Evaluation of The Tumor Volume From Surgical Specimens After Radical Prostatectomy and Its Clinical Impact on The Prognosis of Patients With Localized Prostate Cancer

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Abstract

We evaluated the contribution of tumor volume (TV) to localized prostate cancer (PCa) patients' prognosis. We retrospectively analyzed the data of 2,394 patients who underwent radical prostatectomy (RP) for localized PCa. The effect of TV volume on prostate cancer patients' prognosis was analyzed through Kaplan-Meier and Cox-proportional analysis. The mean prostate volume for all patients was 36.5 ± 15.4 cc, and the mean TV was 5.9 ± 8.3 cc.

A significant positive relationship was observed between the classification by risk group in D' Amico risk classification and the National Comprehensive Cancer Network risk group. ($P < 0.001$). The high TV showed significantly worse pathologic outcomes than the low TV in terms of high rates of extra-capsular extension, seminal vesicle invasion, and positive surgical margin ($P < 0.05$). The patients with high TV had significantly shorter biochemical recurrence-free survivals than those with low TV ($P < 0.001$). Finally, based on multivariate Cox-proportional analyses, TV was revealed to be an independent predictor of postoperative biochemical recurrence as both categorical (hazard ratio [HR]: 1.42, 95% confidence interval [CI]: 1.13–1.78, $P = 0.003$] and continuous variables (HR: 1.04, 95% CI: 1.04–1.05, $P < 0.001$). TV was revealed to be an independent prognostic factor in the postoperative biochemical recurrence. Patients with a high number of positive core and longer tumor length were significantly related to higher TV.

Introduction

Prostate cancer (PCa) is the most frequently diagnosed malignancy and fifth major cause of cancer-related deaths in the United States of America[1]. PCa has unique characteristics, including multi-focality in number and heterogeneity in size and grade[2,3]. Tumor volume (TV) is considered a significant prognostic factor for biochemical recurrence (BCR)-free survival, positive surgical margin, and overall survival in patients with PCa[2,4,5–12]. Other studies produced conflicting results that TV has no prognostic value when combined with pathologic stage or Gleason score[13–17]. Most recently, Uhlman et al analyzed TV and tumor percentage involvement in a large cohort of 3,528 participants and concluded that TV did not show significant results in the multivariate analysis but tumor percentage involvement was predictive of BCR after radical prostatectomy[18]. However, exact imaging or estimating tools to predict the TV of each patient preoperatively are unavailable. Even though the multiparametric magnetic resonance imaging (MRI) has excellent ability to delineate the shape and size of clinically significant PCa, many patients have MRI-invisible clinically-confirmed PCa[19].

Focal therapy is now gaining more attention because of its ability to partially treat PCa and preserve erectile function and urinary continence. Numerous energy sources have been developed for the focal ablation of PCa, but the weak aspect of focal therapy is that precise tumor recognition is difficult and is impossible when conventional imaging modalities are used. However, it would be quite helpful from the standpoint of performing focal therapy to select the best candidate, if we can understand and predict TV in PCa patients. Therefore, we tried to evaluate the actual contribution of TV in localized PCa patients, analyze the prognostic value of TV, and find the significant predictor for large TVs preoperatively.

Methods

The present study does not contain clinical studies or patient data and permitted by Institutional Review Board (IRB No. B-1906-549-101) of Bundang Seoul National University Bundang Hospital. The patient's written informed consent was waived for a retrospective analysis of the prospective database. Study protocol and contents associated with this study followed the Declaration of Helsinki guidelines. After the approval of the institutional review board, we retrospectively analyzed the data of 2,394 patients who underwent radical prostatectomy (RP) for localized PCa from May 2006 to January 2017 at our institution. After further exclusion of some patients (preoperative radiation therapy [n = 4], adjuvant or neoadjuvant hormone therapy [n = 43], and incomplete information [n = 31]), we finally analyzed a total of 2,316 patients. Clinical and pathological information were retrieved from our institutional database, which is prospectively maintained. The RP was performed by open retro-pubic, laparoscopic, or robot-assisted approach. The TNM staging system was used to evaluate tumors according to the 6th edition of the American Joint Committee Cancer guidelines, and adverse pathologic outcomes, including seminal vesicle invasion (SVI), extraprostatic extension (EPE), and positive surgical margin (PSM), were evaluated as previously described. All pathologic evaluations were performed using the modified definition of the 2005 International Society of Urological Pathology Consensus Conference. TV was assessed as described below. After the fixation of pathologic specimens using 20% buffered formalin, the surgical specimens were sectioned in 5 mm intervals. The pathologist determined the number of tumors and dimensions of tumor area from every axial slice of each specimen. Subsequently, TV was calculated by multiplying the percentage of tumor area to the total prostate volume. Postoperative follow-ups were usually performed in two or three month intervals for the initial two years and annually thereafter, in case of no evidence for biochemical recurrence (BCR). The BCR was defined as the continuous elevation of prostate-specific antigen (PSA) over 0.2 ng/ml in more than two consecutive tests.

The independent t-tests and chi-square tests were performed to compare the clinical or pathologic variables between subgroups. Multiple regression tests were performed to identify the possible relationship among the variables; Kaplan-Meier and Cox proportional hazard analyses also compared the survival outcomes among the groups. All statistical analyses were performed using the SPSS software (SPSS 19.0, Chicago, IL, USA); all P-values were presented as two-sided; P-values < 0.05 were considered to be statistically significant.

Results

Clinical characteristics and pathologic outcomes were summarized in Table 1. The mean prostate volume for all patients was 36.5 ± 15.4 cc and mean TV was 5.9 ± 8.3 cc (Table 1). We observed significant positive relationship between increased risk groups and TV ($P < 0.001$). After stratification of patients by the D'Amico risk classification system, the low risk, intermediate risk, and high risk groups had a mean TV of 2.7 ± 3.2 cc, 4.2 ± 4.0 cc, and 11.6 ± 12.5 cc, respectively (Table 2). When we subsequently subdivided the patients according to the National Comprehensive Cancer Network (NCCN) risk groups, TV was 2.0 ± 3.5 cc for the very low risk group, 3.1 ± 3.3 cc for the low risk group, 3.2 ± 3.7 cc for the favorable

intermediate risk group, 5.2 ± 4.8 cc for the unfavorable intermediate risk group, 11.1 ± 12.0 cc for the high risk group, and 20.0 ± 16.2 cc for the very high risk group. We observed a significant positive relationship between the ranks of the NCCN risk groups and TV ($P < 0.001$). However, no significant difference existed between prostate volume, according to the D'Amico and NCCN risk group classification ($P > 0.05$). Analysis of the receiver operating curve of TV to have biochemical recurrence revealed that TV of 5.27 cc indicated the maximal Youden's score, whereas area under the curve of TV was revealed as 0.778 [95% confidence interval (CI): 0.755–0.801]. Subsequently, patients were grouped into high and low TV by using the cut-off of 5.27 cc. Of all the participants, 1,560 patients had low TV whereas 756 subjects had high TV (Table 1). The high TV indicated significantly worse clinical characteristics, in terms of high PSA ($P < 0.001$); pathologic stage ($P < 0.001$); and rate of EPE, SVI, and PSM ($P < 0.001$) (Table 1). Multivariate multiple regression tests revealed that preoperative PSA, clinical stage, D'Amico risk group, ratio of positive biopsy cores (positive/total), and tumor length (longest among the positive biopsies) showed significant relationship to high TV ($P < 0.05$) (Table 3). The Kaplan-Meier analysis showed that the high TV group showed significantly shorter biochemical recurrence-free survival than the low TV ($P < 0.001$) (Fig. 1). Finally, the multi-variate Cox-proportional model revealed that TV was an independent predictor to predict shorter biochemical recurrence-free survival as both a categorical (HR: 1.42, 95% CI: 1.13–1.78, $P = 0.003$] and continuous variable (HR: 1.04, 95% CI: 1.04–1.05, $P < 0.001$) (Table 4).

Table 1
The clinical characteristics and pathologic outcomes according to high and low volume group

Median (interquartile range) or number (percent)	Total (N = 2316)	Low volume (N = 1560)	High volume (N = 756)	p - value
Age (year)	67.0 (62.0–71.0)	67.0 (61.0–71.0)	68.0 (63.0–72.0)	< 0.001
Body mass index (Kg/m^2)	24.4 ± 2.8	24.3 ± 2.7	24.5 ± 3.0	0.070
Damico risk classification				< 0.001
Low	699 (30.2%)	626 (40.1%)	73 (9.7%)	
Intermediate	936 (40.4%)	684 (43.8%)	252 (33.3%)	
High	681 (29.4%)	250 (16.0%)	431 (57.0%)	
NCCN risk classification				< 0.001
Very low	150 (6.9%)	139 (9.7%)	11 (1.5%)	
Low	423 (19.4%)	371 (25.8%)	52 (7.0%)	
Favorable intermediate	416 (19.1%)	356 (24.8%)	60 (8.1%)	
Unfavorable intermediate	523 (24.0%)	327 (22.8%)	196 (26.5%)	
High	626 (28.8%)	236 (16.4%)	390 (52.7%)	
Very High	39 (1.8%)	8 (0.6%)	31 (4.2%)	
Prostate specific antigen (ng/mL)	13.0 ± 16.5	8.5 ± 9.2	22.4 ± 23.1	< 0.001
Prostate volume (g)	36.5 ± 15.4	36.1 ± 14.7	37.4 ± 16.8	0.079
Clinical T stage				< 0.001
T1	1415 (61.1%)	1086 (69.6%)	329 (43.5%)	
T2	673 (29.1%)	421 (27.0%)	252 (33.3%)	
≥ T3	228 (9.8%)	53 (3.4%)	175 (23.1%)	
Biopsy Gleason score				< 0.001
6	921 (39.8%)	769 (49.3%)	152 (20.1%)	

ECE, extracapsular extension; GS, Gleason-score; NCCN, National Comprehensive Cancer Network; PSA, prostate specific antigen; SVI, seminal vesical invasion;

Median (interquartile range) or number (percent)	Total (N = 2316)	Low volume (N = 1560)	High volume (N = 756)	p - value
7	982 (42.4%)	620 (40.1%)	357 (47.2%)	
≥8	403 (17.8%)	166 (10.6%)	247 (32.7%)	
Pathologic results on biopsy				
Number of positive cores	3.8 ± 2.8	2.8 ± 2.0	5.7 ± 3.3	< 0.001
Percentage of positive cores (%)	31.8 ± 23.0	23.6 ± 16.4	49.8 ± 25.2	< 0.001
Median maximal tumor length (cm)	0.5 (0.3–0.8)	0.4 (0.2–0.6)	0.9 (0.5–1.3)	< 0.001
Median length of core (cm)	1.7 (1.4–1.9)	1.7 (1.4–1.8)	1.7 (1.4–1.9)	0.482
Maximal tumor involvement of positive core (%)	38.0 ± 31.1	28.6 ± 22.0	57.5 ± 37.4	< 0.001
Prostate volume (g)	36.0 (30.0–46.0)	36.0 (30.0–44.0)	38.7 (32.0–48.0)	< 0.001
Tumor volume (g)	3.3 (1.6–6.6)	2.1 (1.2–3.3)	9.3 (6.8–15.1)	< 0.001
Pathologic T stage				< 0.001
T2b	221 (9.5%)	209 (13.4%)	12 (1.6%)	
T2c	1354 (58.5%)	1099 (70.4%)	255 (33.7%)	
T3a	505 (21.8%)	209 (13.4%)	296 (39.2%)	
≥T3b	236 (10.2%)	43 (2.8%)	193. (25.6%)	
Pathologic N1 stage	59 (4.4%)	6 (0.9%)	53 (8.3%)	< 0.001
Pathologic Gleason score				< 0.001
6	168 (7.3%)	157 (10.1%)	11 (1.5%)	
7	1824 (78.8%)	1296 (83.1%)	528 (69.8%)	
8	118 (5.1%)	63 (4.0%)	55 (7.3%)	
≥ 9	206 (8.9%)	44 (2.8%)	162 (21.4%)	

ECE, extracapsular extension; GS, Gleason-score; NCCN, National Comprehensive Cancer Network; PSA, prostate specific antigen; SVI, seminal vesical invasion;

Median (interquartile range) or number (percent)	Total (N = 2316)	Low volume (N = 1560)	High volume (N = 756)	p - value
Multifocality (yes)	1884 (81.3%)	1309 (83.9%)	575 (76.1%)	< 0.001
Extracapsular extension	714 (30.8%)	237 (15.2%)	477 (63.1%)	< 0.001
Seminal vesicle invasion	231 (10.0%)	46 (2.9%)	185 (24.5%)	< 0.001

ECE, extracapsular extension; GS, Gleason-score; NCCN, National Comprehensive Cancer Network; PSA, prostate specific antigen; SVI, seminal vesical invasion;

Table 2
Mean tumor volume difference according to NCCN and D'Amico risk classification

D'Amico risk classification	Low (N = 699)	Intermediate (N = 936)	High (N = 681)	p-value
Median prostate volume	36.0 (30.0–44.0)	36.0 (30.0-45.5)	39.0 (32.0–48.0)	< 0.001
Median tumor volume	1.9 (0.9–3.3)	3.4 (1.8–5.8)	7.2 (3.6–14.9)	< 0.001
Multifocality (yes)	505 (74.2%)	591 (84.5%)	788 (84.2%)	< 0.001

NCCN risk classification	Very low (N = 160)	Low (N = 450)	Favorable intermediate (N = 443)	Unfavorable intermediate (N = 556)	High (N = 666)	Very high (N = 41)	p-value
Median prostate volume	44.0 (35.9–55.2)	34.0 (29.0–44.0)	37.0 (30.0–46.0)	35.0 (30.0–44.0)	39.0 (32.0–48.0)	36.0 (30.0–50.0)	0.670
Median tumor volume	1.1 (0.6–2.1)	2.3 (1.2–3.9)	2.4 (1.3–3.8)	4.1 (2.3–6.6)	7.2 (3.5–14.0)	15.0 (7.2–34.8)	< 0.001
Multifocality (yes)	131 (81.3%)	381 (84.6%)	388 (87.5%)	457 (82.2%)	495(74.3%)	26 (64.1%)	< 0.001

NCCN, National Comprehensive Cancer Network; RP, radical prostatectomy;

Table 3
Univariate and multivariate regression analysis for high volume prostate cancer predictor

Variable	Univariate		Multivariate	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Age	1.03 (1.01–1.04)	< 0.001	1.02 (1.00-1.04)	0.119
Body mass index	1.03 (1.00-1.06)	0.061	1.00 (0.96–1.05)	0.852
Diabetes mellitus	1.05 (0.86–1.29)	0.614	1.11 (0.83–1.48)	0.479
Prostate specific antigen	1.12 (1.10–1.13)	< 0.001	1.07 (1.05–1.09)	< 0.001
D'Amico risk classification	4.02 (3.49–4.63)	< 0.001	1.67 (1.23–2.26)	< 0.001
Clinical T stage	2.75 (2.41–3.15)	< 0.001	1.28 (1.03–1.53)	0.023
Prostate volume	1.01 (1.00-1.01)	0.007	1.02 (1.01–1.03)	< 0.001
Biopsy Gleason score	2.43 (2.17–2.73)	< 0.001	1.11 (0.94–1.31)	0.232
Number of positive cores	1.52 (1.46–1.58)	< 0.001	1.02 (0.85–1.21)	0.818
Maximal tumor involvement of positive core	1.06 (1.05–1.07)	< 0.001	1.04 (1.01–1.06)	0.001
Median maximal tumor length	17.37 (13.25–23.01)	< 0.001	2.03 (1.08–5.13)	0.021

Table 4
Multivariate Cox proportional hazards analyses of tumor volume on biochemical recurrence

Variable	Tumor volume (continuous variable)		High volume tumor (categorical variable)	
	HR (95% CI)	p value	HR (95% CI)	p value
Age	1.01 (1.00-1.26)	0.122	0.98(0.97–0.99)	0.005
Prostate specific antigen	1.01 (1.00-1.01)	< 0.001	1.00 (1.00-1.01)	0.048
Tumor volume	1.04 (1.04–1.05)	< 0.001	1.42 (1.13–1.78)	0.003
Pathologic Gleason score		< 0.001		< 0.001
6	Reference		Reference	
7	1.62 (1.08–2.44)	0.021	5.80 (1.85–18.20)	0.003
8	4.08 (2.49–6.67)	< 0.001	13.81 (4.25–44.80)	< 0.001
≥ 9	4.40 (2.68–7.24)	< 0.001	16.86 (5.26–54.06)	< 0.001
Pathologic T stage		0.584		0.045
T2	Reference		Reference	
T3	1.25 (0.45–3.48)	0.669	2.10 (1.12–3.94)	0.022
T4	1.72 (0.51–5.79)	0.379	2.39 (1.02–5.62)	0.046
Pathologic N stage				
N0-Nx	Reference		Reference	
N1	1.80 (1.01–3.21)	0.047	1.84 (1.33–1.54)	< 0.001
Extracapsular extension	2.01 (1.02–3.94)	0.042	1.36 (0.73–2.51)	0.332
Seminal vesicle invasion	2.48 (1.77–3.49)	< 0.001	2.32 (1.83–2.93)	< 0.001
Positive surgical margin	1.01 (0.90–1.14)	0.825	1.91 (1.55–2.36)	< 0.001

Discussion

In this study, we investigated the overall contribution of TV according to the risk group systems from D'Amico criteria and NCCN guidelines and observed that TV significantly increased in the higher risk groups of both systems. The patients of the low risk group exhibited a TV of 2–3 cm^3, with a tumor diameter between 1.4 and 1.6 cm when the tumor is assumed to be spherical, and a TV between 1.3 and

1.4 cm when the tumor is assumed to be a regular hexahedron. Large tumors were significantly related to an increased postoperative BCR in our multi-variate Cox proportional hazard analyses with both categorical and continuous variables. The preoperative PSA, clinical stage, prostate volume, percentage of positive biopsy cores, and maximal tumor length among positive biopsy cores were significantly related to high TV in our multi-variate regression tests.

TV has been presented as a significant prognostic factor of PCa in several papers [2, 4, 5–12]. Stamey et al. reported that cancer volume and high Gleason score were significantly related with worse BCR-free survival after analyzing the results of 379 patients who were treated with radical prostatectomy[2]. They argued that the exact way to predict cancer volume may be helpful in predicting the outcomes of PCa surgery. Subsequently, Nelson et al investigated the effect of TV on pathologic outcomes and biochemical recurrence after surgery[5]. They concluded that TV directly correlated with pathological stage and PSA recurrence after radical prostatectomy; therefore, TV was revealed as an independent predictor for worse prognosis in patients with localized PCa. Another study by Chun et al. showed that cancer volume and high Gleason score were the independent predictors for postoperative BCR in their relatively large cohort of 780 participants treated with radical prostatectomy[4]. However, there were other studies showing contradictory results regarding the use of TV as a predictive prognostic factor[13–16]. Kikuchi et al. also analyzed a larger cohort of 1,302 participants who were also treated with radical prostatectomy. They observed only a weak relationship with postoperative prognosis, but no statistically significant results were obtained from multi-variate analyses[13]. Another study by May et al. reported that absolute TV was unable to predict postoperative BCR, unlike relative TV (TV/total prostate volume), which showed significant results in predicting prognosis[14]. Subsequently, Merrill et al analyzed a large cohort of 1,833 participants who were also treated with radical prostatectomy and found that TV was significantly associated with a higher rate of BCR in the high pathologic Gleason score subgroup (≥ 3 + 4), but not in the Gleason 6 subgroup (3 + 3)[15]. Furthermore, another study by Uhlman et al. analyzed data from a large cohort of 3,528 participants who were treated with radical prostatectomy to evaluate the prognostic influence of TV[16]. They analyzed TV both by categorical and continuous variables and concluded that TV did not show any significant association with BCR-free survival, even though significant difference existed in their BCR-free survival rates after univariate Kaplan-Meier analyses. However, we believe that their study may have some limitations. First, they included patients who were treated from 1988 to 2008 without any pathologic re-review on the Gleason grading. As there was a major update on Gleason grading in 2006 by the International Society of Urologic Pathology (ISUP), there is a possibility of confounding influence from the heterogenous definition for Gleason scoring depending on the time period. Second, our cohort has a more aggressive disease, in terms of pathologic Gleason grade and PSA level, than those in previous studies. As like the aforementioned study by Merrill et al, which showed that TV was associated with postoperative prognosis only in patients with high Gleason scores (≥ 4 + 3), the more aggressive disease profiles of our study may have caused the contrasting results compared with Uhlman et al. Third, we observed a relatively high rate of positive surgical margins from Uhlman et al's study, which may also be connected to confounding effect in their study.

Lately, focal therapy is gaining more attention with clinical benefits in terms of better erectile and urinary functions after treatment[20]. However, there are still limitations for focal therapy, because tumor location cannot be exactly predicted using conventional imaging modalities and biopsy protocols[21]. The understanding of the epidemiology of TV is quite important when planning and finding optimal candidates for focal therapy. We observed from our results that the mean TV was about 2.0 cc for very low risk, 3.1 cc for low risk, and 3.2 cc for favorable intermediate risk group. Patients in the unfavorable intermediate risk group showed significantly larger TV than those in the favorable intermediate risk group (3.2 ± 3.7 cc versus 5.2 ± 4.8 cc, $P < 0.001$). From our volumetric results of TV, we believe that the optimal candidates for focal therapy could be patients between very low risk and favorable intermediate risk groups. However, the patients in the very low risk group should be recommended for active surveillance.

Our study is certainly not without limitations. First, it is limited by its retrospective analyses, even though the data on TV was prospectively accumulated. Second, there is a possibility of selection bias since we only included patients treated with radical prostatectomy. Third, the present study only analyzed the total TV but not the detailed pathologic information about number of tumors and location, which is also important for prognosis of PCa patients. Even so, we believe that we provided the most recent data regarding the actual epidemiology of TV in patients treated with radical prostatectomy, which makes our study clinically meaningful.

Conclusion

TV of PCa was revealed to be an independent prognostic factor in predicting postoperative biochemical recurrence, showing a significantly positive relationship with increase in risk in the risk group system. Further study with more detailed data on tumor location and multifocality is required to understand the nature of PCa.

Declarations

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Author Contributions Statement

Protocol/project development: Hakmin Lee, Sung Kyu Hong

Data collection or management: Seok-Soo Byun, Sung Kyu Hong

Data analysis: Hakmin Lee, Hyeong Dong Yuk

Manuscript writing/editing: Hakmin Lee, Hyeong Dong Yuk

Competing financial interests

The authors declare that the research was conducted in the absence of any competing financial and non-financial interests that could be construed as a potential conflict of interest.

* All authors have no conflict of interest with any institution or product.

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Figures

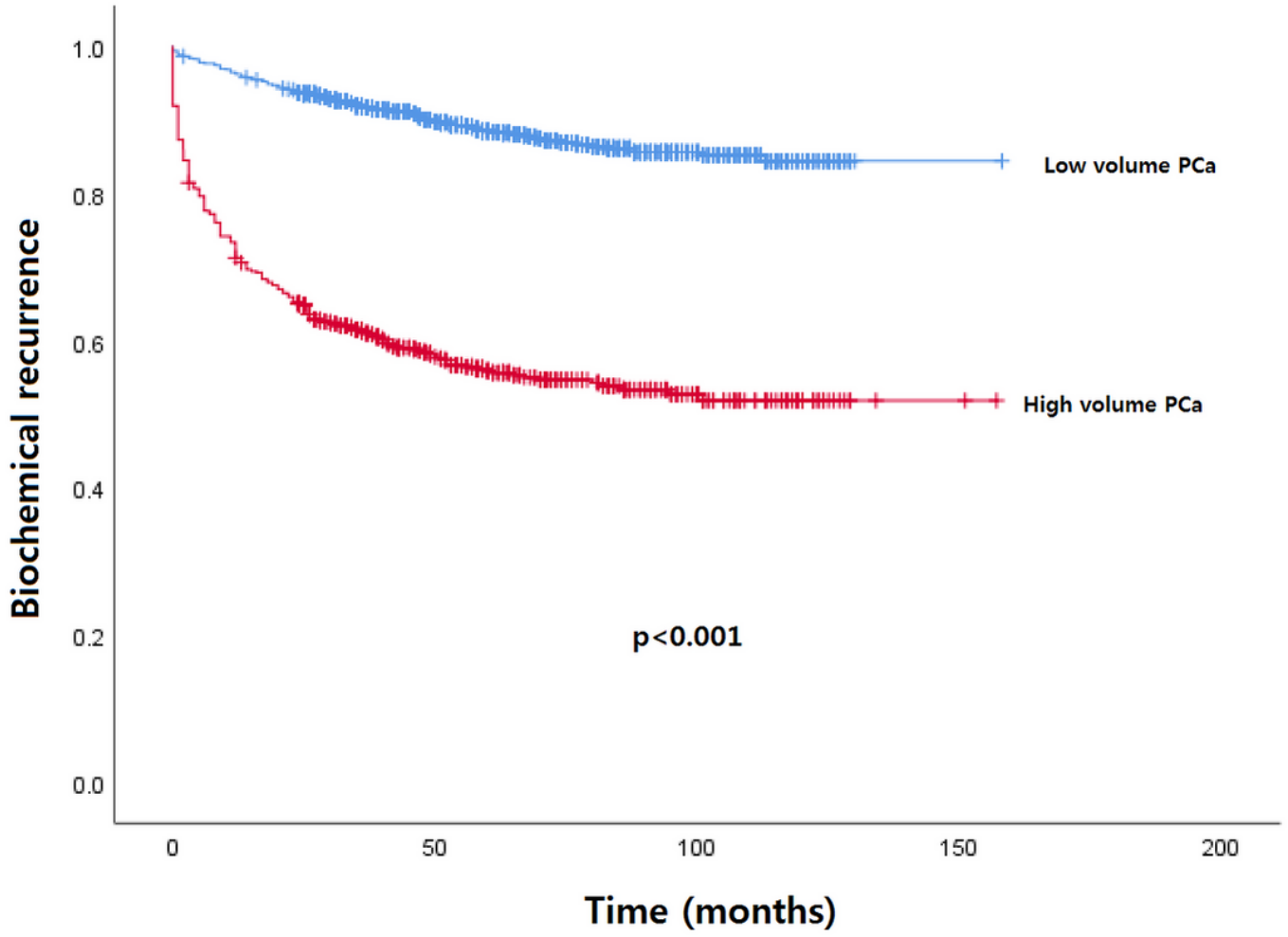

Figure 1

Kaplan-Meier analysis on the biochemical recurrence free survival according to the tumor volum