Comparison of Localized High Volume Tumor and Locally Advanced Low Volume Tumor after Radical Prostatectomy according to Risk Classification

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Purpose: To investigate the percentage of pathologic tumor volume (pTPV) among patients who underwent radical prostatectomy (RP).

Materials and Methods: We reviewed 3,080 patients who underwent RP between September 2003 and March 2015 and with a postoperative follow-up for more than 1 year. The patient population was stratified into 4 disease risk groups according to tumor stage and pTPV (T2 low volume [T2LV], T2 high volume [T2HV], T3 low volume [T3LV], and T3 high volume [T3HV]). Probability of biochemical recurrence (BCR)-free survival was determined using Kaplan-Meier curves. pTPV was evaluated by Multivariate Cox proportional hazard analysis for predicting BCR. Subgroup analyses were performed according to preoperative risk.

Results: The median prostate-specific antigen (PSA) was 7.87 ng/mL, and pTPV was 10%. Among a total of 2,964 patients, T2LV had 1,473 (49.7%), T2HV was 598 (20.2%), T3LV with 199 (6.7%), and T3HV was 694 (23.4%). When comparing T2HV and T3LV, Gleason score and positive surgical margin rate was higher in T3LV. During a 50-month follow-up, BCR-free survival rate was higher in the T2HV group ($p < 0.001$). pTPV was a significant factor to predict BCR in multivariate Cox analysis. In subgroup analyses, T2HV group had similar BCR-free survival rates to T3LV group in the preoperative high risk group while pTPV was significant in the high risk group.

Conclusions: pTPV was a significant predictor of BCR among prostate cancer patients after RP, however T2HV had favorable BCR results. Among patients with a preoperative high PSA and Gleason score, T2HV had similar BCR results to T3LV. (Korean J Urol Oncol 2016;14:165-171)

Key Words: Prostate • Prostate cancer • Recurrence • Tumor volume

INTRODUCTION

Prostate cancer (PCa) is the second most frequently diagnosed cancer and the fifth leading cause of cancer death in males worldwide. It was accountable for 15% of the total new cancer cases and 7% of total male cancer deaths in 2012.¹ Currently, radical prostatectomy (RP) is the only surgical option for patients with localized PCa.² While most localized PCa patients have an excellent 10-year biochemical recurrence (BCR)-free survival rates of 73% to 99%, some cancers will

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eventually recur.^{3,4} Previous studies have identified variables such as prostate-specific antigen (PSA), pathological substage, Gleason score and/or positive surgical margins (PSMs) as predictors of BCR. However, the aforementioned studies had limited accuracy and predictive power. Therefore, studies concerning increased accuracy and prediction of BCR are necessary.

Traditionally, in solid organ cancer, tumor size or tumor volumes (TVs) are important factors to predict cancer related outcomes and prognosis.⁵ The size of a tumor is an important reflection of its biology, determined by complex interacting factors such as cell proliferation, apoptosis and angiogenesis.^{6,7} TV at the time of treatment for clinically localized PCa could reflect important properties that influence its clinical behavior. Despite the biological relevance of tumor size, the status of TV in PCa as an independent predictor of outcome after RP has not been well defined. Some studies demonstrated a positive relationship between TV and cancer progression;⁸ others argued that TV is not an independent predictor of PCa progression when incorporating the more readily determined tumor grade and stage in the analysis.⁹⁻¹¹

Additionally, several studies have reported the predictive value of the percentage of pathologic tumor volume (pTPV) in prediction of BCR.¹²⁻¹⁷ Even though TV shows potential to be a significant factor, there were no studies done on the comparison of localized high volume PCa and low volume advanced PCa. Therefore we investigated the aforementioned issue among PCa patients who underwent RP using pTPV.

MATERIALS AND METHODS

1. Patients

After obtaining Institutional Review Board approval (IRB No. SNUBH-B-1612-375-103), we reviewed the data of 3,080 patients who underwent RP for PCa between September 2003 and March 2015 at Seoul National University Bundang Hospital and were postoperatively followed up for more than 1 year. The patient population was stratified into 4 disease risk groups—T2 low volume group (T2LV), T2 high volume group (T2HV), T3 low volume group (T3LV) and T3 high volume group (T3HV)—according to tumor stage and the median pTPV value of 10%. After excluding patients who underwent neoadjuvant, adjuvant hormone or radiation therapy and pathologic T4 and node positive disease and those with inadequate data, a total of 2,964 patients were included in the final analysis.

2. Pathologic Evaluation

Specimens from RPs were weighed, fixed intact in 20% neutral buffered formalin, and sectioned at 3- to 4-mm intervals with the apical and bladder neck portion sectioned radially to allow evaluation of margin status parallel to urethra. For each pathologic slide, the percent of tumor involvement per slide was estimated, and pTPV was determined by averaging the estimates from all slides using methods previously reported by others.^{13,18}

3. Statistical Analysis

Data assessment included patient age, preoperative PSA level, prostate specimen weight, pTPV, pathologic Gleason score, pathologic stage, surgical margin status, lymph node involvement, and postoperative follow-up PSA data, and was compared according to groups via tumor stage and pTPV by the Mann-Whitney U or Kruskal-Wallis test. BCR was defined as two consecutive rises in PSA of 0.2 ng/mL or higher at a minimum of 2 months following RP.¹⁹ Probability of BCR-free survival was determined using Kaplan-Meier curves with log rank test used to assess statistical significance. Effects of various variables on BCR-free survival were assessed using the Cox proportional hazards model. An additional subgroup analysis was performed via clinical risk classification. The SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. A two-tailed $p < 0.05$ was considered significant for all analyses.

RESULTS

1. Baseline Characteristics

Patient characteristics are shown in Table 1. When stratified into groups (T2LV, T2HV, T3LV and T3HV), 1,473 patients (49.7%) had pathologic T2 and pTPV less than 10% (T2LV), 598 patients (20.2%) had pathologic T2 and pTPV $\geq$ 10% (T2HV), 199 patients (6.7%) were T3LV and 694 patients (23.4%) were T3HV. Among total patients, the median PSA was 7.87 ng/mL, and median pTPV was 10% (mean value; 16.9%). In pT2 patients (n=2,071), the T2HV group had a higher pathologic Gleason score, PSM rate and BCR rate than T2LV ($p < 0.001$). In pT3 patients (n=893), the T3HV group also had a higher pathologic Gleason score, PSM rate, seminal vesicle invasion (SVI) and BCR rate than T2LV ($p < 0.001$).

Table 1. Baseline characteristics of entire patients according to tumor volume and pathologic stage

Characteristic	T2LV	T2HV	T3LV	T3HV	p-value
No. of patients	1,473	598	199	694	
Age (y)	65.45±6.99	65.58±6.91	67.36±6.08	66.66±6.51	<0.001
Body mass index (kg/m ²)	24.43±6.85	24.32±2.91	25.75±16.59	24.45±2.84	0.059
Prostate specific antigen (ng/mL)	6.21±8.84	8.57±11.21	7.45±6.40	14.61±22.20	<0.001
Pathological Gleason score					<0.001
6	291 (19.8)	28 (4.7)	4 (2.0)	6 (0.9)	
7	1,123 (76.2)	524 (87.6)	162 (81.4)	474 (68.3)	
≥8	59 (4.0)	46 (7.7)	33 (16.6)	214 (30.8)	
Prostate volume (mL)	42.46±16.11	36.19±11.46	40.13±12.58	38.96±13.30	<0.001
Tumor volume ratio (%)	4.88±2.85	22.99±61.73	7.24±2.30	38.66±89.87	<0.001
Seminal vesicle invasion	0 (0)	0 (0)	29 (14.6)	221 (31.8)	<0.001
Positive surgical margin	141 (9.6)	151 (25.3)	73 (36.7)	409 (58.9)	<0.001
Biochemical recurrence	87 (5.9)	77 (12.9)	49 (24.6)	310 (44.7)	<0.001
Mean follow-up duration (mo)	46.25	46.94	50.11	45.59	0.480

Values are presented as mean±standard deviation or number (%) unless otherwise indicated.

LV: low volume, HV: high volume.

Table 2. Multivariate Cox proportional hazard analysis to predict biochemical recurrence after radical prostatectomy among total patients

Variable	Hazard ratio	95% CI	p-value
Age	0.995	0.981–1.008	0.439
Prostate-specific antigen	1.010	1.006–1.013	<0.001
Prostate volume	1.002	0.995–1.008	0.602
Pathologic Gleason score	3.409	1.935–6.007	<0.001
Extracapsular extension	2.553	2.039–3.196	<0.001
Seminal vesicle invasion	2.727	2.195–3.389	<0.001
Positive surgical margin	1.951	1.597–2.384	<0.001
Positive tumor volume (10%)	1.569	1.248–1.973	<0.001

CI: confidence interval.

When comparing T2HV and T3LV groups, pathologic Gleason score ($p<0.001$), PSM ($p=0.002$), and BCR ($p<0.001$) were higher in the T3LV group.

2. BCR-free Survival Analysis

Univariate analysis showed that pTPV was associated with BCR-free survival among total patients (log rank $p<0.001$). A multivariate Cox proportional hazards regression model demonstrated that pTPV was an independent predictor of BCR-free survival ($p<0.001$) in the study population after adjusting for age, PSA, prostate volume, pathologic Gleason score, extracapsular extension, SVI, and PSM (Table 2). Among the 4 groups, BCR-free survival rates were significantly different as shown in Fig. 1 (log rank test, all $p<0.001$). The 10-year

Fig. 1. Biochemical recurrence-free survival rate according to tumor stage and percentage of pathologic tumor volume. T2LV: T2 low volume group, T2HV: T2 high volume group, T3LV: T3 low volume group, T3HV: T3 high volume group.

BCR-free survival was calculated as 86.1% in T2LV, 76.0% in T2HV, 59.7% in T3LV, and 26.2% in T3HV.

3. Subgroup Analysis according to Risk Group

In a subgroup analysis according to stratification of risk classification, pTPV was a significant predictor to BCR only in the high risk group and not in the low-intermediate risk group (Table 3). As shown in Fig. 2, T2LV PCa had a significantly higher BCR-free survival rate compared to other groups (vs. T2HV, $p=0.003$; vs. T3LV, $p<0.001$; T3HV, $p<0.001$). However, in the low risk classification groups, there were no

Table 3. Multivariate Cox proportional hazard analysis to predict biochemical recurrence after radical prostatectomy according to risk group

Variable	Low risk group			Intermediate risk group			High risk group		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	0.964	0.924-1.006	0.091	0.984	0.959-1.010	0.236	1.000	0.983-1.018	0.992
PSA	1.111	0.961-1.284	0.206	1.045	1.006-1.086	0.024	1.004	0.996-1.008	0.087
Prostate volume	0.982	0.955-1.010	0.206	0.988	0.974-1.003	0.111	1.004	0.996-1.012	0.302
Pathologic Gleason score	1.226	0.585-2.567	0.590	3.586	1.983-6.484	<0.001	2.110	1.672-2.663	<0.001
ECE	2.567	1.329-4.959	0.005	2.324	1.601-3.375	<0.001	2.016	1.470-2.766	<0.001
SVI	14.917	3.355-66.330	<0.001	1.761	1.058-2.932	0.029	2.011	1.566-2.582	<0.001
PSM	3.795	1.965-7.332	<0.001	2.073	1.460-2.944	<0.001	1.547	1.191-2.010	0.001
PTV (10%)	1.063	0.550-2.054	0.856	0.828	0.569-1.203	0.321	1.914	1.325-2.765	0.001

HR: hazard ratio, CI: confidence interval, PSA: prostate-specific antigen, ECE: extracapsular extension, SVI: seminal vesicle invasion, PSM: positive surgical margin, PTV: pathologic tumor volume.

Fig. 2. Biochemical recurrence-free survival rate according to tumor stage and percentage of pathologic tumor volume. T2LV: T2 low volume group, T2HV: T2 high volume group, T3LV: T3 low volume group, T3HV: T3 high volume group.

significant differences. In the intermediate risk group, T2LV and T2HV had similar BCR-free survival rate and T3LV and T3HV had also similar results for BCR rate. Cox proportional multivariate analysis also showed that pPTV was not a significant predictor to BCR in the low and intermediate risk group (Table 3). However in the high risk group, the T2HV

group had similar BCR-free survival rates when compared to the T3LV group (Fig. 2C) ($p=0.543$). As shown in Table 3, pPTV was a significant predictor to BCR only in the high risk group (hazard ratio, 1.914; 95% confidence interval, 1.325-2.765; $p<0.001$) after adjusting for other factors.

DISCUSSION

In our study, pTPV was observed to be an independent predictor of BCR-free survival following RP among the total subjects. In high pTPV organ confined PCa, BCR free survival rates are favorable compared to locally advanced PCa regardless of pTPV. However in high risk groups who have a higher PSA and Gleason score, PTV could be a significant factor to predict BCR, and our study shows that T2HV disease had similar BCR related results compared to T3LV after RP.

Our finding that TV is an independent prognosticator of BCR agrees with several independent studies.^{8,20-22} Humphrey et al.^{23,24} reported that intraglandular tumor extent measured as percent of carcinoma correlated with disease progression following RP among patients with clinically localized PCa. Moreover, Carvalhal et al.²⁵ and Ramos et al.¹³ observed that pTPV was an independent predictor of BCR among patients who underwent RP for pathologically organ confined disease. Furthermore, a study done by Rampersaud et al.¹⁸ showed that pTPV was a significant factor in disease progression following RP even after adjusting for multiple clinical and pathological characteristics for margin positive or extraprostatic extension of tumor as well as those with pathologically organ-confined disease. On the other hand, Epstein et al.⁹ reported from their series of clinically localized PCa patients treated with RP that PTV did not provide independent information beyond that offered by other factors.

The aforementioned studies are a reflection of the ongoing controversy surrounding the actual value of pTPV as a potential prognostic indicator in patients who underwent RP. There are several possible explanations for the disagreement of the role of volume in risk of recurrence. One explanation of these differences is in the methods used to measure TV. In several series, objective measures of TV, such as by computerized planimetry or measurement of the greatest tumor dimension, have demonstrated prediction of BCR after RP independent of other clinical and pathological variables.^{26,27} Subjective measures, such as visual estimates of tumor size or percentage of gland involvement, have failed to provide prognostic information, although the literature is conflicting.²⁵ A second explanation could be due to a small study cohort or small TV in series in which volume has failed to correlate with outcome. Finally, some studies include large numbers of patients with relatively

low grade cancers. Merrill et al.¹⁵ found that in patients with a pathologic Gleason score of 6 or less, TV failed to predict for BCR. Therefore, the inclusion of patients with Gleason grade 3+3 disease in prognostic models will corrupt the predictive power of TV.

Results from our study show that pTPV was an independent predictor of BCR-free survival following RP. However, the predictive value of pTPV was only significant in the high risk D'Amico classified group, which shows that pTPV could be a significant factor to predict BCR in highly aggressive tumors and in the low or intermediate risk groups, tumor staging is a much more important factor compared to TV.

The Gleason grade represents tumor differentiation while pTPV reflects the tumor burden; these are principal outcome determinants in any solid organ cancer. Pathologic stage represents the disease extent resulting directly from the combination of both factors; all other clinicopathologic factors may have potential to influence outcome. Therefore, in pT2 PCa, prognosis may be primarily determined by pTPV and the Gleason grade; T2HV disease with high a PSA and Gleason score disease should treated and managed in similar fashion to locally advanced PCa.

TV or size is considered as an important prognostic indicator in many cancer types and is often included in pathological staging.²⁰⁻²² However, the importance of TV in the prognosis of PCa has been debated. The main reason for this ongoing debate has been a lack of consensus on the best way to assess cancer volume or extent.²⁸ Some proposed the direct measurements of TV, while others have used percent cancer as a ratio of TV to total prostate volume as an estimate of the percentage of the gland involved with cancer.^{21,22} To date, TV and percent cancer have not been compared directly.

Potential limitations of our study include the retrospective nature of study design. Moreover, we could not control for intra- or interobserver variability in assessing pTPV. Although pTPV in all specimens were calculated by an experienced single uropathologist, pTPV measurement done by computerized morphometric methods would be regarded as a more accurate estimate of the actual tumor burden. The present study was a retrospective analysis with a short median follow-up duration was 48 months in our study. Due to the lack of long term follow up, time to BCR rather than cancer-specific survival was designated as the primary endpoint in our study. A final limitation of the present study is that the different number of sub-

jects according to each group could affect the interpretation of our results. Therefore, the results of this study should be validated in a large scaled cohort study.

CONCLUSIONS

The present study demonstrated that pTPV was a significant predictor of BCR among patients who underwent RP. Patients with a high pTPV, organ confined disease had a favorable BCR-free survival rate compared to locally advanced PCa regardless of pTPV. However in the high risk group, T2HV disease had similar BCR related results when compared to T3LV after RP, therefore, patients with T2HV with a high PSA and Gleason score disease should be approached and managed similarly to locally advanced PCa.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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