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Salvage Low Dose Rate Prostate Brachytherapy: Clinical Outcomes of a Phase II Trial for Local Recurrence after External Beam Radiotherapy (NRG Oncology/0526)

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Abstract

Purpose: We report efficacy of a prospective Phase II trial (NCT00450411) of salvage low dose rate (LDR) prostate brachytherapy (BT) for local failure (LF) after prior external beam radiotherapy (EBRT) with minimum 5- years' follow up.

Materials/Methods: Eligible patients had low/intermediate risk prostate cancer (PCa) prior to EBRT and biopsy-proven LF > 30 months after EBRT, with PSA < 10 ng/mL and no regional/distant disease. The primary endpoint, late GI/GU Adverse Events (AEs) (CTCAE V3.0 ≥ Grade 3) was 14%. With minimum 5-year follow up after salvage BT, secondary clinical outcomes including disease-free (DFS; includes death from any cause), disease-specific (DSS), and overall survival (OS) were estimated using the Kaplan-Meier method and modelled using Cox proportional hazards regression. Local tumor progression (LF), distant and biochemical failure (DF/BF) were estimated using cumulative incidence. Time to LF, DF and BF were modeled by cause-specific Cox proportional hazards regression.

Results: From 05/2007 –01/2014, 20 centers registered 100 patients (92 analyzable). Median follow up is 6.7 years (range: 0.3–11.2); median age 70 years (range: 55–82); median prior EBRT dose 74 Gy (IQR: 70–76) at a median of 85 months prior(IQR: 60–119). Androgen deprivation was combined with salvage BT in 16%. 10-year OS is 70% (95% confidence interval [CI]: 58%–83%). 19 patients died (5 PCa, 10 other, 4 unknown). 10-year failure rates are local 5% (95% CI:1–11), distant 19% (95% CI:10–29) and biochemical 46% (95% CI:34–57). DFS is 61% at 5 years; 33% at 10 years. No baseline characteristic was significantly associated with any clinical outcome.

Conclusion: This is the first prospective multicenter trial reporting outcomes of salvage LDR BT for LF after EBRT. Five-year freedom from BF is 68%, comparable to other salvage modalities. Although further LF is rare (5%), BF climbs to 46% by10-years.

Keywords

Prostate cancer; radiotherapy; local failure; salvage brachytherapy; low dose rate brachytherapy

Introduction

Although local persistence of tumour is not infrequent after external beam radiotherapy (EBRT) for prostate cancer (1) (2) (3) (4) (5), local salvage therapy is rarely employed (6). Several options exist, including salvage prostatectomy, cryotherapy, high intensity focussed ultrasound, or whole gland or partial gland high dose rate (HDR) or low dose rate (LDR) brachytherapy. Most published results are retrospective from single centers(7) (8) (9) (10). Due to advanced patient age, co-morbidities and/or fear of toxicity, the most common approach remains androgen deprivation (11), which may be administered in a delayed or intermittent schedule.

In 2005, the RTOG, now NRG, commenced a phase II trial of salvage whole gland LDR brachytherapy. In 2018 the primary endpoint, the rate of late Grade 3 Gastrointestinal/Genitourinary adverse events (GI/GU AEs) with a minimum 2 years of follow up was reported at 14%. Now, with a minimum 5 years of follow up, we report clinical outcomes for efficacy in terms of survival, and biochemical, local and distant failure.

Materials and Methods

Eligible patients had received EBRT more than 30 months before enrollment (maximum prescribed dose 78 Gy/39 fractions or 81 Gy/45 fractions), had biopsy-proven local recurrence confirmed on central pathology review, prostate specific antigen (PSA) at trial entry < 10 ng/mL, and no evidence of regional or distant metastases on Tc99 bone scan and abdominal/pelvic computed tomography (CT). Original tumour presentation prior to EBRT was favorable or intermediate risk, PSA ≤ 20 ng/mL, Gleason Score ≤ 7 (Grade groups 1,2 and 3) and clinical stage ≤ T2c.

Treatment consisted of transperineal, template-guided LDR brachytherapy using either Iodine-125 (140 Gy minimum target dose) or Paladium-103 seeds (120 Gy minimum target dose). Partial prostate treatment was permitted if the dominant lesion was identified with appropriate biologic imaging (DCE CT, MRI or MRspect). Androgen deprivation therapy (ADT) was permitted in conjunction with salvage brachytherapy at the discretion of the treating physician for a maximum duration of 6 months.

The primary endpoint of late GI/GU AEs was previously reported (12). Secondary endpoints included clinical outcomes of overall survival (OS), disease-specific survival (DSS), disease-free survival (DFS), as well as local, distant and biochemical failure. For all secondary clinical outcome endpoints, all patients were to be followed for a minimum of 5 years. Follow up was mandated every 3 months for the first year post brachytherapy, every 6 months in years 2–5 and then annually. The time to failure was measured from the date of registration to the date of death from any cause for OS, date of death due to prostate cancer (including death in association with clinical tumor progression with or without further salvage therapy, or death from a complication of therapy) for DSS, and date of disease progression or date of death for DFS. DFS and OS were estimated using the Kaplan-Meier method with unadjusted and adjusted hazard ratios (HRs), with corresponding 95% confidence intervals (CIs) calculated from Cox proportional hazards regression models. DSS, local failure (LF), distant failure (DF), and biochemical failure (BF) were estimated using nonparametric estimation of cumulative incidence of the event of interest, accounting for competing risks of death without an event. The time to failure was measured from the date of registration for the trial to the date of LF (determined by clinical exam), BF (PSA ≥ current nadir + 2 ng/mL), or DF (documented lymphatic or hematogenous metastatic disease), respectively. Adjusted and unadjusted HRs for time to death from prostate cancer and LF, DF, and BF were obtained from cause-specific Cox proportional hazards regression models. Adjustment in all models was made for factors such as T-stage, PSA, Gleason score, and age.

Results

From May 2007 to January 2014 100 patients were enrolled from 20 centers. As 8 patients were excluded(12), the subsequent statistical analyses focused on the 92 eligible patients who received protocol treatment (12). Median age at study entry was 70 years. Zubrod performance status was 0 in 92% of eligible patients, and 52% had Gleason score 6 while 48% were Gleason 7. No patient had extracapsular extension clinically at baseline or at the time of salvage. Baseline PSA (prior to EBRT) was ≤10 ng/ml in 84% (median: 7.3 ng/ml). Median PSA prior to salvage LDR brachytherapy was 7.3 ng/ml (IQR: 5.5–9.3 ng/ml). Table 1 provides the clinical characteristics of the patients. Concurrent or prior ADT was prescribed for 16% of patients at the time of salvage. Only 2 patients received a partial prostate implant.

Median follow up is 6.7 years. The 10-year overall survival is 70% (95% CI: 58–83)(Figure 1). Of the 19 patients who died, 5 died due to the prostate cancer, 10 from other causes and 4 of unknown cause.

The 10-year DFS rate is 33% (95% CI: 21–45). The 10-year DSS rate is 70% (95% CI: 58–83). 10-year distant failure rate is 19% (95% CI: 10–29) (Figure 2) and local failure 5% (95% CI: 2–11) (Figure 3). Only 2 of the 14 patients with distant failure also had local failure. Distant failures were detected at a median of 3.9 years (IQR 1.5–6.2). The 10-year biochemical failure rate is 46% (95% CI: 34–57) (Figure 4). The median PSA at 6 years for those patients who are failure free (n=51) was 0.1 ng/ml, suggesting a durable ablative effect of the salvage brachytherapy. Of the 37 patients for whom salvage was unsuccessful, 29 were treated with ADT, 1 received pelvic EBRT, 2 had surgery, and 5 had other forms of treatment.

None of the baseline characteristics, including proportion of the evaluated target volume covered by 100% of the prescription dose (V100) and time from completion of EBRT to brachytherapy implant were significantly associated with any clinical endpoint. Table 2 shows the Cox proportional hazards model.

Discussion

EBRT is the mainstay of non-surgical management in all stages of prostate cancer, often combined with ADT for higher grade or more locally advanced disease. Although highly effective treatment, patients with longer follow up may experience a slowly rising PSA associated with local persistence or recurrence of viable tumour. Morris et al reported that in a randomized trial of 398 men with unfavorable intermediate or high-risk prostate cancer treated with 78 Gy plus 12 months of ADT, only 30% maintained a PSA < 0.2ng/ml while this was evident in 80% of those treated with the combination of EBRT plus brachytherapy and 12 months of ADT (13). Although a dose response relationship for EBRT has been established in multiple randomized trials of dose escalation (14)(15)(16)(17)(18), the optimal dose of EBRT has yet to be reached. Ample evidence exists for the benefit of the increased dose provided by the addition of brachytherapy (19) (20)(21).

Post-radiation biopsies demonstrate residual tumour in 21–51% of cases biopsied 2–3 years after radiotherapy (3)(5)(1). The frequency varies depending on tumor grade and stage, radiation dose and use of ADT (5)(22). Positive post treatment biopsies of 25% are reported even with a dose of 81 Gy or greater (2). Pucar et al have demonstrated through serial MRI and step-sectioning of salvage prostatectomy specimens that recurrence or persistence is usually at the site of the original dominant lesion, indicating relative radioresistance that may still be successfully managed if sufficient dose can be delivered(23). Persistent or recurrent local disease not only predicts biochemical failure but is associated with subsequent distant metastases and death from prostate cancer (2)(1)(3). Zelefsky et al reported on 382 patients who were biopsied at a median of 38 months after radiotherapy, 30% of whom had positive biopsies. With 15-year follow-up, the risk of distant metastases was 2.6 times higher in those with positive post treatment biopsies and the risk of death from prostate cancer twice as high (1).

Despite these potential consequences, local salvage modalities are rarely offered. Fewer than 5% of men with biochemical recurrence undergo biopsy for clarification of the site of disease and subsequent definitive treatment. Many options exist, including salvage prostatectomy, re-irradiation with either brachytherapy or stereotactic body radiotherapy (SBRT) or tissue destructive modalities such as cryotherapy or high intensity focussed ultrasound (HIFU). Patient selection is important in all modalities, but no striking differences exist in efficacy. Reported biochemical no evidence of disease rates (BNED) for whole gland cryotherapy are 67% at 3 years (24) and 39% at 10 years (25). For SBRT, BNED rates range similarly from 3-year 55% (n=100) (26) to 5-year 60% (n=50) (27). For HIFU Crouzet et al reported on 418 patients with a mean follow up of 3.5 years and found 5-year BNED rates of 58% for initially low risk disease, 51% for intermediate and 36% for patients with initially high risk disease (28). Salvage radical prostatectomy yields 5-year BNED rates of 47–82%, and at 10 years 28–53% (29). Reports of robot-assisted laparoscopic prostatectomy are still lacking the follow up to assess oncologic outcomes. Side effects are more frequent than in de novo treatments with each modality.

If local recurrence after prior EBRT is due to insufficient dose initially and is not totally radio-resistant, then further radiotherapy may be potentially curative. The highly conformal dose distribution achievable with brachytherapy is desirable for re-treatment in previously irradiated tissue in order to limit the dose to adjacent sensitive organs. Several single center reports confirmed feasibility and efficacy (7) (8) (9) prior to the RTOG/NRG initiating a multi-center Phase II trial in 2007.

Patient selection

The NRG/RTOG 0526 eligibility criteria concentrated on tumor-related and treatment-related factors and did not specify demographic criteria, which often carry more weight in determining the appropriateness for salvage treatment. Advanced patient age, diminished life expectancy and the presence of significant co-morbidities often preclude consideration of definitive salvage treatment.

NRG/RTOG 0526 only included patients who were more than 2.5 years from their initial treatment. This makes the interpretation of the biopsy more straightforward with fewer

indeterminate results (30) and helps to eliminate those patients whose rising PSA is due to pre-existing metastatic disease (31)(32). All patients had EBRT administered in standard fractionation to a maximum dose of 81 Gy in 1.8 Gy fractions or 78 Gy in 2 Gy fractions. The safety and efficacy of salvage LDR brachytherapy has not been tested following hypofractionated EBRT or SBRT. In addition, to be eligible for NRG/RTOG 0526, the initial presentation of prostate cancer had to be either low or intermediate risk, and the PSA at the time of salvage under 10 ng/ml. Unfortunately, there was no PSA doubling time restriction on eligibility, despite doubling times < 6 months being associated with a component of distant failure (33)(34). The intent was to select a population with a lower risk of pre-existing metastases and a higher chance of ultimate cure. Two-thirds of patients were intermediate risk at initial presentation and despite these precautions, almost 20% of the treated population developed distant metastatic failure by 10 years. As ADT was not mandated in this study and was used for very few patients (16%), its role in combination with salvage brachytherapy cannot be evaluated. Clearly, if the indications for salvage brachytherapy evolve to include the high-risk scenario, ADT will be increasingly important.

Furthermore, the trial antedated availability of prostate specific membrane antigen (PSMA) positron emission tomography (PET) for investigation of patients with a rising PSA following definitive radiotherapy. PSMA-Ga68-PET or other PET-based scanning will play a prominent role in the future for early detection of metastatic disease when selecting patients for definitive salvage treatment. Detection rates with PSA < 0.5 ng/ml are 50–58%, 0.5–2.0 ng/ml 69–93% and > 2.0 ng/ml 86%−97% (35) (36) (37). Given the increased risk of toxicity of salvage treatment compared to the de novo scenario, a negative PSMA PET scan prior to embarking on salvage is recommended. This will be especially important if local salvage is being considered for a patient with initially high-risk disease where co-existent subclinical metastatic disease is more likely.

Partial prostate treatment

Although NRG/RTOG 0526 permitted partial prostate treatment if a focal lesion could be detected by the available metabolic imaging such as SPECT or MR spectroscopy, only 2 of the patients had less than a whole gland implant. The efficacy of focal salvage therapy cannot be evaluated with these data. Because of the available imaging the target for a partial prostate implant was required to be a minimum of 60% of the prostate volume. If focal salvage proves to be effective, toxicity may well be less than whole gland salvage, especially since grade 3 GU toxicity has been shown to be related to higher V100 signifying more complete coverage of the entire gland (12). Focal HDR salvage data is very encouraging with very low rates of grade 3 toxicity reported (38) (39) (40).

Subsequent LF after salvage brachytherapy was observed in only 5% of patients by 10 years. Determination of LF by DRE can be problematic after prostate irradiation such that persistent disease is often unsuspected. This would be especially true after re-irradiation with salvage brachytherapy. Confirmatory biopsies were strongly recommended in the protocol but infrequently collected.

Since LDR brachytherapy provides effective salvage of local recurrence after external beam radiotherapy, could this be preferable use of this modality compared to upfront incorporation

as a “boost” in primary management? The cumulative grade III GU toxicity of LDR boost in primary management of high-risk disease reported in the Ascende trial of 18% is a disturbing disincentive to its use(21). Restricting LDR brachytherapy to those patients with LF after EBRT and no DF on PSMA PET might put fewer patients at risk for toxicity. To counter this argument, much of the grade 3 toxicity in Ascende was successfully managed and persistent toxicity at 5 years was only 8%. Furthermore, other multicenter studies of EBRT plus an LDR boost reported much lower rates of late grade 3 GU toxicity (41,42). Further study of LDR brachytherapy to compare upfront boost vs. delayed salvage could address this question with patient reported outcomes playing a key role.

Conclusion

Whole gland salvage LDR brachytherapy is an effective and well-tolerated modality for salvage of local recurrence after definitive radiotherapy in patients selected to have a reasonable chance of cure based on the initial stage and grade at diagnosis, and the timing of the subsequent recurrence. At 10 years, local failure is 4.9%. The toll of distant failure may be reduced by incorporating advanced imaging in the selection criteria. Even without that, the actuarial rate of biochemical failure at 10 years of 46% compares well to other available modalities.

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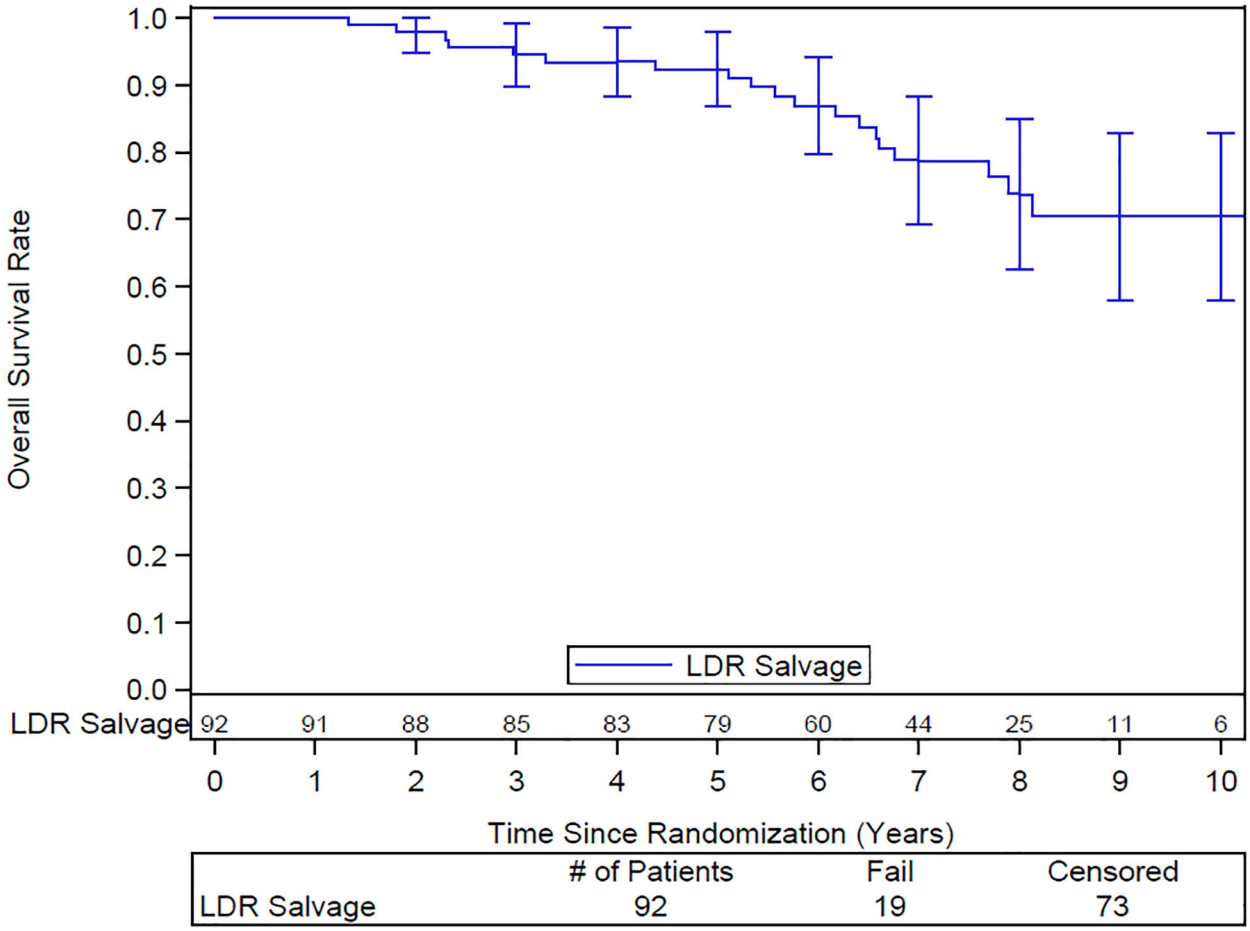

Figure 1:
Overall survival. Numbers of patients at risk are shown above the x-axis.

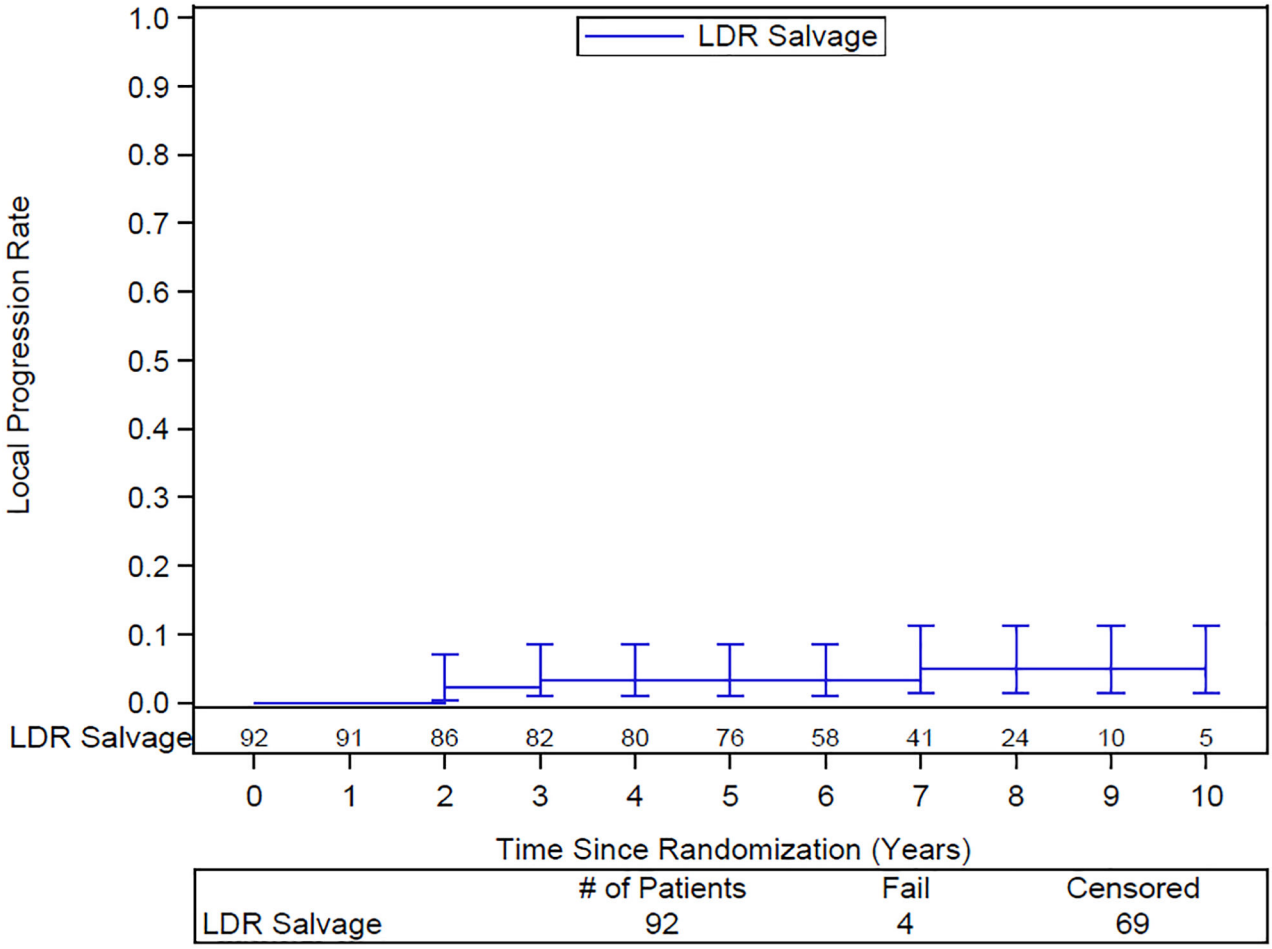

Figure 2:
Actuarial local failure following salvage brachytherapy. Numbers of patients at risk are shown above the x-axis

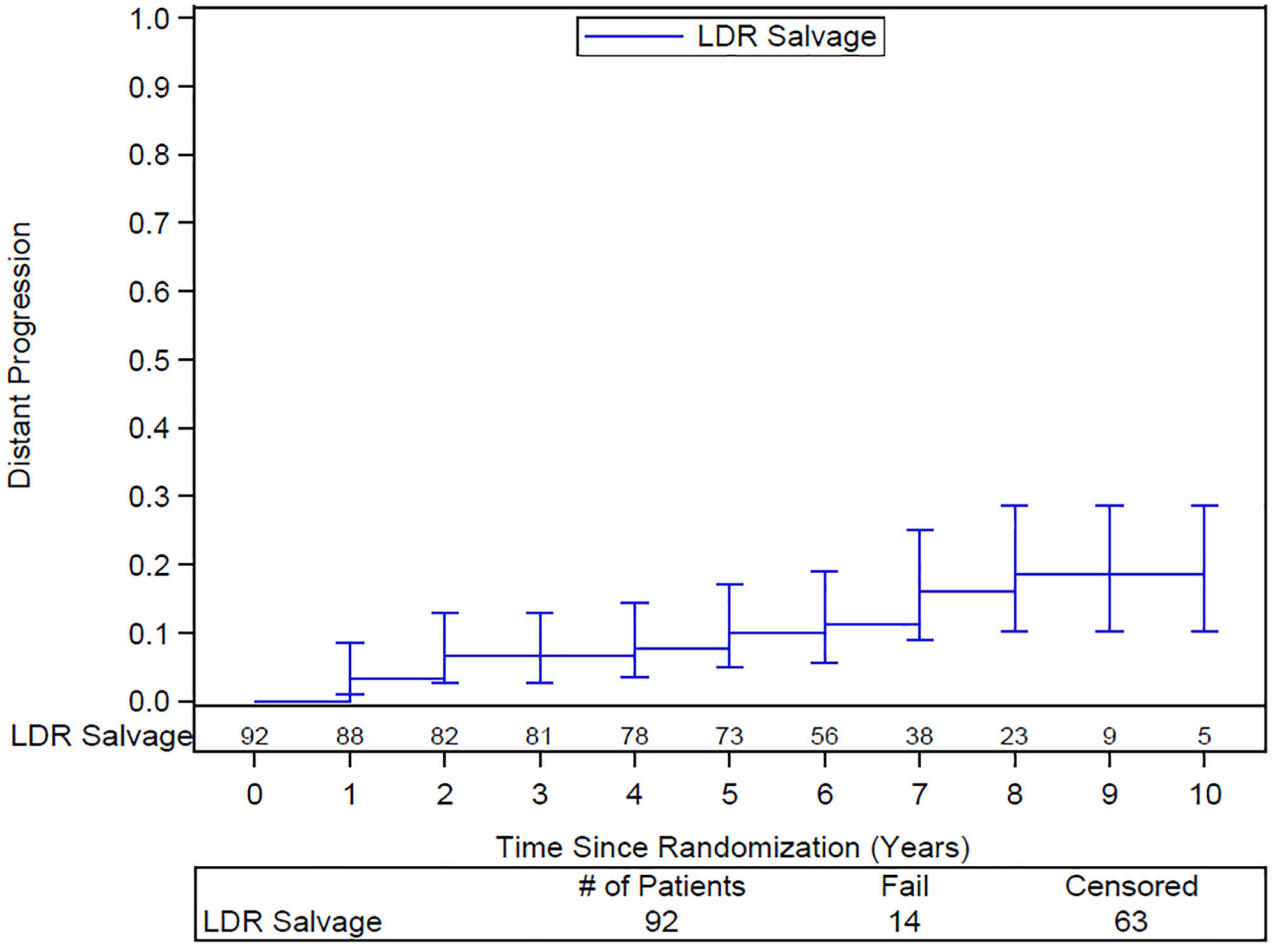

Figure 3:
Actuarial distant failure after salvage brachytherapy. Numbers of patients at risk shown above the x-axis

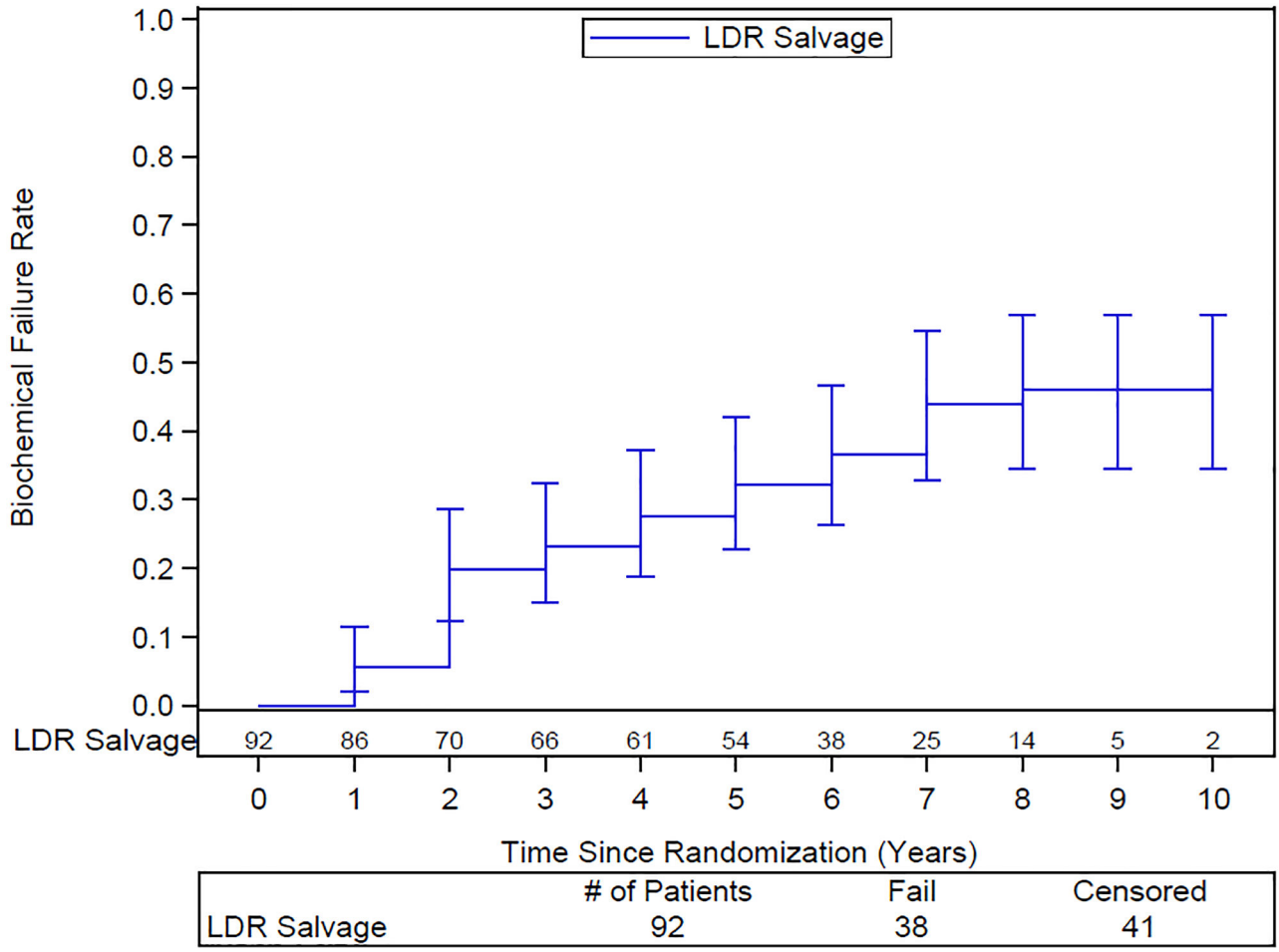

Figure 4:

Actuarial rate of biochemical failure after LDR salvage brachytherapy. Numbers of patients at risk shown above the x-axis

Table 1:

Pre-treatment clinical, tumor and treatment characteristics of the patients.

Factor	Median	Range	Interquartile Range
Age (years)	70	55–82	66–74
TRUS volume (cm^3)	25	14–44	22–31
Interval EBRT to BT (months)	85.4	39.3–199.4	60–119.4
EBRT dose (Gy)	73.8	45–81	70.2–76
Baseline PSA	7.26	0.38–19.56	5.45–9.25
	Proportion	Proportion	
Combined Gleason score	3–6: 52%	7: 48%	
Gleason 1+2	1.1%		
Gleason 2+2	2.2%		
Gleason 2+3	3.3%		
Gleason 3+2	2.2%		
Gleason 3+3	43.5%		
Gleason 3+4	37.0%		
Gleason 4+3	10.9%		
Zubrod Performance Status	0: 92%	1: 8%	
T-Stage	T1: 48.9%	T2: 51.1%	

TRUS= Transrectal Ultrasound; EBRT=external beam radiation therapy, BT=brachytherapy, PSA=prostate specific antigen.

Table 2:

Unadjusted Cox proportional hazards model for influence of clinical factors on efficacy outcomes.

Factor		Overall Survival		Distant Failure		Local Failure		Biochemical Failure	
		HR 95% CI	P value	HR 95% CI	P value	HR 95% CI	P value	HR 95% CI	P value
T stage	T1 vs. T2	1.41 (0.51–3.92)	0.51	0.58 (0.24–1.39)	0.22	0.61 (0.24–1.59)	0.31	0.85 (0.39–1.85)	0.69
PSA	Continuous	1.07 (0.93–1.23)	0.33	0.93 (0.83–1.05)	0.25	0.91 (0.80–1.03)	0.14	0.91 (0.81–1.01)	0.08
Gleason Score	2–6 vs. 7	2.20 (0.78–6.22)	0.14	0.53 (0.22–1.28)	0.16	0.4 (0.15–1.06)	0.07	0.57 (0.26–1.26)	0.16
Age	Continuous	1.09 (0.99–1.20)	0.06	0.95 (0.89–1.02)	0.19	0.96 (0.88–1.03)	0.25	0.98 (0.92–1.04)	0.43
V100	Continuous	0.98 (0.91–1.06)	0.59	1.04 (0.97–1.11)	0.26	1.00 (0.93–1.08)	0.89	1.03 (0.97–1.10)	0.35
Days from EBRT	Continuous	1.00 (0.99–1.02)	0.90	1.00 (0.99–1.02)	0.64	1.00 (0.99–1.02)	0.47	1.01 (0.99–1.02)	0.33
Dose EBRT (Gy)	Continuous	1.01 (0.92–1.10)	0.90	0.94 (0.85–1.04)	0.21	0.97 (0.88–1.06)	0.46	0.92 (0.84–1.00)	0.050

HR=hazard ratio; CI=confidence interval; PSA=prostate specific antigen; EBRT=external beam radiation therapy; V100%=percentage of target volume receiving prescription brachytherapy dose