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The Long-Term Impact of 5-alpha Reductase Inhibitors on the Development of Bladder Cancer and the Need for Radical Cystectomy: A Nationwide Observational Study

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Purpose: To investigate the long-term effects of taking 5-alpha reductase inhibitors (5ARIs) on the development of bladder cancer (BC) and the implementation of radical cystectomy (RC), a standard procedure for advanced BC.

Materials and Methods: From the National Health Insurance Sharing Service database, males aged over 40 years who underwent serum prostate-specific antigen testing from 2006 through 2017 were identified, which is required for the prescription of 5ARIs. The association between the administration duration of 5ARIs and the practice for BC was analyzed.

Results: Of the 3,843,968 subjects, 1,514,713 (39.4%) took 5ARIs for an average of 1.53 years, remaining 2,329,255 (60.6%) as non-5ARI counterparts. The incidence of BC was higher in the non-5ARI than in the 5ARI group (1.25% *vs*. 0.87%, p<0.001), as was the implementation rate of RC (11.1% *vs*. 10.4%, p=0.037). In a multivariate analysis, the non-5ARI group had a significant risk of BC (hazard ratio [HR]=2.289, 95% confidence interval [CI]=2.241–2.338) and RC (HR=2.199, 95% CI=2.061–2.348) than the 5ARI group. Among the 5ARIs group, though the incidence of BC was maintained (slope=-0.002 per year, p=0.79) after an initial increase for two years, the rate of RC decreased (slope=-1.1, p<0.001) consistently for ten years during the administration.

Conclusions: Compared to the untreated group, 5ARIs use was associated with lower rates of BC and RC. In contrast to the increase in BC seen with short-term use of less than two years, long-term use of 5ARIs decreased the rate of RC in a duration-dependent manner for ten years, suggesting a strategy to prevent disease progression.

Keywords: 5-Alpha reductase inhibitors; Cystectomy; Incidence; Urinay bladder neoplasms

INTRODUCTION

Bladder cancer (BC) is the seventh most common cancer in men worldwide and is the most common urinary tract cancer, following prostate cancer [1]. While 75% of BCs are found in non-muscle invasive (NMIBC)

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stages and have a 5-year survival rate of over 90%, 25% are found in muscle-invasive (MIBC) stages or higher, in which case the 5-year survival rate reduces to less than 60%. In contrast to NMIBC, curable mainly by endoscopic transurethral resection of the bladder tumor (TURB), radical cystectomy (RC) with bilateral pelvic lymph node dissection, the standard treatment for a muscle-invasive disease, is associated with significant postoperative morbidity and complications [2,3]. Therefore, the strategies to prevent or slow the progression of NMIBC to MIBC or prevent the need for RC remain a clinical need.

Considering the typical endocrine-related epidemiology of BC that is 3–4 times more prevalent in men than women and more often advanced [4], several studies in preclinical settings have focused on the role of androgen signaling in the tumorigenesis of BC [5-7], as well as in clinical and sizeable population-based cohort studies [8-10]. The 5-alpha reductase inhibitors (5ARIs; including finasteride and dutasteride) inhibit the conversion of testosterone to dihydrotestosterone (DHT), thereby inhibiting prostate growth, and have a long history of clinical use in the management of benign prostatic hyperplasia since their approval in the late 90s [11] and early 2000s [12], respectively. A recent systematic review and meta-analysis similarly reported that 5ARIs might represent a potential strategy to reduce BC recurrence rate, mainly in patients with NMIBC [13]. However, studies to date have not demonstrated whether taking 5ARIs reduces the progression of BC or prevents high-grade cancer requiring RC. If the use of 5ARIs has a preventive effect on the course of bladder cancer requiring RC, a duration-proportional effect would be observed. In this background, this study aims to investigate the impact of 5ARIs on the development of BC and the implantation of RC utilizing national-wide data for a decade.

MATERIALS AND METHODS

1. Data source and study population

South Korea's National Health Insurance covers most people (98%) and provides consistent healthcare coverage. The National Health Insurance Shared Service (NHISS) database provides most medical data, including diagnosis codes, procedures, prescription drugs, and sequelae, including death. Men aged 40 years and older with a serum prostate-specific antigen (PSA) test from 2006 to 2017 were identified from the NHISS database. They were selected for inclusion in the study, given that pre-dose PSA testing is highly recommended before prescribing a 5ARI due to the potential impact on future levels. The PSA testing codes utilized in this study were B5490, C4280, and C7428. The codes for currently available 5ARIs were 159001ATB (finasteride 5 mg) and 458801ACS (dutasteride 0.5 mg), respectively.

Patients newly diagnosed with BC and registered in the NHISS with an International Classification of Diseases, 10th revision code of C67 and V193/194 during the study period were collected. RC, including open and laparoscopic approaches, was identified using reimbursement codes (R3481 and R3482). Robot-assisted RC, which the current version of NHISS did not reimburse, was the only exclusion criteria for this study, considering a relatively minor portion compared to other approaches during the study period.

All personal identification numbers were encrypted before data processing to comply with the privacy guidelines of the Health Insurance Portability and Accountability Act. The Institutional Review Board of Yeungnam University Hospital investigated and approved this study (approval number: YUMC-2019-11-012-002).

2. Study design and endpoints

The subjects were divided into 2 groups: the 5ARI group that prescribed two kinds of 5ARIs (including 126 generics for finasteride 5 mg and 44 generics for dutasteride 0.5 mg) and their counterparts as a non-5ARI group. The association between using 5ARI and the newly registered BC was analyzed. The ultimate goal of the study was to determine whether 5ARI administration would have a sustained long-term effect on the development of bladder cancer or the need for RC. First, the incidence of BC and RC among the patients registered with BC between the 5ARI and the non-5ARI group was compared. Then the difference in the frequency of BC and RC based on the duration of the 5ARIs was investigated.

3. Statistical analysis

To remove the impact of accumulated data from patients in the previous year before the study period and unfinalized data collection from the insurance surveillance system for patients in the last year, the data from 2006 and 2017 were removed for the final

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analysis. Given that the preventive effect on the development of bladder cancer is most likely a result of long-term use of 5ARIs and that dutasteride has a relatively long half-life of 5 weeks, the most extended continuous dosing period was considered the duration of treatment with pauses of more than 3 months. Breaks of administration of less than 3 months were regarded as ongoing treatment. The chi-square test was utilized to compare categorical variables between groups. A multivariable Cox regression test adjusted for age was utilized to compare the 2 groups. A linear regression method was used to identify trends between the duration of 5ARIs, BC development, and RC implementation. For all comparisons, statistical significance was accepted for p-values <0.05. All statistical analyses were performed using SAS 9.4 Software (SAS Institute Inc.).

RESULTS

1. The comparison between the 5ARI group and the non-5ARI group in the development of bladder cancer

Of the 3,843,968 subjects collected, 1,514,713 (39.4%) took 5ARIs for a mean of 1.53 years (standard deviation of 2.21 years), with the remaining 2,329,255 (60.6%) as non-5ARIs. The national distributions of people taking 5ARIs, developing bladder cancer, and undergoing RC during the study period were summarized in Fig. 1. The incidence of BC was higher in the non-5ARI (detected in 29,077 subjects, 1.25%) than in the 5ARI group (seen in 13,208 subjects, 0.87%; p<0.001). Among the registered subjects with BC, RC was performed more frequently in non-5ARI (3,237 cases, 11.1%) than in the 5ARI group (1,380 cases, 10.4%, p=0.037). Multivariate analysis adjusted with age, the non-5ARI group had a significant risk of developing BC (hazard ratio [HR]=2.289, p<0.001; 95% confidence interval [CI]=2.241–2.338) and implantation of RC (HR=2.199, p<0.001; 95% CI=2.061–2.348) than the 5ARI group.

2. The association between the duration of 5ARI administration and the implementation of radical cystectomy

Among the people taking 5ARIs, the number of patients who underwent RC decreased inversely with the duration of the drug (Table 1). Though the percentage of the patients with BC was maintained (slope=-0.002 per year, p=0.79) after an initial increase for 2 years (Fig. 2), the portion of the patients managed with RC among the detected BC was decreased consistently for 10 years of the follow-up period (slope=-1.1 per year, p<0.001; Fig. 3).

DISCUSSION

Despite ongoing technological advances to reduce complications, RC remains a procedure with a high complication rate. In a recent systematic review of articles published up to 2020, the 90-day complication rate after RC was approximately 58.5% (range: 36.1%–80.5%), with an average reoperation rate of 12.3%. The

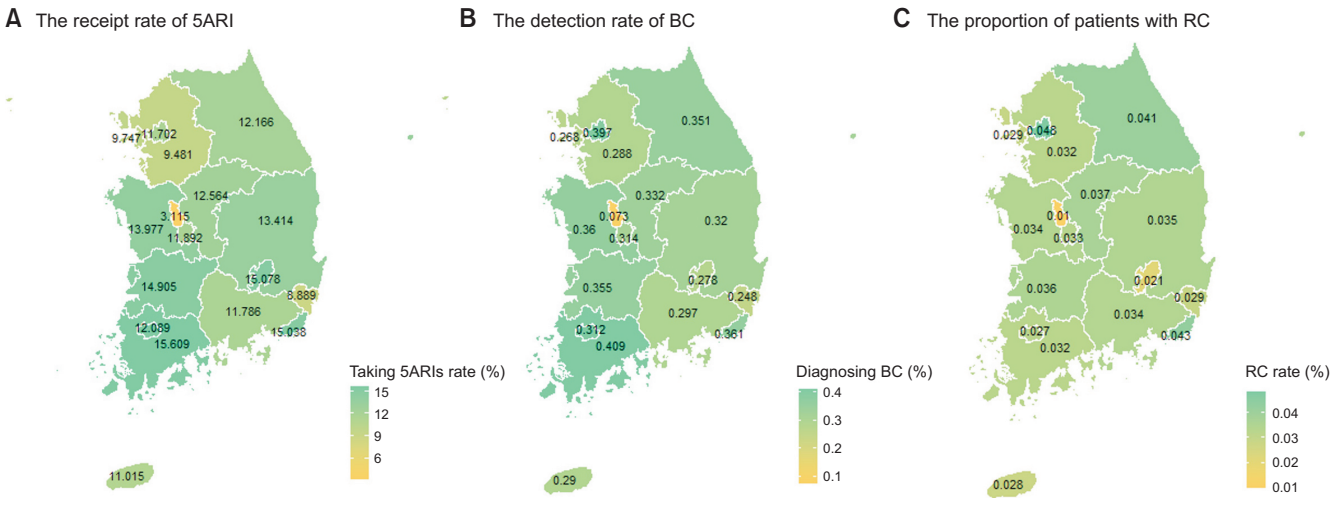

Fig. 1. (A) The national distribution of people taking 5ARIs, (B) developing BC, and (C) undergoing RC. 5ARI: 5-alpha reductase inhibitor, BC: bladder cancer, RC: radical cystectomy.

Table 1. Summary of BC development and RC implementation among subjects receiving 5ARIs

The duration of 5ARIs administration	Subjects with 5ARIs (n)	Subjects detected with BC (n)	Subjects managed with RC among the cases with BC (n)	Percentage of BC patients among the subjects with 5ARIs	Percentage of RC cases among the subjects with 5ARIs
1 y	944,951	6,802	883	0.719825684	0.093443999
2 y	193,514	2,120	221	1.095527972	0.114203624
3 y	109,737	1,216	116	1.108103921	0.105707282
4 y	75,358	861	65	1.142546246	0.086254943
5 y	55,214	635	35	1.150070634	0.06338972
6 y	41,343	497	23	1.20213821	0.055632151
7 y	30,072	353	14	1.173849428	0.046554935
8 y	22,335	268	14	1.199910454	0.062681889
9 y	16,200	171	6	1.055555556	0.037037037
10 y	11,200	136	2	1.214285714	0.017857143
Over 10 y	14,789	149	1	1.007505578	0.006761782
Total	1,514,713	13,208	1,380		

BC: bladder cancer, RC: radical cystectomy, 5ARIs: 5-alpha reductase inhibitors.

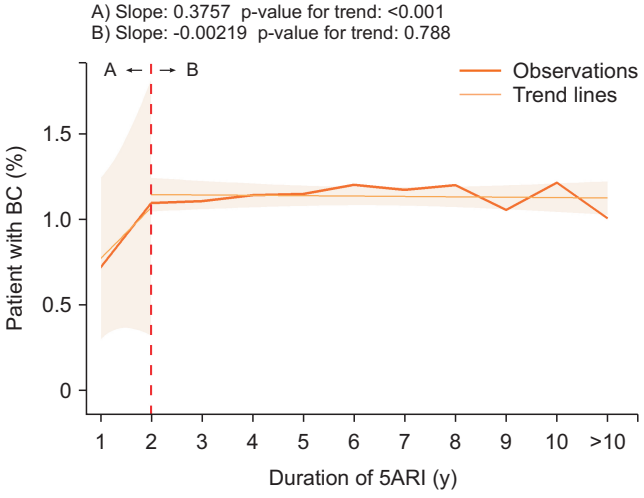

Fig. 2. The slope between the duration of the administration of 5ARIs and the development of BC. 5ARIs: 5-alpha reductase inhibitors, BC: bladder cancer.

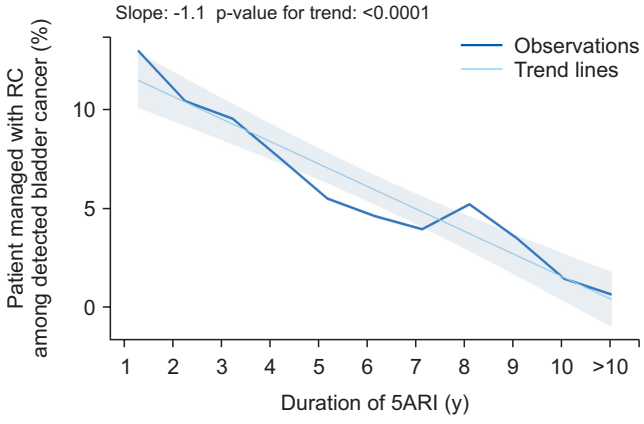

Fig. 3. The slope between the duration of the administration of 5ARI and the implementation of RC. 5ARIs: 5-alpha reductase inhibitors, RC: radical cystectomy.

30-day mortality rate was 2.1% (0.0%–3.7%), and the 90-day mortality rate was 4.7% (0.0%–7.0%) [14]. Even in the era of robotic surgery, complication rates reported by the International Robotic Cystectomy Consortium, the most representative and popular database on robot-assisted RC, were stable between 2001 and 2011, with an overall complication rate of 60%, including 28% of high-grade complications [15]. Considering that age and comorbidities have been found to be the best predictors of these complications [14], complication rates are expected to increase further in Korea, where the average age at the time of RC is aging from 64.6 years in 2010 to 68.5 years in 2021 [16].

As an attempt to evaluate the chemopreventive effect of 5ARIs, especially for the aggravation of the tumor stage that requires RC eventually, we investigated its role from the national-wide database. The bladder is embryologically derived primarily from the urogenital sinus, which in males also gives rise to the prostate, for which the androgen receptor (AR) signals correlate with BC development and progression both *in vitro* and *in vivo* [6]. Boorjian et al [5] reported that the AR was expressed in 26 (53.1%) of 49 BCs and 32 (86.5%) of 37 non-neoplastic bladder epithelium specimens evaluated. Because AR expression decreased with the advanced stage, this study suggests that the loss of AR expres-

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sion is associated with MIBC. Similarly, it has recently been reported that 5ARIs attenuate BC progression by inhibiting the conversion of testosterone to DHT in the presence of membrane AR in BC. At the same time, dutasteride reduces BC progression by blocking SRD5A1, one of the target proteins of 5ARIs [7].

Therefore, reversely, suppressing the androgen signal by reducing the bioavailable androgen may be beneficial in preventing the progression of NMIBC or inhibiting the tumorigenesis of MIBC. Indeed, the current systematic review and meta-analysis consistently suggest the clinical relevance of administering 5ARIs for the preventive purpose of BC. Analyzing nine studies, Kim et al [17] reported that the incidence of BC was significantly reduced (relative risk [RR]=0.69, 95% CI=0.58–0.81) when 5ARIs treatment was initiated before diagnosing BC. When treatment was started after diagnosis of BC, 5ARIs reduced cancer-specific mortality (RR=0.29, 95% CI=0.20–0.42). Based on eight clinical trials, Creta et al [13] reported that the relative risk of BC recurrence after TURB is significantly lower in patients undergoing therapy with 5ARIs (RR=0.50, 95% CI=0.30–0.82).

Going a step further, this is the first report to focus on the long-term association between the implementation of RC and the administration of 5ARIs, utilizing broad population data of nearly 4 million people using an observational dataset from the NHISS. When adjusted for age, those who received 5ARIs had a 45% reduction in the odds of RC compared to those who did not. The proportion of patients who underwent RC among detected BC continued to decline over the 10 years following 5ARI use. However, for the development of BC, the administration of 5ARIs within 2 years increased the odds of BC enrollment. This observation agrees well with results from a previous observational study that matched 93,197 men who started 5ARI treatment 1:1 with men who did not begin 5ARIs. While there was no significant difference in BC diagnosis within two years of 5ARI use (HR=1.05, 95% CI=0.82–1.32), the risk of BC diagnosis was significantly lower in the 5ARI group after 2 or more years of 5ARI use (HR=0.82, 95% CI=0.79–0.94) [10]. An et al [18] recently reported the outcome of a 1:1 propensity-matched study utilizing the nationwide cohort comparing 5,300 men diagnosed with BC. Compared with the control group, the 5ARI group had a lower risk of mortality (HR=0.83, 95% CI=0.75–0.91), bladder instillation (HR=0.84, 95% CI=0.77–0.92), and RC (HR=0.74, 95% CI=0.62–0.88). In particular, the protective effect of 5ARIs against RC was observed only in those taking them for more than 2 years (730 days, HR=0.62; 95% CI=0.42–0.91) compared to those taking them for less than two years (HR=0.74, 95% CI=0.51–1.08).

The authors are well aware of the limitation of this study. First of all, even though our study illustrates the benefits of preventing radical surgery in the management of BC from the national-wide investigation, cause and effect are unclear on the outcome because of the observational characteristics of the study design. To identify a causal relationship, a longer-term follow-up should have confirmed the difference between 5ARIs and no ARIs in a group with similar oncologic features. The biological characteristics of the tumor, including the stage and grade of BC, were not adjusted between groups in this study because of the lack of information from the currently available NHISS dataset. However, in that approximately 40% of subjects took a 5ARI, this study is similar to the prevention results of recently reported 1:1 matched studies, which showed a reduction in BC diagnoses in 93,197 [8] and 5,300 [18] men who initiated 5ARI treatment compared to men who did not start a 5ARI. Second, we did not investigate the clinical outcomes between different formulations of 5ARIs, including finasteride and dutasteride, currently available on the market. In a previous study [8], only finasteride was found to have a protective effect against BC among different types of 5ARIs. Therefore, future studies should be conducted to identify differences in effectiveness between drugs. Third, clinical guidelines strongly recommend that when prescribing 5ARIs, appropriate criteria such as baseline PSA levels (recommended when initial PSA levels are greater than or equal to 1.4 ng/mL) and prostate volume (recommended when the prostate volume is greater than or equal to 40 mL) should be used to select appropriate patients. However, not all 5ARIs are prescribed exclusively by urologists, so cases that did not undergo PSA testing before the administration were not included in this study. Forth, patients who underwent robotic-assisted RC were not assigned a separate code in NHISS, so the difference between the 5ARI and non-5ARI groups was unknown and excluded from the study; however, the number of cases was estimated to be less than 100 cases in each year during the study period, which covered the ten years from 2006–2017, so it is unlikely to have

a significant impact on the results.

As such, the results of this study are more exploratory than conclusive and spur prospective studies. Nevertheless, given that BPH is found in many rapidly aging men and that 5ARIs have long been used clinically to halt the progression of the disease, prospective studies with these agents could be relatively easy to conduct. In fact, in South Korea in 2019, 51.3% of patients at risk for progression of BPH were prescribed 5ARIs [19]. Given the enormous morbidity and mortality associated with RC, our findings suggest 5ARIs as chemopreventive agents for advanced BC. Our results highlight the value of designing future studies.

CONCLUSIONS

Compared to the untreated group, 5ARI use was associated with lower rates of BC and RC. In contrast to the increase of BC seen with short-term use of less than 2 years, long-term use of 5ARIs for ten years decreased the rate of RC in a duration-dependent manner, suggesting a strategy to prevent disease progression. However, due to the lack of causality in an observational study design, these results stimulate the need for randomized clinical trials to develop the clinical acceptance of the 5ARIs to prevent the progression of BC.

Conflict of Interest

The authors have nothing to disclose.

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None.

Author Contribution

Conceptualization: YHK, NHS. Data curation: HSK, YJB. Formal analysis: SWK, NHS. Funding acquisition: YHK. Investigation: SWK, YJB. Methodology: YJB, NHS. Project administration: SWK. Resources: YHK, YJB. Software: HSK, SWK. Supervision: NHS. Validation: NHS, JHP. Visualization: YJB, JHP. Writing – original draft: JHP. Writing – review & editing: YHK, NHS.

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