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Changes in Clinical Characteristics of Patients with an Initial Diagnosis of Prostate Cancer in Korea: 10-Year Trends Reported by a Tertiary Center

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Disclosure

The authors have no potential conflicts of interest to disclose.

ABSTRACT

Background: The Korea Central Cancer Registry reported that incidence rates of prostate cancer have not increased continuously. We used recent trends in the incidence of prostate cancer to generate a preliminary report of the Korean population with prostate cancer.

Methods: Patients initially diagnosed with prostate cancer by prostate biopsy from 2006 to 2015 at our tertiary center were selected. All patients were categorized according to age (< 65, 65–75, > 75 years), time period (2006–2010 vs. 2011–2015), and risk classification. Patients with insufficient data were excluded from the analysis.

Results: Of 675 patients (median prostate-specific antigen [PSA], 9.09 ng/mL), those with a Gleason score (GS) of 6 (32.3%) comprised the largest proportion in our cohort. The proportion with a GS of 8 increased for those aged 65–75 years, despite the lack of increase in PSA. Treatment patterns changed for those with very low to low risk cancer. The overall survival (OS) rate and the cancer-specific survival (CSS) rate for all patients at 5 years were 87% and 90%, respectively. Patients with a low body mass index (BMI; ≤ 23 kg/m²) had worse median OS and CSS rates.

Conclusion: Significant differences in risk classifications and initial treatments were found between 2006–2010 and 2011–2015. Although PSA did not change, the GS did change. Lower BMI (≤ 23 kg/m²) had worse effects on OS and CSS rates for Korean prostate cancer patients.

Keywords: Neoplasms, Prostate; Biopsy; Prostate-Specific Antigen; Gleason Score

INTRODUCTION

According to the GLOBOCAN 2012 database, the incidence rate of prostate cancer has varied widely worldwide, with the highest age-standardized incidence rates in western countries (85–111 per 100,000) and the lowest in Asia.¹ A very strong association between prostate cancer development and the global incidence and mortality of prostate cancer was reported by previous studies.^{2,3} In Korea, the incidence rate of prostate cancer has dramatically increased.⁴ Prostate-specific antigen (PSA) screening campaigns, increased average life expectancy, and changes in western dietary habits have helped to publicize the increase in prostate cancer incidence in Korea.^{4,5} As the prostate cancer incidence has increased, the proportion of localized and locally advanced cancer cases has also increased, but the ratio of metastatic disease has decreased.⁵ Recently, the Korea Central Cancer Registry

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(KCCR) showed that the increasing trend of the incidence rates of prostate cancer (25.6 per 100,000) has not continued after 2011.⁶ Despite changes in incidence rates, there are no recent published data regarding the changes in clinical stage or risk stratification for Korean prostate cancer patients.

The KCCR annually reports prostate cancer stages in Korea according to the Surveillance, Epidemiology, and End Results (SEER) summary of stages. Ratios of localized, regional, distant, and unknown prostate cancer for patients diagnosed in 2013 were 56.3%, 22.3%, 9.1%, and 12.3%, respectively.⁶ However, the registry includes neither Gleason scores (GSs) nor PSA levels, which are dependent on National Comprehensive Cancer Network (NCCN) guideline risk classifications and are used for proper treatment practice.⁷

Therefore, the aim of this study was to evaluate recent trends in the incidence of prostate cancer using a database of registered prostate cancer patients diagnosed at a tertiary center from 2006 to 2015 to generate a preliminary report of the Korean prostate cancer population.

METHODS

A total of 699 patients diagnosed with prostate cancer from January 2006 to December 2015 using prostate biopsy at our institution were initially selected. Patient characteristics including clinico-pathologic data such as age at diagnosis, body mass index (BMI), PSA, prostate volume, disease staging according to the 7th edition of the American Joint Committee on Cancer, and initial treatment options were reviewed.⁸ Treatment options included surgery, radiotherapy (RT), androgen deprivation therapy (ADT), and active surveillance (AS). Surgery included open/laparoscopic/robot-assisted radical prostatectomy (RP). RT included all types of RT such as conformal and intensity-modulated RT. ADT included luteinizing hormone-releasing hormone agonist only, anti-androgen only, and combined androgen blockade. Bone scans were routinely performed during the diagnostic work-up of all patients. Distant metastasis was assessed by bone scan and computed tomography (CT) scan. Magnetic resonance imaging (MRI) was used for patients with low-suspicious distant metastasis.

All patients were categorized according to the NCCN risk stratification published in 2016, the SEER summary of stages category regarding how far the cancer has spread from its origin (localized, regional, and distant), and the Cancer of the Prostate Risk Assessment (CAPRA) score (0–2, low risk; 3–5, intermediate risk; 6–10, high risk).^{7,9} Twenty-four (3.6%) patients without MRI or bone scan data were excluded from the analysis.

Castration-resistant prostate cancer (CRPC) was defined as the progression of disease or increase in serum PSA using the Prostate Cancer Working Group 2 criteria. All patients were stratified to two groups every 5 years according to age.

Pearson's χ^2 test was used to compare distributions of categorical baseline clinical characteristics across treatment methods. For continuous variables, means, medians, and distributions were compared using Student's t-test and Wilcoxon two-sample tests, as appropriate. The Mantel-Haenszel χ^2 test was used to determine the statistical significance of trends regarding stage and initial treatment options. Causes of death were corroborated by reviewing charts. Death certificates were used to assess the cause of death. Univariate and

multivariate Cox proportional hazard regression models were used to identify independent parameters associated with overall survival (OS), cancer-specific survival (CSS), and CRPC. Statistical analyses were performed using the Statistical Package for Social Sciences (version 23.0 for Windows; SPSS Inc., Chicago, IL, USA). All tests were two-sided and performed with a 5% significance level.

Ethics statement

The study was approved by the Institutional Review Board of Gangnam Severance Hospital, Yonsei University College of Medicine (IRB No. 2017-0533-001) and the requirements for informed consents were waived due to the retrospective nature of this study.

RESULTS

Basic characteristics of patients diagnosed with prostate cancer are shown in **Table 1**. A total of 675 (median age, 68.7 years) patients were included in the study from January 2006 to December 2015. The median prostate cancer follow-up duration was 37.5 months. The median PSA was 9.09 (interquartile range [IQR], 5.62–25.06 ng/mL). Those with a GS of 6 (32.3%) comprised the largest proportion in our cohort; 20 (3.0%) had very low risk, 77 (11.4%) had low risk, 202 (29.9%) had intermediate risk, 132 (19.6%) had high risk, 110 (16.3%) had very high risk, 37 (5.5%) had regional risk, and 97 (14.4%) had metastatic risk

Table 1. Comparison of characteristics of patients diagnosed with prostate cancer between 2006 and 2015

Characteristics	Total	2006–2010	2011–2015	P
No. of patients	675 (100.0)	224 (33.2)	451 (66.8)	
Age, yr	68.7 (62.8–74.2)	67.8 (61.3–73.4)	69.3 (63.2–74.5)	0.672
PSA, ng/mL	9.09 (5.62–25.06)	9.13 (5.44–29.11)	8.98 (5.71–23.30)	0.319
Gleason score				0.140
6	218 (32.3)	79 (35.3)	139 (30.8)	
7	180 (26.7)	65 (29.0)	115 (25.5)	
8–10	277 (41.0)	80 (35.7)	197 (43.7)	
NCCN risk stratification				0.001
Very low	20 (3.0)	4 (1.8)	16 (3.5)	
Low	77 (11.4)	12 (5.4)	65 (14.4)	
Intermediate	202 (29.9)	83 (37.1)	119 (26.4)	
High	132 (19.6)	36 (16.1)	96 (21.3)	
Very high	110 (16.3)	37 (16.5)	73 (16.2)	
Regional	37 (5.5)	12 (5.4)	25 (5.5)	
Metastatic	97 (14.4)	40 (17.9)	57 (12.6)	
SEER summary stage				0.189
Localized	398 (59.0)	126 (56.3)	272 (60.3)	
Regional	180 (26.7)	46 (20.5)	97 (21.5)	
Distant	97 (14.3)	52 (23.2)	82 (18.2)	
CAPRA scores	474 (70.2)	152 (67.9)	322 (71.4)	0.663
0–2	159 (33.5)	55 (36.2)	104 (32.2)	
3–5	187 (39.5)	59 (38.8)	128 (39.8)	
6–10	128 (27.0)	38 (25.0)	90 (28.0)	
Initial treatment				0.002
AS	9 (1.3)	2 (0.9)	7 (1.6)	
RP	285 (42.2)	114 (50.9)	171 (37.9)	
RT + ADT	257 (38.1)	64 (28.6)	193 (42.8)	
ADT	124 (18.4)	44 (19.6)	80 (17.7)	

Data are presented as number (%) or median (interquartile range).

PSA = prostate-specific antigen, NCCN = National Comprehensive Cancer Network, SEER = Surveillance, Epidemiology, and End Results, CAPRA = Cancer of the Prostate Risk Assessment, AS = active surveillance, RP = radical prostatectomy, RT = radiotherapy, ADT = androgen deprivation therapy.

cancers. Based on distribution according to initial management chosen by patients, men underwent different initial treatments as follows: 285 (42.2%) chose RP, 257 (38.1%) chose RT plus ADT, and 124 (18.4%) chose ADT. Nine (1.3%) patients enrolled in the AS registry. No patients underwent neoadjuvant ADT before RP or underwent RT only. There were significant differences in NCCN risk classifications and initial treatments for the entire study population between 2006 and 2010 and between 2011 and 2015.

All patients were categorized according to age (< 65, 65–75, > 75 years) to analyze changes in clinical characteristics (Table 2). Men aged 65–75 years and men older than 75 years comprised 46.8% and 21.6% of the study patients, respectively. There were no differences regarding age, PSA, or initial treatment for patients in the entire group between 2006 and 2010 or between 2011 and 2015. Although no differences were found in the NCCN guidelines and SEER summary of stages for patients younger than 65 years, the proportion of those with CAPRA scores 3–5 increased ($P = 0.032$). For patients 65–75 years, the number with very low to low risk cancer increased and the number with intermediate risk cancer relatively decreased ($P = 0.001$). The number of those with a GS of 8 increased as the number with a GS of 9–10 decreased ($P = 0.001$). For men older than 75 years, those with metastasis according to the NCCN risk stratification and SEER summary of stages decreased ($P = 0.016$ and 0.007, respectively).

Table 2. Comparison of characteristics stratified according to age

Characteristics	< 65 yr (n = 213 [31.6])			65–75 yr (n = 316 [46.8])			> 75 yr (n = 146 [21.6])		
	2006–2010	2011–2015	P	2006–2010	2011–2015	P	2006–2010	2011–2015	P
No. of patients	77 (36.2)	136 (63.8)		105 (33.2)	211 (66.8)		42 (28.8)	104 (71.2)	
Age, yr	59.6 (55.8–61.6)	60.2 (57.5–62.6)	0.498	69.2 (66.9–72.0)	69.9 (67.3–72.1)	0.806	79.9 (76.8–82.7)	77.7 (75.8–80.8)	0.382
PSA, ng/mL	6.32 (4.50–12.39)	7.87 (5.61–17.22)	0.380	8.75 (5.73–26.91)	8.71 (5.63–24.47)	0.366	32.09 (12.95–148.93)	11.59 (6.49–33.66)	0.481
Gleason score			0.083			0.001			0.180
6–7	59 (76.6)	84 (61.7)		69 (65.7)	124 (58.7)		16 (38.1)	46 (44.2)	
8	11 (14.3)	30 (22.1)		15 (14.3)	66 (31.3)		11 (26.2)	36 (34.6)	
9–10	7 (9.1)	22 (16.2)		21 (20.0)	21 (10.0)		15 (35.7)	22 (21.2)	
NCCN risk stratification			0.423			0.001			0.016
Very low	2 (2.6)	7 (5.1)		1 (1.0)	9 (4.3)		1 (2.4)	0 (0.0)	
Low	7 (9.1)	20 (14.7)		4 (3.8)	35 (16.6)		1 (2.4)	10 (9.6)	
Intermediate	33 (42.9)	44 (32.4)		45 (42.9)	51 (24.2)		5 (11.9)	24 (23.1)	
High	14 (18.2)	30 (22.1)		17 (16.2)	45 (21.3)		5 (11.9)	21 (20.2)	
Very high	8 (10.4)	13 (9.6)		19 (18.1)	39 (18.5)		10 (23.8)	21 (20.2)	
Regional	8 (10.4)	8 (5.9)		3 (2.9)	10 (4.7)		1 (2.4)	7 (6.7)	
Metastatic	5 (6.5)	14 (10.3)		16 (15.2)	22 (10.4)		19 (45.2)	21 (20.2)	
SEER summary stage			0.296			0.295			0.007
Localized	49 (63.6)	93 (68.4)		64 (61.0)	125 (59.2)		13 (31.0)	54 (51.9)	
Regional	23 (29.9)	29 (21.3)		25 (23.8)	64 (30.3)		10 (23.8)	29 (27.9)	
Distant	5 (6.5)	14 (10.3)		14 (10.3)	22 (10.4)		19 (45.2)	21 (20.2)	
CAPRA scores			0.032			0.157			0.959
0–2	59 (76.6)	106 (77.9)		75 (71.4)	148 (70.1)		18 (42.9)	66 (65.4)	
3–5	32 (54.2)	37 (34.9)		20 (26.7)	54 (36.5)		3 (16.7)	13 (19.1)	
6–10	16 (27.1)	49 (46.2)		36 (48.0)	52 (35.1)		7 (38.9)	27 (39.7)	
6–10	11 (18.6)	20 (18.9)		19 (25.3)	42 (28.4)		8 (44.4)	28 (41.2)	
Initial treatment			0.253			0.050			0.075
AS	0 (0.0)	2 (1.5)		1 (1.0)	5 (2.4)		1 (2.4)	0 (0.0)	
RP	55 (71.4)	80 (58.8)		56 (53.3)	82 (38.9)		3 (7.1)	9 (8.7)	
RT + ADT	14 (18.2)	35 (25.7)		30 (28.6)	90 (42.7)		20 (47.6)	68 (65.4)	
ADT	8 (10.4)	19 (14.0)		18 (17.1)	34 (16.1)		18 (42.9)	27 (26.0)	

Data are presented as number (%) or median (interquartile range).

PSA = prostate-specific antigen, NCCN = National Comprehensive Cancer Network, SEER = Surveillance, Epidemiology, and End Results, CAPRA = Cancer of the Prostate Risk Assessment, AS = active surveillance, RP = radical prostatectomy, RT = radiotherapy, ADT = androgen deprivation therapy.

Table 3. Multivariable analyses of OS, CSS, and CRPC

Variables	OS		CSS		CRPC	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Age, yr					1.01 (0.969–1.051)	0.656
BMI (> 23 vs. ≤ 23 kg/m ²)	0.38 (0.193–0.730)	< 0.001	0.31 (0.140–0.702)	0.005	0.57 (0.318–1.004)	0.052
PSA, ng/mL			1.00 (1.000–1.001)	0.137	1.00 (0.999–1.001)	0.596
PV	1.00 (0.985–1.013)	0.853	0.99 (0.972–1.008)	0.275	1.00 (0.980–1.010)	0.516
Gleason score	1.65 (1.225–2.225)	0.001	1.65 (1.093–2.499)	0.017	1.09 (0.737–1.913)	0.481
T stage (3–4 vs. 1–2)	1.58 (0.598–4.188)	0.356	6.43 (1.368–30.175)	0.018	1.94 (0.920–4.084)	0.082
N stage (1 vs. 0)	1.18 (0.488–2.859)	0.711	1.10 (0.413–2.886)	0.859	2.02 (1.006–4.071)	0.048
M stage (1 vs. 0)	9.12 (4.490–18.521)	< 0.001	15.25 (5.451–42.673)	< 0.001	3.50 (1.815–6.747)	< 0.001

OS = overall survival, CSS = cancer-specific survival, CRPC = castration-resistant prostate cancer, HR = hazard ratio, CI = confidence interval, BMI = body mass index, PSA = prostate-specific antigen, PV = prostate volume.

The OS rate and CSS rate for all patients at 5 years were 87.3% and 90.2%, respectively. The 5-year CSS rate was almost 100% for patients with clinically localized prostate cancer; however, survival rates of those with distant metastases at diagnosis were poor (median survival rate, approximately 4 years). Multivariate analysis of OS indicated that BMI (> 23 vs. ≤ 23 kg/m²; hazard ratio [HR], 0.38; 95% confidence interval [CI], 0.193–0.730; $P < 0.001$), GS (HR, 1.65; 95% CI, 1.225–2.225; $P = 0.001$), and M stage (1 vs. 0; HR, 15.25; 95% CI, 5.451–42.673; $P < 0.001$) were significant risk factors. Multivariate analysis also indicated that BMI (> 23 vs. ≤ 23 kg/m²; HR, 0.31; 95% CI, 0.140–0.702; $P = 0.005$), GS (HR, 1.65; 95% CI, 1.093–2.499; $P = 0.017$), T stage (3–4 vs. 1–2; HR, 6.43; 95% CI, 1.368–30.175; $P = 0.018$), and M stage (1 vs. 0; HR, 6.43; 95% CI, 1.368–30.175; $P < 0.001$) were risk factors for CSS. N stage (1 vs. 0; HR, 2.02; 95% CI, 1.006–4.071; $P = 0.048$) and M stage (1 vs. 0; HR, 3.50; 95% CI, 1.815–6.747; $P < 0.001$) were significant risk factors for CRPC (Table 3).

We evaluated the comparative survival rates of patients after adjustment for covariates considered to be potential predictors by the Cox proportional hazards analysis for OS and CSS. Patients with BMI ≤ 23 kg/m² had worse median OS and CSS rates than those with BMI > 23 kg/m² ($P = 0.007$ and 0.009 , respectively) (Fig. 1).

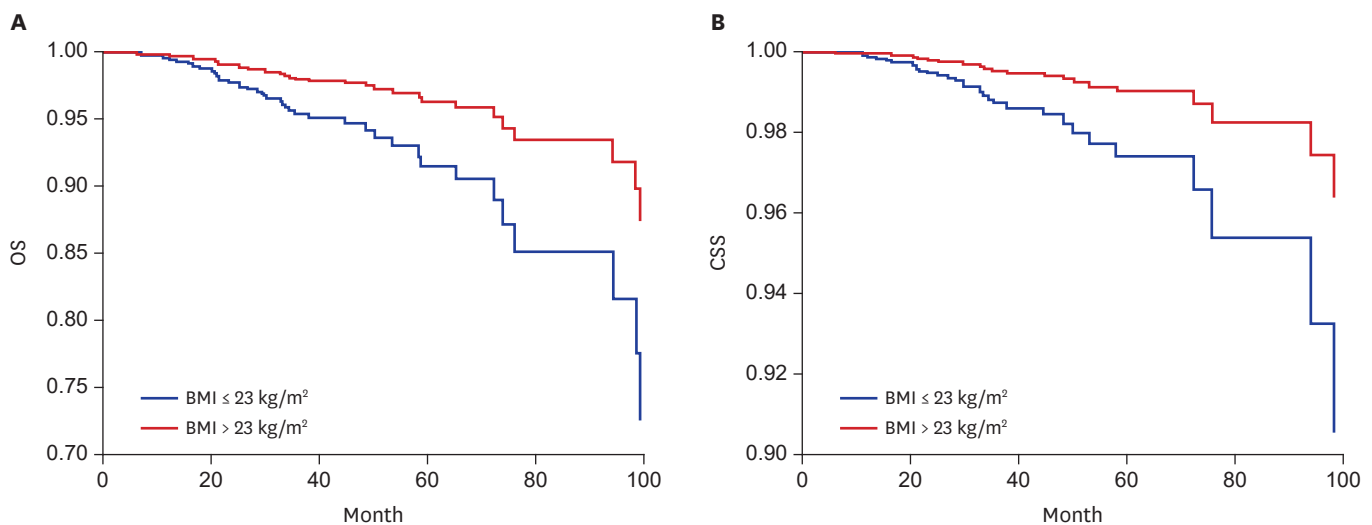


Fig. 1. Comparative survival curves of prostate cancer patients according to BMI. (A) OS and (B) CSS. BMI = body mass index, OS = overall survival, CSS = cancer-specific survival.

DISCUSSION

This preliminary study described the diagnostic characteristics of men diagnosed with prostate cancer in Korea. SEER stages at our center (localized, 59.0%; regional, 26.7%; and metastatic, 14.3%) and 5-year relative survival rates (87.3%) were comparable to the national proportions (56.3%, 22.3%, 9.1%, and 92.5%, respectively) for prostate cancer patients diagnosed from 2009 to 2013, as reported by KCCR. Although our data are not truly representative of the whole Korean population, the present study confirmed the significant changes in incidence and primary treatments according to contemporary risk classifications during one decade.

PSA testing was popularized in the 1990s in the United States.¹⁰ Although its value as a screening test was controversial, PSA testing has been widely used as a common strategy for prostate cancer screening and its effectiveness is well-accepted.^{11,12} In Korea, PSA testing for the diagnosis of prostate cancer has been used for the past 20 years, which is the main reason for the dramatic increase in the incidence rates of prostate cancer. Song et al.¹³ reported changes that occurred during the era when PSA screening was introduced: the proportion of metastatic disease decreased from 40.0% to 17.6% after a comparative analysis involving data from 1997 to 2006. Moreover, they reported that the GS was decreased and that a GS of 7 was the dominant pathologic grade for 758 Korean patients (median PSA, 14.8 ng/mL) diagnosed with prostate cancer at a single center between 1997 and 2006. During an analysis of 1,582 patients treated with RP from 10 centers, the proportion of those with a GS \leq 6 between 2004 and 2007 was higher compared to that between 1995 and 2003.¹⁴ With the continuous decrease in changes of the GS, this study found that a GS of 6 is the most dominant histologic grade in recent decades.

Decreases in PSA were related to relative decreases in the number of men presenting with metastatic disease. However, there are scarce data regarding whether no change in PSA means that there is no change in GS. In an analysis of 21,044 prostate cancer patients in east England, those with a GS of 7 without increased PSA comprised the largest proportion in 2006–2010, although those with a GS of 6 had been prominent during 2000–2005.¹⁵ For the group aged 65–75 years, those with a GS of 8 at the initial diagnosis of prostate cancer dominantly increased without changes in PSA. There are two possible explanations for this. Because the proportion with metastatic disease is continuously decreasing, there is a paradoxical increase in men with a GS of 8 with classified tumor grades. In addition, changes in western dietary habits and hereditary factors in Asians, including family history or genetic background, are potentially linked. Therefore, an investigation of the changes in histological grades should be performed.

After Donald Gleason developed the first grading system for prostate cancer, the Gleason grading system gained worldwide recognition because it allowed for individualized treatment of prostate cancer patients.^{16,17} Tewari et al.¹⁸ reported that there were racial differences in the GS of 4,279 individuals diagnosed with localized prostate cancer between 1980 and 1997. Moreover, Korean prostate cancer patients had worse characteristics than their American counterparts during a comparative analysis of the patients who underwent surgery for localized prostate cancer.¹⁹ For patients with PSA > 10 ng/mL, Koreans had a higher GS than Americans. Regarding those with localized prostate cancer, the proportions of Koreans with CAPRA scores 3–5 (39.5%) and 6–10 (27.0%) were higher than those of Americans according to studies analyzing 11,892 men who contributed to the Cancer of the Prostate Strategic

Urologic Research Endeavor (CaPSURE) registry (29.1% and 10.7%, respectively).²⁰ Regarding the NCCN risk stratification, the fraction of Koreans with high to very high risk cancer (35.9%) was higher than that of the Danish (31.1%).²¹ Therefore, we reconfirmed that Korean men with localized prostate cancer had worse disease features than western populations.

Treatments vary with age, risk stratification, and patient's and clinician's preferences. In our cohort, only 45% of patients with very low risk prostate cancer were enrolled in our AS registry. Almost 73% of men with low risk prostate cancer were managed with watchful waiting or AS in Denmark between 1980 and 1997. Our main strategy for men with very high risk cancer was RT plus ADT (90.0%), not just ADT (90.0%), which is used by the Danish.²¹ The only similarity in our cohort was that treatment with curative intent was primarily used for men with clinically localized prostate cancer; men with higher risk disease were managed without curative intent in accordance with observations by western countries.²⁰⁻²²

With 5-year cancer survival rates approaching 100%, men diagnosed with localized prostate cancer will deal with the consequences of their diagnosis and treatment.²³⁻²⁵ For metastatic prostate cancer patients, initial treatment with chemotherapy can improve survival compared with ADT. Moreover, abiraterone, enzalutamide, and other agents for metastatic CRPC patients can improve survival related to traditional hormonal therapy.²⁶ The American Cancer Society has developed guidelines for prostate survivorship. In these guidelines, health promotion such as diet and exercise were beneficial for quality of life.²⁷⁻²⁹ Unfortunately, there are no guidelines for prostate survivorship for Asians.

Racial disparities may reveal differences in survival for prostate cancer patients. A systematic review of prospective cohort studies showed that obesity is considered a major risk factor associated with fatal prostate cancer.³⁰ Higher BMI, which is a parameter for measuring obesity, was associated with an increased risk of advanced prostate cancer and cancer-specific mortality.³¹ However, Asian men have relatively low BMI compared with western men. Furthermore, to our best knowledge, scarce data regarding the relationship between obesity and the prognosis of prostate cancer were reported for Asians. In the present study, lower BMI (≤ 23 kg/m²) had worse effects on OS and CSS in multivariate analyses, and BMI was not a risk factor for CRPC. Because of the disparity in results, guidelines to promote health in Asian prostate cancer patients should be developed in future.

This report had a number of limitations. First, we analyzed data from a single institute that would not be a representative of Korean populations. Although our study was similar to national studies using several registries regarding the proportion of prostate cancer patients and survival rates, it is possible that there were discrepancies between data obtained from central registries or national databases. Nevertheless, this is the first study to describe diagnostic characteristics among Korean men with prostate cancer according to contemporary risk stratification and primary treatment. Furthermore, we excluded patients diagnosed with prostate cancer but unstaged or diagnosed incidentally after transurethral resection of prostate at our hospital, so there is the possibility of selection bias. To overcome this limitation, data from a large-scale observational longitudinal study are needed. We believe that a large prostate cancer database in Korea will reliably show changes in prostate cancer trends in Korea.

Since introducing PSA screening in Korea, a GS of 6 has become the most dominant histologic grade. As the proportion of those with metastatic disease has decreased, the number of those with a GS of 8 has paradoxically increased for patients aged 65–75 years.

High BMI had positive effects on OS and CSS rates for Korean prostate cancer patients with normal weights.

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