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# Bladder Cancer Recurrence Following Management of Upper Tract Urothelial Carcinoma: Balancing Prevention and Iatrogenicity

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In this issue of *European Urology*, van Doeveren and colleagues [1] report results from the REBACARE trial. This phase 2, single-arm trial included 190 chemotherapy-naïve patients with primary upper tract urothelial carcinoma (UTUC) without prior or concurrent bladder cancer. The study aimed to demonstrate a 40% reduction in the risk of intravesical recurrence (IVR)—from 33.2% to 19.9%—using a single preoperative instillation of mitomycin C (MMC) administered within 3 h of surgery.

First and foremost, the authors are to be commended for successfully establishing a prospective cohort of 190 radical nephroureterectomy (RNU) cases. Conducting high-level studies in UTUC is notoriously challenging. In this context, we, as urologists, should focus on addressing straightforward, practice-changing surgical questions via adequately powered large-scale trials. Unfortunately, the REBACARE trial was negative, with a 2-yr IVR rate of 24%. The study lacked sufficient power to definitively demonstrate the superiority of preoperative MMC instillation in comparison to the expected recurrence rate without MMC instillation. However, several important observations can be made.

1. The IVR rate was notably low in comparison to retrospective findings in the literature. This can be partly attributed to selection of a cohort with no history of bladder cancer. Nevertheless, we cannot rule out the contribution of comprehensive quality management to these results. Notably, quality indicators for UTUC are yet to be systematically implemented.
2. Adherence to preoperative MMC instillation was extremely high.
3. The complication rate associated with the procedure was remarkably low.

One limitation of the trial design is its inability to determine which specific intervention was responsible for reducing the recurrence rate. In this trial, the intervention was not restricted to MMC instillation; patients also underwent continuous saline irrigation of the bladder until the start of bladder cuff excision. The ongoing debate regarding the relative impact of postoperative instillation versus saline irrigation on recurrence rates after transurethral resection of bladder tumor highlights the challenge of interpreting these findings [2,3]. The combination of the two interventions in REBACARE makes it impossible to draw definitive conclusions about the individual effects of either approach. In addition, one of the intended advantages of preoperative over postoperative instillation is its relative simplicity. However, in the context of protocols for early recovery after surgery, the need to maintain a catheter with continuous irrigation for 3 h preoperatively might be perceived as a backwards step.

Comparisons to retrospective historical RNU cohorts without perioperative instillations do little to strengthen the findings. Any differences between the REBACARE cohort and a historical cohort could be attributed to several confounding factors: early ureter clipping (69% vs 25%), differences in stage and grade distribution, perioperative bladder irrigation, diagnostic ureteroscopy rates, and tumor multifocality, among others. While some degree of propensity matching could have been attempted, the sample size is probably insufficient for proper statistical power. This critique applies broadly to much of the existing UTUC literature: confounders are pervasive and the level of evidence for most practice recommendations remains low. Even prospective trials underpinning guidelines for systematic,

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3x lowed IVR for no d-URS

immediate intravesical instillation after RNU suffer from methodological weaknesses, including unbalanced groups, performance and detection biases, and overoptimistic sample size calculations [4,5].

Bladder recurrence is, in part, an iatrogenic consequence of UTUC management. It has been shown that diagnostic ureteroscopy, preoperative biopsies, and tumor mobilization during RNU increase the risk of bladder seeding [6]. In the REBACARE cohort, the risk of IVR was higher for patients who underwent diagnostic ureteroscopy as part of their UTUC workup (hazard ratio 1.83, 95% confidence interval 1.08–3.10; $p = 0.025$). Postoperative instillation to prevent tumor seeding after RNU can also have devastating consequences in cases with MMC leakage, which can lead to chronic pain, abdominal or ureteral obstruction, peritonitis, and even death [7].

The hypothesis behind the REBACARE trial was that preoperative MMC instillation could prevent seeding and that this strategy could avoid the risks associated with postoperative MMC leakage. To formally validate this hypothesis, an ideal study design would be a three-arm randomized trial with sufficient follow-up (ideally 2 yr). The arms would include no instillation, immediate preoperative instillation, and early postoperative instillation. Such a study would need to account for performance and detection biases and ensure a large enough sample size for adequate power and substratification. Is such a trial unrealistic? Probably.

This leaves us with critical unanswered questions.

- Does diagnostic ureteroscopy truly increase the risk of bladder recurrence?
- If so, how can we mitigate this risk without compromising the growing need for ureteroscopy-driven kidney-sparing surgeries?
- Does RNU itself enhance the risk of bladder recurrence?
- If so, how can we adapt surgical techniques to limit this risk and effectively treat the bladder to reduce recurrence without exposing patients to life-threatening complications from MMC leakage?

Although enormous efforts are required, uniting to address one well-defined question at a time with sufficient power could drive meaningful changes in patient treatment.

***Conflicts of interest***: The author has nothing to disclose.

*Use of generative AI and AI-assisted technologies*: During the preparation of this manuscript, the author used ChatGPT to improve the English. After using this tool, the author reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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