tc bone scan, PET/CT, or PET/MRI (tracers included FDG, Na/F, fluciclovine, or ^{68}Ga PSMA).

Treatment received:

Patients received 36 Gy in 6 fractions or 32 Gy in 4 fractions, both over 2 implants; this technique has been described previously (7). Dosimetric constraints included V75 <1cc for the bladder and rectum, urethra V125 < 1cc, and D100 >90% of the planning target volume.

Outcomes and Statistics:

Our primary endpoints were disease free survival (DFS) and overall survival (OS) following sHDRBT, which were estimated using the Kaplan-Meier method. Acute and late toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v5.0). In addition to descriptive statistics, Mann-Whitney tests were used to compare continuous variables while Chi-squared and Cochrane-Armitage tests were used

for non-ordered and ordered categorical variables, respectively. Univariate analysis using Cox's proportional hazards regression model was used to identify predictors of biochemical failure; as no variables were found to be statistically significant, a multivariable analysis was not performed. For all analyses, a 2-sided p-value <0.05 was considered statistically significant. Statistical analysis was performed using SPSS v.25 (IBM Corp, Armonk, NY).

Machine learning

Outcomes for an initial cohort of 45 patients were previously analyzed using a recursive partitioning machines model(***), which found that patients with ≥ 35% positive cores and a disease free interval (DFI) < 4.1 years were more likely to experience biochemical failure (75% vs. 38% among patients who did not meet these criteria). Here we evaluate these clinical criteria in a previously unpublished cohort of 84 patients, as well as with longer follow-up among the original cohort.

Results:

Patient characteristics prior to sHDRBT

Patient characteristics in the entire cohort, as well as separated into the original and validation cohort, are shown in Table 1. The median age at initial diagnosis was 60 years (interquartile range (IQR) 56-66) with a median PSA of 7.77 ng/mL (IQR 5.60-11.75). At initial diagnosis, 35% (45/129) had T1c disease, 37% (48/129) had T2 disease, 11% (14/129) had T3a and 9% (11/129) had T3b disease; initial T stage was unknown in 9% (11/129). At initial diagnosis, 42% (54/129) had Gleason 6 disease, 40% (52/129) Gleason 7, 10% (13/129) Gleason 8, and 5% (7/129) Gleason 9-10. All patients were treated with

definitive radiotherapy (RT). The majority received external beam RT (EBRT) alone (71%, 91/129), while 22% (28/129) received permanent prostate implants (PPI); the remaining 10 patients received HDRBT, protons, or stereotactic body radiotherapy. 44% (57/129) received androgen deprivation therapy (ADT) at the time of initial RT. The median PSA nadir after definitive therapy was 0.60 (IQR 0.10-0.90), with a median DFI of 56 months (IQR 39-84).

All patients underwent trans-rectal ultrasound (TRUS) and biopsy confirming recurrence in the prostate prior to consideration for sHDRBT. The majority of patients underwent evaluation for nodal or distant metastatic disease with CT and bone scan (97/129, 75%) or MRI and bone scan (20/129, 16%) prior to sHDRBT. An additional 4% of patients received Prostacint scans, 2% received ^{68}Ga-PSMA PET/CT or PET/MRI, and an additional 3% received MRI, FDG or NaF PET/CT, or ^{99}Tc bone scan only prior to sHDRBT.

Disease characteristics at sHDRBT

At the time of sHDRBT 24% of patients (31/129) had T1c disease, 29% (37/129) had T2 disease, 19% (25/129) had T3a and 27% (35/129) had T3b disease (Table 1). 5% (7/129) were Gleason 6, 40% (51/129) Gleason 7, 35% (45/129) Gleason 8, and 16% (20/129) Gleason 9-10 at the time of sHDRBT, with a median of 30% positive cores. The median pre-salvage PSA was 4.95 ng/ml (IQR 3.92-6.90). 50% of patients (58/115, 14 unknown) had perineural invasion (PNI) at the time of sHDRBT. Median interval from biochemical failure to sHDRBT was 9 months (IQR 7-18).

Outcomes following sHDRBT

The median post-sHDRBT PSA was 1.07 ng/mL, with a median nadir of 0.18 ng/mL (IQR 0.09-0.51) achieved at a median of 10 months following salvage (IQR 5-21). At a

median follow-up of 68 months (IQR 46-105), 46% of patients (59/129) remained without evidence of disease (Figure 1). The median time to failure after sHDRBT was 64 months (IQR 44-103 months). The Kaplan Meier estimate for 3-year disease free survival was 87% (95% CI 80-93%) and for 5-year disease free survival was 69% (95% CI 60-78%).

Disease free survival was associated with lower post-sHDRBT PSA nadir (0.10 ng/mL in those without evidence of disease at last follow-up (NED) vs. 0.37 ng/mL in those with biochemical failure (BF), $p < 0.001$), as well as longer interval from sHDRBT to PSA nadir (17 months in those who remained NED vs. 7 months in those with BF, $p < 0.001$).

On univariate analysis (Table 2), no pre-treatment variables were significantly associated with biochemical failure. 36% of patients were treated between 8/2009 and 6/2014 and received 32 Gy in 4 fractions (46/129), however the majority of patients received 36 Gy in 6 fractions (64%, 82/129); all patients received 2 implants. There was a trend towards improved DFS in patients treated with 36 Gy in 6 fractions compared to 32 Gy in 4 fractions (52% vs. 33%, $p = 0.053$) with no significant difference in follow-up interval between the two groups (median 63 and 78 months respectively, $p = 0.56$). 28% of patients (36/129) received ADT and 8% (10/129) received hyperthermia at the time of sHDRBT, though neither were associated with disease free survival at last follow-up ($p = 0.37$ and $p = 0.29$, respectively).

<u>Machine learning validation:</u>

Patients who had >35% positive cores at salvage, and a disease free interval <4.1 years were more likely to experience biochemical failure (81% (13/16) vs. 50% (55/109), $p = 0.021$ in the total cohort and 82% (9/11) vs. 49% (35/72) in the new cohort ($p = 0.040$)). As previously predicted(14), when over 100 patients were included in the

analysis, clinical criteria identified using the recursive partitioning machines model was able to identify subpopulations of patients at risk for biochemical failure with statistical significance(15).

Sites of recurrence

70 patients (54%) developed biochemical failure after sHDRBT (Table 3). 46% (32/70) had failure distantly; of these 32 patients, 28 had distant failure only, while 1 had local and distant, 2 had regional and distant, and 1 had both locoregional and distant failure. Isolated local failure was seen in 7% of patients (9/70), isolated regional failure was seen in 2% (3/70), and locoregional failure was seen in 4% (3/70).

In 18% of patients who experienced biochemical failure (23/70), the site of failure was unknown. Site of failure after biochemical recurrence following sHDRBT was unknown in 8% of patients who received ^{68}Ga-PSMA PET imaging (1/12) vs. 38% (22/58) of patients who did not undergo ^{68}Ga-PSMA PET imaging. Of the 12 patients who underwent ^{68}Ga-PSMA PET scans for biochemical failure after sHDRBT (Table 3), 4 patients were identified with local failure, 3 with locoregional failure, 2 with isolated distant failure, 1 with local and distant, 1 with locoregional and distant failure, and one with unknown site of failure.

Toxicity

Genitourinary (GU) and gastrointestinal (GI) toxicities are summarized in Table 4; for the analyses below late is defined as >3 months, though data for late toxicity >9 months is also presented. Acute and late grade 3 or higher GU toxicities were seen in 1% and 6% of patients, respectively. 40% (51/82) of patients with late grade 2 GU toxicity were classified as such solely because they remained on medications such as tamsulosin. Acute and late grade 3 or higher GI toxicities were seen in 0% and 2% of patients, respectively. There was

no association between acute or late grade 3 toxicity and type of prior radiation treatment ($p = 0.99$ and $p = 0.96$ for acute and late GU, and $p = 0.97$ for late GI; no grade 3 or higher acute GI toxicity).

11% of patients (14/129) required a Foley catheter for acute urinary retention following sHDRBT; this was not associated with type of prior RT though there was a trend towards higher rates of Foley use in those who received prior PPI (17% vs. 11% with other RT modalities, $p = 0.09$). Obstruction requiring a Foley was not associated with prostate size at sHDRBT ($p = 0.10$), treatment with hyperthermia ($p = 0.91$), or prior DFI ($p = 0.34$).

15% of patients (19/129) developed strictures at a median of 42 months following sHDRBT (95% CI 27-56 months) (Figure 1c). Stricture development was not associated with type of prior RT ($p = 0.77$), treatment with hyperthermia ($p = 0.71$), prior DFI ($p = 0.18$), or prostate size at salvage ($p = 0.09$).

Four patients developed rectourethral fistulas requiring diversion at 11 months, 13 months, 3.7 years and 6.4 years after completing sHDRBT respectively. Fistula incidence was higher among patients who developed a stricture requiring dilation after sHDRBT (16%, 3/19) than patients who did not develop a stricture requiring dilation (1%, 1/110) ($p = 0.001$). There was no association between fistula development and time from initial RT to salvage ($p = 0.41$), follow-up after sHDRBT ($p = 0.13$), prostate size at salvage ($p = 0.96$), T-stage at salvage ($p = 0.68$), type of prior RT ($p = 1.00$), or hyperthermia at salvage ($p = 1.00$).

Two patients developed a second malignancy in or adjacent to the radiation field, with one rectal cancer and one urothelial carcinoma diagnosed 6.1 and 3.9 years following sHDRBT, respectively.

Discussion

To our knowledge this represents the largest series of sHDRBT to date and suggests that a significant proportion of patients with locally recurrent prostate cancer after definitive radiation can achieve biochemical control with sHDRBT, though this rate declines with time and argues for rigorous patient selection. In our series sHDRBT was relatively well tolerated.

In patients with isolated local failure, local salvage therapy is the only treatment option with curative intent. Though we lack level 1 evidence demonstrating an OS or DFS benefit to local salvage, we have retrospective data that suggests sequential progression in patients with biochemical failure to clinically detectable metastases after 5.4 years, with a median time to prostate cancer specific mortality of 10.5 years(5). Based on data in the setting of biochemical recurrence following radical prostatectomy, we know that the time from initial local treatment to the development of metastatic disease predicts time to death (17). However rates of local therapy following radiation failure have been reported as low as 2%(4). Androgen deprivation therapy is the most common salvage treatment, used in about 94% of patients undergoing salvage, which corresponds to about 66% of all patients with failure after EBRT (18). Unfortunately as a treatment modality, ADT is palliative, with a median survival of 5-6 years after initiation in patients with metastatic disease, and is also associated with decreased quality of life (19).

Our findings are consistent with previously published series of sHDRBT and demonstrate reasonably high rates of biochemical control at short-term follow-up, with attrition over time. Some series have estimated 5-year biochemical control as high as 70-

80% in appropriately selected patients, though rates of approximately 50% are more commonly reported (9, 20-22). These rates of biochemical control are comparable to those achieved with other salvage treatment modalities, including radical prostatectomy (12, 13, 23), low dose rate brachytherapy (24-26), and cryotherapy(27, 28). SBRT has more limited follow-up, however may also be associated 5-year biochemical disease free survival of 60% (29).

The decline in biochemical control between years 3 and 5 suggests that patient selection remains critical. Our current institutional practice is to obtain TRUS and multi-parametric MRI-guided biopsy, CT and bone scan, as well as ^{68}Ga-PSMA or fluciclovine PET imaging if possible. The majority of data using ^{68}Ga-PSMA PET imaging for biochemical recurrence is following radical prostatectomy (30-32). Limited data in patients with biochemical recurrence following definitive EBRT suggests that 17% of patients may have isolated local recurrence, 6% local and regional (pelvic lymph nodes), and 19% isolated regional failure (33). ^{68}Ga-PSMA PET therefore may be a useful tool to identify patients more likely to benefit from local salvage. In our series, regional failure following sHDRBT was seen in 7/42 patients (17%) without prior nodal radiation and 2/17 patients (12%) who received nodal radiation with their initial treatment course ($p = 0.22$). No patients in this series received pelvic nodal radiation at the time of salvage.

We were also able to validate clinical criteria identified using a recursive partitioning machines model for biochemical control. Patients with <35% cores involved or ≥35% cores involved with a disease free interval >4.1 years were less likely to experience biochemical failure following sHDRBT. Additional clinical factors have been shown to be associated with improved disease control after salvage brachytherapy, including PSA

doubling time >6-9 months(34), low PSA < 10 or ≤6(22), and long interval from prior radiation(14) which may also improve toxicity (35).

Retrospective series of salvage brachytherapy suggest acute urinary retention in 4% (4/98) of patients, no acute grade 3/4 genitourinary (GU) toxicity, and 9% (9/98) grade 3/4 late GU toxicity(36). Though the oncologic outcomes for RTOG 0526 are still pending, toxicity data with a median follow-up of 54 months following salvage low-dose-rate brachytherapy demonstrated a 14% rate of late grade 3 GU or GI toxicity, which was not associated with pretreatment variables such as prior treatment dose or interval (37). Our data suggests a slightly higher rate of acute urinary retention, with 11% of patients requiring Foley placement following sHDRBT, however slightly lower rates of late grade 3+ GU or GI toxicity (6%, with late defined as > 9 months per RTOG 0526).

Our stricture rate of 15% was higher than expected based on the 7% seen in Yamada *et al.* (20), as was the prolonged interval of events up to 90 months. Four patients developed rectourethral fistulas, also at a variable duration following sHDRBT of up to 44 months. Our finding that stricture dilation following sHDRBT was associated with increased risk of fistula suggests that additional urologic procedures in patients who have received salvage local therapy warrants careful deliberation and patient education of potential risks. Though our rate of late grade 2 GI or GU toxicity was consistent with previously published series (20), with approximately 40% of these patients requiring medications to manage their urinary symptoms, further consideration of ways to decrease side effects is key.

In addition to urethral sparing during treatment planning(10), focal salvage brachytherapy may be an option in patients with disease localized to one region of the

prostate on both imaging and biopsy, with the potential to limit dose to the urethra and rectum(38, 39). Partial gland sHDRBT to the involved quadrant based on MRI has been reported in a small series of 15 patients and appears well tolerated, with no urinary retention and 7% grade 3 GU toxicity, with a 3-year failure free rate of 61% (40). A technique using sHDRBT to treat the peripheral zone and PET-avid disease has also been reported, with 45% 5-year disease control and no grade 3 toxicity(8). Additional methods using a permanent seed technique have been described, and include treating the whole gland to 108 Gy while escalating dose to the tumor as seen on MR spectroscopy to 144 Gy using ^{131}I or ^{103}Pd seeds (88% biochemical recurrence free survival at a median of 30 months, 1/37 patients with grade 3 toxicity)(41), as well as partial gland salvage using ^{125}I seeds with 70% 3-year biochemical recurrence free survival and one grade 3 GU toxicity(42, 43).

A significant limitation to our analysis is the retrospective nature of our data, with heterogeneous follow-up and potential underestimation of toxicity as a substantial proportion of patients had clinical follow-up with their local referring physicians. Our rate of biochemical failure may be an underestimate if biochemical failure was managed by local referring physicians. In general however, patients who had clinical follow-up closer to home still submitted their PSA measurements to our office and were in communication by MyChart, phone or email. We additionally did not limit our analysis to patients with failure following external beam radiotherapy alone—24% had definitive brachytherapy, 2% had brachytherapy boost, 4% were treated with protons, and 1% treated with SBRT. Increased dose to the urethra during definitive RT with these treatment modalities may help explain our higher than expected stricture rate, as late GU toxicity has been reported to be lower in

patients undergoing salvage SBRT after external beam alone compared to those who were treated with more intensive RT modalities(29).

Despite including patients treated over an 18-year span, our numbers were still limited, precluding identification of additional clinical variables associated with biochemical control or toxicity. Additionally, our institution did not have fixed criteria in place over this period to select patients for sHDRBT. As approximately 30% of patients in this series had T3b disease and almost 50% had Gleason 8-10 disease, our cohort likely does not reflect patients most likely to achieve long-term disease control with sHDRBT. Specific selection criteria for salvage local therapy have been proposed(44), and warrant further investigation. It also must also be noted that we used the Phoenix definition of biochemical failure(15), which was developed to describe outcomes following external beam radiation with or without ADT. Though this definition has been published in other series of salvage brachytherapy after radiation(9, 41) and is the definition used in RTOG 0526, other criteria have also been reported, including 2(24) or 3(34) successive increases in PSA above the nadir.

Conclusions

For patients with local recurrence after definitive radiotherapy, sHDRBT offers the potential for long-term disease control with an acceptable toxicity profile. Optimal patient selection remains critical, and those with ≥ 35% positive cores and prior DFI <4.1 years may be at higher risk of occult metastatic disease.

Figure Captions:

Figure 1. A) Overall survival, B) disease free survival, and C) and stricture-free survival following sHDRBT using the Kaplan Meier method

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Table

Table 1. Patient characteristics

Variable	Total cohort (n=129, %)	Prior cohort (n=45)	Validation cohort (n=84)	p-value
Age at diagnosis, Med (IQR)	60 (56-66)	60 (54-64)	62 (58-71)	0.95
Pre-tx PSA, med ng/mL (IQR)	7.77 (5.60-11.75)	9.00 (6.40-12.60)	6.10 (5.43-9.88)	**0.007**
T-stage at dx				**0.039**
1c	45 (35%)	9 (20%)	36 (43%)	
2a/b	38 (30%)	21 (47%)	17 (20%)	
2c	10 (8%)	1 (2%)	9 (11%)	
3a	14 (11%)	7 (16%)	7 (8%)	
3b	11 (9%)	6 (13%)	5 (6%)	
Unknown	11 (9%)	1 (2%)	10 (12%)	
Pre-tx Gleason score				.60
5	3 (2%)	2 (4%)	1 (1%)	
6	54 (42%)	21 (47%)	33 (40%)	
7 (3+4 and 4+3)	52 (40%)	14 (31%)	38 (45%)	
8	13 (10%)	5 (11%)	8 (18%)	
9/10	7 (5%)	3 (7%)	4 (5%)	
Percent cores at diagnosis, median (IQR)	50% (23-71%)	67% (38-86%)	37% (18-69%)	0.068
Definitive RT				0.057
EBRT alone	91 (71%)	37 (82%)	54 (64%)	
PPI	28 (22%)	5 (11%)	23 (27%)	
HDR	2 (2%)	0 (0%)	2 (2%)	
EBRT+brachy	2 (2%)	2 (4%)	0 (0%)	
Protons	5 (4%)	1 (2%)	4 (5%)	
SBRT	1 (1%)	0 (0%)	1 (1%)	
Prior ADT				**0.044**
Short-term	40 (31%)	16 (36%)	50 (60%)	
Long-term	17 (13%)	9 (20%)	24 (29%)	
No	70 (54%)	20 (44%)	8 (10%)	
Unknown	2 (2%)	0 (0%)	2 (2%)	
PSA nadir after definitive therapy	0.60 (0.10-0.90)	0.60 (0.05-1.12)	0.45 (0.12-0.70)	0.50
Prior disease free interval (mo)	56 (39-84)	53 (33-78)	58 (43-87)	0.27
Time PSA failure to salvage (mo)	9 (7-18)	9 (3-16)	10 (8-21)	0.47
Pre-salvage PSA	4.95 (3.92-6.90)	5.50 (4.12-6.77)	4.75 (3.81-7.75)	0.83
Salvage T stage				0.20
1c	31 (24%)	6 (13%)	25 (30%)	

2a/b 2c 3a 3b Unknown	30 (23%) 7 (5%) 25 (19%) 35 (27%) 1 (1%)	12 (27%) 2 (4%) 16 (36%) 10 (22%) 0 (0%)	18 (21%) 6 (7%) 9 (11%) 25 (30%) 1 (1%)	
Salvage GS 6 7 8 9/10 Unknown	 7 (5%) 51 (40%) 45 (35%) 20 (16%) 6 (5%)	 2 (4%) 8 (18%) 11 (24%) 16 (36%) 4 (9%)	 5 (6%) 13 (15%) 19 (22%) 29 (35%) 16 (19%)	0.43
% positive cores at salvage	30% (15-50%)	40% (23-50%)	31% (15-57%)	0.41
Salvage dose/fx 32 Gy in 4 fx 34 Gy in 5 fx 36 Gy in 6 fx	 46 (36%) 1 (1%) 82 (64%)	 1 (2%) 0 (0%) 44 (98%)	 45 (54%) 1 (1%) 38 (45%)	**<0.001**
Salvage ADT Short term Long term None	 31 (24%) 5 (4%) 93 (72%)	 14 (31%) 4 (9%) 27 (60%)	 17 (20%) 1 (1%) 66 (79%)	**0.026**
Post salvage PSA	1.07 (0.44-2.39)	0.60 (0.21-1.77)	1.68 (0.59-2.48)	**0.013**
Post salvage nadir	0.18 (0.09-1.76)	0.10 (0.05-0.34)	0.23 (0.10-0.72)	**0.006**
Median follow-up (mo)	77 (49-107)	105 (59-140)	62 (49-86)	**<0.001**

Table 2. Univariate analysis for predictors of biochemical failure

Variable	p-value
Prior to definitive treatment	
T-stage	0.23
PSA	0.10
Gleason score	0.75
Percent positive cores	0.66
Perineural invasion	0.20
Definitive treatment with ADT	0.31
Following definitive treatment	
PSA nadir	0.86
Disease free interval (months)	0.41
Failure to SHDRBT (months)	0.43
Clinical variables at sHDRBT	
T-stage	0.25
PSA	0.09
Gleason score	0.21
Percent positive cores	0.50
Perineural invasion	0.48

Table 3. Site of failure after salvage HDR brachytherapy

Site	No ^{68}Ga-PSMA PET	^{68}Ga-PSMA PET	Total
Local	5	4	9
Regional	3	0	3
Distant	26	2	28
Locoregional	0	3	3
Local and distant	1	0	1
Regional and distant	1	1	2
Local, regional, and distant	0	1	1
Unknown	22 (38%)	1 (8%)	23
Total	58	12	70

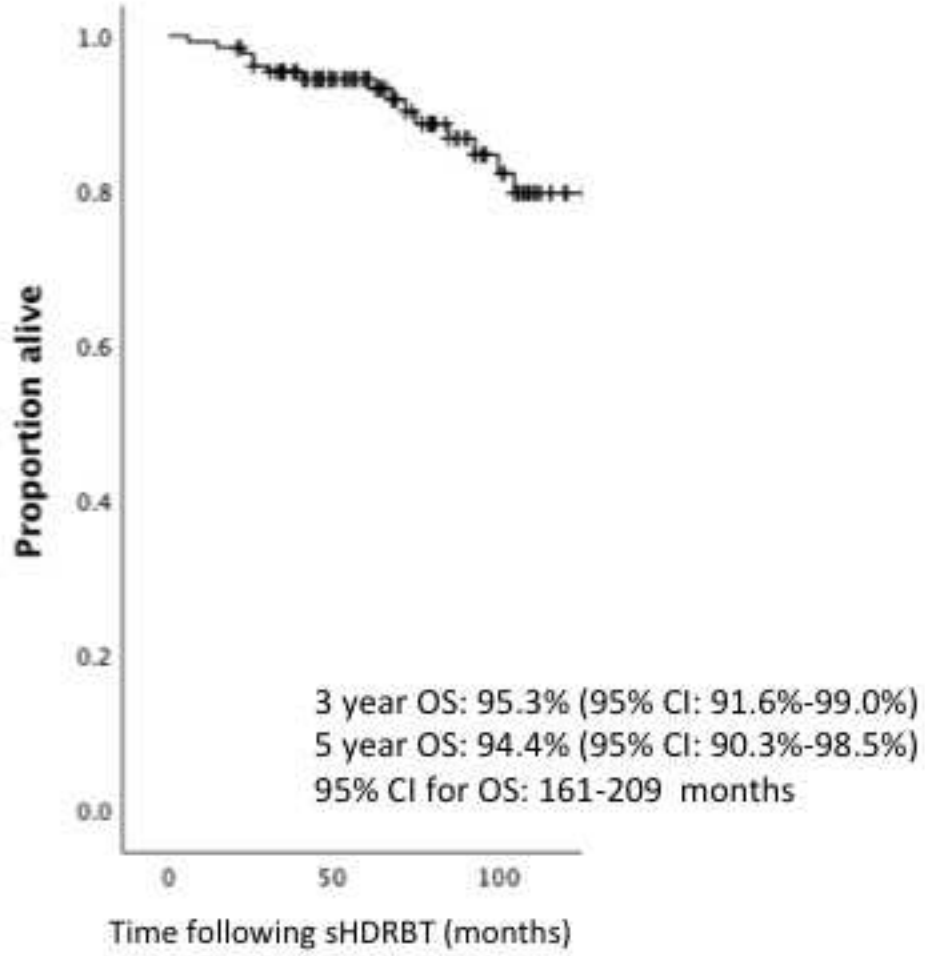
* 2 patients had ^{68}Ga-PSMA PET scans prior to sHDRBT and remain biochemically without evidence of disease

Table 4. Toxicity following salvage HDR brachytherapy

	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Acute, <3 months						
Genitourinary (n=127)	9 (7%)	62 (48%)	55 (42%)	1 (1%)	0 (0%)	0 (0%)
Gastrointestinal (n=126)	97 (75%)	27 (22%)	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Late, >3 months						
Genitourinary (n=125)	14 (11%)	22 (17%)	82 (63%)	6 (5%)	1 (1%)	0 (0%)
Gastrointestinal (n=126)	95 (73%)	25 (19%)	4 (3%)	1 (1%)	1 (1%)	0 (0%)
Late, >9 months						
Genitourinary (n=118)	19 (14%)	23 (18%)	71 (55%)	5 (4%)	1 (1%)	0 (0%)
Gastrointestinal (n=125)	97 (75%)	23 (18%)	3 (2%)	1 (1%)	1 (1%)	0 (0%)

*If insufficient information documented to grade toxicity, patients were excluded from the analysis

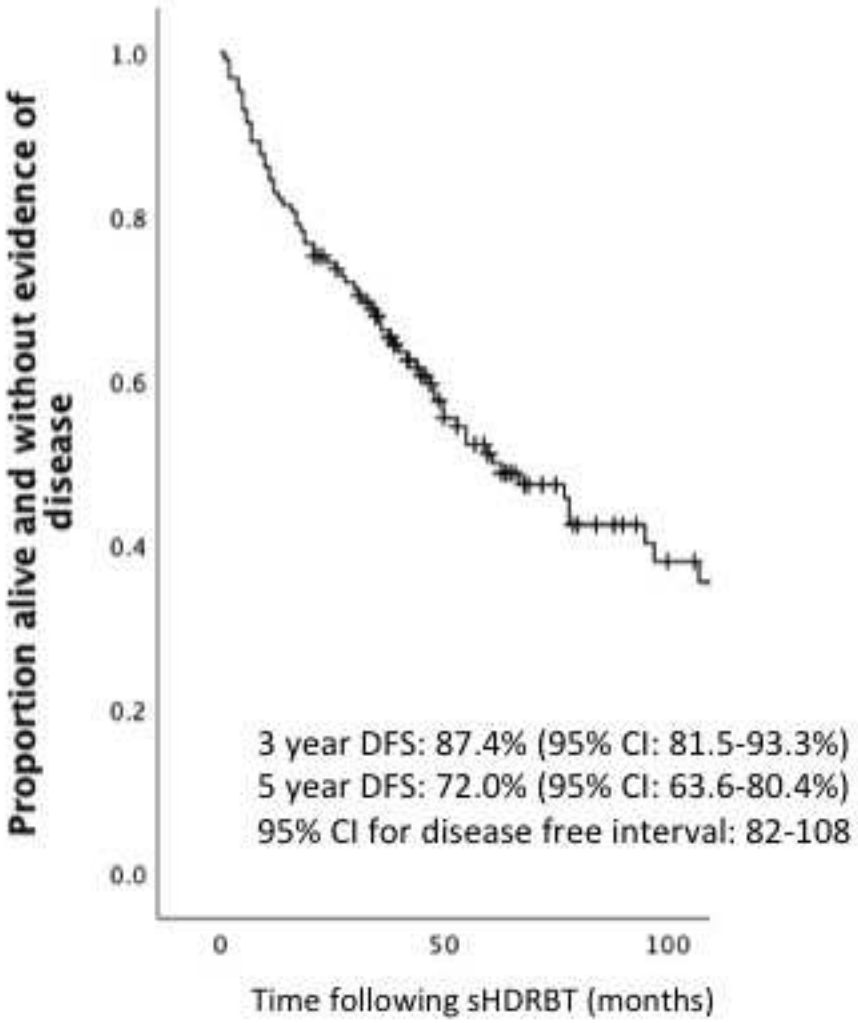
Figure1a



Months	6	24	36	48	90
Number events (death)	1	3	6	7	12
Number at risk	128	124	111	93	42
Censored, lack of follow-up	0	2	12	29	75

Figure1b

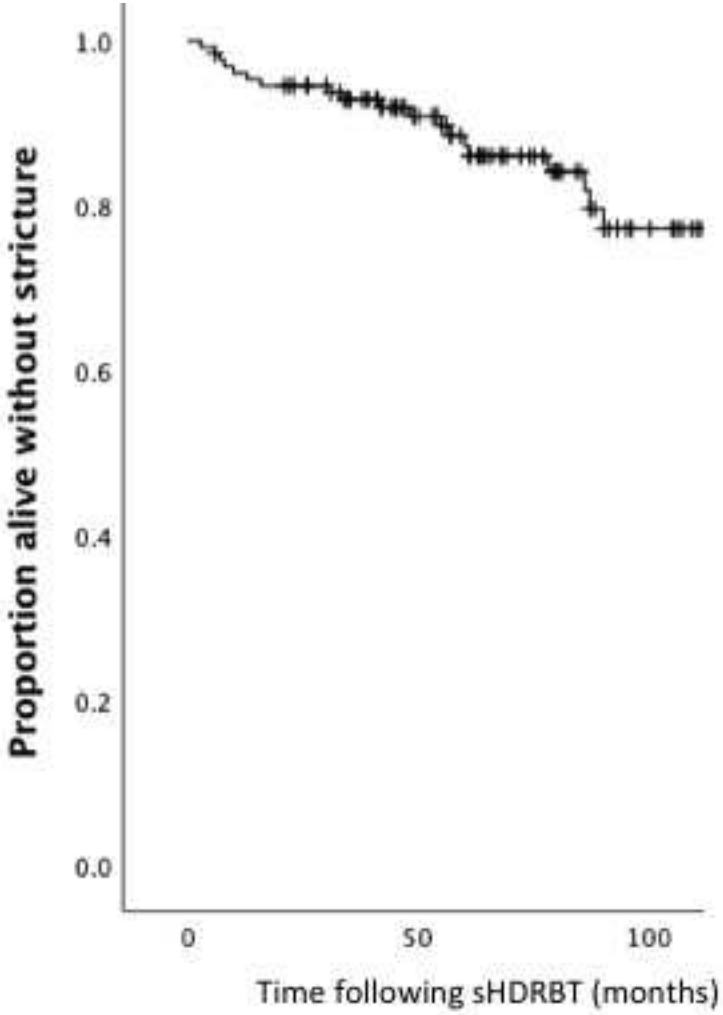
Click here to access/download;Figure;Fig1b.jpg



Months	6	15	24	36	48	70	90
Number events (failure)	2	6	9	16	22	39	45
Number at risk	127	123	117	103	86	53	39
Censored, lack of follow-up	0	0	3	10	23	37	45

Figure1c

Click here to access/download;Figure;Fib1c.jpg



Months	6	12	24	36	48	70	90
Number events (stricture)	2	5	7	9	11	15	19
Number dead w/o stricture	1	1	3	4	6	7	8
Number at risk	126	123	118	104	86	53	31
Censored, lack of follow-up	0	0	2	12	26	54	71