Original Article
Bilateral Seminal Vesicle Invasion as a Strong Prognostic Indicator in T3b Prostate Cancer Patients Following Radical Prostatectomy: A Comprehensive, Multi-Center, Long-Term Follow-Up Study

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Running Title: Prognostic factors in prostate cancer with seminal vesicle invasion

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Abstract

Purpose

Pathologic T3b (pT3b) prostate cancer, characterized by seminal vesicle invasion (SVI), exhibits variable oncological outcomes post-radical prostatectomy (RP). Identifying prognostic factors is crucial for patient-specific management. This study investigates the impact of bilateral SVI on prognosis in pT3b prostate cancer.

Materials and Methods

We evaluated the medical records of a multi-institutional cohort of men who underwent RP for prostate cancer with SVI between 2000 and 2012. Univariate and multivariable analyses were performed using Kaplan-Meier analysis and covariate-adjusted Cox-proportional hazard regression for biochemical recurrence (BCR), clinical progression (CP), and cancer-specific survival (CSS).

Results

Among 770 men who underwent RP without neo-adjuvant treatment, median follow-up was 85.7 months. Patients with bilateral SVI had higher preoperative prostate-specific antigen levels and clinical T stage (all p<0.001). Extracapsular extension, tumor volume, lymph node metastasis (p<0.001), pathologic Gleason grade group (p<0.001), and resection margin positivity (p<0.001) were also higher in patients with bilateral SVI. The 5-, 10-, and 15-year BCR-free survival rates were 23.9%, 11.7%, and 8.5%; CP-free survival rates were 82.8%, 62.5%, and 33.4%; and CSS rates were 96.4%, 88.1%, and 69.5%, respectively. The bilateral SVI group demonstrated significantly lower BCR, CP-free survival rates, and CSS rates all (p<0.001). Bilateral SVI was independently associated with BCR (HR 1.197, 95% CI 1p=0.049), CP (p=0.022), and CSS (p=0.038) in covariate-adjusted Cox regression.

Conclusion

Bilateral SVI is a robust, independent prognostic factor for poor oncological outcomes in pT3b prostate cancer.
Keywords

Prostatic neoplasms, Prostatectomy, Seminal vesicle invasion
Introduction

Prostate cancer is the second most common malignancy in men worldwide and ranks sixth in cancer-related mortality [1]. Seminal vesicle invasion (SVI) is well known adverse prognostic factor in patients with prostate cancer [2]. Despite the earlier stage migration of prostate cancer in the prostate-specific antigen (PSA) era, approximately 5-25% of patients who undergo RP present with SVI [3,4]. The oncological outcomes of patients with SVI remain poor [5].

Prostate cancer patients with SVI in pathologic specimen (pT3b) are a heterogeneous group with presenting diverse oncological outcomes [2,6–8]. These patients were found to have 5-year biochemical recurrence (BCR) free survival rates ranging from 5% to 60% [2]. Oncological outcomes in these patients are influenced significantly by the presence of various clinical and pathologic features, such as pathologic Gleason grade or presence of lymph node involvement [6–8]. Owing to poor oncological outcome in specific population, multimodal treatment strategies have been recommended for high-risk prostate cancer patients with SVI [9–11]. Thus, determining prognostic risk factors in prostate cancer patients with SVI is important for treatment planning, patient counselling, and shared decision making after RP.

The prognostic role of bilateral SVI has been debated for decades [12]. Earlier studies with small populations found an association between bilateral SVI and poor oncological outcomes using univariate analysis, but not multivariate analysis [8,13]. Recent single-center studies have reported conflicting results regarding the prognostic impact of SVI on major oncological outcomes [12,14,15]. Due to the heterogeneous characteristics of the pT3b group, large-scale, multicenter, long-term follow up studies are necessary to reveal the prognostic role of bilateral SVI on oncological outcomes. Additionally, information on adjuvant and salvage treatment after RP is needed to adjust for potential confounding effects.
The present study evaluated the prognostic impact of bilateral SVI on BCR, clinical progression (CP), and cancer-specific survival (CSS) in patients with pT3b prostate cancer after RP at four tertiary referral centers.

Materials and Methods

1. Study population

The medical records of 876 patients with pathologic proven prostate cancer and SVI (pT3b) who underwent RP from January 2000 to December 2012 at four tertiary referral centers were retrospectively evaluated. The 75 patients who underwent neoadjuvant androgen deprivation therapy (ADT) and the 37 who did not have follow-up data were excluded. Finally, 770 of pT3b prostate cancer patients data was used for this analysis.

2. Collected parameters

Patients’ demographic and clinical data, including age at surgery, preoperative PSA level, body mass index (BMI), prostate volume (PV), biopsy Gleason grade group (GGG), and clinical T and N stage were recorded. Pathology specimens collected after RP were evaluated to determine pathologic GGG, percent tumor volume (TV), presence of extracapsular extension (ECE), bilateral involvement of SVI, presence of lymph node (LN) metastasis, and positive surgical margin status. Percent TV was calculated by dividing the volume of the tumor lesion by the total PV. Pathological assessments were conducted by expert genitourinary pathologists at each participating center. It should be noted that there was no retrospective analysis of pathological slides, as all the involved centers had consistently documented and reported these variables throughout the duration of the study period. All biopsy and RP specimens were graded according to 2005 and 2014 International Society of Urological Pathology (ISUP) Consensus...
Conference criteria [16]. Prostate tumors were staged according to the 2019 version of the American Joint Committee on Cancer (AJCC) TNM staging system [17]. Adjuvant treatment was defined as treatment initiated within 3 months after RP without evidence of BCR, while salvage treatment was defined as treatment started after evidence of BCR at any time point after RP. Adjuvant and salvage treatment modality information were separately collected for ADT and radiation therapy (RT).

3. Outcome definition and measurement

Follow-up data were collected from electronic medical health records at each institution. Oncological outcomes included BCR-free survival, clinical progression (CP)-free survival, and cancer-specific survival (CSS). BCR was defined according to the guidelines of the American Urological Association Localized Prostate Cancer Update Panel Report [18]. CP, in this context, was specifically defined as the identification of metastasis via imaging modalities, namely radionuclide bone scans or computed tomography, or through the pathological verification of prostate cancer from biopsies conducted outside the prostatic bed [19]. It is important to note that radiologic or pathologic indications of local recurrence at the anastomosis site were explicitly excluded from the definition of CP for the purposes of this study. CSS was defined based on cancer-related deaths during the follow-up period. Non-parametric survival probability was calculated using the Kaplan–Meier method and oncological outcomes were measured at 5, 10, and 15 years.

4. Statistical analyses

All continuous variables were reported as the median {interquartile range (IQR)}, whereas all categorical variables were reported as frequency (percentage). Factors associated
with BCR, CP, and CSS were evaluated by multivariable Cox-proportional hazard regression analyses. Factors evaluated included clinical parameters (patient age, initial PSA level, BMI, PV) and pathologic parameters (resection margins status, pathologic GGG, pathologic N stage, pathologic TV, pathologic ECE, bilateral SVI involvement). Multivariable model adjusted by treatment information (adjuvant ADT, adjuvant RT, salvage ADT, salvage RT). Pathologic GGG was categorized into ≤3 and ≥4. For evaluating prognostic factors of BCR, clinical and pathologic parameters with adjuvant ADT and RT were used for analysis. For evaluating prognostic factors of CP and CSS, clinical and pathologic parameters with all treatment information were used for analysis.

All statistical analyses were performed using the Python ver. 3.8.5 (www.python.org). Kaplan–Meier analyses and Cox proportional hazard modeling were performed using the lifelines program (ver. 0.25.9) in the Python library. All p-value were two-sided, with the level of significance set at <0.05.

Results

1. Baseline characteristics and survival outcomes in pT3b patients

Median patient age was 67.0 years (IQR, 61.0–70.0 years), and median PSA level before surgery was 14.5 ng/mL (IQR, 8.3–27.4 ng/mL). Of the 770 patients, 386 (50.3%) had clinical T3 or higher, and 59 (7.7%) had clinical node positive disease, as determined by preoperative imaging. At initial diagnosis, 391 (50.8%) patients presented with clinical GGG ≥4. Median follow up was 81.2 months (IQR, 61.8–111.9 months). During follow-up period, 596 (77.4%) patients experienced BCR, 201 (26.1%) experienced CP, and 62 (8.1%) deceased of cancer-related causes. The 5-, 10-, and 15-year BCR-free survival rates were 23.9%, 11.7%, and 8.1%, respectively; the 5-, 10-, and 15-year CP-free survival rates were 82.8%, 62.5%, and
33.4%, respectively; and the 5-, 10-, and 15-year CSS rates were 96.4%, 88.1%, and 69.9%, respectively (Fig. 1).

2. Different characteristics of unilateral and bilateral seminal vesicle invasion

We analyzed the 769 patients with available data, except one patient who did not have information on bilateral or unilateral involvement of the seminal vesicle. Approximately 49% (378/769) of the patients presented with bilateral SVI. The bilateral SVI group had higher serum PSA levels (16.2 vs. 12.4 ng/mL, \(p=0.001\)) and clinical T stage (\(p<0.001\)) than the unilateral SVI group. Bilateral SVI patients shows higher incidence of worse prognostic factors than unilateral SVI, including higher pathologic GG (\(p=0.003\)), ECE (\(p<0.001\)), positive LN metastasis (\(p<0.001\)), and percentage of tumor volume (\(p<0.001\)). Patients with bilateral SVI had a higher risk of resection margin positivity (74.9% vs. 56.0%, \(p<0.001\)) than those with unilateral SVI and received more adjuvant ADT (19.0% vs. 11.5%, \(p=0.005\)) and salvage ADT (65.1% vs. 54.7%, \(p=0.004\)). Adjuvant RT was more frequently provided in the bilateral SVI group than the unilateral SVI group; however, the difference was not statistically significant (24.3% vs. 18.4%, \(p=0.055\)) (Table 2).

3. Difference in BCR, CP free-, and CSS between unilateral and bilateral SVI

During the follow-up period, BCR was experienced by 71.4% (279/391) of patients with unilateral SVI and 83.6% (316/378) of those with bilateral SVI. The CP occurred in 20.2% (79/391) of unilateral SVI patients and 32.3% (122/378) of bilateral SVI patients. 13.0% (51/391) of unilateral SVI patients and 17.5% (66/378) of bilateral SVI patients died from prostate cancer, respectively. Kaplan-Meier analysis and log rank test results showed that all outcomes, including BCR free-survival, CP free-survival, and CSS, were significantly poorer.
in patients with bilateral SVI compared to those with unilateral SVI (all \( p < 0.001 \), Fig. 2).

4. Multivariable cox proportional hazard regression analysis for BCR, CP free-and CSS

After adjusting for the effect of adjuvant therapies, the variables significantly associated with BCR-free survival were PSA level \{Hazard ratio\( (HR) : 1.004, 95\% \) confidence interval \( (CI) : 1.001-1.007, p=0.015 \}, pathological GGG (\( HR : 1.423, 95\% \) CI: 1.196-1.694, \( p<0.001 \)), pathological ECE (\( HR : 1.400, 95\% \) CI: 1.156-1.695, \( p<0.001 \)), positive resection margin (\( HR : 1.325, 95\% \) CI: 1.082-1.624, \( p=0.007 \)), and bilateral SVI (\( HR : 1.197, 95\% \) CI: 1.001-1.432, \( p=0.049 \)). For CP-free survival, pathological GGG (\( HR : 1.703, 95\% \) CI: 1.232-2.355, \( p=0.001 \)), pathological tumor volume (\( HR : 1.007, 95\% \) CI: 1.001-1.013, \( p=0.029 \)), and bilateral SVI (\( HR : 1.459, 95\% \) CI: 1.057-2.015, \( p=0.022 \)) were significant predictors, after adjusting for adjuvant and salvage therapies. Regarding CSS, pathological GGG (\( HR : 2.457, 95\% \) CI: 1.274-4.741, \( p=0.007 \)), positive lymph node metastasis (\( HR : 2.143, 95\% \) CI: 1.193-3.849, \( p=0.011 \)), and bilateral SVI (\( HR : 1.970, 95\% \) CI: 1.038-3.741, \( p=0.038 \)) were significantly associated with worse outcomes, after adjusting for adjuvant and salvage therapies (Table 2).

Discussion

The present study evaluated factors prognostic of the main oncological outcomes (BCR, CP, and CSS) in 770 prostate cancer patients with SVI after RP at four tertiary referral centers in Korea. The BCR-free, CP-free, and CSS rates were 23.9\%, 82.8\%, and 96.4\%, respectively, at 5 years, and 11.7\%, 62.5\%, and 88.1\%, respectively, at 10 years after surgery. Among the clinical and pathologic variables, higher GGG and bilateral SVI were independently and robustly associated all three main oncological outcomes.
Despite disparities in the management patterns and clinical characteristics of prostate cancer across different ethnicities and geographical locations [20,21], there is a notable lack of data from Asian populations [5,7]. Our study fills this gap by providing landmark data on the oncological outcomes of pT3b prostate cancer in the Korean population. Though our cohort showed a lower 5-year BCR-free rate of 23.9% compared to 36.1–40.1% in Western studies [5,7], our CSS rates were comparable. This discrepancy might be attributed to the more aggressive nature of the tumors in our study, reflected by higher median PSA concentrations and a greater proportion of patients with a pathologic Gleason Grade Group of 4-5. The median PSA concentration in the present study, 14.5 ng/mL, was higher than the concentrations of 7.2–10.8 ng/mL measured in prior Western studies [5,7]. Of the patients in the present study, 52.2% had a pathologic GGG of 4-5, a percentage higher than in the previous studies (29.9–33.9%) [5,7]. Nevertheless, our 10-year CP-free and CSS rates align with those previously reported.

Our study identified that GGG and bilateral SVI were significant prognostic factors for BCR, CP free- and CSS after adjusting for the effect of adjuvant or salvage therapies. Earlier studies have yielded mixed results, with some finding bilateral SVI to be a significant factor on univariate analysis but not on multivariate analysis [8,13], while others reported it as a poor prognostic factor for BCR [12] and CP [12,15]. However, these studies were limited by their retrospective designs, relatively small patient numbers, and short follow-up periods [8,12–15]. Given that the risks of CP and CSS are lower than that of BCR, a long-term follow-up of a larger patient population is required to conclusively determine the prognostic factors for CP and CSS. In our study, bilateral SVI showed a strong and robust association with BCR (HR 1.197, p=0.049), CP free- (HR 1.459, p=0.022) and CSS (HR 1.970, p=0.038) which are well known clinical and pathologic prognostic factors. This provides strong evidence of the potential negative impact of bilateral SVI on patient outcomes, emphasizing the importance of this factor.
in risk stratification and treatment decision-making. The strong association of bilateral SVI with poorer outcomes in our study indicates a potential need for its inclusion in the T staging system for prostate cancer, which warrants further investigation.

In present study, resection margin status emerged as an independent prognostic factor for BCR free survival, but not for CP free survival or CSS in pT3b Prostate cancer. The margin positive rate in the present study was 65.3%, similar to the rates of 41.1–66.7% reported in patients with pT3b prostate cancer [22,23]. Although the definition of margin positivity varied before 2009 [24], studies have consistently demonstrated its clinical impact on BCR [25]. However, the influence of margin status on other oncological outcomes remains controversial. A recent meta-analysis reported adverse prognostic effects of margin positivity on other oncological outcomes [26], yet a population-based study from Switzerland did not find margin status to be prognostic of CSS on adjusted multivariate analysis [27]. The discrepancy between BCR and CP or CSS could be attributed to subsequent treatments such as ADT or salvage RT following BCR [2]. Additionally, despite having the longest follow-up in this study, the possibility that sufficient events for CP or CSS have not yet occurred cannot be discounted due to the lengthy disease progression from BCR to CP and CSS. This underlines the need for further research with extended follow-up periods to fully elucidate the prognostic impact of margin positivity on CP and CSS.

This study also had several limitations. Owing to its retrospective nature, the risk of bias could not be avoided. The relatively long study period, changes in PSA screening recommendations [28], and alterations in reporting guidelines for RP specimens [29] during follow up contributed to the heterogeneity of the study population. This study also does not reflect advances in surgical techniques during study periods. Nevertheless, our study presents unique strengths. It comprises the largest data set of pT3b patients from multiple tertiary referral centers, with a
follow-up period exceeding five years. This provides invaluable information on the clinical course of pT3b prostate cancer patients post-RP. Another significant strength is our adjustment for the effects of adjuvant and salvage therapies alongside other prognostic variables, which ensures a more comprehensive evaluation of prognostic factors. The findings from our study are instrumental in improving patient management and counseling, thereby enhancing patient outcomes in the context of pT3b prostate cancer.

In conclusion, bilateral SVI is a robust, independent prognostic factor for poor oncological outcomes in pT3b prostate cancer. Our findings suggest that effective adjuvant treatment for these patients should be offered.

Ethical Statement
The requirement for patient informed consent was waived by the Institutional Review Board of Asan Medical Center.

Author Contributions
Conceived and designed the analysis: Jeong IG, Jeon SS.
Collected the data: Suh J, Jeong IG, Jeon HG, Jeong CW, Lee S, Jeon SS, Byun SS, Kwak C, Ahn H.
Performed the analysis: Suh J, Jeong IG.
Wrote the paper: Suh J, Jeong IG.
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Conflicts of Interest

Conflict of interest relevant to this article was not reported.
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**Fig. 1.** Kaplan–Meier analysis of the probability of main oncologic outcomes of prostate cancer patients with seminal vesicle invasion after radical prostatectomy.
(A) BCR free survival analysis

- SVI bilateral involvement
- SVI unilateral involvement

Survival Probability over Months after Operation:
- 0.0 0.2 0.4 0.6 0.8 1.0
- 24 48 72 96 120 144 168 192

P = <0.001

(B) Clinical progression free survival analysis

- SVI bilateral involvement
- SVI unilateral involvement

Survival Probability over Months after Operation:
- 0.0 0.2 0.4 0.6 0.8 1.0
- 0 24 48 72 96 120 144 168 192

P = <0.001
Fig. 2. A comparison of the main oncologic outcomes for prostate cancer patients who underwent radical prostatectomy, showing differences between those with unilateral seminal vesicle invasion (red) and bilateral seminal vesicle invasion (blue). (A) Biochemical recurrence-free survival, (B) Clinical progression-free survival, (C) Cancer-specific survival.
<table>
<thead>
<tr>
<th>Variables</th>
<th>Unilateral SVI (n=391)</th>
<th>Bilateral SVI (n=378)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, years (median, IQR)</td>
<td>67.0 (62.0–70.0)</td>
<td>67.0 (61.0–70.0)</td>
<td>0.683</td>
</tr>
<tr>
<td>BMI before surgery, kg/m² (median, IQR)</td>
<td>24.4 (22.2–26.3)</td>
<td>24.5 (22.9–26.5)</td>
<td>0.553</td>
</tr>
<tr>
<td>PSA before surgery, ng/mL (median, IQR)</td>
<td>12.4 (7.6–24.1)</td>
<td>16.2 (9.3–30.8)</td>
<td>0.001</td>
</tr>
<tr>
<td>Prostate volume, mL (median, IQR)</td>
<td>31.0 (25.0–43.0)</td>
<td>32.2 (26.0–43.0)</td>
<td>0.615</td>
</tr>
<tr>
<td>Clinical Gleason grade group (No., %)</td>
<td></td>
<td></td>
<td>0.119</td>
</tr>
<tr>
<td>1–3 (Gleason score 6–7)</td>
<td>202 (51.9)</td>
<td>174 (46.0)</td>
<td></td>
</tr>
<tr>
<td>4–5 (Gleason score 8–10)</td>
<td>187 (48.1)</td>
<td>204 (54.0)</td>
<td></td>
</tr>
<tr>
<td>Clinical T stage (No., %)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≤2</td>
<td>228 (58.5)</td>
<td>153 (40.7)</td>
<td></td>
</tr>
<tr>
<td>≥3</td>
<td>162 (41.5)</td>
<td>223 (59.3)</td>
<td></td>
</tr>
<tr>
<td>Clinical N positive (No., %)</td>
<td>23 (5.9)</td>
<td>36 (9.5)</td>
<td>0.078</td>
</tr>
<tr>
<td><strong>Pathologic characteristics</strong></td>
<td></td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Pathologic Gleason grade group (No., %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1–3 (Gleason score 6–7)</td>
<td>212 (54.2)</td>
<td>164 (43.4)</td>
<td></td>
</tr>
<tr>
<td>4–5 (Gleason score 8–10)</td>
<td>179 (45.8)</td>
<td>214 (56.6)</td>
<td></td>
</tr>
<tr>
<td>Positive extracapsular extension (No., %)</td>
<td>220 (56.3)</td>
<td>290 (76.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Percentage of pathologic tumor volume (median, IQR)</td>
<td>30.0 (15.0–50.0)</td>
<td>50.0 (27.8–80.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pathologic N positive (No., %)</td>
<td>36 (9.2)</td>
<td>87 (23.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Resection margin involvement (No., %)</td>
<td>219 (56.0)</td>
<td>283 (74.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Received adjuvant ADT</td>
<td>45 (11.5)</td>
<td>72 (19.0)</td>
<td>0.005</td>
</tr>
<tr>
<td>Received adjuvant RT</td>
<td>72 (18.4)</td>
<td>92 (24.3)</td>
<td>0.055</td>
</tr>
<tr>
<td>Received salvage ADT</td>
<td>214 (54.7)</td>
<td>246 (65.1)</td>
<td>0.004</td>
</tr>
<tr>
<td>Received salvage RT</td>
<td>111 (28.4)</td>
<td>94 (24.9)</td>
<td>0.307</td>
</tr>
</tbody>
</table>

SVI, seminal vesicle invasion; IQR, interquartile range; BMI, body mass index; PSA, prostate specific antigen; ADT, androgen deprivation therapy; RT, radiation therapy.
Table 2. Multivariable cox proportional hazard analyses of factors associated with biochemical recurrence-free, clinical progression free- and cancer specific survival

<table>
<thead>
<tr>
<th>Pathologic characteristics</th>
<th>BCR free survival†</th>
<th></th>
<th>CP free survival‡</th>
<th></th>
<th>CSS ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic Gleason grade group, categorical (4–5 vs. 1–3)</td>
<td>1.423 (1.196-1.694) &lt;0.001</td>
<td></td>
<td>1.703 (1.232-2.355) 0.001</td>
<td></td>
<td>2.457 (1.274-4.741) 0.007</td>
</tr>
<tr>
<td>Seminal vesicle involvement (bilateral vs. unilateral)</td>
<td>1.197 (1.001-1.432) 0.049</td>
<td></td>
<td>1.459 (1.057-2.015) 0.022</td>
<td></td>
<td>1.970 (1.038-3.741) 0.038</td>
</tr>
<tr>
<td>Pathologic extracapsular extension (yes vs. no)</td>
<td>1.400 (1.156-1.695) &lt;0.001</td>
<td></td>
<td>1.318 (0.952-1.826) 0.096</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Positive resection margin (yes vs. no)</td>
<td>1.325 (1.082-1.624) 0.007</td>
<td></td>
<td>1.059 (0.716-1.566) 0.774</td>
<td></td>
<td>0.934 (0.450-1.939) 0.854</td>
</tr>
<tr>
<td>Pathologic tumor volume, continuous</td>
<td>1.002 (0.998-1.005) 0.273</td>
<td></td>
<td>1.007 (1.001-1.013) 0.029</td>
<td></td>
<td>1.009 (0.999-1.020) 0.085</td>
</tr>
</tbody>
</table>

BCR, biochemical recurrence; CP, clinical progression; CSS, cancer specific survival; HR, hazard ration; CI, confidence interval; PSA, prostate cancer specific antigen; ADT, androgen deprivation therapy; RT, radiation therapy. †: adjusted by adjuvant ADT and adjuvant RT, ‡: adjusted by adjuvant ADT, adjuvant RT, salvage ADT and salvage RT.