Natural History of 'Second' Biochemical Failure Following Salvage Radiation Therapy for Prostate Cancer: A Multi-Institution Study

*Vasu Tumati MD[1], *William C. Jackson MD[2], Ahmed E. Abugharib, MD[2], Ganesh Raj[3] MD PhD, Claus Roehrborn MD[3], Yair Lotan MD[3], Kevin Courtney MD PhD[4], Aditya Bagrodia[3] MD, Jeffrey C. Gahan[3] MD, Zachary S. Zumsteg MD[7], Michael R. Folkert[1] MD PhD, Aaron M. Laine MD PhD[1], Raquibul Hannan MD PhD[1], †Daniel E. Spratt MD[2], †Neil B. Desai, MD[1#]

Departments of Radiation Oncology[1], Urology[3], Internal Medicine[4] at the University of Texas Southwestern Medical Center; Departments of Radiation Oncology[2], Urology[6] at the University of Michigan; Department of Radiation Oncology Cedars-Sinai Medical Center[7]

* Contributed equally to first authorship

† Contributed equally to senior authorship.

Running Title: Natural History of Post-Operative Radiation Therapy Failure

Keywords: prostate cancer, salvage radiation, radical prostatectomy, natural history, biochemical failure

#Corresponding Author*:* Neil B. Desai, MD MHS

Assistant Professor of Radiation Oncology

University of Texas Southwestern Medical Center, 2208 Inwood Ave Dallas, TX 75390

Neil.Desai@utsouthwestern.edu Phone: 214-645-8525 Fax: 214-645-7624

Conflicts of Interest: Dr. Spratt has served on an advisory board for Dendreon that is unrelated to the present work. Dr. Courtney has served on an advisory board for Sanofi and receives research funding for a clinical trial that is unrelated to the present work. Dr. Zumsteg is on the external advisory board for the Scripps Proton Therapy Center and has been a paid consultant for EMD Serono unrelated to the present work.

DR. VASU TUMATI (Orcid ID : 0000-0003-3908-6166)

DR. DANIEL E SPRATT (Orcid ID : 0000-0002-5973-4741)

Article type : Original Article

Article category: Urological Oncology

Objectives: To describe the natural history of prostate cancer in men who experience a second biochemical recurrence (BCR) after salvage radiotherapy (SRT) following prostatectomy.

Subjects/Patients and Methods: Following SRT at two institutions from 1986-2013, 286 patients developed second BCR, defined as two rises in PSA of ≥0.2 ng/mL above nadir. Event rates for distant metastasis (DM) or freedom from DM (FFDM), castration-resistant prostate cancer (CRPC), prostate cancer-specific survival (PCSS), and overall survival (OS) were estimated using the Kaplan-Meier method. Cox regression was used for comparative analyses.

Results: At a median 6.1 years following second BCR, rates of DM, CRPC, PCSS, and OS were 41%, 27%, 83%, and 73%, respectively. On multivariable analysis, interval to second BCR <1 year [hazard ratio (HR) 2.66, 95% confidence interval (CI) 1.71-4.14, p<0.001], Gleason score 8-10 (HR 1.65, 95% CI 1.07-2.54, p=0.022), and concurrent ADT during SRT (HR 1.76, CI 1.08-2.88, and p = 0.024) were associated with FFDM, while PCSS was associated with interval to second BCR <1 year (HR 3.00, CI 1.69–5.32, p < 0.001) and concurrent ADT during SRT (HR 2.15, CI 1.13-4.08, p = 0.019). These risk factors were used to stratify patients into three groups, with 6-year FFDM of 71%, 59% and 33% and PCSS of 89%, 79%, and 65%, respectively.

Conclusion: Following second BCR after SRT, clinical progression is enriched in a sub-group of prostate cancer patients, while others remain without DM for long intervals. Stratifying patients into risk groups using prognostic factors may aid counseling and future trial design.

Introduction

Adjuvant post-operative radiotherapy (PORT) is effective in reducing biochemical recurrence (BCR) when radical prostatectomy (RP) reveals adverse pathologic features [1-5]. However, PORT is more commonly implemented as salvage therapy (SRT) only following BCR [6-8]. At time of SRT, the poor sensitivity of existing imaging for ruling out occult micrometastasis and heterogeneous patient presentation contribute to a significant rate of subsequent treatment failure or 'second' BCR [3, 5, 9, 10].

While the natural history of patients who suffer BCR after definitive radiation therapy and RP alone have been described [11-15], detailed outcomes of men who experienced BCR after PORT largely are limited to the adjuvant setting [14, 15]. Because SRT occurs at varying intervals of up to several years from RP, it cannot be assumed that second BCR after SRT confers the same risk for clinical progression to metastasis or death when compared to BCR after definitive radiotherapy, RP, or even adjuvant PORT. Data specific to this cohort of patients in second BCR after SRT is needed to facilitate patient counseling and trial design at this time point.

To determine the natural history and predictors of outcomes in men who biochemically recur after SRT, we performed a multi-institutional retrospective study of men who received SRT and experienced second BCR.

Methods

Patient Cohort

After institutional review board approval, a retrospective review was conducted on 571 treated prostate cancer patients from 1986 to 2013 who underwent salvage radiotherapy (SRT) following radical prostatectomy (RP) at two large institutions (University of Texas Southwestern Medical Center and the University of Michigan). SRT was defined as receipt of post-operative radiotherapy for rising PSA or after at least 4 months following RP in the absence of data on PSA. Of the SRT patients, only patients that had a subsequent BCR were included for this study.

BCR after PORT was defined using the American Urologic Association definition of a PSA rise of 0.2 ng/ml or greater over nadir with a sequential equal or higher value, yielding 286 patients who formed the study cohort.

All men were treated with curative intent RP with limited lymph node sampling, without routine use of extended lymph node dissection. Those men with high risk features were treated at physician's discretion with radiotherapy to pelvic lymph nodes and/or with concurrent androgen deprivation therapy (ADT). Radiation therapy was delivered by 3D conformal radiation planning generally until 2004 at both institutions, at which point IMRT was routine. Total radiation dose varied modestly (interquartile range (IQR) 64.8 – 68.4 Gy) according to era of treatment, physician discretion and institutional preference. Typical follow up included testing of PSA and of testosterone in those who received ADT and physical exam. Imaging was not standardly obtained unless there was evidence of biochemical failure or clinical progression.

Analyses

Following SRT, local recurrence was defined by imaging or digital rectal exam, regional failure by pelvic lymph node involvement on imaging, and distant metastasis by imaging without requirement of pathologic confirmation (almost exclusively by computed tomography and technetium bone scan, with the minority receiving magnetic resonance imaging or positron emission tomography). Castration resistance was defined as 2 or more successive rises in PSA, despite testosterone <50 ng/ml, or evidence of clinical progression of disease despite the use of ADT, similar to the prostate-specific antigen working group definition [16]. Estimates of rates of local recurrence, regional recurrence, freedom from distant metastasis (FFDM) or conversely distant metastasis (DM), prostate cancer specific survival (PCSS), and overall survival (OS) were calculated using the Kaplan Meier method from the time of 'second' BCR after SRT. Groups were compared using the log-rank test.

Univariable and multivariable analyses were performed using Cox regression methods to identify the clinicopathologic variables affecting progression to DM and PCSS. Studied variables included interval to BCR (>1 year vs ≤1 year) from RP, nodal involvement, Gleason grade, T-stage, pre-SRT PSA, and margin status. PSA doubling time was not considered sufficiently robust for analysis due to the low values at time of SRT and lack of multiple measures prior to SRT in many patients. RT dose and/or use of IMRT planning were not

analyzed due to small absolute dose changes (IQR 64.8-68.4 Gy), low isolated recurrence rates after SRT with 'lower' doses in prospective study[10], confounded association of SRT dose with institution in our dataset, and lack of granular data on planning technique for all patients. For those factors found to be prognostic on multivariable analysis for DM or PCSS, we generated risk groupings based on the number of and specific risk factors present. To account for the differing contributions of each prognostic risk factor in our multivariable model for FFDM specifically, the relative influence of the individual risk factors was weighted according to their hazard ratios. Specifically, a risk score for an endpoint was generated based on summing the hazard ratios of each prognostic variable harbored by a patient for the particular endpoint, and the resulting sums were used to generate groupings (**Supplementary Table 1**). Analyses were conducted using IBM SPSS v.23 (SPSS Inc., Chicago, IL USA). An alpha of 0.05 used to define statistical significance with two-sided testing for all evaluations.**Results**

Patient characteristics

The study assessed 286 patients who experienced second BCR after SRT. The median follow up after second BCR was 6.1 years. Comprehensive demographics and treatment details are included in **Table 1**. A small majority of patients constituting our cohort was treated in between 2000-2009 (54.9%). The median pre-RT was PSA 0.6 (interquartile range, IQR 0.3-1.1), 139 men (48.6%) had PSA ≤ 0.5, 92 men (32.1%) had Gleason score ≥8, 172 men (60.1%) had stage ≥pT3, and median RT dose was 66.6 Gy (IQR 64.8-68.4 Gy). Only 18.5% received concurrent ADT with SRT. SRT dose was not associated with time era of treatment (p=0.857) but was associated with institution ($p < 0.001$).

Outcomes

For patients who experienced second BCR after SRT, median time to second BCR was 16 months (IQR 6-38 months). For those patients treated with concurrent ADT, median time to second BCR was 16 months, which was not significantly different than the median 15 months to second BCR for those not receiving ADT (log-rank p=0.232). Following second BCR, six-year local and regional recurrence rates were 4.9% and 7.5%, respectively. The 6-year rates of DM and development of CRPC after second BCR were 41.1% and 27.4%, respectively (**Figure 1A**). Median FFDM from second BCR was 112 months. The 6-year rates of PCSS and OS from second BCR were 82.5%, and 72.9%, respectively, with a median PCSS not reached and median OS of 158 months (**Figure 1B-1C**). The majority of men with second BCR subsequently

received ADT (n=193, 68%). Of the 79 men who developed CRPC, additional therapy exposure was as follows: enzalutamide 24.1%, abiraterone 45.6%, docetaxel 65.8%, cabazitaxel 10.1%, radionuclide therapy 7.6%, sipuleucel-T 3.8%. Multiple lines of therapy were received by 35% of CRPC patients.

Of those 116 men who developed DM, the median time to DM was 36 months (IQR 10.5-66 months) from second BCR. Median OS from initial metastasis was 62 months. As not all men developed metastasis, we sought to determine risk features associated with FFDM after second BCR (**Table 2**). Interval to second BCR <1 year (6-year FFDM 48% vs 67%, p < 0.001), stage ≥pT3 (6-year FFDM 66% vs 54%, p = 0.012), Gleason score 8-10 (6-year FFDM 39% vs 68%, p <0.001), pre-RT PSA > 0.5 (6-year FFDM 55% vs 63%, p = 0.011), and concurrent ADT (6-year FFDM 63% vs 44%, p = 0.001) were each associated with worse FFDM after second BCR on univariable analyses. Pathologic node positivity (p=0.132) approached significant association with FFDM and was included in the multivariable model. On multivariable analysis, interval to second BCR <1 year [hazard ratio (HR) 2.66, 95% confidence interval (CI) 1.71-4.14, p<0.001], Gleason score 8-10 (HR 1.65, 95% CI 1.07-2.54, p=0.022), and concurrent ADT [HR 1.76, CI 1.08-2.88, and p = 0.024) remained significantly predictive of FFDM after second BCR (**Table 2**). We additionally use these features to generate risk groups for development of DM after second BCR. As the hazard ratio for interval to second BCR <1 year was substantially higher than that for Gleason 8-10 or concurrent ADT, this risk grouping relied upon weighting of risk factors according to their hazard ratios, as shown in **Supplementary Table 1**. In this manner, patients could be stratified into three groups: group 1 (0 factors or either concurrent ADT or Gleason ≥ 8 only), group 2 (interval to BCR < 1 year), or group 3 (any two or more risk factors), as shown in **Figure 2A**, with 6-year FFDM from second BCR of 71%, 59%, and 33%, respectively. The proportion of patients in groups 1, 2, and 3 in this schema was 54%, 24%, and 22%, respectively.

We similarly examined prognostic factors for PCSS after second BCR in this patient cohort, of whom fifty-four patients died of prostate cancer (**Table 2**). On univariable analysis, interval to second BCR <1 year (89% v 74%, p = 0.0002), pre-SRT PSA ≤ 0.5 (HR 1.62, CI 1.15-3.30, p = 0.013), and concurrent ADT (HR 1.87, CI 1.01-3.46, p = 0.046) were associated with worse PCSS. Gleason score 8-10 (p = 0.136) approached significant association with worse PCSS and thus was included in the multivariable analysis. On multivariable analysis, interval to

second BCR <1 year (HR 3.00, CI 1.69–5.32, p < 0.001) and concurrent ADT (HR 2.15, CI 1.13-4.08, p = 0.019) remained significantly associated with PCSS. These prognostic features again were used to generate risk groupings. Specifically, patients with 0, 1, or 2 risk demonstrated 6-year PCSS of 89%, 79%, and 65%, respectively (**Figure 2B**). The proportion of patients with 0, 1, or 2 risk factors was 48%, 46%, and 7%, respectively.

Discussion

Determining the natural history of men with second BCR after SRT is important for counseling patients and in directing subsequent therapy. A significant body of literature details the outcomes of PORT and of untreated BCR after RP or definitive radiotherapy [5, 8, 11-14, 17-19]. However, the specific prognosis at time of second BCR after SRT remains poorly described.

As second BCR after SRT represents an exhaustion of local therapy sometimes years after initial RP, one might expect rapid subsequent clinical progression to metastasis and related death. However, median time to DM from second BCR and median OS from second BCR were over 9 years and 13 years, respectively. Allowing for differences in reporting, these intervals compare favorably to outcomes in most series of BCR after initial local therapy, including definitive RT, RP alone, or RP with adjuvant RT (**Table 3**) [11, 12, 14]. They also are consistent with previously reported outcomes in patients experiencing a 'first' BCR after adjuvant PORT [14, 15].

The retention of long interval to detection of metastasis following second BCR in our series is potentially due to underestimation of early ADT interventions and the limited sensitivity of traditional imaging. Second, the median pre-RT PSA 0.4 of our screening cohort of 571 SRT patients reflects the results of a transition to an 'early' SRT approach, which is associated with improved DMFS and PCSS [18, 20]. Third, the apparent better outcome of patients in second BCR after SRT in our series compared to initial BCR after definitive RT [11] is likely attributable to the different and more sensitive definition of second BCR after SRT (confirmed rise 0.2 ng/mL or greater over nadir after SRT compared to nadir + 2mg/mL after definitive RT). Nonetheless, given the interesting similarity of outcomes in our series to natural history series of initial BCR failure after RP [12, 13], one may speculate whether survival has been improved and the disease timeline fundamentally shifted even in these patients ultimately failing SRT.

While these suggested benefits of SRT and long median natural histories are noted, 41% of patients still experienced DM, and the majority were initiated either before or after DM on ADT. In our study, presence of rapid second BCR after SRT (<1 year), high Gleason grade (8-10), or failure despite concurrent ADT with SRT were predictive on multivariable analysis for DM risk. Similarly, studies of the natural history of RP, dose escalated EBRT, and PORT have shown that short interval to failure were significant predictors of DM [11, 12, 15, 19], as well as PCSM [21, 22]. Further, in Boorjan et al.'s analysis of 134 patients in BCR after adjuvant RT, Gleason score was predictive of DM [14]. While lower pre-RT PSA has been associated with improved clinical outcomes following SRT in several series[18, 20, 23] including our own[24], we did not find that pre-RT PSA remained predictive of outcomes for those in second BCR, likely due to fundamentally different determinants of natural history at this time point (i.e. speed of micrometastatic disease progression as opposed to likelihood of cure by SRT). Similarly, while some retrospective SRT series have found a benefit to dose-escalation[25-27], in our dataset, the range of SRT dose was small and confounded by association with institution (not significantly associated with FFDM or PCSS after second BCR when adjusting for institution; data not shown), precluding its analysis. In part, this was due to the study focus on those in second BCR with long follow up, where a minority of patients were treated after 2010 when higher SRT doses might be expected. However, as isolated locoregional relapse rates in both our study and prospective SRT data[10], are infrequently detected, it is also likely that SRT dose has no effect on those who suffer second BCR, where prognosis appears dominated by other metastasis.

Identification of those at highest risk for progression to DM may help trial design in this space and spare overly aggressive management in those at lower risk with competing risks. To this end, we proposed a risk stratification model at time of second BCR after SRT. For instance, study of early cytotoxic therapy such as docetaxel in the setting of recent data for its benefit in earlier metastatic and non-metastatic states[28, 29] may be focused on patients fitting our group 2 or 3 risk categories, whose significant progression rates make feasible a 5-year FFDM endpoint.

The 6-year 18% rate of prostate cancer related-death similarly was spread across patients in heterogeneous manner and in significant association with short interval to BCR <1 year and/or failure despite concurrent ADT, both of which have previously been associated with PCSS in various contexts [15, 19, 30, 31]. Interestingly, second BCR despite concurrent ADT with SRT was associated with both decreased FFDM and PCSS, which is likely a reflection of poor disease

biology and/or delay in detecting second BCR due the prolonged suppressive effect of ADT on PSA particularly for gonadotropin releasing hormone agonists. Notably, those patients who fail aggressive definitive therapy including ADT previously have been suggested to be intrinsically at higher risk for DM and CRPC [31]. Given the now level I data for benefit of adding ADT or anti-androgen therapy to SRT [10, 32], however, it would not be appropriate to hypothesize whether use of ADT itself plays a causative role in early clinical progression amongst those experiencing second BCR. More practically, our study quantified risk groups for PCSS according to interval to second BCR and failure despite use of concurrent ADT with SRT, which should facilitate selection of patients for systemic therapy salvage trials according to their relative risk of death from disease.

This study has several limitations that should be noted. First, the retrospective nature of the study limits interpretation of reasons for imaging and therapeutic interventions after BCR. Second, over the long time period of the study, several changes occurred in management of prostate cancer, such as increasing use of RP in high risk patients, use of early SRT and addition of concurrent ADT, all of which fundamentally may alter the prognosis of patients at time of second BCR in more contemporary patients. In this same vein, as several therapies for CRPC have been introduced since 2010, PCSS would be expected to be prolonged in contemporary patients, as compared to the majority of patients in our study treated before 2010. Conversely, the introduction of more sensitive imaging is likely to affect time at DM detection and time from DM to CRPC and death—an arguably landscape changing effect in prostate cancer natural history analysis for which our we could not yet account. In addition, PSA doubling time, a previously suggested correlate of DM and PCSS in various settings, could not be analyzed at time of second BCR after SRT due to the low PSA values at SRT and lack of multiple measures prior to SRT in many patients.

Nonetheless, this study is the largest to examine specifically the outcomes of men who experienced second BCR after SRT. We show that while many of these men retain prolonged survival, significant proportion is enriched for DM and ensuing morbidity and mortality. Patients with high grade/stage or short intervals to BCR appear to predict for those patients at highest risk for DM and prostate cancer related death in particular. The resultant stratification of risk within this heterogeneous population may help in clinical trial design of new systemic therapy approaches, such as early ADT or docetaxel, and identify populations for early re-staging

imaging with novel ligand PET imaging to identify low burden metastatic states, which may be amenable to novel strategies, such as stereotactic ablative radiotherapy [33].

References:

1. Wright JL, Dalkin BL, True LD, et al. Positive surgical margins at radical prostatectomy predict prostate cancer specific mortality. J Urol. 2010;183: 2213-2218.

2. Swanson GP, Riggs M, Hermans M. Pathologic findings at radical prostatectomy: risk factors for failure and death. Urol Oncol. 2007;25: 110-114.

3. Wiegel T, Bartkowiak D, Bottke D, et al. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. Eur Urol. 2014;66: 243-250.

4. Thompson IM, Jr., Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. JAMA. 2006;296: 2329-2335.

5. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). Lancet. 2012;380: 2018-2027.

6. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. J Clin Oncol. 2007;25: 2035-2041.

7. Trock BJ, Han M, Freedland SJ, et al. Prostate cancer-specific survival following salvage radiotherapy vs observation in men with biochemical recurrence after radical prostatectomy. JAMA. 2008;299: 2760-2769.

8. Cotter SE, Chen MH, Moul JW, et al. Salvage radiation in men after prostate-specific antigen failure and the risk of death. Cancer. 2011;117: 3925-3932.

9. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol. 2009;181: 956-962.

10. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. N Engl J Med. 2017;376: 417-428.

11. Zumsteg ZS, Spratt DE, Romesser PB, et al. The natural history and predictors of outcome following biochemical relapse in the dose escalation era for prostate cancer patients undergoing definitive external beam radiotherapy. Eur Urol. 2015;67: 1009-1016.

12. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. JAMA. 1999;281: 1591-1597.

13. Antonarakis ES, Feng Z, Trock BJ, et al. The natural history of metastatic progression in men with prostate-specific antigen recurrence after radical prostatectomy: long-term follow-up. BJU Int. 2012;109: 32-39.
14. Boorjian SA, Tollefson MK, Thompson RH, Rangel LJ, Bergstralh EJ, Karnes RJ. Natural history of biochemical recurrence after radical prostatectomy with adjuvant radiation therapy. J Urol. 2012;188: 1761-1766.
15. Abdollah F, Boorjian S, Cozzarini C, et al. Survival following biochemical recurrence after radical prostatectomy and adjuvant radiotherapy in patients with prostate cancer: the impact of competing causes of mortality and patient stratification. Eur Urol. 2013;64: 557-564.
16. Bubley GJ, Carducci M, Dahut W, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 1999;17: 3461-3467.
17. Bolla M, van Poppel H, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). Lancet. 2005;366: 572-578.
18. Pfister D, Bolla M, Briganti A, et al. Early salvage radiotherapy following radical prostatectomy. Eur Urol. 2014;65: 1034-1043.
19. Freedland SJ, Humphreys EB, Mangold LA, et al. Risk of prostate cancer-specific mortality following biochemical recurrence after radical prostatectomy. JAMA. 2005;294: 433-439.
20. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. J Clin Oncol. 2016.
21. Denham JW, Steigler A, Wilcox C, et al. Time to biochemical failure and prostate-specific antigen doubling time as surrogates for prostate cancer-specific mortality: evidence from the TROG 96.01 randomised controlled trial. Lancet Oncol. 2008;9: 1058-1068.
22. Johnson S, Jackson W, Li D, et al. The interval to biochemical failure is prognostic for metastasis, prostate cancer-specific mortality, and overall mortality after salvage radiation therapy for prostate cancer. Int J Radiat Oncol Biol Phys. 2013;86: 554-561.
23. Stish BJ, Pisansky TM, Harmsen WS, et al. Improved Metastasis-Free and Survival Outcomes With Early Salvage Radiotherapy in Men With Detectable Prostate-Specific Antigen After Prostatectomy for Prostate Cancer. J Clin Oncol. 2016.
24. Abugharib A, Jackson WC, Tumati V, et al. Very Early Salvage Radiotherapy Improves Distant Metastasis-Free Survival. J Urol. 2017;197: 662-668.

25. King CR, Kapp DS. Radiotherapy after prostatectomy: is the evidence for dose escalation out there? Int J Radiat Oncol Biol Phys. 2008;71: 346-350.
26. King CR, Spiotto MT. Improved outcomes with higher doses for salvage radiotherapy after prostatectomy. Int J Radiat Oncol Biol Phys. 2008;71: 23-27.
27. Pisansky TM, Agrawal S, Hamstra DA, et al. Salvage Radiation Therapy Dose Response for Biochemical Failure of Prostate Cancer After Prostatectomy-A Multi-Institutional Observational Study. Int J Radiat Oncol Biol Phys. 2016;96: 1046-1053.
28. Sweeney CJ, Chen YH, Carducci M, et al. Chemohormonal Therapy in Metastatic Hormone-Sensitive Prostate Cancer. N Engl J Med. 2015;373: 737-746.
29. Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521. 2015 ASCO Annual Meeting. Chicago, IL: J Clin Onco 33 l(suppl; abstr LBA5002), 2015.
30. Messing EM, Manola J, Sarosdy M, Wilding G, Crawford ED, Trump D. Immediate hormonal therapy compared with observation after radical prostatectomy and pelvic lymphadenectomy in men with node-positive prostate cancer. N Engl J Med. 1999;341: 1781-1788.
31. Spratt DE, Zumsteg ZS, Pei X, et al. Predictors of castration-resistant prostate cancer after dose-escalated external beam radiotherapy. Prostate. 2015;75: 175-182.
32. Carrie C, Hasbini A, de Laroche G, et al. Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol. 2016;17: 747-756.
33. Desai NB, Laine AM, Timmerman RD. Stereotactic ablative body radiotherapy (SAbR) for oligometastatic cancer. Br J Radiol. 2017;90: 20160500.

Figure Legends:

Figure 1. Kaplan-Meier plots with numbers at risk for patients suffering biochemical failure after SRT for A) freedom from distant metastasis, B) prostate cancer specific survival, and C) overall survival.

Figure 2. Risk groupings for patients suffering second biochemical failure after SRT for A) freedom from metastasis with stratification based on presence of Gleason 8-10 pathology, interval to second biochemical relapse <1 year, or failure despite concurrent ADT with SRT and B) prostate cancer specific survival with stratification based on presence of interval to second biochemical failure <1 year, and/or BCR despite concurrent ADT with SRT.

Table 1. Patient demographics.

Table 2. Univariate and multivariable analyses of factors predictive of distant metastasis and prostate cancer specific survival.

Table 3. Comparison of natural history series following varying local therapy.

Supplementary Table 1. Methodology of summing hazard ratios for prognostic factors for freedom from distant metastasis into risk groups.

Characteristic	All Patients		Patients with Second BCR	
	No.	%	No.	%
Follow up, Months				
Median	82		98	
Range	1-269		1-269	
Age, Years				
Median	63		63	
Range	29-84		39-84	
PSA, pre-RP				
Median	7.7		8	
Range	0-120		0-120	
PSA, pre-XRT				
Median	0.4		0.6	
Range	0-17.4		0-11.93	
Gleason Score				
≤6	82	14.4%	33	11.5%
3+4	180	31.5%	62	21.7%
4+3	143	25.0%	88	30.8%
8	67	11.7%	40	14.0%
9	83	14.5%	51	17.8%
10	1	0.2%	1	0.3%
Unknown	15	2.6%	11	3.8%
pT-Stage				
T2	253	44.3%	105	36.7%
T3	297	52.0%	169	59.1%
T4	6	1.1%	3	1.0%
Unknown	15	2.6%	9	3.1%
pN stage				
N0	479	83.9%	235	82.2%
N1	28	4.9%	14	4.9%
Nx	64	11.2%	37	12.9%
Margin				
Positive	322	56.4%	136	47.6%
Negative	228	39.9%	137	47.9%
Unknown	21	3.7%	13	4.5%
Concurrent ADT				
Yes	129	22.6%	53	18.5%
No	442	77.4%	233	81.5%
Whole Pelvic RT				

Yes	99	17.3%	40	14.0%
No	472	82.7%	246	86.0%
Decade of Treatment				
1986-1989	10	1.8%	8	2.8%
1990-1999	153	26.8%	97	33.9%
2000-2009	321	56.2%	157	54.9%
2010-2013	85	14.9%	23	8.0%

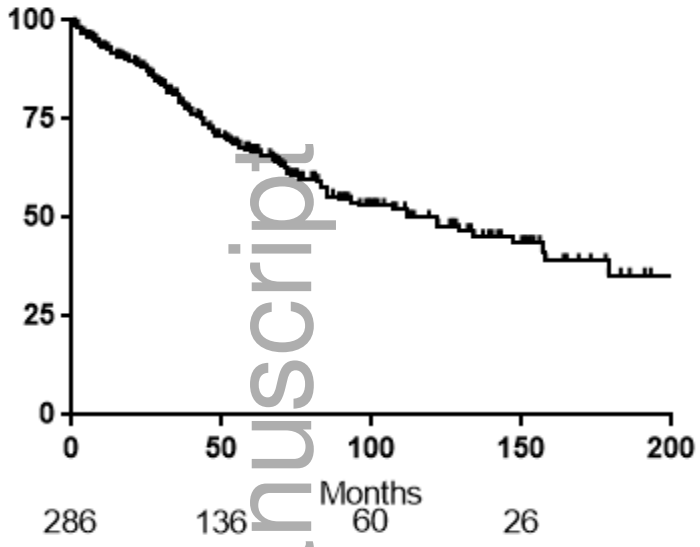
			Distant Metastasis							Prostate Cancer Specific Survival					
Characteristic		6-year FFDM	Univariate			Multivariable			6-year PCSS	Univariate			Multivariable		
			HR	CI	p	HR	CI	p		HR	CI	p	HR	CI	p
Interval to sBCR	>1 year vs ≤ 1 yr	67% vs 48%	2.08	1.44-3.00	*0.00009*	2.66	1.71-4.14	*0.000013*	89% vs 74%	2.81	1.63-4.86	*0.0002*	3	1.69-5.32	*0.0002*
N stage	N0 vs N1	61% vs 48%	1.89	0.826-4.33	0.132	1.96	0.81-4.78	0.137	83% vs 80%	1.66	0.52-5.35	0.397			
Gleason score	≤7 vs 8-10	68% vs 39%	2.02	1.39-2.93	*0.0002*	1.65	1.07-2.54	*0.022*	85% vs 78%	1.51	0.88-2.60	0.136	1.42	0.81-2.51	0.23
pT stage	T1-T2c vs ≥T3a	66% vs 54%	1.64	1.12-2.41	*0.012*	1.34	0.84-2.15	0.22	77% vs 80%	1.42	0.82-2.47	0.214			
Pre-RT PSA	≤ 0.5 vs > 0.5	63% vs 55%	1.63	1.12-2.38	*0.011*	1.37	0.89-2.11	0.151	87% vs 79%	1.95	1.15-3.30	*0.013*	1.62	0.91-2.89	0.104
Concurrent ADT	No vs Yes	63% vs 44%	2	1.31-3.07	*0.001*	1.76	1.08-2.88	*0.024*	84% vs 79%	1.87	1.01-3.46	*0.046*	2.15	1.13-4.08	*0.019*
Margin	negative vs positive	57% vs 61%	0.876	0.60-1.27	0.488				84% vs 80%	0.99	0.58-1.70	0.96			

FFDM - freedom from distant metastasis, PCSS - prostate cancer specific survival, HR - hazard ratio, sBCR - second biochemical recurrence, pT - pathologic T stage

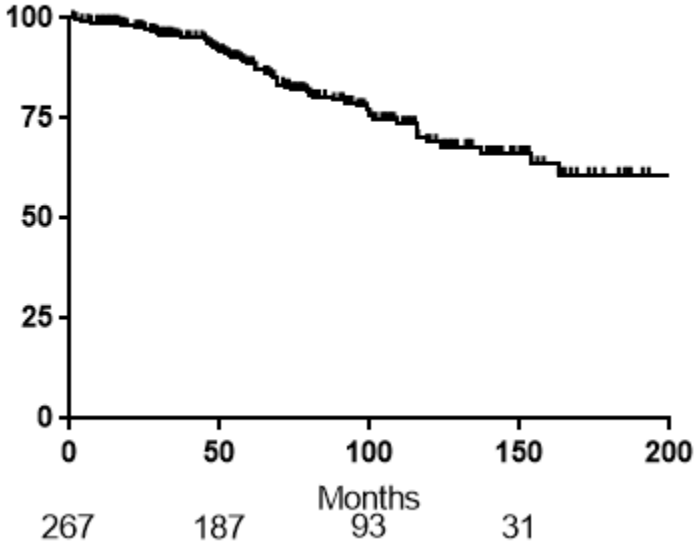
	N	Median follow up after BCR (yr)	Median DMFS (yr)	Median PCSS (yr)	Median OS (yr)
Current Study (PORT sBCR)	297	6	9.3 (6 -yr DM 41%)	Not reached (6 yr PCSS 83%)	13.1 (6-yrOS 73%)
RP/Adjuvant RT fBCR (Boorjan et al)[14]	134	8	Not reached (15-yr DM 45%)	Not reached (15 yr PCCS 65%)	Not reported
RP/Adjuvant RT fBCR (Abdollah et al)[15]	336	5.3	Not reported	Not reached (10 yr PCSS 79%)	Not reported
EBRT fBCR (Zumsteg et al)[11]	609	4.8	5.4 (5-yr DM 47%)	10.5 (5-yr PCSS 82%)	Not reported
RP fBCR (Johns Hopkins)[13,19]	450*	8*	10 (10-yr DM 52%)*	Not reached (10 yr PCSS 73%)*	Not reported

fBCR - first biochemical relapse, sBCR – second biochemical recurrence, PORT - post operative radiotherapy, RP - radical prostatectomy, RT - radiotherapy, EBRT - external beam radiotherapy. * BCR after RP defined as 0.2, median follow up and DMFS reported from Antonarakis et al.[13], PCSS from Freedland et al.[19] ** BCR after RP defined as 0.4

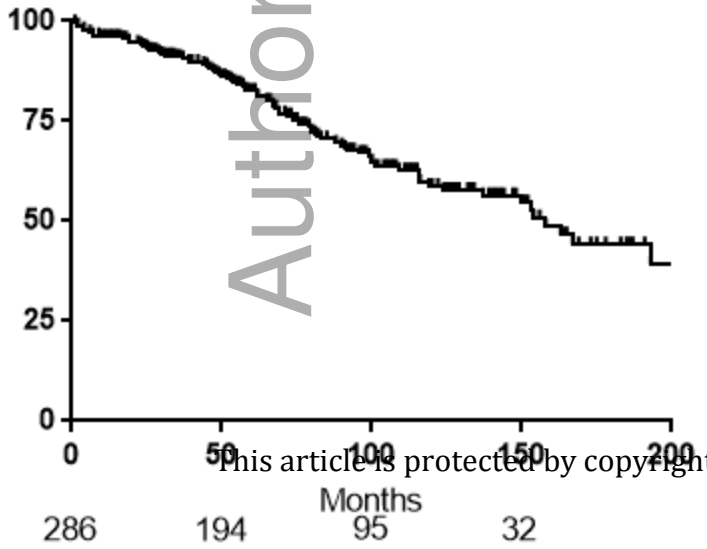
A. Freedom From Distant Metastases



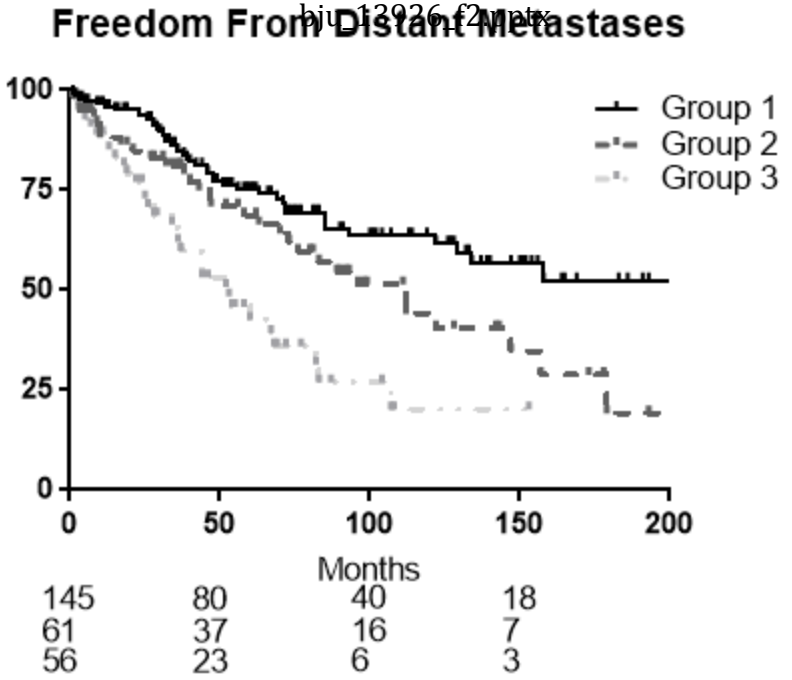
B. Prostate Cancer Specific Survival



C. Overall Survival



A.



B.