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ORIGINAL ARTICLE

Prostate Cancer

The current status of hormone treatment for prostate cancer patients in Korean real-world practice: a multi-institutional observational study

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We aimed to evaluate the current nationwide trend, efficacy, safety, and quality of life (QoL) profiles of hormone treatment in real-world practice settings for prostate cancer (PCa) patients in Korea. A total of 292 men with any biopsy-proven PCa (TanyNanyMany) from 12 institutions in Korea were included in this multi-institutional, observational study of prospectively collected data. All luteinizing hormone-releasing hormone (LHRH) agonists were allowed to be investigational drugs. Efficacy was defined as (1) the rate of castration (serum testosterone ≤50 ng dl^{-1}) at 4-week visit and (2) breakthrough (serum testosterone >50 ng dl^{-1} after castration). Safety assessments included routine examinations for potential adverse events, laboratory tests, blood pressure, body weight, and bone mineral density (BMD, at baseline and at the last follow-up visit). QoL was assessed using the Expanded Prostate Cancer Index Composite-26 (EPIC-26). The most common initial therapeutic regimen was LHRH agonist with anti-androgen (78.0%), and the most commonly used LHRH agonist for combination and monotherapy was leuprolide (64.0% for combination and 58.0% for monotherapy). The castration and breakthrough rates were 78.4% and 6.6%, respectively. The laboratory results related to dyslipidemia worsened after 4 weeks of hormone treatment. In addition, the mean BMD T-score was significantly lower at the last follow-up (mean: −1.950) compared to baseline (mean: −0.195). The mean total EPIC-26 score decreased from 84.8 (standard deviation [s.d.]: 12.2) to 78.3 (s.d.: 8.1), with significant deterioration only in the urinary domain (mean: 23.5 at baseline and 21.9 at the 4-week visit). These findings demonstrate the nationwide trend of current practice settings in hormone treatment for PCa in Korea.

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INTRODUCTION

In current cases of prostate cancer (PCa), distant metastases have been reported in fewer than 5% of newly diagnosed patients, which represents a marked decrease from past data.[1] In Korea, 9.0% of PCa cases had distant metastases at diagnosis between 2006 and 2010 according to the Korean Central Cancer Registry.[2] Hormone treatment, known as androgen deprivation therapy (ADT), was originally introduced as a treatment option for these patients. Notably, despite the substantial decrease in metastatic PCa, the use of ADT increased sharply between 1989 and 2001,[3] which reflects the fact that many patients with non-metastatic and even localized PCa receive ADT, which is not always in accordance with the guidelines.

The advantages of ADT are well documented; it can relieve symptoms caused by metastatic disease or prolong survival when combined with other treatment modalities (*e.g.*, radiation therapy and surgery).[4,5] Importantly, as the use of ADT becomes more widespread, assessing its potential side effects is essential for treatment decision-making and for improving the impact of treatment on each patient's quality of life (QoL).[3,6] Previous studies have demonstrated that ADT increases the risk of mortality and contributes to significant complications, particularly in patients undergoing long-term treatment.[7,8]

Although the prevalence of PCa is lower than that in Western countries, the incidence of PCa in Korea is rapidly increasing (12.3% annually),[9] and it appears that the use of ADT has subsequently increased as well. However, there have been no data to date regarding the real-world practices of hormone treatment in Korean PCa patients. Therefore, we aimed to evaluate this issue through this study, with a

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particular focus on the current nationwide trend, efficacy, safety, and QoL profiles of hormone treatment for PCa in Korea.

PATIENTS AND METHODS

Study cohort

We conducted the current study as an observational design with prospectively collected data from 12 institutions nationwide listed in the affiliations. The study patients included consecutive men aged over 20 years with any stage of biopsy-proven PCa (TanyNanyMany) between March 2014 and December 2017. Patients with (1) a previous history of any hormone or steroid therapy, (2) brain metastasis, (3) Eastern Cooperative Oncology Group performance status >2, or (4) cardiac disease were excluded from our analyses. Researchers from all the 12 institutions obtained Institutional Review Board approval from each hospital listed in the affiliations before entering any data into the registry (approval number: B-1312/230-006, Seoul National University Bundang Hospital Institutional Review Board, Seongnam, Korea). Informed consent was obtained from each patient before participation. Unified data templates were used for consistent data collection at each institution, and data were retrospectively reviewed from medical records. Due to the observational design of the study, neither randomization nor a fixed group was needed. Blinding was not applicable in this study design.

Study methods

A flow diagram of the study process is presented in **Figure 1**. The study period consisted of screening (2 weeks), therapeutic (48 weeks), and follow-up (12 weeks) periods. Following the standardized study protocol, all patients enrolled took hormone treatments appropriate for their disease status throughout the entire therapeutic period (48 weeks). Because we aimed to analyze the trend in real-world practices in hormone treatment, we allowed all luteinizing hormone-releasing hormone (LHRH) agonists (leuprolide, goserelin, *etc.*) and anti-androgens (flutamide, bicalutamide, *etc.*) as investigational drugs; however, we did not include LHRH antagonists. We recommended that physicians not change treatments throughout the full study period, but we permitted changes with records of cause. We assessed compliance based on the number of administrations of hormone therapies for PCa from visit 3 (first treatment visit) until visit 7 (end of the study).

Efficacy, safety, and QoL assessments

We defined efficacy as (1) the rate of castration (serum testosterone ≤50 ng dl^{-1})[10] at 4-week visit and (2) breakthrough (serum testosterone >50 ng dl^{-1} after castration).

Safety assessments included routine examinations for potential adverse events according to the World Health Organization (WHO) classification:[11] laboratory abnormalities including hematology, coagulation, and blood chemistry at 4, 12, 24, 36, 48, and 60 weeks; blood pressure; and body weight. We assessed the bone mineral densities (BMDs) of the femur and lumbar spine at baseline as well as at the last follow-up visit (60 weeks). All patients were assessed prior to each injection unless otherwise stated. In addition, the patients' vital signs were checked 2 h and 4 h after each injection.

We also assessed QoL using the Expanded Prostate Cancer Index Composite-26 (EPIC-26)[12] at baseline and throughout the study period.

Statistical analyses

We used independent or paired *t*-tests, as indicated. We also conducted a comparative analysis between the LHRH agonist with anti-androgen (complete androgen blockade, CAB) and LHRH agonist monotherapy. We performed univariate and multivariate logistic regression analyses in order to determine the significant variables associated with castration and breakthrough. The safety analysis included all patients who received at least one administration of investigational drugs, provided that they had a safety profile. For the safety and QoL analyses, we used the intent-to-treat population, which comprised all patients, regardless of protocol deviations, except for those who had missing testosterone values at 4-week visit. We performed all statistical analyses using SPSS version 21.0 (IBM Corp., Armonk, NY, USA) and considered a two-sided $P < 0.05$ to be statistically significant.

RESULTS

We enrolled a total of 292 patients in the current study. The mean patient age was 74.5 (standard deviation [s.d.]: 7.1) years, and the median follow-up period was 12.8 (range: 1–18) months. The baseline characteristics, including clinicopathological and laboratory data, are summarized in **Table 1**. Mean testosterone at the time of screening was 384.1 (s.d.: 207.3) ng dl^{-1}, and median prostate-specific antigen (PSA) was 26.7 (range: 0.1–2200.0) ng ml^{-1}. Mean total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) cholesterol were 172.8 (s.d.: 35.8) mg dl^{-1}, 135.1 (s.d.: 41.2) mg dl^{-1}, 48.1 (s.d.: 13.3) mg dl^{-1}, and 101.9 (s.d.: 30.8) mg dl^{-1}, respectively. Mean BMD, described as the T-score at baseline, was −0.195. Mean baseline HbA1c and glucose were 5.8% (s.d.: 1.2%) and 118.9 (s.d.: 3.8) mg dl^{-1}, respectively. The visit completion rate was 67.2% at the last follow-up visit (**Supplementary Figure 1**), and the

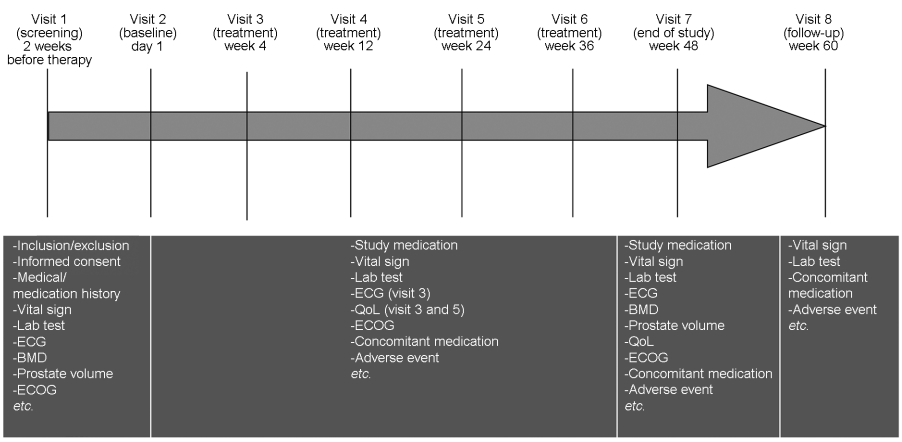

Figure 1: Study flowchart. ECG: electrocardiography; ECOG: Eastern Cooperative Oncology Group Performance Status; BMD: bone mineral density; QoL: quality of life.

therapeutic regimen completion rate was 53.1% at the end of the study (**Supplementary Figure 2**).

The nationwide trend of hormone treatment for PCa

The practice pattern analysis of the 279 patients (95.5%, **Supplementary Figure 2**) found that the most common initial therapeutic regimen was CAB (78.0%), followed by LHRH agonist monotherapy (16.0%) and anti-androgen monotherapy (6.0%). The most commonly used LHRH agonist for combination and monotherapy was leuprolide (64.0% for combination and 58.0% for monotherapy), followed by goserelin (28.0% and 21.0%, respectively) and triptorelin (8.0% and 21.0%, respectively) (**Figure 2**). Only bicalutamide was used for anti-androgen monotherapy (100%). The regimen change rate at the end of the study was 16.0%, and anti-androgen withdrawal was the main reason for change (62.2%, data not shown).

Table 1: Baseline characteristics

Characteristic	*Patients (n=292)*
Age (year), mean±s.d.	74.5±7.1
BMI (kg m^{-2}), mean±s.d.	23.6±3.1
Hypertension (yes), *n* (%)	128 (43.8)
Diabetes (yes), *n* (%)	66 (22.6)
ECOG performance status	
0, *n* (%)	158 (54.1)
1, *n* (%)	134 (45.9)
Testosterone (ng dl^{-1}), mean±s.d.	384.1±207.3
HbA1c (%), mean±s.d.	5.8±0.9
Total cholesterol (mg dl^{-1}), mean±s.d.	172.8±35.8
TG (mg dl^{-1}), mean±s.d.	135.1±41.2
HDL (mg dl^{-1}), mean±s.d.	48.1±13.3
LDL (mg dl^{-1}), mean±s.d.	101.9±30.8
Systolic BP (mmHg), mean±s.d.	127.2±15.4
Diastolic BP (mmHg), mean±s.d.	75.6±10.0
PSA (ng ml^{-1}), median (range)	26.7 (0.1–2200.0)
Total prostate volume (ml), mean±s.d.	48.1±29.2
Clinical stage, *n* (%)	
≤T2	104 (35.6)
≥T3	188 (64.4)
N0	198 (67.8)
N1	94 (32.2)
M0	194 (66.4)
M1	98 (33.6)
Gleason score, *n* (%)	
6	38 (13.0)
7	71 (24.3)
≥8	183 (62.7)

BMI: body mass index; BP: blood pressure; ECOG: Eastern Cooperative Oncology Group; HDL: high-density lipoprotein; LDL: low-density lipoprotein; PSA: prostate-specific antigen; s.d.: standard deviation; HbA1c: glycated hemoglobin; TG: triglyceride

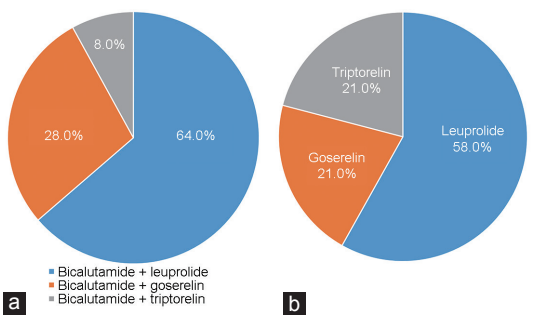

Figure 2: The proportions of LHRH agonists for (**a**) combination therapy and (**b**) monotherapy. LHRH: luteinizing hormone-releasing hormone.

The efficacy analysis: comparison of treatment modalities

In the efficacy analysis among the 255 patients (87.3%, **Supplementary Figure 2**) who completed baseline laboratory testing, the castration rate was 78.4% (**Figure 3a**). The CAB group showed a significantly higher castration rate than the LHRH agonist monotherapy group did (84.5% *vs* 71.4%, P = 0.041; **Figure 3b**). Despite having lower castration levels of testosterone (≤20 ng dl^{-1}),[13] the CAB group still showed a significantly higher castration rate (80.0% *vs* 66.7%, P = 0.05; **Figure 3c**). Notably, mean testosterone at the 4-week visit was significantly higher in the LHRH monotherapy group (75.4 ng dl^{-1} *vs* 37.6 ng dl^{-1}); there were no significant differences between the two groups at the 12-week visit (**Supplementary Figure 3**). Breakthrough occurred in 6.6% and 10.3% of all patients with castration cutoff values of 50 ng dl^{-1} and 20 ng dl^{-1}, respectively (**Supplementary Figure 4a**). The median (interquartile range, IQR) period between castration and breakthrough was 44 (23–44) weeks. The CAB group also showed significantly lower breakthrough rates than the LHRH agonist monotherapy group at both castration cutoff values of 50 ng dl^{-1} and 20 ng dl^{-1} (4.0% *vs* 19.0%, P = 0.002 and 7.5% *vs* 23.8%, P = 0.004, respectively, **Supplementary Figure 4b** and **4c**). Multivariate logistic regression analysis identified age (P = 0.007), body mass index (BMI) (P = 0.008), and initial therapeutic regimen (LHRH agonist monotherapy *vs* CAB, P < 0.001) as significant predictors of breakthrough (**Supplementary Table 1**). In contrast, there were no significant predictors associated with castration (**Supplementary Table 2**).

In addition, in subgroup analysis according to the initial LHRH agonist agent, regardless of the initial therapeutic regimen, leuprolide showed the lowest efficacy in castration rate (72.1% compared to 88.9% [goserelin] and 91.7% [triptorelin], P = 0.002; **Supplementary Table 3**). In terms of PSA profile, mean PSA decreased from the baseline of 180.9 ng ml^{-1} to 25.5 ng ml^{-1} at the 4-week visit, then further to 8.1 ng ml^{-1} at the 12-week visit. It still decreased further to 4.7 ng ml^{-1} at the last follow-up visit (data not shown).

Safety assessment profile

The laboratory results (total cholesterol, TG, HDL, and LDL) related to dyslipidemia worsened after hormone treatment (**Figure 4**). In the early phase, in particular, this phenomenon was observed with statistical significance (all P < 0.05). In addition, the mean BMD T-score was also significantly lower at the last follow-up visit (−1.950) than at baseline

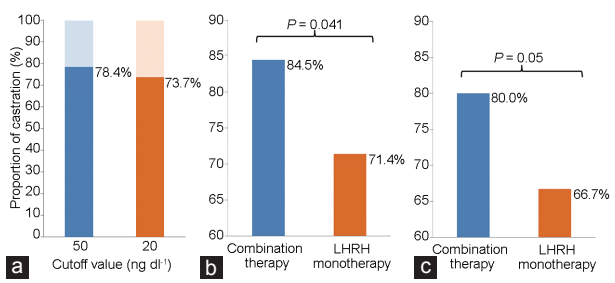

Figure 3: The efficacy analysis with castration. (**a**) The proportion of castration with cutoff values of 50 ng dl^{-1} and 20 ng dl^{-1} (total n = 255). (**b**) Comparative analysis of combination therapy versus LHRH agonist monotherapy with cutoff value of 50 ng dl^{-1} (P = 0.041). (**c**) Comparative analysis of combination therapy versus LHRH agonist monotherapy with cutoff value of 20 ng dl^{-1} (P = 0.05). LHRH: luteinizing hormone-releasing hormone.

(−0.195, $P < 0.001$; **Supplementary Figure 5a**). However, there were no significant changes during the study period in BMI or glucose profile including HbA1c (all $P > 0.05$; **Supplementary Figure 5b** and **6**).

QoL assessment profile

Regarding the EPIC-26 scores, we linearly transformed the responses into a scale of 0–100, with higher scores indicating better QoL. During the study period, the mean total EPIC-26 score decreased from 84.8 (s.d.: 12.2) to 78.3 (s.d.: 8.1). Notably, in comparing the EPIC-26 domain subscales with the mean score, only the urinary domain showed significant deterioration after hormone treatment ($P = 0.039$); there were no significant changes in any of the other domains (all $P > 0.05$; **Figure 5**).

DISCUSSION

To the best of our knowledge, this is the first nationwide study to investigate the current hormone treatment in real-world practice settings for PCa in Korea.

The present study showed that the most common initial therapeutic regimen was CAB, and that the most commonly used LHRH agonist was leuprolide. A previous large cohort study from 14 European Union (EU) countries also demonstrated that the most common preparation was leuprolide (61%), followed by goserelin (25%) and triptorelin (12%).[14] Iannazzo *et al.*[15] showed that leuprorelin 22.5 mg was the most cost-effective treatment in Italy, as compared to leuprorelin 11.25 mg, triptorelin 11.25 mg, and goserelin 10.8 mg. We hypothesized that the current trend in hormone treatment was largely influenced by cost-effectiveness.

In fact, in Korea, leuprorelin 22.5 mg is prescribed since it occupies the lowest price point.[16] In addition, because the leuprolide patent expired in 2014, generic products have entered the Korean market, so subsequent active marketing and price competition have led to even higher usage of leuprolide despite its low efficacy (**Supplementary Table 3**).

In the comparative analysis of clinicopathological features between the initial LHRH agonist monotherapy group and the CAB group, the CAB group showed a significantly higher mean prebiopsy PSA value (210.6 ng ml^{-1} *vs* 30.6 ng ml^{-1}, $P < 0.001$); a significantly higher mean percentage of positive biopsy core number (72.5% *vs* 45.8%, $P < 0.001$); and significantly higher frequencies of high Gleason score ($P = 0.016$), clinical N1 (33.5% *vs* 9.5%, $P = 0.002$), and clinical M1 (38.5% *vs* 4.8%, $P < 0.001$; **Supplementary Table 4**). Despite these adverse features, the efficacy analysis showed the superiority of CAB to LHRH agonist monotherapy in castration and breakthrough (**Figure 3** and **Supplementary Figure 4**). Even with strong rationales for administering CAB, results from previous individual clinical studies have been conflicting.[17–21] In a previous meta-analysis, Samson *et al.*[17] found no statistically significant difference in survival at 2 years between the CAB and monotherapy groups (twenty trials; hazard ratio [HR] = 0.970; 95% confidence interval [CI]: 0.866–1.087). However, they also demonstrated a statistically significant difference in survival at 5 years that favored CAB (ten trials; HR = 0.871; 95% CI: 0.805–0.942). Recently, Usami *et al.*[18] conducted a phase III randomized, double-blind, multicenter trial in Japanese patients and reported that first-line CAB with bicalutamide 80 mg in Japanese patients with advanced PCa offered significant benefits over LHRH agonist alone in time-to-treatment failure and time-to-disease progression. Our current data provide further support for these results, specifically in another Asian population.

In terms of safety profile, the present study showed a significant deterioration of lipid metabolism after 4 weeks of hormone treatment (*i.e.*, total cholesterol, TG, HDL, and LDL; **Figure 4**), as well as a significant deterioration of bone metabolism, according to the BMD results at the last follow-up (**Supplementary Figure 5a**). Consistent with our results, Smith *et al.*[22] reported that serum total cholesterol, HDL, and LDL concentrations each increased at 12-week by 9.4% (s.d.: 2.4%), 9.9% (s.d.: 2.9%), and 8.7% (s.d.: 4.7%), respectively (all $P < 0.05$); serum TG also increased by 23.0% (s.d.: 8.0%; $P = 0.04$) at week 12. The observed increase in this lipid panel was associated with classic metabolic syndrome.[22] In this regard, the science advisory boards from the American Heart Association, American Cancer Society, and American Urological Association presented general preventive strategies for all men who were beginning ADT. These strategies include yearly lipid panels, dietary modification or medication (in the case of abnormal parameters), smoking cessation, weight loss (in the case of being overweight at baseline or becoming overweight thereafter), and regular exercise.[23] However, aggressive treatment is not currently recommended for dyslipidemia; no definite relationship between adverse cardiovascular events and ADT has yet been outlined. Even considering this, we hypothesized that cardiovascular side effects could be decreased further through the early assessment and treatment of dyslipidemia within 4 weeks after treatment, which was a part of the current study protocol.

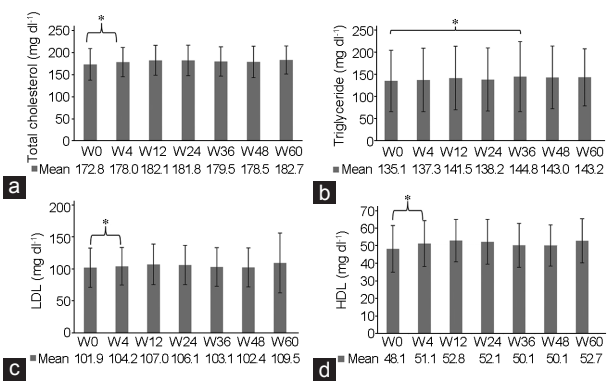

Figure 4: Mean changes in (**a**) total cholesterol, (**b**) triglyceride, (**c**) low-density lipoproteins, and (**d**) high-density lipoproteins from baseline through 60 weeks of treatment. $^*P < 0.05$, the values at baseline versus 4-week (W) visit in **a**, **c**, and **d**; the values at baseline versus 4-, 12-, 24-, and 36-week visits in **b**. LDL: low-density lipoprotein; HDL: high-density lipoprotein; EPIC-26: the Expanded Prostate Cancer Index Composite-26.

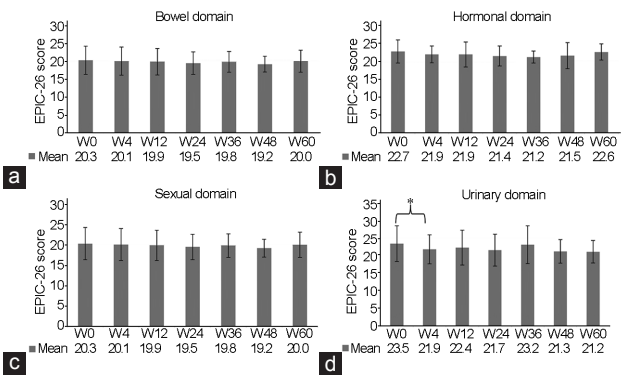

Figure 5: Mean EPIC-26 score changes from baseline to 60 weeks of treatment: (**a**) bowel domain; (**b**) hormonal domain; (**c**) sexual domain; and (**d**) urinary domain. $^*P = 0.039$, the values at baseline versus 4-week (W) visit. EPIC: the Expanded Prostate Cancer Index Composite.

Importantly, in this study, we serially evaluated BMD after ADT in every study participant (baseline and last follow-up), and the mean BMD T-score decreased from −0.195 to −1.950 ($P < 0.001$; **Supplementary Figure 5a**). Skeletal complications, such as decreasing BMD and subsequent fractures (up to 20%), are other well-known consequences of ADT. Although these complications are asymptomatic in most patients, monitoring bone status during the treatment period is highly recommended, due to the negative correlation between the length of ADT and BMD.[24,25] The most commonly used preventive strategies aimed at reducing skeletal side effects include calcium (1500 mg) and vitamin D (800 IU) supplementation; lifestyle modification with increased exercise, decreased alcohol consumption, and cessation of smoking; and normalization of BMI.[26] Notably, Smith *et al*.[27] found that denosumab (human monoclonal antibody against receptor activator of nuclear factor kappa-B ligand), at a dose of 60 mg injected subcutaneously every 6 months, increased BMD and reduced the 3-year risk of new vertebral fractures by 62% in patients treated with ADT.

Health-related QoL profiles provide important information about the impacts of treatment. The current study showed significant deterioration in the urinary domain of the EPIC-26 (**Figure 5**). In contrast, several previous studies have reported improved urinary symptoms with ADT.[28,29] Theoretically, ADT improves urinary symptoms in PCa patients, leading to a complete reduction in prostate size rather than a reduction in the cancer volume itself. Notably, taking this into consideration, several previous studies have shown that testosterone treatment induced bladder neck smooth muscle relaxation and the rapid inhibition of contractility in detrusor smooth muscle preparation.[30,31] Recently, Haider *et al*.[31] reported that long-term testosterone treatment in hypogonadal men resulted in a significant improvement in urinary function. Taking these findings together, we tentatively conclude that the pathophysiologic changes of bladder function due to the testosterone deficiency after castration exacerbated the urinary symptoms.

The present study has several limitations that should be acknowledged. First, the small number of study patients analyzed is a crucial drawback, and therefore, our conclusions cannot be generalized. In addition, patients' compliance was low, as evaluated by visit and therapeutic regimen completion rates (**Supplementary Figure 1** and **2**); accordingly, some of our results deviate from the essence of the data. Second, we did not analyze the results of adverse events and serious adverse events according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 3.0 because the quality of data of this profile was poor, due to the aforementioned low compliance of the study patients (**Supplementary Figure 2**). As a result, we could not evaluate any subjective side effects (*e.g.*, hot flushes, fatigue, sexual side effects, or cognitive function). Finally, we only allowed LHRH agonists; accordingly, we could not consider LHRH antagonists for analysis despite the fact that they currently comprise a substantial proportion of hormone treatments. Previous studies have reported that an LHRH antagonist (degarelix) offers a lower risk of PSA progression or death than leuprolide.[32] However, the use of LHRH antagonists has thus far been limited to current clinical practice settings in Korea due to the reimbursement regulation that requires the response to be evaluated every 3 months through imaging. As such, the present study reflects current real-world practices.

CONCLUSIONS

This is the first nationwide study to demonstrate the current trend in hormone treatment for PCa in Korea. The most common initial therapeutic regimen was CAB, and the most commonly used LHRH agonist was leuprolide. In addition, the efficacy analysis of castration and breakthrough showed the superiority of CAB to LHRH monotherapy. Regarding the safety profile, we found significant deteriorations of lipid and bone metabolisms. Additionally, the current study showed a significant deterioration in the urinary domain of the EPIC-26. These results can contribute to the development of optimized therapeutic strategies for Korean PCa patients.

AUTHOR CONTRIBUTIONS

JKK, JJK, and SSB designed the present study and prepared the manuscript. JKK and SSB reviewed and analyzed the data and revised the manuscript. JJK, TWG, TKK, HSK, SCP, JSP, JYP, SJY, YSJ, JSC, KJJ, and SHH contributed to acquisition of data. JKK and JJK carried out statistical analysis. All authors performed critical review and read and approved the final manuscript.

COMPETING INTERESTS

All authors declare no competing interests.

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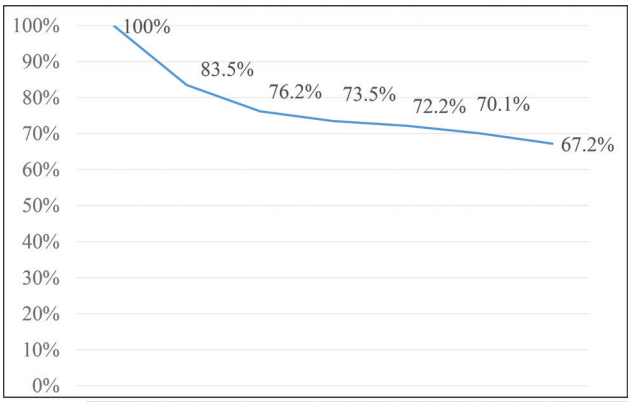
Supplementary Information is linked to the online version of the paper on the *Asian Journal of Andrology* website.

REFERENCES

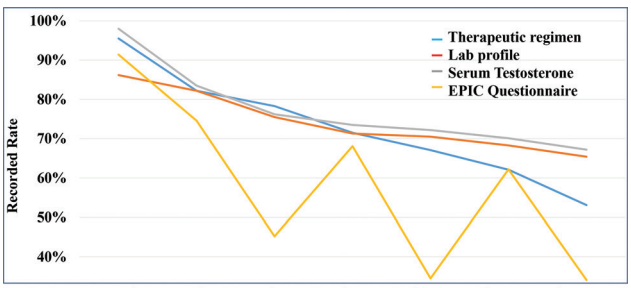
1 Ryan CJ, Small EJ. Early versus delayed androgen deprivation for prostate cancer: new fuel for an old debate. *J Clin Oncol* 2005; 23: 8225–31.
2 Jung KW, Won YJ, Kong HJ, Oh CM, Shin A, *et al*. Survival of Korean adult cancer patients by stage at diagnosis, 2006-2010: national cancer registry study. *Cancer Res Treat* 2013; 45: 162–71.
3 Cooperberg MR, Grossfeld GD, Lubeck DP, Carroll PR. National practice patterns and time trends in androgen ablation for localized prostate cancer. *J Natl Cancer Inst* 2003; 95: 981–9.
4 Pagliarulo V, Bracarda S, Eisenberger MA, Mottet N, Schröder FH, *et al*. Contemporary role of androgen deprivation therapy for prostate cancer. *Eur Urol* 2012; 61: 11–25.
5 Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, *et al*. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomized study. *Lancet Oncol* 2010; 11: 1066–73.
6 Sadetsky N, Greene K, Cooperberg MR, Hubbard A, Carroll PR, *et al*. Impact of androgen deprivation on physical well-being in patients with prostate cancer: analysis from the CaPSURE (Cancer of the Prostate Strategic Urologic Research Endeavor) registry. *Cancer* 2011; 117: 4406–13.
7 Keating NJ, O'Malley AJ, Smith MR. Diabetes and cardiovascular disease during androgen deprivation therapy for prostate cancer. *J Clin Oncol* 2006; 24: 4448–56.
8 Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, *et al*. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the population-based PCBaSe Sweden. *J Clin Oncol* 2010; 28: 3448–56.
9 Park SK, Sakoda LC, Kang D, Chokkalingam AP, Lee E, *et al*. Rising prostate cancer rates in South Korea. *Prostate* 2006; 66: 1285–91.
10 Oefelein MG, Cornum R. Failure to achieve castrate levels of testosterone during luteinizing hormone releasing hormone agonist therapy: the case for monitoring serum testosterone and a treatment decision algorithm. *J Urol* 2000; 164: 726–9.
11 World Health Organization. Conceptual framework for the International Classification for Patient Safety. Version 1.1. Final technical report. World Health Organization; 2009. Available from: http://www.who.int/patientsafety/implementation/taxonomy/icps_technical_report_en.pdf. [Last accessed on 2018 Sep 28].
12 Szymanski KM, Wei JT, Dunn RL, Sanda MG. Development and validation of an abbreviated version of the expanded prostate cancer index composite instrument for measuring health-related quality of life among prostate cancer survivors. *Urology* 2010; 76: 1245–50.
13 Klotz L, O'Callaghan C, Ding K, Toren P, Dearnaley D, *et al*. Nadir testosterone within first year of androgen-deprivation therapy (ADT) predicts for time to castration-resistant progression: a secondary analysis of the PR-7 trial of intermittent versus continuous ADT. *J Clin Oncol* 2015; 33: 1151–6.
14 Merseburger AS, Björk T, Whitehouse J, Meani D. Treatment costs for advanced prostate cancer using luteinizing hormone-releasing hormone agonists: a solid biodegradable leuprorelin implant versus other formulations. *J Comp Eff Res* 2015; 4: 447–53.

15 Iannazzo S, Pradelli L, Carsi M, Perachino M. Cost-effectiveness analysis of LHRH agonists in the treatment of metastatic prostate cancer in Italy. *Value Health* 2011; 14: 80–9.
16 Drug Search, Korea Research-Based Pharmaceutical Industry Association. Seoul; 2009. Available from: http://www.krpia.or.kr/medicine/mediinfo.asp. [Last accessed on 2018 Sep 12].
17 Samson DJ, Seidenfeld J, Schmitt B, Hasselblad V, Albertsen PC, *et al*. Systematic review and meta-analysis of monotherapy compared with combined androgen blockade for patients with advanced prostate carcinoma. *Cancer* 2002; 95: 361–76.
18 Usami M, Akaza H, Arai Y, Hirano Y, Kagawa S, *et al*. Bicalutamide 80 mg combined with a luteinizing hormone-releasing hormone agonist (LHRH-A) versus LHRH-A monotherapy in advanced prostate cancer: findings from a phase III randomized, double-blind, multicenter trial in Japanese patients. *Prostate Cancer Prostatic Dis* 2007; 10: 194–201.
19 Akaza H, Yamaguchi A, Matsuda T, Igawa M, Kumon H, *et al*. Superior anti-tumor efficacy of bicalutamide 80 mg in combination with a luteinizing hormone-releasing hormone (LHRH) agonist versus LHRH agonist monotherapy as first-line treatment for advanced prostate cancer: interim results of a randomized study in Japanese patients. *Jpn J Clin Oncol* 2004; 34: 20–8.
20 Klotz L, Schellhammer P, Carroll K. A re-assessment of the role of combined androgen blockade for advanced prostate cancer. *BJU Int* 2004; 93: 117–82.
21 Prostate Cancer Trialists' Collaborative Group. Maximum androgen blockade in advanced prostate cancer: an overview of the randomised trials. *Lancet* 2000; 355: 1491–8.
22 Smith MR, Lee H, Nathan DM. Insulin sensitivity during combined androgen blockade for prostate cancer. *J Clin Endocrinol Metab* 2006; 91: 1305–8.
23 Levine GN, D'Amico AV, Berger P, Clark PE, Eckel RH, *et al*. Androgen-deprivation therapy in prostate cancer and cardiovascular risk: a science advisory from the American Heart Association, American Cancer Society, and American Urological Association: endorsed by the American Society for Radiation Oncology. *Circulation* 2010; 6: 833–40.
24 Berruti A, Dogliotti L, Terrone C, Cerutti S, Isaia G, *et al*. Changes in bone mineral density, lean body mass and fat content as measured by dual energy x-ray absorptiometry in patients with prostate cancer without apparent bone metastases given androgen deprivation therapy. *J Urol* 2002; 167: 2361–7.
25 Ahmadi H, Daneshmand S. Androgen deprivation therapy: evidence-based management of side effects. *BJU Int* 2013; 111: 543–8.
26 Schulman C, Irani J, Aapro M. Improving the management of patients with prostate cancer receiving long-term androgen deprivation therapy. *BJU Int* 2012; 109 Suppl 6: 13–21.
27 Smith MR, Egerdie B, Hernández Toriz N, Feldman R, Tammela TL, *et al*. Denosumab in men receiving androgen-deprivation therapy for prostate cancer. *N Engl J Med* 2009; 8: 745–55.
28 Anderson J, Al-Ali G, Wirth M, Gual JB, Gomez Veiga F, *et al*. Degarelix versus goserelin (+ antiandrogen flare protection) in the relief of lower urinary tract symptoms secondary to prostate cancer: results from a phase IIIb study (NCT00831233). *Urol Int* 2013; 90: 321–8.
29 Choi H, Chung H, Park JY, Lee JG, Bae JH. The influence of androgen deprivation therapy on prostate size and voiding symptoms in prostate cancer patients in Korea. *Int Neurourol J* 2016; 20: 342–8.
30 Fernandes VS, Barahona MV, Recio P, Martínez-Sáenz A, Ribeiro AS, *et al*. Mechanisms involved in testosterone-induced relaxation to the pig urinary bladder neck. *Steroids* 2012; 77: 394–402.
31 Haider KS, Haider A, Doros G, Traish A. Long-term testosterone therapy improves urinary and sexual function, and quality of life in men with hypogonadism: results from a propensity matched subgroup of a controlled registry study. *J Urol* 2018; 199: 257–65.
32 Tombal B, Miller K, Boccon-Gibod L, Schröder F, Shore N, *et al*. Additional analysis of the secondary end point of biochemical recurrence rate in a phase 3 trial (CS21) comparing degarelix 80 mg versus leuprolide in prostate cancer patients segmented by baseline characteristics. *Eur Urol* 2010; 57: 836–42.



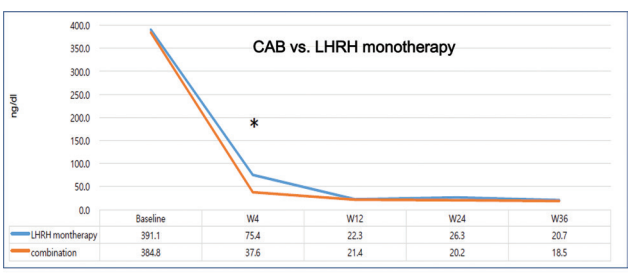
Baseline	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60
N=292	N=247	N=226	N=218	N=214	N=207	N=199

Supplementary Figure 1: Visit completion profile.



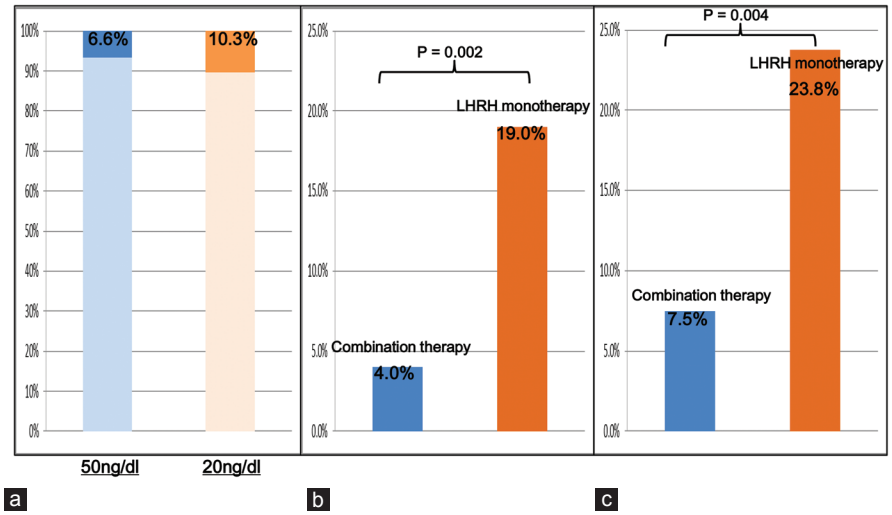
	Baseline	Week 4	Week 12	Week 24	Week 36	Week 48	Week 60
Therapeutic regimen	95.5%	82.2%	78.3%	71.5%	67.1%	62.1%	53.1%
Lab profile	87.3%	82.2%	75.5%	71.3%	70.5%	68.3%	65.4%
Serum Testosterone	98.0%	83.5%	76.2%	73.5%	72.2%	70.1%	67.2%
EPIC Questionnaire	91.4%	74.6%	45.2%	68.1%	34.5%	62.2%	34.1%

Supplementary Figure 2: Therapeutic regimen completion profile.

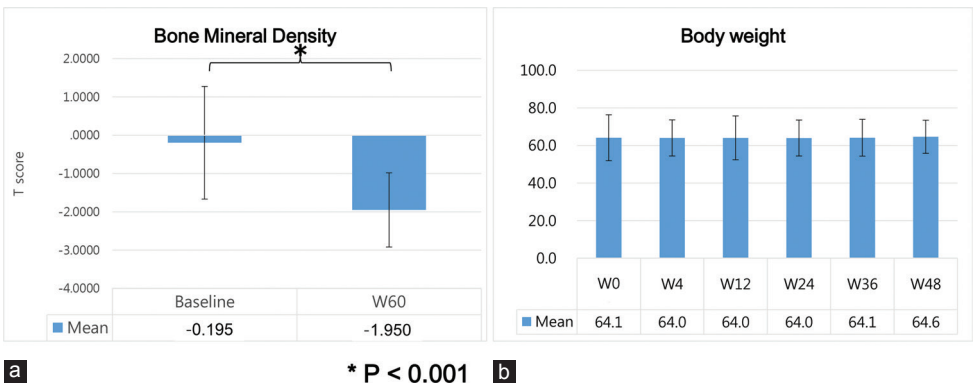


* P < 0.05

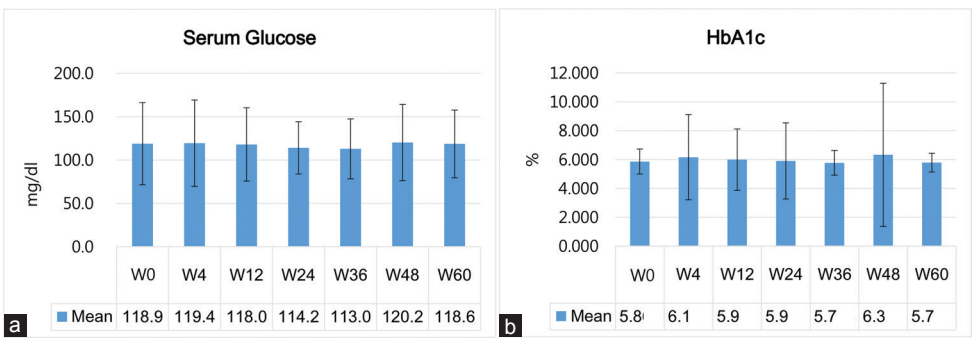
Supplementary Figure 3: Testosterone profile.



Supplementary Figure 4: (**a**) The proportion of breakthrough with castration cutoff value of 50 ng/dL and 20 ng/dL, comparative analysis of combination therapy versus luteinizing hormone-releasing hormone agonist monotherapy with castration cutoff value of (**b**) 50 ng/dL and (**c**) 20 ng/dL.



Supplementary Figure 5: Mean changes in (**a**) bone mineral density (T-score) from baseline to last follow-up visit (week 60) and in (**b**) body weight during the study period.



Supplementary Figure 6: Mean changes in (**a**) serum glucose and in (**b**) glycated hemoglobin during the study period.

Supplemental Table 1. Uni- and multivariate logistic regression analyses results for evaluating variables associated with castration

	Univariate			Multivariate		
Variables	OR	95% CI	P	OR	95% CI	P
Age	1.027	0.986-1.070	0.207			
BMI	1.060	0.959-1.171	0.255			
DM, yes	1.077	0.486-2.389	0.855			
HTN, yes	0.861	0.455-1.628	0.645			
Pre-biopsy PSA	1.001	1.000-1.002	0.232			
Prostate volume	1.010	0.994-1.026	0.213			
Biopsy Gleason Score						
6	Reference					
7	0.527	0.157-1.768	0.300			
≥8	0.393	0.120-1.286	0.123			
Percent of positive core number	1.001	0.993-1.010	0.735			
Clinical T stage						
≤2	Reference					
≥3	1.125	0.603-2.100	0.712			
Clinical N stage						
N0	Reference			Reference		
N1	1.894	0.913-3.928	0.086	1.899	0.816-4.420	0.137
Clinical M stage						
M0	Reference					
M1	1.715	0.858-3.428	0.127			
Therapeutic regimen						
LHRH agonist monotherapy	Reference			Reference		
CAB	2.181	1.008-4.716	0.048	1.621	0.704-3.734	0.257

BMI: body mass index; CAB: complete androgen blockade; CI: confidence interval; DM: diabetes mellitus; HTN: hypertension; LHRH: luteinizing hormone-releasing hormone; OR: odd ratio; PSA: prostate-specific antigen

Supplemental Table 2. Uni- and multivariate logistic regression analyses results for evaluating variables associated with breakthrough

	Univariate			Multivariate		
Variables	OR	95% CI	P	OR	95% CI	P
Age	0.904	0.847-0.966	0.003	0.904	0.840-0.973	0.007
BMI	1.315	1.095-1.578	0.003	1.328	1.076-1.639	0.008
DM, yes	0.311	0.039-2.468	0.269			
HTN, yes	2.078	0.654-6.603	0.215			
Pre-biopsy PSA	0.994	0.985-1.004	0.236			
Prostate volume	0.970	0.931-1.011	0.147			
Biopsy Gleason Score						
6	Reference					
7	0.606	0.126-2.913	0.532			
≥8	0.463	0.087-2.457	0.366			
Percent of positive core number	0.995	0.979-1.010	0.482			
Clinical T stage						
≤2	Reference					
≥3	1.233	0.407-3.735	0.711			
Clinical N stage						
N0	Reference					
N1	1.129	0.371-3.432	0.831			
Clinical M stage						
M0	Reference			Reference		
M1	0.276	0.061-1.264	0.095	0.555	0.235-1.311	0.179
Therapeutic regimen						
LHRH agonist monotherapy	Reference			Reference		
CAB	0.177	0.062-0.504	0.001	0.113	0.034-0.377	<0.001

BMI: body mass index; CAB: complete androgen blockade; CI: confidence interval; DM: diabetes mellitus; HTN: hypertension; LHRH: luteinizing hormone-releasing hormone; OR: odd ratio; PSA: prostate-specific antigen

Supplemental Table 3. Subgroup analysis of efficacy profile according to the initial luteinizing hormone-releasing hormone (LHRH) agonist preparations regardless of initial therapeutic regimen (complete androgen blockade or LHRH agonist monotherapy)

Total (n =254)	Leuprolide (n=158)	Goserelin(n=72)	Triptorelin (n=24)	P
Castration, yes	72.1% (n=114)	88.9% (n=64)	91.7% (n=22)	0.002
Breakthrough, yes	5.0% (n=8)	8.3% (n=6)	8.3% (n=2)	0.525

Supplemental Table 4. Comparative analyses results of variables between initial LHRH agonist monotherapy group and complete androgen blockade group

N(%) or mean±SD	LHRH monotherapy (N=42)	Complete androgen blockade (N=200)	P
Age	75.3 ± 8.4	74.8 ± 6.9	0.706
BMI	23.6 ± 3.2	23.4 ± 3.1	0.712
DM			0.824
Yes	7 (16.7)	31 (15.5)	
No	32 (76.2)	118 (59.0)	
unknown	3 (7.1)	51 (25.5)	
HTN			0.592
Yes	16 (38.1)	69 (34.5)	
No	24 (57.1)	81 (40.5)	
unknown	2 (4.8)	50 (25.0)	
Pre-biopsy PSA, ng/mL	30.6 ± 56.8	210.6 ± 450.3	<0.001
Prostate volume, mL	40.2 ± 18.8	43.9 ± 26.5	0.421
Biopsy Gleason Score			0.016
6	9 (21.4)	19 (9.5)	
7	18 (42.9)	41 (20.5)	
≥8	6 (14.3)	51 (25.5)	
unknown	9 (21.4)	89 (44.5)	
Percent of positive biopsy core number	45.8 ± 29.3	72.5 ± 37.5	<0.001
Clinical T stage			0.101
≤2	19 (45.2)	68 (34.0)	
≥3	19 (45.2)	124 (62.0)	
unknown	4 (9.5)	8 (4.0)	
Clinical N stage			0.002
N0	34 (81.0)	125 (62.5)	
N1	4 (9.5)	67 (33.5)	
unknown	4 (9.5)	8 (4.0)	
Clinical M stage			<0.001
M0	36 (85.7)	115 (57.5)	
M1	2 (4.8)	77 (38.5)	
unknown	4 (9.5)	8 (4.0)	

BMI: body mass index; CI: confidence interval; DM: diabetes mellitus; HTN: hypertension; LHRH: luteinizing hormone-releasing hormone; PSA: prostate-specific antigen