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Changes in Prostate Cancer Aggressiveness over a 12-Year Period in Korea

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Purpose: To investigate whether tumor aggressiveness in patients with prostate cancer has changed in Korea since the introduction of prostate-specific antigen (PSA) testing.
Materials and Methods: The data from 2,508 patients with pathologically confirmed prostate cancer who underwent radical prostatectomy at Asan Medical Center between 2000 and 2011 were reviewed. The patients were divided into four 3-year time series, and the changes between the groups in terms of serum PSA levels, pathological Gleason score (GS), and pathological stage were assessed. The change in GS over time in organ-confined disease and in patients whose PSA was below 10 ng/ml was also analyzed.
Results: The mean PSA levels dropped significantly over the 12-year period ($p<0.001$). The frequency of organ-confined disease increased (55.7% vs. 64.7% vs. 62.9% vs. 63.5%, p=0.043). The frequency of patients with a GS of 8 or more decreased (38.9% vs. 25.7% vs. 18.2% vs. 19.7%) and the frequency of patients with a GS of 6 or less increased (15.0% vs. 18.9% vs. 26.7% vs. 18.2%, p=0.003). However, the vast majority (more than 70%) of all cases had a high GS (7 or greater) at all time points. The GS distribution did not change over time in patients whose PSA levels were below 10 ng/ml or in those who had organ-confined disease.
Conclusions: In 2000 to 2011, the preoperative PSA, pathological stage, and pathological GS dropped. However, the majority of the prostate cancers in Korean men were poorly differentiated, even when the patients had organ-confined disease or their PSA levels were less than 10 ng/ml.

Key Words: *Korea; Neoplasm grading; Prostatic neoplasms*

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INTRODUCTION

Prostate cancer is a very common cancer in Western populations. For example, in the United States in 2010, prostate cancer was the most commonly diagnosed nonskin malignancy among men and the second leading cause of cancer death after lung cancer [1]. By contrast, it is relatively uncommon in Asia. In Korea, prostate cancer ranks as the fifth most common cancer among men. However, prostate cancer rates in Korea, as in other Asian countries, have been increasing rapidly over the past few years [1-4]. Two hypotheses that aim to explain this increased prostate cancer incidence have been proposed. First, the increased incidence may reflect a recent increase in the proportion of older (>50 years old) males who have undergone prostate-specific antigen (PSA) screening for the first time at a Korean health promotion center. Second, the increased incidence may reflect the increasing movement away from the traditional Korean lifestyle to a modern, more Western way of life; in particular, the fat content in diets is increasing in Korea [5,6].

The widespread use of PSA as a diagnostic marker has enabled the diagnosis of prostate cancer in younger patients, in patients with lower PSA concentrations, and in a higher proportion of patients with organ-confined disease [7]. The increasing diagnosis of men with lower PSA values

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means that overall, men who are currently undergoing prostate biopsies in the United States are being diagnosed with less aggressive Gleason patterns compared with the pre-PSA era [8,9]. Such stage and grade migration has also been reported in Europe [10]. It is not clear whether this would also be the case in Korea because not only do different countries and racial/ethnic groups differ markedly in terms of the incidence of prostate cancer, but they also vary with regard to clinicopathological characteristics [11]. Supporting this is our previous study, which revealed that a significant proportion of prostate cancers in Korean men are poorly differentiated, regardless of the initial serum PSA level or the clinical stage at presentation. Such poorly differentiated tumors adversely affect prognosis, causing a greater rate of PSA failure [12]. By contrast, Western men are less likely to have poorly differentiated prostate cancers. The present study asked whether the aggressiveness of prostate cancer in Korean men has changed over the past 12 years, which is when PSA screening was implemented in Korea. To address this, we reviewed data for a large, single series of patients who were treated by radical prostatectomy (RP).

MATERIALS AND METHODS

1. Study population and data collection

After institutional review board approval was obtained, the medical records of 2,851 patients who underwent RP for prostate cancer between January 2000 and December 2011 at Asan Medical Center were retrospectively reviewed. Of these patients, 343 were excluded because they had received hormonal therapy or radiation therapy before RP or because their preoperative clinical or pathological data were inadequate. Finally, 2,508 patients were included in the study cohort.

All patients had undergone a preoperative evaluation, including a clinical examination, blood tests, chest X-ray, magnetic resonance imaging, and bone scanning. The age of the patient at the time of surgery, the preoperative PSA level, the biopsy Gleason score (GS), the clinical stage, the pathological GS, and the pathological stage were recorded. Before a digital rectal examination (DRE) and transrectal ultrasonography (TRUS), PSA concentrations were measured by immunoradiometry by using ^{125}I-IRMA kits (CIS Bio International, Cedex, France). The clinical stage was based on the DRE results (as determined by the clinicians) and the TRUS results. The RP specimens were examined microscopically after formaldehyde fixation and histological sectioning at multiple levels, and pathological staging was determined by using the 6th edition of the American Joint Committee on Cancer tumor-node-metastasis (TNM) staging [13]. For patients who were diagnosed before 2002, the 1997 TNM system was converted to the 2002 TNM system. Patients with negative surgical margins, no extracapsular extension, no seminal vesicle invasion, and no lymph node metastasis were considered to have organ-confined disease. In 2005, an update of the Gleason grading system was published [14]. This changed grading system was applied in our institution in 2007. Tumor differentiation was evaluated by surgical Gleason scoring according to the World Health Organization consensus conference recommendations [15].

2. Division of the cohort into four time series

The incidence of prostate cancer in Korea is increasing and the number of RP procedures performed annually has increased as a result. The patients were divided into four time series to evaluate whether the characteristics of prostate cancer in Koreans had changed: Group 1 had surgery between 2000 and 2002 (n=167), group 2 had surgery between 2003 and 2005 (n=354), group 3 had surgery between 2006 and 2008 (n=731), and group 4 had surgery between 2009 and 2011 (n=1,256). Within each group, the patients were divided into three subgroups on the basis of their preoperative PSA levels (PSA$\leq$10, 10$<$PSA$\leq$20, and 20$<$PSA ng/ml), the pathological GS (6 or less, 7, and 8 or greater), or the pathological stage (organ-confined disease, extracapsular extension, and seminal vesicle invasion).

3. Statistical analysis

The groups were compared with regard to their clinicopathological factors by using analysis of variance test (continuous variables), Pearson's chi-square test, or Fisher exact test (categorical variables). The trends in the preoperative serum PSA, pathological GS, and pathological stage over time were analyzed by using linear regression. All statistical tests were two-tailed, with $p<0.05$ being considered to be significant. The SPSS ver. 12.0 (SPSS Inc, Chicago, IL, USA) was used for all statistical analyses.

RESULTS

Regarding the whole cohort of 2,508 patients, the mean age at presentation was 65 years. In 1,714 patients (68.3%), the preoperative PSA levels were below 10 ng/ml. Moreover, 1,580 patients (63.0%) presented with organ-confined disease, and 1,457 (58.1%) had a pathological GS of 7 and 516 (20.6%) had a pathological GS of 6 or less.

The 2,508 patients were grouped into four 3-year time series. The clinical and pathological characteristics of these four groups are summarized in Table 1. The annual number of RP procedures increased 13-fold over the 12-year study period from 38 in 2000 to 486 in 2011. The number of patients eligible for study inclusion also increased; this can probably be attributed to PSA screening. The four groups did not differ significantly in terms of mean age at surgery (p=0.23) (Table 1). Over time, the preoperative serum PSA levels decreased significantly from 18.1 ng/ml in group 1 to 10.0 ng/ml in group 4 ($p<0.001$) (Table 1). Fig. 1A shows that the proportion of patients whose preoperative PSA levels were below 10 ng/ml increased steadily over time (41.9% vs. 60.2% vs. 71.0% vs. 72.6%, $p<0.001$). There was also a significant increase in the proportion of tumors that were nonpalpable (clinical

TABLE 1. Clinicopathological changes over time

	Overall	2000-2002	2003-2005	2006-2008	2009-2011	p-value
No. of patients	2,508	167	354	731	1,256	
Mean age at surgery (yr)	65.7±6.9	65.9±6.5	65.9±7.0	66.4±6.7	65.2±7.1	0.23
Mean preoperative PSA (ng/ml)	10.9±12.2	18.1±20.1	12.8±12.7	10.0±9.9	10.0±11.5	<0.001
PSA (%)						<0.001
0-10.0	1,714	70 (41.9)	213 (60.2)	519 (71.0)	912 (72.6)	
10.1-20.0	507	53 (31.7)	91 (25.7)	145 (19.8)	218 (17.4)	
>20	287	44 (26.3)	50 (14.1)	67 (9.2)	126 (10.0)	
No. clinical stage (%)						<0.001
T1	1,721	84 (50.3)	128 (36.2)	544 (74.4)	965 (76.7)	
T2	655	72 (43.1)	201 (56.8)	159 (21.8)	223 (17.8)	
T3	132	11 (6.6)	25 (7.1)	28 (3.8)	68 (5.4)	
No. pathological stage (%)						0.043
Organ confined	1,580	93 (55.7)	229 (64.7)	460 (62.9)	798 (63.5)	
Extracapsular extension	637	45 (26.9)	71 (20.1)	201 (27.5)	320 (25.5)	
Seminal vesical invasion	291	29 (17.4)	54 (15.3)	70 (9.6)	138 (11.0)	
No. Gleason score (%)						0.003
6 or less	516	25 (15.0)	67 (18.9)	195 (26.7)	229 (18.2)	
7	1,457	77 (46.1)	196 (55.4)	404 (55.3)	780 (62.1)	
8 or greater	535	65 (38.9)	91 (25.7)	132 (18.1)	247 (19.7)	

PSA, prostate-specific antigen.

stage T1) from 50.3% in group 1 to 76.7% in group 4 ($p < 0.001$) (Table 1). In addition, the proportion of tumors exhibiting seminal vesicle invasion decreased (17.4% vs. 15.3% vs. 9.6% vs. 11.0%, p=0.043) (Table 1 and Fig. 1B). Fig. 1C shows the pathological GS trend over time: the proportion of patients with a GS of 8 or more decreased over time (38.9% vs. 25.7% vs. 18.2% vs. 19.7%) and the proportion of patients with a GS of 6 or less increased (15.0% vs. 18.9% vs. 26.7% vs. 18.2%). Overall, the GS changed significantly (p=0.003) (Table 1).

We then asked whether the GS also changed over time in patients who were likely to have a favorable prognosis. Fig. 1D shows that in patients with PSA≤10 ng/ml, the frequency of tumors with a GS of 8 or more decreased steadily over time (28.6% vs. 16.4% vs. 14.6% vs. 13.8%). However, the frequency of tumors with a GS of 6 or less (24.3% vs. 23.9% vs. 32.2% vs. 22.1%) or a GS of 7 (47.1 % vs. 59.6% vs. 53.2% vs. 64.2%) did not change in a consistent pattern. Overall, there were no significant changes in GS over time in the patients with PSA≤10 ng/ml (p=0.261). In addition, the vast majority of the tumors (68 to 78%) still had an unfavorable GS.

Fig. 1E shows how the GS of patients with organ-confined disease changed over time. Although the frequency of tumors with a GS of 8 or more decreased steadily over time (22.6 vs. 17.0% vs. 9.8% vs. 10.7%), a consistent pattern of change was not observed for the tumors with a GS of 6 or less (24.7% vs. 26.2% vs. 37.6% vs. 26.2%) or 7 (52.7% vs. 56.8% vs. 52.6% vs. 63.2%). Overall, there were no significant changes in GS over time in the patients with organ-confined disease (p=0.149). In addition, the vast majority of the tumors (63 to 75%) still had an unfavorable GS.

DISCUSSION

The present study showed that over the past 12 years, there was a significant downward migration of serum PSA levels, pathological stage, and GS in Korean patients with prostate cancer. However, as was also observed in our previous study [12], the present study showed that Korean men were highly likely to have poorly differentiated prostate cancers, regardless of their initial serum PSA concentrations or the pathological stage.

In 2007, prostate cancer was the fifth most common malignancy in Korean men [16]. The incidence of this cancer in Korea is relatively lower than in Western countries: for example, its age-adjusted incidence in the United State is 155.5 per 100,000 person-years, whereas in Korea in 2002, accord¬ing to the Korean Cancer Registry System, the incidence was 10.1 per 100,000 person-years [17]. However, recently, the incidence in Korea rose dramatically to 20.0 per 100,000 person-years in 2007 [17]. Further supporting this is our recent study [12], and the present study, which showed that the number of prostate cancer patients who underwent RP increased dramatically over time (from 167 in group 1 to 1,256 in group 4). This trend may reflect the fact that the traditional Korean lifestyle is gradually being replaced by a modern, more Western way of life, including higher consumption of dietary fat [5]. However, this increase could also reflect the increased screening for prostate cancer in Korea as well as the increased reliability of several other factors, namely, epidemiological surveys, the screening modalities used, the indications for biopsies, the biopsy methods, and biopsy compliance. Supporting the last is a study by Chi and Chang [3], who showed that the biopsy compliance rate increased from 36% during

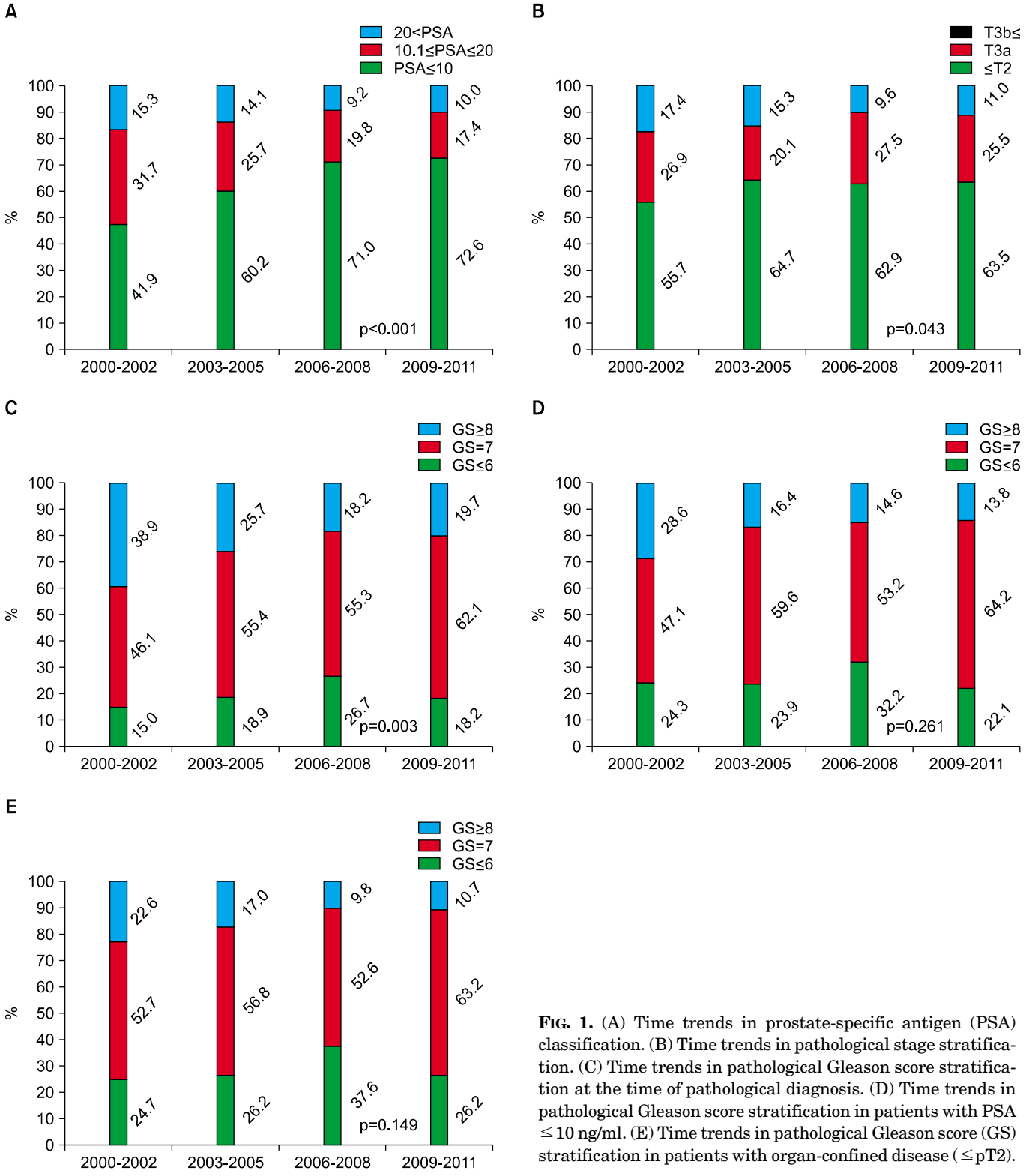

FIG. 1. (A) Time trends in prostate-specific antigen (PSA) classification. (B) Time trends in pathological stage stratification. (C) Time trends in pathological Gleason score stratification at the time of pathological diagnosis. (D) Time trends in pathological Gleason score stratification in patients with PSA ≤10 ng/ml. (E) Time trends in pathological Gleason score (GS) stratification in patients with organ-confined disease (≤pT2).

1997-1998 to 70% during 2005-2006. Moreover, whereas the biopsy procedure was a six-core biopsy until 2002, the number of biopsy cores increased to eight in 2003. This explains why the positive biopsy rate for prostate cancer in men with a PSA level of 4 ng/ml or greater was 17.1% in 1995-2002 and 39.6% in 2003-2008. Owing to this situation, many urologists have asked whether the behavior of prostate cancer differs in Korean men compared with other ethnic groups. However, few studies have examined how ethnic differences in Asians affect the risk factors and characteristics of prostate cancer. The present study was the first to evaluate the characteristics of prostate cancer

in Korean men who were treated in a large, single institution.

Several studies have shown that in patients who were diagnosed with clinically localized prostate cancer during the PSA era and were treated with RP, there has been a dramatic downward migration in the pathological stage of the tumors over time. Thus, Jhaveri et al. [9] observed that the incidence of extracapsular extension at the time of RP dropped from 81% in 1987 to 36% in 1997. In a series of 2,370 men who underwent RP at the Johns Hopkins Hospital, Han et al. [18] reported that the percentage of men with organ-confined disease increased from 37% in 1982-1991 to 61% in 1992-1998; this was associated with a decrease in the number of cases with positive pelvic lymph nodes from 7 to 4%. Similarly, the study by Ung et al. [19] reported that in 1989-1996, 67% of cases had pT3-4 prostate cancer, whereas in 1997-2000, 84% had pT2 prostate cancer. In addition, when Jang et al. [20] examined the data of 2,241 men who were part of a large longitudinal DRE- and PSA-based prostate cancer screening program, they found that the frequency of pathological organ-confined disease in men diagnosed in 1996-2001 (using a PSA threshold of 2.6 ng/ml) was 75%, whereas this frequency was 69% in 1989-1995 (the diagnosis in this period depended on the traditional cutoff of 4.0 ng/ml). Similarly, in the present study, the frequency of organ-confined disease rose steadily over the 12-year period from 55.7% (group 1) to 63.5% (group 4).

Histological tumor grading based on the Gleason grading system is predictive of the biological behavior and prognosis of prostate cancer and is used to facilitate standardized comparisons of end results over time. Although the introduction of PSA screening is known to have resulted in the increased diagnosis of prostate cancer in younger men with lower stage disease and lower PSA levels, it remains unclear at present whether this is matched by changes in the GS distribution. As a result of the widespread PSA testing over the past decade, most patients with prostate cancer now present with clinically localized disease, and their tumors are rarely graded with a GS of less than 6, with a consequent decline in the incidence of low-grade prostate cancer. In addition, differences in PSA production in prostate tumors of different grades may have resulted in a preferential improvement in the detection of moderately differentiated tumors. Moreover, although few data have evaluated the temporal reproducibility of the GS, there is some evidence that pathologists' interpretations of prostate specimens may have shifted over time to higher scores [21]. In the present study, the frequency of patients with GSs of 8 or more dropped over the 12-year period, whereas the frequency of patients with a GS of 6 or less increased. The frequency of patients with a GS of 7 also increased, from 46.1% in group 1 to 62.1% in group 4. Thus, there were significant changes over time in the GS in the present study.

Notably, the frequency of patients with a GS of 6 or less in the present study (15.0 to 26.7%) was lower than that found in earlier studies of Western men (46.1 to 69%) [22-24], even though the frequency of organ-confined disease in the present study was similar to the frequencies reported by Western studies. Although the distribution of GSs varies between studies, about 60% of Western men with prostate cancer have a GS of 6 or less. Indeed, in a recent study, more than 70% of Western men with prostate cancer had a GS of 7 or less [22]. The GS distribution in Asian patients differs from that in Western patients: 86.1% of Chinese and 78.7% of Japanese patients have a GS of 7 or less [25,26]. In the present study, the frequency of patients with high-grade (GS of 7 or greater) tumors did not change over time and exceeded 80% at all time points. This is despite the fact that there was a decline in the seminal vesicle invasion rate and a statistically significant decrease in mean preoperative serum PSA levels over the study period.

Prostate cancer is characteristically a hormone-dependent cancer. Asian men have been reported to have lower total serum testosterone and hormone-binding levels, 5-alpha-reductase levels, and testosterone production rates than white men [27,28]. That Korean men predominantly have high-grade tumors (despite the lower incidence of prostate cancer in Koreans compared with Western men) may reflect the reduced testosterone metabolism in Asians. Supporting this is a study by Hoffman et al., who found that patients with low serum free testosterone levels are more likely to have cancer with a GS of 8 or greater upon biopsy. This suggests that low serum free levels of testosterone may be a marker for more aggressive disease. Similarly, several studies have found an inverse relationship between hormone concentration and tumor grade and that androgen bioactivity is inversely proportional to tumor grade and volume [29,30]. Thus, the prostate cancer in Korean men may be predominantly high-grade tumors because of reduced testosterone metabolism.

It is also possible that the change in cancer grade distribution over time that was observed in the present study is not a true biological change. Instead, it may reflect a recent change in the grading system that yields the GS. This could also explain why there was a high incidence of GS 7 adenocarcinoma in RP specimens in the present study. In 2005, an update of the Gleason grading system was published [14]. As a result of this update and subsequent modifications, cribriform, glomeruloid, and poorly formed glands are now considered to indicate Gleason pattern 4 rather than pattern 3. The recommendation for reporting the Gleason grade is to give the predominant tumor pattern the first score and the highest grade the second score. There is also a growing consensus that low-grade tumors (GS 5) should rarely, if ever, be diagnosed on needle biopsy. This changed grading system was applied in our institution in 2007. This may explain why there was a drop in the frequency of tumors with a GS of 6 or less in 2009 to 2011 (group 4). This could also explain why the frequency of tumors with a GS of 7 increased.

Our study had several limitations. First, our findings were subject to the inherent biases of a retrospective study. Second, because the cohort studied was selected from pa-

tients who underwent RP rather than all those who had biopsy-confirmed prostate cancer, there may have been an unavoidable selection bias. Third, two different GS grading systems were used before and after 2007. Despite these limitations, this is the first study to estimate how the GS in a large cohort in Korea changed during a 12-year period.

CONCLUSIONS

The preoperative PSA levels, pathological stage, and pathological GS dropped over time in this cohort of Korean men. However, a significant proportion of the prostate cancers arising in the Korean men were poorly differentiated, even when the men had organ-confined disease or their initial serum PSA levels were below 10 ng/ml.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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