Peer Review File

Article information: https://dx.doi.org/10.21037/tcr-24-726

Reviewer Comments
The article addresses an important and timely topic in the field of urology: the possibility of bladder sparing management for muscle-invasive bladder cancer (MIBC) patients who exhibit a complete clinical response (CCR) to neoadjuvant chemotherapy (NAC). This is significant given the high morbidity associated with the standard radical cystectomy. The focus on combining imaging, tumor biomarkers, and genomic analyses to assess CCR represents a novel approach, aligning well with current trends towards personalized medicine in oncology.

Comprehensive Literature Review: The paper effectively surveys a wide range of studies, including cohort studies and clinical trials, which lend credibility and depth to the discussion.
Innovative Focus: Emphasis on multimodal approaches and the integration of emerging biomarkers and genomic analyses is a significant forward step, highlighting potential shifts in treatment paradigms.

Reply: Thank you for reviewing our paper and for the feedback.

Areas for Improvement:
Comment 1: Clarity and Structure: The transitions between sections could be smoother to enhance readability and coherence. Some parts, particularly the methods and results sections, are densely packed with information, which might benefit from additional subheadings or bullet points for better readability.

Reply 1: Thank you for your feedback. We have taken steps to enhance the clarity and readability of the article. To improve flow, we have added additional subheadings to better organize and group the information in the Results sections. Further, we have refined transitions between sections to create a smoother and more coherent narrative.

Changes in text:

- **Page 4, line 96:** Included subheading "Establishment of Cisplatin-based NAC."
- **Page 4, line 127:** Included subheading "Investigations into Neoadjuvant Immunotherapy."
- **Page 7, line 181:** Included subheading "TURBT-Based Methods to Assess CCR."
- **Page 7, line 218:** Included subheading "Active Surveillance After Varying Methods to Determine CCR."
- **Page 8, line 260:** Included subheading "Risk of Active Surveillance with T Understaging."
- **Page 9, line 269:** Included subheading "Risk of Observation with Undetected Nodal or Micrometastatic Disease."
- **Page 9, line 292:** Included subheading "mpMRI and Establishment of the VI-RADS Score."
- **Page 10, line 309:** Included subheading "Clinical Efficacy of mpMRI."
- **Page 10, line 325:** Included subheading "Circulating Tumor DNA."
- **Page 11, line 352:** Included subheading "DNA Damage Repair Genes."

- **Page 5, lines 143-146:** Improved transition into Section 3.2: "In addition to NAC, recent guidelines strongly recommend RC and pelvic lymph node dissection (PLND) for non-metastatic MIBC within 12 weeks of systemic therapy.3,6,22 While NAC options have improved significantly over recent years, RC continues to be a major abdominopelvic surgery with significant peri- and postoperative morbidity in an older and comorbid population."
- **Page 5, lines 167-168:** Improved transition into Section 3.3: "Before bladder preservation therapy

can become standard of care, a method to accurately assess a CCR to NAC must be established."

- **Page 7, lines 211-212:** Improved transition into Section 3.4: "TURBT-based staging methods alone may be insufficient to determine a CCR. However, since CCR has been shown to be a favorable prognostic factor…"
- **Page 9, lines 289-291:** Improved transition into Section 3.5: "While TURBT-based staging and clinical assessment alone are insufficient in identifying patients who are truly ypT0, a multimodal approach may provide an avenue toward reliably determining a CCR. This multimodal approach is made possible in part by recent advancements in imaging, particularly mpMRI."

Comment 2: Data Presentation: The inclusion of more detailed tables or figures could help in summarizing the results from various studies mentioned, aiding in quicker comprehension of the data presented.

Reply 2. We agree that the inclusion of more detailed tables will improve readability and better summarize the extensive literature on this topic. In response, we have created three additional tables: one summarizing studies that assess the efficacy of TURBT-based methods for evaluating CCR, another detailing studies on the outcomes of active surveillance following CCR, and another detailing studies investigating tumor biomarkers. These are in addition to our existing table on ongoing RCTs and a new table for the methods.

Changes in text: Please see Tables 2-4

Comment 3: Discussion of Limitations: The discussion could more explicitly address the limitations of the current research, including the heterogeneity of study designs and the small sample sizes in some referenced trials. A more detailed exploration of the challenges in clinical implementation of the discussed technologies and methods would provide a balanced view. In addition to imaging and molecular biomarkers, emerging research on the urinary microbiome suggests its potential in BCa diagnostics and prognosis. A recent study found that specific bacteria like Porphyromonas somerae are notably more abundant in BCa patients, particularly males over 50, potentially serving as a non-invasive predictive biomarker (Reference to PMID: 38298766). This finding could enhance the multimodal diagnostic framework, supporting more tailored therapeutic decisions, including the consideration of bladder sparing strategies

Reply 3: Thank you for your suggestions regarding the discussion of limitations and the potential role of the urinary microbiome.

We have addressed the limitations of the studies included in our review more comprehensively. This includes integrating specific limitations throughout the article, as we note in Reply 4 below, with the corresponding text changes.

We have also included a dedicated "Limitations" section (Section 4). In this section, we focus on the overall limitations of the studies but also the challenges in assessing CCR and bladder-sparing management of MIBC. This leads into our exploration of future directions (Section 4.1).

Changes in text (See Page 13, lines 452-471). "4. Limitations…"

Additionally, we have expanded our discussion to include the emerging role of the urinary microbiome in assessing BCa disease status. We highlight its potential as a predictive biomarker for CCR and disease progression, emphasizing its importance to a multimodal approach.
Changes in text (see Page 12, lines 398-415) "The urinary microbiome…"

Comment 4: Critical Analysis: The paper could benefit from a deeper critical analysis of why previous studies have shown variable success and how the proposed multimodal approach could overcome these limitations. A comparison with other existing approaches in terms of cost-effectiveness, patient compliance, and long-term outcomes would enhance the depth of the review.

Reply 4: We have provided a more thorough examination of the limitations of previous cohort and RCTs, focusing on study design as well as methodological challenges to proposed bladder sparing management. Analyses are integrated throughout the article and are also presented in a dedicated "Limitations" section as mentioned above in Reply 3. By detailing these limitations, we support the case for a multimodal approach, given the variability in outcomes observed in prior studies.

Changes in text:

- **Page 7, lines 186-187:** Included limitation of Kukreja et al's assessment of CCR: "However, they were unable to explicitly assess CCR after NAC due to the lack of restaging data following chemotherapy and instead required only cT0 prior to RC."
- **Page 7, lines 192-193:** Included limitation of Kukreja et al. and Becker et al.: "Nonetheless, given their retrospective nature, both studies faced a significant lack of standardization for restaging protocols."
- **Page 7, lines 205-209:** Included limitations of systemic endoscopic evaluation study and suggestion for exploring a multimodal approach: "A limitation to consider is that institution-specific standardized cystoscopy evaluations may limit generalizability and exhibit discordance with clinical practice. Moreover, given these results, clinical staging with cystoscopy and TURBT cannot be safely used as the only surrogate for ypT0. However, showing some success, it may hold value in a multimodal approach to assessing CCR."
- **Page 8, lines 232-234:** Included limitations of Robins et al. and Mazza et al.: "While indicating durable survival with conservative management, they are limited by retrospective design with restrictive selection criteria, as well as non-standardized protocols for surveillance and indication for radical cystectomy."
- **Page 8, lines 256-259:** Included limitations of Herr et al. and approach to AS: "Notably, Herr et al. found that survival outcomes in patients undergoing active surveillance are also influenced by clinical and pathological factors, such as tumor focality and size. These factors may worsen survival outcomes, highlighting the need to consider aspects beyond the specific active surveillance protocols when evaluating bladder-sparing management."
- **Page 9, lines 296-298:** Included limitations of Heule's findings on mpMRI accuracy: "Of note, this study's limited sample size, particularly its inclusion of only 10 patients with NMIBC, may have contributed to a reduced specificity of mpMRI compared to previous studies."
- **Page 9, lines 303-304:** Included limitations of Ahn et al.'s assessment of VI-RADS: "However, the study did not evaluate intra-reader agreement, limiting the assessment of VI-RADS scoring reproducibility."
- **Page 10, lines 317-319:** Included limitations of mpMRI assessment by PURE-01 with similarity to VI-RADS: "However, similar to the VI-RADS system, this protocol is limited by subjectivity and inter-reader disagreement, as internal assessments only identified pT0 in 62% of patients with no evidence of disease on final pathology compared to 73% for externally evaluated patients."
- **Page 11, lines 347-351:** Included limitations of the ABACUS trial and utility of ctDNA with neoadjuvant treatment: "However, this was a single-arm study with patients not on neoadjuvant chemotherapy and largely exploratory in nature, providing limited guidance on using ctDNA to guide therapy. Still, in the neoadjuvant setting, given its significant association with disease status, ctDNA may have substantial predictive value in identifying patients who can safely pursue surveillance after CCR."

Comment 5: Future Directions: While ongoing trials are mentioned, specific suggestions for future research directions could be elaborated, such as potential studies that could address current gaps in knowledge.

Reply 5: Thank you for your suggestion to elaborate on future research directions as this is still a relatively new area of study. We have now included a dedicated section that outlines proposed future directions. This section discusses increasing the power and generalizability of existing studies, as well as new suggestions such as utilizing tumor banks to enhance molecular profiling and its prognostic value, refining the grading of clinical responses to NAC for more tailored interventions, and investigating the applicability and integration of newly developed techniques to assess CCR, as previously mentioned in the review.

Changes in text (Pages 13-14, lines 472-483): "4.1 Future Directions …"