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TOPIC PAPER

Upper urinary tract instillations in the treatment of urothelial carcinomas: a review of technical constraints and outcomes

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Abstract
Objectives The role of topical upper urinary tract instillation as adjuvant treatment after conservative management of urothelial carcinomas remains unclear. The aim of this article was to review available techniques and protocols proposed to treat urothelial carcinomas of the upper tract (UTUC).
Methods Evidence acquisition on UTUC topical instillations was performed by a Medline search using combinations of the following key words: urothelial carcinomas; upper urinary tract; renal pelvis; ureter; adjuvant therapy; recurrence; bacillus Calmette-Guérin (BCG); mitomycin C. A total of 36 publications were included in analysis.
Results Different approaches have been reported for instillation of the upper tract (UT): percutaneous nephrostomy, retrograde catheterisation and vesico-ureteral reflux. Currently, BCG and mitomycin C are the most commonly agents used for topical treatment of UTUC. A role for BCG in the management of UT carcinoma in situ (CIS) has been demonstrated in retrospective studies, although a definitive efficacy of adjuvant topical therapy after endoscopic resection of Ta/T1 tumours has not yet been proven. No individual study has shown a statistical improvement in survival and recurrence rates.
Conclusion Currently BCG instillation should be considered as first-line treatment for UT CIS managed conservatively in carefully selected patients. The place for adjuvant topical instillation after ablation of Ta/T1 tumours is less evident and should be evaluated on an individual basis.

Keywords Urothelial carcinomas · Upper urinary tract · Renal pelvis · Ureter · Adjuvant therapy · Recurrence · Bacillus Calmette-Guérin (BCG) · Mitomycin C

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Introduction

Urothelial carcinoma of the upper tract (UTUC) is a rare cause of tumours, with an incidence of 2 cases per 100,000 habitants and per year [1]. Until now, radical nephroureterectomy (RNU) remains the gold standard treatment of UTUC. However, therapeutic management has evolved since Huffman et al. [2] description of the first endoscopic treatment of UTUC in 1988. The idea of organ-sparing surgery was first reported in 1941 for ureteric tumours [3]. With advances in endoscopic techniques, it became possible to achieve endoscopic conservative treatment of UTUC. In the last decade, the frequency of per-cutaneous techniques has progressively declined due to the progress of retrograde flexible ureteroscopy. Conservative management of UTUC

was initially considered in imperative cases [4], for patients with bilateral tumours, tumours in solitary kidney, chronic renal failure or severe comorbidities and it spreads subsequently to elective cases [5], for small, low-grade, unifocal tumours [6]. Thus, endoscopic treatment, by percutaneous or ureteroscopic approach, seems to be an alternative option with similar oncologic outcomes when compared with RNU, when it comes to low-volume–low-grade UTUC [7]. However, some patients with conservative management are likely to undergo tumour recurrence (range 30–70 %) [8, 9] with a median recurrence-free survival rate of 10 months [7]. This high rate of recurrence is probably inherent to urothelial carcinomas (UCs), but seeding due to the endoscopic procedure itself may facilitate the process. As a consequence, these patients have to undergo a stringent follow-up, with urine cytology, cystoscopy and iterative flexible ureteroscopies.

Adjuvant chemotherapy or immunotherapy instillations in the UT have been done logically in line with current management of non-muscle invasive bladder UCs. Nevertheless, the role of adjuvant instillations in the upper urinary tract remains a moot point. Technical constraints due to the anatomy and the relative small number of published cases explain the lack of data. Our aim was to review different techniques and outcomes after instillations of UTUC.

Materials and methods

Evidence acquisition on UTUC topical instillations was performed by a Medline search in PubMed (http://www.ncbi.nlm.nih.gov), using combinations of the following key words: urothelial carcinomas; upper urinary tract; renal pelvis; ureter; adjuvant therapy; recurrence; bacillus Calmette-Guérin (BCG); mitomycin C. Selection was limited to English publications between 1982 and 2012. Due to the limited number of publications, articles were selected according to their quality and relevance, including older studies if they were historically relevant to show the evolution of concepts. A total of 36 publications were included in analysis (Fig. 1). To facilitate evaluation of the quality of information provided, levels of evidence (LE) were inserted according to general principles of evidence-based medicine [10].

Types of topical therapies and first experiences

Although the natural history of UTUC differs from that of bladder cancer, UCs share the following pejorative prognostic factors: high tumour grade and stage, tumour diameter, multifocality and existence of carcinoma in situ

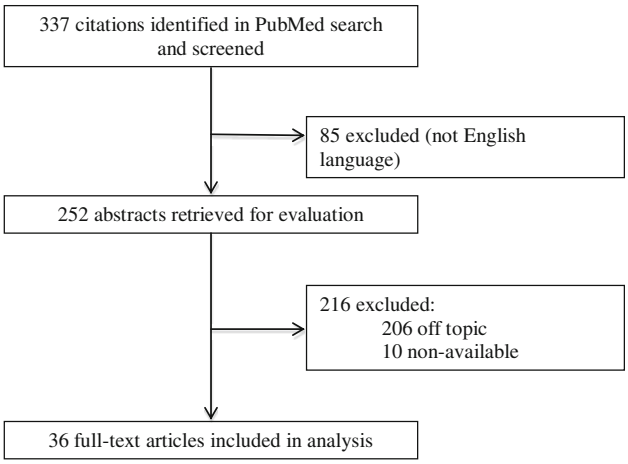

Fig. 1 Selection of publications

(CIS) [11]. The efficacy of endocavitary instillations has been demonstrated in the treatment of primary bladder CIS [12] and in the adjuvant setting after trans-urethral resection of high-risk non-muscle invasive bladder UC [13]. Similarly, in an attempt to reduce the potential for recurrence following conservative treatment of UTUC, several protocols for application of topical chemotherapy or immunotherapy into the upper urinary tract have been reported.

The therapeutic armamentarium includes UT perfusion with several chemotherapeutic agents and immunomodulatory substances [14]. The following agents have been used: BCG, mitomycin C [15–17], epirubicin [18], thiotepa [19] or BCG/interferon [20] either as the primary treatment for CIS or as an adjuvant therapy after resection or ablation of UT papillary tumours. Currently, BCG is the most commonly used agent for topical treatment of UTUC.

The first case of BCG instillation in the UT dates back to 1985, when Herr et al. [21] reported on a patient with a solitary pelvic kidney who had been treated for muscle invasive pT2G3 UTUC associated with multifocal CIS at the pyelo-ureteral junction. After pelvectomy, ureterectomy and autotransplantation with pyelovesical anastomosis, the patient received a course of six weekly BCG perfusions via the bladder because of positive surgical margins for CIS. The urinary cytology became normal and remained negative for more than 13 months, with a patient free of recurrence.

Several studies have shown that BCG could be safely administered in a retrograde fashion using bladder or ileal conduit instillation in the presence of a refluxing system or via ureteral catheter [22, 23]. Mukamel et al. [24] first suggested the potential for more direct application by infusing BCG percutaneously in a pig model, without adverse structural or functional sequel. Topical mitomycin C has also been frequently tested in the upper urinary tract

for its properties of cross-linking agent that in part inhibits DNA synthesis.

In 1987, Smith et al. [25] published the results of five patients treated with percutaneous resection of UTUC who received either BCG instillation ($n = 4$) or mitomycin C ($n = 1$) in an adjuvant setting. Subsequently, Studer et al. [26] used percutaneous application of BCG as sole therapy (i.e. without prior tumour removal) in patients with isolated positive cytology and presumed CIS of the UT. However, published data concern no more than 300 renal units (RUs) so far treated with BCG perfusion and even less for other topical agents. No prospective randomised controlled trial has been published to date.

Techniques of topical instillations for the upper urinary tract

Various approaches have been reported for the administration of topical treatment in the upper urinary tract, including percutaneous nephrostomy for anterograde instillation, retrograde catheterisation and those using vesico-ureteral reflux. Physiologically, the upper urinary tract is drained permanently into the bladder. The major drawback for instillation in the UT relies on whether or not treatment would remain at the tumour site for a sufficient period to cause a satisfactory antitumour effect, with a relative short duration of exposure.

Anterograde instillation

The most reliable access to the upper urinary tract remains via a nephrostomy tube large enough (e.g. 10F) left in place after percutaneous resection or fulguration, or placed under local anaesthesia and in the prone position, under ultrasound control. This procedure allows for reliable and iterative exposure of the urothelium to the topical agent. Some investigators have speculated that contact of the agent with the urothelium was optimised by anterograde administration [26]. The tube is left closed between perfusions. Before each perfusion, unobstructed flow of contrast medium from the renal pelvis to the bladder is verified, and pyelovenous or pyelolymphatic backflow is excluded under fluoroscopy. The agent is instilled by gravity and linked to a manometer to maintain intrarenal pressure below 25 cmH_2O [16]. BCG therapy was the most commonly agent used, and Thalman et al. [27] have proposed a reproducible protocol. A dose of 360 mg Immun BCG Pasteur® or 243 mg Immucyst® is dissolved in 150 mL 0.9 % saline, which is 3 times the dose and volume but the same concentration as that used in the bladder. The flask is then placed 20 cm above the level of the kidney of the supine patient. A continuous flow of approximately 1 mL per minute is maintained for 2 h. After the perfusion is finished, the nephrostomy is closed. Patients receive ampicillin prophylactically and are kept under hospital surveillance for one night. BCG perfusion is repeated on a weekly basis for 6 weeks (one treatment course). If cytology of the retrograde washout remains positive, a further treatment course is initiated and if not, the nephrostomy tube can be removed.

The main criticism of percutaneous instillation is that a significant breach in the integrity of the collecting system could risk tumour recurrence through seeding of cancer cells. However, the risk is only theoretical since we found only two reported cases of UC tract seeding after percutaneous resection, in patients who did not undergo adjuvant therapy [28, 29].

Retrograde instillation

With the development of small calibre flexible digital ureteroscopes, which allow easy inspection of the entire intrarenal collecting system, combined with effective ablative energy sources, the retrograde approach has received considerable interest in recent years.

The topical agent can be delivered by retrograde reflux from the bladder with an indwelling double-J stent in Trendelenbourg position [30]. A 6F or 7F double pigtail ureteral catheter is placed retrogradely in the urinary tract to create a vesico-ureteral reflux. A cystogram is performed with the patient in the Trendelenbourg position to determine the volume necessary to clearly visualise the entire ureter and the renal caliceal system (range 80–250 mL, median 120 mL). The intravesical instillation of the agent is performed with the patient in the Trendelenbourg position, held in position for 15–30 min and voided 30 min to 2 h after instillation. As for anterograde instillation, a course of treatment for BCG includes a weekly instillation for 6 weeks. After evaluation at the end of the course, the ureteral catheter can be removed if the cytology remains negative.

However, the presence of a double-J stent does not guarantee urinary reflux: only 59 % of patients had reflux after cystography according to Yossepowitch et al. [31]. Another alternative has been described by Patel et al. [32] using a transvesical retrograde ureteric catheterisation with a single-J stent secured to the skin of the abdomen and with the extremity positioned in the upper calyx. These instillations were completed using gravity to flow in a retrograde fashion, maintaining pressures ≤ 20 cmH_2O to minimise pyelorenal reflux of BCG. In 2007, Katz et al. [20] described adjuvant combination therapy of BCG and interferon-α2b for the management of UTUC in an outpatient setting, using a 5F open-ended ureteral catheter that was placed in the office before each treatment.

One major drawback with ureteric stents ≥4F is the possible ureteric obstruction and subsequent pyelovenous influx during instillation. Furthermore, a ureteric catheter can theoretically lead to an increased risk of injury of the pyelocaliceal mucosae. In addition, it is often difficult to complete filling of the pyelocaliceal system and often the superior calyx remains unfilled.

Another protocol by Rastinehad et al. [33] consists of bilateral meatotomies with indwelling ureteral stents. After removal of the stents, reflux is confirmed by cystography and volume is recorded. The adjuvant topical protocol consists to perform instillations via the bladder for a total of 1 h of dwell time.

Because of its mode of action, the perfusion of BCG in the upper urinary tract by vesico-ureteral reflux has the potential to cause an efficient immune reaction. Indeed, the antitumour effect of BCG occurs primarily by a local immunologic reaction. The activation of an immune response is initiated by the attachment of the vaccine to the tumour cells or the urothelium and is rapidly developed by the stimulation of mononuclear cells. It has been reported that the attachment of BCG to tumour cells, and the stimulation of mononuclear cells could occur in a short time frame or even by mere contact [34].

Oncological results

Topical instillations as adjuvant therapy after endoscopic management

Overall, we found 12 series that specifically assess topical adjuvant therapy for UTUC (Table 1). The older publications were feasibility studies with limited cases.

Smith et al. [25] first reported in 1987 on six patients with renal pelvic UTUC treated with percutaneous resection who received intracavitary therapy through the nephrostomy tube (mitomycin C in 1 and bacillus Calmette-Guerin in 5). Five patients remain free of recurrence with a follow-up of 3–28 months (mean 9.5 months).

In 1988, a study by Orihuela et al. [18] found a recurrence rate of 80 % in patients who did not receive adjuvant BCG versus 17 % among those who did. However, a follow-up study showed no survival advantage with adjuvant immunotherapy [35].

Schoenberg et al. [36] reported on 10 patients with solitary kidneys and UTUC. The patients received chemotherapy in the form of BCG instillation as an adjunct to percutaneous resection, with no reported morbidity. Six of the patients had no recurrence, one had recurrence at 19 months, and one developed metastases at 15 months. One died from disease progression.

Eastham et al. [16] reported on the use of mitomycin C as topical therapy after endoscopic resection of superficial UC of the renal pelvis or ureter. Seven patients were treated over a 4-year period and were either not fit for more aggressive treatment or had a solitary kidney. No systemic side effects due to perfusion with mitomycin C occurred. Five patients had no evidence of disease while one had a marked decrease in tumour burden.

In 1995, Vasavada et al. [37] also reported the use of BCG in the adjuvant setting for UTUC in 8 patients with anatomically solitary kidney. At a mean follow-up of 23.8 months, 62.5 % of patients were disease free, 25 % of patients died of the disease, and 12.5 % were alive with metastatic disease.

A study by Martinez-Pineiro et al. [38] concerning 42 UTUC treated solely by endourological approach came with a recurrence rate of 24 %. After adjuvant BCG or mitomycin C instillation, the recurrence rate was 12.5 and 14 %, respectively (mean follow-up 30.6 months), compared to 60 % for thiotepa and 40 % for oral combination of 5-fluorouracil and uracil.

In 1998, Patel et al. [32] evaluated the role of combining ureteroscopic tumour ablation with retrograde instillation of BCG through a double-J stent in 17 renal units (RUs) with non-muscle invasive UTUC. At a mean follow-up of 15 months, 15 RUs of 17 (88 %) were preserved and remained tumour-free.

Clark et al. [39] reported a recurrence rate of 6 of 18 RUs (33 %) treated by anterograde instillations of BCG after percutaneous resection. These recurrences occurred at a mean time of 11 months and were treated endoscopically in 4 and with RNU in 2.

In 2002, Studer et al. [27] published a first series completed in 2011 [40], which currently constitutes the largest series with 64 RUs in 55 patients with non-muscle invasive UTUC receiving anterograde BCG perfusion. Among these patients, 22 RUs received BCG with adjuvant intent after ablation of Ta/T1 tumours. Recurrence occurred in 13 of 22 RUs (59 %) and progression occurred in 9 of 22 RUs (41 %) with Ta/T1 tumours.

In a negatively selected patient population, Thalmann et al. reported a recurrence rate of 87 % after anterograde instillation with BCG for papillary UTUC [27]. The author concluded that BCG prevents these patients from requiring dialysis and buys time for some but does not provide cure.

The only comparative studies were retrospective on small cohorts. Jabbour et al. [41] found in their series that patients with grade 1 tumours treated with BCG had a significantly lower recurrence rate: 1 of 7 treated patients (14 %) versus 4 of 8 (50 %) who did not receive BCG (LE: 4).

In 2009, data from Rastinehad et al. [28] concerning BCG perfusion after ablation of Ta/T1 tumours showed no

Table 1 Main series reporting topical instillation of the UT as adjuvant therapy after resection of Ta/T1 UTUC

Study	No patients	No renal units	Type of treatment	Route of instillation	UT recurrence	Follow-up (months)
Smith et al. [25]	6	6	Mitomycin C (1) BCG (5)	Anterograde	17 % (1/6)	9.5
Orihuela et al. [18]	6	6	BCG	Anterograde	17 %	19
Schoenberg et al. [36]	9	9	BCG	Anterograde	11 % (1/9)	24
Eastham et al. [16]	7	7	Mitomycin C	Retrograde	29 % (2/7)	12
Vasavada et al. [37]	8	8	BCG	Anterograde	37 %	24
Martinez-Pineiro et al. [38]	28	31	Mitomycin C (14) BCG (11) Thiotepa (5) IFN 2α (1)	Anterograde or Retrograde	Mitomycin C 14 % BCG 12.5 % Thiotepa 40 %	31
Patel et al. [32]	13	17	BCG	Retrograde	12 % (2/17)	15
Clark et al. [39]	17	18	BCG	Anterograde	33 % (6/18)	11
Jabbour et al. [41]		13	BCG	Anterograde	23 % (3/13)	59
Thalmann et al. [27]	15	16	BCG	Anterograde	87 % (14/16)	42
Rastinehad et al. [28]	NR	50	BCG	Anterograde	18/50 (36 %)	61
Giannarini et al. [40]	NR	22	BCG	Anterograde	13/22 (59 %)	42

significant benefit for adjuvant BCG perfusion after percutaneous resection of UTUC in 50 RUs compared with resection alone in 39 RUs with regard to recurrence and progression rates and time to recurrence, even after stratification by tumour stage and grade (LE: 3). The investigators from the same institution performed a subsequent non-systematic review and found a recurrence rate range from 11 to 85 % although they are closer to 33 % in the 2 largest series. The stratification by grade yields recurrence rate of 25 % for grade 1, 27 % for grade 2 and 35 % for grade 3, from a total of 110 patients [33]. These data showed no significant benefit for adjuvant BCG perfusion after percutaneous resection of Ta/T1 UTUC in 50 RUs compared with resection alone in 39 RUs with regard to recurrence and progression rates and time to recurrence, even after stratification by tumour stage and grade (LE: 3).

Thus, to date, there are no available guidelines about the use of topical therapy as a primary treatment of UTUC recurrence after initial resection.

Topical instillations as curative intent in CIS

In the literature, BCG perfusion for curative treatment of CIS was associated with a uniformly high initial response rates, from 60 to 100 %, and several studies support the use of BCG for UTUC CIS.

In 1989, Studer et al. [26] first used BCG in 10 RUs (eight patients) with cytological evidence of carcinoma in situ. In all but one patient, the cytology became negative.

Since then, many other descriptive studies reported comparable results, as well by anterograde as by retrograde instillation (Table 2). Thus, bacillus Calmette-Guérin (BCG) therapy seems to provide cure in approximately 50 % of renal units with CIS. However, each study included less than 20 RUs treated. The main limitation of these retrospective studies is that the initial diagnosis of CIS was usually made by selective urine cytological examinations rather than biopsy-proven disease. The data were based on normalisation of selective urine cytology rather than more rigorous criterion for success like ureteroscopy and biopsy. Furthermore, of the initial responders in these studies, 25 % experienced upper urinary tract recurrence and metastatic disease developed in almost 10 % of these patients.

In 2006, Kojima et al. [42] retrospectively reviewed the post-treatment course of 17 patients with CIS of the UT who had undergone either a RNU (6 patients) or a BCG therapy (11 patients). No significance was found in either the 5-year recurrence-free survival or the 5-year cancer-specific survival between the 2 groups, so that the authors concluded that BCG therapy was as effective as RNU in long-term outcomes (LE: 3).

In the main series of Giannarini et al. [40] recurrence occurred in 30 of 64 RUs (47 %), 17 of 42 (40 %) with CIS and 13 of 22 (59 %) with Ta/T1 tumours. Progression occurred in 11 of 64 RUs (17 %), 2 of 42 (5 %) with CIS and 9 of 22 (41 %) with Ta/T1 tumours. RNU was eventually performed in 7 of 64 RUs (11 %), 2 of 42 (5 %) with CIS and 5 of 22 (23 %) with Ta/T1 tumours. Patients treated with curative intent for CIS had significantly better progression-free survival ($p < 0.01$) and nephroureterectomy-free survival ($p = 0.05$) compared with those treated

Table 2 Main series reporting BCG instillation of the UT as curative therapy for CIS

Study	No patients	No renal units	Route of BCG instillation	Positive response	UT recurrence	Follow-up (months)
Sharpe et al. [22]	11	17	Retrograde	76 % (13/17)	18 % (2/11)	49
Yokogi et al. [48]	5	8	Anterograde or Retrograde	63 % (5/8)	0 % (0/8)	10–46
Nishino et al. [46]	6	6	Retrograde	100 % (6/6)	0 % (0/6)	22
Nonomura et al. [49]	9	11	Retrograde	82 % (6/11)	22 % (2/9)	NR
Okubo et al. [50]	11	14	Retrograde	64 % (9/14)	45 % (5/11)	18–82
Thalmann et al. [27]	22	25	Anterograde	88 % (22/25)	55 % (12/22)	42
Irie et al. [30]	9	13	Retrograde	100 % (13/13)	11 % (1/9)	36
Miyake et al. [51]	16	16	Anterograde or Retrograde	81 % (13/16)	19 % (3/16)	30
Hayashida et al. [52]	10	11	Anterograde or Retrograde	100 % (11/11)	50 % (5/10)	51
Kojima et al. [42]	11	13	Retrograde	77 % (10/13)	27 % (3/11)	1–76
Giannarini et al. [40]	NR	42	Anterograde	NR	40 % (17/42)	42

with adjuvant intent after ablation of Ta/T1 tumours, although the improvement of the recurrence-free survival was not significant (LE: 3).

In the case of flat lesions, the combination of BCG instillations with new techniques of visualisation, like photodynamic techniques or new digital ureteroscopes with narrow-band imaging (NBI), could probably allow an improved conservative strategy for these lesions [43, 44].

Prevention of UTUC with bladder instillation

After nephroureterectomy, patients may develop bladder cancer in up to 40 %. In this population, a reduction in the bladder recurrence could theoretically reduce the risk of subsequent seeding into the contralateral ureter, and reduce the risk of renal failure from tumour or from damage to the contralateral ureteric orifice during bladder cancer surgery. Recently, O'Brien et al. [45] performed a prospective randomised trial to evaluate the role of a single post-operative mitomycin C instillation in order to prevent bladder recurrence after nephroureterectomy for UTUC. This is the largest randomised trial ever performed on the management of UTUC with 284 patients included. The results have shown a reduction in the risk of bladder cancer in the subsequent year by almost 40 % with little risk of adverse event (LE: 2). Further study is needed to determine the effect on contralateral UTUC recurrence.

Adverse events

Also its efficacy is debatable, topical instillations of the upper urinary tract appear to be safe. The major complications are BCG dissemination and urosepsis secondary to Gram-negative organisms, with both of them being relatively rare occurrences. Minor complications such as fever without infection and the presence of irritative voiding symptoms throughout the treatment period are more common. Colonisation of the nephrostomy tube with skin flora is also frequent. Rastinehad et al. [28] reported one death from sepsis, another patient with a testicular granuloma that led to an orchidectomy, and possibly one case of BCG dissemination suspected by recurrence of febrile episodes of unknown origin.

In one series of 11 patients, there was one case of BCG dissemination [22]. Another study reported two patients with sepsis and one with BCG dissemination of 37 patients treated [27].

Persistent fever after BCG administration was reported in 5 % of patients in combined major series, although this side effect was resolved with appropriate antimicrobial therapy in all cases. It has been reported in up to 67 % of patients in one series [46]. Biopsies during post-BCG nephroscopy may reveal renal granuloma, but this generally have no clinical significance [47].

Topical mitomycin C is also well tolerated in the UT. No systemic side-effect resulting from perfusion of mitomycin C as topical therapy after endoscopic resection of UTUC has been observed [16].

Interestingly, renal function was not impaired after instillations of BCG or mitomycin C, preserving quality of life due to the retained kidney [35]. In most cases, complications from the administration of immunotherapy or chemotherapy can be avoided by maintaining low intracavitary pressures during administration. Furthermore, obstruction and extravasation should be systematically controlled by anterograde or retrograde radiographic opacification before the instillation of these topical agents.

Conclusion

The instillation of BCG or mitomycin C in the upper urinary tract is technically feasible after conservative

treatment of UTUC with complete eradication of the tumour or for the primary treatment of CIS. The medium-term results are similar to those observed for the treatment of bladder tumours but have not been confirmed in long-term studies. A role for BCG in the management of UTUC CIS has been demonstrated in retrospective studies, although a definitive efficacy of adjuvant topical therapy after endoscopic resection of Ta/T1 tumours has still not been proven. The results appear encouraging but no individual study has shown a statistical improvement in survival and recurrence rates.

According to evidence-based medicine, BCG perfusion can be considered as first-line treatment for UTUC CIS before any RNU because the chances for cure are relatively high in carefully selected patients. The place for adjuvant topical instillation after ablation of Ta/T1 tumours is less obvious and should be evaluated on an individual basis. Further studies are needed to clarify the situation.

In case of imperative indications of conservative treatment, in patients in whom radical surgery may present a prohibitive risk or may leave the patient functionally anephric, conservative resection with adjuvant topical chemotherapy/immunotherapy is an option. In this poor-outcome population, kidney sparing could be achieved in up to 90 % of the cases, preventing the development of worsening of chronic renal failure or the need for dialysis and its negative consequences. Furthermore, the local control of the disease prevents or at least delays the occurrence of complications of UTUC such as bleeding or flank pain, improving the quality of life of these patients.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Siegel R, Naishadham D, Jemal A (2012) Cancer statistics, 2012. CA Cancer J Clin 62:10–29. doi:10.3322/caac.20138
2. Huffman JL (1988) Ureteroscopic management of transitional cell carcinoma of the upper urinary tract. Urol Clin North Am 15:419–424
3. Vest SA (1945) Conservative surgery in certain benign tumors of the ureter. J Urol 53:97–120
4. Gadzinski AJ, Roberts WW, Faerber GJ, Wolf JS Jr (2010) Long-term outcomes of nephroureterectomy versus endoscopic management for upper tract urothelial carcinoma. J Urol 183: 2148–2153. doi:10.1016/j.juro.2010.02.005
5. Chen GL, Bagley DH (2000) Ureteroscopic management of upper tract transitional cell carcinoma in patients with normal contralateral kidneys. J Urol 164:1173–1176
6. Roupret M, Zigeuner R, Palou J, Boehle A, Kaasinen E, Sylvester R et al (2011) European guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinomas: 2011 update. Eur Urol 59:584–594. doi:10.1016/j.eururo.2010.12.042
7. Cornu JN, Roupret M, Carpentier X, Geavlete B, de Medina SG, Cussenot O et al (2010) Oncologic control obtained after exclusive flexible ureteroscopic management of upper urinary tract urothelial cell carcinoma. World J Urol 28:151–156. doi:10.1007/s00345-009-0494-x
8. Keeley FX Jr, Bibbo M, Bagley DH (1997) Ureteroscopic treatment and surveillance of upper urinary tract transitional cell carcinoma. J Urol 157:1560–1565
9. Johnson GB, Fraiman M, Grasso M (2005) Broadening experience with the retrograde endoscopic management of upper urinary tract urothelial malignancies. BJU Int 95(Suppl 2):110–113
10. Howick J, Chalmers I, Glasziou P, Greenhalgh T, Heneghan C, Liberati A, et al (2011) Oxford Centre for Evidence-Based Medicine. The Oxford 2011 levels of evidence. http://www.cebm.net/index.aspx?o=5653
11. Stewart GD, Bariol SV, Grigor KM, Tolley DA, McNeill SA (2005) A comparison of the pathology of transitional cell carcinoma of the bladder and upper urinary tract. BJU Int 95:791–793. doi:10.1111/j.1464-410X.2005.05402.x
12. Sylvester RJ, van der MA, Lamm DL (2002) Intravesical bacillus Calmette-Guerin reduces the risk of progression in patients with superficial bladder cancer: a meta-analysis of the published results of randomized clinical trials. J Urol 168:1964–1970. doi:10.1097/01.ju.0000034450.80198.1c
13. Huncharek M, McGarry R, Kupelnick B (2001) Impact of intravesical chemotherapy on recurrence rate of recurrent superficial transitional cell carcinoma of the bladder: results of a meta-analysis. Anticancer Res 21:765–769
14. O'Donoghue JP, Crew JP (2004) Adjuvant topical treatment of upper urinary tract urothelial tumours. BJU Int 94:483–485. doi:10.1111/j.1464-410X.2004.04987.x
15. van Helsdingen PJ, Rikken CH (1986) Treatment of urothelial carcinoma of the upper urinary tract following prostatocystectomy with mitomycin C instillation in the ileal loop. J Urol 136:461–463
16. Eastham JA, Huffman JL (1993) Technique of mitomycin C instillation in the treatment of upper urinary tract urothelial tumors. J Urol 150:324–325
17. Keeley FX Jr, Bagley DH (1997) Adjuvant mitomycin C following endoscopic treatment of upper tract transitional cell carcinoma. J Urol 158:2074–2077
18. Orihuela E, Smith AD (1988) Percutaneous treatment of transitional cell carcinoma of the upper urinary tract. Urol Clin North Am 15:425–431
19. De Kock ML, Breytenbach IH (1986) Local excision and topical thiotepa in the treatment of transitional cell carcinoma of the renal pelvis: a case report. J Urol 135:566–567
20. Katz MH, Lee MW, Gupta M (2007) Setting a new standard for topical therapy of upper-tract transitional-cell carcinoma: BCG and interferon-alpha2B. J Endourol 21:374–377; discussion 377 doi:10.1089/end.2007.9969
21. Herr HW (1985) Durable response of a carcinoma in situ of the renal pelvis to topical bacillus Calmette-Guerin. J Urol 134:531–532
22. Sharpe JR, Duffy G, Chin JL (1993) Intrarenal bacillus Calmette-Guerin therapy for upper urinary tract carcinoma in situ. J Urol 149:457–459; discussion 459-460
23. Ramsey JC, Soloway MS (1990) Instillation of bacillus Calmette-Guerin into the renal pelvis of a solitary kidney for the treatment of transitional cell carcinoma. J Urol 143:1220–1222
24. Mukamel E, Layfield LJ, Hawkins RA, Dekernion JB (1988) The effect of bacillus Calmette-Guerin on the urinary system of pigs. J Urol 139:165–169
25. Smith AD, Orihuela E, Crowley AR (1987) Percutaneous management of renal pelvic tumors: a treatment option in selected cases. J Urol 137:852–856
26. Studer UE, Casanova G, Kraft R, Zingg EJ (1989) Percutaneous bacillus Calmette-Guerin perfusion of the upper urinary tract for carcinoma in situ. J Urol 142:975–977

27. Thalmann GN, Markwalder R, Walter B, Studer UE (2002) Long-term experience with bacillus Calmette-Guerin therapy of upper urinary tract transitional cell carcinoma in patients not eligible for surgery. J Urol 168:1381–1385
28. Rastinehad AR, Ost MC, Vanderbrink BA, Greenberg KL, El-Hakim A, Marcovich R et al (2009) A 20-year experience with percutaneous resection of upper tract transitional carcinoma: is there an oncologic benefit with adjuvant bacillus Calmette Guerin therapy? Urology 73:27–31. doi:10.1016/j.urology.2008.06.026
29. Huang A, Low RK, White deVere R (1995) Nephrostomy tract tumor seeding following percutaneous manipulation of a ureteral carcinoma. J Urol 153:1041–1042
30. Irie A, Iwamura M, Kadowaki K, Ohkawa A, Uchida T, Baba S (2002) 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 59:53–57
31. Yossepowitch O, Lifshitz DA, Dekel Y, Ehrlich Y, Gur U, Margel D et al (2005) Assessment of vesicoureteral reflux in patients with self-retaining ureteral stents: implications for upper urinary tract instillation. J Urol 173:890–893. doi:10.1097/01.ju.0000147747.89028.64
32. Patel A, Fuchs GJ (1998) New techniques for the administration of topical adjuvant therapy after endoscopic ablation of upper urinary tract transitional cell carcinoma. J Urol 159:71–75
33. Rastinehad AR, Smith AD (2009) Bacillus Calmette-Guerin for upper tract urothelial cancer: is there a role? J Endourol 23:563–568. doi:10.1089/end.2008.0164
34. Schneider B, Thanhauser A, Jocham D, Loppnow H, Vollmer E, Galle J et al (1994) Specific binding of bacillus Calmette-Guerin to urothelial tumor cells in vitro. World J Urol 12:337–344
35. Jarrett TW, Sweetser PM, Weiss GH, Smith AD (1995) Percutaneous management of transitional cell carcinoma of the renal collecting system: 9-year experience. J Urol 154:1629–1635
36. Schoenberg MP, Van Arsdalen KN, Wein AJ (1991) The management of transitional cell carcinoma in solitary renal units. J Urol 146:700–702; discussion 702-703
37. Vasavada SP, Streem SB, Novick AC (1995) Definitive tumor resection and percutaneous bacille Calmette-Guerin for management of renal pelvic transitional cell carcinoma in solitary kidneys. Urology 45:381–386
38. Martinez-Pineiro JA, Garcia Matres MJ, Martinez-Pineiro L (1996) Endourological treatment of upper tract urothelial carcinomas: analysis of a series of 59 tumors. J Urol 156:377–385
39. Clark PE, Streem SB, Geisinger MA (1999) 13-year experience with percutaneous management of upper tract transitional cell carcinoma. J Urol 161:772–775; discussion 775-776
40. Giannarini G, Kessler TM, Birkhauser FD, Thalmann GN, Studer UE (2011) Antegrade perfusion with bacillus Calmette-Guerin in patients with non-muscle-invasive urothelial carcinoma of the upper urinary tract: who may benefit? Eur Urol 60:955–960. doi:10.1016/j.eururo.2011.07.051
41. Jabbour ME, Smith AD (2000) Primary percutaneous approach to upper urinary tract transitional cell carcinoma. Urol Clin North Am 27:739–750
42. Kojima Y, Tozawa K, Kawai N, Sasaki S, Hayashi Y, Kohri K (2006) Long-term outcome of upper urinary tract carcinoma in situ: effectiveness of nephroureterectomy versus bacillus Calmette-Guerin therapy. Int J Urol 13:340–344. doi:10.1111/j.1442-2042.2006.01312.x
43. Audenet F, Traxer O, Yates DR, Cussenot O, Roupret M (2012) Potential role of photodynamic techniques combined with new generation flexible ureterorenoscopes and molecular markers for the management of urothelial carcinoma of the upper urinary tract. BJU Int 109:608–613; discussion 613-604 doi:10.1111/j.1464-410X.2011.10363.x
44. Traxer O, Geavlete B, de Medina SG, Sibony M, Al-Qahtani SM (2011) Narrow-band imaging digital flexible ureteroscopy in detection of upper urinary tract transitional-cell carcinoma: initial experience. J Endourol 25:19–23. doi:10.1089/end.2009.0593
45. O'Brien T, Ray E, Singh R, Coker B, Beard R (2011) Prevention of bladder tumours after nephroureterectomy for primary upper urinary tract urothelial carcinoma: a prospective, multicentre, randomised clinical trial of a single postoperative intravesical dose of mitomycin C (the ODMIT-C Trial). Eur Urol 60:703–710. doi:10.1016/j.eururo.2011.05.064
46. Nishino Y, Yamamoto N, Komeda H, Takahashi Y, Deguchi T (2000) Bacillus Calmette-Guerin instillation treatment for carcinoma in situ of the upper urinary tract. BJU Int 85:799–801
47. Bellman GC, Sweetser P, Smith AD (1994) Complications of intracavitary bacillus Calmette-Guerin after percutaneous resection of upper tract transitional cell carcinoma. J Urol 151:13–15
48. Yokogi H, Wada Y, Mizutani M, Igawa M, Ishibe T (1996) Bacillus Calmette-Guerin perfusion therapy for carcinoma in situ of the upper urinary tract. Br J Urol 77:676–679
49. Nonomura N, Ono Y, Nozawa M, Fukui T, Harada Y, Nishimura K et al (2000) Bacillus Calmette-Guerin perfusion therapy for the treatment of transitional cell carcinoma in situ of the upper urinary tract. Eur Urol 38:701–704; discussion 705
50. Okubo K, Ichioka K, Terada N, Matsuta Y, Yoshimura K, Arai Y (2001) 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 Int 88:343–347
51. Miyake H, Eto H, Hara S, Okada H, Kamidono S, Hara I (2002) Clinical outcome of bacillus Calmette-Guerin perfusion therapy for carcinoma in situ of the upper urinary tract. Int J Urol 9:677–680
52. Hayashida Y, Nomata K, Noguchi M, Eguchi J, Koga S, Yamashita S et al (2004) Long-term effects of bacille Calmette-Guerin perfusion therapy for treatment of transitional cell carcinoma in situ of upper urinary tract. Urology 63:1084–1088. doi:10.1016/j.urology.2004.01.046