Editorial

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Changing landscape of diagnosis and treatment of bladder cancer

Urothelial bladder cancer (BC) is predicted to cause an estimated 18,000 deaths, with an expected 76,960 new cases, in 2016. Undoubtedly, BC is one of the leading causes of cancer-related deaths in the United States. Additionally, over 4 billion dollars is spent annually on BC treatment in the United States, making it one of the most expensive cancer treatments to date. As an experienced urologist and scientist working in BC research, I agreed to take on the responsibility of a special guest editor on BC biomarkers and therapy. One of my goals was to provide literature-based evidence of where we are and where we need to go to better take care of the patients we see in the clinic daily. Fortunately, I was able to recruit 10 outstanding multidisciplinary reviewers, consisting of translational scientists and urologists who have strong expertise in the field.

The most important goal in preventing and diagnosing nonmuscle invasive bladder cancer is bladder preservation. The first review titled "Active surveillance for nonmuscle invasive bladder cancer" by Miyake et al. [1] at the Nara Medical University provides an excellent review of the active surveillance (AS) of BC. According to the National Cancer Institute Dictionary of Cancer Terms, AS is defined as "a treatment plan that involves closely watching a patient's condition but not giving any treatment unless there are changes in test results that show the condition is getting worse." The purpose of AS is to avoid or delay the adverse effects of excessive surgical intervention and increased expenses. To be considered for AS, patients should have low-grade and small tumors (<10 mm), no history of high-grade tumors, negative urinary cytology results before and during AS, and most importantly, patient willingness to participate in the surveillance protocol.

In "Dietary factors associated with bladder cancer," by Piyathilake [2] at the University of Alabama at Birmingham provides insight into whether diet is—as we all suspect—an important risk factor for BC prevention. Her extensive review of the available literature suggests that there is no strong (and statistically meaningful) evidence to suggest that diets including red meat or carbohydrate intake are associated with BC risk (e.g., the European Prospective Investigation into Cancer and Nutrition study). However, some studies reported an inverse association between certain diets (such as those containing olive oil) and serum 25-hydroxyvitamin D concentrations, with lower risk of BC. It is also likely that high consumption of processed meat is correlated with increased risk of BC. High cruciferous vegetable consumption, but not consumption of other vegetables and fruits, may reduce BC risk. Interestingly enough, there was little evidence to support the correlation of the intake of supplements (e.g., carotenes; lycopene; lutein/zeaxanthin; vitamins A, E, and C; and folate) with the risk of BC.

As described by Erlich and Zlotta [3] at Mount Sinai Hospital in his review article titled "Treatment of bladder cancer in the elderly," age is an important risk factor in BC progression. Older patients are often associated with higher stages at diagnosis. How can we take better care of elderly patients with BC? Dr. Zlotta provides advice. The first question in our mind is, "how old is old?" According to recent studies, individuals aged 75 years and older are considered elderly patients. These patients stay longer in hospitals after surgery and experience more complications such as depression. Through the use of tools for calculating surgical risk such as the Comprehensive Geriatric Assessment or the American College of Surgeons Surgical Risk Calculator, we can estimate the chance of an unfavorable clinical outcome after surgery. This review also shows a potential

management algorithm for elderly patients with muscle-invasive bladder cancer.

Given that robotic-assisted radical cystectomy (RARC) will become more popular with the public, we also looked into the advantages and disadvantages of RARC compared with open radical cystectomy (ORC). Does RARC really improve patient-important outcomes and maximize patient satisfaction? A review titled "Open versus robotic cystectomy: Comparison of outcomes" by Davis et al. [4] at the Robert Wood Johnson Medical School has the answer to the question. After carefully looking through perioperative factors (e.g., estimated blood loss, length of stay, narcotic requirements, and transfusion rates) and postoperative complications (e.g., oncologic outcomes, recurrence rates, positive surgical margins, lymph node yields, urinary continence, and quality of life), Davis et al.'s answer was "it is hard to say." No significant difference was observed comparing ORC versus RARC. However, the RARC cohort had a shorter time to both flatus and bowel movement and used less morphine than did the ORC group.

"How do we manage high-grade T1 bladder cancer? Conservative or aggressive therapy?" by Yun et al. [5] at the Chungbuk National University provides a review of how to manage primary stage T1 grade 3 (T1G3) BCs. In addition, intravesical bacillus Calmette–Guérin (BCG) therapy or cystectomy is recommended. BCG instillation into the bladder is the gold standard, but has severe local or systemic side effects. However, T1G3 patients without carcinoma *in situ* had a progression of 10% after 1 year and 29% after 5 years. By contrast, these rates for T1G3 patients with carcinoma in situ were 29% and 74%, respectively. Several biomarkers predicting the clinical effects of BCG treatment have been presented. In T1G3 BC, glutathione S-transferase theta 1 (GSTT1)-positiveness is associated with 14 folds higher risk of BCG failure compared with that in GSTT1-null controls. As illustrated in this elegant review article, we may be able to improve the quality of life of patients if molecular risk classifiers (e.g., GSTT1) for predicting progression or BCG response can be considered in the treatment decision-making for T1G3 BC patients.

A distinct biochemical, genetic, or molecular characteristic of a substance that often indicates a particular biological condition or process is called a biomarker. Three articles titled "Aberrantly expressed miRNAs in the context of bladder tumorigenesis," "The role of microRNAs in bladder cancer," and "Can we use methylation markers as diagnostic and prognostic indicators for bladder cancer?" by Lee et al. [6] at the Theragen Etex Bio Institute, Enokida et al. [7] at the Kagoshima University, and Kim and Kim [8], respectively, introduced potential biomarkers for BC diagnosis and prognosis. Epigenetic events such as DNA methylation on CpG islands are key regulatory mechanisms to switch on (or off) gene transcription. In BC, we are interested in the epigenetic silencing of tumor suppressor genes. Recent studies suggest that many genes associated with poor prognosis of BC patients are regulated by DNA methylation (e.g., *RASSF1A, APC, CDH1*, and *CDH13*). High-throughput screening methods coupled with comprehensive bioinformatics approaches have been able to identify methylation markers in voided urine specimens. Some of these methylation markers can achieve greater sensitivity and specificity than cytology, which may serve to distinguish high-risk patients who require aggressive treatment. In addition, to identify BC-associated biomarkers, large-scale profiling of miRNAs, small noncoding RNA eliciting translational repression, and miRNA microarray platforms have been performed in various samples such as urine, tissues, and blood. Drs. Yun and Lee contributed to the overview of miRNA biomarkers and their molecular targets in BC.

We also thought about new treatment interventions for BC patients. In "Autophagy and urotherial carcinoma of the bladder: A review," Chandrasekar and Evans [9] at the University of California Davis explained the role of autophagy in BC progression and treatment resistance to chemotherapy or radiotherapy, along with new therapeutic opportunities offered by autophagy in BC. Previous literature showed an increased expression of autophagosome biogenesis-associated genes such as Beclin-1 and Atg7 in high-grade BC compared with low-grade BC tissues. In addition, autophagy inhibition (by 3-methyladenine or hydroxychloroquine) was shown to enhance apoptosis by pirarubicin treatment by suppressing the function of autophagy.

Given that BC is one of the most highly immunogenic cancer types—which contains a high rate of mutations—BCG has been a standard of care. However, mainly to avoid the severe side effects of BCG therapy, new immune therapies for BC treatment have recently been introduced. As reviewed in "Immune checkpoint blockade therapy for bladder cancer treatment" by Kim [10] at Cedars-Sinai Medical Center and University of California Los Angeles, efforts are accumulating on the activation of antitumor immunity by regulation of tumor microenvironments. She provided new insights into the detailed regulatory aspects of targeting schemes on the cytotoxic T lymphocyte-associated antigen-4, the immune checkpoint PD-L1, or programmed death–1 (PD-1) for preclinical work and ongoing clinical trials.

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This collection of 10 articles was compiled to address the present diagnosis and treatment of BC patients and to stimulate discussion of future directions for how to apply consensus for better patient care. I hope that these review articles provide scientific evidence–based insights to guide the way we should proceed for more promising patient care.

CONFLICTS OF INTEREST

The author has nothing to disclose.

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Wun-Jae Kim
Guest Editor
Department of Urology, Chungbuk National University Hospital, Chungbuk National University College of Medicine, Cheongju, Korea
E-mail: wjkim@chungbuk.ac.kr

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