Serum Testosterone Level Can Be Predictive Factor for Upstaging in Clinically Localized Prostate Cancer

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Purpose: To determine an appropriate surgical technique, it is important to predict pathological results for patients with clinically localized prostate cancer (PCa) eligible for nerve-sparing radical prostatectomy (NSRP). Several studies have highlighted that serum testosterone level was associated with aggressive features of PCa. Therefore, we analyzed factors, including serum testosterone, to predict upstaging and upgrading after surgery for patients with clinically localized PCa eligible for NSRP.

Materials and Methods: We retrospectively evaluated patients who underwent radical prostatectomy (RP) between January 2015 and May 2018 at our institution. Patients with Gleason grade group 1 or 2 on biopsy, prostate-specific antigen <10, and ≤clinical/radiologic stage T2 were included in this study. Upstaging and upgrading were defined as pathological stage ≥T3a and Gleason grade group ≥3, respectively. We evaluated the patients' demographics and outcomes according to upstaging and upgrading after surgery. Predictive factors for upstaging and upgrading were analyzed using a multivariate logistic regression model.

Results: Of 108 patients included in the study, upstaging and upgrading after surgery were observed in 24 (22.2%) and 36 (33.3%), respectively. Low serum testosterone level, small prostate size, and positive core number ≥3 on biopsy were identified as predictive factors for upstaging in multivariate analysis. Although serum testosterone was associated with upgrading in univariate analysis, only clinical/radiologic stage and biopsy Gleason grade group were observed as predictive factors for upgrading in multivariate analysis.

Conclusions: Serum testosterone level was identified as a predictive factor for upstaging after RP for clinically localized PCa eligible for NSRP.

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INTRODUCTION

Prostate cancer (PCa) is among the most common male cancers worldwide, and its incidence is gradually increasing.¹ Several treatment modalities, including active surveillance (AS), radical prostatectomy (RP), radiation therapy, and androgen deprivation therapy, have been established for patients with clinically localized PCa. Generally, RP has been considered as the gold standard definitive treatment for clinically localized PCa. However, RP can cause surgical complications, including urinary incontinence and erectile dysfunction, which can adversely influence quality of life.^{2,3} To mitigate such complications, nerve-sparing radical prostatectomy (NSRP), which preserves the neurovascular bundles, can apply to patients with selected criteria based on preoperative evaluations, such as prostate-specific antigen (PSA), clinical stage, and biopsy grade.^{3,4}

Although NSRP is currently acceptable for selected patients with PCa, it can sometimes cause incomplete tumor excision, depending on the tumor stage.⁵ Additionally, recent studies have shown that pathological stage and Gleason grade after RP are often inconsistent with clinical stage and biopsy Gleason grade.⁶ The discrepancy between preoperative parameters and pathological results is usually observed as upstaging or upgrading.⁶⁻¹¹ Therefore, it is necessary to determine predictive factors for worse pathological outcomes, such as upgrading and upstaging, relative to preoperative findings among patients with PCa amenable to NSRP.

Several studies have revealed that preoperative serum testosterone level is associated with aggressive features of PCa, such as high stage and high grade.¹²⁻¹⁶ Additionally, a recent study showed that low serum testosterone (<300 ng/dL) was associated with a high rate of upgrading and upstaging after RP.⁸ Another study also reported that low serum testosterone was associated with a positive surgical margin in RP specimens.¹⁷

In this study, we evaluated factors, including preoperative serum testosterone, to predict upstaging and upgrading after NSRP for PCa.

MATERIALS AND METHODS

We retrospectively reviewed PCa patients who underwent NSRP, performed by a single experienced surgeon between January 2015 and May 2018 at Kyungpook National University Chilgok Hospital. Patients with biopsy Gleason grade group 1 or 2, PSA<10 ng/mL, and clinical/radiologic stage≤T2 (using the 2009 TNM staging system) on preoperative evaluations were included in this study. We excluded patients who underwent neoadjuvant therapy, such as radiotherapy or hormonal therapy, and those with known medical problems that might affect testosterone status, such as thyroid disease, liver disease, and hypoalbuminemia. Patients with a history of 5αRI medication administration or testosterone replacement therapy were also excluded.

All patients were diagnosed with PCa by 12-core transrectal needle prostatic biopsies at our institution and underwent multiparametric magnetic resonance imaging for preoperative radiologic staging.

All patients underwent open RP or robot-assisted RP according to preoperative counseling. Open RP or robot-assisted RP were conducted in an ante-grade fashion using a nerve-sparing technique and a continuous urethrovesical anastomosis suture in the manner previously reported.¹⁸ Gleason grade was assessed according to the 2014 International Society of Urological Pathology Modified Gleason System.¹⁹ Prostate volume was measured by standard methods using transrectal ultrasonography, and PSA density (PSAD) was calculated by dividing PSA with prostate volume. Using an immunoassay at our institution's laboratory, the preoperative serum testosterone level (ng/dL) was measured. Considering diurnal fluctuations of the testosterone level, serum samples were collected in the morning between 8 AM and 10 AM when testosterone levels are high and stable.

The upstaging and upgrading were defined as nonorgan confined disease (pathological stage≥T3a) and pathological Gleason grade group≥3 after RP, respectively. We evaluated the incidence of upstaging and upgrading after RP in patients with biopsy Gleason grade group 1 or 2, PSA<10 ng/mL, and clinical/radiologic stage≤T2 on preoperative evaluation.

We also compared the patients' characteristics according

to upstaging and upgrading using Student t-test and the chi-square test. Predictive factors for upstaging and upgrading after RP were analyzed using a multivariate logistic regression model. Statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA), and statistical significance was established with p-value of <0.05.

The present study protocol was reviewed and approved by the Institutional Review Board of Kyungpook National University Chilgok Hospital (Reg. No. KNUMC 2019-12-021). Informed consent was submitted by all subjects when they were enrolled.

RESULTS

A total of 108 patients were included in the study. The mean age was 65.5 ± 6.2 years, mean preoperative PSA was 6.3 ± 1.8 ng/mL, and mean preoperative serum testosterone was 347.2 ± 154.1 ng/dL. Clinical/radiologic T stage was cT1c for 18 patients (16.7%) and cT2 for 90 patients (83.3%). Sixty-nine patients (63.9%) were classified as Gleason grade group 1, and 39 patients (36.1%) were classified as grade group 2. Table 1 shows the clinical and pathological characteristics of patients included in this study. Upstaging and upgrading after surgery were observed in 22.2% (24 of 108) and 33.3% (36 of 108) patients, respectively. Among the 24 patients in the upstaging group, 20 (83.3%) were upstaged to pT3a, and 4 (16.7%) were upstaged to pT3b. Among the 36 patients who were upgraded, 30 (83.3%) were upgraded to Gleason grade group 3, and 6 (16.7%) were upgraded to Gleason grade group 4 (Fig. 1).

Table 2 shows patients' characteristics according to upstaging and upgrading status. Mean prostate size was smaller and PSA density was higher among patients who were upstaged compared with those who were not (25.5 ± 5.5 vs. 34.5 ± 10.8 , $p < 0.001$ and 0.28 ± 0.13 vs. 0.20 ± 0.09 , $p = 0.012$, respectively). Mean preoperative serum testosterone was significantly lower in the upstaged patients compared with those who were not upstaged (284.6 ± 108.8 vs. 367.6 ± 156.8 , $p = 0.017$). The proportion of patients with a positive core number ≥ 3 at biopsy was higher in the upstaged group compared with the nonupstaged group (75.0% vs. 35.7%, $p = 0.001$). There were no significant differences in age,

body mass index, PSA, biopsy Gleason grade group, or operative method (robot-assisted RP vs. open RP) according to upstaging status after RP.

In terms of upgrading status, mean preoperative serum testosterone level was significantly lower among upgraded patients compared with those who were not upgraded (308.4 ± 106.9 vs. 369.5 ± 165.7 , $p = 0.047$). In addition, biopsy Gleason grade group and clinical/radiologic stage were significantly different between patients who were upgraded and those who were not ($p = 0.034$ and $p = 0.006$, respectively). Other variables did not show any significance.

The multivariate logistic regression model revealed that preoperative serum testosterone level (odds ratio [OR],

Table 1. Clinical and pathological characteristics of patients included in the study (n=108)

Characteristic	Value
Age (yr)	65.5±6.2
Body mass index (kg/m ²)	24.3±2.9
PSA (ng/mL)	6.3±1.8
Size (mL)	32.2±10.9
PSAD	0.5±3.1
Testosterone level (ng/dL)	347.2±154.1
Total positive core number	3.1±2.3
Positive core number	
≥3	48 (44.4)
<3	60 (55.6)
Biopsy Gleason grade	
Group 1	69 (63.9)
Group 2	39 (36.1)
Pathological Gleason grade	
Group 1	13 (12.0)
Group 2	59 (54.6)
Group 3	30 (27.8)
Group 4	6 (5.6)
Clinical/radiologic stage	
T1c	18 (16.7)
T2	90 (83.3)
Pathological stage	
pT2	84 (77.8)
pT3a	20 (18.5)
pT3b	4 (3.7)
Operative method	
RARP	85 (78.7)
Open RP	23 (21.3)

Values are presented as mean±standard deviation or number (%). PSA: prostate-specific antigen, PSAD: prostate-specific antigen density, RARP: robot-assisted radical prostatectomy, RP: radical prostatectomy.

Fig. 1. The rates of upstaging (A) and upgrading (B) after surgery.

Table 2. Comparison of variables according to upstaging and upgrading after surgery

Variable	Upstaging			Upgrading		
	Yes (n=24)	No (n=84)	p-value	Yes (n=36)	No (n=72)	p-value
Age (yr)	66.7±4.4	65.2±6.7	0.216	65.7±4.8	65.4±6.9	0.828
BMI (kg/m ²)	24.4±3.3	24.3±2.7	0.926	24.5±2.6	24.2±3.0	0.628
PSA (ng/mL)	6.49±2.0	6.26±1.7	0.616	6.15±1.6	6.42±1.8	0.432
Size (mL)	25.5±5.5	34.5±10.8	<0.001	33.4±11.7	32.0±10.0	0.529
PSAD	0.28±0.13	0.20±0.09	0.012	0.21±0.10	0.22±0.11	0.378
Testosterone level (ng/dL)	284.6±108.8	367.6±156.8	0.017	308.4±106.9	369.5±165.7	0.047
Total positive core number	3.8±2.1	2.9±2.3	0.733	2.9±2.0	3.2±2.4	0.564
Positive core number			0.001			1.000
≥3	18	30		16	32	
<3	6	54		20	40	
Biopsy Gleason grade			0.108			0.034
Group 1	12	57		18	51	
Group 2	12	27		18	21	
Clinical/radiologic stage			0.758			0.006
T1c	3	15		1	17	
T2	21	69		35	55	
Operative method			0.286			0.406
RARP	17	68		30	55	
Open RP	7	16		6	17	

Values are presented as mean±standard deviation or number.

BMI: body mass index, PSA: prostate-specific antigen, PSAD: prostate-specific antigen density, RARP: robot-assisted radical prostatectomy, RP: radical prostatectomy.

0.993; 95% confidence interval [CI], 0.987–0.999; $p=0.034$), prostate size (OR, 0.765; 95% CI, 0.669–0.875; $p<0.001$), and a positive core number ≥ 3 at biopsy (OR, 9.856; 95% CI, 2.230–43.557; $p=0.003$) were associated with upstaging after RP (Table 3). The cutoff value for pre-operative serum testosterone level for upstaging was 273.7 ng/dL (sensitivity, 71.3%; specificity, 66.7%, as determined by receiver operating curve analysis) (Fig. 2). In addition,

clinical/radiologic stage (T2 vs. T1c) and Gleason grade group at biopsy (2 vs. 1) were significantly associated with upgrading in the multivariate analysis (OR, 11.260; 95% CI, 1.410–89.914; $p=0.022$ and OR, 2.526; 95% CI, 1.063–5.998; $p=0.036$, respectively).

Table 3. Factors associated with upstaging and upgrading by multivariable logistic regression

Variable	Upstaging		Upgrading	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Testosterone level (continuous)	0.993 (0.987–0.999)	0.034	0.997 (0.994–1.000)	0.072
Prostate size (continuous)	0.765 (0.669–0.875)	<0.001	-	-
Positive core number ≥ 3 vs. <3	9.856 (2.230–43.557)	0.003	-	-
Clinical/radiologic stage T2 vs. T1c	-	-	11.260 (1.410–89.914)	0.022
Biopsy Gleason grade group 2 vs. 1	-	-	2.526 (1.063–5.998)	0.036

OR: odds ratio, CI: confidence interval.

Fig. 2. Receiver-operating characteristic (ROC) curve of pre-operative serum testosterone level for upstaging after surgery. Cutoff point for testosterone level was 273.7 ng/dL (sensitivity, 71.3%; specificity, 66.7%; area under the curve, 0.649) on the ROC curve analysis.

DISCUSSION

Currently, NSRP is a widely accepted surgical method for select patients with clinically localized PCa, to minimize postoperative complications, including erectile dysfunction and postprostatectomy incontinence. However, postoperative upstaging and upgrading—which might have altered the operative technique selection if they had been predicted—are not uncommon after NSRP. Recently, several studies revealed that preoperative serum testosterone reflects tumor aggressiveness among PCa patients.^{12–16} Therefore, we assessed the incidence and predictive factors for upstaging and upgrading among PCa patients after NSRP at our institution. We observed significant incidences of upstaging (22.2%) and upgrading (33.3%). Furthermore, preoperative serum testosterone was negatively associated with upstaging

and upgrading after RP. Multivariate analysis revealed pre-operative serum testosterone as a significant predictor upstaging, despite its lack of a significant association with postoperative upgrading.

The key objectives of RP for PCa include ensuring good postoperative erectile function and urinary continence without compromising oncological outcomes. Techniques that emphasize the preservation of neurovascular bundles during RP have been developed to minimize postoperative complications for appropriately selected patients.³ Several studies have confirmed the benefits of NSRP for the recovery of erectile function and urinary continence.^{20–23} While nerve-sparing techniques have several advantages in terms of quality of life, dissection closer to the prostate capsule during NSRP may increase the risk of incising the tumor or incomplete tumor excision, resulting in a positive surgical margin, and may increase risk of biochemical progression and cancer recurrence.⁵

When choosing the treatment method, particularly when considering NSRP, the surgeon most strongly considered the index PSA, clinical stage, and the biopsy Gleason grade group. However, recent research has shown that pathological stage and grade after surgery are often inconsistent with clinical stage and biopsy grade, and this is usually expressed as upgrading or upstaging.^{6–11} For patients whose real pathological stage and grade exceed the clinical stage and biopsy grade, the selected surgical method—nerve-sparing surgery, for example—could underestimate the aggressiveness of the PCa and compromise cancer control. Therefore, it is necessary to identify predictive factors for upstaging and upgrading for selecting a proper treatment strategy or surgical method for PCa patients for whom there are several options.

Several recent studies have focused on determining pre-

dictors of upstaging and upgrading among PCa patients.⁶⁻¹¹ In a large cohort study including 7,643 patients who underwent RP, 36.3% of patients had their needle biopsy Gleason score upgraded from 5 or 6 to a higher grade after RP.⁶ Sooriakumaran et al.¹⁰ reported that 40.4% patients were either upstaged (3.9%) or upgraded (39.6%) after RP among 750 patients with low-risk PCa, clinically eligible for AS. In a Korean multicenter study with 324 RP specimens from low-risk PCa patients, upstaging and upgrading were observed in 9.6% and 43.8% samples, respectively.⁹ In another study of Korean PCa patients who were eligible for AS (clinical stage T1c/T2a, PSA level 10 ng/mL or less, and Gleason score 6 or less), upstaging and upgrading were observed in 11.0% and 57.8% of 593 patients, respectively.¹¹ A recent study with similar inclusion criteria (biopsy Gleason score ≤ 6 , clinical stage $\leq T2c$, and PSA < 10 ng/mL) to our study revealed that upstaging occurred in 43.7%, and upgrading occurred in 37.1% of 167 patients.⁸ Unlike previous studies, however, our study showed relatively high upstaging (33.3%) and low upgrading (22.2%). We assumed that this discrepancy from previous research was caused by differences in the participant characteristics and radiologic staging using multiparametric magnetic resonance imaging in the present study. This study was conducted on patients eligible for NSRP (biopsy Gleason grade group 1 or 2, PSA < 10 , and clinical/radiologic stage $\leq T2$) at our institution, while previous studies investigated patients who were eligible for AS.

In the present study, preoperative serum testosterone was negatively correlated with upstaging and upgrading after RP, and it was identified as a predictive factor for upstaging in multivariate analysis. Although it is still controversial, testosterone has been widely evaluated as a predictive factor for worse pathological outcomes, such as upstaging and upgrading, and oncologic outcomes.^{13-17,24,25} Previous studies have suggested that serum testosterone level is inversely correlated with tumor aggressiveness, which is a descriptor that encompasses both high stage^{13,14} and high grade.^{15,16} Teloken et al.¹⁷ reported that low serum testosterone levels were associated with positive surgical margins after RP, while not with PSA levels, Gleason score (biopsy or specimen), pathological stage, or capsular perforation. Moreover, Asian studies have identified preoperative serum testosterone level as an independent predictor of biochemical re-

currence after RP among patients with clinically localized PCa.^{24,25}

Recently, several reports have highlighted the association of low serum testosterone levels with upstaging and upgrading after RP among patients with localized PCa.^{8,12} Gao et al.⁸ investigated the association between serum testosterone and upgrading or upstaging among PCa patients with biopsy Gleason scores ≤ 6 , clinical stage $\leq T2c$, and PSA < 10 ng/mL. They confirmed preoperative serum testosterone level as a unique independent predictor of pathological upstaging and upgrading after RP. Moreover, Ferro et al.¹² assessed the impact of serum testosterone for predicting unfavorable outcomes among PCa patients eligible for AS, which is currently considered acceptable for clinically localized PCa. They suggested that patients with hypogonadism were not eligible for AS because low serum testosterone is associated with unfavorable pathological outcomes, including upstaging, upgrading, and positive surgical margins. Our findings also supported the clinical impact of low serum testosterone as a predictive factor of upstaging and upgrading among patients with localized PCa eligible for NSRP on preoperative evaluation. Therefore, surgeons should be cautious when selection of a treatment course and proceeding with NSRP for eligible patients with low serum testosterone.

Recent studies, including the present study, have demonstrated that serum testosterone level is predictive of tumor aggressiveness, including the potential for upstaging and upgrading. Although the exact mechanism is not yet fully understood, it may be assumed that involves the inhibition of testosterone by highly aggressive prostate tumors and negative feedback control of pituitary gonadotropin secretion.⁸ Moreover, metabolic disorders that are associated with hypogonadism might contribute to unfavorable PCa outcomes.^{12,26,27}

In this study, small prostate size and positive core number ≥ 3 on biopsy were also identified as predictive factors for upstaging in multivariate analysis. Previous studies have shown small prostate size and high positive core number on prostate biopsy to be associated with aggressive features of PCa.^{9,11,28-30} Similar with our results, 2 Korean studies found that prostate volume and positive core number were significantly associated with upstaging¹¹ or worsening prognosis⁹ in multivariate analyses. Additionally, a Japanese study²⁹ and a Swedish study³⁰ also reported that smaller

prostate volume was associated with adverse pathology. Regarding the mechanism by which prostate volume and positive core number are predictors of PCa aggressiveness, they might reflect a relatively larger tumor burden with a high probability of disease that has progressed beyond the prostate capsule.

Several limitations of our study should be considered. First, this was a retrospective analysis of the records of a relatively small sample of patients treated at a single institution. Although the criteria for NSRP eligibility were followed in this study, selection bias regarding the surgical indication was unavoidable. Additionally, we did not access to data reflecting long-term oncologic outcomes, such as biochemical recurrence and metastasis-free survival. These limitations highlight the need for more standardized study designs and outcome reporting methods in the future. Furthermore, additional studies are necessary to elucidate the underlying mechanisms involving serum testosterone in relation to PCa. Although this retrospective study had several limitations, it demonstrated that low preoperative serum testosterone level, small prostate size, and positive core number ≥ 3 on biopsy should be considered valuable predictors of upstaging after RP in clinically localized PCa amenable to NSRP. We hope that the results of this study can help clinicians develop appropriate management strategies and choose appropriate surgical methods to treat clinically localized PCa.

CONCLUSIONS

Low preoperative serum testosterone level, small prostate size, and positive biopsy core number ≥ 3 were identified as predictive factors for upstaging after RP in clinically localized PCa eligible for nerve-sparing surgery. Therefore, preoperative serum testosterone should be measured and considered as a predictor of non-organ confined disease in patients with clinically localized PCa eligible for nerve-sparing surgery.

CONFLICT OF INTEREST

The authors claim no conflicts of interest.

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