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Original Article

Prognostic impact of extraprostatic extension on prostate cancer with seminal vesicle invasion

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Abstract: Objectives: Extraprostatic extension (EPE) and seminal vesicle invasion (SVI) are unfavorable factors for biochemical recurrence (BCR) following radical prostatectomy; however, some patients with SVI survive for a long duration without experiencing BCR after prostatectomy in absence of adjuvant therapy. This study aimed to clarify the heterogeneity of locally advanced prostate cancers to better understand prognosis in patients with SVI. Methods: We retrospectively reviewed the medical records of 120 patients with SVI who underwent radical prostatectomy at two institutions. Multivariate logistic regression was used to evaluate the preoperative clinical and postoperative pathological variables as predictors of BCR. We also used Kaplan-Meier and competing risk regression analysis to assess the cumulative incidence and risk of BCR. After excluding patients who received neoadjuvant or adjuvant therapy, 55 patients with SVI were enrolled in this study. Results: BCR occurred in 31 of these patients (56.3%). We found that Grade group and positive EPE were predictors of BCR in patients with SVI ($P < 0.001$ and $P = 0.002$, respectively). Using the multivariate model, EPE was significantly associated with BCR in patients with SVI (hazard ratio: 5.402; 95% confidence interval, 1.247-23.405; $P = 0.012$). Patients who were negative for EPE had significantly lower BCR rates ($P = 0.002$). Conclusions: Among the patients with SVI tumors, prognosis might be different depending on presence or absence of EPE.

Keywords: Biochemical recurrence, extraprostatic extension, prostate cancer, prostatectomy, seminal vesicle invasion

Introduction

Prostate cancer (PCa) is one of the most common malignancies among men worldwide; however, its management remains a significant clinical challenge [1]. Radical prostatectomy has been established as the standard treatment for reducing mortality in men with clinically localized PCa [2]. Furthermore, radical prostatectomy combined with extended pelvic lymph node dissection is a reasonable first-line treatment in patients with high-risk locally advanced PCa, such as cancer with extraprostatic extension (EPE) or seminal vesicle invasion (SVI) [3]. EPE is defined as the extension of prostate cancer beyond the prostate capsule, which is associated with disease progression. SVI is also considered a poor prognostic factor for biochemical recurrence (BCR) after prostatectomy. For patients with EPE or SVI, wide surgical margin resection or non-nerve-sparing prostatectomy may be considered. However, despite advances in surgical techniques, such as robot-assisted surgery, some patients experience BCR after prostatectomy. BCR is generally defined as the asymptomatic increase in serum prostate-specific antigen (PSA) levels to greater than 0.2 ng/mL following radical prostatectomy [4]. Identifying patients at higher risk for BCR remains challenging. Prior studies have shown a significant occurrence of BCR in patients with PCa with high preoperative serum PSA levels, high pathological Gleason score, positive resection margin (RM), maximum index tumor diameter, EPE, and SVI [5-9].

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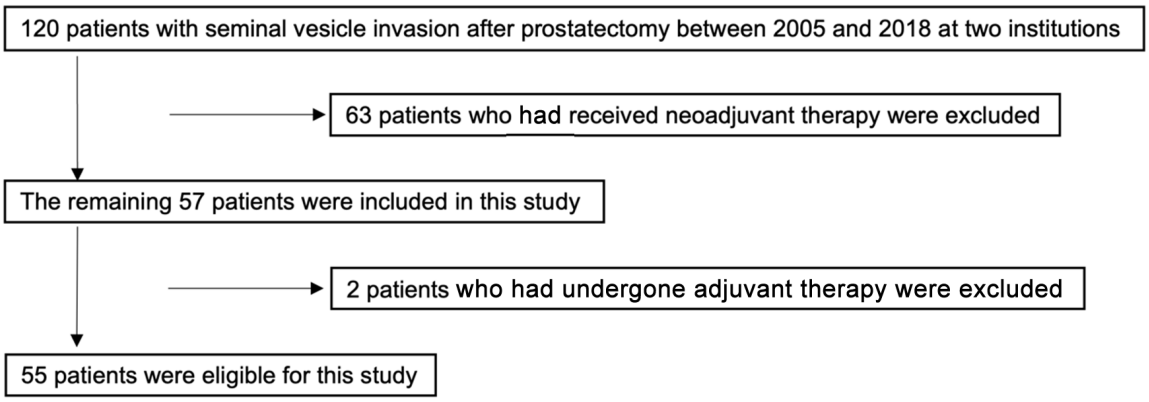

Figure 1. After excluding patients who did not fulfill the inclusion criteria, 55 patients were eligible for this study.

Postoperative adjuvant radiation therapy (RTx) after radical prostatectomy was generally recommended in patients with SVI who were expected to survive for more than 15 years [10-14]. However, currently, early salvage treatment appears to be the preferred treatment strategy compared with adjuvant therapy because adjuvant therapy may result in overtreatment of cases who do not develop BCR [15-17]. Postoperative RTx is defined as radiation administered to the prostatic bed in the absence of signs of recurrence [18-20]; therefore, the risk of adverse events, particularly radiation cystitis, should always be considered.

During their clinical courses, some patients with SVI survive for an extended period without BCR after prostatectomy, in absence of adjuvant RTx. These patients show a similar prognosis to that in individuals with localized cancer; however, there is no established method for identifying them at an early stage. Thus, this study aimed to stratify the clinical and pathological heterogeneity in patients with locally advanced PCa and assess the risk of BCR.

Materials and methods

Patients

We retrospectively reviewed the medical records of patients who underwent radical prostatectomy at Keio University Hospital and Saitama City Hospital between January 2005 and December 2018. Patients were eligible for inclusion if they met all of the following criteria: (1) underwent radical prostatectomy during the study period at either institution, (2) had pathologically confirmed SVI, defined as pT3b according to the TNM classification, (3) had complete clinical and pathological data available for analysis, (4) did not receive neoadjuvant androgen deprivation therapy (ADT) prior to prostatectomy, and (5) did not receive adjuvant therapy, including postoperative RTx or ADT. Patients were excluded if they had received neoadjuvant ADT prior to radical prostatectomy, adjuvant therapy (either RTx or ADT) following surgery, or if they had incomplete or missing clinical or pathological data. A total of 120 patients met these initial criteria. Of these, 63 patients who had received neoadjuvant ADT and two patients who had undergone adjuvant therapy were excluded. Finally, 55 patients were included in the study (**Figure 1**). We assessed serum PSA levels in the patients after RP and defined BCR as a postoperative PSA level greater than 0.2 ng/mL. This study was approved by the Institutional Review Boards of Keio University and Saitama City Hospital. Informed consent was obtained using an opt-out approach. The participants were provided with detailed information on the study, including its purpose, procedures, and their right to withdraw at any time.

Pathology analysis

All patients with PCa were diagnosed histologically before prostatectomy based on ultrasound-guided needle biopsy via either the transrectal or transperineal route. Following radical prostatectomy, all specimens were fixed in 10% formalin embedded in paraffin, and whole-mount sectioned pathology was performed. After seminal vesicle removal, all specimens were cut into thin longitudinal slices that were perpendicular to the urethra, from the apex to

Table 1. Patients characteristics according to clinical and pathological features

No. of patients	median ± SD (IQR)	Biochemical recurrence	
		Negative	Positive
Follow-up period (month)	65 ± 36.8 (36-94)		
Clinical features			
Age at operation (year)	69 ± 6.1 (65-73)		
PSA value at biopsy (ng/mL)	9.0 ± 5.9 (7.0-13.8)		
Prostate volume at biopsy (mL)	31.3 ± 12.4 (22.5-37.6)		
PSA-density at biopsy (ng/mL/mL)	0.34 ± 0.27 (0.21-0.43)		
Clinical T stage			
T1, 2		20	27
T3		4	4
Grade group			
Lower; 1,2,3		21	12
Higher; 4,5		3	19
Pathological features			
Extraprostatic extension			
Negative		10	2
Positive		14	29
Resection margin			
Negative		10	9
Positive		14	22
Lymph node metastasis			
Negative		24	31
Positive		0	0

PSA, prostate-specific antigen; SD, standard deviation; IQR, interquartile range.

the base. All specimens were stained with hematoxylin and eosin and subsequently reviewed by an experienced urologic pathologist (SM). The Gleason score and other pathological parameters, including EPE and SVI, were assessed in each section while the pathologist remained blinded to the patient's clinical data. Gleason scores were initially evaluated according to the 2014 International Society of Urological Pathology (ISUP) consensus guidelines. Subsequently, these were reclassified into ISUP Grade Groups to reflect the current grading system. EPE and SVI were assessed following the American Joint Commission on Cancer TNM classification. EPE was defined as tumor extension beyond the prostatic capsule into the surrounding periprostatic tissue. SVI was defined as tumor invasion into the muscular wall of the seminal vesicles. Other pathological parameters, including resection margins, lymph vascular invasion, and lymph node metastasis, were also recorded. All assessments were performed in a standardized and systematic manner.

Statistical analysis

We evaluated the differences in continuous variables between the groups using the Mann-Whitney U test. We also used the chi-square test to analyze differences in the number of patients between the two groups. Univariate and multivariate analyses were performed to identify predictive factors of BCR using the Cox proportional hazards model with stepwise forward selection, and Kaplan-Meier curves were constructed to evaluate BCR-free survival after prostatectomy. Data are reported as medians ± standard deviations (IQR), all reported *P*-values were two-sided; statistical significance was set at 0.05. Statistical analyses were performed using the R Statistical Language version 3.5.3 program and SPSS version 27.0.

Results

Table 1 summarizes the clinicopathological data of the 55 patients with SVI. The median follow-up period, age at operation, and PSA

Table 2. Univariable and multivariable analysis of the association of clinical and pathological features with biochemical recurrence

	Univariate	Multivariate		
	P-value	HR	95% CI	*P*-value
Clinical features				
Age (year)	0.575			
PSA value at biopsy (ng/mL)	0.054	1.096	1.035-1.162	0.002
Prostate volume at biopsy (mL)	0.151			
PSA density at biopsy (ng/mL/mL)	0.482			
Clinical T stage (T1, 2 vs T3)	0.685			
Grade group (lower; 1,2,3 vs higher; 4,5)	< 0.001	3.551	1.640-7.688	0.001
Pathological features				
EPE (negative vs positive)	0.002	5.402	1.247-23.405	0.012
RM (negative vs positive)	0.333			
LN (negative vs positive)	NA	NA		

CI, confidence interval; EPE, extraprostatic extension; HR, hazard ratio; LN, lymph node; PSA, prostate-specific antigen; RM, resection margin; NA, not assessed.

value were 65 ± 36.8 (36-94) months, 69 ± 6.1 (65-73) years, and 9.0 ± 5.9 (7.0-13.8) ng/mL, respectively. There were 47 (85%) and 8 (15%) patients with clinical T stage 1 or 2 and T stage 3 (cT3), respectively. None of the patients with cT3 had SVI prior to prostatectomy. Lymph node metastases were not detected in any patients in this study.

During the follow-up period, 31 patients (56%) developed BCR, of whom 29 patients (93%) tested positive for EPE. Among the 24 patients without BCR, 10 (42%) tested negative for EPE.

As presented in **Table 2**, the univariate analysis revealed a significant relationship between BCR and the Grade group ($P < 0.001$), as well as between BCR and positive EPE ($P = 0.002$). There were no significant differences in age ($P = 0.575$), PSA level ($P = 0.054$), prostate volume ($P = 0.151$), PSA density ($P = 0.482$), clinical T stage ($P = 0.685$), or resection margin status ($P = 0.333$). One of the eight patients with SVI without EPE had positive resection margins but no BCR. The multivariate analysis showed that higher PSA levels (hazard ratio [HR]: 1.096; 95% confidence interval [CI]: 1.035-1.162, $P = 0.002$), higher Grade group (HR: 3.551; 95% CI: 1.640-7.688, $P = 0.001$), and positive EPE (HR: 5.402; 95% CI: 1.247-23.405, $P = 0.012$) were significant prognostic factors for BCR.

Patients in the lower Grade group and negative EPE groups exhibited significantly lower BCR rates ($P < 0.001$ and $P = 0.002$, respectively).

However, the BCR rate was significantly higher in patients in the lower Grade group who were positive for EPE ($P = 0.019$), while the BCR rate was significantly lower in patients in the higher Grade group who were negative for EPE ($P = 0.027$) (**Figure 2**).

Discussion

The findings of this study showed a difference in the prognosis of PCa with SVI with or without EPE. SVI is a pathological feature associated with locally advanced cancer and poor prognosis; however, not all patients with positive SVI experience BCR. In contrast, EPE indicates tumor spread beyond the prostate and suggests more aggressive tumor behavior [21].

Carefully selected patients are more likely to benefit from observation with early salvage RTx, with reduced overtreatment and adverse effects of adjuvant RTx. In one study, more than 30% of patients with high-risk cancers never relapsed and could, thereby, avoid treatment with adjuvant RTx and its associated toxicity [15]. Similarly, in the present study, 44% of patients with SVI did not experience BCR. This finding suggests that not all patients with SVI necessarily require adjuvant therapy. In other reports, SVI combined with EPE has been associated with a higher frequency of BCR and

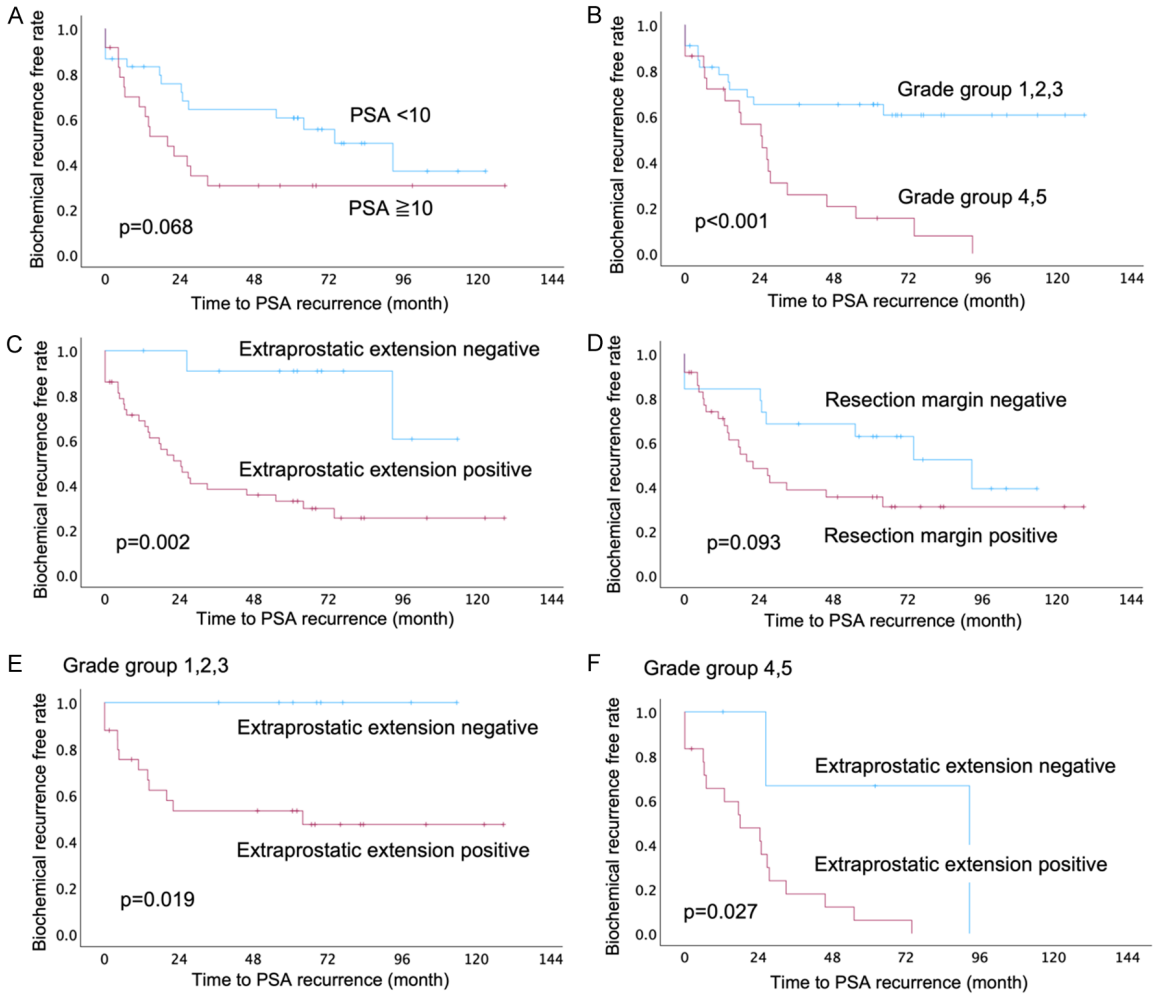

Figure 2. Kaplan-Meier analysis of the biochemical recurrence-free survival of patients who received radical prostatectomy divided by serum prostate level (A), Grade group (B), extraprostatic extension (C), and resection margin (D). The biochemical recurrence-free survival rate was significantly higher in the group without extraprostatic extension (negative group) than in patients with extraprostatic extension (positive group) across Grade group 1, 2, 3 (E) and Grade group 4 and 5 (F).

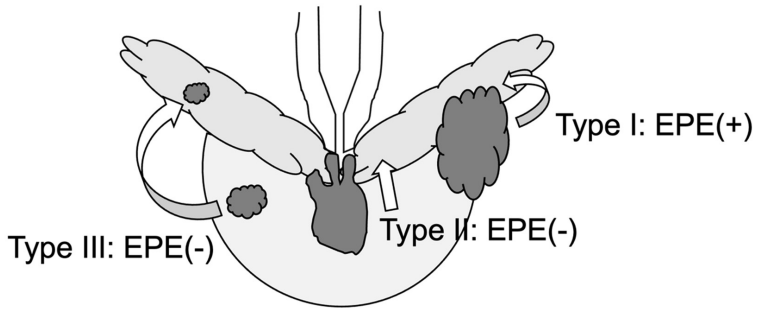

Figure 3. Diagrammatic representation of the three patterns of seminal vesicle invasion. Type I displays invasion through the prostatic capsule and into the seminal vesicle. Type II involves the direct spread of cancer along the ejaculatory duct complex into the seminal vesicle. Type III involves the local metastasis of PCa, remote from the primary intraprostatic index cancer into the seminal vesicle.

lymph node metastasis compared with SVI alone [22, 23]; however, these reports focused on Western populations. The differences in PCa between the Japanese and Western populations include incidence rates, stage at diagnosis, pathological features, treatment approaches, and genetic factors [24]. Furthermore, accurate stratification of the clinical and pathological features in a cohort of Japanese patients with SVI has not yet been reported.

It should be noted that the mechanism underlying favorable prognosis in patients with PCa with SVI but without EPE remains unclear. As shown in **Figure 3**, the extent and route of SVI in patients with PCa have been classified into three subtypes that reflect prognosis [25, 26]. Our classification of SVI was based on the framework proposed by Ohori et al., with modifications to simplify its clinical application. Type I displays invasion through the prostatic capsule and into the seminal vesicle, type II involves direct spread of cancer along the ejaculatory duct complex into the seminal vesicle, and type III involves local metastasis of PCa, remote from the primary intraprostatic index cancer into the seminal vesicle. Type I tumors with EPE are associated with a worse prognosis than is type II or III tumors without EPE. In this retrospective study, accurate stratification of the correct SVI type was difficult because all seminal vesicles were cut longitudinally. Thus, each section should have been examined transversely to adequately assess the SVI type. However, in the other previous report of prognostic analysis by SVI type, tumors with EPE had a better prognosis than did those without EPE [27]. As mentioned in this report, classification by type of SVI includes many mixed patterns, which are difficult to evaluate adequately. Although there have been reports that the presence or absence of EPE is not prognostic in patients with SVI cancers [28, 29], the present study differs in that the previous report included cases from a time when preoperative magnetic resonance imaging was not as commonly performed as it is these days and might include advanced-stage cases.

Despite these limitations, along with the limited number of patients and lack of long-term outcomes, this study is unique in that it simply focused on the invasion pattern of PCa with SVI. The simple postoperative risk stratification based on radical prostatectomy is significantly important [30, 31], and our study results provided a straightforward assessment. Clinicians should evaluate both SVI and EPE postoperatively using pathological analyses. The results of our study may benefit clinical assessments and decision-making for patients with PCa and SVI after RP. In patients with PCa with SVI, there is a difference in the prognosis with or without EPE; therefore, adjuvant therapy is not always necessary, and salvage therapy could be considered during follow-up.

In conclusion, our findings clarify the prognostic impact of EPE in patients with SVI after radical prostatectomy. Further studies are necessary to refine risk stratification strategies and optimize postoperative treatment decisions for managing these patients.

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Informed consent was obtained by using an opt-out approach.

Disclosure of conflict of interest

Takeo Kosaka is an Associate Editorial Board member of American Journal of Clinical and Experimental Urology and a co-author of this article. To minimize bias, Takeo Kosaka is excluded from all editorial decision-making related to the acceptance of this article for publication.

Abbreviations

BCR, Biochemical recurrence; EPE, extraprostatic extension; HR, hazard ratio; PCa, prostate cancer; PSA, prostate-specific antigen; RTx, radiation therapy; SVI, seminal vesicle invasion.

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