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ORIGINAL ARTICLE

Prostate Cancer

Upgrading and upstaging of low-risk prostate cancer among Korean patients: a multicenter study

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Only 54% of prostate cancer cases in Korea are localized compared with 82% of cases in the US. Furthermore, half of Korean patients are upgraded after radical prostatectomy (41.6%–50.6%). We investigated the risk factors for upgrading and/or upstaging of low-risk prostate cancer after radical prostatectomy. We retrospectively reviewed the medical records of 1159 patients who underwent radical prostatectomy at five hospitals in Honam Province. Preoperative data on standard clinicopathological parameters were collected. The radical prostatectomy specimens were graded and staged and we defined a "worsening prognosis" as a Gleason score ≥ 7 or upstaging to ≥ pT3. Multivariate logistic regression models were used to assess factors associated with postoperative pathological upstaging. Among the 1159 patients, 324 were classified into the clinically low-risk group, and 154 (47.5%) patients were either upgraded or upstaged. The multivariable analysis revealed that the preoperative serum prostate-specific antigen level (odds ratio [OR], 1.131; 95% confidence interval [CI], 1.007–1.271; *P* = 0.037), percent positive biopsy core (OR: 1.018; 95% CI: 1.002–1.035; *P* = 0.032), and small prostate volume (≤30 ml) (OR: 2.280; 95% CI: 1.351–3.848; *P* = 0.002) were predictive of a worsening prognosis. Overall, 47.5% of patients with low-risk disease were upstaged postoperatively. The current risk stratification criteria may be too relaxed for our study cohort.

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INTRODUCTION

Treatment options for prostate cancer are based upon risk stratification derived from the Gleason score (GS), prostate-specific antigen (PSA), and clinical stage.[1] According to the risk stratification, patients with prostate cancer are treated by active surveillance (AS), watchful waiting, surgery, radiation, and hormonal therapy. AS is considered the primary treatment strategy for low-risk tumors.

Active surveillance is a relatively novel management strategy that involves serial monitoring of men with low-risk disease features and allows for timely intervention if disease progression is detected. Thus, treatment-related morbidity is avoided or delayed until treatment is required. This strategy is characterized by initial observations with close monitoring of PSA kinetics and serial prostate biopsies to assess cancer progression. AS differs from watchful waiting, which involves a more palliative approach with the goal of reducing morbidity, and is generally reserved for those who are older and not suitable for definitive treatment. Contemporary large institutional series have reported high cancer-specific survival rates with durations of 2–7 years.[2–6] Furthermore, delayed but timely intervention does not appear to pose worse surgical or oncologic outcomes with respect to final pathological stage at radical prostatectomy or recurrence-free survival after treatment.[5,7]

However, recent studies have focused on inappropriate application of AS, which was recommended based on inaccurate reporting of the Gleason sum scores on the initial needle prostate biopsy report.[8–11] Sooriakumaran *et al*. reported that 40.4% of patients with low-risk prostate cancer are either upgraded or upstaged after radical prostatectomy.[8] Hence, it appears that current AS criteria may include patients with higher Gleason sum scores than originally thought of the clinical diagnosis. Upgrading and/or upstaging after radical prostatectomy can worsen the prognosis of some patients under AS. We report our experience in predicting upgrading of the Gleason sum score and/or T stage upstaging of the final pathology in a cohort of AS eligible men who underwent prostatectomy at multiple institutions.

MATERIALS AND METHODS

Patient selection

The Institutional Review Board approved this study and all participating sites providing the necessary data before study initiation. A total of 1159 patients underwent radical prostatectomy at five institutions from 2008 to 2012 using either the open technique, laparoscopic or robotic approaches. We retrospectively reviewed the patient records at each institution. Of these patients, 324 were classified as low-risk prostate cancer (biopsy GS ≤ 6, PSA ≤ 10 ng ml^{-1} and clinical stage ≤ T2a) as defined by D'Amico *et al*.[12]

Data collection

Clinical and pathological data were collected. The clinical data included age, digital rectal exam, body mass index, PSA level, prostate volume by transrectal ultrasound (TRUS), PSA density, and clinical T stage by

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magnetic resonance imaging. The pathological data were GS for the prostate biopsy, percent positive biopsy core (the percentage of the overall number of cores with cancer), pathologic T stage, extracapsular extension, positive surgical margin, and lymph node invasion. TRUS-guided prostate biopsies were performed with an 18-gauge needle biopsy gun by one or two radiologists at each institution. The number of biopsy cores ranged from 6 to 18 in each institution without definite regulation.

Definition of upgrading, upstaging, and worsening prognosis

Patients were analyzed by comparing the pathological result of postprostatectomy specimens. Among the patients with low-risk prostate cancer, we defined upgrading as a GS 7 or more on the postprostatectomy specimen. In addition, pathological T3 stage or more was defined as upstaging. We defined "worsening prognosis" as GS upgrading or upstaging of the pathologic T3 stage.[8]

Statistical analysis

Continuous variables were compared using the two-sample *t*-test, and categorical variables were compared using the Chi-square test. Univariate and multivariate logistic regression analyses were performed. $P < 0.05$ was considered as significant. All analyses were performed using SPSS version 19 statistical software (SPSS Inc., Chicago, IL, USA).

RESULTS

Of the 1159 patients, 324 fulfilled all preoperative selection criteria for low-risk prostate cancer (**Table 1**). A review of these 324 radical prostatectomy specimens showed that 142 demonstrated GS upgrading on final pathology (43.8%). Of the 324 patients, 31 (9.6%) were upstaged to at least pT3, and 154 (47.5%) were either upgraded or upstaged.

Upgrading of Gleason score

Patients with GS upgrading on the final pathology had lower prostate volume ($P = 0.003$), percent positive biopsy core ($P = 0.006$), and a higher preoperative GS ($P = 0.020$) compared with patients who did not display GS upgrading (**Table 2**). In the univariate analysis, PSA (odds ratios [ORs], 1.145; 95% confidence interval [CI], 1.025–1.278; $P = 0.016$), percent positive biopsy core (OR: 1.021; 95% CI: 1.006–1.036; $P = 0.006$), prostate volume (≤30 ml) (OR: 2.210; 95% CI: 1.397–3.532; $P = 0.001$) and a GS of 6 (OR: 3.795; 95% CI: 1.244–11.579; $P = 0.019$) were predictive of upgrading. The multivariable analysis revealed that PSA, prostate volume (≤30 ml), and a GS of 6 were significant contributors to upgrading with ORs (95% CI) of 1.137 (1.012–1.277), 2.235 (1.319–3.787) and 4.864 (1.059–22.586), respectively (**Table 3**).

Table 1: Baseline characteristics of the patient population

Parameter	*Value*
Total patients	324
Age (year, mean±s.d.)	67.34±6.52
BMI (kg m^{-2}, mean±s.d.)	24.22±2.95
Serum PSA (ng ml^{-1}, mean±s.d.)	6.01±2.19
Prostate volume (ml, mean±s.d.)	34.63±17.03
GS sum, *n* (%)	
4	21 (6.5)
5	38 (11.7)
6	265 (81.8)
Clinical T stage, *n* (%)	
T1c	138 (42.6)
T2a	186 (57.4)

PSA: prostate-specific antigen; s.d.: standard deviation; BMI: body mass index; GS: Gleason score

Upstaging more than T stage 3

Age, PSA, percent positive biopsy core, and clinical T2a stage were significant factors (**Table 2**). These variables were predictive of upstaging in the univariate analysis (**Table 4**). In the multivariable analysis, percent positive biopsy core was a significant contributor to upstaging (OR: 1.023; 95% CI: 1.002–1.045; $P = 0.030$) (**Table 4**).

Worsening prognosis

Preoperative PSA, prostate volume (≤30 ml), percent positive biopsy core, and clinical T2a were significant for a worsening prognosis (**Table 2**). Additionally, they were predictive of either upgrading or upstaging in the univariate analysis (**Table 5**). The multivariable analysis revealed that PSA (OR: 1.131; 95% CI: 1.007–1.271; $P = 0.037$), percent positive biopsy core (OR: 1.018; 95% CI: 1.002–1.035; $P = 0.032$), and prostate volume (≤30 ml) (OR: 2.280; 95% CI: 1.351–3.848; $P = 0.002$) were significant contributors to either upgrading or upstaging (**Table 5**).

DISCUSSION

More patients are being diagnosed with early stage prostate cancer in the modern era with PSA screening. Until now, many patients with prostate cancer underwent radical surgery. However, cancer outcome as well as quality of life should be considered. In the Scandinavian Prostate Cancer Group Study Number 4, radical prostatectomy was associated with a reduction in the rate of death.[13] In contrast, as shown in the Prostate Cancer Intervention Versus Observation Trial (PIVOT), radical prostatectomy does not reduce cancer mortality, compared with observation.[14] Furthermore, in long study of PIVOT for low-risk or low PSA patient, observation compared with surgery results in similar long-term overall and prostate cancer survival, prevention of bone metastases. AS can avoid surgical morbidity, and maintains patient performance status. In some cases, we tried noninvasive therapy with prostate cancer and low-risk stratification.

However, it was questionable whether we could apply AS to low-risk patients. Recent studies have reported the difference between preoperative GS or T stage and final pathology from radical prostatectomy specimens. Müntener *et al*.[15] reported that among 6625 radical prostatectomies, 25% had postoperative GS upgrades. They also reported that the upgraded group had significant differences in positive surgical margin, extraprostatic extension, seminal vesicle invasion, and lymphovascular invasion.[15] According to an analysis of 8054 radical prostatectomies in a study by Boorjian *et al*. 20% of the patients had GS upgrading, and the upgrading was related to biochemical recurrence, progression to systematic disease, and cancer-specific survival rate.[16]

Although there are differences by studies, predictors of upgrading or upstaging in postoperative specimens include obesity, PSA, prostate volume, positive biopsy core, cancer volume of the biopsy, and pathologist experience.[9–11,17–19] Dong *et al*.[10] reported that a preoperative serum PSA > 5 ng ml^{-1}, prostate weight ≤ 60 g and more cancer volume at biopsy, defined by cancer involving > 5% of the biopsy tissue, greater than one biopsy core or > 10% of any core, were associated with pathological upgrading. Hong *et al*.[11] reported that preoperative PSA level and number of positive cores may be useful predictors of GS upgrading.

In our study, GS upgrading and pathologic upstaging were recorded in 43.8% and 9.6% of patients, respectively. Although the definition of upgrading or upstaging is different between studies, our results were higher than those of other studies. In univariate and multivariate analyses, smaller prostate volume was a significant predictor of upgrading or upstaging. According to Asian population studies, prostate volume of Asians is smaller than that of western populations.[20–22] This prostate volume difference suggests a considerable

Table 2: Comparison of GS upgrading, upstaging and worsening prognosis

	Upgrading			*Upstaging*			*Worsening prognosis*		
	No-upgrading	*Upgrading*	*P*	*No-upstaging*	*Upstaging*	*P*	*No-worsening*	*Worsening*	*P*
Number of patients	182	142		293	31		170	154	
Age (year, mean±s.d.)	67.18±6.59	67.54±6.45	0.622	67.10±6.43	69.58±7.07	0.044	66.98±6.51	67.73±6.54	0.301
BMI (kg m^{-2}, mean±s.d.)	24.36±3.10	24.04±2.72	0.385	24.28±2.95	23.65±2.86	0.292	24.45±3.12	23.95±2.71	0.167
Serum PSA (ng ml^{-1}, mean±s.d.)	5.80±2.18	6.28±2.19	0.048	5.93±2.15	6.82±2.43	0.030	5.74±2.16	6.30±2.20	0.023
Prostate volume (ml, mean±s.d.)	37.15±17.13	31.23±16.34	0.003	34.96±17.12	31.36±15.89	0.296	37.19±16.92	31.60±16.71	0.004
Percent positive biopsy core (mean±s.d.)	21.10±14.97	26.64±17.94	0.006	22.61±15.78	31.58±20.98	0.007	20.52±14.92	26.84±17.61	0.001
Preoperative Gleason sum, *n* (%)									
4	17 (9.3)	4 (2.8)	0.020	19 (6.5)	2 (6.5)	0.140	15 (8.8)	6 (3.9)	0.133
5	25 (13.7)	13 (9.2)		31 (10.6)	7 (22.6)		22 (12.9)	16 (10.4)	
6	140 (76.9)	125 (88.0)		243 (82.9)	22 (71.0)		133 (78.2)	132 (85.7)	
Clinical T stage, *n* (%)									
1c	85 (46.7)	53 (37.3)	0.090	131 (44.7)	7 (22.6)	0.018	82 (48.2)	56 (36.4)	0.031
2a	97 (53.3)	89 (62.7)		162 (55.3)	24 (77.4)		88 (51.8)	98 (63.6)	
Postoperative pathology, *n* (%)									
Lymph node invasion	0	3 (2.1)	0.083	1 (0.3)	2 (6.5)	0.001			
Positive surgical margin	9 (4.9)	23 (16.2)	0.001	23 (7.8)	9 (29.0)	0.001			
Extraprostatic extension	12 (6.6)	16 (11.3)	0.229	-	-	-			

s.d.: standard deviation; BMI: body mass index; GS: Gleason score; PSA: prostate-specific antigen

Table 3: Univariate and multivariable analysis for predicting of GS upgrading

	Univariate		*Mutivariable*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (per 1-year)	1.009 (0.975–1.043)	0.621	0.996 (0.958–1.035)	0.845
PSA (per 0.01 unit)	1.145 (1.025–1.278)	0.016	1.137 (1.012–1.277)	0.031
Percent positive biopsy core (per 1% increase)	1.021 (1.006–1.036)	0.006	1.015 (0.999–1.032)	0.065
Prostate volume (≤30 ml)	2.221 (1.397–3.532)	0.001	2.235 (1.319–3.787)	0.003
Clinical stage (cT2a)	1.472 (0.940–2.302)	0.091		
GS		0.027		0.117
5	2.210 (0.615–7.940)	0.224	3.904 (0.728–20.933)	0.112
6	3.795 (1.244–11.579)	0.019	4.864 (1.059–22.586)	0.042

PSA: prostate-specific antigen; OR: odds ratio; CI: confidence interval; GS: Gleason score

Table 4: Univariate and multivariable analysis for predicting pathological upstaging

	Univariate		*Mutivariable*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (per 1-year)	1.066 (1.001–1.135)	0.046	1.051 (0.988–1.126)	0.134
PSA (per 0.01 unit)	1.203 (1.016–1.424)	0.032	1.121 (0.927–1.357)	0.240
Percent positive biopsy (per 1% increase)	1.027 (1.006–1.048)	0.010	1.023 (1.002–1.045)	0.030
Prostate volume (≤30 ml)	1.621 (0.726–3.619)	0.238		
Clinical stage (cT2a)	2.772 (1.158–6.637)	0.022	2.440 (0.954–6.242)	0.063
GS		0.156		0.134
5	2.145 (0.403–11.418)	0.371	0.974 (0.155–6.102)	0.978
6	0.860 (0.188–3.936)	0.846	0.363 (0.069–1.897)	0.230

PSA: prostate-specific antigen; OR: odds ratio; CI: confidence interval; GS: Gleason score

difference in degree of upgrading and upstaging between Korean and Western populations.

Prostate volume was associated with worsening prognosis. The relationship between GS upgrading and prostate volume is controversial.[9–11,17–19,23] Turley *et al*.[17] reported that patients with prostate volume < 20 ml have a 5.3 times greater probability of upgrading, compared with patients with > 60 ml. Lim *et al*.[9] reported that smaller prostate volume (<30 ml) is a significant predictor of GS upgrading with an OR of 3.904. Some possible reasons include: patients with a large prostate had higher serum PSA levels caused by benign prostate hyperplasia and patients received prostate biopsy at an earlier stage due to a high PSA.[9] Another reason is the most aggressive characteristics of cancer in a small prostate. Freedland *et al*.[24] reported that predictors of prostate weight are inversely associated with high-grade cancer.

The limitations of this study are as follows. First, the pathological reports varied. Nowadays, 12 core biopsies were common procedure. However, some of the enrolled cases of this study had 6 or 8 core biopsies. In addition, number of cores of biopsy varies between institutions.

Table 5: Univariate and multivariable analysis for predicting a worsening prognosis

	Univariate		*Mutivariable*	
	OR (95% CI)	*P*	*OR (95% CI)*	*P*
Age (per 1-year)	1.018 (0.984–1.053)	0.300	1.005 (0.967–1.044)	0.803
PSA (per 0.01 unit)	1.124 (1.016–1.244)	0.024	1.131 (1.007–1.271)	0.037
Percent positive biopsy (per 1% increase)	1.025 (1.009–1.041)	0.002	1.018 (1.002–1.035)	0.032
Prostate volume (≤30 ml)	2.213 (1.397–3.507)	0.001	2.280 (1.351–3.848)	0.002
Clinical stage (cT2a)	1.631 (1.046–2.545)	0.031	1.260 (0.752–2.111)	0.380
GS		0.145		0.448
5	1.818 (0.579–5.714)	0.306	2.081 (0.523–8.276)	0.298
6	2.481 (0.934–6.591)	0.068	2.177 (0.653–7.254)	0.205

PSA: prostate-specific antigen; OR: odds ratio; CI: confidence interval; GS: Gleason score

Misclassification of upgrading might exist due to a smaller number of cores in some cases. Secondly, this study was retrospective. We could not analyze the clinical effects of GS upgrading. Further studies are needed to compare AS and radical prostatectomy in patients with low-grade prostate cancer. However, we showed the upgrading rate and predictors of upgrading and/or upstaging in low-risk Korean patients with prostate cancer. These results should be considered when a clinician chooses a treatment plan for a patient with low-risk prostate cancer. Recently, there are several recent studies which include percentage positive biopsy cores or prostate volume in risk stratification.[25–27] Our study shows the application of these criteria would be helpful, especially in low-risk group.

CONCLUSION

Overall, 47.5% of patients with low-risk disease were upstaged postoperatively. The current risk stratification criteria are too relaxed for our study cohort. The possibility of postoperative upstaging should be considered for them.

AUTHORS CONTRIBUTIONS

IH and TWK participated in conceiving of the study and drafted the manuscript. DL, YBJ, SCP, JHN and DDK participated in the study design, performed the surgeries, and collected the data. All authors read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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