Asian Journal of Andrology (2016) 18, 54–59

www.asiaandro.com; www.ajandrology.com

*Open Access*

**ORIGINAL ARTICLE**

Prostate Disease

# Effect of serum testosterone and percent tumor volume on extra-prostatic extension and biochemical recurrence after laparoscopic radical prostatectomy

**Eu Chang Hwang[1,*], Seong Hyeon Yu[1,*], Yang Hyun Jo[1], Seung Il Jung[1], Taek Won Kang[1], Dong Deuk Kwon[1], Chan Choi[2], Suk Hee Heo[3], Jun Eul Hwang[4], Sung-Hoon Jung[4], Tae-Young Jung[5]**

**Several studies have revealed that the preoperative serum testosterone and percent tumor volume (PTV) predict extra-prostatic extension (EPE) and biochemical recurrence (BCR) after radical prostatectomy. This study investigated the prognostic significance of serum testosterone and PTV in relation to EPE and BCR after laparoscopic radical prostatectomy (LRP). We reviewed 520 patients who underwent LRP between 2004 and 2012. PTV was determined as the sum of all visually estimated tumor foci in every section. BCR was defined as two consecutive increases in the postoperative prostate-specific antigen (PSA) >0.2 ng ml$^{-1}$. The threshold for serum total testosterone was 3.0 ng ml$^{-1}$. Multivariate logistic regression was used to define the effect of variables on the risk of EPE and BCR. A low serum testosterone (<3.0 ng ml$^{-1}$) was associated with a high serum PSA, Gleason score, positive core percentage of the prostate biopsy, PTV, and all pathological variables. On multivariate analysis, similar to previous studies, the serum PSA, biopsy positive core percentage, Gleason score, and pathological variables predicted EPE and BCR. In addition, low serum testosterone (<3.0 ng ml$^{-1}$, adjusted OR, 8.52; 95% CI, 5.04–14.4, $P$ = 0.001) predicted EPE and PTV (adjusted OR, 1.02; 95% CI, 1.01–1.05, $P$ = 0.046) predicted BCR. In addition to previous predictors of EPE and BCR, low serum testosterone and PTV are valuable predictors of EPE and BCR after LRP.**

*Asian Journal of Andrology* (2016) **18**, 54–59; doi: 10.4103/1008-682X.154317; published online: 5 May 2015

**Keywords:** biochemical recurrence; extra-prostatic extension; prostate neoplasms; prostatectomy; testosterone; tumor burden

## INTRODUCTION

Prostate cancer (PCa) is one of the most commonly diagnosed solid organ malignancies worldwide, and its incidence is increasing gradually. PCa is a heterogeneous disease that varies in spectrum from tumors with a low risk of mortality to highly aggressive malignant disease.[1]

Several primary treatment modalities have been established, including radical prostatectomy, androgen deprivation therapy, and radiation therapy. Of these, radical prostatectomy is the gold-standard definitive therapy for patients with localized PCa. Recently, laparoscopic radical prostatectomy and robotic radical prostatectomy have become popular.[2] However, approximately 25% of males with PCa will develop a postoperative biochemical recurrence (BCR) within 5 years of a radical prostatectomy, and the 10-year risk of BCR is approximately 35%.[3,4] The prognosis after radical prostatectomy is generally based on clinical findings (preoperative prostate-specific antigen [PSA] level and PSA doubling time) and pathological findings (the Gleason score, surgical margin status, extra-prostatic extension, and seminal vesicle invasion).[4,5]

Recently, in addition to the undisputed predictors of prognosis after radical prostatectomy, several studies revealed that the preoperative serum testosterone and prostate tumor volume predicted extra-prostatic extension (EPE) and BCR after radical prostatectomy.[1,2,4,6,7] Nevertheless, the predictors of EPE and BCR after radical prostatectomy are still debated. Therefore, we investigated the prognostic significance of serum testosterone and percent tumor volume (PTV) in relation to EPE and BCR after laparoscopic radical prostatectomy (LRP).

## MATERIALS AND METHODS

### *Study population*

We retrospectively reviewed 520 patients from Chonnam National University Hwasun Hospital, who underwent LRP as the initial treatment for localized or locally advanced PCa between April 2004 and December 2012. The diagnosis of PCa was made using a transrectal ultrasonography (TRUS)-guided biopsy with a minimum of eight fragments. After the LRP, the patients were followed by measuring the serum PSA levels every 3–6 months. Patients administered preoperative hormone or radiation therapy and those without complete clinical or pathological data or postoperative PSA follow-up data available were excluded.

[1]Department of Urology, Chonnam National University Medical School, Gwangju, Republic of Korea; [2]Department of Pathology, Chonnam National University Medical School, Gwangju, Republic of Korea; [3]Department of Radiology, Chonnam National University Medical School, Gwangju, Republic of Korea; [4]Department of Hemato-oncology, Chonnam National University Medical School, Gwangju, Republic of Korea; [5]Department of Neurosurgery, Chonnam National University Medical School, Gwangju, Republic of Korea.
*These authors contributed equally to this work.
Correspondence: Dr. DD Kwon (urokwon@gmail.com, urohwang@naver.com)
Received: 29 October 2014; Revised: 30 December 2014; Accepted: 19 March 2015

Using hospital records, we assessed the following potential predictors of a PCa prognosis: patient age, preoperative PSA, preoperative serum testosterone, preoperative PSA density (PSAD), prostate volume, presence of hypoechoic lesion on TRUS, Gleason score (GS), positive core percentage of the TRUS biopsy, clinical stage, pathological stage, postoperative Gleason score, positive surgical margin, perineural invasion, lymphovascular invasion, EPE, BCR, and D'Amico risk classification. Prostate volume was calculated from the TRUS at the time of prostate biopsy using the formula V = 0.52 (length × width × height),[8] and PSAD was obtained by dividing the serum PSA level by the prostate volume. BCR was defined as two consecutive increases in the postoperative PSA >0.2 ng ml$^{-1}$. The D'Amico risk was classified as low (PSA < 10, cT1-T2a stage and GS ≤6), intermediate (PSA 10–20 and cT2b stage or GS 7), or high (PSA >20 or cT2c-T3a stage or GS 8–10).[9]

***Measuring preoperative serum testosterone***

Using an immunoassay, the preoperative serum testosterone was measured in the morning when testosterone levels are high and stable. Based on a median preoperative testosterone level of 3 ng ml$^{-1}$, the patients were categorized into two groups: serum testosterone <3 ng ml$^{-1}$ (hypogonadism) and preoperative serum testosterone ≥3 ng ml$^{-1}$ (normal).[7] The candidate predictors of the prognosis of PC listed above were compared between two groups.

***Measuring the percent tumor volume***

The LRP specimens were fixed in formalin, inked, sectioned serially at 3-mm intervals in a plane perpendicular to the rectal surface, and embedded in paraffin. Then, the specimens were cut to thicknesses of 5 μm and examined microscopically. One uropathologist (C Choi) examined the slides without knowledge of the patient outcomes. The tumor area was marked on each glass slide, the diameter was measured, and the volume of tumor was calculated. PTV was determined as the sum of all visually estimated tumor foci in every section. A positive surgical margin was defined as tumor cells on the inked surface of the specimen.

***Statistics***

Statistical analyses were performed using SPSS version 17.0 (SPSS, Chicago, IL, USA). The Student's *t*-test and Chi-square test were used to compare baseline clinicopathological characteristics. Univariate and multivariate (stepwise forward procedure) logistic regression analyses were performed to generated an adjusted odds ratio (OR), representing the independent predictive factors. Statistical significance was set at $P < 0.05$ for all analyses.

## RESULTS

***Clinicopathological characteristics***

The clinicopathological characteristics of the normal and hypogonadal patients are summarized in **Table 1**. The median duration of follow-up after LRP was 19.1 (range 0.5–84.2) months. The overall mean age, preoperative serum PSA, preoperative serum testosterone, and PTV were 67.9 ± 5.8 years, 12.4 ± 12.1 ng ml$^{-1}$, 3.6 ± 4.5 ng ml$^{-1}$, and 12.3% ± 12.5%, respectively. BCR developed in 134 patients (25.8%), and the median interval from LRP to BCR was 11.3 (range 0.5–83.3) months. The surgical margin was positive in 145 (27.9%) patients and 126 (24.2%) had EPE. In regard to positive surgical margin, pathologic T2 and T3 positive surgical margin rates for the entire cohort were 19.3% and 54.8% ($P = 0.001$). Of the 520 patients, 320 (61.5%) were normal and 200 (38.4%) had hypogonadism. Comparing two groups, hypogonadism patients had worse clinicopathological features, such as a high preoperative serum PSA, preoperative PSAD, TRUS biopsy positive core percentage, TRUS biopsy Gleason score, clinical MR stage, pathological stage, postoperative Gleason score, and more PTV, lymphovascular invasion, positive surgical margin (pathologic T2 and T3 positive surgical margin rates for hypogonadism patients were 34.7% and 57.6% *vs* 14.0% and 44.4% for normal patients, respectively), perineural invasion, BCR, EPE, and high-risk PCa (**Table 1**).

***Predictors of extra-prostatic extension***

The univariate analyses indicated that the preoperative serum PSA (odds ratio [OR], 1.05, 95% confidence interval [CI], 1.03–1.07, $P = 0.001$), preoperative PSAD (OR, 5.18; 95% CI, 2.90–9.26, $P = 0.001$), TRUS biopsy positive core percentage (OR, 1.02; 95% CI, 1.01–1.03, $P = 0.001$), preoperative serum testosterone (<3 ng ml$^{-1}$, OR, 10.6; 95% CI, 6.57–17.2, $P = 0.001$), clinical stage (≥ T3, OR, 2.11; 95% CI, 1.24–3.58, $P = 0.005$), TRUS biopsy Gleason score (7–10, OR, 2.83; 95% CI, 1.86–4.31, $P = 0.001$), and D'Amico classification (high, OR, 3.22; 95% CI, 2.13–4.89, $P = 0.001$) were associated with EPE, whereas age (≥69), prostate volume, and the presence of a hypoechoic lesion on TRUS were not associated with EPE (**Table 2**).

The multivariate analysis revealed that the preoperative serum PSA (adjusted OR, 1.04, 95% CI, 1.02–1.06, $P = 0.001$), TRUS biopsy positive core percentage (adjusted OR, 1.01; 95% CI, 1.00–1.03, $P = 0.001$), and preoperative serum testosterone (<3 ng ml$^{-1}$, adjusted OR, 8.52; 95% CI, 5.04–14.4, $P = 0.001$) were associated with EPE (**Table 2**).

***Predictors of biochemical recurrence***

The univariate analyses indicated that the preoperative serum PSA (OR, 1.06, 95% confidence interval [CI], 1.04–1.09, $P = 0.001$), preoperative PSAD (OR, 8.22; 95% CI, 4.39–15.3, $P = 0.001$), TRUS biopsy positive core percentage (OR, 1.02; 95% CI, 1.01–2.13, $P = 0.001$), PTV (OR, 1.06; 95% CI, 1.04–1.08, $P = 0.001$), positive surgical margin (OR, 1.99; 95% CI, 1.31–3.03, $P = 0.001$), perineural invasion (OR, 2.86; 95% CI, 1.79–4.57, $P = 0.001$), lymphovascular invasion (OR, 4.05; 95% CI, 2.03–8.08, $P = 0.001$), preoperative serum testosterone (<3 ng ml$^{-1}$, OR, 2.44; 95% CI, 1.63–3.64, $P = 0.001$), TRUS biopsy Gleason score (7–10, OR, 2.50; 95% CI, 1.66–3.76, $P = 0.001$), postoperative Gleason score (OR, 4.01; 95% CI, 2.08–7.74, $P = 0.001$), clinical stage (≥ T3, OR, 1.77; 95% CI, 1.05–3.01, $P = 0.032$), pathological stage (≥ T3, OR, 3.24; 95% CI, 2.10–4.98, $P = 0.001$), and D'Amico classification (high, OR, 3.48; 95% CI, 2.31–5.23, $P = 0.001$) were associated with BCR, whereas, similar to the predictors of EPE, age (≥69 years), prostate volume, and the presence of hypoechoic lesion on TRUS were not associated with BCR (**Table 3**).

The multivariate analysis revealed that the preoperative serum PSA (adjusted OR, 1.04, 95% CI, 1.02–1.07, $P = 0.001$), PTV (adjusted OR, 1.02; 95% CI, 1.01–1.05, $P = 0.046$), perineural invasion (adjusted OR, 2.02; 95% CI, 1.15–3.57, $P = 0.015$), lymphovascular invasion (adjusted OR, 3.64; 95% CI, 1.53–8.66, $P = 0.003$), and TRUS biopsy Gleason score 7–10 (adjusted OR, 1.81; 95% CI, 1.01–2.97, $P = 0.018$) were associated with BCR (**Table 3**).

## DISCUSSION

Identifying preoperative markers that predict disease recurrence and more aggressive PC after a radical prostatectomy is one of the main objectives of prostate oncology research. Several studies have reported that the preoperative serum PSA level, Gleason score, seminal vesicle invasion, surgical margin status, and pathological stage are independent predictors of disease recurrence after a radical prostatectomy.[10] Our results suggest that the preoperative serum testosterone and PTV also predict disease recurrence and progression after LRP.

Testosterone is the principal circulating androgen in males. In the past, the belief that androgens cause *de novo* PCa or accelerate its growth was called the androgen hypothesis. The androgen hypothesis arose from reports beginning in the 1940s that males

**Table 1: Differences in clinical variables between normal and hypogonadal patients**

| *Variables* | *Total (n=520)* | *Normal (n=320, ≥3.0 ng ml$^{-1}$)* | *Hypogonadism (n=200, <3.0 ng ml$^{-1}$)* | *P* |
|---|---|---|---|---|
| Age (mean±s.d.; years) | 67.9±5.8 | 68.1±5.6 | 67.6±6.0 | 0.379* |
| PSA (ng ml$^{-1}$) | 12.4±12.1 | 10.8±10.4 | 14.9±14.2 | 0.001* |
| Serum testosterone (ng ml$^{-1}$) | 3.6±4.5 | 4.5±1.2 | 2.1±0.5 | 0.001* |
| TRUS volume (ml) | 33.5±16.3 | 34.3±17.7 | 32.3±13.8 | 0.174* |
| Preoperative PSAD (ng ml$^{-1}$ ml$^{-1}$) | 0.4±0.3 | 0.4±03 | 0.5±0.4 | 0.001* |
| Positive core (%) | 34.3±22.0 | 32.5±21.9 | 37.3±22.0 | 0.022* |
| Tumor volume (%) | 12.3±12.5 | 10.7±11.5 | 15.0±13.6 | 0.001* |
| TRUS findings, *n* (%) | | | | |
| No hypoechoic lesion | 429 (82.5) | 260 (81.3) | 169 (84.5) | 0.406† |
| Hypoechoic lesion | 91 (17.5) | 60 (18.8) | 31 (15.5) | |
| Biopsy Gleason score, *n* (%) | | | | |
| 6 | 273 (52.5) | 187 (58.4) | 86 (43.0) | 0.001† |
| 7 | 147 (28.3) | 79 (24.7) | 68 (34.0) | |
| 8 | 83 (16.0) | 48 (15.0) | 35 (17.5) | |
| 9 | 13 (2.5) | 6 (1.9) | 7 (3.5) | |
| 10 | 4 (0.8) | 0 (0) | 4 (2.0) | |
| Clinical MR stage, *n* (%) | | | | |
| T1c | 93 (17.9) | 62 (19.4) | 31 (15.5) | 0.038† |
| T2a | 170 (32.7) | 112 (35.0) | 58 (29.0) | |
| T2b | 33 (6.3) | 13 (4.1) | 20 (10.0) | |
| T2c | 152 (29.2) | 95 (29.7) | 57 (28.5) | |
| T3a | 43 (8.3) | 22 (6.9) | 21 (10.5) | |
| T3b | 29 (5.6) | 16 (5.0) | 13 (6.5) | |
| Pathological stage, *n* (%) | | | | |
| T2a | 65 (12.5) | 57 (17.8) | 8 (4.0) | 0.001† |
| T2b | 8 (1.5) | 4 (1.3) | 4 (2.0) | |
| T2c | 321 (61.7) | 232 (72.5) | 89 (44.5) | |
| T3a | 91 (17.5) | 19 (5.9) | 72 (36.0) | |
| T3b | 35 (6.7) | 8 (2.5) | 27 (13.5) | |
| Permanent Gleason score, *n* (%) | | | | |
| 6 | 113 (21.7) | 92 (28.8) | 21 (10.5) | 0.001† |
| 7 | 283 (54.4) | 174 (54.4) | 109 (54.5) | |
| 8 | 62 (11.9) | 30 (9.4) | 32 (16.0) | |
| 9 | 57 (11.0) | 23 (7.2) | 34 (17.0) | |
| 10 | 5 (1.0) | 1 (0.3) | 4 (2.0) | |
| Positive surgical margin, *n* (%) | | | | |
| No | 375 (72.1) | 267 (83.4) | 108 (54.0) | 0.001† |
| Yes | 145 (27.9) | 53 (16.6) | 92 (46.0) | |
| Perineural invasion, *n* (%) | | | | |
| No | 189 (36.3) | 129 (40.3) | 60 (30.0) | 0.001† |
| Yes | 331 (63.7) | 191 (59.7) | 140 (70.0) | |
| Lymphovascular invasion, *n* (%) | | | | |
| No | 484 (93.1) | 307 (95.9) | 177 (88.5) | 0.002† |
| Yes | 36 (6.9) | 13 (4.1) | 23 (11.5) | |
| Biochemical recurrence, *n* (%) | | | | |
| No | 386 (74.2) | 259 (80.9) | 127 (63.5) | 0.001† |
| Yes | 134 (25.8) | 61 (19.1) | 73 (36.5) | |
| Extra-prostatic extension, *n* (%) | | | | |
| No | 394 (75.8) | 293 (91.6) | 101 (50.5) | 0.001† |
| Yes | 126 (24.2) | 27 (8.4) | 99 (49.5) | |
| D'Amico classification, *n* (%) | | | | |
| Low-intermediate | 314 (60.4) | 209 (65.3) | 105 (52.5) | 0.004† |
| High | 206 (39.6) | 111 (34.7) | 95 (47.5) | |

*Student's paired *t*-test; †Chi-square test. PSA: prostate-specific antigen; TRUS: transrectal ultrasonography; PSAD: prostate-specific antigen density; s.d.: standard deviation

**Table 2: Univariate and multivariate analyses of the factors predicting extra-prostatic extension**

| *Variables* | *Univariate* | | *Multivariate* | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *Adjusted OR (95% CI)* | *P* |
| Age (≥69 years) | 0.76 (0.51–1.14) | 0.191 | | |
| PSA (ng ml$^{-1}$) | 1.05 (1.03–1.07) | 0.001 | 1.04 (1.02–1.06) | 0.001 |
| TRUS volume (ml) | 0.99 (0.98–1.01) | 0.929 | | |
| Preoperative PSAD (ng ml$^{-1}$ ml$^{-1}$) | 5.18 (2.90–9.26) | 0.001 | | |
| Positive core (%) | 1.02 (1.01–1.03) | 0.001 | 1.01 (1.00–1.03) | 0.001 |
| TRUS findings (hypoechoic lesion) | 1.23 (0.73–2.05) | 0.427 | | |
| Serum testosterone (<3 ng ml$^{-1}$) | 10.6 (6.57–17.2) | 0.001 | 8.52 (5.04–14.4) | 0.001 |
| Clinical stage (≥T3) | 2.11 (1.24–3.58) | 0.005 | | |
| Biopsy Gleason score (7–10) | 2.83 (1.86–4.31) | 0.001 | | |
| D'Amico classification (high) | 3.22 (2.13–4.89) | 0.001 | | |

PSA: prostate-specific antigen; TRUS: transrectal ultrasonography; PSAD: prostate-specific antigen density; OR: odds ratio; CI: confidence interval

**Table 3: Univariate and multivariate analyses of factors predicting biochemical recurrence**

| *Variables* | *Univariate* | | *Multivariate* | |
|---|---|---|---|---|
| | *OR (95% CI)* | *P* | *Adjusted OR (95% CI)* | *P* |
| Age (≥69 years) | 0.97 (0.65–1.44) | 0.903 | | |
| PSA (ng ml$^{-1}$) | 1.06 (1.04–1.09) | 0.001 | 1.04 (1.02–1.07) | 0.001 |
| TRUS volume (ml) | 1.00 (0.91–1.01) | 0.6 | | |
| Preoperative PSAD (ng ml$^{-1}$ ml$^{-1}$) | 8.22 (4.39–15.3) | 0.001 | | |
| Positive core (%) | 1.02 (1.01–2.13) | 0.001 | | |
| Tumor volume (%) | 1.06 (1.04–1.08) | 0.001 | 1.02 (1.01–1.05) | 0.046 |
| TRUS findings (hypoechoic lesion) | 1.11 (0.66–1.85) | 0.683 | | |
| Positive surgical margin | 1.99 (1.31–3.03) | 0.001 | | |
| Perineural invasion | 2.86 (1.79–4.57) | 0.001 | 2.02 (1.15–3.57) | 0.015 |
| Lymphovascular invasion | 4.05 (2.03–8.08) | 0.001 | 3.64 (1.53–8.66) | 0.003 |
| Serum testosterone (<3 ng ml$^{-1}$) | 2.44 (1.63–3.64) | 0.001 | | |
| Biopsy Gleason score (7–10) | 2.50 (1.66–3.76) | 0.001 | 1.81 (1.01–2.97) | 0.018 |
| Permanent Gleason score (7–10) | 4.01 (2.08–7.74) | 0.001 | | |
| Clinical stage (≥T3) | 1.77 (1.05–3.01) | 0.032 | | |
| Pathologic stage (≥T3) | 3.24 (2.10–4.98) | 0.001 | | |
| D'Amico classification (high) | 3.48 (2.31–5.23) | 0.001 | | |

PSA: prostate-specific antigen; TRUS: transrectal ultrasonography; PSAD: prostate-specific antigen density; OR: odds ratio; CI: confidence interval

with metastatic PCa showed clinical and biochemical improvement with androgen deprivation via castration or estrogen treatment and conversely demonstrated rapid PCa progression with testosterone administration.[11] However, the decades-old beliefs regarding androgens and PCa have changed dramatically with recent evidence and new theoretical constructs. Males with high serum testosterone are not at increased risk of developing PCa, and low serum testosterone provides no protection against the development of PCa.[12,13]

Recently, several studies have reported a correlation between lower serum testosterone and more aggressive PCa. Massengill *et al.*[14] found that patients with extra-prostatic disease had significantly lower preoperative serum testosterone than those with organ confined PCa and suggested that low preoperative serum testosterone predicted EPE. Furthermore, Kim *et al.*[7] found a significant difference in EPE between normal and hypogonadal groups. In our study, there was also a significant difference in EPE between the two groups. Furthermore, low preoperative serum testosterone was an independent predictor of EPE.

In terms of BCR, Yamamoto *et al.*[15] reported that low preoperative serum testosterone was associated with BCR, while Kim *et al.*[7] found that BCR was more frequent in patients with low preoperative testosterone. In line with their results, we also found an association between low preoperative serum testosterone and BCR. Countering this, however, Zhang *et al.*[16] reported that a low preoperative serum testosterone was not associated with BCR in patients who underwent a radical prostatectomy. Lane *et al.*[17] also demonstrated that a low preoperative total testosterone level was found to have a marginal association with a predominance of high-grade PCa at prostatectomy without an association with either the actual or predicted risk of disease progression. This discrepancy might be caused by the different proportion of locally advanced PCa in patients with low preoperative serum testosterone.

The mechanism involving preoperative serum testosterone, disease progression, and prognosis is not yet clear. Many hypotheses regarding the mechanism have been proposed, including changes secondary to the hormonal changes in chronic disease,[18] the inhibition of testosterone levels by high-grade tumors,[16] the central inhibition of the hypothalamic-pituitary axis,[19] the selection of poorly differentiated cancer cells due to low androgen levels, or purely a surrogate of other factors related to the pathological state.[14]

Recently, several studies have suggested that testosterone therapy actually protects against PCa recurrence. In the largest series to date, Pastuszak *et al.*[20] evaluated 103 hypogonadal males who received testosterone therapy after radical prostatectomy and compared BCR with that in 49 eugonadal males. After a median 27.5-month follow-up, there were four BCRs (4%) in the testosterone therapy group versus eight (16%) in the nontestosterone therapy group.[20] This finding is supported by laboratory data demonstrating that androgens promote less aggressive phenotypes and inhibit dedifferentiation in some PCa cell lines.[11] The evidence includes the findings that activation of membrane androgen receptors induced the apoptotic regression of human PCa cells *in vitro* and *in vivo*,[21] androgens triggered the inhibition of cell proliferation at a higher concentration in LNCaP cells,[22] and androgens caused growth suppression and reversion of androgen-independent tumors to an androgen-stimulated phenotype.[23] Studies of the exact mechanism of the effects of low testosterone on prostate cancer are needed.

The ability of tumor volume to predict disease recurrence after radical prostatectomy remains controversial. Some investigators have reported that tumor volume is an independent predictor of disease recurrence.[2,6,24,25] In practice, however, using the tumor volume as a predictive marker is difficult, because no uniform, standardized method of estimating the tumor volume has been accepted by uropathologists, although many investigators have proposed various accurate or practical methods. Maximum tumor diameter,[24] maximum tumor area,[26] tumor volume,[2] PTV,[6] and positive-block ratio[25] have all been suggested as significant, useful predictors of disease recurrence.

In this study, the tumor volume was calculated as the PTV, which was determined as the sum of all visually estimated tumor foci in

every section. In addition, PTV was an independent predictor of BCR in the multivariate analysis. However, compared with other clinicopathological variables in our study, the preoperative serum PSA and lymphovascular invasion were much stronger predictors of BCR than PTV. Our results were consistent with those of previous studies.

Some investigators have failed to demonstrate the prognostic significance of tumor volume.[27] In those studies, contrary to our methodology, the tumor volume was calculated using the equation reported by D'Amico *et al*.[28] Even in those studies, however, tumor volume was uniformly associated with all other clinical and pathological variables. Therefore, further studies are necessary to validate tumor volume as an independent predictor of BCR after radical prostatectomy.

In addition, several studies have found that BCR was significantly associated with prostate volume.[4,29] In those studies, males with smaller prostates were at a significantly higher risk of BCR.[4,29] The reason for this remains unknown, although there are many potential explanations. First, it has been suggested that males with smaller prostates have lower testosterone levels, which has been associated with more aggressive PCa.[14] Second, tumors were detected earlier in males with larger prostates because of PSA-induced biopsies resulting from PSA elevation from an enlarged gland.[30] Third, a tumor within a small prostate has to migrate a shorter distance to escape the prostatic capsule. This is supported by Yadav *et al*.[31] who reported that a decreased prostate volume is a predictor of EPE.

Our study has a number of limitations. First, the number of patients for a common disease such as PC was not sufficiently large ($n$ = 520). Probably due to this, there were some discrepancies in the results. Gleason score, clinical stage, and D'Amico classification which are previously known predictive factors of EPE were not significant in multivariate analysis. Larger cohort should be needed to elucidate these discrepancies. Second, the mean follow-up period was relatively short (median 19.1 months). Extending the follow-up period to 5 years might provide stronger evidence for our conclusions. Third, the visually estimated PTV possesses potential for under- or over-estimating the actual tumor volume. Interobserver variability exists. However, a simpler PTV might be sufficient for individual prognostication because accurately estimating the actual tumor volume might be of significant value for research purposes. Finally, the results of this study might be distorted by the distribution of surgical Gleason score 8–10 disease (23.8% of the population). Of the patients, 19% had biopsy Gleason scores ≥8, and 39.6% had high-risk disease preoperatively. A similar distribution has been reported in previous Asian studies and needs to be considered when interpreting the results.

## CONCLUSION

In addition to previous predictors of PCa progression, such as the preoperative serum PSA and Gleason score, this study showed that the preoperative serum testosterone and PTV were helpful for predicting EPE and BCR after LRP. This information might help urologists to predict postoperative PCa progression and guide patient expectations and disease prognosis.

## AUTHORS CONTRIBUTIONS

ECH and DDK participated in conceiving of the study and drafted the manuscript. DDK performed surgeries. SHY, YHJ, SIJ, TWK, SHH participated in collected the data. CC participated in pathological process. JEH participated in important intellectual content. SHJ and TYJ made a special contribution to the statistical analysis. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declare no competing financial interests.

## ACKNOWLEDGMENTS

This study was financially supported by a grant (HCRI 14029-1) Chonnam National University Hwasun Hospital Research Institute, Republic of Korea.

## REFERENCES

1 Teloken C, Da Ros CT, Caraver F, Weber FA, Cavalheiro AP, *et al*. Low serum testosterone levels are associated with positive surgical margins in radical retropubic prostatectomy: hypogonadism represents bad prognosis in prostate cancer. *J Urol* 2005; 174: 2178–80.
2 Tanaka N, Fujimoto K, Hirayama A, Nakai Y, Chihara Y, *et al*. Calculated tumor volume is an independent predictor of biochemical recurrence in patients who underwent retropubic radical prostatectomy. *Adv Urol* 2012; 2012: 204–15.
3 Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, *et al*. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA* 1999; 281: 1591–7.
4 Cho IC, Kwon WA, Kim JE, Joung JY, Seo HK, *et al*. Prostate volume has prognostic value only in pathologic T2 radical prostatectomy specimens. *J Korean Med Sci* 2011; 26: 807–13.
5 Epstein JI, Partin AW, Sauvageot J, Walsh PC. Prediction of progression following radical prostatectomy. A multivariate analysis of 721 men with long-term follow-up. *Am J Surg Pathol* 1996; 20: 286–92.
6 Song C, Seo S, Ahn H, Byun SS, Cho JS, *et al*. Percent tumor volume predicts biochemical recurrence after radical prostatectomy: multi-institutional data analysis. *Int J Clin Oncol* 2012; 17: 355–60.
7 Kim HJ, Kim BH, Park CH, Kim CI. Usefulness of preoperative serum testosterone as a predictor of extraprostatic extension and biochemical recurrence. *Korean J Urol* 2012; 53: 9–13.
8 Terris MK, Stamey TA. Determination of prostate volume by transrectal ultrasound. *J Urol* 1991; 145: 984–7.
9 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Blank K, *et al*. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998; 280: 969–74.
10 Kattan MW, Wheeler TM, Scardino PT. Postoperative nomogram for disease recurrence after radical prostatectomy for prostate cancer. *J Clin Oncol* 1999; 17: 1499–507.
11 Khera M, Crawford D, Morales A, Salonia A, Morgentaler A. A new era of testosterone and prostate cancer: from physiology to clinical implications. *Eur Urol* 2014; 65: 115–23.
12 Isbarn H, Pinthus JH, Marks LS, Montorsi F, Morales A, *et al*. Testosterone and prostate cancer: revisiting old paradigms. *Eur Urol* 2009; 56: 48–56.
13 Røder MA, Christensen IJ, Berg KD, Gruschy L, Brasso K, *et al*. Serum testosterone level as a predictor of biochemical failure after radical prostatectomy for localized prostate cancer. *BJU Int* 2012; 109: 520–4.
14 Massengill JC, Sun L, Moul JW, Wu H, McLeod DG, *et al*. Pretreatment total testosterone level predicts pathological stage in patients with localized prostate cancer treated with radical prostatectomy. *J Urol* 2003; 169: 1670–5.
15 Yamamoto S, Yonese J, Kawakami S, Ohkubo Y, Tatokoro M, *et al*. Preoperative serum testosterone level as an independent predictor of treatment failure following radical prostatectomy. *Eur Urol* 2007; 52: 696–701.
16 Zhang PL, Rosen S, Veeramachaneni R, Kao J, DeWolf WC, *et al*. Association between prostate cancer and serum testosterone levels. *Prostate* 2002; 53: 179–82.
17 Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. *Urology* 2008; 72: 1240–5.
18 Iversen P, Rasmussen F, Christensen IJ. Serum testosterone as a prognostic factor in patients with advanced prostatic carcinoma. *Scand J Urol Nephrol Suppl* 1994; 157: 41–7.
19 Miller LR, Partin AW, Chan DW, Bruzek DJ, Dobs AS, *et al*. Influence of radical prostatectomy on serum hormone levels. *J Urol* 1998; 160: 449–53.
20 Pastuszak AW, Pearlman AM, Lai WS, Godoy G, Sathyamoorthy K, *et al*. Testosterone replacement therapy in patients with prostate cancer after radical prostatectomy. *J Urol* 2013; 190: 639–44.
21 Hatzoglou A, Kampa M, Kogia C, Charalampopoulos I, Theodoropoulos PA, *et al*. Membrane androgen receptor activation induces apoptotic regression of human prostate cancer cells *in vitro* and *in vivo*. *J Clin Endocrinol Metab* 2005; 90: 893–903.
22 Sonnenschein C, Olea N, Pasanen ME, Soto AM. Negative controls of cell proliferation: human prostate cancer cells and androgens. *Cancer Res* 1989; 49: 3474–81.
23 Chuu CP, Hiipakka RA, Fukuchi J, Kokontis JM, Liao S. Androgen causes growth suppression and reversion of androgen-independent prostate cancer xenografts to an androgen-stimulated phenotype in athymic mice. *Cancer Res* 2005; 65: 2082–4.
24 Eichelberger LE, Koch MO, Eble JN, Ulbright TM, Juliar BE, *et al*. Maximum tumor diameter is an independent predictor of prostate-specific antigen recurrence in prostate cancer. *Mod Pathol* 2005; 18: 886–90.

25 Marks RA, Lin H, Koch MO, Cheng L. Positive-block ratio in radical prostatectomy specimens is an independent predictor of prostate-specific antigen recurrence. *Am J Surg Pathol* 2007; 31: 877–81.
26 Renshaw AA, Chang H, D'Amico AV. Estimation of tumor volume in radical prostatectomy specimens in routine clinical practice. *Am J Clin Pathol* 1997; 107: 704–8.
27 Porten SP, Cooperberg MR, Carroll PR. The independent value of tumour volume in a contemporary cohort of men treated with radical prostatectomy for clinically localized disease. *BJU Int* 2010; 105: 472–5.
28 D'Amico AV, Chang H, Holupka E, Renshaw A, Desjarden A, *et al*. Calculated prostate cancer volume: the optimal predictor of actual cancer volume and pathologic stage. *Urology* 1997; 49: 385–91.
29 Schroeck FR, Sun L, Freedland SJ, Jayachandran J, Robertson CN, *et al*. Race and prostate weight as independent predictors for biochemical recurrence after radical prostatectomy. *Prostate Cancer Prostatic Dis* 2008; 11: 371–6.
30 D'Amico AV, Whittington R, Malkowicz SB, Schultz D, Tomaszewski JE, *et al*. A prostate gland volume of more than 75 $cm^3$ predicts for a favorable outcome after radical prostatectomy for localized prostate cancer. *Urology* 1998; 52: 631–6.
31 Yadav R, Tu JJ, Jhaveri J, Leung RA, Rao S, *et al*. Prostate volume and the incidence of extraprostatic extension: is there a relation? *J Endourol* 2009; 23: 383–6.