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Research Article

# Predictive factors for disease progression after salvage radiation therapy in biochemical recurrent patients treated by radical prostatectomy

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ABSTRACT

**Objective:** Salvage radiation therapy (SRT) is standard treatment for patients after radical prostatectomy (RP). However, the optimal timing of SRT remains to be elucidated.
**Material and methods:** We retrospectively reviewed 133 prostate cancer (PCa) patients who underwent SRT for biochemical recurrence after RP. Disease progression was defined as repeated prostate-specific antigen (PSA) level more than 0.2 ng/mL, greater than the post-SRT nadir or radiographic progression. A receiver operating characteristic curve analysis was used to identify the optimal pre-SRT PSA level for predicting progression after SRT. Cox regression analyses were performed to elucidate the association between clinicopathologic characteristics and disease progression.
**Results:** Fifty-one PCa patients (38.4%) experienced disease progression after SRT. The optimal cutoff value of the pre-SRT PSA for predicting disease progression was 0.44 ng/mL. In multivariable analysis, pre-SRT PSA >0.44 ng/mL was a significant independent predictor of post-SRT disease progression [hazard ratio (HR): 2.02, $P = 0.02$]. Although the pre-SRT PSA >0.44 ng/mL did not maintain its independent association with disease progression in the multivariable analysis of patients with adverse pathology (HR: 1.63, $P = 0.22$), PSA within 4 weeks after RP as a continuous variable was significantly associated with disease progression (HR: 1.19, $P = 0.04$)
**Conclusions:** Our results highlight that in PCa patients who undergo RP, SRT should be performed before their PSA reaches 0.44 ng/mL. In patients with adverse pathology disease, a high PSA level within the 4 weeks after RP might identify those who are likely to have disease progression, and these patients might require systemic therapy.


## 1. Introduction

Although patients with nonmetastatic prostate cancer (PCa) commonly undergo radical prostatectomy (RP) with a curative intent, approximately 40% still experience biochemical recurrence (BCR), with a significant proportion experiencing clinical disease progression within a decade from diagnosis.[1–3] Salvage radiation therapy (SRT) is a standard treatment in clinical practice for PCa patients who develop BCR after RP based on the concept of avoiding overtreatment and treatment-related adverse effects.[4] Three phase 3 trials have revealed that SRT is not inferior to adjuvant radiation therapy in oncological outcomes[5–7]. Additionally, a recent meta-analysis comprising 33 studies has also reported that the outcomes of SRT were not inferior to adjuvant radiation therapy for the majority of PCa patients after RP.[8] Based on recent retrospective studies, current guidelines suggest SRT should be performed before patients have prostate-specific antigen (PSA) >0.5 ng/mL.[9,10] However, due to the lack of randomized controlled or prospective data, the optimal timing of SRT remains to be elucidated.

Stephenson et al.[11] reported in their retrospective cohort study that only half of patients with recurrent PCa after RP have a long-

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term PSA response to SRT. Further, half of those patients developed disease progression, which might lead to mortality. Therefore, it is clinically essential to identify patients who are more likely to experience disease progression after RP, which would allow increased follow-up and improve counseling and decision-making regarding additional treatment, such as systemic hormonal therapy or chemotherapy. PSA testing after RP is routinely used for the early detection of recurrence. Ideally, PSA should decrease to an undetectable level within 4 weeks.[12] PSA persistence after RP has been reported as a prognosticator for worse oncologic and survival outcomes.[13]

In this retrospective study, we investigated the optimal cutoff value of the pre-SRT PSA for predicting post-SRT disease recurrence to determine the optimal timing of SRT in patients with BCR after RP. Furthermore, we elucidated the association between clinicopathologic characteristics, such as the PSA level within 4 weeks after RP and disease progression.

## 2. Material and Methods

### 2.1. Patients

After we obtained the approvals of institutional ethics committees in each center, we identified 133 consecutive patients who received SRT for the treatment of BCR after RP for nonmetastatic PCa between December 2004 and October 2015 at the Jikei University Hospital (Tokyo, Japan) and the Kameda Medical Center (Chiba, Japan). Pelvic lymph nodes were dissected in 33 (24.8%) patients at the discretion of the treating physician based on biopsy results and imaging findings. Patients diagnosed with pathologically node positive at the time of RP with pelvic lymph node dissection were included. Patients who had distant metastases were excluded. All RP specimens were evaluated according to the standard pathological procedure and assigned stage and grade based on the 8th edition of the American Joint Committee on Cancer TNM staging system and the International Society of Urological Pathology, respectively. Adverse pathology was defined as $\geq$ pT3, positive surgical margins, and/or nodal involvement at RP. PSA immediately after RP was defined as the first PSA measurement within 4 weeks after RP. BCR after RP was defined as more than two consecutive increases in PSA by $\geq$0.2 ng/mL following RP. The selection of secondary treatments, including SRT, androgen deprivation therapy (ADT), and surveillance, was dependent on the discussion between the patients and their physicians. ADT includes a gonadotropin releasing hormone agonist, alone, either leuprorelin acetate (3.75 mg, 11.25 mg, or 22.5 mg) or goserelin acetate (10.8 mg), and in some cases, combined with 80 mg/day bicalutamide. The schedule and duration of ADT were decided by the treating physicians.

### 2.2. Treatments

All patients underwent laparoscopic or open RP. The technique for SRT was three-dimensional conformal radiation therapy or intensity-modulated radiotherapy. Until 2007, SRT was administered to the whole pelvis. In the beginning of 2008, most patients received SRT to the prostate bed and two received SRT to the whole pelvis. The SRT dose was dependent on radiation oncologists, although most patients received >65 Gy. All SRT regimens were administered in 1.8-2.0-Gy daily fractions. Computed tomography was used for pre-radiation studies.

### 2.3. Statistical analysis

The optimal pre-SRT PSA for predicting disease progression was determined through a receiver operating characteristic curve analysis using Youden's index (maximum [sensitivity + specificity − 1]).[14] Chi-square test and Mann–Whitney U tests were performed to compare categorical and continuous variables between groups (pre-SRT PSA $\leq$0.44 ng/mL and PSA >0.44 ng/mL). Disease progression was defined as repeated PSA levels more than 0.2 ng/mL,t greater than the post-SRT nadir and/or radiographic progression.[9,15] Kaplan-Meier curves were used to estimate the correlation of PSA with disease progression-free survival. The log-rank test was used to determine the statistical difference between groups. Univariate and multivariate analyses were performed to identify significant predictors of disease progression after SRT using Cox proportional hazard models. As a sub-analysis, we selected patients with adverse pathology ($\geq$pT3, positive surgical margins, and/or positive nodal involvement at RP) and evaluated the optimal timing

**Table 1**
The association of the pre-SRT PSA with clinicopathological characteristics in 133 patients treated with SRT after prostatectomy

| Variables | Total | Pre-SRT PSA (ng/ml) | | *p*-value |
|---|---|---|---|---|
| | | PSA$\leq$0.44 | PSA>0.44 | |
| Number of patients | 133 | 78 (59) | 55 (41) | |
| Age, years, median (IQR) | 63 (58-67) | 63 (59-67) | 63 (58-70) | 0.95 |
| iPSA (ng/ml), median (IQR) | 9.5 (6.6-15.9) | 8.4 (6.0-13.8) | 9.9 (7.4-18.8) | 0.04 |
| D'Amico risk stratification (n, %) | | | | |
| Low | 18 (13.5) | 14 (77.8) | 4 (22.2) | <0.01 |
| Intermediate | 51 (38.4) | 37 (72.6) | 14 (27.4) | |
| High | 64 (48.1) | 27 (42.2) | 37 (57.8) | |
| Gleason sum at RP (n, %) | | | | |
| 6 | 9 (6.8) | 7 (77.8) | 2 (22.2) | 0.10 |
| 7 | 76 (57.1) | 48 (63.2) | 28 (36.8) | |
| 8-10 | 48 (36.0) | 23 (47.9) | 25 (52.1) | |
| With Tertiary 5 | 23 (17.3) | 17 (21.8) | 6 (10.9) | 0.10 |
| Extracapsular extension (n, %) | 66 (50.0) | 36 (46.8) | 30 (54.5) | 0.38 |
| Seminal vesicle invasion (n, %) | 21 (15.8) | 13 (16.7) | 8 (14.5) | 0.74 |
| Positive surgical margin (n, %) | 66 (50) | 38 (49.4) | 28 (50.9) | 0.86 |
| Lymph node status (n, %) | 11 (8.3) | 2 (2.6) | 9 (16.4) | <0.01 |
| PSA immediately after RP, median (IQR) | 0.05 (0.01-0.27) | 0.04 (0.01-0.13) | 0.13 (0.01-1.55) | <0.01 |
| Total SRT (Gy), median (IQR) | 68 (64.8-70) | 68 (66-70) | 66 (64-68.6) | <0.01 |
| Previous hormonal therapy (n, %) | 40 (30.1) | 13 (16.7) | 27 (49.1) | <0.01 |

The PSA immediately after RP was defined as the first PSA measurement within 4 weeks after RP.
iPSA: initial prostate-specific antigen, IQR: interquartile range, PSA: prostate-specific antigen, RP: radical prostatectomy, SRT: salvage radiation therapy.

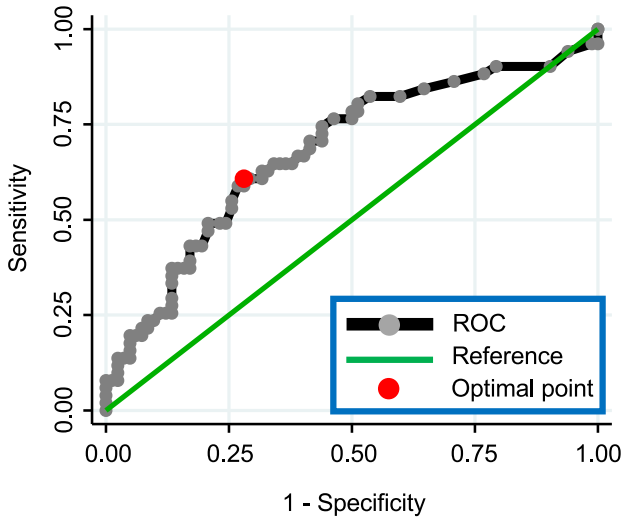


**Figure 1.** The receiver operating characteristic (ROC) curve of the pre-SRT PSA and disease progression. The red point is the optimal cut-off point with the highest Youden index (Youden index J = 0.327, sensitivity = 61%, specificity = 72%). The area under the curve was 0.68. PSA: prostate-specific antigen, SRT: salvage radiation therapy.

of SRT in these patients. Factors with *P* values lower than 0.05, in the univariate analysis, were considered candidates for the multivariate analysis. Statistical analyses were performed using STATA 11.0 (Stata Corp, College Station, TX, USA) and R 3.4.1 (The R Foundation, Vienna, Austria). All tests were two-sided, and $P < 0.05$ was considered statistically significant.

## 3. Results

Patient characteristics are summarized in Table 1. Laparoscopic RP and open RP were performed in 76 (57%) and 57 (43%) patients, respectively. The median follow-up after RP was 101 (interquartile range 67-129) months. Ten patients (7.5%) received neoadjuvant ADT, and 40 (30%) received ADT concurrently with SRT. Eleven patients (8.3%) who underwent SRT had pathologically node positive disease. The standard technique for SRT was 3D-CRT in 127 patients (95%), whereas 6 patients (5%) were treated with intensity-modulated radiotherapy . The most common total radiation dose was 65-70 Gy (41%), followed by ≥70 Gy (32%) and <65 Gy (28%). The irradiated field was the prostate bed alone in 49 patients (37%) and the whole pelvis in 84 patients (63%). Fifty-one patients (38.4%) experienced disease progression after SRT. Out of the 51 patients,

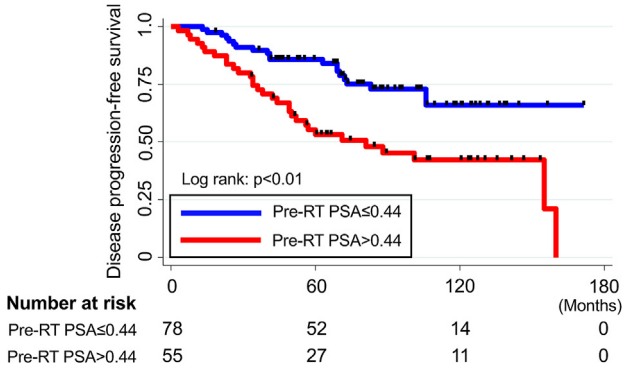


**Figure 2.** The Kaplan-Meier curve of disease progression-free survival after radical prostatectomy according to the pre-SRT PSA level. PSA: prostate-specific antigen, SRT: salvage radiation therapy.

47 patients experienced only repeated PSA levels greater than 0.2 ng/mL above the post-SRT nadir, none of the patients experienced only radiographic progression, and four patients had both. The median PSA level before SRT was 0.37 ng/mL (interquartile range 0.26-0.63 ng/mL). The optimal cutoff value of the pre-SRT PSA for predicting disease progression was 0.44 ng/mL (Fig. 1). The 5-year disease progression-free survival in patients with pre-SRT PSA ≤0.44 ng/mL and PSA >0.44 ng/mL was 85.7% and 53.2%, respectively ($P < 0.01$) (Fig. 2).

The univariate analysis demonstrated that the initial PSA ($P < 0.01$), the D'Amico classification (high vs. low; $P = 0.04$), the PSA immediately after RP ($P < 0.01$), and the PSA before SRT (>0.44 ng/mL vs ≤0.44 ng/mL; $P < 0.01$) were significantly associated with disease progression after SRT (Table 2). In the multivariable analysis, patients with pre-SRT PSA >0.44 ng/mL were likely to experience disease progression after SRT [hazard ratio (HR): 2.02, 95% confidence interval (CI): 1.10-3.69, $P = 0.02$].

We performed a sub-analysis to evaluate the optimal timing of SRT in patients with higher potential of progression, of 133 PCa patients, 96 patients had adverse pathology. In these patients, although pre-SRT PSA >0.44 ng/mL before SRT did not maintain its independent association with disease progression in the multivariable analysis (HR: 1.63, 95% CI: 0.75-3.54, $P = 0.22$), PSA after RP within 4 weeks as a continuous variable was significantly associated with disease progression (HR: 1.19, 95% CI: 1.004-1.41, $P = 0.04$) (Table 3).

## 4. Discussion

In this retrospective study, we investigated the association of disease progression with clinicopathologic features in 133 PCa patients treated with SRT for BCR after RP. To the best of our knowledge, this study included the largest number of patients treated with SRT in Japan. We found that the optimal cutoff value of the pre-SRT PSA for predicting post-SRT disease progression was 0.44 ng/mL, and patients with pre-SRT PSA >0.44 ng/mL were more likely to experience disease progression. We further found that PSA within 4 weeks after RP as a continuous variable was significantly associated with disease progression in patients with adverse pathology, i.e., those who had ≥ pT3, positive surgical margins, and/or nodal involvement at RP.

While the pre-SRT PSA level is known to be a significant predictor of post-SRT disease progression,[11] the optimal timing of SRT is still controversial. Although there is a lack of randomized controlled data, several retrospective studies have shown that PCa patients with a pre-SRT PSA level ≤0.5 ng/mL were more likely to have better oncologic outcomes than those with a pre-SRT PSA level >0.5 ng/mL.[9,11,16–18] In addition, King et al revealed that BCR-free survival decreased by up to 4% with every 0.1 ng/mL increase in the pre-SRT PSA.[19] They reported that waiting to initiate SRT until the PSA reaches 0.6 ng/mL would result in a 20% reduction in the BCR-free survival, when compared with performing SRT when the patient has PSA of 0.1 ng/mL. However, the potential benefit of SRT must be balanced against the possible detrimental effect on functional outcomes, specifically, urinary continence and erectile function.[20] In addition, some patients with what is destined to be indolent BCR will be overtreated with early SRT. In the present study, patients with pre-SRT PSA >0.44 ng/mL were more likely to experience disease progression. Therefore, we propose that SRT should be performed before the patient has a PSA level of 0.44 ng/mL, which is close to the timing recommended by current guidelines.[9,10]

Previous studies have identified significant factors associated with disease progression after SRT, including clinical/pathological T stage, postoperative Gleason score, positive surgical margin, PSA

**Table 2**
Univariable and multivariable Cox regression analyses for the prediction of disease progression in 133 patients treated with SRT after RP

| Variable | Univariable | | | Multivariable | | |
|---|---|---|---|---|---|---|
| | HR | 95%CI | *p* | HR | 95%CI | *p* |
| Age | 1.03 | 0.98-1.07 | 0.23 | - | - | - |
| iPSA | 1.04 | 1.01-1.06 | <0.01 | 1.02 | 0.99-1.05 | 0.09 |
| D'Amico risk stratification | | | | | | |
| Low | ref | | | Ref | | |
| Intermediate | 1.44 | 0.47-4.37 | 0.52 | 1.18 | 0.38-3.62 | 0.78 |
| High | 3.00 | 1.06-8.50 | 0.04 | 1.75 | 0.57-5.36 | 0.32 |
| Gleason score at RP | | | | | | |
| 6 | ref | | | - | | |
| 7 | 1.62 | 0.38-6.84 | 0.51 | - | - | - |
| 8-10 | 2.82 | 0.66-12.0 | 0.16 | - | - | - |
| With tertiary 5 | 0.57 | 0.24-1.33 | 0.19 | - | - | - |
| Extracapsular extension | 1.28 | 0.74-2.22 | 0.38 | - | - | - |
| Seminal vesicle invasion | 0.97 | 0.43-2.15 | 0.93 | - | - | - |
| Positive surgical margin | 1.12 | 0.65-1.95 | 0.68 | - | - | - |
| Lymph node status | 2.00 | 0.85-4.70 | 0.11 | - | - | - |
| PSA immediately after RP (cont.) | 1.23 | 1.08-1.41 | <0.01 | 1.14 | 0.97-1.34 | 0.11 |
| Pre-SRT PSA (ng/ml) (high vs. low, cut-off 0.44) | 2.60 | 1.48-4.57 | <0.01 | 2.02 | 1.10-3.69 | 0.02 |
| Total dose in SRT | 0.97 | 0.89-1.06 | 0.45 | - | - | - |
| Previous hormonal therapy | 1.72 | 0.96-3.05 | 0.07 | | | |

CI = Confidence Interval, HR = Hazard Ratio, iPSA: initial prostate-specific antigen, PSA: prostate-specific antigen, RP: radical prostatectomy, SRT: salvage radiation therapy.

immediately after RP, and pre-SRT PSA.[11,17,21–24] In the present study, the univariate analysis demonstrated that the initial PSA, the D'Amico classification, the PSA immediately after RP, and pre-SRT PSA >0.44 ng/mL were significantly associated with disease progression after SRT. However, in a multivariable analysis, pre-SRT PSA >0.44 ng/mL was the only independent factor for disease progression. To further evaluate the risk factors of progression in patients with higher risk, we examined this question in patients with adverse pathology. In these patients, pre-SRT PSA >0.44 ng/mL did not maintain its independent association with disease progression, but the PSA immediately after RP was a significant factor for predicting disease progression in the multivariable analysis. Although the generalizability of the results might be limited by the small number of patients, this may indicate differences in the role of the PSA for predicting recurrence based on pathology. A certain proportion of PCa recurrence is indolent, and such patients may not require early SRT to control the disease. The median pre-SRT PSA level (0.37 ng/mL) in the total cohort was lower than the optimal cutoff value of the pre-SRT PSA level for predicting disease progression (0.44 ng/mL), which supports our hypothesis that indolent patients may not require early SRT to control the disease. On the other hand, patients with adverse pathology may have aggressive PCa, requiring earlier SRT. In the adverse pathology group, a significant difference in survival was observed based on the PSA immediately after RP, and inducing SRT when the patient has a PSA level of 0.44 ng/mL might be too late. Fossati et al recently determined the best candidates for early SRT.[25] They stratified patients according to clinical and pathological characteristics and found that early SRT has a significant impact in certain proportion of patients, whereas progression after SRT did not change significantly based on the PSA level in patients with indolent or very aggressive PCa. In addition, there was a significant decrease in metastasis-free survival based on the PSA level in the patients without indolent or very aggressive PCa, which revealed that earlier SRT is effective in the group.[25] This may explain the difference in the ability of the PSA to predict outcomes in patients with different aggressiveness in our study. Our results support the current guideline for the timing of SRT. However, in patients with adverse pathology, earlier SRT may be required, or they might not appear to benefit from SRT, as these patients have a relatively constant high rate of metastasis.

**Table 3**
Multivariable Cox regression analyses for the prediction of disease progression in patients with adverse pathology treated with SRT after RP

| | Patients with adverse pathology | | |
|---|---|---|---|
| | Disease progression | | |
| | HR | 95%CI | *p*-value |
| PSA immediately after RP (cont.) | 1.19 | 1.004-1.41 | 0.04 |
| Pre-SRT PSA (ng/ml) (high vs. low, cut-off 0.44) | 1.63 | 0.75-3.54 | 0.22 |

HR = Hazard Ratio; CI = Confidence Interval; PSA: prostate-specific antigen, RP: radical prostatectomy, SRT: salvage radiation therapy.
※adjusted for initial PSA.

Our study had some limitations. This was a retrospective study with a small sample size. This may have induced a selection bias. While the follow-up term was sufficient to assess disease progression, we could not evaluate the effect of SRT on overall survival. The technique for SRT was not standardized. While all SRT regimens were administered in 1.8-2.0-Gy daily fractions, the SRT modality, dose, and area were dependent on the physician. Additionally, although concomitant ADT with SRT was not a significant factor of disease progression in the multivariable analysis, it was administered to 40 patients (30%). Furthermore, in order to validate the clinical significance of the threshold, a prospective study would be imperative. Despite these limitations in our investigation of the association of the timing of SRT and oncological outcomes in PCa patients, we believe our results offer beneficial information in the consideration of the best timing of SRT after BCR in PCa patients after RP.

## 5. Conclusion

In this study, we investigated the pre-SRT prognostic factors for disease progression after SRT for nonmetastatic PCa patients with BCR after RP. In the multivariable analysis, patients with pre-SRT PSA >0.44 ng/mL were more likely to experience disease progression than those with PSA ≤0.44 ng/mL. Although the pre-SRT PSA >0.44 ng/mL did not maintain its independent association with disease progression in the multivariable analysis of patients with adverse pathology, the PSA within 4 weeks after RP as a continuous variable was significantly associated with disease progression. Our

findings support the current guideline for the timing of SRT. However, in patients with adverse pathology, earlier SRT will be required. Further, it may not be advisable to wait until the patient has PSA >0.44 ng/mL as this may not allow patients to benefit from SRT and these patients had a relatively constant high rate of metastasis.

## Conflict of Interest

The authors declare that they have no conflict of interest.

## Contributions

KA, SK, FU: Project development, Data collection, Data analysis, and Manuscript writing. KI: Project development and Manuscript writing. TK, AO, HA: Project development and Manuscript writing. MA: Data collection and Manuscript writing. TK: Project development, Data analysis, and Manuscript writing.

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