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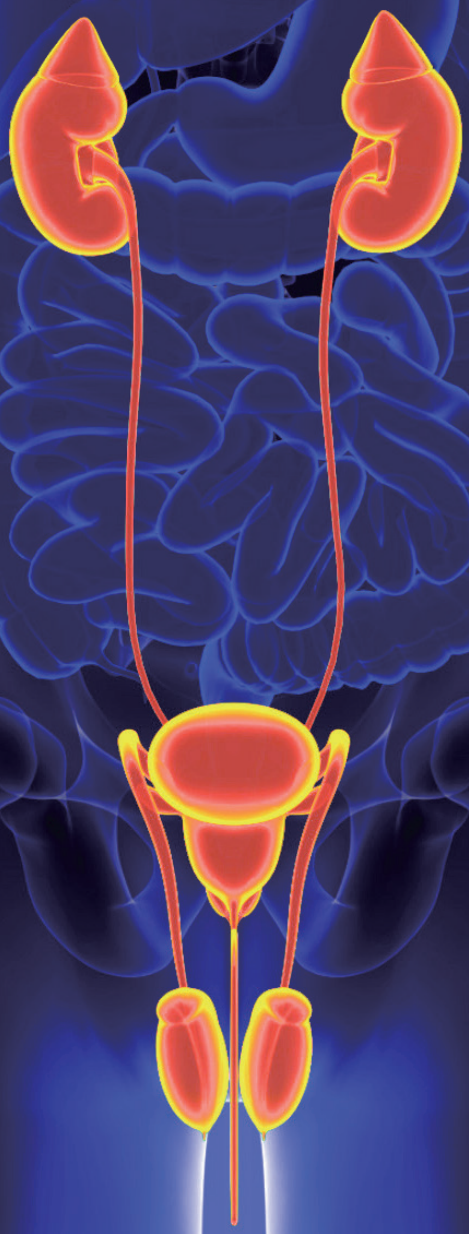

Highlight of JUO in This Issue: The Landscape of Epidemiology in Urologic Cancers

The Korean Urological Oncology Society

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The Korean Urological Oncology Society

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Aims and Scope

The *Journal of Urologic Oncology* (JUO) publishes practical, timely, and relevant clinical and basic science research articles addressing any aspect of urologic oncology. JUO is of interest to urologists, oncologists, radiologists, and clinicians treating patients and to those involved in research on diseases of urologic oncology. JUO publishes original articles, review articles, editorials, rapid communications, brief reports, and letters to the editor. All submitted manuscripts will be peer-reviewed by a panel of experts before being considered for publication. The following is a list of the general topics covered by JUO: prostate cancer; urothelial cancer; kidney cancer; testicular cancer; other genitourinary malignancies; epidemiology, etiology, and pathogenesis; and the detection, diagnosis, prevention, and treatment of urologic oncologic diseases.

About the Journal

The *Journal of Urologic Oncology* (JUO; pISSN 2951-603X, eISSN 2982-7043) is the official journal of the Korean Urological Oncology Society and is an international peer-reviewed journal. The ISO abbreviated journal name is J Urol Oncol. JUO is published three times per year, on the last day of March, July, and November. The journal periodically publishes supplemental issues devoted to areas of current interest to the urologic oncology community. It was first published on March 31, 2003 with Volume 1 and Number 1 under the name Korean Journal of Urological Oncology (pISSN 2234-4977, eISSN 2233-5633), and it was renamed as *Journal of Urologic Oncology* in March 2023. For submission instructions, subscription, and all other information, please visit http://www.e-juo.org.

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Department of Urology, Asan Medical Center, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Korea
Tel: +82-2-3010-3740 Fax: +82-2-477-8928 E-mail: igjeong@amc.seoul.kr

Editorial Office
Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-0817 Fax: +82-2-742-4665 E-mail: journal@e-juo.org

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Editorials

Topic of JUO in This Issue: The Landscape of Epidemiology in Urologic Cancers

Invited Reviews

Topic Articles

Original Articles

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EDITORIAL

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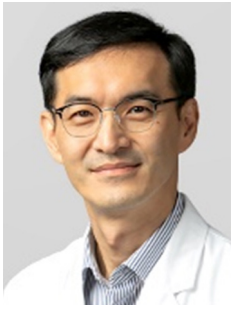
Journal of Urologic Oncology, a Name That Speaks for Itself



Sun Il Kim

President of Korean Urological Oncology Society
Department of Urology, Ajou University School of Medicine, Suwon, Korea

Corresponding author: Sun Il Kim
Email: sikimuro@ajou.ac.kr
https://orcid.org/0000-0003-2674-983X

Welcome to the inaugural issue of the *Journal of Urologic Oncology* (JUO).

Since its foundation in 2003, Korean Journal of Urological Oncology (KJUO), the official journal of the Korean Urological Oncology Society, has published original articles, case reports, and reviews on urological oncology. Published 4 times a year, it has served as a reliable medium for not only our society members but also nonmember urologists at home and abroad to communicate their latest research results and opinions on urological oncology. It has also provided urology residents with a fast and accessible way to achieve the minimum academic requirements for Urology certification. Over the past 20 years, KJUO has made significant progress both quantitatively and qualitatively. Thanks to the contributions of loyal members, dedicated editorial team and thorough peer-reviewers review, it was listed in the Korean Citation Index in 2017, and maintains its status after re-examination in 2020, publishing an average of 26 high-quality papers per year. However, the goal of a scientific paper is not just publication. Its vitality is maintained when fellow scientists read it, inspiring them, and ultimately making them cite the paper in new research. Looking back at the vitality of our papers, the picture is clearly disappointing. Of the 150 papers published between 2015 and 2020, only 28 papers were cited at least once, with 81% of papers going unnoticed. How can this discrepancy exist between self-proclaimed "high quality" and poor citation index? Is the average quality of the papers not good enough? Is the National Research Foundation of Korea doing the right job to keep Korean Citation Index reliable? The sad truth lies within us. KJUO has not received the attention it deserves from its members as the official journal of Korean Urological Oncology Society (KUOS). In fact, we were more interested in getting our work published in a reputable journal than building up the reputation of our journal itself. Is change possible, or is change necessary at all? The answer is yes. The field of urological oncology has not stopped growing worldwide in recent years, at a time when other urological subspecialties have been somewhat stagnant. Amid this global expansion, KUOS has become a large organization attracting young, seriously committed members who aspire to become world leaders in their field. Yes, we see great potential in the new generation. Now, we must provide a more open space where we can disclose our academic achievements more easily,

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more expansively and faster so that our works can be noticed by a wider audience. We must sacrifice the convenience of writing in our own language to gain international attention. A more open space should not be limited to ourselves. We must turn our attention to the needs of our international colleagues and invite them to publish their valuable works in our journal. Science Citation Index Expanded contains only a handful of journals commonly grouped into the category of Oncology and the category of Urology and Nephrology. We must do our part to expand the list and provide publication opportunities to fellow researchers by collaborating with world's leading experts in urological oncology.

I would like to congratulate Professor C. Kwak, the past President of KUOS and the Editor-in-Chief of JUO who had the inspiration and courage to make the difficult decision to convert KJUO to JUO last year amid the turmoil of COVID-19.

I would also like to commend the dedication of Professor Y.H. Ko, the Deputy Editor of JUO and the task force team that made the inaugural issue of JUO possible.

• Conflicts of Interest: The author has nothing to disclose.

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EDITORIAL

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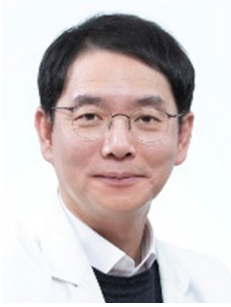
Journal of Urologic Oncology Is Embarking on a Journey to a Global Audience



Cheol Kwak

Editor-in-Chief
Department of Urology, Seoul National University College of Medicine, Seoul, Korea

Corresponding author: Cheol Kwak
Email: mdrafael@snu.ac.kr
https://orcid.org/0000-0002-1987-2111

The *Journal of Urologic Oncology* (JUO) is taking its first steps toward the wider world!

JUO is the official journal of the Korean Urological Oncology Society (KUOS) and is an international peer-reviewed journal. The KUOS started as the "Urological Cancer Research Group" in 1988 and started official academic activities as the KUOS in 1991. For the past 30 years, the hard work and dedication of past presidents, executive directors, directors, committee members, and various members have served as the basis for our society to make rapid progress despite challenges and to become the leading community in the field of urology. The former *Korean Journal of Urological Oncology*, which published its first issue in 2003, is being reborn as JUO in celebration of its 20th anniversary. We will leverage the capabilities of all members so that both domestic and international researchers can submit excellent papers, and we hope that JUO will be listed in Science Citation Index Expanded in the near future.

JUO will publish practical, timely, and relevant clinical and basic science research articles addressing all aspects of urologic oncology, especially 3 primary urinary cancers: prostate, kidney, and bladder. JUO is of interest to urologists, oncologists, radiologists, clinicians treating patients, and those involved in research into diseases of urologic oncology. Every issue of JUO will focus on a timely topic in the field of urologic oncology. This month's issue of JUO investigates the detailed epidemiological characteristics of urologic oncology and provides the most recent updates from renowned authors across the globe.

Three review articles from the world's leading researchers were invited for this issue. Professor I.Y. Kim from Yale University (USA) presents an update on prostate cancer immunotherapy, including all currently available modalities or investigative methods, covering immune checkpoint inhibitors, vaccine-based treatments, adoptive cell therapy, and oncolytic virus therapy [1]. Professor S. Akamatsu from Kyoto University (Japan) carefully summarized the current status and the future of plasma cell-free DNA analysis in urinary malignancies, including prostate, bladder, and kidney cancers, in a very comprehensive way, with beautiful and informative illustrations [2]. To enhance our understanding of the epidemiological characteristics

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of prostate malignancies in Asia, which have not been highlighted in a comparative way in previous publications, we invited professor T. Kimura from Jikei University (Japan) to write an article, and he wonderfully explained the unique epidemiology of prostate cancer in Asia, which is distinct from that in Western countries [3].

In the same context as our focus in this month's issue, we planned key titles and invited domestic urologists with worldwide renown. Professor H.D. Yuk from Seoul National University meticulously analyzed the epidemiology of urologic cancers in Korea over the last 2 decades [4]. Professor S. Yoo from the same institution investigated the risk factors for bladder cancer utilizing nationwide data. Given the low prostate-specific antigen (PSA) testing uptake in many Asian countries, negatively influenced by contemporary Western guidelines [5]. Professor Y.H. Ko from Yeungnam University presented a study showing that the prescription of 5-alpha reductase inhibitors, which encourages repeated PSA testing to select patients based on proper criteria, enhances the detection of prostate cancer in Korea [6]. Professor J. Choi from the Catholic University of Korea described practice patterns for small renal masses among 176 Korean urologists across the country and identified vital indicators in action plans for active surveillance [7].

In addition to the content presented above, interesting original articles were published in this issue, with topics including the 10-year oncological outcomes of bladder preservation with transurethral resection of bladder tumor and intravesical bacillus Calmette-Guérin instillation in selected patients with muscle-invasive bladder cancer [8], the significant prognostic impact of angiolymphatic invasion in patients with bladder cancer beyond the pT2 stage [9], and the prognostic significance of body mass index in nonmetastatic renal cell carcinoma [10]. We believe that all these articles will help provide readers with a comprehensive understanding of these topics. In the second issue set to be published this July, we are planning articles on topics of current interest, including updates on the role of prostate-specific membrane antigen-positron emission tomography in the prostate section, genetic testing in the kidney section, and trends in urine biomarkers in the bladder section.

We are proud to announce the launch of the inaugural issue of JUO. This new publication is dedicated to providing a platform for innovative research and ideas in urology and related fields. We believe that by bringing together experts from all disciplines, we can create an open forum for exchanging knowledge and advancing the field of urology.

We look forward to receiving your contributions!

• Conflicts of Interest: The author has nothing to disclose.

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REVIEW ARTICLE

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Complex Epidemiology of Prostate Cancer in Asian Countries

Kagenori Ito, Takahiro Kimura

Department of Urology, The Jikei University School of Medicine, Tokyo, Japan

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Corresponding author:
Takahiro Kimura
Department of Urology, The Jikei University School of Medicine, Tokyo, Japan
Email: tkimura0809@gmail.com
https://orcid.org/0000-0002-5673-1553

The incidence of prostate cancer (PCa) has increased worldwide in recent years along with the recommendation for prostate-specific antigen testing, and mortality has been declining owing to advances in fragmented and simplified access to treatment care. However, GLOBOCAN (Global Cancer Observatory) data show that this result is not true for all countries. It has been reported that the degree of PCa progression at diagnosis and survival rates differ among racial groups. Based on various comparisons between Caucasians and Asians, it was inferred that survival rates were higher in Asians despite the higher degree of progression at diagnosis, suggesting a better prognosis for life compared with Caucasians. The survey among Asian countries did not reveal any obvious differences among Asian subregions; rather, it inferred that the impact of the level of development among the countries was significant. The development of healthcare systems and medical care could improve PCa survival in developing countries.

Key Words: Prostate cancer, Asia, Epidemiology

INCIDENCE AND MORTALITY OF PROSTATE CANCER IN ASIA

Prostate cancer (PCa) is one of the leading causes of death in humans, the second most common cancer, and the fifth leading cause of mortality worldwide [1]. Older men are more susceptible to PCa, and >80% of patients are diagnosed after 65 years of age. However, the mortality rate of PCa is lower than that of other cancers. The incidence of PCa is 7.3% of the total cancer incidence (developed countries: 3%–15%, developing countries: 3%–4%) [1, 2]. People who die from PCa account for 3.8% of all cancer deaths [1, 3]. In addition, latent PCa has been well identified by autopsy. According to a systematic study of autopsy studies, the prevalence of PCa is 5% in those under 30 years of age and increases to 59% in those over 79 years of age [4]. PCa is characterized by high morbidity and low mortality.

However, the incidence and mortality of PCa differ according to race and country of residence. The incidence of PCa has been increasing, especially in developed countries since the 1990s when prostate-specific antigen (PSA) testing was approved [5]. Oceania (specifically, Australia and New Zealand), North America, and Europe (specifically, Western and Northern Europe) have the highest incidence of PCa in the world. Asian countries have the lowest incidence of PCa in the world [1]. Prevalence of PSA testing and prostate biopsies and racial differences are the main sources of these differences between countries [6]. A Swedish study showed a continuous increase in the incidence of PCa over 30 years despite the low frequency of PSA testing, indicating that there are other influences besides PSA testing [7]. It is questionable whether the reported incidence rates in different countries are true. The reporting of incidence rates is influenced by factors such as ease of access to healthcare,

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quality of care, and accuracy of registration. The incidence in African countries is low compared to that in Asian countries [8]. Global Cancer Observatory (GLOBOCAN) data for 2020 show that the incidence rate in African countries is increasing, while the incidence rate in Asian countries remains at a low level. This is because reliable data are available for African countries but not for Asian countries [1, 9]. Racial differences were highlighted in a migration study. Japanese immigration from Japan to the United States (US) increases the incidence of PCa among Japanese, but still only 50% of the white Americans and 25% of African Americans [10]. PCa has been associated with Western lifestyles, especially a diet high in fat, meat, and dairy products [11, 12]. Not only the country's development in PCa treatment but also racial differences and dietary habits have important roles in PCa incidence. The decline in the number of deaths from other causes may be one of the reasons for the relative increase in PCa mortality. Many factors affect PCa incidence and mortality in each country, which complicates our understanding.

Recently, we have reported Asian epidemiology features in PCa by analyzing GLOBOCAN 2012 database and the statistical information system mortality database of the World Health Organization [13]. According to the GLOBOCAN 2020 database, the incidence tends to be higher in Northern Europe (age-standardized rate [ASR], 83.4), Western Europe (ASR, 77.6), the Caribbean (ASR, 75.8), Australia and New Zealand (ASR, 75.8), and North America (ASR, 73.0) [14]. In contrast, the lowest regions were Asia including South-Central Asia (ASR, 6.3), Southeast Asia (ASR, 13.5), East Asia (ASR, 16.8), and Western Asia (ASR, 28.6) and Africa including Northern Africa (ASR, 16.6), East Africa (ASR, 27.9), and Western Africa (ASR, 33.1). The lowest region had approximately one-thirteenth the incidence of the highest region, which is a clear difference. Generally, developed countries tend to have a high incidence, while developing countries tend to have a low incidence. One can imagine that these findings reflect differences in the availability of medical care, such as testing and early detection, as well as the spread of national cancer registry systems in individual countries. Mortality tended to be higher in the Caribbean (ASR: 27.9) and African descents including those from Central Africa (ASR: 24.8), Southern Africa (ASR, 22.0), Western Africa (ASR, 20.2), Eastern Africa (ASR, 16.3), and Oceania including Polynesia (ASR, 20.5), Melanesia (ASR, 17.0), and Micronesia (ASR, 16.7). In contrast, mortality tended to be low in Asia including South-Central Asia (ASR, 3.1), South Eastern Asia (ASR, 5.4), East Asia (ASR, 4.6), and Western Asia (ASR, 8.4), Southern Europe (ASR, 7.8), Northern Africa (ASR, 8.2), North America (ASR, 8.3), Western Europe (ASR, 9.8), and Australia and New Zealand (ASR, 10.3). Developed countries tend to have low mortality rates, while developing countries tend to have high mortality rates. These results reflect the different environments in which people have access to medical care, including diagnosis, treatment methods, and technologies. Although many Asian countries are still underdeveloped, mortality rates are low, even lower than those in developed countries such as North America and Western Europe. Asian ethnic groups seem to have better survival rates for PCa than other ethnic groups. This result may be partially explained by the differences in dietary habits; however, racial differences remain unclear.

Almost 60% of people live in Asian countries. According to GLOBOCAN 2020 data, only 26.2% of estimated new cases and 32.1% of deaths from PCa worldwide occur in Asia [1]. Incidence and mortality rates vary not only between Asia and the rest of the world, but also between Asian countries. In Fig. 1A, the ASRs of PCa incidence and mortality in the Urological Association of Asia (UAA)-associated countries are shown [14]. The incidence was higher in Oceania including New Zealand (ASR, 92.9) and Australia (ASR, 72.5) than in other Asian countries in UAA (ASR, 3–56.1). Diet habits and racial differences were also associated. PSA testing popularization had the greatest influence in most countries [15]. Incident rates are high in Israel, Japan, Turkey, Singapore, and South Korea, followed by Oceanian countries. This probably reflects the widespread use of PSA testing and the maturity of the cancer registry system. On the other hand, the low incidence in other Asian countries does not seem to reflect the true low prevalence of PCa. This may be due to a variety of factors, including nutritional status, genetics, lifestyle, environmental factors, physical activity, smoking, race, and other characteristics such as registered cancer schemes [16-18]. The mortality-to-incidence rate was lower in Oceania including New Zealand (0.132) and Australia (0.138), Japan (0.087), Israel (0.119), South Korea (0.150),

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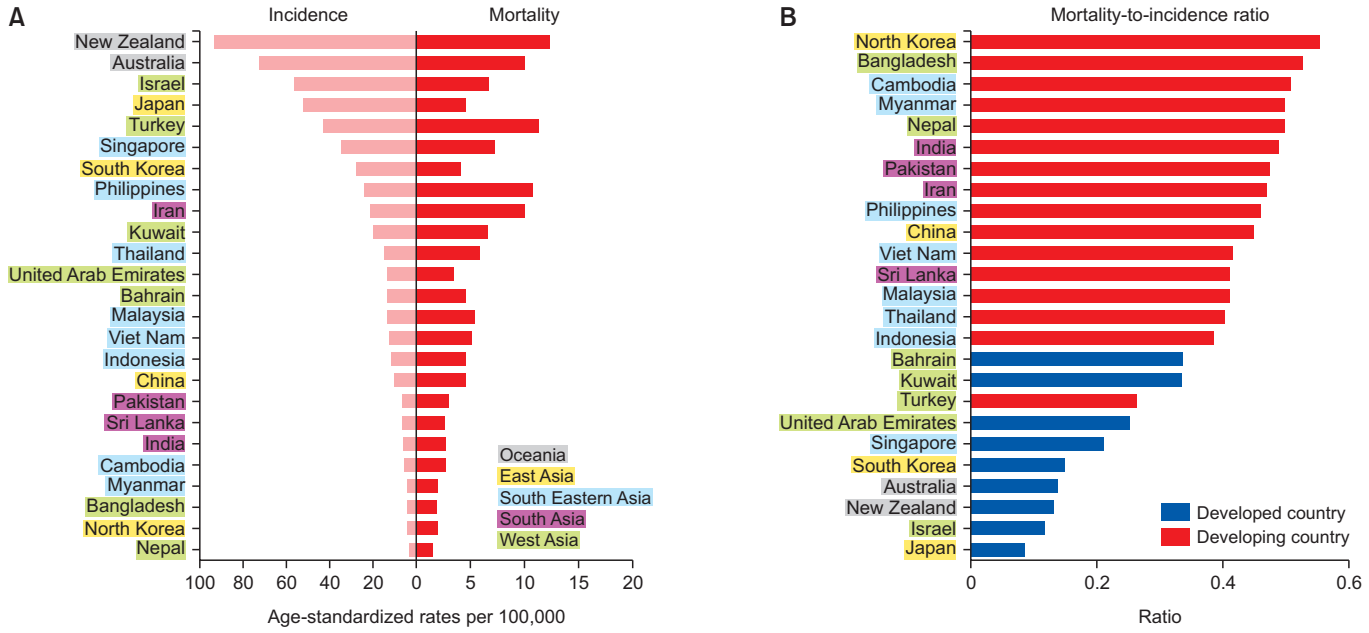

Fig. 1. Incidence and mortality of prostate cancer in Urological Association of Asia (UAA)-associated countries from 2020 GLOBOCAN (Global Cancer Observatory). (A) Age-standardized rates of incidence and mortality in UAA-associated countries are listed in descending order. (B) Mortality-to-incidence ratios are listed in descending order. Developing countries are listed in the Development Assistance Committee list of official development assistance recipients [41].

and Singapore (0.213) than in other Asian countries (0.254–0.556) (Fig. 1B). No significant difference in incidence, mortality, or mortality-to-incidence rate was found by Asian province classification, but it differed between countries. Moreover, developed countries have a lower mortality-to-incidence ratio than developing countries (Fig. 1B). These results indicate that the clinical level is more important than racial differences among Asian countries.

Mortality-to-incidence ratios are practical indicators for assessing the long-term success of cancer surveillance and the effectiveness of cancer control programs, particularly cancer testing [19]. Mortality-to-incidence ratios indicate survival but do not reveal real survival, which needs to be checked and compared.

TRENDS OF INCIDENCE AND MORTALITY FROM PROSTATE CANCER IN ASIA

PCa is now easily detected by the serum PSA test and prostate imaging using multiparametric MRI [20]. PSA is a prostate-specific protein whose serum concentration is increased by prostate diseases such as PCa. PSA was discovered in 1979 and has been widely applied to PCa since its U.S. Food and Drug Administration approval in 1986 because it can detect PCa better than other methods [21]. In New Zealand, Australia, and Israel, the incidence of PCa increased rapidly around 1990 and has generally leveled off since 2000 (Fig. 2A). The incidence of PCa began to increase around 2000 in Turkey, Japan, South Korea, Kuwait, and China and is still increasing. In India and Thailand, the incidence of PCa is increasing slightly. These data are partially explained by the popularization of PSA testing. PSA testing has been highly popularized in Australia, New Zealand, and North America [10, 14]. However, PSA testing remains unpopular in India and Thailand. Although the PSA test rate in South Korea is lower than that in the US and Japan, the incidence of PCa continues to rise, becoming the most common cancer in 2022 [22]. PCa mortality rates in New Zealand, Australia, Israel, and Japan began to rise around 1990, but are now declining (Fig. 2B). In South Korea, PCa mortality began to rise around 2000, but is now declining. In Singapore, PCa mortality increased slightly until approximately 2000, but has generally leveled off since then. Detection of PCa by PSA testing temporarily increased mortality; however, in recent years, mortality has decreased due to improved PCa treatment and possibly the influence of early detection by PSA testing.

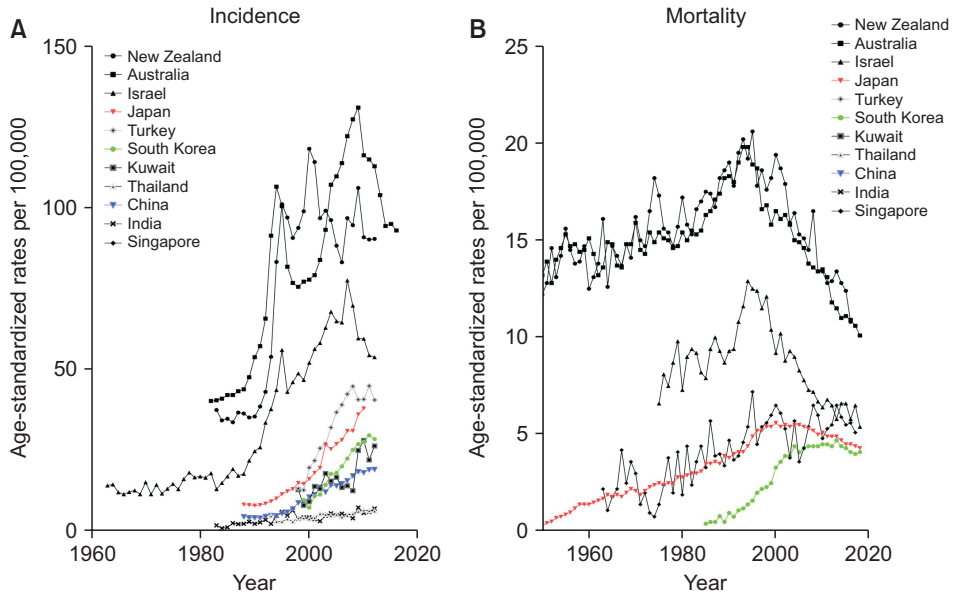

Fig. 2. Incidence and mortality trends in Urological Association of Asia-associated countries. (A) Annual incidence per 100,000 population in the World Health Organization (WHO) Statistical Information System Mortality Database. (B) Annual mortality per 100,000 population in the WHO Statistical Information System Mortality Database.

The incidence rates in Oceanian countries and Israel increased around the 1990s due to the popularization of PSA testing. PSA testing also increases the risk of overdiagnosis and overtreatment of low-risk PCa. Based on this result, the current guidelines in the US, the United Kingdom (UK), Canada, Australia, and Israel do not recommend PSA testing for healthy or asymptomatic men in the 2000s [23-27]. This decision led to the decreased incidence in Oceania and Israel from the 2010s to the 2020s (Fig. 2B). However, from the analysis of the Surveillance, Epidemiology, and End Results (SEER) 18 registry incidence data, a significant increase in the incidence of metastatic PCa was found in men aged 45–74 years (2010–2018) [28]. This phenomenon is related to the decrease in PSA testing recommendations by the US Preventive Services Task Force (USPSTF) [29]. In 2018, the USPSTF changed the PSA testing recommendation from D recommendation (no recommendation) to C recommendation (should not screen men who do not express a preference for testing) for men aged 55–69 years. This may increase the incidence rate in the US, the UK, Canada, Australia, Israel, and other countries. In Japan, PSA testing is strongly recommended, resulting in a continued increase in the incidence [30]. In South Korea and China, PSA testing is not performed in periodic medical check-ups; the incidence declined in South Korea and slightly increased in China [31, 32]. The incidence in Asian countries differs by country: it increased in India, but decreased in the Philippines and Bahrain between 2007–2016 [33].

Mortality rates were once very high in Oceanian countries and Israel in 1990 and have continued to decrease until now. This could be explained by the improvement in treatment care and early-stage detection by PSA testing. Additionally, mortality rates in Singapore, Japan, and South Korea increased slightly in the 2000s but have now slightly decreased, which could be explained by the same reasons. Mortality rates are currently increasing in some Asian countries. The mortality in Uzbekistan, Georgia, Thailand, Kyrgyzstan, and Kuwait increased between 2007–2016 [33]. The recent rise in mortality in many Asian countries may be related to the increased prevalence of risk factors associated with economic development, such as obesity, increased dietary fat consumption, and decreased physical activity, or may reflect improved data collection mechanisms [34].

SURVIVAL RATE TREND IN ASIAN COUNTRIES

PCa has a better survival rate than other cancer types [35]. Even so, survival rates vary between countries, with some countries having poor survival rates. According to data from the CONCORD-3 study, which surveyed cancer survivors worldwide (62 countries) during 1995–2014, although the timing is different, the 5-year survival of PCa is 70%–100% in most countries [35]. In Japan and South Korea, PCa survival

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increased by an average of 12% every 5 years, approaching 90% from 2010 to 2014. Survival was less than 70% in 4 African countries (Algeria, Mauritius, Nigeria, and South Africa), 3 Asian countries (China, India, and Thailand), and 2 European countries (Bulgaria and Gibraltar). India also saw a significant improvement in survival but remained the lowest among Asian countries with 44.3% during 2010–2014.

Asian populations have been reported to be different from the American or African populations in PCa malignancy. Many conflicting reports on PCa malignancy differences in Asia and the US are unclear. PSA level, Gleason score, and clinical TNM (tumor, node, metastasis) stage were reported to be worse in the Asian population than in the American population. The percentage of Caucasians with a Gleason score of 8–10 was 22.9%, whereas the percentages of South Korean, Chinese, and Japanese men in California were 34.5%, 30.9%, and 28.6%, respectively [36]. Among the Asians surveyed, South Koreans had the highest rates of poorly differentiated cancer, high Gleason scores, and advanced stages. Data from the SEER study showed that Asians living in the US had more distant metastases at diagnosis than Caucasians during 1988–1994 [37]. Data from the SEER database also revealed that PSA (median: 7.2 ng/mL vs. 6.7 ng/mL), Gleason score (8–10: 19.1% vs. 18.7%), and disease stage (cT3–4: 2.7% vs. 2.3%) were significantly higher in Asian men compared with US Caucasians [38]. Several other studies have reported that Asians living in North America have more aggressive cancers than Caucasians and African Americans [37]. However, some reports found no racial differences in Gleason scores among Asian US residents compared with Caucasians and African Americans, although Asians accounted for a minority of patients (approximately 5%) [39]. No conclusions have been reached, but the Asian population seems to have more aggressive PCa at the time of diagnosis than Caucasians. Surprisingly, it has been reported that the prognosis of Asian populations is even better than that of Caucasians, even with highly malignant cancers. Chinese, Filipino, Japanese, and South Korean men, except South Asians and Vietnamese men, had significantly better survival than Caucasians [36]. SEER data show that Asians in the US have higher survival rates than other races, such as Caucasians, African Americans, and Hispanics. Caucasian mortality was 22.4 per 100,000 population, whereas Asian mortality was 10.5 per 100,000 population [40]. From these reports, it was speculated that Asian populations have a better survival rate than Caucasians, despite their higher malignancy at diagnosis. This could be explained by the difference in PSA testing popularity between Asian countries and the US. PSA testing is less prevalent in Asian countries than in the US, and it is speculated that PCa is diagnosed at a more advanced stage in Asia. Asians have a good survival rate despite the advanced stage at the time of diagnosis, suggesting a good response to treatment or a slow progression.

To understand the survival difference between Asian countries, we examined the 5-year survival rate of patients with PCa in UAA-associated countries (Fig. 3). No significant difference in the 5-year survival rate was found by Asian province classification, but it differed between countries. All developed countries (Japan, Australia, South Korea, New Zealand, Singapore, Kuwait, and Taiwan) have a survival rate of over 80%. Although no data are available for Israel, the United Arab Emirates, and Bahrain, since the mortality-to-incidence ratio is similar to that in other developed countries, the 5-year survival rate is predicted to be over 80% (Fig. 1B). The Whole Population Cancer Registry was adopted in Australia, New Zealand, Singapore, Hong Kong, and Macao, which made it easy to evaluate 5-year survival chronologically. The 5-year survival rate in Oceania (Australia and New Zealand) increased in the 1990s. In the 2000s, some Asian countries (South Korea, Singapore, and Hong Kong) had increased 5-year survival rates. This may be explained by the early detection of PCa by PSA testing and improvements in PCa treatment. Apart from Hong Kong, all developing countries (Macao, China, Malaysia, Thailand, India, and the Philippines) have a survival rate below 80%. Because of the lack of population-based studies in most developing countries and that of unification in the observation period between countries, it is difficult to simply compare survival rates between countries. However, developing countries with worse survival rates than developed countries can be easily predicted. These results also indicate that the clinical level is more important than racial differences among Asian countries.

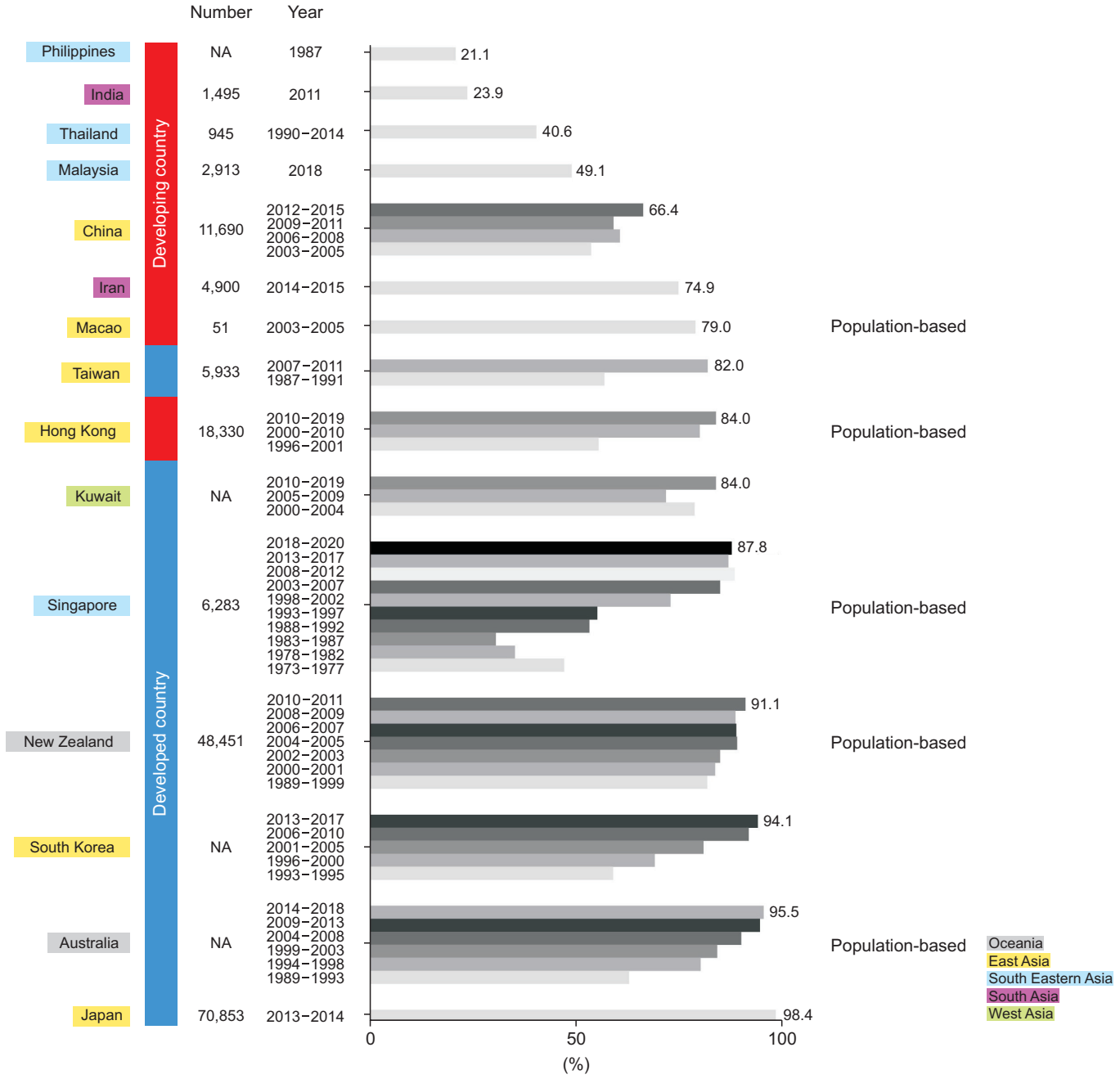

Fig. 3. Five-year overall survival of prostate cancer in Urological Association of Asia-associated countries. Data were selected from each paper or website (the Philippines [42], India [43], Thailand [44], Malaysia [45], China [46], Iran [47], Macao [48], Taiwan [49], Hong Kong [50], Kuwait [51], Singapore [52], New Zealand [53], South Korea [54], Australia [55], Japan [56]).

CONCLUSION

Asians are presumed to have a better prognosis for PCa than Caucasians, as they have lower mortality-to-incidence ratios and higher survival rates, despite being diagnosed with PCa in an advanced state. The situation of PCa in Asian countries was not distinctly different by region; rather, it varied widely between developed and developing countries. The widespread use of PSA testing has led to a temporary increase in PCa cases worldwide. Following the US and Oceania, the number of cases is also on the rise in most developed Asian countries. In the US and Oceania, the number of cases has been declining in recent years as PSA testing has become less recommended; however, in Asian

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countries, PSA testing has continued and has been on the rise. In some developed countries in Oceania and Asia, the number of deaths temporarily increased as the number of PCa diagnoses rose, but has been improving in recent years as medical technology and access to care have improved. Also, the 5-year survival rate is predominantly greater than 80%. On the other hand, some developing countries in Asia previously tended to have a low incidence, a high mortality-to-incidence ratio, and low 5-year survival rates. There are concerns regarding the negative effects of inadequate medical technology and access to medical care. The development of healthcare systems and medical care will likely improve PCa survival in developing countries.

NOTES

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- ORCID

Kagenori Ito: https://orcid.org/0000-0002-4970-1727

Takahiro Kimura: https://orcid.org/0000-0002-5673-1553

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REVIEW ARTICLE

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Current Update on Prostate Cancer Immunotherapy

Juliana E. Kim[1], Kunwoo Lee[2], Isaac Yi Kim[3]

[1]Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, USA
[2]Inha University College of Medicine, Incheon, Korea
[3]Department of Urology, Yale School of Medicine, New Haven, CT, USA

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Corresponding author:
Isaac Yi Kim
Department of Urology, Yale School of Medicine, New Haven, CT, USA
Email: Isaac.kim@yale.edu

Immunotherapy encompasses a wide array of treatment modalities that utilize our natural defense system to fight against cancer and in recent years has contributed to significant improvement in survival and quality of life in patients. However, its use in prostate cancer has been limited due to low efficacy and lack of effective biomarkers. Prostate cancer's unfavorable tumor microenvironment characterized by T-cell exclusion and expansion of T-reg cells, along with the possible inhibitory effect of androgen deprivation therapy (ADT) on the immune system further explains this poor response to immunotherapy. Here, we review current immunotherapies and ongoing clinical trials as well as potential biomarkers being investigated to predict treatment responses to immunotherapy. Finally, we discuss the conflicting results on the best approach to sequencing immunotherapy in relation to ADT.

Key Words: Prostate cancer, Immunotherapy, Clinical trials

INTRODUCTION

Prostate cancer is the most commonly diagnosed cancer in men and the second most diagnosed disease for men in the United States [1]. Although prostate cancer incidence in South Korea is significantly lower than that in Western countries, the malignancy displays minimal symptoms in the early stages and 33.8% of South Korean patients are diagnosed with at least stage III disease [2]. In contrast to the excellent 5-year survival rate of 100% in localized disease, metastatic prostate cancer has a significantly lower 5-year survival rate of 45.9% [3]. The current mainstay of therapy for advanced and metastatic prostate cancer is androgen deprivation therapy (ADT) but cancer cells eventually escape the androgen dependence and become castration resistant.

Immuno-oncological therapy has transformed cancer care by drastically improving survival outcomes and quality of life [4]. Most notably immune checkpoint inhibitors (ICIs) have changed the treatment paradigm in malignancies such as melanoma and lung cancers [5, 6]. Despite its promising results and recent advancements in some solid cancers, immunotherapy's utility in advanced prostate cancer has been limited [7-10]. Pembrolizumab, an ICI with a tissue-agonostic indication, and sipuleucel-T, an autologous cellular vaccine, remain the only immunotherapeutics that have received approval from the U.S. Food and Drug Administration (FDA) [11, 12]. However, the clinical impact of these agents still remains limited by the high cost and modest improvement in survival.

Herein, we review the conventional and experimental immunotherapeutics in prostate cancer. In addition, cellular mechanism and potential factors that limit immunotherapy

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in prostate cancer are discussed. Finally, since ADT is the cornerstone of prostate cancer systemic therapy, we cover conflicting results on how ADT may affect the immune system and question the current standard treatment sequence regarding immunotherapy and ADT.

IMMUNE CHECKPOINT INHIBITORS

Tumor cells evade the body's natural immune response via activation of certain immune checkpoint pathways that typically induce T-cell anergy. ICIs interfere with the T-cell coinhibitory signaling pathways to enhance immune-mediated tumoricidal effect [13]. ICIs have become key players in the treatment of many solid tumors, but their clinical benefits in prostate cancer have been disappointing [14].

(1) Pembrolizumab is an IgG4 monoclonal antibody against programmed cell death protein 1 (PD-1) on lymphocytes and it remains the only ICI with FDA approval for the treatment of prostate cancer. It prevents PD-1-induced self-tolerance and inactivation of lymphocytes. Current National Comprehensive Cancer Network guidelines dictate the usage of pembrolizumab specifically for unresectable or metastatic microsatellite instability-high (MSI-H), deficient mismatch repair (dMMR) gene, or tumor mutational burden (TMB) equal or higher than 10 mutations per megabase (mut/Mb) prostate cancers [15, 16]. Table 1 delineates currently open phase III prostate cancer clinical trials on pembrolizumab—however, 3 out of the 6 trials were discontinued. The KEYLYNK-010 trial combining pembrolizumab to poly ADP-ribose polymerase (PARP) inhibitor olaparib was discontinued due to a higher incidence of serious adverse events without observed benefit in overall survival (OS) or radiographic progression-free survival (PFS) [17]. Likewise, KEYNOTE-921 testing pembrolizumab in combination with chemotherapy failed to show statistically significant improvements [18]. KEYNOTE-991 which compared pembrolizumab with enzalutamide to enzalutamide with placebo in metastatic castration-sensitive prostate cancer will be discontinued after the therapy failed to demonstrate improvements at a planned interim analysis [19]. With these latest updates, KEYNOTE-641 along with KEYNOTE-921, 991 China extension trials are the only phase III trials left, while there is still phase II trial such as KEYNOTE-365 [20, 21].

(2) Ipilimumab is an FDA-approved ICI that targets CTLA-4 but has not been approved for prostate cancer. In 2 recent phase III clinical trials, it failed to improve OS in patients with metastatic castration-resistant prostate cancer (mCRPC) [7, 8]. Currently, there are no phase III trials testing ipilimumab as a monotherapy. However, the NCT03879122 trial is investigating it in combination with nivolumab, as anti-CTLA-4 therapy increases infiltrating T cells and induces interferon-γ which stimulates programmed death ligand-1 (PD-L1) expression [22].

(3) Nivolumab is another anti-PD1 antibody that is cur-

Table 1. Open phase III pembrolizumab trials in prostate cancer

Identifier	Title	Patients	Arms	Enrolled	Estimated completion (month-year)
NCT03834506*	KENOTE-921	NHA-pretreated patients with mCRPC	Experimental: pembrolizumab+docetaxel Comparator: placebo+docetaxel	1,090	Oct-23
NCT03834493	KEYNOTE-641	Patients with mCRPC	Experimental: pembrolizumab+enzalutamide Comparator: placebo+enzalutamide	1,240	Feb-25
NCT04191096*	KEYNOTE-991	mHSPC	Experimental: pembrolizumab+enzalutamide+ADT Comparator: placebo+enzalutamide+ADT	1,232	Sep-26
NCT04934722	KEYNOTE-991 China extension	mHSPC	Experimental: pembrolizumab+enzalutamide+ADT Comparator: placebo+enzalutamide+ADT	186	Jan-28
NCT04907227	KEYNOTE-921 China extension	Enzalutamide or abiraterone-pretreated patients with mCRPC	Experimental: pembrolizumab+docetaxel Comparator: placebo+docetaxel	81	Feb-25
NCT03834519*	KEYLINK-010	Metastatic CRPC	Experimental: pembrolizumab+olaparib Comparator: abiraterone+prednisone or enzalutamide	793	Sep-23

NHA, next generation hormonal agent; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; ADT, androgen deprivation therapy.
*Discontinued trials.

rently being explored, but has not received FDA approval. The STARVE-PC phase II trial demonstrated that nivolumab and ipilimumab immunotherapy for patients with mCRPC disease that expresses the constitutively active androgen receptor (AR) variant AR-V7, had a modest improvement in OS rate, but the effect size was not sufficient for pursuing a phase III trial [23]. A phase II trial CheckMate-650 investigating nivolumab and ipilimumab combination in men with mCRPC disease demonstrated high overall response rates but dosing and scheduling modifications are needed to optimize safety [24]. The ongoing phase III nivolumab trials in prostate cancer are detailed in Table 2. Results from the previous phase II study CheckMate 9KD supported further investigation in the phase III CheckMate-7DX trial which is currently recruiting [25].

(4) Atezolizumab is a PD-L1 inhibitor. Table 3 shows ongoing phase III atezolizumab trials in prostate cancer. CONTACT-02 is still recruiting. IMbassador250 trial results are being reviewed, but the trial failed to show the statistical superiority of atezolizumab over the control. However, in a preplanned subgroup analysis, superior PFS was shown in tumors with high levels of PD-L1 expression or high levels of intratumoral CD8-positive T-cell infiltration [9].

VACCINE-BASED TREATMENTS

Cancer vaccines are a form of active immunotherapy that aims to facilitate the presentation of tumor antigens to the immune system. The proposed prostate cancer's immunosuppressive environment is due in part to the dysfunction of dendritic cells (DCs). Accordingly, DC vaccine therapy has the potential to aid in overcoming the immunosuppressive tumor microenvironment. Currently, sipuleucel-T remains the only vaccine-based therapy with FDA approval for the treatment of prostate cancer. It targets prostatic acid phosphatase and the phase III clinical trial IMPACT (Integrated Model for Patient Care and Clinical Trials) demonstrated that sipuleucel-T had a 22% reduction of relative mortality risk [11]. Since its approval, multiple trials investigating combined immunotherapy have been disappointing [26]. NCT01420965 explored combining pidilizumab, but was terminated early, while NCT01832870 investigated ipilimumab and was terminated without phase I reports. Currently, there is an ongoing phase III trial comparing sipuleucel-T to active surveillance for newly diagnosed localized prostatic cancer (NCT03686683).

No other vaccine treatments have been approved for prostate cancer. VITAL-1 and VITAL-2 were clinical trials with promising results investigating GVAX, a synthesized

Table 2. Open phase III nivolumab trials in prostate cancer

Identifier	Title	Patients	Arms	Enrolled	Estimated completion
NCT04100018	CheckMate 7DX: a Phase 3, randomized, double-blind study of nivolumab or placebo in combination with docetaxel, in men with mCRPC	mCRPC	Experimental: nivolumab+docetaxel+prednisone Comparator: placebo+docetaxel+prednisone	984	Aug-27
NCT03879122	A trial of immunotherapy strategies in metastatic hormone-sensitive prostate cancer	mHSPC	Experimental A: ADT+docetaxel+nivolumab Experimental B: ADT+ipilimumab/docetaxel+nivolumab Comparator: ADT+docetaxel	135	Dec-24

mCRPC, metastatic castration-resistant prostate cancer; ADT, androgen deprivation therapy; mHSPC, metastatic hormone-sensitive prostate cancer.

Table 3. Open phase III atezolizumab trials

Identifier	Title	Patients	Arms	Enrolled	Estimated completion
NCT04446117	CONTACT-02: a phase 3, randomized, open-label, controlled study of cabozatinib in combination with atezolizumab vs. second NHT in subjects with mCRPC	mCRPC	Experimental: cabozatinib+atezolizumab Comparator: either abiraterone+prednisone or enzalutamide	580	Aug-24
NCT03016312	IMbassador250: a phase 3 study of atezolizumab in combination with enzalutamide in men with mCRPC	mCRPC	Experimental: atezolizumab+enzalutamide Comparator: enzalutamide	771	Feb-23

NHT, ovel hormonal therapy; mCRPC, metastatic castration-resistant prostate cancer.

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vaccine using prostate cancer cell lines LNCaP and PC3 secreting granulocyte-macrophage colony-stimulating factor [27]. However, phase III trials were terminated early due to a lack of improved OS and increased mortality.

PROSTVAC is a viral vector containing the PSA gene and several T-cell costimulatory molecules that were used in several clinical trials. Contrary to the promising results in phase II trials, PROSTVAC demonstrated little to no improvement in OS in patients with mCRPC in phase III clinical trials [28-30]. In addition, a phase II trial tested the benefit of using PROSTVAC earlier in the disease compared to active surveillance (NCT02326805) but failed to elicit favorable results [31].

1. Adoptive Cell Therapy

This immunotherapy isolates and manipulates immune cells to increase their capacity to target cancer cells. Chimeric antigen receptor T (CAR T) cell therapy is a classic example and is extremely effective in the treatments of hematologic malignancies due to improved specificity and targeting [32]. CAR T remains a promising treatment option in mCRPC and in other solid tumors, but the safety profile of the treatment remains to be determined [33].

2. Oncolytic Virus Therapy

Oncolytic virus therapy involves utilizing viral vectors to target oncolytic cells and can potentially aid in counteracting tumor-associated immunosuppression and evasion. Conceptually, it is a relatively new mode of therapy as the virus can replicate in situ to have a direct cytocidal effect [34]. Additionally, because the prostate gland is a nonessential organ, oncolytic viral therapy can be used to completely ablate the gland [34]. Oncolytic viral therapy has largely been explored in combination with ICIs [35]. There are several clinical trials exploring this immunotherapy approach and results have been promising but further investigations to clarify the therapeutic potential in prostate cancer are needed.

BARRIERS TO IMMUNOTHERAPY IN PROSTATE CANCER

Despite these diverse immunotherapy modalities, immunotherapy has not been effective in prostate cancer due to its "cold" immune environment. For a robust antitumor immune response, 3 major steps are required: (1) generation of tumor-reactive T cells, (2) physical interaction between target and effector cells, and (3) a microenvironment permissive to immune effector functions [36]. Prostate cancer often lacks distinct characteristics that prevent a clinically meaningful immune response.

Primarily, the TMB of prostate cancer is typically low, resulting in the inefficient generation of tumor-reactive T cells. TMB is increasingly being proposed as a possible predictive marker of response to immunotherapy in various cancers and is associated with high expression levels of neoantigens which correlates with increased immunogenicity [37]. Prostate cancer cells, compared to other cancers successfully treated with immunotherapy such as melanoma, are typically characterized as having low TMB [38, 39].

Next, immune effector cells may be hampered from directly contacting cancer cells, as prostate cancer is characterized by T-cell exclusion. Furthermore, T cells in the adjacent stroma and benign areas often demonstrate anergic and immunosuppressive phenotype. This in part may be explained by the chronic progressive nature of prostate cancer and its inflammatory microenvironment [36].

Additional cellular mechanisms proposed for how prostate cancer maintains an immunosuppressive environment include fibroblasts, T-reg cells, tumor-associated macrophages, mesenchymal stem cells, and myeloid-derived suppressor cells in the tumor stroma. Collectively, these cells secrete mediators that suppress immune activity [40]. Interestingly, as much as 50% of castration-resistant prostate tumors demonstrate phosphatase with tensin homolog (PTEN) inactivation, a tumor suppressor gene. Loss of PTEN function does not affect tumor growth through the loss of its tumor suppressor function but PTEN loss itself can act as an immunosuppressive event, impairing innate and adaptive immunity [41, 42]. Additionally, prostate cancer often produces high levels of transforming growth factor-β, which has a profound inhibitory effect on immune cells including

natural killer (NK) cells resulting in low NK cell infiltration [43, 44]. Finally, tissue aspirate from prostate cancer revealed an increased number of T-reg cells [45]. Taken together, the unfavorable prostate cancer microenvironment is likely a key factor in limiting the efficacy of immunotherapy.

It should be noted that not only the perturbation of immune effector cells and the unfavorable tumor microenvironment pose formidable challenges to developing effective immunotherapeutics in prostate cancer, but factors such as race and previous use of other therapies also add another layer of complexity in prostate cancer immunotherapy. Asian/Pacific islanders have the highest 5-year survival rate in metastatic prostate cancer compared with other races [46], and African Americans respond better to most systemic therapies than Caucasians [47]. ADT can induce T-cell infiltration into the prostate tumor microenvironment [48]. In addition, enzalutamide-resistant prostate cancer expresses higher levels of PD-1 and PD-L1/2 [49]. Therefore, factors such as ethnicity and previous therapies should be considered in developing a rational strategy for immunotherapy in prostate cancer.

PREDICTIVE MARKERS IN IMMUNOTHERAPY

Because immunotherapy is not effective in unselected metastatic prostate cancer patients, predictive biomarkers are needed to identify patients who will likely benefit from immunotherapy.

1. Programmed Death Ligand-1

PD-L1 is used in other tumors as a biomarker for immunotherapy. In prostate cancers, one study reported that the objective response rate to ICI in PD-L1-positive tumors was 5% and in PD-L1-negative tumors, the rate was 3% [10]. Thus, PD-L1 is not considered a viable biomarker of immunotherapy in metastatic prostate cancer.

2. Deficient Mismatch Repair

Deficient MMR genes may result in the overexpression of a variety of immune transcripts including those associated with T cells such as PD-L1 [50]. Underlying dMMR can cause high variation in microsatellite length (MSI-H). Mutations in these genes code for mutant proteins which potentially act as neoantigens that can be recognized by CD8-positive T cells. dMMR/MSI-H tumors showed high response rates and impressive efficacy with ICI treatment [51, 52]. However, dMMR/MSI-H is relatively uncommon in prostate cancer and is reported to be present in 2.2%–12% [50, 51, 53, 54].

3. High TMB

High TMB showed a favorable response to ICI compared with taxanes alone in metastatic prostate cancer. Patients with TMB of 10 mt/Mb or greater had a significantly longer time to the next treatment and OS [55].

4. DNA Homologous Recombination Repair Gene

Homologous recombination repair gene (HRR) mutation, especially the CDK12 mutation showed a favorable response to ICI. CDK12-mutated prostate cancer is linked to poor prognosis and resistance to PARP inhibition, but increased neoantigen load for intratumoral lymphocyte infiltration opens the door to PD-1 targeted therapy [56]. However, CDK12 mutations occur in 5%–7% of patients with mCRPC [57]. There is currently an ongoing phase 2 clinical trial of nivolumab and ipilimumab combination therapy for prostate cancer patients with CDK12 mutation (NCT03570619).

Collectively, effective prostate cancer immunotherapy will require a panel of biomarkers and genomic determinants to identify patients who will likely respond.

IMMUNOTHERAPY IN RELATION TO ANDROGEN DEPRIVATION THERAPY

ADT forms the basis of systemic therapy for advanced prostate cancer and when we consider integrating immunotherapy for prostate cancer treatment, we must consider the interaction between androgens and the immune system. The immunosuppressive effect of androgens has been observed in both rodent and human studies. Women produce more IgM [58] and there is a strong correlation between androgens and genes involved in lipid metabolism that correlate with low

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virus-neutralizing antibody in men [59]. Although variable in ratio, autoimmune diseases are more prevalent in women compared to men and men show increased susceptibility to nonreproductive cancers [60].

Accordingly, castration may restore some of the suppressed immune function. In animal studies, castrated male mice which resulted in the change of sex hormone levels induced a change in immune responsiveness [61]. Androgen deprivation showed enhanced T-cell function and resulted in complete regeneration of male mouse thymus with the restoration of peripheral T-cell function [62]. Castration may also enhance CD4-mediated immune responses [63] and castration temporarily leads to prostate Th1-type T-cell infiltration [64]. Moreover, androgen blockade could mitigate T-cell recognition tolerance and induce prostate-specific T-cell proliferation [65]. Similar findings have been found in human studies where an increase in circulating T cells were found in elderly males undergoing sex steroid ablation therapy for prostate cancer [62]. A separate study showed that patients developed expansion of naïve T-cell compartment after androgen deprivation, along with an increase in effector-cell response to stimulation and prostate tissue-associated IgG responses [66]. Based on these observations, immunotherapy should be combined with or sequenced following ADT.

Conversely, there is a body of data suggesting that ADT may suppress the immune response. For example, Jiang et al. [67] investigated the correlation between hepatocellular carcinoma and sex and reported that androgens down-regulate PD-L1. Interestingly, the same authors did not detect the same negative correlation between AR and PD-L1 in prostate cancer. A more provocative result was reported by Pu et al. [68] in 2016. The team reported that chemical castration, but not surgical castration, suppressed T-cell response in prostate cancer. Similarly, our group has observed that androgens stimulate the antitumorigenic activity of macrophages [69]. Specifically, androgen was shown to induce M1 polarization while in an isolated system, removal of macrophages following orchiectomy partially reversed castration resistance. Taken together, these observations suggest that the clinical efficacy of immunotherapy may need to be assessed in the context of ADT. Indeed, we have proposed that the optimal treatment sequence for immunotherapy in prostate cancer may be prior to the initiation of ADT. Clinical trials are being developed to assess this concept.

CONCLUSION

Despite the progress in understanding tumor immunology over the last decade, immunotherapy has not shown a meaningful clinical effect in prostate cancer. Additional studies are necessary to clarify the mechanisms underlying the "immune-coldness" of prostate cancer. Since ADT is the foundation of prostate cancer systemic treatment and androgens affect the immune system, future immunotherapy trials in prostate cancer should include a rational strategy to assess the interaction between ADT and immunotherapy.

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- ORCID

Juliana E. Kim: https://orcid.org/0000-0003-0763-4279

Kunwoo Lee: https://orcid.org/0000-0002-1651-6269

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REVIEW ARTICLE

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The Current State and Future of Plasma Cell-Free DNA Analysis in Urologic Malignancies

Shusuke Akamatsu[1,2], Kei Mizuno[1], Takayuki Sumiyoshi[1], Takayuki Goto[1], Takashi Kobayashi[1]

[1]Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[2]Department of Urology, Nagoya University Graduate School of Medicine, Nagoya, Japan

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Corresponding author:
Shusuke Akamatsu
Department of Urology, Kyoto University Graduate School of Medicine, Kyoto, Japan
Email:
akamats@med.nagoya-u.ac.jp
https://orcid.org/0000-0002-1394-7506

Genomic medicine based on comprehensive genomic profiling (CGP) has revolutionized cancer treatment. However, there are certain limitations to CGP based on tissue analysis. Liquid biopsy, particularly plasma cell-free DNA (cfDNA), has emerged as a less invasive source of information to complement tissue-based analysis. To use cfDNA analysis effectively in the clinical setting, it is important to know the characteristics and specific limitations of cfDNA analysis. Moreover, the utility of cfDNA testing differs between cancer types, which is not widely recognized. Furthermore, in addition to its use in CGP, there are broader applications for cfDNA testing, including its use in detecting minimal residual disease or even epigenomic profiling. In this review, we first describe the detailed characteristics of cfDNA and the limitations of cfDNA analysis, and then focus on the utility of cfDNA analysis in urologic malignancies.

Key Words: Liquid biopsy, Cell-free nucleic acids, Prostatic neoplasms, Carcinoma, Renal cell, Urinary bladder neoplasms, Ureteral neoplasms

INTRODUCTION

In 2023, cancer genome analysis is clinically available in many parts of the world. Instead of developing and administering drugs for each type of cancer, as in the past, cancer genome medicine, which treats cancer across cancer types based on genomic abnormalities, is now being practiced. Undoubtedly, precision medicine based on the cancer genome, in addition to morphological pathological diagnosis, will be further promoted in the future.

It has been revealed that cancer genomes dynamically change with treatment stress [1]. Considering the dynamic nature of cancer genomes, the most ideal cancer genomic medicine for advanced cancer following multiple lines of treatment would be biopsy of a metastatic lesion and selection of drugs based on genomic information from the tumor tissue. However, biopsy of metastatic lesions may be difficult due to the invasiveness of the procedure in some organs; and bone metastases require ethylenediaminetetraacetic acid decalcification to collect DNA suitable for cancer genome analysis, which may not ensure sufficient quality and quantity of DNA. Furthermore, there is heterogeneity in cancer genomes between metastases in heavily treated patients, and genetic information from a particular metastasis site may not reflect the most important alteration in the overall clinical picture [1-3]. For example, if a patient with prostate cancer maintains lymph node shrinkage with hormonal therapy but only bone metastases worsen, analysis of the cancer genome of metastatic lymph nodes may not identify the genomic abnormality that drives tumor progression at that time. If a

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tissue sample cannot be obtained at the time of progression, an alternative would be to perform cancer genome analysis using a tissue sample from the time of the initial diagnosis of cancer. However, there are 2 major concerns for this approach. First, it is possible that the cancer genome at the time of progression may have changed from the cancer genome at the time of diagnosis. In prostate cancer, *BRCA1* and *BRCA2* mutations, for which the poly(ADP-ribose) polymerase (PARP) inhibitor olaparib is effective, are reported to be already present at the time of diagnosis, and acquisition of new alterations during treatment is rare, except when treated with PARP inhibitors. On the contrary, hormonal therapy, including androgen receptor (AR) pathway inhibitors, significantly alters androgen receptor (*AR*) [1, 4, 5]. In addition, some genes important for prostate cancer progression, such as *TP53* and *RB1*, accumulate new genomic alterations with progression. In the future, as the number of drugs targeting specific genomic alterations increases, the discrepancy between the cancer genome of the biopsied tissue at diagnosis and that at progression may become a clinical problem. The second concern is the degradation of DNA in formalin-fixed paraffin-embedded (FFPE) specimens over time [6]. In particular, the success rate of genomic analysis using large gene panels drops below 50% when FFPE specimens are stored for more than 3 years. Due to these combined factors, the success rate for the analysis of tissue specimens from 4,047 patients analyzed in the Phase III PROfound trial to test the effectiveness of olaparib in metastatic castration-resistant prostate cancer (mCRPC) was unsatisfactory at 69% [7].

Liquid biopsy is expected to complement a diagnosis using tissue specimens. Liquid biopsy examines components such as DNA, RNA, and proteins derived from tumors (or stromal cells around tumors) released in body fluids instead of conventional tissue diagnosis by tumor biopsy. Although cell-free DNA (cfDNA) is the only currently available liquid biopsy clinically, research is ongoing to develop other forms of liquid biopsy, such as circulating tumor cells, circulating free RNA, exosomes, microRNAs, and proteins. In addition to blood, all body fluids, including urine, ascites fluid, spinal fluid, and pancreatic fluid, are also sources for liquid biopsy. Urine is a valuable source of information, particularly in the field of urology, and research on the development of liquid biopsies for urine is vigorously pursued [8]. The common features of all liquid biopsies are that they are less invasive than tissue biopsies, can be repeated in a timely manner, and that they provide information not only on one metastasis, but also on all cancers in the body. In this review, we focus on the utility of plasma cfDNA analysis in urological malignancies.

cfDNA AND ctDNA

cfDNA is fragmented DNA from cells undergoing apoptosis or necrosis, and is released into body fluids; each fragment consists of approximately 170 bases, which is roughly the number of nucleotides constituting a mononucleosome. However, it has been reported that there is variation in the size of cfDNA depending on the organ of origin and tumor or nontumor status, attempts are being made to use the size of cfDNA as a biomarker [9]. Since cfDNA retains the methylation status of cells of origin, in addition to genomic analysis, epigenomic analysis is also possible [10]. However, since cfDNA is fragmented, it does not provide information on transcripts or splice variants. Additionally, although structural variations such as gene fusion can be detected at the DNA level, sensitive identification using cfDNA is difficult because each fragment is very short. This limits the usefulness of cfDNA analysis in tumor types, where fusion genes are more important drivers than gene mutations, such as sarcoma.

A challenge common to all liquid biopsies, including cfDNA, is the discrimination between the information derived from normal cells and cancer cells. cfDNA is released from all cells in the body. Especially in plasma, most of the cfDNA is derived from leukocytes (Fig. 1). Tumor-derived cfDNA is called circulating tumor DNA (ctDNA), and the ctDNA fraction is the percentage of ctDNA among all cfDNA in the plasma. The ctDNA fraction can be as high as 30% or more, or less than 1% [11]. Even when the ctDNA fraction is less than 1%, the ctDNA information is clinically relevant [12], and a highly sensitive analysis system is required to accurately detect such low-frequency mutations. The analysis of cfDNA distinguishes ctDNA from cfDNA derived from normal cells mainly based on single nucleotide mutations. In other words, cfDNAs with mutations that are not found in the germline or human

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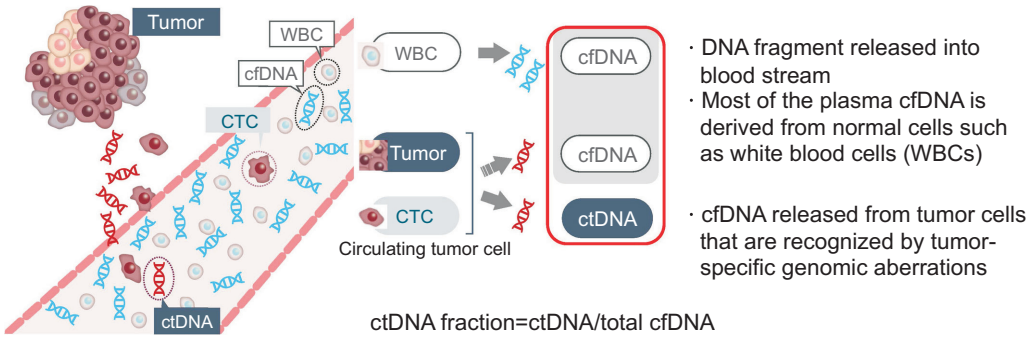

Fig. 1. Schema describing the differences between cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA). CTC, circulating tumor cell.

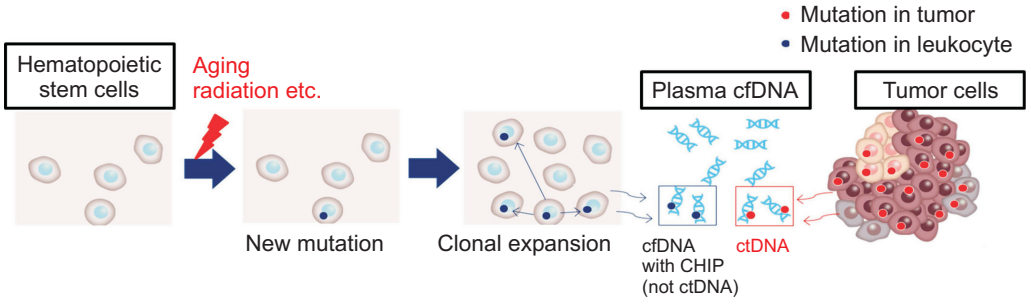

Fig. 2. Schema describing clonal hematopoiesis of indeterminate potential (CHIP). cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.

reference genome are considered ctDNAs. However, it has recently become clear that there is a major pitfall in this discrimination. Traditionally, the germline gene sequence was thought to be inherited by all normal somatic cells and remains unchanged as long as the cells remain normal. In other words, except in patients with hematologic cancers, the leukocyte DNA sequence was considered equivalent to the germline gene sequence. Recently, it was found that normal hematopoietic cells also accumulate gene mutations due to external stimuli, such as aging and radiation, and clonally proliferate (clonal hematopoiesis of indeterminate potential, CHIP) [13]. Therefore, in the plasma of patients with cancer, there is a mixture of cfDNA derived from perfectly normal leukocytes reflecting germline gene sequences, leukocyte-derived DNA with CHIP mutations, and ctDNA (Fig. 2). Thus, the assumption that "mutated DNA"="DNA derived from cancer cells" is no longer valid. To distinguish between CHIP and cancer cell-derived DNA, both cfDNA and leukocyte DNA should be analyzed in the same patient. However, currently commercialized FoundationOne Liquid CDx (Foundation Medicine, Cambridge, MA, USA) and Guardant360 (Guardant Health, Redwood City, CA, USA) both identify ctDNA based on the reference genome. There are many cases where the identified gene mutation is not actually derived from cancer cells, but is CHIP. The frequency of CHIP increases with age [14], and genes such as *ASXL1*, *ATM*, *CBL*, *CHEK2*, *DNMT3A*, *JAK2*, *KMT2D*, *MPL*, *MYD88*, *SF3B1*, *TET2*, *TP53*, and *U2AF1* are known to be susceptible to CHIP. Since CHIP is known to be particularly prevalent among low-frequency mutations [15, 16], CHIP should be strongly suspected, especially when mutations in the above genes are detected at allele frequencies of 1% or less. Among the genes associated with homologous recombination repair that are relevant for the use of PARP inhibitors, in addition to *ATM* and *CHEK2*, CHIP has been reported to be also present in *BRCA1* and *BRCA2*. Therefore, failure to correctly identify CHIP can lead to inappropriate use of PARP inhibitors [12]. The development of commercial gene panels that analyze both cfDNA and leukocyte DNA from the same patient is awaited.

Copy number variations, such as gene amplification, can also be detected by cfDNA analysis. For example, *AR*, the

driver gene for prostate cancer, undergoes amplification at the DNA level in many cases where castration resistance is acquired, often resulting in a 10-fold or higher copy number. Since *AR* is on the X chromosome and there is only one copy per cell, if the ctDNA fraction is 10% and the *AR* copy number is 10-fold, the copy number in the cfDNA analysis is calculated as 1 copy×0.9+10 copies×0.1=1.9, indicating that the cfDNA from the amplified *AR* region has approximately doubled (Fig. 3). However, the detection of copy number loss is difficult unless the ctDNA fraction is high (at least 20%) [17]. For example, in normal cells, there are 2 copies of *PTEN*, a gene often lost in prostate cancer. Assuming diploid status, if the ctDNA fraction is 10% and *PTEN* is lost in both alleles, the copy number in the cfDNA analysis is calculated as 2 copies×0.9+0 copy×0.1=1.8, which means a small decrease from 2 to 1.8 needs to be sensitively detected, which is not possible using current standard methods. Therefore, although FoundationOne Liquid CDx reports abnormalities in gene copy number, in Japan, copy number reports of FoundationOne Liquid CDx have not been approved for use in companion diagnostics. Furthermore, the consistency of blood tumor mutation burden (TMB) with tissue TMB has not been verified, and TMB in FoundationOne Liquid CDx has not been approved in Japan as a companion diagnostic. Microsatellite instability (MSI) can be analyzed using cfDNA, depending on the design method of the gene panel [18]. However, since FoundationOne Liquid CDx was not designed for this purpose, MSI detected with FoundationOne Liquid CDx is also unapproved as a companion diagnostic tool in Japan. In tumors where TMB, MSI, gene copy number alterations, or gene fusions are clinically more frequent and relevant for drug selection, comprehensive genomic profiling (CGP) using tumor tissue is preferable to CGP using cfDNA.

In addition to its use in CGP, ctDNA can also be quantified and used as a surrogate of disease volume. ctDNA fraction or the variant allele frequecy of ctDNA harboring a specific mutation may be used to monitor treatment response during therapy, or to detect minimally residual disease (MRD). Recently, it has also been reported that ctDNA fraction can be a good prognostic marker in 4 major types of cancer with metastasis (prostate cancer, breast cancer, non-small-cell lung cancer, and colorectal cancer) [18]. Even in cases where the shedding of ctDNA is low, methylation status of cfDNA derived from both cancer cells and surrounding stromal cells may be informative as a biomarker, and is actively being explored in research [19]. The role of cfDNA analysis in the clinical setting is expected to further expand beyond mutation detection in the future [20].

UTILITY AND LIMITATIONS OF cfDNA ANALYSIS IN PROSTATE CANCER

Prostate cancer is the most studied urological cancer in terms of liquid biopsy analysis. This is because *AR* is the driver of progression and drug resistance in almost all cases, and because *AR* is a single copy gene, the analysis can be performed without considering the alternate allele. Another advantage is that hotspots of mutations associated with drug resistance are already known. Furthermore, many cases of metastatic prostate cancer have only bone metastases at the time of progression, and biopsy of metastases is technically difficult and highly invasive. Therefore, liquid biopsy is highly anticipated. Prostate cancer has a relatively high ctDNA fraction among urological cancers. It does not have as many passenger mutations as urothelial carcinoma, making it easier to target the gene mutations identified for treatment.

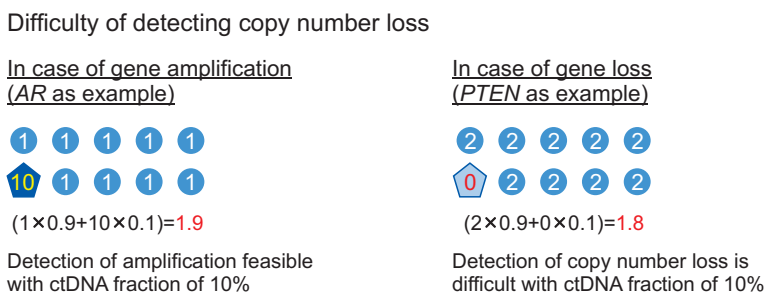

Fig. 3. Schema describing the difficulty of detecting copy number loss using cell-free DNA analysis. ctDNA, circulating tumor DNA.

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The reliability of cfDNA analysis has been demonstrated, for example, in the *post hoc* analysis of the PROfound study. In the PROfound study, the positive concordance rate for *BRCA1*, *BRCA2*, and *ATM* mutations was 81%, and the negative concordance rate was 92% when the results of tissue-based analysis using FoundationOne CDx and cfDNA based analysis by FoundationOne Liquid CDx results were compared [7]. In particular, the concordance rate for single nucleotide aberrations was 93% for nonsense variants, 87% for splice site variants, and 86% for frameshift variants, while the detection sensitivity of ctDNA was 63% for structural variants and 27% for copy number loss. In another *post hoc* analysis of the same study, among the cohort enrolled in the study with *BRCA1*, *BRCA2*, or *ATM* mutations, when the analysis was limited to patients who were also mutation positive using FoundationOne Liquid CDx, there were no differences in the hazard ratio for progression-free survival compared to the overall study group [21].

In cfDNA analysis, tumor volume can affect the detection of ctDNA, since the amount of ctDNA released in the bloodstream depends on tumor volume [22]. If the tumor volume is small, it may result in less ctDNA being released into the bloodstream, causing false-negative results. In fact, in the PROfound study, ctDNA was detected in 81% of all cases, and in approximately 20% of cases, ctDNA was undetectable. Furthermore, cfDNA has a short half-life in the blood, and the ctDNA fraction decreases rapidly after effective treatment. For example, in prostate cancer, the ctDNA fraction significantly decreases within 2 weeks after the initiation of hormonal therapy for untreated metastatic prostate cancer [23]. If cfDNA analysis is conducted in response to current therapy, or immediately after a drug change, the likelihood of false-negative results increases. However, ctDNA has been reported to be detected in 88% of cases of castration-resistant prostate cancer if cfDNA is collected immediately before a change of treatment, even in a cohort that included many cases before the first-line AR pathway inhibitor treatment for mCRPC [12], emphasizing the importance of analysis timing. Generally, CGP testing using tissue samples takes a relatively long time from test submission until the analysis results are reported. In some cases, test results cannot be reported because of problems with DNA quality or quantity. However, CGP testing using cfDNA shortens the time from test submission to reporting of analysis results, and there are few cases of test failure due to poor specimen quality [24]. It is therefore recommended to only perform the cfDNA test after confirming resistance to current therapy.

In Japan, regarding whether a tumor tissue-based test or a cfDNA test should be submitted as a CGP test, the Joint Task Force for the Promotion of Genomic Medicine of the Japanese Society of Clinical Oncology, the Japanese Cancer Association and the Japanese Society of Medical Oncology issued a "Policy Recommendation on the Proper Use of Cancer Genome Profiling Tests Using Circulating Tumor DNA in Blood" [25]. Among all solid tumors, prostate cancer is one of the tumor types for which cfDNA testing is the most clinically useful because (1) there are many cases with only bone metastasis progression; (2) the course of treatment is relatively long, and in many cases, more than 3 years have passed since the initial diagnostic biopsy when a CGP test is performed; (3) currently, fusion genes, TMB, and MSI are relatively less important in prostate cancer for the determination of drug use; (4) the detection rate of ctDNA in large-scale clinical trials is high, and the concordance rate with tumor tissue tests is also high [7, 26]. Alternatively, as mentioned above, cfDNA analysis cannot detect biallelic loss of *BRCA2* due to the low sensitivity of copy number analysis. Therefore, CGP using tumor tissue should be prioritized in cases where good quality DNA can be extracted from FFPE within 3 years of the initial biopsy, or in cases where metastatic sites can be biopsied relatively easily, such as liver or lymph node metastases.

In addition to CGP, cfDNA analysis has been applied for the early diagnosis and detection of MRD in other types of cancer [27]. However, the barrier to clinical application in these areas is high in prostate cancer, because prostate-specific antigen (PSA), a remarkably sensitive and inexpensive biomarker, is already available. There is also growing interest in the use of cfDNA epigenomic markers to diagnose neuroendocrine prostate cancer (NEPC), since a large shift in the epigenome occurs upon transdifferentiation from adenocarcinoma to NEPC [28, 29]. If the feasibility of this approach is confirmed, it would allow the early diagnosis of NEPC without performing a metastatic biopsy.

UTILITY AND LIMITATIONS OF cfDNA ANALYSIS IN UROTHELIAL CARCINOMA

Urothelial carcinoma is one of the most frequently mutated solid tumors [30, 31], and the concordance between tissue-based mutation analysis and cfDNA analysis is relatively high [32]. However, most of them are passenger mutations, and *FGFR3* is the only driver gene that can be targeted. Additionally, some upper urinary tract urothelial cancers are associated with Lynch syndrome and are MSI-high. However, since immune checkpoint inhibitors are approved for advanced urothelial cancers regardless of genomic abnormalities, the likelihood that CGP testing will lead to new treatments based on genomic abnormalities is much lower than for prostate cancer. In contrast, urothelial carcinoma does not have a sensitive biomarker like PSA, making the early diagnosis of recurrence and disease follow-up difficult. Tissue samples are easily obtained during transurethral surgery, cystectomy, or nephroureterectomy for urothelial carcinoma. If the genetic mutations of individual patients can be listed in advance from the sequencing of the tissue samples, and ctDNA can be detected using them as indicators, it will be possible to detect MRD and diagnose recurrence at an early stage. Christensen et al. [33] first extracted patient-specific genetic mutations by whole exon sequencing of tumor tissue in 68 patients with nonmetastatic muscle invasive bladder carcinoma, and then identified 16 patient-specific mutations for each patient. The usefulness of MRD detection using cfDNA was examined by constructing individualized gene panels consisting of 16 mutations per patient and analyzing them by ultradeep sequencing (105,000 × : mutations with allele frequencies of >0.01% can be detected) before and after preoperative adjuvant chemotherapy, before surgery, and periodically after surgery [33]. The results showed that patients who were ctDNA positive before preoperative chemotherapy, before total cystectomy, and after total cystectomy had significantly shorter progression-free survival and overall survival than patients who were ctDNA-negative. In particular, the presence or absence of postoperative ctDNA detection was the strongest predictor of recurrence-free survival in multivariate analysis. Additionally, 85% of patients who were ctDNA positive before chemotherapy but no longer had detectable ctDNA after chemotherapy showed pathological downstaging, while none of the patients in whom ctDNA was still detectable after chemotherapy showed downstaging. Furthermore, postoperative temporal analysis of ctDNA could identify tumor recurrence with 100% sensitivity and 98% specificity, and could detect recurrence approximately 3 months earlier than tumor recurrence identified by imaging studies. In muscle invasive bladder cancer, a 3-month delay in treatment can lead to disease progression and affect the outcome. Therefore, the detection of MRD by ctDNA may improve the outcome of muscle invasive bladder cancer treatment. IMvigor010, a phase III trial of adjuvant atezolizumab in muscle invasive urothelial carcinoma, did not show an improvement in disease-free survival in the general population [32]. However, in this study, a postoperative analysis of cfDNA was conducted using a 16-gene mini-panel generated for each patient based on tumor tissue sequencing data. When stratified by MRD status based on ctDNA, postoperative adjuvant atezolizumab therapy extended progression-free survival in patients who were MRD positive, while no differences were observed in patients who were MRD negative [33]. A new phase III trial (IMvigor011: NCT04660344) is currently ongoing to assess the benefit of postoperative adjuvant atezolizumab in patients who are MRD positive for ctDNA. If the results of the study are positive, it could be a game-changer for treating muscle invasive bladder cancer.

UTILITY AND LIMITATIONS OF cfDNA ANALYSIS IN RENAL CARCINOMA

In contrast to urothelial carcinoma, renal cell carcinoma (RCC) is one of the cancer types that releases the least amount of ctDNA among all cancer types [30]. It is still unclear whether this is due to low ctDNA release or if ctDNA is diluted by cfDNA from the rich stromal components of RCC. Similarly to *AR* in prostate cancer, *VHL* is the main driver of clear cell renal carcinoma, and more than half of cases have *VHL* aberrations. Therefore, detection of ctDNA based on *VHL* mutations could be a useful biomarker. However, a study has shown that even though *VHL* mutations were detected in 71.8% of tumor tissues, the same mutation was detected in cfDNA in only 25% of

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cases in the same patient using an assay system that can accurately detect allele frequencies down to 0.1%, indicating that the agreement between tumor tissues and the results of the cfDNA analysis was disappointingly low [34]. Several reports by various authors have discussed the usefulness of cfDNA analysis in renal cancer. For example, in cases where ctDNA was detectable, ctDNA amount (the allele frequency of ctDNA with specific mutation) was informative to track treatment response to tyrosine kinase inhibitors [34] or immune checkpoint inhibitors [35, 36]. However, in most studies, the concordance rate with tumor tissue for *VHL* mutations was as low as 30% [37-39], suggesting that the usefulness of cfDNA analysis for RCC using genetic mutations as markers is limited, at least with the current detection sensitivity. Further improvement in ctDNA detection method is necessary for clinical implementation. Alternatively, as mentioned previously, cfDNA also allows epigenomic analysis. Nuzzo et al. [19] developed a method to specifically immunoprecipitate methylated cfNA for comprehensive analysis (cfMeDIP-seq). Using this method, the group identified methylation patterns specific to RCC. The methylation information in this case included not only cancer cells, but also cfDNA derived from the surrounding stromal cells. With the model based on the methylation pattern, the authors could diagnose RCC with a high accuracy of area under the curve (AUC) 0.99 for blood cfDNA and AUC 0.85 for urine cfDNA. Although further validation is required, if the clinical application of this detection system is realized, it will become the first highly accurate diagnostic marker for RCC.

SUMMARY

Although liquid biopsy using cfDNA has been clinically implemented as a CGP test, its utility is not limited to CGP. The clinical utility of cfDNA analysis is expected to increase with the development of more sensitive analytical methods and advances in epigenomic analysis.

NOTES

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• Author Contribution: Conceptualization: SA; Data curation: SA; Formal analysis: SA, TS; Methodology: SA, KM, TS; Project administration: SA, TS; Visualization: SJ; Writing - original draft: SA; Writing - review & editing: SA, KM, TS, TG, TK.
• ORCID
Shusuke Akamatsu: https://orcid.org/0000-0002-1394-7506
Kei Mizuno: https://orcid.org/0000-0002-1273-5288
Takayuki Sumiyoshi: https://orcid.org/0000-0001-5321-6014
Takayuki Goto: https://orcid.org/0000-0001-6537-3068
Takashi Kobayashi: https://orcid.org/0000-0003-1069-2816

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ORIGINAL ARTICLE

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Epidemiology of Urologic Cancer in Korea: Nationwide Trends in the Last 2 Decades

Sang Heon Han[1], Hyeong Dong Yuk[1,2]

[1]Department of Urology, Seoul National University Hospital, Seoul, Korea
[2]Department of Urology, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author:
Hyeong Dong Yuk
Department of Urology, Seoul National University Hospital, Seoul National University College of Medicine, Seoul, Korea
Email: armenia8@snu.ac.kr
https://orcid.org/0000-0002-5874-9167

Purpose: This study assessed recent trends in the incidence of urologic cancer and patient survival in Korea.
Materials and Methods: The incidence of urologic cancer in Korea was calculated based on the Korea National Cancer Incidence Database and the South Korean Statistical Information Service Database. Data from 2000 to 2020 were used to determine the incidence, death, prevalence, and survival rates of urologic cancer.
Results: Urologic cancer was diagnosed in 27,514 cases, accounting for 11.1% of the total cancer incidence. In 2020, there were 16,815 prostate cancer cases, 5,946 kidney cancer cases, and 4,753 bladder cancer cases. The age-standardized rate (ASR) for the incidence of prostate, kidney, and bladder cancer increased from 2000 to 2020. The overall ASR was 56 per 100,000 in 2020. In 2000, the ASRs for prostate, kidney, and bladder cancer were 2.9, 3.1, and 4.8 per 100,000, respectively, whereas they were 32.7, 11.6, and 9.3 per 100,000, respectively, in 2020. Urologic cancer has also seen a steady increase in the death rate, prevalence rate, and relative survival rate over the past 20 years. The 5-year relative survival rates for patients diagnosed with prostate cancer, kidney cancer, and bladder cancer during the 5-year period from 2015 to 2019 were 94.4%, 84.7%, and 76.5%, respectively. Among urologic cancers, prostate cancer had the highest survival rate, and bladder cancer had the lowest.
Conclusions: The survival rate for urologic cancer is increasing; however, the incidence and prevalence rates continue to rise.

Key Words: Incidence, Epidemiology, Urinary bladder neoplasms, Kidney neoplasms, Prostate neoplasms, Urologic neoplasms

INTRODUCTION

Cancer is one of the leading causes of death worldwide [1]. According to World Health Organization estimates, there were approximately 19.3 million new cases and 10 million deaths from cancer worldwide in 2020 [1]. In addition, a report on global cancer statistics estimated that one in 5 people may experience cancer and 1 in 6 people will die from cancer [1, 2]. Cancer is a major public health problem worldwide, constituting the second leading cause of death in the United States and the leading cause of death in Korea [2, 3]. According to recent cancer statistics, 247,952 new cancers and 83,776 cancer-related deaths occurred in Korea in 2020 [3]. Furthermore, cancer incidence and death rates are increasing worldwide, and the burden of disease is rapidly increasing [4, 5]. These increases are related to changes in

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population growth, aging, and socioeconomic development [4-6]. Korea is also experiencing an increase in the older population owing to economic development, westernization, and rapid aging [7]. Urologic cancers are among those most closely related to this increase in the older population [1]. The incidence of urologic cancer in Korea has been steadily increasing due to the rapid increase in the older population, which is expected to continue in the future [7]. However, despite the known increase in the number of urologic cancer patients, data related to the epidemiological statistics of urologic cancer in Korea are very limited.

In this study, we report the most recent national statistics on the incidence, survival, prevalence, and death rates, as well as temporal trends, using national epidemiological data for prostate, kidney, and bladder cancers, the 3 most common urologic cancers in Korea.

MATERIALS AND METHODS

1. Data Sources

For annual statistics of urologic cancer, the Korea National Cancer Incidence Database (KNCI DB) [8] and the Korean Statistical Information Service Database data provided by the National Statistical Office of Korea were used [9].

The KNCI DB is a national, population-based database of cancer incidence that is currently used to calculate the National Cancer Registry statistics, which are published annually for data collection and refinement [8].

All carcinomas classified as malignant according to the International Classification of Diseases for Oncology, third edition and the International Classification of Diseases, 10th revision (ICD-10) were included in the analysis and then classified according to 24 carcinoma classifications, modified based on the carcinoma classification used by the International Agency for Research on Cancer [10].

2. Statistical Analysis

Data from 2000 to 2020 were used to determine the incidence and death rates of cancer. In the prevalence, data collection began in 2007 and continued until 2019. Therefore, unlike incidence and mortality, the data spanning from 2007 to 2019 was analyzed and presented. The survival rate was analyzed using data from 2001 to 2019. Data from the National Statistical Office were used to determine whether death had occurred, and the cause of death was coded and classified according to the ICD-10.

The cancer sites were classified as follows: prostate (C61), kidney (C64), and bladder (C67). To determine trends in urologic cancer incidence, the incidence, prevalence, and death rate rates were calculated per 100,000 people (crude rates [CRs]) and age-standardized rates (ASRs) based on the world standard population.

The CRs were calculated as the total number of incidence (crude incidence rate [CIR]), death rate (crude death rate [CDR]), or prevalence (crude prevalence rate [CPR]) cases divided by the annual population per year.

The ASR was standardized using the 2000 registered population and expressed per 100,000 people. In addition, to determine the distribution of urologic cancers according to age, cancer statistics from 2000 to 2020 were used to classify the total number of urologic cancers by age group.

RESULTS

1. Incidence Rate

The number of cancer cases in Korea increased by approximately 2.5 times, from 101,032 in 2000 to 247,952 in 2020. The 3 representative types of urologic cancer are kidney cancer, bladder cancer, and prostate cancer. In 2000, there were 1,455 prostate cancer cases, 979 kidney cancer cancers, and 1,744 bladder cancer cases, totaling 4,178 cases, corresponding to approximately 4.1% of the total cancer incidence rate. In 2020, there were 16,815 prostate cancer cases, 5,946 kidney cancer cases, and 4,753 bladder cancer cases, totaling 27,514 cases, accounting for 11.1% of the total cancer incidence; this number increased by 2.7 times (Table 1).

Regionally, the incidence was highest in Seoul, Gyeonggi Province, and cities with relatively large populations (Fig. 1, Supplementary Table 1).

In 2020, the CIR and ASR of overall urologic cancer incidence were 53.6 per 100,000 (96.7 for men, 10.6 for women) and 56 per 100,000 (106.9 for men, 10.1 for

Table 1. Trends in the incidence, death rate, and the mortality-to-incidence ratio of urologic cancer from 2000 to 2020 in Korea in both sexes

Variable	2000	2005	2010	2015	2020
Incidence (ASR)					
Total	5,091 (10.7)	9,206 (18.9)	15,430 (30.9)	19,175 (37.6)	27,514 (53.6)
Men	4,167 (17.4)	7,837 (32.1)	13,634 (54.6)	17,518 (68.8)	24,776 (96.7)
Women	924 (3.9)	1,369 (5.6)	1,796 (7.2)	2,257 (8.8)	2,738 (10.6)
Deaths (ASR)					
Total	1,843 (3.9)	2,475 (5.2)	3,225 (6.5)	3,951 (7.7)	4,863 (9.5)
Men	1,483 (6.2)	2,033 (8.3)	2,712 (10.9)	3,332 (13.1)	4,193 (16.4)
Women	360 (1.5)	442 (1.9)	513 (2.0)	619 (2.4)	670 (2.6)
M/I ratio (%)					
Total	36.2	26.9	20.9	20.6	17.7
Men	35.6	25.9	19.9	19.0	16.9
Women	39	32.3	28.6	27.4	24.5

Values are presented as number (%) unless otherwise indicated.
ASR, age-standardized rate per 100,000; M/I ratio, morality/incidence rate ratio.

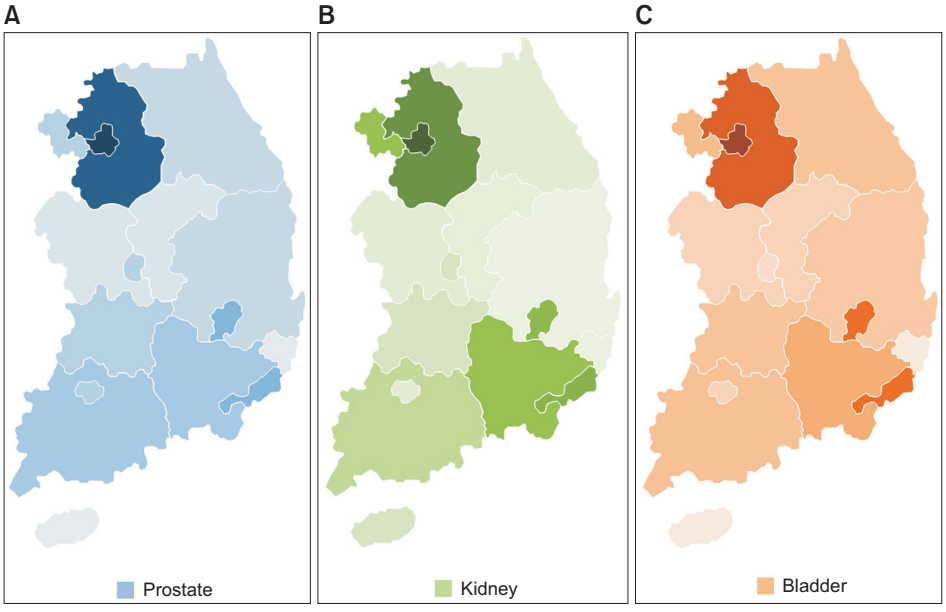

Fig. 1. Incidence map of prostate cancer (A), kidney cancer (B), and bladder cancer (C) by region.

Table 2. Trends in age-standardized incidence rate of urologic cancer from 2000 to 2020 in Korea in both sexes

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Prostate	6.6	8.7	9.5	11.3	13.5	14.3	16.4	19.1	21.6	23.4	24.3	26.0	25.8	25.3	25	24.9	27.7	28.8	31.8	34.5	32.7
Kidney	5.2	5.8	6.1	6.2	6.6	7.5	7.9	8.6	9.1	9.5	9.6	10.1	10.3	10.3	10.5	10.3	11.0	11.4	11.3	12.1	11.6
Male	8.2	8.8	9.2	9.5	10.3	11.5	11.9	13.1	13.8	14.1	14.7	15.2	15.5	15.5	15.8	15.3	15.9	16.5	16.8	17.6	16.9
Female	3.0	3.4	3.6	3.6	3.9	4.4	4.6	4.9	5.2	5.8	5.4	6.0	6.0	6.1	6.1	6.1	6.5	6.7	6.5	7.2	6.7
Bladder	9.8	10.5	10.2	10.6	10.9	11.0	10.8	10.8	10.7	10.3	10.5	10.5	9.9	10.1	10.2	9.8	10.2	9.9	9.9	10.0	9.3
Male	19.7	20.7	20.0	21.1	21.3	21.9	21.8	21.1	21.0	20.1	20.5	20.6	19.5	19.6	19.8	19.1	19.6	18.9	18.6	19.2	17.4
Female	3.5	3.9	3.8	3.8	3.8	3.8	3.6	3.9	3.7	3.6	3.6	3.6	3.3	3.4	3.4	3.4	3.6	3.4	3.5	3.3	3.2

women), respectively. (Table 2, Supplementary Table 2). The difference between the CIR and ASR values can be explained by the fact that the majority of urologic cancer patients are older individuals, while the global standard population has a high proportion of young people.

The ASR for the incidence of prostate, kidney, and bladder cancer increased from 2000 to 2020. This increase was relatively gradual for kidney and bladder cancers, whereas the incidence of prostate cancer has increased rapidly since 2005, and it has had the highest ASR among urologic cancers

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since 2003 (Fig. 2).

The incidence of kidney and bladder cancers was higher in men than in women. However, the annual percent change (APC) pattern of cancer incidence and death showed a greater change in women than in men. In kidney cancer, the APC increased more in women than in men (4.3% vs. 3.8%, respectively), and in bladder cancer, the APC decreased more in women than in men (-0.7% vs. -0.3%, respectively).

1) Incidence rate of prostate cancer

In 2000, there were 1,455 prostate cancer cases, while there were 16,815 cases in 2020—an approximately 11-fold increase. In 2000, the incidence of prostate cancer was lower than that of kidney and bladder cancers. However, it surpassed kidney cancer in 2001 and bladder cancer in 2004, becoming the most common urologic cancer. Since 2008, its incidence has been higher than that of bladder and kidney cancer (Supplementary Table 2).

The ASR showed a similar pattern. In 2000, the ASR was 2.9 per 100,000 people, while it was 32.7 per 100,000 people in 2020, an approximately 11-fold increase. In 2000, the incidence of prostate cancer was lower than that of kidney cancer (ASR, 3.1 per 100,000) and bladder cancer (ASR, 4.8 per 100,000), but it surpassed the ASR of kidney cancer in 2001 and bladder cancer in 2004 and 2008. The ASR of prostate cancer became approximately 2 times as high as those for the incidence of kidney and bladder cancer by 2018, and by 2020, it exceeded the ASRs for kidney and bladder cancer by roughly 3-fold (Table 2).

In an analysis of the incidence rate of prostate cancer by age using 2020 data, the incidence rate increased rapidly from the age of 50 years to peak at the ages of 75–79 years. Meanwhile, the ASR was 0.1 per 100,000 individuals in their 20s (Fig. 3, Supplementary Table 3).

2) Incidence rate of kidney cancer

In 2000, there were 979 cases of kidney cancer, while there were 5,946 cases in 2020—a 6-fold increase. Furthermore, it occurred more than twice as often in men than in women. In 2020, there were more cases of prostate cancer than of bladder cancer. In 2009, bladder cancer was the second most common cancer of the urinary system worldwide. Unlike

Fig. 2. Trends in the age-standardized incidence rate of urologic cancer from 2000 to 2020 in Korea, Urologic cancer (A), kidney cancer by sex (B), and bladder cancer by sex (C).

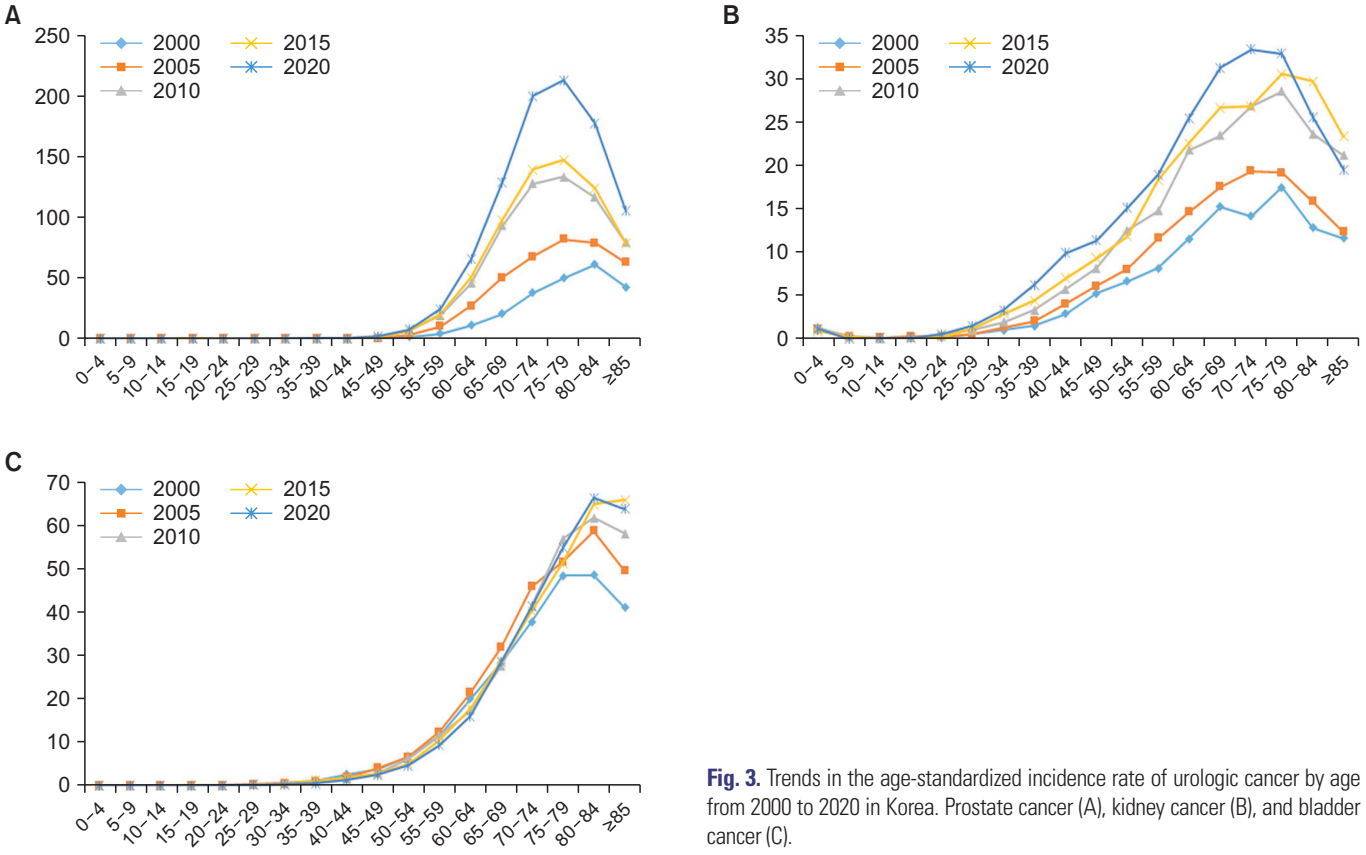

Fig. 3. Trends in the age-standardized incidence rate of urologic cancer by age from 2000 to 2020 in Korea. Prostate cancer (A), kidney cancer (B), and bladder cancer (C).

prostate cancer, which has increased rapidly, kidney cancer showed a gradually increasing incidence pattern, similar to that of bladder cancer (Supplementary Table 2).

In 2000, the ASR was 3.1 per 100,000 people, while it was 11.6 per 100,000 people in 2020, corresponding to an increase of approximately 3.7 times. In 2000, the incidence of kidney cancer was lower than that of bladder cancer (ASR, 4.8 per 100,000 people), but in 2009, it rose higher than the ASR of bladder cancer, showing a consistently high ASR until 2020 (Table 2).

In 2000, the ASR for incidence in men was 8.2 per 100,000, whereas it was 3 per 100,000 in women, showing a 2.7 times higher incidence rate in men than in women. In 2020, the ASR in men was 16.9 per 100,000, while that in women was 6.7 per 100,000, both reflecting more than a 2-fold increase since 2000 (Fig. 2, Supplementary Table 4).

An analysis of the incidence rate of kidney cancer by age using 2020 data showed that the incidence rate increased rapidly from the age of 40 years onward, peaking at the ages of 70–74. When analyzing men and women separately, the rate for men increased rapidly starting at the age of 35 years and reached a peak at the ages of 70–74, while that for women started increasing rapidly at the age of ≥50 years and peaked at the ages of 75–79 (Fig. 3, Supplementary Table 3).

3) Incidence rate of bladder cancer

In 2000, 1,744 cases of bladder cancer were reported, while there were 4,753 cases in 2020—an increase of approximately 2.7 times. Bladder cancer is 5 times more common in men than in women. In 2000, more cases of bladder cancer were observed than of other types of urologic cancer, but in 2020, bladder cancer occurred in fewer cases than prostate and kidney cancer. Unlike prostate cancer, which increased rapidly, bladder cancer showed a gradually increasing incidence pattern, similar to that of kidney cancer (Supplementary Table 2).

In 2000, the ASR was 4.8 per 100,000 people, but it increased to 9.3 per 100,000 people in 2020, approximately doubling. In 2000, the incidence of bladder cancer was higher than that of prostate cancer (ASR, 2.9 per 100,000 people) and kidney cancer (ASR, 3.1 per 100,000 people) (Table 2).

In 2000, the ASR for incidence in men was 19.7 per

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100,000, while it was 3.5 per 100,000 in women, indicating a 5.6 times higher incidence rate in men than in women. In 2005, the ASR in men peaked at 21.9 per 100,000, while the ASR in women peaked at 3.9 per 100,000 in 2007; by 2020, the ASR had decreased to 17.4 per 100,000 in men and 3.2 per 100,000 in women. These findings show a clear trend. Compared to 2000, the ASR of bladder cancer in 2020 was slightly lower in both men and women (Fig. 2).

An analysis of the incidence rate of bladder cancer by age using data from 2020 showed that the incidence rate increased rapidly after the age of 50 years and peaked at the age of 80–84 years. In men, it increased rapidly from the age of 50 years and continued to rise until the age of ≥85 years, while in women, it increased rapidly from the age of ≥65 years and continued to rise until ≥85 years of age (Fig. 3, Supplementary Table 4).

2. Death Rate

The number of all cancer deaths in Korea totaled 59,117 in 2000, and the CDR was 124.5 per 100,000 people. In 2020, there were a total of 83,776 cancer deaths, and the CDR was 164.3 people per 100,000 people. In 2000, there were 548 deaths from prostate cancer, 517 from kidney cancer, and 778 from bladder cancer, totaling 1,843, which corresponded to approximately 3.1% of the total cancer death rate. The CDRs for prostate, kidney, and bladder cancer were 1.2, 1.1, and 1.6 per 100,000 people, respectively. In 2020, there were 2,194 deaths from prostate cancer, 1,076 deaths from kidney cancer, and 1,593 deaths from bladder cancer. These figures correspond to 5.8% of all cancer deaths, and the number of deaths has increased by approximately 2-fold compared to that in 2000. The CDRs for prostate, kidney, and bladder cancer were 4.6, 2, and 3 per 100,000 people, respectively. Compared to 2020, the number of deaths from prostate cancer increased by approximately 4 times, and the number of deaths from kidney and bladder cancer roughly doubled (Table 3).

In men, the CDR in 2000 was 2.3 per 100,000 men for prostate cancer, 1.4 for kidney cancer, and 2.5 for bladder cancer, whereas in 2020, the CDR per 100,000 men was 9.2 for prostate cancer, 2.8 for kidney cancer, and 4.5 for bladder cancer. The CDR for prostate cancer increased by about 4 times, that of kidney cancer roughly doubled, and that of bladder cancer increased by about 1.8 times (Table 3).

In women, the CDR in 2000, the CDR was 0.7 per 100,000 women for kidney cancer and 0.8 for bladder cancer; by 2020, the CDR increased to 1.2 per 100,000 women for kidney cancer and 1.5 per 100,000 women for bladder cancer, corresponding to an increase by about 1.7 times for kidney cancer and 1.9 times for bladder cancer. Men had higher death rates than women due to kidney and bladder cancer (Table 3).

1) Death rate associated with prostate cancer

The number of deaths due to prostate cancer quadrupled from 548 in 2000 to 2,194 in 2020. In 2000, the number of deaths from prostate cancer was higher than that from kidney cancer and lower than that from bladder cancer. However, since 2006, it has outpaced bladder cancer deaths and has been the leading cause of urologic cancer deaths.

The CDR followed a similar pattern. In 2000, the CDR was 1.2 per 100,000 people, and in 2020, it was 4.3 per 100,000 people—an increase of approximately 3.5 times. In 2000, the death rate of prostate cancer was higher than that of kidney cancer (CDR, 1.1 per 100,000 people) and lower than that of bladder cancer (CDR, 1.6 per 100,000 people). In 2020, it had the highest death rate among urologic cancers, with approximately 2 times the CDR of kidney cancer and 1.4 times the CDR of bladder cancer (Fig. 4, Supplementary

Table 3. Trends in the crude death rate of urologic cancer from 2000 to 2020 in Korea in both sexes

Variable	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020
Prostate	1.2	1.3	1.5	1.6	1.9	1.9	2.1	2.3	2.4	2.5	2.7	2.8	2.9	3.2	3.3	3.3	3.4	3.6	3.9	4.0	4.3
Kidney	1.1	1.1	1.2	1.3	1.2	1.4	1.4	1.5	1.3	1.5	1.6	1.7	1.8	1.9	1.9	1.9	2.0	2.0	1.9	1.9	2.1
Male	1.4	1.5	1.6	1.8	1.7	1.8	2.0	1.9	1.9	2.0	2.3	2.3	2.6	2.6	2.6	2.6	2.8	2.7	2.6	2.6	3.0
Female	0.7	0.6	0.8	0.8	0.7	0.9	0.8	1.0	0.8	1.0	0.9	1.0	1.0	1.1	1.1	1.1	1.2	1.2	1.2	1.2	1.2
Bladder	1.6	1.7	1.9	2.0	1.8	1.9	1.9	1.9	2.0	1.9	2.2	2.3	2.4	2.5	2.7	2.5	2.7	2.8	2.7	3.0	3.1
Male	2.5	2.4	3.0	2.9	2.7	2.8	2.9	2.9	3.0	2.9	3.3	3.4	3.6	3.9	4.0	3.8	4.0	4.3	4.1	4.6	4.8
Female	0.8	1.0	0.9	1.0	0.9	1.0	0.9	1.0	1.0	1.0	1.1	1.3	1.2	1.2	1.3	1.3	1.4	1.3	1.3	1.5	1.4

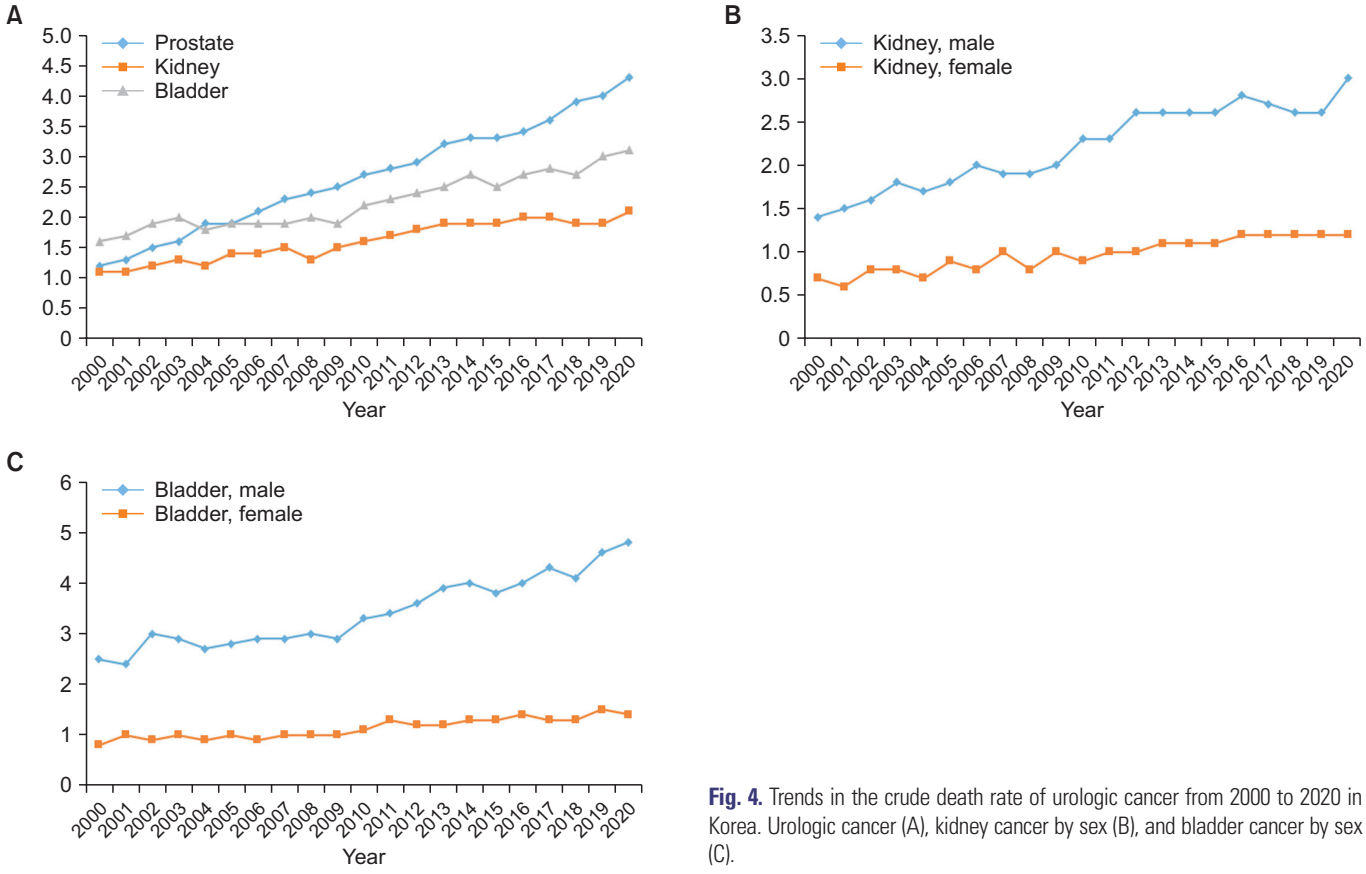

Fig. 4. Trends in the crude death rate of urologic cancer from 2000 to 2020 in Korea. Urologic cancer (A), kidney cancer by sex (B), and bladder cancer by sex (C).

Table 5).

In an analysis of the death rate of prostate cancer by age using 2020 data, the death rate increased rapidly from the age of 70 years and peaks at the ages of 85–89 years. In addition, the CDR was 0.2 per 100,000 people in the 50–54 years age range (Fig. 5).

2) Death rate associated with kidney cancer

The number of deaths from kidney cancer doubled from 517 in 2000 to 1,076 in 2020, with twice as many deaths in men as in women. In both 2000 and 2020, kidney cancer had the lowest number of deaths among urologic cancers. Compared to 2000, the number of deaths in 2020 showed an increase, but this increase was relatively modest compared to the other types of urologic cancer.

In 2000, the CDR of kidney cancer was 1.1 per 100,000 people, and in 2020, it was 2.1 per 100,000 people—an increase of approximately 1.9 times. In 2000, the death rate of kidney cancer was lower than that of prostate cancer (CDR, 1.2 per 100,000 people) and bladder cancer (CDR, 1.6 per 100,000 people) (Fig. 4).

In 2000, the CDR in men was 1.4 per 100,000 people, while that in women was 0.7 per 100,000 people, showing a death rate twice as high for men than for women. In 2020, the CDR in men was 3 per 100,000, while that in women was 1.2 per 100,000; both of these rates more than doubled from 2000, and the death rate for men was approximately 3.6 times higher than that of women (Fig. 4).

An analysis of the death rate of kidney cancer by age using data from 2020 showed that the incidence rate increased rapidly after the age of 70 years and peaked at the ages of 85–89. The rate for men increased rapidly starting at the age of 65 and continued to rise until after the age of 90, while that for women increased rapidly at ≥60 years of age, peaking at the ages of 85–89 (Fig. 5).

3) Death rate associated with bladder cancer

The number of deaths from bladder cancer doubled from 778 in 2000 to 1,593 in 2020, with 3 times more deaths in men than in women. In 2000, bladder cancer accounted for the highest number of deaths among urologic cancers, whereas in 2020, it caused the second-highest number of

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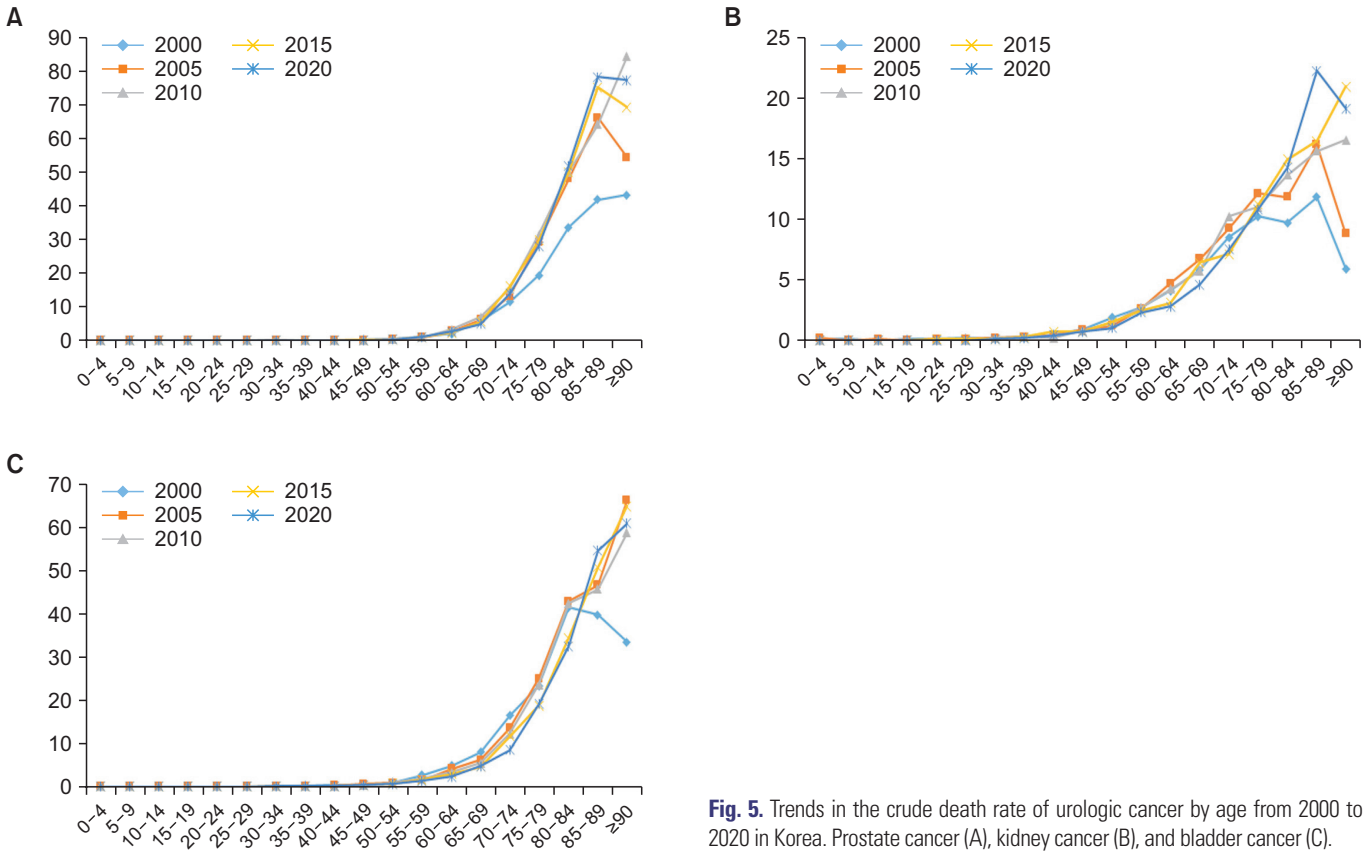

Fig. 5. Trends in the crude death rate of urologic cancer by age from 2000 to 2020 in Korea. Prostate cancer (A), kidney cancer (B), and bladder cancer (C).

deaths. The number of deaths gradually increased.

In 2000, the CDR was 1.6 per 100,000 people, while it was 3.1 per 100,000 people in 2020—an increase of approximately 1.9 times. In 2000, the death rate of bladder cancer was higher than that of prostate cancer (CDR, 1.2 per 100,000 people) and kidney cancer (CDR, 1.1 per 100,000 people) (Fig. 4).

In 2000, the CDR in men was 2.5 per 100,000 people, while that in women was 0.8 per 100,000 people, showing a death rate about 3.1 times higher for men than for women. In 2020, the CDR in men was 4.8 per 100,000 people and that for women was 1.4 per 100,000 people. Compared to 2000, the CDR increased by approximately 1.9 times for men and 1.7 times for women (Fig. 4).

In an analysis of the death rate of bladder cancer by age using data from 2020, the incidence rate increased rapidly from the age of 70 years and continued to rise until ≥90 years of age. The death rate for men increased rapidly from the age of ≥65 years and continued to rise until ≥90 years of age; for women, it increased rapidly from the age of ≥75 years and continued to rise until ≥90 years of age (Fig. 5).

3. Prevalence Rate

The total number of cancer patients in 2020 in Korea was 2,276,792; this number has continued to increase since it exceeded 2 million in 2018. The prevalence of cancer in Korea in 2020 was 4,433.9 per 100,000 people.

In 2020, the prevalence of urologic cancer was 120,423 for prostate cancer, 54,652 for kidney cancer, and 41,835 for bladder cancer, corresponding to rates of 442.4 per 100,000 people for urologic cancer and 234.5, 106.4, and 81.5 per 100,000 people for prostate, kidney, and bladder cancer, respectively.

1) Prevalence rate of prostate cancer

The prevalence of prostate cancer increased by approximately 3.6 times, from 16,549 in 2007 to 60,347 in 2019 (Supplementary Table 6). The prevalence of prostate cancer in 2007 was higher than that of kidney or bladder cancer and remained high through 2019 (Fig. 6).

The CPR and ASR for prevalence followed a similar pattern. In 2007, the CPR was 33.7 per 100,000 people, while

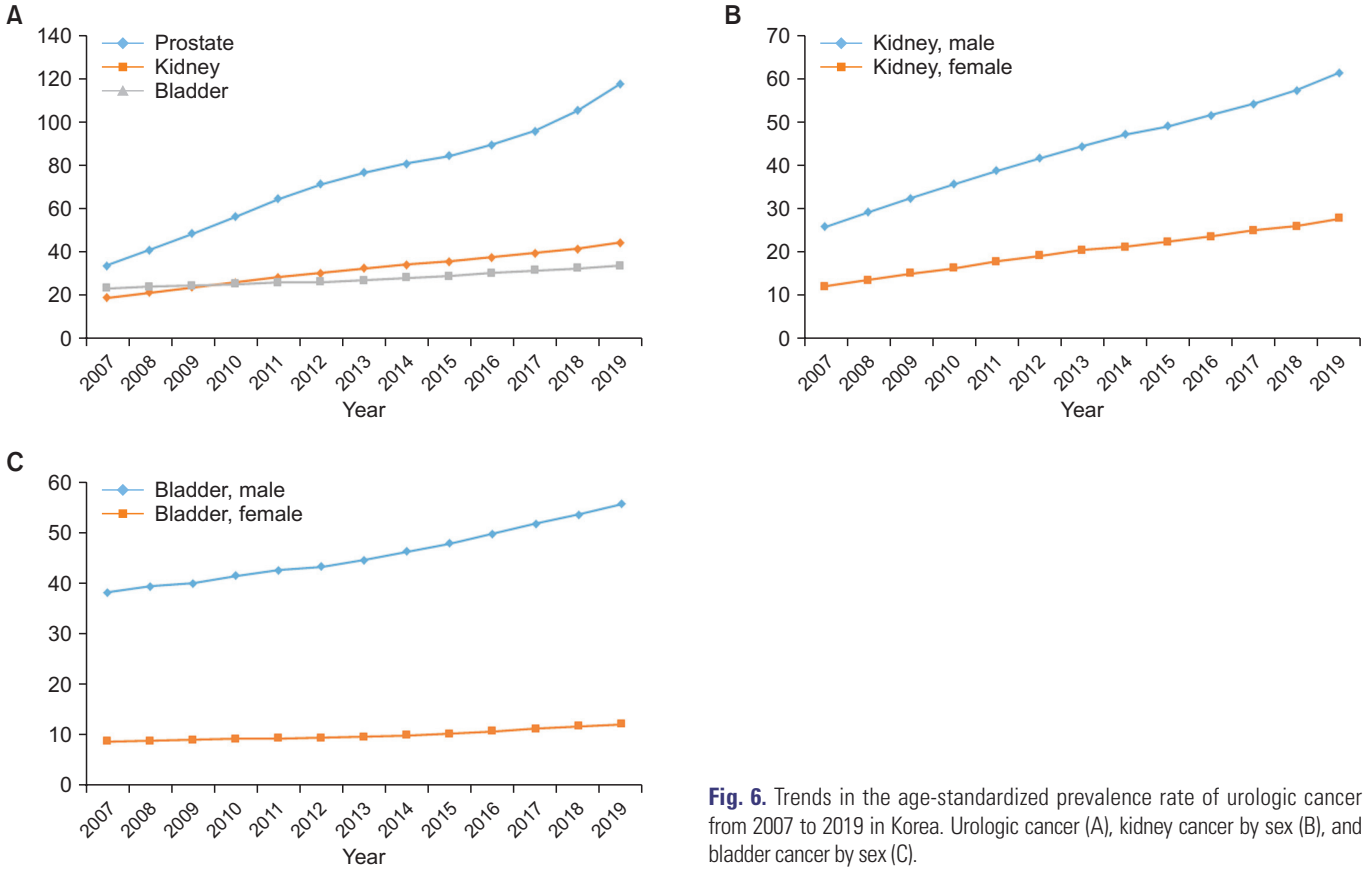

Fig. 6. Trends in the age-standardized prevalence rate of urologic cancer from 2007 to 2019 in Korea. Urologic cancer (A), kidney cancer by sex (B), and bladder cancer by sex (C).

Table 4. Trends in the age-standardized prevalence rate of urologic cancer from 2007 to 2019 in Korea in both sexes

Variable	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
Prostate	25.3	29.6	33.6	37.6	41.5	43.8	45.1	45.7	46.0	47.0	48.2	50.7	54.3
Kidney	15.7	17.2	18.5	19.7	20.9	21.9	22.8	23.4	23.9	24.5	25.3	26.0	27.4
Male	22.9	25.0	26.9	28.7	30.3	31.7	32.9	34.0	34.3	35.2	36.1	37.4	39.1
Female	9.5	10.4	11.2	11.8	12.7	13.2	13.7	13.9	14.2	14.6	15.2	15.4	16.3
Bladder	18.1	17.8	17.2	30.2	31.3	32.1	32.9	32.8	34.5	35.2	40.4	35.9	36.4
Male	35.1	34.7	33.9	33.6	33.0	32.0	31.6	31.5	31.1	30.9	30.6	30.1	29.8
Female	5.9	5.8	5.7	5.5	5.3	5.2	5.1	5.0	5.1	5.2	5.2	5.3	5.3

it was 117.5 per 100,000 people in 2019—an increase of approximately 3.5 times. (Supplementary Table 7). In 2007, the ASR was 25.3 per 100,000 people, while it was 54.3 per 100,000 people in 2019, corresponding to an increase of approximately 2.1 times. In 2007 (Table 4), the prevalence of prostate cancer was higher than that of kidney cancer (CPR, 19.1 per 100,000 people) and bladder cancer (CPR, 23.5 per 100,000 people); in 2019, it was approximately 2.6 times higher than the CPR for kidney cancer and 3.5 times higher than the CPR for bladder cancer. Prostate cancer has the highest prevalence of all urologic cancers (Fig. 6).

An analysis of the prevalence of prostate cancer by age from 2007 to 2019 showed that it increased rapidly after the age of 50 and peaked at the ages of 70–79. Since 2007, the prevalence of prostate cancer increased in all age groups >50 years (Fig. 7, Supplementary Table 8).

2) Prevalence rate of kidney cancer

The prevalence of kidney cancer increased by approximately 2.4 times, from 9,382 in 2007 to 22,817 in 2019. In 2007, the prevalence of prostate cancer was lower than that of kidney or bladder cancer, but it became higher than that of bladder cancer in 2010 and showed a consistently high prevalence until 2019.

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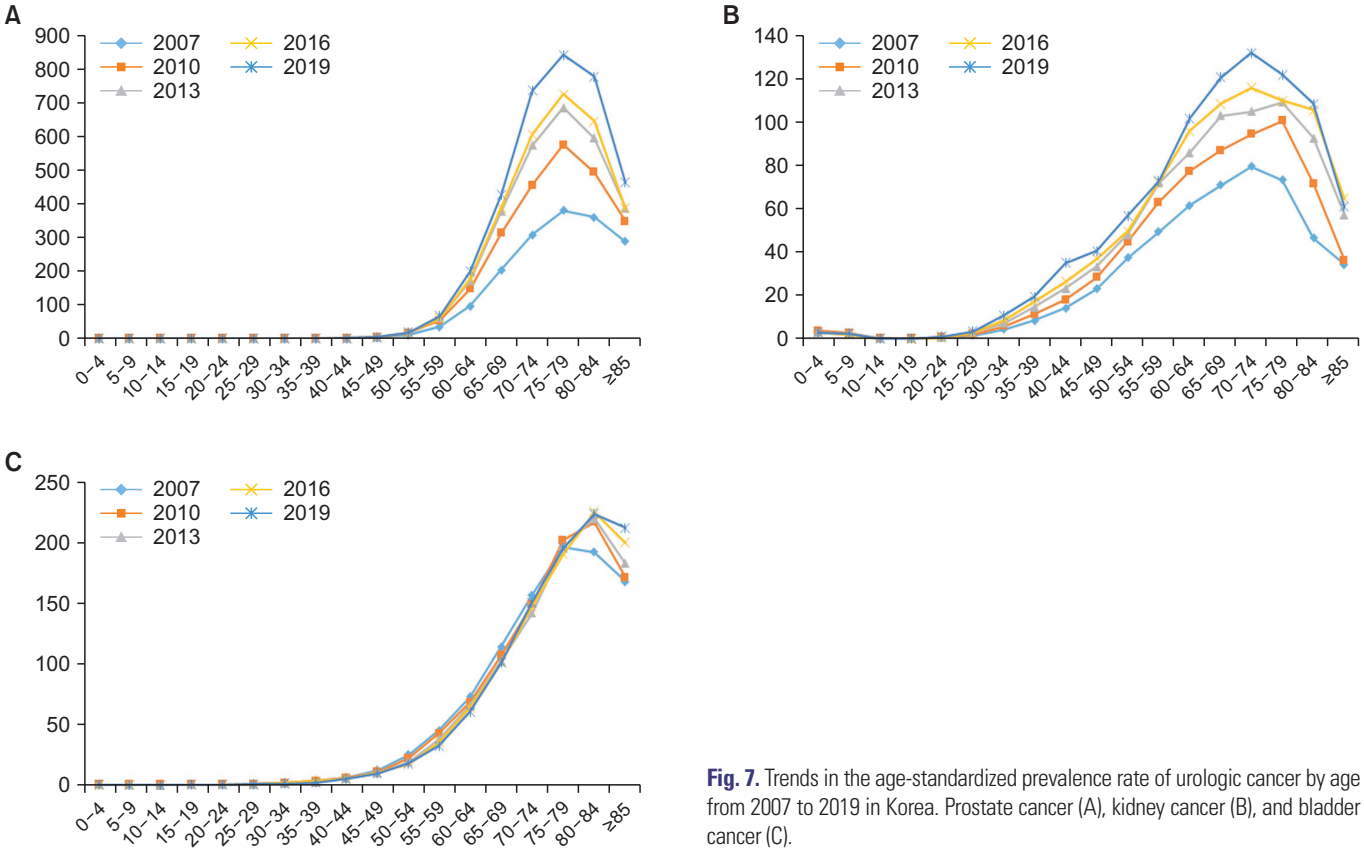

Fig. 7. Trends in the age-standardized prevalence rate of urologic cancer by age from 2007 to 2019 in Korea. Prostate cancer (A), kidney cancer (B), and bladder cancer (C).

The CPR followed a similar pattern. In 2007, the CPR was 19.1 per 100,000 people, while it was 44.4 per 100,000 people in 2019—an increase of about 2.3 times. In 2007, the prevalence of kidney cancer was lower than that of prostate cancer (CPR, 33.7 per 100,000 people) and bladder cancer (CPR, 23.5 per 100,000 people). It consistently showed a higher prevalence than bladder cancer.

In 2007, the CPR in men was 25.9 per 100,000 people, while in women it was 12.2 per 100,000 people, showing a 2.1 times higher prevalence in men than in women. In 2019, the CPR in men was 61.2 per 100,000 people and the CPR in women was 27.5 per 100,000 people, both more than double the corresponding rates in 2007. The prevalence rate in men was approximately 2.2 times higher than that in women.

An analysis of the prevalence of kidney cancer by age from 2007 to 2019 showed that it increased rapidly after ≥30 years of age and peaked at the ages of 70–74. Since 2007, the prevalence of kidney cancer has increased in all age groups >30 years (Fig. 7).

3) Prevalence rate of bladder cancer

The prevalence of bladder cancer increased by approximately 1.5 times, from 11,535 in 2007 to 17,376 in 2019. In 2007, the prevalence of bladder cancer was lower than that of prostate cancer, but higher than that of kidney cancer; it was lower than that of kidney cancer in 2010 and showed the lowest prevalence among urologic cancers until 2019 (Supplementary Table 6).

The CPR followed a similar pattern. In 2007, the CPR was 23.5 per 100,000 people, while it was 33.8 per 100,000 people—an increase of about 1.4 times. In 2007, the prevalence of bladder cancer was lower than that of prostate cancer (CPR, 33.7 per 100,000 people) and higher than that of kidney cancer (CPR, 19.1 per 100,000 people). In 2019, the CPR was 25.4 per 100,000 people, which was lower than that of kidney cancer (CPR, 26 per 100,000 people) (Supplementary Table 7).

In 2007, the CPR in men was 38.1 per 100,000 people, while that in women was 8.8 per 100,000 people, showing a 4.3 times higher prevalence in men than in women. In 2019, the CPR in men was 55.6 per 100,000 people, and the CPR

in women was 12.2 per 100,000 people, both approximately 1.4 times higher than in 2007; the prevalence in men was approximately 4.5 times higher than that in women (Supplementary Table 7).

In 2007, the ASR for prevalence was 18.1 per 100,000 people, while it was 36.4 per 100,000 people—an increase of about 2 times. In 2007, the prevalence of bladder cancer was lower than that of prostate cancer (ASR, 25.3 per 100,000 people) and higher than that of kidney cancer (ASR, 15.7 per 100,000 people). In 2019, the ASR was 36.4 per 100,000 people, which was higher than that of kidney cancer (CPR, 27.4 per 100,000 people) (Table 4).

In 2007, the ASR for prevalence in men was 35.1 per 100,000 people, while it was 5.9 per 100,000 people in women, showing a prevalence 5.9 times higher in men than in women. In 2019, the ASR in men was 29.8 per 100,000 people and 5.3 per 100,000 people in women. Both of these rates were lower than in 2007, and the prevalence in men was approximately 5.6 times higher than that in women (Table 4).

An analysis of the prevalence of bladder cancer by age from 2007 to 2019 showed that it increased rapidly after the age of 40 and peaked at the ages of 80–84. Since 2007, there has been no major increase in the prevalence of bladder cancer in any age group, but it tended to increase in those >75 years of age (Fig. 7).

4. Survival Rate

Over the past 20 years, the relative survival rates of patients with cancer have increased significantly and steadily. The 5-year relative survival rate for all patients diagnosed with cancer during the 5-year period from 2015 to 2019 was 70.7%; the sex-specific rates were 64.5% in men and 77.3% in women.

Urologic cancer has also seen a steady increase in relative survival rates over the past 20 years. The relative survival rates between 1993 and 1995 were 59.1%, 64.2%, and 70.7% for prostate, kidney, and bladder cancer, respectively (Fig. 8). The 5-year relative survival rates for patients diagnosed with prostate cancer, kidney cancer, and bladder cancer during the 5-year period from 2015 to 2019 were 94.4%, 84.7%, and 76.5%, respectively (Fig. 8). Among urologic cancers, prostate cancer had the highest survival rate and bladder cancer had the lowest.

The relative survival rate of kidney cancer showed little difference by sex, with 84.7% for men and 84.8% for women. For bladder cancer, men had a higher relative survival rate than women (78.1% vs. 70%, respectively) (Supplementary Table 9).

DISCUSSION

The significance of this study is that it describes the nationwide cancer incidence, mortality, and prevalence of urologic cancer from 2000 to 2020 in Korea. The prostate, kidney, and bladder represent the most common primary sites of urologic cancer in Korea. Compared to the cancer incidence rate reported in GLOBOCAN 2020, the overall ASR of Korean men for prostate cancer is higher than the global average (ASR, 32.7 vs. 30.7 per 100,000 people) and similar to that reported in Western Africa (ASR, 33.1 per 100,000 people) [1]. The prostate cancer death rate is lower than the global average (ASR, 4.3 vs. 7.7 per 100,000 people) and lower than the Eastern Asian average (ASR, 4.7 per 100,000 people). The incidence rate of prostate cancer changed in the late 2000s in Northern and Western Europe, with a decrease in the incidence due to the limited use of prostate-specific antigen (PSA) tests. A similar, albeit less distinct, pattern was also observed in South America, Central America, and Asia. However, cases in Korea have continued to increase, similar to China or Eastern European countries [11-13]. Prostate cancer mortality has declined since the mid-1990s in developed countries such as those in North America, Northern and Western Europe, and Oceania [11, 14, 15], which likely reflects early detection through increased screening and advances in early-stage treatment and treatment technology [16, 17]. However, in Korea, the mortality rate has continued to rise. Similarly, there the mortality rate has increased in Central and Eastern Europe, Asia, and Africa, likely reflecting the continued increase in incidence in these regions and the increasing effectiveness of screening tests such as PSA testing [16, 17].

The incidence of kidney cancer in Korean men is higher than the global average (ASR, 8.2 vs. 6.1 per 100,000 people). The death rate in Korean men is also higher than the global average (ASR, 3.0 vs. 2.5 per 100,000 people). The incidence

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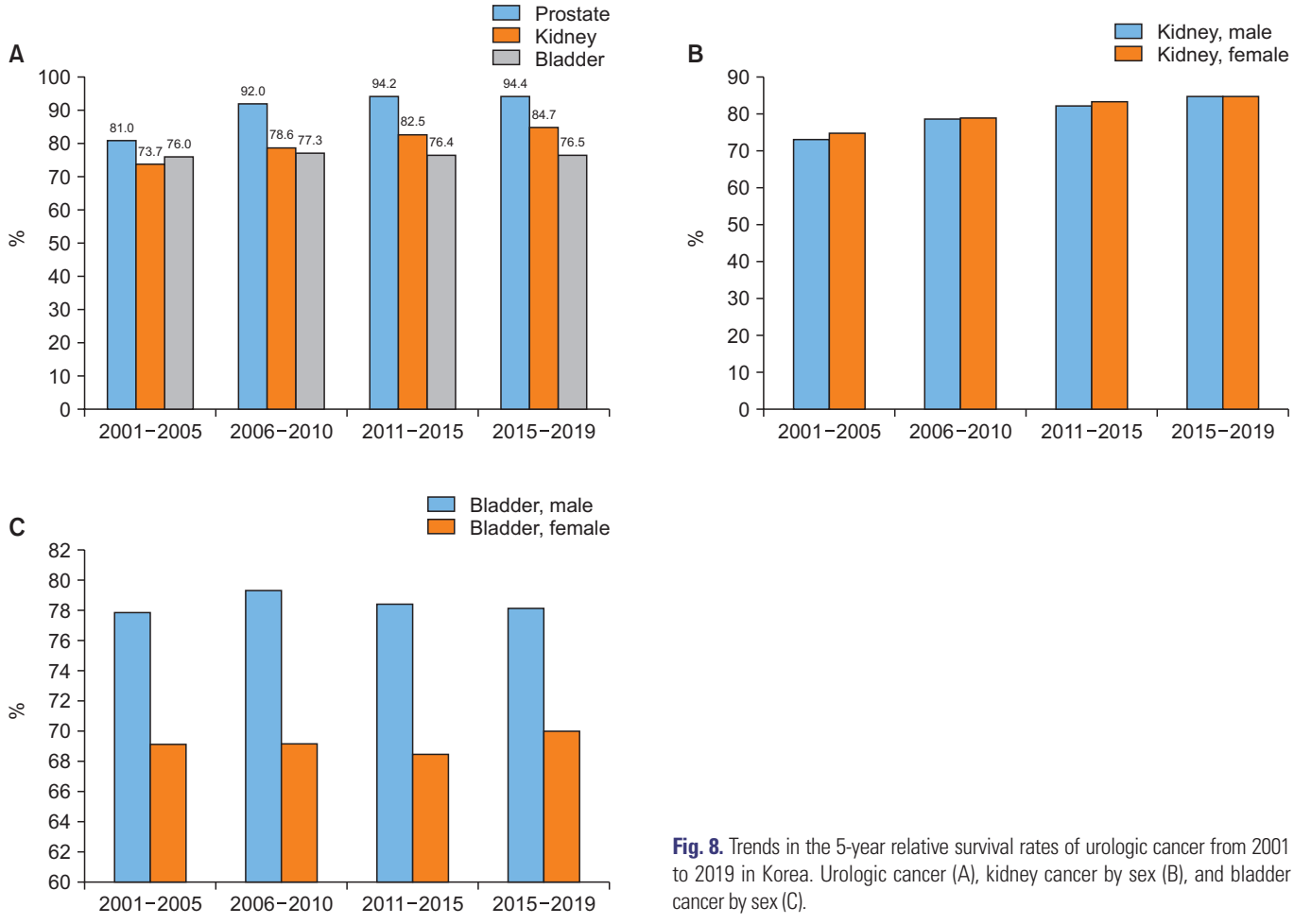

Fig. 8. Trends in the 5-year relative survival rates of urologic cancer from 2001 to 2019 in Korea. Urologic cancer (A), kidney cancer by sex (B), and bladder cancer by sex (C).

of kidney cancer in Korean women is also higher than the global average (ASR, 6.7 vs. 3.2 per 100,000 people). However, the death rate for Korean women was the same as the world average (ASR, 1.2 vs. 1.2 per 100,000 people).

The incidence of bladder cancer in Korean men is also higher than the world average (ASR, 17.4 vs. 9.5 per 100,000 people). It is similar to that of North America (ASR, 18.1 per 100,000 people). However, the death rate for Korean men is similar to the global average (ASR, 3.2 vs. 3.3 per 100,000 people). The incidence of bladder cancer in Korean women is also higher than the global average (ASR, 4.8 vs. 1.2 per 100,000 people). It is also similar to that of North America (ASR, 4.7 per 100,000 people). The death rate of Korean women is also higher than the global average (ASR, 1.4 vs. 0.9 per 100,000 people). Since 2000, the incidence of bladder cancer has been observed to vary by sex in many countries. The incidence in men has tended to stabilize or decrease, while that in women has shown an increasing trend in some European countries [18, 19]. However, Korea has shown increasing incidence in both men and women. The increasing incidence of bladder cancer in women is presumed to be partly related to an increase in women's smoking rate [20]. Bladder cancer mortality has decreased in major developed countries due to the diversification of treatment methods and the development of immunotherapeutic agents, but it has tended to increase in Korea.

CONCLUSIONS

Since 2000, the number of patients with urologic cancer in Korea has increased. The incidence of prostate, kidney, and bladder cancer has also continued to rise. In 2004, prostate cancer surpassed kidney cancer and ranked first among urologic cancers. The morbidity and death rate rates also continued to increase, and men had higher prevalence and death rates than women with kidney and bladder cancers.

As of 2019, the 5-year relative survival rates of patients diagnosed with prostate cancer, kidney cancer, and bladder cancer significantly improved to 94.4%, 84.7%, and 76.5%, respectively. The survival rates for urologic cancer are increasing; however, the incidence and prevalence rates continue to rise.

NOTES

- Supplementary Materials: Supplementary Tables 1–9 can be found via https://doi.org/10.22465/juo.234600080004.
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- ORCID

Sang Heon Han: https://orcid.org/0009-0002-3312-8521

Hyeong Dong Yuk: https://orcid.org/0000-0002-5874-9167

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ORIGINAL ARTICLE

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Bladder Cancer in South Korea: Analysis of Trends and Risk Factors of Bladder Cancer in South Korea Using a Nationwide Database

Sangjun Yoo[1], Kyung-Do Han[2], Kwang Taek Kim[3], Woo Suk Choi[4], Yun-Sok Ha[5], Jeong Hyun Kim[6], Cheol Kwak[7]

[1]Department of Urology, Seoul Metropolitan Government - Seoul National University Boramae Medical Center, Seoul, Korea
[2]Department of Statistics and Actuarial Science, Soongsil University, Seoul, Korea
[3]Department of Urology, Gachon University Gil Medical Center, Incheon, Korea
[4]Department of Urology, Konkuk University Medical Center, Konkuk University School of Medicine, Seoul, Korea
[5]Department of Urology, School of Medicine, Kyoungpook National University, Daegu, Korea
[6]Department of Urology, Kangwon National University School of Medicine, Chuncheon, Korea
[7]Department of Urology, Seoul National University College of Medicine, Seoul, Korea

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Corresponding author:
Cheol Kwak
Department of Urology, Seoul National University College of Medicine, Seoul, Korea
Email: mdrafael@snu.ac.kr
https://orcid.org/0000-0002-1987-2111

Co-Corresponding author:
Jeong Hyun Kim
Department of Urology, Kangwon National University School of Medicine, Chuncheon, Korea
Email: Urodr348@kangwon.ac.kr
https://orcid.org/0000-0002-8942-0188

Purpose: The purpose of this study was to evaluate the incidence rate and trend of bladder cancer in South Korea using a nationwide database. In addition, we aimed to determine the risk factors and their influence on the incidence of bladder cancer.

Materials and Methods: We extracted data from the health insurance database and estimated the incidence rate of newly developed bladder cancer from 2007 to 2019. In addition, we conducted further analysis of 10,210,654 individuals who underwent general health check-ups in 2009 to investigate the risk factors for bladder cancer. Variables associated with bladder cancer were evaluated using Cox regression analysis.

Results: Bladder cancer significantly increased especially in the last 10 years. In 2019, 21.07 people per 100,000 were diagnosed with bladder cancer, whereas 13.62 people per 100,000 were diagnosed with bladder cancer in 2007. The compound annual increase rate from 2007 to 2019 was 3.7%. Among 10,210,654 individuals who had general health check-ups in 2009, bladder cancer was diagnosed in 83 people per 100,000 population in the 10-year follow-up. After adjusting for other variables, smoking-related variables were most significantly associated with bladder cancer incidence, followed by metabolic syndrome and its related variables. In the further analysis of the effect of smoking on bladder cancer according to sex, the smoking amount was more significantly associated with bladder cancer incidence in women compared to that in men.

Conclusions: The crude incidence of bladder cancer continuously increased in South Korea during the last 10 years. Smoking, in addition to sex, age, and metabolic syndrome-related variables, was significantly associated with bladder cancer, especially in women.

Key Words: Incidence, Smoking, Urinary bladder neoplasms

INTRODUCTION

Bladder cancer was ranked as the 10th most common cancer and the 6th most common male cancer worldwide in 2020 [1]. Although the incidence of bladder cancer is higher in men than in women without regional differences [2], it is significantly affected by region: bladder cancer incidence is significantly lower in Asian countries than in Western

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countries [1, 3]. In addition, trends in bladder cancer incidence also vary by region [4]. These findings are thought to be affected by several factors associated with bladder cancer, including smoking behaviors and environmental factors [5, 6].

Not only well-known risk factors, such as smoking, but also ethnicity could influence the incidence and oncological outcomes of bladder cancer [6, 7]. In addition, the policies and awareness about smoking, which also influence secondhand smoking [8], and smoking types, such as nonfilter cigarettes, could vary from country to country. Some studies reported that the relative risk of bladder cancer among the Asian population was lower than that in other populations [9, 10]. In other words, a country-based national analysis of the incidence, incidence trend, and risk factors for bladder cancer is needed to accurately determine the country-specific incidence trend and risk factors for bladder cancer.

In 2019, bladder cancer was the 12th most common cancer and 4,895 patients were newly diagnosed with bladder cancer in South Korea [11]. Bladder cancer severely impairs the quality of life [12]. Moreover, due to the frequent intravesical recurrence after transurethral resection of bladder tumors and intensive follow-up strategies, medical expenses for bladder cancer cannot be ignored [13]. Therefore, it is essential to check the current status of the incidence rate, incidence trend, and risk factors for bladder cancer using a nationwide database in South Korea, which will serve as a basis for future medical policy decisions. To demonstrate the current status of bladder cancer in South Korea, the Korean Urological Oncology Society launched the bladder cancer fact sheet project in 2022. In this study, we aimed to identify the current status of bladder cancer in South Korea and estimate the incidence rate and trend of bladder cancer using a nationwide database. In addition, we sought to determine the risk factors and their influence on the incidence of bladder cancer in a nationwide general health check-up cohort.

MATERIALS AND METHODS

1. Incidence and Trend of Bladder Cancer

In South Korea, medical expenses in approximately 98% of the population were covered by the National Health Insurance Service [14] and the data were collected by the National Health Insurance Sharing Service (NHISS). We extracted 2005–2019 data from the NHISS. Among these, we excluded the patients who visited medical facilities with bladder cancer between 2005 and 2006 to calculate the patients with newly diagnosed bladder cancer after January 2007. Bladder cancer was defined using the Korean Standard Classification of Diseases (KCD) version 6, based on the International Classification of Diseases 10th revision, as code C67 and V193, cancer-specific insurance codes in Korea. Those with ages <20 years were also excluded from the analysis. Using these data, the incidence rate and incidence trend of newly developed bladder cancer per 100,000 population were estimated from 2007 to 2019 after subdividing the population according to sex and age. The compound annual increase rate for newly diagnosed bladder cancer was also calculated.

2. Variables Associated With Newly Diagnosed Bladder Cancer

Among approximately 38 million people, 10.5 million people who underwent general health check-ups in 2009 were initially selected for further analysis. After excluding patients who were diagnosed with bladder cancer from 2005 to 2008 and those without required data, 10,210,654 people were finally included in the further analysis. Baseline characteristics were analyzed using the 2009 health check-up data. Continuous variables were assessed using means±standard deviations and categorical variables were assessed using numbers with percentages.

The presence of hypertension, diabetes, dyslipidemia, abdominal obesity, and metabolic syndrome was determined using the KCD code, medication data, and general health check-up data (Supplementary Table 1). Smoking status, smoking amount, and drinking amount were assessed using the questionnaires included in the general health check-up. Drinking status was categorized as follows: nondrinker; 0 g/day; mild drinker, >0 and <30 g/day; and heavy drinker, ≥30 g/day. The residential areas were classified into 2 groups: urban versus rural. Metropolitan cities were defined as urban areas and the others as rural areas.

The incidence of bladder cancer according to sex and age

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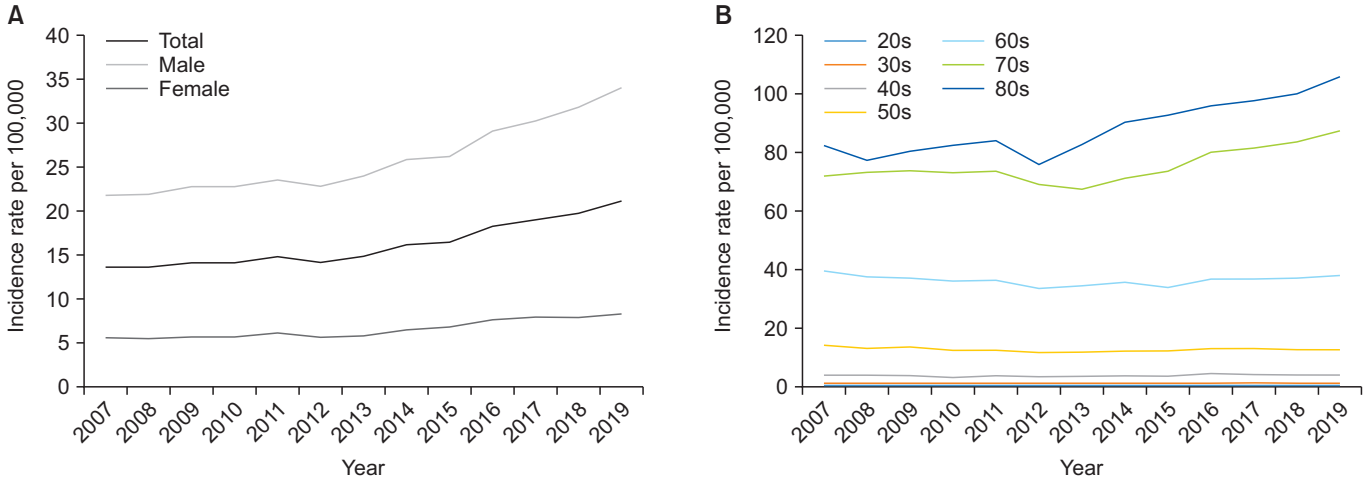

Fig. 1. Trends in bladder cancer incidence. (A) Trends in bladder cancer incidence according to sex. (B) Trends in bladder cancer incidence according to age.

group (≥20 and <40 years, ≥40 and <65 years, and ≥65 years) was determined using Kaplan-Meier analysis and compared using a log-rank test. Using univariate and multivariable Cox regression analysis, we developed 3 models for assessing the effects of variables on the incidence of newly diagnosed bladder cancer: model 1 was unadjusted; model 2 was only adjusted for age and sex; and model 3 was adjusted for all other variables.

As smoking, in addition to sex and age, was determined as the most powerful variable associated with bladder cancer, we further analyzed the interactions between smoking, age, and sex. P-values for interactions in each model were calculated and compared. A p-value of <0.05 was considered statistically significant.

3. Research Ethics

This study was performed according to the Helsinki Declaration (http://www.wma.net/en/30publications/10policies/b3/) and approved the Institutional Review Board (IRB) of Seoul Metropolitan Government - Seoul National University Boramae Medical Center (IRB No. 07-2021-25). A written informed consent is waived by IRB.

RESULTS

The incidence rate of bladder cancer per 100,000 population significantly increased especially during the last 10 years (Fig. 1). In 2019, 21.07 people per 100,000 were diagnosed with bladder cancer, whereas 13.62 per 100,000 persons were diagnosed with bladder cancer in 2007. The compound annual increase rate from 2007 to 2019 was 3.7%. Newly diagnosed bladder cancer significantly increased in both male and female populations. When age stratification was performed, the increment in the incidence of bladder cancer was significant in those older than 70 years, although there were no significant increments in those under 70 years (Supplementary Table 2).

Individuals who underwent health check-ups in 2009 were included in the further analysis. The mean age of this population was 47.1 years and the mean body mass

Table 1. Patients' baseline characteristics (n=10,210,654)

Characteristic	Value
Age (yr)	47.1±14.1
Body mass index (kg/m^2)	23.7±3.2
Hypertension	2,725,576 (26.69)
Diabetes	881,632 (8.63)
Dyslipidemia	1,769,656 (17.33)
Abdominal obesity	2,001,110 (19.6)
Smoking status	
None smoker	6,126,317 (60.0)
Ex-smoker	1,425,970 (14.0)
Current smoker	2,658,367 (36.0)
Smoking amount (pack-year)	6.2±11.6
Drinking status	
None drinker	5,296,037 (51.9)
Mild drinker	4,110,114 (40.3)
Heavy drinker	804,503 (7.9)
Residence	
Urban	4,606,962 (45.1)
Rural	5,603,692 (54.9)

Values are presented as mean±standard deviation or number (%).

index was 23.7 kg/m^2 (Table 1). The percentage of each metabolic component in this population was as follows: hypertension, 26.7%; diabetes mellitus, 8.6%; dyslipidemia, 17.3%; abdominal obesity, 19.6%; and metabolic syndrome, 24.9%. Smoking status was as follows: nonsmoker, 60.0%; ex-smoker, 14.0%; and current smoker, 26.0%. The mean smoking amount was 6.2 pack-years, the mean duration of smoking was 7.2 years, and the mean daily amount of smoking was 0.3 pack.

Bladder cancer was diagnosed in 83 people per 100,000 population in the 10-year follow-up (Fig. 2). The bladder cancer incidence rate was significantly higher in men than women (315 vs. 79 individuals per 100,000 population, p<0.001). In addition, the bladder cancer incidence rate was significantly associated with old age (≥20 and <40 years vs. ≥40 and <65 years vs. ≥65 years: 20 vs. 180 vs. 845 individuals per 100,000 population, p<0.001).

In univariate analysis, all metabolic syndrome-related variables, smoking-related variables, and residential areas were significantly associated with newly diagnosed bladder cancer (Table 2). After age and sex adjustment, smoking-related variables, including smoking status and smoking amount, were the most powerful risk factors for newly diagnosed bladder cancer, followed by metabolic syndrome and metabolic syndrome-related variables. Drinking amount and residential area were also related to newly diagnosed bladder cancer. After adjusting for all variables, smoking-related variables remained the most powerful variables associated with newly diagnosed bladder cancer. Metabolic syndrome-related variables, drinking amount, and residential area were also associated with newly diagnosed bladder cancer.

In the further analysis of the effects of smoking on bladder cancer, the effects of smoking amount on newly diagnosed bladder cancer were more powerful in women than men, not only in the unadjusted model but also in the adjusted model, including models 2 and 3 (Table 3). In addition, the effects of smoking on newly diagnosed bladder cancer were more prominent in older people after adjusting for all variables.

DISCUSSION

The incidence of bladder cancer varies significantly by geographic region and might be affected by several factors including exposure to smoking, occupational factors [15], arsenic in drinks [16], or availability and accessibility to cystoscopy or imaging studies [17]. In addition, these variables are influenced by socioeconomic status, regional characteristics, or sociopolitical situation. In other words, although risk factors for bladder cancer would be similar worldwide, the incidence rate and trend of bladder cancer and the magnitude of the effect of each risk factor on bladder cancer incidence could vary from country to country. In the current study, we identified the current status of bladder cancer in South Korea, including the incidence rate and trend of bladder cancer. In addition, we evaluated the actual magnitude of each risk factor for bladder cancer in Koreans using a nationwide database.

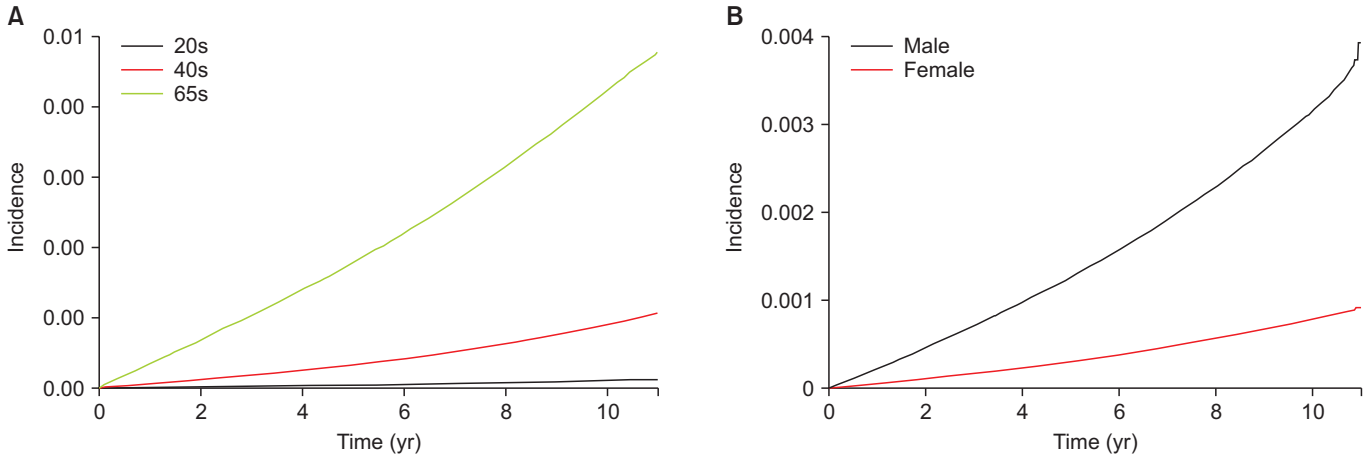

Fig. 2. Incidence of bladder cancer according to age and sex. (A) Age group. (B) Sex.

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Table 2. Variables associated with bladder cancer incidence

Variable	Total (n)	Bladder cancer (n)	Model 1		Model 2		Model 3	
			HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
Diabetes				<0.001		<0.001		<0.001
No	9,329,022	17,836	Reference		Reference		Reference	
Yes	881,632	4,165	2.60 (2.51–2.69)		1.22 (1.18–1.27)		1.13 (1.09–1.18)	
Hypertension				<0.001		<0.001		<0.001
No	7,485,078	10,632	Reference		Reference		Reference	
Yes	2,725,576	11,369	3.04 (2.96–3.12)		1.16 (1.13–1.19)		1.10 (1.07–1.13)	
Dyslipidemia				<0.001		<0.001		<0.001
No	8,440,998	16,532	Reference		Reference		Reference	
Yes	1,769,656	5,469	1.59 (1.54–1.64)		1.17 (1.13–1.20)		1.08 (1.05–1.12)	
BMI (kg/m^2)				<0.001		<0.001		<0.001
<25	6,878,893	13,985	Reference		Reference		Reference	
≥25	3,331,761	8,016	1.18 (1.15–1.21)		1.10 (1.0–1.13)		1.01 (0.97–1.04)	
Abdominal obesity				<0.001		<0.001		<0.001
No	8,209,544	15,495	Reference		Reference		Reference	
Yes	2,001,110	6,506	1.74 (1.69–1.79)		1.17 (1.14–1.21)		1.10 (1.06–1.14)	
Smoking status				<0.001		<0.001		<0.001
None	6,126,317	9,250	Reference		Reference		Reference	
Ex	1,425,970	5,615	2.64 (2.55–2.73)		1.31 (1.26–1.36)		1.30 (1.25–1.35)	
Current	2,658,367	7,136	1.80 (1.74–1.85)		1.61 (1.55–1.66)		1.64 (1.58–1.70)	
Smoking amount (pack-year)				<0.001		<0.001		<0.001
0	6,126,317	9,250	Reference		Reference		Reference	
<10	1,577,998	1,989	0.83 (0.79–0.87)		1.07 (1.02–1.13)		1.08 (1.03–1.14)	
<20	1,181,476	2,834	1.60 (1.53–1.67)		1.31 (1.25–1.37)		1.32 (1.26–1.38)	
≥20	1,324,863	7,928	4.10 (3.98–4.22)		1.66 (1.61–1.72)		1.66 (1.61–1.72)	
Drink status				<0.001		<0.001		<0.001
None	5,296,037	11,423	Reference		Reference		Reference	
Mild	4,110,114	8,274	0.93 (0.90–0.95)		1.00 (0.97–1.03)		0.89 (0.87–0.92)	
Heavy	804,503	2,304	1.33 (1.28–1.39)		1.10 (1.05–1.15)		0.97 (0.93–1.02)	
Residence				0.673		<0.001		<0.001
Urban	4,606,962	9,975	Reference		Reference		Reference	
Rural	5,603,692	12,026	0.99 (0.97–1.02)		0.89 (0.86–0.91)		0.89 (0.87–0.92)	

Model 1, unadjusted; model 2, only adjusted for age and sex; model 3, adjusted for all other variables; HR, hazard ratio; CI, confidence interval; BMI, body mass index.

In the last decade, the crude incidence rate of bladder cancer significantly increased in South Korea, especially in those aged 70 years or older. These findings are thought to be associated with the rapid aging of the Korean population, in addition to increased health check-ups in older people. In 2000, South Korea became an aging society, with over 7% of its population 65 years or older, and in 2017, South Korea became an aged society, with over 14% of its population aged 65 years or older [18]. Based on the cancer statistics in Korea, the compound annual growth rate of bladder cancer incidence from 2008 to 2017 was 3.0%, which is similar to 3.7% in the current study [19, 20]. However, the age-standardized incidence was consistent between 2008 and 2017, which supports our hypothesis. Although the age-standardized incidence of bladder cancer did not change, the increment in the crude incidence of bladder cancer in Korea should not be overlooked because the treatment for bladder cancer in elderly patients is challenging due to the risk of decreasing quality of life without prolonging survival [21, 22]. In addition, considering that the life expectancy in Koreans continues to increase rapidly [23], political support for elderly patients with bladder cancer is urgently needed.

As shown in previous studies, smoking amount and smoking status were the most powerful risk factors for bladder cancer in the current study. However, interestingly, the magnitude of the effects of smoking on bladder cancer was smaller in the current study than that reported in other studies: 1.64-fold vs 2-4-fold for current smokers [24]. A previous Japanese study reported similar results, which the authors attributed to filtered cigarettes [9]. Similar findings, smaller effect sizes of smoking on lung cancer, were also observed in lung cancer research. Although these findings

Table 3. Effects of smoking amount (pack-year) on bladder cancer incidence by sex and age

Variable	Model 1		Model 2		Model 3	
	HR (95% CI)	p-value†	HR (95% CI)	p-value†	HR (95% CI)	p-value†
Sex						
Male		<0.001		<0.001		<0.001
0	Reference		Reference		Reference	
<10	0.41 (0.38–0.43)		1.04 (1.00–1.10)		1.05 (1.00–1.11)	
<20	0.74 (0.70–0.77)		1.29 (1.23–1.35)		1.30 (1.24–1.36)	
≥20	1.89 (1.82–1.95)		1.64 (1.59–1.70)		1.64 (1.59–1.70)	
Female						
0	Reference		Reference		Reference	
<10	0.75 (0.61–0.90)		1.49 (1.23–1.81)		1.52 (1.26–1.85)	
<20	2.12 (1.61–2.79)		1.60 (1.22–2.10)		1.61 (1.23–2.12)	
≥20	4.30 (3.34–5.54)		2.15 (1.67–2.77)		2.15 (1.67–2.77)	
Age						
20–39 Years		<0.001		0.003		0.002
0	Reference		Reference		Reference	
<10	1.75 (1.45–2.10)		0.98 (0.81–1.18)		0.98 (0.82–1.18)	
<20	2.62 (2.14–3.21)		1.10 (0.90–1.35)		1.09 (0.89–1.34)	
≥20	4.43 (3.32–5.91)		1.47 (1.10–1.97)		1.45 (1.09–1.93)	
40–64 Years						
0	Reference		Reference		Reference	
<10	1.75 (1.63–1.88)		1.01 (0.94–1.08)		1.02 (0.95–1.09)	
<20	2.44 (2.30–2.58)		1.27 (1.20–1.35)		1.28 (1.21–1.36)	
≥20	3.85 (3.68–4.02)		1.59 (1.51–1.66)		1.58 (1.50–1.65)	
≥65 Years						
0	Reference		Reference		Reference	
<10	2.36 (2.18–2.54)		1.25 (1.15–1.35)		1.26 (1.16–1.36)	
<20	2.74 (2.57–2.93)		1.36 (1.27–1.46)		1.38 (1.29–1.47)	
≥20	3.44 (3.29–3.58)		1.66 (1.59–1.74)		1.68 (1.61–1.76)	

Model 1, unadjusted; model 2, only adjusted for age and sex; model 3, adjusted for all other variables; HR, hazard ratio; CI, confidence interval.
†p-values for interactions in each model.

need to be validated, smoking patterns, smoking amount, and use of filtered cigarettes could be the reasons for this phenomenon named "smoker's paradox" [25]. As not only the smoking status but also the smoking amount in the current study had smaller effects than those reported in previous Western research [26], we conjecture that the "smoker's paradox" is also present in bladder cancer although more research is warranted.

Interestingly, the magnitude of the effects of smoking on bladder cancer incidence was higher in women as reported in previous studies [26, 27]. Considering the smoking behavioral differences between men and women, such as the number of puffs per cigarette and the size of the remaining cigarette butt after smoking, this finding is quite convincing because women are thought to intake less carcinogen during smoking when compared to men with the same amount of smoking [28]. Considering that the smoking rate did not decrease in Korean women unlike in men [29], it is thought that there is a need to implement active smoking cessation education, especially for female smokers. Although the reason for this finding needs to be elucidated, it is possible to make these data available to the general public to promote their awareness and understanding so as to induce smoking cessation and, hopefully, lower the future risk of bladder cancer, especially in women.

In this study, all metabolic syndrome-related variables were also associated with newly diagnosed bladder cancer although the magnitude of their effects was modest, which is consistent with previous studies [30]. However, due to the complexity of the determination of the association between bladder cancer incidence and metabolic syndrome, it is difficult to conclude the actual influence of metabolic syndrome on bladder cancer. However, it would be important for clinicians to recognize this fact and suspect bladder cancer in patients with hematuria accompanied by metabolic syndrome and carefully examine these patients.

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This study was limited by its retrospective design and operational definition. In addition, the lack of occupational and dietary data is another limitation of the current study. However, considering that this is a nationwide study with a large study population and a long duration of follow-up, it would be useful not only for establishing medical policies in Korea and raising public awareness but also for improving the understanding of clinicians on the current status of bladder cancer in Korea.

CONCLUSIONS

In South Korea, the crude incidence of bladder cancer significantly increased during the last decade, especially in those 70 years or older. The most significant risk factors for newly diagnosed bladder cancer were smoking status and amount, followed by metabolic syndrome-related variables. Considering the magnitude of the effect of smoking on newly diagnosed bladder cancer, especially in women and older people, more active smoking cessation education for these populations is needed.

NOTES

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- ORCID

Sangjun Yoo: https://orcid.org/0000-0003-4992-7053
Kyung-Do Han: https://orcid.org/0000-0002-6096-1263
Kwang Taek Kim: https://orcid.org/0000-0002-3495-369X
Woo Suk Choi: https://orcid.org/0000-0002-8352-578X
Yun-Sok Ha: https://orcid.org/0000-0003-3732-9814
Jeong Hyun Kim: https://orcid.org/0000-0002-8942-0188
Cheol Kwak: https://orcid.org/0000-0002-1987-2111

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ORIGINAL ARTICLE

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The Use of 5-Alpha Reductase Inhibitors Improves the Detection of Prostate Cancer by Increasing Opportunities for Repeated Prostate-Specific Antigen Testing: A Decade-Long (2007–2016) Nationwide Observational Study in Korea

Young Hwii Ko[1], Sang Won Kim[2], Hoseob Kim[3], Yoon-Jong Bae[3]

[1]Department of Urology, College of Medicine, Yeungnam University, Daegu, Korea
[2]Medical Research Center, College of Medicine, Yeungnam University, Daegu, Korea
[3]Department of Data Science, Hanmi Pharm. Co., Ltd., Seoul, Korea

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Corresponding author:
Young Hwii Ko
Department of Urology, College of Medicine, Yeungnam University, Daegu, Korea
Email: urokyh@naver.com
https://orcid.org/0000-0002-9150-4292

Purpose: The aim of this study was to investigate the influence of taking 5-alpha reductase inhibitors (5ARIs) on the detection of prostate cancer (PCa), considering the reported low uptake of prostate-specific antigen (PSA) testing among Korean men.

Materials and Methods: From Korean National Health Insurance Sharing Service data, the number of men older than 40 years who were prescribed 5ARIs from 2007 through 2016 was identified. The association of 5ARI prescriptions with newly registered PCa was analyzed.

Results: In total, 1,528,128 men who took 5ARIs for a mean of 1.523±2.221 years were identified. Among 138,614 patients with PCa, 68,529 (49.4%) took 5ARIs and 70,085 did not. The incidence of PCa was significantly higher in the 5ARI group than in the non-5ARI group during all study years ($p<0.001$) except for 2007. Adjusted for age, the non-5ARI group had a significantly lower likelihood of PCa detection (hazard ratio [HR], 0.854; $p<0.001$) and radical prostatectomy, including robot-assisted procedures (HR, 0.834, $p<0.001$). The mean number of PSA tests was about 2 times higher in the 5ARI group than in the non-5ARI group (3.98 vs. 2.18, $p<0.001$). Among the subjects who took 5ARIs, the incidence of PCa increased up to 3 years of administration, followed by a decreasing trend thereafter ($p<0.001$).

Conclusions: From this observational study in a country with limited PSA testing uptake, the prescription of 5ARIs, for which repeated PSA testing is encouraged to select suitable patients, enhances the detection of PCa, but does not prevent its development.

Key Words: Prostate cancer, 5-Alpha reductase inhibitor, Prostate-specific antigen

INTRODUCTION

Because of the relatively long latency period of prostate cancer (PCa) and treatment-related morbidity in its management of PCa, the utilization of 5-alpha reductase inhibitors (5ARIs) as a chemo-preventive strategy has been highlighted [1]. This strategy was hypothesized to prevent PCa by decreasing intraprostatic dihydrotestosterone levels. Two large, randomized, placebo-controlled cancer prevention trials were initiated to evaluate the effects of

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5ARIs: the Prostate Cancer Prevention Trial (PCPT) for finasteride and the Reduction by Dutasteride of Prostate Cancer Events (REDUCE) trial for dutasteride. Both trials, which were published in the 2000s, demonstrated a similar impact on the risk of PCa development. In the PCPT study, 7 years of finasteride therapy reduced the prevalence of PCa by 24.8% [2]. In the REDUCE trial, dutasteride treatment was associated with a relative risk reduction of 22.8% over 4 years [3], despite the observation of a potentially increased risk of high-grade disease.

Meanwhile, prescriptions of 5ARIs also increased dramatically in Korea, predominantly triggered by the exploding incidence of lower urinary tract symptoms (LUTS), which generally originate from concomitant benign prostate hyperplasia (BPH) along with the extended lifespan. Given the low uptake of prostate-specific antigen (PSA) testing among Korean men (3.1% in 2007 and 7.3% in 2016 among men aged over 40 years [4]) due to the limited social awareness of PCa combined with the lack of a public screening policy [5], the prescription of 5ARIs, for which PSA testing is encouraged to select suitable patients, may promote the identification of PCa by providing repeated opportunities to check men's serum PSA levels. With this background, the purpose of this study was to investigate the influence of 5-ARI prescriptions on the detection of PCa utilizing nationwide data during a recent decade.

MATERIALS AND METHODS

1. Data Source and Study Population

Data were obtained from the National Health Insurance Sharing Service (NHISS). In Korea, national health insurance covers most of its population (98%) and provides universal health coverage. The NHISS database offers most medical data, including diagnostic codes, procedures, prescription drugs, and sequelae, including death.

Men aged over 40 years who underwent PSA testing from 2006 through 2017 were identified from the NHISS database and selected for this study. The PSA test codes utilized in this study were B5490, C4280, and C7428. The code for finasteride (5 mg) and dutasteride (0.5 mg) were 159001ATB and 458801ACS, respectively. Patients newly diagnosed with PCa and registered in the NHISS with an International Classification of Diseases, 10th revision code of C61 or V193/194 each year during the study period were also investigated. Radical prostatectomy, including open and laparoscopic approaches, was identified using reimbursement codes (R3950 and R3960). Robot-assisted radical prostatectomy, which the NHISS did not reimburse, was operationally defined as the absence of a surgery code despite the presence of a general anesthesia code (L1211) and a postoperative pathologic examination code (C5500, C5504, C5505, C5508, C5918, or C5919). Radiation therapy included all radiation modalities, including conformal and intensity-modulated radiation.

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

The subjects were divided into 2 groups: the 5ARI group, which was prescribed two kinds of 5ARIs (including 126 generics for finasteride [5 mg] and 44 generics for dutasteride [0.5 mg]), and their non-5ARI counterparts. For prescriptions of 5ARIs, clinical guidelines have strongly recommended selecting suitable patients using the proper criteria, including the baseline PSA level (recommended when the initial PSA level is over 1.4 ng/mL) and prostate volume (recommended when the prostate is over 40 mL). In the mid-1990s to early 2000s, 5ARIs were introduced into Korea in mid-1990 to early 2000s (the Korea Food and Drug Administration allowed finasteride in 1995 and dutasteride in 2004). Urologists prescribed the majority of 5ARIs during the study period. The reduction of baseline PSA levels after long-term 5ARI administration (over 6 months) has been noticed repeatedly, raising concerns about missing the detection of masked PCa.

The epidemiological characteristics and PCa incidence between the 5ARI and non-5ARI groups were then compared. The number of repetitions of PSA tests was investigated, excluding the number of PSA tests after registration as a

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patient with PCa in the NHISS data. Because registration in the NHISS is mandatory for the official prescription of medications in Korea, the male population over 40 was obtained from the Statistics Korea website. The rates of PSA testing and the incidence of PCa were calculated.

The primary endpoints were (1) the incidence of PCa compared between groups and (2) the rate of PSA testing. The secondary endpoint was the change in PCa incidence over 10 years after 5ARI prescriptions. For patients who were registered as having PCa, the number of PSA tests was limited to tests carried out 3 months before registration in the NHISS, with the removal of all PSA tests after the code of C61 had been assigned for each person.

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 analysis. The chi-square test was used for binary and categorical variables. Since the large number of patients enrolled from the nationwide data tended to have a different age distribution, a multivariable Cox regression test adjusted for age was utilized to compare the 2 groups. The cancer incidence rates were calculated per 1,000 person-years. The Cochran-Armitage trend test was used to investigate PCa trends between the 5ARI and non-5ARI groups and assess the association of variables between these 2 categories. 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., Cary, NC, USA).

RESULTS

1. The Relationship Between the Administration of 5ARIs and the Detection of PCa

Across the research period of a decade (2007–2016), 1,528,128 men who were prescribed 5ARIs for a mean of 1.523±2.221 years were identified. Meanwhile, 138,614 patients with PCa were identified, of whom 68,529 (49.4%) were prescribed 5ARIs, with the other 70,085 subjects constituting the non-5ARI group. The finally analyzed data are summarized in Table 1. Among 312,888 men aged over 40 years who received PSA testing in 2007, 73.4% (n=229,760) were prescribed 5ARIs. As the PSA testing rate increased, the proportion of patients who were prescribed 5ARI decreased (58.8% in 2016). The incidence of PCa was significantly higher in the 5ARI group than in the non-5ARI group during all study years (p<0.001), except in 2007, when the rate of PSA testing was the lowest (3.12% among Korean men aged over 40 years). The mean number of repetitions of PSA testing for the study period was significantly higher in the 5ARI group than in the non-5ARI group (3.98 vs. 2.18, p<0.001).

Table 1. The characteristics of the patients enrolled

Year	Middle-aged male population (≥40 yr)				PSA-tested male population (≥40 yr)						
	Total	Registered PCa	Incidence of PSA test (%)	Incidence of PCa (%)	Total	5ARI group	PCa among 5ARI group	PCa incidence among 5ARI group (%)	PCa among non-5ARI group	PCa incidence among non-5ARI group (%)	p-value†
2007	9,999,912	5,292	3.12	0.052	312,888	229,760	3,272	1.42	2,020	2.42	<0.001
2008	10,337,914	6,471	4.63	0.062	479,046	274,835	3,983	1.44	2,488	1.21	<0.001
2009	10,694,580	7,351	5.34	0.068	571,643	331,232	4,557	1.37	2,794	1.16	<0.001
2010	11,039,633	7,848	5.71	0.071	631,417	365,978	5,092	1.39	2,756	1.03	<0.001
2011	11,386,232	8,952	6.14	0.078	700,040	394,019	5,484	1.39	3,468	1.13	<0.001
2012	11,723,878	9,258	6.44	0.078	755,372	420,822	5,892	1.40	3,366	1.01	<0.001
2013	12,042,751	9,515	6.65	0.079	801,241	457,559	6,483	1.41	3,032	0.88	<0.001
2014	12,354,915	9,785	6.72	0.079	831,495	481,797	6,743	1.39	3,042	0.86	<0.001
2015	12,635,426	10,212	6.83	0.080	863,782	505,933	6,682	1.32	3,530	0.98	<0.001
2016	12,886,340	11,800	7.28	0.091	937,548	551,099	7,707	1.39	4,093	1.05	<0.001

PSA, prostate-specific antigen; PCa, prostate cancer; 5ARI, 5-alpha reductase inhibitor.
†p-value for PCa incidence among 5ARI and non-5ARI groups.

2. The Impact of 5ARIs on the Management of PCa

The outcomes of the Cox proportional hazard model adjusted for age are summarized in Table 2. The non-5ARI group had significantly lower likelihoods of cancer detection (hazard ratio [HR], 0.854; p<0.001) and radical surgery, including robot-assisted procedures (HR, 0.834; p<0.001). In contrast, the non-5ARI group had a significantly higher likelihood of radiation therapy (HR, 1.716; p<0.001) and a higher risk of mortality (HR, 1.96; p<0.001) than the 5ARI group. In the 5ARI group, the incidence of PCa increased for 3 years of administration, followed by a subsequent decreasing trend (Cochran-Armitage trend test, p<0.001) (Fig. 1).

DISCUSSION

Although the benefits of PSA-based mass screening policies have remained a matter of debate since 2012 [6-8], serum PSA testing still plays a pivotal role in detecting PCa. Most early-phase PCa cases do not manifest specific symptoms other than ambiguous LUTS, which more frequently originate from concomitant BPH. Indeed, most PCa cases are detected in the non-metastatic stage in Korea [9]. Therefore, the circumstances in which PSA testing is performed provide opportunities to catch PCa in an earlier phase.

Unlike the United States or Europe, which have a long history of clinical applications, ready access to PSA testing, and greater social awareness of PCa, the incidence of PCa in most Asian countries has soared in very recent years. For example, PCa was a relatively less prevalent cancer in Korea until the end of the 20th century. In 2000, PCa became Korean men's 10th most common malignant disease [9]. However, since 2002, when PCa was first reported to be the fifth most common malignant disease among Korean men, its incidence has consistently increased. In 2016, PCa became the fourth most common incident malignancy in men. In the most recent report (2020), it became the third-most common cancer in men and the second-most common among men over 65 years old.

However, this rapidly increasing incidence of PCa was not accompanied by an enhanced public awareness of the disease and its screening strategies. Indeed, in a general survey of 600 members of the Korean population in 2019, only 9.7% of men aged over 40 years were aware of PSA testing, and 83.3% of them had never received PCa screening [5]. Currently, PSA testing is not included in regular check-ups in Korea, which contrasts with the inclusion of tests for other common malignant diseases in men, such as lung, stomach, colon, and liver cancer, which were the first, second, third, and fifth most prevalent malignant diseases among Korean men in 2019 [9]. The nationwide rate of PSA testing during the recent 10-year period (2006–2016), therefore, remained low in Korean men older than 40 years. Although it reached 7.2% in 2016, that figure is still less than a quarter of that reported in the United States [4]. From 2008 to 2016, only around a

Table 2. Summary of the Cox proportional-hazards model adjusted for age

Variable	HR	95% CI	p-value
The detection of PCa			
5ARI group	1 (reference)		
Non-5ARI group	0.854	0.841–0.867	<0.001
The incidence of radical prostatectomy (including robot-assisted procedure)			
5ARI group	1 (reference)		
Non-5ARI group	0.834	0.814–0.855	<0.001
The incidence of radiation therapy for PCa			
5ARI group	1		
Non-5ARI group	1.716	1.694–1.738	<0.001
Overall mortality			
5ARI group	1		
Non-5ARI group	1.96	1.949–1.971	<0.001

HR, hazard ratio; CI, confidence interval; PCa, prostate cancer; 5ARI, 5-alpha reductase inhibitor.

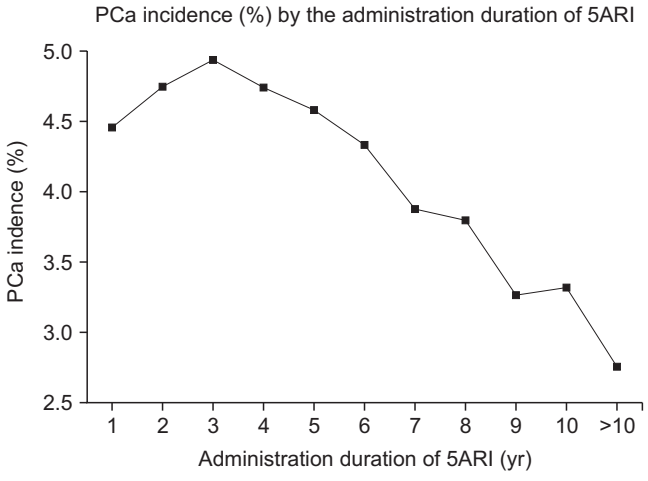

Fig. 1. The incidence of prostate cancer according to the duration of 5-alpha reductase inhibitor (5ARI) administration. PCa, prostate cancer.

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quarter of men with PCa in Korea underwent repeat PSA testing before a pathologic cancer diagnosis was confirmed [10].

The outcomes of this observational study also show how the limited social perception of PSA testing negatively affects PCa detection. In contrast to the well-known randomized controlled trials (RCTs) that were published approximately 2 decades ago, which consistently reported that 5ARIs reduced the development of PCa by 23%–25% [2, 3], the detection of PCa among individuals who were prescribed 5ARIs was instead significantly higher, by about 15%, in this study. Considering the limited opportunities for PSA testing among Korean men during the study period in the absence of a social screening policy and a low social perception of PCa, the prescription of 5ARIs may provide additional opportunities for exposure to PSA testing. In 2007, 73% of nationwide PSA testing was associated with receiving 5ARIs according to this study. In the same year, only 3.12% of men aged 40 received PSA testing [4]. During the study decade, the subjects with 5ARIs had almost twice as high an average number of repeated PSA tests than their non-5ARI counterparts (3.98 vs. 2.18, p<0.001).

Another interesting aspect of this study was that the non-5ARI group had almost twice the overall mortality of the 5ARI group (HR, 1.96; p<0.001), even after adjusting for age. Because the current Korean NHISS does not provide detailed oncologic data, including tumor stage and grade, a direct comparison of tumor aggressiveness between groups was not possible. However, inferences can be made from the data for radiation therapy, which tends to be selected and carried out for patients with advanced stages of disease. Specifically, the fact that PCa patients without previous 5ARI administration had a significantly higher likelihood of radiation therapy implies the more aggressive nature of PCa detected in the non-5ARI group, suggesting possible benefits from earlier cancer detection through more frequent PSA testing. This finding is also inconsistent with those of previous RCTs on 5ARIs, which reported the development of high-grade cancer in patients who received longer-term administration of 5ARIs [11, 12].

If the administration of 5ARIs provokes the biological tumorigenesis of PCa, then a higher incidence of PCa would be observed in subjects with a longer duration of 5ARI administration. With data covering a decade, we could trace the impact of PCa detection among the patients who were prescribed 5ARIs. As shown in Fig. 1, the development of PCa was significantly prevented by the prolonged administration of 5ARIs, especially 3 years after the initial induction and beyond. This observation matches the protective effects of 5ARIs reported in the long-term outcomes of the PCPT and REDUCE trials. At the 16-year follow-up point, Unger et al. [13] reported that men treated with finasteride had a 21.1% lower risk of PCa compared with placebo. Using a registry in Sweden, Wallerstedt et al. [14] evaluated 23,442 men exposed to finasteride or dutasteride for any length of time during an 8-year study period. Treatment with 5ARIs reduced the overall risk of developing PCa, and the effect was more prominent with more prolonged drug exposure (HR, 0.81 for 0.1–2 years vs. HR, 0.31 for 6–8 years).

The authors are well aware of the limitations of this study. First, we could not differentiate significant disease from indolent PCa based on the limited structure of the NHISS. Most RCTs on the efficacy of PSA testing have consistently focused on detecting significant cancer because of the need to consider concerns regarding the overdiagnosis and overtreatment of insignificant PCa. Furthermore, the current version of the NHISS does not contain information on cancer-specific survival, including PCa. Thus, this study could not assess the cost-effectiveness aspect of repeated PSA testing, which was enhanced by the administration of 5ARIs. Second, because the NHISS data did not contain PSA information from private, non-insurance-covered health check-ups, some of those included in the analysis as nonscreened may have been adequately tested. However, given the current reported average retirement age of 51.2 years, according to the most recent employment data among Korean men in 2021 [15], the omission of private PSA testing data likely had a limited impact on the outcomes of this study, since about 90% of the registered PCa cases in Korea are in people older than 60. Furthermore, the reported disparities in PSA testing among Korean men with different socioeconomic statuses should be considered [16]. Third, this observational study design could not identify causal relationships. The advanced age in the 5ARI group may have resulted in the higher detection of PCa than in their

non-5ARI-taking counterparts. Nonetheless, the outcomes from this study, showing that the prescription of 5ARI paradoxically increased the detection of PCa, support the need for expanding a PSA testing-based screening strategy against PCa, balancing the enhanced detection of PCa with cost-effectiveness in prolonging the expected lifespan, given an asymptomatic nature of PCa until its progression into metastatic disease.

CONCLUSIONS

According to this observational study in a country with limited uptake of PSA testing, the prescription of 5ARIs, which encourages repeated PSA testing to select suitable patients, enhanced the detection of PCa more than in their non-5ARI-taking counterparts. With prolonged 5ARI administration, the incidence of PCa increased for 3 years, followed by a continuous decrease thereafter.

NOTES

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- ORCID

Young Hwii Ko: https://orcid.org/0000-0002-9150-4292
Sang Won Kim: https://orcid.org/0000-0003-2648-0340
Hoseob Kim: https://orcid.org/0000-0003-3063-8024
Yoon-Jong Bae: https://orcid.org/0000-0003-1607-8139

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Contemporary Management of Small Renal Masses by Urologic Oncologists: A 2022 Korean Renal Cancer Study Group Practice Pattern Survey

Joongwon Choi[1], Cheryn Song[2], Jungyo Suh[2], Minyong Kang[3,4,5], Chang Il Choi[6], Hyeong Dong Yuk[7], Chan Ho Lee[8], Jung Kwon Kim[9], Jung Ki Jo[10], Won Sik Ham[11], Eu Chang Hwang[12], Chang Wook Jeong[7], Young Hwii Ko[13], Jae Young Park[14], Seong Il Seo[3], Byung Kwan Park[15], Jinsoo Chung[16], Cheol Kwak[7], Sung-Hoo Hong[17]

[1]Department of Urology, Chung-Ang University Gwangmyeoung Hospital, Chung-Ang University College of Medicine, Gwangmyeoung, Korea
[2]Department of Urology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Korea
[3]Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[4]Samsung Genome Institute, Samsung Medical Center, Seoul, Korea
[5]Department of Health Sciences and Technology, SAIHST, Sungkyunkwan University, Seoul, Korea
[6]Department of Urology, Hallym University Dongtan Sacred Heart Hospital, Hallym University School of Medicine, Hwaseong, Korea
[7]Department of Urology, Seoul National University College of Medicine, Seoul, Korea
[8]Department of Urology, Inje University Busan Paik Hospital, Inje University College of Medicine, Busan, Korea
[9]Department of Urology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[10]Department of Urology, Hanyang University Hospital, Hanyang University College of Medicine, Seoul, Korea
[11]Department of Urology, Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[12]Department of Urology, Chonnam National University Medical School, Gwangju, Korea
[13]Department of Urology, Yeungnam University College of Medicine, Daegu, Korea
[14]Department of Urology, Korea University Ansan Hospital, Korea University College of Medicine, Ansan, Korea
[15]Department of Radiology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[16]Department of Urology, Center for Urologic Cancer, National Cancer Center, Goyang, Korea
[17]Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea

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Corresponding author:
Sung-Hoo Hong
Department of Urology, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea
Email: toomey@catholic.ac.kr
https://orcid.org/0000-0002-1952-4010

Purpose: Increased abdominal imaging brought about an explosive increase in the incidental detection of small renal masses (SRMs). In the absence of optimal guidelines for health screening, as well as subsequent diagnostic and therapeutic action plans, incidentally detected SRMs may likewise increasingly become a dilemma, especially in an aging society. In the current study, we aimed to describe the current practice patterns for incidentally detected SRMs among urologic oncologists and to identify key indicators in action plans for active surveillance.

Materials and Methods: A survey containing 18 questions on SRM management patterns was designed. In June 2022, an online survey was sent to all 711 active members of the Korean Urological Oncology Society via email. After response collection, a consensus meeting of the Korean Renal Cancer Study Group, which 19 specialists attended, was held to analyze the results.

Results: In total, 176 responses from participants practicing in an academic setting were obtained (24.8%, 176 of 711). Regarding the age of patients with SRMs, 42.6% (n=72) responded that they would recommend diagnostic evaluation and definitive treatment for anyone under 80 years of age as long as the patient was healthy. The most commonly used target indicators for surveillance termination were a tumor growth rate above a certain velocity (57.9%, n=102) and size increase above a certain diameter (36.9%, n=65). Renal mass biopsy was recommended in very select cases (<10% of all patients) by most respondents (53.4%, n=94), followed by "not using it at all" in 25.6% (n=45).

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Conclusions: We described the current practice patterns for incidentally detected SRMs among urologic oncologists and identified key indicators in action plans for active surveillance. This survey provided robust information, empowering physicians with a detailed knowledge of practice patterns and valuable insights on SRMs.

Key Words: Renal cell carcinoma, Disease management, Surveys and questionnaires

INTRODUCTION

Increased abdominal imaging brought about an explosive increase in the incidental detection of small renal masses (SRMs). Frequently defined as renal tumors 4 cm or smaller in size [1], SRMs encompass a heterogeneous group of tumors with diverse growth kinetics and subsequent progress [2-4]. While most—even if malignant—are presumed to be indolent, especially when small, 10% grow rapidly, 4% progress, and 2% metastasize [5, 6]. Furthermore, the kidney is a vital organ, and every renal unit contributes to glomerular filtration, especially in the elderly population, which is frequently affected by various medico-surgical comorbidities [7]. Thus, not only the absolute size of an SRM but also its size in relation to the kidney on the affected side, its location in relation to the vasculature, as well as the baseline function of both renal units, are all important factors to consider when an SRM is detected and a management decision is contemplated.

In the absence of optimal guidelines for health screening, as well as subsequent diagnostic and therapeutic action plans, incidentally detected SRMs may likewise increasingly become a dilemma, especially in an aging society [8]. Although cancer is the second leading cause of death in both men and women in the United States [9], maintaining an adequate quality of life for the elderly has become a goal equally important as "getting better" [10]. Without a complete understanding of the natural history of SRMs of various histologic subtypes and grades, it is difficult to consider all the competing risks, let alone the cost-effectiveness of surveillance methods, the psychosocial burden, and the subsequent changes in the quality of life brought about by the entire process for patients and their families. The benefits of an accurate diagnosis and definitive treatment must be weighed against potential harms. Despite the increase in SRMs, data on how SRMs are actually managed when they are first detected incidentally in recent practice are scarce. In the current study, we aimed to describe the current practice patterns for incidentally detected SRMs among urologic oncologists and identify key indicators in action plans for active surveillance.

MATERIALS AND METHODS

A survey containing 18 questions on SRM management patterns was designed (Table 1). The survey consisted of questions on practice patterns for the initial management of incidentally detected SRMs, as well as questions inquiring about the rationale behind the decisions. After the predistribution and review process by an expert group, on June 7, 2022, an online survey was sent to all 711 active members of the Korean Urological Oncology Society via email, followed by second and third contacts to nonrespondents on July 7, 2022 and July 14, 2022, respectively. Responses were collected until July 22, 2022. After survey collection, a consensus meeting of the Korean Renal Cancer Study Group, which 19 specialists (including 18 urologists and 1 radiologist) attended, was held in August to discuss the results.

The terms used in the survey were defined as follows: An SRM is a single kidney tumor presumed to be a localized renal cell carcinoma of less than 4 cm in diameter on initial imaging tests that is asymptomatic and incidentally identified. Active surveillance was defined as the initial monitoring of tumor size by serial abdominal imaging (ultrasound, computed tomography [CT], or magnetic resonance imaging) with delayed interventions reserved for tumors showing clinical progression during follow-up. Watchful waiting was defined as following patients without the intention of any subsequent active treatment (as their comorbidities contraindicate any treatment) and thus

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Table 1. Questionnaires on solitary renal mass management patterns (N=176)

Questionnaire	No. (%)
1. How long have you been treating kidney cancer?	
More than 10 years	97 (55.1)
5–10 Years	43 (24.4)
Less than 5 years	36 (20.5)
2. Approximately how many kidney cancer surgeries do you perform every year?	
More than 100 cases	19 (10.8)
50–100 Cases	20 (11.4)
20–50 Cases	64 (36.4)
Less than 20 cases	73 (41.5)
3. In patients with small renal mass, until what age do you recommend active diagnostic evaluations and definitive treatment?	
If healthy, all ages	36 (20.5)
Healthy under 70	19 (10.8)
Healthy under 75	34 (19.3)
Healthy under 80	75 (42.6)
Healthy under 85	12 (6.8)
4. In patients YOUNGER than your answer in #3, what is your size criteria for the renal mass to recommend definitive treatment?	
≥1 cm	35 (19.9)
≥2 cm	99 (56.3)
≥3 cm	26 (14.8)
≥4 cm	16 (9.1)
5. In patients OLDER than your answer in #3, what is your size criteria to recommend definitive treatment?	
≥1 cm	6 (3.4)
≥2 cm	51 (29.0)
≥3 cm	42 (23.9)
≥4 cm	55 (31.3)
Observe without treatment until intolerable symptoms occur	22 (12.5)
6. Do you use indexes to accurately measure patient's health status and comorbidities?	
Charlson Comorbidity Index	77 (43.8)
Chronic Disease Score/Modified-Chronic Disease Score	1 (0.6)
KDIGO classification of CKD risk	7 (4.0)
Do not use	90 (51.1)
7. How often do you recommend diagnostic renal biopsy for a small renal mass?	
Whenever it's helpful (>50% of all patients)	13 (7.4)
Whenever it's helpful (<50% of all patients)	24 (13.6)
Very select cases (<10% of all patients)	94 (53.4)
Do not recommend	45 (25.6)
8. In what situation, do you recommend biopsy? (multiple choices available)	
Before active surveillance	40 (22.7)
When considering surgery	46 (26.1)
Other types of cancer (lymphoma, metastasis) or inflammatory pseudotumor suspected	87 (49.4)
Before thermal ablation	63 (35.8)
9. What would be the reasons for not recommending biopsy? (multiple choices available)	
Concerns about track seeding	23 (13.1)
Nondiagnostic results (high probability of failure)	25 (14.2)
Not alter the treatment plans	23 (13.1)

(continued)

Table 1. Questionnaires on solitary renal mass management patterns (N=176) (continued)

Questionnaire	No. (%)
10. Nephron-sparing surgery is the preferred surgical method for small renal mass recommended in all current treatment guidelines for patients who choose definite treatment. What are the factors that make the choose to consider other methods? (multiple choices available)	
Baseline renal function	104 (23.0)
Tumor morphology	139 (30.7)
Patient's comorbidity	113 (24.9)
Patient's age	97 (21.4)
11. What is your preferred less invasive alternative to nephron-sparing surgery?	
Active surveillance	2 (1.1)
Cryotherapy	11 (6.3)
HIFU	1 (0.6)
Radiofrequency ablation	142 (80.7)
Stereotactic body radiotherapy	12 (6.8)
Always recommend nephron-sparing surgery	8 (4.5)
12. What is your preferred follow-up imaging method in patients on surveillance?	
Computed tomography (CT)	158 (89.8)
Magnetic resonance imaging	2 (1.1)
Ultrasonography	8 (4.5)
No big preference (use multiple methods in turns)	8 (4.5)
13. What is your preferred imaging technique for metastasis workup?	
Bone scan	1 (0.6)
Chest CT	51 (29.0)
Chest CT+bone scan	102 (58.0)
Abdomen & pelvis CT only (no other metastasis workup)	22 (12.5)
14. What do you think the appropriate follow-up interval is in the first year of surveillance?	
3 Months	62 (35.2)
3 Months initially, then 6 months	1 (0.6)
4 Months	10 (5.7)
6 Months	101 (57.4)
1 Year	2 (1.1)
15. Which of the following factors do you emphasize in counseling patients on surveillance?	
Hypertension	8 (4.5)
Diabetes	2 (1.1)
Obesity	4 (2.3)
Smoking	44 (25.0)
Explain everything above	82 (46.6)
I don't think it's very important after the tumor occurs; so, I don't explain.	36 (20.5)
16. What is the target termination indicator that you set when you begin active surveillance? Termination includes both termination of follow-up and transition to active treatment.	
Tumor size increase until radical nephrectomy is necessary	8 (4.5)
Nonmetastasis until target age	1 (0.6)
Increased tumor size above a certain velocity	102 (57.9)
Until the tumor has increased to a certain size	65 (36.9)

(continued)

Table 1. Questionnaires on solitary renal mass management patterns (N=176) (continued)

Questionnaire	No. (%)
17. The following are the criteria AUA 2021 guidelines recommend switching to active treatment during active surveillance. Which do you think is the most important?	
Changes in patient/tumor factors (clinical symptoms, changes to an infiltrative shape, etc.)	8 (4.5)
Growth kinetic (>5 mm/yr)	76 (43.2)
Stage progression	15 (8.5)
Tumor size >3 cm	77 (43.8)
18. Do you have any patients on active surveillance?	
About <10% of solitary renal mass patients	123 (69.9)
About >10% of solitary renal mass patients	26 (14.8)
None	27 (15.3)

KDIGO, Kidney Disease Improving Global Outcomes; CKD, chronic kidney disease; HIFU, high-intensity focused ultrasound; AUA, American Urological Association.

without follow-up imaging unless clinically indicated.

RESULTS

A total of 176 responses were obtained (response rate, 24.8%, 176 of 711). All respondents were practicing in an academic setting, with the number of years treating kidney cancer patients being less than 5 years, between 5 and 10 years, and more than 10 years in 36 (20.5%), 43 (24.4%), and 97 respondents (55.1%), respectively. The approximate number of kidney cancer operations performed per year was fewer than 20 cases, between 20 and 50 cases, between 50 and 100 cases, and more than 100 cases in 73 (41.5%), 64 (36.4%), 20 (11.4%), and 19 respondents (10.8%), respectively (Table 1). The questions were reorganized according to the subject and in the order of the frequency of answers (Table 2). The number of the question is marked next to "#" in Table 2.

1. Age and Competing Risks

Two questions (#3 and #6) independently addressed the issue of age and competing risks, and 2 (#4 and #5) others did so in relation to size criteria. Regarding the age of patients with SRMs, 42.6% (n=72) responded that they would recommend a diagnostic evaluation and definitive treatment for anyone under 80 years of age as long as the patient was healthy. Another 20.5% (n=36) responded that they would recommend it regardless of age if the patient is healthy and

Table 2. Questionnaires summary according to the subject of a question (N=176)

Questionnaire	No. (%)
Age and competing risks	
Age criteria for active treatment (#3)	
1. Healthy under 80	75 (42.6)
2. If healthy, all ages	36 (20.5)
3. Healthy under 75	34 (19.3)
4. Healthy under 70	19 (10.8)
5. Healthy under 85	12 (6.8)
Used index (#6)	
1. Do not use	90 (51.1)
2. Charlson Comorbidity Index	77 (43.8)
3. KDIGO classification of CKD risk	7 (4.0)
4. Chronic Disease Score/Modified-Chronic Disease Score	1 (0.6)
Emphasize in counseling (#15)	
1. Explain everything below	82 (46.6)
2. Smoking	44 (25.0)
3. I don't think it's very important after the tumor occurs; so, I don't explain.	36 (20.5)
4. Hypertension	8 (4.5)
5. Obesity	4 (2.3)
6. Diabetes	2 (1.1)
Size and growth kinetics	
Size criteria for younger age (#4)	
1. ≥2 cm	99 (56.3)
2. ≥1 cm	35 (19.9)
3. ≥3 cm	26 (14.8)
4. ≥4 cm	16 (9.1)
Size criteria for older age (#5)	
1. ≥4 cm	55 (31.3)
2. ≥2 cm	51 (29.0)
3. ≥3 cm	42 (23.9)
4. Observe without treatment until intolerable symptoms occur	22 (12.5)
5. ≥1 cm	6 (3.4)
Preferred AUA guideline indicator (#17)	
1. Tumor size >3 cm	77 (43.8)
2. Growth kinetic (>5 mm/yr)	76 (43.2)
3. Stage progression	15 (8.5)
4. Changes in patient/tumor factors (clinical symptoms, changes to an infiltrative shape, etc.)	8 (4.5)
Termination of surveillance and intervention	
Preferred follow-up imaging method (#12)	
1. Computed tomography (CT)	158 (89.8)
2. Ultrasonography	8 (4.5)
3. No big preference (use multiple methods in turns)	8 (4.5)
4. MRI	2 (1.1)
Preferred imaging technique for metastasis workup (#13)	
1. Chest CT+bone scan	102 (58.0)
2. Chest CT	51 (29.0)
3. Abdomen & pelvis CT only (no other metastasis workup)	22 (12.5)
4. Bone scan	1 (0.6)
First year follow-up interval (#14)	
1. 6 Months	101 (57.4)
2. 3 Months	62 (35.2)
3. 4 Months	10 (5.7)
4. 1 Year	2 (1.1)
5. 3 Months initially, then 6 months	1 (0.6)

(continued)

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Table 2. Questionnaires summary according to the subject of a question (N=176) (continued)

Questionnaire	No. (%)
Active surveillance termination indicator (#16)	
1. Increased tumor size above a certain velocity	102 (57.9)
2. Until the tumor has increased to a certain size	65 (36.9)
3. Tumor size increase until radical nephrectomy is necessary	8 (4.5)
4. Nonmetastasis until target age	1 (0.6)
Factors considering alternative treatment (#10)	
1. Tumor morphology	139 (30.7)
2. Patient's comorbidity	113 (24.9)
3. Baseline renal function	104 (23.0)
4. Patient's age	97 (21.4)
Alternative to nephron-sparing surgery (#11)	
1. Radiofrequency ablation	142 (80.7)
2. Stereotactic body radiotherapy	12 (6.8)
3. Cryotherapy	11 (6.3)
4. Always recommend nephron-sparing surgery.	8 (4.5)
5. Active surveillance	2 (1.1)
6. HIFU	1 (0.6)
Renal mass biopsy	
Renal biopsy recommendation (#7)	
1. Very select cases (<10% of all patients)	94 (53.4)
2. Do not recommend	45 (25.6)
3. Whenever it's helpful (<50% of all patients)	24 (13.6)
4. Whenever it's helpful (>50% of all patients)	13 (7.4)
Reason for recommending biopsy (multiple choices available, #8)	
1. Other types of cancer (lymphoma, metastasis) or inflammatory pseudotumor suspected	87 (49.4)
2. Before thermal ablation	63 (35.8)
3. When considering surgery	46 (26.1)
4. Before active surveillance	40 (22.7)
Reason for NOT recommending biopsy (multiple choices available, #9)	
1. Nondiagnostic results (high probability of failure)	25 (14.2)
2. Concerns about track seeding	23 (13.1)
3. Not alter the treatment plans	23 (13.1)

KDIGO, Kidney Disease Improving Global Outcomes; CKD, chronic kidney disease; HIFU, high-intensity focused ultrasound.

wants active management.

To objectively measure patients' health status in addition to age and comorbidities, 43.8% (n=77) of respondents reported using the Charlson Comorbidity Index, while the majority did not use any indices. Once surveillance was chosen, 79.5% (n=140) said that they counseled patients on control of smoking (25.0%), hypertension (4.5%), diabetes (1.1%), obesity (2.3%), or all of those risk factors (46.6%).

2. Size and Growth Kinetics

Questions relating to tumor characteristics and the clinical decisions made in that regard addressed size criteria in relation to patients' age and subsequent changes influencing a decision. In younger candidates presumed to be fit for definitive treatment, a tumor size criterion of ≥2 cm was the most frequently used, by 56.3% of respondents (n=99). While 19.9% (n=35) responded that they would recommend active treatment for tumors ≥1 cm, 9.1% (n=16) preferred deferring active treatment until tumors grew beyond 4 cm. In contrast, in more elderly candidates presumed to be a better fit for initial surveillance, tumor sizes ≥3 cm or ≥4 cm were considered at similar rates to the ≥2 cm criterion, in 23.9%, 31.3%, and 29.0% of responses, respectively. For this cohort of patients, 12.5% (n=22) of the physicians responded that they would observe the RSM without any investigation or treatment until intolerable symptoms occur.

In addition to the initial tumor size, subsequent changes considered significant were rapid growth (>5 mm/yr) in 43.2% (n=76) of responses and size growth beyond 3 cm in another 43.8% (n=77). Stage progression, in 8.5% (n=15) of responses, and changes in patient and/or tumor factors (e.g., tumor shape), in 4.5% (n=8) of responses, were also considered significant.

3. Termination of Surveillance and Intervention

To evaluate metastasis at the initial diagnosis, 58.0% (n=102) of respondents stated that they checked CT of the chest and a bone scan, and another 29.0% (n=51) and 12.5% (n=22) checked CT of the chest or only abdominal and pelvic CT, respectively. When active surveillance was chosen, the preferred follow-up radiographic method was nearly unanimously CT scans (89.8%), but the intervals significantly differed; most (55.7%, n=44) respondents with less than 10 years of experience in treating kidney cancer abided by initial surveillance intervals of 3–4 months, while those with more than 10 years of experience preferred intervals of 6 months (68.0%, p=0.001). Table 3 shows the differences between physicians with less or more than 10 years of experience in kidney cancer treatment

As a target indicator for surveillance termination, a tumor growth rate above a certain velocity (57.9%, n=102) and a size increase above a certain diameter (36.9%, n=65) were the most commonly used criteria. When patients are converted to definitive therapy, nephron-sparing surgery should be considered as a priority, following the recommendations of

Table 3. Differences by kidney cancer treatment experience

Questionnaires	<10 Years of experience (N=79)	>10 Years of experience (N=97)	p-value
1. How long have you been treating a kidney cancer patient?			<0.001
For more than 10 years	0 (0)	97 (100)	
5–10 Years	43 (54.4)	0 (0)	
Within 5 years	36 (45.6)	0 (0)	
2. Approximately how many kidney cancer patients do you perform surgery a year?			0.006
More than 100 cases	5 (6.3)	14 (14.4)	
50-100 Cases	3 (3.8)	17 (17.5)	
20-50 Cases	34 (43.0)	30 (30.9)	
Within 20 cases	37 (46.9)	36 (37.1)	
3. Until what age do you recommend active diagnosis and treatment of small rental mass?			0.243
If healthy, all ages	15 (19.0)	21 (21.6)	
Healthy under 70	11 (13.9)	8 (8.2)	
Healthy under 75	10 (12.7)	24 (24.7)	
Healthy under 80	37 (46.8)	38 (39.2)	
Healthy under 85	6 (7.6)	6 (6.2)	
4. What is your size criteria to recommend definitive treatment for small renal mass in YOUNGER age as you answered in question number 3?			0.392
≥1 cm	20 (25.3)	15 (15.5)	
≥2 cm	43 (54.4)	56 (57.7)	
≥3 cm	10 (12.7)	16 (16.5)	
≥4 cm	6 (7.6)	10 (10.3)	
5. What is your size criteria to recommend definitive treatment for small renal mass in OLDER age as you answered in question number 3?			0.398
≥1 cm	2 (2.5)	4 (4.1)	
≥2 cm	24 (30.4)	27 (27.8)	
≥3 cm	14 (17.7)	28 (28.9)	
≥4 cm	29 (36.7)	26 (26.8)	
Observe without treatment until severe symptoms occur	10 (12.7)	12 (12.4)	
6. Do you use indexes to accurately measure the patient's comorbidity?			0.637
Charlson Comorbidity Index	38 (48.1)	39 (40.6)	
Chronic Disease Score/Modified-Chronic Disease Score	0 (0)	1 (1.0)	
KDIGO classification of CKD risk	3 (3.8)	4 (4.2)	
Do not use	38 (48.1)	52 (54.2)	
7. Do you recommend renal biopsy for a small renal mass?			0.286
Whenever it's helpful (>50% of all patients)	7 (8.9)	6 (6.2)	
Whenever it's helpful (<50% of all patients)	9 (11.4)	15 (15.5)	
Very select cases (<10% of all patients)	38 (48.1)	56 (57.7)	
Do not recommend	25 (31.6)	20 (20.6)	
8. If renal biopsy is recommended, what is the case? (multiple choices available)			0.652
Before active surveillance	14 (14.3)	25 (15.5)	
When considering surgery	18 (18.4)	36 (22.4)	
Suspect another type of cancer (lymphoma, metastasis) or infection (abscess)	41 (41.8)	55 (34.2)	
Before thermal ablation	25 (25.5)	45 (28.0)	
9. If renal biopsy is NOT recommended, what is the case? (multiple choices available)			0.597
Concerns about seeding	12 (28.6)	11 (37.9)	
I don't think the diagnosis will be accurate (high probability of failure)	16 (38.1)	8 (27.6)	
Not effective in determining the treatment policy	14 (33.3)	10 (34.5)	
10. Nephron-sparing surgery is the preferred surgical method for small renal mass recommended in all current treatment guidelines for patients who choose definite treatment. What are the factors that make the choose to consider other methods? (multiple choices available)			0.718
Preoperative renal function	42 (21.4)	62 (23.0)	
Tumor morphology	65 (33.2)	84 (31.2)	
Patient's comorbidity	52 (26.5)	63 (23.4)	
Patient's age	37 (18.9)	60 (22.3)	

(continued)

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Table 3. Differences by kidney cancer treatment experience (continued)

Questionnaires	<10 Years of experience (N=79)	>10 Years of experience (N=97)	p-value
11. If you choose a less invasive method than nephron-sparing therapy, what is your preferred method?			0.692
Active surveillance	1 (1.3)	1 (1.0)	
Cryotherapy	5 (6.3)	6 (6.2)	
HIFU	0 (0)	1 (1.0)	
Radiofrequency ablation	67 (84.8)	75 (77.3)	
Stereotactic body radiotherapy	4 (5.1)	8 (8.2)	
Always recommend nephron-sparing surgery	2 (2.6)	6 (6.0)	
12. In the AUA 2021 guidelines, follow-up imaging with CT or ultrasonography is recommended, and ultrasonography are recommended to be used more frequently in stable patients. What is the most preferred follow-up imaging method when there is a small renal mass?			0.190
Computed tomography (CT)	70 (88.6)	88 (90.7)	
Magnetic resonance imaging	0 (0)	2 (2.1)	
Ultrasonography	3 (3.8)	5 (5.2)	
No big preference (use multiple methods in turns)	6 (7.6)	2 (2.1)	
13. What is your preferred imaging technique for metastasis workup?			0.489
Bone scan	0 (0)	1 (1.0)	
Chest CT	26 (32.9)	25 (25.8)	
Chest CT+bone scan	45 (57.0)	57 (58.8)	
Abdomen & pelvis CT only (no other metastasis workup)	8 (10.1)	14 (14.5)	
14. The AUA 2021 guideline recommends the initial active surveillance period of 3–6 months. How do you think the appropriate initial 1-year follow-up interval for a small renal mass?			0.001
3 Months	35 (44.3)	27 (27.8)	
3 Months initially, then 6 months	0 (0)	1 (1.0)	
4 Months	9 (11.4)	1 (1.0)	
6 Months	35 (44.3)	66 (68.0)	
1 Year	0 (0.0)	2 (2.1)	
15. Which of the following factors is explained to be actively controlled in patients with small renal mass?			0.373
Hypertension	3 (3.8)	5 (5.2)	
Diabetes	2 (2.5)	0 (0.0)	
Obesity	3 (3.8)	1 (1.0)	
Smoking	21 (26.6)	23 (23.7)	
Explain everything above	37 (46.8)	45 (46.4)	
I don't think it's very important after the tumor occurs; so, I don't explain.	13 (16.5)	23 (23.7)	
16. What is the target end indicator that you usually set when you start active surveillance? Termination included both termination of follow-up and transition to active treatment.			0.153
Tumor size increase until radical nephrectomy is necessary	6 (7.6)	2 (2.1)	
Nonmetastasis until target age	0 (0)	1 (1.0)	
Increased tumor size above a certain velocity	41 (51.9)	43 (44.3)	
Increased tumor size above a certain velocity	5 (6.3)	13 (13.4)	
Until the tumor has increased to a certain size	27 (34.2)	38 (39.2)	
17. The following are the criteria for switching from the AUA 2021 guidelines to active treatment during active surveillance. What is the most important criterion that you consider?			0.681
Clinical changes in patient/tumor factors (clinical symptoms, changes to an infiltrative shape, etc.)	2 (2.5)	6 (6.2)	
Growth kinetic (>5 mm/yr)	36 (45.6)	40 (41.2)	
Stage progression	7 (8.9)	8 (8.2)	
Tumor size >3 cm	34 (43.0)	43 (44.3)	
18. Are there any patients who are currently in active surveillance?			0.911
About <10% of solitary renal mass patients	55 (69.6)	68 (70.1)	
About >10% of solitary renal mass patients	11 (13.9)	15 (15.5)	
None	16 (12.9)	8 (16.3)	

Values are presented as number (%).

KDIGO, Kidney Disease Improving Global Outcomes; CKD, chronic kidney disease; HIFU, high-intensity focused ultrasound; AUA, American Urological Association.

all current guidelines [11-13]. In specific clinical scenarios, however, respondents stated that they considered factors such as tumor morphology (30.7%, n=139), comorbidities (24.9%, n=113), baseline renal function (23.0%, n=104), and age (21.4%, n=97) when deciding upon alternative therapeutic methods, for which radiofrequency ablation was the preferred option (80.7%, n=142)

4. Renal Mass Biopsy

Renal mass biopsies were recommended in very select cases (<10% of all patients) by most respondents (53.4%, n=94), followed by "not using it at all" in 25.6% (n=45). Among the respondents utilizing biopsies, the indications were predominantly to diagnose cancer: to differentiate the mass other types of cancer or an inflammatory condition in 49.4% (n=87), before thermal ablation in 35.8% (n=63), and before active surveillance in 22.7% (n=40). Opinions against performing biopsy were based on concerns about track seeding in 13.1% (n=23) of responses, nondiagnostic results in 14.2% (n=25), and the likelihood that the biopsy results would not change the treatment plan in 13.1% (n=23).

DISCUSSION

We aimed to describe the current practice patterns for incidentally detected SRMs among urologic oncologists and identify key indicators in action plans with regard to active surveillance (Fig. 1). We found that among the respondents, the initial decision to recommend surveillance involved similar key parameters, but the criteria for individual parameters varied independent of years of experience or volume of practice.

In the current survey, most participants were generous with regard to chronological age if patients were healthy and wanted active treatment. Patient-related factors are the most central parameters to consider and, in a society where life expectancy is rapidly increasing, our findings may suggest a potentially significant public health issue. Interest in health screening is high and on the increase, while the cultural sentiment is that active and definitive management of any detected abnormalities is preferred. Without a cost-effectiveness analysis available on abdominal screening [14], no guideline exists on how often and how long abdominal screening needs to be done to remain effective. Thus, the decision and subsequent plan remain to be made by individual practitioners and their patients. In this situation, comorbidity indices and frailty scales may help to objectively measure competing health risks and prioritize them [15,16]. Baseline renal function and the conditions affecting it immediately and long-term [7], access to and coverage by healthcare, the understanding of the surveillance scheme among patients and their caregivers, and motivation and compliance are all relevant patient factors. In this survey, these scales were not a routine practice for most respondents, although the respondents were aware of health risks and the need for counseling about them [17].

Tumor size at initial detection was an important criterion, but diverse patterns were observed, especially in relation to patients' age. Size is critical as it is directly associated with the probability of metastatic disease [18, 19]. In addition to the initial tumor size, the annual growth rate and growth beyond a preset diameter were frequently considered together. In actual practice, additional tumor-related factors, including the location and complexity of the tumor, its shape, and infiltration pattern (with or without identifiable pseudocapsules), always influence decisions [20]. Patient-related factors, such as both ipsilateral and total renal function, and treatment-related factors, such as the availability of less invasive alternatives, are also interlaced [21, 22]. Therefore, while we singled out each factor for our investigation, it would be more meaningful to develop a scoring system with the identified parameters weighted according to their contribution [23, 24]. Such a scoring system could be used in the initial counseling of patients and when deciding whether to surveil, helping to set appropriate goals for each patient.

Similarly, predefining indicators for intervention may be the most difficult part of initiating surveillance because the natural history of the disease is not yet completely understood [25]. Evaluations for metastasis during follow-up in patients undergoing surveillance are usually deferred until symptoms ensue. In the absence of "notable" growth, when to simply stop following may also require a strategy depending on the frailty of the patient population. Even in highly motivated patients, relieving patients of their anxiety

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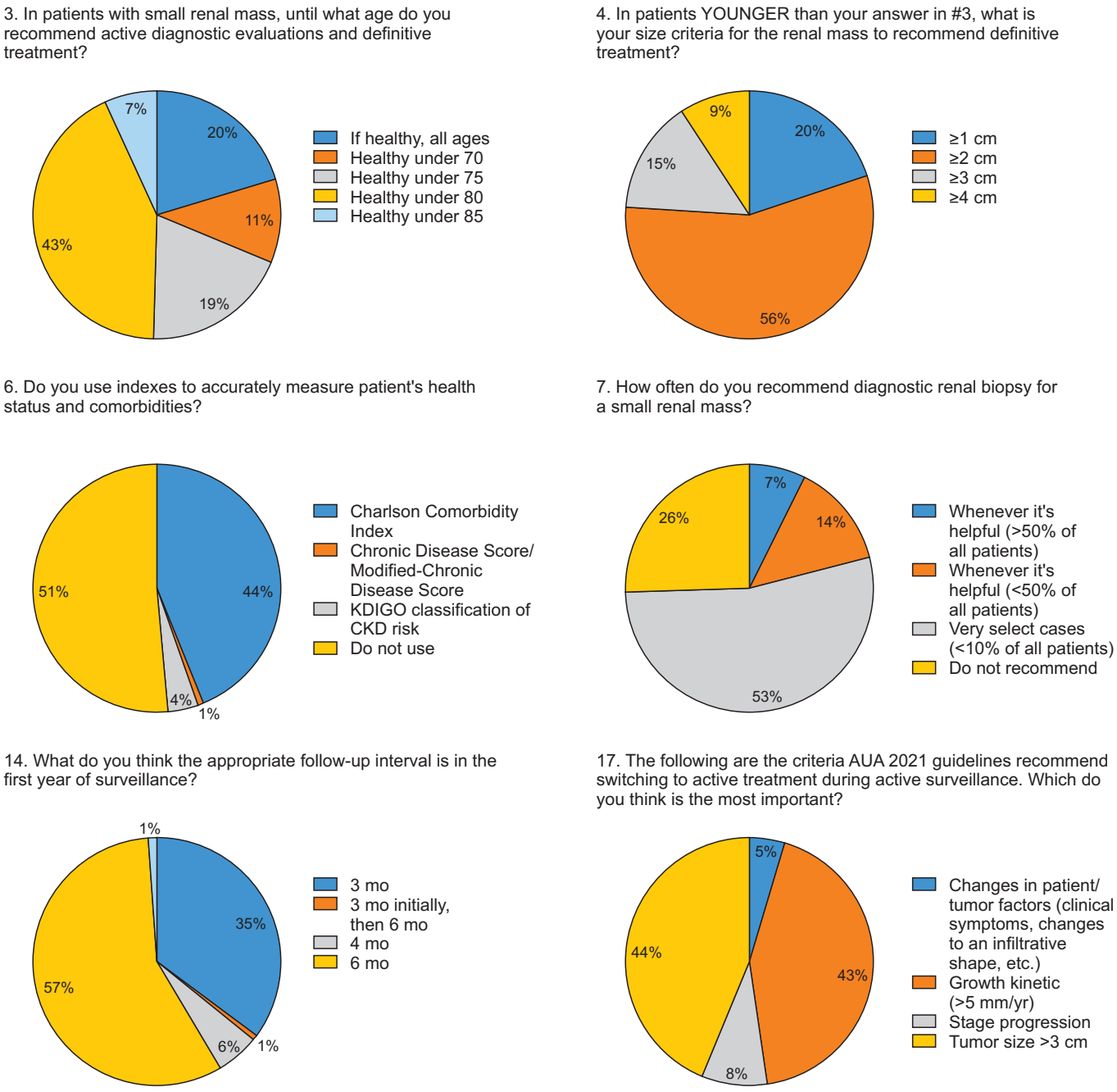

Fig. 1. Key indicators in the action plan with regard to active surveillance. In this survey, 6 key indicators was identified regard to active surveillance method in small renal mass patients. AUA, American Urological Association.

by confirming that their tumors have shown minimal changes and thus improving their general quality of life needs to be balanced against healthcare expenditures [26]. In such a situation, knowing whether the tumor is cancerous or not may often have an impact. Surprisingly, in the survey, we found that renal mass biopsies were not routinely utilized. Concerns about biopsy track seeding and nondiagnostic results were common reasons for opposing biopsy. However, contemporary series on renal biopsy have repeatedly refuted the need for such concerns [27, 28]. Pathological upstaging and progression-free survival have also been reported to be similar irrespective of preoperative biopsy for patients with T1a renal cell carcinoma receiving partial nephrectomy. The likelihood that the biopsy results would not change the treatment plan was another reason, which may stem from the fact that biopsies are not able to reliably detect

high-grade renal cell carcinoma secondary to intratumoral grade heterogeneity [28-30]. Meanwhile, the information that we can currently obtain from biopsies is very limited, which may limit their use. Besides cancer diagnosis, even the nuclear grade is discordant in up to 16% [30]. With accumulating molecular and genetic insights, we hope for more comprehensive prospects in making predictions based on biopsy specimens, which can inform an individualized surveillance strategy.

CONCLUSIONS

We described current practice patterns for incidentally detected SRMs among urologic oncologists and identified key indicators in action plans for active surveillance. This survey has provided robust information, empowering physicians with detailed knowledge of practice patterns and valuable insights on SRMs.

NOTES

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- ORCID

Joongwon Choi: https://orcid.org/0000-0001-5978-8179
Cheryn Song: https://orcid.org/0000-0002-1823-4281
Jungyo Suh: https://orcid.org/0000-0002-3867-4778
Minyong Kang: https://orcid.org/0000-0002-6966-8813
Chang Il Choi: https://orcid.org/0000-0001-6488-1933
Hyeong Dong Yuk: https://orcid.org/0000-0002-5874-9167
Chan Ho Lee: https://orcid.org/0000-0002-7750-6806
Jung Kwon Kim: https://orcid.org/0000-0002-8069-6225
Jung Ki Jo: https://orcid.org/0000-0002-6080-7493
Won Sik Ham: https://orcid.org/0000-0003-2246-8838
Eu Chang Hwang: https://orcid.org/0000-0002-2031-124X
Chang Wook Jeong: https://orcid.org/0000-0002-2200-5019
Young Hwii Ko: https://orcid.org/0000-0002-9150-4292
Jae Young Park: https://orcid.org/0000-0002-6664-6846
Seong Il Seo: https://orcid.org/0000-0002-9792-7798
Byung Kwan Park: https://orcid.org/0000-0002-4114-8859
Jinsoo Chung: https://orcid.org/0000-0003-2251-5331
Cheol Kwak: https://orcid.org/0000-0002-1987-2111
Sung-Hoo Hong: https://orcid.org/0000-0002-1952-4010

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Bladder Preservation With Transurethral Tumor Resection and Intravesical BCG Instillation in Superficial Muscle-Invasive Bladder Cancer: A 10-Year Follow-up

Dong Gyun Kim[1], Ji Eun Heo[1], Kang Su Cho[2], Jongsoo Lee[1], Won Sik Jang[1], Nam Hoon Cho[3], Young Deuk Choi[1]

[1]Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea
[2]Department of Urology, Gangnam Severance Hospital, Yonsei University College of Medicine, Seoul, Korea
[3]Department of Pathology, Yonsei University College of Medicine, Seoul, Korea

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Corresponding author:
Young Deuk Choi
Department of Urology, Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea
Email: youngd74@yuhs.ac
https://orcid.org/0000-0002-8545-5797

Purpose: The aim of this study was to evaluate the 10-year oncological outcomes of bladder preservation with transurethral resection of bladder tumor (TURBT) and intravesical bacillus Calmette-Guérin (BCG) instillation in selected patients with superficial muscle-invasive bladder cancer (MIBC).

Materials and Methods: Patients diagnosed with superficial MIBC (stage T2a) by TURBT between 2001 and 2009 were included. Cystectomy-free survival, recurrence-free survival (RFS), progression-free survival (PFS), and cancer-specific survival (CSS) were estimated using the Kaplan-Meier method. Cox regression analysis was used to identify predictors of each type of survival.

Results: Of 145 patients, 135 underwent bladder preservation and 10 underwent immediate radical cystectomy (RC). Among the latter, 9 patients showed downstaging. During a median follow-up of 132 months (interquartile range, 96–161 months), 13 patients underwent RC, with a 10-year cystectomy-free survival rate of 83.9%. Seventy patients (48.3%) had recurrence, and the 10-year RFS rate was 48.9%. Progression occurred in 12 patients (8.3%), with a 10-year PFS rate of 90.1%. Death occurred only in patients who exhibited progression; 5 patients (3.4%) died of bladder cancer, and the 10-year CSS rate was 96.5%. Tumors greater than 3 cm were associated with RC, and a high tumor grade predicted recurrence. RC was related to progression and cancer-specific mortality.

Conclusions: Although high-grade tumors require careful follow-up, bladder preservation with TURBT and intravesical BCG instillation can enable the successful management of selected patients with stage T2a MIBC less than 3 cm, without carcinoma *in situ* or tumor-associated hydronephrosis, in a nonmetastatic setting.

Key Words: BCG vaccine, Organ preservation, Survival, Transurethral resection of bladder, Urinary bladder neoplasms

INTRODUCTION

Radical cystectomy (RC) has been regarded as the standard treatment for muscle-invasive bladder cancer (MIBC). However, it is associated with high morbidity and diminished quality of life [1, 2]. Various bladder-preserving strategies have been introduced as alternatives for patients unfit for surgery and those unwilling to undergo RC without compromising

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the oncological outcomes [3, 4]. The most representative method of bladder preservation is multimodal therapy (MMT), which includes radical transurethral resection of bladder tumor (TURBT) followed by radiation therapy (RT) with concurrent radiosensitizing chemotherapy. This bladder preservation strategy can provide a better quality of life with acceptable outcomes and may be considered a reasonable alternative to RC in properly selected patients [5].

Another bladder-preserving method is radical TURBT alone. The rationale behind performing TURBT alone lies in the possibility of pathologic absence of tumor (pT0) at RC. Recent RC series reported that the expected incidence of pT0 without neoadjuvant chemotherapy ranged from 6% to 20% [6-8]. RC is indisputably the best approach, even in patients with bladder cancer with pT0 disease, but patients may have missed the opportunity for bladder preservation. This rationale can be opposed by the following considerations: the risk of recurrence in pT0 disease is not zero, clinical and pathological stage discrepancies can occur, and lymphadenectomy can only be performed if RC is performed [9, 10]. Nevertheless, some surgeons have reported favorable outcomes of TURBT alone in selected patients with MIBC. Herr [11] reported a series of 99 patients with a 10-year disease-specific survival of 76%. Solsona et al. [12] reported a similar disease-specific survival of 76.7% at 15 years for 133 selected patients.

Currently, the overall consensus is that radical TURBT alone is a suboptimal treatment for MIBC. However, TURBT alone might provide comparable oncological outcomes to those of RC if candidates are selected more carefully [1, 2]. Superficial MIBC is an essential precondition for bladder preservation, but there is no effective imaging modality for discriminating the depth of proper muscle invasion (superficial vs. deep) [1, 13]. Thus, we diagnosed stage T2a MIBC based on TURBT, and bladder preservation was offered as a treatment option in these patients.

Bacillus Calmette-Guérin (BCG) instillation may have beneficial systemic effects in stage T2a MIBC patients receiving bladder-sparing therapy [14]. Therefore, we performed intravesical BCG instillation in all patients who received radical TURBT. This study aimed to evaluate the 10-year oncological outcomes of bladder preservation with TURBT and intravesical BCG instillation in highly selected patients with stage T2a MIBC.

MATERIALS AND METHODS

This retrospective study was approved by the Institutional Review Board of Yonsei University Severance Hospital (IRB number: 4-2020-0457) for data collection of patients who underwent TURBT for bladder cancer between 2001 and 2009. All procedures were performed by a single surgeon (YDC).

The schematic concept of diagnosing stage T2a based on TURBT is shown in Fig. 1. After a meticulous cystoscopic examination, the gross tumor was completely removed. Next, the tumor base was resected, including the superficial muscle layer. Two consecutive muscle layers below the tumor base were additionally resected until the adipose tissue was exposed and the tumor periphery was included in the resected section. In this procedure, we obtained specimens of the tumor base, deep muscle layer, and deeper muscle layer separately from the main mass. After the resection was complete, the resected surface was fully electrocauterized. We termed this procedure "transurethral layer-section" of the bladder tumor.

Pathological analysis of the specimens was performed at our institution by an experienced uropathologist (NHC) (Fig.

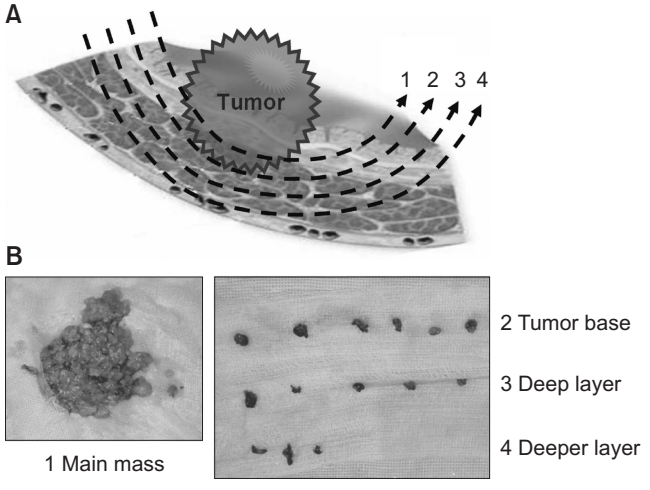

Fig. 1. Muscle layer specimen obtained during transurethral resection of a bladder tumor. (A) Schematic diagram of the concept. Lines 1–4 are resection lines for the main mass, tumor base, deep layer, and deeper layer of muscle, respectively. (B) An example of specimen preparation.

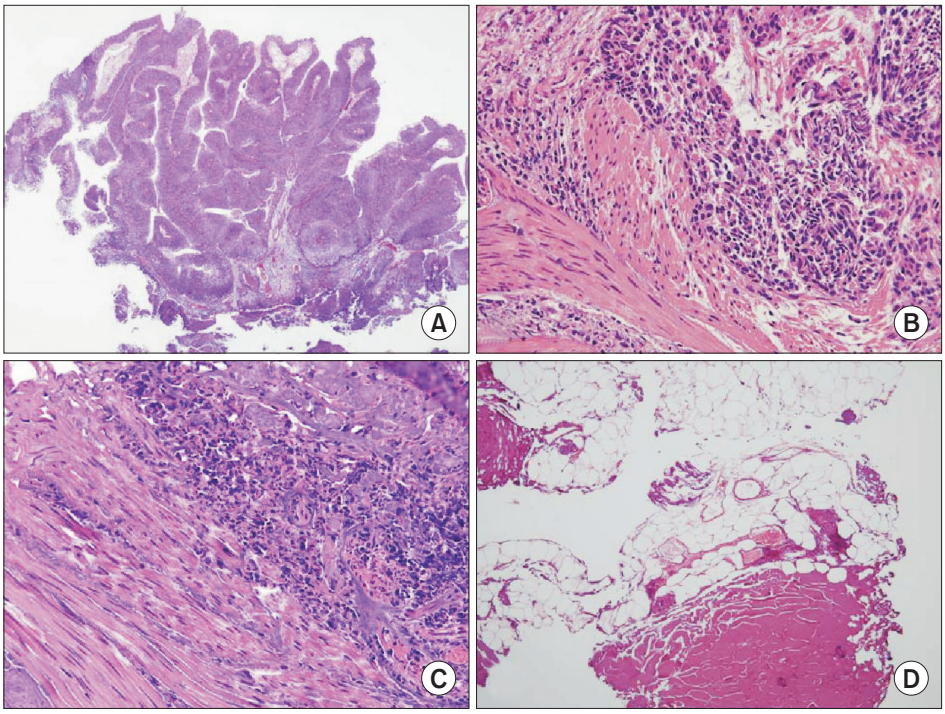

Fig. 2. Histologic findings (hematoxylin and eosin stain). (A) The main mass shows high-grade papillary urothelial carcinoma (magnification, ×40). (B) The tumor base shows muscle-infiltrating carcinoma (magnification, ×400). (C) The deep muscle layer shows muscle tissue without tissue infiltration (magnification, ×400). (D) The deeper muscle layer shows muscle tissue including perivesical fat without tumor invasion (magnification, ×100).

2). The pathological stage and tumor grade were assigned in accordance with the American Joint Committee on Cancer staging system and the World Health Organization classification of bladder tumors, respectively [15, 16]. All specimens were pure urothelial carcinoma, and we excluded variants of urothelial carcinoma. If a tumor was identified in the superficial muscle layer without tumor presence in 2 consecutive layers of deep and deeper muscles, it was considered as stage T2a MIBC without a residual tumor. Radical TURBT was performed in those cases. Preoperative imaging (computed tomography or magnetic resonance imaging [MRI]) was performed in all patients for staging. A Foley catheter was maintained for 7–14 days after surgery.

Bladder preservation without concurrent chemotherapy or RT was considered as an option for patients with stage T2a MIBC. We excluded patients with lymph node or distant metastasis at diagnosis, urothelial carcinoma of the upper urinary tract or prostate, tumor-associated hydronephrosis, or carcinoma *in situ* (CIS), as well as those in whom the largest tumor lesion was greater than 4 cm. Previous studies have indicated that the presence of CIS is not a contraindication for bladder preservation when intravesical BCG therapy is performed [17, 18]. However, we excluded patients with CIS, as the initial presence of CIS is a predictor of cancer progression [17]. A previous study showed that the complication rate of TURBT was significantly higher in masses larger than 4 cm. Therefore, this study only included masses smaller than 4 cm, which are expected to have fewer complications of TURBT [19].

Patients were offered either standard RC or bladder preservation. To confirm the completeness of radical TURBT, repeated TURBT within 6 weeks after the initial operation was suggested. The planned procedures were discussed with each patient and performed after informed consent was obtained.

Intravesical BCG therapy was performed in all patients who selected bladder preservation. All patients received BCG induction 1 month after TURBT and received BCG instillation once a week for 6 weeks. BCG maintenance was not performed. These patients were evaluated regularly with cystoscopy, urine cytology, abdominopelvic computed tomography, bladder MRI, whole-body bone scan, and chest radiography every 3 months for 2 years, every 6 months for the subsequent 3 years, and annually thereafter. The same follow-up plan, except for cystoscopy and bladder MRI, was implemented for patients who underwent RC.

Recurrence was defined as superficial bladder cancer after TURBT or cancer within the soft tissue field of exenteration

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after RC. Progression was considered as deeper tumor invasion of the muscle layer or the presence of lymph node or distant metastasis. If local recurrence after RC or metastasis occurred, patients received chemotherapy and/or RT. Data on mortality and cause of death were collected from the medical records in the Cancer Registry Center database at our institution. Recurrence-free survival (RFS), progression-free survival (PFS), cancer-specific survival (CSS), and cystectomy-free survival were determined from the time of the initial diagnosis of MIBC to the corresponding events or the last follow-up.

Continuous variables are expressed as medians (interquartile ranges [IQRs]), whereas categorical variables are reported as the number of occurrences and frequency (percentage). Survival was estimated using the Kaplan-Meier method and parameters were assessed by Cox regression analysis to identify the predictors. All statistical analyses were performed using IBM SPSS Statistics ver. 26.0 (IBM Co., Armonk, NY, USA).

RESULTS

The patients' baseline characteristics are summarized in Table 1. In total, 145 patients were diagnosed with stage T2a disease. The median age was 64 years (IQR, 56–71 years). High-grade tumors were found in 128 patients (88.3%) and multiple tumor lesions in 83 patients (57.2%). In 74 patients (51.0%), the largest tumor lesion was greater than 3 cm. Complications, such as bladder perforation, urine leakage, or bleeding, were not observed after TURBT. Of the 145 patients, 135 selected bladder preservation and 10 selected immediate RC. In the latter group, 5 patients had pT0 and 4 patients had non-MIBC. Repeated TURBT was performed in 42 patients (13 had T0 and 29 had T1) among those who underwent bladder preservation (Fig. 3).

During a median follow-up of 132 months (IQR, 96–161 months; maximum, 210 months), patients underwent a median of 2 TURBT procedures (IQR, 1–3 procedures; maximum, 13 procedures), and 13 patients eventually underwent RC. The 1-, 5-, and 10-year cystectomy-free survival rates were 89.6%, 85.9%, and 83.9%, respectively. Recurrence was observed in 70 patients (48.3%), and the 1-, 5-, and 10-year RFS rates were 80.1%, 51.6%, and 48.9%, respectively. Progression occurred in 12 (8.3%) patients and the 1-, 5-, and 10-year PFS rates were 100%, 96.3%, and 90.1%, respectively. Death occurred only in patients with disease progression, and 5 patients (3.4%) died of bladder cancer; the 1-, 5-, and 10-year CSS rates were 100%, 98.5%, and 96.5%, respectively (Figs. 3, 4).

In the Cox regression analysis, a tumor lesion size greater than 3 cm was associated with RC (hazard ratio [HR], 2.531; 95% confidence interval [CI], 1.041–6.153; p=0.041). A high tumor grade was the only predictor of recurrence (HR, 6.183; 95% CI, 1.513–25.265; p=0.011). RC (HR, 12.118; 95% CI, 3.645–40.285; p<0.001) and recurrence (HR, 11.494; 95% CI, 1.484–89.037; p=0.019) were associated with progression. This association persisted in the multivariate analysis (RC: HR, 13.233; 95% CI, 3.943–44.413; p<0.001; recurrence: HR, 12.881; 95% CI, 1.642–101.036; p=0.015). RC was also a significant predictor of cancer-specific mortality (HR, 22.972; 95% CI, 2.566–205.662; p=0.005) (Table 2).

Table 1. Patient characteristics (n=145)

Characteristic	Value
Age (yr)	64 (56–71)
Sex	
Male	118 (81.4)
Female	27 (18.6)
Tumor grade	
Low	17 (11.7)
High	128 (88.3)
No. of tumors	
Single	62 (42.8)
Multiple	83 (57.2)
Size of tumor (cm)	
<3	71 (49.0)
≥3	74 (51.0)
Subsequent treatment	
Bladder preservation	122 (84.1)
Radical cystectomy	23 (15.9)
Repeat TURBT	
Performed	42 (29.0)
T1	29 (69.0)
T0	13 (31.0)
Not performed	103 (71.0)
No. of TURBTs	2 (1–3)
Recurrence	70 (48.3)
Progression	12 (8.3)
Cancer-specific mortality	5 (3.4)
Follow-up duration (mo)	132 (96–161)

Values are presented as median (interquartile range) or number (%).
TURBT, transurethral resection of bladder tumor.

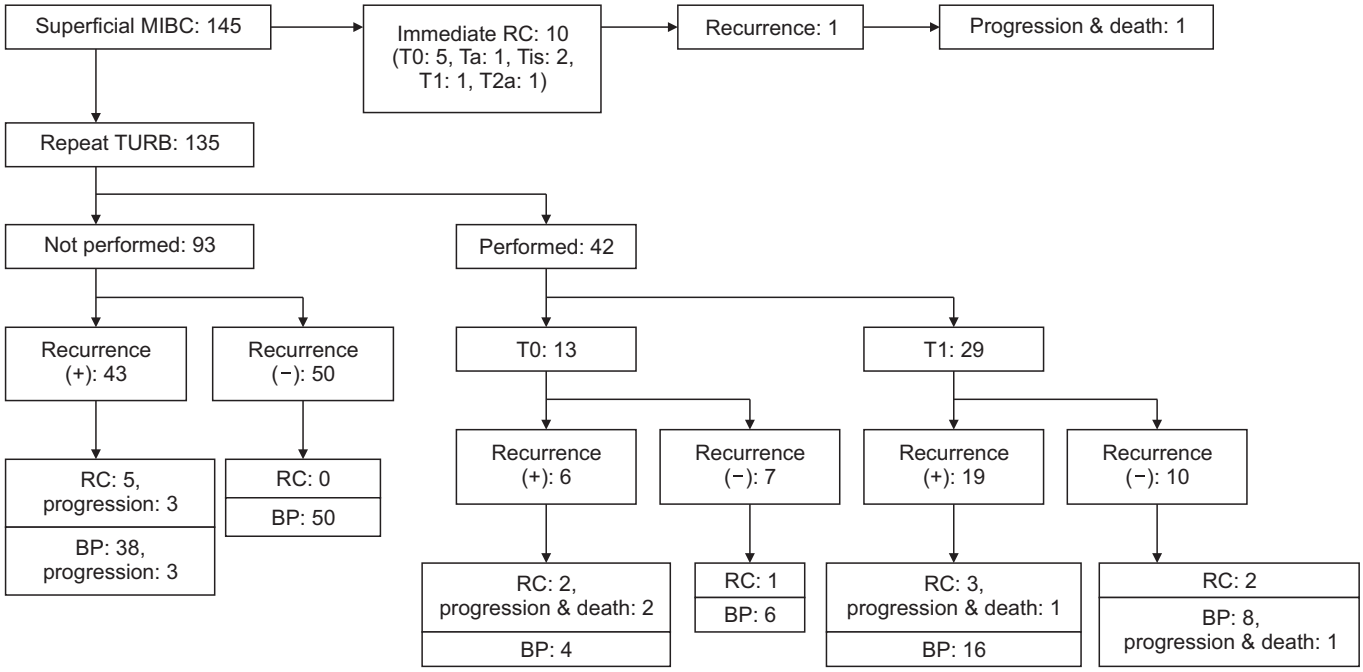

Fig. 3. Flowchart of 145 patients diagnosed with superficial MIBC. MIBC, muscle-invasive bladder cancer; RC, radical cystectomy; TURB, transurethral resection of bladder tumor; BP, bladder preservation.

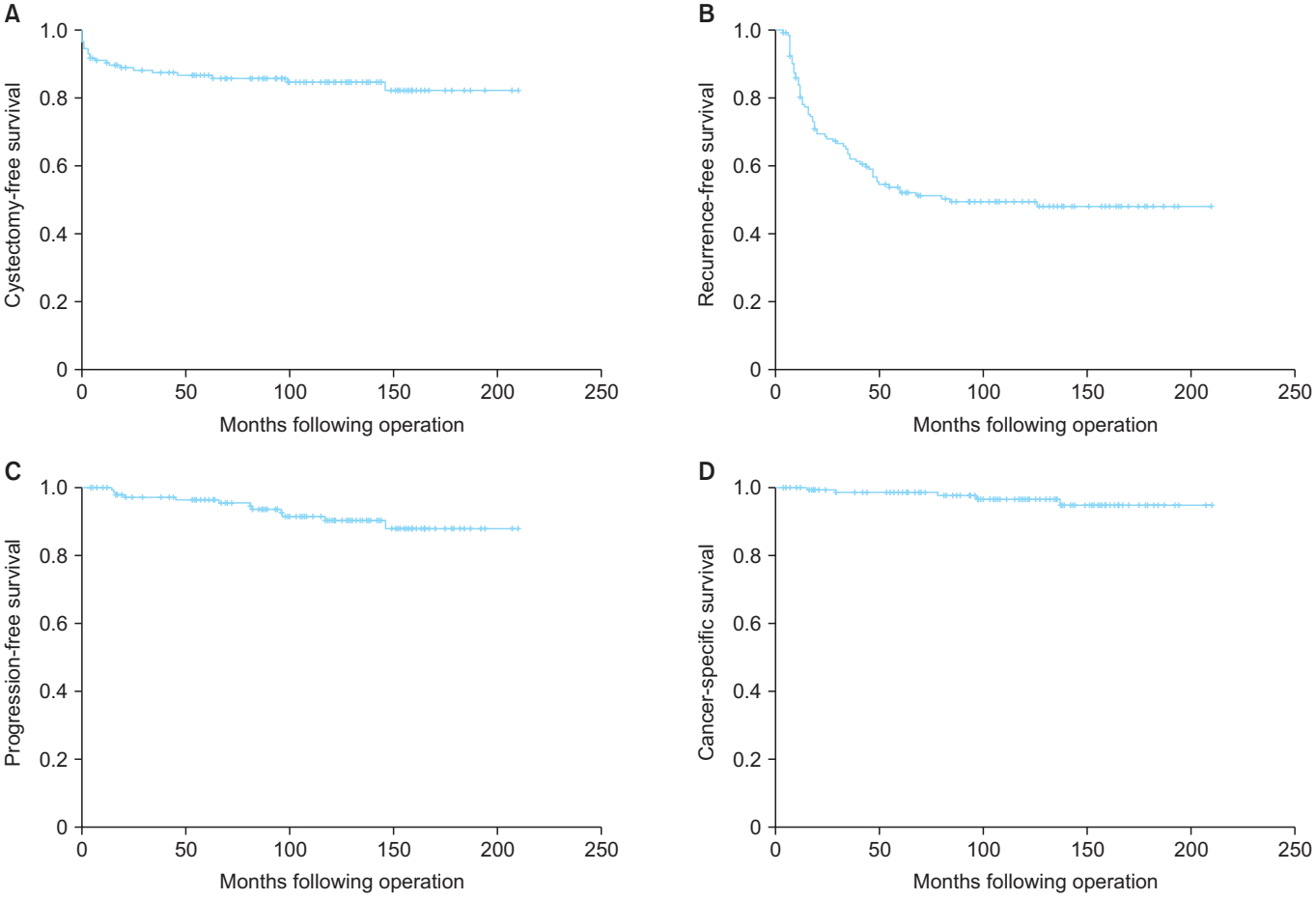

Fig. 4. Kaplan-Meier plots of cystectomy-free survival (A), recurrence-free survival (B), progression-free survival (C), and cancer-specific survival (D).

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Table 2. Cox regression univariate analysis of survival

Variable	Cystectomy-free survival			Recurrence-free survival			Progression-free survival			Cancer-specific survival		
	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.001	0.967–1.036	0.968	1.016	0.995–1.038	0.144	1.050	0.992–1.111	0.092	1.086	0.988–1.192	0.086
Sex												
Male	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
Female	0.614	0.182–2.070	0.431	0.799	0.420–1.521	0.494	0.796	0.174–3.641	0.768	0.921	0.102–8.297	0.942
Tumor grade												
Low	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
High	3.267	0.440–24.253	0.247	6.183	1.513–25.265	0.011	25.316	0.020–3.226×10^5	0.376	25.001	0–2.009×10^6	0.576
No. of tumors												
Single	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
Multiple	1.452	0.615–3.425	0.395	1.061	0.661–1.704	0.806	0.367	0.110–1.220	0.102	0.185	0.021–1.657	0.131
Size of tumor (cm)												
<3	1.000	Reference		1.000	Reference		1.000	Reference		1.000	Reference	
≥3	2.531	1.041–6.153	0.041	1.402	0.876–2.243	0.159	1.061	0.342–3.292	0.918	0.712	0.119–4.259	0.709
Subsequent treatment												
Bladder preservation		-		1.000	Reference		1.000	Reference		1.000	Reference	
Radical cystectomy		-		1.299	0.697–2.420	0.410	12.118	3.645–40.285	<0.001	22.972	2.566–205.662	0.005
Recurrence	1.076	0.474–2.439	0.861		-		11.494	1.484–89.037	0.019	4.064	0.454–36.377	0.210

HR, hazard ratio; CI, confidence interval.

DISCUSSION

This study found that bladder preservation with TURBT and intravesical BCG instillation enabled the successful management of selected patients with stage T2a MIBC. RC with bilateral pelvic lymphadenectomy provides excellent cancer control in patients with localized bladder cancer, with a contemporary series reporting 5-year overall survival rates of 40% to 60% [20]. However, despite improvements in surgical techniques, anesthetic delivery, and perioperative care, RC has a high morbidity rate [20]. Recent studies have reported that 30% to 77% of patients experienced adverse events of any grade, with a mortality rate of 1.7% to 5% at 90 days after RC [21-23]. Advanced age is a risk factor for complications and mortality, and preexisting comorbidities are also associated with high complication rates [2, 24]. Furthermore, any type of urinary diversion after RC has substantial implications for quality of life [25]. Thus, bladder preservation alternatives to RC are attractive to patients and clinicians alike.

The current guidelines recommend bladder preservation based on MMT, including radical TURBT with concurrent chemotherapy and RT, in limited patients with T2 tumors smaller than 6 cm without positive nodes or metastasis, hydronephrosis, or extensive or multifocal CIS [1, 2]. MMT showed comparable outcomes to those of RC in well-selected patients, with 5-year CSS and overall survival rates of 50% to 82% and 36% to 74%, respectively [5]. However, for highly selected patients, radical TURBT alone can be sufficient to achieve favorable oncological outcomes. According to the National Comprehensive Cancer Network Guidelines, TURBT alone may be an option for patients with cT2 or higher stage who are not candidates for cystectomy [1]. Henry et al. [26] documented a 5-year CSS rate of 67% in 43 patients treated with TURBT alone, including 28 with superficial muscle invasion and 15 with deep muscle invasion, and concluded that TURBT was as successful as RC or RT in patients with MIBC. Some researchers have conducted prospective studies on the feasibility of TURBT alone for MIBC and its long-term outcomes. The results support the role of radical TURBT as a successful bladder-conserving treatment strategy in selected patients. Herr [11] demonstrated that MIBC recurred in 34% of 99 patients treated by TURBT alone and that the bladder preservation rate was 82% over more than 10 years of follow-up. Moreover, the cancer-specific mortality rate was 18% in 73 patients with T0 or Tis disease and 42% in 26 patients with T1 disease on restaging TURBT. These 99 patients with at least 10 years of follow-up had comparable outcomes to those who received RC [11]. Solsona et al. [12] reported

the outcomes in 133 patients (including 32 with CIS) with radical TURBT and negative restaging biopsies. Overall, 30% had recurrence and another 30% showed progression. The 5-, 10-, and 15-year PFS rates with bladder preservation were 75.5%, 64.9%, and 57.8%, respectively. The 5-, 10-, and 15-year CSS rates were 81.9%, 79.5%, and 76.7%, respectively.

Complete tumor removal is essential for successful bladder preservation by radical TURBT alone. However, approximately one-third of the lesions had a residual tumor in the tumor base and periphery, even after the surgeon resected all visible tumors [27]. In cases of radical TURBT, tumor negativity of the base and periphery of the resection bed is confirmed by biopsy [17, 20]. In this study, when performing radical TURBT, the tumor base and periphery were also resected to identify any residual tumors, as well as the depth of muscle invasion. When tumor negativity was identified sequentially in the deep and deeper muscle layers, the patient was considered to have stage T2a disease without a residual tumor, and was regarded to have undergone radical TURBT.

A previous prospective study showed encouraging results for TURBTs using intravesical BCG therapy in selected patients with stage T2a bladder cancer. A total of 22 patients with muscle-invasive transitional cell carcinoma of the bladder received 6 weekly BCG instillations after TURBT. The overall 5-year survival rate was 69.1%, while the disease-specific 5-year survival rate was 94% [14]. BCG instillation may reduce the risk of recurrent high-grade superficial transitional cell carcinoma, with a potential systemic effect on stage T2a MIBC.

This study evaluated the long-term oncological outcomes of TURBT and intravesical BCG instillation in selected patients with stage T2a MIBC. Bladder preservation was achieved in 84.1% of patients. The 10-year cystectomy-free survival and CSS rates were 83.9% and 96.5%, respectively. Although recurrence occurred more frequently than reported in previous research, the bladder preservation rate was comparable to previous studies and the CSS was better. These results could be compared to survival in patients who achieve pT0 disease after RC in the cT2 stage at TURBT. Several studies have investigated the oncologic outcomes of pT0 disease without neoadjuvant chemotherapy (i.e., tumor eradication by TURBT). May et al. [28] reported that 79 patients with the cT2/pT0 stage showed a 5-year CSS rate of 87%. Lee et al. [29] demonstrated a 10-year CSS rate of 100% in 11 patients with the cT2/pT0 stage. Focusing on stage T2a disease, Volkmer et al. [30] documented 5- and 10-year CSS rates of 96.2% and 92%, respectively, in 82 patients with the cT2a/pT0 stage. Thus, the survival outcomes in our study are acceptable compared with those in previous studies.

In our study, a tumor lesion size greater than 3 cm was associated with RC. The tumor grade was the only predictor for recurrence, whereas the size and number of tumors were not. Moreover, no pathologic factor was related to progression or survival, whereas RC was a significant risk factor for both. Recurrence itself was associated with progression, not with survival. These findings may appear to be the result of performing salvage RC when recurrence was not controlled by repeated TURBT. Integrating these findings, patients with stage T2a tumors less than 3 cm and without CIS or tumor-associated hydronephrosis in a nonmetastatic setting could be eligible for bladder preservation by radical TURBT and intravesical BCG instillation. However, high-grade tumors require more careful follow-up to recognize recurrence.

Our study has several limitations. First, the study cohort was small and our results may not be generalizable because all data were collected from a single institution. Second, we retrospectively reviewed records of patients without concurrent chemotherapy or RT despite the presence of MIBC. Notwithstanding these study limitations, patients were diagnosed with stage T2a MIBC after TURBT, and bladder preservation by radical TURBT and intravesical BCG instillation showed promising results in highly selected patients.

CONCLUSIONS

We found that following definite determination of muscle invasion by TURBT, patients diagnosed with stage T2a MIBC can be good candidates for bladder preservation. Although more careful follow-up is needed in high-grade tumors, patients with stage T2a tumors less than 3 cm and without CIS or tumor-associated hydronephrosis in a non-metastatic setting can successfully be managed by radical TURBT and intravesical BCG instillation without chemotherapy or RT.

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NOTES

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- ORCID

Dong Gyun Kim: https://orcid.org/0000-0003-3055-4947
Ji Eun Heo: https://orcid.org/0000-0002-4184-8468
Kang Su Cho: https://orcid.org/0000-0002-3500-8833
Jongsoo Lee: https://orcid.org/0000-0002-9984-1138
Won Sik Jang: https://orcid.org/0000-0002-9082-0381
Nam Hoon Cho: https://orcid.org/0000-0002-0045-6441
Young Deuk Choi: https://orcid.org/0000-0002-8545-5797

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The Prognostic Impact of Angiolymphatic Invasion in Bladder Urothelial Carcinoma Patients Undergoing Radical Cystectomy

Jin Hyuck Kim[1], Young Hwii Ko[2], Jong Wook Kim[3], Seok Ho Kang[3], Seung Il Jung[4], Jin Sung Park[5], Ho Kyung Seo[6], Hyung Joon Kim[7], Byong Chang Jeong[8], Tae-Hwan Kim[9], Se Young Choi[10], Jong Kil Nam[11], Ja Yoon Ku[12], Kwan Joong Joo[13], Won Sik Jang[14], Young Eun Yoon[15], Seok Joong Yun[16], Sung-Hoo Hong[17], Jong Jin Oh[1]

[1]Department of Urology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
[2]Department of Urology, Yeungnam University Hospital, Daegu, Korea
[3]Department of Urology, Korea University College of Medicine, Seoul, Korea
[4]Department of Urology, Chonnam National University Medical School, Gwangju, Korea
[5]Department of Urology, Eulji University Hospital, Eulji University School of Medicine, Daejeon, Korea
[6]Department of Urology, Center for Urologic Cancer Hospital, Goyang, Korea
[7]Department of Urology, Myunggok Medical Research Institute, Konyang University College of Medicine, Daejeon, Korea
[8]Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea
[9]Department of Urology, School of Medicine, Kyungpook National University, Daegu, Korea
[10]Department of Urology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Korea
[11]Department of Urology, Pusan National University Yangsan Hospital, Busan, Korea
[12]Department of Urology, Pusan National University Hospital, Busan, Korea
[13]Department of Urology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
[14]Department of Urology, Severance Hospital, Urological Science Institute, Yonsei University College of Medicine, Seoul, Korea
[15]Department of Urology, Hanyang University Hospital, Seoul, Korea
[16]Department of Urology, Chungbuk National University Hospital, College of Medicine, Chungbuk National University, Cheongju, Korea
[17]Department of Urology, Seoul St Mary's Hospital, Seoul, Korea

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Corresponding author:
Jong Jin Oh
Department of Urology, Seoul National University Bundang Hospital, Seoul National University College of Medicine, Seongnam, Korea
Email: bebsuzzang@naver.com
https://orcid.org/0000-0003-0448-5992

Purpose: The aim of this study was to investigate the association between angiolymphatic invasion (ALI) and bladder cancer in patients who underwent radical cystectomy (RC).

Materials and Methods: Multicenter retrospective data from 495 bladder cancer patients who underwent RC between 2007 and 2019 were enrolled in this study. Patients were stratified into 2 groups according to the presence of ALI. The effect of ALI was analyzed by the Kaplan-Meier method and Cox regression hazard models for patients' cancer-specific survival (CSS), overall survival (OS), and recurrence-free survival (RFS).

Results: The median age of the 495 patients in the study was 65 years, with median and mean follow-up durations of 23.3 months and 37.1 months, respectively. ALI was present in 182 patients (36.8%). ALI was significantly associated with worse RFS as well as CSS and OS (p<0.001, p=0.012, and p=0.01, respectively). Adjusting for significant variables, a multivariate analysis showed that tumor stage (over T2) and ALI were independent predictors for CSS, whereas lymph node (LN) metastasis was not. Meanwhile, the adjusted multivariate analysis showed that tumor stage over T2, ALI, LN metastasis, and positive surgical margin were independent predictors for RFS. Otherwise, tumor grade (over grade 2) was not a significant predictor.

Conclusions: The presence of ALI was an independent predictor influencing both CSS and RFS.

Key Words: Carcinoma, Transitional cell, Urinary bladder, Cystectomy, Prognosis, Recurrence, Survival rate

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INTRODUCTION

According to a report from the early 2000s, 10,246 cases of primary bladder cancer occurred in Korea from 1998 to 2002. Furthermore, based on the 2021 Korea National Cancer Incidence Database, bladder cancer is the cancer with the 10th highest burden of incidence and mortality in men [1].

Twenty-five percent of patients who are newly diagnosed with bladder cancer have muscle-invasive bladder cancer. The leading treatment for muscle-invasive bladder cancer or refractory high-grade non–muscle-invasive bladder cancer patients is generally radical cystectomy (RC) with extended bilateral lymphadenectomy. With pathological staging, this procedure can provide an exact evaluation of both bladder cancer and the regional lymph nodes (LNs). Several variables have been identified as significantly related to the disease-specific survival of bladder cancer. LN metastasis, in particular, has been considered as a predictor of bladder cancer-related survival [2, 3]. Several studies have established variables that can be used to predict an adverse prognosis, such as age, tumor stage and LN density, which are used to calculate the COBRA (Cancer of the Bladder Risk Assessment) score [4]. Along with the prognostic value of factors related to the LNs, lymphovascular invasion and angiolymphatic invasion (ALI) remain a matter of debate. ALI has been identified as a poor prognostic factor for other solid tumors, such as upper urinary tract, prostate, liver, and colorectal cancer [5, 6]. Based on the concept that angiolymphatic channels allow the dissemination of invading tumor cells, several articles have reported poor prosnosis for cases of bladder cancer in which RC or even transurethral resection was performed [7]. However, other studies have found ALI not to be significant in comparison to other variables [8] or less significant for urothelial bladder cancer than for squamous cell carcinoma of the bladder [9].

In this study, we aimed to evaluate the prognostic value of ALI in cases of bladder cancer treated with RC.

MATERIALS AND METHODS

1. Study Population

The retrospective, multicenter, full-scale survey study analyzed 495 patients who underwent robot-assisted radical bladder cystectomy between April 2007 and October 2019. The study was approved by the Institutional Review Board of Bundang Seoul National University Hospital (IRB no. 2019AN0102). Of the 495 patients, ALI was present in 182 patients and absent in 313 patients. The exclusion criteria were non-transitional cell carcinoma histology, a history of neoadjuvant therapy, and incomplete data. The surgical technique and the extent of lymphadenectomy (standard, extended, or limited) were decided based on the surgeon's discretion. Regional lymphadenectomy was also performed based on preoperative imaging or an intraoperative examination.

2. Data Collection and Pathologic Evaluation

Clinical and pathological information was also retrospectively obtained from individual medical records from corresponding hospitals for bladder cancer research (a total of 7 medical institutions). Staff pathologists from each institution examined all specimens according to the institutional protocol. The American Joint Committee on Cancer/TNM classification system was used for pathological staging, and the World Health Organization classification was used for pathological staging. The clinicopathologic data included age, sex, comorbidity, tumor stage, tumor grade, surgical margin, presence of ALI, perineural invasion, squamous or glandular metaplasia, and the presence of carcinoma *in situ* (CIS). ALI was defined as the presence of tumor cells within an arterial, venous, or lymphatic lumen. ALI presence was assessed using routine light microscopic examinations with hematoxylin and eosin staining.

3. Statistical Analyses

Descriptive statistics were calculated to evaluate any potential differences in the demographic data and health status of the subjects.

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We divided the patients into ALI and non-ALI groups based on the primary tumor. Differences between these 2 groups were evaluated by the chi-square test for categorical variables and the independent t-test for continuous variables. The Kaplan-Meier method was used to calculate time-dependent outcomes, such as recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) and differences were assessed with the log-rank statistic. Univariate and multivariate survival analyses were performed with a Cox proportional-hazards regression model to evaluate the prognostic significance of the pathological variables. Statistical significance in this study was set at $p<0.05$. All analyses were performed with IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline Characteristics of Patients

The baseline characteristics of all 495 patients in this study are shown in Table 1. Their median age was 65 years, and the median and mean follow-up durations were 23.3 months and 37.1 months, respectively (range, 0–134 months). Most patients were men (418 patients, 84%). ALI was present in 182 patients (36.8%). The baseline characteristics of the ALI-negative group were similar to those of the ALI-positive group (n=313, 63.2%)

The patients with ALI were significantly older (67.3 years vs. 64.6 years, p=0.006), had lower American Society of Anesthesiologists (ASA) physical status classification grades (ASA I: 22.5% vs. 36.1%, p=0.006) and had a higher rate of hydronephrosis (34.6% vs. 19.5%, p=0.001) than the patients without ALI. There were no significant differences in other characteristics, such as body mass index, sex, smoking history, preoperative glomerular filtration rate, or preexisting comorbidities (diabetes mellitus or hypertension) (Table 1).

2. Perioperative and Pathological Outcomes

Among a total of 495 patients who underwent robotic RC, there was no significant difference in average operation time (424 minutes vs. 440 minutes, p=0.236). In estimated blood loss, no significant difference was found (527 vs. 522, p=0.913). The patients with ALI had a higher rate of transfusion (18.1% vs. 16.0%, p=0.444) and a lower complication rate (57.7% vs. 61.7%, p=0.657), but without statistical significance (Table 1).

In terms of the final pathologic outcomes, the presence of ALI was associated with a significantly higher T stage (T3 or T4) and a significantly lower T stage (Ta to T2) ($p<0.001$). Similar relationships were observed for higher tumor grade, such as grade III (74.6% vs. 50.6%, $p<0.001$) and higher rates of LN invasion (48.1% vs. 10.4%, $p<0.001$) in the patients with ALI. The ALI-positive group also showed significantly higher frequencies of perineural invasion (37.6% vs. 8.9%, $p<0.001$), squamous metaplasia (11.6% vs. 6.6%, p=0.010), and glandular metaplasia (7.7% vs. 2.3%, p=0.001). In contrast, CIS was significantly more common in the ALI-negative group (0.6% vs. 17.0%, $p<0.001$). No significant

Table 1. Baseline characteristics and perioperative outcomes among 496 patients who underwent radical cystectomy according to angiolymphatic invasion

Characteristic	All (n=495)	Angiolymphatic invasion		p-value
		Yes (n=182)	No (n=313)	
Age (yr)	65.5±10.4	67.3±10.8	64.6±10.1	0.006*
BMI (kg/m^2)	24.1±3.1	23.8±3.4	24.3±2.9	0.205
Sex				0.558
Male	418 (84.4)	148 (81.3)	271 (86.6)	
Female	77 (15.6)	34 (18.7)	42 (13.4)	
Smoking				0.913
Never	259 (52.3)	91 (50.0)	168 (53.7)	
Former	176 (35.6)	65 (35.7)	111 (35.5)	
Current	60 (12.1)	26 (14.3)	34 (10.9)	
ASA PS classification				0.006*
I	154 (31.1)	41 (22.5)	113 (36.1)	
II	306 (61.8)	120 (65.9)	186 (59.4)	
III	35 (7.1)	21 (11.5)	14 (4.5)	
Preoperative GFR	75.54	72.77	77.11	0.046*
Hydronephrosis				0.001*
No	373 (75.4)	119 (65.4)	252 (80.5)	
Yes	122 (24.6)	63 (34.6)	61 (19.5)	
DM	113 (22.8)	47 (25.8)	66 (21.1)	0.160
HTN	211 (42.6)	84 (46.2)	127 (40.6)	0.130
Perioperative outcomes				
Operation time (min)	434	424	440	0.236
Estimated blood loss (mL)	524	527	522	0.913
Transfusion rate	83 (16.8)	33 (18.1)	50 (16.0)	0.444
Complications	298 (60.2)	105 (57.7)	193 (61.7)	0.657
≥Grade 3	104 (21.0)	32 (17.6)	72 (23.0)	0.210

Values are presented as mean±standard deviation or number (%).
BMI, body mass index; ASA PS, American Society of Anesthesiologists physical status; GFR, glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension.
*p<0.05, statistically significant differences.

difference was found in the percentage of positive surgical margins between the 2 groups (4.4% vs. 2.7%, p=0.185).

3. CSS, OS, and RFS Outcomes

Disease recurrence was observed in 153 patients (30.9%), and 70 patients (14.1%) were dead at the time of final follow-up (except for those lost to follow-up). Recurrence was significantly more common in patients with ALI than in those without ALI (38.5% vs. 26.5%, p<0.001)

The most frequent site of recurrence was the LN, with 47 patients (29.9%), followed by lung (23.6%), bone (17.2%) and liver and neobladder/conduit (12.7%). Other sites of recurrence included the ureter (4.5%) and urethra (3.2%). There was a single incidence of kidney, ureter, and urethra recurrence in the ALI-positive group. LN recurrence was also the most frequent site of recurrence in the ALI-negative group, with 29 patients (34.1%), but in the ALI-positive group, the lung was the most frequent site of recurrence (20 patients, 27.8%). However, no statistically significant differences were observed in recurrence sites between the 2 groups, except for the liver (p=0.017) (Table 2).

Of the 70 dead patients (14.1%), cancer-specific death was recorded in 39 patients. ALI was significantly related to lower RFS, CSS, and OS (p<0.001, p=0.012, and p=0.01, respectively).

The ALI-negative patients showed higher 5-year and 10-year OS, CSS, and RFS. The exact percentages are given in Fig. 1. The mean OS was 95.7 months in the ALI-positive group versus 109.3 months in the ALI-negative group, the mean CSS was 108.7 months in the ALI-positive group versus 120.3 months in the ALI-negative group, and the

Table 2. Pathological and oncological outcomes according to presence of angiolymphatic invasion among patients who underwent radical cystectomy

Variable	All (n=440)	Angiolymphatic invasion		p-value
		Yes (n=181)	No (n=259)	
Pathological outcomes				
T stage				<0.001*
Ta	10 (2.3)	0 (0)	10 (3.9)	
T1	102 (23.2)	8 (4.4)	94 (36.3)	
T2	128 (29.1)	40 (22.1)	88 (34.0)	
T3	156 (35.5)	101 (55.8)	55 (21.2)	
T4	44 (10.0)	32 (17.7)	12 (4.6)	
Carcinoma *in situ*	45 (10.2)	1 (0.6)	44 (17.0)	<0.001*
Lymph node invasion	114 (25.9)	87 (48.1)	27 (10.4)	<0.001*
Grade				<0.001*
I	51 (11.6)	4 (2.2)	47 (18.1)	
II	70 (15.9)	16 (8.8)	54 (20.8)	
III	266 (60.5)	135 (74.6)	131 (50.6)	
Positive surgical margin	15 (3.4)	8 (4.4)	7 (2.7)	0.185
Perineural invasion	91 (20.7)	68 (37.6)	23 (8.9)	<0.001*
Squamous metaplasia	38 (8.6)	21 (11.6)	17 (6.6)	0.010*
Oncological outcomes	All (n=495)	Yes (n=182)	No (n=313)	
Recurrence	153 (30.9)	70 (38.5)	83 (26.5)	<0.001*
Recurrence site				
Neobladder/conduit	20 (12.7)	6 (8.3)	14 (16.5)	0.158
Lymph node	47 (29.9)	18 (25.0)	29 (34.1)	0.293
Lung	37 (23.6)	20 (27.8)	17 (20.0)	0.181
Bone	27 (17.2)	14 (19.4)	13 (15.3)	0.427
Liver	20 (12.7)	4 (5.6)	16 (18.8)	0.017*
Other	63 (40.1)	30 (41.7)	33 (38.8)	0.524
Cancer-specific mortality	39 (7.9)	19 (10.4)	20 (6.4)	0.012*
Overall mortality	70 (14.1)	31 (17.0)	39 (12.5)	0.010*

Values are presented as number (%).
*p<0.05, statistically significant differences.

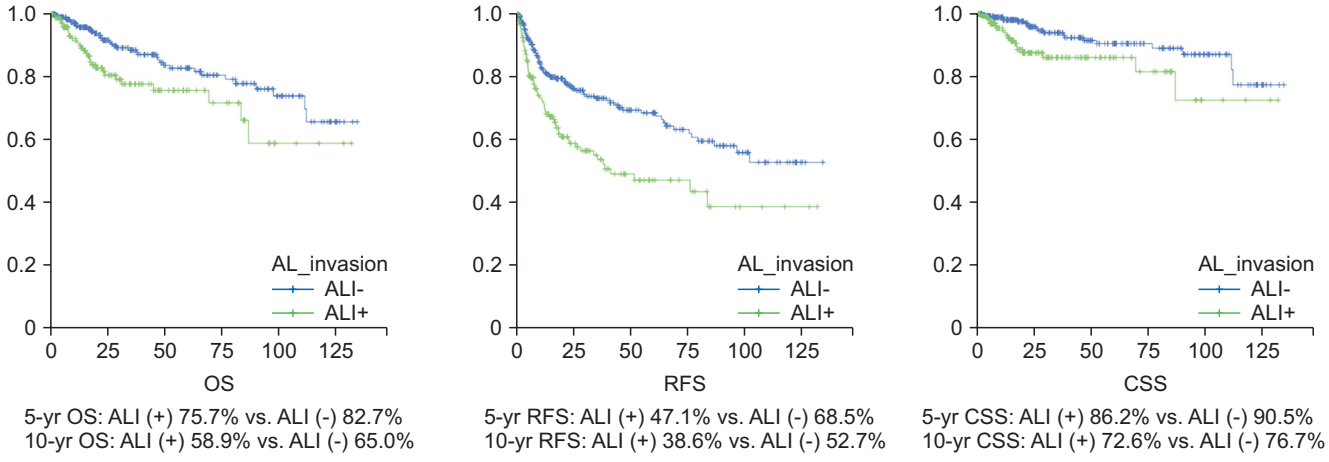

Fig. 1. Oncological outcomes (OS, CSS, and RFS) according to presence of angiolymphatic invasion among patients who underwent radical cystectomy. OS, overall survival; ALI, angiolymphatic invasion; RFS, recurrence-free survival; CSS, cancer-specific survival.

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mean RFS was 65.9 months in the ALI-positive group versus 89.1 months in the ALI-negative group (Fig. 1).

Multivariate and univariate Cox proportional hazard models to predict bladder cancer recurrence and survival among all 495 patients in the study are shown in Table 3, with all variables calculated in the analysis. Tumor stage (over T2), ALI, and LN metastasis were all associated with bladder cancer-specific death in the univariate analysis. Adjusting for those significant variables, the multivariate analysis showed that tumor stage (over T2) and ALI were independent predictors of CSS (hazard ratio [HR], 1.632; 95% confidence interval [CI], 1.035–2.571, p=0.035; HR, 2.396; 95% CI, 1.256–4.571, p=0.008, respectively), while LN metastasis was not (p=0.209) (Table 3).

For RFS, tumor stage (over T2), tumor grade (over grade 2), ALI, LN metastasis, and a positive surgical margin showed significant associations in the univariate analysis. The adjusted multivariate analysis showed that tumor stage over T2, ALI, LN metastasis, and positive surgical margin were independent predictors of RFS. Tumor grade (over grade 2) was not a significant predictor (Table 4).

Table 3. Uni- and multivariate Cox proportional hazard analysis among patients who underwent radical cystectomy for cancer-specific survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.026	0.993–1.060	0.121	-	-	-
Sex, female vs. male	0.899	0.376–2.149	0.811	-	-	-
Body mass index	0.907	0.817–1.007	0.067	-	-	-
Tumor stage, ≥T2 or not	2.398	1.099–5.232	0.028*	1.632	1.035–2.571	0.035*
Tumor grade, ≥2 or not	1.652	0.638–4.276	0.301	-	-	-
CIS+	0.962	0.340–2.720	0.942	-	-	-
Angiolymphatic invasion	2.253	1.191–4.260	0.012*	2.396	1.256–4.571	0.008*
LN+	2.414	1.238–4.703	0.010*	1.647	0.757–3.583	0.209
Positive surgical margin	1.530	0.208–11.241	0.676	-	-	-
Preoperative GFR	0.997	0.983–1.011	0.639	-	-	-
Presence of preoperative DM	1.529	0.760–3.076	0.234	-	-	-
Presence of preoperative HTN	0.723	0.371–1.408	0.340	-	-	-
History of smoking	1.702	0.899–3.223	0.103	-	-	-

HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*; LN, lymph node; GFR, glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension.
*p<0.05, statistically significant differences.

Table 4. Uni- and multivariate Cox proportional hazard analysis among patients who underwent radical cystectomy for recurrence-free survival

Variable	Univariate analysis			Multivariate analysis		
	HR	95% CI	p-value	HR	95% CI	p-value
Age	1.006	0.991–1.021	0.450	-	-	-
Sex, female vs. male	0.749	0.497–1.128	0.167	-	-	-
Body mass index	0.982	0.932–1.034	0.485	-	-	-
Tumor stage, ≥T2 or not	2.713	1.817–4.049	<0.001*	1.938	1.209–3.107	0.006*
Tumor grade, ≥2 or not	1.700	1.030–2.805	0.038*	1.087	0.580–2.037	0.794
CIS+	0.780	0.442–1.378	0.393	-	-	-
Angiolymphatic invasion	1.875	1.361–2.582	<0.001*	1.717	1.071–2.753	0.025*
LN+	2.702	1.939–3.765	<0.001*	1.837	1.254–2.692	0.002*
Positive surgical margin	2.910	1.425–5.943	0.003*	4.090	1.831–9.137	0.001*
Preoperative GFR	0.998	0.991–1.005	0.565	-	-	-
Presence of preoperative DM	1.003	0.682–1.475	0.988	-	-	-
Presence of preoperative HTN	0.805	0.579–1.118	0.195	-	-	-
History of smoking	1.074	0.782–1.474	0.660	-	-	-

HR, hazard ratio; CI, confidence interval; CIS, carcinoma *in situ*; LN, lymph node; GFR, glomerular filtration rate; DM, diabetes mellitus; HTN, hypertension.
*p<0.05, statistically significant differences.

DISCUSSION

Identifying prognostic factors associated with the survival and recurrence of bladder cancer is crucial for selecting among treatment options. Several guidelines include pathological stage, LN metastases, and tumor size as prognostic factors for survival and recurrence. However, the prognostic value of ALI for bladder cancer patients who have undergone RC remains a matter of debate. Some studies have shown that this pathological property was associated with worse survival outcomes [10-14], while others have reported discordant findings [8, 15-18]. A subgroup analysis showed that ALI was not correlated with lower RFS in Asian populations [19]. Canter et al. [20] demonstrated that ALI showed significance only in pT3 patients based on univariate analysis of OS, CSS, and RFS. In the multivariate analysis, ALI was also a significant predictor for worse OS and disease-specific survival ($p<0.01$ and $p=0.007$, respectively), but not for RFS ($p=0.1$). According to a multi-institutional retrospective study conducted by Lotan et al. [21], ALI showed significance for predicting survival and recurrence, specifically for LN-negative patients. They also reported that the prevalence of ALI was 9% in pT1 and 78% in pT4 disease. Our study also showed similar results for the prevalence of ALI (7.8% in pT1, 72.7% in pT4). Regarding the N stage, 72% of LN-positive patients had ALI, while only 26% of LN-negative patients had ALI. Similarly, our study showed that 76% of LN-positive patients were ALI-positive.

We retrospectively analyzed a multi-institutional database of patients who underwent RC to evaluate the influence of ALI on tumor survival and recurrence. ALI showed significant associations with poor OS, CSS, and RFS. The 5-year OS was 82.7% in patients without ALI and 75.7% in patients with ALI. The 10-year OS was 65.0% in patients without ALI and 58.9% in those with ALI. This aligns with other studies that reported lower 5-year or 10-year OS or CSS in patients with ALI [8, 14]. Furthermore, in line with previous reports [19, 21], ALI was pathologically found in 36% of specimens.

A multivariate analysis was also done to clarify whether ALI can serve as an independent prognostic factor for recurrence and survival. In our analysis, ALI was an independent predictor for both RFS and CSS in univariate analysis ($p=0.025$ and $p=0.008$, respectively). Other factors, such as tumor stage and LN metastasis, were also related to both RFS and CSS, and tumor grade and a positive surgical margin were also related to RFS in the univariate analysis. In the multivariate analysis, higher T stage, LN metastasis, ALI, and a positive surgical margin were significant factors associated with recurrence, while only higher T stage and ALI were significant factors associated with CSS. Bassi et al. [22] reported that tumor stage and LN metastasis (but not ALI) were valuable factors for predicting survival through a multivariate analysis. In contrast, Canter et al. [20] demonstrated that ALI-positive patients showed lower OS, CSS, and RFS in the univariate analysis ($p<0.001$), and only OS and CSS showed significance in the multivariate analysis ($p<0.01$ and $p=0.007$, respectively). As shown by the above summary, several studies have reported different findings for independent predictors of survival and recurrence depending on the analysis type.

In our study, ALI-positive patients had a tendency for recurrence in the LNs, followed by the lung, neobladder/conduit, bone, and liver. This pattern of recurrence or progression was previously shown by Elsayed et al. [23], where metastasis occurred most frequently in the LNs (5%) and lung (6%). However, given the limited number of studies on the relationship between ALI and the progression or recurrence site, further study would help analyze the relevance of ALI for local and distal recurrence patterns.

Several previous studies of patients with other urological cancers, such as penile and prostate cancer, have established a relationship between ALI in LN-positive patients and a poorer prognostic outcome [5]. As ALI is theoretically related to both the lymphatic and vascular systems, this pathological property can be strongly associated with cancer cell spread [24]. Based on this characteristic of ALI as an important prognostic factor, the TNM staging for some cancers includes ALI. This may facilitate more precise cancer staging and improved decision-making by physicians. There has also been some debate about including ALI in the TNM staging of bladder cancer, based on studies that showed ALI to have prognostic value for worse progression-free survival and OS in RC patients (pooled HRs of 1.57 and 1.59, respectively) [25, 26]. However, due to the difficulty of assessing ALI at a morphological level and the rare clinical use of

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immunohistochemical markers that enable differentiating lymphatic and vascular invasion at the pathological level, ALI is not yet appropriate for inclusion into the TNM staging system [27, 28].

This study has several limitations. First, as a retrospective study, there is a risk of inherent bias. As this was a multicenter study, the pathological reports from each center for ALI may have been different or the criteria of ALI may have changed during the 12-year follow-up period. It is important to propose absolute morphological criteria to define ALI as vascular invasion or lymphatic invasion or combined in a standardized manner.

Our study also did not assess the extent of pelvic LN dissection, which may have generated bias; however, previous reports have shown no difference in RFS, CSS, or OS between extended and limited PLND [29]. However, these results remain uncertain. Even though extended LND is considered a standard procedure for RC, differences in the extent of PLND might affect the outcomes. The bias incurred by this limitation may have influenced our results for the relationship between LN metastasis and CSS. Fewer than 10 nodes were dissected in 101 out of 440 cases, corresponding to the lowest nodal yield for determining surgical quality. This result demonstrates that an inappropriate PLND extent and deficiency of the nodal yield might have influenced the results, as a bias incurring a higher likelihood for false negatives. Additional information will be needed on how to define the range of PLND.

Finally, since therapeutic options have changed rapidly since the 2000s, our study's long follow-up may not have accurate implications for newly diagnosed patients. The follow-up period of this study marks a transition from the beginning to the middle of robotic surgery. The learning curve for surgery might have biased the outcomes. Regarding this limitation, future large-scale randomized prospective trials with stringent criteria will provide insights into the effects of ALI on patients' prognoses.

CONCLUSIONS

In conclusion, the presence of ALI in bladder cancer patients who underwent RC was associated with significantly worse outcomes both in terms of survival and recurrence. Furthermore, along with a high T stage, the presence of ALI was an independent predictor influencing both CSS and RFS. Future prospective studies should be performed to further validate our results.

NOTES

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- ORCID

Jin Hyuck Kim: https://orcid.org/0000-0002-8702-7008
Young Hwii Ko: https://orcid.org/0000-0002-9150-4292
Jong Wook Kim: https://orcid.org/0000-0003-2228-0640
Seok Ho Kang: https://orcid.org/0000-0002-1524-5233
Seung Il Jung: https://orcid.org/0000-0002-7166-8732
Jin Sung Park: https://orcid.org/0000-0001-6158-3359
Ho Kyung Seo: https://orcid.org/0000-0003-2601-1093
Hyung Joon Kim: https://orcid.org/0000-0003-3975-3045
Byong Chang Jeong: https://orcid.org/0000-0002-5399-2184
Tae-Hwan Kim: https://orcid.org/0000-0003-4924-4826
Se Young Choi: https://orcid.org/0000-0002-4615-0966
Jong Kil Nam: https://orcid.org/0000-0002-3424-2417
Ja Yoon Ku: https://orcid.org/0000-0003-3460-9386
Kwan Joong Joo: https://orcid.org/0000-0003-2352-4387
Won Sik Jang: https://orcid.org/0000-0002-9082-0381
Young Eun Yoon: https://orcid.org/0000-0001-8059-6649
Seok Joong Yun: https://orcid.org/0000-0001-7737-4746
Sung-Hoo Hong: https://orcid.org/0000-0002-1952-4010
Jong Jin Oh: https://orcid.org/0000-0003-0448-5992

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ORIGINAL ARTICLE

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The Prognostic Significance of Body Mass Index in Patients Undergoing Nephrectomy for Nonmetastatic Renal Cell Carcinoma

Hee Jae Yoo[1], Sun Il Kim[1], Se Joong Kim[1], Il Won[2], Dae Sung Cho[1]

[1]Department of Urology, Ajou University School of Medicine, Suwon, Korea
[2]Department of Urology, Bundang Jesaeng General Hospital, Seongnam, Korea

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Corresponding author:
Dae Sung Cho
Department of Urology, Ajou University School of Medicine, Suwon, Korea
Email: urocho@aumc.ac.kr
https://orcid.org/0000-0002-0348-9548

Purpose: The aim of this study was to evaluate the impact of body mass index (BMI) on survival in patients with nonmetastatic renal cell carcinoma (RCC) treated with radical or partial nephrectomy.

Materials and Methods: Between June 1994 and December 2021, 482 patients with RCC underwent radical or partial nephrectomy. Among those patients, 21 patients with lymph node or distant metastasis were excluded. The medical records of the remaining 461 patients were retrospectively reviewed. The prognostic significance of various clinicopathological variables, including BMI, was evaluated in univariate and multivariate analyses.

Results: Of the total 461 patients, 171 (37.1%) were categorized as normal-weight, 118 (25.6%) as overweight, and 172 (37.3%) as obese. Forty-eight patients (10.4%) developed local recurrence or distant metastasis, and 26 patients (5.6%) died from the disease during the follow-up period. In the multivariate analysis, BMI (p=0.017), tumor size (p<0.001), T stage (p<0.001), Fuhrman nuclear grade (p=0.016), and lymphovascular invasion (p=0.012) were independent predictors of recurrence-free survival. Furthermore, BMI (p=0.025), tumor size (p<0.001), T stage (p<0.001), Fuhrman nuclear grade (p=0.047), and lymphovascular invasion (p=0.033) were independent predictors of cancer-specific survival.

Conclusions: Our results suggest that overweight and obese patients with nonmetastatic RCC treated with radical or partial nephrectomy have a more favorable prognosis. These findings indicate that BMI could be an important factor for predicting recurrence or survival in patients undergoing nephrectomy for nonmetastatic RCC.

Key Words: Body mass index, Recurrence, Renal cell carcinoma, Survival

INTRODUCTION

Renal cell carcinoma (RCC) is the most common malignant tumor of the kidney, and its incidence has been steadily increasing in recent decades [1]. Although several clinical, anatomical, and histological risk factors are associated with the disease prognosis in patients with RCC, only a handful of factors, such as tumor size, pathological stage, and nuclear grade, are recommended for use in routine clinical practice [2].

The relationship between body mass index (BMI) and the prognosis of various cancers is not well established. Previous studies have reported that a high BMI was associated with a favorable prognosis for a variety of cancers, including esophageal, colorectal, and head and neck cancers [3-5]. In contrast, similar analyses have found that higher BMI was

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associated with poorer prognoses of breast and prostate cancer [6, 7].

Among the most common risk factors, tobacco smoke exposure, obesity, and hypertension have all been consistently associated with RCC [8]. This apparent link between obesity and RCC has been attributed to a combination of factors, including increased expression of insulin-like growth factor-1, higher circulating estrogen levels, arteriolar nephrosclerosis, and local inflammation [9]. However, although these factors have all been linked to RCC, whether there is an association between obesity and disease prognosis is not known. To address this apparent discrepancy in clinical findings, we evaluated the impact of BMI on survival in patients with nonmetastatic RCC treated with radical or partial nephrectomy.

MATERIALS AND METHODS

1. BMI and Patient Data

This study was approved by the Institutional Review Boards of Ajou University Hospital and Bundang Jesaeng Hospital (AJIRB-MED-MBD-21-558, DMC 2021-02-003). Between June 1994 and December 2021, radical or partial nephrectomy was performed in 482 patients with RCC at these 2 hospitals. Lymph node dissection was limited to patients with either palpable enlarged lymph nodes identified during surgery or abnormal findings on preoperative imaging studies. Follow-up examinations were performed every 3 months during the first 2 years after surgery, every 6 months during the next 2 years, and annually thereafter. Routine checkups, such as physical examinations, basic laboratory examinations, and chest x-ray examinations, were performed at each follow-up visit. Abdominopelvic computed tomography was performed every 6 months for the first 2 years and annually during follow-up or when clinically indicated. Disease recurrence was defined as a local mass in the tumor bed, regional lymph node involvement, or distant metastasis. Tumor staging was reassessed according to the 2010 TNM classification system, and the nuclear grade was assigned according to Fuhrman's nuclear grading system [10].

Patients were classified into 3 BMI groups on the basis of the World Health Organization recommendation for Asians [11], with <23.5, 23.5–25, and >25 kg/m^2 representing normal-weight, overweight, and obese, respectively. Clinicopathological data were collected and analyzed for each group.

2. Statistical Analysis

The chi-square test was used to assess the relationship between BMI and clinicopathological variables, including age, sex, smoking history, diabetes mellitus, hypertension, tumor histology, tumor size, T stage, Fuhrman nuclear grade, coagulative tumor necrosis, lymphovascular invasion, and nephrectomy type. Recurrence-free survival (RFS), cancer-specific survival (CSS), and overall survival (OS) were estimated using the Kaplan-Meier method, stratified by BMI, and the log-rank test was used to compare the groups. The prognostic significance of BMI was calculated using a Cox proportional hazards model. All tests were 2-sided, with p-values <0.05 considered statistically significant. The statistical analysis was performed using IBM SPSS Statistics ver. 21.0 (IBM Co., Armonk, NY, USA).

RESULTS

Among the 482 patients with RCC who underwent radical or partial nephrectomy, 21 were excluded due to lymph node involvement or distant metastasis. The medical records of the remaining 461 patients with nonmetastatic RCC (307 men and 154 women) were retrospectively reviewed and analyzed. The mean age of the patients was 55.9 years (range, 18–83 years), and the median follow-up duration was 71 months (mean, 73.5 months; range: 4–272 months). The clinicopathological data of the entire cohort are summarized in Table 1.

Of the 461 patients included in this study, 171 (37.1%) were categorized as normal-weight, 118 (25.6%) as overweight, and 172 (37.3%) as obese (Table 1). The associations of BMI with the clinicopathological characteristics of the 461 patients included in this study are shown in Table 2. Obesity was significantly associated with younger age (p=0.002), hypertension (p=0.003), small tumor size (p=0.021), lower T stage (p=0.008), and the absence of lymphovascular invasion

Table 1. Clinicopathological data of 461 patients with renal cell carcinoma

Characteristic	No. of patients (%)
Age (yr)	
≤60	283 (61.4)
>60	178 (38.6)
Sex	
Male	307 (66.6)
Female	154 (33.4)
Smoking history	
Never	189 (41.0)
Ever	272 (59.0)
Diabetes mellitus	
No	384 (83.3)
Yes	77 (16.7)
Hypertension	
No	292 (63.3)
Yes	169 (36.7)
Body mass index (kg/m^2)	
<23	171 (37.1)
23–24.9	118 (25.6)
≥25	172 (37.3)
Histology	
Clear cell	400 (86.8)
Papillary	23 (5.0)
Chromophobe	31 (6.7)
Collecting duct	2 (0.4)
Unclassified	5 (1.1)
Tumor size (cm)	
≤7	381 (82.6)
>7	80 (17.4)
T stage	
T1	320 (69.4)
T2	42 (9.1)
T3	95 (20.5)
T4	4 (0.9)
Grade	
1	31 (6.7)
2	148 (32.1)
3	239 (51.8)
4	43 (9.3)
Coagulative tumor necrosis	
No	389 (84.4)
Yes	72 (15.6)
Lymphovascular invasion	
No	432 (93.7)
Yes	29 (6.3)
Nephrectomy type	
Partial	37 (8.0)
Radical	424 (92.0)

(p=0.014). No associations were seen for sex, smoking history, diabetes mellitus, tumor histology, Fuhrman nuclear grade, coagulative tumor necrosis, or nephrectomy type (Table 2). Local recurrence or distant metastasis developed in 48 patients (10.4%), and 26 patients (5.6%) died from the disease during the follow-up period.

Table 2. Clinicopathological characteristics of patients grouped by body mass index (BMI) category

Variable	BMI category			p-value†
	Normal	Overweight	Obese	
Age (yr)				0.002*
≤60	94 (33.2)	67 (23.7)	122 (43.1)	
>60	77 (43.3)	51 (28.7)	50 (28.1)	
Sex				0.939
Male	117 (38.1)	73(23.8)	117 (38.1)	
Female	54 (35.1)	45(29.2)	55 (35.7)	
Smoking history				0.470
Never	62 (32.8)	58 (30.7)	69 (36.5)	
Ever	109 (40.1)	60 (22.1)	103 (37.9)	
Diabetes mellitus				0.485
No	147 (38.3)	94 (24.5)	143 (37.2)	
Yes	24 (31.2)	24 (31.2)	29 (37.7)	
Hypertension				0.003*
No	126 (43.2)	66 (22.6)	100 (34.2)	
Yes	45 (26.6)	52 (30.8)	72 (42.6)	
Tumor histology				0.983
Clear cell	148 (37.0)	103 (25.8)	149 (37.3)	
Nonclear cell	23 (37.7)	15 (24.6)	23 (37.7)	
Tumor size (cm)				0.021*
≤7	132 (34.6)	100 (26.2)	149 (39.1)	
>7	39 (48.8)	18 (22.5)	23 (28.8)	
T stage				0.008
Low (T1+T2)	123 (34.0)	95 (26.2)	144 (39.8)	
High (T3+T4)	48 (48.5)	23 (23.2)	28 (28.3)	
Grade				0.051
Low (G1+G2)	57 (31.8)	47 (26.3)	75 (41.9)	
High (G3+G4)	114 (40.4)	71 (25.2)	97 (34.4)	
Coagulative tumor necrosis				0.444
No	144 (37.0)	95 (24.4)	150 (38.6)	
Yes	27 (37.5)	23 (31.9)	22 (30.6)	
Lymphovascular invasion				0.014*
No	154 (35.6)	112 (25.9)	166 (38.4)	
Yes	17 (58.6)	6 (20.7)	6 (20.7)	
Nephrectomy type				0.987
Partial	14 (37.8)	9 (24.3)	14 (37.8)	
Radical	157 (37.0)	109 (25.7)	158 (37.3)	

Values are presented as number of patients (%).
*p<0.05, statistically significant differences. †Analyzed by chi-square test.

Kaplan-Meier curves for RFS, CSS, and OS according to the BMI category showed lower RFS, CSS and OS rates in the normal-weight group (Figs. 1–3). In the univariate analysis, obesity, tumor size, T stage, Fuhrman nuclear grade, coagulative tumor necrosis, and lymphovascular invasion were all significant prognostic factors for RFS. Meanwhile, obesity, tumor size, T stage, Fuhrman nuclear grade, and lymphovascular invasion were significant prognostic factors for CSS and OS. In the multivariate analysis, the independent prognostic factors for RFS, CSS, and OS were obesity, tumor size, T stage, Fuhrman nuclear grade, and lymphovascular

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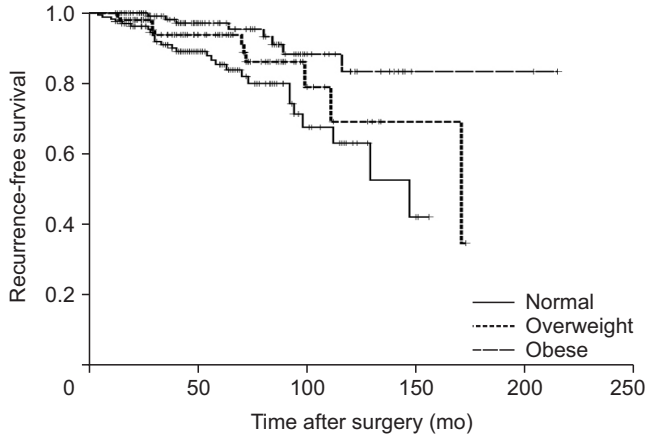

Fig. 1. Kaplan-Meier recurrence-free survival curves according to body mass index category.

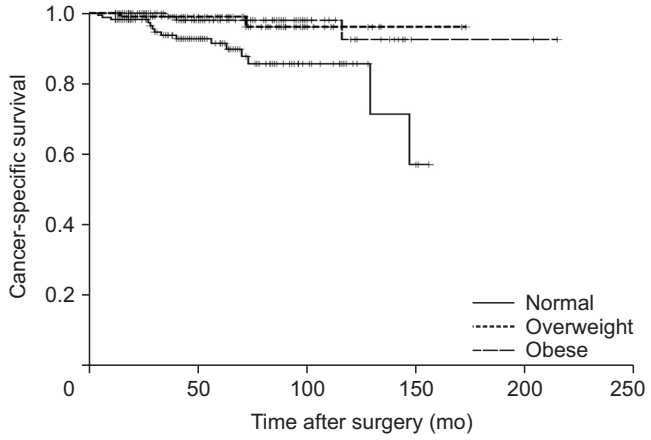

Fig. 2. Kaplan-Meier cancer-specific survival curves according to body mass index category.

invasion (Tables 3–5).

DISCUSSION

Several studies have suggested that obesity is a risk factor for the development of RCC [8, 9]. Obesity is also generally considered to be a major risk factor for complications during and after surgery due to the high rate of comorbidities [12]. However, there is considerable debate regarding whether obesity is a risk factor for disease progression and shorter survival in RCC. The initial findings of Yu et al. [13], who reported an apparently paradoxical association between obesity and both overall and disease-free survival in RCC, prompted several other studies to examine this relationship. The most extensive of these studies was a retrospective review

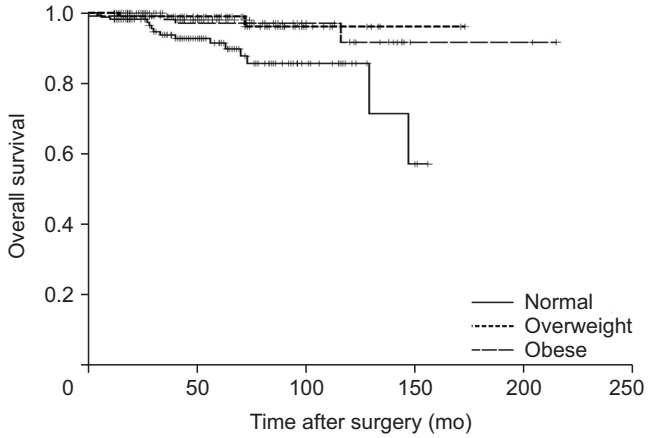

Fig. 3. Kaplan-Meier overall survival curves according to body mass index category.

Table 3. Univariate and multivariate analysis of recurrence-free survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.187	1.299 (0.700–2.413)	0.407
Sex, male vs. female	0.851	1.652 (0.620–4.398)	0.315
Smoking history, never vs. ever	0.469	1.465 (0.571–3.758)	0.427
Diabetes mellitus, no vs. yes	0.851	0.963 (0.397–2.338)	0.934
Hypertension, no vs. yes	0.325	0.605 (0.288–1.269)	0.183
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.135	2.276 (0.890–5.819)	0.086
Normal, <23	0.001*	2.926 (1.298–6.600)	0.010*
Tumor histology, conventional vs. nonconventional	0.827	1.130 (0.456–2.802)	0.791
Tumor size, ≤7 cm vs. >7 cm	<0.001*	3.730 (1.941–7.172)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	5.592 (2.796–11.186)	<0.001*
Grade, G1+G2 vs. G3+G4	<0.001*	3.163 (1.299–7.701)	0.011*
Coagulative tumor necrosis	0.005*	1.153 (0.563–2.358)	0.697
Lymphovascular invasion	<0.001*	2.296 (1.113–4.740)	0.025*
Nephrectomy type, partial vs. radical	0.430	0.471 (0.102–2.178)	0.335

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

of 400 patients undergoing nephrectomy for RCC, in which Kamat et al. [14] confirmed a more favorable prognosis and disease-specific survival in overweight and obese patients than in normal-weight patients.

Many studies have since reported an inverse linear correlation between obesity and RCC prognosis, commonly referred to as the "obesity paradox," although the mechanism underlying this phenomenon remains poorly understood. One hypothesis is that obese patients are less likely to have

Table 4. Univariate and multivariate analysis of cancer-specific survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.036*	2.120 (0.782–5.744)	0.140
Sex, male vs. female	0.888	0.690 (0.191–2.489)	0.571
Smoking history, never vs. ever	0.786	0.927 (0.271–3.171)	0.904
Diabetes mellitus, no vs. yes	0.575	0.875 (0.229–3.339)	0.845
Hypertension, no vs. yes	0.970	0.857 (0.284–2.588)	0.785
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.355	0.608 (0.113–3.273)	0.563
Normal, <23	0.014*	2.760 (1.003–7.592)	0.049
Tumor histology, conventional vs. nonconventional	0.392	0.501 (0.108–2.327)	0.377
Tumor size, ≤7 cm vs. >7 cm	<0.001*	6.955 (2.696–17.947)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	6.198 (2.248–17.088)	<0.001*
Grade, G1+G2 vs. G3+G4	0.004*	3.340 (1.023–10.906)	0.046*
Coagulative tumor necrosis	0.503	0.603 (0.199–1.827)	0.371
Lymphovascular invasion	<0.001*	2.997 (1.071–8.384)	0.037*
Nephrectomy type, partial vs. radical	0.648	0.286 (0.031–2.602)	0.266

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

Table 5. Univariate and multivariate analysis of overall survival in 461 patients with renal cell carcinoma

Variable	Univariate	Multivariate	
	p-value†	Hazards ratio (95% CI)	p-value‡
Age, ≤60 yr vs. >60 yr	0.138	1.370 (0.563–3.331)	0.488
Sex, male vs. female	0.737	0.668 (0.201–2.216)	0.509
Smoking history, never vs. ever	0.411	1.195 (0.383–3.727)	0.759
Diabetes mellitus, no vs. yes	0.737	1.042 (0.329–3.301)	0.945
Hypertension, no vs. yes	0.767	1.260 (0.475–3.343)	0.643
BMI (kg/m^2)			
Obesity, ≥25	Reference	Reference	
Overweight, 23–24.9	0.407	0.557 (0.166–2.978)	0.489
Normal, <23	0.013*	2.884 (1.112–8.780)	0.047*
Tumor histology, conventional vs. nonconventional	0.456	0.376 (0.085–1.662)	0.197
Tumor size, ≤7 cm vs. >7 cm	<0.001*	6.100 (2.557–14.547)	<0.001*
T stage, T1+T2 vs. T3+T4	<0.001*	5.710 (1.582–13.702)	0.003*
Grade, G1+G2 vs. G3+G4	0.005*	2.981 (1.220–8.803)	0.048*
Coagulative tumor necrosis	0.615	0.526 (0.181–1.527)	0.238
Lymphovascular invasion	<0.001*	3.626 (1.380–9.525)	0.015*
Nephrectomy type, partial vs. radical	0.725	0.271 (0.055–1.341)	0.220

CI, confidence interval; BMI, body mass index.
*p<0.05, statistically significant differences. †Analyzed by log-rank test. ‡Analyzed by Cox proportional hazards regression model.

aggressive tumor biology. A genomic study of 2,119 patients with clear cell RCC revealed that obese patients had tumors with downregulated expression of the metabolic and fatty acid genes essential for tumor growth [15]. Other hypotheses propose a role of excessive perirenal fat as a protective barrier, or that high nutritional status can protect against treatment-related stress [16]. However, studies of the obesity paradox have been criticized due to various methodological problems, including the limitations of BMI, confounding factors, detection and selection bias, and reverse causation; nonetheless, the consistency with which the obesity paradox has been observed in clinical studies renders it virtually undeniable.

Several proteins and signaling factors capable of attenuating RCC progression have been reported in adipose tissue. For example, adipose tissue synthesizes leptin, the circulating levels of which are strongly related to obesity. Leptin has also been shown to play an important role in stimulating pro-inflammatory T helper (Th) 1 immune responses [17]. In contrast, a change in the predominant immunologic response from Th1 to Th2 is strongly correlated with higher RCC stages [18]. Therefore, leptin expression may play a pivotal role in delaying RCC progression.

To better understand the obesity paradox, several studies have conducted subgroup analyses given the high degree of heterogeneity seen among RCC cases. An epidemiological study of 2,769 patients with nonmetastatic RCC indicated that higher BMI was associated with a good prognosis for clear cell RCC, an unclear prognosis for papillary RCC, and a poor prognosis for chromophobe RCC [19]. Another study of 2,097 patients with nonmetastatic clear cell RCC revealed significant inverse correlations of obesity with RFS and CSS in men, but not in women [20]. The present study evaluated the association of BMI with the prognosis of patients with RCC, and found that obese and overweight patients had superior survival outcomes compared to normal-weight and underweight patients. However, significant relationships were not observed in subgroup analyses based on factors such as age, sex, and histologic subtype.

Our study had several limitations. First, it used a retrospective design, which is known to pose a risk of bias. In particular, as shown in Table 2, obese patients had smaller tumors, lower rates of tumors with a high T stage, and a lower frequency of lymphovascular invasion. Therefore, these disparities in the distribution between the patient groups might have resulted in a higher survival rate in

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obese patients. Second, we were unable to adjust for several potential confounding factors, such as RCC-associated molecular markers and nutritional status, although we did include the most widely accepted prognostic factors of nonmetastatic clear cell RCC. Third, we were unable to assess other indices of obesity, such as waist circumference, waist-to-hip ratio, and visceral adiposity. While BMI remains the most commonly used obesity index in clinical studies and real practice, the use of these other factors might improve our understanding of the prognostic value of obesity for RCC. Finally, our study included only Korean patients, such that our findings may not be generalizable to other ethnic groups, particularly Western populations.

CONCLUSIONS

Our results suggest that overweight and obese patients with nonmetastatic RCC, treated with radical or partial nephrectomy, have a more favorable prognosis than normal-weight patients. Thus, BMI could be an effective tool for predicting recurrence or survival in patients undergoing nephrectomy for nonmetastatic RCC.

NOTES

- Conflicts of Interest: The authors have nothing to disclose.
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- ORCID

Hee Jae Yoo: https://orcid.org/0000-0003-0113-365X
Sun Il Kim: https://orcid.org/0000-0003-2674-983X
Se Joong Kim: https://orcid.org/0000-0002-4221-2461
Dae Sung Cho: https://orcid.org/0000-0002-0348-9548

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Instructions for Authors

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GENERAL INFORMATION

Aims and Scope

The *Journal of Urologic Oncology* (JUO) publishes practical, timely, and relevant clinical and basic science research articles addressing any aspect of urologic oncology. JUO is of interest to urologists, oncologists, radiologists, and clinicians treating patients and to those involved in research on diseases of urologic oncology. JUO publishes original articles, review articles, editorials, rapid communications, brief reports, and letters to the editor. All submitted manuscripts will be peer-reviewed by a panel of experts before being considered for publication. The following is a list of the general topics covered by JUO: prostate cancer; urothelial cancer; kidney cancer; testicular cancer; other genitourinary malignancies; epidemiology, etiology, and pathogenesis; and the detection, diagnosis, prevention, and treatment of urologic oncologic diseases.

About the Journal

The *Journal of Urologic Oncology* (JUO; pISSN 2951-603X, eISSN 2982-7043) is the official journal of the Korean Urological Oncology Society and is an international peer-reviewed journal. The ISO abbreviated journal name is J Urol Oncol. JUO is published three times per year, on the last day of March, July, and November. The journal periodically publishes supplemental issues devoted to areas of current interest to the urologic oncology community. It was first published on March 31, 2003 with Volume 1 and Number 1 under the name *Korean Journal of Urological Oncology* (pISSN 2234-4977, eISSN 2233-5633), and it was renamed as *Journal of Urologic Oncology* in March 2023. For submission instructions, subscription, and all other information, please visit http://www.e-juo.org.

RESEARCH AND PUBLICATION ETHICS

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4. Readership

JUO is primarily for clinicians and researchers who seek tailored information to adopt in their research and practice, but its readership can be expanded to other roles: researchers can obtain knowledge on recent topics of clinical research in urologic oncology field and detailed research methods; clinicians in the field can receive new information and learn about recent developments in patient care; medical educators can access and adopt a variety of data for medical education; allied health professionals, including nurses, can obtain recent information for patient care in urologic oncology; medical students can understand the recent trends in the field and learn about interesting cases for their work; policymakers can reflect the results of the articles in nationwide health care policies for patients with urologic cancer; the public, especially family members of patients with urologic oncologic diseases, can learn about advances in the diseases affecting their family member in order to obtain better knowledge about the diseases and enhance their confidence in clinicians' devotion to their family member's care.

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A redundant publication is defined as "reporting (publishing or attempting to publish) substantially the same work more than once, without attribution of the original source(s)." The characteristics of reports that are substantially similar include the following: (1) "at least one of the authors must be common to all reports (if there are no common authors, it is more likely plagiarism than redundant publication)," (2) "the subject or study populations are often the same or similar," (3) "the methodology is typically identical or nearly

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A clinical trial defined as "any research project that prospectively assigns human subjects to intervention and comparison groups to study the cause-and-effect relationship between a medical intervention and a health outcome," and clinical trials should be registered in a primary registry prior to publication.

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JUO adheres to the research and publication ethics policies outlined in the International Standards for Editors and Authors (http://publicationethics.org) and the Uniform Requirements for Manuscripts Submitted to Biomedical Journals (http://icmje.org). Any studies involving human subjects must comply with the principles of the World Medical Association Declaration of Helsinki. Clinical research should be approved by the Institutional Review Board and obtain patient consent. A patient's personal information generally cannot be published in any form. However, if it is absolutely necessary to use a patient's personal information, the consent of the patient or his/her guardian will be needed before publication. Animal studies should be performed in compliance with all relevant guidelines, observing the standards described in the NIH Guide for the Care and Use of Laboratory Animals.

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1. Formatting by Manuscript Type

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- Review Articles are reserved for important subjects relevant to the field of urologic oncology that is selected by the Editorial Committee. Authors are invited based on articles published in JUO and other journals. The length of the manuscript and the number of references should not exceed 3,500 words and 100, respectively. The decision to publish the manuscript is made after review by the Editorial Committee. The manuscript format may vary in review articles.
- Systematic Reviews are critical assessments of the literature and data sources pertaining to clinical topics, emphasizing factors such as the cause, diagnosis, prognosis, therapies, and prevention. Systematic Reviews without a meta-analysis are published as reviews; those with a meta-analysis are published as Original Articles (see Meta-Analyses).
- Meta-Analyses are systematic, critical assessments of the literature and data sources pertaining to clinical topics, emphasizing factors such as the cause, diagnosis, prognosis, therapies, and prevention, that include a statistical technique for quantitatively combining the results of multiple studies that measure the same outcome into a single pooled or summary estimate. The requirements for the format of the abstract and the main text follow those for Original Articles.
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- Rapid Communications report novel, exciting urologic oncology research. The focus may be basic, translational, or clinical and can include all aspects of urologic oncology. The format is shorter than original articles, and the best-suited articles for this category are those with a concise presentation.
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- Letters to the Editor discuss a recent article in this journal and should be submitted within 4 weeks of the article's publication in print.
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Type	Abstract			Max. words of the main text	Max. tables	Max. references
	Max. words	Max. key words	Format			
Review Article	300	6	Unstructured	3,500	5	100
Original Article	300	6	Structured	3,000	5	30
Rapid Communication	200	6	Unstructured	1,500	2	15
Brief Report	200	6	Unstructured	1,500	2	15
Editorial	×	×	×	500	-	10
Letter to the Editor	×	×	×	500	-	10

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The title page contains the article title, and full names of all authors with their institutional affiliations both. The type of manuscript (original article, review article, letter to the editor, brief communication) should also be indicated. If the work includes multiple authors with different affiliations, the institution where the research was mainly conducted should be spelled out first, and then be followed by footnotes in superscript Arabic numerals beside the authors' names to describe their affiliations in the consecutive order

of the numbers.
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3. Abstract

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An abstract should include brief descriptions of the purpose, materials and methods, results, and conclusion, as well as a detailed description of the data. An abstract containing 300 words or less is required for original articles and review articles.
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The introduction should address the purpose of the article concisely, and include a presentation of the background relevant to the purpose of the paper. A more detailed review of the literature should be addressed in the discussion section.

5. Materials and Methods

The article should record the research plans, objectives, and methods in order, as well as the data analysis strategies and methods implemented to control bias. Sufficient details should be furnished for the reader to understand the method(s) without reference to another work described in the study.
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Logical answers to the questions raised in the Introduction section should be proposed. The Discussion should be limited to new and important issues raised by the study results. Citing references not related to the results should be avoided. Data/measurements already described in the Results section should not be repeated.

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Conclusions should be comprehensive, be in accordance with the observations stated in the Results and Discussion sections, and befit the purpose of the study. A simple summary of the results should be avoided. An attempt at presenting future study directions

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- Djavan B. Nickel JC, de la Rosette J, Abrams P. The urologist view of BPH progression: results of an international survey. Eur Urol 2002;41:490-6.

(2) Other samples

- Shen HM, Zhang QF. Risk assessment of nickel carcinogenicity and occupational lung cancer. Environ Health Perspect 1994;102 Suppl 1:275-82.
- Payne DK, Sullivan MD, Massie MJ. Women's psychological reactions to breast cancer. Semin Oncol 1996;23(1 Suppl 2):89-97.
- Ozben T, Nacitarhan S, Tuncer N. Plasma and urine sialic acid in non-insulin dependent diabetes mellitus. Ann Clin Biochem 1995;32(Pt 3):303-6.
- Poole GH, Mills SM. One hundred consecutive cases of flap lacerations of the leg in ageing patients. N Z Med J 1994;107(986 Pt 1):377-8.
- Turan I, Wredmark T, Fellander-Tsai L. Arthroscopic ankle arthrodesis in rheumatoid arthritis. Clin Orthop 1995;(320):110-4.
- Enzensberger W, Fischer PA. Metronome in Parkinson's disease [letter]. Lancet 1996;347:1337.
- Clement J, De Bock R. Hematological complications of hantavirus nephropathy (HVN) [abstract]. Kidney Int 1992;42:1285.

*2) **Books***

(1) Personal author(s)

- Coe FL, Favus MJ, Pak CY, Tu GW, Miller HC, Kim YS, et al. Kidney stones: medical and surgical management. New York (NY): Lippincott-Raven; 1996;85-100.

(2) Editor(s), compiler(s) as author

- Norman IJ, Redfern SJ, editors. Mental health care for elderly people. New York (NY): Churchill Livingstone; 1996.

(3) Organization as author and publisher

- Institute of Medicine (US). Looking at the future of the Medicaid program. Washington (DC): The Institute; 1992.

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- Reiter RE, deKernion JB. Epidemiology, etiology, and prevention of prostate cancer. In: Walsh PC, Retik AB, Vaughan ED Jr, Wein AJ, editors. Campbell's urology. 8th ed. Philadelphia (PA): Saunders; 2002. p. 3003-24.

3) Conference proceedings

- Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Proceedings of the 10th International Congress of EMG and Clinical Neurophysiology; 1995 Oct 15-19; Kyoto, Japan. Amsterdam: Elsevier; 1996.

4) Conference paper

- Bengtsson S, Solheim BG. Enforcement of data protection, privacy and security in medical informatics. In: Lun KC, Degoulet P, Piemme TE, Rienhoff O, editors. MEDINFO 92. Proceedings of the 7th World Congress on Medical Informatics; 1992 Sep 6-10; Geneva, Switzerland. Amsterdam: North-Holland; 1992. p. 1561-5.

5) Scientific or technical report

- Smith P, Golladay K. Payment for durable medical equipment billed during skilled nursing facility stays. Final report. Dallas (TX): Dept. of Health and Human Services (US), Office of Evaluation and Inspections; 1994 Oct. Report No.: HHSIGOEI69200860.

6) Dissertation

- Kaplan SJ. Post-hospital home health care: the elderly's access and utilization [dissertation]. St. Louis (MO): Washington Univ.; 1995.

7) Patent

- Larsen CE, Trip R, Johnson CR, inventors; Novoste Corporation, assignee. Methods for procedures related to the electrophysiology of the heart. US patent 5,529,067. 1995 Jun 25.

8) Newspaper article

- Lee G. Hospitalizations tied to ozone pollution: study estimates 50,000 admissions annually. The Washington Post 1996 Jun 21;Sect. A:3 (col. 5).

9) In press

- Leshner AI. Molecular mechanisms of cocaine addiction. N Engl J Med Forthcoming 1997.

10) Websites

- Polgreen PM, Diekema DJ, Vandeberg J, Wiblin RT, Chen YY, David S, et al. Risk factors for groin wound infection after femoral artery catheterization: a casecontrol study. Infect Control Hosp Epidemiol [Internet] 2006 [cited 2010 Jan 5];27:34-7. Available from: http://www.journals.uchicago.edu/ICHE/journal/issues/v27n1/2004069/2004069.web.pdf.
- U.S. Food and Drug Administration, Center for Drug Evaluation and Research. Index to drug-specific information [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; [updated 2009 Jun 4; cited 2009 Jun 10]. Available from: https://www.fda.gov/drugs/postmarket-drug-safety-information-patients-and-providers/index-drug-specific-information.

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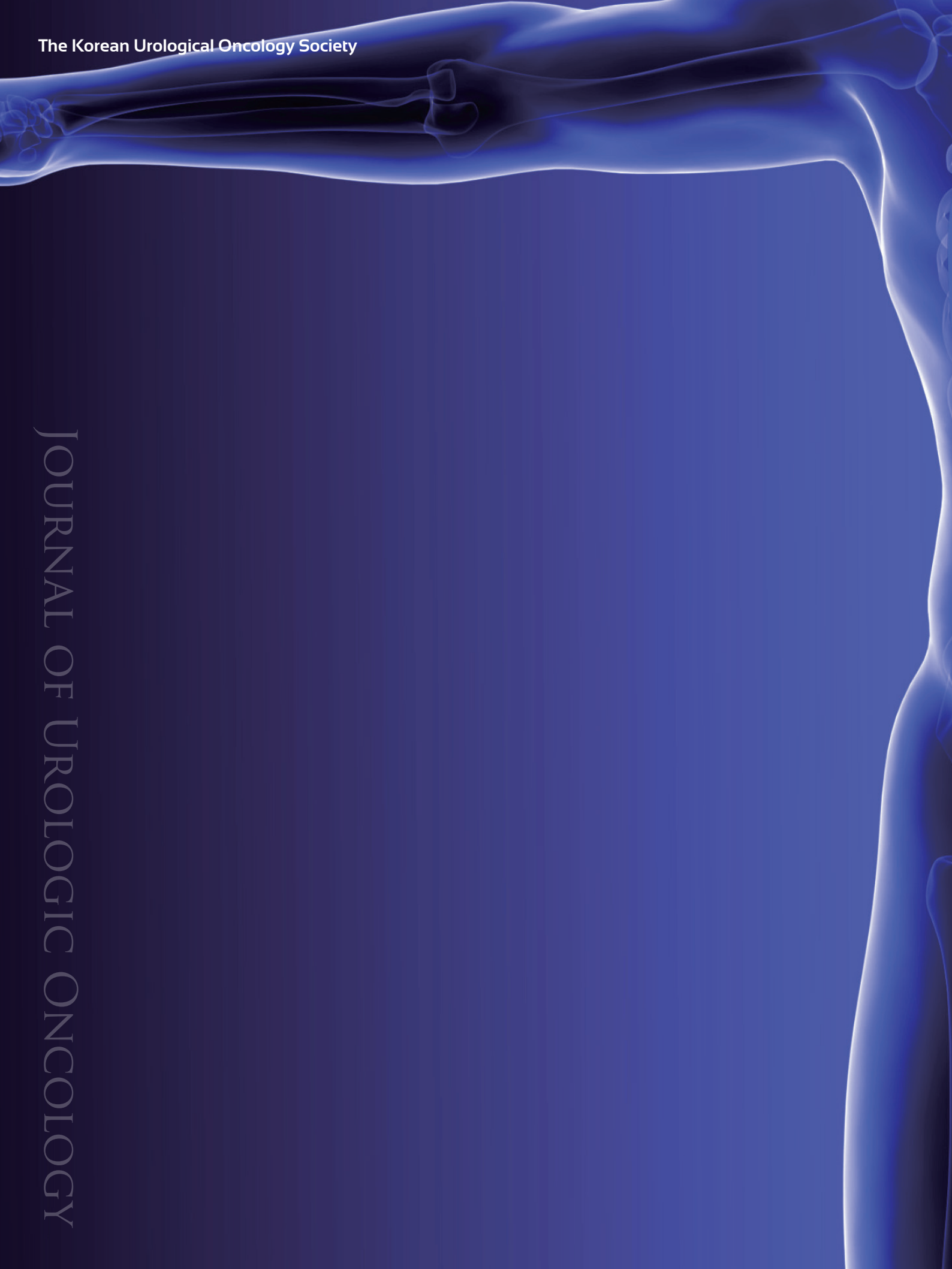

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