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 study² 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 studies³⁴ 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 study⁵ 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 serum total 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...
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 χ² 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 upgrading 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, \( P = 0.01 \)).

When we defined testosterone as a categorical variable at 3 ng ml\(^{-1}\), the χ² 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.4–8 According to previous studies,6–8 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 trials12–14 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 studies19,20 repudiated the predictive value of age for upgrading. Meanwhile, both Hong et al.19 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,25 number of positive cores,26 and the maximum percentage of cancer

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

| 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) |
| 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 means±s.d. BMI: body mass index; PSA: prostate-specific antigen; TT: total testosterone; s.d.: standard deviation; GS: Gleason Score.
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)     | 0.05  | 70.0 (53.0–81.0) | 69.0 (52.0–80.0)     | 0.41  |
| Means.d.      | 70.86±5.12       | 69.04±6.65           |       | 70.14±5.55       | 69.38±6.07           |       |
| BMI (kg m⁻²)  |                  |                      |       |                  |                      |       |
| Median (range)| 21.00 (17.00–31.00) | 21.00 (15.00–31.00)  | 0.42  | 22.0 (15.0–29.0)  | 21.0 (15.0–31.0)     | 0.63  |
| Means.d.      | 22.23±3.41       | 21.76±3.78           |       | 22.08±3.63       | 21.81±3.67           |       |
| PSA (ng ml⁻¹) |                  |                      |       |                  |                      |       |
| Median (range)| 7.23 (1.84–9.65) | 7.41 (2.30–9.85)     | 0.43  | 7.30 (1.84–9.74)  | 7.34 (2.30–9.85)     | 0.53  |
| Means.d.      | 6.77±2.00        | 7.01±1.86            |       | 6.82±2.08        | 7.00±1.78            |       |
| Volume (ml)   |                  |                      |       |                  |                      |       |
| Median (range)| 37.2 (20.6–109.8)| 49.9 (13.1–98.7)     | 0.03* | 44.1 (13.1–103.3) | 47.6 (20.3–109.8)    | 0.81  |
| Means.d.      | 45.24±21.22      | 51.85±18.00          |       | 49.19±20.59      | 49.55±18.64          |       |
| TT (ng ml⁻¹)  |                  |                      |       |                  |                      |       |
| Median (range)| 3.48 (0.54–7.77) | 4.32 (0.26–8.87)     | <0.01** | 3.66 (0.54–7.77) | 4.47 (0.26–8.87)     | 0.01* |
| Means.d.      | 3.72±1.77        | 4.56±1.74            |       | 3.84±1.69        | 4.57±1.83            |       |

*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

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per core²⁶ 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. Botton 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 multivariable 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,²⁶ 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* |
| Age | 1.03 (0.97–1.10) | 0.29 | TT <3 ng ml⁻¹ | 1.04 (0.98–1.10) | 0.21 |
| BMI | 1.04 (0.95–1.14) | 0.39 | Age | 1.03 (0.94–1.13) | 0.52 |
| PSA | 0.91 (0.77–1.09) | 0.33 | BMI | 0.92 (0.78–1.10) | 0.37 |
| Volume | 0.98 (0.97–1.00) | 0.08 | PSA | 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* |
| Age | 1.00 (0.95–1.06) | 0.99 | TT <3 ng ml⁻¹ | 1.01 (0.96–1.07) | 0.73 |
| BMI | 1.04 (0.95–1.13) | 0.44 | Age | 1.02 (0.94–1.12) | 0.60 |
| PSA | 0.94 (0.80–1.11) | 0.48 | BMI | 0.95 (0.80–1.12) | 0.52 |
| Volume | 1.00 (0.99–1.02) | 0.84 | PSA | 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. CTJ, 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.

REFERENCES
1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015; 65: 5–29.
2. Epstein JI, Feng Z, Tock BJ, Pierorazio PM. Upgrading and downgrading of prostate cancer from biopsy to radical prostatectomy: incidence and predictive factors using the modified Gleason grading system and factoring in tertiary grades. Eur Urol 2012; 61: 1019–24.
3. Hong SK, Han BK, Lee ST, Kim SS, Min KE, et al. Prediction of Gleason score upgrading in low-risk prostate cancers diagnosed via multi (> or=12)-core prostate biopsy. World J Urol 2009; 27: 271–6.
4. Gershman B, Dahl DM, Olumi AF, Young RH, McDougal WS, et al. Smaller prostate gland size and older age predict Gleason score upgrading. Urol Oncol 2013; 31: 1033–7.
5. Teloken C, Da RC, Caraver F, Weber FA, Cavaileiro 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.
6. Sooriakumaran P, Srivastava A, Christos P, Grover S, Shevchuk M, et al. Predictive models for worsening prognosis in potential candidates for active surveillance of presumed low-risk prostate cancer. Int Urol Nephrol 2012; 44: 459–70.
7. Colleselli D, Pelzer AE, Steiner E, Ongarello S, Schafer G, et al. Upgrading of Gleason score 6 prostate cancers on biopsy after prostatectomy in the low and intermediate tPSA range. Prostate Cancer Prostatic D 2010; 13: 182–5.
8. Moreira LK, Camara-Lopes LH, Dall’Oglio FC, Cury J, Antunes AA, et al. Upgrading the Gleason score in extended prostate biopsy: implications for treatment choice. Int J Radiat Oncol Biol Phys 2009; 73: 353–6.
9. Chiu FK, Steuber T, Erbendobler A, Cunlin E, Walz J, et al. Development and internal validation of a nomogram predicting the probability of prostate cancer Gleason sum upgrading between biopsy and radical prostatectomy pathology. Eur Urol 2006; 49: 820–6.
10. Fukagai T, Namiki T, Namiki H, Carlile RG, Shimada M, et al. Discrepancies between Gleason scores of needle biopsy and radical prostatectomy specimens. Pathol Int 2001; 51: 364–70.
11. Sved PD, Gomez P, Manoharan M, Kim SS, Soloway MS. Limitations of biopsy Gleason grade: implications for counseling patients with biopsy Gleason score 6 prostate cancer. J Urol 2004; 172: 98–102.
12. Witt TJ, Brawer MK, Jones KM, Barry MJ, Aronson WJ, et al. Radical prostatectomy versus observation for localized prostate cancer. N Engl J Med 2012; 367: 203–13.
13. Lane JA, Donovan JL, Davis M, Walsh E, Dedman D, et al. Active monitoring, radical prostatectomy, or radiotherapy for localised prostate cancer: study design and diagnostic and baseline results of the ProtecT randomised phase 3 trial. Lancet Oncol 2014; 15: 1109–18.
14. Tosoian JJ, Tock BJ, Landis P, Feng Z, Epstein JI, et al. Active surveillance program for prostate cancer: an update of the Johns Hopkins experience. J Clin Oncol 2011; 29: 2185–90.
15. Soloway MS, Soloway CT, Williams S, Ayashhuri R, Kava B, et al. Active surveillance; a reasonable management alternative for patients with prostate cancer: the Miami experience. BJU Int 2008; 101: 165–9.
16. Dall’Era MA, Koneyte BR, Cowan JE, Shinohara K, Stauf F, et al. Active surveillance for the management of prostate cancer in a contemporary cohort. Cancer 2008; 112: 2664–70.
17. Heidenreich A, Bastian PJ, Bellmunt J, Bolla M, Joniau S, et al. EAU guidelines on prostate cancer. Part I: screening, diagnosis, and local treatment with curative intent-update 2013. Eur Urol 2014; 65: 124–37.
18. Busch J, Maghei L, Leva N, Ferrari M, Kramer J, et al. Higher rates of upgrading and upstaging in older patients undergoing radical prostatectomy and qualifying for active surveillance. BJU Int 2014; 114: 517–21.
19. Richstone L, Bianco FJ, Shah HH, Kattan MW, Eastham JA, et al. Radical prostatectomy in men aged ≥70 years: effect of age on upgrading, upstaging, and the accuracy of a preoperative nomogram. BJU Int 2008; 101: 541–6.
20. Gofrit ON, Zorn KC, Taxy JB, Lin S, Zagaja GP, et al. Predicting the risk of patients with biopsy Gleason score 6 to harbor a higher grade cancer. J Urol 2007; 178: 1925–8.
21. Moussa AS, Li J, Soriano M, Klein EA, Dong F, et al. Prostate biopsy clinical and pathological variables that predict significant grading changes in patients with intermediate and high grade prostate cancer. BJU Int 2009; 103: 43–8.
22. Krane LS, Menon M, Kaul SA, Siddiqui S, Wambi C, et al. Role of PSA velocity in predicting pathologic upgrade for Gleason 6 prostate cancer. Urol Oncol 2011; 29: 372–7.
23. de Cobelli O, Terracciano D, Tagliabue E, Raimondi S, Galasso G, et al. Body mass index was associated with upstaging and upgrading in patients with low-risk prostate cancer who met the inclusion criteria for active surveillance. Urol Oncol 2015; 33: 201.e1–8.
24. Lotan TL, Carvalho FL, Peskoe SB, Hicks JL, Good J, et al. PTEN loss is associated with upgrading of prostate cancer from biopsy to radical prostatectomy. Mod Pathol 2009; 22: 128–37.
25. Moon SJ, Park SY, Lee TY. Predictive factors of Gleason score upgrading in localized and locally advanced prostate cancer diagnosed by prostate biopsy. Korean J Urol 2010; 51: 677–82.
26. Stav K, Judith S, Merald H, Leibovici D, Lindner A, et al. Does prostate biopsy Gleason score accurately express the biologic features of prostate cancer? Urol Oncol 2007; 25: 383–6.
27. Botto H, Neuzillet Y, Lebret T, Camparo P, Moline V, et al. High incidence of
predominant Gleason pattern 4 localized prostate cancer is associated with low serum testosterone. *J Urol* 2011; 186: 1400–5.

28 Xylinas E, Ploussard G, Durand X, Fabre A, Salomon L, et al. Low pretreatment total testosterone (<3 ng/mL) predicts extraprostatic disease in prostatectomy specimens from patients with preoperative localized prostate cancer. *BJU Int* 2011; 107: 1400–3.

29 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.

30 Makarov DV, Trock BJ, Humphreys EB, Mangold LA, Walsh PC, et al. Updated nomogram to predict pathologic stage of prostate cancer given prostate-specific antigen level, clinical stage, and biopsy Gleason score (Partin tables) based on cases from 2000 to 2005. *Urology* 2007; 69: 1095–101.