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Original Article

Optimal Definition of Biochemical Recurrence in Patients Who Receive Salvage Radiotherapy Following Radical Prostatectomy for Prostate Cancer

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Purpose This study proposed the optimal definition of biochemical recurrence (BCR) after salvage radiotherapy (SRT) following radical prostatectomy for prostate cancer.

Materials and Methods Among 1,117 patients who had received SRT, data from 205 hormone-naïve patients who experienced post-SRT prostate-specific antigen (PSA) elevation were included in a multi-institutional database. The primary endpoint was to determine the PSA parameters predictive of distant metastasis (DM). Absolute serum PSA levels and the prostate-specific antigen doubling time (PSA-DT) were adopted as PSA parameters.

Results When BCR was defined based on serum PSA levels ranging from 0.4 ng/mL to nadir+2.0 ng/mL, the 5-year probability of DM was 27.6%-33.7%. The difference in the 5-year probability of DM became significant when BCR was defined as a serum PSA level of 0.8 ng/ml or higher (1.0-2.0 ng/mL). Application of a serum PSA level of ≥ 0.8 ng/mL yielded a c-index value of 0.589. When BCR was defined based on the PSA-DT, the 5-year probability was 22.7%-39.4%. The difference was significant when BCR was defined as a PSA-DT ≤ 3 months and ≤ 6 months. Application of a PSA-DT ≤ 6 months yielded the highest c-index (0.660). These two parameters complemented each other; for patients meeting both PSA parameters, the probability of DM was 39.5%-44.5%; for those not meeting either parameter, the probability was 0.0%-3.1%.

Conclusion A serum PSA level > 0.8 ng/mL was a reasonable threshold for the definition of BCR after SRT. In addition, a PSA-DT ≤ 6 months was significantly predictive of subsequent DM, and combined application of both parameters enhanced predictability.

Key words Prostatic neoplasms, Prostatectomy, Radiotherapy, Prostate-specific antigen

Introduction

Regular monitoring of serum prostate-specific antigen (PSA) is important during follow-up after curative treatment for prostate cancer, because an increased serum PSA level is usually the first sign of disease recurrence, preceding distant metastasis (DM) and prostate cancer-specific death by 7 and 15 years, respectively [1]. Biochemical recurrence (BCR) is defined as an increase in the serum PSA level above a particular value after curative treatment, depending on the type of treatment. Generally, when prostate cancer patients undergo radical prostatectomy (RP), a serum PSA level > 0.2 ng/mL is considered BCR, while in definitive radiotherapy, a serum PSA level > nadir+2.0 ng/mL is the widely adopted definition (the Phoenix definition).

Salvage radiotherapy (SRT) is the treatment of choice for patients who develop BCR during follow-up after RP. The percentage of prostate cancer patients who undergo SRT is relatively high, because > 30% of those who undergo RP eventually experience disease recurrence [2]. PSA monitoring remains an important method of evaluation during follow-up after SRT, and retrospective series have shown

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that approximately 60%-75% of patients present with a biochemical response after SRT [3,4]. Although early detection of treatment failure after SRT is marked by elevated PSA levels, no widely accepted consensus has been reached on the optimal definition of BCR in SRT patients. Despite the need, few studies have sought the optimal definition of BCR for prediction of clinical outcomes after SRT.

The Korean Radiation Oncology Group (KROG) 18-01 protocol was designed to evaluate the efficacy of SRT after RP in patients with localized prostate cancer, based on data from more than 1,000 patients included in a multi-institutional database. Using this study population, we determined the optimal PSA levels and kinetics for prediction of the probability of DM, a critical event that contributes to cancer-specific mortality. Hence, this study was performed to propose the optimal definition of BCR after SRT.

Materials and Methods

Data from 1,117 consecutive patients with prostate cancer who received postoperative radiotherapy after RP between 2001 and 2012 at 19 institutions participating in the KROG 18-01 protocol were collected. The inclusion and exclusion criteria and evaluation methods for the KROG 18-01 protocol have been described previously [5]. Of the subjects, 579 patients were excluded because they received androgen deprivation therapy (ADT) perioperatively or concurrently with or after SRT. Among the 538 (48.1%) remaining hormone (ADT)-naïve patients, 205 experienced post-SRT PSA elevation and 333 did not. These 205 patients included those with histories of re-salvage treatment after SRT (n=177), or persistent PSA elevation after SRT (n=6), or re-elevation after reaching the post-SRT nadir (n=22). The flow of subjects through the study is summarized in Fig. 1.

The details of treatment of the patients included in the KROG 18-01 protocol have been described previously [5]. Briefly, all patients received SRT following RP, and a median RT dose of 66.7 Gy (interquartile range [IQR], 64.6 to 70.0) was delivered to the treatment target encompassing the prostate and seminal vesicle bed. After completion of SRT, patients' serum PSA levels were measured at regular follow-up evaluations every 3 months for 1 year, every 6 months for the next 4 years, and every 12 months thereafter. When PSA elevation was detected after 1 year, the evaluation interval reverted to 3 months. The median interval between SRT and post-SRT PSA elevation was 37.8 months (IQR, 17.5 to 66.0). For assessment of PSA kinetics, the PSA doubling time (PSA-DT) was calculated using at least three PSA measurements obtained at a 3-month interval before re-salvage treatment after SRT. The PSA-DT is the number of months required for the PSA level to double and may be associated with prostate cancer cell proliferation [6].

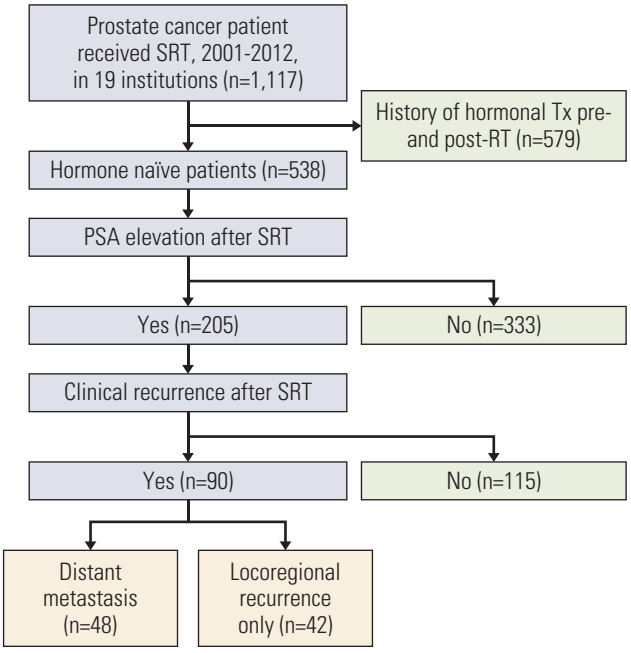

Fig. 1. The flow chart of the study subjects. PSA, prostate-specific antigen; SRT, salvage radiotherapy; Tx, therarpy.

The primary endpoint of this study was to determine the PSA parameters predictive of DM following SRT. Patients lost to follow-up were censored at the last known date on which they were alive. The ability of various definitions of BCR to predict DM was tested using the absolute serum PSA level and the PSA-DT before re-salvage treatment. The PSA-DT was not calculated for 18 patients (8.7%) due to a lack of adequate serial PSA measurements.

The Mann-Whitney U, chi-square, and Fisher exact tests were used to analyze the clinicopathological variables, as appropriate. Survival curves were plotted using the Kaplan-Meier estimator, and the log-rank test was used to compare survival curves between groups. The probability of DM according to the BCR definition was assessed with Harrell's c-index (also known as the concordance index), which is commonly used to evaluate risk models in a survival analysis in which data may be censored. p-values < 0.05 were considered significant, and all reported p-values are two-sided. IBM SPSS software ver. 27 (IBM Corp., Armonk, NY) was used to perform the statistical analyses.

Table 1. Patient characteristics (n=205)

Characteristic	Value
Age (yr)	65 (60-69)
Gleason score sum	
6	6 (2.9)
7	120 (58.0)
8	33 (15.9)
9	48 (23.2)
Pathologic staging	
pT2	57 (27.5)
pT3	140 (67.6)
pT4	10 (4.8)
RM status	
Negative	86 (41.5)
Positive	121 (58.5)
PSA information	
Initial PSA (ng/mL)	11.7 (7.0-19.2)
Pre-SRT PSA (ng/mL)	0.5 (0.3-0.9)
Post-SRT PSA nadir	
< 0.2 ng/mL	138 (67.3)
≥ 0.2 ng/mL	67 (32.7)
Absolute PSA reduction after SRT	
Increased	33 (16.1)
< 0.5 ng/mL decrease	104 (50.7)
≥ 0.5 ng/mL decrease	68 (33.2)
Interval between SRT to post-RT nadir[a] (mo)	5.49 (3.03-10.58)

Values are presented as median (IQR) or number (%). IQR, interquartile range; PSA, prostate-specific antigen; RM, resection margin; RT, radiotherapy; SRT, salvage radiotherapy. [a]Twelve pts the date of nadir was same as the date of post-SRT PSA elevation.

Results

1. Patient and tumor characteristics

The characteristics of the 205 patients with post-SRT PSA elevation are summarized in Table 1. The most common Gleason's score for the pathologic specimens was seven (58.0%), followed by nine (23.2%) and eight (15.9%). More than 70% of patients were diagnosed with pT3 or more advanced disease. More than half of the patients had positive resection margins. For these patients, the median serum PSA values at the time of initial diagnosis and SRT were 11.7 ng/mL (IQR, 7.0 to 19.2) and 0.5 ng/mL (IQR, 0.3 to 0.9), respectively. The median follow-up times from the days of RP and SRT were 120.3 months (IQR, 92.9 to 143.6) and 99.2 months (IQR, 75.9 to 121.8), respectively. Of the 205 patients with post-SRT PSA elevation, 90 (43.9%) developed clinical recurrence; of these, 48 (23.4%) developed DM and 42 (20.5%) had only locoregional recurrences. Among those who developed DM, the median lag time between the time of post-SRT PSA elevation and DM was 17.2 months (IQR, 2.2 to 43.8). The PSA-DT was assessable for 187 patients (91.2%).

2. BCR definition using serum PSA values

Nine definitions of BCR based on serum PSA levels ranging from 0.4 ng/mL to the nadir+2.0 ng/mL, were evaluated. Depending on the definition used (Table 2), the number of diagnoses of BCR after SRT ranged from 79 (PSA level > nadir+2.0 ng/mL) to 172 (PSA level > 0.4 ng/mL). The 5-year probability of DM ranged from 27.6% (PSA level > 0.4 ng/mL) to 33.7% (serum PSA level > 2.0 ng/mL). Among the nine definitions, the probability of DM was significantly higher based on the following five definitions compared to the counterparts: serum PSA level > 0.8 ng/mL, a PSA level > 1.2 ng/mL, a PSA level > 2.0 ng/mL, a PSA level > nadir +0.5 ng/mL, and a PSA level > nadir+2.0 ng/mL. The difference in the 5-year probability of DM became significant when BCR was defined as a serum PSA level of 0.8 ng/ml or higher (1.0, 1.2, and 2.0 ng/mL). Survival curves for the probabilities of DM based on two representative definitions (PSA level > 0.8 ng/mL and > 2.0 ng/mL) are depicted in Fig. 2. Harrell's c-index values for DM prediction using these definitions of BCR ranged from 0.526 to 0.589 (Table 2). To define BCR based on serum PSA levels, a level > 0.8 ng/mL was a useful threshold for prediction of DM, with a c-index value of 0.589 (95% confidence interval [CI], 0.525 to 0.654).

3. Definition of BCR using PSA-DT

Five definitions of BCR based on PSA-DTs of 3-24 months were evaluated. Depending on the definition used (Table 3), the number of diagnoses of BCR after SRT ranged from 40 (PSA-DT ≤ 3 months) to 165 (PSA-DT ≤ 24 months); the 5-year probability of DM ranged from 22.7% (PSA-DT ≤ 24 months) to 39.4% (PSA-DT ≤ 3 months). Among the five definitions, the probability of DM was significantly higher for a PSA-DT ≤ 3 months and a PSA-DT ≤ 6 months. Survival curves for the probability of DM based on the two representative definitions based on PSA-DT (≤ 3 months and ≤ 6 months) are depicted in Fig. 3. Harrell's c-index values for prediction of the probability of DM using the PSA-DT ranged from 0.510 to 0.660 (Table 3); a PSA-DT ≤ 6 months had the highest c-index value (0.660 [95% CI, 0.582 to 0.738]).

4. Combined use of the serum PSA level and the PSA-DT to predict DM

Two different DM probability patterns, illustrated in Figs. 2 and 3, were observed. Definition of BCR using serum PSA levels resulted in a relatively linear pattern of increased DM over time (Fig. 2), whereas definition of BCR using the PSA-

Table 2. Various BCR definitions using serum PSA value and its predictability of subsequent DM

BCR definitions by PSA values	No. of patients (%)	5-Year probability of DM (%)	p-value[a]	Harrell's c-index (95% CI)
> 0.4 ng/mL				
Yes	172 (83.9)	27.6	0.118	0.541 (0.489-0.593)
No	33 (16.1)	9.6		
> 0.6 ng/mL				
Yes	149 (72.7)	29.9	0.052	0.565 (0.502-0.629)
No	56 (27.3)	9.4		
> 0.8 ng/mL				
Yes	139 (67.8)	31.7	0.011	0.589 (0.525-0.654)
No	66 (32.2)	8.1		
> 1.0 ng/mL				
Yes	125 (61.0)	30.8	0.056	0.562 (0.487-0.636)
No	80 (39.0)	13.5		
> 1.2 ng/mL				
Yes	116 (56.6)	33.4	0.006	0.588 (0.513-0.663)
No	89 (43.4)	11.9		
> 2.0 ng/mL				
Yes	101 (49.3)	33.7	0.011	0.572 (0.493-0.651)
No	104 (50.7)	14.8		
> Post-SRT nadir+0.5 ng/mL				
Yes	145 (70.7)	30.1	0.022	0.583 (0.520-0.645)
No	60 (29.3)	12.5		
> Post-SRT nadir+1.0 ng/mL				
Yes	110 (53.7)	29.7	0.159	0.526 (0.446-0.605)
No	95 (46.3)	18.5		
> Post-SRT nadir+2.0 ng/mL				
Yes	79 (38.5)	33.4	0.027	0.550 (0.472-0.629)
No	126 (61.5)	19.0		

BCR, biochemical recurrence; CI, confidence interval; DM, distant metastasis; PSA, prostate-specific antigen; SRT, salvage radiotherapy.
[a]Log-rank test.

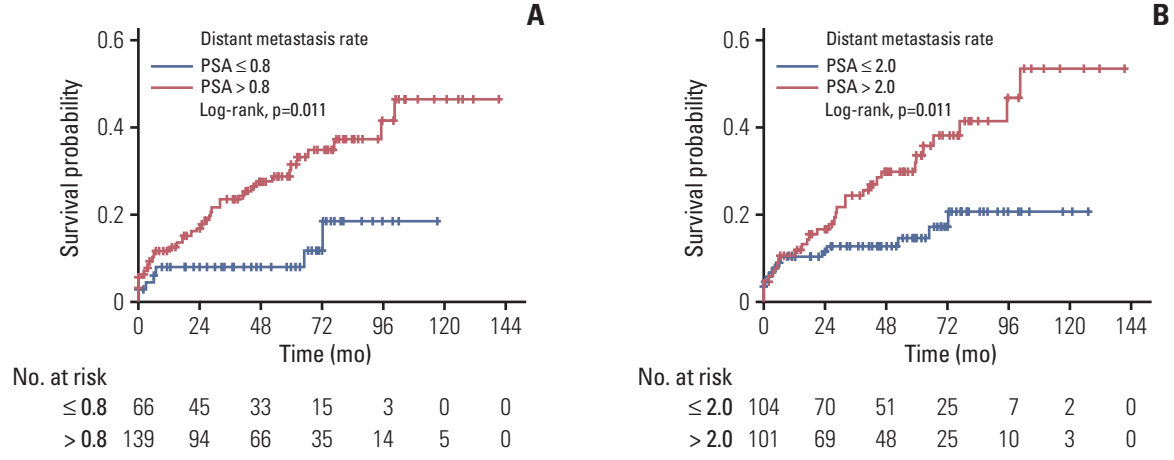

Fig. 2. The survival curves of probability of distant metastasis by biochemical recurrence definitions using serum prostate-specific antigen (PSA) value: (A) serum PSA > 0.8 ng/mL, (B) serum PSA > 2.0 ng/mL.

Table 3. Various BCR definitions using PSA doubling time and its predictability of subsequent DM

BCR definitions by PSA-DT	No. of patients (%)	5-Year probability of DM (%)	p-value[a)]	Harrell's c-index (95% CI)
≤ 3 months				
Yes	40 (21.4)	39.4	0.020	0.607 (0.524-0.689)
No	147 (78.6)	16.7		
≤ 6 months				
Yes	76 (40.6)	33.7	0.001	0.660 (0.582-0.738)
No	111 (59.4)	13.7		
≤ 12 months				
Yes	127 (67.9)	25.3	0.060	0.585 (0.526-0.644)
No	60 (32.1)	16.7		
≤ 18 months				
Yes	155 (82.9)	23.3	0.456	0.523 (0.472-0.574)
No	32 (17.1)	17.4		
≤ 24 months				
Yes	165 (88.2)	22.7	0.692	0.510 (0.467-0.553)
No	22 (11.8)	20.5		

BCR, biochemical recurrence; CI, confidence interval; DM, distant metastasis; PSA, prostate-specific antigen; PSA-DT, PSA doubling time.
[a)]Log-rank test.

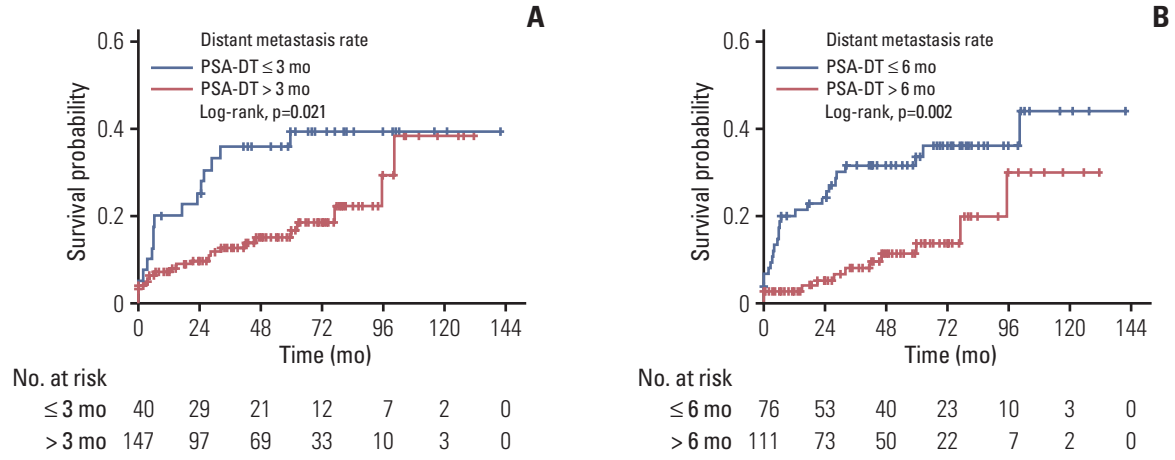

Fig. 3. The survival curves of probability of distant metastasis by biochemical recurrence definitions using prostate-specific antigen doubling time (PSA-DT): (A) PSA-DT ≤ 3 months, (B) PSA-DT ≤ 6 months.

DT yielded a pattern in which DM occurred in a relatively large percentage of patients during the early period (within 1 year after BCR diagnosis) and then plateaued after about 4 years. Definition of BCR using the PSA-DT and PSA levels tended to yield good short-term and long-term prediction of DM, respectively. Thus, these two parameters complemented each other. The 5-year probability of DM was determined based on combination of the absolute PSA level and PSA-DT (Table 4). Four absolute PSA levels (0.8, 1.2, 2.0, and the nadir 0.5 ng/mL) were combined with a PSA-DT ≤ 6 months. For patients meeting both PSA parameters (higher absolute PSA level and shorter PSA-DT), the probability of DM was 39.5%-44.5%. For those meeting one of the two PSA parameters, the probability was 14.3%-22.6%. For patients who did not meet either PSA parameter, the probability was 0.0%-3.1%. Survival curves of the probability of DM obtained with the combination of the two representative definitions, such as PSA > 0.8 ng/mL with a PSA-DT ≤ 6 months and PSA > 2.0 ng/mL with a PSA-DT ≤ 6 months, are presented in Fig. 4. Patients with PSA-DTs ≤ 6 months had a notably greater probability of DM within 1-2 years in both subgroups defined according to PSA values (> 0.8 and ≤ 0.8 ng/mL) (Fig. 4A). In contrast,

Table 4. Probability of DM according to combination of PSA values and PSA-DT

Combination		No. of patients (%)	5-Year probability of DM (%)	p-value[a]
Absolute PSA	PSA-DT (mo)			
> 0.8 ng/mL	≤ 6	54 (28.9)	39.6	0.001
	> 6	74 (39.6)	18.8	
≤ 0.8 ng/mL	≤ 6	22 (11.8)	18.2	
	> 6	37 (19.8)	0.0	
> 1.2 ng/mL	≤ 6	47 (25.2)	43.1	0.001
	> 6	62 (33.3)	21.2	
≤ 1.2 ng/mL	≤ 6	29 (15.5)	17.6	
	> 6	48 (25.8)	2.1	
> 2.0 ng/mL	≤ 6	39 (20.9)	44.5	< 0.001
	> 6	56 (29.9)	22.6	
≤ 2.0 ng/mL	≤ 6	37 (19.8)	22.5	
	> 6	55 (29.4)	1.9	
> Nadir+0.5 ng/mL	≤ 6	61 (32.7)	39.5	0.004
	> 6	79 (42.4)	18.6	
≤ Nadir+0.5 ng/mL	≤ 6	15 (8.0)	14.3	
	> 6	31 (16.6)	3.1	

DM, distant metastasis; PSA, prostate-specific antigen; PSA-DT, PSA doubling time. [a]Log-rank test.

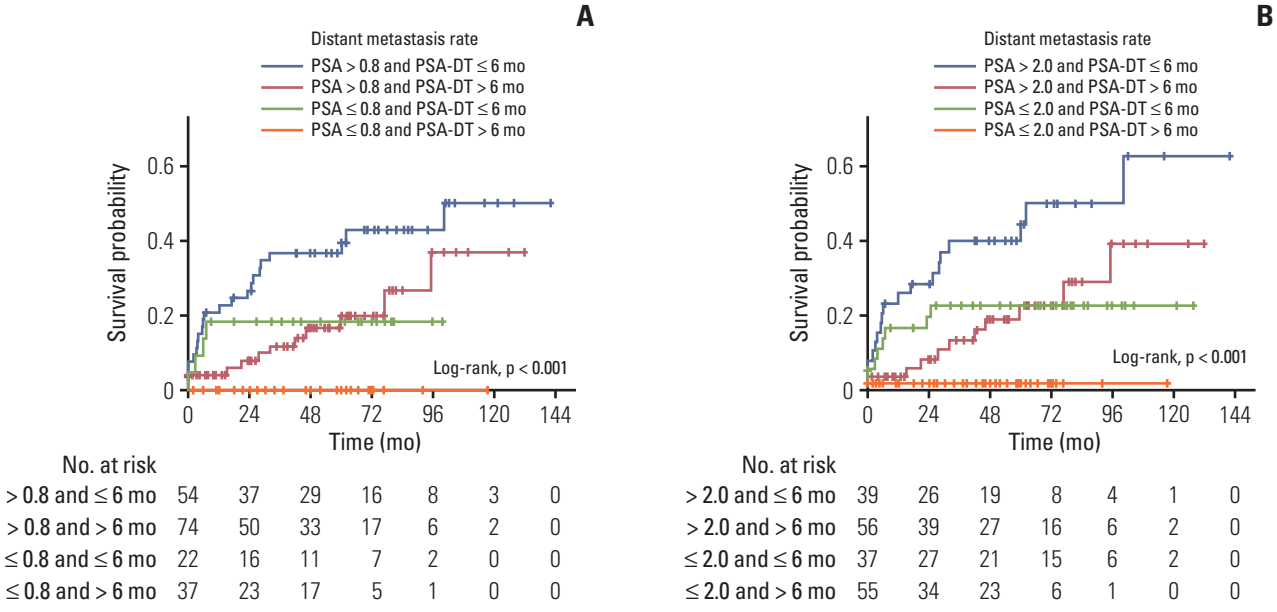

Fig. 4. The survival curves of probability of distant metastasis by biochemical recurrence definitions using combination of prostate-specific antigen (PSA) 0.8 ng/mL and prostate-specific antigen doubling time (PSA-DT) 6 months (A) and PSA 2.0 ng/mL and PSA-DT 6 months (B).

for patients with PSA levels > 0.8 ng/mL, the difference in the probability of DM within 2 years was minimal compared to those with PSA levels ≤ 0.8 ng/mL, but increased gradually after 2 years in both the PSA-DT ≤ 6 months and > 6 months subgroups. As a result, patients who met two PSA parameters had a ≥ 40% 5-year probability of DM according to the combinations assessed. Similar patterns were observed in patients with PSA levels > 2.0 and < 2.0 ng/mL (Fig. 4B).

Discussion

After curative treatment for prostate cancer, proper definition of BCR is essential to enable earlier assessment of treatment failure and timely administration of salvage treatment. Two different definitions of BCR, based on the presence or absence of the prostate after definitive therapy, have been widely accepted. For example, BCR is defined as a postoperative increase in the PSA level ≥ 0.2 ng/mL after RP and as post-RT PSA elevation ≥ nadir+2 ng/mL. We assumed that the purpose of SRT was to sterilize microscopic cancer cells in the prostate bed after RP. Thus, we speculated that a particular PSA level between 0.2 ng/mL and the nadir+2.0 ng/mL would be a reasonable candidate for a definition of BCR after SRT. Various PSA levels, such as a single value of 0.4 ng/mL [7,8] and the nadir+0.3 ng/mL [9], have been used in previous studies of the efficacy of SRT and adopted as definitions of BCR in measurements of BCR-free survival.

For the first, we set the probability of DM as the primary endpoint to assess the predictive ability of various definitions of BCR, based on a report on the International Intermediate Clinical Endpoints in Cancer from the Prostate Working Group [10]. In that report, metastasis-free survival was a strong surrogate for overall survival in patients with localized prostate cancer [10]. Gharzai et al. [11] also demonstrated the surrogacy of metastasis-free survival as an intermediate clinical endpoint for prostate cancer, and reported that improvements in local failure rates alone are less likely to translate into improvements in overall survival, presumably because local recurrence can be indolent or curable by salvage therapy [10]. In previous studies conducted to establish a definition of BCR after RP, the probability of DM was adopted as the primary endpoint [12]. As described in the "Results", locoregional recurrence after SRT was also observed as many as subsequent DM. As seen in S1 Table, there was no significant difference between locoregional recurrence (–) and (+) cases in terms of serum PSA level and PSA-DT, especially showed relatively longer PSA-DT compared to DM. According to the previous study which tested the association between post-prostatectomy PSA-DT and type of recurrence [13], they also demonstrated short PSA-DT of DM and long PSA-DT of locoregional recurrence. Therefore, we'd like to suggest that the definitions of BCR in our study would not be optimal for the prediction of subsequent locoregional recurrence after SRT.

The ability of serum PSA levels ranging from 0.4 ng/mL to the nadir+2.0 ng/mL to predict DM was tested. Among them, a serum PSA level of 0.8 ng/mL was the most useful single PSA value for prediction of DM after SRT. Use of this threshold did not result in an overwhelmingly higher c-index value relative to the use of other values, such as 1.2 and 2.0 ng/mL. However, 0.8 ng/mL was the lowest PSA value that resulted in a significant difference in the probability of DM, and its c-index value was higher than those for 1.2 and 2.0 ng/mL. If a diagnosis of BCR could be made at a lower PSA level (0.8 ng/mL vs. 1.2 or 2.0 ng/mL), re-salvage treatment could be initiated earlier, before further progression. As described, c-index values of PSA 0.8 ng/mL and nadir+0.5 ng/mL were 0.589 (95% CI, 0.525 to 0.654) and 0.583 (95% CI, 0.520 to 0.645), respectively, and we believe that both values are valid to predict DM. However, the interval between SRT and BCR was shorter for the group with PSA > 0.8 ng/mL (mean±standard deviation, 43.89±34.10 months) than the group with nadir+0.5 ng/mL (47.40±35.89 months). In addition, the 5-year probability of DM was high (12.5%), even in patients with PSA levels ≤ nadir+0.5 ng/mL. Therefore, we decided to pick cutoff value of PSA > 0.8 ng/mL predicting DM for a subsequent early intervention in our study.

We also confirmed that the PSA-DT, particularly a PSA-DT ≤ 6 months, is an important measurement for a post-SRT definition of BCR, with the highest c-index value. In a previous study, the rate of PSA increase was notably greater in patients who subsequently developed DM. As suggested by Hanks et al. [14], the mathematical expression of the PSA-DT may be a useful indicator of recurrent prostate cancer tumor biology and the speed of PSA increase. No study has involved assessment of the PSA-DT in cases of post-SRT PSA elevation like ours, but several studies have been conducted to evaluate the prognostic value of the PSA-DT at the time of the first BCR after RP. According to Jackson et al. [15], a PSA-DT < 6 months before receipt of SRT for a postoperative BCR was a significant prognostic factor for metastasis and cancer-specific death. Nevertheless, definition of post-SRT BCR using the PSA-DT alone is limited because the PSA-DT sometimes cannot be calculated and is a weak predictor of long-term events (Fig. 3).

The ability to predict subsequent DM improved with the combined use of the serum PSA level and the PSA-DT. These parameters may complement each other, as the definitions of BCR based on them showed strength in long-term and short-term predictions of DM, respectively (Fig. 4). The 5-year probability of DM was approximately 40% or more for patients meeting two PSA parameters (PSA-DT ≤ 6 months and PSA level > 0.8 ng/mL), and extremely low for patients who did not meet either PSA parameter. Although our results should be interpreted with caution, we suggest that patients with PSA-DTs > 6 months should be observed closely until their PSA level reaches 2.0 ng/mL, at which point the 5-year probability of DM in this study was only 1.9%.

The significance of our study derives from the examination of a large population over a long follow-up period, with well-performed PSA monitoring coupled with clinical

examinations before and after SRT. The limitations of this study are due primarily to the multi-institutional, retrospective nature of the data. We selectively analyzed patients with prostate cancer who had received SRT and had post-SRT PSA elevation. This approach may have introduced unrecognized selection biases. The most challenging aspect of this study was that some patients with BCR are administered re-salvage hormonal therapy before they show further PSA elevation predictive of subsequent DM. For this reason, we assessed the PSA-DT in this retrospective analysis. Even when the last serum PSA level before re-salvage treatment is relatively low, the likelihood of subsequent metastatic progression can be assumed to be high when the PSA-DT is remarkably short. In addition, re-salvage hormone therapy may influence pattern or time sequence of subsequent DM developments. However, designing a prospective study to assess the optimal definition of BCR would be difficult because of the protracted time between BCR and detectable clinical recurrence, the need for a large population because of the relatively low clinical recurrence rate after curative treatment, and ethical issues with the delay of re-salvage treatment until macroscopic clinical recurrence.

In conclusion, various serum PSA levels and the PSA-DT were assessed to propose an optimal definition of BCR for prediction of subsequent DM. Based on our results, a PSA level > 0.8 ng/mL is a reasonable threshold for the definition of post-SRT BCR. In addition, a PSA-DT ≤ 6 months was significantly predictive of subsequent DM, and the combined use of the serum PSA value and the PSA-DT enhanced the predictive ability. To our knowledge, this report is the first to propose an optimal definition of BCR for patients who receive SRT following RP. A more universal definition of BCR is needed for these patients. We believe that use of this optimal definition of BCR can lead to the best management of prostate cancer and ultimately improve the clinical outcomes of these patients.

Electronic Supplementary Material

Supplementary materials are available at Cancer Research and Treatment website (https://www.e-crt.org).

Ethical Statement

The Institutional Review Board of the National Cancer Center approved this protocol (NCC 2018-0116). The protocols of the other participating institutions were approved by their respective institutional review boards. The data were managed by the assignment of hospital-specific case numbers and anonymization. Data analysis was performed centrally at the National Cancer Center of Korea. The requirement for written informed consent was waived due to the retrospective nature of the study.

Author Contributions

Conceived and designed the analysis: Lee SU, Park W, Cho KH.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.

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