Highlight of JUO in This Issue

Perioperative Considerations and Treatment for Advanced Renal Cell Carcinoma

Influence of Body Composition on the Perioperative and Survival Outcomes of Renal Cell Carcinoma

Preoperative Renal Artery Embolization Before Radical Nephrectomy for Nonmetastatic Renal Cell Carcinoma: A Propensity Score Matched Analysis

The Future of Adjuvant Therapy in Renal Cell Carcinoma: Recent Insights and Prospects

Role of Radiotherapy in Metastatic Renal Cell Carcinomas: An Evolutionary Journey in a Misunderstood Histological Type

Optimal Management for BCG Unresponsive Non-Muscle-Invasive Bladder Cancer

Optimal Management of Bacillus Calmette-Guérin– Refractory Non–Muscle-Invasive Bladder Cancer in 2023

Early Experience With Pembrolizumab in Bacillus Calmette-Guérin Unresponsive Non–Muscle-Invasive Bladder Cancer

Clinical Outcomes of Patients With Variant Histology of Urothelial Carcinoma After Radical Cystectomy

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Negative Delta-Prostate-Specific Antigen Time Ratio as Potential New Marker of Progression-Free Survival in Castration-Resistant Prostate Cancer Patients Treated With First-Line Enzalutamide or Docetaxel
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.

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Ja Yoon Ku, Md Nazmul Huda, Eu Chang Hwang, Chan Ho Lee, Kyung Hwan Kim, Dong Deuk Kwon, Hong Koo Ha
Welcome to the latest issue of the Journal of Urologic Oncology (JUO)! We look closely at cutting-edge research and advances in managing urologic cancers in this issue. The editorial team has curated many articles to focus on 3 crucial areas of interest: perioperative considerations and treatment for advanced renal cell carcinoma (RCC), optimal management for bacillus Calmette–Guérin (BCG) unresponsive non–muscle-invasive bladder cancer (NMIBC), and clinical predictors of androgen-receptor targeting agent (ARTA) response in metastatic prostate cancer.

1. Perioperative Considerations and Treatment for Advanced RCC

Advances in imaging technology have increased the number of incidentalomas in kidney cancer, especially in localized stages, leading to the introduction of perioperative measures to reduce complications and recurrence. Noting previous reports of better prognosis in overweight patients, Dr. Viraj A. Master [1] of Emory University, summarizes objective methods to measure body composition and convincingly presents the relevance between the muscle/fat mass and kidney cancer prognosis in each stage. Professor Jung Kwon Kim [2] of Seoul National University reports on the effectiveness of preoperative renal artery embolization in 820 nonmetastatic kidney cancer patients in terms of reduced recurrence rates. Dr. Joo Han Lim [3], a medical oncologist at Inha University, reviews the adjuvant therapies available after surgery in localized staging, including recent immunotherapy agents, and these articles are valuable in that they summarize the options for improving prognosis before or after surgery. In the treatment of kidney cancer that has recurred after surgery and for which metastasectomy is an already-proven option, stereotactic ablative radiotherapy can be an effective means of treatment. Dr. Jaeho Cho [4] from the Department of Radiation Oncology at Yonsei University summarizes the latest findings in this field, expanding the range of postoperative treatment options to include radiation therapy.
2. Optimal Management for BCG Unresponsive Non-Muscle-Invasive Bladder Cancer

BCG unresponsive NMIBC is one of the themes that has driven innovation in bladder cancer over the past few years. Prof. Hyun Hwan Sung [5] of Samsung Medical Center presents a timely review of this from the perspective of 2023, with a nicely summarized table. Among these treatment options offered to date, Prof. Byung Chang Jeong [6] from Samsung Medical Center contributed a valuable report on the first 24 patients’ experience and response to pembrolizumab, the first drug available in Korea. In muscle-invasive bladder cancer, treatment for the variant histology type remains a challenge. Prof. Jong Kil Nam [7] from Pusan National University shows the prognosis of 55 patients who were not pure urethral carcinoma among 300 radical cystectomy patients.

3. Clinical Predictors of ARTA Response in Metastatic Prostate Cancer

While the drug landscape for castration-resistant prostate cancer is becoming increasingly complex with multiple ARTAs, taxanes, RARP inhibitor, and doublet or triple combinations of these agents, the clinical prognostic factors for these newly proposed therapies have received relatively little attention. In this session on prostate cancer at JUO, we will introduce studies on clinical predictors. In the field of metastatic hormone-sensitive prostate cancer, Prof. Bumjin Lim [8] from Asan Medical Center has proposed a clinical indicator of response to abiraterone. In the area of metastatic castration-resistant prostate cancer, Prof. Doo Yong Chung [9] from Inha University has proposed a new prostate-specific antigen kinetics indicator called negative delta-prostate-specific antigen time ratio.

As Editor-in-Chief of JUO, I would like to extend my sincere thanks to all the researchers, authors, and peer reviewers who made this issue possible. Their contributions have advanced our understanding of urologic cancer and paved the way for better patient care. We encourage readers to explore the diverse articles on this issue and believe that the insights presented here will inspire continued advances in the field of urologic oncology.

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

REFERENCES

INTRODUCTION

Renal cell carcinoma (RCC) is among the most common and fatal cancers in the United States, with an estimated 81,800 new diagnoses and 14,890 deaths in 2023 [1]. Obesity is recognized as a primary risk factor for RCC development; however, overweight patients have, interestingly, demonstrated more favorable survival outcomes following treatment [2-4]. This phenomenon, known as “the obesity paradox,” suggests that obesity may be protective in cancer patients, prolonging overall survival (OS) and improving systemic treatment response; however, this benefit may be cancer-specific [5-8].

Traditionally, obesity is measured by body mass index (BMI, kg/m²) as a quantitative representation of a patient’s adiposity, with elevated BMI considered indicative of poor health [9]. However, BMI is recognized as a poor indicator of total percent body fat, fails to differentiate between lean muscle mass, and inconsistently predicts perioperative and survival outcomes in RCC. Recent studies have suggested that objective measurements of lean and fat body masses from various compartments have strong prognostic utility. Low muscle mass (i.e., sarcopenia) and low visceral adiposity are often associated with poorer survival outcomes in localized and advanced RCC. These patients tend to experience higher rates of recurrence, progression, treatment failure, and death from kidney cancer. Given the influence of body composition in RCC outcomes, further characterization of the role of prehabilitation programs is warranted to evaluate the feasibility and efficacy of interventions targeting these modifiable factors.

Key Words: Renal cell carcinoma, Body composition, Body mass index, Sarcopenia, Adiposity, Survival
nostic utility in patients with RCC. We first describe the common definitions and methods in body composition analysis. Then, we characterize the influence of BMI, muscle, and fat in predicting perioperative and survival outcomes in localized and metastatic RCC (mRCC). Furthermore, we describe the role of body composition in systemic treatment efficacy and tolerance in locally advanced RCC and mRCC. Finally, we discuss how exercise and nutritional prehabilitation programs may impact body composition and associated outcomes.

DEFINITIONS AND EVALUATION OF BODY COMPOSITION MEASUREMENTS

1. Body Composition in RCC: Definitions

Muscle quantity is the most frequently considered body composition metric in patients with RCC. Sarcopenia, defined as a clinically significant deficiency of skeletal muscle mass and function, is closely associated with aging and poor health status [13]. Around 10% of patients in their 50s are believed to have sarcopenia, with the prevalence rising to 35%–50% in patients with RCC [14]. Sarcopenia results from several factors, including physical inactivity, malnutrition, comorbidities, hormonal alterations, neuromuscular changes, and inflammation [13]. Malignancy-associated muscle loss may be linked to similar factors, but is additionally associated with acutely increased systemic inflammation [13]. Muscle mass is typically measured as the skeletal muscle index (SMI, cm²/m²), with various thresholds reported in the literature to determine high versus low mass, often stratified by sex and BMI [13]. There is no universally agreed-upon threshold for SMI, which can lead to differing sarcopenia prevalence rates reported by various studies [13]. The global prevalence varies widely depending on the patient population and classification [15].

Skeletal muscle quality has recently been recognized as a critical contributor to patient body composition. Skeletal muscle density (SMD) represents infiltration by fat tissue, with each 1 Hounsfield unit decrease in density representing an increase in adiposity of 1 g per 100-mL increase in adiposity, and correlates with muscle functionality [16,17]. SMD has been linked to inflammatory processes, while mass may relate more closely to nutrition and catabolic status [17]. SMD serves as a useful prognostic tool in multiple cancers, particularly when comparing patients with similar muscle mass but differing degrees of myosteatosis [18]. Various methods of fat measurement are also implemented that offer more insight than BMI alone, with visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) being most often considered. Additionally, intramuscular adipose tissue (IMAT) is related to the aforementioned SMD. Visceral fat is believed to pose greater negative health implications, with SAT playing a lesser role, given the metabolic activity of VAT and the associated secretion of proinflammatory adipokines and cytokines [10,19,20]. These measurements are predominantly classified using median values from study cohorts to define high versus low fat content.

2. Body Composition in RCC: Techniques

For patients with RCC, the predominant method of measuring body condition is using cross-sectional abdominal imaging, with both computed tomography and magnetic resonance imaging, routinely obtained in diagnosis, staging, and follow-up [13]. Given its representation of total body composition, the level of the third lumbar vertebra (L3) is primarily considered. With the use of specialized software, such as Slice-O-Matic (TomoVision, Quebec, Canada), semimanual mapping of body compartments can be conducted to generate quantitative data. An example of a completed L3 body composition analysis is presented in Fig. 1.

Although beyond the scope of this review, other methods to expedite and ease body composition analysis (e.g., artificial intelligence, linear segmentation, psoas muscle measurements) have been frequently explored. However, technique standardization, threshold determination, and quality control remain crucial to minimize subjectivity for future research and clinical incorporation. For a full review on body composition imaging techniques and muscle analysis outcomes in patients with RCC, please refer to the review article by Schmeusser et al. [13]. Furthermore, a video article detailing the methods for body composition analysis using Slice-O-Matic software was published by Steele et al. [21].

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BODY COMPOSITION MEASUREMENTS IN RELATION TO RCC OUTCOMES

1. Influence of BMI

BMI has been recognized as a principal risk factor for the development of kidney cancer, with obesity (BMI ≥30 kg/m$^2$) increasing risk 2- to 3-fold compared with normal-weight individuals (BMI <25 kg/m$^2$) [2]. BMI became a popular preoperative measurement given its association with prolonged operative time, risk of postsurgical complications, and higher mortality rates, although inconsistent results have been reported [22-24]. Table 1 provides a summary of the findings regarding BMI.

1) Perioperative outcomes

According to a series of studies examining perioperative outcomes following minimally invasive nephrectomy, BMI may have an association with estimated blood loss (EBL); however, it has not shown any major associations with complication rates or changes in the glomerular filtration rate, suggesting that surgery can be performed safely in obese patients [25-27]. Among patients undergoing retroperitoneal laparoscopic radical nephrectomy (RN) for T1–2 RCC, no association was observed between elevated BMI (≥25.0 kg/m$^2$) and operative duration, EBL, or postoperative complications [28]. In a separate cohort, obesity increased the risk of wound infections and extended length of stay (LOS) following nephrectomy for non-mRCC, whereas the remaining body composition measures were nonpredictive [29].

2) Localized RCC outcomes

The role of BMI in RCC often supports the concept of the obesity paradox, as described above. Separate studies from the United States and France demonstrated an association between elevated BMI and longer OS following nephrectomy for localized RCC, compared to patients with lower BMI [29,30]. In a prospective randomized trial of high-risk RCC patients receiving adjuvant girentuximab, a monoclonal antibody to carbonic anhydrase IX that triggers antibody-dependent cell-mediated cytotoxicity, obesity was associated with improved recurrence-free survival (RFS) and OS rates [31]. Furthermore, when compared to normal-weight individuals, patients with a BMI of 30.0–30.49 kg/m$^2$ (hazard ratio [HR], 0.50; 95% confidence interval [CI], 0.31–0.81) and ≥35.0 kg/m$^2$ (HR, 0.24; 95% CI, 0.09–0.60) had lower mortality risks [31].

3) Metastatic and locally advanced RCC outcomes

Kim et al. [27] reviewed the favorable impact of BMI on progression-free survival (PFS), cancer-specific survival (CSS), and OS in mRCC. However, in a series of mRCC patients receiving vascular endothelial growth factor (VEGF) inhibitors, obesity did not influence the prognosis, but patients with elevated BMI in combination with sarcopenia experienced lower rates of sorafenib and sunitinib dose-limiting toxicity (DLT) [32-34]. The role of BMI in immunotherapy patients has recently been described. De Giorgi et al. [35] examined the interplay between BMI and systemic
<table>
<thead>
<tr>
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<tr>
<td>Darbas et al. 2020</td>
<td>BMI, SMI, VAT, SAT</td>
<td>Survival outcomes in localized RCC</td>
<td>5-year DFS &amp; OS No association between BMI, DFS, or OS was seen</td>
</tr>
<tr>
<td>Mano et al. 2014</td>
<td>BMI, VAT, SAT</td>
<td>Survival outcomes in localized RCC</td>
<td>OS: BMI association on univariable analysis only (p=0.028) No association between BC parameters and OS on multivariable analysis</td>
</tr>
<tr>
<td>Donin et al. 2016</td>
<td>BMI</td>
<td>Survival outcomes in metastatic RCC</td>
<td>OS: BMI 30-34.9 kg/m² (HR, 0.77; 95% CI, 0.56–1.05); ≥35 kg/m² (HR, 0.24; 95% CI, 0.09–0.60)</td>
</tr>
<tr>
<td>Steffens et al. 2011</td>
<td>BMI, VAT, SAT</td>
<td>Survival outcomes in metastatic RCC</td>
<td>PFS: low VAT (HR, 3.26; p=0.006); low SAT (HR, 2.66; p=0.010) OS: low VAT (HR, 2.97; p=0.006); low SAT (HR, 3.41; p=0.001)</td>
</tr>
<tr>
<td>Antoun et al. 2010</td>
<td>BMI, SMI</td>
<td>Survival outcomes in metastatic RCC</td>
<td>DLT: 41% prevalence in sarcopenia + low BMI &lt;25.0</td>
</tr>
<tr>
<td>Huillard et al. 2013</td>
<td>BMI, SMI</td>
<td>Survival outcomes in metastatic RCC</td>
<td>DLT: Sarcopenia + low BMI (OR, 4.1; p=0.01) No association of BMI or sarcopenia alone with DLT</td>
</tr>
<tr>
<td>De Giorgi et al. 2019</td>
<td>BMI, SII, NLR, PLR</td>
<td>Survival outcomes in metastatic RCC</td>
<td>OS: low BMI (HR, 1.58; p=0.01); BMI &lt;25.0 + SII ≥1,375 (HR, 3.37; p&lt;0.0001)</td>
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<tr>
<td>Lalani et al. 2021</td>
<td>BMI</td>
<td>Survival outcomes in metastatic RCC</td>
<td>OS: high BMI (79% vs. 66%; HR, 0.75, p=0.03) ORR: high BMI (30% vs. 21%; OR, 1.51, nonsignificant) TTF: high BMI (7.4 vs. 4.9 months; HR, 0.98, nonsignificant)</td>
</tr>
<tr>
<td>Martini et al. 2020</td>
<td>BMI, MLR, distant metastases</td>
<td>Survival outcomes in metastatic RCC</td>
<td>OS: very poor (HR, 4.1), poor (HR, 1.36), intermediate (HR, 1.70) vs. favorable risk</td>
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<tr>
<td>Boi et al. 2020</td>
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</tr>
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</table>

RCC, renal cell carcinoma; RN, radical nephrectomy; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; RP, retroperitoneal; EBL, estimated blood loss, mL; SMI, skeletal muscle index; IMAT, intermuscular adipose tissue; PN, partial nephrectomy; LOS, length of stay, days; DFS, disease-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; BC, body composition; AJCC, American Joint Cancer Committee; cc, clear cell; WHO, World Health Organization; mRCC, metastatic RCC; VEGF, vascular endothelial growth factor; DLT, dose-limiting toxicity; SII, systemic immune inflammation index; NLR, neutrophil-to-lymphocyte ratio; PFS, progression-free survival; OR, objective-response rate; TTF, time to treatment failure; aRCC, advanced RCC.
inflammation in relation to survival in patients with mRCC treated with nivolumab. Normal weight, compared with BMI >25.0 kg/m$^2$, independently predicted worse OS (HR, 1.59), and when high inflammatory markers were included, mortality risk was tripled (HR, 3.37) [35]. According to Lalani et al. [36], in 735 advanced RCC patients receiving immune checkpoint inhibitors (ICIs), elevated BMI improved 1-year OS (79% vs. 66%; HR, 0.75; p=0.03), the objective-response rate (30% vs. 21%), and time-to-treatment failure (7.4 months vs. 4.9 months). Martini et al. [37] developed a novel risk score for mRCC patients on ICIs, finding that a BMI ≥24 kg/m$^2$ was a protective factor in OS and PFS. However, in a multicenter study of 76 mRCC patients receiving nivolumab or pembrolizumab, obesity reduced the treatment response rate (73% vs. 44%), PFS, and OS [38].

Histopathology may explain these conflicting findings. Among patients with obesity, tumors showed greater angiogenesis and inflammation of peritumoral adipose tissue, which may permit lymphocytic infiltration [39]. This could clarify the survival advantage and improved immunotherapy response. However, obese mRCC mouse models revealed increased intratumoral interleukin-1β levels, which can inhibit the action of ICIs and limit their efficacy [38].

2. Influence of Muscle Measurements

Sarcopenia is highly prevalent among RCC patients and is associated with poor survival across a variety of malignancies, including RCC [40]. Table 2 provides a summary of the relevant findings.

1) Perioperative outcomes

Although sarcopenia has been associated with postoperative complications and 30-day mortality in patients undergoing oncological surgery, little has been reported regarding sarcopenia in patients with RCC [41]. In 2 series of patients undergoing nephrectomy with inferior vena cava tumor thrombectomy, no significant differences in surgical complications or LOS were found according to whether patients had sarcopenia [42,43]. However, in 137 American Joint Cancer Committee stage III–IV RCC patients undergoing RN, Peyton et al. [44] found that the psoas muscle index (PMI) was associated with the risk of high-grade Clavien complications, although PMI as a marker of total skeletal muscle mass is relatively unreliable [45].

Given the complexity and high complication rates of these procedures, it will be of interest in the future to examine perioperative outcomes of sarcopenic patients following nephrectomy for localized disease.

2) Localized RCC outcomes

In a group of 387 non-mRCC patients following RN, Psutka et al. [46] found that sarcopenia predicted worse 5-year CSS (79% vs. 85%, p=0.05) and OS (65% vs. 74%, p=0.005). Furthermore, Lee et al. [47] found sarcopenia to be a risk factor for all-cause mortality (HR, 2.58; 95% CI, 1.02–6.54) and cancer-specific mortality (HR, 3.07; 95% CI, 1.38–6.83) in over 600 pT1–2 RCC patients. In contrast, Darbas et al. [29] found no association between body composition measurements, including BMI, SMI, and VAT index and 5-year RFS, though this study was limited by the sample size and included only overweight patients. Nonetheless, multiple studies of various patient populations have repeatedly shown a connection between low skeletal muscle mass and shorter CSS and OS in localized RCC patients, which supports this association [47-50]. Patients who have sarcopenia present with larger, higher-grade, and higher-stage tumors with an increased risk of lymphovascular invasion, which may explain the poorer oncological outcomes [51]. In RCC, clinicopathologically aggressive tumors produce inflammatory cytokines and promote proinflammatory states, diminishing skeletal muscle mass and strength [52,53]. Therefore, sarcopenia is a significant prognostic factor in non-mRCC and may suggest clinically aggressive malignancy.

3) Metastatic and locally advanced RCC outcomes

Sarcopenia has further demonstrated its prognostic utility for mRCC. In 92 patients with mRCC, Fukushima et al. [54] found a high prevalence (68%) of sarcopenia, and the 3-year OS rates were 31% and 73% in patients with and without sarcopenia, respectively. Low SMI increased the risk of death nearly 3-fold. Sarcopenia at the time of CN has been shown to be highly prevalent and negatively associated with OS (HR, 2.13; p=0.016; 15.0 months vs. 29.4 months; p=0.04) [55,56].

Sarcopenia has also been examined in relation to survival and tolerance in patients receiving medical therapy. In those
Table 2. Notable studies investigating the impact of skeletal muscle measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma

<table>
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<td>Watanabe et al. 2021</td>
<td>Advanced RCC after nephrectomy and IVC thrombectomy (83)</td>
<td>SMI</td>
<td>Operative time, EBL, postoperative complications, LOS</td>
<td>Sex-specific SMI thresholds</td>
<td>Operative time: sarcopenia (366 min vs. 372 min; p=0.974) EBL: sarcopenia (1,750 mL vs. 1740 mL; p=0.903) Complications: sarcopenia (27.6% vs. 19.8%; p=0.492) LOS: sarcopenia (11 days vs. 10 days; p=0.148)</td>
</tr>
<tr>
<td>Schmeusser et al. 2023</td>
<td>Non-mRCC after nephrectomy and IVC thrombectomy (115)</td>
<td>SMI</td>
<td>90-day high-grade complications</td>
<td>Sex-specific SMI thresholds</td>
<td>No association with preoperative sarcopenia (HR, 2.04; 95% CI, 0.66–6.42)</td>
</tr>
<tr>
<td>Peyton et al. 2016</td>
<td>AJCC stage III–IV RCC after RN (128)</td>
<td>PMI</td>
<td>EBL, complications, LOS, high-grade complications</td>
<td>Sex-specific cohort quartiles (sarcopenia = bottom quartile)</td>
<td>EBL: sarcopenia (613 mL vs. 809 mL; p=0.49) LOS: sarcopenia (6.0 days vs. 4.7 days; p=0.15) Clavien grade ≥III complication: sarcopenia (18% vs. 5%; OR, 4.2; p=0.03)</td>
</tr>
<tr>
<td>Psutka et al. 2016</td>
<td>Non-mRCC after RN (387)</td>
<td>SMI</td>
<td>5-yr CSS, OS</td>
<td>Sex-specific SMI thresholds</td>
<td>CSS: sarcopenia (79% vs. 85%; HR, 1.70; p=0.047) OS: sarcopenia (65% vs. 74%; HR, 1.46; p=0.039)</td>
</tr>
<tr>
<td>Noguchi et al. 2020</td>
<td>Localized ccRCC in males (316)</td>
<td>PMI</td>
<td>RFS</td>
<td>Cohort median threshold for PMI</td>
<td>RFS: Low PMI (HR, 2.31; p=0.022)</td>
</tr>
<tr>
<td>Mao et al. 2021</td>
<td>Localized RCC after PN or RN (443)</td>
<td>SMI, PMI</td>
<td>OS, CSS</td>
<td>Sex-specific SMI, PMI thresholds</td>
<td>OS: sarcopenia (SMI-HR, 2.9; p&lt;0.001) &amp; (PMI-HR, 2.8; p&lt;0.001) CSS: sarcopenia (SMI-HR, 2.6; p=0.009) &amp; (PMI-HR, 2.2; p=0.031)</td>
</tr>
<tr>
<td>Lee et al. 2022</td>
<td>pT1-2 RCC after RN (632)</td>
<td>SMI</td>
<td>10-yr CSS, OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: sarcopenia (HR, 2.58; p=0.045) CSS: sarcopenia (HR, 3.07; p=0.006)</td>
</tr>
<tr>
<td>Midenberg et al. 2023</td>
<td>Localized RCC after PN or RN (473)</td>
<td>SMI, Albumin</td>
<td>10-yr RFS, CSS, OS</td>
<td>Sex-specific SMI threshold</td>
<td>No association between sarcopenia + hypoalbuminemia (HR, 2.62; p&lt;0.001)</td>
</tr>
<tr>
<td>Darbas et al. 2020</td>
<td>Localized RCC in overweight patients (96)</td>
<td>BMI, SMI, VAT, SAT, IMAT</td>
<td>5-yr DFS &amp; OS</td>
<td>Sex-specific SMI thresholds</td>
<td>DFS: no associations between BC parameters</td>
</tr>
<tr>
<td>Makino et al. 2023</td>
<td>Non-mRCC after PN or RN (299)</td>
<td>SMI, PMI</td>
<td>10-yr OS, MFS</td>
<td>Optimal cutoff analysis for PMI</td>
<td>MFS: sarcopenia (HR, 118; p=0.628)</td>
</tr>
</tbody>
</table>

https://doi.org/10.22465/juo.234600500025
Table 2. Notable studies investigating the impact of skeletal muscle measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma (continued)

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort (n)</th>
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<th>Outcome(s) of interest</th>
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<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fukushima et al. 2016 [54]</td>
<td>mRCC at initial diagnosis (92)</td>
<td>SMI</td>
<td>3-yr OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia (31% vs. 73%; HR, 2.58; p=0.015)</td>
</tr>
<tr>
<td>Sharma et al. 2015 [55]</td>
<td>mRCC after CN (93)</td>
<td>SMI</td>
<td>OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia (7 mo vs. 23 mo; HR, 2.13; p=0.016)</td>
</tr>
<tr>
<td>Khan et al. 2022 [56]</td>
<td>mRCC after CN (158)</td>
<td>SMI, VAT, SAT, IMAT</td>
<td>OS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia negatively associated (15.0 mo vs. 29.4 mo; p=0.04)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cohort median thresholds for other BC measures</td>
<td>No significant associations with adiposity parameters</td>
</tr>
<tr>
<td>Lee et al. 2021 [57]</td>
<td>mRCC receiving sunitinib (78)</td>
<td>SMI</td>
<td>PFS, OS</td>
<td>Sex-specific SMI thresholds</td>
<td>Mean dose reduction: Sarcopenia (20.3% vs. 6.3%; p=0.004) PFS: Sarcopenia (HR, 2.62; p=0.001) OS: Sarcopenia (HR, 1.78; p=0.038)</td>
</tr>
<tr>
<td>Antoun et al. 2010 [33]</td>
<td>mRCC receiving sorafenib (55)</td>
<td>BMI, SMI</td>
<td>DLT</td>
<td>BMI ≥25.0 kg/m² Sex-specific SMI thresholds</td>
<td>DLT: 41% prevalence in sarcopenia + low BMI</td>
</tr>
<tr>
<td>Huillard et al. 2013 [34]</td>
<td>mRCC receiving sunitinib (61)</td>
<td>BMI, SMI</td>
<td>DLT</td>
<td>BMI ≥25.0 kg/m² Sex-specific SMI thresholds</td>
<td>DLT: Sarcopenia + low BMI (OR, 4.1; p=0.01)</td>
</tr>
<tr>
<td>Aslan et al. 2022 [58]</td>
<td>mRCC receiving ICI therapy (62)</td>
<td>SMI, Albumin, NLR</td>
<td>OS, PFS</td>
<td>Cohort median threshold for cachexia index [(SMI x albumin)/NLR]</td>
<td>PFS: ≥5% SMI loss (4 mo vs. 17 mo; HR, 2.8; p=0.007)</td>
</tr>
<tr>
<td>Ged et al. 2022[59]</td>
<td>mCRC receiving ICI therapy (205)</td>
<td>BMI, SMI, VAT, SAT</td>
<td>2-yr OS, PFS</td>
<td>Sex-specific SMI thresholds</td>
<td>OS: Sarcopenia (HR, 1.65; p=0.036); High BMI (HR, 0.66; p=0.036) Lyness et al. 2014</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Cohort median thresholds for other BC parameters</td>
<td>No association with sarcopenia &amp; high BMI after IMDC score adjustment</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>No association with adiposity parameters and OS</td>
</tr>
<tr>
<td>Fukushima et al. 2017 [60]</td>
<td>mRCC after CN (37)</td>
<td>SMI</td>
<td>3-yr OS</td>
<td>Continuous &amp; % change categorization for SMI</td>
<td>3-yr OS rates: 19% (&gt;5% SMI loss), 76% (stable SMI), 100% (&gt;5% SMI gain) HR, hazard ratio; CI, confidence interval; LOS, length of stay; mRCC, metastatic RCC; AJCC, American Joint Cancer Committee; RN, radical nephrectomy; PMI, psoas muscle index; CSS, cancer-specific survival; OS, overall survival; ccRCC, clear cell RCC; PN, partial nephrectomy; RFS, recurrence-free survival; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMAT, intermuscular adipose tissue; DFS, disease-free survival; BC, body composition; MFS, metastasis-free survival; CN, cytoreductive nephrectomy; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; IMDC, International Metastatic RCC Database Consortium; LVEF, left ventricular ejection fraction; TAT, total adipose tissue.</td>
</tr>
<tr>
<td>Gu et al. 2017 [61]</td>
<td>mRCC receiving targeted therapy (101)</td>
<td>SMI</td>
<td>PFS, OS</td>
<td>% change in SMI</td>
<td>% SMI change greater in patients with toxicity (9.7% vs. 0.2%; p=0.04)</td>
</tr>
<tr>
<td>Ozaki et al. 2023 [62]</td>
<td>mRCC receiving targeted therapy (57)</td>
<td>PMI</td>
<td>PFS, OS</td>
<td>% change in PMI</td>
<td>PFS: ≥10% PMI loss (HR, 4.95; p=0.011)</td>
</tr>
<tr>
<td>Kazemi-Bajestani et al. 2019 [63]</td>
<td>mRCC receiving sorafenib or sunitinib (47)</td>
<td>SMI, SAT, TAT, NLR</td>
<td>Cardiotoxicity (LVEF fall &gt;10% to absolute &lt;55%)</td>
<td>Sex-specific TAT median threshold</td>
<td>High TAT associated with toxicity (1.05% vs. 0.4%; p=0.02)</td>
</tr>
</tbody>
</table>

RCC, renal cell carcinoma; IVC, inferior vena cava; SMI, skeletal muscle index; EBL, estimated blood loss; HR, hazard ratio; CI, confidence interval; LOS, length of stay; mRCC, metastatic RCC; AJCC, American Joint Cancer Committee; RN, radical nephrectomy; PMI, psoas muscle index; CSS, cancer-specific survival; OS, overall survival; ccRCC, clear cell RCC; PN, partial nephrectomy; RFS, recurrence-free survival; BMI, body mass index; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; IMAT, intermuscular adipose tissue; DFS, disease-free survival; BC, body composition; MFS, metastasis-free survival; CN, cytoreductive nephrectomy; DLT, dose-limiting toxicity; ICI, immune checkpoint inhibitor; NLR, neutrophil-to-lymphocyte ratio; IMDC, International Metastatic RCC Database Consortium; LVEF, left ventricular ejection fraction; TAT, total adipose tissue.
receiving sunitinib, sarcopenia was associated with a mean dose reduction, and predicted poorer PFS and OS [57]. Low SMI, in conjunction with BMI, increased DLT rates for those receiving sunitinib or sorafenib, which may explain the worse survival outcomes seen in these patients, although it should be noted that SMI alone was not predictive of toxicity [33,34]. Inconsistent evidence has been reported regarding sarcopenia and immunotherapy. Aslan et al. [58] found that sarcopenia alone did not predict outcomes in mRCC patients receiving ICI treatment; however, when markers of inflammation (e.g., albumin and the neutrophil-to-lymphocyte ratio) were included, this new index was significantly predictive of PFS (HR, 2.6) and OS (HR, 4.5). In a separate study, SMI was associated with OS in clear cell RCC (ccRCC) patients receiving ICIs, although this was no longer significant when adjusting for the IMDC score [59]. However, Ged et al. [59] found that tumors from patients with sarcopenia displayed increased angiogenic, inflammatory, and myeloid signals, which warrants further investigation into the interplay between sarcopenia and the efficacy and tolerability of immunotherapy.

Changes in muscle mass over the course of treatment have been a significant focus in the study of metastatic disease. Fukushima et al. [60] further characterized postoperative changes in muscle mass following cytoreductive nephrectomy and found that there was significant variation in 3-year OS between tiers: 19% for >5% SMI loss, 76% for stable SMI, and 100% for >5% gain (p<0.001). In a series of mRCC patients receiving targeted therapy, ≥5% muscle loss demonstrated strong predictive ability for poorer PFS (HR, 1.744; p=0.024) and OS (HR, 2.367; p=0.008) [61]. This was further echoed by Ozaki et al. [62], who found that a loss of muscle mass during treatment with targeted therapy predicted OS, as opposed to a low initial SMI; this change was further associated with a low score on the prognostic nutritional index, indicating that declining nutritional status may account for this change and impact tolerability and overall efficacy. A greater percent loss of SMI has also shown an association with increased cardiotoxicity in patients receiving antiangiogenic therapy [63]. The impact of changes in muscle mass during immunotherapy in mRCC remains relatively underexamined.

4) Other methods of examining muscle

Further methods of examining sarcopenia by including measures of inflammation and muscle quality have proven insightful. Interleukin-6 (IL-6) is an inflammatory tumor cytokine correlated with mortality in RCC and overall muscle mass loss; the combination of IL-6 with low SMI demonstrated the strongest predictive ability for OS (26.1 months vs. not reached, p<0.001) and risk of mortality (HR, 5.95) in a group of stage I-IV ccRCC patients [52,64,65]. When including the modified Glasgow Prognostic Score (mGPS), a metric of inflammation, Higgins et al. found that high-risk patients (with sarcopenia and high mGPS) demonstrated a higher area under the curve in comparison with SSIGN and IMDC scores in predicting 5-year RFS and CSS [66]. Sarcopenia combined with inflammation has shown a strong association with the likelihood of cancer recurrence and death in RCC, along with treatment response. Myosteatosis, as evaluated by SMD, is prognostic for worse OS in multiple malignancies, including RCC [18]. Across cohorts, high SMD has proven to be a protective factor in both localized and advanced-stage RCC, and can help predict improved response to targeted therapies in mRCC [16,67]. The role of myosteatosis in immunotherapy is unclear in RCC, although results have been mixed for other malignancies [7,68].

3. Influence of Fat Measurements

Although BMI is readily measurable, its association with outcomes in kidney cancer is inconsistent. Originally intended to detect fat, BMI fails to account for age, comorbid metabolic conditions, and muscle mass, therefore limiting its interpretation and applicability [10]. Fat measurements are more accurate representations of body composition and demonstrate stronger correlations with cancer development and prognosis [10,12,69]. Table 3 provides a summary of the findings discussed in this section.

1) Perioperative outcomes

Studies that included visceral adiposity along with elevated BMI showed associations with increased operative time and EBL alongside postsurgical complications, LOS, and expenses [25,70]. In 2 studies conducted in Japan and China,
Table 3. Notable studies investigating the impact of adipose measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort (n)</th>
<th>Study measurements(s)</th>
<th>Outcome(s) of interest</th>
<th>Cutoffs used</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Perioperative outcomes</strong></td>
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</tr>
<tr>
<td>Hagiwara et al. 2012 [25]</td>
<td>T1-3a &lt;10 cm RCC after laparoscopic RN (121)</td>
<td>BMI, VAT, SAT, TAT</td>
<td>Operative time</td>
<td>BMI ≥25.0 kg/m², VAT area ≥100 cm²</td>
<td>Higher BMI (r=0.316, p&lt;0.001) &amp; VAT (r=0.348, p&lt;0.001) showed a correlation with longer operative time (OR, 3.70; p=0.009)</td>
</tr>
<tr>
<td>Zhai et al. 2018 [70]</td>
<td>AJCC stage I–III ccRCC after RN (76)</td>
<td>BMI, VAT</td>
<td>Operative time, EBL, LOS, Complications, Total expenses</td>
<td>BMI &lt;20.0 kg/m² (Chinese obesity threshold), VAT area ≥100 cm²</td>
<td>Operative time: High VAT (172 vs. 141 min; p=0.012); High BMI (197 min vs. 153 min; p=0.013)</td>
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<tr>
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<td>EBL: High VAT (132 mL vs. 84 mL; p=0.018); High BMI (215 mL vs. 93 mL; p=0.013)</td>
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<tr>
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<td></td>
<td>Complications: High VAT alone (26.9% vs. 4.2%; p&lt;0.045)</td>
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<tr>
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<td></td>
<td>LOS: High VAT alone (8.7 days vs. 7.5 days; p=0.013)</td>
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<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td>Total expenses: High VAT ($7.6k vs. $2.7k; p=0.029)</td>
</tr>
<tr>
<td>Yuge et al. 2015 [71]</td>
<td>Laparoscopic RN (167)</td>
<td>VAT</td>
<td>Operative time</td>
<td>VAT area ≥100 cm²</td>
<td>High VAT with nonexpert surgeon (&lt;50 cases/year) associated with prolonged time (HR, 5.15; p=0.004)</td>
</tr>
<tr>
<td>Darbas et al. 2020 [29]</td>
<td>Localized RCC after PN or RN in overweight patients (96)</td>
<td>BMI, SMI, VAT, SAT, IMAT</td>
<td>Postoperative infections, LOS &gt;7 days (PN) or &gt;10 days (RN)</td>
<td>WHO BMI categorization, Sex-specific SMI thresholds for adiposity</td>
<td>No significant associations of BC parameters with perioperative outcomes measured, except BMI &gt;30.0 with increased risk of infections and LOS</td>
</tr>
<tr>
<td>Demirel &amp; Dilek 2023 [72]</td>
<td>Localized RCC after PN or RN (210)</td>
<td>SMI, VAT, SAT, IMAT</td>
<td>High-grade complications</td>
<td>Continuous</td>
<td>No associations between BC parameters in patients with versus without HG complications</td>
</tr>
<tr>
<td>Akahata et al. 2013 [28]</td>
<td>T1-2 RCC after laparoscopic RP RN (96)</td>
<td>BMI, anterior perirenal fat distance</td>
<td>Operative time, EBL, Complications</td>
<td>BMI ≥25.0 kg/m², Continuous fat distances</td>
<td>Operative time: anterior perirenal fat (r=0.252, p=0.016)</td>
</tr>
<tr>
<td>Gorin et al. 2013 [73]</td>
<td>Localized RCC after MI-PN (257)</td>
<td>BMI, VAT, SAT</td>
<td>Operative time, LOS, Complications</td>
<td>Continuous BC measurements</td>
<td>All-grade complications: VAT only (OR, 1.05; p=0.005)</td>
</tr>
<tr>
<td>Raman et al. 2016 [74]</td>
<td>Localized RCC after RPN (240)</td>
<td>Perinephric fat, perinephric to subcutaneous fat ratio</td>
<td>Ischemic time, EBL, Complications, LOS</td>
<td>Continuous BC measurements</td>
<td>All-grade complications: perinephric to subcutaneous fat ratio (OR, 1.82; p=0.020)</td>
</tr>
<tr>
<td>Ioffe et al. 2013 [75]</td>
<td>Localized RCC after MI-PN (118)</td>
<td>VAT, perinephric fat</td>
<td>Ischemic time, EBL, Complications</td>
<td>Cohort specific tertiles for adiposity parameters</td>
<td>No significant associations of adiposity parameters with perioperative outcomes measured</td>
</tr>
<tr>
<td>Davidiuk et al. 2014 [76]</td>
<td>Localized RCC after RPN (100)</td>
<td>MAP score</td>
<td>Adherent perinephric fat</td>
<td>Perinephric fat stranding</td>
<td>Presence of adherent fat: MAP score (0%, 1 (16%), 2 (31%), 3-4 (73%), 5 (100%)</td>
</tr>
<tr>
<td><strong>Survival outcomes in localized RCC</strong></td>
<td></td>
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<tr>
<td>Naya et al. 2010 [77]</td>
<td>Localized RCC after PN or RN (117)</td>
<td>VAT</td>
<td>Pathologic features, CSS</td>
<td>Cohort median threshold for VAT</td>
<td>Low VAT associated with advanced disease (AJCC II–IV, p&lt;0.022), microvascular invasion (p=0.026), decreased CSS (p=0.026)</td>
</tr>
<tr>
<td>Maurits et al. 2022 [67]</td>
<td>AJCC Stage I–III RCC</td>
<td>SMI, SMD, VAT, SAT</td>
<td>OS, RFS</td>
<td>Sex-specific median thresholds for BC parameters</td>
<td>OS: low VAT (Men: HR, 1.38, 95% CI, 1.05–1.83) &amp; (Women: HR, 1.67, 95% CI, 1.01–2.78)</td>
</tr>
<tr>
<td>Park et al. 2014 [78]</td>
<td>Localized RCC after PN or RN (706)</td>
<td>VAT%, VAT, SAT</td>
<td>RFS</td>
<td>Cohort VAT% Quartiles</td>
<td>RFS: VAT% (lowest quartile: HR, 3.2; p=0.038) &amp; (highest quartile: HR, 4.8; p=0.010)</td>
</tr>
</tbody>
</table>

(continued)
### Table 3. Notable studies investigating the impact of adipose measurements on perioperative, survival, and treatment-related outcomes in localized, locally advanced, and metastatic renal cell carcinoma (continued)

<table>
<thead>
<tr>
<th>Study</th>
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<tbody>
<tr>
<td>Kaneko et al. 2015 [79]</td>
<td>Localized RCC after PN or RN (285)</td>
<td>VAT</td>
<td>5-yr RFS</td>
<td>VAT area ≥120 cm²</td>
<td>RFS rates: all histologies, low VAT (76.9% vs. 91.3%; p=0.037) Low VAT only predictor of RFS in ccRCC (HR, 1.374; p=0.042)</td>
</tr>
<tr>
<td>Preza-Fernandes et al. 2022 [80]</td>
<td>Localized RCC after PN or RN (137)</td>
<td>SMI, VAT, SAT, perinephric fat</td>
<td>PFS, OS</td>
<td>Cohort tertiles for BC parameters</td>
<td>PV: high perinephric fat area (HR, 0.3; p=0.019)</td>
</tr>
<tr>
<td>Maurits et al. 2022 [82]</td>
<td>AJCC Stage I–IV RCC (1039)</td>
<td>BMI, SMI, VAT, SAT, TAT, VAT%</td>
<td>Pathologic features, TNM stage</td>
<td>10-unit BC parameter increases</td>
<td>Stage IV in males: VAT (OR, 0.93; p&lt;0.001), TAT (OR, 0.95; p&lt;0.001), VAT% (OR, 0.97; p&lt;0.001)</td>
</tr>
<tr>
<td>Tan et al. 2022 [83]</td>
<td>Localized vs. mRCC (188)</td>
<td>BMI, SMI, SAT, VAT</td>
<td>BC differences according to RCC stage</td>
<td>Continuous comparison</td>
<td>VAT: localized vs. mRCC (19867 vs. 1523.2 cm³; p=0.020) No associations with other BC parameters and higher-stage RCC</td>
</tr>
<tr>
<td>Thiel et al. 2016 [81]</td>
<td>Localized RCC (456)</td>
<td>MAP score</td>
<td>PV</td>
<td>Dichotomized MAP score: low (1–3) vs. high (4–5)</td>
<td>PFS: High MAP (HR, 2.20; p=0.032)</td>
</tr>
<tr>
<td>Steffens et al. 2011 [32]</td>
<td>mRCC receiving anti-VEGF therapy (156)</td>
<td>BMI, VAT, SAT</td>
<td>PV</td>
<td>Coefficient median thresholds for BC parameters</td>
<td>PV: Low VAT (HR, 3.26; p=0.006); Low SAT (HR, 2.96; p=0.010)</td>
</tr>
<tr>
<td>Ladoire et al. 2011 [84]</td>
<td>mRCC receiving anti-VEGF therapy (113)</td>
<td>BMI, VAT, SAT</td>
<td>PV</td>
<td>Coefficient median thresholds for BC parameters</td>
<td>Low SAT (HR, 3.41; p=0.001) PV: High VAT (HR, 2.97; p=0.006); Low SAT (HR, 3.41; p=0.001)</td>
</tr>
<tr>
<td>Gu et al. 2015 [85]</td>
<td>aRCC receiving targeted therapy (124)</td>
<td>VAT, SAT</td>
<td>OS</td>
<td>Continuous &amp; sex-specific optimal cutoff analysis</td>
<td>OS: association with higher VAT (HR, 0.38; p&lt;0.002) &amp; higher SAT (HR, 0.987; p=0.048)</td>
</tr>
<tr>
<td>Ning et al. 2022 [86]</td>
<td>mRCC receiving anti-VEGF therapy (358)</td>
<td>BMI, VAT, SAT, perinephric fat</td>
<td>PFS, OS</td>
<td>Coefficient median thresholds for BC parameters</td>
<td>PV: High perinephric fat (HR, 0.78; 95% CI, 0.61–0.98) PV: High perinephric fat (HR, 0.57; 95% CI, 0.35–0.93)</td>
</tr>
<tr>
<td>Park et al. 2020 [88]</td>
<td>mRCC receiving sunitinib (211)</td>
<td>BMI, SAT</td>
<td>DLT, PFS, CSS</td>
<td>Continuous &amp; Cohort median thresholds for BC parameters</td>
<td>DLT: increasing VAT (OR, 1.013; p=0.29) PV: Low VAT (13.0 vs. 26.0 months; p=0.006) DLT: increasing VAT (OR, 1.013; p=0.29)</td>
</tr>
<tr>
<td>Kazemi-Bajestani et al. 2018 [83]</td>
<td>mRCC receiving sunitinib or sorafenib (47)</td>
<td>SMI, TAT</td>
<td>Cardiotoxicity (LVEF fall &gt;10% absolute &lt;55%)</td>
<td>% change in SMI; sex-specific median threshold for TAT</td>
<td>High TAT associated with toxicity (87.5% vs. 41.0%; p=0.02) % SMI change greater in patients with toxicity (-7% vs. 0%; p=0.04)</td>
</tr>
<tr>
<td>Martin et al. 2021 [89]</td>
<td>mRCC receiving ICI therapy (79)</td>
<td>SMI, SAT, IMAT, VAT, TAT</td>
<td>PFS, OS, ORR</td>
<td>Cohort optimal cutoff analysis Risk score including IMAT, SAT</td>
<td>ORR: poor risk (HR, 4.19; p&lt;0.001); low TAT (HR, 1.91; p=0.025) ORR: poor risk (HR, 0.23; p=0.044); low TAT (OR, 0.25; p&lt;0.001)</td>
</tr>
<tr>
<td>Wang et al. 2023 [90]</td>
<td>mRCC receiving ICI therapy (244)</td>
<td>BMI, SMI, VAT, SAT, SAT%</td>
<td>PFS, OS</td>
<td>Continuous BC parameters</td>
<td>PV: SAT% (HR, 0.02; 95% CI, 0.00–0.04) SAT% (HR, 0.08; 95% CI, 0.01–0.72) NO significant associations between MAP and PFS or OS</td>
</tr>
</tbody>
</table>

RCC, renal cell carcinoma; RN, radical nephrectomy; BMI, body mass index; VAT, visceral adipose tissue; OR, odds ratio; HR, hazard ratio; CI, confidence interval; SAT, subcutaneous adipose tissue; TAT, total adipose tissue; AJCC, American Joint Cancer Committee; ccRCC, clear cell RCC; EBL, estimated blood loss; LOS, length of stay; PN, partial nephrectomy; IMAT, intermuscular adipose tissue; WHO, World Health Organization; SMI, skeletal muscle index; BC, body composition; HG, high-grade; RP, retroperitoneal; MI, minimally invasive; RPN, robotic PN; MAP, Mayo Adhesive Probability; CSS, cancer-specific survival; SMD, skeletal muscle density; RFS, recurrence-free survival; OS, overall survival; PFS, progression-free survival; mRCC, metastatic RCC; VEGF, vascular endothelial growth factor; DLT, dose-limiting toxicity; LVEF, left ventricular ejection fraction; ORR, objective-response rate; ICI, immune checkpoint inhibitor; aRCC, advanced RCC.
elevated VAT was associated with prolonged operative time, increased EBL, longer LOS, and a higher rate of complications in patients undergoing laparoscopic RN for T stage I–III RCC [25,70]. However, in a separate Japanese cohort using the same VAT area cutoff (≥100 cm²), elevated VAT was only associated with prolonged operative time (HR, 5.15; p=0.004) among nonexpert surgeons (<50 laparoscopic RN procedures per year) [71]. Furthermore, Darbas et al. [29] analyzed 96 overweight patients following nephrectomy, and found no association between body composition measures, including VAT and SAT indices (cm²/m²), and the risk of infection or LOS, though this study was limited by its sample size and the inclusion of only overweight patients. In another study examining 210 patients undergoing nephrectomy, no significant difference in fat tissue distribution was found between those with and without high-grade postoperative complications [72].

Given the somewhat inconsistent influence of VAT on complications of nephrectomy, alternative visceral adipose surrogates have been considered. Akaihata et al. [28] found that anterior perirenal fat distance was predictive of higher operative time and EBL during retroperitoneal laparoscopic RN. Among patients undergoing minimally invasive partial nephrectomy (PN), excess intra-abdominal fat, as measured by distance from the posterior renal capsule to abdominal wall, increased the probability of all-grade (OR, 1.05; p=0.005) and grade 3–4 (OR, 1.05; p=0.04) Clavien complications; however, the operative time and LOS were not impacted [73]. These findings were supported by Raman et al. [74], who showed that perinephric fat thickness, including the SAT proportion, posed an increased risk for all complications without affecting EBL, ischemic time, or LOS. Ioffe et al. [75] used perinephric, visceral, and subcutaneous fat thicknesses at pre-specified levels on cross-sectional imaging to categorize 118 patients into low, medium, and high tertiles; however, in this cohort of minimally invasive PN with a single surgeon, none of the measurements were associated with EBL, ischemic time, or postoperative complications. There is moderate support for perinephric fat measurement as a predictor of the risk for postoperative complications, but its association with other perioperative outcomes is uncertain.

Furthermore, the Mayo Adhesive Probability (MAP) score utilizes both quantitative and qualitative perinephric fat measurements to determine the degree of PN complexity [76]. Scores are determined via the degree of perinephric fat stranding, in addition to distances between the posterior renal capsule to the posterior abdominal wall and from the lateral renal capsule in alignment with the renal vein to the abdominal wall. A higher score was strongly predictive of the presence of adherent perinephric fat, and therefore surgical difficulty [76].

2) Localized RCC outcomes

Although elevated visceral adiposity may promote tumorigenesis, it has often been described as a protective factor during localized malignancy treatment [69]. In a cohort of 117 patients undergoing nephrectomy for T1–3 RCC, VAT was significantly lower in patients with microvascular invasion and more advanced disease pathologically, and patients with elevated VAT, based on median cutoff, reported improved CSS [77]. Lee et al. [47] examined over 2000 localized and advanced RCC patients who underwent nephrectomy at a single South Korean institution and found that lower VAT predicted worse CSS (HR, 2.19; p=0.004) and OS (HR, 2.22; p=0.003). This finding was echoed by Maurits et al. in 719 T1–3 non-mRCC patients, finding an association between low VAT and worse OS for both men (HR, 1.38) and women (HR, 1.67) [67]. The percent VAT according to total adipose tissue (TAT) was analyzed by Park et al. [78] in 706 Japanese patients; interestingly, the highest (HR, 3.198, p=0.036) and lowest (HR, 4.760, p=0.010) VAT quartiles were associated with RFS. Furthermore, Kaneko et al. [79] found after curative surgery for localized RCC, patients with VAT <120 cm² exhibited shorter RFS (HR, 1.974; p=0.042), although this was only significant for clear cell histology. Perinephric fat has also been examined given its association with VAT and potential for direct tumor interaction. Preza-Fernandes et al. [80] found that a greater area was associated with improved PFS and OS. MAP was also applied to examine survival outcomes in patients treated surgically for localized RCC. In 456 pT1–T2 patients, Thiel et al. [81] found that high MAP scores (4–5) were associated with decreased PFS (HR, 2.20; p=0.032). Overall, a consistent association has been observed in patients with low visceral adiposity and aggressive, higher-stage kidney tumors with
worse oncological outcomes [82,83].

3) Metastatic and locally advanced RCC outcomes

A study by Steffens et al. [32] at a single German institution among 77 mRCC patients treated with antiangiogenic therapies found that higher VAT was associated with significantly longer PFS (11.5 months vs. 8.4 months, \( p=0.005 \)) and OS (32.3 months vs. 16.9 months, \( p=0.04 \)). In contrast, Ladoire et al. [84] reported on 64 French patients receiving antiangiogenic therapy, finding that high VAT was associated with shorter PFS (HR, 3.22) and OS (HR, 6.26). The positive impact of visceral adiposity on survival could be explained by a high nutritional status with resistance to malignancy-associated fat loss or a potential signaling effect from adipose tissue; in contrast, the angiogenic factors produced by adipocytes may promote tumor spread and limit the response to targeted therapy [32,84]. Furthermore, in a series of 124 mRCC patients receiving targeted therapy, higher levels of the continuous VAT (HR, 0.981; \( p=0.002 \)) and SAT (0.987; \( p=0.048 \)) indices remained positively associated with OS [85]. In addition, above-median perirenal fat thickness has shown predictive ability for improved OS and PFS in those receiving anti-VEGF therapy [86]. However, Schmeusser et al. [87] also examined the ability of MAP, which include markers of perirenal fat thickness, to predict OS and PFS in localized T3–4 RCC, and found no significant associations. Patients with high perirenal fat thickness had increased angiogenic gene expression, suggesting that this feature may instead aid in drug delivery to the tumor for improved response [86].

The role of adiposity in drug tolerance has also been examined. Across 8 sites in South Korea, a higher VAT index was associated with early-onset sunitinib-induced DLT; however, these patients experienced longer PFS [88]. VAT is a risk factor for fatty liver disease, and Park et al. [88] proposed that this could lower the metabolism of sunitinib, increase concentration, and promote DLT. Further evidence supports this finding, where patients with an above-median TAT index, adjusted by sex, demonstrated increased rates of sorafenib and sunitinib-associated cardiotoxicity [63].

Measurements of fat may play a role in immunotherapy. Martini et al. [89] developed a risk score for mRCC patients receiving ICIs based on body composition metrics, including SAT and IMAT indices; the poor-risk category demonstrated shorter OS (HR, 6.37; \( p<0.001 \)), PFS (HR, 4.19; \( p<0.001 \)), and lower clinical benefit (OR, 0.23; \( p=0.044 \)) than the favorable risk group [89]. Overall, a below-median TAT index was associated with shorter OS, PFS, and lower clinical benefit than patients with a high TAT index. In contrast, Wang et al. [90] analyzed fat composition measurements in relation to survival outcomes in 251 Chinese mRCC patients receiving immunotherapy; only percent SAT was predictive of improved PFS and OS. Fat composition appears to predict immunotherapy responses in mRCC; however, further research is warranted to identify the principal contributing factors and biologic explanations.

**FUTURE APPLICATIONS**

Body composition has significant implications for perioperative and survival outcomes in patients with RCC. A principal question is whether body composition is practically modifiable to help direct clinical management. Prehabilitation programs aim to improve a patient’s functional status prior to surgery via medical optimization, physical exercise, nutritional supplementation, and psychological support [91]. Evidence suggests that interventions encourage positive muscle and fat changes [92,93]. A recent study of surgical patients randomized to a preoperative program involving activity, pulmonary function, nutrition, and mindfulness [94]. However, in a review of prehabilitation exercises before prostate, bladder, and kidney cancer surgery, although presurgical fitness measures improved, no impact was observed on complications, mortality, LOS, or readmission rates [95].

The influence of prehabilitation programs on survival outcomes remains unexplored in RCC. In general, physical inactivity is associated with increased likelihood of death from kidney cancer [96]. Indeed, regular exercise may help prevent cancer development and improve treatment outcomes in patients with cancer diagnoses [97,98]. There may also be a prognostic role for diet in cancer-related outcomes, although existing studies vary widely and are dominated by select cancers [99,100]. Traditionally healthy diets may decrease RCC incidence, but further research is...
needed to characterize the impact of nutrition throughout the disease course [101].

The early evidence for prehabilitation before and during other cancer treatments is encouraging. Halliday et al. [92] found, in a study of patients undergoing multimodal therapy for esophageal cancer, that exercise was feasible, mitigated SMI loss, and reduced VAT, leading to a lower risk of complications. In a separate study of 40 esophageal cancer patients receiving neoadjuvant chemotherapy, the exercise prehabilitation group experienced greater tumor regression and downstaging, possibly due to a decreased inflammatory response [102]. The physiological effects of exercise may reduce inflammation and limit muscle loss while promoting a decline in VAT. Visceral adiposity may represent nutritional status or the degree of disease aggressiveness; therefore, unintentional loss could indicate worsening oncologic outcomes, whereas intentional loss may correlate with improving health status and inflammation. Similar methodology is needed to evaluate the potential benefits and biological implications of prehabilitation programs for patients with RCC.

CONCLUSIONS

Accurate body composition measurements beyond BMI for patients with kidney cancer have become increasingly feasible and clinically accessible. Strong evidence supports low muscle mass as a predictor of shortened survival outcomes in both localized and advanced RCC; the prognostic utility becomes even stronger when combined with markers of inflammation and malnutrition. Fat quantity and quality measurements hold significant roles in prognosticating perioperative outcomes as well. Decreased visceral adiposity has been shown to negatively impact survival in patients with localized and advanced RCC; however, this may be reflective of nutritional status and the degree of tumor aggressiveness. Strategies aimed at maximizing these metrics hold significant promise in improving outcomes for RCC patients.

NOTES

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REFERENCES


68. Zhai T, Zhang B, Qu Z, Chen C. Elevated visceral obesity quantified by CT is associated with adverse postoperative outcome of laparoscopic radical nephrectomy for renal clear cell carcinoma patients. Int Urol Nephrol 2018;50:845-50.
with localized renal cell carcinoma progression-free survival. Urology 2016;89:54-60.
INTRODUCTION

Renal cell carcinoma (RCC) is the most frequent type of renal malignancy, accounting for 2.4% of all adult cancers in South Korea [1]. Surgical resection is currently acknowledged as the standard treatment for localized RCC [2,3]. The most recent guidelines from the European Association of Urology (EAU) [4] recommend partial nephrectomy (PN) for clinical T1 stage RCC. For advanced localized RCC, radical nephrectomy (RN) is the preferred treatment. PN may also
be an option for T2–3a RCC, but the risks and benefits must be carefully weighed. Since cytoreductive nephrectomy can offer oncologic benefits for patients with metastatic RCC [5,6], the clinical significance of RN in treating advanced RCC is substantial.

Percutaneous renal arterial embolization (RAE) was first introduced into clinical practice in the 1970s [7]. Initially, its applications were confined to treating symptomatic hematuria and providing palliation for metastatic RCC. Over time, the indications for RAE have expanded to include a variety of conditions such as persistent bleeding, hemorrhagic angiomyolipoma, arteriovenous fistulae, and vascular malformations [8,9]. Furthermore, performing RAE prior to PN in RCC patients has been shown to reduce blood loss during surgery [10]. At present, RAE is recognized as a safe procedure with few complications, the majority of which are postinfarction syndromes such as pain, fever, nausea, and vomiting [8].

In advanced RCC cases, preoperative renal artery embolization (PRAE) has begun to be implemented prior to RN to induce preoperative infarction, thereby facilitating tumor resection with less blood loss compared to RN alone [11,12]. Numerous retrospective series that have evaluated the use of PRAE before surgical resection have reported reductions in intraoperative blood loss, operation time, and involvement of adjacent organs, thus enabling a more comprehensive resection [13,14]. It is generally recommended to perform PRAE less than 48 hours before RN to minimize the distress caused by postinfarction syndrome [15]. In terms of oncologic outcomes, some studies have reported that PRAE does not improve the prognosis following surgery [16]. Conversely, other studies have suggested that PRAE results in a better prognosis after RN than RN alone [17,18]. These improvements in survival may be due to immunotherapeutic responses, including lymphoproliferative responses and the enhancement of natural killer cell activity, which follow tumor necrosis after PRAE [15,19,20]. However, all these previously published studies were non-randomized and had a selection bias. Therefore, the true role of PRAE remains undetermined [21].

Thus, the objective of this study was to assess the effects of PRAE for nonmetastatic RCC before RN on perioperative and oncologic outcomes.

MATERIALS AND METHODS

We conducted a retrospective analysis of data from patients who underwent RN for nonmetastatic RCC. This took place at a single tertiary center between June 2003 and May 2022. This study was approved by the Institutional Review Board (IRB) of Seoul National University Bundang Hospital (IRB No. B-2212-801-107).

Patients aged over 20 years, with nonmetastatic RCC staged as clinically T1-T4/N0-N1, who had undergone RN were included in this study. All patients were definitively diagnosed with RCC via a pathological report following RN. We excluded patients with bilateral synchronous tumors, von Hippel-Lindau syndrome, or histology inconsistent with RCC. The procedures performed included open RN, hand-assisted laparoscopic RN, laparoscopic RN, and robot-assisted laparoscopic RN. Tumor size was determined by the longest diameter of the tumor, as measured by preoperative computed tomography (CT) scan or magnetic resonance imaging (MRI). The renal nephrometry score [22], based on CT or MRI, was used to evaluate the anatomical features and complexity of the tumors.

There were no standardized guidelines for conducting PRAE. Surgeons individually determined the necessity of PRAE in patients who were considered surgically challenging or who had aggressive forms of cancer. Various anatomical features identified in the images, including complex vasculature with multiple feeding vessels, potential adhesions surrounding the tumor, or exceptionally large tumors, were viewed as challenging surgical conditions or indicative of an aggressive tumor.

Radiologists at the center performed PRAE within 24 hours prior to surgery to mitigate postinfarction symptoms such as pain, fever, nausea, vomiting, and the like. Arteriography was conducted via a common femoral artery puncture to visualize the ipsilateral renal arterial structure and hypervascular tumor staining. Following the identification of the vascular anatomy, PRAE was carried out using a polyvinyl alcohol particle, Gelfoam, and a detachable coil. If complete occlusion of the target vessel was confirmed, PRAE was deemed technically successful [23].

In this retrospective study, propensity score matching (PSM) was utilized to minimize the selection bias of potential
confounders. Prior to implementing PSM, significant
differences were observed in baseline characteristics such as
sex (p=0.047), clinical stage (p=0.001), and Fuhrman grade
(p<0.001) among the 830 patients included in the study. We
applied 1:2 PSM using the nearest-neighbor method, taking
into account variables such as age, sex, body mass index,
diabetes, hypertension, chronic kidney disease performance
status, clinical stage, and pathologic reports. As a result, we
successfully matched 121 patients with PRAE to 242 control
patients.

The primary endpoints of our study were oncologic
outcomes, which included the recurrence rate, overall
survival (OS), cancer-specific survival (CSS), and recurrence-
free survival (RFS). Local recurrence, recurrence at ipsilateral
regional structures (such as retroperitoneal lymph nodes and
the psoas muscle), and distant recurrence were included. The
secondary endpoints were perioperative and postoperative
outcomes, which included operation time, estimated blood
loss during surgery, the number of patients who required
postoperative transfusion, the volume of transfusion (pack),
and the length of hospital stay.

The baseline characteristics were analyzed using
descriptive statistics. The differences between the 2 groups
were examined with the chi-square test for categorical
variables and the independent t-test for continuous variables.
RFS, CFS, and OS were evaluated using Kaplan-Meier
analysis with univariate and multivariate logistic regression.
P-values of less than 0.05 indicated statistical significance. All
statistical analyses were performed using IBM SPSS Statistics
ver. 25.0 (IBM Co., Armonk, NY, USA).

### RESULTS

The basic characteristics of both groups, both before and
after PSM, are presented in Table 1. Statistically significant
differences were observed in sex (p=0.047), clinical stage ≥T3
(p<0.001), clinical stage N1 (p=0.001), and the distribution of
Fuhrman grade (p<0.001). However, after PSM, the baseline
characteristics between the 2 groups were well balanced
and comparable. The mean age at the time of operation

<table>
<thead>
<tr>
<th>Variable</th>
<th>Before propensity score matching</th>
<th>After propensity score matching</th>
<th>Control group (n=699)</th>
<th>PRAE group (n=121)</th>
<th>p-value</th>
<th>Control group (n=242)</th>
<th>PRAE group (n=121)</th>
<th>p-value</th>
<th>Standardized difference</th>
<th>Standardized difference</th>
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<td>58.1±12.5</td>
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<td>58.3±13.3</td>
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<td>47 (38.8)</td>
<td>0.047</td>
<td>0.194</td>
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<td>96 (39.7)</td>
<td>47 (38.8)</td>
<td>0.970</td>
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<td>BMI (kg/m²)</td>
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<td>24.0±3.4</td>
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<td>44 (18.2)</td>
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<td>120 (49.6)</td>
<td>57 (47.1)</td>
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<tr>
<td>≥T3</td>
<td>107 (15.3)</td>
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<td>191 (78.9)</td>
<td>100 (82.6)</td>
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<td>Chromophobe type</td>
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<td>7 (5.8)</td>
<td>10 (4.1)</td>
<td>7 (5.8)</td>
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<tr>
<td>Fuhrman grade</td>
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Values are presented as mean±standard deviation or number (%).
PRAE, preoperative renal artery embolization; BMI, body mass index; CKD, chronic kidney disease; ECOG, European Cooperative Oncology Group.
was 58.2±13.0 years, with 143 (39.3%) of the patients being female. In terms of clinical stages, 150 (41.3%) were ≥cT3 and 42 (11.5%) were cN1. The pathology report indicated that 291 (80.1%) patients had clear-cell type RCC, and 334 (89.3%) had a Fuhrman grade of ≥3. After PSM, there was no significant difference in tumor size (76.4±32.6 mm vs. 79.2±27.3 mm, p=0.471) or renal nephrometry score (10.0±7.6 vs. 9.84±1.6, p=0.825).

The perioperative outcomes for both groups are detailed in Table 2. The PRAE group exhibited a higher postoperative transfusion rate (18.2% vs. 10.7%, p=0.049) and a greater amount of postoperative transfusion (0.7±1.9 packs vs. 0.3±0.9 packs, p=0.025) than the control group. However, there was no significant difference between the PRAE group and the control group in operation time (166.6±95.3 minutes vs. 155.5±74.2 minutes, p=0.263), estimated blood loss (360.4±732.0 mL vs. 293.4±596.6 mL, p=0.384), or length of hospital stay (7.7±4.9 days vs. 7.7±3.7 days, p=0.961).

The median follow-up period was 42.0 months. In terms of oncologic outcomes, the recurrence rate was significantly lower in the PRAE group compared to the control group (20.7% vs. 34.3%, p=0.007). However, no significant difference was observed between the PRAE group and the control group in terms of cancer-specific death (8.3% vs. 9.1%, p=0.793) or overall death (8.3% vs. 12.0%, p=0.281) (Table 3). Furthermore, the Kaplan-Meier analysis revealed no significant difference in RFS (p=0.283), CSS (p=0.173), or OS (p=0.442) between the 2 groups (Fig. 1).

Univariate analysis revealed that a higher recurrence rate was associated with clinical T stage ≥3 (odds ratio [OR], 4.275; p<0.001) and clinical N1 stage (OR, 2.407; p<0.008). Additionally, the absence of PRAE (OR, 2.005; p<0.008) was also linked to a higher recurrence rate. In the multivariate analysis, clinical T stage ≥3 (OR, 4.365; p<0.001), clinical N1 stage (OR, 2.405; p=0.020), and the absence of PRAE (OR, 2.293; p=0.004) were identified as independent predictive factors of recurrence (Table 4).

**DISCUSSION**

Before RAE was introduced for the management of RCC [24], it was utilized in the treatment of various renal diseases. It has been acknowledged as a safe procedure with a low incidence of major complications [8]. However, the role of PRAE in the management of RCC remains a contentious issue among urologists [19]. According to the guidelines of the American Urological Association [25] and the National Comprehensive Cancer Network [2], there are no recommendations for PRAE prior to RN. Only the EAU guideline [4] suggests the use of RAE for the palliation of symptoms such as flank pain and hematuria, and notes that only selective PRAE could reduce intraoperative blood loss during PN. The current EAU guideline also states that there is no benefit to PRAE before routine RN.

The clinical role of PRAE prior to RN has been the subject of extensive debate in numerous studies. May et al. [16] reported that there was no survival advantage following PRAE in patients with RCC. In patients with RCC and an inferior vena cava thrombus, Subramanian et al. [26] have reported that PRAE not only fails to provide survival benefits, but also increases mortality and perioperative complications. Conversely, Zielinski et al. [17] have retrospectively assessed the role of PRAE in RN. In their study, patients were divided into a PRAE group (n=118) and a control group (n=116). The PRAE group exhibited statistically significant higher 5-year and 10-year survival rates. Some research has suggested that PRAE, followed by RN, may be associated with immunotherapeutic benefits due to lymphoproliferative responses and subsequent tumor necrosis, which could contribute to additional survival gains [20,27]. Bakke et

<table>
<thead>
<tr>
<th>Parameter</th>
<th>PRAE group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operation time (min)</td>
<td>166.6±95.3</td>
<td>155.5±74.2</td>
<td>0.263</td>
</tr>
<tr>
<td>Estimated blood loss (mL)</td>
<td>360.4±732.0</td>
<td>293.4±596.6</td>
<td>0.384</td>
</tr>
<tr>
<td>Postoperative transfusion</td>
<td>22 (18.2)</td>
<td>26 (10.7)</td>
<td>0.049</td>
</tr>
<tr>
<td>Postoperative transfusion (pack)</td>
<td>0.7±1.9</td>
<td>0.3±0.9</td>
<td>0.025</td>
</tr>
<tr>
<td>Hospital days (day)</td>
<td>7.7±4.9</td>
<td>7.7±3.7</td>
<td>0.961</td>
</tr>
</tbody>
</table>

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

**Table 3. Oncologic outcomes between PRAE group and control group**

<table>
<thead>
<tr>
<th>Variable</th>
<th>PRAE group</th>
<th>Control group</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>25 (20.7)</td>
<td>83 (34.3)</td>
<td>0.007</td>
</tr>
<tr>
<td>Cancer-specific death</td>
<td>10 (8.3)</td>
<td>22 (9.1)</td>
<td>0.793</td>
</tr>
<tr>
<td>Overall death</td>
<td>10 (8.3)</td>
<td>29 (12.0)</td>
<td>0.281</td>
</tr>
</tbody>
</table>

Values are presented as number (%).

PRAE: Preoperative renal artery embolization.
al. [19] have also reported an increase in natural killer cells following PRAE in patients with RCC, which may be influenced by interferon released from macrophages activated by tumor necrosis. However, there is currently no definitive evidence to suggest that PRAE provides survival benefits through an immunotherapeutic response in patients.

### Table 4. Univariate and multivariate logistic regression analysis for probability of recurrence

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Age</td>
<td>1.019 (1.001–1.038)</td>
<td>0.035</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.219 (0.765–1.941)</td>
<td>0.405</td>
</tr>
<tr>
<td>BMI</td>
<td>0.950 (0.886–1.019)</td>
<td>0.154</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1.449 (0.826–2.541)</td>
<td>0.195</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1.257 (0.801–1.973)</td>
<td>0.319</td>
</tr>
<tr>
<td>CKD</td>
<td>1.923 (0.506–7.304)</td>
<td>0.337</td>
</tr>
<tr>
<td>ECOG =1</td>
<td>1.029 (0.554–1.913)</td>
<td>0.928</td>
</tr>
<tr>
<td>ECOG ≥2</td>
<td>2.482 (0.902–6.832)</td>
<td>0.078</td>
</tr>
<tr>
<td>cT ≥3</td>
<td>4.275 (2.651–6.894)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>cN1</td>
<td>2.407 (1.252–4.626)</td>
<td>0.008</td>
</tr>
<tr>
<td>Clear-cell type</td>
<td>1.229 (0.688–2.196)</td>
<td>0.486</td>
</tr>
<tr>
<td>Fuhrman grade ≥3</td>
<td>2.527 (1.026–6.221)</td>
<td>0.044</td>
</tr>
<tr>
<td>PRAE</td>
<td>2.005 (1.199–3.351)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; BMI, body mass index; CKD, chronic kidney disease; ECOG, European Cooperative Oncology Group; PRAE, preoperative renal artery embolization.

Fig. 1. Kaplan-Meier analysis of recurrence-free survival (A), overall survival (B), and cancer-specific survival (C) comparing PRAE group and control group. PRAE, preoperative renal artery embolization.
with nonmetastatic advanced RCC [1].

Other studies have proposed that PRAE is a safe and beneficial procedure, offering distinct technical advantages during subsequent RN in advanced high-risk RCC, including a reduction in surgical blood loss [11,12,28]. However, our study did not reveal a significant difference in operation time or estimated blood loss during surgery between the PRAE group and the control group. Moreover, contrary to previous studies, a higher percentage of patients who received postoperative transfusion (18.2% vs. 10.7%, p=0.049) and a greater number of red blood cell packs were used during transfusion in the PRAE group (0.7±1.9 packs vs. 0.3±0.9 packs, p=0.025). This was a retrospective study without randomization, and PRAE was performed on patients who were deemed to be surgically challenging or had aggressive tumors (thus, anticipated to have substantial intraoperative blood loss). Apart from tumor size and the renal nephrometry score, other anatomical features such as complex vasculature, which prompted the surgeons to perform PRAE, were challenging to quantify and statistically analyze accurately. Therefore, our results could have been affected by selection bias despite PSM.

Despite the issue of selection bias, the recurrence rate was notably lower in the PRAE group compared to the control group (20.7% vs. 34.3%, p=0.007). PRAE emerged as a statistically significant factor associated with the recurrence rate, alongside clinical T stage and N stage, in the multivariate analysis. The immunotherapeutic effects suggested by previous studies [19,20] may influence circulating cancer cells, potentially preventing recurrence. Given that a PSM was conducted with the clinical stage and pathologic report, it can be inferred that patients in both the PRAE group and the control group likely had similar oncologic characteristics. Moreover, there was no significant statistical difference in tumor size or the renal nephrometry score. However, considering the potential selection bias due to PRAE being performed on patients with challenging conditions, it can be inferred that the PRAE group may have had similar or even worse oncologic characteristics compared to the control group. Despite this, the PRAE group demonstrated a lower recurrence rate, suggesting an additional role for PRAE prior to RN. Further studies are needed to clarify the effects and roles of this procedure in advanced RCC patients. There were no significant differences in overall death or cancer-specific death between the 2 groups. Similarly, there was no significant difference in the Kaplan-Meier analysis of CSS or OS. However, given the relatively short follow-up period, the effect of PRAE on survival may have been underestimated. Therefore, studies with longer follow-up periods are necessary for a more comprehensive evaluation of the effects of PRAE.

This study has some potential limitations. First, due to the retrospective nature of the study, there may be potential selection bias, although we did employ PSM to mitigate this bias. Second, our study population was relatively small and our follow-up period was relatively brief, which may have contributed to the lack of significant difference observed in the Kaplan-Meier analysis. Third, we did not take into account the potential impacts of changes in medical practice and technology over nearly 2 decades on the study’s results. Changes in guidelines or technical advancements could have made potential RN candidates suitable for PN, which could also have introduced selection bias. Additionally, there were insufficient guidelines for PRAE for asymptomatic patients. As a result, PRAE may have been applied to patients who could potentially benefit from the procedure.

**CONCLUSIONS**

The results of our study suggest that PRAE for advanced nonmetastatic RCC could reduce recurrence rate. Therefore, performing PRAE before RN could be useful in the management of advanced nonmetastatic RCC. Considering that in our study, PRAE was performed on patients deemed to be surgical challenges or those with aggressive cancer, as assessed by our surgeons. Consequently, we cautiously propose the consideration of PRAE before RN when surgeons evaluate a patient as having an aggressive condition. However, we should also emphasize that proper guidelines or indications for PRAE are currently absent. The results should be interpreted with caution and further prospective randomized research is needed to provide evidence of our results.
NOTES

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- **Author Contribution:** Conceptualization: JN, GHJ; Data curation: JN, SHS; Formal analysis: JN, GHJ; Methodology: JN; Project administration: JKK, SKH; Visualization: JN SCL; Writing - original draft: JN; Writing - review & editing: JN, JKK, SSB
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REFERENCES


INTRODUCTION

Renal cell carcinoma (RCC) remains a significant challenge in oncology, prompting thorough investigations into adjuvant treatments aimed at enhancing both survival and quality of life for patients. In this review, we explore the complex landscape of adjuvant treatments for managing RCC, highlighting the pivotal roles and efficacy of tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs). This review article presents a detailed exploration of both historical and contemporary trials involving TKIs, spotlighting their capabilities, successes, and limitations in the adjuvant setting. Furthermore, we examine the emerging significance of ICIs, analyzing recent trials and assessing their impact on outcomes such as disease-free survival and overall survival. Additionally, this review provides insights into the application, adaptation, and outcomes of these adjuvant therapies within the specific context and circumstances of Korean healthcare.

Key Words: Renal cell carcinoma, Adjuvant, Chemotherapy
therapy have not demonstrated notable improvements in either overall survival (OS) or disease-free survival (DFS). Although these trials sought to improve the long-term prospects of patients confronting the challenges of relapsed or metastatic RCC, the results have not confirmed significant benefits in terms of prolonged survival or disease management. Therefore, the pursuit of more effective adjuvant therapies persists, necessitating ongoing research and investigation to discover innovative strategies for improving outcomes and quality of life for individuals dealing with this daunting disease. In the early 2000s, a noteworthy breakthrough in comprehending the underlying causes of RCC led to the development of a promising treatment strategy: tyrosine kinase inhibitors (TKIs), specifically those targeting the vascular endothelial growth factor (VEGF) family [8]. While these TKIs transformed the management of metastatic RCC, signifying a crucial moment in the battle against RCC and presenting new opportunities for improved patient care, numerous clinical trials did not corroborate the hoped-for improvements in either DFS or OS. In addition to TKIs, researchers have explored various treatment approaches over the years, but their efficacy has remained indeterminate. Despite these challenges, the search for effective adjuvant therapies for RCC continues, propelled by the necessity to improve the outcomes of patients confronting this challenging disease. As immune checkpoint inhibitors (ICIs), including programmed cell death-1 (PD-1) inhibitors and cytotoxic T lymphocyte antigen-4 inhibitors, have also proven to be effective against RCC, various treatment options have emerged [9,10]. Consequently, recent clinical trials have been conducted to assess the efficacy and safety of new drugs in adjuvant settings.

This comprehensive review seeks to examine the current landscape of adjuvant therapy for RCC, highlighting recent trials that investigate the effectiveness of treatment modalities such as TKIs and ICIs.

**TKIs AS ADJUVANT THERAPY**

Over the last 2 decades, targeted therapies such as VEGFR-TKIs (e.g., sunitinib, sorafenib, axitinib, and pazopanib) have revolutionized the treatment of metastatic RCC, propelling the initiation of clinical trials aimed at identifying effective adjuvant treatments. Globally, 5 phase 3 trials have been conducted; however, they have yielded inconsistent results for DFS. A summary of these studies is presented in Table 1.

### 1. S-TRAC Trial

The S-TRAC trial, a pivotal phase 3 study, evaluated sunitinib as an adjuvant treatment in RCC patients with clear cell histology, involving 615 high-risk locoregional clear-cell RCC (ccRCC) patients and assigning them randomly to receive either sunitinib or a placebo [11]. Patients on sunitinib showed a noticeable increase in median DFS, recording 6.8 years compared to 5.6 years with placebo (p=-0.03), though the trial did not demonstrate a definitive between-group difference in the median OS. Sunitinib’s approval by the U.S. Food and Drug Administration (FDA) as an adjuvant therapy for high-risk RCC patients, following the success of the S-TRAC trial, marked a significant advancement in RCC management. However, despite its demonstrated benefits for DFS, questions persist regarding its impact on OS, and its application remains a matter of medical debate due to potential toxicities and side effects, including diarrhea, fatigue, hypertension, and rashes, that can impinge upon patients’ quality of life [12,13].

### 2. Other VEGFR-TKI Trials

The ASSURE study examined sunitinib and sorafenib as additional treatments in 1943 RCC patients at high risk of recurrence [14]. Both sunitinib (adjusted from 50 to 37.5 mg) and sorafenib (adjusted from 400 to 200 mg twice daily) required dose changes due to side effects. However, the study did not find any differences in DFS or OS. In the later SORCE study, sorafenib failed to show any benefits in terms of DFS or OS compared to a placebo [15]. The trial included patients with intermediate-risk or high-risk ccRCC as well as non-clear cell RCC (nccRCC), as defined by the Leibovich risk model. They were given sorafenib or a placebo for 3 years, and after 10 years, the survival rates were similar among these groups. The PROTECT study tested adjuvant pazopanib in patients with locally advanced RCC who were at a high risk of recurrence after surgery [16]. Unfortunately, the study did not meet its main goal of showing improved
Table 1. Overview of adjuvant clinical trials utilizing tyrosine kinase inhibitors in renal cell carcinoma treatment

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Starting dose</th>
<th>Adjusted dose</th>
<th>Treatment duration</th>
<th>AEs (grade 3 or worse)</th>
<th>Most common AEs</th>
<th>No.</th>
<th>Treatment regimen</th>
<th>Time</th>
<th>Primary end point</th>
<th>Outcome</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASSURE</td>
<td>3</td>
<td>50-mg sunitinib, 800-mg sorafenib</td>
<td>37.5-mg sunitinib, 800-mg sorafenib</td>
<td>54 Weeks</td>
<td>63% sunitinib, 800-mg sorafenib</td>
<td>Sunifatinib: hypertension, fatigue (17%), hand-foot syndrome (15%), diarrhea (10%); Sorafenib: hand-foot syndrome (33%), hypertension (16%), rash/desquamation (15%)</td>
<td>1,943</td>
<td>Sorafenib or sunitinib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>No significant differences, Sorafenib; 5.8 years HR, 1.02; 97.5% CI, 0.85 to 1.23; p=0.8038 Sunitinib; 5.8 years HR, 0.97; 97.5% CI, 0.80 to 1.17; p=0.7184</td>
<td>Dose reduction of sunitinib and sorafenib midtrial because of higher-than-expected rates of discontinuation</td>
</tr>
<tr>
<td>S-TRAC</td>
<td>3</td>
<td>50-mg sunitinib</td>
<td>-</td>
<td>1 Year</td>
<td>63%</td>
<td>Hand-foot syndrome (50%), Hypertension (37%)</td>
<td>615</td>
<td>Sunitinib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>Significant differences, Sunitinib; 6.8 years HR, 0.76; 95% CI, 0.59 to 0.98; p=0.03 Led to FDA approval of sunitinib in the adjuvant setting for RCC</td>
<td>ccRCC</td>
</tr>
<tr>
<td>PROTECT</td>
<td>3</td>
<td>800-mg pazopanib</td>
<td>600-mg pazopanib</td>
<td>1 Year</td>
<td>60%</td>
<td>Hypertension (25%), LFT elevation (16%), diarrhea (7%)</td>
<td>1538</td>
<td>Pazopanib vs. placebo</td>
<td>1 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 0.86; 95% CI, 0.70 to 1.06; p=0.165 Dose reduction of pazopanib midtrial because of higher-than-expected rates of discontinuation</td>
<td>ccRCC</td>
</tr>
<tr>
<td>ATLAS</td>
<td>3</td>
<td>10-mg axitinib</td>
<td>-</td>
<td>1–3 Years</td>
<td>61%</td>
<td>Hypertension (60%), diarrhea (47%), dysphonia (38%)</td>
<td>724</td>
<td>Axitinib vs. placebo</td>
<td>3 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 0.870; 95% CI, 0.665 to 1.147; p=0.3211 Terminated early because of lack of response at interim analysis</td>
<td>&gt;50% component of ccRCC</td>
</tr>
<tr>
<td>SORCE</td>
<td>3</td>
<td>800-mg sorafenib</td>
<td>400-mg sorafenib</td>
<td>1 or 3 Years</td>
<td>58% sorafenib 1 year 64% sorafenib 3 years</td>
<td>Sorafenib 1 year: hypertension (26%), hand-foot syndrome (24%), rash (7%); Sorafenib 3 years: hypertension (24%), hand-foot syndrome (24%), rash (10%)</td>
<td>1711</td>
<td>Sorafenib vs. placebo</td>
<td>3 Year</td>
<td>DFS</td>
<td>No significant differences, HR, 1.01; 95% CI, 0.83 to 1.23; p=0.95 More than 50% of patients stopped treatment early because of adverse events</td>
<td>More than 50% of patients stopped treatment early because of adverse events</td>
</tr>
</tbody>
</table>

AEs, adverse events; DFS, disease-free survival; HR, hazard ratio; CI, confidence interval; ccRCC, clear cell renal cell carcinoma; nccRCC, non-clear cell renal cell carcinoma; UISS, UCLA Integrated Staging System; FDA, Food and Drug Administration; SSIGN, stage, size, grade and necrosis; pT, pathological tumor; N, node; M, metastasis; G, grade.
DFS. No significant differences in OS were found between the pazopanib and placebo groups. In the ATLAS trial, which involved 724 patients who had more than 50% ccRCC and had undergone nephrectomy, patients received axitinib or a placebo for over 3 years. However, axitinib did not reach the main goal of improving DFS compared to the placebo [17]. OS also showed no significant difference between the treatment arms. The results of these trials indicate that VEGFR-TKIs did not enhance survival outcomes in the adjuvant setting [18].

3. EVEREST Trial

The EVEREST study initially investigated an mTOR inhibitor, everolimus, as a postsurgery adjuvant treatment for RCC and provided key insights into disease management, even though it did not significantly improve recurrence-free survival (RFS) across all patient groups [19]. Administered for up to a year, everolimus demonstrated a nuanced pattern of efficacy, with subgroup analyses revealing a tangible RFS benefit among very high-risk patients, while showing no such benefit in intermediate-high-risk patients. Notably, the 5-year RFS was 67% with everolimus versus 63% with placebo, although this difference did not reach the pre-specified p-value for statistical significance. The study, which included 1,545 patients, highlighted the complexity and urgency of preventing metastatic progression in early-stage RCC, especially given the diverse responses among different risk stratifications. The findings from the EVEREST study underline the importance of focused investigations into mTOR inhibition, particularly for very high-risk RCC patients, and suggest the possibility of an approach where everolimus is considered concomitantly with a precise patient selection strategy that centers around identifying those at the highest risk for recurrence [20]. Despite 46% of patients experiencing grade 3 or higher adverse events (AEs) with everolimus compared to 11% with placebo, the EVEREST study offers vital insights into its application as an adjuvant treatment for RCC. Nonetheless, there is a need for more refined studies, aimed at enhancing risk assessment tools and selecting optimal patients for treatment, by going beyond conventional TNM staging and investigating the complex molecular diversity within RCC.

Regarding the use of adjuvant TKIs in RCC, sunitinib has been approved both in the United States and in Korea for adjuvant therapy, specifically in patients with a high risk of recurrence, a decision grounded on the demonstrable DFS advantage observed in the S-TRAC trial. Specifically, in Korea, it is authorized for use in high-risk RCC patients who have undergone nephrectomy. However, a prevailing issue remains that it is not covered by national insurance, requiring patients to bear the financial burden. Conversely, other trials of anti-VEGF agents have not successfully met their primary efficacy endpoints, and not one, sunitinib included, has shown a clear benefit for OS. Furthermore, a meta-analysis revealed no noticeable benefit in terms of DFS or OS and reported a significant increase in AEs [18,21].

ADJUVANT IMMUNOTHERAPY IN RCC: SHIFTING THE PARADIGM

Immunotherapy (IO), whether utilized alone or in combination with other treatments, has significantly advanced the therapy for metastatic RCC. This progress has mirrored its postoperative successes in melanoma, through stimulating immune responses against residual disease and distant micro-metastases. Consequently, ICIs—particularly agents that inhibit PD-1 and its ligand (PD-L1)—have emerged as a promising adjuvant treatment, prompting extensive research in the setting of adjuvant treatment for kidney cancer. Recent randomized studies have explored the influence of IO-based treatments in the adjuvant setting for RCC, reporting a spectrum of results. Key trials on IO drugs in the adjuvant setting are organized and presented in Table 2.

1. KEYNOTE-564 Trial

Several clinical trials have explored the role of IO in the adjuvant setting, and some of them are still ongoing. One of the most noteworthy among them is the adjuvant pembrolizumab trial (KEYNOTE-564) [22]. Pembrolizumab demonstrated promising potential in reducing recurrence risk in RCC patients, as evidenced by the KEYNOTE-564 trial. While it is used as a monotherapy and is not FDA-approved for the metastatic setting, it has demonstrated benefits for DFS and potentially even OS when used in the...
adjuvant setting. The results of the KEYNOTE-564 trial led to the FDA’s approval of pembrolizumab as an adjuvant treatment for high-risk RCC patients by demonstrating a 32% decrease in disease recurrence risk, with a DFS hazard ratio (HR) of 0.68 (95% CI, 0.53–0.87; p=0.001). However, while data on DFS have been optimistic, OS data are still under examination, necessitating long-term follow-up to confirm potential long-term survival benefits. Subgroup analyses highlighted a noteworthy DFS benefit in M1 patients with no evidence of disease [23].

Despite the advancements presented by the trial, ongoing and further explorations are critical for understanding pembrolizumab’s potential and limitations from a holistic standpoint. Its immune-related AEs and the implications for subsequent treatment following metastatic disease relapse warrant consideration, emphasizing the necessity for continued scrutiny in future clinical practices and patient discussions [24]. While the role of pembrolizumab has solidified, particularly for high-risk RCC patients, ongoing investigations and long-term follow-up studies are crucial to ensure that its therapeutic applications are both thoroughly understood and judiciously applied in clinics.

2. Other IO Trials in an Adjuvant Setting

While the results from the KEYNOTE-564 trials showed noteworthy findings, the results from other clinical trials, especially the Phase 3 IMmotion010 trial, have introduced a complex narrative in the adjuvant IO landscape. The IMmotion010 trial scrutinized the impact of adjuvant atezolizumab (an anti-PD-L1 antibody) on resected RCC patients, identified with either a clear cell or sarcomatoid component, who were at an increased risk of recurrence [25]. Enrolled patients, reflecting demographics similar to prior studies, were randomized to receive atezolizumab or a placebo for 1 year, after nephrectomy with or without metastasectomy. With a median follow-up of 44.7 months, no significant difference was observed in DFS between the treatment and control arms, with a median investigator-assessed DFS of 57.2 versus 49.5 months (HR, 0.93; 95% CI: 0.75–1.15; p=0.50). Furthermore, no distinct patient subgroups, including M1 patients with no evidence of disease (HR, 0.93; 95% CI, 0.58–1.49), demonstrated discernible benefits from the therapy. Additionally, although OS data have yet to fully mature, current signals do not point toward a significant benefit, with an HR of 0.97 for a reduced mortality risk and a 3-year OS rate of 90.3% versus 89.8% when compared to the placebo.

The CheckMate 914 trial was conducted to examine the effectiveness of the adjuvant nivolumab/ipilimumab combination versus placebo (part A) and nivolumab monotherapy versus placebo (part B) [26]. Enrolled patients, particularly those with clear cell histology and a higher risk of recurrence, were the focus of CheckMate 914. Part A randomized patients with completely resected RCC (predominantly of clear cell histology) and an increased risk

Table 2. Summary of clinical trials employing immune checkpoint inhibitors as adjuvant therapy for renal cell carcinoma

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>No.</th>
<th>Tumor features</th>
<th>Treatment arms</th>
<th>Duration of treatment</th>
<th>DFS HR, 95% CI</th>
<th>RFS HR, 95% CI</th>
<th>OS HR, 95% CI</th>
<th>Grade 3 or worse AEs</th>
</tr>
</thead>
<tbody>
<tr>
<td>KEYNOTE-564</td>
<td>994</td>
<td>Intermediate-high-risk M0 M1</td>
<td>Pembrolizumab Placebo</td>
<td>1 Year</td>
<td>HR, 0.63; 95% CI: 0.50–0.80; p=0.0001</td>
<td>75.2% (95% CI, 70.8–78.1); 65.5% (95% CI, 60.3–70.9)</td>
<td>HR, 0.52; 95% CI: 0.31–0.86; p=0.0048</td>
<td>32%</td>
</tr>
<tr>
<td>IMmotion010</td>
<td>778</td>
<td>Intermediate-high-risk M0 M1</td>
<td>Atezolizumab Placebo</td>
<td>1 Year</td>
<td>HR, 0.93; 95% CI: 0.75–1.15; p=0.50</td>
<td>N/A</td>
<td>N/A</td>
<td>28%</td>
</tr>
<tr>
<td>Checkmate-914</td>
<td>816</td>
<td>Intermediate-high-risk M0 Clear-cell RCC sarcomatoid</td>
<td>Nivolumab+Ipilimumab Placebo</td>
<td>At least 24 weeks</td>
<td>HR, 0.92; 95% CI: 0.71–1.20</td>
<td>N/A</td>
<td>N/A</td>
<td>28.5%</td>
</tr>
<tr>
<td>PROSPER</td>
<td>819</td>
<td>Intermediate-high-risk M0 or M1 NED RCC of any histology</td>
<td>Nivolumab neoadjuvant Adjuvant placebo</td>
<td>40 Weeks (one dose prior to surgery followed by 9 doses)</td>
<td>N/A</td>
<td>HR, 0.97 (95% CI: 0.74–1.28; P1-sided=0.43)</td>
<td>HR, 1.48; (95% CI: 0.89–2.48; P1-sided=0.93</td>
<td>20%</td>
</tr>
</tbody>
</table>

DFS, disease-free survival; RFS, relapse-free survival; OS, overall survival; AEs, adverse events; NED, no evidence of disease; RCC, renal cell carcinoma; HR, hazard ratio; CIs, confidence intervals; N/A, not applicable.
of recurrence based on TNM stage and histologic grade. They were assigned to receive a 6-month treatment of either combined ipilimumab/nivolumab therapy or a placebo. Following a median follow-up of 37 months in part A, no significant difference in median DFS was observed (not reached vs. 50.7 months; HR, 0.92; 95% CI, 0.71–1.19). The 24-month DFS rates stood at 76.4% and 74% in the experimental and control arms, respectively. Although patients with sarcomatoid features, a small subgroup, seemed to significantly benefit from the ipilimumab/nivolumab combination, the advantage was offset by a notable 29% discontinuation of treatment due to AEs and a 23% necessity for corticosteroid use to manage immune-related AEs in the combination treatment arm. Part B of the ongoing trial, investigating the role of nivolumab monotherapy as an adjuvant treatment, is anticipated to expand the current understanding of single PD-1 inhibition in the adjuvant setting.

The PROSPER trial adopted a unique phase 3 trial design, randomizing 819 patients to receive either perioperative nivolumab or surgery alone [27]. The regimen involved administering one dose of nivolumab before surgery, followed by 9 adjuvant doses (480 mg intravenously every 4 weeks). Of the patients enrolled, 53% were diagnosed with cT2 disease, 47% with cT3/4, 17% with N+, and 4% with cM1, and 83% exhibited clear cell histology. The Data Safety and Monitoring Board prematurely halted the trial due to its futility for RFS (HR, 0.97; p=0.43). Although the OS data remain immature, initial indicators do not suggest a beneficial outcome (HR, 1.48; 95% CI, 0.89–2.48; p=0.93).

The results from IMmotion010, CheckMate 914, and PROSPER have not shown progress in DFS, thus raising questions regarding the exact role of IO in an adjuvant setting. The exact reasons behind these trial shortcomings remain elusive and might relate to differences in patient populations, the mechanisms of ICIs, and the duration of follow-up [28]. Given the disappointing outcomes from these trials, ongoing inquiry and evaluation are essential for expanding our understanding of how to prevent recurrence and improve outcomes for patients with RCC [29,30].

### COMPARING IO AND TKIs IN THE ADJUVANT SETTING

In the adjuvant treatment landscape for RCC, a comparative analysis between TKIs and ICIs has emerged as a critical consideration. These 2 major classes of therapeutics offer distinct mechanisms of action and have undergone rigorous evaluations. As mentioned above, sunitinib gained FDA approval as the first adjuvant therapy based on data from the S-TRAC trial. This phase 3 trial demonstrated an improvement in DFS with sunitinib. However, updated data did not reveal a significant difference in OS. The introduction of IO into adjuvant RCC treatment marked a significant paradigm shift. The KEYNOTE-564 trial evaluated adjuvant pembrolizumab and reported statistically significant and clinically meaningful DFS benefits. This trial resulted in FDA approval for high-risk RCC patients. Conversely, ICIs’ DFS benefits have the potential to translate into long-term survival advantages, although more extended follow-up is required for definitive confirmation. Analyzing the data between TKIs and IO uncovers subtleties. TKIs, while showing benefits for DFS, have not consistently translated to OS advantages. In contrast, IO’s DFS benefits have the potential to lead to OS benefits, although more extended follow-up is needed to confirm this. Additionally, the consideration of toxicity is also very important, as ICIs may induce immune-related AEs, necessitating a meticulous risk-benefit evaluation. Moreover, the utilization of ICIs as adjuvant therapy can significantly impact subsequent treatment decisions in cases of disease relapse with metastasis [31]. The selection between TKIs and ICIs in adjuvant RCC therapy is complex. The choice depends on individual patient factors, risk profiles, and the significance placed on DFS versus OS. Ongoing research continues to shape our understanding of the comparative efficacy and safety of these approaches.

### ONGOING AND FUTURE TRIALS

The dynamic landscape of adjuvant therapy for RCC continues to evolve with ongoing and future trials. International phase 3 adjuvant RCC studies, including RAMPART and LITESPARK-022, are actively enrolling patients, offering the promise of further improving outcomes for RCC patients.
following resection. The LITESPARK 002 study is examining belzutifan, a hypoxia-inducible factor 2 alpha (HIF-2α) inhibitor, in combination with pembrolizumab, as compared to a placebo plus pembrolizumab. Belzutifan targets a key mechanism in kidney cancer development linked to VHL mutations, effectively blocking HIF-related transcription. The trial targets ccRCC patients at intermediate-high or high risk, including those identified as M1 with no evidence of disease. The primary endpoint is DFS, and the study aims to enroll 1,600 patients [32]. The study is anticipated to be ongoing until approximately July 2024. Another phase 3 trial, RAMPART, is exploring the impact of durvalumab and tremelimumab on intermediate- to high-risk RCC patients postsurgery [33]. The trial will evaluate DFS and OS, with 1,750 patients planned for enrollment. Expected to achieve its primary completion by approximately July 2024, a distinct aspect of this trial is that it includes patients with Leibovich risk scores between 3 and 5, constituting 25% of the trial populations, as well as various RCC cell types.

In total, the RAMPART and LITESPARK 002 phase 3 trials together plan to recruit over 3,000 patients. The eligibility percentages vary due to different criteria. The collective efforts of patients participating in these trials, coupled with collaborative analysis, will guide the selection of the most appropriate adjuvant therapy for each individual with RCC in clinical practice. These trials aim to further refine treatment strategies, expand therapeutic options, and address unanswered questions.

**CHALLENGES IN ADJUVANT THERAPY SELECTION IN KOREA**

In Korea, applying adjuvant IO in a real-world setting demands careful consideration of several interconnected factors. Decisions about adjuvant therapy are significantly influenced by the country’s healthcare system and its strict reimbursement policies [34]. In Korea, as of 2023, the administration of adjuvant chemotherapy for RCC is entirely non-reimbursable, meaning that patients are required to pay the full cost of the medication themselves. These policies impose certain limitations on physicians regarding the selection of available adjuvant treatments for RCC patients.

Beyond financial aspects, addressing concerns about the potential for persistent and long-term AEs in some patients undergoing IO is vital. Identifying the most appropriate patients for treatment, taking into account variables such as distinct histological features and disease stage, is crucial. Alongside this, maintaining awareness of the limitations of IO—most notably, its relatively low objective response rate and the absence of predictive biomarkers—is essential for clarifying its applicability and efficacy across varied RCC patient demographics. Moreover, as we investigate further into therapeutic strategies, deciding on the next steps when adjuvant IO fails becomes necessary. Choosing between an ICI + ICI combination and an ICI + TKI regimen after recurrence requires a comprehensive approach that takes into account both patient-centered factors and the broader clinical perspective. This situation illustrates the complex challenges involved in integrating adjuvant IO into South Korea’s healthcare landscape. Furthermore, if RCC recurs, utilizing IO as a primary palliative treatment is neither approved nor logistically feasible following adjuvant IO treatment. These factors jointly highlight the complex interaction between healthcare policies and patient care in South Korea, emphasizing the necessity for continual evaluation and potential policy modifications to enhance patient access to optimal treatments.

**CONCLUSION**

No firmly established consensus exists regarding adjuvant chemotherapy for RCC, despite recent successful trials. Although VEGF inhibitors have shown a survival benefit, previously conducted trials of TKIs in the adjuvant setting have failed. Two recent meta-analyses also reported no benefits in DFS and OS [21,22]. The differences between successful and failed trials remain somewhat unclear. One contributor to the results may be the high toxicity rates. Patients treated with VEGF inhibitors commonly experienced toxicity. This can lead to poor compliance or low completion rates for TKIs, causing failure to extend DFS or OS. While VEGF inhibitors remain an effective treatment option for metastatic or unresectable RCC, they have failed to demonstrate a survival benefit in patients undergoing curative surgical resection. Further research will be needed to explain the mechanism underlying these discrepancies.
Pembrolizumab is currently the recommended adjuvant therapy for high-risk RCC. However, its application in nccRCC lacks substantial supporting evidence. ccRCC is the predominant subtype among diagnosed patients, and the majority of research has concentrated on this specific type. Conversely, our understanding of nccRCC remains limited, coupled with relatively weak treatment-related evidence. As a result, a pressing need exists for additional research studies focusing on individuals with nccRCC, aiming to improve our understanding and establish more effective treatment strategies within this patient subgroup. Moreover, we need to identify patients who notably benefit from adjuvant chemotherapy. A need persists to investigate more effective and established adjuvant treatments for these patients.

NOTES

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REFERENCES


Role of Radiotherapy in Metastatic Renal Cell Carcinomas:
An Evolutionary Journey in a Misunderstood Histological Type

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INTRODUCTION

Kidney cancer affects approximately 400,000 patients worldwide annually year, resulting in nearly 200,000 fatalities [1]. Renal cell carcinoma (RCC), the most common histological subtype of kidney cancer, accounts for over 90% of all cases. This type of cancer is most prevalent in developed regions, including North America and Western Europe. In Korea, the incidence of RCC has reached levels comparable to those seen in Western countries. In 2020, kidney cancer accounted for over 2% of new cancer diagnoses and approximately 1% of cancer-related deaths in Korea [2]. Data from the Surveillance, Epidemiology, and End Results database indicate that the survival rate for patients with RCC has gradually improved over the past few decades, mirroring trends seen in other types of malignancies [3]. As patients’ survival duration increases, the need to address metastatic disease becomes increasingly urgent. The survival rate for patients with metastatic RCC (mRCC) is also expected to rise due to the approval of immune checkpoint inhibitors such as pembrolizumab, nivolumab, avelumab, and ipilimumab. These can be used either as standalone treatments or in combination with tyrosine kinase inhibitors (TKIs) [4-7].

Radiotherapy (RT) plays a fundamental role in cancer treatment, with the primary objectives being to cure the disease, prevent its recurrence, and provide palliative relief from symptoms. Historically, due to the prevailing belief that RCC is radioresistant [8], the use of RT in managing mRCC has been largely limited to symptom management, particularly in addressing pain or neurological symptoms caused by bone or brain metastases. In fact, the use of RT has seen a decline from 1998 to 2010 for localized, locally advanced, and mRCC, as per the National Cancer Database [9]. However, with the advent of technological advancements...
in RT that allow for the precise delivery of radiation beams to the target while minimally impacting surrounding healthy tissues, a shift in the role of RT in managing (oligo)metastatic RCC is taking place. The American Society of Clinical Oncology, European Association of Urology, and National Comprehensive Cancer Network guidelines now recommend RT as a treatment option for mRCC, either as a metastasis-directed ablative or palliative treatment [10-12]. In this review, our aim is to discuss the current evidence and future perspectives on the emerging, or perhaps already established, role of RT in treating extracranial (oligo)metastatic RCC.

**RADIOSENSITIVITY OF RCC**

RCC has long been considered a histological type of cancer that is resistant to conventionally fractionated RT, with doses of ≤1.8–2 Gy per fraction. In a study by Deschavanne and Fertil [8], RCC was found to be the most radioresistant among 76 types of isolated cancer and normal cells. It required the highest radiation dose for cell inactivation and demonstrated the highest survival rate at 2-Gy irradiation in vitro. DiBiase and colleagues observed clinically that in patients with mRCC who underwent palliative RT for symptomatic lesions, a lower RT dose below the biologically effective dose (BED = total dose × [1 + daily dose/(α/β ratio)]) of 50 Gy (using an α/β ratio of 10 Gy) resulted in a significantly lower complete symptomatic response rate (59% vs. 39%). This implies that RCC cells may not respond effectively to lower RT doses [13]. Additionally, RCC has been observed to upregulate the α-subunits of the hypoxia-inducible factors (HIF-1α), which could potentially be associated with radioresistance in hypoxic conditions. The regulation of HIF-1α is influenced by mutations or methylation of the von Hippel-Lindau tumor suppressor gene, a common occurrence in most clear-cell RCCs [14]. These findings have led to the widespread misconception that RCC is radioresistant.

However, a paradigm shift has occurred in the field of RT, spurred by technological advancements that allow for precise tumor targeting and the delivery of a higher biological RT dose to the tumor, while sparing normal tissues. This represents a significant improvement over past methods [15]. Ning et al. [16] studied 2 human RCC cell lines (Caki-1 and A498) and reported that the α/β ratio of RCC cells ranged from 2.6 to 6.9 Gy, which is lower than the dose delivered to most radiosensitive tumor types (α/β ratio of approximately 10 Gy). From a radiobiological perspective, this suggests that a higher dose per fraction of RT could be more effective in killing RCC cells. It has also been reported that endothelial cell apoptosis, which may contribute to cancer cell death, can be inhibited by activated HIF-1α when irradiated at a dose range of 1.8–3 Gy per fraction in vitro [17]. When a dose of ≥8 Gy per fraction was used, endothelial cell apoptosis led to cancer cell death.

**DOSE-RESPONSE RELATIONSHIP IN RT FOR mRCC**

Promising results have been reported for primary RCC using a higher fractional dose, radiosurgery, or ultrahigh-dose stereotactic “ablative” RT (SABR or stereotactic body radiation therapy) [18-20]. SABR is an ultra-hypofractionated form of RT, which is a highly focused form of RT that delivers an intense dose per fraction (>5 Gy) concentrated on a tumor while limiting the dose to the surrounding organs. This therapy is typically administered in 1 to 5 fractions. Staepler et al. [18] reported an impressive local control rate of 98% at 9 months and a complete remission rate of 42.2% in 45 primary renal tumors, including RCC and transitional cell carcinoma of the renal pelvis, using CyberKnife robotic radiosurgery. The International Radiosurgery Oncology Consortium for Kidney reported an excellent 4-year local control rate of 97.8% in 223 patients receiving single-fraction SABR with a median dose of 25 Gy or multifraction SABR of 40 Gy in 4 fractions for primary RCC [19]. Although the estimated glomerular filtration rate declined by 5.5±13.3 mL/min/1.73 m² from baseline after SABR, this treatment strategy could be a valuable option for patients who are inoperable or may require hemodialysis after surgery. According to a previous meta-analysis, the most commonly used SABR schedule for primary RCC is 26 Gy in one fraction and 40 Gy in 5 fractions [20]. These treatments resulted in a random-effect estimated local control rate of 97.2%, and local failure tended to occur in low-dose arms.
including symptom relief and tumor control. In the study conducted by DiBiase et al. [13], a BED (using an $\alpha/\beta$ ratio of 10 Gy) of more than 50 Gy led to significantly improved symptom relief. This contrasts with earlier studies that used conventional fractionation with moderate doses in the treatment of RCC. Wersäll et al. [21] reported a high local control rate following RT with a high dose-per-fraction (8–15 Gy per fraction) regimen in patients with either primary or mRCC lesions. After administering dose-fractionation schedules of 8 Gy × 4 fractions, 10 Gy × 4 fractions, and 15 Gy × 3 fractions, recurrence was noted in only 3 out of 162 treated patients, the majority of whom had metastatic lesions. A retrospective study from the Memorial Sloan-Kettering Cancer Center assessed the effectiveness of a single fraction of 18–24 Gy and hypofractionation with 20–30 Gy in 3 to 5 fractions in 105 patients with mRCC lesions [22]. Compared to a single fraction of 24 Gy, corresponding to the highest BED, a single fraction of less than 24 Gy or hypofractionation resulted in a significantly lower 3-year local progression-free survival (PFS) rate (88% vs. 17%–21%, respectively). However, this finding should be interpreted with caution, as this study is among those that reported the lowest local control following fractionated SABR.

Despite the notably higher tumor control rates associated with high total doses of RT and increased doses per fraction using SABR, it is important to exercise caution when using RT for metastatic lesions from RCC due to potential treatment-related toxicity. Thibault et al. [23] conducted a multi-institutional analysis of osteolytic vertebral metastases from RCC, finding a 43% incidence of vertebral compression fractures in patients treated with a single 24 Gy fraction of SABR. In contrast, the rates were 24% and 14% in patients treated with 20–23 Gy and less than 20 Gy, respectively. However, the crude 1- to 2-year local control of metastatic lesions from RCC treated with a higher total dose and higher dose per fraction, particularly with SABR, is reported to be approximately 85%–100% in the literature. While a balance between tumor control and toxicity must be considered, there is a clear RT dose-response relationship in RCC. The impressive local control rates associated with high-dose RT suggest that RCC is no longer resistant to high-dose regimens. From our perspective, a BED of at least 100 Gy or higher (using an $\alpha/\beta$ ratio of 3 Gy) is necessary to locally control lesions with an RCC histology. Moreover, we recommend a higher BED through the use of SABR when feasible, as most reported and ongoing studies have utilized SABR and a BED of over 100 Gy in the treatment of mRCC. This will be further discussed later in this review.

**EMERGING ROLE OF RT IN OLIGOMETASTATIC CANCER**

The survival rate of patients with metastatic cancer has gradually improved over the past several decades. This is primarily due to advancements in cancer treatment strategies, which are based on a more profound understanding of cancer biology and the prognosis of oligometastatic cancer [24]. In this context, RT serves to eliminate primary or metastatic cancer sites or to alleviate progressively worsening symptoms [25]. The term “oligometastasis” was first introduced by Hellman and Weichselbaum in 1995 to describe tumors with a limited number of distant metastases [26]. There is ongoing debate regarding the establishment of a threshold for metastatic sites, whether it be 3, 4, or more. However, it is clear that patients with a limited number of metastases have significantly longer survival rates than those with extensive metastases [27]. The “seed and soil” concept, which emphasizes the importance of eradicating the metastatic tumor niche, is widely accepted today. This concept has demonstrated clinical relevance over the past 5 years across various types of cancers (Table 1) [28-38].

The most revolutionary study published in recent years is the SABR-COMET phase II trial conducted by Palma et al. [28,29]. This trial involved 99 patients with various types of cancer, all of whom had ≤5 metastatic lesions and a life expectancy of >6 months. These patients were randomly assigned to receive either the standard of care (SOC) or SOC in conjunction with SABR for all metastatic sites. After a median follow-up period of 51 months, it was found that SABR not only improved PFS, but also significantly increased overall survival (OS). The 5-year survival rate was 42.3% for the SABR group, compared to 17.3% for the SOC group, with a median survival benefit of 22 months [29]. The success of this phase II trial led to the initiation of 2 phase III trials, SABR-COMET-3 [30] and SABR-COMET-10 [31]. These trials are exploring the benefits of adding SABR to
SOC in the standard treatment of patients with ≤3 and 4–10 metastases, respectively.

Individual trials for specific types of cancer have demonstrated the benefits of incorporating metastasis-directed SABR without causing excessive toxicity in patients with oligometastasis. The ORIOLE/EXTEND [32,33] and STOMP [34] phase II trials have indicated that adding metastasis-directed SABR to the standard treatment for patients with hormone-sensitive oligometastatic prostate cancer enhances both the PFS and androgen deprivation therapy-free survival. Moreover, the Italian ARTO phase II study reported a significant improvement in PFS when metastasis-directed SABR of BED (α/β ratio of 3 Gy) exceeding 100 Gy was included with abiraterone acetate in the treatment of patients with castrate-resistant prostate cancer with ≤3 bone or lymph node metastases [35]. The beneficial impact of metastasis-directed SABR (or surgery) on PFS and OS has also been confirmed in patients with oligometastatic non-small cell lung cancer through several prospective clinical trials [36-38]. When combined with first-line TKI, metastasis-directed RT significantly extended the OS from 17.4 to 25.5 months, as reported in the SINDAS trial conducted on patients with oligometastatic non-small cell lung cancer [38]. In general, SABR for oligometastatic cancer achieves a 1-year local control rate of approximately 95% and a 1-year OS rate of 85%, with acute and late grade 3 or higher toxicity rates of approximately 1%–2% [39].

The role of RT is increasingly recognized as significant in the treatment of patients with metastatic cancer, with the aim of mitigating the severe consequences associated with metastasis. A recent study by Gillespie et al. [40] showed that prophylactic RT for high-risk asymptomatic bone metastases can significantly reduce the risk of subsequent skeletal-related events. These events include pathologic fractures, spinal cord compression, orthopedic surgery to the bone, and/or palliative RT for pain [40]. High-risk asymptomatic bone metastasis was defined in the study as: a bulky site of disease (≥2 cm); disease involving the hip, shoulder, or sacroiliac joints; disease in the long bones occupying one-third to two-thirds of the cortical thickness; disease in the vertebrae of the junctional spine (C7–T1, T12–L1, and L5–S1); and/or disease with posterior element involvement.

### RT FOR OLIGOMETASTATIC RCC

One of the earliest reports of successful oligometastasis eradication in RCC was documented in 1939 by Barney and Churchill [41]. They performed a nephrectomy and subtotal lobectomy on a patient with kidney adenocarcinoma and a single lung metastasis. The patient lived for over 5 years without any signs of the disease. Since that time, cytoreductive nephrectomy of the primary disease has significantly improved OS, providing an absolute benefit of several months for patients with mRCC [42-44]. Surgical metastasectomy also appears to extend OS (with a median survival of 36–142 months) compared to cases where surgical metastasectomy was not performed (with a median survival of 8–27 months) in patients with oligometastatic RCC. A subset of patients with mRCC can be safely monitored for a certain period before starting systemic treatment, particularly those with fewer International Metastatic Database Consortium adverse risk factors or metastatic disease sites [45,46].

### Table 1. Summary of randomized trials demonstrating the benefit of radiotherapy in oligometastatic cancers

<table>
<thead>
<tr>
<th>Histology</th>
<th>Study</th>
<th>Year of publication</th>
<th>Treatment</th>
<th>Endpoint</th>
<th>Beneficial outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>SABR-COMET [28,29]</td>
<td>2019</td>
<td>RT</td>
<td>OS and PFS</td>
<td>OS: 28 → 50 months (p=0.006)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>PFS: 5.4 months → not reached (p=0.001)</td>
</tr>
<tr>
<td>Prostate</td>
<td>ORIOLE [32]</td>
<td>2020</td>
<td>RT</td>
<td>PFS</td>
<td>5.8 → Not reached (p=0.002)</td>
</tr>
<tr>
<td></td>
<td>EXTEND [33]</td>
<td>2023</td>
<td>RT</td>
<td>PFS</td>
<td>15.8 → Not reached (p=0.001)</td>
</tr>
<tr>
<td></td>
<td>STOMP [34]</td>
<td>2018</td>
<td>RT or surgery</td>
<td>ADT-free survival</td>
<td>13 → 21 Months (p=0.11)</td>
</tr>
<tr>
<td></td>
<td>ARTO [35]</td>
<td>2023</td>
<td>RT</td>
<td>6-month biochemical response PFS</td>
<td>6-Month biochemical response: 68.3% → 92% (p=0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Biochemical PFS: 36 months → not reached (p=0.002)</td>
</tr>
<tr>
<td>NSCLC</td>
<td>Gomez et al. [36]</td>
<td>2016</td>
<td>RT or surgery</td>
<td>PFS</td>
<td>3.9 → 11.9 Months (p=0.005)</td>
</tr>
<tr>
<td></td>
<td>Iyengar et al. [37]</td>
<td>2018</td>
<td>RT</td>
<td>PFS</td>
<td>3.5 → 9.7 Months (p=0.01)</td>
</tr>
<tr>
<td></td>
<td>SINDAS</td>
<td>2023</td>
<td>RT</td>
<td>PFS and OS</td>
<td>PFS: 12.5 → 20.2 months (p&lt;0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OS: 17.4 → 25.5 months (p&lt;0.001)</td>
</tr>
</tbody>
</table>

RT, radiotherapy; OS, overall survival; PFS, progression-free survival; ADT, androgen deprivation therapy; NSCLC, non-small cell lung cancer.
These findings imply that RT could have a significant role in mRCC, potentially aiding in the cytoreduction of metastatic tumor sites or postponing the start of systemic treatment.

1. Retrospective Studies on SABR in Oligometastatic/Oligoprogressive RCC

To date, several published retrospective studies have reported excellent local control and safety of SABR for metastatic sites in patients with oligometastatic RCC [47]. Here, we discuss some of the most notable studies found in the literature [47-52]. Each of these studies was a retrospective review and included fewer than 100 patients.

Stenman et al. [48] reported the outcomes of SABR and/or surgical metastasectomy for oligometastatic RCC in the era of targeted agents. They found a median survival time of 51 months, which was significantly longer than anticipated. Of the 60 patients treated with curative intent, 15% remained relapse-free, with a median follow-up period of 87 months. Zhang et al. [49] examined the role of SABR in postponing the systemic treatment of patients with oligometastatic RCC. They found a local control rate of 91.5% at 2 years, with no reported grade 3 or higher toxicities following SABR. The median duration of freedom from systemic therapy was 15 months post-SABR. Schoenhals et al. [50] reported a median PFS of 9 months and a 1-year local control rate of 93% following SABR with a median dose of 36 Gy in 3 fractions. Notably, patients who received immunotherapy showed a significantly longer PFS than those who did not (>28 months vs. 9 months, p=0.0001). Researchers from the MD Anderson Cancer Center reported a 1-year PFS rate of 52% following SABR with a BED (α/β ratio of 2.63 Gy) of >100 Gy for patients with oligometastatic RCC [51]. In this study, the PFS was similar among patients who escalated, maintained, or discontinued systemic treatment at oligoprogression. This result underscores the potential value of SABR in delaying the escalation of systemic treatments, leading to decreased toxicity and improved quality of life. A previous meta-analysis of 28 studies assessing the outcomes of SABR for oligometastatic RCC, which included over 1,000 extracranial metastatic lesions, reported 1-year survival and local control rates of 86.8% and 89.1%, respectively [47]. Only 0.7% of the patients developed grade 3–4 toxicity.

2. Prospective Studies on SABR in Oligometastatic or Oligoprogressive RCC

Unfortunately, no prospective phase III randomized trials have assessed the role of metastasis-directed SABR in oligometastatic RCC. However, a number of single-arm prospective studies have demonstrated encouraging results with SABR, either in terms of postponing the start of systemic treatments or in its combination with systemic therapies such as TKI or immune checkpoint blockade (ICB) (Table 2) [53-57].

In the multicenter prospective Volga trial conducted by Dengina et al. [54], 17 patients with mRCC who had maintained stable disease for at least 4 months following TKI or ICB therapy were enrolled. In this study, SABR was administered to selected target lesions, while nontarget lesions in the same organ were identified and deliberately excluded from the RT field. As a result, only a subset of the metastatic lesions received irradiation, and a third of the patients had only a single metastatic site. A higher response rate was observed when the fraction size exceeded 10 Gy per fraction and the equivalent dose was 100 Gy or higher (2-Gy per fraction; α/β ratio of 2.6 Gy). Despite reporting a promising response rate of 76% for the irradiated lesions, this study did not provide data on PFS and OS. This omission hinders further interpretation and the clinical application of partial irradiation of metastatic lesions in mRCC.

SABR could potentially delay the initiation of systemic treatment in patients with oligometastatic mRCC, which could positively affect their quality of life. A prospective phase II feasibility study was conducted by our colleagues at MD Anderson Cancer Center to explore the use of SABR as an alternative to systemic therapy in patients with oligometastatic mRCC, defined as having 1–5 metastases [55]. All metastatic sites underwent metastasis-directed SABR; the most commonly used RT dose-fractionation regimen was 50 Gy in 4 fractions. All patients had either stopped or had never started systemic treatment before SABR. In the first round of RT, a total of 43 lesions in 30 patients were irradiated. The median PFS and local control rates were 22.7 months and 97%, respectively. While the OS outcomes of this “upfront” approach combined with SABR are still unknown, given the significant toxicity burden associated with systemic
treatments, this strategy, as explored by Tang et al. [55], merits further investigation.

In addition to the “upfront” strategy, where all metastatic lesions are irradiated before systemic treatment begins, the “oligoprogression” strategy can also be considered for patients already receiving systemic treatment. A prospective phase II trial in Canada assessed the role of SABR during TKI treatment in patients with oligoprogressive mRCC, defined as having 1–5 progressive sites [56]. SABR was administered to all oligoprogressive sites, with a predetermined RT dose fractionation for each anatomical site. The PFS following SRT was 9.3 months, and the 1-year local control rate was 93%, suggesting that most treatment failures occurred after the first year of treatment. The “oligoprogression” strategy showed a somewhat shorter PFS compared to the “upfront” strategy, as reported by Tang et al. [55]. This difference is likely due to the emergence of a subclinical disease that may have developed resistance to the patient’s ongoing TKI treatment. However, this strategy did prevent changes to the systemic treatment regimen for over a year in nearly half of the patients.

Recently, ICBs have been used to treat patients with mRCC, either with or without TKIs [4-7]. In summary, SABR has the potential to enhance the effectiveness of ICBs by functioning as an in situ vaccine and initiating proinflammatory processes within the tumor microenvironment. Following the initiation of immunogenic cell death via RT, tumor-associated antigens are released from the cancer cells, leading to the recruitment of cytotoxic T cells [58-60]. Clinical trials that have combined ICBs with RT have demonstrated promising results, particularly in the case of non-small cell lung cancer [61,62].

As previously mentioned, Schoenhals et al. [50] reported that the combination of SABR, delivered at a median dose of 36 Gy in 3 fractions, with ICBs resulted in superior PFS compared to the combination of SABR and other systemic treatments. In the RAPPORT trial, as reported by Siva et al. [57], a single-fraction SABR of 20 Gy was administered to all metastatic sites, followed by 8 cycles of pembrolizumab in 30 patients with oligometastatic (1–5 metastases) mRCC. A total of 83 oligometastases were irradiated, resulting in 2-year local control and PFS rates of 92% and 45%, respectively. Future research should focus on addressing several key issues: the optimal RT dose-fractionation regimen when combined with ICBs, the sequence of combination, the duration of maintenance, and the dosage of ICBs.

When considering the combination of SABR and ICBs, in

<table>
<thead>
<tr>
<th>Study</th>
<th>Year of publication</th>
<th>Trial phase</th>
<th>No. of lesions</th>
<th>RT dose</th>
<th>Systemic treatment</th>
<th>Outcome</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Svedman et al. [53]</td>
<td>2006</td>
<td>II</td>
<td>82</td>
<td>8 Gy × 4 fractions</td>
<td>Any</td>
<td>Local control: 98%</td>
<td>Approximately 19% of patients were followed up for less than 6 months.</td>
</tr>
<tr>
<td>VOLGA [54]</td>
<td>2019</td>
<td>Ib</td>
<td>17</td>
<td>Mean equivalent dose in 2-Gy fraction (EQD2), 114 Gy (range, 40–276 Gy)</td>
<td>TKI or immune checkpoint inhibitors</td>
<td>Complete or partial remission: 76%</td>
<td>Not all lesions were irradiated; fraction size of 10 Gy or higher (EQD2 dose of 100 Gy or higher) most often led to complete response (p&lt;0.01).</td>
</tr>
<tr>
<td>Tang et al. [55]</td>
<td>2021</td>
<td>II</td>
<td>43</td>
<td>1–5 fractions with 7 Gy or higher per fraction (the most common regimen, 50 Gy in 4 fractions)</td>
<td>None</td>
<td>PFS: 22.7 months</td>
<td>All patients had nephrectomy prior to treatment.</td>
</tr>
<tr>
<td>Cheung et al. [56]</td>
<td>2021</td>
<td>II</td>
<td>57</td>
<td>Lung: 48–60 Gy in 3–8 fractions</td>
<td>Last &gt;3 months of TKI</td>
<td>1-yr local control: 93%</td>
<td>Oligoprogresive patients during TKI treatment</td>
</tr>
<tr>
<td>RAPPORT [57]</td>
<td>2022</td>
<td>I/II</td>
<td>83</td>
<td>20 Gy × 1 fraction</td>
<td>Pembrolizumab following RT</td>
<td>2-yr local control: 92%</td>
<td>Four patients (13%) with grade 3 toxicity</td>
</tr>
</tbody>
</table>

SABR, stereotactic ablative radiotherapy; RT, radiotherapy; TKI, tyrosine kinase inhibitor, PFS, progression-free survival.

https://doi.org/10.22465/juo.234600560028
vitro studies have suggested that a fractional dose of 8–12 Gy may be the most effective for antitumor immunity [63,64]. A pivotal report by Vanpouille-Box et al. [63] showed that RT fractions exceeding 12–18 Gy can elevate the expression of the endonuclease Trex1, which in turn can lead to diminished immunogenicity. However, in practical applications, a higher fractional dose and total BED might enhance clinical outcomes in patients with oligometastasis, irrespective of antitumor immunity. While the optimal dose-fractionation regimen for oligometastasis-directed SABR in RCC still needs to be established, a recent phase III randomized trial reported that a single fraction of 24 Gy (BED 432 Gy with $\alpha/\beta$ ratio of 3 Gy) led to a significantly improved local control rate compared to 27 Gy in 3 fractions (BED 108 Gy with $\alpha/\beta$ ratio of 3 Gy) [65]. Importantly, distant metastasis was also significantly reduced with a higher BED at 3 years (5.3% vs. 22.5%, p=0.010). Eight patients (6.8%) participating in this study had renal cancers [65]. Therefore, further research is necessary.

3. Palliative RT for Bone Metastasis From RCC

Historically, RT has been extensively utilized for several decades to alleviate symptoms associated with metastatic lesions from RCC, and its effectiveness is well-documented [66-69]. However, the correlation between the dose-response relationship and the effectiveness of treatment in symptom relief remains a topic of debate. Lee et al. [69] carried out a prospective phase II trial to evaluate the effectiveness of palliative RT, using a regimen of 30 Gy in 10 fractions, which is the most commonly employed RT regimen for symptom relief. While pain relief was noted in 83% of patients following RT, the median duration of site-specific pain response was a mere 3 months, which is suboptimal.

Moreover, although not confined to the RCC histology (renal cancer, 7%), Sprave et al. [70] reported that a single-fraction SABR dose of 24 Gy resulted in a superior 6-month pain response compared to a 30 Gy SABR dose delivered in 10 fractions for patients with painful spinal metastases. In the NRG Oncology/RTOG 0631 phase III trial, which compared a single-fraction 16–18 Gy dose with a single-fraction 8 Gy dose for vertebral metastases, no significant difference was observed in patient-reported pain response at 3 months post-RT [71]. However, only 15% of patients had a “radioresistant” histology such as RCC, melanoma, and soft tissue sarcoma. Sahgal et al. [72] conducted a comparison of the efficacy of a 24 Gy dose in 2 fractions versus a 20 Gy dose in 5 fractions for painful spinal metastases (RCC accounted for 8.7% of cases) in a phase II/III randomized trial. The complete response rate for pain was significantly higher in patients treated with 24 Gy in 2 fractions, and this difference was maintained at 6 months post-RT. The patients included in this study had relatively stable vertebrae, as indicated by a Spinal Instability in Neoplasia Score of ≤12. A recent retrospective study, in which 30% of patients had radioresistant histology (including gastrointestinal, RCC, thyroid, sarcoma, and melanoma), suggested that a slight difference between 24 Gy in 2 fractions and 28 Gy in 2 fractions might lead to better local control without increasing the risk of vertebral compression fracture [73]. For patients with painful metastases, this marginal dose difference could be associated with a durable response. Following treatment with intermediate hypofractionated RT delivered in 24 fractions (2.5 Gy per fraction; total dose: 60 Gy; BED: 110 Gy with an $\alpha/\beta$ ratio of 3 Gy), all infiltrative and expansile bone lesions disappeared. A durable response was observed for more than 2 years, and reossification occurred in the treated bones [74].

Given the “radioresistance” of RCC to low-dose conventional fractionation, a hypofractionated regimen with a higher BED could potentially yield more favorable outcomes. These outcomes could include symptom relief and the achievement of a durable response [8,13-17,74]. However, the optimal dose fractionation for patients with mRCC still needs to be determined in future studies. When choosing an RT dose regimen, factors such as the symptomatic response rate, the probability of a durable response, and the risk of RT-related toxicity should be taken into account.

ONGOING RANDOMIZED TRIALS ON RT FOR mRCC

1. Cytoreduction of Primary Disease in Patients With mRCC

The CYTOSHRINK (NCT04090710) trial is a phase II randomized study that evaluated the effectiveness of
Ipiilimumab plus nivolumab, in comparison to the combination of ipilimumab, nivolumab, and SABR (30–40 Gy in 5 fractions) for primary renal mass in patients with mRCC. The goal of this trial was to improve survival outcomes by employing cytoreductive nephrectomy, which offers a more convenient approach for cytoreduction in patients who are either unwilling or unsuitable for nephrectomy [42-44]. Similarly, the NRG-GU012 trial (also known as the SAMURAI study, NCT05327686) assessed the efficacy of ICB, with or without cytoreductive SABR, for primary renal tumors in patients with inoperable mRCC.

2. Metastasis-Directed SABR in mRCC

In the GETUG-StORM-01 (NCT04299646) trial, patients with oligoprogressive clear-cell RCC (1–3 lesions) will be randomized to either receive systemic treatment with SABR at all progressive sites, or without it. This trial is anticipated to offer further insights into the role of RT in managing oligoprogressive mRCCs. The EORTC 1945 OligoRARE trial is also open to patients with oligometastatic RCC (1–5 metastases), but it excludes those with lung, breast, colon, and prostate cancers. In this trial, patients with oligometastatic cancer will be assigned to 1 of 2 groups: one will receive standard palliative treatment with SABR at all metastatic sites, and the other will receive the same treatment but without SABR.

SUMMARY AND FUTURE PERSPECTIVES

In summary, due to advancements in technology that allow for the precise delivery of high-dose RT targeted at the tumor, metastasis-directed RT in mRCC has emerged as a strategy to either mitigate or delay systemic treatment, or to enhance survival when used in conjunction with TKIs and ICBs. While this review primarily discussed SABR as the form of RT for patients with mRCC, it is important to note that not only SABR, but also various RT dose-fractionation regimens delivering higher (ablative) doses, can be utilized for this purpose. In this context, the treating radiation oncologist must strike a careful balance between the tumor control probability and the normal tissue complication probability. Future studies should aim to establish the optimal RT dose fractionation and the best sequence for combining it with systemic treatments. Factors such as the probability of local and overall disease control, antitumor immunity, and the risk of toxicity should all be considered in a comprehensive manner. Thus, a new chapter in the understanding of RCC, which has been mischaracterized as a "radioresistant" histology for decades, has begun.

NOTES

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- **Author Contribution:** Conceptualization: JC; Data curation: CWW, JC; Methodology: CWW, JC; Project administration: CWW, JC; Writing - original draft: CWW; Writing - review & editing: JC.
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REFERENCES


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INTRODUCTION

Bacillus Calmette-Guérin (BCG) therapy for bladder cancer is the most efficacious immunotherapeutic intervention employed against human neoplasms [1]. The United States Food and Drug Administration (U.S. FDA) granted approval for this immunotherapy in 1990, marking a historic milestone as the first cancer immunotherapeutic agent to attain such authorization.

In the management of intermediate- and high-risk non–muscle-invasive bladder cancer (NMIBC), standard treatment entails intravesical BCG instillation, which effectively reduces the risk of recurrence [2,3]. Furthermore, BCG maintenance therapy significantly decreases the risk of progression [4]. Despite being the cornerstone of NMIBC treatment, a substantial proportion of patients (approximately one-third) do not respond to BCG therapy. Furthermore, more than 50% of those who initially respond subsequently experience recurrence or progression during follow-up [5]. Moreover, local or systemic adverse events occur in approximately 70% of patients, leading to roughly 5% to 9% of patients discontinuing treatment prematurely and not completing the planned BCG course [6,7]. Patients encountering recurrence or progression to muscle-invasive bladder cancer (MIBC) following BCG therapy are considered to have experienced BCG failure. The objectives of this study were to define BCG failure and explore potential treatment approaches for patients who do not respond to BCG therapy.
DEFINING BCG-UNRESPONSIVE PATIENTS: CRITERIA AND CONSIDERATIONS

The concept of BCG failure involves various considerations [8-10]. First, patients with low-grade recurrence during or after BCG treatment are not categorized as cases of BCG failure. Second, the detection of MIBC at any point during the follow-up period is deemed a treatment failure. Third, BCG intolerance refers to severe side effects that hinder further BCG instillation. Finally, the occurrence of high-grade disease following adequate therapy is primarily defined according to Table 1 of the European Association of Urology Guidelines [11].

A particularly important point is that the BCG-unresponsive category includes both BCG-refractory and certain BCG-relapsing tumors. This definition was formulated in collaboration with the U.S. FDA, with a specific focus on facilitating single-arm trials to establish primary evidence of effectiveness in this context. In this definition, adequate BCG treatment is defined as the administration of a minimum of 5 out of 6 doses during the initial induction course, coupled with at least 2 out of 6 doses during the second induction course, or 2 out of 3 doses of maintenance therapy.

RADICAL CYSTECTOMY AS THE CURRENT STANDARD FOR PATIENTS WITH BCG-UNRESPONSIVE NMIBC

Expert committees, along with various clinical guidelines, recommend radical cystectomy as the standard therapeutic approach for BCG-unresponsive NMIBC [11-14]. Delayed cystectomy in patients with NMIBC recurrence following BCG may be associated with unfavorable cancer-specific survival outcomes [15]. Furthermore, in a retrospective study that involved patients who experienced T1 recurrence after BCG therapy, those who underwent radical cystectomy exhibited a lower cancer-related mortality rate (31% vs. 48%) than patients who underwent repeated transurethral resection of the bladder tumor and intravesical BCG therapy [16]. Nonetheless, radical cystectomy is linked to a spectrum of postoperative complications (30%–70%) and mortality risk (approximately 3%) [17-20].

Taking these factors into account, it is imperative to offer thorough counseling to patients, particularly those undergoing radical cystectomy. This approach aims to optimize oncologic outcomes while weighing the relatively elevated risk of morbidity, mortality, and impact on quality of life associated with the procedure. Consequently, bladder preservation strategies employing diverse mechanisms have been extensively explored for patients who decline surgery or are ineligible (Table 2); some of these strategies have shown promising results.

INTRAVESICAL CHEMOTHERAPY

1. Valrubicin

In 1998, valrubicin, a lipid-soluble semisynthetic analog of doxorubicin, was approved by the U.S. FDA for the treatment

Table 1. Classifying high-grade recurrence during or after BCG treatment

<table>
<thead>
<tr>
<th>BCG-refractory tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. If T1 HG/G3 tumor is present at 3 months</td>
</tr>
<tr>
<td>2. If Ta HG/G3 tumor is present after 3 months and/or at 6 months, after either reinduction or first course of maintenance</td>
</tr>
<tr>
<td>3. If CIS (without concomitant papillary tumor) is present at 3 months and persists at 6 months after either reinduction or first course of maintenance. If patients with CIS present at 3 months, an additional BCG course can achieve a complete response in &gt;50% of cases</td>
</tr>
<tr>
<td>4. If HG tumor appears during BCG maintenance therapy</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BCG-relapsing tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence of HG/G3 tumor after completion of BCG maintenance, despite an initial response</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BCG-unresponsive tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCG-unresponsive tumors include all BCG refractory tumors and those who develop T1/Ta HG recurrence within 6 months of completion of adequate BCG exposure or develop CIS within 12 months of completion of adequate BCG exposure</td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette-Guérin; CIS, carcinoma in situ; HG, high grade.
of BCG-refractory carcinoma in situ (CIS) in patients ineligible for cystectomy due to morbidity and mortality concerns; this approval was supported by data from a pivotal phase 3 study. In this open-label, noncomparative pivotal phase 3 study, 90 patients with recurrent CIS following multiple unsuccessful intravesical therapies, including at least one course of BCG, were treated with 800 mg of intravesical valrubicin for 6 consecutive weeks, resulting in a complete response (CR) rate of 21%, with 7 patients maintaining disease-free status during the median follow-up period of 30 months [21]. A comprehensive evaluation of valrubicin’s efficacy, utilizing updated efficacy data from a pivotal phase 3 trial along with data from a supportive phase 2/3 study, reported that in both studies, the CR rate remained only 18% at the 6-month follow-up, leading to limited further research in this area [22].

2. Gemcitabine

Gemcitabine, an anticancer antimetabolite, blocks DNA synthesis and induces apoptosis in tumor cells through the formation of active metabolites.

Dalbagni et al. [23] investigated the efficacy of intravesical gemcitabine in patients with NMIBC that was refractory or intolerant to intravesical BCG therapy who were unwilling to undergo cystectomy. Two courses of intravesical gemcitabine were administered twice weekly at a dose of 2,000 mg/100 mL for 3 consecutive weeks, with a week of rest between each course. Among the 30 eligible patients, 15 of 30 (50%) achieved CR at the 8-week follow-up, and the 1-year recurrence-free survival rate for patients with CR was 21%.

In a comparative study of mitomycin C (MMC) in patients with a history of previously treated recurrent NMIBC, intravesical gemcitabine demonstrated a higher recurrence-free rate, with an absence of recurrence noted in 39 of 54
patients (72%) compared to 33 of 55 (61%) in the MMC group [24]. Additionally, the incidence of chemical cystitis was significantly lower in the gemcitabine group than in the MMC group (p=0.012), indicating that gemcitabine was less toxic than MMC.

Another study also compared the efficacy of gemcitabine and secondary BCG in the context of initial BCG failure [25]. In this prospective, randomized phase 2 trial, eligible patients with high-risk NMIBC and one failed BCG course were randomly assigned to receive either intravesical gemcitabine or intravesical BCG treatment. Eighty participants, with 40 in each group, were enrolled, and the results revealed a lower disease recurrence rate in the intravesical gemcitabine group (52.5%) than in the intravesical BCG group (87.5%) (p=0.002) and a significantly higher 2-year recurrence-free survival rate in the intravesical gemcitabine group (19%) than in the intravesical BCG group (3%) (p<0.008).

Skinner et al. [26] evaluated the durability of intravesical gemcitabine therapy. Eligible patients with recurrent NMIBC after at least 2 prior courses of BCG were treated with 2 g of gemcitabine in 100 mL normal saline intravesically on a weekly basis for 6 weeks. Subsequently, this regimen continued on a monthly basis for up to 12 months. Out of the 58 enrolled patients, 47 were could be evaluated for their response, and at the initial 3-month evaluation, 47% were disease-free. However, the study found that fewer than 30% of patients had a durable response at 12 months, even with maintenance therapy, with 28% and 21% remaining disease-free at 1 and 2 years, respectively.

A Cochrane review published in 2021 on intravesical gemcitabine identified 6 relevant randomized trials with a total of 704 patients [27]. The review indicated that a single dose of gemcitabine immediately following surgery was ineffective based on one study. Additionally, gemcitabine exhibited potentially greater activity and lower toxicity than MMC; in comparison to intravesical BCG therapy, it demonstrated comparable effects in patients with intermediate risk, lower efficacy in patients with high risk, and superior outcomes in patients with BCG-refractory disease.

1) Gemcitabine + MMC

Combination therapy has been further investigated to enhance its effectiveness in targeting diverse tumor cells and reducing therapy resistance. In a retrospective review of 47 patients with NMIBC who received 6 weekly treatments of sequential intravesical gemcitabine (1 g) for 90 minutes followed by MMC (40 mg) for an additional 90 minutes, the CR rates at 6 weeks after induction and the 1-year and 2-year recurrence-free survival rates were 68%, 48%, and 38%, respectively, with a median recurrence-free survival of 9 months (range, 1–80 months) [28]. Fourteen out of 47 patients (30%) remained free of recurrence with a median follow-up time of 26 months (range, 6–80 months). Another study identified patients who received sequential weekly instillations of gemcitabine and MMC for 6–8 weeks; 10 out of the enrolled patients (37%) showed no evidence of disease, with a median follow-up duration of 22.1 months [29]. However, the observed outcomes appear to be less effective than those achieved with subsequently explored alternative medications, and no further investigations are currently underway in this regard.

3. Docetaxel

Docetaxel, a microtubule depolymerization inhibitor, exhibits antitumor activity against a broad range of cancers. In 2006, findings from a phase 1 trial evaluating intravesical docetaxel for BCG-refractory NMIBC were reported [30]. The study demonstrated a promising 56% response rate with minimal toxicity in 18 patients who received a single 6-week course of intravesical instillation, following the phase 1 dose escalation protocol.

In a larger cohort of 33 patients with refractory NMIBC receiving salvage intravesical docetaxel therapy, 36% experienced grade 1 or 2 local toxicity, and no cases of grade 3 or 4 local or systemic toxicity were observed [31]. Out of these patients, 61% achieved CR after undergoing 6 weekly induction treatments, as evaluated 4–6 weeks after the instillation.

Moreover, the long-term outcomes of salvage intravesical docetaxel treatment were reported in 54 patients with BCG refractory NMIBC, revealing a 59% rate of initial CR following 6 weekly instillations [32]. Among initial responders, those who received additional monthly maintenance treatments experienced a longer median time to
recurrence (39.3 months vs. 19.0 months), and the 1- and 3-year recurrence-free survival rates for the entire cohort were 40% and 25%, respectively, suggesting that adding maintenance treatments may prolong recurrence-free survival.

Research on the combination of docetaxel and gemcitabine for potential therapeutic applications is ongoing.

1) Gemcitabine and docetaxel

In 2015, Steinberg et al. [33] introduced the concept of sequential gemcitabine and docetaxel treatment. Patients received 6 weekly instillations of gemcitabine (1 g in 50 mL of sterile water) for 60 minutes, followed immediately by docetaxel (37.5 mg in 50 mL of saline) for an additional 60 minutes. The treatment success rates were 66% at the first surveillance, 54% at 1 year, and 34% at 2 years after initiating induction.

Subsequent retrospective studies explored the outcomes of 59 patients who received complete gemcitabine/docetaxel treatment for NMIBC [34]. Overall, disease-free survival rates were 49% at 1 year and 29% at 2 years. For patients in whom multiple induction courses of BCG had failed, the overall disease-free survival rates were 48% at 1 year and 32% at 2 years. Moreover, among patients eligible for maintenance therapy who received ≥1 induction courses of BCG, disease-free survival rates at 1 year were 42% for observed patients and 81% for those receiving maintenance therapy, while at 2 years, they were 34% for observed patients and 59% for those receiving maintenance therapy. In another study involving 276 patients, the 1- and 2-year recurrence-free survival rates were 60% and 46%, respectively, and the high-grade recurrence-free survival rates were 65% and 52%, respectively [35].

Further evaluations are necessary because no prospective studies have been conducted to date. Currently, although there appear to be no ongoing studies specifically investigating the combination of gemcitabine and docetaxel alone for patients unresponsive to BCG, there are ongoing prospective clinical trials combining gemcitabine and docetaxel with immunotherapy for BCG-unresponsive cases. Additionally, other studies are exploring the use of gemcitabine and docetaxel in patients who have not previously received BCG treatment.

4. Paclitaxel

Nanoparticle albumin-bound (nab)-paclitaxel is a modified taxane with improved solubility and lower toxicity than other taxanes that exerts anticancer effects through tubulin polymerization, microtubule stabilization, cell cycle arrest, and apoptosis induction.

A single-center, single-arm, phase 2 trial investigated the use of intravesical nab-paclitaxel (500 mg/100 mL) in patients with recurrent NMIBC after failure of at least one prior regimen of intravesical BCG [36]. Among the 28 enrolled patients, 35.7% exhibited CR at 6 weeks after initial treatment. Furthermore, after 1 year, all of these responses continued to be sustained with the aid of maintenance therapy. Treatment-related adverse events were limited to grade 1 or 2, indicating that intravesical nab-paclitaxel demonstrated minimal toxicity and a promising response rate in heavily pretreated patients with NMIBC and prior BCG failure.

In another phase 2 trial of intravesical nab-paclitaxel involving 28 patients with NMIBC after prior intravesical BCG failure, 36% of patients achieved CR at 6 weeks following the final instillation, with a recurrence-free survival rate of 18% at a median follow-up of 41 months (range, 5–76 months) [37].

However, the routine use of this agent still awaits independent validation. A phase 3, single-arm study (NCT 05024773) evaluating the efficacy and safety of ONCOFID-P-B (paclitaxel-hyaluronic acid conjugate) administered intravesically to patients with BCG-unresponsive CIS with or without Ta-T1 papillary disease is currently recruiting patients, and the estimated primary completion date is November 2025.

DEVICE-ASSISTED THERAPY

1. Device-Assisted Instillations of MMC

The superiority of gemcitabine over standard MMC in a head-to-head randomized controlled trial for BCG failure [24] implies that standard MMC may not be a suitable treatment option following BCG failure. As an alternative, methods for enhancing MMC efficacy using devices have
been developed to achieve better outcomes.

1) Chemohyperthermia

Arends et al. [38] compared the efficacy of chemohyperthermia (CHT) using MMC with BCG as adjuvant treatments for intermediate- and high-risk NMIBC in patients without a history of BCG therapy. Among the 184 patients included, only 10 had a history of BCG treatment. The 24-month intention-to-treat recurrence-free survival rate was 78.1% in the CHT group compared to 64.8% in the BCG group (p=0.08). The 24-month recurrence-free survival rates in the per-protocol analysis were 81.8% in the CHT group and 64.8% in the BCG group (p=0.02). Both groups had progression rates of less than 2%, and no new safety concerns were identified. However, the study’s premature closure resulted in an underpowered analysis, warranting caution when interpreting the results.

In a recent study comparing the radiofrequency-induced thermo-chemotherapy effect (RITE) with institutional standard second-line therapy (control) in patients with NMIBC experiencing recurrence following induction/maintenance BCG, no significant difference was observed in disease-free survival time between the treatment arms [39]. Additionally, a subgroup analysis of patients with CIS with or without papillary disease, demonstrated that disease-free survival time was significantly lower in the RITE group than in the control group (hazard ratio, 2.06; 95% confidence interval [CI], 1.17–3.62; p=0.01).

2) Electromotive drug administration

Electromotive MMC demonstrated superior transport rates compared to passive transport. In a clinical trial involving 108 patients with high-risk NMIBC, electromotive MMC demonstrated superior CR rates at 3 and 6 months compared to passive MMC (53% vs. 28%, p=0.036 and 58% vs. 31%, p=0.012, respectively), and a longer median time to recurrence (35 months vs. 19.5 months, p=0.013) [40]. Peak plasma MMC levels were significantly higher with electromotive MMC, indicating increased bladder content absorption.

In a prospective, single-center, single-arm phase 2 study involving 26 consecutive patients with BCG-refractory high-grade NMIBC, with a 3-year follow-up, the electromotive drug administration (EMDA®)-MMC treatment—comprising 40 mg of MMC diluted in 100 mL of sterile water retained in the bladder for 30 minutes with 20 mA pulsed electric current—demonstrated efficacy in preserving the native bladder in 61.5% of patients. Additionally, it showed disease-free rates of 75%, 71.4%, 50%, and 25% for TNM classifications of TaG3, T1G3, Cis, TaT1G3 + Cis, respectively [41]. However, adverse events, including hypersensitivity to MMC in 11.5% of patients and local side effects in 26.1% of patients, were reported during the study. The encouraging outcomes observed in BCG-refractory patients clearly warrant further research to assess the efficacy and safety of EMDA-MMC treatment in comparison to existing therapies.

2. Photodynamic Therapy

In 2023, interim findings were released, detailing the outcomes of a phase 2 clinical study on intravesical photodynamic therapy for patients with BCG-unresponsive CIS with or without papillary disease (NCT03945162) [42]. The study involved intravesical instillation of the photosensitizer TLD-1433 (0.70 mg/cm²), followed by activation using a 520-nm intravesical laser (Study Device TLC-3200) and consequently delivering a total of 90 J/cm² of laser light under general anesthesia. Among the 45 enrolled patients, the data showed CR rates of 50% at 90 days, 35% at 360 days, and 21% at 450 days. Eight serious adverse events were identified in the study. The study is currently ongoing, with recruitment in progress, and the estimated completion date is December 2025.

IMMUNOTHERAPY WITH CHECKPOINT INHIBITORS

Immunotherapy holds promise for patients with NMIBC due to the higher mutational load of tumors, which triggers an immune response and results in improved efficacy for immune checkpoint inhibitors [43]. Furthermore, BCG infection induces programmed death-ligand 1 (PD-L1) expression in regulatory T cells, making combination or sequential checkpoint inhibitor therapy a potential strategy for patients unresponsive to BCG [44].
Numerous ongoing clinical trials are investigating various immunotherapeutic agents and their combinations with other therapeutic options. Presentation of their results is currently in progress.

1. Intravesical Immunotherapy

Immunotherapy is currently being investigated more extensively through systemic (intravenous) administration than through intravesical administration. Two ongoing small single-group assignment studies—NCT02808143 (phase 1) assessing intravesical pembrolizumab with concurrent BCG for high-grade disease or BCG-refractory and NCT03759496 (phase 2) assessing intravesical durvalumab in patients with high-grade disease or BCG nonresponsiveness—are actively recruiting patients to assess the tolerance and efficacy of these treatments.

2. Systemic Immunotherapy

1) Pembrolizumab

A recent publication detailing the KEYNOTE-057 (NCT 02625961) trial described the assessment of pembrolizumab, a PD-1 inhibitor, to determine its efficacy and safety in managing high-risk NMIBC that had proven unresponsive to BCG therapy [45]. Conducted as an open-label, single-arm, multicenter, phase 2 study, pembrolizumab was administered intravenously at 200 mg every 3 weeks for a maximum of 24 months or until specified endpoints were reached. The data revealed a notable CR rate (39 patients; 41%; 95% CI, 30.7%–51.1%) at 3 months among the cohort of 96 patients with BCG-unresponsive CIS with or without papillary tumors. The median duration of CR was 16.2 months (95% CI, 6.4–36.2 months), and 46% (18 patients) of initial responders had a CR lasting for 12 months or longer. Grade 3 or 4 treatment-related adverse events occurred in 13% of the patients, with arthralgia affecting 2% and hyponatremia affecting 3%. Additionally, 8% of the patients experienced serious treatment-related adverse events. Based on these findings, pembrolizumab was approved by the FDA in 2020. Additionally, a recent analysis of KEYNOTE-057 Cohort B, which focused exclusively on patients with papillary tumors without concomitant CIS, observed that 43.5% of patients remained disease-free 1 year after initiating treatment [46].

2) Atezolizumab

The results of a single-arm phase 2 registration trial (SWOG S1605; NCT 02844816) investigating the efficacy and safety of atezolizumab, an anti-PD-L1 agent, in patients with BCG-unresponsive high-risk NMIBC were reported in 2020 [47]. The study aimed to enroll 135 eligible patients who were ineligible for or declined radical cystectomy, and the analyzed subset comprised 73 patients with CIS with or without concomitant Ta/T1 tumors. At 3 and 6 months, CR was observed in 41.1% and 26.0% of the patients with CIS, respectively. Treatment-related adverse events were reported in 83.6% of the patients, with the most common being fatigue, pruritus, hypothyroidism, and nausea. Grade 3–5 adverse events occurred in 12.3% of the patients, and one treatment-related death due to myasthenia gravis with respiratory failure and sepsis was reported.

3) Durvalumab

According to interim data reported in 2023 from multicenter phase 1/2 trial (ADAPT-BLADDER; NCT03317158), the safety and preliminary efficacy of anti-PD-L1 directed therapy with durvalumab (D), either alone or in combination with intravesical BCG (durvalumab + BCG) or external beam radiation therapy (durvalumab + EBRT), were assessed in patients with BCG-unresponsive NMIBC [48]. The patients received 1,120 mg of durvalumab intravenously every 3 weeks for 8 cycles. The combination therapies demonstrated encouraging preliminary efficacy, with a 3-month CR observed in 64% of all patients. The rates varied within the durvalumab alone, durvalumab + BCG, and durvalumab + EBRT subgroups (33%, 85%, and 50%, respectively). At the 12-month mark, CR rates were achieved in 46% of all patients, and notably in 73% of the durvalumab + BCG patients and 33% of the durvalumab + EBRT patients. Importantly, one patient in the durvalumab + EBRT cohort experienced a grade 3 dose-limiting toxicity event of autoimmune hepatitis, which was the only dose-limiting toxicity event reported in the study. This study is currently ongoing and actively recruiting participants, with an estimated completion date of December 31, 2025.
4) Nivolumab

Currently, 2 major clinical trials are in progress in the field of NMIBC immunotherapy. CheckMate 9UT (NCT 03519256) is a phase 2, randomized open-label study investigating the safety and efficacy of nivolumab (anti-PD-1) alone or in combination with linrodostat mesylate or intravesical BCG in patients with BCG-unresponsive high-risk NMIBC. Another trial (NCT04149574) is a phase 3, randomized, double-blind study comparing nivolumab in combination with intravesical BCG to standard-of-care BCG alone in participants with high-risk NMIBC that persisted or recurred after BCG treatment.

ANTIBODY-DRUG CONJUGATES

1. Vicinium (Oportuzumab Monatox, VB4-845)

Vicinium is a recombinant fusion protein comprising an epithelial cell adhesion molecule-specific antibody fragment linked to a variant of *Pseudomonas* exotoxin A. This potent inhibitor of protein synthesis leads to tumor cell death, resulting in the display of immunogenic cell death signals and neo-antigens that promote adaptive T-cell mediated antitumor responses.

In a phase 2 study, the efficacy and tolerability of Vicinium were evaluated in 46 patients with BCG-refractory CIS [49]. Patients received one induction cycle of 6 or 12 weekly intravesical Vicinium instillations of 30 mg, followed by up to 3 maintenance cycles every 3 months. Notably, 20 patients (44%) achieved CR, and the most common adverse events were mild-to-moderate reversible bladder symptoms.

In the phase 3 VISTA study (NCT02449239), 89 patients with CIS or papillary disease were treated with Vicinium. Among the patients with evaluable CIS, a CR rate of 40% was observed at the 3-month mark, with a median duration of response of 9.4 months [50]. The recurrence-free rates for the patients with evaluable papillary were 71%, 58%, 50%, and 37% at 3, 6, 12, and 24 months, respectively.

Although Vicinium showed clinically favorable antitumor activity and was well tolerated in this phase 3 study, its development has been voluntarily discontinued since 2022, following the FDA’s decision of non-approval.

2. N-803 (IL-15 Superagonist)

N-803 is an innovative mutant interleukin (IL)-15-based immunostimulatory fusion protein complex (IL15RaFc) that selectively stimulates the proliferation and activation of natural killer cells and CD8+ T cells while sparing regulatory T cells. According to the results of an open-label, multicenter study (QUILT 3.032; NCT03022825) involving 160 patients with BCG-unresponsive high-grade NMIBC (83 with CIS and 77 with papillary disease) treated with an intravesical mixture of N-803 and BCG, the CR rate in patients with CIS was 71% (59 out of 83), with responders showing a median CR duration lasting 24.1 months [51].

In patients with papillary disease, the 12-month disease-free survival rate was 57%, the 24-month disease-free survival rate was 48%, and 95% of these patients avoided cystectomy. When comparing N-803 alone with BCG plus N-803, the combination therapy demonstrated greater effectiveness [52]. Researchers suggested that the efficacy and safety profile of N-803 plus BCG combination therapy may surpass those of other available intravesical and systemic treatment options for BCG-unresponsive NMIBC.

However, in May 2023, the approval decision for N-803 was postponed by FDA, with the agency requesting additional data and a safety update, prompting keen attention to both the manufacturer’s response and the FDA’s subsequent actions.

INTRAVESICAL GENE THERAPY

1. Adstiladrin (Nadofaragene Firadenovec [rAd-IFNα2b/Syn3])

Adstiladrin (Nadofaragene firadenovec [rAd-IFNα2b/Syn3]) is a replication-deficient recombinant adenovirus vector carrying the human IFN-α2b gene. Upon intravesical administration, rAd-IFN enters the bladder epithelium, prompting the synthesis and expression of significant amounts of the IFN-α2b protein.

A phase 3 clinical trial (NCT02773849) conducted in
patients with BCG-unresponsive NMIBC aimed to evaluate the efficacy of intravesical Adstiladrin [53]. A total of 157 patients were enrolled and treated with a single intravesical dose of the drug, with repeated dosing at 3, 6, and 9 months provided there was no high-grade recurrence. Data reported in 2020 revealed that among 103 patients with CIS (with or without a high-grade Ta or T1 tumor), 53.4% achieved CR within 3 months of the first dose, and this response was sustained in 45.5% of the patients at 12 months. The most common grade 3–4 drug-related adverse event was micturition urgency; no treatment-related deaths occurred.

Adstiladrin, with prolonged exposure to a therapeutic agent compared to conventional instillation, demonstrated clinical efficacy and safety in patients with BCG-unresponsive NMIBC. Based on a positive phase 3 trial (NCT02773849), Adstiladrin was approved by the FDA in December 2022 for the treatment of high-risk BCG-unresponsive NMIBC in adult patients with CIS with or without papillary tumors.

2. CG0070

The first-in-human phase 1 study of CG0070, a granulocyte-macrophage colony-stimulating factor-expressing oncolytic adenovirus, published in 2012, reported that intravesical CG0070 demonstrated a tolerable safety profile and exhibited anti-bladder cancer activity [54].

The interim results of an open-label, single-arm, phase 2 multicenter study (BOND2; NCT02365818) evaluating the safety and efficacy of CG0070 in patients with BCG-unresponsive NMIBC were reported in 2018 [55]. Out of 45 patients with residual high-grade Ta, T1, or CIS ± Ta/T1, the overall 6-month CR rate was 47%. The CR rate for pure CIS was 58%, that of CIS ± Ta/T1 was 50%, and that of pure Ta/T1 was 33%. The treatment was generally well tolerated, with urinary bladder spasms, hematuria, dysuria, and urgency reported as main treatment-related adverse events at 6 months. Immunological-treatment-related adverse events included flu-like symptoms and fatigue. No grade IV or V treatment-related adverse events were observed. The study demonstrated a particularly strong response and limited progression in patients with pure CIS.

An ongoing phase 3 clinical trial (BOND-003; NCT 04452591) aims to validate the clinical activity of CG0070 in patients with BCG-unresponsive NMIBC.

**ONGOING CLINICAL TRIALS INVESTIGATING THERAPEUTIC AGENTS**

Various treatment modalities and combinations are currently being evaluated in clinical trials (Table 3).

**CONCLUSION**

BCG-unresponsive NMIBC, which represents an unmet clinical need, poses a substantial challenge for both clinicians and patients. Although radical cystectomy remains a standard treatment option, its association with high morbidity, mortality, and impact on the patients' quality of life necessitates the exploration of various bladder preservation strategies. Currently, FDA-approved treatments for BCG-unresponsive NMIBC include intravesical valrubicin, Adstiladrin, and systemic pembrolizumab, each of which has its unique advantages and disadvantages (Table 4). Ongoing research holds promise for the future, as potential avenues include combination therapies such as intravesical chemotherapy and novel immunotherapy utilizing checkpoint inhibitors, as well as intravesical gene therapy using viruses.

The focus of this review was to present a wide range of treatment options, including both established and experimental approaches, that aim to improve patient outcomes in cases of BCG-unresponsive NMIBC. Patients should be informed about the off-label status of certain regimens and the substantial risks associated with recurrence and disease progression. These factors may necessitate contemplation of radical cystectomy.

Considering the diversity of options available for bladder preservation, the importance of tailoring treatment to individual patients is underscored. This approach ensures effective outcomes while mitigating the risks associated with radical cystectomy.
Table 3. Current investigational clinical trials on therapeutic agents for BCG-unresponsive NMIBC

<table>
<thead>
<tr>
<th>Trial number</th>
<th>Study title</th>
<th>Intervention</th>
<th>Status/estimated study completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT04172675</td>
<td>A Randomized Phase 2 Study of Erdafitinib Versus Investigator Choice of Intravesical Chemotherapy in Subjects Who Received Bacillus Calmette-Guerin (BCG) and Recurred With High Risk Non-Muscle-Invasive Bladder Cancer (NMIBC) and FGFR Mutations or Fusions</td>
<td>Oral Erdafitinib vs. intravesical chemotherapy (gemcitabine or mitomycin C)</td>
<td>Recruiting/March 29, 2024</td>
</tr>
<tr>
<td>NCT04154082</td>
<td>Phase II Trial of Intravesical Gemcitabine and MK-3475 (Pembrolizumab) in the Treatment of Patients With BCG-Unresponsive Non-Muscle Invasive Bladder Cancer</td>
<td>Intravesical gemcitabine plus intravenous pembrolizumab</td>
<td>Recruiting/March 31, 2024</td>
</tr>
<tr>
<td>NCT04106115</td>
<td>A Phase Ib/II Study to Assess the Safety and Activity of Durvalumab (MEDI4736) in Combination With S-488210/S-488211, vAccine in Non-Muscle Invasive Bladder CancEr (DURANCE)</td>
<td>Intravenous durvalumab plus S-488210/S-488211 (5-peptide cancer vaccine)</td>
<td>Recruiting/May 31, 2024</td>
</tr>
<tr>
<td>NCT03950382</td>
<td>Bladder PReEsrVation by RadioTherapy and Immunotherapy in BCG Unresponsive Non-muscle Invasive Bladder Cancer (PREVERT)</td>
<td>Intravenous avelumab plus radiation</td>
<td>Not yet recruiting/ June 15, 2024</td>
</tr>
<tr>
<td>NCT04736830</td>
<td>A Single-arm, Open-Label, Multicenter, Phase II Clinical Study of HX008 in Subjects With BCG-Unresponsive Non-muscle Invasive Bladder Cancer</td>
<td>Intravenous HX008 (PD-1 antibody)</td>
<td>Recruiting/December 1, 2023</td>
</tr>
<tr>
<td>NCT04752272</td>
<td>A Phase 1/2 Study of EG-70 as an Intravesical Administration to Patients With BCG-Unresponsive Non-Muscle Invasive Bladder Cancer (NMIBC) and High-Risk NMIBC Patients Who Are BCG Naive or Received Incomplete BCG Treatment</td>
<td>Intravesical EG-70 (nominal gene therapy encoding 2 RIG-1 agonists)</td>
<td>Recruiting/May 2027</td>
</tr>
<tr>
<td>NCT04387461</td>
<td>A Phase 2, Single Arm Study of CG0070 Combined With Pembrolizumab in Patients With Non Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Bacillus Calmette-Guerin (BCG)</td>
<td>Intravesical CG0070 plus intravenous pembrolizumab</td>
<td>Active, not recruiting/ June 2023</td>
</tr>
<tr>
<td>NCT04640623</td>
<td>Phase 2b Clinical Study Evaluating Efficacy and Safety of TAR-200 in Combination With Cetrelimab, TAR-200 Alone, or Cetrelimab Alone in Participants With High-Risk Non-Muscle Invasive Bladder Cancer (NMIBC) Unresponsive to Intravesical Bacillus Calmette-Guerin (BCG) Who Are Ineligible for or Elected Not to Undergo Radical Cystectomy (SunRISe-1)</td>
<td>Intravenous cetrelimab (PD-1 inhibitor), intravesical TAR-200 (continuous intravesical release gemcitabine) or combination</td>
<td>Recruiting/July 2, 2027</td>
</tr>
<tr>
<td>NCT02202777</td>
<td>A Phase I Trial for the Use of Intravesical Cabazitaxel, Gemcitabine, and Cisplatin (GCC) in the Treatment of BCG-Refractory Non-muscle Invasive Urothelial Carcinoma of the Bladder Cancer</td>
<td>Intravesical cabazitaxel, gemcitabine and cisplatin</td>
<td>Recruiting/December 2024</td>
</tr>
</tbody>
</table>

BCG, Bacillus Calmette-Guérin; NMIBC, non–muscle-invasive bladder cancer.

Table 4. Pros and cons of FDA-approved agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intravesical valrubicin</td>
<td>Relatively long history of use</td>
<td>Relatively low efficacy and sustainability, Irritative symptoms of bladder</td>
</tr>
<tr>
<td>Intravesical Adstiladrin</td>
<td>Fewer instillation, Prolonged exposure of therapeutic agent</td>
<td>Risk for disseminated adenovirus infection (contraindicated to immunocompromised patients), Irritative symptoms of bladder</td>
</tr>
<tr>
<td>Intravenous pembrolizumab</td>
<td>No catherization, Relatively high efficacy and sustainability</td>
<td>Systemic and immune-related adverse effect, Variations in response based on tumor PD-L1 expression</td>
</tr>
</tbody>
</table>

FDA, Food and Drug Administration; PD-L1, programmed death-ligand 1.

NOTES

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- **Author Contribution**: Conceptualization: JY, HHS; Data curation: JY, HHS; Formal analysis: JY, HHS; Methodology: JY, HHS; Project administration: JY, HHS; Visualization: JY, HHS; Writing - original draft: JY, HHS; Writing - review & editing: JY, HHS.
REFERENCES


INTRODUCTION

Bladder cancer (BC) is the tenth most prevalent cancer globally, with an annual incidence of approximately 573,000 cases, and 213,000 deaths [1]. The most common subtype is urothelial BC. Approximately 75% of patients initially present with non–muscle-invasive bladder cancer (NMIBC) confined to the bladder mucosa and submucosa [2,3].

Early Experience With Pembrolizumab in Bacillus Calmette-Guérin Unresponsive Non–Muscle-Invasive Bladder Cancer

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Purpose: Radical cystectomy (RC) is recommended for patients with non–muscle-invasive bladder cancer (NMIBC) who are unresponsive to intravesical bacillus Calmette-Guérin (BCG) instillation. However, RC is a very risky treatment, and some patients cannot undergo RC due to old age, patient preference, and comorbidities. In this study, we investigated the efficacy of pembrolizumab, a programmed cell death protein 1 inhibitor, in patients with NMIBC unresponsive to intravesical BCG instillation.

Materials and Methods: Between December 2016 and February 2023, 24 patients who experienced recurrence after BCG treatment and subsequently received pembrolizumab were enrolled. We evaluated the patients’ response to pembrolizumab therapy using urine cytology, cystoscopic examination (with/without biopsy), and/or computed tomography imaging. The primary endpoint was the complete response (CR) rate 3 months after the first dose of pembrolizumab. Patients were followed up every 3 months for the first 2 years and every 6 months thereafter. Kaplan-Meier survival analysis was used to illustrate CR and the individual treatment course was demonstrated.

Results: The median follow-up period was 16 months (range, 2–68 months) and the median number of pembrolizumab administrations was 5 times (range, 3–39 times). Thirteen of the 18 patients (54.2%) with BCG-unresponsive NMIBC achieved CR at 3 months. The median duration of CR maintenance was 15 months (range, 5–47 months). Five patients (20.8%) showed no recurrence for 12 months after pembrolizumab administration. Seven patients underwent RC, and pathological reports showed T2 stage in 3 patients. To date, 1 patient (4.2%) has died.

Conclusions: Our early experience with pembrolizumab treatment for BCG-unresponsive NMIBC showed better results than those of the KEYNOTE-057 trial, which reported a CR rate of 40% at 3 months. However, long-term data and more cases are required to establish pembrolizumab therapy in patients with BCG-unresponsive NMIBC in a real-world setting.

Key Words: BCG vaccine, Non-muscle invasive bladder neoplasms, Pembrolizumab
Treatment of NMIBC primarily consists of localized treatment and surveillance. The high prevalence of this stage is due to its nonaggressive characteristics. In cases of NMIBC with a high risk of cancer recurrence and progression, adjuvant intravesical instillation of bacillus Calmette-Guérin (BCG) immunotherapy is considered [2,3].

Intravesical BCG instillation after transurethral resection of bladder tumor (TURBT) has been demonstrated to decrease recurrence significantly [4]. However, recurrence is identified within 5 years of starting BCG treatment in approximately half of high-risk cases, and the prognosis for patients with BCG treatment failure is poor [5-7]. Several guidelines recommend radical cystectomy (RC) for patients who develop carcinoma in situ (CIS) and/or high-grade tumor recurrence despite sufficient BCG therapy due to the significant risk of disease progression [2,3].

However, as RC can degrade the quality of life [8], many patients opt for bladder preservation. Furthermore, many patients suffer from concurrent illnesses such as cardiovascular or pulmonary diseases due to tobacco exposure, which makes them unsuitable candidates for RC. Hence, there is a clinical need for alternative bladder-preserving treatments for patients with NMIBC who do not respond to BCG.

Pembrolizumab, a U.S. Food and Drug Administration (FDA)-approved immune checkpoint inhibitor (ICI), is an IgG4 anti-programmed cell death protein 1 (PD-1) humanized antibody. It functions by attaching to PD-1, thereby blocking the binding between PD-1 and its ligands, programmed death-ligand 1 (PD-L1) and programmed death-ligand 2. FDA approval was granted based on a randomized, phase 3 trial known as KEYNOTE-045, which was an open-label study that assigned 542 randomly selected patients who had recurrence or progression following platinum therapy [9]. Pembrolizumab also gained approval as a first-line therapy for cisplatin-ineligible patients with metastatic urothelial carcinoma based on early data from the phase 2 KEYNOTE-052 study [10,11].

The KEYNOTE-057 study demonstrated that pembrolizumab monotherapy was well tolerated and showed promising results in patients with BCG-unresponsive NMIBC who were unsuitable for or refused RC [12]. Consequently, it should be considered as a clinically active nonsurgical treatment alternative for this challenging patient population. In this study, we investigated the efficacy of pembrolizumab, a PD-1 inhibitor, in patients with NMIBC that was unresponsive to intravesical BCG administration in a real-world setting.

**MATERIALS AND METHODS**

This study was approved by the Institutional Review Board of the Samsung Medical Center (IRB No. 2023-07-146-001), which waived the requirement for informed consent because of the retrospective nature of this study. All the study protocols were performed in accordance with the principles of the Declaration of Helsinki.

We retrospectively reviewed the records of patients who experienced recurrence after BCG treatment and subsequently received pembrolizumab treatment between December 2016 and February 2023. Patients who experienced recurrence after intravesical BCG instillation were included in this study. They were pathologically diagnosed with urothelial carcinoma by TURBT before intravesical BCG instillation, and NMIBC was confirmed by TURBT before pembrolizumab administration. Among the included patients, 1 patient was diagnosed with muscle-invasive BC at the first TURBT; however, the patient wanted bladder preservation. Intravesical BCG instillation was performed as part of the treatment, and then NMIBC was confirmed by TURBT before pembrolizumab administration.

When intermediate-to-high NMIBC was confirmed after TURBT, intravesical BCG induction was initiated and performed 6 times weekly. After intravesical BCG induction, the response was evaluated through a cystoscopic examination with or without biopsy after 3 months. Depending on the response, a second intravesical BCG induction or intravesical BCG maintenance was performed 3 times weekly, and after 3 months, post-BCG cystoscopic examination with/without biopsy was used to evaluate the response. In the absence of recurrence, intravesical BCG maintenance was continued every 6 months.

BCG-unresponsive NMIBC was defined as persistent CIS, high-grade Ta tumors, or high-grade T1 tumors at 6 months after receiving adequate BCG therapy. Adequate BCG therapy referred to the administration of at least 5 of
6 induction doses and 2 of three maintenance treatments of BCG, or at least 2 of 6 instillations of a second induction course when maintenance BCG was not provided.

The definition of BCG-unresponsive NMIBC also included patients who experienced recurrences of high-grade Ta or T1 NMIBC within 6 months, or CIS within 12 months following a disease-free state after BCG treatment; patients who continued to exhibit persistent high-grade Ta or CIS, or showed progression to T1 disease after BCG therapy, were also considered to have BCG-unresponsive NMIBC.

Patients with BCG-unresponsive NMIBC received intravenous pembrolizumab 200 mg every 3 weeks. We evaluated the patient’s response to pembrolizumab therapy via urine cytology, cystoscopic examination (with/without biopsy), and/or CT imaging after 4 administrations. Patients were followed up every 3 months for the first 2 years and every 6 months thereafter. The primary endpoint was the complete response (CR) rate 3 months after the first dose of pembrolizumab. Secondary outcomes included duration of response, progression-free survival, complications, and recurrence after pembrolizumab treatment.

Descriptive statistics included frequencies and proportions of categorical variables. Continuous variables are presented as median (range). Kaplan-Meier survival analysis was used to illustrate CR and demonstrate the individual treatment course. All statistical analyses were performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Baseline Characteristic

In total, 24 patients who experienced recurrence after BCG treatment and subsequently underwent pembrolizumab treatment were analyzed. As shown in Table 1, the median age was 70.5 years (range, 47–85 years), and 5 patients had a history of surgery for upper urinary tract carcinoma (3 and 2 patients had undergone radical nephroureterectomy and distal ureterectomy, respectively). Eight patients (33.3%) had CIS on the initial TURBT, and 15 patients (62.5%) had CIS on TURBT just before the administration of pembrolizumab. The median number of pembrolizumab administration was 5 times (range, 3–39 times) and the duration was 3 months (1–64 months). The total follow-up period was 16 months (2–68 months).

2. Response to Pembrolizumab

The primary outcome, CR at the first assessment (usually 3 months after pembrolizumab administration), was observed in 54.2% (13 patients) in this study. CR was maintained for 15 months (range, 5–47 months) in these patients. Eleven patients (45.8%) showed CR at the second assessment (usually 6 months after pembrolizumab administration). Five patients (20.8%) maintained a recurrence-free status 1 year after pembrolizumab administration (Table 2).

The median duration of CR at onset was 22 months (95% confidence interval, 9.1–34.9), and 5 of 13 patients (38.5%) had CR for 12 months or longer (Fig. 1). The detailed responses and clinical courses of the individual patients are shown in Fig 2.

Eight patients (33.3%) experienced adverse events following pembrolizumab administration. Fatigue was the most

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>70.5 (47–85)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>21 (87.5)</td>
</tr>
<tr>
<td>Female</td>
<td>3 (12.5)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>25.2 (20.4–29.9)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>16 (66.7)</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>History of upper tract urothelial carcinoma</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Pathology at 1st TURB</td>
<td></td>
</tr>
<tr>
<td>CIS only</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Ta</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>T1</td>
<td>13 (52.0)</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>T2</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Pathology before pembrolizumab</td>
<td></td>
</tr>
<tr>
<td>CIS only</td>
<td>6 (25.0)</td>
</tr>
<tr>
<td>Ta</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Ta + CIS</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>T1</td>
<td>7 (29.2)</td>
</tr>
<tr>
<td>No. of pembrolizumab administration</td>
<td>5 (3–39)</td>
</tr>
<tr>
<td>Duration of pembrolizumab administration (mo)</td>
<td>3 (1–64)</td>
</tr>
<tr>
<td>Total follow-up (mo)</td>
<td>16 (2–68)</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>8 (33.3)</td>
</tr>
</tbody>
</table>

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

BCG, bacillus Calmette-Guérin; NMIBC, non–muscle-invasive bladder cancer; TURB, transurethral resection of bladder tumor; CIS, carcinoma in situ.
common symptom, followed by pruritus, and features of hyperthyroidism (Table 3).

### Table 2. Complete response and recurrence-free survival in patients with BCG-unresponsive NMIBC (N=24)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with complete response at 3 months</td>
<td>13 (54.2)</td>
</tr>
<tr>
<td>Duration of complete response (mo)</td>
<td>15 (5–47)</td>
</tr>
<tr>
<td>Patients who were free from recurrence</td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td>10 (41.7)</td>
</tr>
<tr>
<td>9 Months</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>12 Months</td>
<td>5 (20.8)</td>
</tr>
</tbody>
</table>

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

BCG, bacillus Calmette-Guérin; NMIBC, non–muscle-invasive bladder cancer.

### Table 3. Treatment-related adverse events (N=24)

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any</td>
<td>8 (33.3)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>4 (16.7)</td>
</tr>
<tr>
<td>Pruritis</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>2 (8.3)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Rash</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Diaphoresis</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>1 (4.2)</td>
</tr>
<tr>
<td>Constipation</td>
<td>1 (4.2)</td>
</tr>
</tbody>
</table>

3. Treatment for Patients With Recurrence After Pembrolizumab

No CR was observed in 11 patients during the first assessment. Eight patients (72.7%) either underwent RC or planned RC (Fig. 2). Three patients either planned or underwent other intravesical therapies, including gemcitabine and mitomycin.

In total, 7 patients (29.2%) underwent RC because of recurrence after pembrolizumab administration. There was no aggravation of pathological results after TURBT when comparing the pathology before RC with that before pembrolizumab administration. When comparing the pathology of RC with that before pembrolizumab administration, aggravation of pathology was observed in 3 patients (Table 4).

### Fig. 1. Kaplan-Meier survival analysis depicting the complete response rate after the first dose of pembrolizumab.

### Fig. 2. Detailed response and clinical course for individual patients following the first dose of pembrolizumab. RCx, radical cystectomy; CR, complete response.
Although platinum-based combination chemotherapy continues to be the primary treatment for advanced BC, the surge in the understanding of the biological intricacies of BC has spurred a growing interest in ICIs and molecularly targeted treatments [13]. BC is characterized by frequent mutations [14], and its high tumor mutational burden makes it susceptible to ICIs targeting PD-1 and its ligand, PD-L1 [15,16]. Consequently, ICIs that inhibit PD-1 or PD-L1 have gained FDA approval for the first- and second-line treatment of metastatic BC.

Additionally, a role for the PD-1–PD-L1 pathway in fostering resistance to BCG in NMIBC has been proposed. Tumors that have recurred or progressed following BCG treatment have been found to exhibit a noticeable increase in PD-L1 expression compared to tumors that have never been treated with BCG. Furthermore, increased PD-L1 expression has been associated with recurrence and progression [17].

Despite RC being recommended as a treatment option for BCG-unresponsive NMIBC by several guidelines [2,3], the demand for alternative treatments has surged because of the high complication rate associated with RC and patients’ preference for preserving the bladder. Based on the findings of the PD-L1 study, pembrolizumab is expected to be a viable treatment option for BCG-unresponsive NMIBC.

This study aimed to investigate the efficacy of pembrolizumab in patients with NMIBC who did not respond to intravesical BCG instillation through our initial experience. The tolerability and antitumor activity of pembrolizumab in patients with BCG-unresponsive NMIBC were reported in the KEYNOTE-057 study [12]. However, there have been no studies on pembrolizumab in patients with NMIBC in a clinical setting. In real clinical situations, a patient’s disease state is not constant, and there are various factors to be considered. Our study demonstrated the efficacy of pembrolizumab in patients with BCG-unresponsive NMIBC.

In our study, the primary outcome, CR at the first assessment (usually at 3 months after pembrolizumab administration), was observed in 54.2% of patients; among them, 38.5% maintained a recurrence-free status at 1 year after pembrolizumab administration. The KEYNOTE-057 study showed a 41% CR rate at 3 months after the administration of pembrolizumab for patients with BCG-unresponsive CIS of the bladder with or without papillary tumors, and 46% of responders remained in CR for 12 months or longer [12]. In terms of complications, 33.3% of patients had treatment-related adverse events in our study, and 66% of patients had treatment-related adverse events in KEYNOTE-057. Our study showed better results than the KEYNOTE-057 study.

Additionally, we analyzed the pathological results of patients who underwent RC after the failure of pembrolizumab treatment. Seven patients underwent RC; among them, 3 patients showed upgrading of T stage to T2, and 1 patient showed downgrading of T stage to TX. Although the patients experienced aggravation of the disease stage, they were able to receive appropriate treatment by undergoing RC. Therefore, the period before surgical treatment can be extended by administering pembrolizumab. Although pembrolizumab treatment results in failure of disease control, it can be properly managed by RC, and we can confirm that pembrolizumab could affect pathological complete remission. Therefore, clinicians should consider pembrolizumab administration to patients with BCG-unresponsive NMIBC.

### DISCUSSION

Table 4. Pathological stage at the time of radical cystectomy in patients who discontinued pembrolizumab

<table>
<thead>
<tr>
<th>Pathology before pembrolizumab</th>
<th>Pathology before RCx.</th>
<th>Interval between initial dose of pembrolizumab and RCx. (mo)</th>
<th>Interval between last dose of pembrolizumab and RCx. (mo)</th>
<th>No. of pembrolizumab doses</th>
<th>Pathology after RCx.</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 + CIS</td>
<td>T1</td>
<td>7</td>
<td>4</td>
<td>5</td>
<td>T1</td>
</tr>
<tr>
<td>T1</td>
<td>T1</td>
<td>5</td>
<td>2</td>
<td>6</td>
<td>T2 + CIS</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>CIS</td>
<td>6</td>
<td>2</td>
<td>6</td>
<td>T2</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>T1</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>TX</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>T1G3 + CIS</td>
<td>4</td>
<td>2</td>
<td>4</td>
<td>T1</td>
</tr>
<tr>
<td>T1 + CIS</td>
<td>Ta + CIS</td>
<td>7</td>
<td>2</td>
<td>4</td>
<td>T1 + CIS</td>
</tr>
<tr>
<td>T1</td>
<td>-</td>
<td>6</td>
<td>2</td>
<td>7</td>
<td>T2</td>
</tr>
</tbody>
</table>

RCx., radical cystectomy; CIS, carcinoma in situ.
Previous studies suggest a variance in the 1- to 2-year recurrence-free survival rates, ranging from 18% to 43%, following diverse salvage therapies in patients experiencing BCG treatment failure [18-23]. Consequently, the International Bladder Cancer Group posits a benchmark for clinical significance, advocating for an initial CR rate of 50% at the 6-month interval, coupled with sustained response rates of 30% at 12 months and 25% at 18 months in patients with BCG-unresponsive CIS. In instances of BCG-unresponsive papillary disease, recurrence-free benchmarks of 30% at 12 months and 25% at 18 months are deemed clinically significant [5]. Our study, albeit lacking a control cohort of NMIBC patients not treated with pembrolizumab, demonstrates that pembrolizumab surpasses the efficacy of extant salvage therapies, aligning with the recommendations of the International Bladder Cancer Group.

Some studies have attempted to demonstrate the efficacy of novel treatment options in patients with BCG-unresponsive NMIBC. One concerns hyperthermic intravesical chemotherapy for BCG-unresponsive NMIBC. The study reported that the 3-month, 6-month, 9-month, and 1-year cumulative incidence rates of disease recurrence/progression were 25%, 35%, 44%, and 53%, respectively [24]. Another option is intravesical gemcitabine treatment. There have been some reports on intravesical gemcitabine use in patients with NMIBC with recurrence after intravesical BCG instillation. Hurle et al. [25] reported a disease-free survival rate of 68.8% after induction (once a week for 6 consecutive weeks) and 44.4% disease-free survival after 12 months of treatment. Skinner et al. [19] reported 47% and 28% CR rates at 3 and 12 months, respectively. Another study reported on intravesical nadofaragene firadenovec gene therapy for BCG-unresponsive NMIBC. Boorjian et al. [26] reported 53.4% and 45.5% CR rates at 3 and 12 months, respectively, after initial administration. Direct comparison between these treatments is difficult because each study has a different group of patients and research methods; however, based on the results of our study, it can be suggested that pembrolizumab can also be considered as a treatment option in patients with BCG-unresponsive NMIBC.

Despite the strengths of this study, it has several limitations. First, the retrospective design may have resulted in a significant selection bias. Second, it is limited to establishing the effect of pembrolizumab, and additional analysis of factors such as treatment success was not possible due to the relatively small cohort. Third, the patients were not uniform in terms of tumor characteristics or previous therapy. Additionally, the absence of PD-L1 testing in this study represents a missed opportunity for more detailed understanding of pembrolizumab’s clinical implications. Further, well-designed studies are required to determine the clinical significance and efficacy of pembrolizumab therapy in patients with BCG-unresponsive NMIBC.

CONCLUSIONS

Our early experience with pembrolizumab treatment for BCG-unresponsive NMIBC showed better results than those of the KEYNOTE-057 trial. Pembrolizumab treatment can be considered in patients with BCG-unresponsive NMIBC who decline or are not eligible for RC. However, long-term data and more cases are needed to establish pembrolizumab treatment for patients with BCG-unresponsive NMIBC in real-world settings.

NOTES

- **Conflicts of Interest**: MK and HHS, members of the Editorial Board of *Journal of Urologic Oncology*, is the co-first authors of this article. However, they played no role whatsoever in the editorial evaluation of this article or the decision to publish it. The other authors have nothing to disclose.
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REFERENCES


Clinical Outcomes of Patients With Variant Histology of Urothelial Carcinoma After Radical Cystectomy

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Original Article

INTRODUCTION

Bladder cancer (BC) ranks as the 10th most prevalent cancer type globally [1]. The most common pathological type is pure urothelial carcinoma (PUC), but this form of carcinoma is known for its tendency towards divergent differentiation. As a result, these tumors often show variant histology (VH) in conjunction with urothelial histology [2]. The 2016 World Health Organization’s classification of the urothelial tract includes several histologic variants:

1. Micropapillary
2. Plasmacytoid
3. Sarcomatoid
4. Squamous differentiation
5. Glandular differentiation
6. Lipoid
7. Nested

Small cell carcinoma, pure adenocarcinoma, pure squamous cell carcinoma, and lymphoma BC were excluded from analysis. The progression-free survival (PFS) and overall survival (OS) rates were evaluated using Kaplan-Meier analysis and Cox regression.
micropapillary, plasmacytoid, sarcomatoid variants of urothelial carcinoma (UC), squamous cell neoplasms, glandular neoplasms, neuroendocrine tumors, and others [3]. These are divided into urothelial and nonurothelial variants. Urothelial variants demonstrate urothelial differentiation alongside other morphologies, while nonurothelial variants display distinct characteristics.

VH is associated with important prognostic and therapeutic implications. Several reports have described the presence of VH as a poor prognostic factor. Compared to PUC, VH has a worse prognosis due to more locally advanced disease and occult regional lymph node metastasis at the time of diagnosis [4]. Since VH often presents at a more advanced stage, it is important to estimate the prognosis after adjusting for stage [5]. Unfortunately, the clinical staging of BC is inadequate due to the relative inaccuracy of transurethral bladder tumor resection results. As such, reported findings are often inconsistent, and definitive data on the effect of the histological type on survival are currently lacking [6].

Although there are defined criteria for managing VH in BC, they are largely based on subgroup analyses, relatively small studies, and expert consensus [7]. In some cases, the risk associated with VH necessitates aggressive treatment, such as early radical cystectomy (RC). Histological types such as micropapillary, plasmacytoid, and sarcomatoid are considered for early RC due to their significant risk of progressing to muscle-invasive and potentially metastatic diseases [8-10]. At present, the early administration of neoadjuvant chemotherapy followed by local treatment (either cystectomy or radiotherapy) is recommended for patients with small cell carcinoma of the bladder [11]. However, the survival outcomes for squamous or glandular differentiation, nested variants, and other rare variants are comparable to those of PUC. Consequently, these are managed in the same manner as UC of the same stage [7].

Given the considerable impact of RC on postoperative complications and patient quality of life, it is essential to determine whether the presence of higher-risk VH justifies aggressive treatment with early RC. Our study evaluated the clinical outcomes and survival expectancies of post-cystectomy patients with VH based on their stratified risk profile.

**MATERIALS AND METHODS**

1. **Data Collection**

We identified 327 BC patients who had undergone RC at our institution from February 2010 through June 2021 (Fig. 1). This study retrospectively analyzed patients who were eligible for follow-up observation for at least 2 years after surgery. Patients with nonurothelial variants, such as
pure squamous cell carcinoma, pure adenocarcinoma, and lymphoma, and any metastasis were excluded, resulting in a total of 299 patients. Patients were categorized by histology into PUC (n=244) and VH (n=55) groups using the 2016 World Health Organization classification. The differentiation patterns included in the study were squamous differentiation, glandular differentiation, lipoid variant, nested variant, tubular type differentiation, and giant cell differentiation variants of urothelial cancer, small cell carcinoma, micropapillary, plasmacytoid, and sarcomatoid variants of urothelial cancer. This study was approved by the Institutional Review Board of Pusan National University Yangsan Hospital (approval No. 05-2023-173). Anonymized and deidentified information was used for analyses; therefore, informed consent was not obtained.

2. Patient Management

Patients underwent routine evaluations, including laboratory tests, cystoscopy, biopsy with transurethral resection of the bladder tumor, abdominal-pelvic and chest computed tomography (CT), and a bone scan. All of them underwent RC with urinary diversion and pelvic lymphadenectomy. The surgical procedures included RC with continent and incontinent urinary diversion. Tumor stage and lymph node status were assigned according to the tumor, node, metastasis (TNM) staging system [12].

For postoperative surveillance, laboratory tests and CT scans were performed every 3 months for the first 2 years, followed by biannual checkups. Disease progression was confirmed when local recurrence, metastasis to regional lymph nodes, or distant metastasis was detected. Patients without any event during follow-up were censored at the time of their last visit. Those lost to follow-up because of deaths unrelated to BC were censored at their time of death. The cause of death was determined by medical record review or death certificates alone.

3. Statistical Analysis

We retrospectively evaluated the clinical data of 299 BC patients who were treated with RC. Patients were analyzed according to age, sex, stage, grade, administration of chemotherapy, and type urinary diversion (continent vs. incontinent). Patients with VH were stratified by the researchers into aggressive (n=35) and more aggressive (n=20) groups (Fig. 2) with reference to the 2022 NCCN (National Comprehensive Cancer Network) Guidelines for Bladder Cancer. The more aggressive histologic types included micropapillary, plasmacytoid, and sarcomatoid.

Finally, multivariable Cox proportional hazards models were fitted to predict the clinicopathologic variables influencing overall survival (OS) and progression-free survival (PFS) rates. OS and PFS were estimated with the Kaplan-Meier method. Categorical data were compared using the chi-square test, and quantitative variables were compared using the t-test. All statistical analysis was performed using IBM SPSS Statistics ver. 27.0 (IBM Co., Armonk, NY, USA).

![Histologic grouping of 299 patients who met the inclusion criteria.](https://via.placeholder.com/150)
A p-value <0.05 was considered statistically significant.

**RESULTS**

From 2010 to 2021, 327 patients with surgically resected BC were identified. Of these, 244 (74.61%) were found to have PUC, and 55 (16.82%) had VH. Squamous differentiation was the most common histological type observed (6.73%), followed by micropapillary variant (3.34%) and glandular differentiation (1.83%) (Table 1).

Table 2 summarizes the clinicopathologic features of 299 patients. Our cohort included 266 men and 33 women. The median age at diagnosis was 69 years (range, 63–75 years). Age, sex, grade, and type of urinary diversion did not show statistical significance. Overall, 29.8%, 18.4%, 29.4%, and 22.4% of patients presented with pathologic T stages pT1, pT2, pT3–4 and any pT with a positive lymph node, respectively. The UC with VH group was more likely to show advanced T stage (pT3–4: 23.4% vs. 56.3%) and to be greater than or equal to pN1 or cM1 (21.3% vs. 27.3%). In conclusion, the presence of VH was significantly associated with an advanced pathologic tumor stage (p<0.001).

The rate of pathologic upstaging or downstaging relative to the clinical stage after RC was measured to evaluate the likelihood of VH being upstaged. Any increase from the initial cT stage and/or cN stage was defined as pathologic upstaging. Upstaging was recorded in 25.1% of patients. More aggressive VH showed the highest incidence of upstaging (58%), followed by less aggressive VH (39%) and PUC (22%) (Fig. 3).

During a median follow-up of 35 months, 75 patients experienced disease progression (22.9%), and 49 (21.4%)

<table>
<thead>
<tr>
<th>Table 1. Patient distribution according to histologic type</th>
<th></th>
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</thead>
<tbody>
<tr>
<td>Histologic type</td>
<td>Pure UC (74.62%)</td>
</tr>
<tr>
<td>Pure UC</td>
<td>244 (74.62)</td>
</tr>
<tr>
<td>UC with variant histology</td>
<td></td>
</tr>
<tr>
<td>More aggressive variant</td>
<td></td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>22 (6.73)</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>13 (4.35)</td>
</tr>
<tr>
<td>Plasmacytoid</td>
<td>4 (1.22)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>2 (0.61)</td>
</tr>
<tr>
<td>Less aggressive variant</td>
<td></td>
</tr>
<tr>
<td>Squamous differentiation</td>
<td>22 (6.73)</td>
</tr>
<tr>
<td>Micropapillary</td>
<td>13 (4.35)</td>
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<tr>
<td>Plasmacytoid</td>
<td>4 (1.22)</td>
</tr>
<tr>
<td>Sarcomatoid</td>
<td>2 (0.61)</td>
</tr>
<tr>
<td>Glandular differentiation</td>
<td>6 (1.83)</td>
</tr>
<tr>
<td>Lipoid variant</td>
<td>3 (0.92)</td>
</tr>
<tr>
<td>Nested variant</td>
<td>2 (0.61)</td>
</tr>
<tr>
<td>Tubular type differentiation</td>
<td>1 (0.31)</td>
</tr>
<tr>
<td>Giant cell</td>
<td>1 (0.31)</td>
</tr>
</tbody>
</table>
| UC, urothelial carcinoma.

<table>
<thead>
<tr>
<th>Table 2. Patient characteristics</th>
<th>Pure urothelial carcinoma (74.62%)</th>
<th>Urothelial carcinoma with variant histology (16.82%)</th>
</tr>
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<tr>
<td>Characteristic</td>
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<tr>
<td>Age (yr), median (IQR)</td>
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<td>72 (63–76)</td>
</tr>
<tr>
<td>Sex</td>
<td>Male</td>
<td>221</td>
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<tr>
<td></td>
<td>Female</td>
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<tr>
<td>T stage</td>
<td>≤pT1</td>
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<tr>
<td></td>
<td>pT2</td>
<td>51</td>
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<tr>
<td></td>
<td>pT3–4</td>
<td>57</td>
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<td>Any pT with positive lymph node</td>
<td>52</td>
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<td>Grade</td>
<td>Low grade</td>
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<td>High grade</td>
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<td>Chemotherapy</td>
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<td>159</td>
</tr>
<tr>
<td></td>
<td>No</td>
<td>85</td>
</tr>
<tr>
<td>Type of surgery</td>
<td>Neobladder</td>
<td>97</td>
</tr>
<tr>
<td></td>
<td>Incontinence urinary diversion</td>
<td>147</td>
</tr>
</tbody>
</table>
| IQR, interquartile range.

**Fig. 3.** The rate of upstaging and downstaging relative to clinical stage after radical cystectomy in patients with pure urothelial carcinoma (A), more aggressive variant (B), and less aggressive variant (C).
died. The median time to progression was 18 months (range, 1–142 months). The 5-year PFS rates of PUC and UC with VH were 56.6% and 3.6%, respectively. Kaplan-Meier analysis was used to estimate OS and PFS according to the following categories: pure UC versus UC with VH (Fig. 4A, B) and pure UC versus UC with aggressive VH versus UC with more aggressive VH (Fig. 4C, D). No statistically significant differences were identified between patients with PUC and those with UC with VH in terms of OS and PFS (Fig. 4A, B). Although the UC with VH group had a lower PFS rate than the PUC group, no statistical significance was found between the survival curves (Fig. 4B). However, UC with more aggressive VH demonstrated significant differences in OS (p=0.013) and PFS (p=0.002) (Fig. 4C, D).

Univariate and multivariate analyses identified clinicopathologic parameters associated with disease progression and mortality after RC. On multivariate analysis, the presence of more aggressive VH was significantly associated with both OS (odds ratio [OR], 2.07; 95% confidence interval [CI], 1.76–3.98; p=0.030) and PFS (OR, 2.79; 95% CI, 1.33–5.91; p=0.070) when compared to PUC (Table 3). However, the survival outcomes of UC with less aggressive VH were comparable to PUC: OS (OR, 1.17; 95% CI, 0.68–2.03; p=0.560) and PFS (OR, 0.90; 95% CI, 0.41–1.99; p=0.800). The odds of mortality were 1.94 times higher for patients with pathologic T stage higher than 2 than for patients with pathologic T stage lower than 2 (OR 1.94; 95% CI, 1.26–2.88; p=0.002). The odds of progression were 1.87 times higher for patients with stage>pT2 (OR, 1.87; 95% CI, 1.03–3.61; p<0.016). Incontinent urinary diversion was associated with OS (OR, 3.32; 95% CI, 2.04–5.44; p=0.013) and PFS (OR, 2.14; 95% CI, 1.11–4.12; p<0.009).

Fig. 4. Overall survival (A) and progression free survival (B) in patients with pure urothelial carcinoma vs. urothelial carcinoma with variant histology. Overall survival (C) and progression free survival (D) in patients with pure urothelial carcinoma versus urothelial carcinoma with less aggressive variant versus urothelial carcinoma with more aggressive variant.
DiscusSion

UC is known to manifest in diverse morphological variants. Approximately 25% of BC cases are thought to have VH. Previous studies have reported prevalence rates of 2%–5% for the micropapillary variant, 1%–3% for the plasmacytoid variant, and less than 1% for the sarcomatoid variant [13]. The incidence rates found in this study align with these figures, with rates of 4.35%, 1.22%, and 0.61% for the micropapillary, plasmacytoid, and sarcomatoid variants, respectively. These 3 variants have been suggested in prior studies to be associated with poorer oncologic outcomes than PUC [14,15]. Conversely, the survival rates for squamous differentiation, glandular differentiation, and other rare types have been found to be comparable to those of PUC [13].

However, studies have presented findings that challenge previous research. In particular, the outcomes for patients with T1 micropapillary BC have been contentious. Some studies suggest that upfront cystectomy can provide a survival benefit, while others indicate that bladder sparing is not necessarily inferior. These conflicting results may be attributed to selection bias, and thus are subject to debate [16,17].

As a result, definitive data regarding the impact of histology type on survival have not yet been established [18]. For instance, a meta-analysis conducted by Abufaraj et al. [19] found that the micropapillary variant did not correlate with lower recurrence-free, cancer-specific, or OS rates compared to those observed in individuals with PUC.

The presence of VH has significant implications for disease management. Currently, guidelines on managing BC with VH are primarily based on subgroup analyses, relatively small studies, and expert consensus. The definition of treatment strategies is vague, and recommendations often lean towards a conservative approach to minimize patient harm. Experts agree that VH in non–muscle-invasive bladder cancer (NMIBC) patients should be considered a high-risk feature. Despite the absence of robust evidence, early RC should be considered as an aggressive treatment option [20]. Typically, immediate cystectomy is recommended for micropapillary, sarcomatoid, and plasmacytoid variants [16,21,22]. Other variants, such as squamous differentiation, glandular differentiation, and nested variants, are treated in the same way as conventional UC. For NMIBC patients, several series have shown promising results with bladder preservation therapy in carefully selected patients [13]. Systemic chemotherapy followed by RC or radiotherapy is suggested as a standard treatment for small cell carcinomas [7]. However, there is no evidence supporting the use of chemotherapy for other types of VH [23].

Accurately predicting survivability is crucial for physicians when determining treatment plans. As such, we conducted

| Table 3. Overall and progression-free survival according to clinicopathologic variables |
|-----------------------------------------------|---------------------|--|---------------------|--|
| Variable                                       | Univariate (OR [95.0% CI]) | p-value | Multivariate (OR [95.0% CI]) | p-value | Univariate (OR [95.0% CI]) | p-value | Multivariate (OR [95.0% CI]) | p-value |
| Age, >70 yr vs. ≤70 yr                         | 1.85 (1.15–2.96)        | <0.001* | 1.7 (1.08–2.67)              | 0.021*  | 1.04 (0.60–1.79)           | 0.499   |                           |
| Sex, male vs. female                           | 1.42 (0.68–2.91)        | 0.194   |                           |         | 1.24 (0.19–2.45)           | 0.326   |                           |
| Stage, >T2 vs. ≤T2                             | 4.13 (2.51–6.79)        | <0.001* | 1.94 (1.26–2.88)            | 0.002*  | 3.91 (2.16–7.08)           | <0.001* | 1.87 (1.03–3.61)           | 0.016*  |
| Grade, HG vs. LG                               | 1.36 (0.29–1.84)        | 0.512   |                           |         | 1.68 (0.48–5.94)           | 0.411   |                           |
| Chemotherapy, yes vs. no                       | 1.29 (0.77–2.15)        | 0.332   |                           |         | 3.14 (1.72–5.74)           | <0.001* | 2.46 (1.36–4.44)           | 0.003*  |
| Type of surgery                                |                           |         |                           |         |                           |         |                           |
| Neobladder                                     | Ref.                  |         | Ref.                      |         | Ref.                      |         |                           |
| Incontinence urinary diversion                 | 1.24 (0.63–2.43)        | 0.533   | 3.32 (2.04–5.44)           | 0.013*  | 3.19 (1.57–6.51)           | <0.001* | 2.14 (1.11–4.12)           | 0.009*  |
| Variant vs. pure UC                            | 1.45 (0.38–1.25)        | 0.216   |                           |         | 0.72 (0.37–1.41)           | 0.338   |                           |
| Histology                                      | Purpure UC             | Ref.    | Ref.                      |         |                           |         |                           |
| Less aggressive variant                        | 0.92 (0.38–2.23)        | 0.859   | 1.17 (0.68–2.03)           | 0.564   | 1.290 (0.63–2.65)          | 0.485   | 0.90 (0.41–1.99)           | 0.795   |
| More aggressive variant                        | 2.462 (0.96–6.34)       | 0.033*  | 2.07 (1.76–3.98)           | 0.030*  | 2.46 (1.44–6.34)           | 0.047*  | 2.79 (1.33–5.91)           | 0.070*  |

OR, odds ratio; CI, confidence interval; HG, high grade; LG, low grade; UC, urothelial cancer.
*p<0.05, statistically significant difference.
a retrospective investigation into the clinical outcomes and survival rates of high-risk VH subtypes in RC specimens, aiming to highlight their increased clinical risk compared to PUC and aggressive variants. Generally, patients with VH exhibited higher T stages than those with PUC, indicating a higher prevalence of locally advanced disease. Furthermore, the presence of VH was associated with a high likelihood of pathologic upstaging, particularly in patients who had UC with a more aggressive VH type.

The Kaplan-Meier estimates revealed no significant difference in survival rates between the overall VH group and the PUC group (Fig. 4). In the multivariable analysis, both OS and PFS were similar between PUC and VH types. However, when the variant types were stratified into less aggressive and more aggressive VH, the results aligned with previous research findings. The more aggressive variant demonstrated poorer survival rates for both OS and PFS (Fig. 4). Furthermore, it was linked with a higher risk of progression and death compared to PUC in the multivariate analysis. These findings suggest that our prognostic analysis may be utilized to reinforce the current recommendations for managing UC in cases of BC with VH.

This study has some limitations. Due to its retrospective design, this study is subject to bias. The relatively small sample size and short follow-up period in the VH group compared to the PUC group may render our analysis underpowered, limiting the generalizability of the results on survival. A prospective study starting at transurethral resection with a follow-up of at least 5 years would better meet the objective of this study. Pure squamous cell carcinoma, adenocarcinoma, and small cell carcinoma were excluded from the study because they were not primary BCs and their inclusion could have confounded the results. However, in 2017, two patients with small cell carcinoma were treated with upfront cystectomy due to the lack of established treatment recommendations at that time. Patients in the aggressive VH group had a higher stage at presentation, which could have also contributed to biased results since the baseline demographics were not the same in all groups. Lastly, incontinent urinary diversion was performed on individuals with high morbidity or low-performance scores; this may have reduced their likelihood of survival, which in turn may have contributed to surgery type being identified as a predictor of survival in the multivariate analysis.

CONCLUSIONS

Our study provides a clinical risk stratification of histologic variants in patients with BC postcystectomy. Within the study cohort, 16.82% of the patients analyzed exhibited VH, with 34.5% of these belonging to the more aggressive variant type. Histologic variations such as squamous differentiation, glandular, nested variant, and others, predicted a prognosis similar to PUC. Conversely, the more aggressive variants were linked with pathological upstaging and a poor prognosis in both Kaplan-Meier and multivariate models. As such, it serves as an independent predictor of poor survival and recurrence following RC. Consistent with previous studies, our findings indicate that cystectomy specimens with a more aggressive type tend to have a worse prognosis in MIBC patients. We propose that analyzing histologic characteristics through transurethral bladder tumor resection could aid in therapeutic decision-making between upfront RC and chemotherapy, a topic we plan to explore in further research.

NOTES

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INTRODUCTION

Prostate cancer is a major health concern for men, and it is the second most common cancer and the fifth leading cause of cancer-related deaths worldwide [1]. In addition, there is a steady increase in prostate cancer in Korea, and according to statistics released by the National Cancer Information Center in 2022, it ranked third in age-standardized prevalence rate [2]. At the time of initial diagnosis, approximately 6% of men with prostate cancer are diagnosed with metastatic prostate cancer [3]. Historically, the first-line treatment for metastatic prostate cancer has been androgen-deprivation therapy (ADT), which was introduced by Dr. Charles Huggins in the 1940s and earned him the Nobel Prize in Physiology or Medicine in 1966 [4]. Despite the initial response to ADT, the cancer can progress to a more aggressive form known as metastatic castration-resistant prostate cancer (mCPRC) within a mean time of 2–3 years [5]. mCPRC is associated
with a poor prognosis, and the survival time of patients is only 16–18 months [6,7]. Several therapies have emerged to treat mCRPC, including chemotherapy, hormonal therapy, immunotherapy, and targeted therapy. Chemotherapy agents such as docetaxel and cabazitaxel have demonstrated efficacy in extending the survival of patients with mCRPC. Second-generation antiandrogens, such as abiraterone and enzalutamide, have shown promising results by targeting the androgen receptor signaling pathway.

These drugs have also exhibited effectiveness in treating metastatic hormone-sensitive prostate cancer (mHSPC) when used in combination with ADT, leading to improvements in the overall survival. The chemohormonal therapy versus androgen ablation randomized trial for extensive disease in prostate cancer (CHAARTED) study provided evidence for the benefit of early chemotherapy by revealing that the addition of docetaxel to ADT significantly improved the overall survival in patients with mHSPC [8]. Similarly, the STAMPEDE (systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy) trial demonstrated that the addition of docetaxel chemotherapy or abiraterone acetate, a second-generation anti-androgen, to standard ADT resulted in substantial improvements in the overall survival of patients with advanced prostate cancer, including mHSPC [9]. The ARCHES trial further supported the efficacy of enzalutamide in combination with ADT, showing superior outcomes in radiographic progression-free survival, time to prostate-specific antigen (PSA) progression, and overall survival to placebo plus ADT in patients with mHSPC [10].

In addition, a triplet therapy that uses ADT + androgen receptor signaling inhibitor (ARSI) + docetaxel was found to have a therapeutic effect on mHSPC. In the PEACE-1 trial, the addition of abiraterone to ADT and docetaxel significantly improved the overall survival (hazard ratio [HR], 0.75; 95.1% confidence interval [CI], 0.59–0.95; p=0.017) and radiographic progression-free survival (HR, 0.50; 99.9% CI, 0.34–0.71; p<0.001). In the ARASENS trial, the combination of darolutamide, ADT, and docetaxel demonstrated significantly longer overall survival than placebo plus ADT and docetaxel (HR, 0.68; 95% CI, 0.57–0.80; p<0.001) [11,12]. These treatments are now listed in the guidelines for mHSPC treatment.

Although triplet therapy can increase survival, no evidence shows that it is better than abiraterone alone, and compared with abiraterone therapy, triplet therapy in all patients with mHSPC is associated with higher costs and unexpected side effects. Therefore, this study aimed to identify the predictive factors of response to abiraterone therapy in patients with high-risk mHSPC.

**MATERIALS AND METHODS**

1. **Patient Population**

This study was approved by the Institutional Review Board (IRB) of Asan Medical Center (IRB No. 2022-1516). The study retrospectively screened medical records of patients diagnosed with high-risk mHSPC between 2018 and 2021. A total of 167 patients who were diagnosed with de novo high-risk mHSPC and initiated ADT and abiraterone were enrolled. However, patients were excluded if their pretreatment stage examinations (including PSA, computed tomography [CT], magnetic resonance imaging [MRI], bone scan, and biopsy results) were unclear or if they had inadequate regular follow-up at the hospital.

Metastatic prostate cancer is defined when a histologically confirmed prostate cancer has at least one metastatic lesion identified through thoracic abdominal pelvic CT and bone scan.

The study referred to the LATITUDE studies and CHAARTED trial for the definition of high-risk and high volume, respectively. A high-volume disease was defined as the presence of visceral metastasis, or ≥4 bone lesions with at least one lesion located beyond the vertebral bodies and pelvis. A high-risk disease was defined as meeting at least 2 of the following 3 criteria: (1) Gleason score of ≥8, (2) presence of 3 or more lesions on a bone scan, and (3) presence of measurable visceral lesions [8,13,14].

CRPC is defined as a castration level of serum testosterone plus one of the following: (1) 3 consecutive rises (over the nadir) in PSA levels at least 1 week apart and a PSA >2 ng/mL (biochemical progression) and (2) development of 2 or more new lesions in bones or progressive disease according to Response Evaluation Criteria in Solid Tumors version 1.1 criteria (radiographic progression) [15-18].
Data on metastatic burden and site were collected from bone, CT, or MRI scans conducted within 3 months before ADT initiation. Patients underwent clinical examination, imaging examination, and serum PSA analysis every 3–6 months for evaluation.

2. Statistical Analysis

Regarding patient characteristics, quantitative data were reported as either mean with standard deviation or median with interquartile range, whereas categorical variables were presented as absolute values with percentages. Univariate and multivariate logistic regression analyses were performed to examine the response to ADT and abiraterone. The associations between outcomes and evaluated variables were expressed as HRs with their corresponding 95% CIs. CRPC-free survival based on risk factors was assessed using Kaplan-Meier survival analysis. All statistical analyses were performed using IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA).

RESULTS

The study included 167 patients with mHSPC. The clinical characteristics of patients are listed in Table 1. The mean patient age, height, and weight were 71.62±8.12 years, 166.06±5.71 cm, and 68.46±10.34 kg, respectively, resulting in an average body mass index of 24.82±3.51 kg/m². The initial PSA levels varied widely, with a median of 218 ng/mL (interquartile range, 70–654 ng/mL). The follow-up period ranged from 0.9 to 56.7 months, with a median of 13.5 months. In addition, the biopsy results showed varying International Society of Urological Pathology (ISUP) grade, with the majority of patients having a ISUP grade of 5 (71.4%) or 4 (27.4%). Metastasis was predominantly observed in the bone (98.8%) and lymph nodes (80.8%), and a subset of patients was experiencing visceral metastasis (29.9%), lung metastasis (28.7%), and liver metastasis (3.0%). Other evaluated factors were the presence of high-volume disease (86.2%), high-risk disease (100%), development of CRPC (25.7%), and mortality (18.0%).

Univariate and multivariate Cox proportional hazards regression analyses were performed to evaluate the association between the characteristics of patients and CRPC-free survival (Table 2). In the univariate Cox regression analysis, age, BMI, and initial PSA levels were not significantly associated with CRPC-free survival. Similarly, the presence of bone metastasis, visceral metastasis, lung metastasis, liver metastasis, lymph node metastasis, and high volume did not demonstrate significant predictive value. However, a Gleason grade of 5 and the presence of bone lesions ≥10 was found to be significant predictors of CRPC-free survival in the univariate analysis. In the multivariable Cox regression analysis, which was adjusted for multiple factors simultaneously, both the Gleason grade of 5 and the presence of bone lesions ≥10 remained significant predictors of CRPC-free survival. The adjusted HR for a Gleason grade of 5 was 2.888 (95% CI, 1.133–7.361), and the adjusted HR for bone lesions ≥10 was 4.194 (95% CI, 1.760–9.997). This indicates that patients with a Gleason grade of 5 and those with bone lesions ≥10 have a higher risk of experiencing CRPC progression.

Table 1. Clinical characteristics of the study patients (n=167)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>71.62±8.12</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>166.06±5.71</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>68.46±10.34</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>24.82±3.51</td>
</tr>
<tr>
<td>Initial PSA (ng/mL), median (IQR)</td>
<td>218 (70–654)</td>
</tr>
<tr>
<td>Follow-up period (mo), median (range)</td>
<td>13.5 (0.9–56.7)</td>
</tr>
<tr>
<td>ISUP grade</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>3</td>
<td>1 (0.6)</td>
</tr>
<tr>
<td>4</td>
<td>45 (27.4)</td>
</tr>
<tr>
<td>5</td>
<td>117 (71.4)</td>
</tr>
<tr>
<td>6</td>
<td>118 (72)</td>
</tr>
<tr>
<td>Metastasis site</td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td>165 (98.8)</td>
</tr>
<tr>
<td>Bone lesion ≥10</td>
<td>106 (63.5)</td>
</tr>
<tr>
<td>Lymph node*</td>
<td>135 (80.8)</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td>50 (29.9)</td>
</tr>
<tr>
<td>Lung metastasis</td>
<td>48 (28.7)</td>
</tr>
<tr>
<td>Liver metastasis</td>
<td>5 (3.0)</td>
</tr>
<tr>
<td>High volume</td>
<td>144 (86.2)</td>
</tr>
<tr>
<td>High-risk</td>
<td>167 (100)</td>
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<tr>
<td>CRPC</td>
<td>43 (25.7)</td>
</tr>
<tr>
<td>Death</td>
<td>30 (18.0)</td>
</tr>
</tbody>
</table>

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

PSA, prostate-specific antigen; IQR, interquartile range; ISUP, International Society of Urological Pathology; CRPC, castration-resistant prostate cancer.

* Lymph node (LN) meta was analyzed in all cases, including extrapelvic LN meta and N1.
Univariate and multivariate Cox proportional hazards regression analyses were also performed to determine predictors of cancer-specific survival by assessing the association between patient characteristics and cancer-specific survival (Table 3). In the univariate Cox regression analysis, age, BMI, and initial PSA levels were not significantly associated with cancer-specific survival. Similarly, the presence of bone metastasis, visceral metastasis, lung metastasis, liver metastasis, lymph node metastasis, and high volume did not show a significant predictive value. However, the presence of bone lesions ≥10 and a Gleason grade of 5 were found to be significant predictors of cancer-specific survival. In the multivariable Cox regression analysis, the presence of bone lesions ≥10 remained a significant predictor of cancer-specific survival. The adjusted HR for bone lesions ≥10 was 3.185 (95% CI 1.215–8.348). This suggests that patients with bone lesions ≥10 have a higher risk of cancer-related mortality.

**DISCUSSION**

Prostate cancer shows a 5-year survival of >99% in the case of localized lesions but a 5-year survival of 32% in the case of metastatic lesions, and treatment for this has been steadily studied [19]. The introduction of ADT as the first-line treatment has been a significant advancement in disease management. However, the development of mCRPC remains a challenge, and alternative treatments have emerged to address this issue. Chemotherapy agents such as docetaxel and cabazitaxel have shown effectiveness in extending the survival of patients with mCRPC [20-22]. Furthermore, second-generation antiandrogens such as...
abiraterone and enzalutamide have demonstrated promising results by targeting the androgen receptor signaling pathway [23,24]. The CHAARTED and STAMPEDE trials have provided evidence supporting the addition of docetaxel to ADT, resulting in improved overall survival for patients with mHSPC [8,9]. The ARCHES trial also showed the efficacy of enzalutamide in combination with ADT for patients with mHSPC [10].

Recently, the PEACE-1 study and ARASENS trial have shown therapeutic benefits for mHSPC through triplet therapy involving ADT, anti-ARSIs, and docetaxel [11,12]. Although adding ARSIs to docetaxel is said to be beneficial, no evidence suggests its superiority over abiraterone alone. Moreover, triplet therapy in all patients with mHSPC has been associated with higher costs and unexpected side effects than abiraterone alone. In the CHAARTED trial, the rate of adverse events of grade ≥3 among patients who received the docetaxel-containing regimen was 29.6%. The rate of grade 3 or 4 febrile neutropenia was 6.2%; grade 3 or 4 infection with neutropenia, 2.3%; and grade 3 sensory neuropathy and grade 3 motor neuropathy, 0.5% [8].

Consequently, identifying the predictors of the decision to treat using ADT plus abiraterone plus docetaxel as a triplet therapy in patients with mHSPC is important. Therefore, in this study, we aimed to identify predictors of response to abiraterone therapy in patients with mHSPC to determine the patients for whom triplet therapy with docetaxel would be more effective than ADT plus abiraterone therapy.

The study included 167 patients with mHSPC and evaluated various clinical characteristics. The results showed that age, BMI, and initial PSA levels were not significant predictors of CRPC-free survival or cancer-specific survival. However, the presence of bone lesions ≥10 and a Gleason grade of 5 were found to be significant predictors in both univariate and multivariate Cox regression analyses.

In the multivariable Cox regression analysis, adjusting for multiple factors simultaneously, a Gleason grade of 5 (HR, 3.185; p=0.001) remained a significant predictor. This indicates that patients with bone lesions ≥10 have a higher risk of cancer-related mortality.

The findings of this study highlight the importance of considering a Gleason grade of 5 and the presence of bone lesions ≥10 when determining the response to abiraterone therapy in patients with mHSPC. In other words, if a patient has a Gleason grade 5 or bone lesion ≥10, docetaxel as part of the triplet therapy can be added instead of using ADT plus abiraterone therapy.

Several studies have reported predictive or prognostic factors for prostate cancer treatment; however, this study has the following advantages. First, unlike other studies that has evaluated prognostic factors based on response to drug use or treatment results, the present study focuses on identifying prognostic factors at the beginning of treatment. In a retrospective study of patients with mCRPC treated with abiraterone, a PSA response was observed as a prognostic factor [25]; however, this is a factor that can determine the patient’s prognosis after treatment begins. On the contrary, this study has the advantage of examining clinical characteristics before the initiation of abiraterone therapy in patients with mHSPC, which provides early predictive factors for treatment response and assists in treatment selection.

Although studies have investigated prognostic factors in patients with mHSPC, the present study focused on identifying predictive factors for response to abiraterone therapy. It narrows down the analysis to the effects of abiraterone alone, providing insights into the factors that can influence the effectiveness of this treatment modality. In addition, with a sample size of 167 patients, which is relatively large in these conditions, the results of this study are meaningful. In a multicenter, retrospective study of a similar study, a Gleason pattern of 5, performance status, and hemoglobin could be potential predictors of progression-free survival in 112 patients with high-risk mHSPC treated with abiraterone [26].

Finally, this study assessed CRPC-free survival. Usually, many studies have focused solely on overall survival or cancer-specific survival as the primary outcome measure. However, the present study expands the scope by assessing CRPC-free survival as a separate endpoint. By analyzing this distinct survival outcome, the study provides a more...
comprehensive understanding of the effect of prognostic factors on disease progression and cancer-related mortality.

This study has several limitations. First, it is a retrospective study. Second, although the study includes a relatively large number of patients within a particular patient group, the absolute sample size is still relatively small. This limited sample size may affect the generalizability and statistical power of the findings, warranting caution in extrapolating the results to a larger population. Third, the study lacks a comprehensive exploration of the underlying mechanisms that drive the observed results, leaving gaps in understanding the biological and physiological explanations. Fourth, the follow-up period of patients who received abiraterone therapy was short; this may restrict the assessment of long-term treatment outcomes and the durability of the observed effects. Therefore, prospective studies with larger and more diverse patient populations are needed to validate and expand upon the findings of this study.

CONCLUSIONS

The study identified significant predictors of response to abiraterone therapy in patients with high-risk mHSPC. The presence of bone lesions ≥10 and a Gleason grade of 5 emerged as important prognostic factors for CRPC-free survival. Patients with bone lesions ≥10 demonstrated a higher risk of cancer-specific survival. Therefore, adding docetaxel as part of the triplet therapy may be more effective than using ADT plus abiraterone therapy in patients with mHSPC who have these high-risk features.

NOTES

- **Conflicts of Interest:** HJA, a member of the Editorial Board of *Journal of Urologic Oncology*, is the co-author of this article. However, he played no role whatsoever in the editorial evaluation of this article or the decision to publish it. The other authors have nothing to disclose.
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REFERENCES

9. James ND, de Bono JS, Spears MR, Clarke NW, Mason MD, Dearnaley DP, et al. Abiraterone for prostate cancer not pre-


Nonregional Lymph Node Metastasis as a Predictor of Early Progression When Using Androgen Receptor Targeting Agents in Patients With Metastatic Castration-Resistant Prostate Cancer Without Previous Chemotherapy

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Department of Urology, Inha University College of Medicine, Incheon, Korea

INTRODUCTION

Prostate cancer is the most frequently diagnosed solid tumor worldwide and the second leading cause of cancer-related deaths among the male population [1]. Most patients are diagnosed with localized cancer. However, some patients...
develop metastatic disease after the treatment of localized cancer. Moreover, 8% of patients are diagnosed with de novo metastatic hormone-sensitive prostate cancer (mHSPC) [2].

Over the past 15 years, the treatment of metastatic prostate cancer has undergone drastic changes owing to the development of androgen receptor-targeted agents (ARTA) and immuno-targeting agents [3-5]. Based on the development of these drugs, large-scale randomized controlled trial studies using or combining chemotherapy and ARTA have been recently conducted in patients with mHSPC. Therefore, various treatments have progressed away from androgen deprivation therapy (ADT), which was traditionally used to treat mHSPC [6,7].

ARTAs were initially studied in patients with metastatic castration-resistant prostate cancer (mCRPC). In mCRPC, docetaxel chemotherapy has been the preferred first-line drug since the TAX327 study [8]. However, after the publication of the COU-AA-302 [9] and PREVAIL studies [10] conducted in patients with mCRPC who had not received chemotherapy, the introduction of ARTA as a first-line treatment was one of the major changes in mCRPC treatment. In chemo-naive patients with mCRPC, ARTA resulted in a statistically significant improvement in overall survival (OS) [9,10] In addition, the use of ARTA was relatively advantageous even in patients who had difficulty receiving chemotherapy for various reasons [11].

Although it is clear that ARTA helps increase OS in these patients, in practice, some patients still show early disease progression [12]. It is difficult to predict the duration of treatment response to these ARTAs. Therefore, it will be of great help to know the predictive factors when using ARTA as the first-line treatment for mCRPC. Therefore, we investigated the data of patients with mCRPC who received ARTA without chemotherapy at Inha University Hospital. We studied the factors predicting the drug effect-response period of ARTA in mCRPC.

MATERIALS AND METHODS

1. Patients and Study Design

We retrospectively retrieved clinical and pathological data of patients with prostate cancer who received ARTA for mCPRC at Inha University Hospital between January 2010 and January 2023. The Institutional Review Board (IRB) of the Inha University Hospital approved this study (IRB approval No. 2023-07-034). Patients who received chemotherapy before ARTA and those with incomplete pathological or follow-up data were excluded from the study.

mCRPC is defined as the presence of castration levels of testosterone (50 ng/dL or 1.7 nmol/dL) and an increase in prostate-specific antigen (PSA) by more than 50% with 2 consecutive measurements at least 1 week apart and an absolute value of 2.0 ng/dL. Radiographic progression was defined as 2 or more new bone lesions on bone scans or new soft-tissue lesions using the Response Evaluation Criteria for Solid Tumors (RECIST). The clinical characteristics of these patients, including age, body mass index, initial PSA at diagnosis, PSA kinetic, International Society of Urological Pathology grade group (ISUP GG), visceral metastasis, bone metastasis, and lymph node (LN) metastasis (regional and nonregional) were obtained through a review of medical records. In most patients, the initial PSA changes after using ARTA were greatest. Thus, the PSA kinetic was determined based on the change value 3 months after using ARTA.

2. Follow-up

Follow-up was calculated from the time of the start of ARTA to the date of the last known contact with the patient or the date of death. During the follow-up period, PSA level measurement, sequential radiography such as computed tomography (CT) or magnetic resonance imaging (MRI), and bone scanning were performed for efficacy evaluation every 3 months. The currently used ARTA was discontinued, and the regimen was changed to another drug such as another ARTA or chemotherapy, when 2 or more of the following were observed: PSA elevations, radiologic progression, and worsening of clinical symptoms. Radiographic progression was defined as progression in soft-tissue lesions as measured using CT or MRI, according to RECIST criteria, or progression on bone scanning according to criteria adapted from the Prostate Cancer Working Group 3.
3. Statistical Analysis

We compared clinical and pathological characteristics between groups by using Mann-Whitney U-tests for continuous data and χ² tests for dichotomous variables. Univariate and multivariate logistic regression analyses were performed to assess the association between baseline parameters and residual cancer. Significant variables in the univariate analysis were included in the multivariate analysis.

In addition, the Kaplan-Meier method and log-rank test were performed in parallel to estimate and compare the OS rate according to the ARTA response. A p-value of <0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS Statistics ver. 23.0 (IBM Co., Armonk, NY, USA).

RESULTS

1. Patient and Disease Characteristics

Seventy patients with mCRPC received ARTA without chemotherapy and were included in the study. The median follow-up duration from ARTA start was 16.95±13.79 months. The mean age for all patients was 76.07±8.09 years. Among the pathology specimens, 5 (7.1%) exhibited ISUP GG 3, 18 (25.7%) exhibited ISUP GG 4, and 47 (67.1%) exhibited ISUP GG 5.

The mean initial PSA value at the diagnosis of prostate cancer was 355.64±788.54 ng/mL. At the time of ARTA initiation, 62 patients (88.6%) had bone metastases, 30 (42.9%) had visceral metastases, and 39 (55.7%) had LN metastasis. Among them, 17 had limited regional LN metastasis and 22 had nonregional LN metastasis. The mean ARTA treatment period until discontinuation owing to cancer progression was 334.9±364.71 days.

We divided the patients into 2 groups, early and late progression groups, according to the cancer response period to ARTA for 12 months. There were 44 and 26 patients in the early and late progression groups, respectively. The characteristics of each group are summarized in Table 1.

2. OS Following First ARTA Response Duration for Prechemo mCRPC

During the follow-up period, cancer-specific deaths were observed in 18 patients (25.7%); 11 and 7 patients in the early

### Table 1. Baseline patient characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (n=70)</th>
<th>Early progression group (n=44)</th>
<th>Late progression group (n=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>76.07±8.09</td>
<td>77.36±6.97</td>
<td>73.88±2.29</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>22.52±3.68</td>
<td>22.29±3.58</td>
<td>22.39±3.9</td>
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<tr>
<td>Initial PSA (ng/mL)</td>
<td>355.64±788.54</td>
<td>298.1±453.55</td>
<td>456.9±1173.22</td>
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<tr>
<td>Time to mCRPC (mo)</td>
<td>37.04±32.64</td>
<td>33.93±31.28</td>
<td>42.13±34.79</td>
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<td>Follow-up (mo)</td>
<td>16.95±13.77</td>
<td>10.93±11.48</td>
<td>27.14±11.28</td>
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<tr>
<td>ARTA treatment period (day)</td>
<td>334.9±364.71</td>
<td>128.48±69.99</td>
<td>684.23±395.97</td>
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<td>Hb (g/dL)</td>
<td>11.89±2.19</td>
<td>11.65±2.33</td>
<td>12.28±1.9</td>
</tr>
<tr>
<td>ALP (U/L)</td>
<td>280.38±457.88</td>
<td>355.3±556.67</td>
<td>156.46±154.98</td>
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<td>ARTA Medication type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abiraterone</td>
<td>27/70 (38.57)</td>
<td>14/44 (31.82)</td>
<td>13/26 (50.00)</td>
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<td>Enzalutamide</td>
<td>43/70 (61.43)</td>
<td>30/44 (68.18)</td>
<td>13/26 (50.00)</td>
</tr>
<tr>
<td>Gleason grade group</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ISUP GG3</td>
<td>5/70 (7.14)</td>
<td>3/44 (6.82)</td>
<td>2/26 (7.69)</td>
</tr>
<tr>
<td>ISUP GG4</td>
<td>18/70 (25.71)</td>
<td>12/44 (27.27)</td>
<td>6/26 (23.08)</td>
</tr>
<tr>
<td>ISUP GG5</td>
<td>47/70 (67.14)</td>
<td>29/44 (65.91)</td>
<td>18/26 (69.23)</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>62/70 (88.57)</td>
<td>37/44 (84.09)</td>
<td>25/26 (96.15)</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td>30/70 (42.88)</td>
<td>22/44 (50.00)</td>
<td>8/26 (30.77)</td>
</tr>
<tr>
<td>Lymph node metastasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional</td>
<td>17/70 (24.29)</td>
<td>9/44 (20.45)</td>
<td>8/26 (30.77)</td>
</tr>
<tr>
<td>Nonregional</td>
<td>22/70 (31.43)</td>
<td>18/44 (40.91)</td>
<td>4/26 (15.38)</td>
</tr>
</tbody>
</table>

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

BMI, body mass index; PSA, prostate-specific antigen; mCRPC, metastatic castration-resistant prostate cancer; ARTA, androgen receptor targeting agents; Hb, hemoglobin; ALP, alkaline phosphatase; ISUP GG, International Society of Urological Pathologists grade group.
and late progression groups, respectively, had cancer-specific deaths. Additionally, the Kaplan-Meier curves showed a significant increase in OS in the late progression group for ARTA (log-rank test, p=0.001) (Fig. 1).

3. Predictors Associated With First ARTA Response Duration for Prechemo mCRPC

In this study, we used univariate and multivariate logistic regression analyses to identify predictors of ARTA response duration.

In these analyses, age (odds ratio [OR], 1.154; 95% confidence interval [CI], 1.043–1.251; p=0.005) and nonregional LN metastases (OR, 8.819; 95% CI, 1.165–66.746; p=0.035) were independent predictors of ARTA response duration in prechemo mCRPC in both univariate and multivariate models (Table 2).

DISCUSSION

Currently, the primary standard treatments for mCRPC are chemotherapy and ARTA [13]. Although no direct randomized controlled trials (RCT) study has been conducted among these treatments, it is difficult to determine which treatment is superior through a meta-analysis [14,15]. Therefore, the optimal treatment of mCRPC has not been determined. Both ARTA and chemotherapy have become standard treatments, and currently, the choice of drugs depends on the clinician’s judgment.

The usefulness of ARTA for oncologic outcomes in chemotherapy-naive patients with mCRPC has already been demonstrated in large-scale RCTs [9,10]. However, some studies have shown that docetaxel-based chemotherapy has a good prognosis in patients with mCRPC. In particular, studies have reported that patients with a high tumor burden respond poorly to ARTA [16,17]. However, the definition of high tumor burden is ambiguous across studies. Additionally, not all patients can withstand the adverse effects of chemotherapy [18]. Therefore, ARTA may be the preferred treatment for these patients. The choice of the first-line agent in patients with mCRPC is important when

<p>| Table 2. Univariate and multivariate analyses of factors associated early progression |
|-----------------------------------------|-------------|---------|-------------|</p>
<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.098 (1.022–1.180)</td>
<td>1.154 (1.043–1.251)</td>
</tr>
<tr>
<td>BMI</td>
<td>0.952 (0.820–1.105)</td>
<td>0.996 (0.793–1.210)</td>
</tr>
<tr>
<td>Initial PSA</td>
<td>1.000 (0.999–1.000)</td>
<td>1.003 (0.996–1.010)</td>
</tr>
<tr>
<td>PSA kinetics</td>
<td>0.988 (0.995–1.000)</td>
<td>0.988 (0.968–1.001)</td>
</tr>
<tr>
<td>Time to mCRPC</td>
<td>1.000 (0.999–1.000)</td>
<td>1.000 (0.999–1.001)</td>
</tr>
<tr>
<td>ARTA medication type, abiraterone vs. enzalutamide</td>
<td>0.467 (0.172–1.264)</td>
<td>0.325 (0.065–1.623)</td>
</tr>
<tr>
<td>Gleason grade group, GG3 and GG4 vs. GG5</td>
<td>0.690 (0.242–1.910)</td>
<td>0.281 (0.055–1.429)</td>
</tr>
<tr>
<td>Bone metastasis</td>
<td>0.211 (0.024–1.826)</td>
<td>3.125 (0.147–66.261)</td>
</tr>
<tr>
<td>Regional LNs metastasis</td>
<td>0.579 (0.191–1.754)</td>
<td>0.806 (0.141–4.622)</td>
</tr>
<tr>
<td>Nonregional LNs metastasis</td>
<td>3.808 (1.121–12.938)</td>
<td>8.819 (1.165–66.746)</td>
</tr>
<tr>
<td>Visceral metastasis</td>
<td>2.250 (0.810–6.247)</td>
<td>1.079 (0.223–5.224)</td>
</tr>
</tbody>
</table>

OR, odds ratio; CI, confidence interval; BMI, body mass index; PSA, prostate-specific antigen; mCRPC, metastatic castration-resistant prostate cancer; LN, lymph node.
considering their response to subsequent treatment. The response to subsequent treatment is unlikely to be better than that of the first treatment. Cross-resistance between treatments, reported in previous studies, is thought to be one of the causes [19]. Antonarakis et al. [20] suggested that the levels of androgen receptor splice variant 7 (AR–V7) in circulating tumor cells are a potentially informative pretreatment prognostic marker [20]. Although the exact mechanisms have not yet been revealed [21], our study showed similar results. For this reason, research on the optimal sequence continues and clinical trials such as the OSTRICh study (NCT03295565), are underway to find the optimal subsequent treatment for patients with mCRPC with poor prognosis [22]. Therefore, it is of great significance to study the factors that predict the response duration to ARTA as the first treatment and determine appropriate treatment sequences for each patient.

In our study, older patients with mCRPC and those with nonregional LN metastases appeared to have poor therapeutic responses to ARTA without chemotherapy. In addition, in our study, OS was low in patients with early progression with first-line ARTA. Previous studies have also predicted responses to ARTA. Verzoni et al. [23] analyzed data from an Italian multicenter database. They reported that the duration of abiraterone response in mCRPC significantly correlated with PSA and ISUP GG. Kato et al. [24] reported that patients with early PSA response to enzalutamide had a good prognosis. Additionally, one study reported that the duration of ADT uses until progression to CRPC had an effect [25]. However, these studies were not limited to prechemotherapy patients with CRPC. A recent study published by Jeong et al. [26] reported that the use of abiraterone in patients with mCRPC before chemotherapy resulted in better results after chemotherapy. Considering the aforementioned cross-resistance, there may be differences between patients with mCRPC without chemotherapy and with chemotherapy. There are few studies on the factors predicting ARTA response duration in chemo-naive patients with mCRPC such as the present study.

Based on our results, we believe that the presence or absence of nonregional LN metastasis has a significant impact on the treatment response to ARTA in chemo-naive patients with mCRPC. Similar to our findings, a previous study published by Ali et al. [27] found that prostate cancer patients with M1a and M1b stages had poor prognoses. Because their study was conducted on patients with mHSPC, it differs from ours. However, because most patients in our study also had M1b, the poor prognosis of patients with M1a and M1b was similar in both studies. Therefore, we believe that it is similar to the aim of our study that patients with M1a and M1b tumors should be considered for more aggressive combination therapy.

Age also showed a statistically significant difference in our study. However, most of the patients included in our study were elderly, with an average age of 76.07±8.09 years. Therefore, it was difficult to perform the analysis based on the age of 75 or 70 years, as in previous studies [28]. In this study, age statistics were conducted using continuous variables, and since all patients were elderly, we think it is difficult to attach great significance to this result. Relatively young patients were indeed treated with ARTA for a long period; however, as in previous studies, the elderly patients included in this study also had no major side effects while using ARTA. Therefore, the use of ARTA is considered safe for elderly patients.

Our study had several limitations. First, this was a retrospective review of data from patients with prostate cancer treated at a single institution, and the number of patients included was small. Therefore, our results were affected by a selection bias, which limits their generalizability, and a multicenter prospective study is warranted. For these reasons, our findings may differ from previous RCT studies [9,10]. For example, it was not statistically significant in patients with visceral metastases. However, our study also showed a tendency for early progression in patients with visceral metastasis. Therefore, we do not mean that it is different from previous RCT studies. In addition, the enrolled patients in the current study were mostly diagnosed with mCRPC that occurred after using only ADT for mHSPC, and the study was limited to mCRPC without chemotherapy. Therefore, it may be difficult to apply the results of this study to patients with mHSPCs. Lastly, in our study, we were unable to conduct a comparative analysis of treatments other than ARTA in mCRPC patients with nonregional LN metastasis. Therefore, in order to find a better treatment, it would be meaningful to conduct additional comparative
analysis on ARTA monotherapy and chemotherapy or ARTA and chemotherapy combination therapy.

Numerous studies have been conducted on mHSPC. Based on these studies, ARTA, chemotherapy, or combination therapy is used in patients with mHSPC [29,30]. Therefore, the number of chemo-naive patients with mCRPC may gradually decrease. However, there are still patients using ADT alone for mHSPC and patients developing mCRPC while using ADT after treatment for localized prostate cancer. Therefore, the first-choice treatment for patients with mCPRC is still important. We believe that this study provides valuable information for patients and clinicians.

CONCLUSIONS

We believe that nonregional LN metastasis is a predictor of early progression when ARTA is used in patients with mCRPC without chemotherapy. Therefore, caution should be exercised when using ARTA as a first-line treatment in patients with mCRPC with nonregional LN metastasis.

NOTES

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REFERENCES

13. Schaeffer EM, Srinivas S, Adra N, An Y, Barocas D, Bitting R,


Negative Delta-Prostate-Specific Antigen Time Ratio as Potential New Marker of Progression-Free Survival in Castration-Resistant Prostate Cancer Patients Treated With First-Line Enzalutamide or Docetaxel

Tae Hwan Kim, Seol Ho Choo, Kang Hee Shim, Sun Il Kim

Purpose: We propose a new potential marker of progression-free survival (PFS) called negative delta-prostate-specific antigen (PSA) time ratio (NDPSATR) and compare it with conventional PSA response, defined as PSA decline ≥50% at 12 weeks from pretreatment baseline (PSAR50) in metastatic castration-resistant prostate cancer (mCRPC) patients treated with first-line enzalutamide (ENZ) or docetaxel (DTX).

Materials and Methods: All patients diagnosed as mCRPC at Ajou University Hospital from 2016 were included. Delta-PSA days is PSA change between 2 consecutive measurements during a regimen multiplied by interval days. A negative delta-PSA days value represents a positive PSA response. NDPSATR is calculated by dividing the sum of days on negative delta-PSA days by total days on the regimen. Student t-test was used to compare mean values and Kaplan-Meier survival curves for PFS were obtained.

Results: Of 57 patients identified, 22 and 35 were treated with ENZ and DTX, respectively. Rates of PSAR50 for ENZ and DTX were 72.7% and 20.6%, respectively. Mean NDPSATR for ENZ and DTX were 0.40 and 0.46, respectively and the difference was not statistically significant. For ENZ, median PFS (mPFS) of PSAR50 and non-PSAR50 were 14.3 and 4.8 months, respectively and there was significant difference in PFS (p=0.002). For DTX, mPFS of PSAR50 and non-PSAR50 were 15.0 and 6.5 months, respectively but there was no significant difference in PFS (p=0.055). At cutoff value of 0.4, rate of NDPSATR ≥0.4 for ENZ and DTX were 36.4% and 62.9%, respectively. For ENZ, mPFS of NDPSATR ≥0.4 and NDPSATR <0.4 were not achieved and 14.1 months, respectively and there was no significant difference in PFS (p=0.895). For DTX, mPFS of NDPSATR ≥0.4 and NDPSATR <0.4 were 9.7 and 6.3 months, respectively and there was a significant difference in PFS (p=0.045).

Conclusions: NDPSATR ≥0.4 may be a good marker of PFS in CRPC patients treated with DTX and may replace PSAR50.

Key Words: Prostate neoplasms, Docetaxel, Prostate-specific antigen, Survival

INTRODUCTION

Serum prostate-specific antigen (PSA) is the most practical, if not the most reliable marker of response to therapy in prostate cancer patients. In castration-resistant prostate cancer (CRPC), PSA has been advocated as one of the markers of response to therapy along with radiologic response and symptomatic response. PSA response, defined
as PSA decline ≥50% at 12 weeks from pretreatment baseline (PSAR50) is the most commonly used marker of progression-free survival (PFS) [1]. Landmark phase 3 studies that gave birth to current standard-of care CRPC regimen, such as docetaxel (DTX) and androgen-receptor targeting agents (ARTAs) all used the rate of PSAR50 as secondary endpoints [2-4]. In real-world, retrospective data, DTX achieved PSAR50 in 41%–56% of CPRC patients which is remarkable, and comparable to 50% observed in the landmark phase 3 study of DTX and estramustine combination [2,5-7]. However, PSA level checked at a predetermined time may not faithfully reflect the efficacy of treatment in all patients equally. Well recognized measures of PSA kinetics such as time to PSA nadir, PSA halving time, PSA doubling time, PSA at 12 weeks, and other PSA-based parameters have shown limited potential as novel predictive markers of progression in DTX-only era [8,9]. Moreover, these PSA-based markers assume that all responders will show initial decline of PSA, which is not always true. In the current era where DTX is not the stand-alone therapy for CRPC patients, timely transition from first-line DTX to an ARTA and vice-versa is important to optimize treatment and prolong patients survival. We introduce a potential new marker of response to therapy based on PSA kinetics named total negative delta-PSA time ratio (NDPSATR) that can be easily evaluated any time and could be used during the course of treatment in CRPC patients.

MATERIALS AND METHODS

Using the clinical data warehouse, all male patients >40 years of age who were prescribed any one of the standard-of care pharmacotherapy agents used in CRPC at Ajou University Hospital were searched. These agents included abiraterone, cabazitaxel, DTX, and enzalutamide (ENZ). Once patients were identified, their history of prescription of antineoplastic agents including hormonal agents along with dosing dates were searched and downloaded in a spreadsheet file. Also, their PSA values along with test dates were searched and downloaded in a spreadsheet file. Then, the 2 spreadsheet files were merged so that patient’s identification number and dosing/test dates are aligned in same reciprocal columns. Sorting the spreadsheet successively in an ascending order for dosing/test dates and for patient identification number gave a report form whereby treatment and response (PSA value) are arranged in a chronological order for individual patients. This allowed us to assess the date and value of initial PSA, treatment regimen used, date and value of nadir PSA during the initial androgen-deprivation therapy (ADT), date of CRPC according to the PSA definition of CRPC (>25% increase in serum PSA within 2 consecutive measurements separated by at least 1 week, and an absolute value >2.0 ng/mL) and the last follow-up date, which was usually the date of the last PSA or the date of the last drug prescription. Using appropriate spreadsheet functions, important periods were calculated such as duration of each therapeutic regimen that is equivalent to PFS, initial treatment duration, time to nadir PSA, duration of hormone-sensitive prostate cancer, duration of CRPC, and time to first metastasis if applicable. NDPSATR based on PSA kinetics during a certain regimen were calculated. Delta-PSA days is PSA change between 2 consecutive measurements during a regimen multiplied by interval days. This mimics the pack-year equation, which measures the relative amount of cigarettes smoked by a person over the entire time he/she smoked. A negative delta-PSA days value will represent a positive PSA response and a positive delta-PSA days will represent PSA unresponsiveness. NDPSATR is calculated by dividing the sum of days on negative delta-PSA days by total days on the regimen. PSAR was calculated by dividing PSA change at 12 weeks from the start of the regimen by the baseline PSA. Fig. 1 shows 2 representative examples of PSA kinetics after ENZ and DTX treatment, respectively. For ENZ case (orange line), NDPSATR is calculated as NDPSATR=t1/∑t=0.06. For DTX case (blue line), NDPSATR is calculated as NDPSATR=(t2+t4+t6+t8+t9+t10+t12+t14)/∑t=0.56.

Patients were divided into ENZ and DTX groups according to the first-line treatment given at CRPC. Bivariate correlation analysis was used to calculate Pearson correlation coefficient (PCC) between PSAR and NDPSATR. Kaplan-Meier survival curves for PFS were obtained and the difference was compared using log-rank test. IBM SPSS Statistics ver. 25.0 (IBM Co., Armonk, NY, USA) was used for statistical analyses.
RESULTS

Fifty-seven patients were identified, 22 in the ENZ group and 35 in the DTX group. Clinicopathological data are summarized in Table 1. Figs. 2 and 3 show waterfall plots of PSAR and NDPSATR of individual patients during ENZ and DTX treatment, respectively. In the ENZ group, there was moderate correlation between PSAR and NDPSATR, which was not statistically significant (PCC=0.337, p=0.125). In the DTX group, there was moderate correlation between PSAR and NDPSATR, which was statistically significant (PCC=0.389, p=0.023). The rate of PSAR50 for ENZ and DTX were 72.7% and 20.6%, respectively. Median NDPSATR for ENZ and DTX were 0.35 and 0.47, respectively. Figs. 4–7 show Kaplan-Meier curves for PFS in ENZ and DTX.

Table 1. Clinicopathological characteristics of metastatic castration-resistant prostate cancer patients treated with enzalutamide or docetaxel as the primary therapy

<table>
<thead>
<tr>
<th>Variable</th>
<th>ENZ group (n=22)</th>
<th>DTX group (n=35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean (range)</td>
<td>70.3 (51.6–84.1)</td>
<td>68.2 (51.2–89.5)</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>3</td>
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<td>9</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>10</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Mean follow-up (mo)</td>
<td>27.8</td>
<td>34.1</td>
</tr>
<tr>
<td>Status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing</td>
<td>12</td>
<td>11</td>
</tr>
<tr>
<td>Dead of disease</td>
<td>3</td>
<td>8</td>
</tr>
<tr>
<td>Dead of other cause</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up loss</td>
<td>7</td>
<td>15</td>
</tr>
</tbody>
</table>

Values are presented as mean (range) or number unless otherwise indicated. ENZ, enzalutamide; DTX, docetaxel.

Fig. 1. Two representative examples of PSA kinetics in long-term responders to ENZ and DTX treatment, respectively. PSA, prostate-specific antigen; t, time interval between 2 consecutive PSA measurements; 3M PSAR, 3-month prostate-specific antigen response; NDPSATR, negative delta-PSA time ratio; DTX, docetaxel; ENZ, enzalutamide.

Fig. 2. Waterfall plot of PSAR and NDPSATR for individual patients during first-line ENZ treatment in ascending order for PSAR. ENZ, enzalutamide; NDPSATR, negative delta-PSA time ratio; PSAR, prostate-specific antigen response; PSA, prostate-specific antigen.

Fig. 3. Waterfall plot of PSAR and NDPSATR for individual patients during first-line DTX treatment in ascending order for PSAR. DTX, docetaxel; NDPSATR, negative delta-PSA time ratio; PSAR, prostate-specific antigen response; PSA, prostate-specific antigen.
groups, and compare between PSAR50 and non-PSAR50, and between NDPSATR ≥0.4 and NDPSATR <0.4. In ENZ group, median PFS (mPFS) for PSAR50 and non-PSAR50 were 14.3 and 4.8 months, respectively and there was a statistically significant difference in PFS (p=0.002). In DTX group, mPFS of PSAR50 and non-PSAR50 were 15.0 and 6.5 months, respectively but there was no statistically significant difference in PFS (p=0.055). NDPSATR ≥0.4 for ENZ and DTX were 36.4% and 62.9%, respectively. In ENZ group, mPFS of NDPSATR ≥0.4 and NDPSATR <0.4 were not achieved and 14.1 months, respectively and there was no statistically significant difference in PFS (p=0.895). In DTX group, mPFS of NDPSATR ≥0.4 and NDPSATR <0.4 were 9.7 and 6.3 months, respectively and there was a statistically significant difference in PFS (p=0.045).

**DISCUSSION**

PSA will often rise initially with DTX treatment only to fall gradually, a phenomenon which is rarely seen with ARTA. This flare-up phenomenon has been observed in 11%–15% of CRPC patients on DTX [7,10]. However, most of the patients who showed initial PSA flare-up had their successive PSA decline and demonstrated similar oncological outcome with patients who showed initial PSA response. Other than this initial flare-up, PSA will often fluctuate going up and down during the treatment for a long stable period (Fig. 1). This particular PSA kinetics with DTX may make PSA response
criteria of >50% decline often obsolete. This may also lead to premature termination of DTX when it is still effective. NDPSATR was discovered during an effort to compensate for the unsatisfactory performance of PSAR50 at the clinic. NDPSATR ranges from 0 meaning no PSA response at all to 1 meaning continuous and uninterrupted PSA decline during treatment. In real-world practice, NDPSATR value of 0 coupled with a negative PSAR will signify primary resistance to treatment. As all mCRPC patients will ultimately progress on a treatment, NDPSATR value of 1 signifies either the treatment was prematurely stopped for some reason during a responsive period, or the treatment is still ongoing. As PSA rise usually precedes radiologic progression that mostly determines the discontinuation of a treatment by a few months, it can be expected that NDPSATR value of most patients who had their diseases progressed after an initial response will fall somewhere between 0 and 0.5. Median NDPSATR values of 0.35 and 0.47 are in line with these observations. Cutoff value of 0.4 was set arbitrarily based on our patients’ data showing meaningful prognostic value at this level. Our results showed PSAR50 rate of 73% with ENZ which is comparable to 78% shown in the landmark phase 3 study [3]. However, our PSAR50 rate with DTX was only 21%, which is much lower than results from previous studies and not clearly explained. In addition, PSAR50 was predictive of PFS in ENZ, but not in DTX. On the contrary, NDPSATR ≥0.4 rate was 63% in DTX and only 36% in ENZ. Also, NDPSATR ≥0.4 was predictive of PFS.

Differences in PSA kinetics between ENZ and DTX shown in our study are not new; similar differences are found in the literature. With the advent of ARTAs in the treatment of CRPC, multiple real-world studies have consistently shown that PSA markers exhibiting earlier, and more profound PSA decline after initiation of treatment are strong predictors of good prognosis [11-13]. If the PSA kinetics during first-line ARTAs in CRPC are similar to those during ADT in the initial castration-naïve state, the behavior of PSA during DTX is in sharp contrast. In a retrospective single center analysis of 41 CRPC patients who received DTX as first-line therapy, time to nadir PSA of <16 weeks was an independent predictor of shorter duration of chemotherapy response and shorter time to PSA progression [8]. In another retrospective series, 52 CRPC patients who showed initial sensitivity to DTX were given median holidays of 16 to 18 weeks before initiating DTX retreatment which ranged from 2 to 8 series [9]. In this study, various PSA kinetics were calculated during on- and off-treatment periods of which absolute PSA decline and type I PSA progression (increase of ≥25% from the nadir) were the only independent predictors of survival. On the other hand, PSA decline >50% and absolute and relative PSA values were not independent predictors of survival. In addition, type II PSA progression based on a PSA value above the baseline level, was not predictive of survival.

There are several limitations in our study. The study population was small and there was a significant disparity in the number of patients between the ENZ and DTX groups, making the statistical power limited as a result. A multicenter study would be ideal to prove the usefulness of NDPSATR. Also, the mPFS values used in the study were relatively short. Longer-term observations may be necessary, and additional studies may be required to evaluate PFS over a more extended period. Cutoff value of 0.4 was arbitrary and may not apply universally. NDPSATR presented in this study is the sum of all delta-PSA day values from the start of a regimen to progression, which is not practical as a predicting marker on a par with PSAR50 which is usually obtained at 12 weeks of the start of treatment. An interim NDPSATR should be studied in the future.

**CONCLUSIONS**

NDPSATR ≥0.4 may be a good marker of PFS in CRPC patients treated with DTX and may replace PSAR50 in the future. Further studies should be performed to improve and validate NDPSATR in a larger multicenter cohort.

**NOTES**

- **Conflicts of Interest:** The authors have nothing to disclose.
- **Funding/Support:** This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.
- **Author Contribution:** Conceptualization: SIK; Data curation: THK, KHS; Formal analysis: SIK; Methodology: SIK; Project administration: KHS; Visualization: THK; Writing - original draft:THK; Writing - review & editing:

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REFERENCES

Clinical Significance of Rab27a as a Urinary Biomarker in Patients With Bladder Cancer

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In this paper, the second author was unintentionally omitted. Thus, the second author was added as follows:
Ja Yoon Ku1,2, Md Nazmul Huda2, Eu Chang Hwang3, Chan Ho Lee3, Kyung Hwan Kim5, Dong Deuk Kwon3, Hong Koo Ha2,5
GENERAL INFORMATION

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

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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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1. Research Ethics

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.

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

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The article should record the research plans, objectives, and methods in order, as well as the data analysis strategies and methods implemented to control bias. Sufficient details should be furnished for the reader to understand the method(s) without reference to another work described in the study.
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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.

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Conclusions should be comprehensive, be in accordance with the observations stated in the Results and Discussion sections, and benefit 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.

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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).

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List the first six authors followed by et al.

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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. □
   • Review Articles should be composed of no more than 3,500 words, excluding references, tables, and figures. □
   • 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]. □
   • All references cited in the text must be both listed and cited by the reference number (footnotes are not accepted). □
   • When more than 2 references are cited at a given place in the manuscript, use hyphens to join the first and last numbers of a closed series; use commas without space to separate other parts of a multiple citation. □
   • If there are more than 6 authors in the end-reference list, name only the first 6 authors and then use et al. □

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. □
   • Figures are submitted individually, not incorporated into one file. □
   • The preferred file formats for figures are JPG (JPEG) or TIF (TIFF), with a resolution of 300 dpi or more (Line art should have resolution of 1,200 dpi or more). □
   • Table and figure footnotes should be indicated with superscript symbols in sequence, *, †, ‡, §, ||, ¶, **, ††, ‡‡, etc. □
Highlight of JUO in This Issue

- Perioperative Considerations and Treatment for Advanced Renal Cell Carcinoma
- Influence of Body Composition on the Perioperative and Survival Outcomes of Renal Cell Carcinoma
- Preoperative Renal Artery Embolization Before Radical Nephrectomy for Nonmetastatic Renal Cell Carcinoma: A Propensity Score Matched Analysis
- The Future of Adjuvant Therapy in Renal Cell Carcinoma: Recent Insights and Prospects
- Role of Radiotherapy in Metastatic Renal Cell Carcinomas: An Evolutionary Journey in a Misunderstood Histological Type

Optimal Management for BCG Unresponsive Non-Muscle-Invasive Bladder Cancer

- Optimal Management of Bacillus Calmette-Guérin–Refactory Non–Muscle-Invasive Bladder Cancer in 2023
- Early Experience With Pembrolizumab in Bacillus Calmette-Guérin Unresponsive Non–Muscle-Invasive Bladder Cancer
- Clinical Outcomes of Patients With Variant Histology of Urothelial Carcinoma After Radical Cystectomy

Clinical Predictors of ARTA Response in Metastatic Prostate Cancer

- Predictive Factors of Abiraterone Response in Patients With High-Risk Metastatic Hormone-Sensitive Prostate Cancer
- Nonregional Lymph Node Metastasis as a Predictor of Early Progression When Using Androgen Receptor Targeting Agents in Patients With Metastatic Castration-Resistant Prostate Cancer Without Previous Chemotherapy
- Negative Delta-Prostate-Specific Antigen Time Ratio as Potential New Marker of Progression-Free Survival in Castration-Resistant Prostate Cancer Patients Treated With First-Line Enzalutamide or Docetaxel