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Original Article

Is it important to see the coexistent seminal vesicle invasion and extracapsular extension at the radical prostatectomy specimen reports?

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Abstract

Aim: To evaluate the effect of coexistent extracapsular extension and seminal vesicle invasion on biochemical reccurence free survival rates in patients who had undergone open radical retropubic prostatectomy.

Material and Methods: The data of 307 patients with clinically localized prostate cancer who had undergone radical retropubic prostatectomy between January 2000 and May 2019 were evaluated retrospectively. According to extension of tumor on surgical specimens, patients were classified into five groups as; organ-confined disease, extracapsular extension, isolated seminal vesicle invasion, extracapsular extension in addition to seminal vesicle invasion and lymph node involvement. Patient groups were analyzed categorically with regard to biochemical reccurence free survival rates by using Kaplan Meier analysis, log-rank and chi-square tests. The effect of pathological features of surgical specimens on biochemical reccurence was evaluated by using univariate and multivariate Cox regression analysis.

Results: There were statistically significant differences on biochemical reccurence free survival rates among the five groups, and pathological stage and biochemical reccurence rates increased correspondingly. Multivariate Cox regression analysis showed that coexistent extracapsular extension and seminal vesicle invasion, and lymph node involvement are the two significant factors that negatively effect the biochemical reccurence free survival rate.

Conclusion: Coexistence of extracapsular extension and seminal vesicle invasion is a worse prognostic factor compared to their isolated forms

Keywords: Biochemical reccurence; extracapsular extension; prostate cancer; radical retropubic prostatectomy; seminal vesicle invasion

INTRODUCTION

Prostate cancer is one of the major health problems of the male population. Prostate cancer remains the most commonly diagnosed non-skin cancer and the second leading cause of cancer mortality among men (1).

Prostate cancer consists of localized stage (organ-confined) disease, locally advanced disease, metastatic disease and hormonal treatment resistant disease, respectively. The treatment of prostate cancer varies according to risk of prostate cancer. Depending on the tumour characteristics, oncological outcomes after initial treatment vary widely. Specifically, patients with high-risk prostate cancer are at higher risk of biochemical recurrence (BR) after initial treatment, as well as at higher risk of metastatic progression and cancer-specific mortality in comparison to low- or intermediate-risk prostate cancer (2).

The issue of choosing the most appropriate treatment for all stages of prostate cancer is still very controversial. With its high success and low morbidity rates, radical retropubic prostatectomy (RRP) is the most appropriate treatment method for patients with clinically localized prostate cancer with a life expectancy of more than 10 years (3).

Prognostic factors in RRP sample are Gleason score (GS), histologic type, extracapsular extension (ECE), seminal vesicle invasion (SVI), lymph node involvement (LNI), perineural invasion, lymphovascular involvement, surgical

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margin positivity, tumor location and distribution, tumor progression and vascular invasion. Demonstration of the invasiveness of the seminal vesicle muscle wall by prostate cancer after RRP is considered a poor prognostic factor for prostate cancer and has been associated with PSA recurrence and metastasis following surgery (4-6).

Seminal vesicles are not completely extraprostatic organs, and most of the proximal segment is located at the base of the prostate. SVI may occur by internal pathway (by ductus deferens) and external pathway (extracapsular spread), and in the internal pathway isolated SVI can occur without ECE (7,8). From this view of aspect, we aim to delineate whether it makes a difference in terms of prognosis or BR of prostate cancer between coexistent and isolated forms of SVI and ECE in patients for whom RRP was performed due to localized prostate cancer.

MATERIAL and METHODS

By the approval of the Local Ethics Committee, we included our 307 prostate cancer patients who underwent RRP due to clinically localized disease between January 2000 and May 2019 in our clinic.

Clinical and pathological data of the patients were retrospectively reviewed. All patients were diagnosed with prostate cancer by a pathologic examination of prostate needle biopsy from a digital rectal examination (DRE) abnormality and / or serum PSA elevation (> 4 ng / mL).

2002-TNM staging system was used in clinical and pathological staging. Clinical staging of patients was performed with DRE, serum PSA value, chest X-ray, whole body bone scintigraphy and pelvic radiographic imaging. Clinical and radiological examination of the patients showed no evidence of metastasis. None of the patients received hormonal therapy or radiotherapy prior to surgery.

RRP operation was performed under general anesthesia, at least 6 weeks after the date of the prostate biopsy. Additional pelvic lymphadenectomy was performed to the patients who have a life expectancy of more than 10 years.

Surgical materials were evaluated in terms of Gleason grade and score, high grade prostatic intraepithelial neoplasia, perineural invasion, lymphovascular invasion, ECE and SVI. In the pathological examination of the surgical specimens, microscopic spread of tumor cells beyond the prostate capsule were regarded as ECE, infiltration of the muscular wall of the seminal vesicle was assessed as SVI, and cancer limited to prostate was assessed as organ-confined prostate cancer.

Postoperative patients were called for control every 3 months in the first year, 6 months for the next 6 years, and then every year thereafter. DRE was performed in the control and patients were assessed for PSA for biochemical failure and local or distant metastases. BR was accepted as 0.2 ng / mL and higher in serum PSA levels in two consecutive measurements (at least 1 month apart) after RRP. Local recurrence was treated with adjuvant radiotherapy and / or and distant metastases was treated with androgen suppression therapy or bilateral orchiectomy.

Clinical and pathological data of the patients before and after surgery were evaluated in our study. According to extension of tumor on surgical specimens, patients were classified into five groups as; organ-confined disease, ECE, isolated SVI, ECE in addition to SVI and LNI. The distribution of these groups according to biochemical failure was studied. The statistical evaluation of the results was performed using "Statistical Package for the Social Sciences (SPSS) for Windows 18.0 (SPSS Inc., Chicago, IL)". Chi-square test was used in the categorical examination of patients who were divided into 5 groups according to extension of tumor in the RRP sample. Univariate and multivariate cox regression analysis was used to assess the factors affecting biochemical failure. Associated variables determined with univariate analysis were selected for multivariate analysis based on the logistic regression model. Relative risk and 95% CI (confidence interval) were calculated for each independent variable. Kaplan Meier and log rank analysis were used to assess biochemical recurrence-free survival rates (BRFS). A two-tailed p-value < 0.05 was considered statistically significant.

RESULTS

Preoperative clinical and biopsy parameters of the 307 patients are shown in Table 1. The postoperative surgical material was assessed for ECE, isolated SVI, additional ECE presence in SVI, LNI and organ-confined disease.

Table 1. Clinicopathological features of 307 patients

	Mean±SD
Age (y)	62.8 ± 6.1 (44-75)
PSA (ng/ml)	10.7 ± 6.8 (1.1-35)
Prostate Volume (ml)	46.1 ± 22 (12-190)
GS on biopsy specimen	5.7±1.3
GS on RRP specimen	6.1±1.3
Clinical Stage	
cT1a	14 (4.6%)
cT1b	28 (9.1%)
cT1c	122 (39.7%)
cT2a	78 (25.4%)
cT2b	44 (14.3%)
cT2c	21 (6.8%)
Pathological Stage	
pT0	2 (0.7%)
pT2a	87 (28.3%)
pT2b	52 (16.9%)
pT2c	64 (20.8%)
pT3a	59 (19.2%)
pT3b+T4	43 (14%)
Patient distribution according to serum PSA level	
<10ng/ml	176 (57.3%)
10-20 ng/ml	96 (31.3%)
>20 ng/ml	35 (11.4%)
Organ-confined	204 (66.4%)
ECE	58 (18.8%)
Isolated SVI	12 (3.9%)
SVI&ECE	17(5.5%)
LNI	16 (5.2%)

Mean follow-up time was 74.2 ± 37.2 months. Thirty patients were lost to contact. During the follow-up, BR was found in 23.4% (n=65) of the patients. BR was detected in 16 patients (9%) of the organ-confined group, 17 patients (17.5%) of the ECE group, 7 patients (58.3%) of the isolated SVI group, 14 patients (82.4%) of the ECE in addition to SVI group and 11 patients (78.6%) of the LNI group. As the pathological stage increased, the BR rate increased and the results were statistically significant (p = 0.0001).

The mean duration of BRFS was 115.5 ± 3.5 months (95% CI: 108.6-122.4). There was a statistically significant difference between the groups in terms of BRFS rates (p = 0.0001). The Kaplan-Meier graphic showing the BRFS curves of the groups is shown in Figure 1.

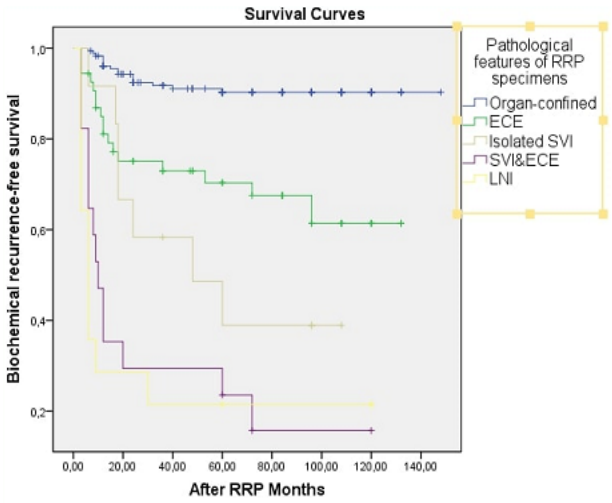

Figure 1. Biochemical recurrence-free survival rates of the groups

Table 2. Univariate Cox regression analysis of BR related factors after RRP

	RR	p-value	%95 CI	
			Low	High
Age (y)		0.24		
<60	1	-	-	-
60-70	1.60	1.1	0.89	2.87
>70	1.68	1.19	0.76	3.72
Preoperative serum PSA value (ng/ml)				
<10	1	-	-	-
10-20	1.74	0.05	1.00	3.03
>20	3.27	0.0001	1.73	6.17
Pathological features of RRP specimen				
Organ-confined	1	-	-	-
ECE	4.12	0.0001	2.08	8.16
Isolated SVI	7.37	0.0001	3.03	17.92
ECE in addition to SVI	16.72	0.0001	8.11	34.48
LNI	20.22	0.0001	9.30	43.95
RRP GS				
≥4+3	5.31	0.0001	3.25	8.68

The univariate Cox regression analysis of our study factors that may be associated with BR were evaluated. They were pathological features of RRP specimen (organ-confined, ECE, isolated SVI, ECE in addition to SVI and LNI), postoperative GS, patient age (> 60, 60-70,> 70) and preoperative serum PSA level (<10 ng / ml, 10-20 ng / ml,> 20 ng / ml). Risk factors associated with BR in univariate Cox regression analysis of our study were; preoperative serum PSA> 20 ng / ml (RR 3.27, 95% CI 1.73-6.17, p = 0.0001), ECE (RR 4.12, 95% CI 2.08-8.16, p = 0.0001), isolated SVI (RR 7.37, 95% CI 3.03-17.92, p = 0.0001), ECE in addition to SVI (RR 16.72, 95% CI 8.11-34.48, p = 0.0001), LNI (RR 20.22 95% CI 9.30-43.95, p = 0.0001) and RRP specimen GS≥ 4 + 3 (RR 5.31, 95% CI 3.25-8.68, p = 0.0001) (Table 2).

Table 3. Factors related to BR after RRP multivariate Cox regression analysis (backward stepwise)

Pathological Features of Groups	RR	p-value	95% CI	
			Low	High
Organ- Confined	1	-	-	-
ECE	2.02	0.083	0.91	4.48
Isolated SVI	2.78	0.050	0.99	7.76
ECE in addition to SVI	5.41	**0.0001**	2.20	13.30
LNI	5.33	**0.001**	1.99	14.26

Independent risk factors associated with BR in multivariate Cox regression analysis (Backward stepwise) of our study were; ECE in addition to SVI (RR 5.41, 95% CI 2.20-13.30, p = 0.0001) and LNI (RR 5.33, 95% CI 1.99-14.26, p = 0.001). There was no statistically significant correlation between ECE and isolated SVI groups in terms of BR. (Table 3).

DISCUSSION

Recent studies have frequently emphasized that SVI is a poor prognostic factor for recurrence of prostate cancer after RRP, as well as associated with distant metastasis and high failure rates (9). New studies have reported 5-year BRFS rates of between 17% and 56% (10). There are several reasons for such differences in long-term follow-up. Differences in GS, tumor volume, preoperative tumor stage, and these multiple pathologic parameters cause differences in the prognosis of patients with SVI (11). However, SVI variations are less well-known of these prognostic differences. There are few studies on this subject. The route of SVI has served as an obvious source of potential differentiation of tumors with SVI into prognostic groups (8). The route of SVI and its clinical significance has been the subject of debate, and several studies have been conducted on this topic and it has been shown that SVI is occured in three possible ways (7) (Figure 2).

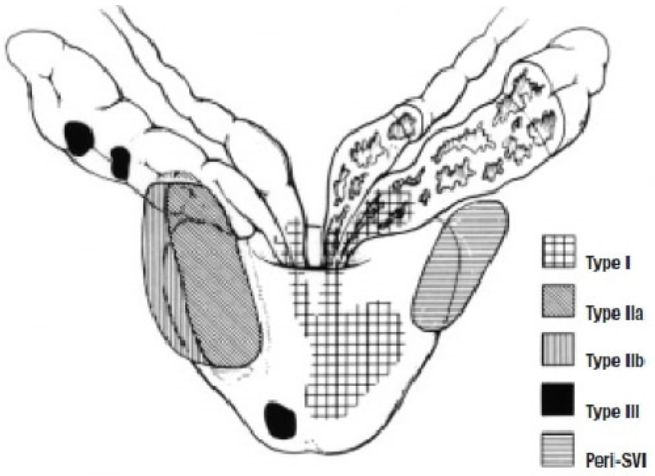

Figure 2. Diagrammatic representation of patterns of seminal vesicle invasion

According to this following factors were detected;

Type 1: Direct spread of prostate cancer along the ejaculatory duct complex into the seminal vesicle

Type 2: Invasion occurring through the prostatic capsule and into the seminal vesicle

2A: Direct spread of prostate cancer between the base of the prostate and the seminal vesicle

2B: Retrograde growth of the prostate cancer into the seminal vesicle from periprostatic nerve involvement

Type 3: Prostate cancer metastases in the seminal vesicle remote from the primary intraprostatic cancer focus.

In the study examining the prognostic significance of these routes of invasion conducted by Ohori et al., tumors demonstrating type 1 invasion were associated with a worse prognosis than were tumors revealing type 3 invasion (7). The study by Billis et al. confirms the results of Ohori et al. and they did not detect BR in any of the type 3 invasion and correlated this with the absence of ECE in this group (12). Villers and colleagues reported that the majority of SVI occurred at the ejaculatory duct sheath, either penetrating the muscular wall of the ejaculatory duct or extending up the ejaculatory duct and into muscle of the seminal vesicle wall. In addition, they reported that a minority of tumors penetrated the prostatic capsule and invaded the seminal vesicle either directly or by extension into periprostatic soft tissue and then into the seminal vesicle (13).

Consequently, if tumor extends via the ejaculatory duct into the seminal vesicles but not into the periprostatic soft tissue, some investigators would report an absence of ECE and believe that there is no clear difference in prognosis between these lesions and truly organ-confined lesions on the basis of the absence of ECE in these lesions (14,15).

In the light of current studies, it is argued that SVI might develop in the absence of ECE and furthermore, ECE accompanied by SVI can make difference regarding the prognosis. Despite the poor prognostic outcome of SVI, the results of our study support that the patient group with isolated SVI is not different in terms of cancer progression from the patient group with isolated ECE, but in the presence of ECE in addition to SVI, this patient group has a greater risk of cancer progression. We believe that these results should be supported by more comprehensive and prospective studies.

CONCLUSION

In clinical practice, SVI is considered as a type of ECE by the majority of urologists and the presence or absence of additional ECE is ignored in many situations. Contrary to common belief, SVI might occur with/without ECE. If there is additional ECE, this situation further increases the likelihood of BR after RRP, compared to isolated SVI. We encourage the urologists to be more careful in terms of cancer progression in this patient group.

Competing interests: The authors declare that they have no competing interest.

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