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**ORIGINAL ARTICLE**

Prostate Disease

# Low serum testosterone predicts upgrading and upstaging of prostate cancer after radical prostatectomy

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**Often, pathological Gleason Score (GS) and stage of prostate cancer (PCa) were inconsistent with biopsy GS and clinical stage. However, there were no widely accepted methods predicting upgrading and upstaging PCa. In our study, we investigated the association between serum testosterone and upgrading or upstaging of PCa after radical prostatectomy (RP). We enrolled 167 patients with PCa with biopsy GS ≤6, clinical stage ≤T2c, and prostate-specific antigen (PSA) <10 ng ml$^{-1}$ from April 2009 to April 2015. Data including age, body mass index, preoperative PSA level, comorbidity, clinical presentation, and preoperative serum total testosterone level were collected. Upgrading occurred in 62 (37.1%) patients, and upstaging occurred in 73 (43.7%) patients. Preoperative testosterone was lower in the upgrading than nonupgrading group (3.72 *vs* 4.56, $P < 0.01$). Patients in the upstaging group had lower preoperative testosterone than those in the nonupstaging group (3.84 *vs* 4.57, $P = 0.01$). In multivariate logistic regression analysis, as both continuous and categorical variables, low serum testosterone was confirmed to be an independent predictor of pathological upgrading ($P = 0.01$ and $P = 0.01$) and upstaging ($P = 0.01$ and $P = 0.02$) after RP. We suggest that low serum testosterone (<3 ng ml$^{-1}$) is associated with a high rate of upgrading and upstaging after RP. It is better for surgeons to ensure close monitoring of PSA levels and imaging examination when selecting non-RP treatment, to be cautious in proceeding with nerve-sparing surgery, and to be enthusiastic in performing extended lymph node dissection when selecting RP treatment for patients with low serum testosterone.**

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## INTRODUCTION

In 2015, 220 800 new cases of prostate cancer (PCa) and 27 540 deaths are projected to occur in the US.[1] With the widespread use of prostate-specific antigen (PSA), PCa has always been diagnosed at a low-risk stage. For low-risk PCa patients, we have many therapeutic options such as active surveillance (AS), watchful waiting (WW), radical prostatectomy (RP), and definitive radiotherapy (DRT). Biopsy Gleason Score (GS) and clinical stage are principal elements for selecting therapy. However, recent research and our experiences have shown that pathological GS and stage are often inconsistent with biopsy GS and clinical stage, and in most cases, it was upgrading or upstaging. A large study[2] of 7643 patients with RP and corresponding needle biopsies revealed that 36.3% of the cases were upgraded from a needle biopsy GS 5–6 to a higher grade at RP. It was necessary to determine an effective predictor of upgrading and upstaging to assist selecting therapy. Several studies[3,4] have demonstrated that a small prostate and high PSA level are two factors that predict GS upgrading after prostatectomy for biopsy GS 6. However, they are still controversial.

The prostate is an androgen-dependent organ and serum testosterone contributes to the growth and development of PCa. Low serum testosterone has been shown to predict a high GS and to be an indicator of PCa aggressiveness. One study[5] even reported that low-testosterone was associated with a positive margin in RP specimens. In this study, we evaluated the association between testosterone and upgrading or upstaging after RP.

## MATERIALS AND METHODS

From April 2009 to April 2015, 167 patients with biopsy GS ≤6, clinical stage ≤T2c, and PSA <10 ng ml$^{-1}$ PCa underwent laparoscopic radical prostatectomy (LRP) by one single experienced surgeon, and extended lymph node dissection (eLND) was performed in accordance with European Association of Urology (EAU) guidelines. All patients had been assessed for PCa by 12-core transrectal needle prostatic biopsies before LRP, and patients received LRP at least 4 weeks after prostate biopsy.

Data including age, body mass index (BMI), preoperative PSA level, comorbidity, clinical presentation, and preoperative testosterone level were collected. Blood samples were collected on the morning of prostatic surgery between 07:00 and 09:00 h, and patients were divided into two groups according to testosterone level such as low-testosterone group (<3 ng ml$^{-1}$) and normal TT group (≥3 ng ml$^{-1}$). Clinical stage was

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assessed by digital rectal examination and magnetic resonance imaging by the attending surgeon according to TNM staging (2009). GS upstaging was regarded as pathological stage ≥T3a after RP with clinical stage ≤T2c. GS upgrading was defined as GS ≥7 in RP specimens with GS ≤6 in biopsy specimens. Patients who accepted any kind of neoadjuvant hormonal therapy or suffered from incurable endocrine diseases were excluded.

Unpaired *t*-test was used to compare continuous variables (age, BMI, PSA, and testosterone level), and $\chi^2$ test was used to compare categorical variables (categorical testosterone). Multivariate unconditional logistic regression models were used to evaluate the independent contribution of characteristics in the prediction of upgrading and upstaging. In all analyses, $P < 0.05$ was considered statistically significant. For statistical analysis, we used SAS version 9.2 (SAS Institute, Cary, NC, USA).

## RESULTS

A total of 167 patients were included in this study. **Table 1** shows the clinical and pathological characteristics of patients included in the study such as mean age of the patients was 69.71 ± 5.84 years, PSA was 6.92 ± 1.91 ng ml$^{-1}$, and preoperative testosterone was 4.25 ± 1.80 ng ml$^{-1}$. Of the 167 patients, upgrading occurred in 62 (37.1%) and upstaging in 73 (43.7%) patients.

**Table 2** shows the results of the *t*-test for the association between patients and tumor characteristics with upgrading or upstaging. No difference was found in age, BMI, and PSA. The prostate volume in the upgrading group was smaller than in the nonupgrading group (45.24 *vs* 51.85, $P = 0.03$), but no significant difference was seen between the upstaging and nonupstaging groups (49.19 *vs* 49.55, $P = 0.81$). In contrast, preoperative serum testosterone was lower in the upgrading than nonupgrading group (3.72 *vs* 4.56, $P < 0.01$). Meanwhile, patients in the upstaging group had lower preoperative serum testosterone than those in the nonupstaging group (3.84 *vs* 4.57, $P = 0.01$).

**Table 1: Clinical and pathological characteristics of patients included in the study**

| | *Patients sample validation cohort (n=167) (%)* |
|---|---|
| Age (year) | 69.71±5.84 |
| BMI (kg m$^{-2}$) | 21.93±3.64 |
| PSA (ng ml$^{-1}$) | 6.92±1.91 |
| prostate volume (ml) | 49.40±19.46 |
| preoperative TT (ng ml$^{-1}$) | 4.25±1.80 |
| Biopsy GS | |
| <6 | 37/167 (22.2) |
| 6 | 130/167 (77.8) |
| Pathological GS | |
| <6 | 21/167 (12.6) |
| 6 | 84/167 (50.3) |
| 7 | 41/167 (24.6) |
| >7 | 21/167 (12.6) |
| Clinical stage | |
| cT1 | 84/167 (50.3) |
| cT2 | 83/167 (49.7) |
| Pathological stage | |
| pT2 | 94/167 (56.3) |
| pT3 | 73/167 (43.7) |
| Upgrading | 62/167 (37.1) |
| Upstaging | 73/167 (43.7) |

Data are presented as mean±s.d. BMI: body mass index; PSA: prostate-specific antigen; TT: total testosterone; s.d.: standard deviation; GS: Gleason Score

When we defined testosterone as a categorical variable at 3 ng ml$^{-1}$, the $\chi^2$ test demonstrated that upgrading occurred in 26 (56.5%) low-testosterone patients, but only 36 (29.8%) normal-testosterone patients. Patients with serum testosterone <3 ng ml$^{-1}$ were more likely to be upgraded ($P < 0.01$). At the same time, upstaging occurred in 27 (58.7%) low-testosterone patients, but only 46 (38.0%) normal-testosterone patients ($P = 0.02$, **Table 3**).

According to multivariate logistic regression analysis, prostate volume was not regarded as an independent predictor of PCa upgrading. Low-testosterone, as both a continuous and categorical variable, was confirmed to be an independent predictor of upgrading ($P = 0.01$ and $P = 0.01$) and upstaging ($P = 0.01$ and $P = 0.02$) after RP (**Tables 4** and **5**).

## DISCUSSION

The biopsy GS and clinical stage contributed most for surgeons in selecting therapy of PCa; however, pathological upgrading and upstaging after RP were common.[6–8] According to previous studies,[2,6,9] the rate of upgrading after RP was 30%–60%, means nearly half of the biopsy grades were not correctly presenting the real malignancy. Epstein *et al.* attributed upgrading after RP to pathological error, borderline grades, and sampling error, emphasizing that a tertiary higher grade pattern in RP should be recorded in needle biopsy.[2] Studies have proven that upgrading demonstrates an association with poor outcome, including adverse pathological features and risk of biochemical progression.[10,11]

Some large prospective clinical trials[12–14] have suggested that compared with RP, AS did not show any treatment delay during long-term follow-up. Therefore, AS was widely recognized as a reasonable treatment for low-risk PCa.[15,16] According to EAU guidelines, patients with clinically confined PCa (T1–T2), GS ≤6, and PSA <10 ng ml$^{-1}$ are eligible for AS.[17] In patients who undergo RP, it is possible to determine real pathological grade and stage by specimen examination, so that surgeons can adjust therapy accordingly. However, for patients whose real pathological grade and stage exceed the biopsy grade and clinical stage, selecting non-RP treatment such as AS could underestimate PCa aggressiveness and delay timely treatment. At the same time, even selecting RP, an incorrect biopsy GS and clinical stage could influence our surgical methods such as eLND and nerve-sparing surgery. Therefore, many studies have focused on figuring out predictions of upgrading and upstaging.

Gershman *et al.*[4] evaluated 1836 patients with GS 6 on prostate biopsy and found that older age and smaller prostate size were significantly associated with GS upgrading, owing to increased high-grade disease in smaller organs. Busch *et al.*[18] confirmed the association between age and upgrading and also found that patients aged ≥65 years were more likely to be upstaged. However, some studies[19,20] repudiated the predictive value of age for upgrading. Meanwhile, both Hong *et al.*[3] and Moussa *et al.*[21] reported multivariate analyses in which preoperative PSA level was an independent predictor of GS upgrading but, conversely, the study of Krane *et al.*[22] disagreed. Recently, a study by de Cobelli *et al.*[23] defined BMI as a continuous and categorical variable. They demonstrated that high BMI significantly predicted upgrading, upstaging, and seminal vesicle invasion, indicating BMI as a selection criterion for low-risk PCa patients in AS programs. Another recent study found that phosphatase and tensin homolog protein loss could help identify upgrading of PCa from biopsy to RP.[24] At the same time, number of biopsy cores,[20] number of positive cores,[25] and the maximum percentage of cancer

**Table 2: Univariate analysis for the association between patient and tumor characteristics with upgrading or upstaging**

| *Variables* | *Upgrading (n=62)* | *Nonupgrading (n=105)* | *P* | *Upstaging (n=73)* | *Nonupstaging (n=94)* | *P* |
|---|---|---|---|---|---|---|
| Age (year) | | | | | | |
| Median (range) | 71.0 (62.0–80.0) | 69.0 (52.0–81.0) | | 70.0 (53.0–81.0) | 69.0 (52.0–80.0) | |
| Mean±s.d. | 70.86±5.12 | 69.04±6.15 | 0.05 | 70.14±5.55 | 69.38±6.07 | 0.41 |
| BMI (kg m$^{-2}$) | | | | | | |
| Median (range) | 21.00 (17.00–31.00) | 21.00 (15.00–31.00) | | 22.0 (15.0–29.0) | 21.0 (15.0–31.0) | |
| Mean±s.d. | 22.23±3.41 | 21.75±3.78 | 0.42 | 22.08±3.63 | 21.81±3.67 | 0.63 |
| PSA (ng ml$^{-1}$) | | | | | | |
| Median (range) | 7.23 (1.84–9.65) | 7.41 (2.30–9.85) | | 7.30 (1.84–9.74) | 7.34 (2.30–9.85) | |
| Mean±s.d. | 6.77±2.00 | 7.01±1.86 | 0.43 | 6.82±2.08 | 7.00±1.78 | 0.53 |
| Volume (ml) | | | | | | |
| Median (range) | 37.2 (20.6–109.8) | 49.9 (13.1–98.7) | | 44.1 (13.1–103.3) | 47.6 (20.3–109.8) | |
| Mean±s.d. | 45.24±21.22 | 51.85±18.00 | 0.03* | 49.19±20.59 | 49.55±18.64 | 0.81 |
| TT (ng ml$^{-1}$) | | | | | | |
| Median (range) | 3.48 (0.54–7.77) | 4.32 (0.26–8.87) | | 3.66 (0.54–7.77) | 4.47 (0.26–8.87) | |
| Mean±s.d. | 3.72±1.77 | 4.56±1.74 | <0.01** | 3.84±1.69 | 4.57±1.83 | 0.01* |

*$P$<0.05; **$P$<0.01. s.d.: standard deviation; BMI: body mass index; PSA: prostate-specific antigen; TT: total testosterone

**Table 3: Comparison of upgrading and upstaging of patients with low versus normal TT**

| *Variable* | *Low TT (<3 ng ml$^{-1}$) (%)* | *Normal TT (≥3 ng ml$^{-1}$) (%)* | *P* |
|---|---|---|---|
| Upgrading | | | |
| Yes | 26 (56.5) | 36 (29.8) | <0.01** |
| No | 20 (43.5) | 85 (70.2) | |
| Upstaging | | | |
| Yes | 27 (58.7) | 46 (38.0) | 0.02* |
| No | 19 (41.3) | 75 (62.0) | |

*$P$<0.05; **$P$<0.01. TT: total testosterone

per core[26] were reported to be associated with upgrading or upstaging. Nevertheless, all predictors are still controversial, and little is known about the relationship between pathological upgrading or upstaging and testosterone, which has a crucial role in prostate growth and PCa progression.

Testosterone has been widely evaluated for its role in prediction of GS, pathological stage, biochemical recurrence, and even survival. Botto *et al.*[27] assessed 431 patients with PCa and found that low serum testosterone was associated with a higher percentage of predominant Gleason pattern 4, which is a signature of PCa aggressiveness. Xylinas *et al.*[28] examined serum testosterone and pathological specimens of 107 patients and claimed that low serum testosterone (<3 ng ml$^{-1}$) predicted high GS (>7) and locally advanced pathological stage (pT3, pT4).

In our study, we found that patients with upgrading or upstaging had lower testosterone than patients who did not. In multivariate statistical analysis, when controlling for age, PSA, BMI, and prostate volume, we confirmed the inverse association between testosterone and upgrading or upstaging. As most previous studies had shown 3 ng ml$^{-1}$ as a threshold between low and normal-testosterone,[29] we classified testosterone as a dichotomous variable and categorized patients as hypogonadism or eugonadism according to testosterone level of 3 ng ml$^{-1}$. We also found that hypogonadism led to a high rate of upgrading and upstaging. We thought that it was related to an increased incidence of high-grade disease in low-testosterone PCa, mainly resulting from inhibition of testosterone by high-grade PCa and negative feedback control of pituitary gonadotropin secretion. Our findings corroborated those of earlier studies, in which low serum testosterone may predict high malignancy for low-risk PCa patients.

Our results remind us to be cautious when selecting AS treatment for patients with PCa and hypogonadism, in whom it is better to ensure close monitoring of PSA levels and imaging examination. Based on nomograms,[30] patients with GS <7 are less likely to have lymph node metastasis and undergo unnecessary eLND. However, for upgrading patients whose real GS ≥7, eLND is recommended. Nerve-sparing RP is safe in most patients with localized PCa and is recommended. However, in upgraded patients who are not low-risk, nerve-sparing RP would probably lower the tumor clearance rate. Although intraoperative observation and frozen-section analysis could help eliminate nerve-sparing surgery and remove the neurovascular bundle, their accuracy and cost are limiting. Therefore, even though we selected RP therapy for low-testosterone patients, we should be cautious about proceeding with nerve-sparing and enthusiastic about eLND.

The merits of this study are that to our knowledge, it is the first to investigate the association between upgrading or upstaging and testosterone level, which is important in PCa. Low-testosterone may be an effective predictor of upgrading and upstaging in the future. Meanwhile, all prostate biopsies and RP were performed by the same surgeon at one single center, and none of the enrolled patients had received neoadjuvant hormonal therapy or had other comorbidities that may have affected testosterone.

However, our study still had some limitations. First, it was a retrospective small sample analysis with inherent bias. In addition, as most cases were from the past 5 years, we were short of long-term follow-up data, which we will publish in the future. Finally, we lacked data about free and bioavailable testosterone, which may be more important for PCa grade.

## CONCLUSION

We suggest that low serum testosterone is associated with a high rate of upgrading and upstaging after RP, regardless of whether as a continuous or categorical variable. It is better for surgeons to ensure close monitoring of PSA levels and imaging examination when selecting non-RP treatment to be cautious to proceed with nerve-sparing surgery and to be enthusiastic to perform eLND when selecting RP treatment for patients with low serum testosterone.

**Table 4: Multivariate logistic regression analysis of predictors for upgrading after radical prostatectomy**

| *Variable* | *OR (95% CI)* | *P* | *Variable* | *OR (95% CI)* | *P* |
|---|---|---|---|---|---|
| Continuous TT | 0.78 (0.63–0.95) | 0.01* | TT ≥3 ng ml$^{-1}$ | 0.35 (0.17–0.73) | 0.01* |
| | | | TT <3 ng ml$^{-1}$ | | |
| Age | 1.03 (0.97–1.10) | 0.29 | Age | 1.04 (0.98–1.10) | 0.21 |
| BMI | 1.04 (0.95–1.14) | 0.39 | BMI | 1.03 (0.94–1.13) | 0.52 |
| PSA | 0.91 (0.77–1.09) | 0.33 | PSA | 0.92 (0.78–1.10) | 0.37 |
| Volume | 0.98 (0.97–1.00) | 0.08 | Volume | 0.98 (0.97–1.00) | 0.06 |

*$P$<0.05. TT: total testosterone; BMI: body mass index; PSA: prostate-specific antigen; OR: odds ratio; CI: confidence interval

**Table 5: Multivariate logistic regression analysis of predictors for upstaging after radical prostatectomy**

| *Variable* | *OR (95% CI)* | *P* | *Variable* | *OR (95% CI)* | *P* |
|---|---|---|---|---|---|
| Continuous TT | 0.78 (0.65–0.95) | 0.01* | TT ≥3 ng ml$^{-1}$ | 0.44 (0.22–0.89) | 0.02* |
| | | | TT <3 ng ml$^{-1}$ | | |
| Age | 1.00 (0.95–1.06) | 0.99 | Age | 1.01 (0.96–1.07) | 0.73 |
| BMI | 1.04 (0.95–1.13) | 0.44 | BMI | 1.02 (0.94–1.12) | 0.60 |
| PSA | 0.94 (0.80–1.11) | 0.48 | PSA | 0.95 (0.80–1.12) | 0.52 |
| Volume | 1.00 (0.99–1.02) | 0.84 | Volume | 1.00 (0.98–1.02) | 0.96 |

*$P$<0.05. TT: total testosterone; BMI: body mass index; PSA: prostate-specific antigen; OR: odds ratio; CI: confidence interval

## AUTHOR CONTRIBUTIONS

YG contributed to project development and also wrote the manuscript. CYJ, SKM, and DC performed data collection and management. KYH, WZ, and QJ performed data analysis. BMH performed all 167 LRP operations. BMH, SJX, and YR contributed to the manuscript editing and supervised the project. All authors read and approved the final manuscript.

## COMPETING INTERESTS

All authors declared no competing financial interests.

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