Author's response to reviews

Title: The Diagnostic Value of Circulating Tumor Cell Detection in Bladder and Urothelial Cancer: a Systematic Review and Meta-analysis

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Author's response to reviews: see over
Please find below our responses to each reviewer’s comments:

Reviewer 1:

**Reviewer Comment:** “I read the article - I would call it low priority, well written but not that interesting.”

**Response:** An early step in the metastatic process is the intravasation of tumor cells (circulating tumor cells; CTCs) in the circulation. Although recent advances in molecular techniques have improved the sensitivity of CTC detection, their biological significance is under debate. With regards to bladder and other urothelial cancers, clinical reports have given contradictory results with some studies indicating that CTC detection may be related to higher stage disease while others failed to demonstrate this association.

Because a critical body of published literature evaluating CTC detection in patients with bladder and other urothelial cancers now exists, we used meta-analytic approaches to pool together and quantitatively summarize the available evidence with regards to the diagnostic accuracy of CTC detection in these tumors as well as clarify the association of CTC positivity with higher stage disease. The present paper is the first meta-analysis of circulating bladder cancer cell studies in the literature. Our results indicate that CTC detection has high specificity and can thus be used to confirm the diagnosis of bladder and other urothelial cancers. Furthermore, our meta-analysis demonstrated that CTC detection can be used to identify patients who are more likely to have extra-organ and/or metastatic disease. This key finding was consistently observed throughout subsequent subgroup stratifications. On the other hand, our analysis shows that CTC detection techniques have limited diagnostic sensitivity as they fail to identify approximately two-thirds of patients and show moderate positive and negative diagnostic likelihood ratios. We accordingly concluded that current CTC detection methods are inappropriate for initial bladder/urothelial cancer screening.

Based on the above results and conclusions, we strongly believe that our analysis is of interest and merits publication as it provides a clearer view of the usefulness and limitations bladder/urothelial CTC detection techniques in clinical practice and can guide physicians and clinical investigators who may wish to implement such methods in clinical research or as diagnostic tools.

Reviewer 2:

We would like to thank the reviewer for his helpful comments and constructive input regarding the manuscript. Below is our response to the reviewer’s comments:

**Minor Essential revisions:**

**Reviewer Comment:** “Page 4: Author should correct the sentence in which they claim that bladder is leading cause of morbidity and mortality worldwide. Bladder cancer is not leading cause of mortality worldwide. Lung cancer,
stomach cancer, and liver cancer are among leading causes of cancer-related mortalities.”

Response: This statement was accordingly rephrased.

Reviewer Comment: “Page 5: Immune surveillance (not immunosurveillance) happens everywhere in body, not specifically in lymph nodes. Lymph nodes represent highly specialized lymphoid organs for antigen-presentation and initiation of adaptive immune response.”

Response: This sentence was revised following the reviewer’s comment.

Reviewer Comment: “Page 5: EpCAM is correct abbreviation of this adhesion molecule.”

Response: This abbreviation error has now been corrected.

Reviewer Comment: “Page 7: Meeting abstracts should be excluded from search criteria.”

Response: The exclusion criteria have accordingly been clarified.

Reviewer Comment: “Page 13: DU-145 is prostate cancer cell line. Authors should exclude data which are not related to bladder cancer.”

Response: Following the reviewer’s recommendation, in vitro detection sensitivity data using cells other than bladder/urothelial cancer have been excluded. Page 13 of the manuscript and supplementary table 1 have thus been accordingly revised.