Research Article

# The impact of the definition of biochemical recurrence following salvage radiotherapy on outcomes and prognostication in patients with recurrent prostate cancer after radical prostatectomy: a comparative study of three definitions

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## ARTICLE INFO

## ABSTRACT

**Purpose:** The clinical management and follow-up of patients with recurrent prostate cancer after salvage radiotherapy (SRT) has not yet been established, and no standardized definition of biochemical recurrence (BCR) after SRT exists. We compared the impact of applying three different definitions of BCR following SRT on patient outcomes and prognostication.
**Subjects:** Patients who received salvage androgen-deprivation therapy before the completion of SRT were excluded. The data of 118 men who had undergone salvage radiation as monotherapy for BCR after radical prostatectomy were reviewed. In all patients, SRT comprised irradiation to the prostatic bed (70 Gy) using three-dimensional conformal radiotherapy techniques. Treatment outcomes, including BCR-free survival and prognostic factors, were analyzed and compared among three definitions: The Nara, Radiation Therapy Oncology Group (RTOG) 9601, and GETUG-AFU 16 definitions.
**Results:** The BCR rate differed significantly among the applied definitions. Multivariate analyses identified the same four independent prognostic factors, including primary Gleason pattern 4 or 5, negative resection margin, prostate-specific antigen (PSA) level before SRT 0.5 or more, and PSA doubling time before SRT <6 months, using the RTOG 9601 and GETUG-AFU 16 definitions, whereas only two of the four factors were identified using the Nara definition. Although the results obtained using the RTOG 9601 and GETUG-AFU 16 definitions were similar, the prognostic value of the four factors differed. According to the RTOG 9601 definition of BCR, a negative resection margin on prostatectomy specimens and short PSA doubling time before SRT were associated with no subsequent response in PSA level.
**Conclusions:** The applied definition of BCR after SRT can influence the reported BCR-free rate and the potential prognostic factors. Establishment of the standardized definition is needed for the optimal management of patients with recurrent prostate cancer undergoing SRT.
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## 1. Introduction

Radical prostatectomy is often selected as initial therapy for patients with localized prostate cancer. A nationwide observational study by the Japan Prostate Cancer Study Group reported that 32% of patients with newly diagnosed prostate cancer underwent radical prostatectomy as initial treatment [1]. Our data from Nara Uro-Oncological Research Group showed a similar trend, with radical prostatectomy performed in approximately 30% of such patients and in 40% of those with intermediate-risk prostate cancer [2,3]. However, 15—40% of patients experience recurrence. Biochemical recurrence (BCR), which manifests as an elevation of the serum prostate-specific antigen (PSA) level, occurs before clinical and radiographic evidence of cancer is apparent [4,5]. The standard treatment option for BCR after radical prostatectomy is

salvage radiotherapy (SRT) to the surgical prostate bed. Despite this, at least 50% of patients experience further prostate cancer progression, particularly those with aggressive cancers, indicated by a high Gleason score, high pre-SRT PSA concentration, and short PSA doubling time (PSADT) [6–9].

A critical issue in clinical management is to determine whether an elevated PSA level after radical prostatectomy represents isolated local recurrence at the surgical prostate bed and/or remote micrometastases. The former can potentially be eradicated by SRT, especially if the tumor is radiosensitive and has a low burden [9]. Phase III randomized controlled trials (RCTs) demonstrated that radiotherapy and androgen-deprivation therapy (ADT) in combination improved survival in patients with treatment-naïve localized prostate cancer [10–12]. Therefore, this combination seems a reasonable approach to prolonging progression-free and overall survival in patients experiencing BCR after radical prostatectomy. Two RCTs evaluating the potential benefit of this combination were recently published, one by Shipley et al [the Radiation Therapy Oncology Group (RTOG) 9601] [13] and one by Carrie et al (GETUG-AFU 16) [14]. When combined with SRT, both 24 months of bicalutamide (150 mg daily) and 6 months of ADT using goserelin resulted in better clinical outcomes, including second BCR-free survival, compared with SRT alone. However, in a substantial proportion of patients, it might be possible to eradicate recurrent disease using SRT alone, without additional ADT.

Although BCR-free survival has become a surrogate marker of treatment efficacy, the definition of BCR following local or systemic therapy is controversial [15]. Given the variety of definitions of BCR following SRT, variability exists in reported prognostic factors [6–9,13,14]. Moreover, the definition of treatment failure is vital in the process of developing treatment strategies. In a study published in 2014, we proposed a salvage treatment strategy based on BCR-free survival and clinicopathologic features that stratified patients into three risk groups according to Gleason score, resection margin, and PSA velocity (PSAV) [9]. The definition we used for BCR after SRT corresponded to the definition for BCR after radical prostatectomy; this was named the "Nara definition" for convenience.

In the present study, we compared outcomes using three different definitions of BCR: The Nara definition [9], RTOG definition [13], and GETUG definition [14]. We assessed BCR-free survival and identified prognostic factors to determine which subgroup derived the greatest benefit from SRT, which needed SRT and ADT in combination, and which was not expected to benefit from SRT. To our knowledge, this is the first study addressing the impact of various definitions of BCR on treatment outcomes using a single cohort of patients who underwent SRT.

## 2. Subjects

### 2.1. Ethical considerations

The Ethics Committee of Nara Medical University approved the study protocol (reference ID: 1256). The study was conducted in compliance with the protocol and in accordance with the provisions of the Declaration of Helsinki (2013). All participants provided informed consent.

### 2.2. Patients and data collection

Between November 2006 and June 2015, a total of 155 consecutive patients underwent SRT for the treatment of BCR after radical prostatectomy at Nara Medical University Hospital. Of these, 35 patients were excluded because salvage ADT (luteinizing hormone–releasing hormone agonist and/or antiandrogen) was initiated before the completion of SRT, and two were excluded because of insufficient follow-up data. Thus, 118 (76.1%) patients, who completed SRT monotherapy as initial treatment, were eligible for the analysis (Supplementary Fig. S1). Their medical records were reviewed for relevant clinicopathologic information.

All hematoxylin and eosin-stained specimens obtained via prostate biopsy and radical prostatectomy were reviewed by two experienced uropathologists (T.F. and N.K.) to determine T-stage (2010 AJCC Cancer Staging system, 7th edition) and Gleason score and to assess the surgical resection margin. No patients had findings suggestive of distant metastases. PSA kinetics, including PSADT and PSAV, were calculated between the postprostatectomy PSA nadir value and the value at initiation of SRT using at least two PSA measurements with a 3-month interval.

### 2.3. SRT to the surgical prostatic bed

SRT was administered as previously described [9]. Briefly, 70 Gy was delivered in daily fractions of 2.0 Gy using three-dimensional conformal radiotherapy techniques with the treatment fields encompassing the prostatic and seminal vesicle bed plus periprostatic tissues.

### 2.4. Post-SRT follow-up and definition of second BCR

After SRT was completed, patients were followed up with PSA measurements every 3 months for 1 year, every 6 months for the next 4 years, and every 12 months thereafter. The primary endpoint of this study was BCR-free survival after SRT (second BCR-free survival). Fig. 1A shows the ideal PSA outcome, considered indicative of successful SRT.

Using the Nara definition—based on the thought that SRT should be the second curative option after radical prostatectomy [9,16]—two patterns of second BCR emerged: Nara–BCR pattern 1 represents a decline in PSA concentration to < 0.2 ng/mL after SRT, followed by a rise to ≥ 0.2 ng/mL at two consecutive points, one of which is the last measurement (Fig. 1B, left). Nara–BCR pattern 2 represents a rise in PSA level without a decline to PSA <0.2 ng/mL after SRT (Fig. 1B, right). Using the RTOG definition [13], second BCR was classified into three patterns according to the decrease in PSA level after completing SRT (Fig. 1C). Using the GETUG definition [14], second BCR was defined as an increase in PSA level above the nadir of 0.5 ng/mL (Fig. 1D).

### 2.5. Statistical analysis

The Mann–Whitney U, Chi-square, and Fisher's exact tests were used to analyze clinicopathologic variables, as appropriate. Survival curves were plotted using the Kaplan–Meier method, and the log-rank test was applied for between-group comparisons. We used multivariate Cox proportional hazards regression models to identify independent prognostic factors, expressed as hazard ratios (HRs) and 95% confidence intervals. Variables with a $P < 0.1$ in the univariate analysis were considered for inclusion in the multivariate models. Statistical significance was set at $P < 0.05$, and all reported $P$ values were two-sided. IBM SPSS, version 21, (SPSS Inc., Chicago, IL, USA) and PRISM software, version 7.00, (GraphPad Software, Inc., San Diego, CA, USA) were used to perform the statistical analyses and data plotting, respectively.

## 3. Results

### 3.1. Overview of the enrolled patients

The characteristics of the 118 patients are listed in Table 1. The median follow-up period after completion of SRT was 49.2 months
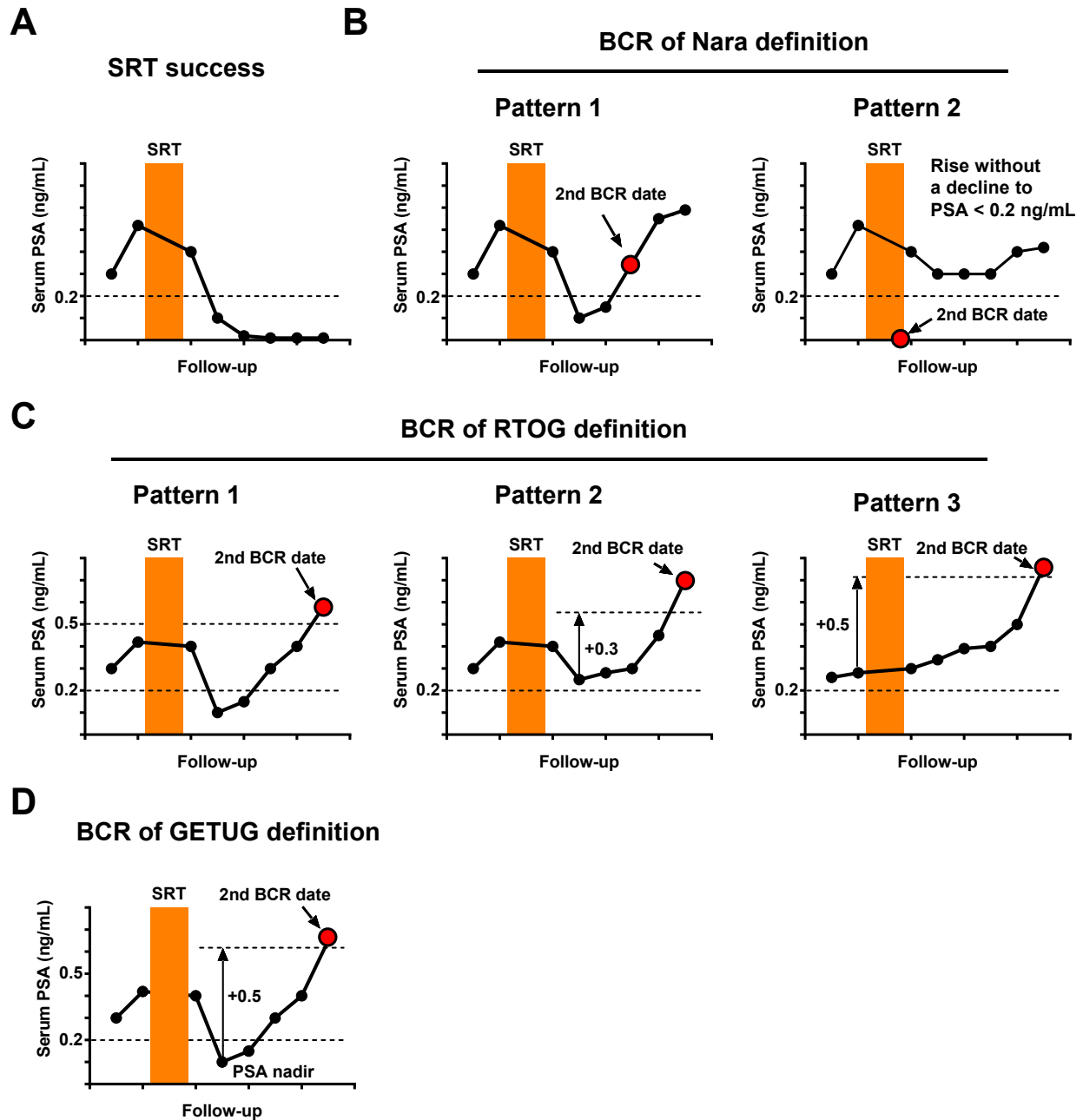
**A**

**SRT success**



**B**

**BCR of Nara definition**

**Pattern 1**

**Pattern 2**



**C**

**BCR of RTOG definition**

**Pattern 1**

**Pattern 2**

**Pattern 3**



**D**

**BCR of GETUG definition**



**Fig. 1. Changes in serum PSA levels after undergoing salvage radiotherapy**. (A) Successful SRT was defined as a sustained decline in PSA level to <0.2 ng/mL. (B, left) Using the Nara definition of BCR, Nara-BCR pattern 1 was defined as a decrease in PSA level to <0.2 ng/mL followed by a rise at two consecutive points with the last PSA level being ≥0.2 ng/mL. (B, right) Nara-BCR pattern 2 was defined as a PSA level that did not decrease to <0.2 ng/mL. Using the RTOG definition, second BCR was defined as the first occurrence of one of the following events: (C, left) if the PSA level decreased to <0.2 ng/mL, second BCR was defined as an increase in PSA level after protocol treatment to ≥0.5 ng/mL; (C, middle) if the PSA level decreased but remained ≥ 0.2 ng/mL, second BCR was defined as an increase in PSA level after protocol treatment of ≥0.3 ng/mL above the lowest detectable level; and (C, right) if the PSA level did not decrease, second BCR was defined as an increase in PSA level after protocol treatment of ≥0.5 ng/mL above the PSA level at entry. (D) Using the GETUG definition, second BCR was defined as an increase in PSA level above the nadir of 0.5 ng/mL, confirmed by a second PSA measurement.
BCR, biochemical recurrence; PSA, prostate-specific antigen; RTOG, Radiation Therapy Oncology Group; SRT, salvage radiotherapy.

(interquartile range = 30.5−64.4). During follow-up, 51 patients were treated with salvage ADT. The median salvage ADT-free survival was 55.3 months (Supplementary Fig. S2A). Five patients progressed to metastatic disease, three died of prostate cancer, and one died of heart disease. Five-year metastasis-free, cancer-specific, and overall survival rates were all >95% (Supplementary Fig. S2B−D). Adverse events of grade 3 and above (Common Terminology Criteria for Adverse Events, version 4.0) were observed in three (2.5%) patients during follow-up after SRT: two had grade 3 hematuria and one had a grade 3 rectal hemorrhage.

*3.2. Prognostication using three different definitions for second BCR after SRT*

Using the Nara, RTOG, and GETUG definitions, 62 (52.5%), 53 (44.9%), and 46 (40.0%) patients, respectively, had second BCR

**Table 1**
Characteristics of 118 patients undergoing SRT after radical prostatectomy.

| Variables | Total ($n = 118$) | % |
|---|---|---|
| Median age at SRT (IQR) | 71 (66−74) | — |
| Initial PSA (mean, SD) | 13.4 ± 15.6 | — |
| Clinical T stage | | |
| cT1c | 44 | 37.3 |
| cT2a-c | 54 | 45.8 |
| cT3a-b | 20 | 16.9 |
| Pathological T stage | | |
| pT2a-c | 67 | 56.8 |
| pT3a-b | 51 | 43.2 |
| Gleason sum | | |
| 6 | 16 | 13.6 |
| 7 | 68 | 57.6 |
| (3 + 4/4 + 3) | (36/32) | (30.5/27.1) |
| 8 | 16 | 13.6 |
| 9 | 18 | 15.3 |
| Primary Gleason pattern | | |
| 3 | 54 | 45.8 |
| 4 | 59 | 50.0 |
| 5 | 5 | 4.2 |
| Resection margin | | |
| Negative | 57 | 48.3 |
| Positive | 61 | 51.7 |
| Time to PSA nadir after prostatectomy, months (IQR) | 2.4 (1.6−4.0) | — |
| PSA nadir after prostatectomy, ng/mL (IQR) | 0.053 (0.014−0.15) | — |
| Pre-SRT PSA, ng/mL (IQR) | 0.37 (0.26−0.68) | — |
| PSADT after PSA recurrence, months (IQR) | 5.6 (3.1−10.8) | — |
| PSAV after PSA recurrence, ng/mL/year (IQR) | 0.41 (0.21−0.92) | — |
| Follow-up period after SRT, months (IQR) | 49.2 (30.5−64.4) | — |

IQR, interquartile range; PSA, prostate-specific antigen; PSADT, PSA doubling time; PSAV, PSA velocity; SD, standard deviation; SRT, salvage radiotherapy.

after SRT ($P = 0.11$). Of 62 patients having second BCR in the Nara definition, nine patients (15%) did not have second BCR in the RTOG definition and 16 (26%) did not have second BCR in the GETUG definition. Fig. 2A shows the calculated BCR-free survival rates 2- and 5-years after SRT. Although the Nara definition was the strictest, similar outcomes were observed using the RTOG and GETUG definitions. Univariate survival analysis demonstrated that second BCR was significantly associated with higher Gleason score, primary Gleason pattern ≥4, pre-SRT PSA ≥0.5 ng/mL, PSADT <6 months, PSA velocity >0.4 ng/mL/year, and a negative resection margin (Fig. 2B−E and Supplementary Tables S1−3). The cut-off value of pre-SRT PSA (0.5 ng/mL) and PSADT (6 months) were based on the previous articles [6,8,9]. The optimal cut-off of PSAV was set as 0.4 ng/mL by testing all the data points yielding the highest *P* value in each intergroup comparison [9]. There was no significant association between clinical outcome and clinical T-stage, pathologic T-stage, and PSA nadir after radical prostatectomy. These results were similar across all three definitions.

The results of univariate and multivariate analyses using the Nara, RTOG, and GETUG definitions are shown in supplementary Tables S1−3, respectively. Spearman's correlation analysis showed a strong correlation between PSADT and PSAV ($P < 0.0001$; correlation coefficient $\rho = -0.71$, 95% confidence interval $= -0.78$ to $-0.60$). PSADT was a better predictor than PSAV according to the univariate analysis (higher HR and lower *P* value); hence, PSADT was selected for inclusion in the multivariate analysis. The same four independent prognostic factors were identified by both the RTOG and GETUG definitions, whereas the Nara definition identified only two (primary Gleason score and pre-SRT PSA) factors (Table 2). Although the results were similar using the RTOG and GETUG definitions, the HRs and *P* values of the four factors differed.

### 3.3. Predictive factors for non-response to SRT using the RTOG definition

In the RTOG 9601 RCT [13], three BCR patterns were set out to define second BCR after SRT (Fig. 1C). It is supposed that patients with BCR pattern 3 did not benefit from SRT; they demonstrated nonresponse to SRT. To avoid unnecessary SRT, we need to determine which variables distinguish patients who are likely to present RTOG BCR pattern 3. The patients' clinicopathologic characteristics were compared by BCR pattern (Supplementary Table S4). Although no variable was statistically significant, age at SRT, resection margin, and PSADT approached significance ($0.5 \leq P < 1.0$). These three variables were highlighted and additional statistical tests were performed. While patients with RTOG BCR pattern 2 were older than those in the other groups, no age difference between patterns 1 and 3 was seen (Fig. 3A). The PSADT was shorter in the BCR pattern 3 group than in the other groups (Fig. 3B). Moreover, 92% of patients with BCR pattern 3 had a negative resection margin on radical prostatectomy, whereas <50% of patients with the BCR patterns 1 or 2 had a negative resection margin (Fig. 3C). In our cohort, of the six patients with negative resection margin and PSADT <2 months, four (75%) demonstrated RTOG BCR pattern 3. A negative resection margin and short PSADT could distinguish nonresponders to SRT.

## 4. Discussion

The main finding of this study is that the definition of second BCR after SRT significantly influences reported treatment failure rates following SRT for recurrent prostate cancer after radical prostatectomy. Serum PSA level has become an accepted tool for detecting prostate cancer relapse, but the definition of BCR after SRT has not yet been standardized. Following radical prostatectomy, the PSA level reaches a nadir of <0.2 ng/mL by 6 months postsurgery. BCR after radical prostatectomy is defined as two consecutive PSA values that are >0.2 ng/mL and rising [16]. When SRT is used as the second radical treatment approach after radical prostatectomy has failed, the definition of BCR after SRT should be similar to that for BCR after radical prostatectomy. Based on that thought, we applied the Nara definition to diagnose BCR or treatment failure after SRT [9,16]. Of the three definitions assessed, the Nara definition was the strictest as it included the following definition of treatment failure: A PSA level increase without a prerequisite decline to <0.2 ng/mL; when this condition was fulfilled, the second BCR date was the date that SRT was completed (Fig. 1B). Using the Nara definition, the BCR-free rate was much lower than the rates obtained using the other two definitions (Fig. 2A). In a review of studies on the outcomes of SRT following radical prostatectomy, Sia et al reported a biochemical control rate ranging from 20% to 60% [17]. However, the radiotherapy doses used in the included studies were inconsistent, and the definitions of BCR after SRT were not uniform.

The Nara definition did not detect resection margin and PSADT as the risk factor of second BCR in this study, whereas other two definitions detected. The Nara definition was drastically different from definitions applied in other two studies in terms of cut-off of the PSA levels and second BCR date (Fig. 1), which probably made the discrepancy. As different studies used different definitions, the standardized definition for the second BCR is needed for establishment of optimal management of the patients.

Both the RTOG 9601 and GETUG-AFU-16 RCTs demonstrated a clinical benefit of adding ADT to SRT. However, it is uncertain whether the addition of ADT just attributed to delay of relapse after SRT or better radical cure rate of recurrent disease. Accumulating evidence will clarify the mechanism by which the addition of ADT
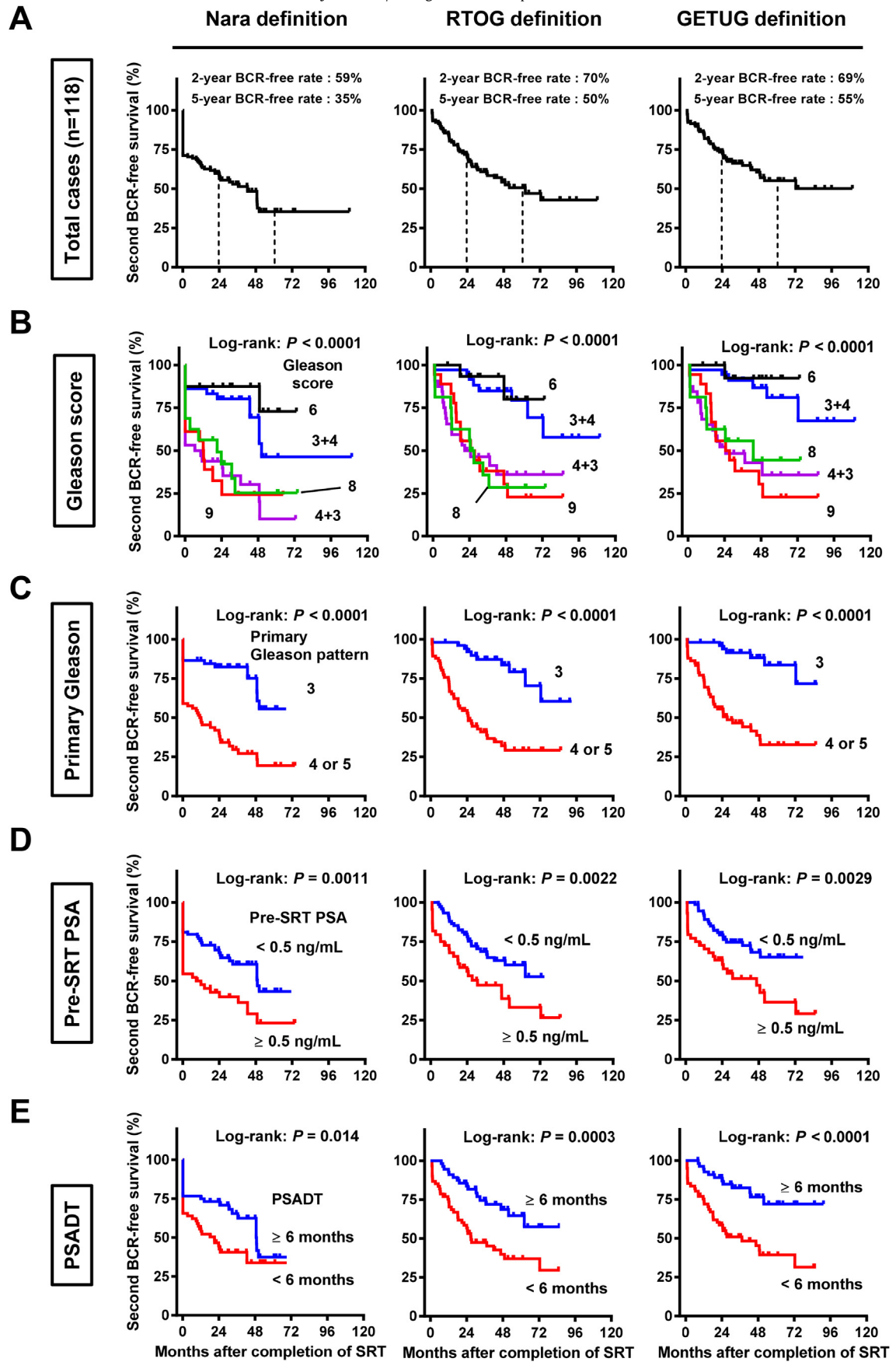
Fig. 2. **Second biochemical recurrence-free survival curves after salvage radiotherapy, stratified by three definitions of biochemical recurrence**. Kaplan–Meier analysis estimates of BCR in all patients (A) and of second BCR-free survival stratified by prostatectomy Gleason score (B), primary Gleason pattern (C), pre-SRT PSA (D), and PSA doubling time (E).

BCR, biochemical recurrence; PSA, prostate-specific antigen; PSADT, PSA doubling time; RTOG, Radiation Therapy Oncology Group; SRT, salvage radiotherapy.

**Table 2**
Multivariate Cox regression analyses of independent risk factors for second BCR by three definitions.

| Variables | Nara definition | | | RTOG definition | | | GETUG definition | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P | HR | 95% CI | P |
| Primary Gleason pattern | | | | | | | | | |
| 3 | Ref | | | Ref | | | Ref | | |
| 4 or 5 | 3.42 | 1.90—6.19 | <0.001 | 4.81 | 2.43—9.55 | <0.001 | 6.63 | 2.91—15.2 | <0.001 |
| Resection margin | | | | | | | | | |
| Positive | Ref | | | Ref | | | Ref | | |
| Negative | 1.47 | 0.86—2.51 | 0.16 | 1.79 | 1.02—3.16 | 0.044 | 2.09 | 1.13—3.86 | 0.018 |
| Pre-SRT PSA (ng/mL) | | | | | | | | | |
| < 0.5 | Ref | | | Ref | | | Ref | | |
| ≥ 0.5 | 1.87 | 1.11—3.14 | 0.018 | 2.47 | 1.42—4.31 | 0.0014 | 2.6 | 1.44—4.69 | 0.0015 |
| PSADT (months) | | | | | | | | | |
| ≥ 6 months | Ref | | | Ref | | | Ref | | |
| < 6 months | 1.53 | 0.89—2.63 | 0.13 | 2.68 | 1.45—4.50 | 0.0016 | 3.48 | 1.73—6.98 | <0.001 |

BCR, biochemical recurrence; CI, confidence interval; HR, hazard ratio; PSA, prostate-specific antigen; PSADT, PSA doubling time RTOG, Radiation Therapy Oncology Group; SRT, salvage radiotherapy.
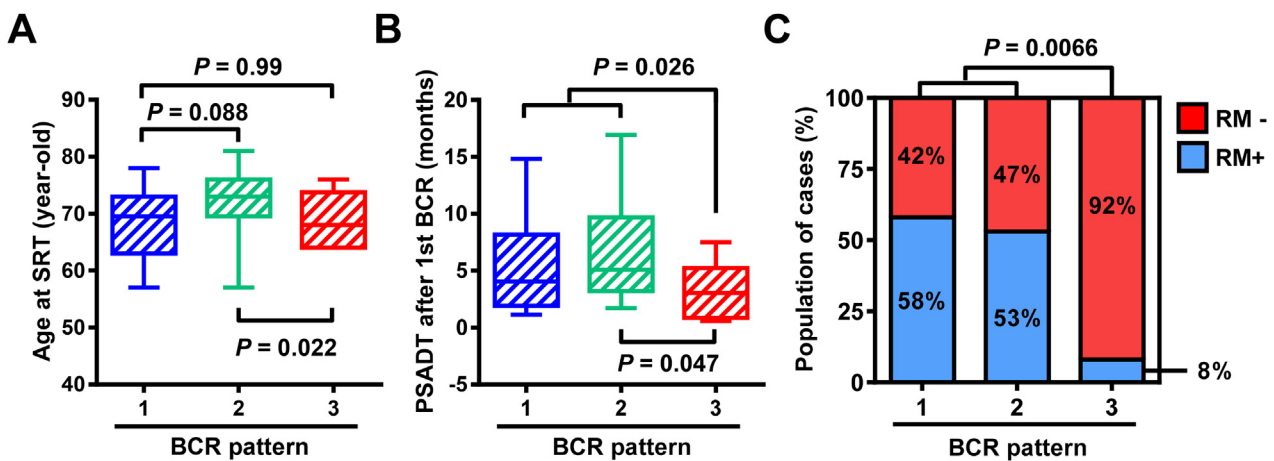


**Fig. 3. Clinicopathologic differences among patients with three patterns of BCR based on the RTOG definition (*n* = 53).** Age at SRT (A) and PSADT (B) are depicted by Tukey box plots. Horizontal lines within boxes indicate median levels. In the analysis of resection margin (C), blue and red bars indicate proportion of patients with positive and negative resection margins, respectively.
BCR, biochemical recurrence; SRT, salvage radiotherapy; PSADT, prostate-specific antigen doubling time.
Mann—Whitney U test (A, B) or Fisher's exact test (C) were used.

exerts a clinically beneficial effect. In the RTOG 9601 RCT, the addition of 24 months of bicalutamide resulted in significantly longer overall survival and cancer-specific survival [13]. Although these are major endpoints in an oncologic clinical trial, a secondary goal is to establish accurate risk stratification that will enable clinicians to select the most appropriate patients for SRT monotherapy, SRT—ADT combination therapy, or ADT monotherapy. The latter two options should not be selected in patients expected to be cured using SRT monotherapy, because ADT often causes deleterious effects on a patient's quality of life, increases the risk of serious health concerns, and causes psychological distress [18,19]. Unfortunately, the topic of salvage ADT-free survival after SRT failure has not been addressed in previous publications. In this study, we focused not only on second BCR-free survival but also on salvage ADT-free survival after SRT, as in the clinical setting, a close relationship exists between second BCR and induction of salvage ADT.

The definition of treatment failure after radiotherapy is generally complicated because measurement of serum PSA does not fully reflect whether all functioning prostate cells have been ablated. Previous articles have demonstrated that definitions of BCR significantly affect the interpretation of treatment failure following primary radiotherapy for primary localized prostate cancer

[15,20—22]. The American Society for Therapeutic Radiology and Oncology (ASTRO) consensus conference held in 1996 recommended three consecutive rises in PSA level determined at unspecified intervals of 3—6 months after the PSA nadir [23]. However, subsequent studies pointed out a number of fundamental methodologic limitations of this definition [15,24].

The RTOG-ASTRO Phoenix Consensus Conference in 2005 concluded that a rise in PSA value of >2.0 ng/mL from the PSA nadir represents the best definition of treatment failure following external beam radiotherapy [25]. Nielsen et al summarized the performance characteristics and BCR-free survival rates according to different definitions of BCR in patients treated with external beam radiotherapy monotherapy [15]. The sensitivity and specificity values, respectively, to predict subsequent clinical failure were 61% and 80% using the ASTRO definition, 74% and 82% using the Phoenix definition, and 91% and 9% using the definition for radical prostatectomy (PSA > 0.2 ng/mL). Based on that exploration, the Phoenix definition has become the current standard definition of BCR after radiotherapy as the primary treatment. Unlike the long and considerable effort made to find the best definition of BCR after primary radiotherapy, clinical management and follow-up strategies for recurrent prostate cancer after SRT have neither been debated nor refined.

There are several limitations to the current study, including its retrospective study design. There was no ability to comment on clinically meaningful events such as cancer-specific mortality and overall mortality because of limited follow-up duration. Moreover, we acknowledge that the relatively small number of patients ($n = 118$) may have led to selection bias. However, our cohort comprised patients treated with a uniform radiation dose (70 Gy/35fr) and treatment modality (three-dimensional conformal radiotherapy) at a single-center, reducing treatment bias. Validation of these results by prospective multicenter studies is needed.

In conclusion, the applied definition of BCR after SRT can dramatically influence the reported BCR-free rate and the potential prognostic factors used in deciding on the most appropriate treatment. To our knowledge, this is the first study evaluating different definitions of BCR in patients who underwent SRT after radical prostatectomy. The findings highlight the importance of finding a more universal definition of BCR after SRT that can be used across multiple disciplines. We believe that our findings will raise a number of questions regarding patient selection for SRT monotherapy, SRT–ADT combination therapy, and ADT monotherapy and will stimulate further research where a current gap exists.

## Conflicts of interest

The authors declare that they have no potential conflicts of interest.

## Funding source

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.prnil.2018.04.005.

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