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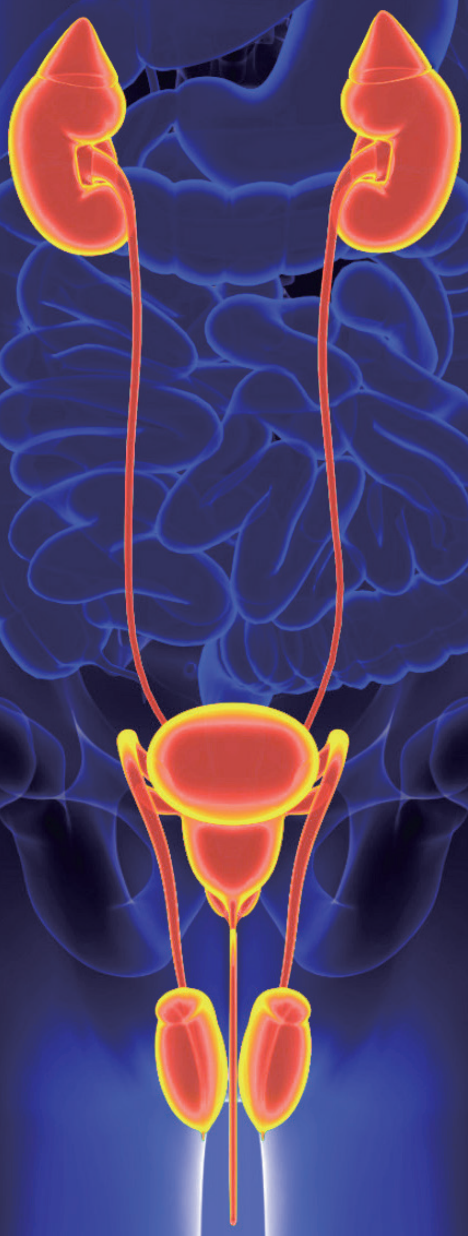

Highlight of JUO in This Issue

Prostate Cancer

Kidney Cancer

Bladder Cancer

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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Original Article

Bladder Cancer

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Systemic Review and Meta-analysis

Erratum

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EDITORIAL

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JUO, the *Journal of Urologic Oncology*, Celebrates Its Second Anniversary

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The newly established *Journal of Urologic Oncology* (JUO), which succeeded the *Korean Journal of Urologic Oncology*, which was founded in 2003 as the official journal of the Korean Urologic Oncology Society, is celebrating its second year of publication with a complete English translation in 2023. Over the past year, JUO has published timely reviews of emerging research trends in the fields of prostate, kidney, and bladder cancer by world-renowned experts in the field, as well as topical feature articles on the most updated topics in urological oncology, which it claims have helped to keep readers abreast of the latest treatment trends.

This year's JUO will further mature last year's experimental attempts in content and format to become a journal that meets our goal of becoming an SCIE-rated journal. First, from this issue 4, we have introduced reporting guidelines to help readers understand the title and format. We have adopted the CONSORT guideline for randomized clinical trials, the RPISMA statement for systemic reviews, and the STROBE guideline for observational studies, and we will continue to strive to ensure that these policies are reflected in the submission and revision of articles. Regarding quality, we aim to be a multinational journal by allowing researchers worldwide to submit original articles and review articles on significant treatment trends. In the March issue of JUO in 2024, we have 2 systemic reviews and 3 invited reviews on each cancer type from world-leading researchers.

1. Prostate Cancer

The role of prostate-specific antigen (PSA) testing in the diagnosis of prostate cancer is pivotal, yet US Preventive Services Task Force (USPSTF) guidelines prohibiting PSA screening have had a global impact since 2012. Guidelines based on the USPSTF in the West may not be equally applicable in countries in Asia, where prostate cancer is just beginning to emerge as a primary cancer killer. Professor Chang Wook Jeong [1] from Seoul National University shows a narrative review demonstrating the value of ethnicity-specific PSA screening. In locally advanced cancer, the addition of radiotherapy can cause fatal dysuria in cases of patients who have already undergone radical prostatectomy.

Professor Hanjong Ahn [2] from Seoul Medical Center presents the latest data on this topic. In the 2020s, PSMA-based theranostics are emerging as a significant treatment for refractory prostate cancer. Professor Gi Jeong Cheon [3] from the Department of Nuclear Medicine at Seoul National University has contributed an excellent review on this topic.

Professor Se Hoon Park [4] from the Division of Hematology-Oncology, Samsung Medical Center, suggested a novel treatment strategy for metastatic hormone-sensitive prostate cancer in an article entitled "Enzalutamide Maintenance Following Docetaxel in Metastatic Castration-Naive Prostate Cancer: A Pilot Feasibility Study".

2. Kidney Cancer

In a metastatic setting, metastasectomy is one of the clinically important treatment strategies, but different outcomes can be achieved depending on which systemic treatment is used in combination. No randomized clinical trials have yet been reported on the role of metastasectomy in immunooncology+tyrosine kinase inhibitor (TKI), the current standard of care for metastatic kidney cancer, but a systematic review by Professors Sun Il Kim and Dongdeuk Kwon [5] from Chonnam National University shows the effectiveness of the combination of TKI and metastasectomy, which immediately precedes it and provides important insights. As the largest bibliometric analysis to explain research trends in renal cell carcinoma (RCC), an article from Professor Ji Woong Hwang [6], from Chung-Ang University provides an overview of kidney cancer articles. For advanced cases with venous thrombus, Professor Jungyo Suh [7] from Asan Medical Center has provided a valuable analysis of 30 years of data. For *TFE3*-rearranged/*TFEB*-altered RCC, a relatively rare type of tumor, Professor Se Hoon Park [8] from the Division of Hematology-Oncology, Samsung Medical Center, has provided important information on drug selection.

3. Bladder Cancer

Nephron-sparing surgery as an alternative to traditional nephroureterectomy in upper tract urothelial carcinoma is accepted as a universal treatment strategy in recently updated guidelines. Professor Seth P. Lerner [9] of Baylor College of Medicine, a world-renowned expert in this field, has reviewed the latest developments. In the field of bladder cancer, where there is less research on the prognostic value of clinical factors other than biological cancer compared to other cancers, Professor Victoria K. Cortessis [10] from the Keck School of Medicine of the University of Southern California contributed a systematic review of the prognostic value of diabetes.

We hope that all these studies in this issue of JUO will be helpful to our readers in their practice and research. We look forward to your continued support and interest in JUO as we expand globally.

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

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REVIEW ARTICLE

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Prostate-Specific Antigen-Based Prostate Cancer Screening: One for All or Individualized for Each Race? – A Narrative Review

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Prostate cancer (PCa) is the second most common cancer globally. However, significant disparities in incidence and mortality exist between countries, especially between Western and Asian regions. This review discusses the applicability of Western-based randomized controlled trials on prostate-specific antigen-based PCa screening in other regions such as Korea, where PCa is less frequently diagnosed but tends to present more aggressive features compared to Western countries. The paper also reviews major guidelines and landmark trials, emphasizing the importance of an individualized approach in the context of regional diversity in PCa incidence and mortality.

Key Words: Prostatic neoplasms, Prostate-specific antigen, Early detection of cancer, Mass screening

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

INTRODUCTION

Prostate cancer (PCa) is the second most common cancer and its incidence has increased globally in recent years [1]. Despite a reduction in prostate-specific antigen (PSA) testing since 2018 [2], PCa still ranks as the most diagnosed cancer in men in the United States as of 2023. Moreover, after 2 decades of decreasing rates, the incidence of PCa has been rising by 3% annually from 2014 to 2019 [3]. However, significant disparities in incidence and mortality rates are observed between countries according to the data from the International Agency for Research on Cancer [4]. This data reveals notably lower incidences of PCa in Asian countries compared to Western regions. However, this varies by country, and recently, some Asian countries have also experienced a rapid increase in incidence [1]. For example, PCa is expected to be the most commonly diagnosed cancer in Korean men from 2022 onward [5,6].

Several factors, including genetic susceptibility and culturally influenced lifestyles, may play a role in the notably lower incidence and mortality rates of PCa in Asian countries [7]. Regarding genetic differences, studies in Western populations have shown a high prevalence of *ERG* gene mutations in PCa, while research focusing on Asian populations has revealed a relatively higher occurrence of *FOXA1* gene mutations [8]. The variations in diagnostic practices could also be a significant factor contributing to the international differences in PCa incidence rates [7]. A significant portion

of the disparity in PCa prevalence can be attributed to the less frequent utilization of PSA testing [9].

Due to such clinical or genetic characteristics, Asian countries shows a lower survival rate after diagnosis compared to Western countries [3,10,11], indicating a high potential for improving cancer management through early detection. However, the current guidelines for PCa screening using PSA testing are primarily based on prospective randomized controlled trials (RCTs) conducted in the United States and Europe in the early 2000s [12-16]. Despite RCT offering the highest level of evidence, their applicability is limited to specific study populations and intervention types. A uniform approach to PCa screening overlooks the considerable variability in cancer risk by regions and individuals. This represents the broader challenge of balancing evidence-based medicine with personalized medicine, where recommendations are customized for each individual [17]. In this context, the question arises: Should the policy for PSA-based PCa screening be uniform for all, or should it be individualized according to each country and/or race? We will review the current guidelines and their important evidences to assess whether it is appropriate to apply these guidelines uniformly, even when considering the varying characteristics across different countries and races. We will discuss it using Korean data as an example.

MAJOR GUIDELINES REGARDING PSA-BASED PCa SCREENING

In 2012, the US Preventive Services Task Force (USPSTF) recommended against routine PSA screening for men of all ages, a stance marked as a grade D recommendation [18]. Initial observations from this approach indicated that both the incidence of rate of PSA testing and early-stage PCa have declined [18], but a rise in more high-risk cases subsequently [19]. Predictive models have raised concerns that abandoning PSA screening entirely might reduce cases of overdiagnosis, yet could lead to an increase in patients presenting with advanced, metastatic disease, potentially boosting PCa mortality by 13% to 20% by 2025 [20]. A cohort study involving 836,282 patients with PCa, using data from the SEER (Surveillance, Epidemiology, and End Results) database spanning from 2004 to 2018, revealed that the incidence rates of metastatic PCa have increased significantly and coincide temporally with the USPSTF recommendations against PSA-based PCa screening across races and age groups [21]. Other nationwide epidemiologic study using comprehensive PCa mortality data through 2019 also demonstrated decreasing PCa mortality rates that flattened or increased after the 2012 USPSTF grade D recommendation [22]. Between 1999 and 2012, and then from 2014 to 2017, there was a significant increase in the age-adjusted incidence of metastatic PCa, particularly in men aged 60 years or older [22]. These changes were seen across ages, races and ethnicities, urbanization categories, and US Census regions. Consequently, the updated 2018 USPSTF guideline endorsed shared decision-making for men aged 55 to 69 years regarding individualized PSA-based screening, although it continued to recommend against screening in men aged 70 years and older [23].

In light of this, many professional society recommend a more nuanced, shared decision-making process, weighing the pros and cons of PSA screening, along with individual patient preferences and the uncertainties involved [13-15,24]. There remains, however, a divide in the specific guidelines about how to best implement screening for those opting in, especially concerning the ideal age for commencement and cessation, as well as the optimal screening frequency. Furthermore, the guidelines lack specific considerations for regions or ethnic groups, with the exception of African-Americans. The National Comprehensive Cancer Network emphasized the shared decision-making process and recommend PSA-based screening since 45 years of age [13,14]. They suggest testing intervals based on baseline PSA, digital rectal exams (DREs) and age. The European Association of Urology advises conducting an initial baseline PSA test in the 40s, adopting a risk-adapted strategy that takes into account factors such as family history, African-American ethnicity, and baseline PSA levels, after counseling patients about the potential risks and benefits [15]. The American Urological Association advised offering PSA screening to men between 55 and 69 years, with a more individualized approach for those aged 40 to 55, and suggests biennial screenings to mitigate potential risks [24]. In their latest revision, the guideline now supports initiating PSA-based screening for younger men aged 45 to 50 years, with

an emphasis on shared decision-making [16]. Additionally, it strongly recommends beginning PSA-based screening from age 40 to 45 years for individuals at increased risk of PCa based on the following factors: Black ancestry, germline mutations, and a strong family history of PCa, backed by evidence level grade B.

LANDMARK TRIALS AND THEIR LIMITATIONS

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial, a multicenter RCT, enrolled participants in the United States from 1993 through 2001. The study randomly assigned participants aged 55 to 74 to either a screening group (n=38,340) or a control group (n=38,345) [25]. The primary endpoint was PCa-specific mortality, compared between the 2 groups. For the screening group, PCa screening was recommended using PSA tests and DRE for the first 4 years, followed by PSA testing alone for the next 2 years. The control group received routine medical care. Individuals were recommended a prostate biopsy for a PSA>4 ng/mL or suspicious DRE.

The analysis of the PLCO trial showed no significant difference in PCa-specific mortality between the screening and control groups [25-27]. However, this outcome was anticipated, considering that about 91% of men in the usual care arm underwent PSA testing [28]. This high rate of contamination, reflected in the low incidence of advanced and metastatic PCa in both groups (1.9% and 2.7% in the screening group, 1.4% and 2.1% in the control group), undermines the study's findings. Furthermore, this trial had also other limitations. In the PLCO trial, some participating centers enrolled less than 10% of the total candidates in the study, contrasting with the European Randomized Study of Screening for Prostate Cancer (ERSPC), which included up to 75% of candidates. Additionally, prostate biopsies were recommended in cases with PSA>4 ng/mL or suspicious DRE, but only 30%–40% of these cases actually underwent biopsy. Despite these limitations, nonurological organizations interpreted the results as evidence against routine PSA screening. In contrast, specialists in urology and radiation oncology contended that the trial should not be viewed as conclusive evidence against PSA screening.

The ERSPC randomly allocated men aged 55 to 69 years to screening (N=72,891) or control (N=89,352) from 8 European countries from 1991 to 2005 [29,30]. A screening interval of 2 to 4 years using a serum PSA test was employed. For the indication of a biopsy, a PSA level of ≥3.0 ng/mL was used as the cutoff. The intention-to-screen analysis of the ERSPC indicated that PSA-based screening significantly reduced mortality about 20% over a median follow-up period upto16 years [29]. Moreover, individuals who underwent PSA test at least once showed a 25% reduction, while those who were screened more than twice demonstrated a 48% reduction in PCa mortality compared to the control group. Analysis of Rotterdam section of the ERSPC showed very low nonattendance rate (5.4%) in the screening arm and true PSA contamination (defined as PSA testing in the absence of symptoms, 19.4%) in the control arm [31]. These indicators suggest that the quality and reliability of the ERSPC study are significantly higher compared to the PLCO study. Therefore, most guidelines on PCa screening from professional society regard the ERSPC as the only reliable large-scale RCT.

Following studies have suggested the potential benefits of initiating screening at an even earlier age. A Swedish study using stored serum samples revealed that elevated baseline PSA levels at ages 45 to 49 years were associated with an increased long-term risk of metastasis and PCa mortality [32]. Notably, 44% of all PCa mortality within 25 to 30 years occurred in men who were in the highest 10th percentile of the PSA distribution (≥1.6 ng/mL) at ages 45 to 49. In contrast, men with baseline PSA levels below the median of 0.68 ng/mL at this age range had less than a 0.1% risk of developing metastatic disease over the following 15 years. Thus, a randomized trial focusing on risk-adapted screening for PCa, known as the PROBASE trial, is currently underway. This study compares men who start screening at age 45 with those beginning at age 50. To date, 23,301 patients have participated in the first round of the trial [33].

DIVERSITY OF PCa BY REGION

The GLOBOCAN 2020 estimates highlight that cancer significantly contributes to morbidity and mortality globally, affecting every world region regardless of the level of human development [1]. It's crucial to note the remarkable diversity

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of cancer by region, influenced by factors such as genetics, environment, healthcare accessibility, economic status, and the human development index. Therefore, the report also emphasizes that adopting a tailored approach to health planning at the national level can significantly reduce the future burden and suffering caused by cancer worldwide. This also implies the need for an individualized approach in the application of PCa screening plan, taking into account the differences between countries.

Incidence rates of PCa are 3 times higher in transitioned countries compared to transitioning countries (37.5 vs. 11.3 per 100,000), while mortality rates show less variation (8.1 vs. 5.9 per 100,000) (Fig. 1) [1]. The incidence rates across regions range from 6.3 to 83.4 per 100,000 men, with the highest rates observed in Northern and Western Europe, and the Caribbean, and the lowest in Asia and Northern Africa. However, the patterns of mortality rates do not mirror those of incidence; the highest mortality rates are found in the Caribbean and sub-Saharan Africa. This diversity in PCa incidence and mortality can be attributed to several factors, including advancing age, family history, specific genetic mutations (e.g., *BRCA1* or *BRCA2*), ethnicity (e.g., African-American or Caribbean descent), and potentially lifestyle or environmental factors (e.g., smoking history or obesity). However, the most significant factor contributing to the global variation in PCa incidence is the regional differences in diagnostic practices for PCa including exposure rate of PSA testing [7,9].

We can notice that aggressiveness of the diagnosed PCa is higher in Africa and Asia, despite the higher incidence rate in Europe and America, when calculating mortality/incidence ratio (Fig. 1) [1]. In regions where the frequency of diagnosis is low and lethal cancers are more prevalent, implementing more aggressive PCa screening could potentially be more effective and cost-effective.

EPIDEMIOLOGY AND CHARACTERISTICS OF PCa IN SOUTH KOREA

Metastatic PCa is almost incurable and typically progress to castration-resistant PCa, ultimately leading to death. While the overall 5-year survival rate of men with PCa in Korea is 96.0%, the survival rate for those with metastatic PCa is significantly lower, at only 48.8% [34]. According to the National Cancer Registry data (2017–2021), the percentage of distant metastasis and regional disease in Korea was 10.1% and 25.6%, respectively. In comparison, data of from the Surveillance, Epidemiology, and End Results Prostate with Watchful Waiting Database in the United States (2010–2015)

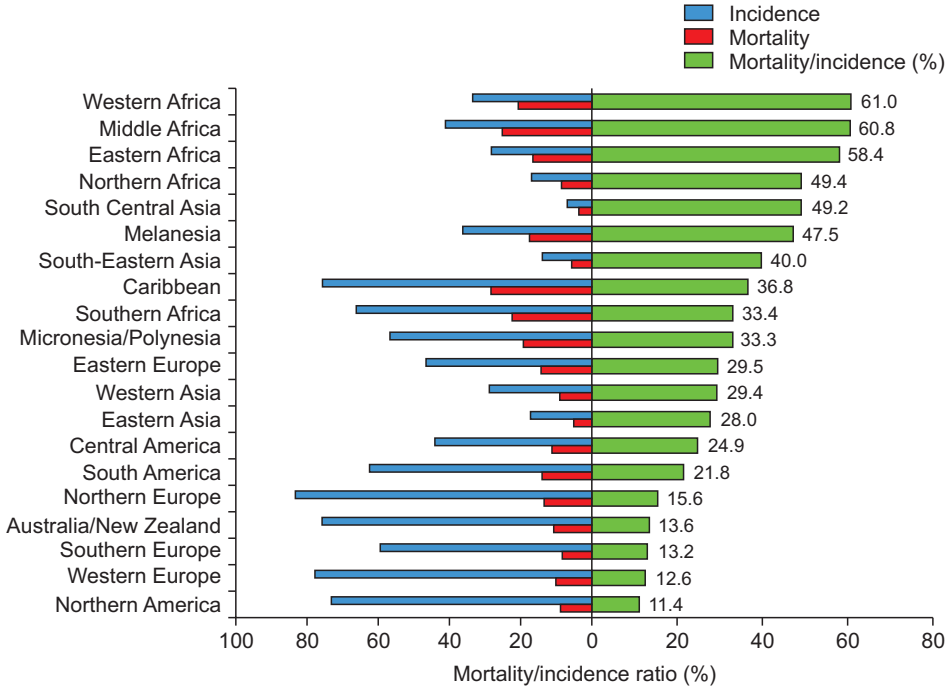

Fig. 1. Region-specific mortality/incidence ratio (%) based on incidence and mortality age-standardized rates for prostate cancer in 2020. Modified from Sung H, et al. CA Cancer J Clin 2021;71:209-49, with permission of John Wiley & Sons, Inc. [1].

showed corresponding rates of 5.8% for distant metastasis and 3.3% for pelvic lymph node metastasis [35]. In addition, in Korea, high-risk disease dominates even in localized PCa, accounting for over 60% of cases, which is significantly higher compared to about 30% in the United States [35-37]. One retrospective analysis comparing men who underwent radical prostatectomy in Korea and the United States showed that Korean patients had higher proportion of ≥T3 stage (34.8%) and Gleason score 8–10 (19.4%) compared to Caucasian (13.3% and 5.5%, respectively), and even compared to African-American (18.2% and 6.1%, respectively) [38]. These findings suggest a substantially increased risk of recurrence and progression posttreatment in Korea.

In Asia, a notable distinction in PCa compared to the Western countries is its rising incidence primarily among the elderly population. In Japan, where PCa became the most prevalent male cancer in 2016, approximately two-thirds of diagnosed patients were aged ≥75 years [39]. Similarly, in Korea, about 90% of the registered PCa patients were ≥60 years old, with about a third being ≥75 years old. In contrast, in the US, the proportion of men aged ≥75 years among PCa patients decreased from approximately 50% in 1975 to 20% in 2015 [35]. Moreover, South Korea is experiencing a rapid increase in its elderly population. South Korea ranks highly in terms of longevity, with the life expectancy of 83.7 years for both sexes in 2021 [40]. On average Korean men (80.4 years) have a 6.1-year longer lifespan compared to men in the United States (74.3 years). This indicates that Korean men, after being diagnosed with PCa, are likely to have a longer period of competing with PCa mortality against other cause mortality. Therefore, early PCa. detection would be more effective than the United States.

PSA TESTING AND SCREENING IN SOUTH KOREA

Although many evidences suggest that PSA-based PCa screening could be effective in Korea, PCa and the PSA test awareness remains low in the country. According to a 2020 report, an online survey on awareness revealed that only 9.7% (58 out of 600 respondents) were aware of the PSA test, and a mere 16.7% had ever undergone an opportunistic PSA test in their lifetime [41]. This is significantly lower compared to the approximately 91% PSA contamination rate in the control arm of the PLCO trial [28], indicating that exposure to PSA testing in Korea is still very limited. Additionally, the frequency of PSA testing shows considerable variation between different residential areas, with disparities observed between urban and rural regions [42]. Therefore, this suggests that organized PSA screening in Korea could potentially be quite effective.

Actually, a nationwide study for PSA testing and prostate biopsy was conducted in Korea, targeting men aged 55 years or older in 2007 [43]. A total of 3,943 individuals underwent PSA testing, and among them, 719 (18.2%) were recommended for biopsy due to PSA levels >3 ng/mL. Of these, 268 (37.3%) actually underwent biopsy, and PCa was diagnosed in 76 cases (28.5%). Consequently, the estimated PCa detection rate was 3.36%, which is considerably higher compared to estimates derived from national cancer statistics [5,11].

In a study conducted in Yokosuka City, Japan, which shares demographic and genetic characteristics with Korea, the 15-year results indicated that patients diagnosed with PCa through PSA screening had a higher long-term survival rate compared to those who were not screened [44]. The hazard ratio for these screened patients was 1.58 (95% confidence interval, 1.065–2.356; p=0.023). Therefore, it can be inferred that, unlike in Western populations, PSA-based PCa screening in populations like Korea and other East Asian countries could provide a significant survival benefit.

CONCLUSIONS

Although RCTs provide the highest level of evidence, their applicability is often limited to specific populations and intervention types. The characteristics of PCa incidence and mortality vary widely by region. Therefore, direct adoption of the results from RCTs conducted in Western countries for PCa related policies may not be appropriate for other regions. There is substantial evidence suggesting that PSA-based PCa screening could provide significant survival benefits in Asian countries, including Korea. In this context, it is essential to establish individualized screening plans that are specifically tailored to each region. Moreover, conducting clinical trials within each region to gather more relevant and impactful

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evidence is strongly recommended.

NOTES

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REVIEW ARTICLE

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Multidisciplinary Team Approach in Prostate-Specific Membrane Antigen Theranostics for Prostate Cancer: A Narrative Review

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In managing prostate cancer, the integration of multidisciplinary team (MDT) with prostate-specific membrane antigen (PSMA) theranostics marks a significant advancement, addressing the disease's spectrum from indolent forms to aggressive metastatic stages. MDTs, comprising urology, oncology, radiation oncology, pathology, radiology, and nuclear medicine experts, are pivotal in delivering tailored, evidence-based care, essential for the varied clinical presentations of prostate cancer. The introduction of PSMA-targeted theranostics and PSMA positron emission tomography imaging has impacted the approach to diagnosis and treatment, offering enhanced precision in disease localization and enabling more nuanced management strategies for conditions such as oligometastatic prostate cancer, metastatic hormone-sensitive prostate cancer, and metastatic castration-resistant prostate cancer. The collaborative approach of MDTs in utilizing PSMA-targeted radioligand therapy emphasizes meticulous patient selection, predictive assessment of therapy response, and careful management of therapy-related toxicities. Additionally, recent strategies, including combination therapies from ENZA-P and Lu-PARP trials, show potential for improving treatment efficacy. This unified approach showcases the critical role of MDTs in optimizing treatment outcomes, underscoring the importance of collaboration in advancing the treatment of prostate cancer with PSMA-targeted therapies, thereby setting a new paradigm in personalized prostate cancer management.

Key Words: Prostatic neoplasms, Prostate-specific membrane antigen, Multidisciplinary team, Theranostics

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MULTIDISCIPLINARY TEAM APPROACH IN PROSTATE CANCER

The management of prostate cancer, characterized by its biological heterogeneity and complex clinical presentations, demands a multifaceted and nuanced approach [1,2]. This variability, ranging from indolent to aggressive metastatic disease, underscores the necessity for personalized treatment strategies that are sensitive to the risks of both undertreatment and overtreatment. It is within this context that multidisciplinary team (MDT) becomes indispensable, combining expertise from urology, medical oncology, radiation oncology, pathology, radiology, and nuclear medicine to ensure a coordinated and evidence-based approach to patient care [3]. The emerging concept of prostate-specific membrane antigen (PSMA) targeted theranostics further

exemplifies the need for such a collaborative approach, as it introduces novel diagnostic and therapeutic options that require integrated expertise for optimal application in clinical practice [4].

MDTs significantly enhance prostate cancer management by facilitating a comprehensive evaluation of each patient's case, thus ensuring that all treatment options are considered and that management strategies are tailored to individual patient preferences and clinical profiles. Studies have shown that MDTs can lead to changes in treatment plans, reduce biases, and increase adherence to evidence-based guidelines, potentially improving clinical outcomes [3,5-11]. Gomella et al. [7] conducted a retrospective analysis comparing outcomes for newly diagnosed localized prostate cancer patients managed by a single-center MDT with those from the SEER (Surveillance, Epidemiology, and End Results) database. The findings revealed significantly longer overall survival (OS) for MDT-managed patients with stage III disease (p=0.0007) and a trend towards longer OS for Stage IV disease (p=0.0847), with over 90% of patients reporting the MDT clinic experience as good or very good. Similarly, Knipper et al. [9] examined the impact of adherence to MDT recommendations for adjuvant radiotherapy on clinical outcomes in patients at high risk of recurrence postradical prostatectomy. Their analysis showed that adherence to MDT recommendations led to significant improvements in outcomes, including biochemical recurrence-free survival (57.7% vs. 20.1%), metastasis-free survival (76.5% vs. 75.4%), cancer-specific survival (91.7% vs. 87.4%), and OS (80.4% vs. 75.8%) at 8 years. By leveraging the collective expertise of MDTs, patients are afforded access to the most advanced care options, including PSMA-targeted treatments, which have been shown to significantly impact disease progression and patient quality of life. This collaborative model not only optimizes the utilization of emerging therapies but also fosters a patient-centered approach to care, ensuring that decisions are made with a comprehensive understanding of the potential benefits and risks of each treatment option.

CONCEPT OF PSMA THERANOSTICS

Theranostics, a pivotal advancement in personalized medicine, integrates diagnostic and therapeutic functionalities into a singular platform, enabling clinicians to precisely visualize and target diseases [12,13]. Central to this approach is the concept of using ligands attached to radioisotopes, which can switch between diagnostic and therapeutic functions. This innovative principle, "We see what we treat, and we treat what we see," is materialized by administering a diagnostic radioisotope to accurately image and locate disease sites, followed by a therapeutic radioisotope to deliver targeted treatment to the same sites [14]. This seamless transition from diagnosis to therapy not only ensures that treatment is directly aimed at the disease but also significantly enhances the specificity and effectiveness of treatment, minimizing damage to surrounding healthy tissues.

PSMA has emerged as a particularly promising target for theranostic applications in prostate cancer due to its significant overexpression in prostate cancer cells—up to 1,000 times higher than in normal tissues [15,16]. This differential expression provides a unique advantage for the selective targeting and treatment of prostate cancer cells. Furthermore, PSMA-targeted ligands are designed with a cell internalization moiety, which, upon binding to PSMA, facilitates the internalization of the ligand-radioisotope complex into cancer cells [17]. This process enhances the retention of therapeutic radioisotopes within the cells, increasing the efficacy of the treatment.

The chemistry of PSMA ligands has evolved from earlier methods using monoclonal antibodies to the current use of urea-based small-molecule PSMA inhibitors, characterized by structures such as glutamate-urea-glutamate or glutamate-urea-lysine dimers [18]. These molecular designs are essential for attaching to PSMA's catalytic domain, marking a significant shift towards treatments with improved specificity and quicker clearance from the body. The combination of targeted ligand design and refined chemistry has propelled PSMA to the forefront of theranostic targets, offering a promising pathway for the development of more effective prostate cancer treatments.

APPLICATION OF PSMA IMAGING IN PROSTATE CANCER MDT

The clinical breakthrough of ^{68}Ga-based PSMA radioligands, particularly ^{68}Ga-PSMA-11, since its introduction

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in 2011 and U.S. Food and Drug Administration approval in 2020, has set a precedent for PSMA-targeted imaging [19]. The radiopharmaceutical agents ^{68}Ga-PSMA-11, ^{68}Ga -PSMA-I&T, ^{18}F-DCFPyL, ^{18}F-PSMA-1007, and ^{18}F-rhPSMA-7 are at the forefront of clinical adoption and/or receiving regulatory clearance [20-23]. These radioligands exhibit variations in radionuclide labeling, radiochemical foundations, and patterns of distribution in organs. Distinct differences in physiological distribution and challenges in interpreting imaging have been identified. Yet, up to this point, no conclusive evidence suggests that any specific PSMA radioligand outperforms others in terms of diagnostic accuracy or clinical outcomes [22].

Currently, in Korea, ^{68}Ga-PSMA-11 and ^{18}F-PSMA-1007 are clinically available. Reimbursement policies in Korea cover the deployment of PSMA-ligand imaging under particular clinical circumstances. Initially, this includes the staging process where prostate cancer diagnosis is confirmed via histological analysis or when the probability of cancer is high based on alternative imaging modalities. In instances of potential biochemical recurrence, which is indicated by a postsurgical serum prostate-specific antigen (PSA) level increase to more than 0.2 ng/mL, or a rise of more than 2.0 ng/mL above the lowest level after radiotherapy. Reimbursement is also provided for evaluating the effectiveness of ongoing treatment and guiding potential adjustments to the treatment plan through PSMA-ligand positron emission tomography (PET) scans.

1. PSMA Imaging for Oligometastatic Prostate Cancer

The condition known as oligometastatic prostate cancer represents a state of cancer characterized by a limited but potentially curable number of metastases [24]. This stage calls for a coordinated effort from a team that includes urologists, medical and radiation oncologists, radiologists, and nuclear medicine experts. The advent of PSMA PET imaging has brought significant advancements in this area, enabling the detection of metastatic lesions at lower PSA levels and driving a reevaluation of disease classifications and treatment methodologies [25].

The influence of PSMA PET imaging on the management of oligometastatic prostate cancer is particularly evident in the realm of metastasis-directed therapy (Fig. 1). Highlighted by the ORIOLE trial, the use of stereotactic body radiation therapy (SBRT) has been shown to delay the need for androgen deprivation therapy (ADT), with patients undergoing SBRT experiencing a median ADT-free survival of 21 months, a notable increase from the 13 months observed in patients under surveillance [26]. A noteworthy aspect of the ORIOLE trial was the utilization of PSMA PET scans in the SBRT arm to track disease progression. The findings revealed that only 5% of patients without any untreated PSMA-avid lesions showed disease progression at 6 months, as opposed to 38% of those who had untreated lesions (p=0.03). This underscores the precision of PSMA PET in identifying metastatic sites and its potential to guide targeted therapy. Long-term outcomes of metastatic-directed SBRT were highlighted in a retrospective study, covering a

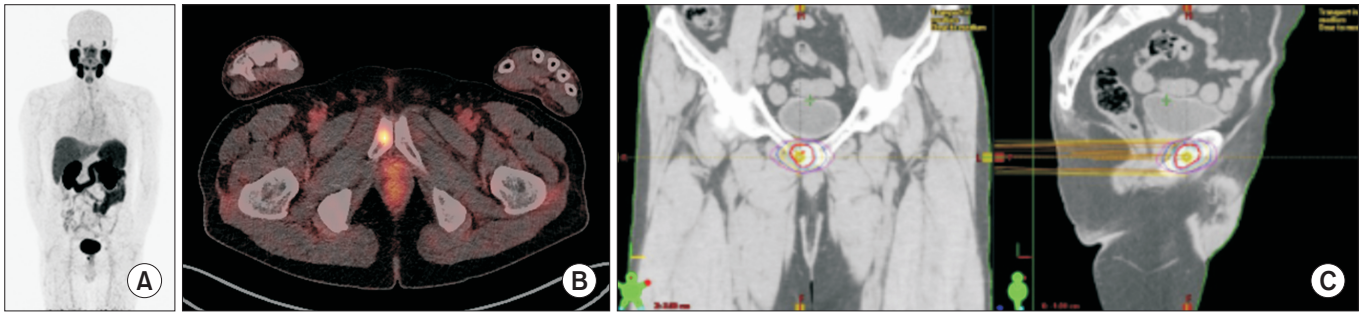

Fig. 1. A 69-year-old patient with metastatic castration-resistant prostate cancer involving the left pelvis. Initial management included leuprorelin therapy, followed by a combination of triptorelin and bicalutamide. Despite these treatments, the patient exhibited a gradual increase in serum prostate-specific antigen (PSA) levels from 0.074 ng/mL to 0.212 ng/mL within 8 months. (A, B) Prostate-specific membrane antigen (PSMA) positron emission tomography identified a focal PSMA-avid lesion in the right pubic bone. (C) Subsequently, the patient underwent stereotactic ablative radiotherapy to the right pubis with a single fraction of 22 Gy, leading to a reduction in PSA levels from 0.212 ng/mL to 0.053 ng/mL.

cohort of 103 patients with a median follow-up period of 5 years [27]. The study discloses that 15% of participants remained free from any biochemical failure at 5 years, with a median time to biochemical failure of 1.1 years. Notably, at 5 years, 39% of patients had never received any ADT and 55% had not started ADT for relapse with a median time to ADT for relapse of 5.5 years, endorsing the potential of metastasis-directed therapy to delay disease progression and the need for ADT.

Recent clinical trials increasingly incorporate PSMA PET imaging to define oligometastasis and to further delineate the role of PSMA PET in the treatment of oligometastatic prostate cancer [28-31]. The SPARKLE trial, a multicentre randomized phase III trial, focuses on whether the addition of short-term ADT during 1 month or short-term ADT during 6 months together with an androgen receptor pathway inhibitor (ARPI) to metastasis-directed therapy significantly prolongs polymetastasis free survival [30]. Oligometastatic prostate cancer in the study is defined by a maximum of 5 extracranial metastases identified using PSMA PET scans. Findings from the trials are awaited to provide evidence of the benefits of treatment strategies informed by PSMA PET (Table 1). These developments emphasize the importance of an MDT approach in leveraging the collective expertise of specialists to advance patient outcomes in the treatment of prostate cancer with oligometastatic spread.

2. Redefining Prostate Cancer Tumor Burden With PSMA PET

The advent of PSMA PET imaging has introduced a paradigm shift in the stratification of metastatic hormone-sensitive prostate cancer (mHSPC), presenting a nuanced challenge to traditional disease burden assessment methodologies. Historically, pivotal trials like CHAARTED and STAMPEDE have delineated treatment protocols based on tumor burden assessed through conventional imaging modalities, such as computed tomography, magnetic resonance imaging, and bone scans. These trials underscored the significance of accurately gauging tumor volume to predict treatment response, with CHAARTED demonstrating the benefits of chemohormonal therapy in high-volume disease patients, and STAMPEDE showing improved failure-free survival with radiotherapy in low-volume disease patients [32,33]. However, the high sensitivity of PSMA PET in detecting prostate cancer lesions necessitates a reevaluation of these volume-based classifications, as it identifies a greater number of lesions than traditional imaging, potentially altering disease categorization and subsequent treatment pathways.

A retrospective study aimed to align PSMA PET findings with the CHAARTED/STAMPEDE criteria, highlighting the impact of enhanced detection capabilities [34]. In this study, PSMA PET identified additional lesions in 62% of mHSPC patients, resulting in a hypothetical migration from CHAARTED-defined low-volume disease to high-volume disease in approximately 19% of cases. Similarly, a preliminary study, incorporating data from 4 international centers, demonstrates a notable stage migration in patients when assessed by PSMA PET, with 38.6% experiencing a shift in disease volume classification [35]. Particularly, 22% were upstaged to high-volume disease, while 22.8% were downstaged, indicating a considerable discrepancy between conventional imaging and PSMA PET evaluations. This

Table 1. Ongoing clinical trials employing PSMA PET

Study	Trial phase	Definition of oligometastasis	Intervention	Outcome
NCT05352178	Phase III	1–5 extracranial metastases in any organ, detected on PSMA PET	SBRT/surgery vs. SBRT/surgery + 1 month of ADT vs. SBRT/surgery + 6 months of ADT + anzalutamide	Poly-metastatic free survival
NCT04619069	Phase I/II	1–3 PSMA-avid areas of metastatic disease	Hormone therapy vs. SBRT + hormone therapy	Proportion of eligible patients who enroll onto the study
NCT04983095	Phase III	1–3 skeletal or extra pelvic lymph node metastases detected by PSMA PET	ADT + local radiotherapy vs. SBRT + ADT + local radiotherapy	Failure-free survival
NCT04302454	Phase III	1–4 lesions (bone + lymph nodes) in total, without evidence of visceral metastases detected by PSMA PET	Radiotherapy vs. radiotherapy + hormonal therapy	Metastases progression-free survival

PSMA, prostate-specific membrane antigen; PET, positron emission tomography; SBRT, stereotactic body radiation therapy, ADT, androgen deprivation therapy.

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nuanced understanding emphasizes the need for cautious interpretation of existing trial data and the integration of PSMA PET imaging in future research to refine treatment selection.

The introduction of PSMA PET-based criteria into clinical practice highlights an urgent need for their validation by linking them with actual clinical outcomes, beyond their capability for enhanced detection. Such validation is crucial to confirm that the increased sensitivity of PSMA PET translates into tangible benefits for patient care and treatment outcomes. Furthermore, the complex data provided by PSMA PET necessitate a multidisciplinary approach to treatment, underlining the importance of collaborative decision-making in interpreting the implications for disease classification and therapy planning. It is imperative to integrate a thorough understanding of how PSMA PET's comprehensive disease mapping affects the choice and effectiveness of both systemic and localized treatments. Current research lacks in providing a clear association between tumor burden as defined by PSMA PET and clinical outcomes, indicating a gap in the evidence-based application of these new criteria. Therefore, there is a significant need for further studies to establish and validate new definitions of tumor burden based on PSMA PET findings, ensuring they are effectively correlated with patient outcomes before they are adopted into routine practice.

MDT APPROACH FOR PSMA RADIOLIGAND THERAPY

Radioligand therapy consists of 2 components: a ligand that seeks out and binds to specific surface molecules on cancer cells, and a radioactive isotope that delivers radiation causing lethal DNA damage to the targeted cells and nearby microenvironment, leading to cell death and tumor regression [36] (Fig. 2). The only regulatory-approved PSMA-targeted radioligand therapy to date is ^{177}Lu–PSMA-617 in the setting of metastatic castration-resistant prostate cancer (mCRPC) [37]. The efficacy of ^{177}Lu -PSMA-617 in treating mCRPC was highlighted by the VISION study, a phase III trial that showed improved radiographic progression-free survival (rPFS; median, 8.7 vs. 3.4 months; hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.29–0.57) and OS (median, 15.3 vs. 11.3 months; HR, 0.62; 95% CI, 0.52–0.74; p<0.001) in patients treated with ^{177}Lu-PSMA-617 compared to standard care alone [38]. This led to FDA approval in 2022 for PSMA-positive mCRPC patients. The TheraP phase II study, comparing ^{177}Lu-PSMA-617 to cabazitaxel, revealed a higher PSA response rate (66% vs. 37%, p<0.000) and fewer grade 3 or higher adverse effects (33% vs. 53%) in the ^{177}Lu-PSMA-617 group, indicating not just an efficacy advantage but also a potentially more favorable tolerability profile [39]. These studies collectively underpin the specified indication for PSMA radioligand therapy with ^{177}Lu-PSMA-617, in patients with PSMA-positive mCRPC, who progressed under at least one ARPI (e.g., enzalutamide or abiraterone) and at least one taxane regimen [40,41].

1. Patient Selection for PSMA Radioligand Therapy

The effectiveness of PSMA-targeted therapy hinges on

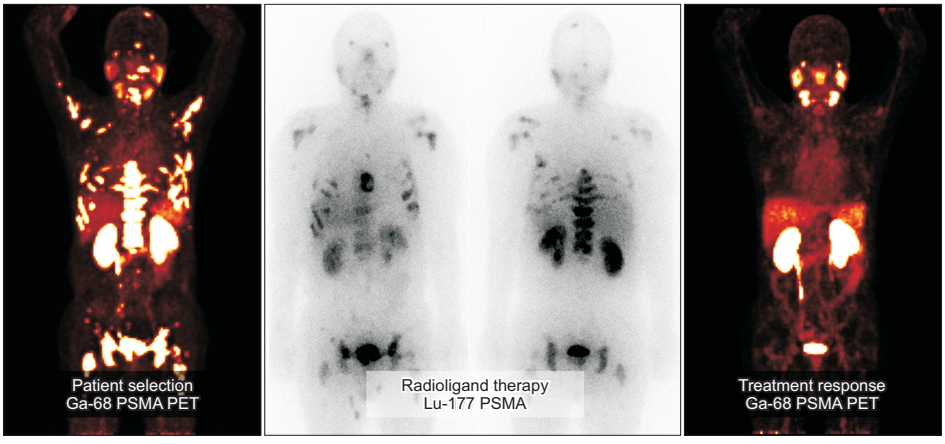

Fig. 2. Theranostic process in a 64-year-old male patient with metastatic prostate cancer who underwent hormone therapy followed by 2 cycles of chemotherapy. Despite these treatments, the patient continued to develop metastatic lesions, prompting referral for radioligand therapy. Pretreatment prostate-specific membrane antigen (PSMA) positron emission tomography (PET) showed multiple PSMA-avid metastases. Following PSMA radioligand therapy, prostate-specific antigen levels dramatically decreased from 823.8 ng/mL to 0.53 ng/mL, indicating a substantial response to treatment.

the presence of sufficient PSMA expression on tumor lesions [42]. In the VISION study, PSMA-positive mCRPC was defined as having at least one tumor lesion with ^{68}Ga-PSMA-11 uptake greater than the normal liver [38]. Patients were excluded from enrollment if any lesions, defined by the conventional imaging, exceeding certain size criteria in the short axis had uptake less than or equal to uptake in normal liver. Under these criteria, 13% of patients were excluded from the enrollment. The definition of "PSMA-positive" for the trial was carefully crafted to ensure tumors with sufficient target expression were identified for likely response to therapy, avoiding reliance on standardized uptake value (SUV) cutoffs due to variability across sites [43]. The criteria developed were based on visual assessment against the liver as an internal reference, deemed more consistent than the spleen and avoiding the need for measuring SUVs, with a binary assessment chosen for clarity. This methodology underlines the intricate balance between ensuring a robust and feasible selection process that aligns with existing criteria and the practical execution of global clinical trials. However, there are several considerations when deciding whether to treat an individual patient.

Firstly, patient outcomes may differ according to the PSMA uptake. Post hoc analysis of the VISION trial, revealed a significant correlation between higher PSMA expression, as quantified by SUVs (mean SUV [SUVmean] and maximum SUV [SUVmax]), and improved clinical outcomes such as rPFS and OS [44]. Notably, patients with higher whole-body SUVmean, particularly those in the highest quartile (SUVmean ≥10.2 for rPFS; ≥9.9 for OS), exhibited a median rPFS and OS of 14.1 and 21.4 months, respectively, compared to significantly lower survival rates in the lowest quartile. Furthermore, a preliminary study suggests that clinically meaningful anti-tumor activity predominantly occurs in patients exhibiting more than one-fold parotid uptake across the majority of lesions (approximately SUV>10), emphasizing the necessity for consideration of treatment sequencing in patients with suboptimal PSMA uptake [45]. Secondly, different PSMA ligands may show variable tumor and normal organ uptake [22,23]. ^{18}F-PSMA-1007 shows higher liver and gall bladder accumulation than ^{68}Ga-PSMA-11 due to hepatobiliary excretion and no or only minimal excretion via the urinary system [46,47]. Furthermore, organ uptake may show variability due to scanner calibration parameters, which further complicates the patient selection process.

The decision to proceed with ^{177}Lu-PSMA radioligand therapy involves a thorough evaluation by an MDT, considering not only the PSMA PET imaging results but also the patient's overall health, prior treatments, and the potential for response based on PSMA expression levels [5]. This MDT approach ensures that all aspects of the patient's condition are considered, allowing for personalized treatment planning. As research continues to refine the criteria for PSMA radioligand therapy eligibility, the goal remains to optimize outcomes for mCRPC patients through targeted, effective therapy that minimizes exposure to non-responsive individuals.

2. Treatment-related Toxicity of PSMA Radioligand Therapy

The ability to visualize the distribution of radiopharmaceuticals before treatment provides predictive insight into potential radiation effects on normal organs, allowing for a more individualized assessment of risk and benefit [36]. Expected short-term toxicities associated with PSMA radioligand therapy include dose-dependent myelosuppression and xerostomia [40]. In the VISION trial, the most common adverse events (AEs) reported were fatigue, dry mouth, and nausea, predominantly of grade 1 or 2 severity [38]. A preliminary study provides insight into the long-term (at least 6 months of follow-up) toxicity profile of various PSMA-targeted radioligand therapies, indicating that most AEs could be attributed to alternate etiologies [47]. In particular, only 2 grade ≥3 AEs were attributed to possibly being related to PSMA radioligand therapy: 1 case of grade 4 renal dysfunction (creatinine elevation) and 1 case of grade 3 ALT elevation. Studies collectively affirm the safety and efficacy of PSMA-targeted radioligand therapy in treating mCRPC, with manageable toxicity profiles [48,49].

However, it's important to acknowledge the limitations in predicting specific adverse effects that may manifest in individual patients. Patients exhibiting impaired renal function, extensive prior chemotherapy, or prolonged hematological toxicity may have a higher susceptibility

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to experiencing more severe myelotoxicity [50]. There is limited clinical data on patients with moderately impaired renal function (GFR 30–50 mL/min), suggesting a gap in understanding the full impact of ^{177}Lu-PSMA radioligand therapy in this subgroup [51,52]. In cases where patients began ^{177}Lu-PSMA radioligand therapy with already diminished kidney function, worsening renal conditions were observed, though these could also be attributed to the typical risk factors associated with chronic kidney disease [52,53]. These observations indicate a crucial need for careful patient selection and monitoring within MDT, particularly for those with pre-existing conditions that might elevate the risk of adverse outcomes from radioligand therapy.

The management of AEs in radioligand therapy, including marrow toxicity and dry mouth, generally follows symptom-based approaches similar to those used for conventional chemotherapy side effects. For marrow toxicity, strategies include delaying subsequent treatments to allow for marrow recovery, especially in patients responding well to treatment; administering supportive care such as platelet or red blood cell transfusions; and considering the use of marrow-stimulating agents, albeit with caution due to the risk of exacerbating toxicity in future cycles [40,41,50]. For dry mouth, a common toxicity in PSMA radioligand therapy, assessing severity through careful history-taking at baseline and follow-ups is crucial. Although no consensus exists on reducing salivary gland toxicity, symptomatic relief can be sought through lubricating rinses, and treatment delays may help in salivary gland function recovery [54]. Decisions regarding treatment delays or symptom management should be made comprehensively, taking into account the overall benefit-risk balance for the patient.

3. Enhancing PSMA Radioligand Therapy Through Strategic Combinations

In the evolving landscape of mCRPC treatment, studies like the ENZA-P (NCT04419402) and Lu-PARP (NCT03874884) trials offer promising insights into enhancing treatment responses through innovative combination therapies. The ENZA-P trial underscores the potential of combining enzalutamide, an ARPI, with PSMA-targeted radioligand therapy, predicated on the premise that ARPI upregulates PSMA expression, thereby potentially enhancing the efficacy of PSMA-targeted therapies [55]. This synergy was hinted at in preclinical studies and observed through PSMA PET in men commencing enzalutamide treatment, suggesting that a combined approach might improve treatment outcomes without significantly increasing toxicity [56,57]. Similarly, the Lu-PARP trial addresses the intersection of DNA repair gene mutations and prostate cancer aggressiveness, highlighting the vulnerability of such cancers to PARP inhibitors. This approach leverages the interconnectedness of PARP-associated DNA repair pathways and androgen receptor signaling, suggesting that targeting these mechanisms concurrently could offer a more effective treatment strategy [58]. However, PARP inhibitors (such as olaparib and talazoparib) did not enhance the DNA-damaging effects of ^{177}Lu-PSMA radioligand therapy *in vitro*, which indicates that further validation is required [59]. Both trials emphasize the critical role of MDT in integrating the latest treatment advances and selecting the most suitable therapy for individual patients. This approach not only ensures that patients receive the most up-to-date and effective treatments but also highlights the importance of tailoring therapy to the patient's specific disease characteristics and genetic profile, thereby maximizing therapeutic efficacy while minimizing unnecessary toxicity.

CONCLUSION

In conclusion, the integration of the MDT approach with PSMA theranostics in prostate cancer treatment highlights the importance of further investigation. There are unanswered questions regarding how the high sensitivity of PSMA imaging in detecting more lesions impacts patient outcomes, the identification of predictive markers for patient selection in PSMA-targeted radioligand therapy, and the potential benefits of combination therapies. Addressing these areas through focused research within the MDT framework is essential to ensure that the clinical application of PSMA theranostics leads to improved patient care and outcomes. This effort requires collaboration among clinicians, researchers, and patient advocacy groups to advance prostate cancer management.

NOTES

- **Author Contribution:** Conceptualization: MS, GJC; Visualization: MS, GJC; Writing - original draft: MS, GJC; Writing - review & editing: MS, GJC.
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ORIGINAL ARTICLE

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High-Grade Late Urinary Toxicity Following Salvage Radiotherapy After Radical Prostatectomy: A Retrospective Cohort Study

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Purpose: To find out the incidence and predictors for late high-grade genitourinary (GU) toxicity following salvage radiotherapy (SRT), we investigated the consecutive patients who were treated with SRT after radical prostatectomy.

Materials and Methods: Patients who underwent SRT for biochemical recurrence after radical prostatectomy were reviewed. The incidence of GU toxicity was assessed and risk factors for grade ≥2 and ≥3 GU toxicity were evaluated. The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guided the reporting of this study.

Results: Among the total of 217 patients, 88 patients (40.5%) showed late grade ≥2 GU toxicity. The incidence of late grade ≥3 GU toxicity was 11.5%. The presence of grade ≥2 baseline GU dysfunction (hazard ratio [HR], 6.097; 95% confidence interval [CI], 3.280–11.333; p<0.001) and short interval (<1 year) from surgery to SRT (HR, 1.994; 95% CI, 1.182–3.365; p=0.01) were associated with late grade ≥2 GU toxicity. A short interval from surgery to SRT was an independent predictor of late grade ≥3 GU toxicity (HR, 2.975; 95% CI, 1.135–7.794; p=0.027).

Conclusions: The incidence of late high-grade GU toxicity was not uncommon after SRT. Thus, care should be taken when we consider SRT in patients with baseline urinary dysfunction and a short interval from surgery to SRT, to determine an optimal treatment strategy with balancing quality of life and oncologic outcome of patients.

Key Words: Prostatic neoplasms, Radical prostatectomy, Salvage radiotherapy, Urinary toxicity

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INTRODUCTION

Salvage radiotherapy (SRT) is the potentially curative treatment option for patients with prostate-specific antigen (PSA) recurrence after radical prostatectomy (RP) but no evidence of distant metastatic disease, through the eradication

of microscopic residual disease [1,2]. SRT after RP is applied to the prostatic bed and possibly to the surrounding tissues, including lymph nodes [3]. Regarding survival outcomes of SRT in postprostatectomy patients, we previously reported that SRT with or without subsequent androgen deprivation therapy (ADT) demonstrated better clinical progression-free survival compared to ADT only [4]. Several studies of SRT demonstrated that 5-year biochemical progression-free survival outcomes following SRT ranged from 40% to 90% and better results are achieved with a lower PSA at initiation of SRT [5-12]. However, SRT could result in an increasing risk of morbidity in relation to acute and late toxicity following irradiation [6,8]. Genitourinary (GU) toxicity plays a major role in the post-treatment quality of life in patients who have undergone SRT, because SRT could aggravate the RP complications such as urinary incontinence or urethral stricture [8,13,14]. In the current study, we investigated the acute and late GU toxicity of patients, and evaluated the pre-SRT clinical factors which predict late grade ≥2 and ≥3 GU toxicity not only to aid selecting patients who would benefit more from SRT but also to determine an optimal treatment strategy before SRT.

MATERIALS AND METHODS

The STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines were followed to conduct this retrospective cohort study. After obtaining approval from the Institutional Review Board of University of Ulsan College of Medicine, Asan Medical Center (No. 2017-1036), the medical records of prostate cancer patients who underwent SRT with a curative intent for biochemical recurrence (defined as 2 consecutive postoperative PSA values ≥0.2 ng/mL) after a period of undetectable PSA or persistent postoperative PSA between 1998 and 2015 at University of Ulsan College of Medicine, Asan Medical Center, were reviewed. Patients with incomplete data or short follow-up periods of less than 1 year were excluded from the analysis. Finally, a total of 217 patients were evaluated in this study. Our institutional protocol of SRT was described in our previous report [4]. Briefly, computed tomography simulation was performed before SRT. External beam radiotherapy (RT) was delivered for SRT, including either the whole pelvis or prostate bed according to the Roach score [15]. Patients with a Roach score ≥15% received whole-pelvis RT, whereas the others received prostate bed RT. After 45–50 Gy of whole-pelvis RT, a reduced field boost, up to a mean of 66.5 Gy, was delivered in patient treated with whole-pelvis RT. Sixty-five patients (30.0%) were treated with 3-dimensional conformal RT (3D-CRT) using four-field box technique. The remaining 152 patients (70.0%) were treated according to intensity-modulated RT (IMRT) schemes using 5 to 7 fields which were created using Eclipse 10.0 (Varian Medical Systems, Palo Alto, CA, USA). The planning target volume was a 5- to 7-mm expansion of the clinical target volume. A median (range) dose of 66.0 Gy (47.8–77.0 Gy) with a daily fraction size of 1.8–2.0 Gy was delivered with a 15-MV x-ray from a linear accelerator (Clinac 1800, 2100 C/D, Varian Medical System).

Patients had follow-up visits every 3 to 6 months after SRT up to 3 years, and then annually thereafter. Acute toxicities were those occurring during treatment or within 3 months after treatment. Late toxicities were those occurring after 3 months of treatment or those that started acutely and lasted for 3 months after treatment. Acute and late gastrointestinal (GI) and GU toxicities were graded according to the Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. The CTCAE displays grades 1 through 5 with clinical descriptions of severity for each adverse event. Briefly, grade 2 is defined as moderate adverse event (minimal, local or noninvasive intervention indicated), and grade 3 is defined as severe or medically significant but not immediately life-threatening adverse event (hospitalization or prolongation of hospitalization indicated, limiting self-care activities of daily living). Because we assumed that a substantial proportion of patients had urinary dysfunction such as frequency, urgency, or urinary incontinence following RP, baseline GU dysfunction was assessed for every patient before SRT and it was graded according to the same criteria as toxicity grading.

Kaplan-Meier analyses were used to determine the 5-year risk of late grade ≥2 and ≥3 GU toxicity. To identify the predictive factors for the high-grade late GU toxicity, the following factors were analyzed: age, body mass index, presence or absence of hypertension and diabetes, time interval from RP to SRT, whether patients were taking ADT or not, RT modality, RT dose, RT field, year of RT, and

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baseline GU dysfunction. Univariable and multivariable Cox regression models were used for predictive analysis. SPSS ver. 18.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analyses; $p<0.05$ was considered statistically significant.

RESULTS

The baseline and treatment characteristics of the 217 patients are summarized in Table 1. The median age was 64 years. The median time interval from RP to SRT was 22.7 months. ADT was administered in 97 patients (44.7%). Most patients (70.0%) were treated with IMRT, while the remaining 30.0% of patients were treated with 3D-CRT.

Table 1. Clinical characteristics of 217 patients who underwent salvage radiotherapy after radical prostatectomy

Characteristic	Value
Age (yr)	64 (59–68)
Preoperative PSA (ng/mL)	13.8 (7.7–27.1)
<10	81 (37.3)
10–20	61 (28.1)
≥20	75 (34.6)
Pathologic Gleason score	
≤6	9 (4.2)
7	99 (46.7)
8–10	104 (49.1)
Extracapsular extension	83 (38.2)
Seminal vesicle invasion	65 (30.0)
Positive surgical margins	131 (60.4)
PSA before radiotherapy (ng/mL)	0.66 (0.39–1.0)
<0.5	74 (34.1)
0.5–1.0	91 (41.9)
≥1.0	52 (24.0)
Time from RP to RT (mo)	22.7 (11.8–39.8)
<12	57 (26.3)
12–24	57 (26.3)
≥24	103 (47.4)
ADT	97 (44.7)
Radiotherapy modality	
3D-CRT	65 (30.0)
IMRT	152 (70.0)
Radiotherapy dose (Gy)	66.0 (66.0–70.0)
Radiation fields	
Prostatectomy bed	66 (30.4)
Whole pelvis	151 (69.6)
Year of radiotherapy	
1998–2008	56 (25.8)
2009–2010	72 (33.2)
2011–2013	89 (41.0)

Values are presented as median (interquartile range) or number (%).
PSA, prostate-specific antigen; RP, radical prostatectomy; RT, radiotherapy; ADT, androgen deprivation therapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

The median RT dose was 66.0 Gy and most patients (86.6%) were treated with total dose of ≥66 Gy. Whole-pelvis RT was performed in 151 patients (69.6%).

Forty-eight patients (22.1%) had acute grade ≥2 GU toxicity. The frequency (66.0%) was the most common acute grade 2 GU toxicity followed by urinary incontinence (22.6%). Four patients had acute grade 3 GU toxicity with urethral stricture, ureteral stricture, and urinary incontinence.

The overall incidence of late grade ≥2 GU toxicity was 40.5%. Urinary incontinence (57.7%) was most common late grade 2 GU toxicity followed by hematuria (22.5%). Although these patients were treated with medication, their symptoms waxed and waned over the years. Twenty-five patients (11.5%) had late grade 3 GU toxicity. Hematuria (56%) was the most common late grade 3 GU toxicity followed by urinary incontinence (36%). No grade 4 or higher acute and late GU toxicities were reported (Table 2). The 5-year risk of late grade ≥2 GU toxicity was 43.0% and that of late grade 3 GU toxicity was 11.6% (Fig. 1). The median time to development of first late grade ≥2 and grade 3 GU toxicity was 20.3 (interquartile range [IQR], 11.1–31.5) and 28.7 (IQR, 22.6–48.4) months, respectively.

A total of 57 patients received SRT within 1 year after RP. Among them, 36 (63.2%) and 14 patients (24.6%) developed late grade ≥2 and grade 3 GU toxicity, demonstrating a high risk of late GU toxicity, compared to patients who had received SRT ≥1 year after RP (late grade ≥2 toxicity; 32.5%, grade 3 GU toxicity; 6.9%).

Of the 22 patients with a baseline grade ≥2 GU dysfunction, 18 (81.8%) and 6 patients (27.3%) developed late grade ≥2 and grade 3 GU toxicity, while 35.9% and 9.7% of patients with a baseline grade ≤1 GU dysfunction developed late grade ≥2 and grade 3 GU toxicity, respectively. A similar trend was observed with respect to urinary incontinence. Of

Table 2. The incidence of acute and late toxicity after salvage radiotherapy (n=217)

Grade of toxicity	Baseline GU dysfunction	Incidence of acute GU toxicity	Incidence of late GU toxicity
0	167 (76.9)	99 (45.6)	75 (34.6)
1	28 (12.9)	70 (32.3)	54 (24.9)
2	21 (9.7)	44 (20.3)	63 (29.0)
3	1 (0.5)	4 (1.8)	25 (11.5)

Values are presented as number (%).
GU, genitourinary.

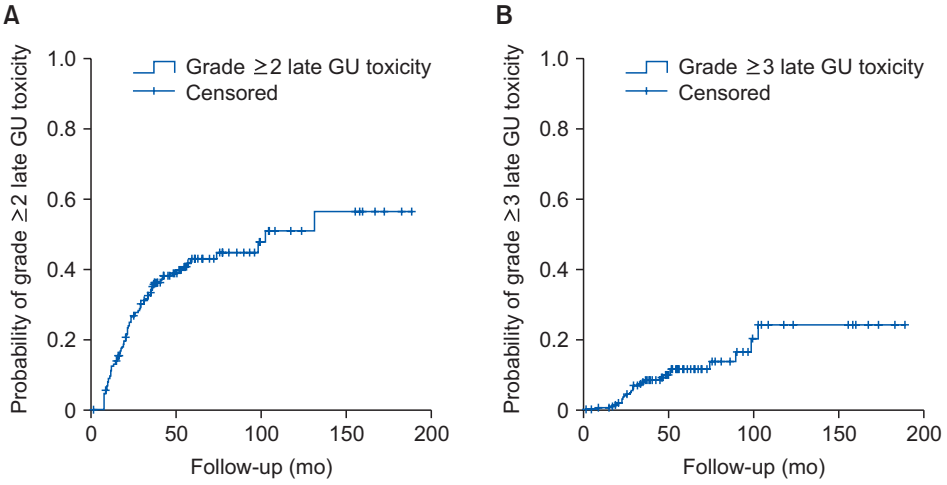

Fig. 1. Risk of 5-year late (A) grade ≥2 and (B) grade 3 urinary toxicity. GU, genitourinary.

the 15 patients with baseline grade ≥2 urinary incontinence, 9 (60%) and 3 patients (20%) reported late grade ≥2 and grade 3 urinary incontinence, while 17.8% and 3.0% of patients with baseline grade 0–1 urinary incontinence reported late grade ≥2 and grade 3 urinary incontinence, respectively.

Multivariable analysis demonstrated that a short time interval (<1 year) from RP to SRT (hazard ratio [HR], 1.994; 95% confidence interval [CI], 1.182–3.365; p=0.01) and baseline grade ≥2 GU dysfunction (HR, 6.097; 95% CI, 3.280–11.333; p<0.001) were independent predictive factors for late grade ≥2 GU toxicity. A short time interval from RP to SRT was an also independent predictive factor for late grade ≥3 GU toxicity (HR, 2.975; 95% CI, 1.135-7.794; p=0.027). Although it was not statistically significant, baseline grade ≥2 GU dysfunction showed a trend toward increasing risk of late grade ≥3 GU toxicity (HR, 2.500; 95% CI, 0.905-6.904; p=0.077) (Table 3).

With respect to GI toxicity, acute grade ≥2 GI toxicity was reported in 34 patients (15.7%). Most of acute grade 2 GI toxicity was diarrhea (40.0%). One patient had acute grade 3 GI toxicity with rectal hemorrhage. The overall incidence of late grade ≥2 GI toxicity was 6.9%. Most of late grade 2 GI toxicity was proctitis (58.3%). Three patients had late grade 3 GI toxicity including rectal hemorrhage and proctitis. No grade ≥4 GI toxicity was reported (Table 2). The 5-year risk of late grade ≥2 GI toxicity was 7.9% and that of late grade 3 GI toxicity was 2.1%.

DISCUSSION

Previous studies have demonstrated the low incidence of GI and GU toxicity following SRT after RP reporting serious late toxicity rates of 10% or less and suggested that SRT appears to be well-tolerated in patients [5,6,13,14,16,17]. In daily clinical practice, however, it is not uncommon that we face patients who complain of late urinary toxicity after SRT. Cozzarini et al. [18] reported higher than expected severe late urinary toxicity after hypofractionated adjuvant RT (ART) or SRT demonstrating 18% of a 5-year risk of late grade ≥3 urinary toxicity. Van Dessel et al. [8] reported late grade ≥2 toxicity for GU was 29.9% after SRT in accordance with our results. These results might be affected by hypofractionation, radiation dose, and the potential bias linked to the more vigilant attitude toward urinary toxicity in patients treated more recently. However, patients' quality of life is as important as survival outcomes and treatment related toxicity is an important factor for planning treatment strategy for patients [3]. In that sense, a vigilant attitude toward the toxicity of patients is required to clinicians in daily practice. In the current study, we reviewed acute and late toxicity of patients after SRT in detail. Furthermore, we investigated predictive factors of grade ≥2 and ≥3 late GU toxicity not only for better selection of patients before SRT, but also for better decision making regarding the timing of SRT, along with balancing the oncologic outcome and safety of patients.

According to prior studies assessed GI and GU toxicity after SRT, the incidence of acute grade ≥2 GI and GU toxicity

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Table 3. Predictive factors for late grade ≥ 2 or grade 3 GU toxicity

Variable	Late grade ≥2 GU toxicity			Late grade 3 GU toxicity		
	Univariate	Mutivariate		Univariate	Mutivariate	
	p-value	HR (95% CI)	p-value	p-value	HR (95% CI)	p-value
Age (yr)	0.035	1.029 (0.991–1.067)	0.133	0.311	1.021 (0.957–1.089)	0.527
BMI (kg/m^2)	0.317	0.988 (0.905–1.079)	0.792	0.522	1.039 (0.879–1.228)	0.651
HTN	0.334	1.265 (0.782–2.045)	0.338	0.938	1.200 (0.486–2.964)	0.692
DM	0.833	1.237 (0.687–2.225)	0.479	0.519	0.656 (0.175–2.463)	0.532
Time from RP to SRT (mo)						
≥24	Reference			Reference		
12–24	0.389	1.559 (0.870–2.792)	0.135	0.980	1.013 (0.367–3.843)	0.985
<12	<0.001	1.994 (1.182–3.365)	0.010	0.005	2.975 (1.135–7.794)	0.027
ADT	0.072	0.670 (0.421–1.068)	0.092	0.748	1.028 (0.428–2.469)	0.950
Radiotherapy modality						
3D-CRT	Reference			Reference		
IMRT	0.593	0.374 (0.135–1.037)	0.059	0.786	0.988 (0.245–3.983)	0.986
Radiotherapy dose (Gy)						
≤66	Reference			Reference		
>66	0.807	1.106 (0.639–1.912)	0.719	0.435	1.570 (0.587–4.201)	0.369
Radiation field						
Prostatectomy bed	Reference			Reference		
Whole pelvis	0.440	0.712 (0.399–1.270)	0.250	0.786	1.883 (0.577–6.142)	0.294
Year of radiotherapy						
1998–2008	Reference			Reference		
2009–2010	0.280	1.240 (0.648–2.372)	0.516	0.414	1.241 (0.331–4.652)	0.749
2011–2012	0.169	1.786 (0.798–3.995)	0.158	0.284	2.875 (0.610–13.548)	0.182
Baseline GU dysfunction						
Grade 0–1	Reference			Reference		
Grade ≥2	<0.001	6.097 (3.280–11.333)	<0.001	0.004	2.500 (0.905–6.904)	0.077

GU, genitourinary; HR, hazard ratio; CI, confidence interval; BMI, body mass index; HTN, hypertension; DM, diabetes; RP, radical prostatectomy; SRT, salvage radiotherapy; ADT, androgen deprivation therapy; 3D-CRT, 3-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

was reported by 10%–18% and 9%–20%, respectively [5,6,11-14,18]. The incidence of acute grade 3 GI and GU toxicity was less than 5% in these studies. Although the incidence of acute grade ≥2 GU toxicity (22.1%) was slightly higher in the current study, our findings with respect to the incidence of acute toxicity were in accordance with prior studies.

The 5-year risk of late grade ≥2 and grade 3 GI toxicity (7.9% and 2.1%) was similar to previous reports (≤10% and ≤5%) [5,6,14,16,17,19]. However, the overall incidence and 5-year risk of late grade ≥2 and grade 3 GU toxicity of the current study was higher than other published reports (grade ≥2; 10%–30%, grade ≥3; 1%–10%) [5,6,12,13,16-19]. Possible explanations for this discrepancy are retrospective character of some series, and different materials and methods of those studies including statistical analysis, SRT protocol, and toxicity grading system.

In our study, short time interval (<1 year) from RP to SRT was associated with late high-grade (grade ≥2 or ≥3) GU toxicity. Time interval from RP to SRT was not clearly demonstrated for a predictive factor, or not associated with late high-grade GU toxicity in several prior studies [5,6,13,17,18]. However, these results should be interpreted carefully, because predictive analyses were not clearly demonstrated and several possible confounding factors were not adjusted in their studies. In addition, a small number of patients with a short time interval (<1 year) from RP to SRT in those studies might be the possible reason for their inconsistent results. We evaluated as many as possible confounding variables based on published reports assessed toxicity after SRT, and patients with incomplete data were excluded from the analysis. The median time interval from RP to SRT of the current study (22.7 months) was short, compared with other studies (29–36 months) [5,6,13]. This might be the reason for our high risk of late grade ≥2 and grade 3 GU toxicity. Moreover, results of the recent 3 randomized controlled trials (GETUG, RADICALS, RAVES)

that compare the efficacy and safety of ART versus SRT support our findings [11,12,20]. All these trials demonstrated that SRT results in similar biochemical control to ART, and is associated with significantly lower amounts of GU toxicity. One of these studies concluded that observation with salvage treatment for PSA biochemical progression should be the current standard of care after RP [20]. Thus, we can assume that short time interval from RP to RT increased the risk of high-grade GU toxicity, and a longer time interval between RP and RT might lower the risk of toxicity.

CTCAE is a well-defined and standardized grading scale system that can be utilized for adverse event reporting. However, it seems that grading of toxicity is rather subjective, because adverse events are usually determined and graded by clinicians largely based on their beliefs and practices. In that sense, the perspective of radiation oncologists and urologists may be different. Several studies confirmed different practice patterns between radiation oncologists and urologists [21,22]. In our study, urologists tended to prescribe medication (CTCAE grade 2) for patients who complained of urinary symptoms, while radiation oncologists did not (CTCAE grade 1) do the same for the same patients (data not shown). Indeed, almost all prior studies that assessed toxicity after SRT were written by radiation oncologists [5,6,13,16-18]. Further study would be needed to verify this tendency, but this might have affected our results.

Goenka et al. [5] demonstrated that baseline GU dysfunction grade ≥2 (HR; 2.7, p=0.01) was associated with increased late grade ≥2 GU toxicity after SRT. Furthermore, poor baseline urinary incontinence was associated with an increased risk of developing late grade ≥2 urinary incontinence (HR, 4.21; p<0.01). We confirmed these findings in the current study demonstrating an increased risk of late grade ≥2 GU toxicity in patients with a baseline grade ≥2 GU dysfunction (HR, 6.1; p<0.001). Although not significant, a baseline grade ≥2 GU dysfunction was associated with increased late grade 3 GU toxicity (HR, 2.5; p=0.077).

With respect to oncologic outcomes, early SRT at the low PSA level and higher SRT dose were associated with improvement in survival outcomes after SRT [7,9,11,12,23,24]. Our findings would be helpful to determine the patient selection and timing of SRT maintaining the balance between oncologic outcome and toxicity. For instance, we can consider ADT before SRT, and followed by high-dose SRT in patients with a baseline GU dysfunction and a short time since RP. Although the type and optimal duration of ADT in combination with SRT remains controversial, we can expect not only improved survival but also a reduced risk of late high-grade GU toxicity in these patients [11,25]. In our data, among the patients who showed biochemical recurrence within 1 year after RP, 35 patients received SRT ≥1 year after RP due to a period of ADT before SRT. The incidence of late grade ≥2 and grade 3 GU toxicity of these patients was lower than that of patients who received SRT <1 year after RP (late grade ≥2 toxicity, 25.7% vs. 63.2%; grade 3 GU toxicity, 2.9% vs. 24.6%). Furthermore, the 5-year biochemical progression-free survival rates following SRT were better in the former group than those of the latter group (57% vs. 33%). These findings support our suggestion regarding the patient selection and timing of SRT with a balancing between the oncologic outcome and toxicity.

Our study had several limitations including the potential bias inherent in retrospective studies. The patients who received ART were not analyzed in the current study. Therefore, our findings cannot be generalized to ART. However, recent 3 randomized controlled trials demonstrated that ART increases the risk of urinary morbidity with no benefit for biochemical control compared with SRT [11,12,20]. Our findings will provide additional information for the management strategy of patients in relation to toxicity after SRT.

CONCLUSIONS

Our results showed the high incidence of late high-grade GU toxicity after SRT. In addition, a baseline grade ≥2 GU dysfunction and a short time (<1 year) interval from surgery to SRT are associated with an increased risk of late high-grade GU toxicity. Therefore, more time for potential recovery from urinary dysfunction or an alternative treatment strategy should be provided to patients so that they can benefit more from SRT maintaining a balance between the oncologic outcome and treatment related toxicity.

NOTES

• **Author Contribution:** Conceptualization: HA; Data cura-

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tion: SKC, SML; Formal analysis: SKC; Methodology: SKC, MK; Project administration: HA; Visualization: SKC; Writing - original draft: SKC; Writing - review & editing: SKC, MK, SML, CS, JHH, CSK.

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ORIGINAL ARTICLE

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Enzalutamide Maintenance Following Docetaxel in Metastatic Castration-Naive Prostate Cancer: A Pilot Feasibility Study

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Purpose: To assess the feasibility and short-term efficacy of maintenance enzalutamide following first-line docetaxel plus androgen deprivation therapy (ADT) in patients with high-volume, metastatic castration-naive prostate cancer (mCNPC).

Materials and Methods: The present study included 38 consecutive patients with mCNPC who did not have disease progression with ADT plus docetaxel between October 2022 and October 2023. Patients received a switch maintenance therapy with enzalutamide until progression, unacceptable toxicity, or patient withdrawal. Endpoints included time to prostate-specific antigen (PSA) progression and safety.

Results: Among the 38 patients, the median age was 68 years, and the most frequently observed metastatic site was bone (n=36), followed by lymph nodes (n=28), lung (n=8), and liver (n=1). The median duration of first-line docetaxel was 2.8 months (range, 2.7–5.0 months). At the time of commencing maintenance enzalutamide, the median PSA was 3.2 ng/mL (range, 0.01–258 ng/mL). Maintenance enzalutamide was generally well-tolerated. A total of 11 patients (28%) discontinued enzalutamide, and the main reasons included adverse events (prolonged fatigue of grade 1 or 2, n=6), disease progression (n=3) and financial burdens (n=2). Median time to PSA progression was not reached, and 93% were PSA progression-free at 12 months.

Conclusions: Maintenance enzalutamide is a feasible treatment option with potential clinical benefit for patients with high-volume mCNPC who were progression-free after first-line ADT+docetaxel.

Key Words: Enzalutamide, Prostatic neoplasms, Castration-naive

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- **Research Ethics:** The study protocol was approved by the Institutional Review Board of Samsung Medical Center (IRB No. 2023-07-103), and all patients provided a written informed consent prior to both starting docetaxel and switch to enzalutamide.
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

In Korea, prostate cancer is one of the greatest growing cancers, with an incidence of >10,000 cases annually [1]. If a patient with prostate cancer develops or is diagnosed with metastatic disease, androgen deprivation therapy (ADT), which includes bilateral orchiectomy or medical castration with gonadotropin-releasing hormone agonists/antagonists

can provide palliation of symptoms and prolong survival [2]. More recently, based on findings from clinical trials [3-8], guidelines have established the addition of docetaxel or novel androgen receptor targeting agents (ARTAs; i.e., abiraterone acetate, enzalutamide, or apalutamide) to ADT as the standard of care for those with metastatic castration-naive prostate cancer (mCNPC) [9].

Although the long-term follow-up of clinical trials confirmed the benefit of adding docetaxel to ADT persisted regardless of metastatic burden [10], it is suggested that docetaxel might be under-used in clinical practice [11]. Use of docetaxel plus ADT in mCNPC setting is limited to patients with high-volume disease, provided they are willing and fit enough to receive cytotoxic chemotherapy. A major challenge with docetaxel is balancing the toxicity with clinical benefit. Duration of first-line docetaxel is limited to 4 to 6 months [3,4]. Therefore, there is a growing interest in switch maintenance therapy as a strategy for prolonging the benefit with first-line docetaxel while minimizing toxicity. In phase III trials involving first-line enzalutamide in mCNPC (ENZAMET and ARCHES) [6,7], prior treatment with docetaxel was permitted. Based on these considerations, from Oct 2022, we adopted a maintenance therapy with enzalutamide following 6 to 8 cycles of docetaxel as an institutional standard regimen for patients with high-volume, high-risk mCNPC. The present study was conducted to evaluate the feasibility of the regimen in anticipation of initiating a prospective, formal phase II study.

MATERIALS AND METHODS

We retrospectively collected and reviewed the medical records of 38 men with mCNPC who did not have disease progression with first-line ADT plus 6 to 8 cycles of docetaxel between Oct 2022 and Oct 2023. Enrolled patients had histologically confirmed prostate adenocarcinoma, documented metastatic disease before the receipt of ADT and first-line docetaxel for high-volume disease, no disease progression (i.e., no prostate-specific antigen [PSA] elevation and no evidence of progression on imaging studies) after 6 to 8 cycles of docetaxel chemotherapy, an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and acceptable major organ functions to receive enzalutamide. High-volume disease was defined as bone metastases beyond the axial skeleton and/or visceral involvement, regardless of PSA level. The choice of first-line docetaxel was determined by a multidisciplinary urologic oncology team composed of urologists, radiologists, pathologists, radiation and medical oncologists.

Patients and initial tumor characteristics, docetaxel treatment duration, intervening therapies, and clinical outcomes were recorded. Analytical data with potential prognostic value, PSA decline and time to PSA progression were collected for both first-line docetaxel and maintenance enzalutamide treatments. First-line treatment consisted of docetaxel 20–25 mg/m^2/week biweekly or tri-weekly regimen. Oral prednisone was given at a dose of 5 mg twice daily. After 6 to 8 cycles of docetaxel, clinical response was evaluated with PSA level, computed tomography scans, bone scans, or by the same tests that were initially used to stage the tumor. Patients without evidence of disease progression were eligible to switch to maintenance enzalutamide 160 mg orally per day. At the same time, patient who had not undergone surgical castration were required to continue ADT. The adverse events were recorded and graded according to the National Cancer Institute criteria (NCI-CTCAE). Endpoints of the present retrospective study included the PSA and radiologic responses, and safety during maintenance enzalutamide. PSA response and progression were defined as a >50% decline from baseline, and as an increase >25% and >2 ng/mL, respectively. Radiologic response and progression were evaluation according to the PCWG (Prostate Cancer Clinical Trials Working Group 2) criteria [12]: if a patient had no measurable lesions other than bone metastases, then the response was only classified as stable disease or disease progression. All statistical analyses were performed using R for Windows v2.11.1 (https://www.r-project.org).

RESULTS

The baseline patient characteristics and outcomes relating to prior docetaxel therapy are listed in Table 1. The duration of first-line docetaxel was 2.8 months (range, 2.7–5.0 months). All 38 patients had a PSA response with docetaxel, and radiologic responses were seen in 21 patients (58%). With ADT plus docetaxel, their PSA value was decreased

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Table 1. Baseline patient characteristics and outcome of first-line docetaxel (N=38)

Characteristic	Value
Age (yr)	68 (46–82)
Gleason score	9 (7–10)
7 or 8	18 (47)
9 or 10	20 (53)
Prior treatment to primary tumor	
Prostatectomy	5 (13)
Radiotherapy	2 (5)
PSA (ng/mL)	
Prior to ADT	222.0 (3.3–10,000.0)
Prior to docetaxel	147.0 (0.2–4,580.0)
Prior to enzalutamide	3.2 (0.01–258.0)
Performance status	
No symptoms	20 (53)
Symptomatic	18 (47)
Metastatic sites	
Bone	35 (92)
Lymph nodes	28 (74)
Lung	8 (21)
Liver	1 (3)
Treatment duration of first-line docetaxel (mo)	2.8 (2.7–5.0)

Values are presented as median (range) or number (%).
PSA, prostate-specific antigen; ADT, androgen deprivation therapy.

Table 2. Maximum grade adverse events per patient

Adverse event	Grade 1	Grade 2
Anemia	19 (50)	4 (11)
Fatigue	20 (53)	4 (11)
Pain	10 (26)	2 (8)
Nail changes	8 (21)	0 (0)
Sensory neuropathy	8 (21)	0 (0)
Anorexia	15 (40)	0 (0)
Nausea	4 (11)	0 (0)
Stomatitis	4 (11)	0 (0)
Edema	11 (29)	0 (0)
Urinary tract symptoms	16 (42)	1 (3)

Values are presented as number (%).

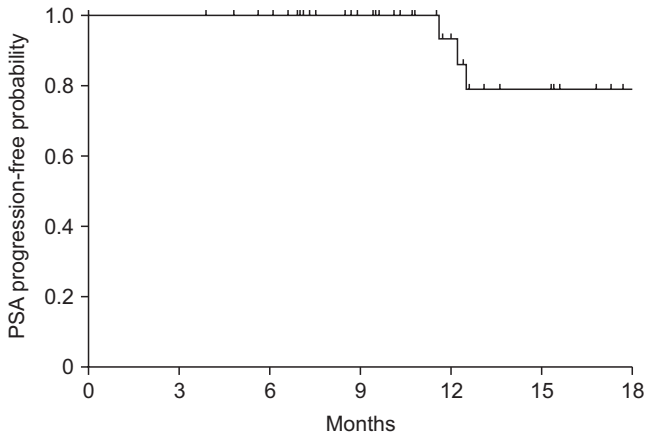

Fig. 1. Kaplan-Meier curve for time to prostate-specific antigen (PSA) progression.

from a median of 222.0 ng/mL (range, 3.3–10,000 ng/mL) to 3.2 ng/mL (range, 0.01–258.0 ng/mL). Most patients had metastases confined to bone and/or lymph nodes. Nine patients (24%) had visceral metastases (lung and/or liver). At the start of enzalutamide, their median age was 68 years (range, 46–82 years) and 47% had symptomatic (i.e., ECOG performance status of 1) disease.

With a median follow-up duration of 10 months (95% confidence interval, 9–12), 27 patients (71%) were still receiving maintenance enzalutamide. The main reasons for discontinuation of enzalutamide included adverse events (prolonged fatigue of grade 1 or 2, n=6), disease progression (n=3) and financial burdens (n=2). Two patients received a subsequent anticancer therapy: rechallenge docetaxel (n=1) and cabazitaxel (n=1). Maintenance enzalutamide was generally well-tolerated: adverse events of any grade occurred in 34 patients (90%) (Table 2) but none of the adverse events were grade 3 or higher. Two patients discontinued enzalutamide due to prolonged grade 1 or 2 fatigue but they are on ADT alone without evidence of disease progression. Eight patients (21%) demonstrated PSA response, and there was no radiologic response during enzalutamide therapy. PSA and/or radiologic progression was noted in 3 patients, thereby 93% were PSA progression-free at 12 months (Fig. 1).

DISCUSSION

The present study shows that maintenance therapy with enzalutamide is a feasible treatment option with potential therapeutic benefit for patients with high-volume mCNPC, progression-free following first-line docetaxel plus ADT. The finding is consistent with previous studies [6,7] in which the effect of enzalutamide for mCNPC was substantial regardless of early docetaxel treatment. Although the number of patients and follow-up duration are limited in the present study, baseline characteristics were generally consistent with those seen in these phase III studies, with the only exception that we included high-volume disease.

Although there are more than a few newly developed treatment options for mCNPC [5,8], it is not possible to replace ADT plus docetaxel, for high-volume disease in

particular. It is suggested that the high tumor burden is a poor prognostic factor, and patients are suffering from symptoms of metastatic disease. The addition of docetaxel to ADT is often preferred in patients with mCNPC based on a high-volume of disease and potentially the symptomatic burden [13]. On the other hand, considering most cases are diagnosed in elderly patients, hematologic toxicities of docetaxel can be a major hurdle for general application to mCNPC. In general, the safety profile of ARTAs seems more tolerable than docetaxel [13], although a direct comparison has never been made. Another difference between docetaxel and other ARTAs is the treatment duration. Patients with mCNPC receive ADT plus either <6 months of docetaxel or long-term (i.e., until progression or unacceptable adverse events) ARTAs [3,5-7]. The omission of excessive docetaxel cycles may avoid unnecessary cumulative toxicity which may sometimes be severe. Conversely, the majority of patients will progress after the cessation of first-line therapy. In our prospective phase II study involving first-line docetaxel plus ADT in mCNPC patients [14], the median PFS was 26 months.

Despite major advancements in prostate cancer treatment, mCNPC remains an incurable condition where the aim of treatment is to improve survival and to palliate symptoms. In general, systemic therapy in mCNPC should be focused on prolongation of time to PSA progression, as well as preserving the quality of life of the patients. Most patients are elderly, and usually a frail population with multiple comorbidities and poor tolerance to cytotoxic chemotherapy. Switch maintenance therapy with an active and tolerable treatment regimen in a well-selected patient population may have a beneficial effect on quality of life, as a direct effect of the improvement in clinical outcome. The major limitation of this study is its retrospective, noncomparative design. Patients received maintenance enzalutamide following first-line docetaxel at the discretion of the treating medical oncologist. As a result, it may be that clinical judgment withheld the use of cytotoxic chemotherapy from patients at high risk of adverse events or those with poor performance status. The definition of high-volume disease was not well-defined but judged by treating physicians. In general, guidelines included the presence of extensive bone metastases and/or visceral disease as a predictor for poor prognosis [9,15]. Patients included men with newly diagnosed metastatic disease and a small proportion of patients with recurrent disease. It seems unlikely to look for statistically different results in patients with recurrent disease, as the estimates of the effect of docetaxel were consistent with that seen in the whole population in previous trials [3,4]. In addition, the small number of patients led to biases and lack of significance of some considerations that otherwise would probably provide more consistent results. These questions are currently being addressed in our prospective study (ClinicalTrials.gov, NCT06015321; CRIS.nih.go.kr, KCT0009086), which aims to assess treatment outcomes with enzalutamide first-line maintenance, following 6 to 8 cycles of ADT plus docetaxel.

CONCLUSIONS

In conclusion, our data provide the evidence of feasibility and tolerable safety of enzalutamide first-line maintenance in patients with high-volume mCNPC, who were progression-free following ADT+docetaxel. The findings warrant further investigation and the prospective study is under way.

NOTES

- **Author Contribution:** Conceptualization: SHL, SWC, SHP; Data curation: JHJ, WS, MK, HHS, HGJ, BCJ, SIS, SSJ, SHP; Formal analysis: SHL, SWC; Methodology: SHP; Project administration: SHP; Visualization: SWC, SHP; Writing - original draft: SHL, SWC; Writing - review & editing: All authors.
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ORIGINAL ARTICLE

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Targeted Therapy Following Metastasectomy for Metastatic Renal Cell Carcinoma: A Systematic Review and Meta-analysis

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Purpose: The aim of this study was to assess the effects of tyrosine kinase inhibitors (TKIs) following metastasectomy in patients with metastatic renal cell carcinoma (mRCC).

Materials and Methods: A systematic search of multiple electronic databases was conducted. The inclusion criteria encompassed randomized clinical trials evaluating the use of TKIs after metastasectomy in mRCC patients. Study outcomes were relapse-free survival (RFS)/disease-free survival (DFS), overall survival (OS), and adverse events of TKIs.

Results: Two studies with 197 randomized participants that compared TKIs following metastasectomy versus metastasectomy alone were identified. According to these studies, TKIs following metastasectomy may result in little to no difference in RFS/DFS (hazard ratio [HR], 1.01; 95% confidence interval [CI], 0.65–1.57; I^2=29%; low-certainty evidence). TKIs after metastasectomy may slightly increase OS, but the CI crossed the line of no effect (HR, 0.80; 95% CI, 0.06–9.87; I^2=86%; low-certainty evidence). TKIs after metastasectomy likely resulted in a large increase in adverse events (risk ratio, 2.76; 95% CI: 1.65–4.62; I^2=not applicable; moderate-certainty evidence).

Conclusions: TKIs following metastasectomy did not improve RFS/DFS, but slightly improved OS. It is likely that TKIs following metastasectomy increase adverse events compared to surgery only. The certainty of evidence ranged from moderate (signaling confidence that the reported effect size is likely close to the true effect) to low (indicating that the true effect may be substantially different from the effect estimate). The findings of this study should help to inform future guidelines and clinical decision-making at the point of care.

Key Words: Renal cell carcinoma, Metastasectomy, Tyrosine kinase inhibitors, Recurrence, Survival

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- **Research Ethics:** Ethical approval was waived due to the nature of this study.
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

Metastatic renal cell carcinoma (mRCC) accounts for approximately 20%–30% of all kidney cancer cases; it has limited treatment options and is associated with a poor prognosis [1]. Surgical metastasectomy (i.e., the removal of metastatic lesions) has been considered a treatment option for carefully selected patients with limited metastases, aiming to prolong survival and improve the quality of life [2]. However, mRCC is characterized by a high rate of recurrence and metastasis, even after surgical intervention [3].

Tyrosine kinase inhibitors (TKIs) have transformed the treatment landscape for advanced RCC, demonstrating significant efficacy as both first-line and subsequent therapies [4]. Consequently, the use of TKIs following metastasectomy as an adjuvant therapy has been explored as a possible way to improve outcomes in patients with mRCC [5]. However, the optimal timing, duration, and patient selection for adjuvant TKI therapy after metastasectomy remain debatable.

Several clinical studies have investigated the role of TKIs after metastasectomy in mRCC patients, but the results are unclear. This systematic review and meta-analysis aimed to systematically evaluate the available evidence and quantify the impact of TKIs on relapse-free/disease-free survival (RFS/DFS), overall survival (OS), and adverse events of TKIs in mRCC patients.

MATERIALS AND METHODS

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines [6].

1. Literature Search

A comprehensive literature search was conducted using electronic databases, including MEDLINE (Ovid), Embase, Scopus, Web of Science, Cochrane Central Library, KoreaMed, and KMbase, to analyze relevant studies published up to October 6, 2021. The search strategy included keywords related to mRCC, metastasectomy, and TKIs (Supplementary Material). Clinical trial registries were also searched, including the United States National Institutes of Health Ongoing Trials Register Clinical Trials and the World Health Organization International Clinical Trials Registry Platform.

2. Study Selection and Outcomes

Two researchers (ECH and HMG) independently reviewed all studies that appeared to fit the inclusion criteria. All authors were involved in the final decision regarding the inclusion or exclusion of each study. Studies were considered eligible if they met the following criteria: (1) evaluated the use of TKIs after metastasectomy in patients with mRCC; (2) reported survival outcomes (OS and/or RFS/DFS); and (3) were randomized clinical trials (RCTs) published as original articles, abstracts, or brief communications. Prospective or retrospective cohort studies, case reports, and review articles were excluded. If patient data were reported more than once by the same institution, the most informative and recent article was included in the analysis. RFS/DFS was defined as the interval from metastasectomy date until the detection of tumor recurrence. OS extended from the metastasectomy date until death from any cause. Adverse events during TKI therapy were recorded.

3. Data Extraction and Risk of Bias Assessment

For studies that fulfilled the inclusion criteria, 2 review authors (ECH and HMG) independently extracted the following information: (1) study characteristics, including the names of the authors, study region, and sample size; (2) treatment regimens, including TKI agents and dosages; and (3) survival data, including OS and RFS/DFS. The risk of bias for RCTs was assessed using the Cochrane Risk of bias tool [7]. When the 2 authors disagreed, a final consensus was decided on by a third author (JHJ).

4. Statistical Analysis

Using a random-effects model, pooled hazard ratios (HRs), relative risk (RR), and 95% confidence intervals (CIs) were calculated for RFS/PFS, OS, and adverse events. The HRs, RR, and 95% CIs were extracted directly from the articles. Heterogeneity among the studies was evaluated using the Cochran chi-square test and the Higgins I^2 statistic. A p-value

less than 0.10 was considered statistically significant for the Cochran chi-square test, and an I^2 greater than 50% indicated substantial heterogeneity among the studies. All statistical tests were 2-sided, and a p-value less than 0.05 indicated statistical significance. A meta-regression or subgroup analysis was not conducted and publication bias was not assessed since only 2 studies were available. All statistical tests were performed using Review Manager 5.4.1 software (Cochrane Collaboration, Copenhagen, Denmark).

5. Summary of Findings

The certainty of evidence (CoE) was rated on a per-outcome basis using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework, which considers 5 criteria related to internal validity (risk of bias, inconsistency, imprecision, and publication bias) and external validity (generalizability of the results) [8]. For each comparison, 2 review authors (ECH and HMG) independently rated the CoE for each outcome as "high," "moderate," "low," or "very low" using the GRADEpro software, and summary of findings tables were constructed. Discrepancies were resolved by consensus. For each comparison, these tables provided key information about the best estimate of relative and absolute effects for each outcome [9]. The GRADE guidance was used to describe the CoE and magnitude of the effect size [10].

RESULTS

1. Study Identification and Selection

The initial literature search found 2,117 potentially relevant studies. The systematic review process is shown in the PRISMA flowchart (Fig. 1). Seventeen studies did not meet the inclusion criteria or were irrelevant to the review question. Ultimately, 2 studies met the inclusion criteria and were included in the meta-analysis, comprising 197 RCC patients [11,12].

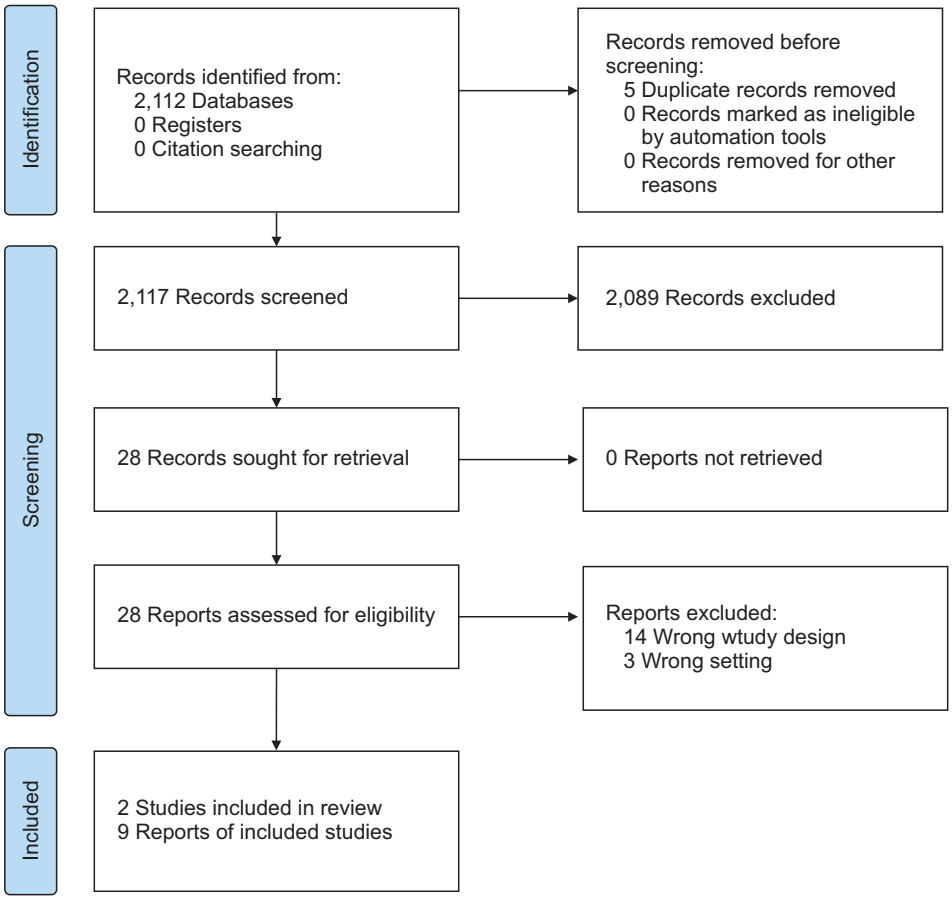

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

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2. Study Characteristics

All randomized patients in the included studies underwent metastasectomy, with or without adjuvant therapy. The studies were performed in the United States [11] and Italy [12]. One study compared pazopanib after metastasectomy to no additional treatment after metastasectomy [11], and the other study compared sorafenib after metastasectomy with metastasectomy only [12]. In the former study, reported as an abstract, the demographic characteristics of the patients were not ascertainable [11]. In the latter study, there was a single site of metastasis in 81% (n=26) of the patients in the sorafenib arm and 80% (n=29) in the observation arm. The lung was the most common metastatic site (27%, n=15), followed by the adrenal gland (22%, n=12) in both arms. In patients with multiple metastatic sites, the lung with other sites were the most common sites, and all included participants had no residual lesions following metastasectomy [12]. Data on OS and RFS/DFS were available in the 2 studies [11,12], but adverse events were only available in 1 study [12]. Table 1 provides additional details of the included studies [11,12].

3. Risk of Bias of the Included Studies

One RCT was only an abstract; therefore, all domains were rated as having an unclear risk of bias [11]. The study by Mennitto et al. [12] had a high risk of performance bias and an unclear risk of detection bias since this study was open-label. The risk of bias summary of the included studies is summarized in Fig. 2.

4. Effect of Intervention

1) Relapse-free survival/disease-free survival

TKIs after metastasectomy may result in little to no difference in RFS/DFS compared to metastasectomy only (HR, 1.01; 95% CI, 0.65–1.57; I^2=29%; 2 studies [11,12]; low-certainty evidence) (Table 2, Fig. 3).

2) Overall survival

TKIs after metastasectomy may increase OS slightly compared to metastasectomy only, but the CI crossed the line of no effect (HR, 0.80; 95% CI, 0.06–9.87; I^2=86%; 2 studies

Table 1. Included studies characteristics

Study cohort	Year	Study region	Research time	Follow-up (mo)	Population	Treatment	Patients characteristics
E2810 [11] abstract only	2019	Probably US	2012–2017	Median (range): 30 (0.4–66.5)	Patients with no evidence of disease after metastasectomy for metastatic renal cell carcinoma	Metastasectomy + pazopanib (800 mg daily) vs. metastasectomy + placebo	NA
Mennitto et al. [12]	2021	Italy	2012–2017	Median (IQR): 42 (31–58)	Patients with no evidence of disease after metastasectomy for metastatic renal cell carcinoma	Metastasectomy + sorafenib vs. metastasectomy only	Sorafenib arm n=32 (%) Age (yr), median (range): 65 (44–76) Sex: male, 20 (62); female, 12 (38) ECOG performance status: 0, 27 (84); 1, 5 (16) Histology, clear cell: 32 (100) Fuhrman grade: high (grade 3 or 4), 15 (47); low (grade 1 or 2), 15 (47) Missing: 2 (6) Disease-free interval between nephrectomy and metastasectomy (mo): ≤12, 9 (28); >12, 23 (72) Observation arm n=36 (%) Age (yr), median (range): 59 (45–80) Sex: male, 27 (75); female, 9 (25) ECOG performance status: 0, 33 (92); 1, 3 (8) Histology, clear cell: 36 (100) Fuhrman grade: high (grade 3 or 4), 22 (61); low (grade 1 or 2), 14 (39) Missing: 0 Disease-free interval between nephrectomy and metastasectomy (mo): ≤12, 15 (42); >12, 21 (58)

NA, not available; IQR, interquartile range; ECOG, Eastern Cooperative Oncology Group.

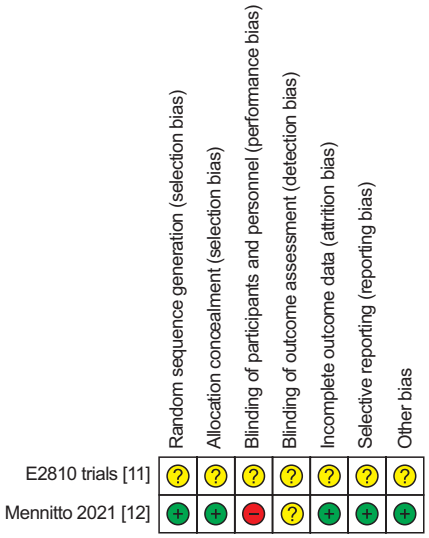

Fig. 2. Risk of bias summary for randomized clinical trials, review authors' judgments about each risk of bias item for each included study

[11,12]; low-certainty evidence) (Table 2, Fig. 3).

3) Adverse events

TKIs after metastasectomy likely resulted in a large increase in adverse events compared to metastasectomy only (risk ratio, 2.76; 95% CI, 1.65–4.62; I^2=not applicable; one study [12]; moderate-certainty evidence) (Table 2, Fig. 3).

DISCUSSION

This meta-analysis provides evidence against the use of TKIs as an adjuvant therapy after metastasectomy in patients with mRCC. These findings show no significant improvement in RFS/DFS with the addition of TKIs to surgery. To some extent, these results align with previous studies demonstrating the efficacy of upfront cytonephrectomy in selected patients with advanced mRCC [13].

Table 2. Metastasectomy after tyrosine kinase inhibitor compared to metastasectomy for metastatic renal cell carcinoma

Outcomes	No. of participants (studies)	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Plain language summary
				Risk with metastasectomy	Risk difference with metastasectomy after tyrosine kinase inhibitor	
Relapse-free/disease-free survival MCID: 5% relevant absolute risk difference	197 (2 RCTs)	⊕⊕◯◯: Low[a,b]	HR 1.01 (0.65–1.57)	626 per 1,000	3 fewer per 1,000 (147 fewer to 112 more)	Metastasectomy after tyrosine kinase inhibitor may result in little to no difference in disease-free survival compared to metastasectomy.
Overall survival MCID: 2% relevant absolute risk difference	197 (2 RCTs)	⊕⊕◯◯: Low[a,c,d]	HR 0.80 (0.06–9.87)	111 per 1,000	61 more per 1,000 (111 fewer to 765 more)	Metastasectomy after tyrosine kinase inhibitor may increase overall survival slightly compared to metastasectomy, but the confidence interval crossed the line of no effect.
Adverse events follow-up: median, 42 months MCID: 5% relevant absolute risk difference	68 (1 RCT)	⊕⊕⊕◯: Moderate[a]	RR 2.76 (1.62–4.62)	306 per 1,000	538 more per 1,000 (189 more to 1106 more)	Metastasectomy after tyrosine kinase inhibitor likely results in a large increase in adverse events compared to metastasectomy

Patient or population: Patients with metastatic renal cell carcinoma; Setting: likely outpatient; Intervention: Metastasectomy after tyrosine kinase inhibitor; Comparison: Metastasectomy.

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

GRADE, Grading of Recommendations Assessment, Development, and Evaluation; CI, confidence interval; MCID, minimal clinical important difference; RCT, randomized controlled trial; HR, hazard ratio; RR, risk ratio.

GRADE Working Group grades of evidence—high certainty: we are very confident that the true effect lies close to that of the estimate of the effect; moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different;
low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a]Downgrade by one level for risk of bias: High risk of performance bias and unclear risk of detection bias. [b]Downgrade by one level for imprecision: confidence interval crosses assumed clinical important threshold. [c]Downgrade by one level for inconsistency: substantial unexplained heterogeneity I^2=86%. [d]We did not rate down for imprecision because wide confidence interval results from inconsistency.

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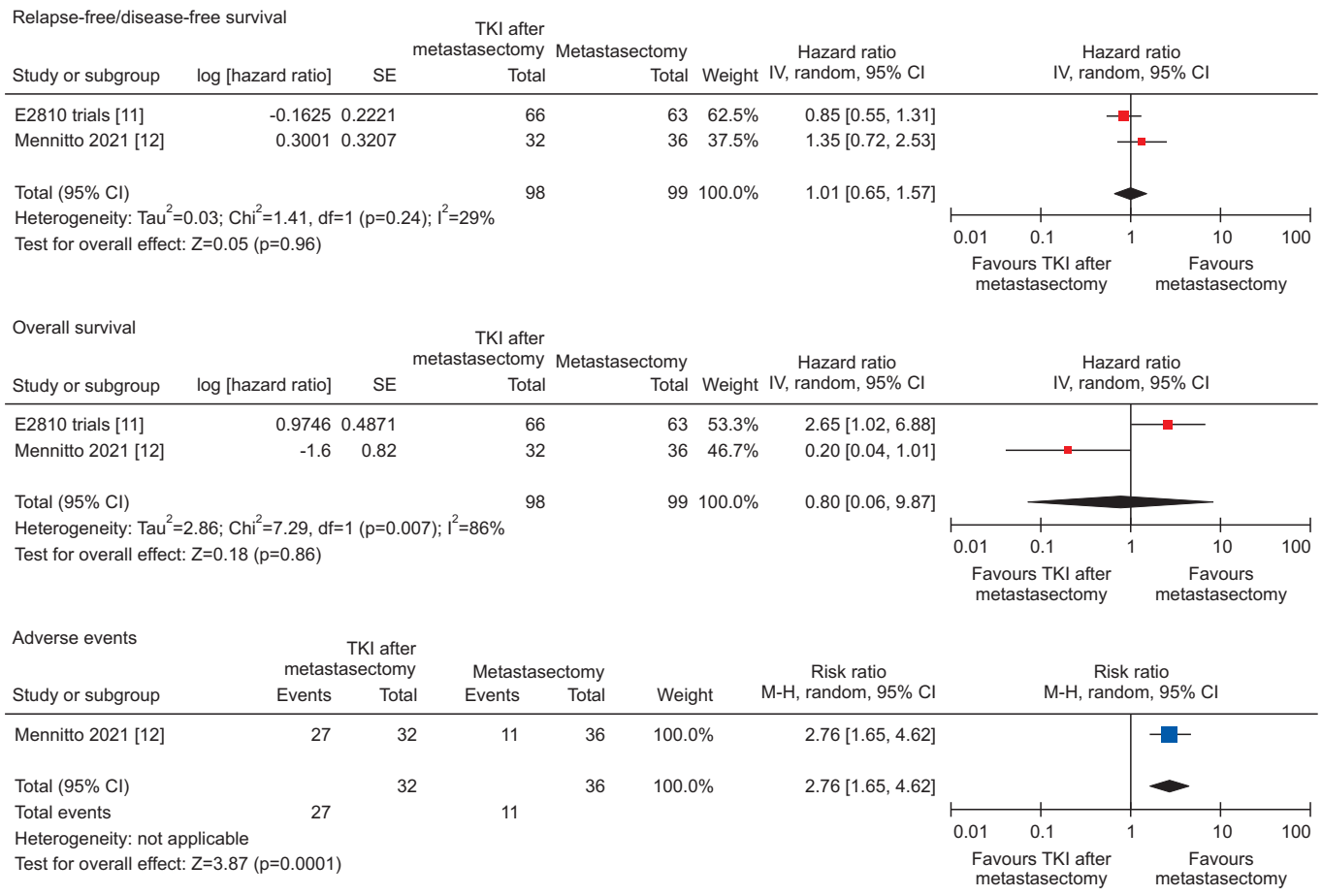

Fig. 3. Forest plots for relapse-free/disease-free survival, overall survival, and adverse events. TKI, tyrosine kinase inhibitor; SE, standard error; IV, inverse variance; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel.

Like other cancers, RCC is a heterogeneous disease with various histopathological subtypes, molecular phenotypes, and clinical features. Tumor biology determines the response to targeted therapies (TTs), and a remission period after the beginning of a TT is often followed by disease progression as tumors adapt and utilize alternative molecular pathways. This clinical pattern of tumor behavior may be explained by the significant genetic heterogeneity that exists between regions of the same primary tumor or between the primary tumor and metastatic lesion [14]. Alterations in the mammalian target of rapamycin pathway (SETD2, PTEN, and KDM5C) have been identified in different metastatic lesions within the same patient. In addition, Callea et al. [15] showed discordance in programmed cell death protein 1 expression between primary clear cell RCCs and metastatic sites in approximately 20% of patients. Various characteristics of the tumor phenotype and microenvironment play an important role in the progression and development of metastasis. In RCC, tumor progression and metastasis have been linked to the upregulation of VEGRF, MET, and AXL [14]. Therefore, developing a precision oncological approach deriving from molecular profiling of an individual's tumor may allow for personalized therapeutic targets. This approach may also identify patients more likely to benefit from metastasectomy.

TKIs targeting angiogenesis through the inhibition of vascular endothelial growth factor receptor (VEGFR) were associated with substantial response rates and improved survival, thus transforming the prognosis of mRCC [16]. However, most patients eventually developed drug resistance and disease progression while on therapy, including in the adjuvant setting after nephrectomy [17-19]. The biological rationale related to the failure of adjuvant TKI treatment remains unclear. It is possible that the differential TKI inhibitor activity of these drugs, as well as discrepancies in trial inclusion criteria, might have influenced the conflicting results observed in the S-TRAC [20] and ASSURE trials [21].

In the light of the failure of the ASSURE trial, we could speculate on the possible mechanisms of action of sunitinib or sorafenib in the biological scenario of micrometastatic residual disease; hypothetical possibilities could include a limited weight of angiogenesis-driven tumor growth, decreasing the sensitivity to VEGF/VEGFR inhibition, or a limited or even bad impact on immune response of sunitinib or sorafenib [12,22,23]. However, further studies are needed to clarify the biological pathways underlying these results.

The European Association of Urology (EAU) guidelines on managing mRCC strongly recommend not offering TKI treatment to mRCC patients with no evidence of disease (NED) after metastasectomy [24]. This recommendation is driven by the same trial results [11,12] that we meta-analyzed. Based on the recommendation of the EAU guidelines and the results of our meta-analysis, we conclude that TKI therapy provides no survival benefit to mRCC patients with NED after metastasectomy.

Recently, immune checkpoint inhibitors (ICIs), which target tumor or immune cell surface receptors triggering immune tolerance, have been shown to be effective in both pretreated and treatment-naïve patients with mRCC [19]. The randomized, phase 3 KEYNOTE-564 study was designed to investigate adjuvant pembrolizumab monotherapy (novel ICI) versus placebo after nephrectomy for participants with high-risk localized RCC or complete metastasectomy for mRCC patients [25]. In an updated analysis after 30 months of follow-up, subgroup analyses showed the benefit of adjuvant pembrolizumab irrespective of the disease risk category, in particular, metastatic patients after metastasectomy (DFS: HR, 0.28; 95% CI, 0.12–0.66). However, only 6% of patients were included in the experimental and placebo arm, and the results should be interpreted cautiously [26]. Another adjuvant ICI study with the PD-L1 inhibitor atezolizumab (IMmotion010) also included a complete metastasectomy subgroup, but showed no DFS advantage [27], contradicting the KEYNOTE-564 study. Patients who have undergone a successful nephrectomy or complete metastasectomy are considered to be disease-free but remain at a high risk of recurrence or mortality within 5 years after surgery in the absence of suitable adjuvant options [26,27]. Therefore, an optimal biomarker study to find suitable patients who respond to adjuvant therapy is needed.

This study has several limitations. First, the enrolled studies and sample sizes are too small to draw definitive conclusions. Second, the follow-up durations varied, and the TKIs differed (pazopanib and sorafenib) among the studies. Despite these limitations, to our knowledge, this is the first systematic review conducted with a rigorous methodology using the GRADE approach.

CONCLUSIONS

TKIs following metastasectomy did not improve RFS/DFS, but slightly improved OS. Furthermore, TKIs following metastasectomy increased adverse events compared with surgery only. The CoE ranged from moderate (signaling confidence that the reported effect size is likely close to the true effect) to low (indicating that the true effect may differ substantially from the estimated effect). The findings of this study should help to inform future guidelines and clinical decision-making at the point of care.

NOTES

- **Supplementary Material:** Supplementary material can be found via https://doi.org/10.22465/juo.244600140007.
- **Author Contribution:** Conceptualization: ECH, DK, SIK; Data curation: HMG, MHK; Formal analysis: ECH, HMG; Funding: ECH; Methodology: JHJ, MAH; Writing original draft: HMG; Review & Editing: SHL, IGJ, SIJ; Supervision: DK.
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ORIGINAL ARTICLE

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Global Renal Cell Carcinoma Research Trends Over 30 Years: A PRISMA-Compliant Bibliometric Analysis

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Purpose: Renal cell carcinoma (RCC) is a relatively common malignancy of the urinary tract. Over the past few decades, methodologies for diagnosing and managing patients with RCC have shown various developmental stages. This study was designed to provide insights into RCC research trends over that period.

Materials and Methods: To understand RCC research trends over the past 30 years, we conducted a bibliometric analysis, an appropriate method for evaluating scholarly output. Data were acquired by searching the Web of Science for articles published between 1991 and 2020. Bibliometric analysis and VOSviewer were used to visualize and statistically analyze the research trends.

Results: A total of 18,172 articles were identified. The most productive country was the United States (n=4,461, 26.5%), followed by China (n=3,503, 19.9%), and Japan (n=1,950, 11.9%). During keyword analysis, 3 clusters were identified, relating to gene expression, surgical outcomes, and immunotherapy. Over the last 10 years, research has mostly focused on emerging immunotherapy-related drugs.

Conclusions: Our bibliometric analysis has explained the characteristics of RCC research trends over the past 30 years.

Key Words: Kidney neoplasms, Renal cell carcinoma, Bibliometrics, Trend analysis

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- **Research Ethics:** As this study was a bibliometric analysis, ethical approval was not required.
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

Renal cell carcinoma (RCC) is a relatively common malignancy worldwide, accounting for 3%–5% of all oncological diagnoses [1]. Furthermore, its incidence has been increasing by 2% a year over the last 2 decades [2]. RCC is the most common form of solid lesion in the kidneys, with a rate of up to 85% [1]. It is more common in men than women, with an average age at diagnosis of 64 years [3]. These developments in diagnostic trends are mainly due to the use of noninvasive abdominal imaging procedures, such as computed tomography, ultrasonography, and magnetic resonance imaging, which detect incidental renal lesions [4]. Given an increase in early-stage, low-grade diagnoses, surgical treatment for RCC has shifted from radical to partial nephrectomy [5]. Furthermore, over the past 20 years,

medical treatment for advanced RCC transitioned from a nonspecific immune approach (cytokines) to targeted therapy and now on to novel immunotherapeutic agents [6]. Some antiangiogenic agents have shown improved clinical outcomes and have thus replaced cytokine therapy [7]. Recently, immunotherapeutic agents have attracted attention for the treatment of metastatic RCC. Against this background, the foci of RCC-related research have continually changed over time, including aspects such as diagnosis, surgery, and nonsurgical treatment options.

In examining research publication trends in relation to specific diseases, bibliometric analysis can be used to identify aspects such as top authors, journals, and countries, as well as topic changes [8]. Over the past 10 years, diverse bibliometric analyses have been conducted in numerous fields owing to an increase in the number of publications for analysis as well as the availability of user-friendly analytic computer programs. Some authors have applied a bibliometric approach to urology studies [9-11]. These trend analyses have focused on localized RCC treatments, but the overall trends of RCC research have not been investigated using a bibliometric approach [12]. To fill this gap, this study aimed to analyze the characteristics and trends of RCC research over the last 30 years based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for bibliometric analyses.

MATERIALS AND METHODS

As this study was a bibliometric analysis, ethical approval was not required. The study was conducted in accordance with the PRISMA guidelines [13].

1. Source of Research Data

We searched the Thomson Reuters Web of Science (Clarivate Analytics, Philadelphia, PA, USA) database from January 1, 1991, to December 31, 2020. The terms used in the search were "clear-cell cancer," "kidney cancer," "renal cell carcinoma," and "RCC." A total of 34,743 articles published between 1991 and 2020 were identified. Among these, we excluded editorials, reviews, comments, perspectives, and letters, as well as articles not published in English. Finally, 18,172 articles were included in the analysis (Fig. 1).

2. Bibliometric Analysis

Data analysis was performed using the Bibliometrix package in R 4.2.1 software (http://www.bibliometrix.org); the web-based application "Biblioshiny 4.0" was used to visualize the results. The following parameters were collected and analyzed: publication year, country of origin, corresponding author, citation number, publishing journal, title, abstract, and keywords.

VOSviewer (version 1.6.15; Leiden University, Leiden, The Netherlands) was used to evaluate the relationships between keywords and produce a keyword map [14]. Prior to VOSviewer analysis, the authors manually standardized the keywords included in the article titles or abstracts (because different representations of the same keyword can inaccurately increase the total number of keywords) [8]. Each node in the resulting map represents a keyword. Nodes with higher frequencies appear larger, and lines between nodes indicate keyword co-occurrence. Related keywords are grouped into clusters of the same color. An overlay visualization represents developments over time by calculating the average number of appearances per keyword and visualizing them on a network map to demonstrate trends in keyword appearance.

RESULTS

1. Number of Annual Publications

In the 2000s, the number of publications on RCC steadily increased; by 2007, it had increased markedly to more than 500 articles per year. Subsequently, the number of RCC-related articles continued to rise, exceeding 1, 000 in 2015 and reaching 2,000 by 2020 (Fig. 2). Therefore, the doubling period of RCC-related publications gradually shortened during the analyzed period.

2. Contribution Trends of Countries and Authors

The articles were categorized according to their country of publication. The United States published the largest

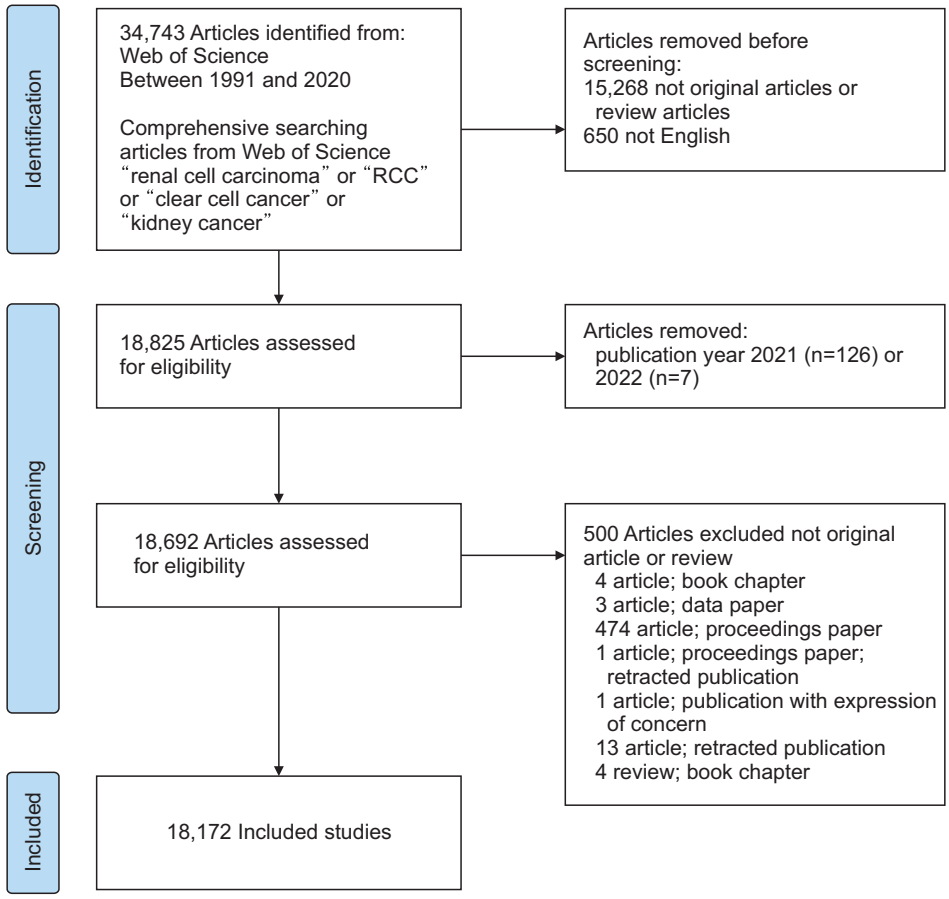

Fig. 1. Data acquisition flowchart.

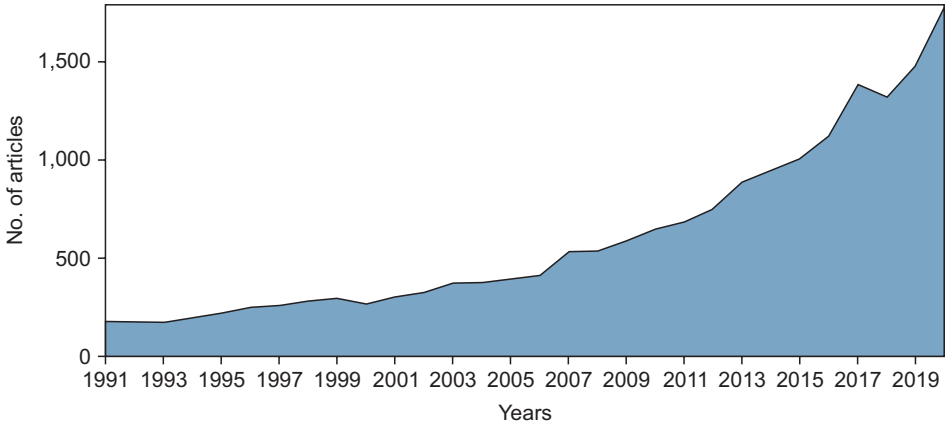

Fig. 2. The annual numbers of published articles on renal cell carcinoma.

number of papers (4,661), accounting for 26.5% of the total (Table 1, Fig. 3A). China and Japan published 3,503 (19.9%) and 1,950 articles (11.1%), respectively. We also assessed collaboration tendencies among countries by measuring domestic/international publication ratios. Asian countries such as China, Japan, and Turkey tended to publish articles without international collaboration. In contrast, international publication ratios were higher than 0.10 in Western countries (Canada, 0.44; United Kingdom, 0.31; France, 0.26; USA, 0.18). The characteristics of international collaborations are summarized in Fig. 3B. Looking at the United States' collaborations, the width of ties (i.e., number of connections) with Canada, China, and Japan are very thick; significant collaborations also occurred with Germany, Italy, and France.

The 10 most productive authors participating in RCC studies are summarized in Table 2. Motzer, who works for the Memorial Sloan-Kettering Cancer Center in New York,

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Table 1. Top 10 countries by corresponding author and domestic vs. international collaboration

Rank	Country	No. of articles	Frequency	Domestic studies	International studies	Domestic-international ratio
1	US	4,661	0.2648	3,818	843	0.1809
2	China	3,503	0.199	3,228	275	0.0785
3	Japan	1,950	0.1108	1,832	118	0.0605
4	Germany	1,144	0.065	912	232	0.2028
5	Italy	788	0.0448	615	173	0.2195
6	Korea	640	0.0364	589	51	0.0797
7	France	593	0.0337	437	156	0.2631
8	Canada	454	0.0258	250	204	0.4493
9	UK	444	0.0252	308	136	0.3063
10	Turkey	338	0.0192	329	9	0.0266

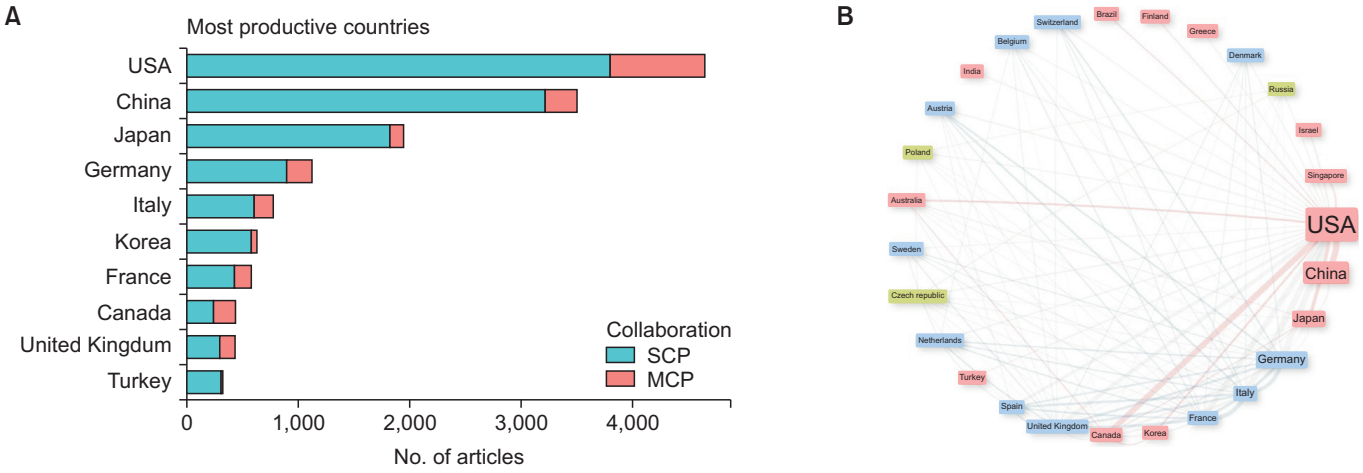

Fig. 3. The distribution of authors' countries and collaborations. (A) The 10 most productive countries according to corresponding author. (B) Specific relationships forming international collaborations. SCP, single-country publication; MCP, multicountry publication. Assigning colors based on the frequency of collaboration or patterns of collaboration in specific research fields can visually compare different relationship formation patterns between countries within the network.

Table 2. Top 10 most prolific authors

Rank	First author	No. of publications	H-index	G-index	M-index (first year)	Local citations
1	Motzer RJ	238	85	221	2.741935	49,072
2	Escudier B	230	75	188	2.5	35,745
3	Rini BI	226	78	168	3.12	28,979
4	Choueiri TK	225	66	161	3.882353	26,580
5	Leibovich BC	151	53	101	2.65	10,864
6	Wood CG	148	49	95	2.45	9,741
7	Figlin RA	141	60	141	1.875	22,970
8	Ljungberg B	141	47	98	1.46875	10,065
9	Cheville JC	139	56	119	1.931034	14,337
10	Porta C	134	38	105	1.461538	11,351

has published the largest number of articles (238 articles, 49,072 citations). Following Motzer, Escudier (n=230), Rini (n=226), and Choueiri (n=225) each published more than 200 articles. We also conducted a time series analysis of the publication status of the top 10 most prolific authors (Fig. 4A). Five authors—Figlin, Ljungberg, Motzer, Escudier, and Cheville—have continuously published articles for almost 30 years. The most active authors in the last 5 years were Choueiri, Escudier, Motzer, Rini, and Porta. Although Choueiri, Leibovich, and Wood only started publishing their research in the early 2000s, they were included in the list of the top 10 authors.

Citation networks indicate that Motzer and Escudier were strongly connected and made a central contribution to the

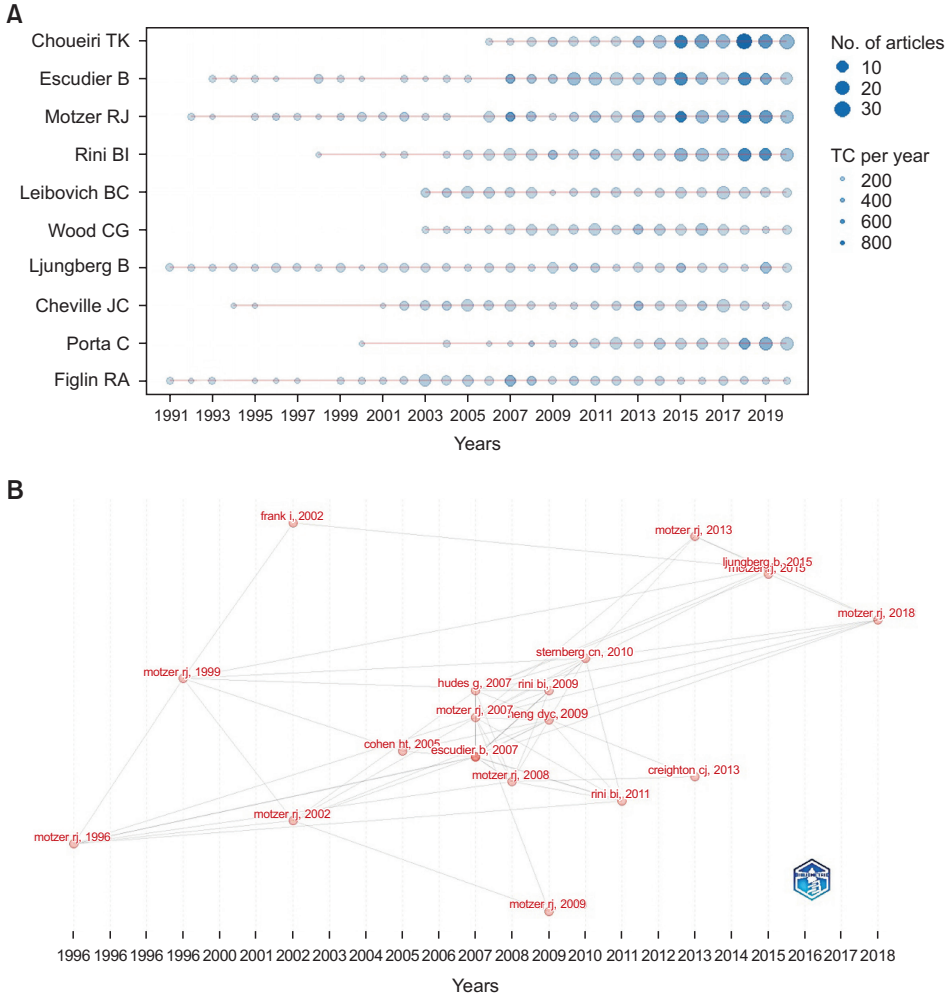

Fig. 4. Characteristics of articles published by top 10 authors. (A) Annual numbers of published articles and citations over time. (B) Historical direct citation network. TC, total citation.

Table 3. The most active journals in terms of publishing renal cell carcinoma-related research

Rank	Journal	No. of publications	IF[†]	5-years IF[†]	Total citations	H-index[‡]
1	*Journal of Urology*	702	7.450	6.413	39,631	100
2	*Urology*	429	2.649	2.564	12,611	54
3	*Clinical Genitourinary Cancer*	347	2.872	2.989	4,514	30
4	*Urologic Oncology: Seminars and Original Investigations*	346	3.498	3.491	4,544	31
5	*BJU International*	342	5.588	5.225	11,246	54
6	*European Urology*	317	20.096	21.259	22,613	79
7	*Cancer*	261	6.860	7.921	15,205	66
8	*International Journal of Urology*	261	3.369	2.986	3,762	29
9	*Oncotarget*[§]	259	5.168	N/A	5,141	34
10	*Clinical Cancer Research*	239	12.531	12.836	18,083	78

[†]Impact factor (IF) of each journal was obtained from Journal Citation Reports. [‡]The H-index is defined as the maximum value of h, such that a given journal has published h papers cited at least once. [§]The IF of *Oncotarget* was obtained from 2016 data because it was deselected from the Science Citation Index-Expanded in 2018.

publication of RCC articles (Fig. 4B). The figure shows that this network of prominent authors—which was most active during 2007–2009—began with an article published by Motzer in 1996. Looking at the chronological direct citation pattern, 4 articles published in 2007 showed a tendency to be widely cited, suggesting they influenced later articles.

3. Journal and Citation Trends

The top 10 journals for RCC research (i.e., most publications) are listed in Table 3. The *Journal of Urology* published the most articles (n=702), followed by *Urology* (n=429), and *Clinical Genitourinary Cancer* (n=347). Although *European*

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Table 4. Top 10 most cited publications related to renal cell carcinoma

Rank	First author	Title	Citations
1	Motzer RJ	Sunitinib versus interferon alfa in metastatic renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):115-24.	1,854
2	Escudier B	Sorafenib in advanced clear-cell renal-cell carcinoma. N Engl J Med. 2007 Jan 11;356(2):125-34.	1,341
3	Fuhrman SA	Prognostic significance of morphologic parameters in renal cell carcinoma. Am J Surg Pathol. 1982 Oct;6(7):655-63.	1,322
4	Hudes G	Temsirolimus, interferon alfa, or both for advanced renal-cell carcinoma. N Engl J Med. 2007 May 31;356(22):2271-81.	1,154
5	Motzer RJ	Overall survival and updated results for sunitinib compared with interferon alfa in patients with metastatic renal cell carcinoma. J Clin Oncol. 2009 Aug 1;27(22):3584-90.	865
6	Motzer RJ	Efficacy of everolimus in advanced renal cell carcinoma: a double-blind, randomised, placebo-controlled phase III trial. Lancet. 2008 Aug 9;372(9637):449-56.	851
7	Sternberg CN	Pazopanib in locally advanced or metastatic renal cell carcinoma: results of a randomized phase III trial. J Clin Oncol. 2010 Feb 20;28(6):1061-8.	832
8	Motzer RJ	Nivolumab versus Everolimus in Advanced Renal-Cell Carcinoma. N Engl J Med. 2015 Nov 5;373(19):1803-13.	793
9	Motzer RJ	Renal-cell carcinoma. N Engl J Med. 1996 Sep 19;335(12):865-75.	785
10	Heng DY	Prognostic factors for overall survival in patients with metastatic renal cell carcinoma treated with vascular endothelial growth factor-targeted agents: results from a large, multicenter study. J Clin Oncol. 2009 Dec 1;27(34):5794-9.	782

Urology had the highest impact factor (5-year impact factor=21.259; Journal Citation Reports), its number of RCC publications was relatively small (n=317), ranking it in sixth place.

The most frequently cited articles are presented in Table 4. Among the top 10 most cited articles, the top 4 articles had more than 1,000 citations. Motzer was first author in 5 of the top 10 articles. The ranking demonstrates that interest in therapeutics for RCC has been high; 8 out of the top 10 papers were associated with targeted drugs and immuno-oncologic therapies, such as sunitinib, sorafenib, temsirolimus, everolimus, pazopanib, and nivolumab.

4. Trends of RCC-Related Keywords

The most frequently occurring keywords are listed in Table 5. Among analyzed articles, the keyword "cancer" appeared the most frequently. This was followed by "expression," "survival," and "interferon-alpha." The most frequent treatment drug was "sunitinib," which was mentioned 1,349 times. Excluding old immunotherapeutic agents such as "interferon-alpha" and "interleukin-2," "sorafenib" and "everolimus" appeared with high frequencies. This indicates that RCC research has focused on novel immunotherapeutic agents. Unexpectedly, the keyword analysis identified breast cancer as a frequently occurring keyword. This is probably due to similarities in gene expression and immunotherapy between breast cancer and kidney cancer. Among the keywords related to surgical approaches to RCC, radical nephrectomy appeared 864 times and was ranked in 8th place.

Table 5. List of the most frequently appearing keywords

Term	Frequency	Term	Frequency
Cancer	5,083	Protein	525
Expression	2,835	Breast cancer	523
Survival	2,647	Apoptosis	514
Interferon-alpha	1,665	Invasion	512
Tumors	1,645	Features	509
Sunitinib	1,349	Disease	505
Therapy	1,331	Everolimus	504
Radical nephrectomy	864	Risk	490
Kidney	808	Masses	488
Growth	800	Impact	472
Classification	733	Targeted therapy	471
Metastasis	732	Experience	469
Management	725	Immunotherapy	468
Gene	705	Diagnosis	459
Identification	684	Interleukin-2	457
Endothelial growth factor	678	Double-blind	449
Proliferation	671	Tumor-suppressor gene	436
Nephrectomy	639	Neoplasms	433
Progression	638	Mutations	427
Sorafenib	614	Prognosis	402
Activation	586	Angiogenesis	400
Kidney cancer	564	Prognostic factors	400
Efficacy	558	Outcomes	398
Trial	558	Surgery	396
Tumor	537	Gene expression	370

5. Co-occurrence Network Analysis

The co-occurrence network analysis between keywords is shown in Fig. 5A. Co-occurrence analysis aims to evaluate the relationships between core terms based on the number

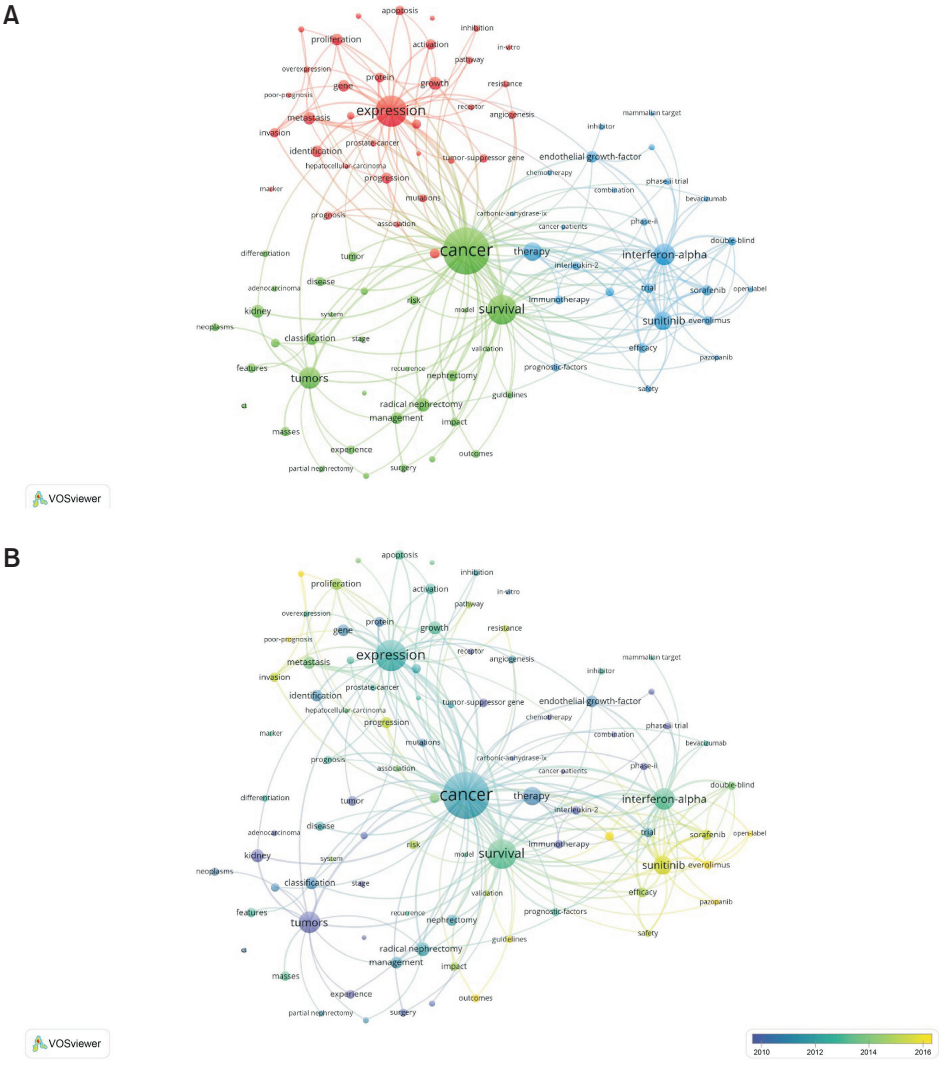

Fig. 5. A co-occurrence network of "keywords plus" from articles on renal cell carcinoma (RCC) from 1991 to 2020. (A) Clustering of keywords in the RCC field. (B) Average year of publication distribution of keywords (purple indicates earlier publication and yellow indicates more recent publication).

of articles in which they appear together. Circle sizes indicate the number of articles in which the terms were presented. We clustered the keywords into 3 major categories according to their correlation and frequency of appearance. Green clusters are related to surgical treatment, such as surgical outcomes, tumor stage, surgical procedures, and survival rates. The blue categories are associated with trends related to medical management. In this category, interferon-alpha and sunitinib had the largest circles. Interleukin-2, pazopanib, everolimus, bevacizumab, and sorafenib were associated with small circular nodes. Finally, the red clusters relate to gene and protein expression or suppression. Keywords with similar topics or meanings are grouped and represented with the same color. This helps visually identify specific thematic areas within the network. Time series analysis (Fig. 5B) showed that keywords related to surgical methods were more popular in the past, before research interest shifted to treatment drugs for advanced or metastatic RCC, such as immunotherapy and targeted therapy. This is likely to be related to the developmental history of drugs used to treat patients with RCC. Overlay visualization in the figure represents developments over time by demonstrating the network map of the trend topics according to the keywords. While the earliest nodes were painted with purple, the most recent ones were colored with yellow.

DISCUSSION

This study is the largest bibliometric analysis in the field of RCC, including 18,172 articles. We aimed to include all published articles that could be accessed online and included RCC-related keywords. Recently, 2 studies have analyzed

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RCC using a bibliometric approach [12,14]. However, these studies limited their investigation to publications on the surgical method of partial nephrectomy in patients with RCC. Hence, our analysis provides a broader overview of the RCC field. In relation to other urological cancers, many bibliometric analyses have been produced. For example, He et al. analyzed the top 100 articles on immunotherapy for urological cancer [15]. Mainwaring et al. [16] reviewed big data relating to more than 40,000 articles and reported the top manuscripts on bladder cancer. Similarly, Shen et al. [17] studied global research patterns on prostate cancer.

The number of RCC manuscripts has been steadily increasing over the past 3 decades, though this increase became much more pronounced after 2007; we suggest this can be explained as follows. In 2007, when the results of a phase III clinical trial related to sunitinib were announced, targeted therapy for metastatic RCC generated a huge amount of interest [18]. Furthermore, the therapeutic effects of sorafenib were first reported in 2007; oral sorafenib prolonged progression-free survival in patients with metastatic RCC [19]. Thus, the success of targeted therapy may have driven the increase in RCC articles since 2007 [20]. Although Xu et al. reported a research trend in the use of tyrosine kinase inhibitors for RCC from 2000 to 2022, they only demonstrated a trend toward focusing on immune checkpoint inhibitors [21]. Furthermore, the development of surgical techniques for the treatment of small RCC has contributed to the rapid growth of RCC-related studies. As laparoscopic and robot-assisted surgeries have become more popular, many studies have compared their surgical outcomes with those of conventional open surgery [22]. Additionally, as diagnostic technologies for small renal masses (SRMs) have developed, surgical skills for partial nephrectomy have also developed and begun to replace conventional radical nephrectomy.

Overall, RCC research can be categorized into surgical and drug treatments. Surgical excision is the gold standard treatment for nonmetastatic RCC, and various surgical techniques have been developed for this purpose. Specifically, trends in surgical strategies have changed as the detection rate of SRMs increased. Previously, all RCCs, including SRMs, were treated with aggressive surgery; however, the scope of partial nephrectomy has recently expanded. Furthermore, less invasive and conservative treatment modalities have emerged [23,24]. Among the most frequent keywords, those related to surgical methods were "radical nephrectomy" and "surgery." The keywords associated with prognosis were "survival," "progression," "efficacy," "risk," "prognosis," and "outcomes." Keywords such as "SRM," "active surveillance," "radiofrequency ablation," and "cryoablation" were not identified in the ranking list, because they primarily relate to recently emerging research. Hence, the number of articles on novel surgical techniques is relatively low, and the majority of research articles we examined relate to traditional surgical techniques.

Unlike other malignant epithelial tumors, RCC is highly resistant to cytotoxic chemotherapy. Despite their low efficacy, interleukin-2 and interferon-alpha were used to treat metastatic RCC until the early 2000s [25]. Targeted therapeutic agents, including sunitinib, pazopanib, temsirolimus, everolimus, and axitinib, have replaced cytokine therapy for metastatic RCC [26]. Recently, immunotherapeutic agents and combination strategies have been developed for metastatic RCC treatment [7]. Thus, this study successfully demonstrated the trends of changing therapeutic drugs over time. Considering that the latest drug treatment strategies are included among the top-ranked keywords, it can be seen that research on the latest drugs is being actively conducted. This is different to the trends in surgical method-related research.

In summary, the present study makes valuable contributions by analyzing big data on RCC. However, it has some limitations. Although our study reflects RCC-related research trends over the last 3 decades, it does not reflect physicians' decisions regarding the direction of diagnosis and treatment of individual RCC patients. Therapeutic determinations should be made considering not only the RCC size and location but also the patient's renal function, underlying diseases, and even sociodemographic characteristics such as religion or sex [27]. Because bibliometric analysis is a keyword-oriented analytical method, it cannot identify the overall contextual meaning of the identified articles. Since the articles included in the bibliometric analysis were very diverse, it is difficult to understand exactly why each keyword appeared in each article. Additionally, although some keywords had similar

meanings, they were recognized distinctly. To minimize the subjective intervention of researchers, technical improvements, such as contextual or semantic analyses, are required to clearly classify and cluster keywords. Finally, because data acquisition was performed only in relation to English-language articles, some excellent articles published in other languages were not included, leading to selection bias.

With respect to future research prospects, research on RCC is progressing toward the diagnosis and treatment of incidental SRMs. Surgical techniques have continuously improved toward minimally invasive surgeries, such as single-port surgery, small robot devices, flexible instruments, and ablative therapy. Researchers could conduct distinct trend analyses relating to these aspects to obtain more specific and suggestive research results. In advanced or metastatic RCC, various comparative studies of other novel antitumor drugs have been reported. The emerging research topic of publications regarding the treatment of RCC has been related to targeted therapy using vascular endothelial growth factor tyrosine kinase and immunotherapy with immune checkpoint inhibitors [28]. Additionally, various drugs based on targeted and immuno-oncological therapies have been used to treat RCC. Recently, targeted therapies for metastatic RCC have evolved into third-line therapies [29]. Targeted therapies have improved the survival rate of patients with metastatic RCC [30]. Although the number of articles regarding immuno-oncologic therapy in patients with metastatic RCC has a small range (approximately 10 years), a significant therapeutic outcome can be found when analyzing large-scale articles closely.

CONCLUSIONS

This is the largest bibliometric analysis to explain research trends in RCC; accordingly, it provides an overview of kidney cancer articles. Publications on RCC have increased over the last 30 years. Whether conducted domestically or as part of international collaborations, the United States made the largest contribution to kidney cancer research. After 2007, publishing rates markedly increased in response to the development of targeted therapy, immune checkpoint inhibitors, and less invasive minimal surgery. Overall, this bibliometric analysis of RCC provides an understanding of research trends; it may provide insights to practitioners with respect to counseling patients about their disease and treatment plans.

NOTES

• **Author Contribution:** Conceptualization: JHK; Data curation: JWH; Funding acquisition: JHK; Methodology: JWH; Visualization: JWH; Writing - original draft: JHK; Writing - review & editing: JHK

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ORIGINAL ARTICLE

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Prognostic Factors and Cancer-Specific Survival of Surgically Managed Renal Cell Carcinoma With Venous Thrombus: A 30-Year Experience at a Tertiary Referral Center

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Purpose: This study investigated the prognostic factors and cancer-specific survival (CSS) of patients who had renal cell carcinoma (RCC) with venous thrombus and underwent radical nephrectomy with thrombectomy (RNTx).

Materials and Methods: From January 1990 to December 2022, we retrospectively reviewed the medical records of patients diagnosed with RCC with venous thrombus who underwent RNTx at a single tertiary medical center. Univariate and multivariable Cox proportional hazard regression analyses were conducted to identify significant prognostic factors affecting CSS. A Kaplan-Meier model was used to calculate CSS rates at 1, 3, and 5 years after RNTx.

Results: We included 262 patients in the final analysis (median age, 59 years) with a median follow-up of 28 months. The 1-, 3-, and 5-year CSS rates were 84.1%, 62.5%, and 46.4%, respectively. Multivariable analysis revealed that pathologic T4 stage (hazard ratio [HR], 3.711; 95% confidence interval [CI], 1.599–8.611, p=0.002), pathologic N1 stage (HR, 2.371; 95% CI, 1.231–4.567; p=0.01), sarcomatoid differentiation (HR, 1.89; 95% CI, 1.027–3.477; p=0.041), and tumor necrosis (HR, 2.993; 95% CI, 1.132–7.914; p=0.027) were associated with CSS.

Conclusions: Approximately one-third of all RCC patients with venous thrombus remained disease-free, and half survived 5 years after RNTx. Sarcomatoid differentiation and the presence of tumor necrosis in pathology predicted poorer CSS outcomes in our study. Further retrospective studies are required to validate these findings.

Key Words: Renal cell carcinoma, Tumor thrombus, Thrombectomy, Survival analysis

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- **Research Ethics:** This study was approved by the Institutional Review Board of Asan Medical Center, and the requirement for informed consent from patients was waived due to the retrospective nature of the study (2023-1310).
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

Renal cell carcinoma (RCC) is the most common neoplasm in the kidney, accounting for almost 4% of all incident malignancies in adults [1]. In the United States, an estimated 79,000 patients were newly diagnosed with RCC in 2022,

among whom 13,920 died [1]. RCC often extends into the renal vein, forming a thrombus that can further progress into the inferior vena cava (IVC). A venous thrombus in the IVC was observed in approximately 10% of patients with RCC at the time of diagnosis [2].

Radical nephrectomy with thrombectomy (RNTx) is considered an effective treatment option for RCC with venous thrombus [3]. However, it is accompanied by surgical challenges, including the risk of massive bleeding, and the potential need for cardiopulmonary bypass in cases of high-level tumor thrombus [4]. Although the 5-year survival rates after surgical management exceeded 50%, the postoperative mortality rates also reached almost 50% [5].

Several studies have been conducted to identify perioperative and postoperative prognostic factors for RCC with venous thrombus or RNTx, including operation time, vascular resection margin, sarcomatoid differentiation, tumor necrosis, venous thrombus level, TNM stage, and the histologic type of RCC [6-8]; however, the findings remain highly debated.

In this study, we retrospectively reviewed the medical records of RCC patients with venous thrombus who underwent RNTx at a single tertiary referral medical center over 30 years. We aimed to identify prognostic factors for cancer-specific survival (CSS).

MATERIALS AND METHODS

1. Study Population

This retrospective study reviewed the medical records of patients diagnosed with RCC with venous thrombus who underwent RNTx at a single tertiary medical center between January 1990 and December 2022. This study was approved by the Institutional Review Board of Asan Medical Center, and the requirement for informed consent from patients was waived due to the retrospective nature of the study (2023-1310).

The parameters included age, sex, lateralization of tumor location, tumor size, level of venous thrombus, histologic subtype, TNM stage, Fuhrman nuclear grade, presence of sarcomatoid differentiation, presence of lymphovascular invasion, presence of tumor necrosis, presence of a positive renal vein resection margin, date of final follow-up, and CSS and overall survival (OS). Preoperative computed tomography (CT) or magnetic resonance imaging reports from radiologists were reviewed to determine the size of the tumor, as well as the presence and level of venous thrombus. These reports were manually reviewed again for accuracy. The pathologic report was examined to determine the histologic type, Fuhrman nuclear grade, presence of sarcomatoid differentiation, presence of lymphovascular invasion, presence of tumor necrosis, and presence of positive renal vein resection margin. The TNM stage was determined according to the 2017 American Joint Committee on Cancer (AJCC) TNM classification system [9]. The histologic subtype was categorized as clear cell RCC, papillary RCC, chromophobe RCC, and other types of RCC. The Fuhrman nuclear grade was categorized as grades 1 and 2, grade 3, and grade 4. The surgical method for RNTx included open RNTx, laparoscopic RNTx, and hand-assisted laparoscopic RNTx. Robot-assisted RNTx was not performed.

The venous thrombus level data were also collected and classified according to the Mayo classification system [10], as follows: level 0, venous thrombus is limited to the renal vein; level 1, venous thrombus extends into the IVC to no more than 2 cm above the renal vein; level 2, the venous thrombus extends into the IVC to more than 2 cm above the renal vein but below the hepatic vein; level 3, venous thrombus extends into the IVC to above the hepatic vein but below the diaphragm; level 4, the venous thrombus extends above the diaphragm or right atrium. CT images before RNTx were used to calculate the venous thrombus level.

2. Statistical Analyses

Continuous data are presented as the median with the interquartile range (IQR), and categorical data are presented as the number and percentage of patients. Univariate and multivariate Cox proportional hazard regression analyses were used to identify significant prognostic factors affecting CSS. The hazard ratio (HR) and 95% confidence interval (CI) were used for the results of the univariate and multivariate Cox proportional hazard regression. A Kaplan-Meier model was used to calculate CSS rates at 1, 3, and 5 years after RNTx. Statistical significance was set at $p<0.05$. All statistical

analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline Characteristics of the Study Population

A total of 262 patients who had RCC with venous thrombus were identified (Table 1). The median patient age was 59 years (IQR, 51–67 years) and comprised 80.15% (210 of 262) male and 19.85% (52 of 262) female patients. There were 110 right-sided tumors (41.98%) and 152 left-sided tumors (58.02%). The median tumor size was 9.5 cm (IQR, 7.5–11.6 cm). The histopathologic findings were reported as follows: clear cell RCC in 211 patients (80.53%), papillary RCC in 17 patients (6.49%), chromophobe RCC in 6 patients (2.29%), and other types of RCC in 28 patients (10.69%). Among them, 36 patients (13.74%) were staged as T4, 56 (21.37%) as N1, and 68 (25.95%) as M1. The venous thrombus was level 0 in 97 patients (37.02%), level 1 in 64 (24.43%), level 2 in 42 (16.03%), level 3 in 30 (11.45%), and level 4 in 29 (11.07%). The Fuhrman nuclear grade was grade 1 or 2 in 35 patients (13.36%), grade 3 in 108 (41.22%), and grade 4 in 115 (43.89%). Sarcomatoid differentiation was present in 58 patients (22.14%), lymphovascular invasion in 176 (67.18%), and tumor necrosis in 152 (58.02%). Furthermore, the renal vein resection margin was pathologically positive in 72 patients (27.48%). The operation period was categorized based on the year in which patients underwent RNTx (through the end of 2011, in 2012 and beyond). The number of patients who underwent RNTx through the end of 2011 was 129, while 133 patients underwent RNTx in 2012 and beyond.

Table 1. Baseline characteristics of study population (n=262)

Characteristic	Value
Age (yr)	59 (51–67)
Sex	
Male	210 (80.15)
Female	52 (19.85)
Side	
Right	110 (41.98)
Left	152 (58.02)
Median tumor size (cm)	9.5 (7.5–11.6)
Histology	
Clear cell	211 (80.53)
Papillary	17 (6.49)
Chromophobe	6 (2.29)
Others	28 (10.69)
T stage	
Under T4	226 (86.26)
T4	36 (13.74)
Venous thrombus level	
Level 0	97 (37.02)
Level 1	64 (24.43)
Level 2	42 (16.03)
Level 3	30 (11.45)
Level 4	29 (11.07)
Fuhrman nuclear grade	
Grade 1–2	35 (13.36)
Grade 3	108 (41.22)
Grade 4	115 (43.89)
Sarcomatoid differentiation	58 (22.14)
Lymphovascular invasion	176 (67.18)
Tumor necrosis	152 (58.02)
Pathologic renal vein resection margin positive	72 (27.48)

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

2. Cancer-Specific Survival

Cox proportional hazard model data for CSS are presented in Table 2. In the univariate analysis, papillary histologic type (HR, 2.306; 95% CI, 1.225–4.341, p=0.01), pathologic T4 stage (HR, 2.171; 95% CI, 1.345–3.504; p=0.002), pathologic N1 stage (HR, 1.928; 95% CI, 1.270–2.929; p=0.002), pathologic M1 stage (HR, 2.643; 95% CI, 1.811–3.857; p<0.001), Fuhrman nuclear grade 4 (HR, 1.607; 95% CI, 1.113–2.321; p=0.011), sarcomatoid differentiation (HR, 2.111; 95% CI, 1.211–3.680; p=0.008), lymphovascular invasion (HR, 2.084; 95% CI, 1.117–3.889; p=0.021), tumor necrosis (HR, 3.813; 95% CI, 1.667–8.721; p=0.002) and pathologic renal vein resection margin positivity (HR, 1.560; 95% CI, 1.063–2.288; p=0.023) were significantly associated with CSS. In the multivariate analysis, pathologic T4 stage (HR, 3.711; 95% CI, 1.599–8.611; p=0.002), pathologic N1 stage (HR, 2.371; 95% CI, 1.231–4.567; p=0.01), sarcomatoid differentiation (HR, 1.890; 95% CI, 1.027–3.477; p=0.041) and tumor necrosis (HR, 2.993; 95% CI, 1.132–7.914; p=0.027) were statistically associated with CSS.

The Kaplan-Meier results for CSS according to pathologic T4 stage, pathologic N1 stage, sarcomatoid differentiation, and tumor necrosis, which were significantly associated with CSS in the multivariate analysis, are presented (Figs. 1–4), respectively. For pathologic T4 stage, the 1, 3, and 5-year CSS rates were 60.8%, 39.4%, and 21.9%, respectively, compared

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Table 2. Cox proportional hazard model for cancer-specific survival

Variable	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	0.989 (0.972–1.006)	0.204	-	-
Sex	1.115 (0.721–1.724)	0.624	-	-
Tumor size	0.998 (0.982–1.014)	0.813	-	-
Histology				
Clear cell	Reference			
Papillary	2.306 (1.225–4.341)	0.010	-	-
Chromophobe	2.188 (0.689–6.947)	0.184	-	-
Other	1.419 (0.773–2.603)	0.259	-	-
Pathologic T4	2.171 (1.345–3.504)	0.002	3.711 (1.599–8.611)	0.002
Pathologic N1	1.928 (1.270–2.929)	0.002	2.371 (1.231–4.567)	0.010
Pathologic M1	2.643 (1.811–3.857)	<0.001	-	-
Fuhrman G4	1.607 (1.113–2.321)	0.011	-	-
Thrombus level				
Level 1	0.797 (0.488–1.301)	0.365	-	-
Level 2	0.978 (0.584–1.637)	0.932	-	-
Level 3	1.005 (0.543–1.861)	0.986	-	-
Level 4	1.174 (0.633–2.176)	0.611	-	-
Sarcomatoid differentiation	2.111 (1.211–3.680)	0.008	1.890 (1.027–3.477)	0.041
Lymphovascular invasion	2.084 (1.117–3.889)	0.021	-	-
Tumor necrosis	3.813 (1.667–8.721)	0.002	2.993 (1.132–7.914)	0.027
Pathologic margin positive	1.560 (1.063–2.288)	0.023	-	-
Operation period	0.854 (0.581–1.255)	0.423	-	-

HR, hazard ratio; CI, confidence interval.

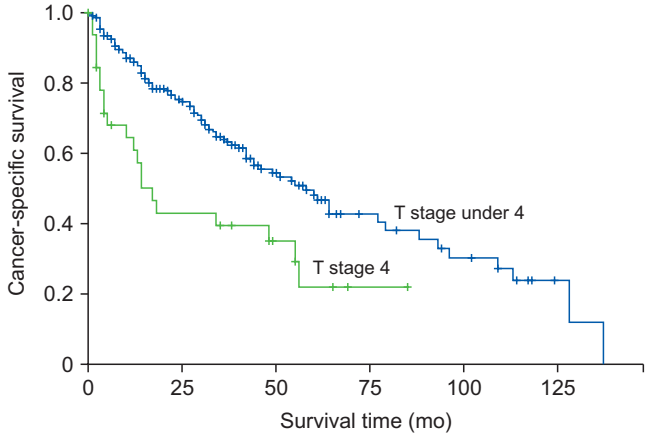

Fig. 1. Kaplan-Meier model for cancer-specific survival (T stage 4).

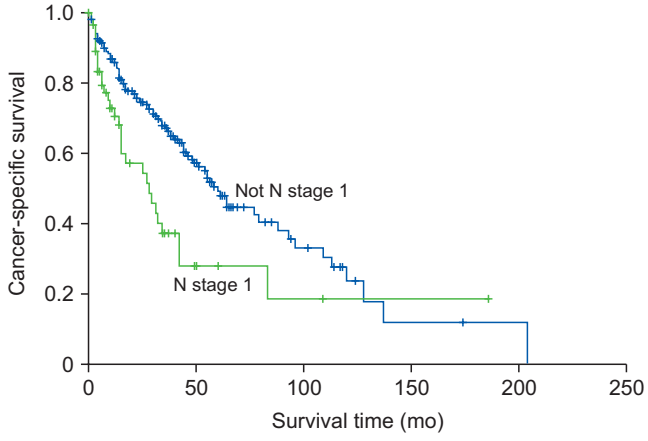

Fig. 2. Kaplan-Meier model for cancer-specific survival (N stage 1).

with 85.9%, 63.9%, and 48.1%, respectively for patients with pathologic T stage under 4 (p=0.001). For pathologic N1 stage, the 1, 3, and 5-year CSS rates were 83.8%, 37.1%, and 27.9%, respectively, compared with 85.8%, 67.1%, and 49.2%, respectively, for patients with pathologic N0 disease (p=0.002). For sarcomatoid differentiation, the 1, 3, and 5-year CSS rates were 71.0%, 47.3%, and 36.8%, respectively, compared with 89.6%, 69.6%, and 52.0%, respectively, in patients with no sarcomatoid differentiation (p=0.007). For tumor necrosis, the 1, 3, and 5-year CSS rates were 79.6%, 53.8%, and 38.3%, respectively, compared with 94.8%, 84.8%, and 76.3%, respectively, in patients with no tumor necrosis (p=0.001).

DISCUSSION

The analysis of pathological reports in this study revealed that pathologic T4 stage, pathologic N1 stage, sarcomatoid

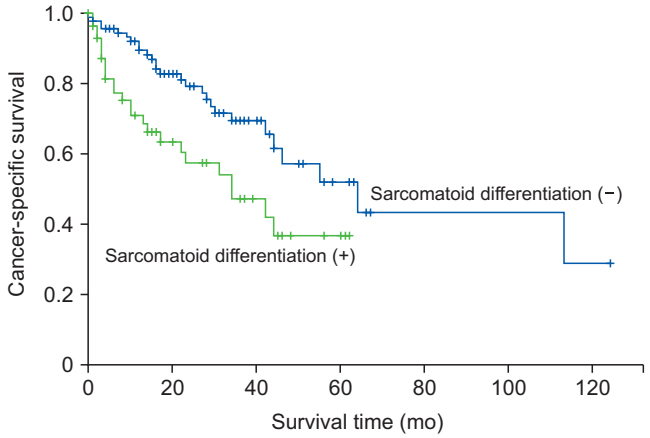

Fig. 3. Kaplan-Meier model for cancer-specific survival (sarcomatoid differentiation).

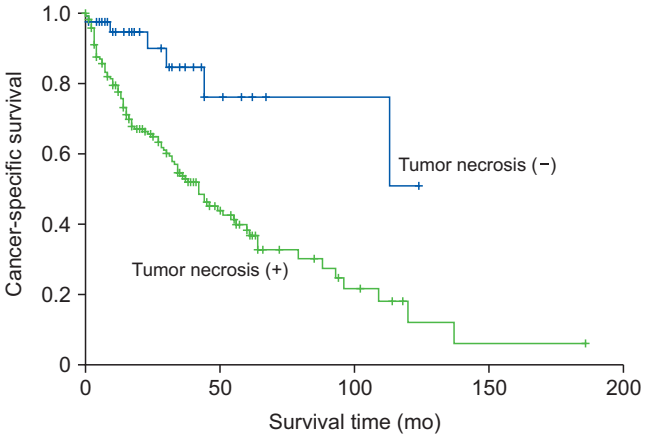

Fig. 4. Kaplan-Meier model for cancer-specific survival (tumor necrosis).

differentiation, and tumor necrosis were associated with poor CSS. Furthermore, tumor size, histologic type of RCC, Fuhrman nuclear grade, thrombus level, lymphovascular invasion, and positive renal vein resection margin were not associated with CSS.

Our findings showed that the venous thrombus level was not associated with CSS, which has been reported in several studies [11,12]. Shiff et al. [11] reported that venous thrombus level was not a significant prognostic factor for CSS, even for recurrence-free survival (RFS) and OS in 228 nonmetastatic RCC patients with venous thrombus who underwent RNTx. They categorized patients into 3 groups according to venous thrombus level (level 0, levels 1–2, and levels 3–4), and found no significant differences in CSS, RFS, or OS among the 3 groups. Klatte et al. [12] also concluded that venous thrombus level was not a prognostic factor for CSS. After identifying the medical records of 321 RCC patients with venous thrombus who underwent RNTx at a single medical institution, the patients were categorized into 3 groups based on thrombus level, classified as renal vein thrombus, IVC thrombus, and right atrium thrombus. We observed no association between venous thrombus level and CSS. In contrast, Mager et al. [13] reported that venous thrombus level was significantly associated with CSS, similar to pathologic N stage, distant metastasis, and perinephric fat invasion. They retrospectively reviewed the medical reports of patients who had RCC with venous thrombus and underwent RNTx at 16 institutions across the United States and Europe. In their study, they excluded patients who had RCC with venous thrombus limited to renal vein thrombus. This exclusion might have increased the average venous thrombus level, leading to opposite outcomes compared with our study. Tang et al. [14] also reported that the venous thrombus level was a prognostic factor for CSS in the entire population and nonmetastatic subgroup. Furthermore, the level 2 subgroup had a better prognosis than the level 3 and 4 subgroups, and the level 1 and 2 subgroups had a better prognosis compared with the level 3 and 4 subgroups. In their study, patients categorized as stage T4 and those who underwent palliative cytoreductive nephrectomy were excluded. This might have led to a relatively small number of patients with lower severity, who had higher venous thrombus levels, possibly explaining their results, which were inconsistent with our own.

Yang et al. [15]. reported on the significance of sarcomatoid differentiation in RCC patients with venous thrombus who underwent RNTx. In this retrospective study at a single institution involving 125 patients, RCC with sarcomatoid differentiation tended to lead to worse progression-free survival (PFS) and CSS than RCC without sarcomatoid differentiation. Sarcomatoid differentiation was associated with larger tumor size, a higher risk of necrosis, and a higher tumor stage, and was also more frequently observed in clear cell RCC [16]. The proportion of patients with metastasis in our study was 26%, and we identified sarcomatoid differentiation as a significant factor. The relationship between sarcomatoid differentiation and RCC metastasis remains a matter of debate. Sarcomatoid

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differentiation was also associated with PFS and OS in metastatic RCC, and it predicted a poor response to target therapy in metastatic RCC [16,17]. Thus, we hypothesized that there is an association between metastasis of RCC and sarcomatoid differentiation.

Zhang et al. [18] conducted a meta-analysis that identified a significant association between histologic tumor necrosis and CSS, OS, RFS, and PFS in patients with RCC. They reviewed 34 studies investigating the relationship between RCC and tumor necrosis and concluded that tumor necrosis could be a poor prognostic factor for RCC. The proportion of tumor necrosis was related to the degree of intratumoral hypoxia, resulting from the rapid growth of the tumor outpacing the growth of the blood vessels. Tumor necrosis was associated with a poor prognosis and a higher likelihood of vulnerability to radiotherapy and chemotherapy [19]. In our study, the 5-year survival rate for patients with no tumor necrosis was 76.3%, which exceeded the average 5-year survival following RNTx. Coons et al. [20] reported that tumor necrosis in the pathologic report was associated with OS, CSS, and RFS. They highlighted that patients who had no tumor necrosis had better OS, CSS, and RFS outcomes, particularly with a 5-year survival rate exceeding 60% compared with the overall CSS and RFS rates, which were approximately 50%. Their study included over 100 patients with T3b RCC according to the 2002 AJCC TNM staging criteria, wherein the tumor involves the renal vein or vena cava below the diaphragm, corresponding with the T3a and T3b 2010 TNM staging criteria [21]. Additionally, their patients had similar stage and metastasis ratios. Nevertheless, the 5-year CSS in patients with tumor necrosis was approximately 25% in their study, compared with 38.3% in ours. The higher survival rates for tumor necrosis and the absence of tumor necrosis in our study can be attributed to their use of patient data from 1988 to 2006, whereas our study covered the period from 1990 to 2022. Across these different periods, there might have been variations in surgical skills, surgical instruments, and postoperative care, leading to more favorable survival outcomes.

In our previous report in 2010 [22], we discussed the surgical and survival outcomes following RNTx. We concluded that tumor thrombus level was not significantly associated with OS, a finding consistent with our current study. However, pathologic T stage was also not a significant prognostic factor for OS in our previous study, but it did emerge as significant in our current study. This could be attributed to an increase in the number of patients analyzed in this study compared with the previous analysis.

Our study had several limitations. First, it was a retrospective review conducted at a single institution, which risks selection bias; however, we evaluated a larger number of patients than in other single-institutional studies on RNTx. Next, our study included a heterogeneous group of patients, and we could not conduct a subgroup analysis owing to the insufficient number of cases. Additionally, we did not have information on medical treatment. However, despite the limitations of our single-institutional study, there was low variability in surgical factors, enabling a detailed review with long-term follow-up.

CONCLUSION

In this retrospective study conducted at a single tertiary referral center, focusing on RCC patients with venous thrombus who underwent RNTx, pathologic T4 stage, pathologic N1 stage, sarcomatoid differentiation, and tumor necrosis were identified as significant prognostic factors for CSS. However, the venous thrombus level was not significantly associated with CSS. Further prospective studies are warranted to elucidate the prognostic factors for CSS in RCC patients with venous thrombus who undergo RNTx.

NOTES

- **Author Contribution:** Conceptualization: HA, JS; Data curation: HYL, YK; Formal analysis: HYL; Methodology: JS, HYL; Project administration: JS; Visualization: HYL; Writing – original draft: HYL, YK; Writing – review & editing: BL, CS, DY, IGJ, JHH, BH.
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ORIGINAL ARTICLE

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Clinical Characteristics and Outcomes of TFE3-Rearranged/TFEB-Altered Renal Cell Carcinoma with Systemic Therapies, Including Tyrosine Kinase Inhibitors or Immune Checkpoint Inhibitors: An Observational Study

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Purpose: *TFE3*-rearranged/*TFEB*-altered renal cell carcinoma (RCC) is a rare subtype of RCC. Due to its rarity, there is an unmet medical need for effective therapies in advanced settings. The study aims to investigate the clinical and histopathological characteristics of patients with microphthalmia transcription factor family/transcription factor E (MiTF/TFE) translocation RCC and the clinical outcomes of systemic therapies, including tyrosine kinase inhibitors (TKIs) or immune checkpoint inhibitors (ICIs).

Materials and Methods: This was a single-center, retrospective study. We identified 32 eligible patients among a total of 37 patients diagnosed with MiTF/TFE translocation RCC between January 2004 and September 2021, and the study included 9 patients who were treated with systemic therapies. We collected data on clinical characteristics, targeted sequencing, and clinical outcomes.

Results: The median age of the 32 patients was 45.5 years. Histologically, 26 patients (81.3%) had *TFE3*-rearranged RCC, and only 1 patient (3.1%) had *TFEB*-altered RCC. Curative or cytoreductive nephrectomy was performed in all 27 patients (84.4%), and 4 patients (12.6%) were diagnosed with metastatic disease at the time of the initial diagnosis. Nine patients (28.1%) were treated with systemic therapy with TKIs, 2 (6.3%) of whom received simultaneous TKI and ICI treatment. The response to systemic therapy (TKI or ICI) and duration of response ranged from complete response to progressive disease. Excluding 1 patient who was treated with a TKI in the adjuvant setting, the overall response rate in 8 metastatic patients was 50% and the complete response rate was 37.5%. The median follow-up period was 29 months. The median progression-free survival was 21 months, median overall survival was not achieved, and 2 deaths occurred.

Conclusions: Our findings suggest that TKI for treatment for metastatic *TFE3*-rearranged RCC is efficacious, with an overall response rate of 50% and a median progression-free survival of 21 months.

Key Words: *TFE3*-rearranged, *TFEB*-altered, Renal cell carcinoma, Tyrosine kinase inhibitors, Immune checkpoint inhibitors

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- **Research Ethics:** This study was performed in accordance with the Declaration of Helsinki and was approved by the Institutional Review Board of Samsung Medical Center (approval no. 2021-11-088-001; November 22, 2021). While consent to participate was waived by Institutional Review Board of Samsung Medical Center due to its retrospective nature, consent to perform next-generation sequencing was performed.
- **Conflicts of Interest:** The authors have nothing to disclose.

INTRODUCTION

In 2020, there were more than 430,000 new cases of kidney cancer globally and 179,000 deaths globally [1]. Smoking, obesity, and hypertension are established risk factors for renal cell carcinoma (RCC), which is a heterogeneous disease comprised of several histological subtypes with different genetic and clinicopathological characteristics. Among the histologic subtypes of RCC, clear cell carcinoma is the most common, accounting for 75% to 90% of total kidney cancers [2]. The remaining 20% include non-clear cell RCCs, such as papillary, chromophobe, and other rare subtypes. A single patient with RCC can sometimes harbor more than one subtype.

The benefits of vascular endothelial growth factor receptor (VEGFR)-targeted therapies for advanced RCC have long been known in palliative settings. Although the therapeutic options for advanced RCC have expanded in recent years to include immune checkpoint inhibitors (ICIs), such as pembrolizumab and nivolumab, VEGFR-targeted tyrosine kinase inhibitors (TKIs) remain the backbone of most current treatment guidelines [3-6]. However, novel therapeutic strategies have primarily focused on clear cell RCC, and few studies have evaluated ICIs in non-clear cell RCC.

In the latest (2022) World Health Organization (WHO) Classification of Urinary and Male Genital Tumors, rare subtypes of RCC were newly categorized according to their molecular features [7]. Most notably, the 2022 WHO classification introduced a new category of molecularly-defined renal tumors in addition to a morphology-based classification of renal tumors.

Microphthalmia transcription factor family (MiTF) translocation RCC was first described as an Xp11 translocation RCC by the WHO classification in 2004 [2]. Xp11 translocation RCC is characterized by chromosomal translocations involving the *TFE3* transcription factor gene located at the chromosome Xp11.2 locus. The fusions include *PRCC*, *ASPL*, and *SFPQ*/*PSF* as partner genes [8,9]. Meanwhile, t(6;11) translocation RCC is characterized by fusion between *TFEB* on chromosome 6p21.2 and *Alpha*/*MALAT1* on chromosome 11q13 [10]. Because of the rarity of t(6;11) translocation RCC, and because it was believed that translocation RCCs with *TFE3* or *TFEB* rearrangements share clinical and histopathological features, these tumors were previously grouped as MiTF/TFE translocation RCC [11,12]. However, as described above, TFE3-rearranged RCC and TFEB-altered RCC were separated into 2 distinct molecularly-defined subtypes in the 2022 WHO classification. MiTF/TFE translocation RCC represents up to 40% of all pediatric and adolescent RCCs and 1% to 4% of adult RCCs [13]. Due to the morphological overlap with more common subtypes, the frequency of translocation RCC in adults is probably underestimated in the absence of specific molecular studies [14].

Although more than a decade has passed since MiTF/TFE translocation RCC was recognized, effective therapies for these tumors represent an unmet medical need. Radical or nephron-sparing nephrectomy is considered for localized tumors, but there are few studies of systemic therapies in advanced settings. The available treatment options have all been based on the extrapolation of data from studies conducted almost exclusively in more common types of RCC. Due to the lack of a full understanding of molecular carcinogenesis, as well as the rarity of the disease, there have only been retrospective studies on VEGFR-targeted agents, mammalian target of rapamycin (mTOR) inhibitors, and ICIs [15-19].

Considering the difficulties in conducting a prospective study, we designed the present study to describe clinical and histopathological characteristics of patients with MiTF/TFE translocation RCC. We also investigated the clinical outcomes of existing systemic therapies.

MATERIALS AND METHODS

This was a single-center, retrospective study. Patients with MiTF/TFE translocation RCC were identified through an electronic medical record search of the patient database for the period between January 2004 and September 2021 in Samsung Medical Center (Seoul, Korea). We identified 32 eligible patients among a total of 37 patients diagnosed with MiTF/TFE translocation RCC, and 9 of those patients who were treated with systemic therapies were included in the present retrospective study (Fig. 1). Eligibility criteria were adult patients (20 years or older) with MiTF/TFE

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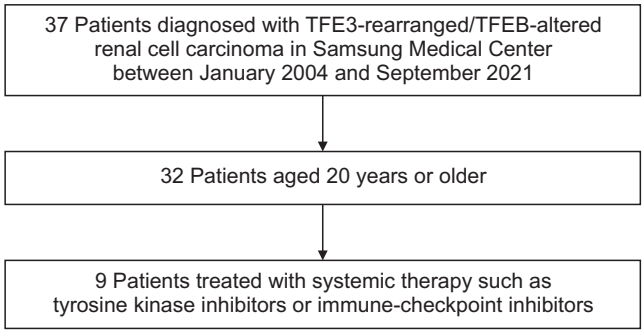

Fig. 1. Flowchart of patient inclusion. TFE3, transcription factor E3; TFEB, transcription factor EB.

translocation RCC diagnosed by a dedicated genitourinary pathologist utilizing immunohistochemistry (IHC) and/or fluorescent *in situ* hybridization (FISH) and treatment with at least one dose of TKIs or ICIs.

The medical records of the patients were reviewed, and information on patient death was obtained from census data. The demographic, histological, and clinical characteristics of patients at diagnosis were described and used for the analysis. Treatment and clinical outcomes of the patients were obtained from medical records. The data cutoff date was July 2022. Targeted sequencing of primary tumors using TruSight Oncology 500 (Illumina, San Diego, CA, USA) was performed in 6 of the 9 eligible patients. Tumor samples from 3 patients who were lost to follow-up were not available for targeted sequencing.

We collected tumor samples from archival tissues obtained from surgery. Genomic DNA was extracted and the DNA quality and quantity were assessed in a similar manner to a previous study [20]. DNA libraries were prepared using the hybrid capture-based TruSight Oncology 500 Library Preparation Kit (Illumina) following the manufacturer's instructions. Because this study was retrospective in nature, matched normal tissues were not available. The tumor mutational burden, microsatellite instability calls, germline variants, and called variants were generated and filtered in a similar manner to another study [21].

Because the sample was small, the endpoints of the present study were mainly descriptive in nature. Data were collected on patients' baseline characteristics, including sex, age, International Metastatic RCC Database Consortium (IMDC) risk score, performance status, American Joint Committee on Cancer TNM stage, and metastatic sites, as well as primary treatment were collected. In addition, indices for clinical outcomes such as types of therapy, clinical responses, and survival status were also collected. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method. Statistical analyses were performed with R for Windows v4.2.0 software (R Core Team, Vienna, Austria; http://www.Rproject.org).

Table 1. Baseline characteristics of 32 patients with MiTF/TFE translocation renal cell carcinoma

Variable	Value
Age (yr)	45.5 (20–67)
Sex	
Male	13 (40.6)
Female	19 (59.4)
Stage at diagnosis	
Stage 1	15 (46.9)
Stage 2	3 (9.4)
Stage 3	5 (15.6)
Stage 4	4 (12.5)
Not available	5 (15.6)
Subtypes	
TFE3	26 (81.3)
TFEB	1 (3.1)
Not available	5 (15.6)
Surgical treatment	
Curative nephrectomy	22 (68.8)
Cytoreductive nephrectomy	5 (15.6)
Not available	5 (15.6)
Systemic treatment	
Tyrosine kinase inhibitors	9 (28.1)
Immune checkpoint inhibitors	2 (6.3)
Not performed	18 (56.3)
Not available	5 (15.6)

Values are presented as median (range) or number (%).
MiTF/TFE, microphthalmia transcription factor family/transcription factor E; TFE3, transcription factor E3; TFEB, transcription factor EB.

RESULTS

1. Demographic and Clinical Characteristics of Patients

As described in the Methods section, 32 patients diagnosed with MiTF/TFE translocation RCC between January 2004 and September 2021 were eligible for this study (Table 1). Their median age was 45.5 years (range, 20–67 years). Histologically, 26 patients (81.3%) had *TFE3*-rearranged RCC and only 1 patient (3.1%) had *TFEB*-altered RCC. The others (15.6%) were morphologically diagnosed with MiTF/TFE

translocation RCC. Except for 5 patients (15.6%) whose electronic medical records were not available, curative or cytoreductive nephrectomy was performed in all 27 patients (84.4%), and 4 patients (12.6%) were diagnosed with metastatic disease at the time of initial diagnosis. Nine patients (28.1%) were treated with systemic therapy with TKIs, 2 (6.3%) of whom received simultaneous TKI and ICI treatment.

2. Patients Treated With TKIs or ICIs

All 9 MiTF/TFE translocation RCC patients treated with TKIs had *TFE3*-translocation RCC, with 8 patients having positive IHC staining for *TFE3*. The baseline characteristics before TKI or ICI administration are shown in Table 2. Five patients were men and 4were women. The median patient age was 47 years. Among the 9 patients, 4 were IMDC intermediate-risk, 3 were favorable-risk, and the other 2 were poor-risk before TKI or ICI administration. Five patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0, and the other 4 patients had an ECOG performance status of 1. Eight patients had distant metastases before TKI or ICI administration, and only 1 patient exhibited a complete response (CR) after left radical nephrectomy with lymph node dissection. This patient underwent adjuvant TKI treatment for more than 10 regional lymph node metastases in surgical specimens, which indicated a high risk of relapse. Regarding metastasis sites before TKI or ICI administration, 4 patients had distant lymph node metastasis to the mediastinal or supraclavicular lymph nodes. There were also liver, lung, bone, soft tissue, and peritoneal seeding metastases. All 9 patients underwent nephrectomy with curative or cytoreductive intent. Among them, 7 underwent curative or cytoreductive nephrectomy, radiofrequency ablation, or metastasectomy before TKI administration. The other 2 underwent interim cytoreductive nephrectomy while receiving TKIs in combination with ICIs because of partial response (PR) to treatment.

3. Efficacy of TKIs and ICIs

Treatment with TKIs and ICIs and the resulting clinical outcomes are shown in Table 3. Among 9 patients, 6 were treated with sunitinib, 2 with axitinib and pembrolizumab, and the remaining patient received pazopanib as the first TKI exposure. Eight patients were treated with systemic therapy in a palliative setting, and 1 patient was treated with a TKI as adjuvant therapy. Seven received their first TKI or ICI exposure as first-line therapy, while the other 2 patients received their first TKI exposure as second-line treatment after an mTOR inhibitor or bevacizumab with interferon-α. The response to systemic therapy (TKI or ICI) and the duration of response were variable, ranging from CR to progressive disease (Fig. 2). Five of the 9 patients achieved an overall response to the TKI or ICI to which they were first exposed, with 4 exhibiting CR and 1 showing PR. Excluding 1 patient who was treated with TKI in the adjuvant setting, the overall response rate in 8 metastatic patients was 50% and the CR rate was 37.5%. During the median follow-up of 29 months, the median PFS was 21 months, the median OS

Table 2. Histological and clinical characteristics* of 9 patients treated with systemic therapy (TKI or ICI)

Case No.	Age (yr)	Sex	ECOG PS	IMDC Risk	IHC	Treatments before systemic therapy (TKI or ICI)	TNM stage, AJCC 8th†
1	61	Female	0	Intermediate	TFE3	Curative radical nephrectomy	pT3aN1 (cM0)
2	51	Male	0	Intermediate	TFE3	Cytoreductive nephrectomy	pT3aN1 (cM1)
3	20	Male	1	Intermediate	TFE3	Interim cytoreductive nephrectomy	cT3aN0M1
4	55	Male	1	Poor	TFE3	Interim cytoreductive nephrectomy	cT1aN0M1
5	29	Female	0	Poor	TFE3	Cytoreductive nephrectomy	pT3a (cT3bN0M1)
6	40	Male	0	Favorable	TFE3	Curative nephrectomy → metastasectomy → temsirolimus	pT3aN0 (cM0)
7	60	Female	1	Favorable	Morphologically diagnosed	Curative nephrectomy → metastasectomy	pT1a (cN0M0)
8	47	Female	1	Intermediate	TFE3	Cytoreductive nephrectomy → bevacizumab+interferon-α	pT1aM1 (cN0)
9	20	Male	0	Favorable	TFE3	Curative nephrectomy → metastasectomy → RFA → RFA → metastasectomy	pT1b (cN0M0)

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; ECOG PS, Eastern Cooperative Oncology Group performance status; IMDC, International Metastatic RCC Database Consortium; IHC, immunohistochemistry; AJCC, American Joint Committee on Cancer; TFE3, transcription factor E3; RFA, radiofrequency ablation.
*Before TKI or ICI administration. †Initial stage.

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Table 3. Treatment and clinical outcomes of 9 patients treated with systemic therapy (TKI or ICI)

Case No.	Age (yr)	Sex	TKI or ICI	Lines of treatment	Setting	Best response	Last response	Subsequent treatment	PFS (mo)	OS (mo)	Status
1	61	Female	Pazopanib	1	Adjuvant	CR	PD	RT → sorafenib → everolimus	18	33	Deceased
2	51	Male	Sunitinib	1	Palliative	SD	PD	Cabozantinib and RT	5	32	Alive
3	20	Male	Axitinib/pembrolizumab	1	Palliative	CR	CR	Nephrectomy	15	15	Alive
4	55	Male	Axitinib/pembrolizumab	1	Palliative	PR	PR	Nephrectomy	15	15	Alive
5	29	Female	Sunitinib	1	Palliative	SD	PD	Cabozantinib	5	8	Lost to follow-up
6	40	Male	Sunitinib	2	Palliative	CR	CR	Off	63	63	Alive
7	60	Female	Sunitinib	1	Palliative	CR	CR	Off	79	79	Alive
8	47	Female	Sunitinib	2	Palliative	SD	PD	Everolimus and RT	24	29	Deceased
9	20	Male	Sunitinib	1	Palliative	PD	PD	HD IL-2 → everolimus	2	14	Lost to follow-up

TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; PFS, progression-free survival; OS, overall survival; CR, complete response; PR, partial response; PD, progressive disease; RT, radiotherapy; SD, stable disease; HD IL-2, high-dose interleukin-2.

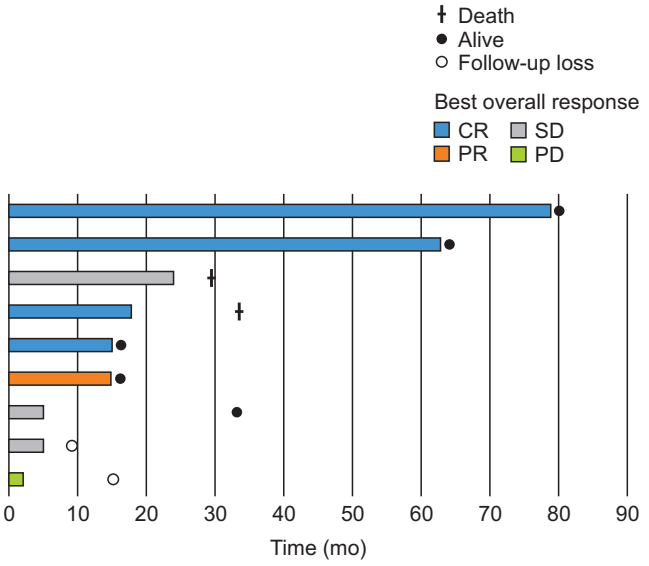

Fig. 2. Duration of clinical benefits. CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

Table 4. Clinical outcomes of systemic therapy (TKI or ICI)

Variable	Value
Best response of first-exposed TKI or ICI	
CR	4 (44.4)
PR	1 (11.1)
SD	3 (33.3)
PD	1 (11.1)
Overall response	
CR	3 (33.3)
PR	1 (11.1)
PD	5 (55.5)
Progression-free survival (mo)	21 (2–79)
Overall survival (mo), median	Not reached

Values are presented as number (%) or median (range).
TKI, tyrosine kinase inhibitor; ICI, immune checkpoint inhibitor; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease.

was not reached, and 2 deaths occurred (Table 4, Fig. 3). The median PFS was not reached and 5 months for the CR group (3 patients) and non-CR group (5 patients), respectively (p=0.041). The median OS was not reached and 29 months for the CR group and non-CR group, respectively (p=0.32).

4. Tumor Mutational Profiles With Targeted Sequencing

Tumor samples from 6 of the 9 patients were available for targeted sequencing analysis with TruSight Oncology 500 (Illumina). The top 10 mutated genes among the 221 genes were *FAT1*, *FANCA*, *SPTA1*, *ANKRD26*, *GEN1*, *NUTM1*, *ALK*, *FGFR4*, *MSH3*, and *EML4* (Fig. 4A). Each of these mutations existed in all 6 samples. While missense mutations were most common, there were also in-frame deletions and insertions, nonsense mutations, frameshift deletions and insertions, and splice site mutations (Fig. 4B).

DISCUSSION

Until recently, MiTF/TFE translocation RCC was defined as kidney cancers harboring gene fusions involving members of the MiT family of transcription factors, including *TFE3* and *TFEB*. Subsequently, the latest WHO classification (2022) separated *TFE3*-rearranged RCC and *TFEB*-altered RCC as 2 distinct molecularly-defined entities. These entities may overlap with each other and with other RCC subtype morphologies [22]. These overlapping morphological features may lead to misdiagnosis if specific IHC analyses are missing.

TFE3-rearranged RCC comprises 20%–75% of RCCs in

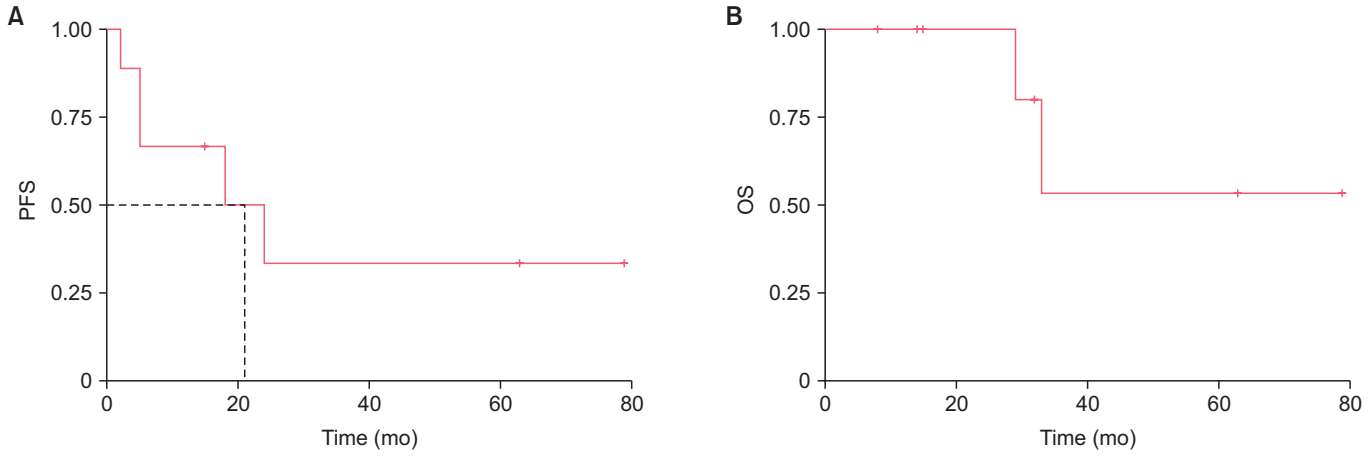

Fig. 3. Kaplan-Meier curves for progression-free survival (PFS) (A) and overall survival (OS) (B).

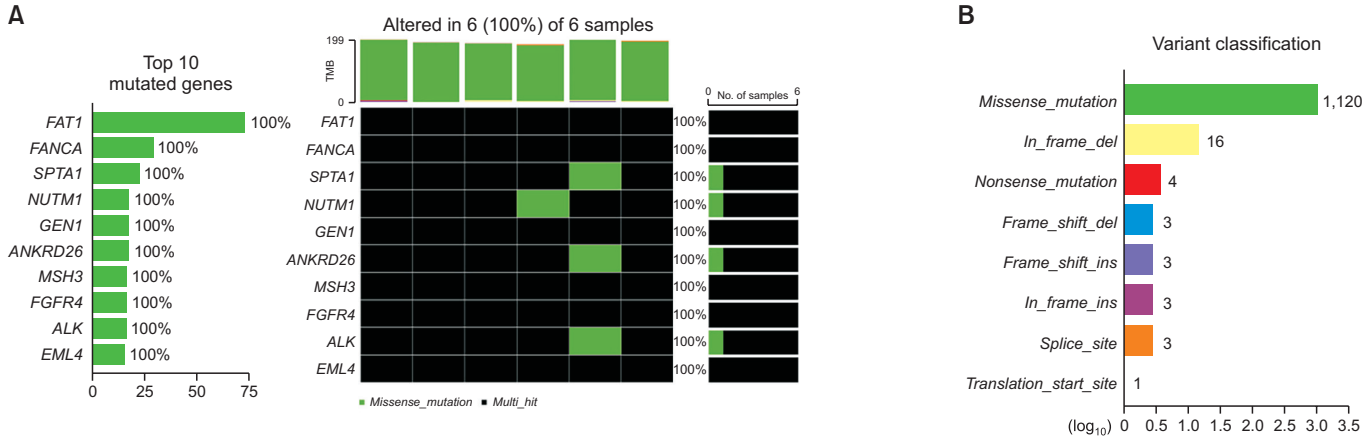

Fig. 4. Tumor mutational profiles based on targeted sequencing. The top 10 mutated genes (A) and variant classification (B).

children and 1%–4% of adult RCCs, with a median age of onset of 33 years [23]. As explained above, the incidence of *TFE3*-rearranged RCC in adults may be underestimated due to their morphological overlap with more common RCC subtypes such as papillary and clear cell carcinoma. Similar to other RCC subtypes, one-third of all *TFE3*-rearranged RCC patients are asymptomatic and often incidentally diagnosed. *TFEB*-altered RCC is a much rarer subtype, accounting for only 0.02% of all kidney tumors and comprising 6p21.1 translocated RCC and 6p21.1 amplified RCC [23]. The t(6;11) translocation fuses the gene for *TFEB*, located on chromosome 6, resulting in overexpression of *TFEB*. As a *TFE3*-rearranged tumor, *TFEB*-altered RCC does not have distinctive microscopic findings. Clinically, most cases with *TFE3*-rearranged and *TFEB*-altered RCCs are found incidentally, with median PFS and OS of 72 and 198 months, respectively [24]. Retrospective studies have shown that age and T stage at presentation and the presence of metastases were associated with aggressive behavior [24,25].

In metastatic settings, although no consensus exists regarding the optimal systemic therapy for *TFE3*-rearranged/*TFEB*-altered RCC, clinicians often extrapolate from treatment guidelines for clear cell RCC. The juvenile RCC network reported a series of 11 patients treated with sunitinib in the first-line setting, with a median PFS of 8.2 months [17]. Choueiri et al. [16] reported another series of 15 adult patients with metastatic Xp11 translocation RCC who received sunitinib, with 3 responders (20%) and a median PFS of 7.1 months. Subsequently, several attempts have been made to explore the efficacy of systemic therapies in patients with non-clear cell disease [26-28]. In these prospective studies, although sunitinib appeared to

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have clinically meaningful activity in non-clear cell RCC, each study included a diverse mix of histologic subtypes and no information was available on the clinical benefits for each distinct subtype. Although our small sample size poses a limitation for evaluating the efficacy of first-exposure systemic therapy of TKI and ICI, the median PFS in 9 patients with metastatic *TFE3*-rearranged RCC was 21 months.

There is no consensus regarding predictive factors for choosing the best systemic therapy for an individual patient. Interestingly, activation of the NRF2 pathway, which has recently been identified as a hallmark of *TFE3*-rearranged RCC, was previously shown to be associated with resistance to VEGFR-targeted TKIs [29]. Moreover, MiTF/TFE translocation RCCs are known to harbor strong expression of *MET*. Cabozantinib, a TKI with activity against VEGFR-2 and MET, has been evaluated in patients with clear cell RCC and, more recently, in patients with MiTF/TFE translocation RCC [30-32]. In 2 retrospective studies of patients with *TFE3*-rearranged/*TFEB*-altered RCC treated with cabozantinib, the promising disease control rates of 63%–82% suggest a therapeutic role for this TKI [31,32]. Prospective and larger studies are warranted to confirm these results. In addition to MET, PD-L1 expression by tumor cells and tumor-infiltrating mononuclear cells was reported in 30% and 90% of *TFE3*-rearranged/*TFEB*-altered RCC cases, respectively, suggesting that ICIs may be beneficial in these populations [33]. In addition, programmed cell death ligand 1 (PD-L1) expression in MiTF/TFE translocation RCC has been reported to be associated with a poor prognosis [34,35]. Boilève et al. [15] reported the efficacy of ICIs in 24 MiTF/TFE translocation RCC patients, with a response rate of 17% and median PFS of 2.5 months. They also reported that mutations in bromodomain-containing genes (*PBRM1* and *BRD8*) might be associated with clinical benefit for ICIs, consistent with a previous report on clear cell RCC [36]. In parallel with advancement of the standard of care for metastatic clear cell RCC, several combinations involving ICIs and TKIs are being investigated in non-clear cell RCC, including *TFE3*-rearranged/*TFEB*-altered RCC [3,4].

The small number of patients and retrospective nature are limitations of the present study. Four of 9 patients were diagnosed less than 2 years before the data search, which indicates that MiTF/TFE translocation RCC was diagnosed recently. This might have been due to greater clinical alertness to this rare disease, and vigorous suspicion might have led to a larger number of diagnoses. In addition, all 9 patients were diagnosed with *TFE3*-rearranged RCC rather than *TFEB*-altered RCC, and FISH was not performed routinely for diagnosis. This might be due to the much lower prevalence of *TFEB*-altered RCC than *TFE3*-rearranged RCC or the frequency of misdiagnosis of *TFEB*-altered RCC as conventional RCC or *TFE3*-rearranged RCC. In addition to IHC for several markers, performing FISH for *TFE3* or *TFEB* gene rearrangements or gene sequencing for identifying gene amplification can help differentiate diagnoses. In addition, TKI treatment was not uniform among patients, although 6 of 9 patients were treated with sunitinib. The absence of normal samples for comparison is another limitation of our analysis of mutational profiles. Whole genome sequencing or whole exome sequencing might give more information. Moreover, the small number of tumor samples analyzed was insufficient to draw solid conclusions.

CONCLUSION

Despite these limitations, we demonstrated the efficacy of TKI or ICI treatment for MiTF/TFE translocation RCC, a rare disease. With the further development of novel TKIs in combination with ICIs in other RCCs—mainly the clear cell type—these treatments could be expanded to MiTF/TFE translocation RCC. Further studies evaluating the efficacy of this therapeutic strategy and identifying predictive markers for treatment are warranted.

NOTES

- **Author Contribution:** Conceptualization: JHH, SHP; Data curation: JHH, GYK, MYK, SIS, SHP; Formal analysis: JHH; Methodology: JHH, SHP; Project administration: SHP; Visualization: JHH; Writing - original draft: JHH; Writing - review & editing: JHH, GYK, MYK, SIS, SHP.
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REVIEW ARTICLE

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Nephron-Sparing Surgery for Upper Urinary Tract Urothelial Carcinoma

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Radical nephroureterectomy (RNU) remains the gold standard for the surgical management of upper tract urothelial carcinoma (UTUC) from the ureterovesical junction to the renal pelvis. However, the removal of the ipsilateral intact kidney causes morbidity due to renal functional deterioration after RNU. Recently, the indications for nephron-sparing surgery (NSS) in UTUC have been expanded to preserve the intact kidney. Minimally invasive surgical approaches, including endourological, laparoscopic, and robotic-assisted techniques for segmental resection of the distal ureter with ureteral reimplantation have shown favorable oncological and clinical outcomes (for both noninvasive and invasive ureteral tumors). The established guidelines for UTUC have limited indications for NSS. Because of low tumor burden, stage Ta/T1 UTUC is considered the best indication for NSS. NSS requires close follow-up and managing the risk of recurrence in the preserved ipsilateral ureter and/or renal pelvis. To overcome these limitations, adjuvant administration of various immuno-chemotherapeutic agents is being explored to overcome the resistance to therapeutic cell death and evasion of immune destruction from current therapies with better prognostic outcomes. The aim is to reduce urothelial cancer recurrence improving the effectiveness of NSS and to achieve comparable outcomes to RNU in UTUC. In this review article, we have comprehensively discussed the different types of NSS in UTUC, the indications for NSS in the international guidelines, and oncological outcomes of each of the NSS techniques.

Key Words: Urologic neoplasms, Transitional cell, Endoscopy, Ureteral neoplasm, Ureteroscopy

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INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is relatively uncommon, and accounts for only 5%–10% of all urothelial tract tumors. The annual incidence of UTUC in Western countries is estimated to be approximately 2 cases per 100,000 individuals [1]. At present, due to improved detection techniques and better survival outcomes of patients with bladder cancer, the rate of detection of UTUC has increased. However, despite these advancements, approximately two-thirds of patients with UTUC have progressed to invasive disease at the time of initial diagnosis [2].

To improve survival outcomes of patients with UTUC, the current guidelines emphasize prevention and early diagnosis

of UTUC at both the individual and population levels [3]. The standard treatment of high-risk UTUC is open radical nephroureterectomy (RNU) with simultaneous complete bladder cuff excision [1]. However, with the emergence of improved endoscopic technology, it has become feasible to manage UTUC by removal of the intraureteral tumor itself endoscopically or percutaneously by partial ureterectomy, while preserving the kidney [4]. The advancements in endoscopic management and adjuvant intraureteral instillation regimens have provided an incentive over RNU as endoscopic management protects against loss of kidney function, which is associated with the aggressive surgical approach.

Nephron-sparing surgery (NSS) is the surgical concept of preserving the kidney and removing only the tumor or the affected ureteral segment. It has become an alternative to RNU in UTUC, which avoids renal functional deterioration that occurs after RNU in patients with solitary kidneys, bilateral disease, or renal insufficiency. Clinicians are now encouraged to use NSS with achievable success by applying the endoscopic approach [4]. NSS provides the advantage of reducing postoperative complications as it shortens the operation time and length of hospital stay without affecting survival, especially in older patients [5]. The wide array of NSS includes endoscopic ablation and surgical techniques using robot-assisted segmental ureterectomy (SU) [6]. Despite heterogeneous patient and tumor characteristics, several retrospective series and systemic reviews have consistently demonstrated comparable and acceptable oncologic outcomes after SU and standard RNU in terms of overall survival (OS), 3- and 5-year cancer-specific survival (CSS), and intravesical tumor recurrences, emphasizing SU as the first-line treatment for low-risk UTUC [7-10]. In this review, we have discussed the diverse surgical techniques of NSS and their recommended indications and surgical outcomes.

INDICATIONS IN THE RECOMMENDED GUIDELINES

There are concerns regarding tumor recurrence within the remnant UTUC with NSS. However, recent evidence on the outcomes of NSS in individuals suitable for these techniques is less controversial, leading to the establishment of several guidelines for using NSS for UTUC management [7,11]. These guidelines highlight risk stratification based on several clinicopathologic characteristics to assist in clinical decision-making. However, these guidelines are derived from evidence-based suggestions for selecting patients suitable for NSS based on (1) stratifying tumors into low- and high-risk of progression to identify patients who are more likely to benefit from NSS versus RNU. (2) In real practice, as tumor staging is difficult to perform clinically in patients with complex UTUC, about half of the urologists still perform endoscopic NSS without adhering to the guidelines of tumor-grade recommendations. NSS using endoscopic surgery was recommended even in patients with high-risk multifocality, with multiple studies providing evidence that low-grade multifocal UTUC was not related to progression-free survival [12,13].

Globally, NSS is indicated for patients with low-risk UTUC, especially those with a single-functioning kidney, chronic renal failure, or bilateral disease, irrespective of the status of the contralateral kidney, although RNU is considered the best surgical modality for UTUC [7,11]. The National Comprehensive Cancer Network (NCCN) guidelines 2024 v1.0 stratify UTUC based on favorable or unfavorable clinical and low and high-grade pathological criteria, including tumor size, grade, focality, and invasiveness for nephron preservation [11,14,15]. Favorable cases include low-grade tumors based on cytology and biopsy, papillary architecture, tumor size <1.5 cm, unifocal tumor, and cross-sectional imaging showing no concerns of invasive disease. Less favorable cases include multifocal tumors, flat or sessile tumor architecture, tumor size ≥1.5 cm, high-grade tumors, cT2–T4 tumors, midureteral and proximal ureteral tumors (due to technical challenges), and tumors crossing the infundibulum or ureteropelvic junction.

The European Association of Urology (EAU) guidelines stratify UTUC patients into "low risk" and "high risk" according to tumor focality, size, grade, variant histology, clinical stage on computed tomography (CT), and hydronephrosis based on clinical, endoscopic, radiographic, and histopathologic factors [16]. Low-risk cases include unifocal disease, tumor size <2 cm, low-grade cytology and/or ureteroscopic (URS) biopsy, and noninvasive disease on imaging. High-risk cases include hydronephrosis, multifocal

disease, tumor size ≥2 cm, high-grade cytology and/or URS biopsy, invasive disease on imaging, and prior radical cystectomy. Although it may be feasible to treat high-grade tumors with NSS endoscopically, it is not in line with either the NCCN or EAU guidelines, or the common practice of most urologists [17].

The main concerns about NSS are related to more procedures requiring stringent endoscopic surveillance, residual tumors, recurrence, disease progression, and the burden of repeat treatments. Urologists are getting more inclined towards endoscopic management, especially for patients with low-grade UTUC as research has proven that it reduces morbidity, such as the loss of kidney function associated with RNU without compromising the oncological outcomes, including CSS and OS, which were equivalent to those with RNU [7]. NSS is valuable for high-grade UTUC, predominantly in patients with imperative indications for NSS, who possess unfavorable factors for an invasive surgical approach, and those requiring palliative treatment [18]. Thus, patients with UTUC who will benefit from NSS have to be identified along with formulating an efficient follow-up strategy for surveillance.

IMPORTANCE OF THE DIAGNOSTIC MODALITY

The diagnostic precision of UTUC within the ureter segment is crucial for choosing the optimal NSS option of either open surgery or endoscopic surgery. An accurate determination of the tumor grade and stage enables successful NSS. Nevertheless, tumor staging is difficult in UTUC because of the difficulty in assessing the tumor depth and stage, especially with ureteroscopy [19]. Consequently, tumor grade is routinely used to approximate staging given the association between high-grade pathology and invasive disease [20].

Diverse diagnostic methods for UTUC include endoscopic modalities, biopsy, and cytologic techniques. Flexible ureteroscopy is essential and enables direct visualization of the tumor and specimen retrieval [21]. Optical coherence tomography and confocal light endomicroscopy offer visual means for tissue diagnosis with high sensitivity and specificity for tumor invasion, and staging concordance with the final histopathology [22]. Barbotage cytology is another important tool to rule out high-grade UTUC and has been shown to be an equally efficient tool in detecting cancer compared to histological biopsy if the lower urinary tract has been completely evaluated and determined to be cancer negative [23].

In UTUC, there is difficulty in determining the pathological stage based on the biopsy grade for selecting the appropriate surgical option [24]. The smaller tissue size and individualized morphology of UTUC necessitates different biopsy approach strategies, and various new biopsy techniques and equipment have been introduced and improved, such as sheath, forceps, light, and magnifying scope for better acquisition of tissues, higher yielding rate, and greater accuracy [18,19]. For example, basket devices can be used to debulk large amounts of tissue and provide an accurate diagnosis for large papillary lesions; the flat-wire basket was shown to be the most accurate device, with a diagnosis rate of 94% and grade determination rate of 93% [8], whereas forceps devices may be preferable for smaller, sessile, or nonpapillary lesions [9].

PROGNOSTIC OUTCOMES OF NSS AND RNU

No randomized studies have compared NSS and RNU, and most of the relevant studies encompassed fewer than 100 patients, with mostly small-sized, low-grade tumors. A meta-analysis of 8 published retrospective studies reported that endoscopic NSS had similar OS and CSS to RNU using pooled data of 1,002 patients with organ-localized UTUC [25]. Systemic reviews of retrospective studies have also reported consistent conclusions based on heterogeneous evidence that NSS has comparable survival outcomes to RNU in low-risk patients or patients with favorable disease criteria [7,9,16,17,26,27]. Recurrence of UTUC is common and occurs in most patients, which mandates regular surveillance [28]. Thus, the risks of poor oncologic control and tumor progression with endoscopic management must be weighed against the perioperative risks, such as poor life expectancy associated with end-stage renal failure and consequent hemodialysis, which are associated with RNU [28]. Thus, the endoscopy-based approach is indicated for compliant

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patients who will adhere to a strict follow-up regimen [9].

SURGICAL MODALITIES

1. Segmental Ureterectomy

NSS comprises several surgical techniques: endoscopic resection and SU with ureteroureterostomy or ileal ureter substitution or distal ureterectomy. The fundamental principles for SU have not been standardized yet; however, they include atraumatic, "no-touch" ureteral dissection, identification of the limits of the ureteral tumor (with or without the use of concomitant ureteroscopy), isolation of the affected ureteral segment to prevent tumor spillage [29], and tumor resection with adequate (1–2 cm) safety margins considering the patient's underlying comorbidity and tumor grade, size, and stage, along with negative frozen biopsy of the remaining tumor within the ipsilateral ureter [30]. If a wide margin with SU has been achieved, it gives favorable perioperative, functional, and oncologic outcomes, provides accurate pathologic staging and grading, and completely preserves ipsilateral renal function [6,31-33].

SU was shown to have acceptable oncological results regarding local, metastatic, and bladder recurrence, similar to those of RNU [34]. A study of 3,061 patients with UTUC from The National Cancer Database showed SU as a valid surgical method that did not meaningfully sacrifice oncologic control in appropriately selected patients with UTUC [35]. Tumor recurrence rate in the urinary tract, including the ipsilateral ureter, after SU was between 4.1% and 7%, with a mean time to procedure of 33.3–54 months [36,37]. A recent propensity-matched study reported a recurrence rate of 6.8% for distal ureterectomy and bladder cuffing [38].

The NCCN and EAU guidelines have highlighted SU with distal ureterectomy with concomitant ureteroneocystostomy or segmental ureteral resection with ureteroureterostomy as the most radical approach for distal ureteral tumors [7,11]. The most "radical" and extirpative way of performing SU would be a complete ureterectomy with ileal ureter replacement with/without lymphadenectomy of which the degree and implementation of bladder cuffing have not been clearly described [17,39].

For proximal and midureteral tumors, ureteroureterostomy is the simplest alternative to SU, but no guidelines recommend SU as the primary treatment option [8,9,29]. Especially, SU for tumor in the proximal two-thirds of the ureter is associated with high failure rates than for distal ureter tumor [10,40]. Therefore, distal ureterectomy with ureteroneocystostomy is indicated for low-risk tumors in the distal ureter that cannot be removed completely endoscopically [10].

For high-risk cancer with an imperative indication, distal ureterectomy with/without lymph node dissection could be an alternative option, provided it is low grade [8,9,29]. The EAU guidelines recommend complete distal ureterectomy with neocystostomy with/without lymph node dissection for high-risk distal tumors [16], whereas the NCCN guidelines selectively recommend distal ureterectomy with ureteral reimplantation and regional lymphadenectomy for high-grade tumors only in the distal ureter [8,9,14].

Indeed, the standard surgical management for the high-grade UTUC is RNU and the role of lymph node dissection during RNU has not accumulated sufficient evidence to support its adherence to the guideline recommendation recommended in real-world practice [11,14,41]. However, the role of lymph nodal dissection (LND) during RNU for high-grade UTUC improves lymph node staging and prognostication in order to identify patients who may benefit from adjuvant treatment. Patients who underwent LND have better disease-free survival, CSS and OS compared with those who did not. In addition, the pathological node positivity (pN+) is associated with poor survival outcome compared with pN0 and higher number of lymph nodes removed is associated with improved CSS and OS, even in pT0 patients [42-46].

2. Endoscopic Surgery

The ureteroscopic resection of intraureteral tumors is performed to preserve the upper urinary tract (UUT) above the tumor. The existing approaches of endoscopic surgery for intraluminal UTUC are either retrogradely through the distal urethra or by a percutaneous anterograde approach via the renal parenchyma. The principal advantage of the percutaneous approach is the ability to use larger-diameter endoscopic resectoscopes for more efficient resection and

debulking of the tumor [11,20]. For tumors located in the lower caliceal system that are inaccessible or difficult to manage even with flexible ureteroscopy, percutaneous (anterograde) access can be utilized. The disadvantages of the percutaneous approach include a higher complication rate of up to 30% including transfusion, renal failure, and emergency nephrectomy or angioembolization [28]. It is also associated with greater invasiveness of renal parenchyma with a higher risk of tumor seeding along the nephrostomy tube, compared to the retrograde approach [11,47,48].

Endoscopic surgery comprises an initial debulking with a cold cup or basket, followed by ablated cauterization via electricity or laser [8,9,14,29,49,50]. Laser is more recommended because of complete achievable tumor resection or destruction [16], and lesser risk of ureteral stricture [19,21,51]. A frequently used energy source, named holmium yttrium aluminum garnet (Ho:YAG), provides an achievable safety depth of penetration (<0.4 mm) for surgical ablation of UTUC. However, for high-grade disease secondary to imperative indications (i.e., solitary renal unit, baseline renal insufficiency, inability to tolerate surgery) for endoscopic surgery, a median OS of 29.2 months with a 2-year OS rate of 54% were not superior compared to those with other surgical modalities [52].

Endoscopic management for UTUC differs from RNU in several aspects, such as the approach, either antegrade or retrograde. Larger tumors, low-grade UTUC in the renal pelvis (>1.5–2.0 cm), and tumors in the lower caliceal system should be preferably managed with an anterograde approach by obtaining a percutaneous tract through the kidney parenchyma because of the difficult access and management via flexible URS [7,11]. Regarding percutaneous access with endoscopic management, stringent surveillance is necessary because of the risk of disease progression [53,54] and tumor seeding [55], despite various studies showing comparable and equivalent efficacy of endoscopic resection and RNU in terms of disease-specific and OS in patients with low-grade UTUC [52,56-58].

The classic retrograde approach by using a ureteroscope is good for small-sized tumors in the distal ureter [21]. Middle and distal ureter tumors are generally accessed using semirigid URS. The recent popularity of flexible devices has enabled access to middle and distal ureter tumors via retrograde endoscopic ablation to obtain maximal debulking of the tumor within the ureter [16,39]. The percutaneous approach with a resectoscope through the renal parenchyma and electrocautery with adequate energy generators such as Ho:YAG laser and Nd:YAG (neodymium-doped yttrium aluminum garnet) laser was performed successfully for large tumors >2 cm due to the high rate of ipsilateral recurrence and risk of tumor seeding [49,55,59]. Scotland et al. [23] showed a 90.5% ipsilateral recurrence rate for retrograde endoscopic treatment of tumors larger than 2 cm, with an OS of 75% and CSS of 84% in a 5-year follow-up. However, other studies have shown that retrograde endoscopic treatment is feasible with good oncologic outcomes even for tumors larger than 2 cm and multifocality when the tumor is low-grade with a progression-free rate of 93.2% in a median follow-up of almost 2 years [50].

3. Robot-Assisted Laparoscopic Segmental Ureterectomy

Endoscopic minimal invasive surgery has been applied to UTUC using robot-assisted laparoscopic SU (RALSU) [60-62]. Patients with a low-grade distal ureteral tumor, impaired renal function, and high-grade distal UTUC are ideal candidates for SU with ureteral reimplantation, as well as RALSU [28,47,63,64]. The required reduction in the length of the ureter for optimal oncological results is challenging during SU for UTUC. Still, robotic surgery with 3-dimensional magnified instrumental view helps to overcome these limitations of conventional laparoscopic and open approaches by the application of tension-free ureteral reimplantation procedures for reconstruction after SU. Several reports have proven the feasibility of RALSU with acceptable oncological outcomes, including surgical morbidity [39,60,61,65,66]. Furthermore, the safety and feasibility of the reimplantation and anastomosis techniques has also been demonstrated [61]. Robot-assisted ureteric reimplantation with Boari flap (RABFUR) and psoas hitch (RAPHUR) have shown favorable 1-year outcomes. However, it is worth noting that robotic surgical procedures require a high level of experience similar to laparoscopy, and the learning process is vital for patient safety as well as the oncological outcome of RALSU [67].

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4. Laparoscopic Segmental Ureterectomy

Similarly to RALSU, laparoscopic segmental ureterectomy (LSU) is an alternative surgical option for distal ureteral tumors in a setting where robot laparoscopy is not available [62,68,69]. Not many groups have performed LSU because laparoscopic nephroureterectomy has been the preferred surgical option for UTUC. No consensus has been achieved yet on the preferred surgical technique for LSU; however, several research groups have established the safety profile and feasibility of LSU with psoas hitch ureteral reimplantation for distal UTUC, including optimal perioperative, renal functional, and oncologic outcomes [68].

5. Intravesical Instillation Therapy

Endoscopic treatments offer acceptable outcomes for patients with low-grade/low-volume disease despite a higher rate of ipsilateral remnant ureteral recurrence compared to RNU (15%–90% vs. 3%–33%) [9]. Therefore, intraluminal instillation of adjuvant agents into the UUT has been attempted to reduce the likelihood of tumor recurrence in the ipsilateral renal pelvis and ureter while preserving renal function [67,70].

A systematic review and meta-analysis assessing the oncological outcomes of patients with papillary UTUC or carcinoma *in situ* (CIS) of the UUT treated with NSS and adjuvant intraluminal treatment found no difference between the drug administration methods (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS. The recurrence rates following adjuvant instillations were comparable to those reported in the literature for untreated patients, calling their efficacy into question [71].

Bacillus Calmette- Guerin (BCG) has been the best-studied adjuvant therapy despite the uncertainty regarding its dosage and mechanism of action as intraluminal therapy for UTUC because of variable institutional results [27,71]. It has been recommended for papillary tumors and CIS by the non–muscle-invasive bladder cancer guidelines [9]. Carmignani et al. revealed that an induction course of BCG in CIS could convert positive cytology to negative with a mean recurrence rate of 32% at 19 to 57 months follow-up [72].

Mitomycin C (MMC) is another reported adjuvant intraluminal agent [12,73]. A study of 28 patients with UTUC stage Ta,/T1 tumors receiving postoperative intraluminal MMC showed 3-year recurrence-free, progression-free, nephrouretectomy-free, and OS rates of 60%, 80%, 76%, and 92.9%, respectively [73]. Another series of 20 patients with low-grade UTUC receiving MMC therapy showed a recurrence-free survival of 65% at a mean follow-up of 24 months without any postoperative renal impairment [74].

Jelmyto (UGN-101, formerly MitoGel, UroGen Pharma, Israel) is an enhancing gelatinous form of the MMC matrix that achieves more sustained contact with the UUT. A single-arm phase 3 trial using UGN-101 instillation in a chemoablation setting via a retrograde catheter in the renal pelvis and calyces showed significantly promising results, with complete response in 42 patients (59%) with low-grade UTUC (<15 mm), among which 52% of the patients sustained complete remission for 12 months, with an estimated durability rate of 82% [70,75].

FOLLOW-UP

The aims of follow-up after either SU or endoscopic surgery for UTUC are to detect locally recurrent or new primary tumors within the remnant urothelium, including the bladder, and to detect regional and distant metastases based on the individual patient's NSS type and tumor characteristics. Importantly, endoscopic management has a risk of understating and undergrading UTUC with a higher risk of recurrences [16]. Therefore, thorough ureteroscopy and UUT imaging at 3- to 12-month intervals should be considered [14,16].

A more frequent and stricter follow-up regimen than that for RNU should be planned with prolonged surveillance of the ipsilateral ureter via cystoscopy, ureteroscopy, and urine cytology. The EAU guidelines recommend these follow-up modalities every 3 and 6 months, then every 6 months for 2 years, and annual investigations thereafter for the remnant ureter, including annual CT or ureteroscopy [16]. The NCCN guidelines recommend imaging of the upper tract collecting system or ureteroscopy at 3- to 12-month intervals and radiologic evaluation including abdominal/pelvic CT or magnetic resonance imaging with or without contrast,

and chest imaging after NSS. Long-term surveillance 5 years after NSS includes urine cytology, radiologic evaluation of the UUT, and endoscopic inspection due to the high risk of disease recurrence [14].

For low-risk tumors without any upstaging and upgrading, an early second-look ureteroscopy should be scheduled after 6–8 weeks of NSS [53], with cystoscopy and CT urography at 3 and 6 months, and then yearly for 5 years [76]. For high-risk tumors, the surveillance regimen might be influenced by the consequences of recurrent disease. The ipsilateral UUT still requires careful and long-term follow-up owing to the high risk of disease recurrence [77] and progression, even beyond 5 years [78]. Stage pT0 or pT1 tumors should be followed up with serial cystoscopies at 3-month intervals for the first year and longer intervals in case of a negative test.

CONCLUSION

NSS has some advantages over standardized RNU in UTUC, as nephron sparing prevents major postoperative morbidity, such as renal functional deterioration. The advanced technologies of NSS have expanded the surgical indications for UTUC despite the existing limitations of intraureteral detection and identification of tumor staging with a risk of under-staging and grading of UTUC. However, NSS has demonstrated comparable efficacy to RNU in terms of oncological outcomes of low-volume/low-grade UTUC. Furthermore, the improved efficacy of endoscopic surgery and SU have expanded the indications of UTUC, although the current guidelines still suggest a narrow range of indications for SU and endoscopic surgery in patients with UTUC. However, improvements in the technology of endoscopic equipment and introduction of diverse adjuvant instillation regimens suggests positive future perspectives for NSS in UTUC. Further clinical trials with improved diagnostics and treatment regimens may shift this paradigm and are eagerly anticipated in UTUC.

NOTES

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ORIGINAL ARTICLE

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Poorer Outcomes in Bladder Cancer Patients With Diabetes: A Systematic Review and Meta-analysis Addressing Over 226,472 Bladder Cancer Patients

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Purpose: Diabetes mellitus, a frequent comorbid condition in cancer patients, has been shown to increase risk of all-site cancer mortality. This relationship has not been systematically studied in bladder cancer patients. This systematic review and meta-analysis aimed to identify, evaluate, and synthesize available evidence on the relationship between history of diabetes and outcomes in bladder cancer patients.

Materials and Methods: Systematic searches interrogated OVID MEDLINE, Embase, Web of Science, Google Scholar, and Cochrane Library to identify scholarly reports relating diabetes to all-cause mortality, bladder cancer-specific mortality, recurrence, and progression in bladder cancer patients. After critical review, meta-analysis was used to quantitively synthesize qualifying data and assess potential influence of publication bias, clinical heterogeneity, and residual confounding.

Results: We synthesized data on over 226,472 patients treated with curative intent uniquely represented in 28 studies that met quality metrics. Having diabetes was positively associated with each outcome. Hazard ratio estimates were indistinguishable for mortality from any cause, 1.22 (95% confidence interval [CI], 1.12–1.33) and bladder cancer-specific mortality, 1.28 (95% CI 1.17–1.41) and notably stronger in patients with muscle-invasive and high-risk non–muscle-invasive bladder cancer, 1.32 (95% CI, 1.15–1.50) and 1.48 (95% CI, 1.06–2.06). Neither publication bias, systematic error, nor confounding by factors such as smoking or obesity is likely to explain the observed associations.

Conclusions: Bladder cancer patients with diabetes experience elevated mortality that is not explained by diabetes-related comorbidities or complications. Future research should explore type, severity, and duration of diabetes in relation to unfavorable bladder cancer outcomes.

Key Words: Bladder cancer, Diabetes mellitus, Treatment outcome, Urinary bladder neoplasm, Urologic cancer

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

INTRODUCTION

Bladder cancer is the 10th most common cancer worldwide, and 6th most diagnosed malignancy of men in the United States (US) [1]. The American Cancer Society projected 17,100 deaths from bladder cancer in 2022 in the US alone [2]. Muscle-invasive bladder cancer (MIBC) has a 5-year survival rate of 38% [3] while non–muscle-invasive bladder cancer (NMIBC) has a recurrence rate of up to 87% and progression rate of up to 45% [4]. Bladder cancer is the most expensive cancer to treat, costing about 4 billion dollars per year in the US [5]. Most bladder cancer is diagnosed in adults 65 or older; half of the increase in world population is projected to consist of adults ages 60 or older [6]. This demographic change will increase bladder cancer occurrence, prevalence, and mortality, augmenting financial and clinical burdens.

Diabetes mellitus is a major public health challenge, and prevalence is increasing worldwide [7]. There is abundant evidence that those with diabetes have elevated risks of developing numerous malignancies [8-12], and diabetes is one of the most frequent comorbid conditions in cancer [13].

Diabetic cancer patients reportedly have 20% greater all-site cancer mortality than cancer patients without diabetes [12]. Such differences have not been systematically assessed for cancer at each organ site. Diabetes' influence on cancer survival remains poorly understood. The elevated mortality could be due entirely to complications of diabetes such as wound infection or cardiac events; conversely, diabetes may influence processes that increase host vulnerability or encourage aggressive behavior of cancer. Goals of this research were to learn whether bladder cancer patients with diabetes have greater mortality than other bladder cancer patients and, should such a difference be evident, to estimate its magnitude and investigate its origins. We reasoned that if excess mortality is due to complications of diabetes, diabetic patients would be found to have greater all-cause mortality than those without diabetes, but similar magnitudes of bladder cancer-specific mortality, recurrence, and progression. Conversely, if diabetes or processes inherent to diabetes contribute to oncogenesis, associations of all-cause mortality and bladder cancer-specific mortality with diabetes would have similar magnitudes.

MATERIALS AND METHODS

1. Protocol and Registration

The study protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO Identification: CRD42021251175) and is available online. Reporting followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [14].

2. Eligibility Criteria

Using the PICO (Person, Independent variable, Comparator, Outcome) method to define the research question, we specified person to be humans with bladder cancer, intervention to be diabetes, comparator to be bladder cancer patients without diabetes, and outcomes to be all-cause mortality, bladder cancer-specific mortality, bladder cancer recurrence and bladder cancer progression. Studies which reported on original, individual level, human data that assessed bladder cancer outcomes in relation to history of diabetes were included. Reviews and studies of non-human data were excluded. There were no limitations regarding year of publication, geography, language, or length of follow-up.

3. Information Sources

Systematic searches of OVID MEDLINE, Embase, Web of Science, Google Scholar, and Cochrane Library were conducted by professional librarians using controlled vocabulary and keywords. To query the intersection between urinary bladder neoplasms, diabetes mellitus and an extensive set of outcomes, we combined terms for each domain with the Boolean operator 'OR' then identified their intersection with 'AND' (Supplementary Material). Searches were implemented from inception of each database and repeated upon initial completion of the meta-analysis on May 6, 2021.

4. Study Selection

Deduplicated title and abstract citations were loaded into Covidence software and screened to eliminate clearly ineligible reports by 2 independent investigators, who

reviewed full text of remaining reports to identify those satisfying inclusion criteria. Discrepancies were resolved by consensus with occasional adjudication by a third reviewer. For each report meeting inclusion criteria, we reviewed cited references and conducted a Web of Science citation search seeking additional reports meeting inclusion criteria. If multiple studies provided data on the same base population, we included only information from the most recent report. All contributing studies were cohort studies. Information extraction is described in Supplementary Material.

5. Outcome Definitions

All-cause mortality, also called overall survival, was defined as time from bladder cancer diagnosis to death from any cause. Bladder cancer-specific mortality, also called bladder cancer-specific survival, was defined as time from cancer diagnosis until death from bladder cancer, with death due to alternate causes censored. Recurrence was defined as time elapsed between initiation of curative treatment and documented recurrence, with death from any cause before recurrence being censored. Recurrence-free survival (RFS) was similarly defined except death from any cause before recurrence was counted as an event. Progression was defined as time from initial treatment to any increase in grade or stage after repeat treatment for recurrence, with death from any cause censored. Progression-free survival (PFS) was similarly defined except death before progression was counted as an event. In all studies, patients who did not experience the event under investigation were censored at the time of last follow-up. Outcomes were scored according to these definitions using information provided in the methods section of each report. If the original authors did not fully describe the outcome, the stated outcome was assumed to be defined as indicated above. We recognized that if diabetes were associated with mortality during follow-up, then censoring death would introduce negative bias into studies of recurrence and progression. For completeness we nonetheless summarized data on all 5 outcomes. Finding clear evidence of greater mortality among diabetic patients, we base our inferences on only results for mortality, RFS and PFS.

6. Risk of Bias in Individual Studies

We critically reviewed methodology used in each study for vulnerability to bias, assessing potential for information bias (if methodology allowed significant error in measurement of diabetes or bladder cancer outcomes), participation bias (if nonrepresentative participants were enrolled), and confounding (if bladder cancer risk/protective factors were inadequately controlled).

7. Data Harmonization

We used several procedures to harmonize estimates of diabetes-outcome associations to include in meta-analysis. If estimates were calculated separately for males and females or within categories of race, subgroup-specific estimates were combined using fixed effect meta-analysis [15-17]. If multiple groups of patients with diabetes were compared to the same diabetes-free reference group, dose response methods were used to calculate a diabetic vs non-diabetic estimate using appropriate weights [15,18-20]. If not provided, RRs were calculated from study data when possible [19,21-24]. If a 95% CI was not provided, it was calculated using the p-value [25,26]. Descriptions of these methods appear in Supplementary Material.

8. Synthetic Meta-analysis

We calculated summary estimates of effect size for each outcome reported for 2 or more studies (all-cause mortality, bladder cancer-specific mortality, recurrence, RFS, progression), using random-effects and fixed effect models. We base inferences largely on random-effects analyses because available information provides little basis for assuming a single true effect size for all source populations contributing to each analysis. Heterogeneity was characterized by I^2, which represents the proportion of dispersion not explained by random error, corresponding p-value, and tau^2, which represents between-study variance. For each synthetic analysis we created a forest plot displaying results of individual contributing studies and summary estimate, and a funnel plot.

We conducted cumulative meta-analyses ordered by publication year (earliest to latest) and examined resulting cumu-

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lative forest plots and funnel plots for patterns characteristic of publication bias. We report results of synthetic analyses in graphic and tabular forms.

9. Sensitivity Analyses

We evaluated influence of individual studies by 'leave one out' analyses in which synthetic analyses were repeated omitting each study individually and compared resulting summary estimates to the full summary estimate. To evaluate influences of model form used in original analyses we repeated random-effects meta-analyses omitting sets of studies that reported estimates of the risk ratio (RR) or odds ratio (OR) rather than the hazard ratio (HR). To evaluate influence of decisions for redundantly reported data we repeated analyses substituting excluded estimates for included estimates based on the same population.

To investigate influences of potential confounders, we conducted analyses stratified on whether each study controlled potential confounding by age, sex, tumor stage, tumor grade, history of smoking tobacco, and body mass index (BMI), then compared summary estimates from studies that did and did not address each factor. In a further effort to learn whether reported associations were likely to reflect appreciable residual confounding by smoking, we regressed effect size on the score for measure of smoking used in each study, ordered from poorest to best (0, no assessment; 4, assessment of intensity and/or duration).

Due to greater incidence of bladder cancer in males and recognizing that few original studies provided sex-specific estimates enabling synthetic analyses separately for each sex, we conducted study-level analyses, regressing effect size on proportion cases who were female. We implemented these analyses using linear regression weighted by inverse variance of each estimate.

Analyses were implemented using R-Studio (version 4.2.1).

RESULTS

Our searches identified 4868 unique records. After title and abstract screening, 175 full text articles were assessed; 43 met eligibility criteria. Citation searches of the 43 articles identified 3 more (Fig. 1). The 46 articles were reviewed in full. After critical appraisal, data from 28 studies were included in quantitative analyses (Table 1). Of 18 studies excluded during critical appraisal, 3 provided redundant data, 1 used an inappropriate data structure, 1 used enrollment criteria creating extreme vulnerability to bias, and 13 did not report on effect measures of interest (Supplementary Table 1). Included studies investigated over 226,472 bladder cancer patients who were treated with curative intent, among whom over 36,699 were diabetic.

1. All-Cause Mortality

Thirteen studies [16,18,19-24,27-31] provided estimates of the association between diabetes and all-cause mortality. The random-effects summary estimate of this association was 1.22 (95% CI, 1.12–1.33; Fig. 2A). This result was statistically robust: cumulative meta-analysis ordered on study weight revealed that only 2 studies were needed to identify a statistically significant association (Supplementary Fig. 1A), and summary estimate was not materially changed by omitting any individual study (Supplementary Fig. 1B). Between study heterogeneity was moderate but did not achieve statistical significance (I^2=34%, p=0.11). Neither the funnel nor the cumulative forest plot ordered on date (Fig. 2B, C) had features characteristic of publication bias. We found no indication that the association arose by confounding: comparable results were obtained in studies that did or did not address each potential confounder (Table 2), and meta-regression on smoking measure identified a nonsignificant and only slightly lower effect size in studies with poorer measures of smoking (Supplementary Fig. 1C). The summary estimate was strongest in 7 studies in which all patients were treated by cystectomy (1.35 [95% CI, 1.20–1.52]) and similarly high in 5 studies that enrolled only patients with MIBC or high-risk NMIBC (1.32 [95% CI, 1.15–1.50]). By comparison, it was 1.00 [95% CI, 0.63–1.58] in 2 studies of NMIBC patients who did not receive cystectomy. Estimates did not differ appreciably in subgroups defined by other patient characteristics or features of study design investigated by sensitivity analysis (Table 3). Sex did not appear to modify effect size; meta-regression on proportion female participants defined a fitted line with slope not significantly different from 0 (p=0.418) (Supplementary

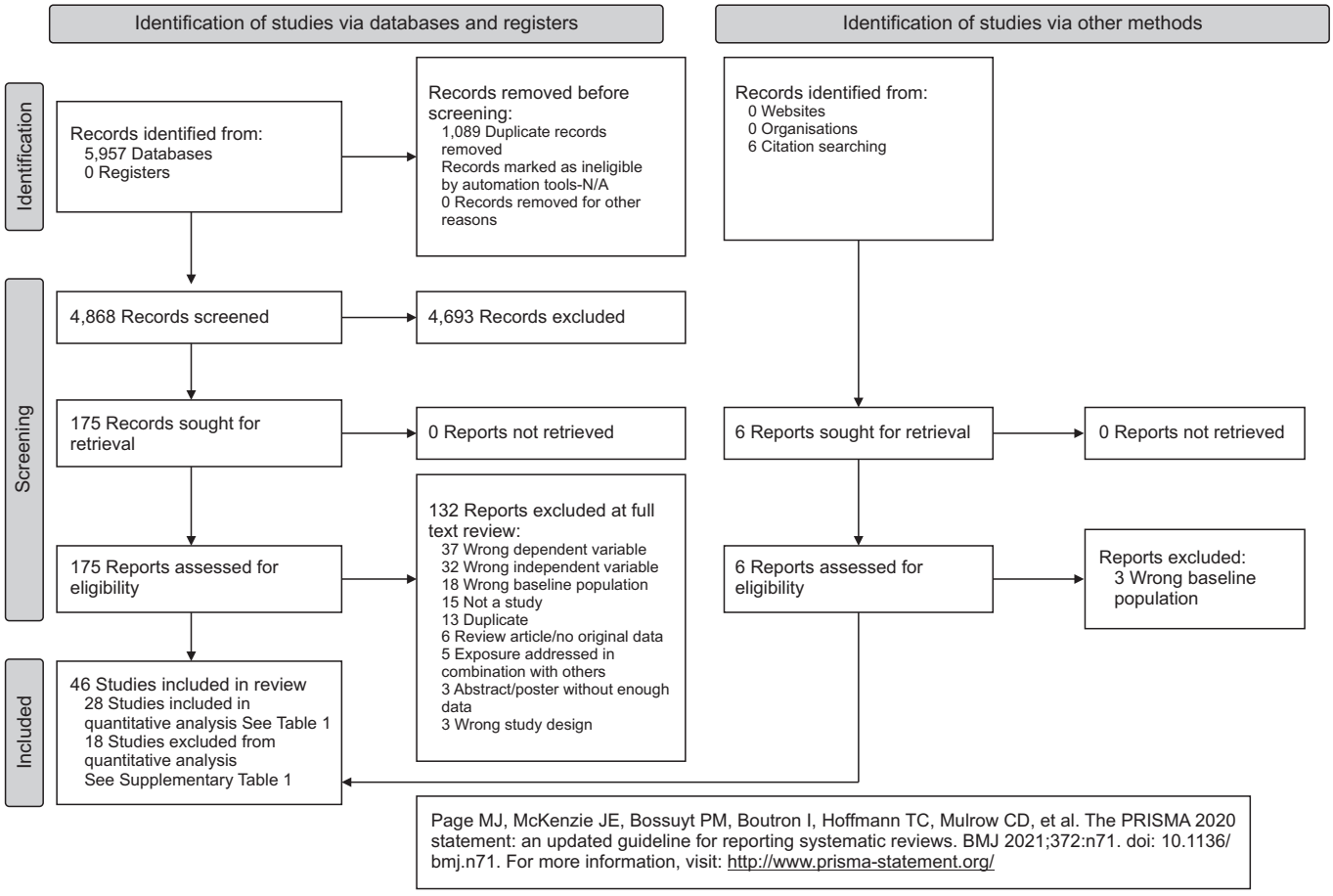

Fig. 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) diagram illustrating flow of data through the systematic review and meta-analyses.

Fig. 1D).

2. Bladder Cancer-Specific Mortality

Nine studies [15,17,18,21,24,27,31-33] provided estimates of association between diabetes and bladder cancer-specific mortality. The random-effects summary estimate was 1.28 (95% CI, 1.17–1.41; Fig. 2D), strongest in 5 studies that enrolled only patients with MIBC or high-risk NMIBC (1.48 [95% CI 1.06–2.06]). There was no apparent association in the single study of NMIBC patients who did not receive cystectomy (0.91 [95% CI, 0.29–2.87]). There was appreciable between study heterogeneity (I^2=72%, p<0.01) indicating variation between studies is unlikely to be due to chance alone. Funnel and cumulative forest plots (Fig. 2E, F) did not show signs of publication bias. These results were statistically robust (Supplementary Fig. 2A and B) and the summary estimate was not materially changed in any sensitivity analysis (Tables 2, 3). Slopes from meta-regression on smoking measure and proportion female participants did not achieve statistical significance (p=0.952 and p=0.619, respectively) (Supplementary Fig. 2C and D).

3. Recurrence and RFS

Eleven studies [15,16,20,24,30,31,34-39] provided estimates of the association between history of diabetes and bladder cancer recurrence; 4 [26,31,40,41] provided estimates for RFS. Random-effects summary estimates were 1.26 (95% CI, 1.13–1.40) for recurrence and 1.33 (95% CI 95% CI 1.24–1.43) for RFS (Fig. 3A, D). Because deaths were scored as events in RFS but not in recurrence, the somewhat stronger association of diabetes with RFS accords with results for mortality described above. There was no indication of heterogeneity for either outcome (recurrence: I^2=0%, p=0.57; RFS: I^2=15%, p=0.32). Funnel and cumulative forest plots

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Table 1. Sources of published data included in quantitative analyses

Year of publication	Last name of first author	No. of participants		Proportion female	Tumor stages included	Initial treatment received	Percent urothelial carcinoma	Addressed age as covariate? (Y/N)	Addressed sex as covariate? (Y/N)	Addressed stage as covariate? (Y/N)	Addressed grade as covariate? (Y/N)	Addressed smoking as covariate? (Y/N)	Addressed BMI/obesity as covariate? (Y/N)	Point and (95% CI) of HR, RR[a], or OR[b] estimate of association between diabetes and outcome of bladder cancer			
		#with DM	#without DM		NMIBC:T0, Ta, Tis, T1 /MIBC:T2, T3, T4									All-cause mortality	Bladder cancer-specific mortality	Recurrence-free survival or recurrence[c]	Progression-free survival or progression[d]
2010	Schade [34][e]	179				Induction BCG		N	N	Y	Y	N	N			2.112[c] (1.183–3.773)	4.19[d] (1.397–12.566)
2012	Liu [32]	849	47,840					Y	Y	N	N	Y	Y		1.33 (1.18–1.49)		
2012	Currie [28]	675	5,968					Y	Y	N	N	Y	N	1.16 (1.02–1.32)			
2012	Karlin [29]	68	831	0.2				Y	Y	N	N	N	N	0.91 (0.63–1.32)			
2013	Rieken [20]	125	992	0.235	Ta, Tis, T1	TUR		Y	N	Y	Y	N	N	1.245[g] (0.905–1.712)		1.159[c,g] (0.887–1.514)	1.974[d,g] (1.171–3.329)
2014	Rieken [18]	200	1,302	0.216	T0, Ta, Tis, T1, T2, T3, T4	RC	100	Y	Y	Y	Y	Y	Y	1.347[g] (1.063–1.707)	1.364[g] (1.039–1.790)	1.178[c,g] (0.920–1.507)	
2014	Ranc [15]							Y	Y	N	N	N	N		1.258[g] (1.195–1.341)		
2014	Rausch [25]	52	140	0.17	Ta, T1			N	N	N	N	N	N			1.2212[c] (0.474–3.1434)	0.7729[d] (0.364–1.6435)
2015	Xu [35]	64	339	0.26	Ta, T1	TUR	100	N	N	N	N	N	N			1.805[c] (1.255–2.596)	3.439[d] (1.636–7.229)
2015	Zhang [30]	25	99	0.19	T1, T2, T3, T4	RC	100	Y	Y	Y	Y	Y	Y	1.678 (0.918–2.029)			
2015	Oh [21]	28	172	0.12	Ta, Tis, T1, T2, T3, T4	RC	100	N	N	Y	N	N	N	1.281 (1.052–1.468)	1.785 (1.252–2.295)	1.117[c,g] (0.171–7.312)	
2015	Dybowski [22]	10	53	0.27	T0, T1, T2, T3, T4	RC	100	N	N	N	N	N	N	1.403[a,g] (0.893–2.204)			
2016	Wang [33]	12	91	0.2427	T1, T2, T3, T4	RC	100	N	Y	Y	Y	N	N		0.104 (0.014–0.786)		
2016	Faiena [19]	16,682	73,603	0.16		RC		Y	Y	N	N	N	N	2.569[b,g] (0.972–6.79)			
2016	Ahn [36]	127	518	0.15	Ta, T1	TUR		Y	Y	Y	Y	Y	N			1.22[c] (0.89–1.67)	1.54[d] (0.95–2.50)
2016	Cao [37]	72	170	0.264	Ta, T1	TUR	100	N	N	N	N	N	N			1.08[c] (0.75–1.56)	
2017	Kwiatkowska [23]	8	36	0.43		RC		N	N	N	N	N	N	1.929[a,g] (0.344–10.808)			
2017	Strele [16]	169	1,658	0.23				Y	N	N	N	N	N	1.252[g] (0.941–1.667)			
2017	Downs [26][e]	120	184			TUR		N	N	N	N	N	N			1.3 (1.27–1.33)	
2018	Hong [27]	21	72	0.3	T2	TUR (n=27) RC (n=66)	100	N	N	N	N	Y	N	2.74 (1.09–6.83)	3.32 (1.28–8.69)	1.45[c] (0.70–3.01)	
2018	Lam [17]	14,199	46,182	0.267				Y	Y	Y	N	N	N		1.162[g] (1.134–1.192)		
2019	Sekar [42][e]	3,563	5,211					Y	Y	Y	N	N	N		1.21[f] (1.01–1.45)		1.113[d,g] (1.008–1.229)
2020	Brooks [40]	104	471	0.2	Ta, Tis, T1	Induction BCG	96	N	Y	Y	Y	Y	Y			1.57 (1.2–2.1)	
2020	Evers [38]	198	1,235	0.172	Ta, Tis, T1		99.4	Y	Y	Y	Y	Y	Y			1.22[c] (0.98–1.54)	1.16[d] (0.76–1.76)
2020	Ferro [41]	231	941	0.169	T1	Induction BCG		Y	Y	Y	Y	Y	Y			1.41 (1.20–1.66)	1.27 (0.99–1.63)
2020	Huang [39]	61	226		T1 , Tis	TUR	100	Y	Y	Y	Y	Y	Y			1.11[c] (0.57–2.19)	
2020	Wang [24]	22	100	0.172	Ta, Tis, T1	Induction BCG	100	Y	N	Y	Y	N	N	0.779[a,g] (0.536–1.132)	0.909[a,g] (0.288–2.872)		
2020	Zhao [31]	14	160	0.2		RC	100	N	N	N	N	N	N	1.00 (0.43–2.30)	0.92 (0.37–2.29)	0.81 (0.30–2.24)	

DM, diabetes mellitus; NMIBC, non–muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; BMI, body mass index; CI, confidence interval; HR, hazard ratio; RR, risk ratio; OR, odds ratio; BCG, bacillus Calmette-Guerin; TUR, transurethral resection; RC, radical cystectomy.

[a]RR. [b]OR. [c]Recurrence. [d]Progression. [e]Information provided only in abstract form, not full text report. [f]Bladder cancer-specific mortality results reported in this abstract excluded from quantitative analysis to avoid redundant use of information provided in full report of Lam 2018. [g]Estimates calculated from information provided in report as described in supplementary methods.

Blank cells indicate that information was not provided in the original report.

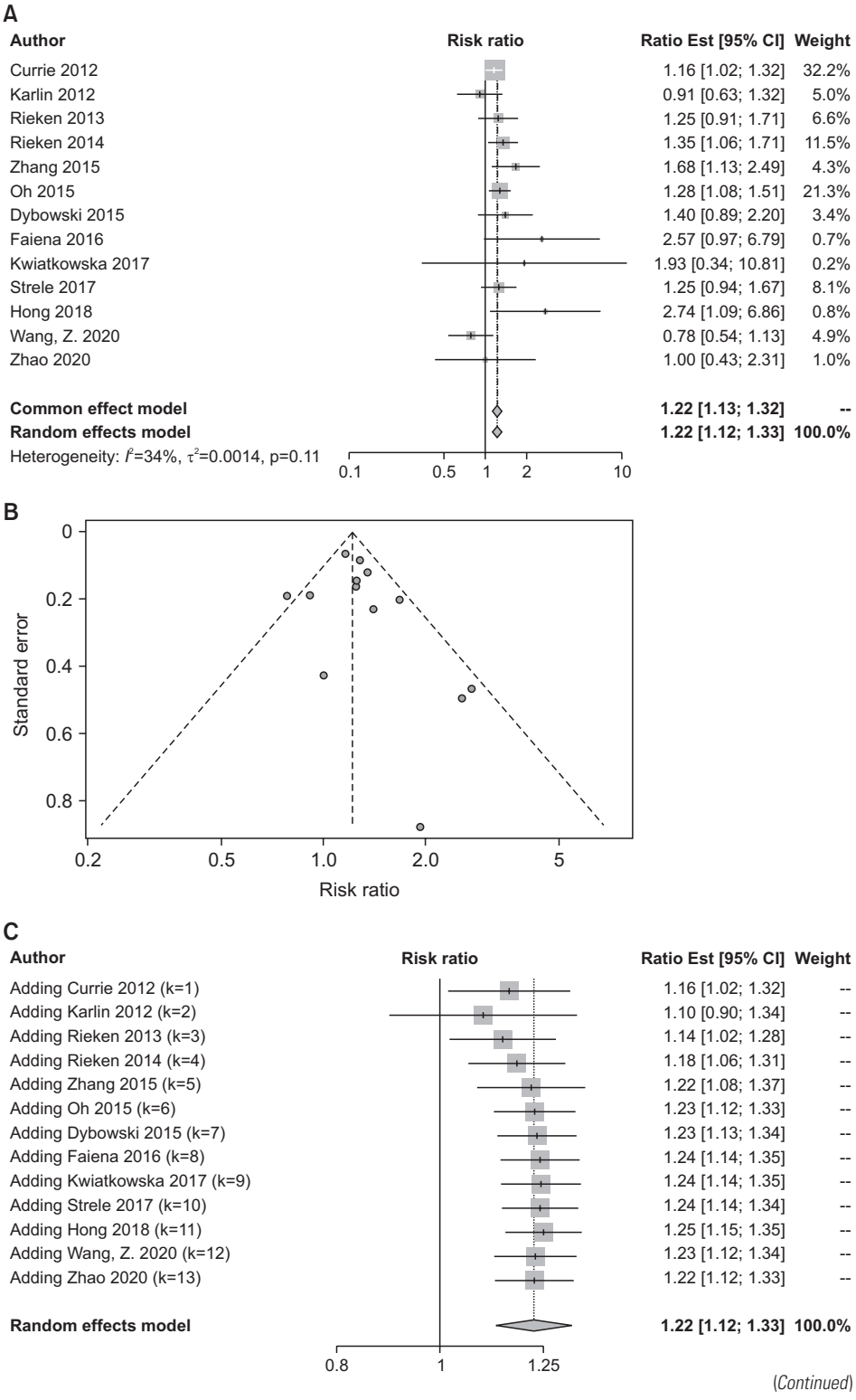

Fig. 2. Results of meta-analyses estimating associations between history of diabetes and mortality outcomes among bladder cancer patients. (A) All-cause mortality, forest plot from synthetic meta-analysis. (B) All-cause mortality, funnel plot. (C) All-cause mortality, forest plot from cumulative meta-analysis by date. (D) Bladder cancer-specific mortality, forest plot from synthetic meta-analysis. (E) Bladder cancer-specific mortality, funnel plot. (F) Bladder cancer-specific mortality, forest plot from cumulative meta-analysis by date. CI, confidence interval.

(*Continued*)

(Fig. 3B, C, E-F) did not show signs of publication bias. Summary estimates for recurrence and RFS were statistically robust (Tables 2, 3; Supplementary Figs. 3A-B, 4A-B). Because mortality was associated with diabetes, we regard RFS as the appropriate measure of recurrence. Available data were not adequate for meta-regression of RFS on proportion female participants, but regression on smoking measure revealed a slight slope consistent with negative confounding

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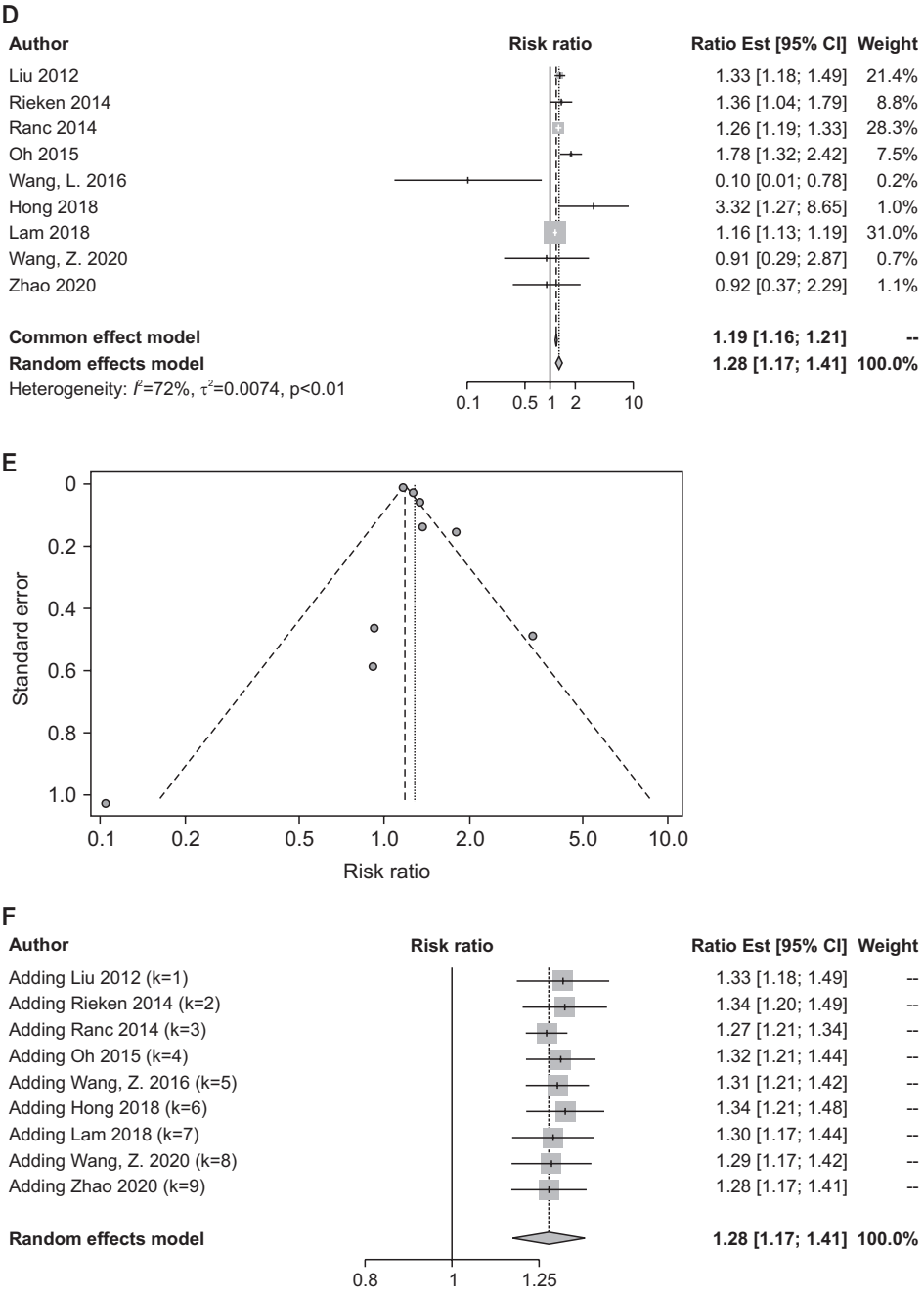

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that did not achieve statistical significance (p=0.136, Supplementary Fig. 4C).

4. Progression and PFS

One study [41] estimated the association between diabetes and PFS, 1.27 (95% CI 0.99–1.63), the more appropriate measure of progression. Seven studies [20,25,34-36,38,42] provided estimates of the association between history of diabetes and bladder cancer progression. The random-effects summary estimate was 1.55 (95% CI, 1.08–2.22; Fig. 3G). Substantial heterogeneity (I^2=71%, p<0.01) indicates that appreciable between study variance may not be due to chance. Funnel and cumulative forest plots (Fig. 3H-I) did not show signs of publication bias. The summary estimate was statistically robust (Supplementary Fig. 5A and B) and largely unchanged in studies that enrolled only bladder cancer patients with urothelial carcinoma. Subgroup analysis that distinguished studies by location resulted in a summary estimate of 2.19 (95% CI, 1.00–4.77) for studies in Asia

Table 2. Summary estimates of association between diabetes and each of 4 bladder cancer outcomes, in full set of contributing studies and subgroups defined by the features of the original studies

Set of studies	Summary estimate (95% CI)	No. of studies	Heterogeneity parameters		
			I^2	p-value	Tau^2
All-cause mortality					
All contributing studies [16,18,19-24,27-31]	1.22 (1.12–1.33)	13	34	0.11	0.0014
Studies located in US and Europe only [18,19,20,22,23,28,29]	1.21 (1.10,1.33)	8	0	0.48	0.0000
Studies located in Asia only [21,24,27,30,31]	1.27 (0.89–1.81)	5	65	0.02	0.0991
Studies which reported time to event data (HR) [16,18,19,20,21,27-31]	1.23 (1.14–1.34)	9	17	0.29	<0.0001
Studies limited to urothelial cell carcinoma [18,21,24,27,30,31]	1.28 (0.99–1.64)	6	57	0.04	0.0529
Studies restricted to type 2 DM [21,28]	1.20 (1.09–1.33)	2	0	0.36	0.0000
Studies which did not differentiate between types 1 and 2 DM [16,18-20,22,23,24,27,29-31]	1.25 (1.06–1.49)	11	42	0.07	0.0307
Studies limited to subjects who underwent radical cystectomy [18,19,21,22,23,30,31]	1.35 (1.20–1.52)	7	0	0.69	0.0000
Studies limited to subjects who did not undergo radical cystectomy [20,24]	1.00 (0.63–1.58)	2	71	0.06	0.0785
Studies which did not limit by treatment or did not specify treatment [16,27-29]	1.16 (1.04–1.30)	4	43	0.15	<0.0001
Studies limited to MIBC and high-risk NMIBC only [18,21,23,27,31]	1.32 (1.15–1.50)	5	0	0.53	0.0000
Studies limited to NMIBC only [20,24]	1.00 (0.63–1.58)	2	71	0.06	0.0785
Bladder cancer-specific mortality					
All contributing studies [15,17,18,21,24,27,31-33]	1.28 (1.17,1.41)	9	72	<0.01	0.0074
Studies located in US and Europe only [15,17,18,32]	1.24 (1.15–1.33)	4	73	0.01	0.0032
Studies located in Asia only [21,24,27,31,33]	1.16 (0.52–2.58)	5	67	0.02	0.5573
Studies which reported time to event data (HR) [15,17,18,21,27,31,32,33]	1.29 (1.17,1.42)	8	76	<0.01	0.0079
Studies limited to urothelial cell carcinoma [18,21,24,27,31,33]	1.43 (0.90–2.07)	6	61	0.02	0.0489
Studies restricted to type 2 DM [21,32]	1.49 (1.12–1.97)	2	68	0.08	0.0296
Studies which did not differentiate between types 1 and 2 DM [15,17,18,24,27,31,33]	1.21 (1.13–1.31)	7	66	<0.01	0.0026
Studies limited to subjects who underwent radical cystectomy [18,21,31,33][a]	1.29 (0.84,1.97)	4	69	0.02	0.0942
Studies limited to subjects who did not undergo radical cystectomy [24]	0.91 (0.29–2.87)	1	-	-	-
Studies which did not limit subjects by treatment or did not specify treatment [15,17,27,32]	1.24 (1.15–1.34)	4	80	<0.01	0.0037
Studies limited to MIBC and high-risk NMIBC only [18,21,27,31,33]	1.48 (1.06,2.06)	5	67	0.02	0.0538
Studies limited to NMIBC only [24]	0.91 (0.29,2.87)	1	NA	NA	NA
Recurrence-free survival (death counted as an event)[b]					
All contributing studies [26,31,40,41]	1.33 (1.24–1.43)	4	15	0.32	0.0015
Studies located in US and Europe only [26,40,41]	1.34 (1.23–1.45)	2	25	0.27	0.0022
Studies located in Asia only [31]	0.81 (0.30–2.21)	1	NA	NA	NA
Progression-free survival (death counted as an event)[b]					
All contributing studies [41]	1.27 (0.99–1.63)	1	NA	NA	NA
Recurrence (death was censored)[c]					
All contributing studies [18,20,21,25,27,34-39]	1.26 (1.13–1.40)	11	0	0.57	0.0000
Studies located in US and Europe Only [18,20,25,34,38]	1.23 (1.07–1.41)	5	0	0.46	0.0000
Studies located in Asia Only [21,27,35-39]	1.31 (1.05–1.64)	6	0	0.47	0.0159
Studies which reported time to event data (HR) [18,20,27,34-39]	1.26 (1.13–1.40)	9	6	0.38	<0.0001
Studies limited to urothelial cell carcinoma [18,21,27,35,36,37,39]	1.27 (1.08–1.49)	7	0	0.54	0.0042
Studies restricted to type 2 DM [21,36,38]	1.09 (0.89–1.35)	3[d]	0	0.66	0.0000
Studies which did not differentiate between types 1 and 2 DM [18,20,25,27,34,35,37,38,39]	1.30 (1.11–1.53)	9[d]	5	0.39	0.0107
Studies limited to MIBC and high-risk NMIBC only [18,21,27]	1.20 (0.95–1.52)	3	0	0.87	0.0000
Studies limited to NMIBC only [20,25,34-39]	1.28 (1.12–1.47)	8	14	0.32	0.0054
Progression (death was censored)[c]					
All contributing studies [20,25,34-36,38,42]	1.55 (1.08–2.22)	7	71	<0.01	0.1538
Studies located in US and Europe only [20,25,34,38,42]	1.34 (0.93–1.92)	5	63	0.03	0.0976
Studies located in Asia only [35,36]	2.19 (1.00–4.77)	2	68	0.08	0.2204
Studies which reported time to event data (HR) [20,34-36,38,42]	1.66 (1.15–2.47)	6	74	<0.01	0.1487
Studies limited to Urothelial Cell Carcinoma [25,35,36]	1.60 (0.72–3.55)	3	74	0.02	0.381
Studies restricted to type 2 DM [36,38]	1.19 (0.78–1.79)	2[d]	56	0.13	0.0521
Studies which did not differentiate between types 1 and 2 DM [20,24,34,35,38,42]	1.66 (1.04–2.65)	6[d]	74	<0.01	0.2289

CI, confidence interval; US, United States of America; DM, diabetes mellitus; MIBC, muscle-invasive bladder cancer; NMIBC, non–muscle-invasive bladder cancer; HR, hazard ratio; NA, not applicable.

[a]Fixed effect estimate reported to address extreme differences in study weights. [b]Results presented in the body of the paper and basis of inferences. [c]Results provided for completeness. [d]Evers 2020 reported both overall diabetes and type 2 diabetes only estimates and was included in both subgroups.

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Table 3. Summary estimates of association between diabetes and each of 4 bladder cancer outcomes by subgroups defined by whether or not study addressed the covariate of interest

Covariate	Addressed					Did not address				
	Summary estimate (95% CI)	No. of studies	Heterogeneity parameters			Summary estimate (95% CI)	No. of studies	Heterogeneity parameters		
			I^2	p-value	Tau^2			I^2	p-value	Tau^2
All-cause mortality										
Age	1.20 (1.04–1.37)	8 [16,18,19,20,24,28-30]	49	0.06	0.0143	1.31 (1.13–1.53)	5 [21,22,23,27,31]	0	0.00	0.5200
Sex	1.26 (1.04–1.52)	5 [18,19,28,29,30]	52	0.02	0.0800	1.22 (1.07–1.40)	8 [16,20-24,27,31]	28	0.20	0.0049
Stage	1.24 (1.03–1.50)	5 [18,20,21,24,30]	54	0.07	0.0246	1.19 (1.07–1.32)	8 [16,19,22,23,27,28,29,31]	21	0.26	0.0000
Grade[a]	1.22 (0.91–1.63)	4 [18,20,24,30]	65	0.03	0.0590	1.21 (1.11–1.33)	9 [16,19,21-23,27,28,29,31]	15	0.31	0.0000
Smoking[b]	1.36 (1.10–1.68)	4 [18,27,28,30]	55	0.09	0.0214	1.17 (1.01–1.36)	9 [16,19,20-24,29,31]	29	0.19	0.0123
BMI	1.43 (1.16–1.75)	2 [18,30]	0	0.35	0.0000	1.19 (1.09–1.29)	11 [16,19,20-24,27,28,29,31]	32	0.15	<0.0001
Bladder cancer-specific mortality										
Age	1.24 (1.15–1.33)	5 [15,17,18,24,32]	65	0.02	0.0031	1.12 (0.36–3.49)	4 [21,27,31,33]	73	0.01	1.0581
Sex	1.23 (1.15–1.33)	5 [15, 17,18,32,33]	76	<0.01	0.0031	1.63 (1.07–2.48)	4 [21,24,27,31]	38	0.18	0.0593
Stage	1.30 (1.02–1.65)	5 [17,18,21,24,33]	73	<0.01	0.0354	1.27 (1.21–1.34)	4 [15,27,31,32]	40	0.17	<0.0001
Grade[a]	0.69 (0.19–2.44)	3 [18,24,33]	69	0.04	0.9049	1.30 (1.15–1.47)	6 [15,17,21,27,31,32]	77	<0.01	0.0119
Smoking[b]	1.35 (1.21–1.50)	3 [18,27,32]	42	0.18	<0.0001	1.25 (1.05–1.49)	6 [15,17,21,24,31,33]	74	<0.01	0.02
BMI	1.34 (1.20–1.49)	2 [18,32]	0	0.87	0.0000	1.30 (1.06–1.59)	7 [15,17,21,24,27,31,33]	75	<0.01	0.0315
Recurrence-free survival										
Age	1.41 (1.20–1.66)	1 [41]	-	-	-	1.33 (1.18–1.49)	3 [26,31,40]	23	0.27	0.0039
Sex	1.45 (1.26–1.67)	2 [40,41]	0	0.51	0	1.30 (1.27–1.33)	2 [26,31]	0	0.36	0
Stage	1.45 (1.26–1.67)	2 [40,41]	0	0.51	0	1.30 (1.27–1.33)	2 [26,31]	0	0.36	0
Grade[a]	1.45 (1.26–1.67)	2 [40,41]	0	0.51	0	1.30 (1.27–1.33)	2 [26,31]	0	0.36	0
Smoking[b]	1.45 (1.26–1.67)	2 [40,41]	0	0.51	0	1.30 (1.27–1.33)	2 [26,31]	0	0.36	0
BMI	1.45 (1.26–1.67)	2 [40,41]	0	0.51	0	1.30 (1.27–1.33)	2 [26,31]	0	0.36	0
Recurrence										
Age	1.19 (1.05–1.35)	5 [18,20,36,38,39]	0	1.00	0.0000	1.48 (1.11–1.98)	6 [21,25,27,34,35,37]	12	0.34	0.0372
Sex	1.20 (1.04–1.39)	4 [18,36,38,39]	0	0.99	0.0000	1.38 (1.09–1.75)	7 [20,21,25,27,34,35,37]	20	0.27	0.0319
Stage	1.22 (1.08–1.38)	7 [18,20,21,34,36,38,39]	0	0.71	0.0000	1.39 (1.00–1.91)	4 [25,27,35,37]	23	0.27	0.0378
Grade[a]	1.22 (1.08–1.38)	6 [18,20,34,36,38,39]	0	0.59	<0.0001	1.38 (1.01–1.89)	5 [12,25,27,35,37]	0	0.41	0.0352
Smoking[b]	1.21 (1.05–1.39)	5 [18,27,36,38,39]	0	0.99	0.0000	1.38 (1.06–1.80)	6 [20,21,25,34,35,37]	33	0.19	0.0408
BMI	1.20 (1.02–1.41)	3 [18,38,39]	0	0.96	0.0000	1.34 (1.11–1.61)	8 [20,21,25,27,34-37]	10	0.35	0.0170
Progression										
Age	1.30 (1.01–1.66)	4 [20,36,38,42]	49	0.12	0.0307	2.15 (0.74–6.25)	3 [25,34,35]	80	<0.01	0.6894
Sex	1.13 (1.03–1.24)	3 [36,38,42]	0	0.43	0.0000	2.07 (1.02–4.22)	4 [20,25,34,35]	70	0.02	0.3706
Stage	1.44 (1.06–1.95)	5 [20,34,36,38,42]	64	0.02	0.0657	1.63 (0.38–7.05)	2 [25,35]	87	<0.01	0.9683
Grade[a]	1.66 (1.14–2.36)	4 [20,34,36,38]	48	0.12	0.0541	1.40 (0.62–3.16)	3 [25,35,42]	79	<0.01	0.4258
Smoking[b]	1.31 (0.95–1.80)	2 [36,38]	0	0.39	0.0000	1.75 (0.98–3.12)	5 [20,25,34,35,42]	79	<0.01	0.3209
BMI	1.16 (0.76–1.77)	1 [38]	-	-	-	1.67 (1.07–2.61)	6 [20,25,34,35,36,42]	76	<0.01	0.2097

CI, confidence interval; BMI, body mass index.

[a]Fixed effect estimate reported to address extreme differences in study weights. [b]Studies which controlled for smoking did so at the level of yes/no, ever/never, current/former/never, measures of intensity and/or duration, or using a proxy measure (i.e., chronic obstructive pulmonary disease).

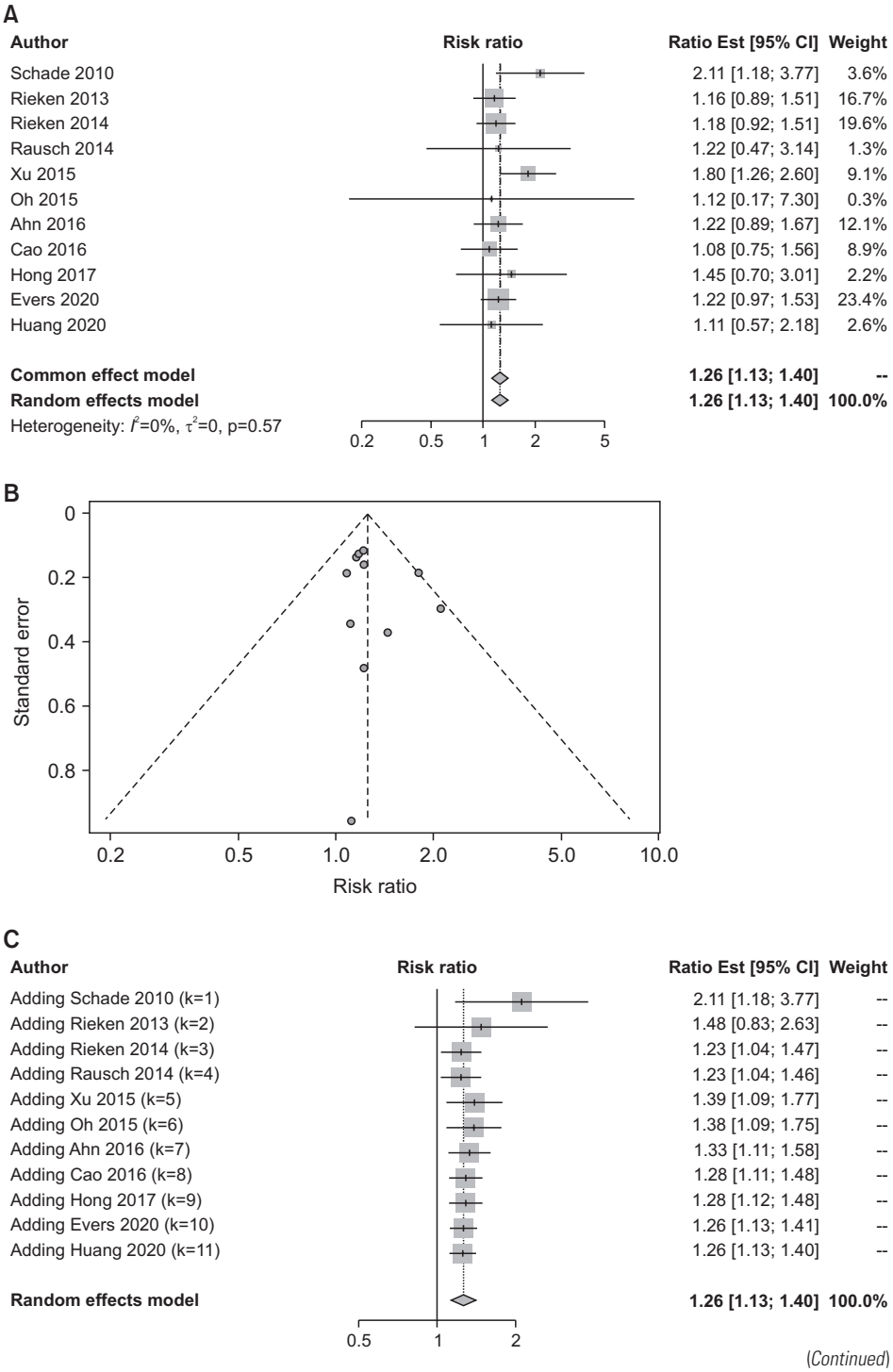

Fig. 3. Results of meta-analyses estimating associations between history of diabetes and recurrence and progression outcomes among bladder cancer patients. (A) Bladder cancer recurrence, forest plot from synthetic meta-analysis. (B) Bladder cancer recurrence, funnel plot. (C) Bladder cancer recurrence, forest plot from cumulative meta-analysis by date. (D) Bladder cancer recurrence-free survival, forest plot from synthetic meta-analysis. (E) Bladder cancer recurrence-free survival, funnel plot. (F) Bladder cancer recurrence-free survival, forest plot from cumulative meta-analysis by date. (G) Bladder cancer progression, forest plot from synthetic meta-analysis. (H) Bladder cancer progression, funnel plot. (I) Bladder cancer progression, forest plot from cumulative meta-analysis by date.

(*Continued*)

(n=2), but 1.34 (95% CI, 0.93–1.92) for studies in the US and Europe (n=5); it is noteworthy that studies conducted in Asia enrolled only patients with urothelial carcinoma. The summary estimate for studies of patients with types 1 and 2 diabetes was 1.66 (95% CI, 1.04–2.65), while for studies that included only type 2 diabetics it was 1.19 (95% CI, 0.78–1.79; Table 2). Meta-regression on proportion female defined a slope that did not differ from 0 (p=0.135; Supplementary Fig. 5C).

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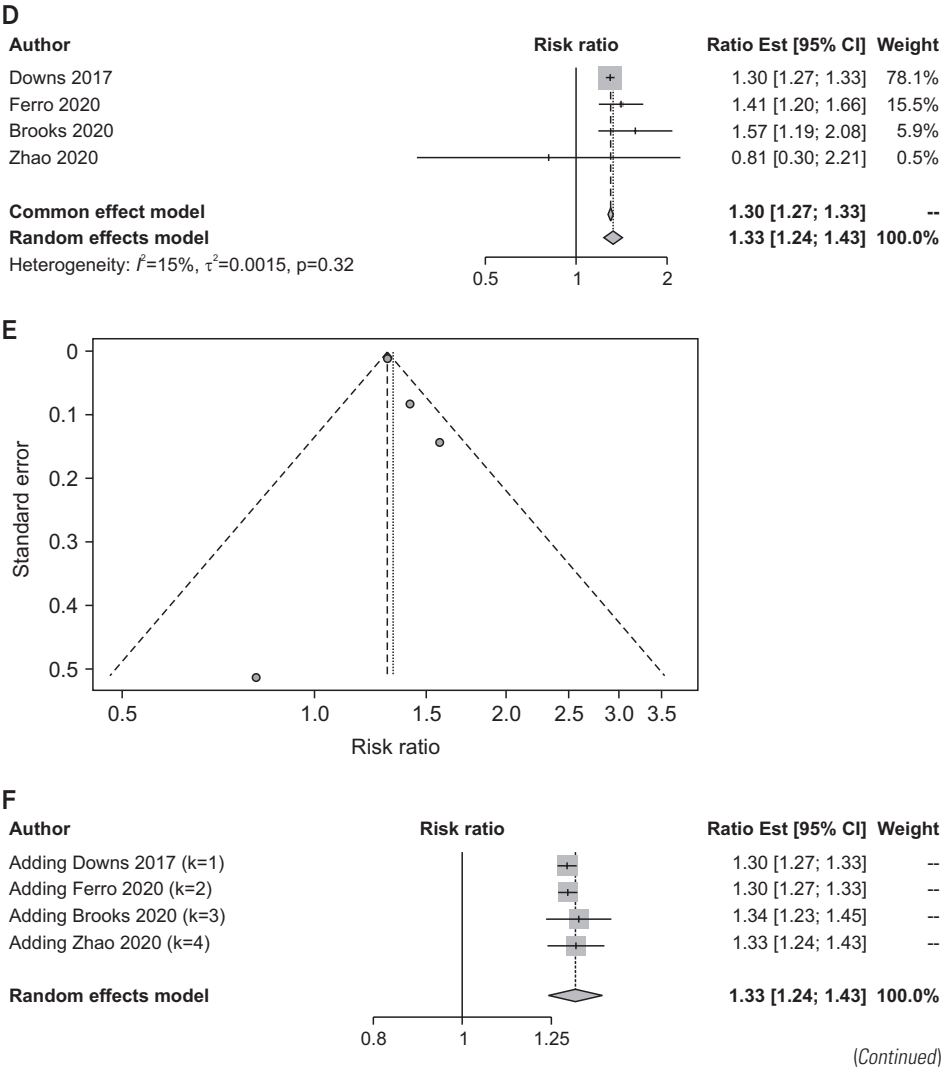

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(*Continued*)

DISCUSSION

Among bladder cancer patients treated with curative intent, those with diabetes more frequently experienced each of the unfavorable outcomes investigated. Estimates of effect size for all-cause mortality and bladder cancer-specific mortality were comparable, as expected if increased risk of death in diabetics were not due predominately to diabetes-related comorbidities or complications (i.e., cardiovascular disease, wound infections), instead resulting from influence of diabetes on persistence and/or evolution of bladder cancer itself. Consistent with this hypothesis, the meta-analysis identified greater frequency of bladder cancer recurrence and progression in diabetics compared to nondiabetics. Mechanisms by which diabetes may contribute to oncogenesis remain undefined; however, hyperglycemia, hyperinsulinemia, and IGF have all been implicated in cell proliferation and mitogenesis [43]. The plausibility of diabetes-related oncogenesis mediated by these or other mechanisms is supported by separate research identifying elevated cancer-specific mortality in diabetic patients with other cancer types. In a recent review, Shahid et al. [44] reported this finding in diabetic patients with a variety of other cancers. Excess mortality among diabetics is attributed largely to complications of diabetes, predominantly cardiovascular disease [45]. But in a large population-based study of cancer patients by van de Poll-Franse et al. [46], although cardiovascular disease was more prevalent among diabetics than nondiabetics, mortality was greater in those with diabetes after controlling for cardiovascular disease. The relationship of diabetes to recurrence and progression of cancer has been less studied, although diabetics have been

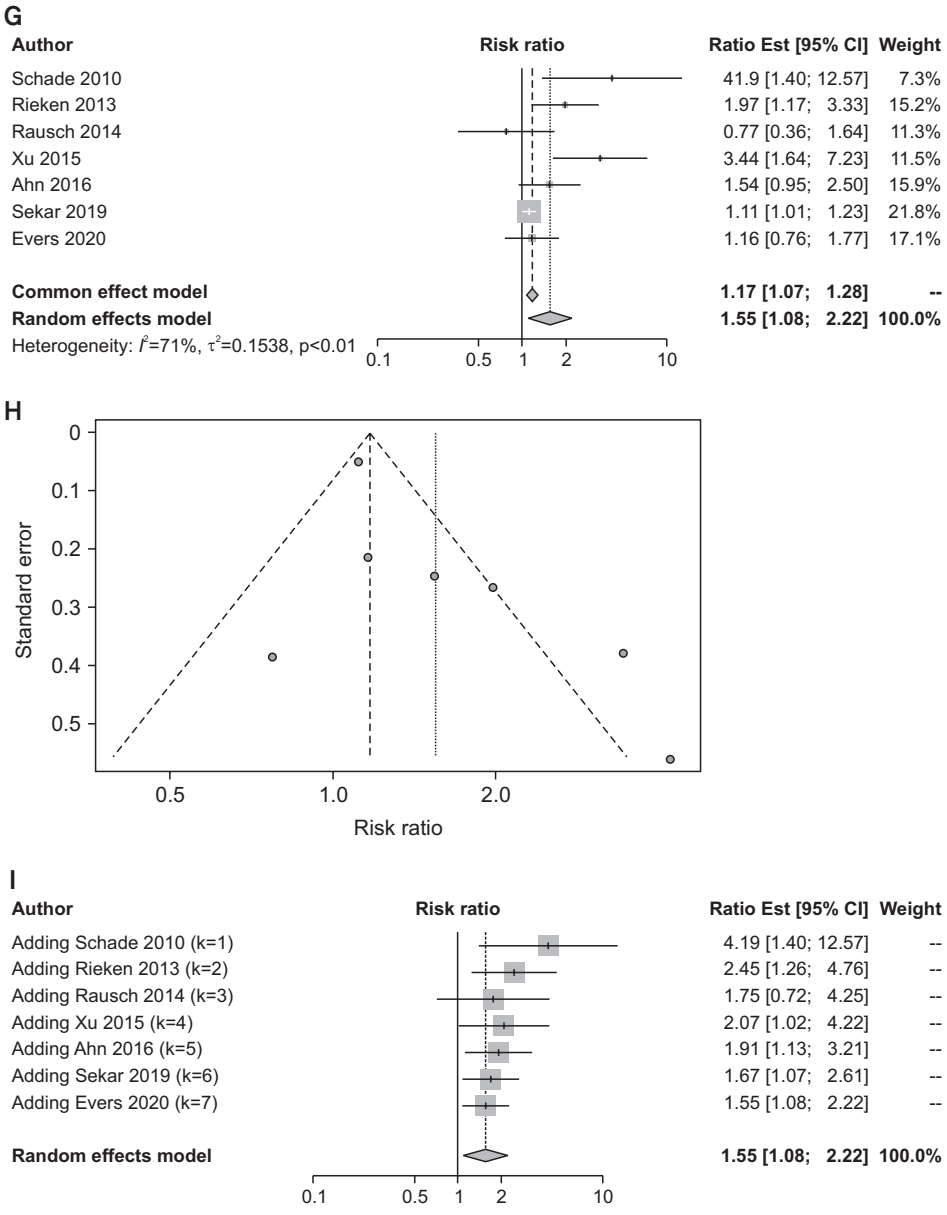

Fig. 3. Results of meta-analyses estimating associations between history of diabetes and recurrence and progression outcomes among bladder cancer patients. (A) Bladder cancer recurrence, forest plot from synthetic meta-analysis. (B) Bladder cancer recurrence, funnel plot. (C) Bladder cancer recurrence, forest plot from cumulative meta-analysis by date. (D) Bladder cancer recurrence-free survival, forest plot from synthetic meta-analysis. (E) Bladder cancer recurrence-free survival, funnel plot. (F) Bladder cancer recurrence-free survival, forest plot from cumulative meta-analysis by date. (G) Bladder cancer progression, forest plot from synthetic meta-analysis. (H) Bladder cancer progression, funnel plot. (I) Bladder cancer progression, forest plot from cumulative meta-analysis by date. (Continued)

shown to have elevated recurrence of colon cancer [47].

Critical appraisal identified several potential sources of systematic error in studies included in our meta-analyses, but these are unlikely to explain elevated mortality amongst diabetic patients. Diabetes care could lead to earlier detection of recurrence or progression in some bladder cancer patients with diabetes. Consequently, differential misclassification could account for some of the positive association between diabetes and some outcomes, but could not create associations with mortality outcomes, because being followed more closely does not make death more apparent. The first sign of bladder cancer is often hematuria detected on a routine urinalysis [48], and diabetics may undergo more frequent urinalysis to screen for glucose or ketones [49] leading to earlier diagnosis of bladder cancer, resulting in lead-time-bias creating spurious impressions of better outcomes in diabetic patients. This would attenuate rather than create the positive associations reported here. Prior studies document that cancer patients with diabetes were treated less aggressively than those without diabetes [46], and specific treatments may be avoided in diabetic patients with MIBC [50]. If some patients with severe or uncontrolled diabetes were not treated surgically for their bladder cancer, they would be underrepresented in studies of patients who

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underwent radical cystectomy. Such exclusions would introduce downward bias if severe diabetes influences course of bladder cancer more strongly than milder forms, and introduce no bias otherwise. Thus, although these forms of systematic error cannot be ruled out, their presence would not create spurious positive associations between diabetes and mortality, and may have introduced downward bias causing summary results to underestimate true effects.

Studies contributing to the meta-analysis were inconsistent in addressing potentially confounding variables. Older age is associated with mortality, and females have been reported in several studies to have slightly poorer bladder cancer outcomes. In subsets of studies that controlled for each of these factors, summary estimates revealed statistically elevated occurrence of all outcomes among diabetics. Smoking is related to bladder cancer mortality [51] and a risk factor for developing type 2 diabetes [52] and mortality among diabetics [53]. Meta-regression on quality of smoking measure used in each study provided no indication of positive residual confounding that might explain observed associations. Tumor stage and grade are important predictors of bladder cancer outcome, but incidental detection of hematuria in diabetics could result in a distribution of lower stage among diabetics as described above [46,48,49]. To the extent that this occurred, negative confounding could be anticipated in studies that did not address these factors. In subsets of studies that controlled for stage or grade, positive associations approaching or achieving statistical significance were observed in all but one analysis. The exception was an inverse association of diabetes and bladder cancer-specific survival estimated for the small set of studies controlled for grade; this cannot be explained by positive confounding, so may represent random error. Obesity is a risk factor for type 2 diabetes [54]. Obese individuals have been reported to experience elevated bladder cancer recurrence [55], so studies that did not control for obesity could be subject to positive confounding. Sensitivity analyses identified little difference in effect size between studies which did or did not address BMI. These considerations provide reassurance that confounding is unlikely to explain observed associations between diabetes and unfavorable outcomes.

Meta-regression did not identify differences in effect size for males and females, but data required to investigate other potential sources of heterogeneity were not available. For example, previous research revealed inconsistent associations between use of diabetic medications and oncogenesis [56]. Metformin has been associated with decreased cancer risk [57] while other diabetic medications may increase cancer risk [58]. Possible influences of diabetic medications on bladder cancer survival have not been characterized. Thus, differing levels of control for use of antidiabetic medications could explain some of the heterogeneity observed. Other possible sources of heterogeneity include differences in methods of classifying diabetes, different proportions of type 1 and type 2 disease among diabetic participants, differing degrees of glycemic control among diabetic participants, and differing follow-up periods.

CONCLUSION

In summary, we report a systematic review and quantitative summary of published data identifying a clear pattern of poorer outcomes of bladder cancer in patients with diabetes. Despite limitations of studies included in the meta-analysis, bias is unlikely to explain these results. Our study therefore implicates features of diabetes such as hyperinsulinemia and hyperglycemia in an unfavorable course of bladder cancer and identifies diabetes care as a possible component of personalized management of bladder cancer. Further investigation is warranted to pursue these possibilities and to rectify the dearth of scholarly information on diabetes in relation to clinical course of bladder cancer. New research should be implemented with careful control of potential confounders, and with detailed consideration and reporting of types and severity of diabetes, diabetes treatment during cancer care, elements of bladder cancer treatment, whether bladder cancer diagnosis was incidental to diabetes care, and whether patients with severe diabetes are advised to forego elements of usual bladder cancer care at participating institutions. Meanwhile, although mechanisms by which diabetes may lead to worse outcomes for patients with bladder cancer are not established, these results support a multidisciplinary approach to the management of bladder cancer in patients with diabetes in which endocrinologists and urologists coordinate care to improve outcomes [44,46].

NOTES

- **Supplementary Materials:** Supplementary Material, Table 1 and Figs. 1-5 can be found via https://doi.org/10.22465/juo.244600020001
- **Author Contribution:** Conceptualization: SF, VC, PZ, LK, RJ, SP, SD; Data curation: SF, VC, PZ, LK, RJ; Formal analysis: KS, RM, SF, VC; Methodology: SF, VC, PZ, RM, KS; Project administration: SF, KS, VC; Visualization: SF, RM, KS, VC; Writing - original draft: SF, VC, PZ; Writing - review & editing: SF, PZ, RM, SP, SD, KS, VC
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ERRATUM

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Declaration of Conflict of Interest for Editorial Board Members' Articles

Editorial Office, Korean Urological Oncology Society

The journal's policy in handling editors' or in-house staff's manuscript was posted on January 1, 2023 at the "instructions for authors (https://www.e-juo.org/authors/authors.php)" and "principles of transparency and best practice (https://www.e-juo.org/about/best_practice.php)" sections as follows:

"All manuscripts from editors, employees, or members of the editorial board are processed the same as other unsolicited manuscripts. During the review process, submitters will not engage in the decision process. Editors will not handle their own manuscripts, although they are commissioned ones. We neither guarantee the acceptance without review nor very short peer review times for unsolicited manuscripts. Commissioned manuscripts also were reviewed before publication."

Therefore, the conflict of interest declaration of the following 7 articles are added as follows:

1. Ito K, Kimura T. Complex Epidemiology of Prostate Cancer in Asian Countries. Journal of Urologic Oncology 2023;21(1):5-13. https://doi.org/10.22465/juo.234600140007.

Conflict of Interest

Takahiro Kimura has been an editorial board member of Science Editing since 2023 but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported. The opinions provided in this manuscript reflect the authors' personal views and do not represent that of their affiliated organizations.

2. Kim JE, Lee K, Kim IY. Current Update on Prostate Cancer Immunotherapy. Journal of Urologic Oncology 2023;21(1):14-22. https://doi.org/10.22465/juo.234600100005.

Conflict of Interest

Isaac Y. Kim has been an editorial board member of Science Editing since 2023 but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported. The opinions provided in this manuscript reflect the authors' personal views and do not represent that of their affiliated organizations.

3. Akamatsu S, Mizuno K, Sumiyoshi T, Goto T, Kobayashi T. The Current State and Future of Plasma Cell-Free DNA Analysis in Urologic Malignancies. Journal of Urologic Oncology 2023;21(1):23-31. https://doi.org/10.22465/juo.234600060003.

Conflict of Interest

Shusuke Akamatsu has been an editorial board member of Science Editing since 2023 but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported. The opinions provided

in this manuscript reflect the authors' personal views and do not represent that of their affiliated organizations.

4. Ko YH, Kim SW, Kim H, Bae YJ. 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. Journal of Urologic Oncology 2023;21(1):53-58. https://doi.org/10.22465/juo.234600020001.

Conflict of Interest

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5. Choi J, Song C, Suh J, Kang M, Choi CI, Yuk HD, et al. Contemporary Management of Small Renal Masses by Urologic Oncologists: A 2022 Korean Renal Cancer Study Group Practice Pattern Survey. Journal of Urologic Oncology 2023;21(1):59-69. https://doi.org/10.22465/juo.234600120006.

Conflict of Interest

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6. Kim JH, Ko YH, Kim JW, Kang SH, Jung SI, Park JS, et al. The Prognostic Impact of Angiolymphatic Invasion in Bladder Urothelial Carcinoma Patients Undergoing Radical Cystectomy. Journal of Urologic Oncology 2023;21(1):79-87. https://doi.org/10.22465/juo.224400340017.

Conflict of Interest

Young Hwii Ko, Jong Wook Kim, and Jong Jin Oh have been an editorial board member of Science Editing since 2023 but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported. The opinions provided in this manuscript reflect the authors' personal views and do not represent that of their affiliated organizations.

7. Ku JY, Gu HM, Yu SH, Hwang EC, Han MA, Jung JH, et al. Korean Urologic Oncology Society Guidelines: Does Angioembolization Improve the Quality of Life for Renal Cell Carcinoma Patients With Intractable Symptoms Who Are Unfit for Surgery? Journal of Urologic Oncology 2023;21(2):140-147. https://doi.org/10.22465/juo.234600180009.

Conflict of Interest

Cheol Kwak has been an editorial board member of Science Editing since 2023 but has no role in the decision to publish this article. Except for that, no potential conflict of interest relevant to this article was reported. The opinions provided in this manuscript reflect the authors' personal views and do not represent that of their affiliated organizations.

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Instructions for Authors

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GENERAL INFORMATION

Aims and Scope

Aims: *Journal of Urologic Oncology* aims to free humanity suffering from urologic neoplasms from the agony of diseases.

Scope: It publishes practical, timely, and relevant clinical and basic science research articles addressing any aspect of urologic oncology, including follows: 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.

Regional scope: Its regional scope is mainly Korea, but it welcomes submissions from all over the world.

Its readership includes urologists, oncologists, radiologists, and clinicians treating patients and to those involved in research on diseases of urologic oncology.

Its publication type includes original articles, review articles, editorials, rapid communications, brief reports, and letters to the editor.

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

1. Research Ethics

All manuscripts should be prepared with strict observation of the research and publication ethics guidelines presented by the Council of Science Editors (https://www.councilscienceeditors.org/), International Committee of Medical Journal Editors (ICMJE; https://www.icmje.org/), World Association of Medical Editors (WAME; https://www.wame.org/), and the Korean Association of Medical Journal Editors (KAMJE; https://www.kamje.or.kr/en/main_en).

Any study including human subjects or human data must be reviewed and approved by a responsible institutional review board (IRB). Authors should refer to the principles embodied in the Declaration of Helsinki (https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/) for all investigations involving human materials.

Animal experiments should also be reviewed by an appropriate committee for the care and use of animals (e.g., the Institutional Animal Care and Use Committee). Studies with pathogens requiring a high degree of biosafety should pass review by a relevant committee (e.g., the Institutional Biosafety Committee). JUO always requests the submission of copies of informed consent forms from human subjects in clinical studies or IRB approval documents.

2. Conflicts of Interest

A conflict of interest exists when an author or the author's institution, reviewer, or editor has financial or personal relationships that inappropriately influence or bias his or her actions. Such relationships are also known as dual commitments, competing interests, or competing loyalties. These relationships vary from being negligible to having a great potential for influencing judgment. Not all relationships represent a true conflict of interest. Nonetheless, the potential for conflict of interest can exist regardless of whether

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The Editor will decide whether information on the conflict should be included in the published paper. If necessary, before publishing such information, the Editor will consult with the corresponding author. In particular, all sources of funding for a study should be explicitly stated.

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Authors are required to clearly state their contributions to a manuscript in the cover letter. To be listed as an author, one should have contributed substantially to all four categories established by the ICMJE: (1) conception and design, or acquisition, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published; and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Each author should be accountable for the parts of the work he or she has done. In addition, each author should be able to identify which coauthors are responsible for specific other parts of the work and should have confidence in the integrity of the contributions of any coauthors. All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors.

When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. When submitting a manuscript authored by a group, the corresponding author should clearly indicate the preferred citation and identify all individual authors as well as the group name. Journals generally list other members of the group in the Acknowledgments. Acquisition of funding, collection of data, or general supervision of the research group alone does not constitute authorship. Authors are responsible for replying to all questions asked by reviewers or editors that relate to the accuracy or integrity of any part of the work. All persons who have made a substantial contribution, but who are not eligible to be considered authors, should be named in the acknowledgments. Authors are expected to consider carefully the way authors should be listed and ordered before submitting their manuscript, and to provide a definitive list of authors with their original submission. Any addition, deletion, or rearrangement of author names in the authorship list should be made before the manuscript has been accepted—and only if approved by the journal Editor. To request such a change, the Editor must receive the following from the corresponding author: (1) the reason for requesting a change in the list of authors; and (2) written confirmation (by email or letter) from all authors saying that they agree with the addition, removal, or rearrangement.

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.

5. Redundant Publication and Plagiarism

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

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When submitting a manuscript, authors should include a letter informing the Editor of any potential overlap with other already published material or material being evaluated for publication and should also state how the manuscript submitted to JUO differs substantially from this other material. If all or part of the patient population was previously reported, this should be mentioned in the Materials and Methods, with citation of the appropriate reference(s).

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6. Obligation to Register Clinical Trials

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.

JUO accepts the registration in any of the primary registries that participate in the WHO International Clinical Trials Portal (http://www.who.int/ictrp/about/details/en/index.html), as well as https://www.anzctr.org.au/, www.clinicaltrials.gov, www.umin.ac.jp/ctr/index/htm and www.trialregister.nl. The clinical trial registration number shall be published at the end of the abstract.

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When the journal faces suspected cases of research and publication misconduct, such as a redundant (duplicate) publication, plagiarism, fabricated data, changes in authorship, undisclosed conflicts of interest, an ethical problem discovered with the submitted manuscript, a reviewer who has appropriated an author's idea or data, complaints against editors, and other issues, the resolving process will follow the flowchart provided by the Committee on Publication Ethics (http://publicationethics.org/resources/flowcharts). The Editorial Board will discuss the suspected cases and reach a decision. We will not hesitate to publish errata, corrigenda, clarifications, retractions, and apologies when needed.

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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Honest errors are a part of science and publishing and require publication of a correction when they are detected. Corrections are needed for errors of fact. The minimum standards are as follows: First, the journal shall publish a correction notice as soon as possible, detailing changes from and citing the original publication on both an electronic and numbered print page that is included in an electronic or a print Table of Contents to ensure proper indexing; second, the journal shall post a new article version with details of the changes from the original version and the date(s) on which the changes were made through CrossMark; third, the journal shall archive all prior versions of the article, and this archive can be directly accessible to readers; and fourth, previous electronic versions shall prominently note that there are more recent versions of the article via CrossMark.

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Post-publication discussions can be conducted through letters to the editor. If any readers have a concern about any articles published, they can submit a letter to the editor about the issue. If any errors or mistakes in the article are found, the article can be corrected through an erratum, corrigendum, or retraction.

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1. General Guideline

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1. Formatting by Manuscript Type

- Original Articles should be composed of no more than 3,000 words, excluding the references, tables, and figures, and organized in the order of title, abstract, introduction, materials and methods, results, discussion, conclusion, references, tables, and figures or illustrations.
- 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.
- Special Articles are invited with the intention of special introduction of medical information in the field of urologic oncology. The format of the abstract and manuscript may be structured or unstructured. The length of the manuscript should not exceed 3,500 words. More extensive manuscripts will be considered and judged on their merits; however, authors are urged to be as concise as possible.
- 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.
- Brief Reports are articles with a simple and short structure that nonetheless deserve to be reported within the urologic oncology field, especially in clinical and research areas. This is not a section for case reports; instead, it is appropriate for basic/clinical research that deals with a timely and important urologic oncology issue, but needs a more elaborate statistical analysis, for example. The format is shorter than original articles, and the best-suited articles for this category are those with a concise presentation.
- 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.
- Text should be written in a 12-point font with double line spacing.
- The detailed formatting recommendations for each type are shown in the table below.

Summary Table of Manuscript Types

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

Note: Exceptions may be made to the above specifications according to the decision of the editorial committee.

2. Title Page

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.

The title page also contains the postal address and email address of the corresponding author at the bottom of the page, as well as information on any previous presentation of the manuscript in conferences and funding resources, if necessary.

The title should be concrete and not exceed 20 words, and the running title should not exceed 50 characters, including spaces.

3. Abstract

Abstracts for articles presenting clinical or laboratory research should contain the following sections: purpose, materials and methods, results, and conclusion. However, these sections are not necessary for other types of studies.

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.

Abstracts can be revised by the decision of the Editorial Board, and some sentences can be modified as a result of revision.

A list of key words, with a minimum of 3 items and maximum of 6 items, should be included at the end of the abstract. The selection of key words should be based on Medical Subject Heading (MeSH) of Index Medicus and the website (http://www.nlm.nih.gov/mesh/MBrowser.html).

4. Introduction

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.

When reporting experiments with human subjects, the authors must document the approval received from the local IRB. When reporting experiments with animal subjects, the authors should indicate whether the handling of the animals was supervised by the research board of the affiliated institution or a similar entity. The IRB approval number must be noted.

Photographs disclosing patients must be accompanied by a signed release form from the patient or the patient's family permitting publication.

Authors should ensure correct use of the terms sex (when reporting biological factors) and gender (identity, psychosocial, or cultural factors), and, unless inappropriate, report the sex and/or gender of study participants, the sex of animals or cells, and describe the methods used to determine sex and gender. If the study was done involving an exclusive population, for example in only one sex, authors should justify why, except in obvious cases (e.g., prostate cancer). Authors should define how they determined race or ethnicity and justify their relevance.

6. Results

Only important findings observed or results that directly answer the study purposes should be described. Results should be presented logically, matching the order appearing in the Materials and Methods section. Tables and graphs should be used to show numerical data, while descriptive sentences should be reserved for only important data. Demographic data of study subjects, such as age and the sex/gender distribution, should not be mentioned in this section. The repetitive enumeration of findings shown in tables and graphs should be avoided. The past tense should be used.

7. Discussion

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.

8. Conclusions

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 or expected benefits is not recommended.

9. References

All references should be numbered consecutively in the order in which they are first mentioned in the text. In using in-text reference citation, each reference should be cited in square brackets as [1], [1,2], or [1-3]. The reference format should conform to the Vancouver form (N Engl J Med 1997;336:309-15; https://www.nejm.org/doi/full/10.1056/nejm199701233360422).

Use the style of the examples below, which are based on the formats used by the U.S. National Library of Medicine (NLM) in Index Medicus. The titles of journals should be abbreviated according to the style used in Index Medicus. Authors should consult the List of Journals Indexed in Index Medicus, published annually as a separate publication by the library and as a list in the January issue of Index Medicus. The list can also be obtained through the library's web site: https://www.nlm.nih.gov/bsd/aim.html.

Avoid using abstracts as references. References to papers accepted but not yet published should be designated as "in press" or "forthcoming"; authors should obtain written permission to cite such papers as well as verification that they have been accepted for publication. Information from manuscripts submitted but not accepted should be cited in the text as "unpublished observations" with written permission from the source.

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The references must be verified by the author(s) against the original documents.

The "Uniform Requirements" style (the Vancouver style) is based largely on an ANSI standard style adapted by the NLM for its databases.

1) Articles in Journals

(1) Standard journal article

List the first six authors followed by et al.

- Babaian RJ, Toi A, Kamoi K, Troncoso P, Sweet J, Evans R, et al. A comparative analysis of sextant and an extended 11-core multisite directed biopsy strategy. J Urol 2000;163:152-7.
- 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.

(4) Chapter in a book
- 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.

10. Tables
- Tables should be created using the table formatting and editing feature of Microsoft Word and should not be provided in non-editable image format.
- The title of the table must be noted. Tables cannot be submitted in a picture format.
- Each table should be inserted on a separate page, with the table number, table title and legend above the table.
- Tables should be concise and not duplicate information found in figures.
- The significance of results should be indicated by an appropriate statistical analysis.

- Unnecessary longitudinal lines should not be drawn. Horizontal lines should be used as sparingly as possible.
- All symbols and abbreviations should be described below the table.
- Table footnotes should be indicated with superscript symbols in sequence: *, †, ‡, §, ||, ¶, **, ††, ‡‡, etc.
- All units of measurement and concentrations should be designated.

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- Figures should have resolution of 300 dpi or above and should be submitted individually—namely, if Figure 1 is divided into A, B, C, and D, do not combine them into one, but submit each of them separately. The preferred file formats for figures are JPG (JPEG) or TIF (TIFF).
- Figure files should be named according to the figure name (example: Fig. 1A.tif). If the quality of the photographs is considered inappropriate for printing, the journal may request resubmission.
- Authors should submit figures in black and white if they want them to be printed in black and white. Authors are responsible for any additional costs of producing color figures, as determined by the Editorial Board.
- Line art should have resolution of 1,200 dpi or more in JPG or TIF format.
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- The text should be written in 12-point font with double line spacing. ☐
- The original article should be prepared in the following order: title page, abstract, key words, introduction, materials and methods, results, discussion, conclusion, references, table, and figure legends. ☐
- English-language editing is done before submitting a manuscript. ☐

2. Title page

- The title page should be a separate file, and must contain the names and affiliations of all authors and contact information of the corresponding author. ☐
- The title should be concrete and not exceed 20 words. A running title must be included, consisting of no more than 50 characters/spaces. ☐

3. Abstract

- The abstract should be no longer than 300 words for original articles and review articles. ☐
- The abstract of clinical or laboratory research studies has the following sections: Purpose, Materials and Methods, Results, Conclusion. ☐
- A list of key words, with a minimum of 3 items and maximum of 6 items, is included at the end of the abstract. ☐
- Key words are selected based on Medical Subject Headings (MeSH). ☐

4. Manuscript

- Original Articles should be composed of no more than 3,000 words, excluding references, tables, and figures, and organized in the order of title, abstract, introduction, materials and methods, results, discussion, conclusion, references, tables, and figures or illustrations. ☐
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- The IRB No. is provided if subjects are human. ☐

5. References

- All references should be numbered consecutively in the order in which they are first mentioned in the text. In using in-text reference citation, each reference should be cited in square brackets as [1], [1,2], or [1-3]. ☐
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6. Tables, Figures, and Illustrations

- Tables should be created using the table formatting and editing feature of Microsoft Word and should not be provided in noneditable image format. ☐
- Tables and figures are prepared in separate files. ☐
- Each table should be inserted on a separate page, with the table number, table title and legend above the table. ☐
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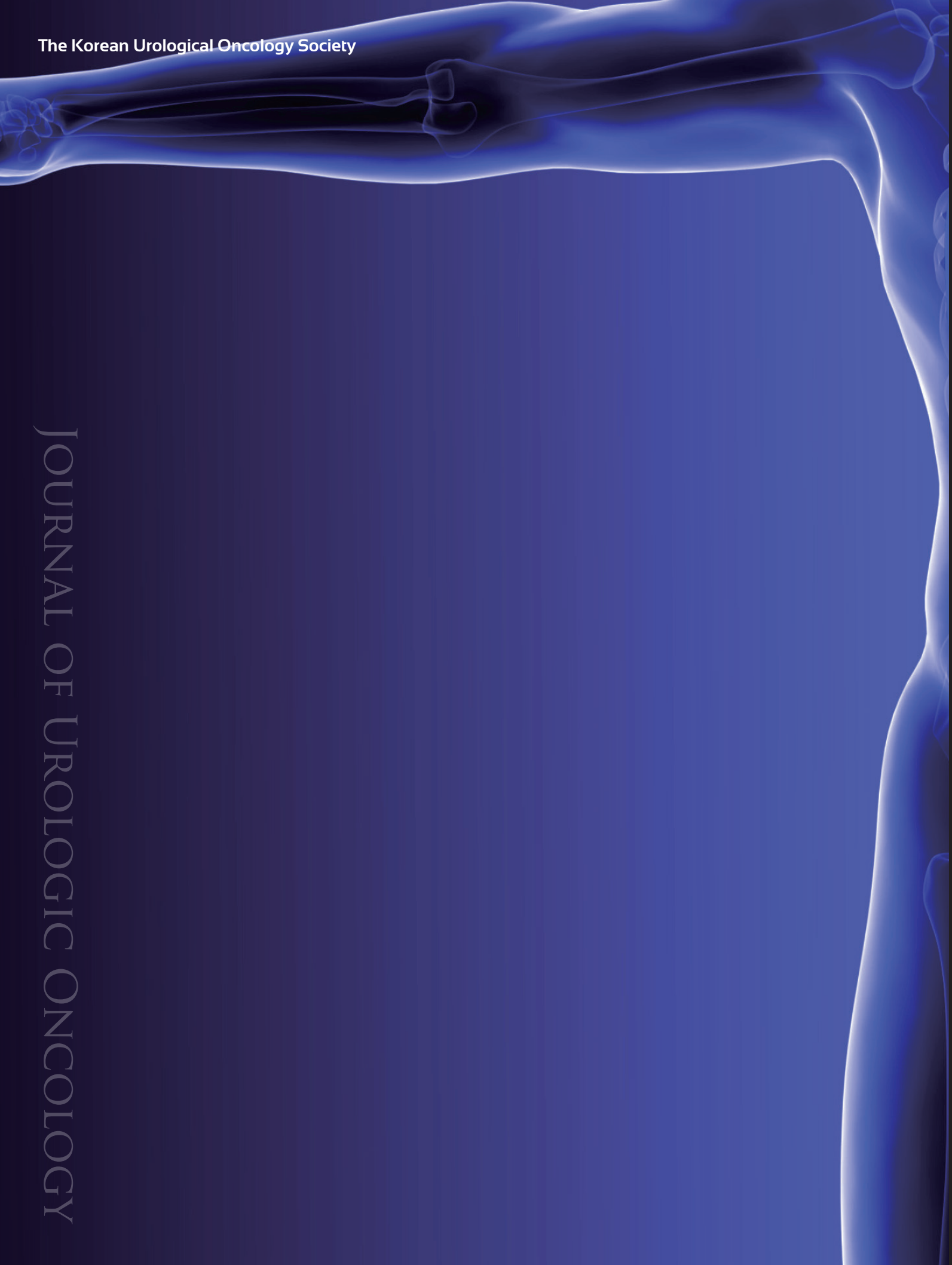

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