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Review article

Endocavitary treatment for upper tract urothelial carcinoma: A meta-analysis of the current literature

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Abstract

Purpose: To assess the oncologic impact of adjuvant endocavitary instillation after kidney-sparing surgery (KSS) in the treatment of upper tract urothelial carcinoma (UTUC). *Methods:* A meta-analysis of the available literature was performed using PUBMED and MEDLINE on June 2018. No time or language restrictions were applied. All included participants were substratified into 2 groups: Ta/T1 UTUC and upper tract (UT) carcinoma in situ. Subjects with higher stage disease, involvement of the bladder, or urethra were excluded. Predefined endpoints of interest were rates of cytology response, UT recurrence, UT progression, cancer-specific survival, and overall survival. *Results:* Overall, 27 eligible reports for a total of 438 patients were identified and 18 studies included for quantitative analyses. All included reports were nonrandomized observational case series. Among studies that reported on UT recurrence, 154 (35%) patients developed UT recurrence during a median follow-up of 30 months. The overall pooled estimates for adjuvant instillations in Ta-T1 patients were 40% for UT recurrence, 94% for cancer-specific survival, and 71% for OS. Subanalyses stratified by regimen used and instillation approach did not show any significant differences. In patients with UT carcinoma in situ treated with BCG, the pooled estimates for cytology response, UT recurrence, and progression were 84%, 34%, and 16%, respectively. Similarly, comparison between instillation approaches did not show any significant differences. *Conclusions:* In this meta-analysis of presumed nonmuscle invasive patients treated with kidney-sparing surgery, endocavitary instillations for noninvasive UTUC, did not reveal any differences between the regimens and instillations approaches. Patients with Ta-T1 UTUC had an UT recurrence rate comparable to that reported in the literature for nontreated patients. To date, the efficacy of endocavitary instillations in UTUC remains to be demonstrated. Upcoming novel drugs promise to change this paradigm.

Keywords: UTUC; Endocavitary instillations; Recurrence; Kidney-sparing surgery; BCG

1. Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5% of all urothelial cancers, with an estimated annual incidence of 1 to 2 cases per 100,000 [1]. UTUC exhibits aggressive clinical behavior with 5-year cancer-specific survival (CSS) rates varying from 10% to 70%, mainly depending on tumor stage and lymph-nodal status at diagnosis [2–5]. To date, the standard treatment for nonmetastatic UTUC remains radical nephro-ureterectomy with bladder cuff excision. At some centers, perioperative cisplatin-based

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combination chemotherapy is administered followed by surgery with lymphadenectomy [6]. In recent years, a kidney-sparing approach to UTUC patients has become more acceptable with the aim of preserving renal function and preventing the long-term complications associated with chronic kidney disease, without compromising oncologic outcomes and surgical safety [7,8]. To date, kidney-sparing surgery (KSS) is indicated in patients harboring a tumor size ≤2 cm, unifocal disease, low-grade cytology, low-grade cancer on ureteroscopic biopsy, and no evidence of invasion or extra-organ spread on computer tomography [6,9–13].

In patients treated with KSS, recurrence in the upper and lower urinary tract is quite common, affecting 15% to 90% of patients, depending on the case mix and follow-up [14,15]. Therefore, similar to the management of nonmuscle invasive bladder cancer (NMIBC), adjuvant endocavitary instillations have been proposed in patients treated with KSS, with the aim of reducing recurrence and progression rates in low risk papillary UTUCs and to treat upper tract (UT) carcinoma in situ (CIS); however, adjuvant endocavitary treatment is not routinely recommended by any national or international guidelines [6]. The evidence supporting the use of endocavitary instillations is scarce and mainly consists of small, single-center series, characterized by a relatively short follow-up, retrospective study design and the problems associated with reporting bias [16]. The widespread use of adjuvant instillations after KSS has been limited by concerns regarding the method of administration and the unsatisfactory oncologic results. The major challenge of adjuvant endocavitary treatment resides in specific anatomic and physiologic characteristics of the upper urinary tract which has no storage capacity and is bathes continuously by the downward flow of urine produced by the kidneys [14].

To overcome these limitations, novel methods such as slow-release formulations including stents and hydrogel polymers with reverse-thermal gelation properties (liquid at cold temperature and soft, adherent gel at body temperature) and mitomycin C (MMC) have been developed and tested in preclinical models [17–19]. The aim of this review and meta-analysis was to investigate the oncologic efficacy of endocavitary therapies for the treatment of UTUC to create an up-to-date reference point for comparison to these new methods of drug delivery. The primary endpoints of our study were endocavitary recurrence, progression, and mortality. Bladder recurrence was not assessed in this study.

2. Materials and methods

2.1. Study eligibility

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement [20]. The literature search was performed nonsystematically by 2 authors to identify studies investigating UT instillation therapies in UTUC patients. We searched PubMed and MEDLINE in June 2018 using the following string terms: ("UTUC" OR "urothelial carcinoma" OR "upper tract" OR "upper urinary tract") AND ("instillation" OR "instillation therapy" OR "intracavitary treatment" OR "endocavitary treatment" OR "Mitomycin" OR "Bacillus Calmette-Guérin). No time or language restrictions were applied. Furthermore, we checked the references of reports for additional publications.

The population, intervention, comparator, outcome, and study design approach was used to define the inclusion criteria. Studies were selected when patients with Ta/Tis/T1 UTUC (P) who received UT instillation treatment with adjuvant/curative intent (I) using different drugs (MMC/ bacillus Calmette-Guérin) and instillation methods (antegrade/retrograde) (C) were examined for treatment response and oncologic survival outcomes (O) regardless of study type (S). Predefined endpoints of interest were rates of cytology response, UT recurrence, UT progression, disease-specific survival, and overall survival. All included participants were substratified into 2 main comparison groups, such as Ta/T1 UTUC patients and UT CIS patients. Subjects with higher stage disease, involvement of the bladder or urethra were excluded. The antegrade instillation approach was performed through a nephrostomy tube. Retrograde instillation was either applied directly through a mono-J-catheter or through a bladder filling procedure when a double-J-catheter was already in place.

All potentially relevant studies were evaluated as full text. In case of multiple reports of the same cohort, the most recent and comprehensive was selected. We made exceptions when studies investigated different outcomes. Predefined data were independently extracted by 2 authors (SB, BF) using standard data extraction templates. Disagreements were resolved by consensus.

2.2. Statistical analysis

In summary statistics, median follow-up durations were calculated of given median or mean values. To avoid small sample bias, only studies with the minimum of 10 patients were included for pooling of outcome data. Proportions of treatment response and oncologic outcomes were pooled with the metaprop program [21] of STATA/MP version 14.2 (Stata-Corp., College station, TX) using Freeman-Tukey double arcsine transformation. Statistical pooling of proportions was based on the level of heterogeneity among studies. Significant heterogeneity was indicated by a P value <0.05 in Cochrane Q test, and a ratio >50% in I^2 statistics, which led to the use of a random-effects model according to the DerSimonian and Laird method [22]. When the observed heterogeneity was not significant, a fixed-effects model through the inverse-variance method was used. All statistical analyses were performed using STATA/MP 14.2 (Stata-Corp., College station, TX).

3. Results

We identified 27 eligible reports and included 18 studies for quantitative analyses. All included reports were nonrandomized

observational analyses or case series with sample sizes ranging from 5 to 50 patients. All selected studies comprised a total of 438 participants who received UT instillation therapy for Ta, T1, or Tis UTUC. Among studies that reported on UT recurrence, 154 (35%) patients developed UT recurrence during a median follow-up of 30 months.

3.1. Instillation therapy for Ta/T1 upper tract urothelial carcinoma

Twelve studies reported on treatment outcomes of overall 212 patients who underwent endoscopic laser ablation and instillation therapy for Ta/T1 UTUC [15,16,23–32]. Table 1 summarizes the instillation methods, median follow-up durations and oncologic outcomes. During a median follow-up of 31 months, 82 (39%) patients developed UT recurrence. Among 161 patients with information on cancer-specific mortality, 12 (7%) patients eventually succumbed to their disease.

Cumulative analysis, which included nine studies with ≥ 10 participants, comprised a total of 189 patients and is shown in Fig. 1 [15,16,25–30,32]. Overall pooled estimates showed that the rates of UT recurrence, CSS, and OS were 40% (95% confidence interval [CI] 29–52%), 94% (95% CI 86–99%), and 71% (95% CI 47–90%), respectively. Subanalyses stratified by drug use and instillation approach did not show significant differences (Fig. 1). Follow-up time was too heterogeneous to report time-dependent cancer recurrence probabilities.

3.2. Instillation therapy for carcinoma in situ (CIS) of the upper urinary tract

The outcome of BCG instillation treatment in patients with UT CIS was examined in 15 studies [32–46] containing information about a total of 226 patients (Table 2). Fourteen studies reported on cytology response, UT recurrence and progression with a total of 211, 226, and 226 participants, respectively. Among these patients, 177 (84%) had a full cytology response, 72 (32%) developed UT recurrence, and 38 (17%) experienced disease-progression during a median follow-up of 31 months, respectively.

Eleven studies with ≥10 participants qualified for quantitative analyses [32,33,36,37,39–43,45,46] comprising 182 patients (Fig. 2). The pooled estimates for cytology response, UT recurrence and progression were 84% (95% CI 75–92%), 34% (95% CI 27–41%) and 16% (95% CI 11–22%), respectively. Comparison between instillation approaches did not show any statistically significant differences. Among patients having initial full cytology response, the cumulative rates for UT recurrence and progression were 10% (95% CI 5–16%) and 25% (95% CI 8–33%), respectively (Fig. 3). Data on mortality were not available.

4. Discussion

In this pooled analysis, we investigated the oncologic outcomes (excluded bladder recurrence) of patients with papillary UTUC or CIS of the UT treated with KSS and adjuvant endocavitary treatment. We separately analyzed the therapeutic effect of adjuvant therapies (i.e., chemotherapeutic agents and/or immunotherapy with BCG) after KSS for papillary noninvasive (Ta-T1) UTUCs and of adjuvant BCG for the treatment of UT CIS.

We found no difference between the way of drug administration (antegrade vs. retrograde vs. combined approach) in terms of recurrence, progression, CSS, and OS, both in patients with papillary Ta-T1 UTUC and in those with UT CIS. After KSS, topical agents can be administered with an antegrade approach through a nephrostomy tube, by a retrograde approach directly through a ureteral catheter or mimicking a vesicoureteral reflux through a double-J placement [14]. Several concerns exist regarding the time of contact

Table 1
Studies investigating upper tract instillation therapies for Ta/T1 UTUC

Study Author, Year	Participants *N*	Drug (%, BCG/MMC)	Instillation approach (%, *A/R*)	Median FU months	UT recurrence *n* (%)	UT CSS *n* (%)	OS *n* (%)
Schoenberg, 1991 [23]	9	Both	Both (40/60)	24[a]	4 (36)	8 (89)	8 (89)
Eastham, 1993 [24]	7	MMC	Both (30/70)	12[a]	2 (29)		
Martinez-Pineiro, 1996 [25]	21	Both (30/70)	Both	31	3 (14)	19 (90)	
Keeley, 1997 [26]	19	MMC	Retrograde	30[a]	10 (53)	19 (100)	17 (89)
Patel, 1998 [27]	13	Both (90/10)	Retrograde	15[a]	2 (15)	13 (100)	
Clark, 1999 [28]	16	BCG	Antegrade	21[a]	5 (31)	14 (88)	11 (69)
Goel, 2003 [29]	15	MMC	Both (50/50)	64[a]	8 (53)	14 (93)	12 (80)
Palou, 2004 [30]	19	Both (75/25)	Both (75/25)	51[a]	11 (58)		
Katz, 2007 [31]	7	BCG	Retrograde	29[a]	0 (0)		
Rastinehad, 2009 [16]	50	BCG	Antegrade	61	18 (36)	49 (98)	
Giannarini, 2011 [32]	18	BCG	Antegrade	42	11 (61)	13 (72)	7 (39)
Cutress, 2012 [15]	18	MMC	Both	54	8 (44)		

Abbreviations: CSS = Cancer-specific survival; OS = overall survival; UT = upper tract; FU: follow-up.
[a] Mean values; BCG: bacillus Calmette-Guérin; MMC: Mitomycin C.

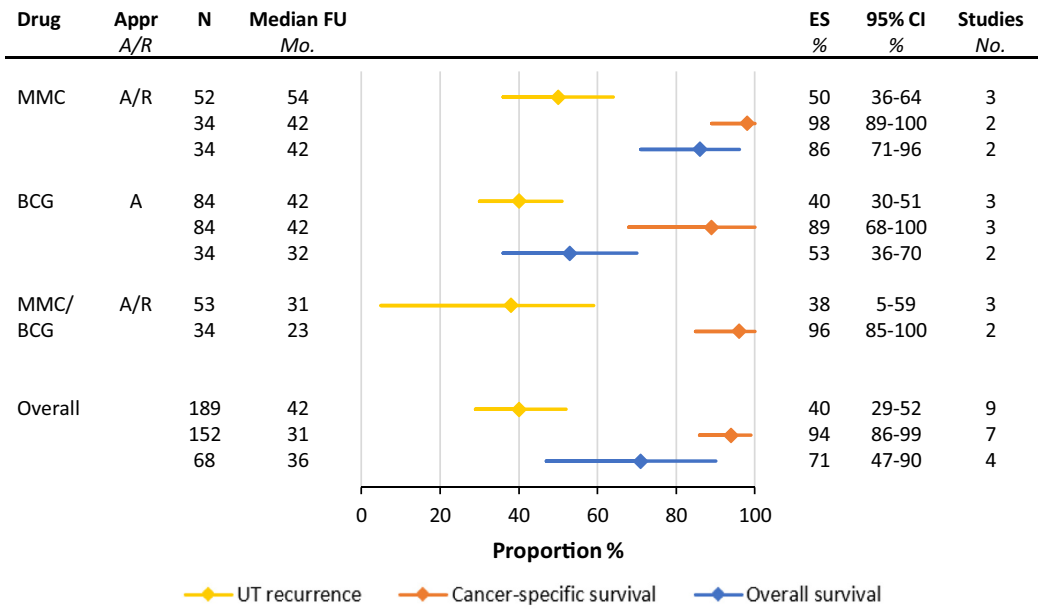

Fig. 1. Pooled analysis of studies ($N \geq 10$) investigating instillation therapies for Ta/T1 UTUC.

between the drug and the urothelial surface and the drug concentration in the UT, especially in case of double-J approach: few authors have suggested that the contact of the drug with the urothelium could be facilitated by the antegrade approach [47]. As suggested by Yossepowitch et al., refluxing of the therapeutic agent is unlikely to be successful [48]. Ex and in vivo studies on porcine models indicate that retrograde infusion by an open-ended ureteral catheter is an ideal approach for endocavitary therapy compared to antegrade infusion and vesico-ureteral reflux via indwelling ureteric stents [49,50]. However, no studies comparing the oncologic results of 2 approaches have been published so far and, we could not detect the differences between the two approaches.

We found no difference between the type of drug (MMC vs. BCG) used for the adjuvant treatment of papillary Ta-T1 UTUC treated with KSS in terms of RFS, CSS, and OS. This is in contrast to the data from studies of NMIBC which suggest superiority of intravesical BCG to chemotherapy in preventing disease recurrence and delaying or decreasing the chance of disease progression in high-grade tumors [51].

In our pooled analysis, we found that 39% of patients with papillary Ta-T1 UTUC treated with KSS and adjuvant therapy experienced an UT recurrence. This finding is concordant with that reported in series of patients undergoing KSS and observation. Cutress et al., for example, analyzed the oncological outcomes of patients treated with endoscopic vs.

Table 2
Studies investigating upper tract instillation therapy with Bacillus Calmette-Guérin for UT carcinoma in situ (CIS)

Study *Author, Year*	Participants *N*	Instillation approach (% *A/R*)	Cytology response *n* (%)	Median follow-up months	UT recurrence *n* (%)	UT progression *n* (%)
Sharpe, 1993 [33]	11	Retrograde	8 (73)	49	2 (18)	2 (18)
Yokogi, 1996 [34]	5	Both (60/40)	3 (60)	16	2 (40)	1 (20)
Nishino, 2000 [35]	6	Retrograde	6 (100)	22[a]	0 (0)	0 (0)
Nonomura, 2000 [36]	11	Retrograde	9 (82)	20[a]	3 (27)	3 (27)
Okubo, 2001 [37]	11	Retrograde	6 (55)	49	6 (55)	4 (36)
Irie, 2002 [38]	9	Retrograde	9 (100)	21	1 (11)	0 (0)
Miyake, 2002 [39]	16	Both (30/70)	16 (100)	30	3 (19)	2 (13)
Thalmann, 2002[b] [40]	22	Antegrade	19 (86)	—	—	—
Hayashida, 2004 [41]	10	Both (40/60)	10 (100)	51[a]	5 (50)	3 (30)
Kojima, 2006 [42]	11	Retrograde	8 (73)	58	3 (27)	2 (18)
Giannarini, 2011 [32]	37	Antegrade	NR	42	14 (38)	2 (5)
Shapiro, 2012 [43]	11	Retrograde	8 (73)	14	1 (11)	0 (0)
Anan, 2013 [44]	9	Retrograde	9 (100)	33[a]	1 (11)	1 (11)
Horiguchi, 2018 [45]	38	Retrograde	30 (79)	49	17 (45)	9 (24)
Tomisaki, 2018 [46]	41	Retrograde	36 (88)	26	14 (34)	9 (22)

Abbreviations: A = antegrade; R = retrograde; UT = upper tract.
[a] Mean values.
[b] Same cohort as in Giannarini et al., but reported on cytology response.

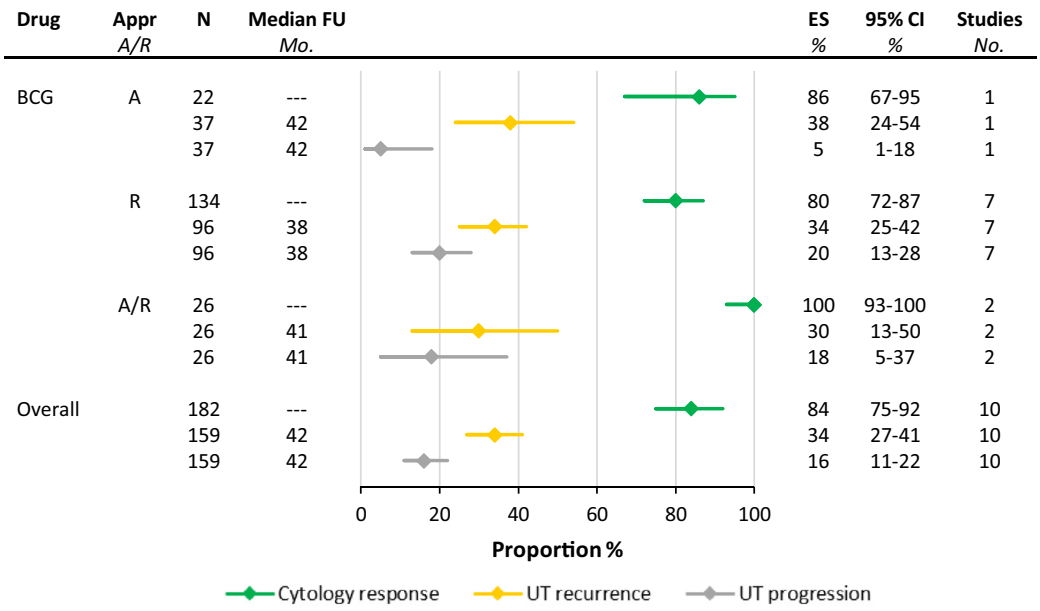

Fig. 2. Pooled analysis of studies ($N \geq 10$) investigating instillation therapies for UT CIS (Tis).

laparoscopic surgery for noninvasive UTUC and reported a UT recurrence rate of 50% in patients who received KSS within 5 years [52]. Similarly, Bagrodia et al. reported a 5-year recurrence rate of 31% for patients undergoing partial ureterectomy [53].

Recently, to overcome the above-discussed limitations of endocavitary instillations and to improve oncological outcomes of patients undergoing KSS, a new compound has been developed. This is composed of a mixture of a hydrogel polymer with reverse-thermal reaction (liquid at cold temperature and jelly at body temperature) and MMC, and aims to allow the permanence of MMC in the UT, increasing its urothelial absorption [18]. Two different groups of researchers recently demonstrated the safety of this novel drug formulation and the feasibility of serial instillations in the UT of animal models [17,18]. Two clinical trials (NCT02701023 and NCT02793128) evaluating the efficacy of this compound in UTUC and NMIBC patients are ongoing and may provide a basis for future investigation. Early results of clinical trial NCT02793128 reported at the American Urological Association annual meeting in 2018 revealed preliminary evidence of efficacy in low grade UTUC, with a complete response rate (defined as a negative ureteroscopic evaluation and a negative wash cytology after treatment) of 59%; durability data are also preliminary and additional information is expected as more patients achieve follow up milestones. Several factors limit the strength of these findings such as the selection bias, the small sample size, the variable, and limited follow-up, the absence of an endoscopic second-look and detection bias inherent the limitations of ureteroscopy and CT-scan [54].

Finally, a new biodegradable ureteral stent that can be impregnated with the most commonly used anticancer

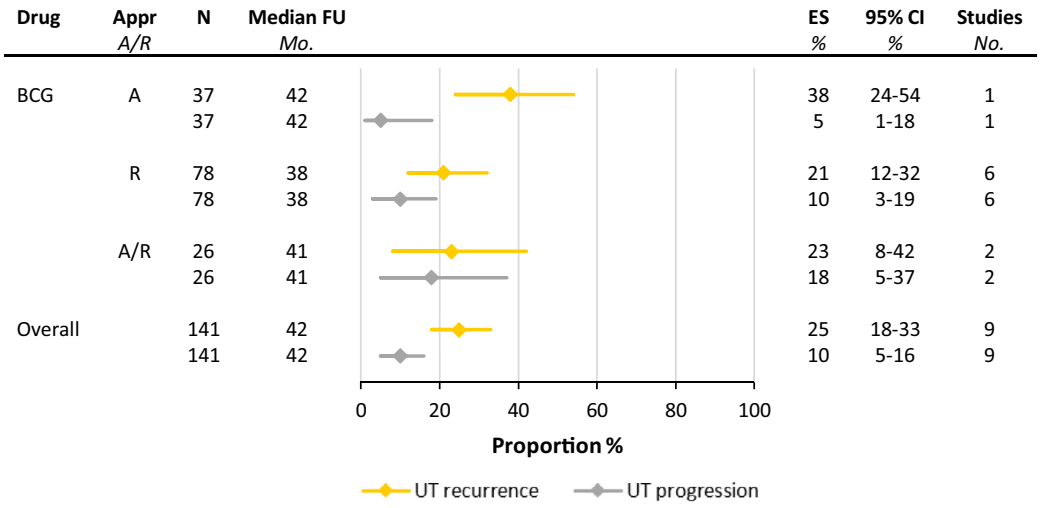

Fig. 3. Pooled analysis of studies investigating outcomes for UT CIS patients with cytology response.

agents has been developed. An in vitro study showed a fast release of the drug in the first 72 hours; after this time a plateau was achieved and the stent degraded after 9 days [19]. The antitumor effect was confirmed by exposing a cancer cell line to the biodegradable stent, demonstrating a new potentially effective approach for the adjuvant treatment of noninvasive UTUC patients.

Our review and pooled analysis are not devoid of limitations, mainly inherent to the quality of the studies included. Actually, the methods of the studies included in the meta-analysis are suboptimal. Not all the oncological outcomes of interest were assessed in each report and, therefore some analyses cannot be conducted (i.e., there were no available data on mortality for patients with CIS). Studies did not report individual data and, consequently, the separate role of clinical and pathologic variables (i.e., age, gender, and stage) cannot be assessed. Other limitations include the observational and nonrandomized design of the studies as well as the small sample size of patients evaluated in each study.

5. Conclusions

In this meta-analysis, we investigated the oncological outcomes of patients with noninvasive UTUC treated with endocavitary instillations. We found no differences between the type of drug used (MMC vs. BCG) for the adjuvant treatment of patients with Ta-T1 UTUC in terms of RFS, CSS, and OS. Moreover, both in patients with Ta-T1 UTUC and in those treated with BCG for UT CIS, no differences were found with regards to the type of approach used for instillations (antegrade vs. retrograde). Finally, we demonstrated that recurrence rates of patients treated with adjuvant instillations are comparable to those reported in the literature in untreated patients. To date, the efficacy of adjuvant endocavitary therapy in the treatment of UTUC patients is suboptimal. Novel drug delivery technologies promise to change this paradigm by favoring drug exposure in the UT leading to higher treatment efficacy.

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