

Intracavitary Chemotherapy after kidney-Sparing Therapy for Upper Tract Urothelial Carcinoma: A Meta-Analysis

Hang Zhou^{1#}, Yang Pan^{1#}, Mingming Xu^{1#}, Shangren Wang¹, Yuezheng Li¹, Xiaoqiang Liu^{1*}

Purpose: Intracavitary chemotherapy is one of the current treatment options for kidney-sparing treatment of upper tract urothelial carcinoma (UTUC). The purpose of this meta-analysis was to assess the efficacy and safety of intracavitary perfusion.

Methods: We carefully selected publications for study from four databases (Embase, PubMed, Web of Science, and Scopus) up to January 2023. The R 4.0.4 software was used to calculate the pooled ratio and its 95% confidence intervals (95% CIs). The I2 score was used to test heterogeneity, and the funnel plot was used to estimate the publication bias.

Results: Thirty-four studies with a total of 788 patients were included in this study. The overall survival at a median follow-up of 26.3 months was 87.2% (95% CI 0.80–0.93). The cancer-specific survival at a median follow-up of 30 months was 94.1% (95% CI 0.89–0.98). At a median follow-up of 30 months, the recurrence rate of UTUC was 27.5% (95% CI 0.21–0.34). By subgroup analysis, we found that the recurrence rate in patients with T1 / Ta stage was 35.1% and CIS stage 29.0%. The recurrence rates of BCG, Mitomycin C, and Mitomycin Gel (UGN101) were 31.2%, 41.3% and 12.9%, respectively. The recurrence rates for anterograde and retrograde perfusion were 28.5% and 21.8%, respectively.

Conclusion: With the advent of new drugs, including UGN101, patients with UTUC have a better prognosis. Therefore, kidney preservation therapy for patients with UTUC would be promising.

Keywords: upper tract urothelial carcinoma; intracavitary perfusion; kidney-sparing therapy; recurrence rate; meta-analysis

INTRODUCTION

Upper tract urothelial carcinoma (UTUC) is a rare tumor of the urinary tract, accounting for only 5-10% of all urothelial carcinomas, with an annual incidence of 1-2 cases per 100,000 people⁽¹⁾. Depending on tumor stage, grade, and presence or absence of metastases, 5-year cancer-specific survival (CSS) for UTUC ranges from 10% to 70%⁽²⁻⁴⁾. According to the EAU guidelines⁽¹⁾, the standard treatment for nonmetastatic UTUC is radical nephroureterectomy with bladder cuff excision, but renal element preservation may be recommended for patients with anatomically or functionally isolated kidneys, bilateral disease, severe chronic renal insufficiency, or medical comorbidities that make primary surgery intolerable. However, minimally invasive techniques for managing upper tract cancers are currently posing a threat to the gold standard for open radical nephroureterectomy. A meta-analysis⁽⁵⁾ demonstrated that there was no significant difference in overall survival (OS) and CSS between radical nephrectomy and kidney sparing surgery, with relative hazard ratios of 1.47 and 0.96, respectively. Unplanned nephrectomy can reduce quality of life. As a result, kidney-sparing surgery (KSS), including segmental ureteral excision and endoscopic ablation, may be required in some patients with small, localized, low-grade upper-tract tumors⁽⁶⁾.

However, patients undergoing kidney-sparing surgery often experience recurrence. Following local tumor resection, numerous hospitals recommend intraluminal infusion of chemotherapeutic drugs to decrease tumor recurrence and improve patient survival. BCG and mitomycin C (MMC) were the two drugs that were used most frequently in local chemotherapy. The experimental drug UGN-101, a formulation based on sustained release hydrogel polymers containing MMC, is currently being tested in clinical trials to treat UTUCs⁽⁷⁾.

Currently, there is no comprehensive overview of the efficacy and risks of intracavitary chemotherapeutic medication infusion after KSS. Due to the unsatisfactory effect of the existing renal preservation therapy of UTUC, the sample size of postoperative intracavitary chemotherapy is small, the follow-up time is short, and there is no article to summarize the effectiveness and safety. We organized tumor survival information and summarized the recurrence rate of various drugs, perfusion techniques, and tumor stages. The purpose of this meta-analysis was to evaluate the efficacy and safety of intracavitary chemotherapy for UTUC and to provide advice for future treatment of UTUC.

MATERIALS AND METHODS

Search strategy

The current meta-analysis was designed, performed,

¹Department of Urology, General Hospital of Tianjin Medical University, Tianjin, 300052, China.

contributed equally to this work.

*Correspondence: Email: xiaoqiangliu1@163.com

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Table 1. The main characteristics and the perfusion status of all included studies.

Author	Year	Country	Medicine	Perfusion Time	Dose (mg/mL)	Methods	Approach (%)	Participants, N	Mean age	Tumor staging	Median follow-up months
Schoenberg (10)	1991	USA	BCG/MMC	0.5h	NR	NR	A/R (40/60)	10	70.8	Ta/T1	24
Eastham (11)	1993	USA	MMC	24h	NR	One time after surgery	A/R (30/70)	7	78	Ta/T1	12
Sharpe (12)	1993	Canada	BCG	1h	1.2	Once a week, 6 weeks	R	11	66a	CIS	49
Yokogi (14)	1996	Japan	BCG	2h	1.0	Once a week, 6 weeks	A/R (60/40)	5	66	CIS	16
Pineiro (13)	1996	Spain	BCG/MMC	1h	NR	Once a week, 6 weeks	A/R	21	NR	Ta/T1	30.7b
Keeley (15)	1997	USA	MMC	0.5h	1.3	One time after surgery	R	19	73	Ta	30
Patel (16)	1998	USA	BCG/MMC	NR	NR	NR	R	13	59.7	Ta	14.6b
Clark (17)	1999	USA	BCG	NR	NR	Once a week, 6 weeks	A	16	72.2	Ta/T1	20.5b
Nishino (18)	2000	Japan	BCG	2h	0.8	~NR	R	6	72.8	CIS	22b
Nonomura (19)	2000	Japan	BCG	0.5h	2.0	Once a week, 6 weeks	R	11	72.2	CIS	20b
Okubo (20)	2001	Japan	BCG	1h	0.8	Once a week, 6 weeks	A/R (20/80)	11	69	CIS	60
Irie (21)	2002	Japan	BCG	0.25-0.5h	NR	Once a week, 6 weeks	R	9	64.9	CIS	36
Goel (22)	2003	UK	MMC	NR	1.0	Once a week, 6 weeks	A/R	15	NR	Ta/T1	64
Hayashida (23)	2004	Japan	BCG	1-2h	0.8-1.6	Once a week, 6 weeks	A/R	10	71.7a	CIS	50.9
Palou (24)	2004	Spain	BCG/MMC	NR	NR	NR	R	12	NR	Ta/T1	45.5
Kojima (25)	2006	Japan	BCG	1h	1.0-2.0	Once a week, 8 weeks	R	11	66.6	CIS	58.3
Katz (26)	2007	USA	BCG	1h	NR	NR	R	7	NR	Ta/T1	24
Rastinehad (27)	2009	USA	BCG	1h	1.6	6 times a week, one week	A	50	70.9	Ta/T1	61
Giannarini (28)	2011	Switzerland	BCG	2h	2.4	6 times a week, one week	A	18	69a	Ta/T1	42
Cutress (29)	2012	UK	MMC	NR	NR	One time after surgery	A/R	18	NR	Ta/T1	54b
Shapiro (30)	2012	USA	BCG	1h	0.8	Once a week, 6 weeks	R	11	73	CIS	14
Aboumarzouk (31)	2013	UK	MMC	1h	1.0	One time after surgery	R	19	72	T1/Ta	24b
Motamedinia (32)	2016	USA	BCG/MMC	NR	NR	NR	A	73	73a	T1/Ta	66
Metcalfe (33)	2017	USA	MMC	2h	2.0	Once a week, 6 weeks	A/R	21	NR	T1/Ta	19
Balassubramanian (34)	2018	USA	MMC/ BCG/other	2h	NR	Once a week, 6 weeks	A/R	17	NR	T1/Ta	36.5
Horiguchi (35)	2018	Japan	BCG	2h	0.5	6 times a week, one week	R	38	74a	CIS	49
Tomisaki (36)	2018	Japan	BCG	2h	0.8	8 times a week, one week	A/R	41	72a	CIS	26.3
Kleinmann (37)	2019	USA	UGN101	NR	2.0-6.0	6 times a week, one week	A/R	18	75a	NR	NR
Kleinmann (38)	2020	USA	UGN101	NR	4	6 times a week, one week	R	41	70.4	NR	11
Matin (39)	2022	USA	UGN101	NR	NR	6 times a week, one week	R	41	72	NR	11.8
Rosen (40)	2022	USA	UGN101	NR	NR	6 times a week, one week	A	8	68	NR	7
Rose (41)	2022	USA	UGN101	NR	4	Once a week-6 weeks	A	32	74.5a	NR	13
Territo (42)	2022	Spain	BCG	2h	1.6	One time a week-6 weeks	A	16	75a	CIS	36
Woldu (43)	2022	USA	UGN101	NR	NR	NR	A/R	132	73.9a	NR	6.7

^a Median age ^b Mean follow-up months

Abbreviations: A=Anterograde; R=Retrograde; CSS = Cancer-specific survival; OS = overall survival; NR=not report

and reported according to the quality standards for the reporting of meta-analyses⁽⁸⁾. Terms including "Upper Urinary Tract Urothelial Carcinoma," "Perfusion," "Mitomycin," "BCG," and "UGN 101" were used to systematically search Embase, PubMed, Scopus, and the Web of Science between January, 1990, and January, 2023. The detailed search formula is shown in the Supplemental Material. This study was registered in PROSPERO (CRD42022350429).

Selection criteria

Articles included in this study had to meet all the following criteria: (1) the research subjects of interest were UTUC; (2) the exposure of interest was intracavitary perfusion after kidney sparing therapy; (3) the primary outcomes were the survival and recurrence rates after this treatment; (4) the proportion estimates were reported with their corresponding 95% CIs or sufficient data were provided to calculate them. Articles were excluded if they met these criteria: (1) animal experiment; (2) no English language; (3) reviews, comments, letters, editorials, interviews, or reports; (4) duplicate studies; (5) incomplete data.

Quality assessment

Two reviewers (YP, a urologist with three years of

clinical experience and MMX, a urology postgraduate) independently evaluated the articles to determine eligibility according to strict inclusion and exclusion criteria, and any disagreements were resolved by discussion with a third reviewer (SRW, a physician with six years of clinical experience). All three of these have a good foundation in statistical research and experience in meta-analytic data processing. The Newcastle-Ottawa Scale (NOS) was introduced to assess the quality of included studies studied by two independent reviewers. NOS is a 9-star system that includes 3 dimensions: selection (4 items), comparability (1 item), and exposure/outcome (3 items). Each item represents 1 point, except for comparability (2 points). The included articles have NOS scores of at least 5.

Data extraction

The following data from each included study were recorded: first the author's surname, publication year, the country where the study was conducted, sample size, tumor staging of UTUC, chemotherapy drugs, and ways of perfusion. Other data included tumor recurrence, CSS, OS during follow-up, and the incidence of complications.

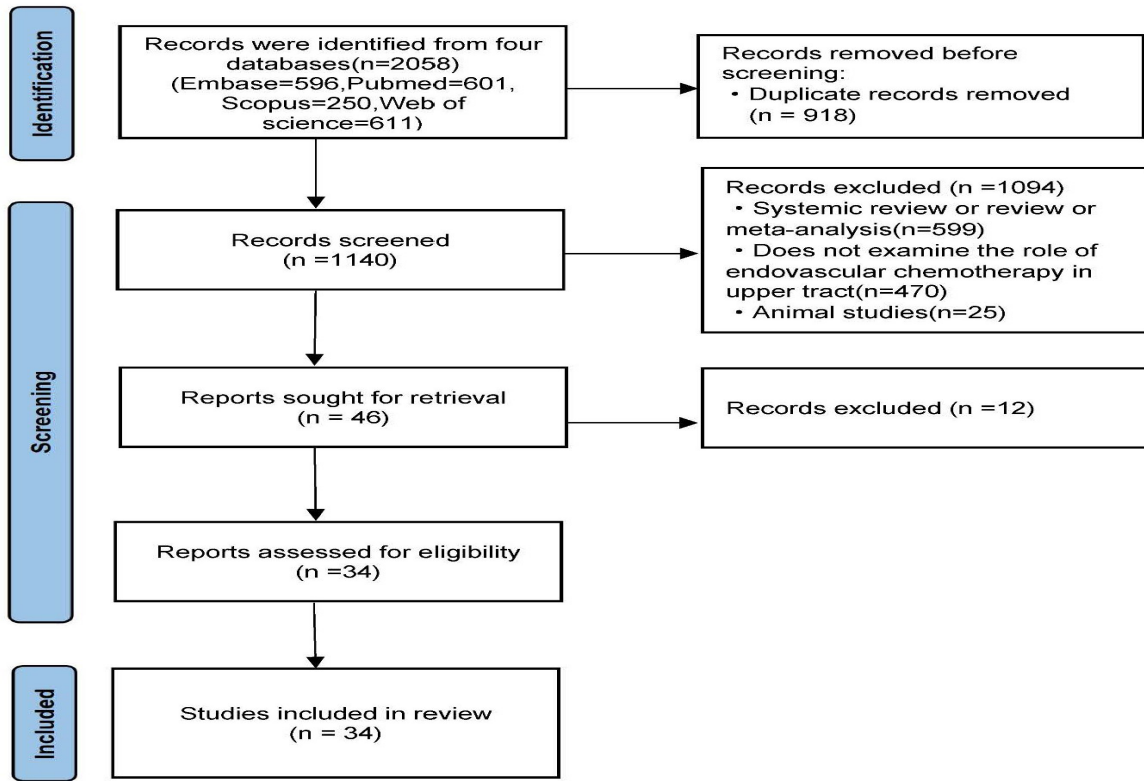


Figure 1. Flow diagram of identification and screening of eligible studies (PRISMA flow diagram).

Data analysis

Software version 4.0.4 of R was employed for statis-

tical analysis. We used the single group rate as an effect size, which provides the total number of people

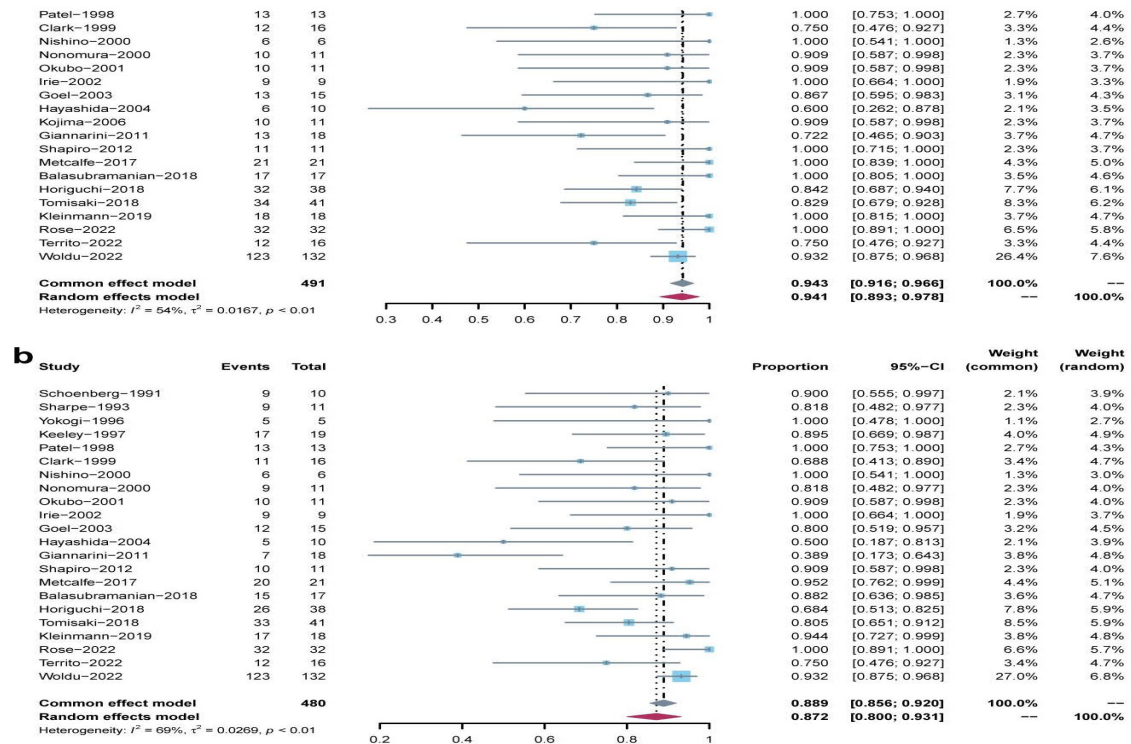


Figure 2. Forest plots for (a) cancer-specific survival and (b) overall survival in patients with UTUC.

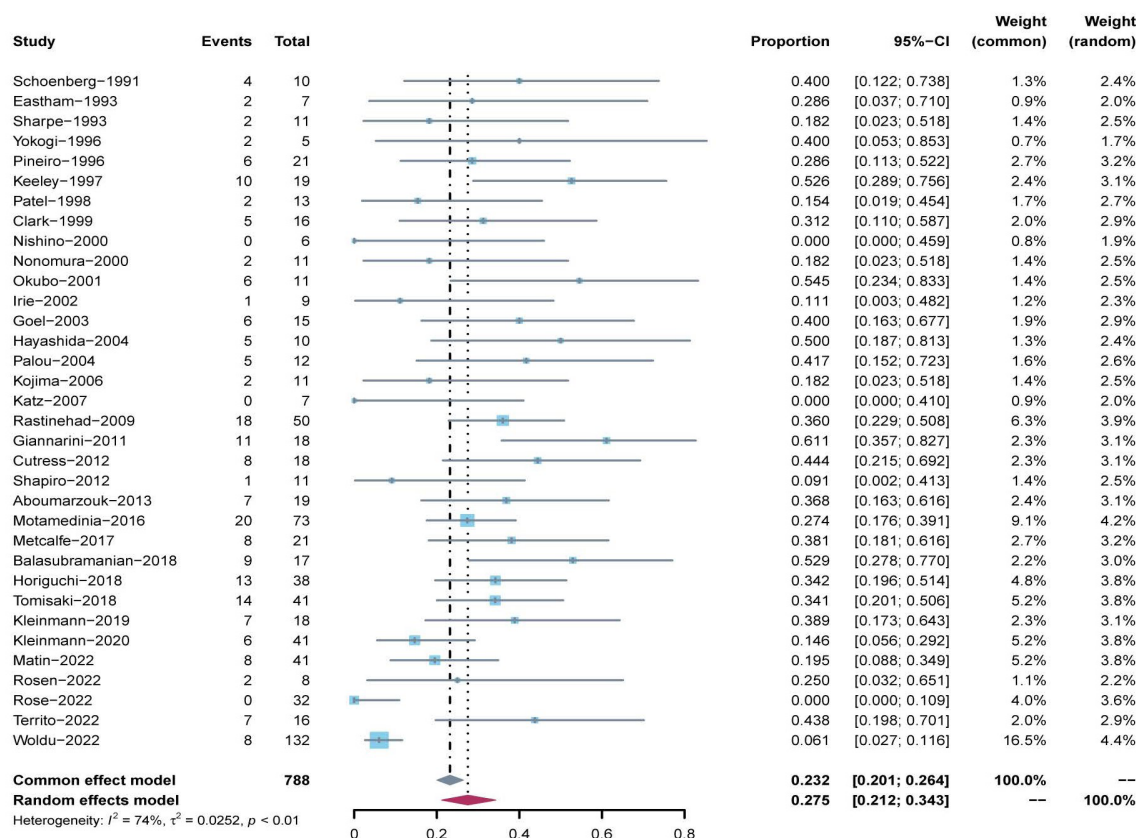


Figure 3. Forest plot for the total recurrence rate of UTUC.

and the number of events in a population. We pooled the tumor recurrence rate, cancer-specific survival rate, overall survival rate, and the incidence of complications separately. The I^2 score was also used to determine the degree of heterogeneity ($I^2 > 50\%$, no obvious heterogeneity; $I^2 > 50\%$, large or extreme heterogeneity). When $I^2 > 50\%$, the random effects model was used; otherwise, the fixed effects model was used. A p -value of less than 0.05 was considered statistically significant. To reduce the heterogeneity of the data, we applied the Freeman-Tukey double-arcsine transformation to the data with a partial rate of zero. Subgroup analyses were performed for several variables based on tumor types, chemotherapy drugs, and administration methods. In terms of sensitivity analysis, a meta-analysis was performed to omit each study in turn. The funnel plot was used to evaluate potential publication bias⁽⁹⁾.

RESULTS

Study searches and characteristics

The detailed process of conducting a literature search is shown in Figure 1. This meta-analysis finally included 34 studies (10-43) in total. These studies were carried out in the following countries: United States ($n = 17$), Japan ($n = 9$), the United Kingdom ($n = 3$), Spain ($n = 3$), Canada ($n = 1$), and Switzerland ($n = 1$). The Newcastle-Ottawa Scale (NOS) grades quality on a scale from 5 to 6. The tumors in 34 studies were always upper urothelial carcinomas, which were treated with local tumor resection or local ablation combined with drug chemotherapy. The language of all publications included in the study is English. Additional details are

listed in Table 1.

CSS and OS of UTUC

We collected data on CSS at a median follow-up of 30 months from 23 studies. The cancer-specific survival rate during the follow-up period was 94.1% (95%CI 0.89-0.98; $I^2 = 54.1\%$; $P < .001$) (Figure 2a). At a median follow-up of 26.3 months, the OS was 87.2% (95%CI 0.80-0.93; $I^2 = 69.0\%$; $P = .036$) (Figure 2b). In a subgroup analysis of CSS, T1/Ta (ES = 94.2%; 95% CI = 0.84-1.00; $I^2 = 64.3\%$; $P = .034$) had better cancer-specific survival than CIS (ES = 89.6%; 95% CI 0.84-0.94; $I^2 = 26.8\%$; $P = .038$). Cancer-specific survival was higher in patients treated with MMC (ES = 99.2%; 95% CI = 0.95-1.00; $I^2 = 1.1\%$; $P < .001$) compared to BCG (ES = 87.3%; 95% CI = 0.82-0.92; $I^2 = 30.8\%$; $P = .044$) and UGN101 (ES = 97.5%; 95% CI = 0.93-1.00; $I^2 = 64.0\%$; $P < .001$) (Table S1).

Recurrence rate of UTUC

A total of 788 cases from 34 studies of UTUC were reported, most with stage CIS-T1 disease. At a median follow-up of 30 months, the recurrence rate was 27.5% (95% CI 0.21-0.34; $I^2 = 74.3\%$; $P = .053$) (Figure 3). We performed the subgroup analysis of the recurrence rates. The recurrence rate in patients with a stage of T1/Ta was 35.1% (95% CI 0.30-0.41; $I^2 = 30.5\%$; $P = .030$) and a stage of CIS was 29.0% (95% CI 0.22-0.36; $I^2 = 31.8\%$; $P = .708$) (Figure 4).

Different chemotherapeutic agents were used for perfusion in different studies: BCG ($n = 16$), MMC ($n = 6$), and UGN 101 ($n = 6$). The recurrence rate of BCG per-

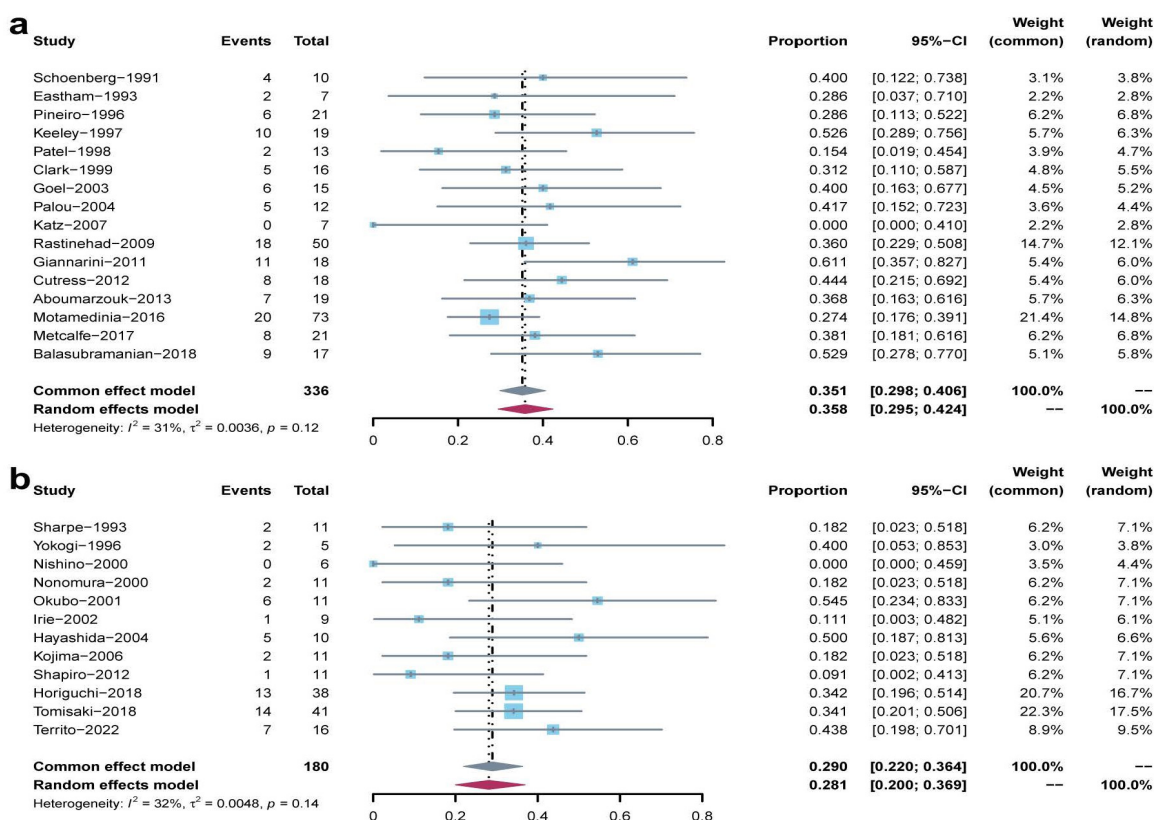


Figure 4. Forest plots of the recurrence rate for (a) Ta/T1 and (b) CIS.

fusion during a median follow-up period of 36 months was 31.2% (95% CI 0.25-0.37; $I^2 = 46.8\%$; $P = .367$). The recurrence rates of MMC and UGN101 after perfusion were, respectively, 41.3% (95% CI 0.31-0.52; $I^2 = 0.0\%$; $P = .608$) and 12.9% (95% CI 0.03-0.27; $I^2 = 80.2\%$; $P = .934$) (Figure 5). Anterograde perfusion was used in 7 studies and retrograde perfusion in 14 studies. Other studies did not specify any particular perfusion technique or the combination of both. The recurrence rates for anterograde and retrograde perfusion were respectively 28.5% (95% CI 0.12-0.48; $I^2 = 85.2\%$; $P = .146$) and 21.8% (95% CI 0.16-0.28; $I^2 = 43.6\%$; $P = .539$) (Figure 6).

Complications

A total of 22 studies mentioned complications. We collected the number of cases with complications and found that there were four common complications. Bladder irritation was the most common complication, with an incidence of 42.9% (95% CI 0.16-0.73; $I^2 = 93.1\%$; $P = .056$). Hematuria was the least common complication, with an incidence of 13.8% (95% CI 0.06-0.23; $I^2 = 70.5\%$; $P = .141$). The incidence of the other two complications, including infection and urethral stricture, was 18.7% (95% CI 0.09-0.31; $I^2 = 80.4\%$; $P = 0.324$) and 16.2% (95% CI 0.09-0.25; $I^2 = 68.8\%$; $P = 0.405$) (Figure 7). However, the heterogeneity of all studies was high.

Sensitivity analysis and publication bias

We performed sensitivity analysis and a publication bias test on 34 articles. The sensitivity analysis confirmed that no individual studies influenced the results (Figure S1). There was no evidence of publication bias

in this meta-analysis, as indicated by the funnel plot (Figure S2).

DISCUSSION

In this article, the majority of these patients received local chemotherapeutic perfusion following percutaneous tumor excision or laser ablation. In this meta-analysis, we evaluated survival outcomes in patients with UTUC and explored four possible complications of conservative management. At a median follow-up time of 26.3 and 30 months, OS and CSS were 87.2% and 94.1%, respectively, demonstrating good survival performance. It was discovered by subgroup analysis of the CSS reporting group that patients who used MMC had better survival outcomes than those who used BCG. Following local chemotherapeutic medication infusion, the overall recurrence rate was 27.5%. The subgroup analysis revealed that patients with stage T1/Ta had a recurrence rate of 35.1% and those with CIS had a recurrence rate of 29.0%. After renal-sparing surgery and local chemotherapy, the recurrence rate of carcinoma in situ is decreased, which may indicate that tumor recovery is directly related to the initial tumor stage. Compared to BCG and MMC, the new drug UGN101 exhibited a reduced recurrence rate. However, no high-level controlled trials have been performed to examine the disparity in efficacy between it and the other two drugs. The two most common chemotherapy drugs used for UTUC were MMC and BCG. Although BCG perfusion can cause urinary tract irritation, MMC has fewer negative effects. According to our specific data, the recurrence rate of BCG perfusion ($ES = 31.2\%$) was

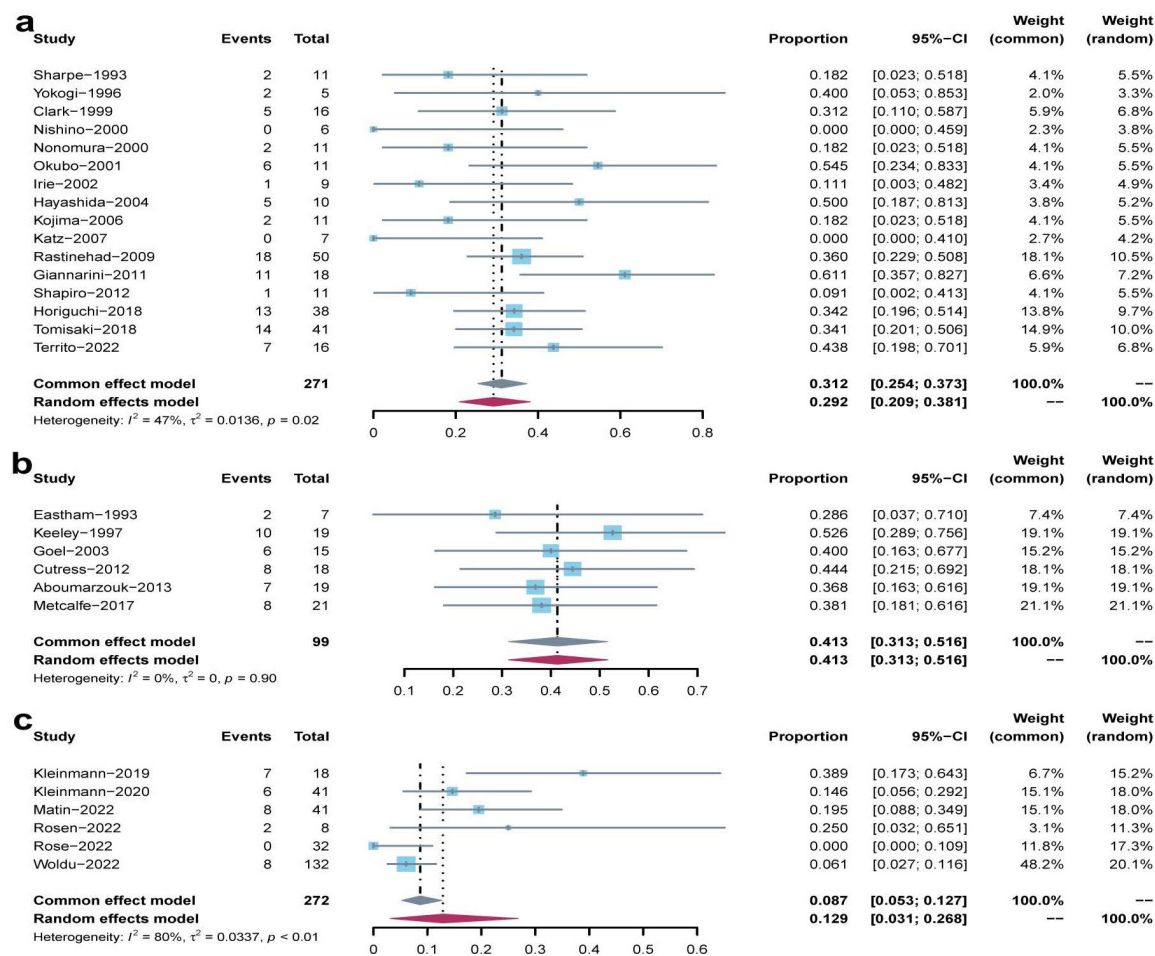


Figure 5. Forest plots of the recurrence rate for (a) BCG, (b) MMC and (c) UGN101.

lower than MMC perfusion (ES = 41.3%). But it was not statistically significant. Patients utilizing MMC had higher survival results than those using BCG, according to CSS subgroup analysis. The mechanism of destruction of tumor cells by mitomycin is primarily attributed to DNA alkylation and consequent inhibition of DNA synthesis, and can modify the REDOX cycle, inhibit RNA, and regulate thioredoxin reductase activity⁽⁴⁴⁾. Due to the large molecular weight of MMC, systemic absorption is limited when injected into the upper tract. Recurrence rates of UTUC tend to be high with the use of traditional chemotherapy drugs^(45,46). Therefore, experts have recently proposed a gel-shaped MMC for the treatment of UTUC patients undergoing kidney preservation surgery. This new therapy option prolongs the time that drugs are retained in the upper urinary tract in cases with low-grade UTUC while also improving the cure rate. Through the local infusion of particular medications, this strategy for the conservative treatment of UTUC can be considered promising.

After kidney preservation therapy, the medication can be administered anteriorly through a nephrostomy tube, retrogradely directly through the ureter, or by double J implantation to mimic vesicoureteral reflux⁽⁴⁷⁾. Urine production limits drug delivery to the calyceal system and the effectiveness of intracavitary chemotherapy by flushing the drug away, reducing residence time, and making direct contact with the urothelium. This

results in an unmet need for efficient local treatment of epithelial cancer of the upper urinary tract (UTUC). In this meta-analysis, anterograde and retrograde perfusion were performed for UTUC, and the recurrence rates were respectively 28.5% and 21.8%. However, $p > 0.05$, which was not considered statistically significant. According to certain research, perfusion through a renal fistula is more practical and riskier than retrograde perfusion through the ureter⁽⁴⁸⁾. But in this article, we found that retrograde perfusion had a lower recurrence rate, which may be related to longer drug retention. Patients with UTUC had greater recurrence rates following retrograde ureteral procedures, including retrograde pyelography⁽⁴⁹⁾, diagnostic ureteroscopy⁽⁵⁰⁾, and ureteroscopy⁽⁵¹⁾. Song et al.⁽⁵²⁾ suggested that multiple reversals through the ureter may increase the risk of recurrence. Therefore, deciding which perfusion technique is appropriate for a patient may require a detailed evaluation depending on the location of the tumor and the physical health of the patient. The basic situation of perfusion is presented in Table 1. Each cycle of treatment lasts six weeks and the average perfusion time is one hour. The concentration of the medications used varies depending on their type. There were no appreciable differences in the rates of recurrence between the various investigations. However, the length of time that a drug stays in the upper urinary system is associated with the progression of the disease. It's crucial to think about how pa-

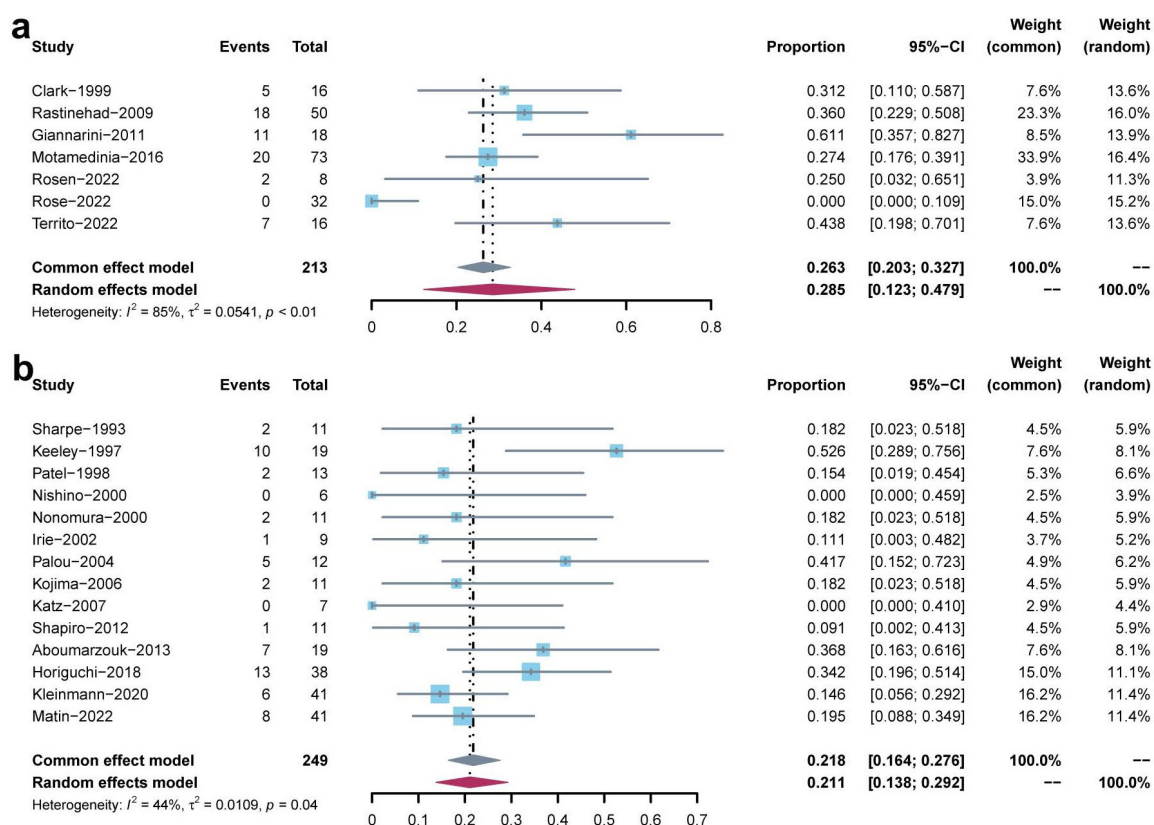


Figure 6. Forest plots of the recurrence rate for (a) anterograde perfusion and (b) retrograde perfusion.

tients can be impacted by a drug's own negative effects. According to the summary of the number of complications in various studies, the following four complications were the most frequent: bladder irritation symptoms (ES = 42.9%), infection (ES = 18.7%), ureteral stricture (ES = 16.2%), and hematuria (ES = 13.8%). However, statistical analysis showed high heterogeneity among different studies. The prevalence of postoperative infection and fever was 18.7%, but there was significant heterogeneity between the studies, presumably because some of them used preventive antibiotics. The operation of the ureter during treatment and follow-up, including irrigation and ureteral evaluation, is linked to the occurrence of complications^(49,50), which is another factor contributing to high heterogeneity. If patients develop complications, symptomatic management can be given to ensure that local perfusion can be carried out normally. For patients with ureteral strictures, some temporary relief can be achieved on its own, but for those with no relief, stent drainage may be considered, or radical nephrectomy may be an alternative. Antibiotics may be used as a preventative measure if the patient is at risk of infection or fever. For patients who may have complications, doctors should not only pay close attention to possible risks after administering the drugs, but also treat symptoms and stop patients from taking the drugs if necessary.

The limitation is the lack of prospective and case-control studies with large sample sizes. At the same time, because of ethical issues, a placebo group was not considered. Another important limitation of this study is the neglect of the overall weights, leading to biased es-

timates of the combined proportions. The effectiveness of chemotherapy after kidney-sparing therapy will require numerous prospective case-control studies in the future, as well as prolonged follow-up. This will give more details on the benefits and drawbacks of intracavitary perfusion for patients with upper urothelial carcinoma who have received conservative treatment, and it might give more treatment options.

CONCLUSIONS

In this meta-analysis, we summarized the efficacy and safety of conservative treatment for UTUC. In general, local tumor resection combined with local chemotherapy for upper urothelial carcinoma often leads to better results. With the emergence of new agents, including UGN101, which has better efficacy and fewer side effects, intracavitary perfusion may become an effective treatment for UTUC after conservative treatment in the future.

CONFLICT OF INTEREST

The authors certify that there is no conflict of interest regarding this manuscript.

APPENDIX

We have provided supplementary materials, including a table (Table S1), two figures (Figures S1 and S2) and

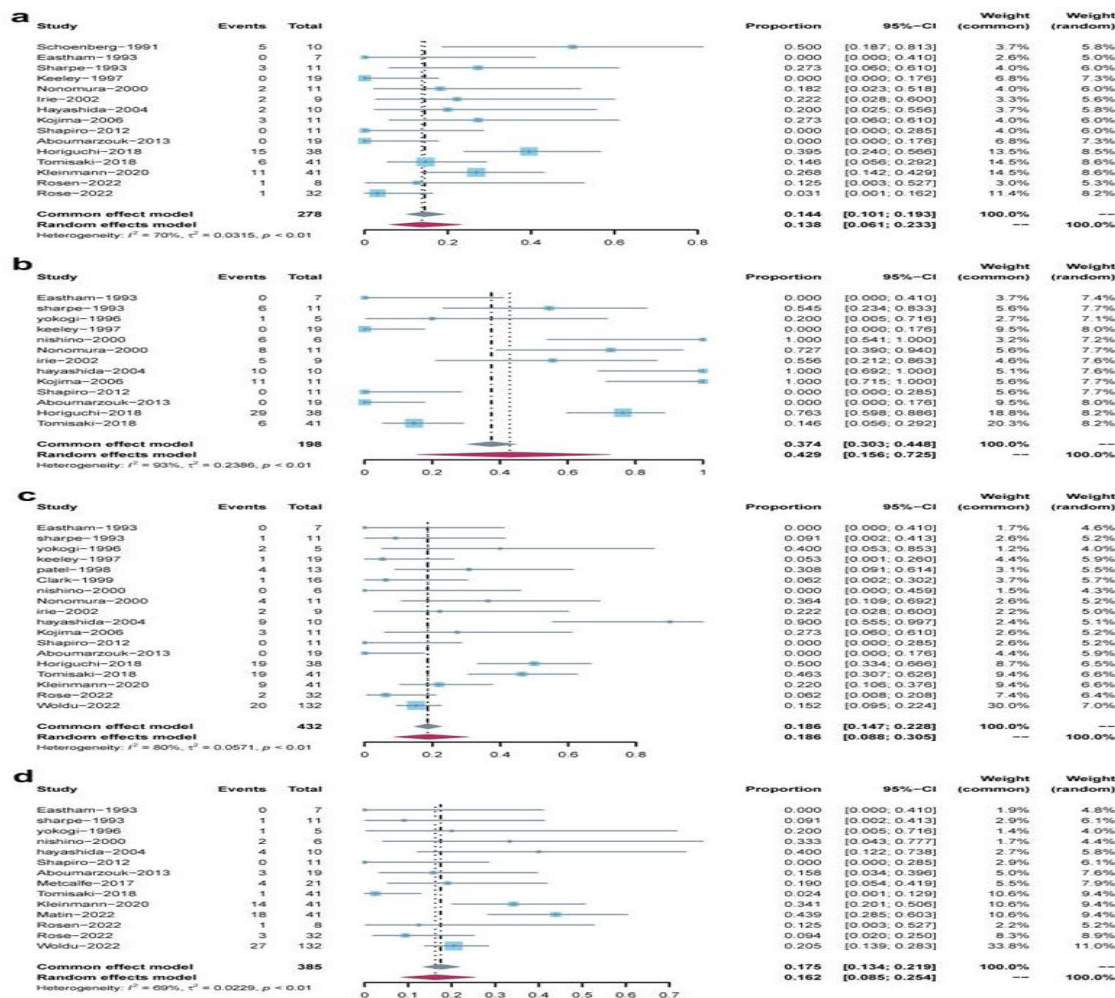


Figure 7. Forest plots of the complication rates for (a) hematuria, (b) symptoms of bladder irritation, (c) infection, and (d) ureteral stricture.

the search formula.

<https://journals.sbm.ac.ir/ur/ij/index.php/uj/libraryFiles/downloadPublic/55>

REFERENCES

- Rouprêt M, Babjuk M, Burger M et al. European Association of Urology Guidelines on Upper Urinary Tract Urothelial Carcinoma: 2020 Update. *Eur Urol.* 2021; 79:62-79.
- Ploussard G, Xylinas E, Lotan Y et al. Conditional survival after radical nephroureterectomy for upper tract carcinoma. *Eur Urol.* 2015; 67:803-12.
- Lughezzani G, Burger M, Margulis V et al. Prognostic factors in upper urinary tract urothelial carcinomas: a comprehensive review of the current literature. *Eur Urol.* 2012; 62:100-14.
- Cha EK, Shariat SF, Kormaksson M et al. Predicting clinical outcomes after radical nephroureterectomy for upper tract urothelial carcinoma. *Eur Urol.* 2012; 61:818-25.
- Yakoubi R, Colin P, Seisen T et al. Radical nephroureterectomy versus endoscopic procedures for the treatment of localised upper tract urothelial carcinoma: a meta-analysis and

- a systematic review of current evidence from comparative studies. *Eur J Surg Oncol.* 2014; 40:1629-34.
- Smith P, Mandel J, Raman JD. Conservative nephron-sparing treatment of upper-tract tumors. *Curr Urol Rep.* 2013; 14:102-8.
- Bhattacharjee S, Maiti B, Bhattacharya S. First report of charge-transfer induced heat-set hydrogel. Structural insights and remarkable properties. *Nanoscale.* 2016; 8:11224-33.
- Liberati A, Altman DG, Tetzlaff J et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. *Bmj.* 2009; 339:b2700.
- Seagroatt V, Stratton I. Bias in meta-analysis detected by a simple, graphical test. Test had 10% false positive rate. *Bmj.* 1998; 316:470.
- Schoenberg MP, Van Arsdalen KN, Wein AJ. The management of transitional cell carcinoma in solitary renal units. *J Urol.* 1991; 146:700-2.
- Eastham JA, Huffman JL. Technique of mitomycin C instillation in the treatment of upper urinary tract urothelial tumors. *J Urol.*

- 1993; 150:324-5.
12. Sharpe JR, Duffy G, Chin JL. Intrarenal bacillus Calmette-Guerin therapy for upper urinary tract carcinoma in situ. *J Urol.* 1993; 149:457-9.
 13. Martínez-Piñeiro JA, García Matres MJ, Martínez-Piñeiro L. Endourological treatment of upper tract urothelial carcinomas: analysis of a series of 59 tumors. *J Urol.* 1996; 156:377-85.
 14. Yokogi H, Wada Y, Mizutani M, Igawa M, Ishibe T. Bacillus Calmette-Guérin perfusion therapy for carcinoma in situ of the upper urinary tract. *Br J Urol.* 1996; 77:676-9.
 15. Keeley FX, Jr., Bagley DH. Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. *J Urol.* 1997; 158:2074-7.
 16. Patel A, Fuchs GJ. New techniques for the administration of topical adjuvant therapy after endoscopic ablation of upper urinary tract transitional cell carcinoma. *J Urol.* 1998; 159:71-5.
 17. Clark PE, Strem SB, Geisinger MA. 13-year experience with percutaneous management of upper tract transitional cell carcinoma. *J Urol.* 1999; 161:772-5.
 18. Nishino Y, Yamamoto N, Komeda H, Takahashi Y, Deguchi T. Bacillus Calmette-Guerin instillation treatment for carcinoma in situ of the upper urinary tract. *Bju International.* 2000; 85:799-801.
 19. Nonomura N, Ono Y, Nozawa M et al. Bacillus Calmette-Guerin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. *European Urology.* 2000; 38:701-4.
 20. Okubo K, Ichioka K, Terada N et al. Intrarenal bacillus Calmette-Guerin therapy for carcinoma in situ of the upper urinary tract: long-term follow-up and natural course in cases of failure. *Bju International.* 2001; 88:343-7.
 21. Irie A, Iwamura M, Kadowaki K et al. Intravesical instillation of bacille Calmette-Guerin for carcinoma in situ of the urothelium involving the upper urinary tract using vesicoureteral reflux created by a double-pigtail catheter. *Urology.* 2002; 59:53-7.
 22. Goel MC, Mahendra V, Roberts JG. Percutaneous management of renal pelvic urothelial tumors: long-term followup. *J Urol.* 2003; 169:925-9.
 23. Hayashida Y, Nomata K, Noguchi M et al. Long-term effects of bacille Calmette-Guérin perfusion therapy for treatment of transitional cell carcinoma in situ of upper urinary tract. *Urology.* 2004; 63:1084-8.
 24. Palou J, Piovesan LF, Huguet J et al. Percutaneous nephroscopic management of upper urinary tract transitional cell carcinoma: recurrence and long-term followup. *J Urol.* 2004; 172:66-9.
 25. Kojima Y, Tozawa K, Kawai N et al. Long-term outcome of upper urinary tract carcinoma in situ: Effectiveness of nephroureterectomy versus bacillus Calmette-Guerin therapy. *International Journal of Urology.* 2006; 13:340-4.
 26. Katz MH, Lee MW, Gupta M. Setting a new standard for topical therapy of upper-tract transitional-cell carcinoma: BCG and interferon-alpha2B. *J Endourol.* 2007; 21:374-7.
 27. Rastinehad AR, Ost MC, Vanderbrink BA et al. A 20-year experience with percutaneous resection of upper tract transitional carcinoma: is there an oncologic benefit with adjuvant bacillus Calmette Guérin therapy? *Urology.* 2009; 73:27-31.
 28. Giannarini G, Kessler TM, Birkhäuser FD, Thalmann GN, Studer UE. Antegrade perfusion with bacillus Calmette-Guérin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? *Eur Urol.* 2011; 60:955-60.
 29. Cutress ML, Stewart GD, Zakikhani P et al. Ureteroscopic and percutaneous management of upper tract urothelial carcinoma (UTUC): systematic review. *BJU Int.* 2012; 110:614-28.
 30. Shapiro EY, Lipsky MJ, Cha DY et al. Outcomes of Intrarenal Bacillus Calmette-Guerin/Interferon-alpha 2B for Biopsy-Proven Upper-Tract Carcinoma in Situ. *Journal of Endourology.* 2012; 26:1645-50.
 31. Aboumarzouk OM, Somani B, Ahmad S et al. Mitomycin C instillation following ureterorenoscopic laser ablation of upper urinary tract carcinoma. *Urol Ann.* 2013; 5:184-9.
 32. Motamedinia P, Keheila M, Leavitt DA et al. The Expanded Use of Percutaneous Resection for Upper Tract Urothelial Carcinoma: A 30-Year Comprehensive Experience. *J Endourol.* 2016; 30:262-7.
 33. Metcalfe M, Wagenheim G, Xiao L et al. Induction and Maintenance Adjuvant Mitomycin C Topical Therapy for Upper Tract Urothelial Carcinoma: Tolerability and Intermediate Term Outcomes. *J Endourol.* 2017; 31:946-53.
 34. Balasubramanian A, Metcalfe MJ, Wagenheim G et al. Salvage topical therapy for upper tract urothelial carcinoma. *World J Urol.* 2018; 36:2027-34.
 35. Horiguchi H, Yoneyama T, Hatakeyama S et al. Impact of bacillus Calmette-Guerin therapy of upper urinary tract carcinoma in situ: comparison of oncological outcomes with radical nephroureterectomy. *Medical Oncology.* 2018; 35.
 36. Tomisaki I, Kubo T, Minato A, Fujimoto N. Efficacy and Tolerability of Bacillus Calmette-Guerin Therapy as the First-Line Therapy for Upper Urinary Tract Carcinoma In Situ. *Cancer Investigation.* 2018; 36:152-7.
 37. Kleinmann N, Wirth G, Lin JS et al. Thermo Reversible Hydrogel Based Delivery of Mitomycin C (UGN-101) for Treatment of Upper Tract Urothelial Carcinoma (UTUC). *Bladder Cancer.* 2019; 5:21-9.
 38. Kleinmann N, Matin SF, Pierorazio PM et al.

- Primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel (OLYMPUS): an open-label, single-arm, phase 3 trial. *Lancet Oncol.* 2020; 21:776-85.
39. Matin SF, Pierorazio PM, Kleinmann N et al. Durability of Response to Primary Chemoablation of Low-Grade Upper Tract Urothelial Carcinoma Using UGN-101, a Mitomycin-Containing Reverse Thermal Gel: OLYMPUS Trial Final Report. *J Urol.* 2022; 207:779-88.
 40. Rosen GH, Nallani A, Muzzey C, Murray KS. Antegrade Instillation of UGN-101 (Mitomycin for Pyelocalyceal Solution) for Low-Grade Upper Tract Urothelial Carcinoma: Initial Clinical Experience. *J Urol.* 2022.
 41. Rose KM, Narang G, Rosen G et al. Antegrade administration of mitomycin gel for upper tract urothelial carcinoma via percutaneous nephrostomy tube: a multi-institutional retrospective cohort study. *BJU Int.* 2022.
 42. Territo A, Fontanet S, Meneghetti I et al. Management of primary upper urinary tract carcinoma in situ diagnosed by ureteroscopic biopsy: Is bacillus Calmette-Guerin an alternative to nephroureterectomy? *Actas Urol Esp (Engl Ed).* 2022.
 43. Woldu SL, Labbate C, Murray KS et al. Early experience with UGN-101 for the treatment of upper tract urothelial cancer – A multicenter evaluation of practice patterns and outcomes. *Urologic Oncology: Seminars and Original Investigations.* 2022.
 44. Paz MM, Zhang X, Lu J, Holmgren A. A new mechanism of action for the anticancer drug mitomycin C: mechanism-based inhibition of thioredoxin reductase. *Chem Res Toxicol.* 2012; 25:1502-11.
 45. Xylinas E, Rink M, Margulis V et al. Multifocal carcinoma in situ of the upper tract is associated with high risk of bladder cancer recurrence. *Eur Urol.* 2012; 61:1069-70.
 46. Li WM, Shen JT, Li CC et al. Oncologic outcomes following three different approaches to the distal ureter and bladder cuff in nephroureterectomy for primary upper urinary tract urothelial carcinoma. *Eur Urol.* 2010; 57:963-9.
 47. Seisen T, Colin P, Rouprêt M. Risk-adapted strategy for the kidney-sparing management of upper tract tumours. *Nat Rev Urol.* 2015; 12:155-66.
 48. Knoedler JJ, Raman JD. Intracavitary therapies for upper tract urothelial carcinoma. *Expert Rev Clin Pharmacol.* 2018; 11:487-93.
 49. Ko YH, Song PH, Park T, Choi JY. Retrograde pyelography before radical nephroureterectomy for upper tract urothelial carcinoma is associated with intravesical tumor recurrence. *Int Braz J Urol.* 2020; 46:778-85.
 50. Baboudjian M, Al-Balushi K, Michel F et al. Diagnostic ureteroscopy prior to nephroureterectomy for urothelial carcinoma is associated with a high risk of bladder recurrence despite technical precautions to avoid tumor spillage. *World J Urol.* 2020; 38:159-65.
 51. Katims AB, Say R, Derweesh I et al. Risk Factors for Intravesical Recurrence after Minimally Invasive Nephroureterectomy for Upper Tract Urothelial Cancer (ROBUUST Collaboration). *J Urol.* 2021; 206:568-76.
 52. Song Y, Du Y, Qin C, Xu T. Comment on "Durability of response to primary chemoablation of low-grade upper tract urothelial carcinoma using UGN-101, a mitomycin-containing reverse thermal gel: OLYMPUS trial final report". *World J Urol.* 2022; 40:1251-2.