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ORIGINAL ARTICLE

Time to biochemical relapse after radical prostatectomy and efficacy of salvage radiotherapy in patients with prostate cancer

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Abstract

Background To investigate the prognostic and therapeutic implications of time to biochemical relapse (BCR) in patients with prostate cancer after radical prostatectomy.

Methods The records of 3210 consecutive men with prostate cancer who underwent radical prostatectomy between January 1998 and June 2013 were retrospectively reviewed. Patients with BCR were divided into three groups based on quartiles of time to BCR, namely an early group (first quartile), an intermediate group (second and third quartiles) and late group (fourth quartile).

Results 817 (25.5%) patients experienced BCR at a median of 24.9 months after surgery. The 8-year rate of distant metastasis-free survival (64.3% vs. 41.3%, $p=0.002$) and cancer-specific survival (86.6% vs. 63.4%, $p<0.001$) was higher in the salvage radiotherapy (SRT) group than the androgen deprivation therapy (ADT) group in patients with early BCR, whereas those rates (91.3% vs. 87.9%, $p=0.607$ and 100.0% vs. 93.1%, $p=0.144$, respectively) were similar in patients with late BCR. In the intermediate BCR group, the impact of SRT over ADT on 8-year cancer-specific survival was modest (91.9% vs. 82.3%, $p=0.057$) and was limited to patients with pT2 or pT3a disease.

Conclusions SRT may decrease the risk of distant metastasis and cancer-specific mortality in patients with early BCR. However, a survival benefit for those with late BCR was not apparent. For patients with intermediate BCR, SRT was associated with a cancer-specific survival benefit in patients with pT2 or pT3a disease. Novel genomic tests and imaging modalities may support clinical decision-making in these patients.

Keywords Prostatic neoplasm · Prostatectomy · Radiotherapy · Survival

Introduction

Although men with localized prostate cancer who undergo radical prostatectomy can expect favorable oncologic outcomes, biochemical relapse (BCR) has been reported in up to 35% of patients [1, 2]. A recent report by the International Intermediate Clinical Endpoints in Cancer of the Prostate working group suggests that biochemical-based endpoints cannot be considered to be surrogate indicators of more meaningful survival outcomes [3]. However, a rise in prostate-specific antigen (PSA) frequently precedes clinical recurrence, despite the long interval to distant metastasis or death [4], suggesting that BCR is of clinical value as an early endpoint after radical prostatectomy [5].

In general, BCR has been found to precede clinical recurrence and cancer-specific death by an average of 7 and 15 years, respectively [6]. However, the likelihood of clinical recurrence is dependent on the duration of BCR-free

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survival after radical prostatectomy, making conventional estimates of survival less relevant. Studies assessing the association between time to BCR and survival outcomes in patients with prostate cancer treated with radical prostatectomy have yielded inconsistent results [9, 2, 4, 6–8, 10–13]. In addition, while approximately 6–23% of patients are reported to experience BCR more than 5 years after radical prostatectomy [2, 14, 15], optimal management strategies for patients with later recurrence have not yet been fully determined. Surveillance has been favored, because late recurrence rarely progresses to metastasis or cancer death [11, 14], whereas others report that the recurrence-free interval is not a significant factor [4, 16].

This study was designed to assess oncologic outcomes according to time from surgery to BCR in patients with prostate cancer after radical prostatectomy. In addition, the study analyzed predictors of survival and assessed the efficacy of salvage radiotherapy according to time from surgery to BCR.

Materials and methods

The study protocol was approved by the institutional review board of the Asan Medical Center (no. 2017–1036). Patients were excluded if they had received neoadjuvant or adjuvant therapy, had not achieved undetectable PSA levels (< 0.1 ng/ml) after surgery, or had incomplete clinical information. The records of 3,210 men with prostate cancer who underwent radical prostatectomy at the Asan Medical Center between January 1998 and June 2013 were retrospectively reviewed. Patient data, including demographics and clinical characteristics, treatment-related variables, and survival outcomes, were also evaluated.

Pre-operative staging included a digital rectal examination, serum PSA level determination, bone scanning, and pre-operative MRI. Post-operative PSA concentrations were measured every 3 months for the first 2 years after radical prostatectomy, every 6 months for the third and fourth years, and annually thereafter. BCR was defined as two consecutive PSA increases of ≥ 0.2 ng/ml after radical prostatectomy. Most patients who experienced BCR after surgery were advised to undergo secondary treatments before clinical recurrence occurred; these included salvage radiotherapy (SRT) with or without androgen deprivation therapy (ADT), or ADT alone, with treatment selection being made according to the preference of the patient or physician. For SRT after radical prostatectomy at our institution, 3D-conformal radiotherapy was performed until 2012 and intensity-modulated radiotherapy after 2012. Pelvic nodal irradiation was performed when the Roach score was 15% or greater for the risk of lymph node involvement [17]. Detailed information on SRT, including the planning target volume, doses, and fractionation schemes used at our institution, have been described previously [18, 19]. Abdominopelvic computed tomography (CT) and bone scanning were routinely performed at the time of BCR and at the time of biochemical progression after secondary treatments. Clinical recurrence was evaluated by CT or magnetic resonance imaging (MRI) for soft-tissue disease and by bone scanning for bone disease.

Oncologic outcomes, including distant metastasis-free survival, cancer-specific survival, and overall survival, were analyzed relative to BCR-free survival. To investigate the differences between patients who experienced BCR at early and late time intervals, we categorized the patients into three groups based on quartiles of time to BCR, namely, an early group (first quartile), an intermediate group (second and third quartiles) and late group (fourth quartile).

Clinical and pathological data were expressed as frequencies and means. Between-group differences in continuous variables were assessed by Student's *t*-tests or analysis of variance (ANOVA), and differences in categorical variables were assessed by the chi-square test. Survival outcomes were determined using the Kaplan–Meier method and compared with log rank tests. Factors significantly prognostic for survival were assessed by multivariate analysis using the Cox proportional hazard model with a stepwise backwards elimination approach. All statistical tests were two tailed, with a significance level of 0.05. All statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY, USA).

Results

The clinical and pathological characteristics of the 3,210 men with prostate cancer who underwent radical prostatectomy are summarized in Table 1. Of these, 817 patients (25.5%) experienced BCR at a median of 24.9 months after surgery. BCR occurred in 219 (26.8%), 174 (21.3%), 153 (18.7%), 111 (13.6%), 55 (6.7%), and 105 (12.9%) patients at < 1, 1–2, 2–3, 3–4, 4–5, and ≥ 5 years after surgery, respectively. The median follow-up duration for enrolled patients was 93.8 months. Distant metastases, cancer-specific deaths, and all-cause deaths were observed in 163 (5.1%), 105 (3.3%), and 358 (11.2%) patients during follow-up, respectively. When patients with BCR were categorized into four quartiles based on time from surgery to BCR, the median times to BCR were 8.5 (4.0–11.9), 17.5 (11.9–24.9), 33.2 (24.9–42.9), and 70.0 (42.9–195.0) months, respectively. PSA levels, National Comprehensive Cancer Network (NCCN) risk groups, pathological Gleason score (GS), pathological stage, surgical margin status, and PSA doubling time (PSADT) differed significantly according to time from surgery to BCR, with patients in the early BCR group exhibiting poorer clinical and pathological characteristics than those with late recurrence.

Table 1 Baseline patient characteristics

	Overall, $N=3210$	Quartiles by time from radical prostatectomy to biochemical relapse, months				
		Q1 $N=204$	Q2 $N=204$	Q3 $N=205$	Q4 $N=204$	*P* value
Median time to BCR, months (range)		8.5 (4.0–11.9)	17.5 (11.9–24.9)	33.2 (24.9–42.9)	70.0 (42.9–195.0)	< 0.001
Mean age, years	65.1	65.2	65.3	64.1	64.3	0.120
Mean body mass index, kg/m^2	24.7	25.0	24.8	24.6	24.8	0.563
Diabetes mellitus, *n* (%)	508 (15.8)	42 (20.6)	33 (16.2)	35 (17.1)	37 (18.1)	0.680
Pre-operative mean PSA, ng/ml	11.8	24.5	19.2	18.0	13.2	< 0.001
NCCN risk group, *n* (%)						< 0.001
Low	970 (30.2)	6 (3.0)	16 (7.9)	31 (15.1)	29 (14.2)	
Intermediate	1230 (38.3)	37 (18.1)	67 (32.8)	65 (31.7)	87 (42.7)	
High	1010 (31.5)	161 (78.9)	121 (59.3)	109 (53.2)	88 (43.1)	
Pathologic Gleason score, *n* (%)						< 0.001
6	657 (20.5)	4 (2.0)	9 (4.4)	12 (5.9)	20 (9.8)	
7	1866 (58.1)	73 (35.8)	92 (45.1)	103 (50.2)	122 (59.8)	
8	294 (9.2)	34 (16.6)	42 (20.6)	34 (16.6)	30 (14.7)	
9–10	393 (12.2)	93 (45.6)	61 (29.9)	56 (27.3)	32 (15.7)	
Pathologic T-stage, *n* (%)						< 0.001
T2	2021 (63.0)	31 (15.2)	60 (29.4)	84 (41.0)	95 (46.6)	
T3a	815 (25.4)	77 (37.7)	81 (39.7)	75 (36.6)	69 (33.8)	
T3b	374 (11.6)	96 (47.1)	63 (30.9)	46 (22.4)	40 (19.6)	
Positive lymph nodes, *n* (%)	179 (5.6)	28 (13.7)	25 (12.3)	17 (8.3)	13 (6.4)	0.050
Positive surgical margins, *n* (%)	1081 (33.7)	146 (71.6)	131 (64.2)	119 (58.0)	105 (51.5)	< 0.001
Mean PSA doubling time, months		4.3	6.3	6.3	9.0	< 0.001
Secondary treatments, *n* (%)						< 0.001
ADT alone		95 (46.5)	110 (53.9)	119 (58.0)	115 (56.4)	
Radiotherapy (± ADT)		105 (51.5)	87 (42.7)	76 (37.1)	67 (32.8)	
None		4 (2.0)	7 (3.4)	10 (4.9)	22 (10.8)	

ADT androgen deprivation therapy, *BCR* biochemical relapse, *NCCN* National Comprehensive Cancer Network, *PSA* prostate-specific antigen

Distant metastasis-free survival, cancer-specific survival, and overall survival as a function of duration of BCR-free survival after surgery are shown in Supplementary Fig. 1. Distant metastasis-free survival, cancer-specific survival, and overall survival increased gradually with increasing duration of BCR-free survival years. The 8-year cancer-specific mortality rate from the time of PSA rise was significantly higher than other-cause mortality rates in patients in the first (24.7% vs. 7.0%, log rank $p=0.0007$; Fig. 1) and second quartiles (15.7% vs. 7.0%, log rank $p=0.046$), but not in patients in the third (9.1% vs. 9.7%, log rank $p=0.480$) and final quartiles (4.7% vs. 9.9%, log rank $p=0.090$).

Figure 2 shows the probability of distant metastasis, cancer-specific mortality, and overall mortality from time of PSA rise in patients with BCR by quartile. Kaplan–Meier analysis showed that patients in the first quartile of time to BCR had significantly worse distant metastasis-free survival (log rank $p<0.0001$), cancer-specific survival (log rank $p=0.0002$), and overall survival (log rank $p=0.0041$) from the time of PSA rise than patients in the other quartiles.

The characteristics of patients who experienced clinical recurrence according to time from radical prostatectomy to BCR are shown in Table 2. Distant metastasis was more frequent than local recurrence in patients with earlier BCR, whereas local recurrence was more frequent than distant metastasis in patients with clinical recurrence after later BCR.

Survival outcomes based on salvage treatments and time from surgery to BCR are shown in Fig. 3. The median SRT dose was 67 Gy and the median pre-SRT PSA level was 0.56 ng/ml. In the early BCR group, patients who underwent SRT had better 8-year rates of distant metastasis-free survival (64.3% vs. 41.3%, log rank $p=0.002$) and cancer-specific survival (86.6% vs. 63.4%, log rank $p<0.001$) than those who received ADT alone. However, the 8-year rates of distant metastasis survival (91.3% vs. 87.9%, log rank $p=0.607$) and cancer-specific survival (100.0% vs. 93.1%, log rank $p=0.144$) from the time of BCR were similar between SRT- and ADT-treated patients in the late BCR group. In patients with intermediate BCR,

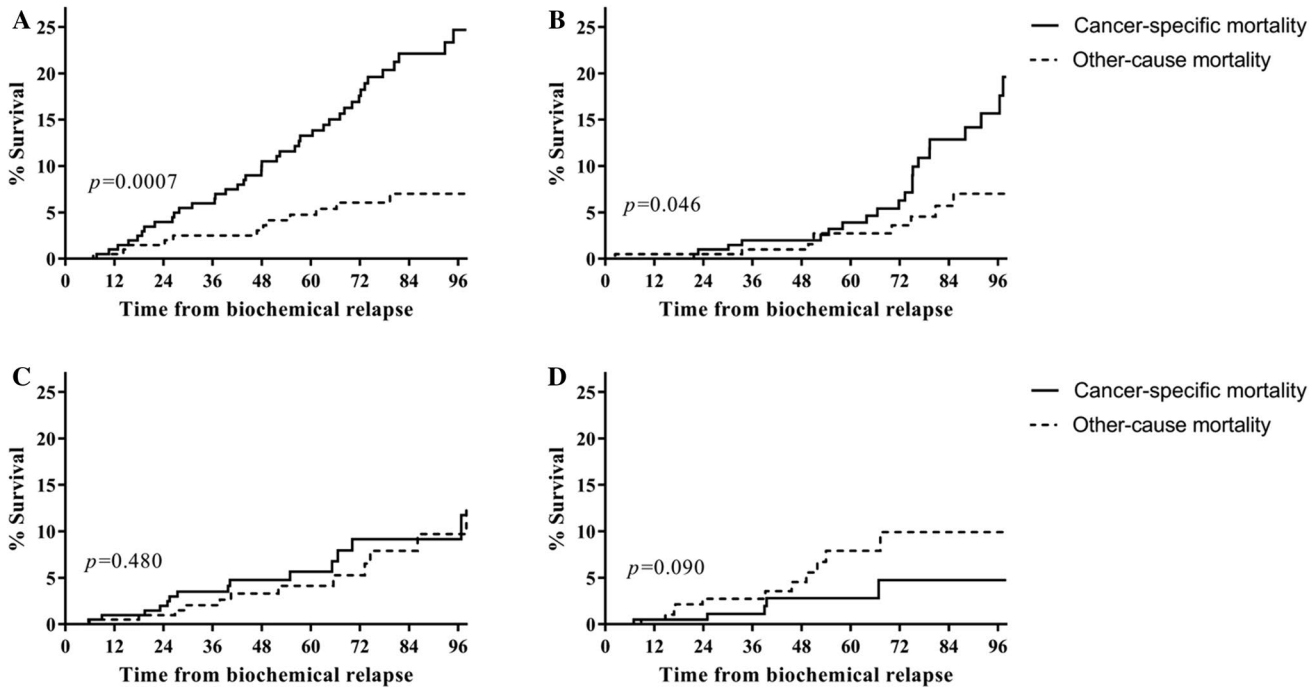

Fig. 1 Kaplan–Meier analyses of cancer-specific and other-cause mortality in patients with biochemical relapse according to quartile of time from surgery to relapse. **a** First quartile (earliest), **b** second quartile, **c** third quartile, **d** fourth quartile (latest)

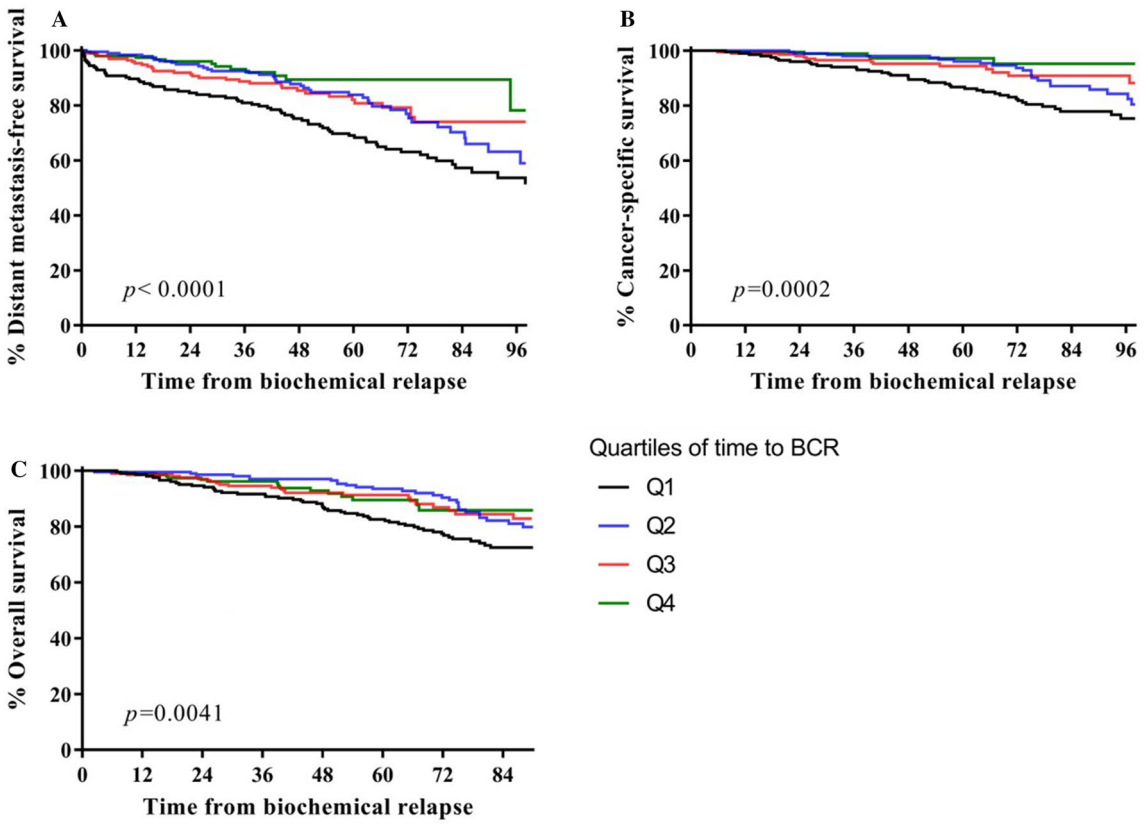

Fig. 2 Kaplan–Meier analyses of the probability of **a** distant metastasis, **b** cancer-specific mortality, and **c** overall survival as a function of time from biochemical relapse

Table 2 Characteristics of clinical recurrence according to time from radical prostatectomy to biochemical relapse

	Quartiles by time from radical prostatectomy to biochemical relapse, months				*P*-value
	Q1	Q2	Q3	Q4	
Median time from biochemical relapse to clinical recurrence, months	39.2	49.2	34.9	24.4	0.099
Clinical recurrence, *n*	84	59	55	31	
Local recurrence, *n* (%)	22 (26.2)	22 (37.3)	25 (45.5)	21 (67.7)	0.001
Distant metastasis, *n* (%)	72 (85.7)	40 (67.8)	35 (63.6)	15 (48.4)	< 0.001
Bone	56	29	27	10	
Lymph node	33	15	9	8	
Solid organ	13	6	3	1	

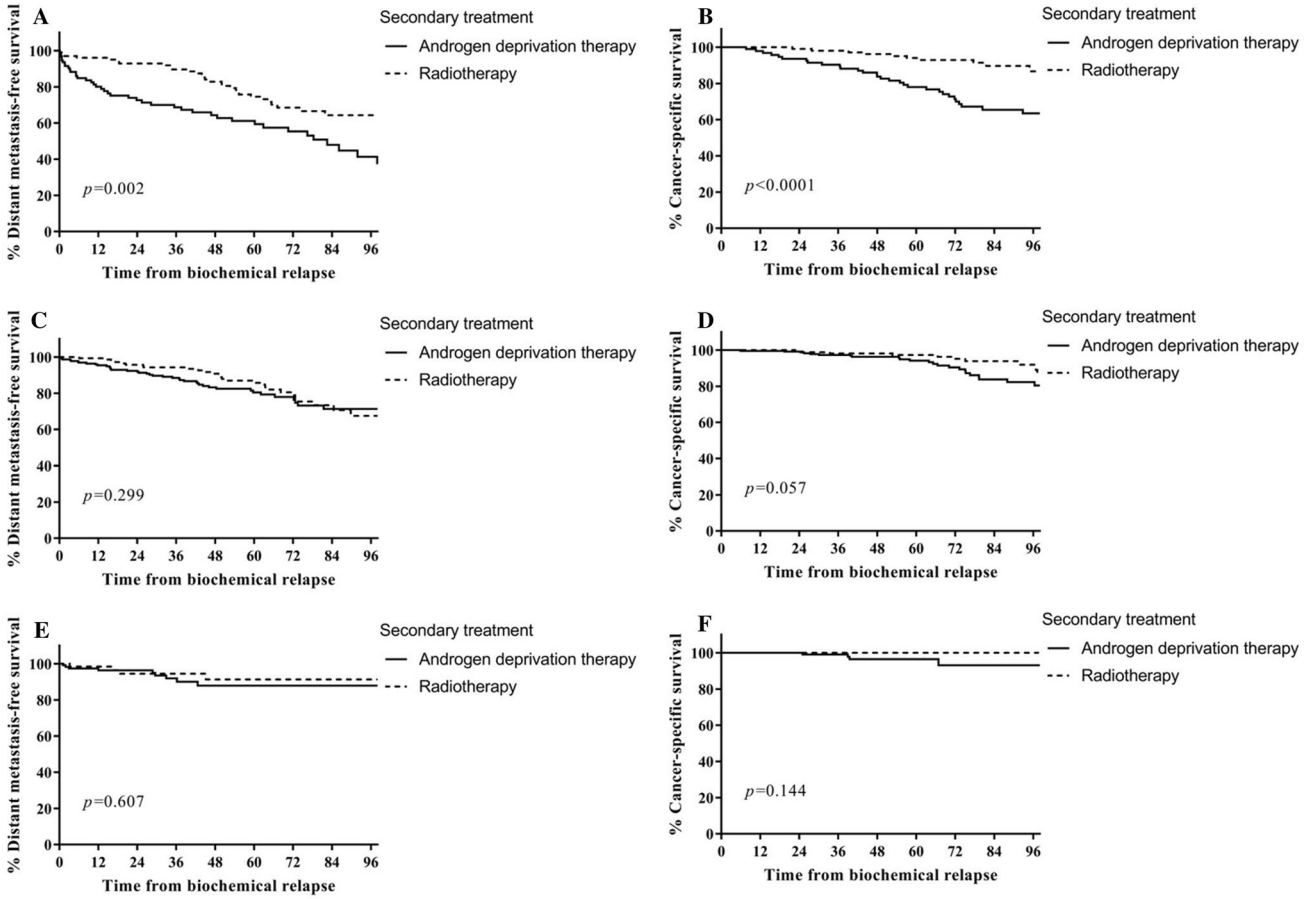

Fig. 3 Kaplan–Meier analyses of outcomes based on salvage treatments and quartile of time from surgery to relapse. **a** Distant metastasis-free survival in the first quartile, **b** cancer-specific survival in the first quartile, **c** distant metastasis-free survival in the second and third quartiles, **d** cancer-specific survival in the second and third quartiles, **e** distant metastasis-free survival in the latest quartile, **f** cancer-specific survival in the latest quartile

the 8-year cancer-specific survival rates were higher in the SRT than the ADT group, although this difference did not reach statistical significance (91.9% vs. 82.3%, log rank $p = 0.057$). In a sub-analysis of the intermediate BCR group, SRT was associated with a cancer-specific survival benefit in patients with pT2 or pT3a disease (log rank $p = 0.016$; Fig. 4).

Multivariate analyses showed that, in the overall population (Table 3A), pathologic GS 8–10 [vs. ≤ 7; hazard ratio (HR) = 2.19; 95% CI 1.28–3.77; $p = 0.004$], seminal

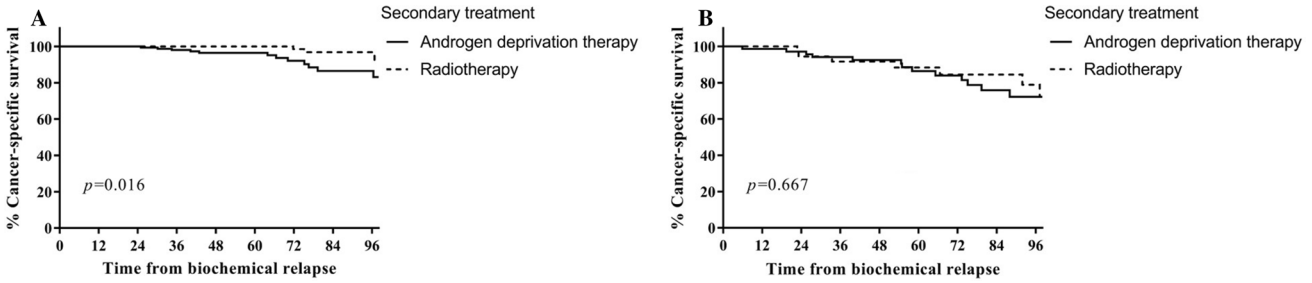

Fig. 4 Kaplan–Meier analyses of cancer-specific survival based on pathologic T-stage in the second and third quartiles. **a** Patients with pathologic stage T2 or T3a disease, **b** patients with pathologic disease stage ≥ T3b

Table 3 Multivariable Cox regression analyses evaluating the risk of cancer-specific mortality from the time of biochemical relapse

(a) Overall population

	Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age, continuous	1.03 (0.99–1.07)	0.074		
Body mass index, continuous	0.99 (0.92–1.07)	0.887		
Pathologic GS 8–10 vs. ≤ 7	3.73 (2.22–6.25)	< 0.001	2.19 (1.28–3.77)	0.004
Extraprostatic extension	3.14 (1.67–5.90)	< 0.001	1.30 (0.62–2.76)	0.489
Seminal vesicle invasion	3.66 (2.38–5.63)	< 0.001	2.16 (1.23–3.60)	0.003
Lymph node involvement	3.41 (2.15–5.41)	< 0.001	1.93 (1.18–3.15)	0.008
Positive surgical margins	1.34 (0.86–2.07)	0.194		
Time from surgery to biochemical relapse, months[a]				
Fourth quartile	1 [Reference]		1 [Reference]	
Third quartile	2.73 (0.92–8.13)	0.071	2.26 (0.76–6.79)	0.145
Second quartile	3.20 (1.10–9.27)	0.032	1.85 (0.63–5.46)	0.265
First quartile	5.74 (2.06–15.98)	0.001	3.34 (1.17–9.51)	0.024
PSA doubling time < 3 months vs. ≥ 3 months	2.12 (1.40–3.22)	< 0.001	1.60 (1.04–2.46)	0.034
Secondary treatments				
ADT alone	1 [Reference]		1 [Reference]	
Radiotherapy, ± ADT	0.41 (0.25–0.65)	< 0.001	0.43 (0.26–0.70)	0.001

(b) Hazard ratios for secondary treatments predicting cancer-specific mortality from the time of biochemical relapse

	Unadjusted (univariate)		Adjusted[b] (multivariate)		*P*-value for interaction
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	
Radiotherapy vs. ADT					
Q1 (earliest)	0.29 (0.15–0.56)	< 0.001	0.34 (0.17–0.68)	0.002	
Q2–Q3	0.51 (0.26–1.03)	0.061	0.62 (0.30–1.25)	0.180	0.186
Q4 (latest)	0.34 (0.08–1.54)	0.161	0.30 (0.06–1.36)	0.118	

ADT androgen deprivation therapy, *CI* confidence interval, *GS* Gleason score, *HR* hazard ratio, *PSA* prostate-specific antigen

[a]Time from surgery to biochemical relapse, when evaluated as a continuous variable, was not significant in the multivariable analyses (HR = 0.99; 95% CI 0.98–1.00; $p = 0.113$)

[b]Adjusted for pathologic Gleason score, extraprostatic extension, seminal vesicle invasion, lymph node involvement, and prostate-specific antigen doubling time

vesicle invasion (HR = 2.16; 95% CI 1.23–3.60; $p = 0.003$), lymph node involvement (HR = 1.93; 95% CI 1.18–3.15; $p = 0.008$), the first quartile of time to BCR (vs. The fourth quartile; HR = 3.34; 95% CI 1.17–9.51; $p = 0.024$), PSADT < 3 months (vs. ≥ 3 months; HR = 1.60; 95% CI 1.04–2.46; $p = 0.034$), and SRT (vs. ADT alone; HR = 0.43;

95% CI 0.26–0.70; $p = 0.001$) were independent predictors of cancer-specific mortality from the time of BCR. When stratified by quartile of time from surgery to BCR, SRT was seen to be associated with a significant cancer-specific survival benefit versus ADT only in patients in the first quartile (Table 3B; HR = 0.34, $p = 0.002$).

Discussion

BCR after radical prostatectomy is not uncommon in patients with prostate cancer. In the present study, 25.5% of patients experienced BCR at a median of 24.9 months after surgery, which is consistent with the results seen in previous studies, although the PSA rise occurred earlier than has previously been observed [1, 2, 4]. The relatively early rate of recurrence observed in the present study may be due to the high proportion of patients with high-risk (31.5%), high-grade (GS 8–10: 21.4%) tumors and an advanced pathologic stage (T3: 37.0%; N1: 5.6%).

There is no consensus regarding the appropriate cut-off points for defining early recurrence. Pound et al. reported that time to BCR ≤ 2 years independently predicts metastatic progression [10]. Freedland et al. reported that time to BCR ≤ 3 years was a significant risk factor for prostate cancer deaths [6], while one recent study reported that BCR at 1 year or less after surgery was prognostic of mortality [9]. In this study, time to BCR was divided by quartile distribution instead of by arbitrary cut-off points. We considered it more appropriate to classify the earliest 25% of time to BCR in our study cohort as early BCR, and the latest 25% as late BCR.

The cancer-specific mortality rate has previously been reported to be lower than the other-cause mortality rate in patients with BCR following surgery, regardless of the time from surgery to BCR [4]. In one study, only 9.1% of patients who experienced early BCR died of prostate cancer, compared with 15% who died from other causes [4]. By contrast, the current study found the 8-year cancer-specific mortality rate to be significantly higher than the other-cause mortality rate in patients with earlier recurrence, although this was not seen in patients with later recurrences. These disparate outcomes may have been due to differences in the clinicopathologic features of the study cohort and the use of neoadjuvant, adjuvant, or salvage treatments.

Patterns of initial clinical recurrence were found to differ according to time from surgery to BCR. Distant metastases were more frequent in patients who experienced earlier BCR, whereas local recurrence was more frequently observed in patients with later BCR. Several factors may explain these observations. First, patients experiencing later BCR had a less aggressive tumor biology than those with earlier BCR. In general, local recurrence is more frequently observed in patients with low-grade, organ-confined disease, indicating that local recurrence has low metastatic potential [10, 20]. Second, the secondary treatment pattern may have contributed to differences in the recurrence patterns between patients with earlier and later recurrences. Patients with earlier recurrence were more likely to receive SRT for local control than were those with later recurrence, resulting in the latter group having a lower probability of developing local recurrence.

The impact of time from treatment to BCR on oncologic outcomes has been investigated in patients with prostate cancer undergoing radical prostatectomy [2, 4, 6–10, 12] and radiation therapy [16, 21]. Earlier BCR has been associated with an increased risk of death from prostate cancer [6, 8], and a shorter interval from surgery to BCR (< 12 months) is reported to be an independent predictor of metastatic progression, cancer-specific mortality, and overall mortality [9]. By contrast, other studies have reported that the time interval from surgery to BCR was not independently associated with the risk of systemic progression or death from prostate cancer [4, 12, 13, 16]. In the present study, Kaplan–Meier curves showed that distant metastasis-free survival and cancer-specific survival from the time of BCR were significantly worse in patients in the first quartile of time to BCR than in those in other quartiles. After adjusting for clinicopathologic variables, the first quartile of time to BCR remained an independent predictor of cancer-specific survival.

SRT is the standard of care for recurrent prostate cancer after radical prostatectomy [22, 23]. Pre-SRT PSA levels have shown a significant association with SRT outcome [24]. In the current study, the mean pre-SRT PSA levels and the proportion of patients who received early SRT were similar in each quartile but SRT was associated with a significant survival benefit compared with ADT only in patients in the first quartile, who experienced BCR within 12 months. These results may be due to the differences in PSADT between the patients in the first quartile and the other quartiles. PSADT has been reported to be a strong predictor of prostate cancer progression and mortality in most studies conducted to date [4, 6–9, 12, 13, 21]. Similarly, PSADT was a significant predictor of cancer-specific mortality from the time of BCR in the present study. One study reported that PSADT < 3 months was an adverse predictor of early progression and survival in patients who received ADT after radical prostatectomy [25]. Consistent with this finding, the present study showed the effect of ADT to be significantly lower than that of SRT in patients with PSADT < 3 months (Supplementary Fig. 2). By contrast, patients with PSADT ≥ 3 months who received salvage ADT showed similar cancer-specific survival results to those who received SRT. These data suggest that the large proportion of patients with a shorter PSADT in the first quartile

contributed to the poorer outcomes observed in this group of patients who received ADT alone.

Identifying patients who had benefited from SRT in the intermediate BCR group is important, because SRT was shown to be clearly effective in patients with early BCR, and the mortality rate of the late BCR group was low regardless of secondary treatment approaches. Our analysis showed that SRT was associated with a cancer-specific survival benefit among patients in the intermediate BCR group with pT2 or pT3a disease. These results are consistent with those of previous studies that reported an association between seminal vesicle invasion and increased risk of SRT failure [24, 26]. The study results highlight the importance of selecting patients who may benefit from SRT. Recent genomic tests and novel imaging modalities may help to support clinical decision-making in patients who experience BCR after radical prostatectomy [27, 28].

The current study has several limitations. First, the retrospective design may be subject to the inherent bias associated with observational studies. However, retrospective analysis is necessitated by the fact that randomization according to BCR-free interval is challenging. Other limitations that may have introduced bias include the exclusion of patients who received neoadjuvant or adjuvant therapy and the lack of prospective standardized protocols for salvage treatments. SRT was performed at our hospital only on 41.5% of patients because of the distance patients needed to travel to the facility and the nature of a metropolitan tertiary center. Therefore, complete information on radiation field and radiation technique was not available, which may have influenced the survival outcomes. Furthermore, although the study included a large patient cohort, the number of patients who experienced clinical recurrence after late BCR was small and the relatively short duration of follow-up precluded subgroup analysis of survival outcomes. In addition, a relatively high proportion of patients in this study had advanced tumors, suggesting that this population may not be representative of general populations of patients with prostate cancer. Nevertheless, we believe that the present study provides useful information to support the management and counseling of patients who experience BCR after radical prostatectomy.

Conclusions

SRT may help to decrease the risk of distant metastasis and cancer-specific mortality in patients with early BCR; however, the survival benefit for those with late BCR was not apparent. For patients with intermediate BCR, SRT was associated with cancer-specific survival benefit in patients with pT2 or pT3a disease. Novel genomic tests and imaging modalities may support the clinical decision-making in these patients.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

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