Round 1:

Dear Editorial Office,

We would like to thank you and the reviewers for your thorough and constructive feedback on our manuscript titled Concurrent Occurrence of Adenocarcinoma and Urothelial Carcinoma in the Prostate Gland: An Uncommon Case Report. Below are our responses to each of the reviewers' comments and the corresponding revisions we have made to our manuscript.

1. **Comment:** It was notable that some previous studies have registered for such cases, for example, PMID: 35288430; PMID: 23671490; PMID: 25847902. It was not appropriate for the authors to say: “first known instance” or “first to document the simultaneous presence” in this paper. Also, it would be better to make a case summary and literature review based on previous studies.

   **Response:** After reviewing the literature, most cases of urothelial carcinoma (UC) in the prostate were found to have a prior history of UC in the urinary bladder. Additionally, the diagnosis of concurrent UC in the urinary bladder and prostate was typically made incidentally following cystoprostatectomy. In the case we present, there was no UC in the urinary bladder. However, the coexistence of UC and adenocarcinoma in the prostate was incidentally discovered during a prostate biopsy. We have revised our manuscript and included literature review to provide a comprehensive context based on previous studies.

2. **Comment:** It seems like the patient received neoadjuvant ADT before the surgery for PC, when did the authors determine to conduct the surgery after
such treatment? A treatment fishbone diagram for the case would be appreciated.

**Response:** The patient initially underwent androgen deprivation therapy for adenocarcinoma of the prostate, as the patient and their family preferred non-surgical intervention. Consequently, leuprorelin and bicalutamide were prescribed for several months, followed by immunotherapy with nivolumab and chemotherapy with gemcitabine and cisplatin for four cycles. Although the patient's PSA level decreased to 8.78 ng/mL after four months of treatment, they sought a second opinion at our hospital. Based on tumor restricted to the prostate stroma without prostatic urethra involvement, confirmed by cystoscopy and MRI and the patient's good Eastern Cooperative Oncology Group performance status, a radical cystoprostatectomy was recommended. However, after thorough discussion and explanation, the patient opted for a robotic-assisted radical prostatectomy and bilateral pelvic lymph node dissection for bladder-sparing surgery. We have added a treatment fishbone diagram to illustrate this process in the revised manuscript.

3. **Comment:** The patient also received gemcitabine and cisplatin, and immunotherapy with nivolumab; these treatments aimed to treat the UC. What is the evidence for these treatments since the stage of UC was very early in this case?

**Response:** Systemic chemotherapy with gemcitabine and cisplatin for four cycles for urothelial carcinoma of the prostate was initially administered at another hospital based on the physician’s clinical experience for the stromal
invasive urothelial carcinoma of the prostate. Second-line systemic immunotherapy with nivolumab was prescribed sequentially. We have provided additional context and references to support these treatment decisions in the revised manuscript.

4. **Comment:** It was not enough for the differential diagnosis by the IHC markers including AMACR, GATA3 in this case, more markers are needed since UC can mimic PC (PMID: 27385897; PMID: 27385897) or invade into the prostate.

**Response:** According to previous research on the differential immunohistochemical profiles used to distinguish between prostate carcinoma and urothelial carcinoma, the sensitivities of prostatic markers in prostate adenocarcinoma were as follows: 100% for PSA, 83.8% for prostate-specific membrane antigen, 91.9% for prostate acid phosphatase, 93.7% for P501s, 88.3% for NKX 3.1, and 66.7% for AMACR. In contrast, the sensitivities of urothelial markers in UC were 75.4% for CK34βE12, 73.9% for p63, 45.7% for thrombomodulin, 22.5% for S100P, and 84.8% for GATA3. The IHC staining results of the prostate sample in our patient showed positivity for both AMACR and GATA3. This strongly suggests the coexistence of adenocarcinoma and UC. We have included these details and further discussion on differential diagnosis markers in the revised manuscript.

5. **Comment:** The potential mechanisms for synchronous PC and UC should be addressed in the discussion.
Response: We propose three possible hypotheses about the potential mechanisms for synchronous adenocarcinoma and UC in the prostate. Firstly, metaplastic transformation may account for this phenomenon. Metaplastic transformation involves the conversion of one differentiated cell type into another. In this context, certain glandular cells within the prostate may have undergone metaplastic transformation into urothelial cells, potentially driven by chronic inflammation or other local environmental factors. Secondly, the presence of multipotent stem cells within the prostate could explain the coexistence of both adenocarcinoma and urothelial carcinoma. Multipotent stem cells have the capacity to differentiate into various cell types, including glandular and urothelial cells. This pluripotency might lead to the simultaneous emergence of adenocarcinoma and urothelial carcinoma in the same tissue. Finally, intraluminal spread of urothelial carcinoma cells from an occult site within the urinary tract to the prostate may be another plausible explanation. This spread could occur without a documented history of primary urothelial carcinoma, particularly if the primary site is very small or has regressed. These hypotheses provide various potential explanations for the simultaneous presence of adenocarcinoma and urothelial carcinoma cells in the prostate. We have expanded the discussion to include these potential mechanisms.

We appreciate the reviewers' valuable comments, which have significantly improved the quality of our manuscript. We hope the revised manuscript now meets the standards for publication in *World Journal of Clinical Cases*. Thank you for your consideration.

Sincerely,
Round 2:

The authors have revised the paper according to the comments; and its quality was improved. I would like to recommend it for publication.