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Original Article

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Intravesical Instillation of Chemotherapy Before Radical Surgery for Upper Urinary Tract Urothelial Carcinoma: The REBACARE Trial

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Abstract

Background and objective: Intravesical instillation of chemotherapy (IIC) after radical surgery for upper urinary tract urothelial carcinoma (UTUC) reduces the risk of intravesical recurrence (IVR). However, compliance is low because of possible extravesical leakage after bladder cuff excision. The aim of this study was to evaluate the efficacy of preoperative IIC in reducing the risk of IVR.

Methods: In this prospective, single-arm, multi-institutional, phase 2 clinical trial, 190 chemonaïve patients with primary UTUC without prior or concurrent bladder cancer received a single intravesical instillation of mitomycin C for 1–2 hr within 3 h before surgery. The primary endpoint was the 2-yr histologically confirmed IVR rate, with a target reduction of >40% (from 33.2% according to literature data to <20%). A historical cohort of 247 patients with UTUC who did not receive perioperative IIC served as the reference. Secondary endpoints included compliance, toxicity, and IVR-free survival, which was

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Phase 2 trial
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analyzed via multivariable Cox regression and stratified by previous diagnostic ureteroscopy (d-URS).

Key findings and limitations: The 2-yr IVR rate was 24% (95% confidence interval [CI] 18–31%) on intention-to-treat analysis and 23% (95% CI 13–32%) on per-protocol analysis. Multivariable analysis revealed that d-URS was associated with higher IVR risk. In the REBACARE cohort, patients without d-URS had threefold lower IVR risk (hazard ratio 0.33, 95% CI 0.12–0.87) in comparison to the reference cohort. Compliance with preoperative instillation was 96% and no grade >2 toxicity occurred.

Conclusions and clinical implications: Preoperative IIC with mitomycin C was feasible and well tolerated and significantly reduced IVR risk for patients without d-URS. These findings suggest that preoperative IIC is a viable strategy for this subset of UTUC patients and that d-URS should be performed judiciously.

ADVANCING PRACTICE

What does this study add?

This phase 2 clinical trial demonstrated that a single preoperative intravesical instillation of mitomycin C significantly reduced the 2-yr rate of intravesical recurrence (IVR) in patients with upper urinary tract urothelial carcinoma (UTUC) undergoing radical surgery without prior diagnostic ureteroscopy. The intervention had a high compliance rate of 96% and was well tolerated, with no significant toxicity observed. The results indicate that diagnostic ureteroscopy is an important risk factor for IVR in primary UTUC and should be performed judiciously.

Clinical Relevance

The role of diagnostic ureteroscopy in patients with upper tract urothelial cancer has been increasingly scrutinized. While the effectiveness of a single postoperative intravesical instillation of mitomycin C following nephroureterectomy in reducing the risk of intravesical recurrence is well established, this prospective, single-arm, multi-institutional phase 2 clinical trial sought to explore its impact further. Chemo-naïve patients with primary upper tract urothelial cancer, without prior or concurrent bladder cancer, received a single instillation of mitomycin C within three hours before undergoing nephroureterectomy or distal ureterectomy with ipsilateral bladder cuff excision. Their outcomes were compared to a historical cohort that did not receive this preoperative treatment. Although the trial did not achieve its prespecified goal of reducing the two-year intravesical recurrence rate by more than 40%, it identified a significant reduction in recurrence among patients who did not undergo diagnostic ureteroscopy as part of their preoperative evaluation. Notably, patients who underwent diagnostic ureteroscopy exhibited a five-fold higher risk of intravesical recurrence, emphasizing the importance of a cautious approach to its use. This study supports preoperative intravesical mitomycin C as a feasible and well-tolerated intervention that significantly reduces the risk of intravesical recurrence in patients with upper tract urothelial cancer who do not undergo diagnostic ureteroscopy prior to radical surgery. Associate Editor: Sarah P. Psutka, MD MS.

Patient Summary

Our clinical trial showed that a single bladder instillation with chemotherapy before surgery for cancer in the upper urinary tract was safe and feasible. This treatment reduced the 2-year risk of bladder cancer recurrence in patients who had not undergone ureteroscopy, in which a small telescope is inserted up through the bladder into the ureters.

1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) has an annual incidence rate of two to three cases per 100 000 individuals in Western Europe and accounts for 5–10% of urothelial carcinoma diagnoses, with a notable increase in incidence in recent decades [1–4]. Patients with non-metastatic UTUC undergo radical nephroureterectomy (RNU) with excision of the ipsilateral bladder cuff, with or without lymph node dissection [2]. Adjuvant platinum-based systemic chemotherapy is recommended for patients with locally advanced UTUC to improve disease-free survival [2,5]. In selected patients with low-risk UTUC, kidney-sparing surgery is an alternative treatment option [2].

A significant challenge in the clinical management of UTUC is the high risk of intravesical recurrence (IVR) after RNU. The rate of IVR within 2 yr for patients who did not receive a perioperative intravesical instillation has been reported as 22–47% [6,7]. It is hypothesized that IVR arises from seeding of cancer cells from the upper urinary tract

to the bladder, which might occur before clinical diagnosis [8–10]. It has been reported that diagnostic ureteroscopy (d-URS), used in the diagnostic workup for UTUC, is associated with higher risk of IVR [11,12].

Current guidelines recommend a single postoperative intravesical instillation with chemotherapy to mitigate IVR risk [2,13,14]. However, adoption of this strategy in clinical practice is hampered by concerns over extravesical chemotherapy leakage after bladder cuff excision, which can lead to severe morbidity and even mortality [15–20].

We hypothesized that an intravesical instillation of chemotherapy immediately before radical surgery for UTUC may offer a comparable reduction in IVR risk without the risk of extravesical leakage and could potentially enhance physician compliance. Therefore, we initiated the Reduce Bladder Cancer After Radical Nephroureterectomy (REBACARE) study to assess the efficacy, safety, and compliance rate with a preoperative Mitomycin C (MMC) instillations in patients with nonmetastatic localized primary UTUC scheduled for radical surgery.

2. Patients and methods

2.1. Study population

Eligible participants were adults diagnosed with primary UTUC, stage cTanyN0-1M0, scheduled for radical surgery. The UTUC diagnosis relied on a biopsy during d-URS and/or computed tomography (CT) urography together with urine cytology suspicious of high-grade urothelial cancer cells. Surgery comprised open or laparoscopic (conventional or robotic) RNU or partial ureterectomy with ipsilateral bladder cuff excision. Exclusion criteria included prior or synchronous bladder carcinoma, contralateral UTUC, prior intravesical chemotherapy, >50% aberrant histology on preoperative biopsy, MMC allergy, acute urinary tract infection (UTI), or pregnancy. Patients with postoperative histology showing absence of cancer or >50% aberrant histology were also excluded, as well as patients who received a postoperative instillation with chemotherapy.

The study, approved by the institutional review board of the Erasmus Medical Center, obtained enforceability permission for all sites (METC 2017-227 NL60919.078.17). It adhered to the Declaration of Helsinki and Good Clinical Practice and was registered at clinicaltrialsregister.eu (EudraCT number: 2017-000949-53). All patients provided written informed consent before study inclusion. The informed consent procedure has been previously described in detail [21].

2.2. Study design

The single-arm phase 2 REBACARE trial was conducted across 18 Dutch hospitals. Patients were included from November 2017 to August 2020 and received a single intravesical MMC instillation (40 mg in 50 ml of sterile saline) within 3 h before radical surgery. MMC was administered via an indwelling catheter and had to remain in the bladder for 1–2 h, if tolerable for the patient. The bladder was then continuously rinsed with 0.9% NaCl solution to remove MMC remnants and possible floating tumor cells. Bladder irrigation continued during radical surgery and was stopped at the start of bladder cuff excision. Surgery had to commence within 3 h after removal of MMC. RNU or partial ureterectomy was performed in accordance with local guidelines in the participating centers, but the distal ureter had to be clipped at the beginning of the procedure after first identification of the ureter. En bloc bladder cuff excision was mandatory when possible. The decision on whether to perform lymph node dissection was at the discretion of the treating physician. Follow-up was in accordance with the European Association of Urology (EAU) UTUC guidelines, encompassing cytology and cystoscopy every 3 mo and CT imaging every 6 mo for 2 yr. If cystoscopy findings were suspicious for bladder tumor, transurethral biopsy or resection of the tumor was mandatory. Toxicity and adverse events were assessed using the National Cancer Institute Common Toxicity Criteria v4.0 and Common Terminology Criteria for Adverse Events v4.0 from inclusion up to 6 mo after surgery, and were reported using the Clavien-Dindo classification [22].

2.3. Endpoints and sample size calculation

The primary endpoint was the histologically confirmed 2-yr IVR rate. Using literature data, we estimated that the 2-yr IVR rate after RNU in the absence of postoperative instillation is 33.2% [7,13,14,23,24]. By assuming a >40% reduction in IVR risk (from 33.2% to 19.9%), because of the beneficial effect of preoperative chemotherapy instillation, a total of 170 patients was required for the REBACARE trial (two-sided superiority test for comparing two independent proportions; power of 80%, two-sided p value of 0.05). Inclusion was increased to 190 because of a larger than expected number of dropouts (MEC-2017-227, amendment 10, March 19, 2020, NL60919.078.17, v11).

Secondary endpoints included the compliance and toxicity rates for preoperative MMC instillation, and IVR-free, metastasis-free, cancer-specific, and overall survival. For calculation of metastasis-free survival, patients were censored at the date of their last CT imaging scan. For cancer-specific and overall survival, patients were censored at the last date on which they were alive.

2.4. Reference cohort

A historical cohort of patients with primary pT any N0–1 M0 UTUC treated with radical surgery with no intravesical chemotherapy (either before or after surgery) and no history of bladder cancer served as the reference group. The group comprised patients from four Dutch hospitals (2000–2018) and an existing international retrospective cohort (2005–2020) from 18 institutions across Europe, Asia, and the USA [25,26]. The goal of the REBACARE trial was to assess the efficacy of preoperative intravesical MMC instillation in reducing the risk of IVR in comparison to this historical UTUC cohort.

2.5. Statistical analysis

Descriptive analyses were performed to characterize the patient, tumor, and treatment characteristics of the REBACARE and reference cohort. Time-to-event endpoints were

assessed using the Kaplan-Meier method and Cox proportional-hazards regression and were calculated from time of inclusion (T0). The primary endpoint was evaluated in intention-to-treat and per-protocol analyses. Multivariable Cox proportional-hazards regression, adjusted for various factors, including d-URS (yes vs no) as an *interaction term* was used to assess whether d-URS had different effects in the study cohorts. The model including the interaction between d-URS and cohort showed a statistically better fit to the data than a model with the main effects alone ($p = 0.019$). A detailed description of the statistical analyses is provided in the Supplementary material. Analyses were performed using SPSS version 28.0.1 (IBM, Armonk, NY, USA) and R version 4.3.1. (R Foundation for Statistical Computing, Vienna, Austria).

3. Results

3.1. Patient characteristics and compliance rate

Between November 2017 and August 2020, 190 patients were enrolled in the REBACARE trial (Fig. 1). Twelve

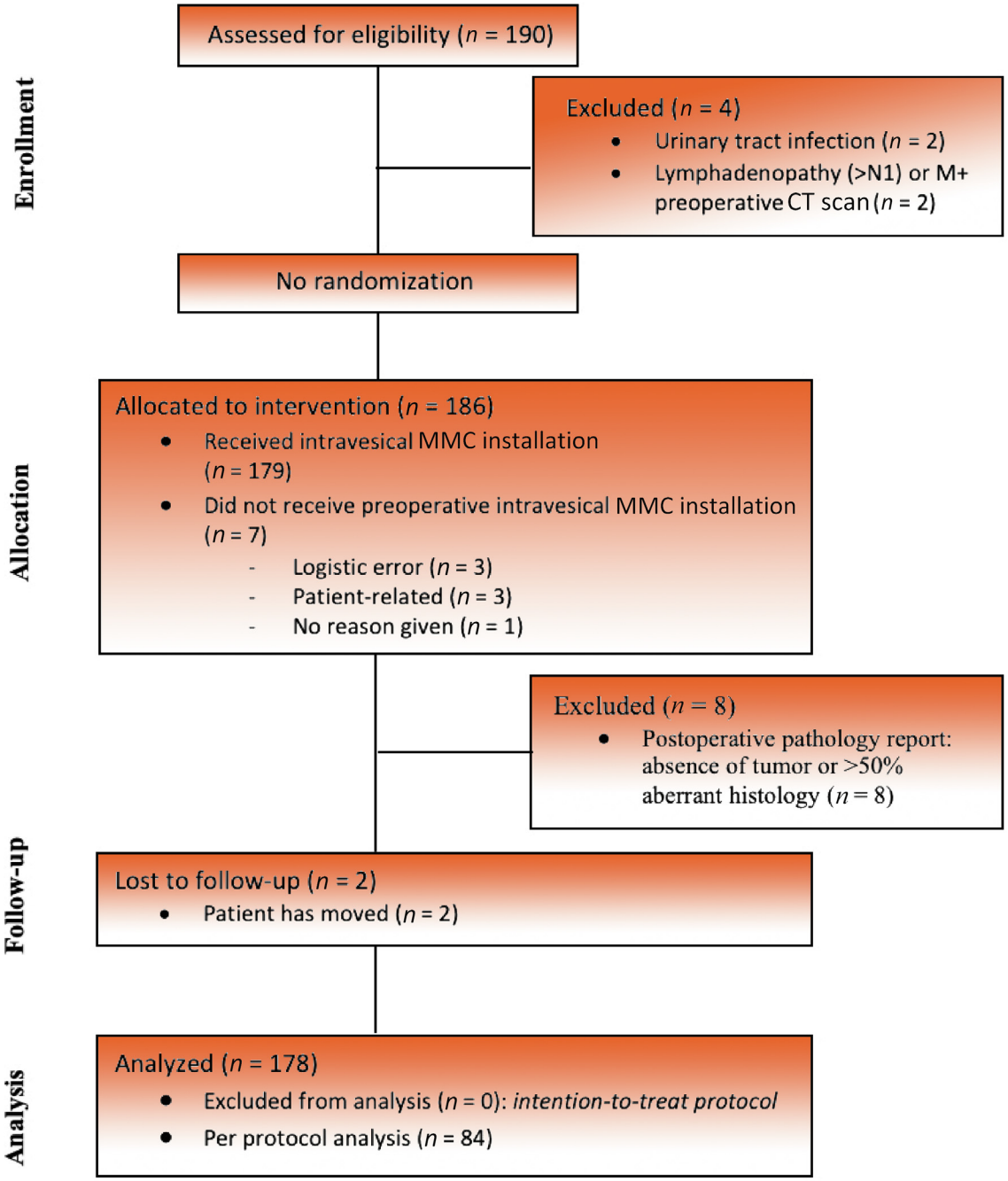

Fig. 1 – Flow diagram for the REBACARE trial according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines. Of 190 patients with primary upper tract urothelial carcinoma, 186 met the inclusion criteria. No randomization was performed because of the single-arm design. A total of 179 patients ultimately received an intravesical MMC instillation before surgery. After surgery, eight patients were excluded because of the absence of tumor or >50% aberrant histology, leaving a total of 178 patients for inclusion in the intention-to-treat analysis. CT = computed tomography; MMC = mitomycin C.

patients were excluded: eight because of the absence of cancer or >50% aberrant histology in the surgical resection specimens, and four because they did not meet the inclusion criteria (two with acute UTI and two with lymphadenopathy >cN1 and/or distant metastasis on preoperative CT imaging; Supplementary Table 1). Most patients were male (69%) and the median age was 70 yr (interquartile range [IQR] 63–75; Table 1). A d-URS procedure was performed in 104 patients (59%), with biopsy in 78 (44%). The vast majority of patients (n = 169, 95%) underwent RNU, with lymphadenectomy in 32 (18%). Pathological T stage was ≥pT2 in 79 patients (42%) and six (7.6%) were staged as pN+.

Table 1 – Baseline characteristics of patients with primary upper urinary tract urothelial carcinoma (any cT stage, N0–1, M0) in the REBACARE trial and the historical reference cohort

Parameter	REBACARE trial (n = 178)	Reference cohort (n = 247)
Female, n (%)	55 (31)	83 (34)
Median age, yr (interquartile range)	70 (63–75)	69 (60–76)
Age category, n (%)		
<50 yr	9 (5.1)	10 (4.0)
50–59 yr	20 (11)	50 (20)
60–69 yr	53 (30)	67 (27)
70–79 yr	85 (48)	90 (36)
>80 yr	11 (6.2)	30 (12)
Preoperative urinary cytology, n (%)		
Not done	26 (15)	83 (34)
Benign	54 (30)	68 (28)
Atypia/inconclusive	39 (22)	4 (2)
High grade, malignant	57 (32)	38 (15)
Data missing	2 (1.1)	54 (22)
Diagnostic ureteroscopy, n (%)		
No	73 (41)	128 (52)
Yes, without biopsy	26 (15)	41 (17)
Yes, with biopsy	78 (44)	70 (28)
Data missing	1 (0.6)	8 (3)
Type of surgery, n (%)		
Radical nephroureterectomy, open	22 (13)	43 (17)
Radical nephroureterectomy, laparoscopic/robot-assisted	147 (83)	195 (79)
Partial ureterectomy, open	5 (2.8)	8 (3.2)
Partial ureterectomy, laparoscopic/robot-assisted	4 (2.2)	0 (0)
Lymph node dissection, n (%)	32 (18)	32 (13)
Data missing	4 (2.3)	0 (0)
Pathological tumor stage, n (%)		
pTis	4 (2.3)	28 (11)
pTa	63 (35)	57 (23)
pT1	31 (17)	36 (15)
pT2	25 (14)	8 (3.2)
pT3	49 (28)	91 (37)
pT4	5 (2.8)	27 (11)
pTx	1 (0.6)	0 (0)
Tumor grade, n (%)[a]		
Grade 1	19 (11)	8 (3.2)
Grade 2	70 (39)	39 (16)
Grade 3	81 (45)	51 (21)
Data missing	8 (4.5)	149 (60)
Lymph node involvement, n (%)		
N0	25 (14)	39 (16)
N1	6 (3.4)	7 (2.8)
N2	1 (0.6)	0 (0)
Nx	146 (82)	201 (81)
Concomitant carcinoma in situ, n (%)	17 (10)	41 (17)
Data missing	2 (1.1)	4 (1.6)
Primary tumor location, n (%)		
Renal pelvis or proximal ureter	122 (69)	173 (70)
Mid- or distal ureter	56 (32)	74 (30)
Multifocality, n (%)	23 (13)	50 (20)

[a]World Health Organization 1973 classification.

Clinicopathological characteristics of the REBACARE and reference cohort were largely similar, except for distribution of previous d-URS (59% vs 45%), clipping of the ureter (69% vs 25%), proportion of patients with pT3 (28% vs 37%) and pTa stage (35% vs 23%), and multifocality (13% vs 20%).

A total of 171 patients (96%) received preoperative MMC instillation (Supplementary Table 2). The median instillation duration was 75 min (IQR 60–105), with surgery starting at a median of 105 min after removal of the MMC instillation. Eighty-four patients (44%) were not treated according to the study protocol for the following reasons: no bladder cuff excision (n = 20), no ureter clipping (n = 32), instillation duration <60 min (n = 14), and initiation of radical surgery >3 h after MMC instillation (n = 24).

Median follow-up was 24 mo (IQR 24-24) for patients without IVR or death in the REBACARE trial, and 24 mo (IQR 20–24) for the historical cohort.

3.2. IVR rate

On intention-to-treat analysis, the 2-yr IVR rate was 24% (95% CI 18–31%), so the prespecified risk reduction target of >40% (IVR rate <20%) was not achieved. The median time to IVR was 7.5 mo (IQR 5.0–14.0) and the IVR-free survival rate at 1 yr was 83% (95% CI 78–89%). In the reference cohort, the 2-yr IVR rate was 26% (95% CI 20–31%). The 2-yr IVR-free survival was 75% (95% CI 69–82%) in the REBACARE cohort versus 70% (95% CI 64–77%) in the reference cohort (Fig. 2A, B). On per-protocol analysis, the 2-yr IVR rate was 23% (95% CI 13–32%). As the IVR rates were similar for the per-protocol and intention-to-treat analyses, subsequent analyses were limited to the latter.

For the REBACARE subgroup of patients who did not undergo d-URS (n = 73, 41%), multivariable analysis revealed threefold lower risk of IVR (hazard ratio [HR] 0.33, 95% CI 0.12–0.87; p = 0.025) in comparison to patients without d-URS in the reference cohort (Table 2, Fig. 3, and Supplementary Table 3). For the REBACARE subgroup of patients who underwent d-URS as part of their UTUC workup, the risk of IVR was significantly higher (HR 1.83, 95% CI 1.08–3.10, p = 0.025). In the reference cohort, the risk of IVR was higher for the subgroup with a history of d-URS than for those without d-URS, but the difference did not reach statistical significance. Lastly, UTUC located in the mid- or distal ureter was associated with higher risk of IVR in both cohorts.

To assess whether there was an association between the date of radical surgery and the risk of IVR in the reference cohort, a new model that included year of surgery was developed using the predictors from the model described above. This new model showed that year of surgery was not a significant predictor for IVR (HR 1.04, 95% CI 0.98–1.11) and no adjustments for trends over time were necessary.

3.3. Survival in the REBACARE cohort

In the REBCARE cohort, 2-yr survival rates were 77% (95% CI 71–83%) for metastasis-free survival (Supplementary Fig. 1), 90% (95% CI 85–94%) for cancer-specific survival, and 86% (95% CI 81–91%) for overall survival.

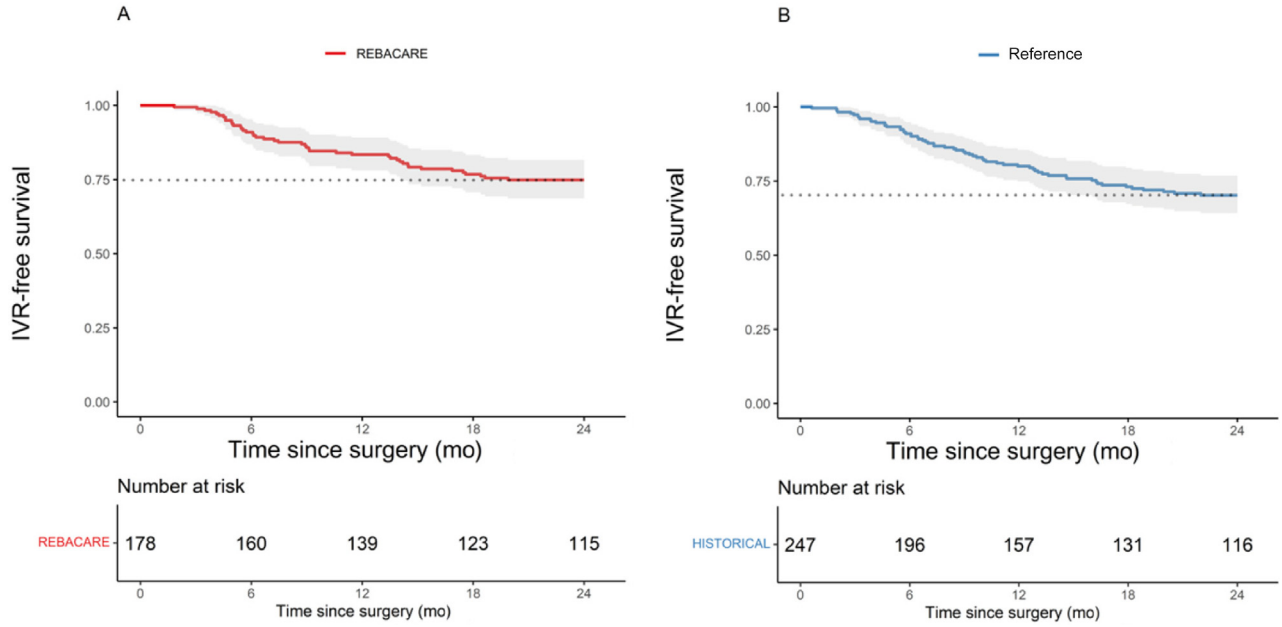

Fig. 2 – Intravesical recurrence (IVR)-free survival for (A) patients with primary nonmetastatic upper urinary tract urothelial cell carcinoma who received a preoperative instillation of mitomycin C in the REBACARE cohort and (B) the reference cohort of patients who had not received a perioperative instillation of chemotherapy. The dashed line indicates the 2-yr IVR-free survival rate.

Table 2 – Multivariable Cox proportional-hazards regression results for factors associated with intravesical recurrence in patients with primary upper urinary tract urothelial carcinoma, with d-URS included as an interaction term

Parameter	HR (95% CI)	*p* value[a]
pT stage		
Tis/Ta/Tx	Reference	
T1–2	0.80 (0.43–1.37)	0.4
T3–4	0.85 (0.54–1.33)	0.5
Female sex (vs male)	0.66 (0.42–1.04)	0.077
Preoperative cytology		
Not done or unknown	Reference	
Benign or atypia	0.77 (0.48–1.28)	0.3
High grade	0.88 (0.50–1.53)	0.6
Age per 10-yr increment	0.92 (0.76–1.11)	0.4
Mid- or distal ureter tumor location (vs renal pelvis or PU)	1.83 (1.23–2.73)	**0.003**
Concomitant carcinoma in situ (yes vs no)	1.04 (0.58–1.86)	0.9
Multifocality (yes vs no)	1.11 (0.66–1.87)	0.7
Group		
Historical cohort without d-URS	Reference	
Historical cohort with d-URS	1.67 (0.98–2.83)	0.057
REBACARE cohort without d-URS	0.33 (0.12–0.87)	**0.025**
REBACARE cohort with d-URS	1.83 (1.08–3.10)	**0.025**

CI = confidence interval; d-URS = diagnostic ureteroscopy; HR = hazard ratio; PU = proximal ureter.
[a] Statistical significance was set at $p < 0.05$; significant values are denoted in bold font.

3.4. *Toxicity and adverse events*

Twenty-seven patients (15%) experienced surgical complications (hemorrhage, urine leakage, wound infection, and bowel motion) within 30 d after surgery, of which only two (7.4%) were Clavien-Dindo grade >II complications (both hemorrhage). Grade ≥III adverse events within 6 mo after surgery were reported for 48 patients (27%), none of which were related to MMC. A total of 23 treatment-related complications were reported, the most frequent of which was bladder spasms (n = 13, 56%), with medication prescribed in 11 cases. The second most frequent complication was hematuria (n = 6, 26%), for which two patients received a temporary indwelling catheter for continuous rinsing.

4. Discussion

REBACARE is the first prospective trial to assess the efficacy and feasibility of an intravesical MMC instillation before radical surgery for primary UTUC. Although the prespecified reduction of >40% in the 2-yr IVR rate was not achieved, a significant reduction was observed in the group of patients who had not undergone d-URS in the diagnostic workup for UTUC. Therefore, a single preoperative MMC instillation could be a viable strategy for this subgroup of patients. We observed an excellent safety profile for the study intervention, and achieved almost 100% compliance. Although d-URS still may contribute to the diagnostic workup of UTUC (ie, patient selection for radical or kidney-sparing surgery), careful consideration on a per-patient basis is warranted because of its strong association with the risk of IVR.

The guideline recommendation of postoperative chemotherapy instillation after radical surgery for UTUC is based on outcomes from the THP Monotherapy Study Group and ODMIT-C trials [13,14], which were initiated because of the benefits in reducing the risk of IVR observed after transurethral resection of the bladder [27,28]. The theory of seeding of cancer cells, supported by molecular studies [8–10], posits that IVR may arise from intraluminal seeding of cancer cells during surgery for UTUC. Hence, the aim of postoperative chemotherapy instillation is to mitigate IVR risk by killing residual cancer cells in the bladder. Although it has been reported that a postoperative instillation after

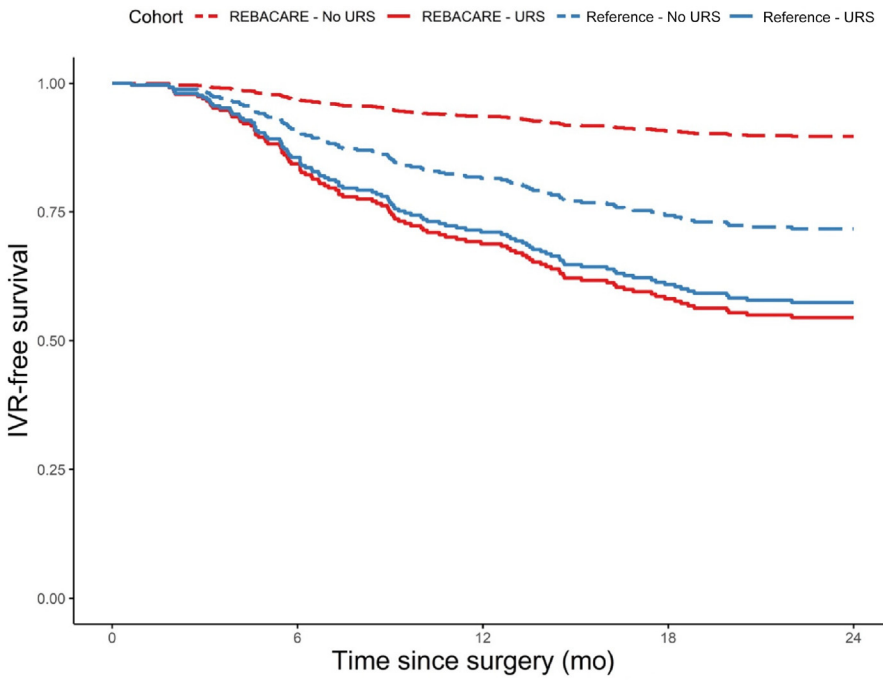

Fig. 3 – Intravesical recurrence–free survival predicted via multivariable Cox proportional-hazards regression analysis for the REBACARE and reference cohorts, stratified by diagnostic ureteroscopy (URS) in the diagnostic workup for upper tract urothelial carcinoma. Characteristics: pT1–2, male, similar age, benign or atypia finding on preoperative cytology, tumor in the mid- or distal ureter, no concomitant carcinoma in situ, and no multifocality.

RNU is safe, the potential risk of extravesical leakage remains a concern, contributing to compliance rates of <50% in real-world clinical practice [17–20,29]. By contrast, a preoperative instillation bypasses this risk, and the REBACARE results demonstrate excellent safety and compliance rates. It is hypothesized that a preoperative MMC instillation may prevent implantation of tumor cells in the urothelium, as neoadjuvant device-assisted instillation of MMC before transurethral resection of bladder tumor has been effective in non–muscle-invasive bladder cancer [30]. Continuous bladder irrigation with saline solution might also inhibit implantation of tumor cells.

Although the prespecified IVR reduction threshold of >40% was not achieved, the IVR rate of 24% was lower than the mean rate of 33.2% derived from study populations who did not receive a preoperative or postoperative instillation [7,13,14,23,24,31]. This suggests the potential benefit of a preoperative instillation. Furthermore, it is noteworthy that the 2-yr IVR rate for the reference cohort (26%) was also much lower than the mean rate in the literature. This might be because of more favorable characteristics of the reference cohort, such as stage <pT2 UTUC and a lower proportion of patients with a history of a d-URS (45% vs 59%). In the REBACARE cohort, 38/43 patients who developed IVR had undergone d-URS (88%), with biopsy performed during d-URS in 30 of these 38 patients (79%). In addition, underreporting of IVR might have occurred in the retrospective reference cohort.

The 2-yr IVR rate of 24% in REBACARE trial may be deemed inadequate in comparison to rates reported for the two trials that evaluated a postoperative instillation with chemotherapy. In the study by Ito et al [13], patients were randomized to receive a single dose of pirarubicin within 48 h after RNU (n = 36) versus observation (n = 36). The authors reported IVR rates of 17% versus 32% at 1 yr, and 17% versus 42% at 2 yr, respectively, favoring the intervention arm. The ODMIT-C trial, in which patients were randomized to receive a single dose of MMC after RNU before catheter removal (<10 d after surgery) versus observation, was limited by a follow-up duration of 1 yr. The IVR rate reported was 16% versus 27% in favor of the intervention arm in the per-protocol analysis (88% of the study population; p = 0.03) [14]. The intention-to-treat analysis revealed no statistically significant difference between the treatment arms. Importantly, histological confirmation of IVR was not mandatory, with potential for under-reporting of the IVR rate. It is important to consider whether the outcomes of these two trials accurately reflect real-world daily clinical practice, as a substantial proportion of patients do not receive a postoperative instillation because of concerns about extravesical leakage of chemotherapy.

Almost 60% of patients in our study underwent d-URS during diagnostic workup for UTUC, which may have contributed to the risk of IVR, which was fivefold higher in the d-URS group than in the group without d-URS (HR 0.33 vs 1.83). No benefit of preoperative instillation was observed in this subgroup, indicating that d-URS was an important confounder. The time lapse between d-URS and radical surgery, which allows tumor cells to implant in the urothelium of the bladder, might explain why a perioperative instillation was of limited benefit in these patients.

The necessity for d-URS in the diagnostic workup for UTUC is debatable. While offering advantages, such as histopathological diagnosis and upper urinary tract inspection, d-URS also has limitations, including a risk of understaging when biopsy is performed, ureter perforation,

urinary tract infection, a delay in time to definitive treatment, and higher risk of IVR, which might be even higher when biopsy is performed [11,32,33]. Hence, our study results underscore the need to carefully consider d-URS on a per-patient basis and to adhere to the EAU guidelines on UTUC, which recommend d-URS only when other diagnostic modalities are inconclusive. Future studies should explore alternative strategies such as chemotherapy bladder instillations around the time of URS to optimize IVR prevention in patients with UTUC [34].

The limitations of our study are largely related to the single-arm design. Owing to the rarity of UTUC, a randomized controlled trial to compare preoperative versus postoperative instillation was not considered feasible. Furthermore, because the recommendation for postoperative instillation was only included in the guidelines just before the REBACARE trial started, it was not possible to compile a reference cohort with a representative number of cases who had received a postoperative instillation. In addition, <50% of the patients were treated according to the study protocol, which included ureteral clipping, bladder cuff excision, instillation for 1–2 h, and <3 h between instillation and surgery. However, the per-protocol analysis demonstrated similar results to the intention-to-treat analysis, suggesting that deviations from the protocol may not have significantly influenced the outcomes. Moreover, since repeat cystoscopy between d-URS and radical surgery was not mandatory, small IVRs could have developed before radical surgery. Finally, other risk factors for IVR have been identified, but the numbers of participants and expected events meant that we were constrained in the number of variables included without risking underpowered or overfitted analyses. The most significant risk factors according to the literature were included [24].

5. Conclusions

In conclusion, the REBACARE trial demonstrated that a single preoperative instillation of MMC before radical surgery for primary UTUC was safe and feasible and significantly reduced the risk of IVR in patients without a history of d-URS. Therefore, a preoperative instillation of MMC seems a viable strategy for a subset of UTUC patients. Since d-URS was strongly associated with higher risk of IVR, it should be performed judiciously and restricted to patients in whom imaging and/or urine cytology are inconclusive.

Author contributions: Thomas van Doeveren had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: van Doeveren, van Leeuwen, Boormans, Aben.
Acquisition of data: All author.
Analysis and interpretation of data: van Doeveren, van Leeuwen, Boormans, Aben, Remmers.
Drafting of the manuscript: van Doeveren, van Leeuwen, Boormans, Aben, Remmers.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: van Doeveren, van Leeuwen, Boormans, Aben, Remmers.
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Supplementary data

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