Long-term Outcome of Prostate Cancer Patients Who Exhibit Biochemical Failure Despite Salvage Radiation Therapy After Radical Prostatectomy

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Objectives: Salvage radiation therapy (SRT) is an effective treatment for recurrent prostate cancer (PCa) after radical prostatectomy. We report the long-term outcome of men who developed biochemical recurrence (BCR) after SRT and were treated >14 years ago.

Methods: In total, 61 patients treated with SRT from 1992 to 2000 at our institution were identified. Survival was calculated by Kaplan-Meier method. Log-rank test and Cox regression were used to determine significance of clinical parameters.

Results: The median follow-up was 126 months (interquartile range, 66-167 mo). Thirty-four (56%) had prostate-specific antigen (PSA) failure after SRT. At 10 years, overall survival (OS) was 67%, freedom from PSA failure (FFPF) was 33%, prostate cancer-specific survival (PCSS) was 84%, and distant metastases-free survival (DMFS) was 84%. Pathologic T-stage, Gleason score, seminal vesicle involvement, and pre-SRT PSA were associated with FFPF. For patients who failed SRT, the median time to BCR after SRT was 30 mo. A total of 19 (68%) received androgen deprivation therapy. The median OS was 13.6 years. At 10 years from time of BCR, OS was 59%, PCSS was 73%, DMFS was 75%, and castration-resistant-free survival was 70%. Early SRT failure correlated with significantly decreased DMFS and PCSS. Ten-year DMFS from SRT was 43% (BCR $\leq$ 1 y) versus 91% (BCR > 1 y).

Conclusions: Extended follow-up demonstrates that despite SRT failure, PCSS remains high in select patients. Early failure ($\leq$1 y after SRT) predicted for significantly worse outcome and may represent a subgroup with more aggressive disease that may be considered for further prospective clinical studies.

Key Words: salvage radiation therapy, biochemical failure, long-term follow-up, prostate cancer, radical prostatectomy

(*Am J Clin Oncol* 2017;40:612–620)

Prostate cancer (PCa) is the most common cancer and the second leading cause of cancer death in men, with estimated annual incidence and mortality of 233,000 and 29,480 in the United States, respectively.[1] Up to 91% of PCa cases are locally confined at diagnosis,[2] and radical prostatectomy remains a first-line therapeutic option. Unfortunately, approximately one-third of the patients recur after prostatectomy.[3] In patients who develop prostate-specific antigen (PSA) failure after prostatectomy, timely administration of salvage radiation therapy (SRT) before the development of distant metastases can be an effective treatment for local control and can result in decreased rate of distant metastases and improved cancer-free survival.[4–18] We previously reported our institution's SRT experience.[19] However, there is little data on long-term outcomes in men after SRT. In this study, we evaluated the long-term outcomes of patients treated with SRT with a median follow-up of 126 months after SRT.

METHODS

Patients

Between 1992 and 2000, 61 patients with biochemically recurrent PCa after prostatectomy who underwent SRT were identified at the University of Texas Southwestern Medical Center (Dallas, TX). Biochemical recurrence (BCR) of the disease after surgery was defined as persistently detectable PSA $\geq$ 0.05 ng/mL or 2 consecutive PSA rises $\geq$ 0.1 ng/mL that triggered initiation of SRT. Failure of SRT was defined as a single rise of PSA $\geq$ 2 ng/mL from nadir, 2 consecutive PSA rises $\geq$ 0.2 ng/mL, initiation of salvage treatment, or clinical disease recurrence. Patients who underwent adjuvant radiation therapy (ART) without a rise in PSA postprostatectomy were excluded. Patients were followed up to 238 months after SRT. Follow-up was defined as last office visit or last date of PSA measurement from time of initiation of SRT. PSA response after SRT was defined as a drop in PSA level after SRT. Clinical characteristics were retrospectively extracted from medical records and summarized in Table 1.

Procedures

SRT was delivered to the prostate bed at a median total dose of 6480 cGy (interquartile range [IQR], 6300 to 6840 cGy). Pelvic lymph nodes were not routinely treated. The radiation dose was delivered using megavoltage photon and conventional fractionation (180 to 200 cGy/fraction) with 4-field techniques. One patient received 5040 cGy and 12 patients received $\geq$ 7020 cGy. Concurrent androgen deprivation therapy (ADT) was allowed at the discretion of physicians but was not routinely given.

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The authors declare no conflicts of interest.

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ISSN: 0277-3732/17/4006-0612

DOI: 10.1097/COC.0000000000000207

TABLE 1. Patient Characteristics

Characteristics	All Patients (n = 61)	Patients Who Developed SRT Failure (n = 34)
Median follow-up post-SRT (mo)	126 (3-238)	158 (13-238)
Median follow-up post-SRT failure (mo)		112 (0-209)
Median age at SRT (y)	62 (46-83)	64 (50-83)
Ethnicity (n [%])		
White	56 (92)	30 (88)
African American	4 (7)	4 (12)
Asian	1 (2)	0 (0)
Pathologic stage (n [%])		
T2	22 (37)	16 (47)
T3	38 (63)	18 (53)
N0	58 (95)	32 (94)
N1	3 (5)	2 (6)
Pathologic Gleason score (n [%])		
4-6	16 (26)	7 (21)
7	36 (59)	21 (62)
8-10	9 (15)	6 (18)
Positive margins (n [%])		
Positive	35 (59)	17 (52)
Negative	24 (41)	16 (48)
Unknown	2	1
Seminal vesicle invasion (n [%])	15 (25)	12 (35)
Extracapsular extension (n [%])	29 (48)	16 (47)
Pre-RP PSA (n [%]) (ng/mL)		
< 10	33 (57)	19 (61)
10-20	17 (29)	6 (19)
> 20	8 (14)	6 (19)
Unknown	3	3
Median pre-RP PSA (ng/mL)	8.85 (1.6-70)	8.2 (1.9-41)
Persistently detectable post-RP PSA (n = 58) (n [%])	26 (45)	15 (44)
Median time to BCR post-RP (mo)	3 (0-48)	3 (0-44)
Median time to SRT post-RP (mo)	24 (2-95)	24 (3-9)
Pre-SRT PSA (n [%]) (ng/mL)		
< 0.5	30 (51)	14 (41)
0.5-1.0	18 (31)	11 (32)
1.0-2.0	5 (9)	4 (12)
> 2.0	6 (10)	5 (15)
Unknown	2	0
Median pre-SRT PSA (ng/mL)	0.45 (0.06-11.93)	0.6 (0.1-11.93)
Median total SRT dose	6480 (5040-7290)	6480 (5040-7290)
SRT concurrent hormone therapy (n [%])		
Yes	11 (22)	5 (19)
No	38 (78)	22 (81)
Unknown	12	7
PSA drop post-SRT (n [%])	53 (87)	27 (79)
Median max post-SRT PSA (ng/mL)	1.56 (0-5377)	6.05 (0.38-5377)
Median time to BCR post-SRT (mo)	NA	30 (3-138)
Hormone therapy post-SRT failure (n [%])		
Yes	19 (35)	19 (68)
No	36 (65)	9 (32)
Unknown	6	6

BCR indicates biochemical recurrence; PSA, prostate-specific antigen; RP, radical prostatectomy; SRT, salvage radiation therapy.

Study Outcome and Statistical Analysis

Overall survival (OS), prostate cancer-specific survival (PCSS), freedom from PSA failure (FFPF), castration-resistant-free survival (CRFS), and distant metastasis-free survival (DMFS) were constructed using Kaplan-Meier method from time of initiation of SRT or time of treatment failure when evaluating patients after SRT failure. PCa-specific mortality was defined as death due to PCa, SRT toxicity, or unknown cause with distant metastasis or castration resistance. Castration resistance was defined as 2 consecutive rises in PSA while on hormone therapy with testosterone level ≤ 50 ng/dL. Radiation Therapy Oncology Group (RTOG) criteria were used to grade acute (within 90 d of onset of SRT) and late (>90 d from onset of SRT) SRT-related toxicity. Univariate log-rank test and Cox regression were used to determine the significance of clinicopathologic parameters with survival endpoints. Categorical outcomes were compared using the χ^2 test. All P-values corresponded to 2-sided tests, and a P-value < 0.05 indicates statistically significant effects. Multivariable analysis was performed on variables with $P < 0.15$ on univariate analysis.

RESULTS

The median follow-up after SRT was 126 months (IQR, 66 to 167 mo) for the 61 patients (Table 1). The median age at SRT after prostatectomy was 62 years (range, 46 to 83 y). The median presurgery PSA was 8.85 ng/mL (range, 1.6 to 70 ng/mL), and only 14% had presurgical PSA > 20 ng/mL. A total of 45% had a persistent detectable PSA level postoperatively, with a median PSA of 0.23 (IQR, 0.1 to 0.4). Approximately 70% of the patients had either locally advanced disease with either seminal vesicle involvement (SVI) or extraprostatic extension (eg, pathologic stage T3 or above) (63%) or with positive surgical margin (59%) at the time of surgery.

The median time from prostatectomy to initiation of SRT was 24 months (range, 2 to 95 mo). The median PSA level to initiate SRT was 0.45 ng/mL (range, 0.06 to 11.93 ng/mL). A total of 41% received SRT with PSA level < 0.4 ng/mL. A total of 22% received concurrent ADT in conjunction with SRT. A total of 87% had a PSA drop after SRT. With a median follow-up of 126 months after SRT, 26 patients (42.6%) died, including 10 (16.4%) from PCa. The median OS and FFPF after SRT were 14.7 and 5.5 years, respectively. The OS were 91% and 67%, FFPF were 51% and 33%, PCSS were 98% and 84%, and DMFS were 94% and 84% at 5 and 10 years, respectively (Fig. 1). In total, 49% of the patients had grade 1+, 15.25% had grade 2+, and 0% had grade 3+ acute gastrointestinal (GI) toxicity, whereas 75% of the patients had grade 1+, 3.4% had grade 2+, 16.9% had grade 3+, and 0% had grade 4+ acute genitourinary (GU) toxicity. In total, 49% and 75% of patients experienced acute GI and GU toxicities, respectively. Of 27 patients who survived 10 years, 37% had grade 1+, and 3.7% had grade 2/3+, and 0% had grade 4+ delayed GU toxicity, whereas 14.8% had grade 1+ and 0% had grade 2+ delayed GI toxicity.

Of all 61 patients, 34 (56%) experienced PSA failure after SRT. For these 34 patients with BCR, the median follow-up after SRT was 157.5 months (IQR, 88.8 to 188.5) and the median follow-up from time of PSA failure was 112 months (IQR, 54 to 131). Five (19%) received concurrent ADT with SRT. The median time to BCR after SRT was 30 months (range, 3 to 138 mo). Nineteen (68%) received salvage ADT. This therapy was initiated at the discretion of the physicians. The median time from BCR to initiating salvage ADT was 48 months (range, 0 to 151 mo). The median OS from time of PSA failure was 13.6 years in those who failed SRT.

Measuring from time of SRT initiation, OS of patients who developed BCR were 91% and 65%, PCSS were 97% and 80%,

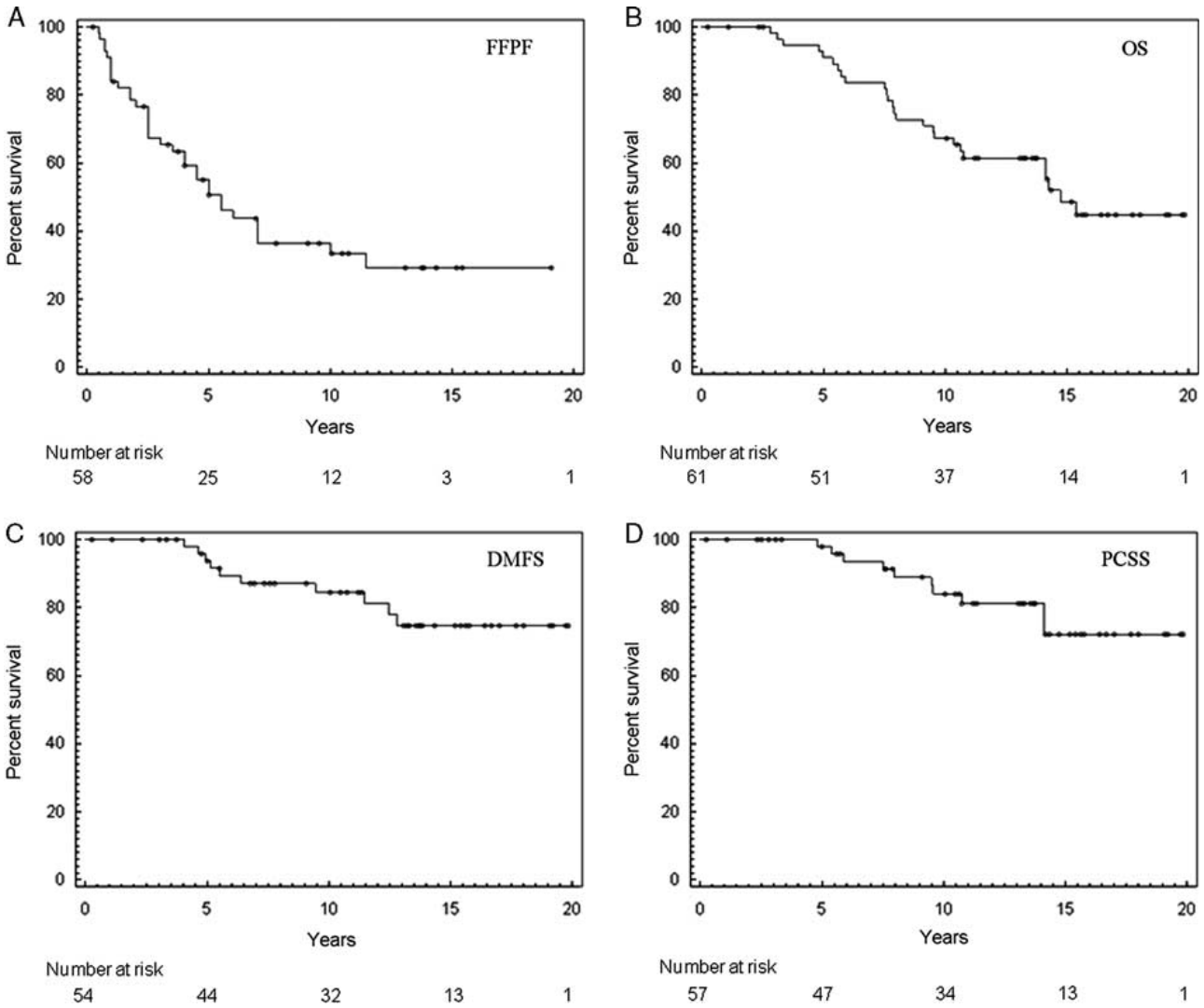

FIGURE 1. Kaplan-Meier survival curves after the start of salvage radiation therapy, n = 61. Freedom from prostate-specific antigen (PSA) failure (A); overall survival (B); distant metastasis-free survival (C); prostate cancer-specific survival (D). DMFS indicates distant metastases-free survival; FFPF, freedom from PSA failure; OS, overall survival; PCSS, prostate cancer-specific survival.

DMFS were 87% and 76%, and CRFS were 85% and 81% at 5 and 10 years, respectively (Fig. 2). Measuring from time of PSA failure, outcome were as follows: OS were 79% and 59%, PCSS were 89% and 73%, DMFS were 75% and 75%, and CRFS were 81% and 70% at 5 and 10 years, respectively.

Univariate analysis showed pathologic T-stage, Gleason score, SVI, and preradiation PSA level were correlated to FFPF after SRT (Table 2A). Only pathologic Gleason score was correlated with all outcome measures studied (OS, DMFS, PCSS, and CRFS) on univariate analysis (Tables 2A–E). On multivariable analysis, pathologic Gleason score, pre-SRT PSA levels, margin status, and hormone therapy remained significantly correlated to FFPF outcomes (Table 2A). Pre-SRT PSA level showed a possible associative benefit in CRFS on univariate analysis, but it was not significant on multivariable analysis (Table 2E).

Of the 34 patients with BCR after SRT, 9 patients had a time to BCR after SRT $\leq$ 1 year. Univariate analysis was performed as a hypothesis generating study to determine factors that may correlate with early BCR ($\leq$ 1 y) and which could be considered for future studies of salvage radiation therapy patients with a larger sample size. Factors evaluated included age, ethnicity, pathologic nodal status, pathologic Gleason score, presence of extracapsular extension, seminal vesicle invasion, lymphovascular invasion, perineural invasion, PSA doubling time, margin status, and hormone therapy use. Gleason score of 8 or higher ($P = 0.0005$) and the presence of extracapsular extension ($P = 0.03$) were significantly correlated with early BCR in this analysis. The median OS (from initiation of SRT) of patients with time to BCR after SRT $\leq$ 1 year was 90 months. When considering only those who failed SRT, time to BCR after SRT $\leq$ 1 year correlated significantly with decreased OS (10 y 33% vs. 80%, $P = 0.0010$, hazard ratio [HR] 5.7, 2.0 to 15.9), DMFS (10 y 43% vs. 91%, $P = 0.0027$, HR 7.7, 2.0 to 28.9), PCSS (10 y 50% vs. 90.5%, $P = 0.0010$, HR 10.6, 2.6 to 43.4), and CRFS (10 y 38% vs. 95%, $P = 0.0037$, HR 8.9, 2.0 to 39.0) on univariate analysis (Tables 2B–E) when measured from initiation of SRT (Fig. 3). On multivariate analysis, PCSS and DMFS remained significant ($P = 0.007$), whereas CRFS ($P = 0.08$) and OS ($P = 0.058$) trended toward significance.

DISCUSSION

This study has a median follow-up of 126 months after SRT and 112 months after SRT failure, which is among the longer

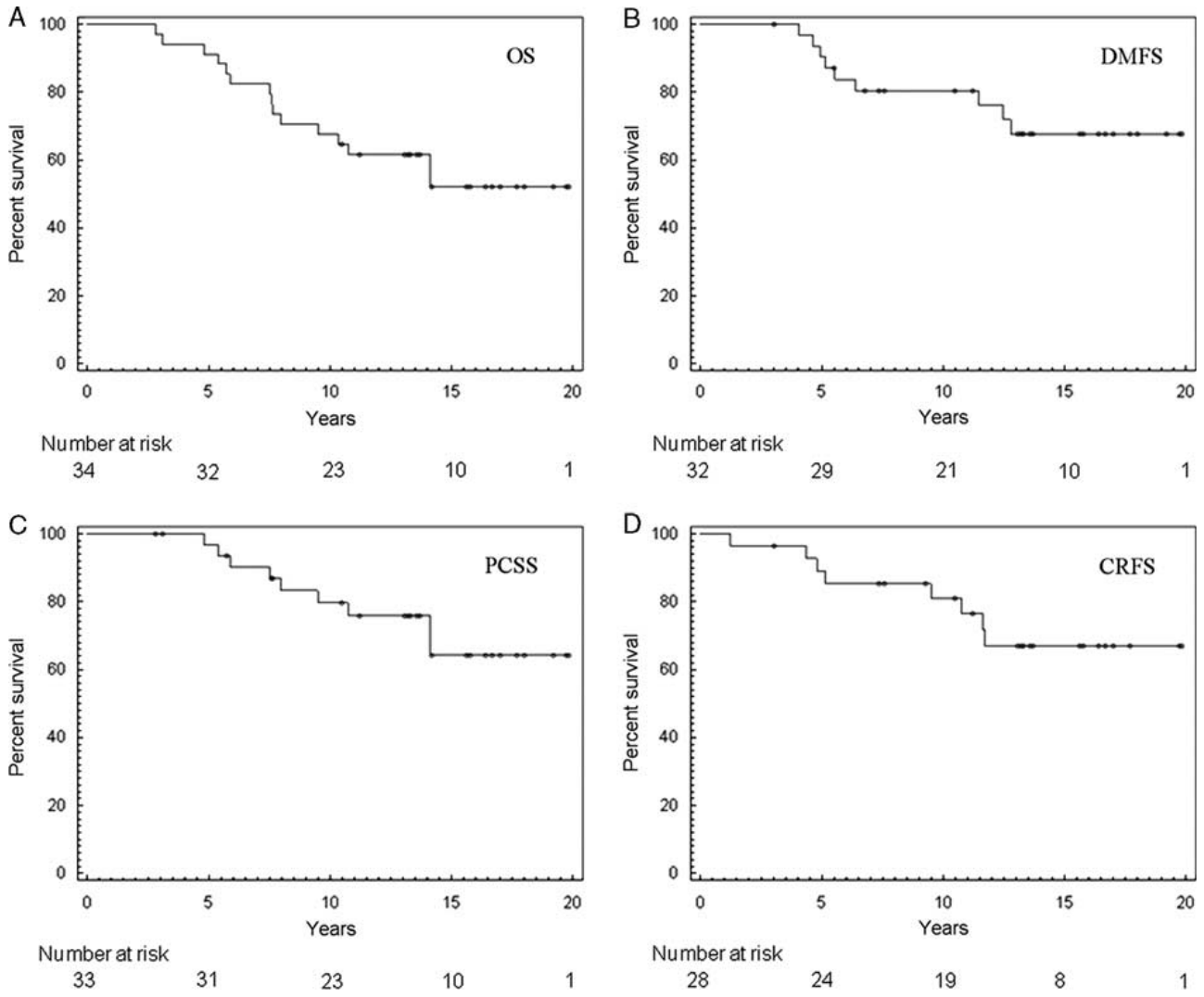

FIGURE 2. Kaplan-Meier survival curves after the start of salvage radiation therapy of patients who developed biochemical recurrence (BCR), n = 34. Overall survival (A); distant metastasis-free survival (B); prostate cancer-specific survival (C); castration-resistant-free survival (D). CRFS indicates castration-resistant-free survival; DMFS, distant metastases-free survival; OS, overall survival; PCSS, prostate cancer-specific survival.

follow-up studies in literature for SRT after prostatectomy (Table 3).[4–18] Most studies reported to date have a median follow-up of <90 months after SRT. Studies with long follow-up are particular insightful for disease, such as PCa, with slow progression rate with other competing causes of mortality. For example, randomized studies such as SWOG 8794 required 12 years before survival benefit of ART was apparent.[20]

Because of our long-term follow-up, we were able to make observations in those patients who recurred despite SRT. Specifically, the survival after SRT was long, with a median survival of 13.6 years despite biochemical failure. The 10-year PCa-specific, metastasis-free, and castration-resistant-free survival (from the time of their PSA failure after SRT) were in excess of 70%. A study on natural history after PSA failure demonstrated that the median time to distant metastasis was 8 years after PSA failure after radical prostatectomy, and roughly 1 in 3 patients developed distant metastases within 5 years without radiation therapy.[21] In our series, DMFS at 5 years was 94% for all patients, and was 75% for those who failed after SRT. About 30% of our patients went on to develop castration resistant disease at 10 years after SRT failure, suggesting that 70% of the cancer was still androgen sensitive at 10 years after SRT failure. Most of our patients received early SRT intervention with 41% having PSA < 0.4 ng/mL at the time of SRT, and this may have contributed to the prolonged survival, as will be discussed further in the discussion.

There were few prior studies with >10-year follow-up after SRT.[10,11] Swanson et al[11] reported on 92 patients with a median follow-up of 13.9 years. That cohort had pathologic Gleason score 8-10 (14%), positive margin (52%), and SVI (24%) comparable with our study. The median time from prostatectomy to initiation of SRT and the PSA response after SRT were comparable with our series (24 vs. 25 mo, and 85% vs. 87% PSA response after radiation). Another series with a follow-up of 11.3 years (from time of PSA failure after surgery) reported 37.6% all-cause mortality in all patients who failed surgery, and SRT statistically improved all-cause mortality regardless of PSA doubling time.[10] Although our study cannot directly compare survival outcome in patients who did not receive SRT, our 10 years survival of 67% compares favorably with that reported by Swanson and colleagues.[10,11]

In this series, only about two-third of our patients who had PSA failure after SRT went on to receive salvage ADT at a median time of 48 months. Although most of those who did not

TABLE 2. Univariate and Multivariable Analysis

		Univariate Analysis			Multivariable Analysis		
	10 y FFPF	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
(A) Freedom from PSA failure (FFPF)							
Patient characteristics							
Age at SRT (<60 vs. ≥60 y)	0.46 vs. 0.32	0.696	0.332-1.459	0.3368			
Ethnicity (black vs. white)	0.00 vs. 0.40	2.265	0.785-6.535	0.1304	6.552	1.402-30.631	0.0169
Tumor characteristics							
Pre-RP PSA (<10 vs. ≥10 ng/mL)	0.34 vs. 0.46	1.451	0.702-2.998	0.3148			
T-stage status (≥pT3b vs. ≤pT3a)	0.19 vs. 0.41	2.406	1.164-4.971	0.0178	4.761	0.429-52.878	0.204
N stage status (pN+ vs. pN0)	0.33 vs. 0.37	1.019	0.243-4.269	0.9797			
Pathologic Gleason score (8-10 vs. ≤7)	0.19 vs. 0.40	4.099	1.603-10.483	0.0032	11.975	2.620-54.726	0.0014
Seminal vesicle involvement (positive vs. negative)	0.16 vs. 0.44	2.067	1.018-4.193	0.0444	0.125	0.010-1.578	0.1081
Extracapsular extension (positive vs. negative)	0.34 vs. 0.39	1.095	0.557-2.150	0.7824			
Surgical margin status (negative vs. positive)	0.23 vs. 0.45	1.796	0.902-3.577	0.0957	2.652	1.226-5.735	0.0132
Clinical characteristics before SRT							
Pre-SRT max PSA (≥0.5 vs. <0.5 ng/mL)	0.21 vs. 0.49	2.267	1.137-4.522	0.0202	1.178	0.533-2.603	0.6855
Velocity (≥0.5 vs. <0.5 ng/mL/y)	0.19 vs. 0.32	1.677	0.768-3.660	0.1946			
PSADT (<6 vs. ≥6 mo)	0.21 vs. 0.28	1.527	0.704-3.309	0.2838			
Time to BCR after RP (≥3 vs. <3 mo)	0.25 vs. 0.42	0.857	0.436-1.686	0.6553			
Time to BCR after RP (≥1 vs. <1 y)	0.16 vs. 0.43	0.699	0.348-1.406	0.3151			
Treatment and response to SRT							
ADT during SRT (no vs. yes)	0.36 vs. 0.53	1.283	0.484-3.404	0.62			
	10 y OS (mean)	**Univariate analysis**			**Multivariable analysis**		
(B) Overall survival (OS)							
Patient characteristics							
Age at SRT (<60 vs. ≥60 y)	0.71 vs. 0.65	0.796	0.354-1.787	0.5796			
Ethnicity (black vs. white)	1.00 vs. 0.65	0.33	0.04-2.453	0.2786			
Tumor characteristics							
Pre-RP PSA (<10 vs. ≥10 ng/mL)	0.66 vs. 0.74	1.22	0.542-2.750	0.6305			
T-stage (≥pT3b vs. ≤pT3a)	0.50 vs. 0.73	1.815	0.806-4.089	0.1504			
N stage (pN+ vs. pN0)	0.67 vs. 0.67	0.602	0.081-4.492	0.6206			
Gleason score (8-10 vs. ≤7)	0.38 vs. 0.72	3.885	1.623-9.30	0.0023	1.689	0.504-5.656	0.3953
Seminal vesicle involvement (positive vs. negative)	0.47 vs. 0.75	2.084	0.941-4.613	0.0703	1.551	0.629-3.825	0.3402
Extracapsular extension (positive vs. negative)	0.67 vs. 0.68	1.283	0.586-2.809	0.5333			
Surgical margin (negative vs. positive)	0.75 vs. 0.67	1.089	0.469-2.529	0.8429			
Clinical characteristics before SRT							
Pre-SRT max PSA (≥0.5 vs. <0.5 ng/mL)	0.69 vs. 0.70	1.649	0.732-3.717	0.2273			
PSA velocity (≥0.5 vs. <0.5 ng/mL/y)	0.61 vs. 0.72	1.855	0.704-4.886	0.211			
PSADT (<6 vs. ≥6 mo)	0.73 vs. 0.62	0.576	0.202-1.641	0.3017			
Time to BCR after RP (≥3 vs. <3 mo)	0.72 vs. 0.67	1.512	0.671-3.407	0.3182			
Time to BCR after RP (≥1 vs. <1 y)	0.72 vs. 0.68	1.375	0.570-3.318	0.4788			
Treatment and response to SRT							
ADT during SRT (no vs. yes)	0.68 vs. 0.75	1.186	0.35-4.1	0.79			
Any ADT after RP (no vs. yes)	0.61 vs. 0.74	1.165	0.468-2.901	0.7423			
Time to BCR after SRT (<1 vs. ≥1 y)	0.33 vs. 0.80	5.655	2.015-15.870	0.0010	2.818	0.965-8.231	0.0582
	10 y PCSS (mean)	**Univariate analysis**			**Multivariable analysis**		
(C) Prostate cancer-specific survival (PCSS)							
Patient characteristics							
Age at SRT (<60 vs. ≥60 y)	0.89 vs. 0.81	0.987	0.278-3.500	0.984			
Ethnicity (black vs. white)	1.00 vs. 0.83	NA	NA	NA			
Tumor characteristics							
Pre-RP PSA (<10 vs. ≥10 ng/mL)	0.80 vs. 0.94	6.465	0.808-51.717	0.0785	1.796	0.157-20.486	0.6375
T-stage (≥pT3b vs. ≤pT3a)	0.83 vs. 0.84	1.373	0.354-5.334	0.6467			
N stage (pN+ vs. pN0)	1.00 vs. 0.83	NA	NA	NA			
Gleason score (8-10 vs. ≤7)	0.63 vs. 0.87	6.517	1.826-23.256	0.0039	0.357	0.030-4.263	0.4154
Seminal vesicle involvement (positive vs. negative)	0.84 vs. 0.85	1.336	0.343-5.195	0.6761			
Extracapsular extension (positive vs. negative)	0.91 vs. 0.79	0.727	0.205-2.585	0.6227			
Surgical margin (negative vs. positive)	0.83 vs. 0.85	2.553	0.711-9.161	0.1505			
Clinical characteristics before SRT							
Pre-SRT max PSA (≥0.5 vs. <0.5 ng/mL)	0.80 vs. 0.87	3.152	0.815-12.198	0.0963	1.301	0.188-8.991	0.7893
PSA velocity (≥0.5 vs. <0.5 ng/mL/y)	0.73 vs. 0.81	2.506	0.626-10.032	0.1943			
PSADT (<6 vs. ≥6 mo)	0.79 vs. 0.75	0.954	0.255-3.560	0.9436			
Time to BCR after RP (≥3 vs. <3 mo)	0.77 vs. 0.92	0.673	0.190-2.390	0.5405			
Time to BCR after RP (≥1 vs. <1 y)	0.80 vs. 0.86	1.112	0.285-4.331	0.8787			

Treatment and response to SRT							
ADT during SRT (no vs. yes)	0.87 vs. 1.00	NA		NS			
Any ADT after RP (no vs. yes)	0.91 vs. 0.80	0.237	0.030-1.896	0.1748			
Time to BCR after SRT (<1 vs. ≥1 y)	0.50 vs. 0.905	10.580	2.581-43.368	0.0010	43.337	2.717-691.215	0.0076
	10 y DMFS (mean)	Univariate analysis			Multivariable analysis		
(D) Distant metastases-free survival (DMFS)							
Patient characteristics							
Age at SRT (<60 vs. ≥60 y)	0.83 vs. 0.85	1.096	0.309-3.884	0.8876			
Ethnicity (black vs. white)	1.00 vs. 0.83	NA	NA	NA			
Tumor characteristics							
Pre-RP PSA (<10 vs. ≥10 ng/mL)	0.79 vs. 0.93	3.058	0.634-14.741	0.1637			
T-stage (≥pT3b vs. ≤pT3a)	0.81 vs. 0.85	0.895	0.190-4.219	0.8881			
N stage (pN+ vs. pN0)	1.00 vs. 0.84	NA	NA	NA			
Gleason score (8-10 vs. ≤7)	0.53 vs. 0.88	5.554	1.424-21.655	0.0135	0.496	0.058-4.267	0.5233
Seminal vesicle involvement (positive vs. negative)	0.83 vs. 0.85	0.843	0.179-3.977	0.8296			
Extracapsular extension (positive vs. negative)	0.87 vs. 0.83	0.772	0.218-2.737	0.6883			
Surgical margin (negative vs. positive)	0.79 vs. 0.88	2.306	0.650-8.172	0.1957			
Clinical characteristics before SRT							
Pre-SRT max PSA (≥0.5 vs. <0.5 ng/mL)	0.81 vs. 0.88	3.287	0.849-12.727	0.085	2.241	0.410-12.248	0.3519
PSA velocity (≥0.5 vs. <0.5 ng/mL/y)	0.73 vs. 0.81	2.697	0.67 -10.817	0.1615			
PSADT (<6 vs. ≥6 mo)	0.85 vs. 0.71	0.952	0.255-3.552	0.941			
Time to BCR after RP (≥3 vs. <3 mo)	0.78 vs. 0.91	0.719	0.203-2.550	0.61			
Time to BCR after RP (≥1 vs. <1 y)	0.82 vs. 0.86	1.251	0.323-4.843	0.7461			
Treatment and response to SRT							
ADT during SRT (no vs. yes)	0.87 vs. 1.00	NA		NS			
Any ADT after RP (no vs. yes)	0.91 vs. 0.80	0.221	0.028-1.770	0.1549			
Time to BCR after SRT (<1 vs. ≥1 y)	0.43 vs. 0.91	7.652	2.024-28.933	0.0027	12.764	1.982-82.191	0.0074
	10 y CRFS (mean)	Univariate analysis			Multivariable analysis		
(E) Castration-resistant-free survival (CRFS)							
Patient characteristics							
Age at SRT (<60 vs. ≥60 y)	0.79 vs. 0.92	1.662	0.415-6.648	0.473			
Ethnicity (black vs. white)	1.00 vs. 0.86	NA	NA	NA			
Tumor characteristics							
Pre-RP PSA (<10 vs. ≥10 ng/mL)	0.76 vs. 1.0	5.932	0.729-48.256	0.096	4.066	0.330-50.065	0.2735
T-stage (≥pT3b vs. ≤pT3a)	0.64 vs. 0.93	2.127	0.506-8.946	0.3032			
N stage (pN+ vs. pN0)	1.00 vs. 0.86	NA	NA	NA			
Gleason score (8-10 vs. ≤7)	0.43 vs. 0.94	8.428	2.065-34.394	0.003	0.526	0.048-5.705	0.5973
Seminal vesicle involvement (positive vs. negative)	0.65 vs. 0.93	2.022	0.479-8.534	0.338			
Extracapsular extension (positive vs. negative)	0.78 vs. 0.92	1.517	0.378-6.082	0.5562			
Surgical margin (negative vs. positive)	0.87 vs. 0.86	1.181	0.295-4.731	0.8145			
Clinical characteristics before SRT							
Pre-SRT max PSA (≥0.5 vs. <0.5 ng/mL)	0.76 vs. 0.95	10.279	1.258-84.013	0.0297	7.639	0.708-82.463	0.0939
PSA velocity (≥0.5 vs. <0.5 ng/mL/y)	0.60 vs. 1.00	NA	NA	NA			
PSADT (<6 vs. ≥6 mo)	0.77 vs. 0.80	2.364	0.457-12.228	0.3048			
Time to BCR after RP (≥3 vs. <3 mo)	0.90 vs. 0.82	1.873	0.447-7.843	0.3904			
Time to BCR after RP (≥1 vs. <1 y)	0.92 vs. 0.83	4.09	0.503-33.271	0.1879			
Treatment and response to SRT							
ADT during SRT (no vs. yes)	0.89 vs. 1.00	NA		NS			
Any ADT after RP (no vs. yes)	1.00 vs. 0.79	NA	NA	NA			
Time to BCR after SRT (<1 vs. ≥1 y)	0.38 vs. 0.95	8.901	2.032-38.983	0.0037	11.248	0.729-173.465	0.0829

ADT indicates androgen deprivation therapy; BCR, biochemical recurrence; CI, confidence interval; HR, hazard ratio; NA, not available (due to insufficient sample size or events, correlative analysis was not feasible); NS, not significant; PSA, prostate-specific antigen; PSADT, PSA doubling time; RP, radical prostatectomy; SRT, salvage radiation therapy.

receive ADT had slower doubling time before SRT, a specific trigger or threshold PSA policy was not implemented, and initiation of ADT was left to the discretion of the treating physician. Despite relatively delayed use of ADT, PCSS and DMFS remained high at 73% to 75% in those who failed SRT, comparable with other reports in literature.[11,12] Interestingly, Swanson and colleagues reported a similar 10-year cancer-specific survival (82%) in their long-term salvage cohort, but the majority of their patients (>80% to 90%) received salvage ADT and the median time to salvage ADT initiation was 14 months. As it was in our series, the initiation of ADT in their series was left to the discretion of the treating physician.[11]

This study, as well as other retrospective studies, demonstrated that the benefit of SRT is most apparent when the preradiotherapy PSA level is <0.5 ng/mL.[4,7,8,11,18,22–24] Trock et al[7] demonstrated treating local recurrence early with SRT (eg, within 2 y of biochemical failure) translated to improved PCSS even in biologically aggressive disease. The importance of the timing of postoperative radiation was further demonstrated by Trabulsi et al[22] with a match-control analysis that reported inferior long-term biochemical progression with SRT compared with early ART. Our data show a 2.3-fold increase in FFPF when SRT was given before the PSA level rose to 0.5 ng/mL. Most of our patients underwent SRT before PSA

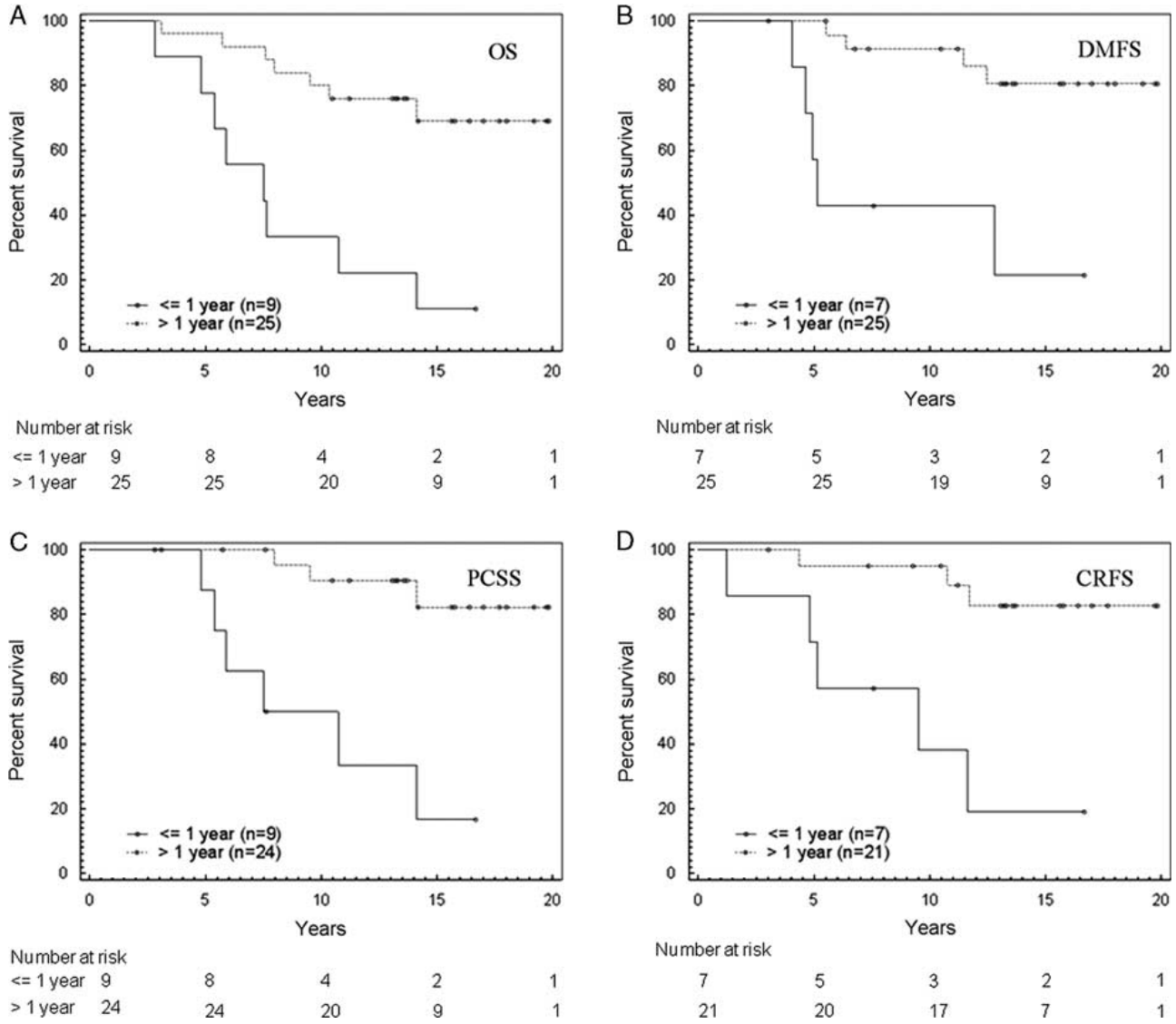

FIGURE 3. Kaplan-Meier survival curves after the start of salvage radiation therapy according to rapidity of failure (failure $\leq$ 1 y vs. failure > 1 y), n = 34. Overall survival (A); distant metastasis-free survival (B); prostate cancer-specific survival (C); castration-resistant-free survival (D). CRFS indicates castration-resistant-free survival; DMFS, distant metastases-free survival; OS, overall survival; PCSS, prostate cancer-specific survival.

reached 1 ng/mL, with a median level of 0.45 ng/mL, suggesting that the outcomes seen in this patient population would be comparable with those treated with contemporary recommendations for early intervention.[4,24] The long-term follow-up in this study minimizes lead-time bias and is able to support the prolonged benefit of early SRT. A recent study by Lohm et al[15] demonstrated incremental beneficial effect to biochemical progression-free survival after initiating SRT at a PSA level as low as <0.15 ng/mL, whereas a systematic review has suggested an average of 2.6% loss of relapse-free survival for each incremental 0.1 ng/mL PSA at time of SRT.[25] These results are highly suggestive of the importance of earlier intervention to maximize outcomes in PCa. The effectiveness of initiating therapy at a lower PSA level may be due to a lower local disease burden with a minimal chance of cancer metastasis. However, the absolute threshold of <0.5 ng/mL to initiate SRT remains debatable at present, and determining thresholds based on different pathologic features is an active topic under investigation.

Pathologic T3 disease and/or positive surgical margin are considered indications for ART as demonstrated in multiple prospective studies.[20,26,27] In our series, the majority (70%) of patients would have been candidates for ART after prostatectomy based on their pathologic stage and margin status. Although it intuitively makes sense that patients with the highest likelihood of microscopic residual disease locally in the prostate fossa are more likely to benefit from earlier intervention with radiation, without concrete evidence from randomized clinical trials one must seriously consider the advantages and disadvantages of ART versus SRT. The decision on whether to use ART or SRT remains an area of active debate, and prospective randomized trials are currently underway to attempt to answer this question.[28]

There may be other strategies to improve SRT outcomes. For instance, preliminary reports of RTOG 96-01, as well as several institutional reviews, have suggested that select patients may benefit from the use of ADT at the time of SRT.[6,29,30] Studies also have suggested potential benefit for pelvic RT in the presence[6] or absence of ADT in select patients undergoing SRT.[14] Although ADT impacted FFPF in our patients, given our small sample size and lack of OS benefit

TABLE 3. Summary of Reported Salvage Radiation Therapy Experiences (Not All Inclusive)

References	Accrual Period	N	Median Follow-up (mo)	Median SRT Dose (Gy)	Outcome
De Meerleer et al[16]	2002-2007	135	30	75	5 y BRFS 67%
Neuhof et al[18]	1991-2004	171	39	60-66	5 y OS 93.8% 5 y BRFS 35.1%
Wiegel et al[17]	1997-2004	162	41.5	66.6	3.5 y bNED 54%
Bernard et al[8]	1987-2007	426	70	64.8	5 y BF 50%
Geinitz et al[12]	1993-2002	96	70	64.8	5 y OS 88% 5 y PCSS 90% 5 y DM 18%
Trock et al[7]	1982-2004	238	72	66.5	5 y PCSS 96% 10 y OS 86%
Choo et al[9]	1998-2002	75	76.8	66	5 y FFPF 91.5% 7 y FFPF 78.6% 5 and 7 y OS 93.2%
Mishra et al[13]	1990-2009	122	88	66.6	5 y OS 95% 10 y OS 80% 10 y FFPF 41%
Stephenson et al[4]	1987-2005	1540	90	64.8	6 y PFP 32%
Cotter et al[10]	1988-2008	519 (219 received radiation therapy)	135.6*	66	All-cause mortality—37.6% for all patients after PSA failure with or without radiation therapy
Swanson et al[11]	1990-1995	92	167	65	5 y OS 86% 10 y OS 67% 10 y FFPF 26%
This study	1992-2000	61	126	64.8	5 y OS 91% 10 y OS 67% 10 FFPF 33%

*Follow-up measured from time of prostate-specific antigen (PSA) failure after surgery.

bNED indicates biochemically no evidence of disease; BF, biochemical failure; BRFS, biochemical recurrence-free survival; DM, distant metastases; FFPF, freedom from PSA failure; NA, not available; OS, overall survival; PCSS, prostate cancer-specific survival; PFP, progression-free probability; SRT, salvage radiation therapy.

clear conclusions cannot be made. These hypotheses are being tested by the ongoing RTOG 0534 phase III randomized trial.

Finally, our study shows statistically significantly worse outcomes in patients who fail SRT early (BCR $\leq$ 1 y). Rapid development of BCR after SRT is independently predictive of worse PCSS ($P = 0.007$) and DMFS ($P = 0.007$) and strongly trended toward significance with worse OS ($P = 0.058$) and CRFS ($P = 0.08$) on multivariate analysis (Table 2). To our knowledge, no other study has reported on the outcome of patients after SRT according to rapidity of SRT failure. According to our univariate analysis (Tables 2A–E), compared with those who develop BCR after 1 year, patients who develop BCR within 1 year are 7.7 times (95% confidence interval [CI], 2.0-28.9) more likely to develop distant metastasis, 8.9 times (95% CI, 2.6-43.4) more likely to develop castration resistant PCa, 10.6 times (95% CI, 2.6-43.4) more likely to die from PCa, and 5.7 times (95% CI, 2.0-15.9) more likely to die due to any cause during our 112-month median follow-up period after failure of SRT. At 10 years (from start of SRT), 57% developed distant metastasis in the BCR $\leq$ 1 year subgroup compared with only 9% in the BCR > 1 year subgroup (Fig. 3). Such poor survival outcome and significantly higher distant metastasis rate in patients who fail SRT early suggests the need for close observation and timely PSA monitoring during the first 12 months after SRT. Furthermore, these results may also indicate the need for more aggressive salvage treatment for early PSA failure after SRT, such as earlier use of systemic therapy for concerns of risk of microscopic metastatic dissemination. Systemic treatments beyond standard ADT should be considered, given that these patients develop castration resistant PCa almost 9 times more frequently than those who fail SRT in a more delayed manner. A number of agents are now available for systemic treatment including, but not limited to, docetaxel, cabazitaxel, abiraterone, enzalutamide, and radium-223. Further prospective randomized studies are warranted to establish clear guidelines for the timing and method of using additional systemic agents.

In conclusion, this study, with a median follow-up >10 years, supports previously published clinicopathologic parameters for predicting outcomes after SRT. Although limited by a small sample size and its retrospective nature, this study nevertheless adds to the body of literature where there remains paucity of prospective data. It supports a long-lasting survival benefit of early SRT at a lower PSA level. It suggests that SRT is effective in preventing PCa-specific mortality and decreasing the rate of distant metastases. Patients with early PSA failure after SRT may represent a more aggressive subgroup that needs close follow-up and further improvement of therapy, which may be tested in future prospective studies.

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