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Prostate Volume has Prognostic Value Only in Pathologic T2 Radical Prostatectomy Specimens

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The objective of this study was to evaluate the prognostic roles of the prostate volume, tumor volume, and tumor percentage as a function of the pathologic T stage in radical prostatectomy specimens. This study included 259 patients who underwent radical prostatectomy between 2005 and 2010. The mean follow-up period was 41.2 months. In all of the specimens, prostate volume ($P = 0.021$), the Gleason score ($P = 0.035$), and seminal vesicle invasion ($P = 0.012$) were independent predictors of biochemical recurrence (BCR). In the T2 group, multivariate analysis showed that the BCR was significantly associated with prostate specific antigen (PSA) ($P = 0.028$), a lower prostate volume ($P = 0.004$), and the Gleason score ($P = 0.040$). The Kaplan-Meier survival curve showed that a smaller prostate volume was significantly associated with a greater risk of BCR (< 30 vs ≥ 30 mL; $P = 0.010$). In the T3 group, patients with seminal vesicle invasion had a significantly shorter mean BCR-free survival ($P = 0.030$). In this study, tumor volume and tumor percentage did not predict BCR. Notably, a lower prostate volume is an independent predictor for BCR only in the organ-confined radical prostatectomy specimens. But, prostate volume could not predict BCR in most locally advanced tumors.

Key Words: Prostate; Prostatic Neoplasms; Prostatectomy; Volume

INTRODUCTION

Recently, Korea has faced a very rapid change and increase in the incidence of prostate cancer, which draws much attention in public health. According to the Korea National Cancer Incidence Database, the incidence for prostate cancer increased annually by 13.4% from 1999 to 2007 (1, 2). The early detection of prostate cancer with prostate specific antigen (PSA) testing allows many patients the option of radical treatment with curative intent. However, approximately 25% of patients will develop a post-operative biochemical recurrence (BCR) by the time of the 5-yr follow-up, and the 10-yr risk of BCR is approximately 35% (3-6). The prognosis after radical prostatectomy is usually based on clinical findings (pre-operative PSA level and the PSA doubling time) and pathologic findings (the Gleason score, surgical margin status, extra-prostatic extension, and seminal vesicle invasion) (7, 8).

Several investigators have suggested that tumor volume and tumor percentage are independent predictors of recurrence (9-11). Freedland et al. (12) have suggested that prostate volume may be an important prognostic variable to predict BCR and men with smaller prostates have more high-grade cancers, more advanced disease, and at greater risk of progression after radical prostatectomy. However, others have argued that prostate volume, tumor volume, and tumor percentage are not independent predictors of prostate cancer progression when incorporating the more readily determined tumor grade and stage in the analysis (13, 14). Despite the biological relevance of tumor burden, the status of prostate volume, tumor volume, and tumor percentage as independent predictors of outcome after radical prostatectomy has not been well-defined. Furthermore, late in the PSA era, no study has investigated the importance of prostate volume, tumor volume, and tumor percentage in predicting outcome, especially in patients with pathologically organ-confined tumors.

In this study we evaluated and compared prostate volume, tumor volume, and tumor percentage as independent predictors of BCR after radical prostatectomy by pathologic T stage. This is the first study to examine the role of prostate volume, tumor volume, and tumor percentage as it relates to BCR in men stratified by pathologic T stage.

MATERIALS AND METHODS

Study population

Two hundred fifty-nine Korean men, 49-80 yr of age, with clinically localized or locally advanced adenocarcinoma of the prostate were included in this retrospective study. The patients un-

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derwent radical prostatectomy at our institution between February 2005 and February 2010. We excluded from analysis patients who received hormone or radiation therapy before surgery, used 5α-reductase inhibitor therapy, had pathologic T0 disease, and those with incomplete clinical or pathologic data. After the radical prostatectomies, patients were followed by measurements of serum PSA levels at ≤ 3 month intervals for the first 2 yr and every 6 months thereafter. A BCR was defined as a postoperative serum PSA of at least 0.2 ng/mL, increasing at least 1 subsequent estimation. Irrespective of the pathologic findings, suggesting a poor prognosis, none of the patients received any adjuvant therapy until the BCR was detected.

Specimen collection

Fresh specimens were weighed and fresh weight was used as a surrogate for total prostate volume. Actual prostate weight was measured after removal at radical prostatectomy, and after removing the seminal vesicles, with the exception of the base. The apex and bladder base were amputated. Prostate volume was determined by assuming that prostatic tissue was composed primarily of water and converting weight in gram to mL (1 g H_2O = 1 mL H_2O). The specimens were then fixed in formalin and serially-sectioned at 3-mm intervals in a plane perpendicular to the rectal surface and embedded in paraffin. Specimens were then cut at a thickness of 5 μm and examined microscopically. One professional uropathologist examined slides without knowledge of patient outcome. The tumor area was marked on the glass slide, the diameter was measured, the vol% was calculated, and the specimen was graded according to the Gleason system (15). Tumor volume was determined using a visual estimation. The area of the tumor was measured in x and y diameters and multiplied by the depth, based on the presence of tumor in subsequent sections and the thickness of the sections. The sum total of all foci of tumor was the estimated tumor volume. This method of visual estimation was previously described and validated in other studies (16). Tumor involvement of each slide was estimated by the percentage of the slide containing tumor. Estimation of the tumor percentage for the entire prostate was completed by summing each individual slide and averaging the results from all slides that were analyzed. The individual slides were also examined for the presence of standard pathologic indices, including pathologic stage, margin status, Gleason score, lymph node involvement, seminal vesicle invasion, and extracapsular extension of the tumor.

Statistical analysis

Patients were divided into two groups on the basis of the pathologic T stage (T2 and T3). A Cox proportional hazard model with stepwise selection of the co-variates was used to determine whether or not the prostate volume, tumor volume, tumor percentage, PSA, Gleason score, surgical margin status, or seminal vesicle invasion predicted the BCR. Univariate and multivariate analyses were performed for each group to determine the significance of the prostate volume, tumor volume, or tumor percentage as predictors of BCR within these subsets. Patients were stratified by prostate volume (≥ 30 mL or < 30 mL). Cut-off points for the variable prostate volume was chosen to separate the patient populations by median value. A BCR-free survival curves was plotted according to the Kaplan–Meier method. A log-rank test was applied to determine the relationship between prognostic markers and BCR. The levels of statistical significance were set at a $P < 0.05$ (two-sided), and the Statistical Package for the Social Sciences for Windows (version 12.0) was used for statistical analysis.

Ethics statement

The study protocol was approved by the institutional review board at the National Cancer Center Hospital (Goyang, Korea; IRB registration number-NCC NCS 05-049). An informed consent was obtained from each patient.

RESULTS

Clinico-pathologic characteristics

Two hundred fifty-nine patients were included in this study. The median duration of follow-up after radical prostatectomy was 40 months (range, 6-63 months). The data on patient age, PSA, pathologic features, and BCR are summarized in Table 1. During the present observation period, BCR developed in 59 of 259 patients (22.8%). Within the entire group, 29.7% of the patients

Table 1. Patient characteristics stratified by organ confinement

Variables	Organ confinement		*P* value
	Organ-confined (n = 182)	Extra-prostatic (n = 77)	
Mean (range) age (yr)	64.3 (50-80)	64.6 (49-78)	0.520
Mean (range) PSA (ng/mL)	17.5 (0.8-173.6)	24.7 (3.7-95.8)	0.082
Prostate volume (range) (mL)	33.2 (10.6-91.0)	28.6 (6.0-88.8)	0.032
Tumor volume (range) (mL)	4.9 (0.3-40.2)	8.4 (0.4-28.8)	0.001
Tumor percentage (range) (%)	14.2 (2.0-80.0)	27.9 (5.0-80.0)	< 0.001
Biopsy GS (%)			< 0.001
5-7	172 (94.5)	56 (72.5)	
8-10	10 (5.5)	21 (27.5)	
Post-operative GS (%)			0.004
5-7	145 (97.3)	42 (79.2)	
8-10	4 (2.7)	11 (20.8)	
Surgical margin status (%)			0.470
Positive	52 (28.6)	27 (35.3)	
Negative	130 (71.4)	50 (64.7)	
Seminal vesicle invasion (%)			< 0.001
Positive	0 (0.0)	25 (33.3)	
Negative	182 (100.0)	51 (66.7)	
BCR (%)			< 0.001
Occurred	23 (12.6)	36 (47.1)	
Did not occur	159 (87.4)	41 (52.9)	

PSA, prostate-specific antigen; GS, Gleason score; BCR, biochemical recurrence.

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had stage pT3, 30.5% were surgical margin-positive, and 9.6% had evidence of seminal vesicle invasion. The mean serum PSA value for patients with organ-confined and extra-prostatic disease was 17.5 and 24.7 ng/mL, respectively. Extra-prostatic disease was associated with biopsy Gleason score ($P < 0.001$), post-operative Gleason score ($P = 0.003$), seminal vesicle invasion ($P < 0.001$), BCR ($P < 0.001$), lower prostate volume ($P = 0.032$), higher tumor volume ($P = 0.001$), and higher tumor percentage ($P < 0.001$).

The impact of prostate volume, tumor volume, and tumor percentage on BCR in all specimens

There were BCRs in 59 of 259 patients (22.8%). We evaluated the predictive value of several clinicopathologic factors for BCR. By univariate Cox proportional hazards analysis, most of the parameters, except surgical margin status ($P = 0.324$), significantly influenced the time to BCR. Multivariate Cox proportional hazards analysis revealed that BCR was significantly associated with a prostate volume (hazard ratio [HR] = 0.919, $P = 0.021$), biopsy Gleason score (HR = 2.150, $P = 0.035$), seminal vesicle invasion (HR = 6.650, $P = 0.012$), and extra-prostatic extension (HR = 2.006, $P = 0.048$; Table 2). The Kaplan-Meier survival curve showed that a smaller prostate volume was significantly associated with a greater risk of BCR (comparing < 30 vs ≥ 30 mL; $P = 0.001$; Fig. 1A).

The impact of prostate volume, tumor volume, and tumor percentage on BCR in stage pT2 specimens

There were BCRs in 23 of 182 patients (12.6%) with stage pT2. Based on univariate Cox proportional hazards analysis, the PSA ($P = 0.006$), prostate volume ($P = 0.007$), and high biopsy Gleason score ($P = 0.015$) significantly influenced the time to BCR. Multivariate Cox proportional hazards analysis revealed that BCR was significantly associated with a PSA level (HR = 1.016, $P = 0.028$), prostate volume (HR = 0.885, $P = 0.004$), and biopsy Gleason score (HR = 2.121, $P = 0.040$; Table 3). The Kaplan-Meier survival curve showed that a smaller prostate volume was significantly associated with a greater risk of BCR (< 30 vs ≥ 30 mL; $P = 0.010$; Fig. 1B).

The impact of prostate volume, tumor volume, and tumor percentage on BCR in stage pT3 specimens

There were BCRs in 36 of 77 patients (47.1%) with stage pT3. Based on univariate Cox proportional hazards analysis, the PSA ($P < 0.001$), tumor volume ($P = 0.020$), tumor percentage ($P =$

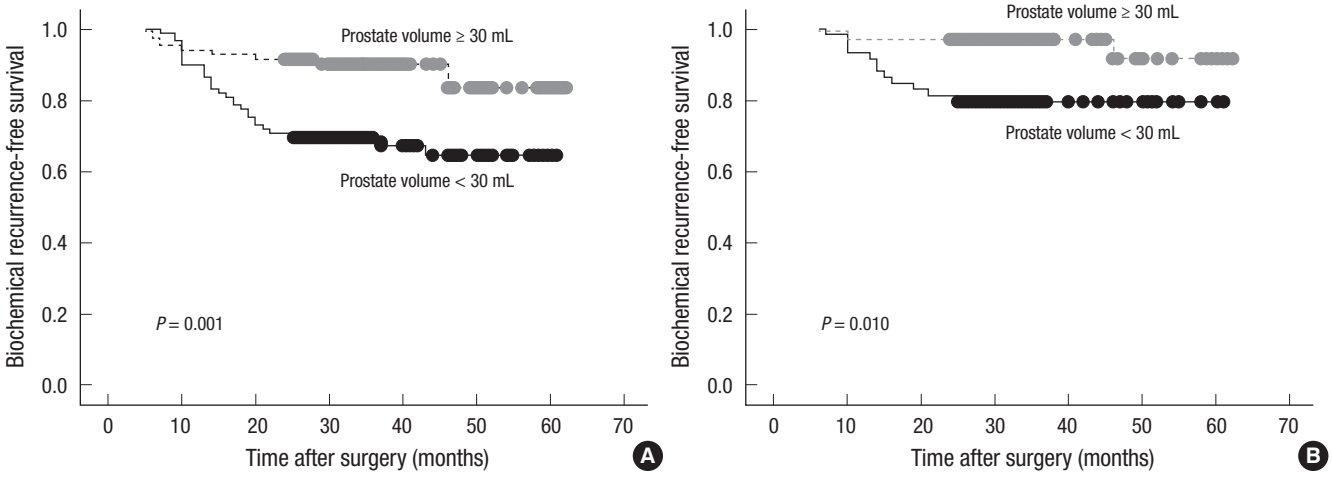

Fig. 1. BCR-free survival curves according to the prostate volume in all (**A**) and pT2 (**B**) specimens.

Table 2. Univariate and multivariate analyses of prognostic factors for biochemical recurrence in all specimens (n = 259)

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PSA	1.015 (1.009-1.023)	< 0.001	1.003 (0.983-1.024)	0.748
Prostate volume	0.951 (0.919-0.980)	0.003	0.918 (0.855-0.987)	0.021
Tumor volume	1.051 (1.014-1.089)	0.008	1.109 (0.885-1.388)	0.365
Tumor percentage	1.035 (1.020-1.047)	< 0.001	0.991 (0.917-1.071)	0.823
Biopsy GS (5-7 vs 8-10*)	4.830 (2.473-9.435)	< 0.001	2.150 (1.576-2.941)	0.035
Post-operative GS (5-7 vs 8-10*)	4.255 (1.558-11.623)	0.007	1.626 (0.451-5.865)	0.459
Surgical margin status (negative vs positive*)	1.393 (0.721-2.694)	0.324	-	-
Seminal vesicle invasion (absence vs presence*)	7.893 (3.997-15.591)	< 0.001	6.644 (1.573-28.061)	0.012
Extra-prostatic extension (absence vs presence*)	4.440 (2.328-8.479)	< 0.001	2.005 (1.202-2.835)	0.048

*Reference category. PSA, prostate-specific antigen; GS, Gleason score; HR, hazard ratio; CI, confidence interval.

Table 3. Univariate and multivariate analyses of prognostic factors for biochemical recurrence in stage pT2 specimens (n = 182)

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PSA	1.014 (1.003-1.026)	0.007	1.016 (1.002-1.031)	0.028
Prostate volume	0.902 (0.843-0.965)	0.005	0.881 (0.811-0.959)	0.004
Tumor volume	0.983 (0.889-1.088)	0.748	-	-
Tumor percentage	1.016 (0.985-1.046)	0.264	-	-
Biopsy GS (5-7 vs 8-10*)	4.953 (1.392-17.623)	0.015	2.119 (1.438-3.011)	0.040
Post-operative GS (5-7 vs 8-10*)	4.598 (0.574-36.884)	0.154	-	-
Surgical margin status (negative vs positive*)	1.039 (0.328-3.286)	0.948	-	-

*Reference category. PSA, prostate-specific antigen; GS, Gleason score; HR, hazard ratio; CI, confidence interval.

Table 4. Univariate and multivariate analyses of prognostic factors for biochemical recurrence in stage pT3 specimens (n = 77)

Variables	Univariate		Multivariate	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value
PSA	1.032 (1.015-1.048)	< 0.001	1.020 (0.998-1.042)	0.077
Prostate volume	0.988 (0.947-1.031)	0.593	-	-
Tumor volume	1.067 (1.010-1.127)	0.020	0.987 (0.864-1.128)	0.849
Tumor percentage	1.030 (1.011-1.048)	0.001	1.025 (0.982-1.069)	0.258
Biopsy GS (5-7 vs 8-10*)	2.579 (1.137-5.849)	0.023	1.666 (0.634-4.376)	0.301
Post-operative GS (5-7 vs 8-10*)	2.110 (0.634-7.021)	0.223	-	-
Surgical margin status (negative vs positive*)	1.376 (0.610-3.104)	0.443	-	-
Seminal vesicle invasion (absence vs presence*)	4.395 (1.904-10.145)	0.001	2.665 (1.273-6.706)	0.030

*Reference category. PSA, prostate-specific antigen; GS, Gleason score; HR, hazard ratio; CI, confidence interval.

0.001), high Gleason score ($P = 0.023$), and seminal vesicle invasion ($P = 0.001$) significantly influenced the time to BCR. Multivariate Cox proportional hazards analysis revealed that BCR was significantly associated with only seminal vesicle invasion (HR = 2.665, $P = 0.030$; Table 4).

DISCUSSION

The ability to predict disease recurrence after a radical prostatectomy is important because this will allow for the identification of patients who may be candidates for adjuvant therapy. Numerous studies, mostly performed before the widespread use of PSA testing, have shown that the pre-operative PSA level, Gleason score, seminal vesicle invasion, surgical margin status, and pathologic stage are independent predictors of cancer recurrence after treatment with radical prostatectomy (17). In the present study, the prostate volume, tumor volume, and tumor percentage represented independent variables in the progression of prostate cancer after radical prostatectomy. These factors predict BCR in men who undergo a radical prostatectomy with clinically localized prostate cancer (12, 18, 19). Though these variables have been analyzed independently in the past, the relationship has not been previously examined in men stratified by pathologic T stage.

Our results revealed that BCR was significantly associated with prostate volume, biopsy Gleason score, and seminal vesicle invasion in all specimens. When grouping data by pathologic stage, the univariate model for pT2 showed that PSA, prostate volume, and biopsy Gleason score were significant factors; however, tumor volume, tumor percentage, post-operative Gleason score, and surgical margin status were not significant factors. The multivariate model showed that PSA, prostate volume, and biopsy Gleason score were independent predictors of cancer recurrence. The univariate model for pT3 showed that PSA, tumor volume, tumor percentage, biopsy Gleason score, and seminal vesicle invasion were significant factors, but prostate volume, post-operative Gleason score, and surgical margin status were not significant factors. The multivariate model demonstrated the significance of seminal vesicle invasion when controlling for PSA, tumor volume, tumor percentage, and biopsy Gleason score.

In agreement with previous reports (20, 21), we showed that men with smaller prostates were at a significantly higher risk of BCR. The reason for this remains unknown; however, many potential explanations exist. First, it has been suggested that men with smaller prostates may have lower levels of testosterone, which has been shown to correlate with more aggressive prostate cancer (22). Second, men with larger prostates had their tumors detected earlier because of PSA-driven biopsies resulting from PSA elevation from an enlarged gland. This lead-time bias would be expected to result in better outcomes (23). As shown in Table 1, the extra-prostatic group had a higher PSA than the organ-confined group. The PSA range was 3.7-95.8 ng/mL. Thus, a PSA-driven biopsy group that had a large portion of benign tissue is difficult to be included. Third, a tumor within a small prostate has to migrate a lesser distance to escape the prostatic capsule, as demonstrated by Yadav et al. (24), who showed

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that decreased prostate volume is a predictor of extra-prostatic extension. It is likely that a combination of these factors leads to a greater chance of BCR after treatment for men with smaller prostate volume. The most important finding in our study was obtained from the analysis of prostate volume stratified by pathologic T stage. Our data showed that prostate volume was not prognostic in the pT3 group.

Extra-prostatic extension is an important prognostic factor, and that was expected far stronger than other prognostic factors, such as the prostate volume. In pT2 specimens, as a continuous variable, prostate volume was significantly associated with BCR (HR, 0.881; $P = 0.004$). The reduction in BCR risk may initially seem unimpressive; however, when considered in the context with other variables, it becomes more significant. The prognostic value of PSA in this model had a HR of 1.016; however, when the inverse was used, the HR was 0.984. Taking the reciprocal of PSA showed, as expected, that a decrease in PSA was predictive of decreased BCR risk. Interestingly, the predictive value is similar to that of prostate volume. PSA is a major factor in the stratification of risk for BCR for patients with prostate cancer (3, 25). Prostate volume may offer additional information that should be considered when counseling patients about their risk of BCR after radical prostatectomy, especially in organ-confined cases.

In the current study, survival analyses using the prostate volume categories were provided in all and pT2 settings. Our stratification and analysis of prostate volume in subgroups < 30 and ≥ 30 mL, is one of only a few studies to analyze prostate volume in a range that has immediate clinical relevance.

In the present, retrospective, single-center study performed late in the PSA era, we found that prostate volume was a significant predictive factor in the entire cohort of patients undergoing radical prostatectomy for localized prostate cancer. Patients with lower prostate volume had a greater risk of BCR compared with patients with higher prostate volume. On multivariate analysis, prostate volume remained a significant factor in patients with pT2 prostate cancer. In those with a pT3, the prostate volume was not significantly associated with BCR, reflecting that the pT3 group is relatively low volume.

The present findings differ from previous studies which found the tumor volume and tumor percentage to be significant predictors of BCR after radical prostatectomy (26-29). In the all subgroup analysis, we found that tumor volume and tumor percentage were not independent predictors of cancer recurrence on multivariate analysis when controlling for other variables. Nelson et al. (28) concluded that tumor volume is an independent predictor of BCR in 431 men treated by radical prostatectomy. In that study, the mean tumor volume was associated with pathologic stage and was significantly different between patients with and without recurrence (6.8 and 2.6 mL, respectively). Based on multivariate analysis, tumor volume predicted BCR when considered as a continuous variable. Recent findings by Merrill et al. (14) in a large population undergoing radical prostatectomy for localized prostate cancer again confirmed this observation, finding that regardless of tumor volume, low-risk patients had a low rate of cancer recurrence. Notably, they found that tumor volume was a significant independent predictor of BCR in patients with a GS ≥ 7. Manoharan et al. (27) and Carvalhal et al. (26) reported tumor percentage to be an independent predictor of BCR. In contrast, the present findings are consistent with the findings of Epstein et al. (13), who examined 185 men with clinical stage B prostate cancer and found that the tumor volume and tumor percentage did not provide independent prognostic information in a stepwise regression analysis; however, Gleason score and surgical margin status were independent predictors of recurrence. In our study, the tumor volume and tumor percentage were not meaningful for organ-confined cancers; however, the prognostic potential of tumor volume and tumor percentage was proposed for locally advanced cancers in univariate analyses.

The interpretation of these results may vary; however, the prognostic value of prostate volume is clearly present. It is important to note, our results suggest that some of the value of prostate volume was composed of lead time bias during the PSA era. Furthermore, anatomic and biologic factors are strongly related to the association between prostate volume and prognosis.

In the case of pT3, we suggest that the tumor volume or tumor percentage can reflect the degree of extra-prostatic tumor extension indirectly. Thus, the tumor volume or tumor percentage has some prognostic role in pathologic-extra-prostatic disease. These are the reasons that the prostate volume, tumor volume, and tumor percentage should be analyzed separately depending on the pathologic stage.

This conclusion has several clinical implications for the treatment of patients with pT2 prostate cancer. First, regardless of other factors, patients with a low PSA and a high prostate volume are at low risk for BCR, and does not appear to place the patient in a higher risk group at the time of radical prostatectomy. Therefore, routine resection of the neurovascular bundles is not recommended, and adjuvant therapy is of little benefit. Second, recognizing the limitations of tumor volume and tumor percentage in accurately predicting the BCR in every case, it seems likely that tumor volume or tumor percentage alone would not justify adjuvant therapy.

A number of factors may contribute to the variation between the findings of the current study and earlier studies. First, this is the first study to examine the role of prostate volume, tumor volume, and tumor percentage as it relates to BCR in men stratified by pathologic T stage. Second, in the current study, unlike existing studies, a well-defined and relatively homogeneous group of patients was subjected. In a number of earlier studies, a heterogeneous group of patients with pathologic stages ranging from pT1-pT4 was used, with some studies including patients with lymph node metastasis. As a result, substantial variation in

the risk of BCR would relate to tumor stage and would potentially contribute to a weakening of the prognostic value of the prostate volume, tumor volume, and tumor percentage.

There were several limitations to this study. First, a sample size of 259 men in such a common disease as prostate cancer is not sufficiently large. Second, our follow-up time was relatively short (median, 40.0 months). Extending the follow-up period by revisiting this study in 5 yr might provide stronger evidence for our conclusions. Third, our conclusions addressed the predictive values of prostate volume, tumor volume, and tumor percentage in the post-operative patient only. It would be beneficial to compare the pre-operative biopsy volume in this same population to identify useful correlations in predicting BCR.

The results of this study suggest that a lower prostate volume is a significant and independent predictor for BCR only in the organ-confined radical prostatectomy specimens. In contrast, prostate volume will not predict BCR in most locally advanced tumors. Additionally, tumor volume and tumor percentage could have some prognostic roles in pathologic extra-prostatic disease.

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AUTHOR SUMMARY

Prostate Volume has Prognostic Value only in Pathologic T2 Radical Prostatectomy Specimens

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The objective of this study is to evaluate the prognostic roles of the prostate volume, tumor volume, and tumor percentage as a function of the pathologic T stage in radical prostatectomy specimens. In the T2 group, multivariate analysis showed that the biochemical recurrence is significantly associated with PSA ($P = 0.028$), lower prostate volume ($P = 0.004$), and biopsy Gleason score ($P = 0.040$). The Kaplan-Meier survival curve showed that a smaller prostate volume is associated with a greater risk of biochemical recurrence (comparing < 30 vs ≥ 30 mL; $P = 0.010$). According to this study, tumor volume and tumor percentage can not predict for biochemical recurrence in all radical prostatectomy specimens. Notably, the lower prostate volume is an independent predictor for biochemical recurrence only in the organ-confined specimens.