Natural history of 'second' biochemical failure after salvage radiation therapy for prostate cancer: a multi-institution study

Vasu Tumati*, William C. Jackson†, Ahmed E. Abugharib†, Ganesh Raj‡, Claus Roehrborn‡, Yair Lotan‡, Kevin Courtney§, Aditya Bagrodia‡, Jeffrey C. Gahan‡, Zachary S. Zumsteg**, Michael R. Folkert*, Aaron M. Laine*, Raquibul Hannan*, Daniel E. Spratt† and Neil B. Desai*

Departments of *Radiation Oncology, ‡Urology, §Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX, USA, Department of †Radiation Oncology, University of Michigan, Ann Arbor, MI, USA, and **Department of Radiation Oncology Cedars-Sinai Medical Center, Los Angeles, CA, USA

V. T. and W.C.J. are equal first authors.
D.E.S. and N.B.D. are equal senior authors.

Objectives

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

Patients and Methods

After undergoing SRT at one of two institutions between 1986 and 2013, 286 patients experienced a second BCR, defined as two rises in prostate-specific antigen (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 of 6.1 years after second BCR, DM, CRPC, PCSS and OS rates 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, 95% CI 1.08–2.88; $P = 0.024$) were associated with FFDM, while PCSS was associated with interval to second BCR <1 year (HR 3.00, 95% 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 rates of 71%, 59% and 33%, and PCSS rates of 89%, 79%, and 65%, respectively.

Conclusion

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

Keywords

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

Introduction

Adjuvant postoperative radiotherapy (RT) is effective in reducing biochemical recurrence (BCR) when radical prostatectomy (RP) reveals adverse pathological features [1–5]; however, a strategy of salvage radiotherapy (SRT) after post-RP BCR is more commonly used [6–8]. At the time of SRT, the poor sensitivity of existing imaging for excluding 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 experience BCR after definitive RT and RP alone has been described [11–15], detailed outcomes of patients who experienced BCR after postoperative RT are largely 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 of clinical progression to metastasis or death when compared with BCR after definitive RT, RP, or even adjuvant postoperative RT. Data specific to this cohort of patients with second BCR after SRT is needed to facilitate patient counselling and inform trial design.

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

Methods

Patient Cohort

After obtaining institutional review board approval, a retrospective review was conducted of 571 patients treated for prostate cancer between 1986 and 2013 who underwent SRT after RP at two large institutions (University of Texas Southwestern Medical Center and the University of Michigan). SRT was defined as receipt of postoperative RT for a rising PSA level or SRT performed at least 4 months after RP in the absence of data on PSA. Of the patients who received SRT, only those who subsequently experienced BCR were included in the present study. BCR after postoperative RT was defined using the AUA definition of a PSA rise of ≥0.2 ng/mL above nadir with a sequential equal or higher value, yielding 286 patients who formed the study cohort.

All the patients were treated with curative intent RP with limited lymph node sampling, without routine use of extended lymph node dissection. Those patients with high risk features were treated at their physician's discretion with RT to pelvic lymph nodes and/or with concurrent androgen deprivation therapy (ADT). RT was generally delivered by three-dimensional conformal radiation planning until 2004 at both institutions, after which intensity-modulated RT 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 examination. Imaging was not routinely obtained unless there was evidence of biochemical failure or clinical progression.

Analyses

After SRT, local recurrence was defined by imaging or DRE, regional failure by pelvic lymph node involvement on imaging, and distant metastasis (DM) by imaging without requirement of pathological confirmation (almost exclusively by CT and technetium bone scan, with the minority receiving MRI or positron-emission tomography). Castration resistance was defined as two or more successive rises in PSA level, despite testosterone level <50 ng/mL, or evidence of clinical progression of disease despite the use of ADT, similar to the

PSA working group definition [16]. Estimates of rates of local recurrence, regional recurrence, freedom from DM (FFDM) or, conversely, 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 clinicopathological 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 level, and margin status. PSA doubling time was not considered sufficiently robust for analysis because of the low values at time of SRT and lack of multiple measures prior to SRT in many patients. RT dose and/or use of intensity-modulated RT planning were not analysed because of small absolute dose changes (IQR 64.8–68.4 Gy), low isolated recurrence rates after SRT with 'lower' doses in a 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 [HRs]. Specifically, a risk score for an endpoint was generated based on summing the HRs of each prognostic variable harboured by a patient for the particular endpoint, and the resulting sums were used to generate groupings (Table S1). Analyses were conducted using IBM SPSS v.23 (SPSS Inc., Chicago, IL, USA). An α value of 0.05 was 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 the present cohort, was treated between 2000 and 2009 (54.9%). The median (IQR) pre-RT PSA level was 0.6 (0.3–1.1) ng/mL, 139 patients (48.6%) had a PSA ≤ 0.5 ng/mL, 92 (32.1%) had Gleason score ≥8, 172 (60.1%) had stage ≥pT3, and the median (IQR) RT dose was 66.6 (64.8–68.4) Gy. Only 18.5% of patients received concurrent ADT with SRT. SRT dose was not associated with time era of treatment ($P = 0.857$) but was associated with institution ($P < 0.001$).

Table 1 Patient demographics.

Characteristic	All patients	Patients with second BCR
Median (range) follow-up, months	82 (1–269)	98 (1–269)
Median (range) age, years	63 (29–84)	63 (39–840
Median (range) PSA, pre-RP	7.7 (0–120)	8 (0–120)
Median (range) PSA, pre-SRT	0.4 (0–17.4)	0.6 (0–11.93)
Gleason score, *n* (%)		
≤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)

ADT, androgen deprivation therapy; BCR, biochemical recurrence; RP, radical prostatectomy; RT, radiotherapy; SRT, salvage radiotherapy.

Outcomes

For patients who experienced second BCR after SRT, the median (IQR) time to second BCR was 16 (6–38) months. For those patients treated with concurrent ADT, the median time to second BCR was 16 months, which was not significantly different from the median 15 months to second BCR for those not receiving ADT (log-rank $P = 0.232$). After second BCR, 6-year local and regional recurrence rates were 4.9% and 7.5%, respectively. The 6-year rates of DM and development of castration-resistant prostate cancer (CRPC) after second BCR were 41.1% and 27.4%, respectively (Fig. 1A). The median FFDM time 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 a median OS time of 158 months (Fig. 1B and C). The majority of patients with second BCR subsequently received ADT ($n = 193$, 68%). Of the 79 patients who developed

CRPC, the proportions of patients with additional therapy exposure were as follows: enzalutamide 24.1%; abiraterone 45.6%; docetaxel 65.8%; cabazitaxel 10.1%; radionuclide therapy 7.6%; and sipuleucel-T 3.8%. Multiple lines of therapy were received by 35% of patients with CRPC.

Of the 116 patients who developed DM, the median (IQR) time to DM was 36 (10.5–66) months from second BCR. The median OS time from initial metastasis was 62 months. Because not all patients developed metastasis, we sought to determine the 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 ng/mL (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. Pathological 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 (HR 2.66, 95% 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, 95% CI 1.08–2.88; $P = 0.024$) remained significantly predictive of FFDM after second BCR (Table 2). We additionally used these features to generate risk groups for development of DM after second BCR. As the HR for interval to second BCR <1 year was substantially higher than that for Gleason 8–10 or concurrent ADT, this risk grouping relied on weighting of risk factors according to their HRs, as shown in Table S1. 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 Fig. 2A, with 6-year FFDM rates from second BCR of 71%, 59% and 33%, respectively. The proportions of patients in groups 1, 2 and 3 in this schema were 54%, 24% and 22%, respectively.

We similarly examined prognostic factors for PCSS after second BCR in this patient cohort, of whom 54 patients died from prostate cancer (Table 2). On univariable analysis, interval to second BCR <1 year (89% vs 74%; $P < 0.001$), pre-SRT PSA ≤ 0.5 ng/mL (HR 1.62, 95% CI 1.15–3.30; $P = 0.013$), and concurrent ADT (HR 1.87, 95% 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, 95% CI 1.69–5.32; $P < 0.001$) and concurrent ADT (HR 2.15, 95% CI 1.13–4.08; $P = 0.019$) remained significantly associated with PCSS. These prognostic features again were used to generate risk groupings. Specifically, in

Fig. 1 Kaplan–Meier plots with numbers at risk for patients with biochemical failure after salvage radiotherapy for (**A**) freedom from distant metastasis, (**B**) prostate cancer-specific survival and (**C**) overall survival.
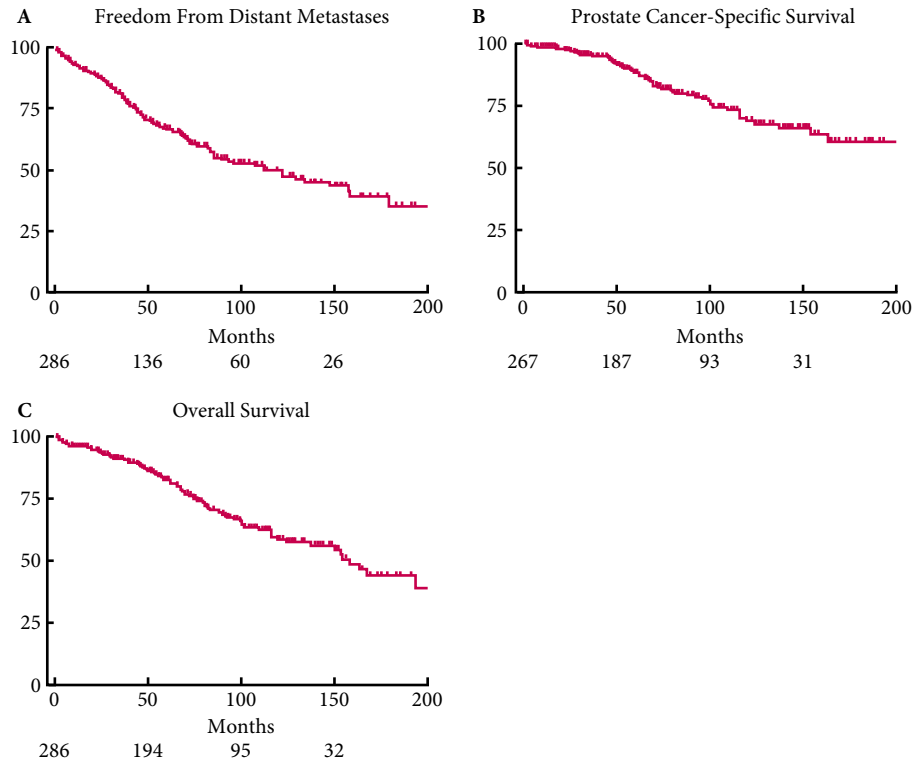
patients with 0, 1 or 2 risk factors, 6-year PCSS rates were 89%, 79% and 65%, respectively (Fig. 2B). The proportion of patients with 0, 1 or 2 risk factors was 48%, 46% and 7%, respectively.

Discussion

Determining the natural history of men with second BCR after SRT is important for counselling patients and in directing subsequent therapy. A significant body of literature details the outcomes of postoperative RT and of untreated BCR after RP or definitive RT [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 >9 years and 13 years, respectively. Allowing for differences in reporting, these intervals compare favourably with 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 are also consistent with previously reported outcomes in patients experiencing a 'first' BCR after adjuvant postoperative RT [14,15].

The retention of a long interval to detection of metastasis after second BCR in the present series is potentially attributable to underestimation of early ADT interventions and the limited sensitivity of traditional imaging. Second, the median pre-RT PSA level of 0.4 ng/mL in our screening cohort of 571 patients undergoing SRT reflects the results of a transition to an 'early' SRT approach, which is associated with improved DM-free survival and PCSS rates [18,20]. Third, the apparently better outcome of patients in second BCR after SRT in our series compared with initial BCR after definitive RT [11] is probably attributable to the different and more sensitive definition of second BCR after SRT (confirmed rise ≥0.2 ng/mL above nadir after SRT compared with nadir + 2 mg/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 the present 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

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

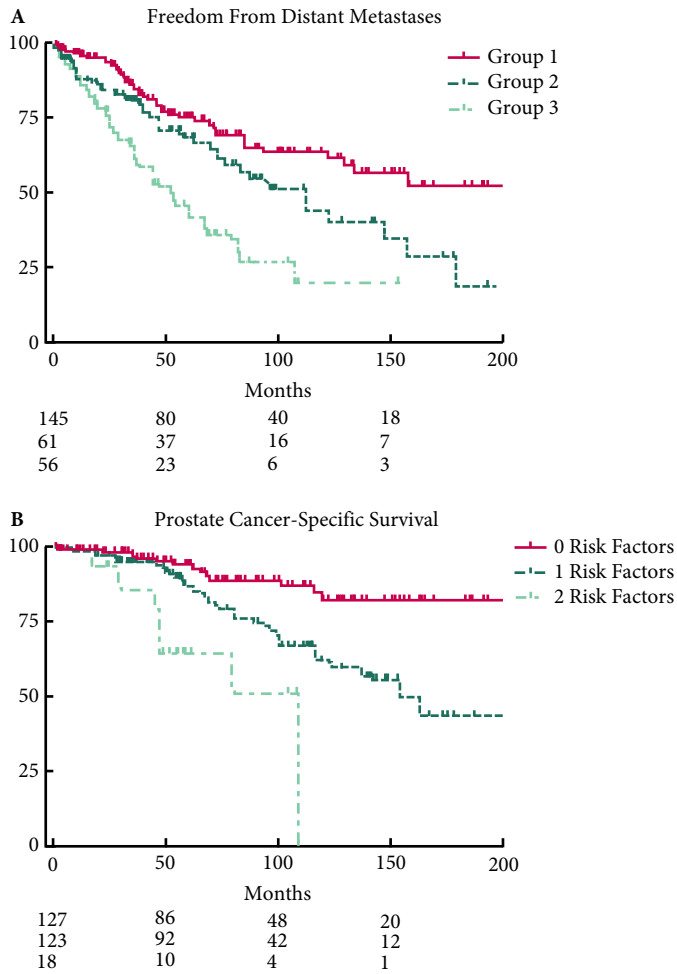| Variable	6-year FFDM	DM Univariate HR	CI	P	DM Multivariable HR	CI	P	6-year PCSS	PCSS Univariate HR	CI	P	PCSS Multivariable HR	CI	P
Interval to second BCR: >1 year vs ≤ 1 year	67% vs 48%	2.08	1.44–3.00	<0.001	2.66	1.71–4.14	<0.001	89% vs 74%	2.81	1.63–4.86	<0.001	3	1.69–5.32	0.0002
N stage: N0 vs N1	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	<0.001	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 ng/mL	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			

ADT, androgen deprivation therapy; BCR, biochemical recurrence; FFDM, freedom from distant metastasis; HR, hazard ratio; PCSS, prostate cancer specific survival. Italicized values represent statistically significant findings.

multivariable analysis for DM risk. Similarly, studies of the natural history of RP, dose-escalated external-beam RT, and postoperative RT have shown that short interval to failure were significant predictors of DM [11,12,15,19], as well as prostate cancer-specific mortality [21,22]. Further, in an analysis of 134 patients with BCR after adjuvant RT by Boorjan et al. [14], Gleason score was predictive of DM. While lower pre-RT PSA level has been associated with improved clinical outcomes after 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 with second BCR, probably as a result of 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 because of the study focus on those with second BCR with long follow-up; a minority of patients were treated after 2010 when higher SRT doses might be expected. Because isolated locoregional relapse rates in both the present study and prospective SRT data [10] were infrequently detected, however, it is also likely that SRT dose has no effect on those who experience second BCR, where prognosis appears dominated by other metastasis.

Identification of those at highest risk for progression to DM may help inform trial design in this area 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 on 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 was similarly spread across patients in a heterogeneous manner and in significant association with a 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 probably a reflection of poor disease biology and/or delay in detecting second BCR because of the prolonged suppressive effect of ADT on PSA level, particularly for GnRH agonists. Notably, those patients who fail aggressive definitive therapy, including ADT, have previously been suggested to be intrinsically at higher risk of DM and CRPC [31]. Given the level 1 data on the benefit of adding ADT or anti-androgen therapy to SRT [10,32], it

Fig. 2 Risk groupings for patients with second biochemical failure after salvage radiotherapy (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 androgen deprivation therapy (ADT) with SRT and (**B**) prostate cancer-specific survival with stratification based on presence of interval to second biochemical failure <1 year, and/or biochemical recurrence despite concurrent ADT with SRT.

A Freedom From Distant Metastases

Group 1
Group 2
Group 3

Months

145	80	40	18
61	37	16	7
56	23	6	3

B Prostate Cancer-Specific Survival

0 Risk Factors
1 Risk Factors
2 Risk Factors

Months

127	86	48	20
123	92	42	12
18	10	4	1

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, in the present study, we 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.

The present study has several limitations. 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 the 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 may fundamentally 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 with 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 we were unable to account. In addition, PSA doubling time, a previously suggested correlate of DM and PCSS in various settings, could not be analysed at time of second BCR after SRT because of 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 patients who experienced second BCR after SRT. We show that, while many of these patients have prolonged survival, a significant proportion is enriched for DM and ensuing morbidity and mortality. High Gleason grade, failure despite concurrent ADT with SRT, or short intervals to BCR appear to predict those patients at highest risk of DM and prostate cancer-related death in

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

	N	Median follow-up after BCR, years	Median DM-free survival, years	Median PCSS, years	Median OS, years
Current Study (postoperative RT second BCR)	297	6	9.3 (6-year DM 41%)	Not reached (6-year PCSS 83%)	13.1 (6-year OS 73%)
RP/adjuvant RT first BCR (Boorjan et al. [14])[†]	134	8	Not reached (15-year DM 45%)	Not reached (15-year PCCS 65%)	Not reported
RP/adjuvant RT first BCR (Abdollah et al. [15])	336	5.3	Not reported	Not reached (10-year PCSS 79%)	Not reported
EBRT first BCR (Zumsteg et al. [11])	609	4.8	5.4 (5-year DM 47%)	10.5 (5-year PCSS 82%)	Not reported
RP first BCR (Johns Hopkins) [13,19]	450*	8*	10 (10-year DM 52%)*	Not reached (10-year PCSS 73%)*	Not reported

BCR, biochemical recurrence; DM, distant metastasis; EBRT, external beam radiotherapy; OS, overall survival; PCSS, prostate cancer-specific survival; RP, radical prostatectomy; RT, radiotherapy. *BCR after RP defined as PSA ≥0.2 ng/mL above nadir, median follow-up and DM-free survival reported from Antonarakis et al. [13], PCSS from Freedland et al. [19]. [†]BCR after RP defined as PSA 0.4 ≥ ng/mL.

particular. The resultant stratification of risk within this heterogeneous population may help with the 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 positron-emission tomography to identify low burden metastatic states, which may be amenable to novel strategies, such as stereotactic ablative RT [33].

Conflict 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.

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Correspondence: Neil B. Desai, Assistant Professor of Radiation Oncology, University of Texas Southwestern Medical Center, 2280 Inwood Road Dallas, TX 75390, USA.

e-mail: Neil.Desai@utsouthwestern.edu.

Abbreviations: BCR, biochemical recurrence; CRPC, castration-resistant prostate cancer; DM, distant metastasis; FFDM, freedom from DM; HR, hazard ratio; IQR, interquartile range; OS, overall survival; PCSS, prostate cancer-specific survival; RP, radical prostatectomy; RT, radiotherapy; SRT, salvage radiotherapy.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1 Methodology of summing hazard ratios for prognostic factors for freedom from distant metastasis into risk groups.