

Intravesical instillation of chemotherapy before surgery for upper tract urothelial cancer

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Urothelial cancer that occurs in the bladder following radical surgery for upper tract urothelial cancer (UTUC) occurs in 22–47% of cases within two years.^{1,2} There are many proposed reasons for this occurring including the possibility of pan-urothelial cancer diathesis, recurrence of previously treated bladder cancer, technical factors including not taking a complete bladder cuff at the time of radical nephroureterectomy (RNU),³ not clipping the distal ureter early on in the case,⁴ or whether/and how the diagnosis of UTUC was made, as evidence of a contributory role for diagnostic ureteroscopy has become compelling.⁵ To try to reduce this recurrence rate, two randomized prospective trials (each with their own flaws) have “demonstrated” that a single postoperative instillation of chemotherapy^{6,7} does reduce one- and two-year bladder recurrences. However, in part because of concern about potential extravasation of the chemotherapy, postoperative instillations have not been widely adopted into practice.^{7,8}

For this reason, van Doeveren and colleagues conducted a single arm trial (REBACARE) to determine if a preoperative instillation of mitomycin C (MMC) within three hours before RNU (or distal ureterectomy and bladder cuff) could reduce recurrence within the bladder.⁹ Because UTUC is relatively uncommon, the authors felt that a randomized trial was impractical to conduct, so as a comparator control group a historical cohort of patients with pT any, N0-N1, M0 UTUC without any prior (or concurrent) bladder cancer, who had undergone radical surgery for UTUC in four Dutch hospitals between 2000–2018 and an international retrospective cohort (2005–2020) from 18 institutions across Europe, Asia and the United States^{10,11} was used. Eligible patients for the REBACARE trial conducted from 2017–2020 came from 18 Dutch hospitals, could not have had prior or concomitant bladder cancer, contralateral UTUC, prior intravesical chemotherapy or >50% variant histology if a prior biopsy was done.

Participants received 40 mg MMC in 50 ml saline within three hours before surgery. The chemotherapy remained in the bladder for 1–2 h and then continuous saline irrigations

were given up to the time of taking the bladder cuff. The distal ureter was clipped early in the case, and a formal bladder cuff taken. No patient received prior systemic therapy for UTUC. Follow up after RNU included cystoscopy and cytology every three months for two years with mandatory transurethral resection/biopsy of any suspicious lesions and computed tomographic (CT) imaging every 6 months for two years. The authors assumed a 33.2% recurrence rate at two years without intravesical (pre or post operative) chemotherapy would improve by 40% (to <20% recurrences by two years). Secondary endpoints were compliance with, and toxicity from the preoperative MMC instillation, increased recurrence-free, metastasis-free, cause specific and overall survival.

So, what did they find? Almost all of the 186 patients who agreed to take part in the study received preoperative MMC (96.2%) but eight were excluded from analysis for intravesical recurrence because they had no cancer or >50% variant histology on the surgical specimen. 178 patients were analyzed. Importantly, the reference cohort was not identical to those in the REBACARE group including the former undergoing fewer preoperative diagnostic ureteroscopies (45% “control” vs 59% REBACARE) and ureteral clipping (25% controls vs 69% REBACARE) and the reference group had higher-pathological stage disease in general (pT3a 37% vs. 28% REBACARE, pTa 23% vs. 35% REBACARE). However, 44% of patients in the REBACARE group were not treated according to protocol including no bladder cuff excision, no ureteral clipping, and variations in the duration of MMC instillations and the time from instillation to surgery. The instillation of MMC was

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safe and well tolerated with only 7.4% Clavian grade ≥ 3 complications- none related to the MMC instillation.

Was the treatment effective in preventing bladder cancer occurrence at two years? This was only found in the minority of REBACARE patients who had not had preoperative diagnostic ureteroscopy ($P = 0.025$) compared with the reference cohort (who had not undergone ureteroscopy); but for the over all REBACARE cohort the two-year bladder cancer occurrence rate was 24% vs 26% in the reference cohort, not remotely reaching the prespecified goal of reducing intravesical recurrences by 40%. However, it had already been reported that preoperative ureteroscopy (particularly with biopsy) might lead to increased risk of bladder cancer,^{5,12,13} although those reports were published after the REBACARE cohort began accruing (2017). Moreover, details about how ureteroscopy was preformed (e.g., ureteral dilation, post operative stent insertion, rigid or flexible ureteroscopy, use of ureteral access sheath to perform ureteroscopy – particularly with biopsy) all of which theoretically can (and probably do) affect the likelihood of subsequent bladder cancer developing^{14,15} were not reported for the REBACARE or reference cohorts. Additionally, while patients in the REBACARE cohort could not have had prior intravesical chemotherapy before the MMC instillation and RNU, such instillation immediately after ureteroscopy $\pm$ biopsy have been proposed as a means of preventing intravesical recurrences.^{12,16} Finally, at least in the United States where these patients are admitted the day of surgery it is cumbersome for busy hospital units to admit patients several hours early for the preoperative chemotherapy instillation, let alone the extra psychological burden on patients and their families for this to take place.

Thus, for all the reasons above, while pre RNU intravesical MMC instillations are safe and well tolerated, given the limitations of this trial (including its lack of randomization, non-identical control group—particularly in factors which affect intravesical recurrence rates, the issues concerning preoperative ureteroscopy, the logistical matters discussed, and the trial's negative results) it's difficult to conclude that this is an advance that will be widely adopted into clinical practice, when the two positive randomized prospective trials of post RNU intravesical chemotherapy have not been.

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