

# Intracavitary Immunotherapy and Chemotherapy for Upper Urinary Tract Cancer: Current Evidence

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A review of the literature was performed to summarize current evidence regarding the efficacy of topical immunotherapy and chemotherapy for upper urinary tract urothelial cell carcinoma (UUT-UCC) in terms of post-treatment recurrence rates. A Medline database literature search was performed in March 2012 using the terms *upper urinary tract*, *urothelial cancer*, *bacillus Calmette-Guérin (BCG)*, and *mitomycin C*. A total of 22 full-text articles were assessed for eligibility, and 19 studies reporting the outcomes of patients who underwent immunotherapy or chemotherapy with curative or adjuvant intent for UUT-UCC were chosen for quantitative analysis. Overall, the role of immunotherapy and chemotherapy for UUT-UCC is not firmly established. The most established practice is the treatment of carcinoma in situ (CIS) with BCG, even if a significant advantage has not yet been proven. The use of BCG as adjuvant therapy after complete resection of papillary UUT-UCC has been studied less extensively, even if recurrence rates are not significantly different than after the treatment of CIS. Only a few reports describe the use of mitomycin C, making it difficult to obtain significant evidence.

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## KEY WORDS

Upper urinary tract • Urothelial cell carcinoma • Bacillus Calmette-Guérin • Mitomycin C • Chemotherapy • Immunotherapy

According to the 2011 update of the European Guidelines for the diagnosis and management of upper urinary tract urothelial cell carcinoma (UUT-UCC),<sup>1</sup> urothelial carcinomas are the fourth most common tumors after prostate and breast cancer, lung cancer, and colorectal cancer. Bladder tumors account for 90% to 95% of urothelial carcinomas; UUT-UCC are relatively uncommon and account for only 5% to 10% of urothelial carcinomas. The annual incidence of UUT-UCC in Western countries is approximately one or two new cases per 100,000 inhabitants. Pyelocaliceal tumors are approximately twice as common as ureteral tumors. In 8% to 13% of cases, concurrent bladder cancer is present, and 60% of UUT-UCC are invasive at diagnosis, compared with only 15% of bladder tumors. This kind of carcinoma has a peak incidence in people in their 70s and 80s, with a higher prevalence in men.

Radical nephroureterectomy (RNU) with excision of the bladder cuff represents the gold standard treatment for UUT-UCC, regard-

low-stage tumors. Endoscopic ablation can be considered if a flexible ureteroscope, laser generator, and pliers (pluck) for biopsies are available, if the patient is informed of the need for closer follow-up, and if a complete resection is advocated.

Segmental ureteral resection with wide margins provides adequate pathologic specimens for definitive staging and grade analysis while also preserving the ipsilateral kidney. Segmental resection is possible for the treatment of low- and high-risk tumors of the distal ureter, whereas segmental resection of the iliac and lumbar ureter is associated with a greater failure rate. Open resection of tumors of the renal pelvis or calices has almost disappeared.

Percutaneous management can be considered for low-grade or non-invasive UUT-UCC that are inaccessible or difficult to manage by ureteroscopy, even if a theoretical risk of seeding exists in the puncture tract and if perforations occur during the procedure.

After conservative treatment of UUT-UCC or for the treatment of

According to a recent review,<sup>2</sup> topical therapy appears to be safe, although its efficacy is debatable. Complications from the administration of topical immunotherapy or chemotherapy can be avoided by maintaining low intracavitary pressures during administration. Renal function does not seem to be impaired after instillation of BCG or MMC.<sup>3</sup> No systemic side effects result from perfusion with MMC, and persistent fever was reported in 5% of patients in combined major series after BCG administration; therefore, this side effect was resolved with appropriate antimicrobial therapy in all cases. Furthermore, up to 25% of patients may have granulomatous involvement of the urinary tract after BCG.

This review summarizes current evidence about the efficacy of topical immunotherapy and chemotherapy in terms of post-treatment recurrence rates.

## Evidence Acquisition

A literature search was performed in March 2012 using the Medline database. We searched using the terms *upper urinary tract, urothelial cancer, bacillus Calmette-Guérin*, and *mitomycin C* across the "Title" and "Abstract" fields with the following limits: humans and language (English).

After we screened the results, 22 full-text articles were assessed for eligibility. We selected for quantitative analysis 19 studies reporting the outcomes of cohorts of patients who underwent immunotherapy or chemotherapy with curative or adjuvant intent for UUT-UCC.

An article by Elliott and colleagues<sup>4</sup> was excluded from this review because data about recurrences were provided without distinguishing between chemotherapy and immunotherapy. Two articles, one by Palou and associates<sup>5</sup> and one by Goel and colleagues,<sup>6</sup>

*Conservative surgery for low-risk UUT-UCC allows for preservation of the upper urinary renal unit; conservative management can be considered in imperative cases (renal insufficiency, solitary functional kidney) or in elective cases (ie, when the contralateral kidney is functional) for low-grade, low-stage tumors.*

less of the location of the tumor in the upper urinary tract.<sup>1</sup> Lymph node dissection associated with RNU is of therapeutic interest and allows for optimal staging of the disease.

Conservative surgery for low-risk UUT-UCC allows for preservation of the upper urinary renal unit; conservative management can be considered in imperative cases (renal insufficiency, solitary functional kidney) or in elective cases (ie, when the contralateral kidney is functional) for low-grade,

carcinoma in situ (CIS), the instillation of bacillus Calmette-Guérin (BCG) or mitomycin C (MMC) is technically feasible by means of a percutaneous nephrostomy or even through a ureteric stent.

Different agents have been used for topical therapy, including BCG, MMC, epirubicin, and thiotepa. Topical chemotherapeutic agents can be administered after endoscopic management, whereas instillations of BCG need to be postponed until the urothelium heals to avoid systemic side effects.

were excluded because outcomes of patients who received immunotherapy or chemotherapy were not selectively reported.

The included articles were distinguished according to the grade of evidence for therapy/prevention/etiology/harm studies, as stated by Phillips and colleagues.<sup>7</sup> Two reports were retrospective studies comparing contemporary series of patients (level of evidence: 3b)<sup>8,9</sup>; 17 studies were observational studies without control (level of evidence: 4).<sup>10-26</sup>

We analyzed the use of BCG with curative intent for CIS or as adjuvant therapy after endoscopic resection of papillary tumor and the use of MMC as adjuvant therapy after endoscopic resection of papillary tumor. One report dealt with the use of BCG as salvage therapy in patients not eligible for surgery.<sup>24</sup>

The main outcome evaluated was recurrence of the urothelial disease, defined as a positive biopsy result, imaging evidence, or a positive selective cytology after intracavitary immunotherapy/chemotherapy.

## Evidence Synthesis

### Statistical Analyses

The data available in the selected articles were collected and entered into an electronic database. Cumulative analysis was conducted using Review Manager Version 5.1 (Cochrane Collaboration, Oxford, United Kingdom), designed for composing Cochrane Reviews.

Statistical heterogeneity was tested using the  $\chi^2$  test. A *P* value < .05 was used to indicate heterogeneity. Random effects models were used in case of heterogeneity.

### BCG With Curative Intent for CIS

A total of 11 articles reported outcomes of patients who received

BCG with curative intent for UUT CIS (Table 1).

In 1989, Studer and colleagues<sup>23</sup> reported the treatment of 10 UUT CIS in 8 patients. Diagnosis of CIS was made by selective ureteral catheterization. BCG was administered weekly by percutaneous nephrostomy for 6 weeks. If cytology remained positive 6 weeks later, a further treatment course was started. Median follow-up was 23 months (range, 18-28), and one recurrence (10%) after 24 months was reported.

Sharpe and colleagues<sup>22</sup> treated 11 patients with BCG 17 UUT CIS. CIS was defined as the presence of positive selective urinary cytology with no radiographic evidence of papillary transitional cell carcinoma (TCC). Treatment was repeated weekly for 6 weeks by means of a 4 Fr ureteral catheter, and repeated if cytology remained positive. Median follow-up was 49 months (range, 11-64), and three recurrences (17.65%) were reported.

Martínez-Piñeiro and colleagues<sup>15</sup> reported a large case study dealing with the endourological treatment of UUT-UCC. Only one UUT CIS was treated with BCG (weekly for 6 weeks), showing no recurrence.

Yokogi and associates<sup>25</sup> treated 8 UUT patients (3 by nephrostomy, 2 with a ureteral catheter). CIS diagnosis was made in the presence of positive selective upper tract cytology in urine collected directly and by washing with normal saline after ureteric catheterization with no abnormalities on retrograde pyelography. BCG was administered weekly for 6 weeks. Median follow-up was 28 months (range, 10-46), and three recurrences were observed (37.5%).

Nonomura and coauthors<sup>19</sup> stated the following diagnostic criteria for UUT CIS: positive urinary cytology, negative multiple

random biopsy of the bladder and prostatic urethra, negative radiographic findings in the UUT, and two serial positive cytologies in selective ipsilateral urine sampling from the pyeloureteral system. A total of 11 UUT CIS were treated in 11 patients. After placing a 6 Fr double-J (DJ), BCG was administered into the bladder weekly for 6 weeks. Median follow-up was 19.6 months (range, 4-41), and three recurrences were reported (27.27%).

The study conducted by Nishino and colleagues<sup>18</sup> included 6 men (8 UUT CIS, defined as positive selective upper urinary cytology results with no radiographic evidence of papillary TCC on either intravenous or retrograde pyelography). BCG was administered weekly for 4 to 8 weeks by means of a ureteral catheter. Median follow-up was 22 months (range, 9-38), and only a ureteral recurrence (12.5%) at 22 months was reported.

Okubo and coauthors<sup>20</sup> studied 11 patients (14 UUT CIS). Diagnostic criteria included positive voided urinary cytology and negative multiple random biopsies of the bladder and prostatic urethra; negative radiographic studies including computed tomography (CT), and two serial positive cytology results in selective ipsilateral urine samples. Twelve renal patients were treated by selective retrograde catheterization, and two units were treated using the percutaneous antegrade approach. BCG was administered weekly for 6 weeks. Median follow-up was 49.4 months (range, 18-82), and six recurrences were recorded (42.86%).

A total of 16 cases of UUT CIS were treated by Miyake and colleagues.<sup>16</sup> The diagnostic criteria were the same as for Okubo and coauthors.<sup>20</sup> BCG was administered weekly for 6 weeks through a nephrostomy tube, a single-J

**TABLE 1**
**BCG With Curative Intent for UUT CIS**

Study	Country	Patients (N)	UUTs	Scheme	Median Follow-up (mo)	Range (mo)	CIS	Recurrences (%)
Studer UE et al <sup>23</sup>	Switzerland	8	10	6 wk + every 6 wk	23.0	18.0-28.0	10	1 (10.00)
Sharpe JR et al <sup>22</sup>	Canada	11	17	6 wk + every 6 wk	49.0	11.0-64.0	17	3 (17.64)
Martínez-Piñero JA et al <sup>15</sup>	Spain	32	33	6 wk	30.6	2.0-119.0	1	0 (0.00)
Yokogji II et al <sup>25</sup>	Japan	5	8	6 wk	28.0	10.0-46.0	8	3 (37.5)
Nonomura N et al <sup>19</sup>	Japan	11	11	6 wk	19.6	4.0-41.0	11	3 (27.27)
Nishino Y et al <sup>18</sup>	Japan	6	8	4-8 wk	22.0	9.0-38.0	8	1 (12.5)
Okubo K et al <sup>20</sup>	Japan	11	14	6 wk	49.4	18.0-82.0	14	6 (42.86)
Miyake H et al <sup>16</sup>	Japan	16	16	6 wk	30.0	9.0-90.0	17	4 (23.52)
Irie A et al <sup>13</sup>	Japan	9	13	6 wk	36.0	8.0-97.0	13	3 (23.08)
Hayashida Y et al <sup>12</sup>	Japan	10	11	6 wk	50.9	12.0-134.0	11	5 (45.45)
Kojima Y et al <sup>8</sup>	Japan	11	13	8 wk	57.3	39.0-76.0	13	7 (53.85)
Giannarini G et al <sup>11</sup>	Switzerland	55	64	6 wk	42.0	2.0-237.0	42	17 (40.47)
<b>TOTAL</b>		<b>185</b>	<b>218</b>				<b>165</b>	<b>53 (32.12)</b>

BCG, bacillus Calmette-Guérin; UUT, upper urinary tract; CIS, carcinoma in situ.

(SJ) catheter, or urethral catheter for patients carrying a DJ stent. Median follow-up was 30 months (range, 9-90), and four recurrences were reported (25%).

Irie and colleagues<sup>13</sup> treated 13 UUT CIS using the vesicoureteral reflux created by a DJ catheter. The diagnosis of UUT CIS was made when the irrigated fluid of the UUT collected by retrograde ureteral catheterization revealed class 4 or 5 at least two times. BCG was administered weekly for 6 weeks. Median follow-up was 36 months (range, 8-97), and recurrences were found in three UUT (23.08%).

Hayashida and associates<sup>12</sup> studied 10 patients (11 UUT CIS). The diagnostic criteria were positive voided urinary cytology (more than class 4), positive cytology in

weekly for 8 weeks. Median follow-up was 57.3 months (range, 39-76). In the RNU group, two patients had contralateral recurrence, whereas in the BCG group, seven UUTs showed a recurrence (53.84%). There was no significant difference in 5-year recurrence-free survival between the two groups (67% vs 78%;  $P = .55$ ); the 5-year cancer-specific survival was also not significantly different (80% vs 91%;  $P = .62$ ).

The latest study was conducted by Giannarini and associates<sup>11</sup> who described a large cohort of patients treated for UUT-UCC. A total of 42 UUT CIS were administered BCG for 6 weeks through a 10 Fr nephrostomy. Median follow-up was 42 months (range, 2-237), and 17 recurrences (40.47%) were observed.

UUT CIS (weekly for 6 weeks). Mean follow-up was 30.6 months (range, 2-119), and one recurrence (12.5%) was observed.

Patel and Fuchs<sup>21</sup> conducted a study on 13 patients who underwent ureteroscopic tumor ablation for 17 papillary UUT-UCC. Sixteen renal units were administered BCG weekly for 6 weeks. Median follow-up was 14.6 months (range, 6-36), and two recurrences (12.5%) were observed.

From July 1985 to January 1998, Clark and associates<sup>10</sup> attempted definitive percutaneous management of 18 papillary UUT-UCC in 17 patients. All 18 UUT were administered BCG weekly for 6 weeks. Median follow-up was 20.5 months (range, 1.7-75.5); six recurrences (33.33%) were observed.

Between 1997 and 2005, Montanari and coauthors<sup>17</sup> treated four patients with papillary UUT-UCC by means of percutaneous resection. After the resection, all the UUT were perfused with MMC. Second-look nephroscopy with multiple biopsies was performed in all cases after 7 days and an 8 Fr nephrostomy was inserted. Second-look biopsy was negative in all cases; therefore, BCG was administered weekly through the nephrostomy for 6 weeks. Median follow-up was 71 months (range, 10-97), and no recurrences were reported.

Rastinehad and colleagues<sup>9</sup> performed a retrospective analysis of 133 patients (89 renal units) who underwent percutaneous resection of papillary UUT-UCC. Thirty-nine renal units received no adjuvant therapy after resection, whereas 50 were administered BCG weekly for 6 weeks. Median follow-up was 61 months (range, 6-115.9). Recurrences were 12 (30.77%) versus 18 (36%), with no statistically significant differences ( $P > .05$ ).

*In our cumulative analysis, we found 165 UUT CIS that were administered BCG. There were 53 recurrences (32.12%).*

selective urine samples, negative radiographic findings of UUT, and negative multiple random biopsies of the bladder and prostatic urethra. BCG was administered weekly for 6 weeks by means of a percutaneous nephrostomy, an SJ stent or using the vesicoureteral reflux created by a DJ stent. Median follow-up was 50.9 months (range, 12-134), and five recurrences (45.45%) were found.

Kojima and colleagues<sup>8</sup> conducted a comparative study. UUT CIS was diagnosed in cases of positive voided urinary cytology; negative multiple random biopsy of the bladder and prostatic urethra; no abnormality on radiographic examinations including excretory urogram, retrograde pyelography, and CT; three serial positive cytologies in selective UUT urine sample. A total of 6 patients were treated with RNU, whereas 11 patients (13 UUT CIS) were administered BCG

In our cumulative analysis, we found 165 UUT CIS that were administered BCG. There were 53 recurrences (32.12%).

#### ***BCG as Adjuvant Therapy After Resection of Papillary UUT-UCC***

Six of the included reports described the use of BCG as adjuvant therapy after resection of papillary UUT-UCC (Table 2).

In 1995, Jarrett and colleagues<sup>14</sup> described 36 patients (64 UUT) who underwent percutaneous resection of papillary UUT-UCC. Nineteen renal units received BCG weekly for 6 weeks. Median follow-up was 55 months, and only 1 recurrence (5.26%) was reported.

In the previously reported study by Martínez-Piñeiro and colleagues,<sup>15</sup> eight UUT were administered BCG after endoscopic ablation of papillary UUT-UCC. The schedule was the same as for

**TABLE 2**

**BCG With Adjuvant Intent After Resection of Papillary UUT-UCC**

Study	Country	Patients (N)	UUTs	Scheme	Median Follow-up (mo)	Range (mo)	Papillary	Recurrences (%)
Jarrett TW et al <sup>14</sup>	United States	19	19	6 wk	55.0	NA	19	1 (5.26)
Martínez-Piñero JA et al <sup>15</sup>	Spain	32	33	6 wk	30.6	2.0-119.0	7	1 (14.28)
Patel and Fuchs <sup>21</sup>	United States	13	17	6 wk	14.6	6.0-36.0	16	2 (12.50)
Clark PE et al <sup>10</sup>	United States	17	18	6 wk	20.5	1.7-75.5	18	6 (33.33)
Montanari F et al <sup>17</sup>	Italy	4	4	6 wk	71.0	10.0-97.0	4	0 (0.00)
Rastinehad AR et al <sup>9</sup>	United States	50	89	6 wk	61.0	6.0-115.9	50	18 (32.72)
Giannarini G et al <sup>11</sup>	Switzerland	55	64	6 wk	42.0	2.0-237.0	22	13 (59.09)
<b>TOTAL</b>		<b>190</b>	<b>244</b>				<b>136</b>	<b>41 (30.15)</b>

BCG, bacillus Calmette-Guérin; NA, not available; UUT, urinary tract; UUT-UCC, upper urinary tract urothelial cell carcinoma.

**TABLE 3**

**MMC With Adjuvant Intent After Resection of Papillary UUT-UCC**

Study	Country	Patients (N)	UUTs	Scheme	Median Follow-up	Range (mo)	Gx/G0	Recurrences (%)			Recurrences (%)		
								G1	G2	G3			
Martínez-Piñero JA et al <sup>15</sup>	Spain	32	33	6 wk	30.6	2.0-119.0	3	6	1 (16.66)	4	1 (25.00)	1	0 (0.00)
Keeley and Bagley <sup>26</sup>	United States	19	19	3 wk	30			7	2 (28.57)	8	4 (50.00)	4	1 (25.00)
Patel and Fuchs <sup>21</sup>	United States	13	17	6 wk	14.6	6.0-36.0		1	0 (0.00)				
<b>TOTAL</b>		<b>64</b>	<b>64</b>		<b>25.07</b>		<b>3</b>	<b>14</b>	<b>3 (21.43)</b>	<b>12</b>	<b>5 (41.66)</b>	<b>5</b>	<b>1 (20.00)</b>

MMC, mitomycin C; UUT, urinary tract; UUT-UCC, upper urinary tract urothelial cell carcinoma.

In the report by Giannarini and coauthors,<sup>11</sup> 22 UUT were administered BCG weekly for 6 weeks after ablation of papillary UUT-UCC. Median follow-up was 42 months (range, 2-237), and 13 recurrences (59.09%) were observed.

In our cumulative analysis, we found 136 papillary UUT-UCC that were administered BCG. Recurrences were 41 (30.15%).

### *BCG as Salvage Therapy in Patients Not Eligible for Surgery*

In 2002, Thalmann and colleagues<sup>24</sup> described their experience with BCG therapy of UUT-UCC in patients not eligible for surgery. Twenty-two patients (25 UUTs) presented UUT CIS, whereas 15 patients (16 UUTs) had papillary disease (TaG1 in 2, TaG2 in 6, TaG3 in 2, T1G3 in 2, and Tx in 4). Recurrence was observed in 8 UUT in the CIS group (32%), and 13 recurrences occurred in the papillary group (81.25%).

### *MMC as Adjuvant Therapy After Resection of Papillary UUT-UCC*

Three of the included reports described the use of MMC as adjuvant therapy after resection of papillary UUT-UCC (Table 3).

In the previously cited report by Martínez-Piñero and colleagues,<sup>15</sup> 14 UUT were administered MMC (3-6 times) after endoscopic ablation of papillary UUT-UCC. Mean follow-up was 30.6 months (range, 2-119), and two recurrences (14.28%) were observed.

In 1997, Keeley and Bagley<sup>26</sup> reported on 19 patients (19 renal units) who underwent ureteroscopic treatment of upper tract TCC, followed by the weekly administration of topical MMC by means of a ureteral catheter for 3 weeks. Seven UUT-UCC were G1, 8 were G2, and 4 were G3. Median

follow-up was 30 months. There were two recurrences (28.57%) in the G1 group, and four (50%) in the G2 group. Two patients with G3 TCC in three renal units died of unrelated causes, and one had a marked decrease in tumor burden.

Patel and Fuchs<sup>21</sup> described one renal unit who was treated with MMC, with no recurrence of the disease in 13 patients who underwent ureteroscopic tumor ablation for 17 papillary UUT-UCC.

In our cumulative analysis, we found 34 papillary UUT-UCC that were administered MMC. A total of nine recurrences were observed (26.47%).

## Discussion

The gold standard for treatment of UUT-UCC for patients with a normal contralateral kidney and no

cancer of the bladder has been firmly established, the topical treatment of UUT-UCC remains problematic because agents must be delivered to renal pelvis and ureter to be effective,<sup>29</sup> and the literature dealing with this topic is scarce. No randomized studies have been completed to evaluate the true value of such therapy, and most studies have set the number of instillations empirically.<sup>27</sup>

In 1985, the first case of adjuvant topical BCG immunotherapy for a UUT-UCC was described by Herr: a patient with a solitary kidney and T2 TCC underwent excision of the renal pelvis and ureter, followed by a pyelovesical anastomosis.<sup>30</sup> The margins of the renal pelvis and infundibola were positive for CIS, so the patient underwent weekly vesical administrations of BCG for

*Patients with solitary kidney, bilateral disease, poor renal function, small tumor burden, or low-grade disease force the clinician to consider other treatment options, such as segmental ureterectomy and ureteroscopic or percutaneous resection.*

evidence of metastatic disease is nephroureterectomy with excision of the bladder cuff. This therapeutic option offers 5-year survival rates of 91% for stages Ta, T1, and CIS, 43% for T2, and 23% for T3 and T4 disease.<sup>27</sup> This choice is also supported by the presence of polychronotropism, the low risk of contralateral TCC (3%), and the high recurrence rate associated with open nephron-sparing surgery.<sup>28</sup>

Patients with solitary kidney, bilateral disease, poor renal function, small tumor burden, or low-grade disease force the clinician to consider other treatment options, such as segmental ureterectomy and ureteroscopic or percutaneous resection.<sup>26</sup>

Whereas the role of intravesical immunotherapy/chemotherapy in nonmuscle-invasive urothelial

6 weeks. Urinary cytology became normal and remained negative for more than 13 months.

Afterward, BCG perfusion has been proposed with either curative intent for CIS or adjuvant intent after ablation of papillary UUT-UCC.<sup>11</sup>

Most available evidence deals with the treatment of CIS, and most are case series. No randomized, controlled trials (RCT) were conducted. Furthermore, in our review, we encountered various definitions of CIS, as we reported in the evidence synthesis. With our search criteria, we found 12 studies reporting outcomes of the treatment of CIS with BCG (185 patients, 218 UUT, 165 CIS). Except for the case series by Nishino and colleagues,<sup>18</sup> who proposed administration schemes of 4 to 8 weeks, all other series adopted a 6-week

scheme. Studer and colleagues<sup>23</sup> and Sharpe and associates<sup>22</sup> started another 6 weeks of treatment if urinary cytology remained positive after the first attempt. In our cumulative analysis, we found a recurrence rate of 32.12%.

Seven of the included studies described patients who underwent endoscopic resection of a papillary UUT-UCC and then underwent intracavitary treatment with BCG

The administration of MMC after percutaneous resection of a UUT-UCC in a solitary kidney was first described in 1986 by Stroom and Pontes.<sup>31</sup>

Our literature search found only three studies (64 patients, 64 UUTs, 34 papillary UUT-UCC) providing outcomes of a small series of patients treated with MMC after endoscopic resection of papillary UUT-UCCs. According to our

literature search. The most established practice is the treatment of CIS with BCG, even if a significant advantage has not yet been proven. The use of BCG as adjuvant therapy after complete resection of papillary UUT-UCC has been studied less extensively; according to our cumulative analysis, recurrence rates were not significantly different than that after the treatment of CIS. Only a few reports described the use of MMC, making it difficult to obtain significant evidence. ■

*In our cumulative analysis, BCG showed the same efficacy when used with curative intent for UUT CIS as when used with adjuvant intent after endoscopic resection for papillary UUT UCC: recurrences were 32.15% versus 30.15%, respectively (P = .71).*

(190 patients, 244 UUTs, 136 papillary tumors). All studies applied a 6-week scheme. Montanari and colleagues first performed a one-shot MMC perfusion right after resection. Cumulative analysis showed a recurrence rate of 30.15%.<sup>17</sup>

In our cumulative analysis, BCG showed the same efficacy when used with curative intent for UUT CIS as when used with adjuvant intent after endoscopic resection for papillary UUT UCC: recurrences were 32.15% versus 30.15%, respectively ( $P = .71$ ).

cumulative analysis, 3 UUT-UCCs were Gx/G0, 14 were G1, 12 were G2, and 5 were G3. Recurrence rates were 0%, 21.43%, 41.66%, and 20%, respectively.

### Conclusions

Although immunotherapy and chemotherapy for UUT-UCC has been described since the 1980s, their role has not been firmly established. The low prevalence of the disease makes it difficult to undertake RCTs, and only two comparative studies were found in the

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### MAIN POINTS

- Although immunotherapy and chemotherapy for upper urinary tract urothelial cell carcinoma (UUT-UCC) has been described since the 1980s, their role has not been firmly established. The low prevalence of the disease makes it difficult to undertake randomized controlled trials, and only two comparative studies were found in the literature search.
- The gold standard for treatment of UUT-UCC for patients with a normal contralateral kidney and no evidence of metastatic disease is nephroureterectomy with excision of the bladder cuff. This therapeutic option offers 5-year survival rates of 91% for stages Ta, T1, and CIS, 43% for T2, and 23% for T3 and T4 disease.
- The most established practice is the treatment of carcinoma in situ (CIS) with bacillus Calmette-Guérin (BCG), even if a significant advantage has not yet been proven. The use of BCG as adjuvant therapy after complete resection of papillary UUT-UCC has been studied less extensively; according to our cumulative analysis, recurrence rates were not significantly different than that after the treatment of CIS.
- Only a few reports described the use of mitomycin C, making it difficult to obtain significant evidence.

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