

Review Article

Endoscopic Management of Upper Urinary Tract Urothelial Carcinoma

Bong Hee Park, Seong Soo Jeon¹

Department of Urology, Incheon St. Mary's Hospital, The Catholic University of Korea College of Medicine, Incheon, ¹Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea

Upper urinary tract urothelial carcinoma (UTUC) is relatively uncommon. Radical nephroureterectomy with an ipsilateral bladder cuff excision has been the gold standard treatment for UTUC. However, recent advances in technology have made possible the increased use of endoscopic management for the treatment of UTUC. The definitive goal of endoscopic management of UTUC is cancer control while maintaining renal function and the integrity of the urinary tract. Endoscopic management includes both the retrograde ureteroscopic and antegrade percutaneous approaches. The endoscopic management of UTUC is a reasonable alternative for patients with renal insufficiency or a solitary functional kidney, bilateral disease, or a significant comorbidity that precludes radical surgery. Select patients with a functional contralateral kidney who have low-grade, low-stage tumors may also be candidates for endoscopic management. The careful selection of patients is the most important point for the successful endoscopic management of UTUC. It is crucial that patients are compliant and motivated, because a lifetime protocol of strict surveillance is necessary. Adjuvant topical therapy with Bacillus Calmette-Guerin or mitomycin C can be used after endoscopic management of UTUC in an attempt to reduce recurrence. In this article, we review current endoscopic techniques, indications for endoscopic treatment, clinical outcomes of endoscopic management, adjuvant topical therapy, and surveillance in patients with UTUC.

Keywords: Adjuvant treatment; Endoscopy; Percutaneous resection; Transitional cell carcinoma; Ureteroscopy

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Corresponding Author:

Seong Soo Jeon
Department of Urology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Korea
TEL: +82-2-3410-3555
FAX: +82-2-3410-6992
E-mail: seongsoo.jeon@samsung.com

INTRODUCTION

Upper urinary tract urothelial carcinoma (UTUC) is uncommon, accounting for only 5% to 6% of all urothelial carcinomas [1]. The estimated annual incidence in Western countries is about 2 new cases per 100,000 individuals [2]. The peak incidence of UTUC is in the seventh and eighth decades of life, and UTUC occurs three times more frequently in men than in women [3]. Whereas just 15% to 25% of bladder tumors are invasive at diagnosis, 60% of UTUCs are invasive at diagnosis [4] and UTUCs have a poorer prognosis. Radical nephroureterectomy (RNU) with excision of the ipsilateral bladder cuff is considered to be the gold standard treatment for UTUC [5].

However, despite radical surgical intervention, it has become increasingly recognized that a significant proportion of patients still die from their disease, possibly as a result of micrometastasis at the time of operation, with a 5-year disease-specific mortality of 15% to 30% [6]. Thus, endoscopic management of UTUC has gained interest. Several facets of endoscopic management, including the potential benefits of nephron-sparing surgery, the multifocal recurrent nature of UTUC, and the evolution in endoscopic technology, have contributed to this interest.

The recently published 2013 European Association of Urology Guidelines indicate that conservative management of UTUC can be considered in imperative or elective cases for low-grade, low-stage tumors [2]. In this article, we

review the current literature with regard to the endoscopic management of UTUCs.

ENDOSCOPIC MANAGEMENT

Advances in endoscopic technology, including the development of improved optics, progressively smaller and more durable rigid and flexible endoscopes, actively deflecting telescopes, and adjunctive instrumentation, have enabled endoscopic management to become more practical and efficacious when used for both diagnostic and therapeutic purposes in UTUC cases [7]. Traditionally, endoscopic management of UTUC was recommended only for patients with imperative indications, such as renal insufficiency or a solitary functional kidney, bilateral disease, or a significant comorbidity that precluded radical surgery. Recently, however, the 2013 European Association of Urology Guidelines suggested that endoscopic management of UTUC could also be used for elective cases (when the contralateral kidney is functional) if specific criteria are met, such as a unifocal tumor, tumor size < 1 cm, low-grade tumor (cytology or biopsies), no evidence of an infiltrative lesion on computed tomography (CT) urography, and an understanding of the necessity of close follow-up [2].

Direct visualization of upper urinary tract tumors can be obtained by using tumor biopsy specimens and selective urine cytology. Tumor grading in this setting is very accurate and is 90% in agreement with the grade of the final histopathological specimen [7]. Although ureteroscopy has not been demonstrated to be a dependable method of staging and therefore has been characterized by some authors as unreliable in determining stage [8], recent reports suggest a highly reliable concordance between biopsy grade and histopathological stage [9]. In addition, CT urography can detect with high accuracy evidence of UTUC extending beyond the wall of the ureter or renal pelvis [10]. Therefore, more accurate UTUC characterization can be obtained through the combination of tumor grading on biopsy and clinical staging by CT urography. Endoscopic management of UTUC can be performed via either an ureteroscopic retrograde or a percutaneous antegrade approach.

URETEROSCOPIC MANAGEMENT

Advances in ureteroscopic techniques and instruments allow for retrograde access to the entire upper urinary tract. Small-diameter rigid and flexible ureteroscopes with greater deflecting abilities have been combined with endoscopic biopsy techniques and devices for tissue ablation to offer practical approaches to managing upper urinary tract tumors [11]. The principal advantage of retrograde endoscopy is its low morbidity while maintaining urothelial integrity [12]. However, the ureteroscopic approach is limited by the size of the instruments that can be adjusted in the ureter and the size of tumor that can be adequately managed. Some parts of the upper urinary tract, such as the lower calyces, are less accessible when using the retro-

grade approach. Also, the retrograde ureteroscopic approach is difficult in patients who have undergone a previous urinary diversion.

Following retrograde access, a UTUC of the distal ureter is cleared with a rigid ureteroscope, and the remains of the ureter and renal pelvis are observed with a flexible ureteroscope. After an initial biopsy of the lesion, available management options are performed and can include mechanical debulking (cold-cup forceps or stone basket), electrofulguration, electroresection, laser photo-coagulation, or ablation. Mechanical removal of small UTUCs can be very effective, and the biopsy process can remove significant volumes of tumor. An electrosurgical technique was first used for the management of ureteral tumors, but the use of this technique is mostly confined to the distal ureter owing to the rigid design of the resectoscope.

In particular, the holmium:yttrium aluminum garnet (Ho:YAG) and neodymium:yttrium aluminum garnet (Nd:YAG) lasers used to cauterize and ablate UTUCs, which are supplied through small-diameter, flexible fibers, permit the management of relatively large UTUCs. The Ho:YAG laser is effective because it can both coagulate and ablate tissue and has minimal tissue penetration (< 0.5 mm) and therefore can be used for ureteric lesions [7]. The Nd:YAG laser has been used widely for the treatment of both bladder and upper tract tumors. It has a greater depth of penetration (4–6 mm) and provides a deeper coagulation and ablative effect on the tumor [13]. The two lasers can be used in combination. The Nd:YAG laser, penetrating to a depth of several millimeters, is used to coagulate the major volume of the tumor, and then the coagulated tissue can be removed with the Ho:YAG laser [14].

Treatment outcomes from the current literature of ureteroscopic management for UTUC are summarized in Table 1. Upper urinary tract and bladder recurrence rates for patients managed ureteroscopically are reported to be 20% to 90% and 15% to 53%, respectively, and several studies with limited follow-up have suggested 45% to 100% overall survival (OS) and 82% to 100% cancer-specific survival (CSS). Cutress et al. [6] recently reviewed the oncologic outcomes of 73 patients undergoing ureteroscopic management of UTUC. Upper urinary recurrence occurred in 68% (50/73), and 19% of the patients (14/73) eventually proceeded to nephroureterectomy. The estimated OS and CSS were 69.7% and 88.9%, respectively, at 5 years, and 40.3% and 77.4%, respectively, at 10 years. The estimated mean and median OS times were 119 months and 107 months, respectively. The median follow-up was 54 months. Similar results were reported by Cornu et al. [15] in 35 patients undergoing ureteroscopic resection of UTUC. The 3-year cancer-specific and recurrence-free survival rates were 100% and 35%, respectively. The median interval to recurrence was 10 months, and four patients ultimately underwent nephroureterectomy.

The foremost complications associated with ureteroscopic management are postoperative stricture and ureteral perforation. Complication rates have decreased with de-

TABLE 1. Outcomes of series using ureteroscopic management for UTUC

Series	No. of patients	Bx (G1/G2/G3) (n)	Follow-up (mo)	UT Rec (%)	BL Rec (%)	OS (%)	CSS (%)	NUx (%)
Fajkovic et al. [32]	20	17 (LG14/HG3)	Mean, 20	25	15	45	95	0
Cutress et al. [6]	73	59 (34/19/6)	Median, 54	68	53	60	90	19
Cornu et al. [15]	35	22 (LG16/HG6)	Mean, 24	60	40	100	100	11
Pak et al. [33]	57	NR	Mean, 53	90	NR	93	95	19
Lucas et al. [34]	39	39 (LG27/HG12)	Median, 33	46	NR	62	82	28
Johnson et al. [35]	35	35 (35/0/0)	Mean, 32	68	NR	NR	100	3
Deligne et al. [36]	61	53 (21/24/8)	Mean, 40	25	23	76	85	18
Keeley et al. [37]	41	40 (21/14/5)	Median, 26	20	37	NR	100	20

UTUC, upper urinary tract urothelial carcinoma; Bx, biopsy; FU, follow-up; UT Rec, upper urinary tract recurrence; BL Rec, bladder recurrence; OS, overall survival; CSS, cancer-specific survival; NUx, patients proceeding to nephroureterectomy; LG, low grade; HG, high grade; NR, not reported.

velopments in instrumentation and technique. The incidence of perforation is 0% to 10%, and perforations are treated by ureteral stenting or percutaneous nephrostomy drainage [7]. The stricture rate ranges from 5% to 14% [16]. Evidence suggests that a lower incidence of stricture is associated with lesions treated by laser ablation rather than by electrocoagulation [12]. Most strictures can be treated by ureteral stenting, laser incision, or balloon dilation [17]. Generally, ureteroscopic management has a notably lower requirement for blood transfusion and a lower overall complication rate than does percutaneous management [18].

Proper patient selection is crucial when considering primary ureteroscopic treatment of UTUC. Painter et al. [19] classified 45 patients who underwent ureteroscopic treatment of UTUC into elective, relative (patients who rejected radical surgery), and imperative groups. At 24 months of follow-up, the CSS was 100% in the elective group. In comparison, 12 of 16 patients in the relative group required nephroureterectomy, and 6 patients had stage pT2 or greater disease on the final histopathological examination. Thus, ureteroscopic management should be considered for low-volume, low-grade UTUC in healthy populations who are candidates for radical treatment. Boorjian et al. [20] compared 121 patients who underwent nephroureterectomy, 75 patients who underwent nephroureterectomy after ureteroscopic biopsy, and 12 patients who underwent tumor ablation. No significant difference was found in CSS among the three groups (85%, 81%, and 83%, respectively) at a mean follow-up of 37 months. An important point is that ureteroscopic biopsy or ablation before radical surgery does not adversely affect the oncologic outcomes compared with immediate radical nephron-ureterectomy.

PERCUTANEOUS MANAGEMENT

Although the ureteroscopic retrograde approach has the benefit of conserving a closed urinary system, the percutaneous antegrade approach can be considered for low-grade or noninvasive UTUC in the renal cavities [2]. The principal advantage of the percutaneous approach is that it al-

lows for the removal of a larger tumor volume from any site of the collecting system owing to the use of instruments with larger working channels, which allows better visualization and faster resection [7]. The percutaneous approach also allows better access to the lower caliceal system, which is inaccessible by flexible ureteroscopy.

After the establishment of a percutaneous tract, the lesion is initially biopsied and subsequently debulked. Various techniques have been used for tumor ablation, including monopolar and bipolar electrocautery, rollerball electrodes, lasers, and electrovaporization [21]. The whole tumor is ablated, and the base of the lesion is resected or fulgurated. The base of the UTUC is separately resected and sent for staging. Hemostasis is achieved by laser ablation or electrocautery. The established nephrostomy tract can be maintained, allowing for repeated treatment or administration of topical adjuvant therapy [14].

Treatment outcomes in the current literature for the percutaneous management of UTUC are summarized in Table 2. Upper urinary tract and bladder recurrence rates for patients managed percutaneously are reported to be 13% to 65% and 15% to 42%, respectively, and several studies with limited follow-up suggested OS of 68% to 96% and CSS of 75% to 100%. Palou et al. [22] retrospectively reviewed 34 patients who underwent percutaneous management of UTUC; 15% had grade 3 tumors with either a solitary kidney or bilateral disease. During 51 months of follow-up, upper urinary tract recurrence was found in 44% of cases, at a median time of 24 months. Nine patients required nephroureterectomy. Kidney preservation was achieved in 74% of cases. The rates of OS and CSS were 74% and 94%, respectively.

In a more recent study, Roupret et al. [23] reported on the outcomes of 24 patients who underwent a percutaneous approach for UTUC. During follow-up, which was a median of 62 months, eight recurrences were detected at a median time of 17 months. Three recurrences were in the ipsilateral ureter, one in the contralateral ureter, and four in the bladder. Five patients with high-grade or invasive tumors subsequently required nephroureterectomy; one pa-

TABLE 2. Outcomes of series using percutaneous management for UTUC

Series	No. of patients	Bx (G1/G2/G3) (n)	Follow-up (mo)	UT Rec (%)	BL Rec (%)	OS (%)	CSS (%)	NUx (%)
Rastinehad et al. [25]	89	89 (LG50/HG39)	Mean, 61	33	NR	68	NR	13
Roupret et al. [23]	24	24 (LG17/HG7)	Median, 62	13	17	79	83	21
Palou et al. [22]	34	33 (7/21/5)	Mean, 51	44	NR	74	94	26
Goel et al. [38]	20	20 (LG15/HG5)	Mean, 64	65	15	NR	75	50
Clark et al. [39]	18	18 (6/8/4)	Mean, 24	33	NR	75	82	12
Patel et al. [40]	26	23 (11/11/1)	Mean, 45	35	42	75	91	6
Fuglsig and Krarup [41]	26	NR	Mean, 21	31	NR	96	100	35

UTUC, upper urinary tract urothelial carcinoma; Bx, biopsy; FU, follow-up; UT Rec, upper urinary tract recurrence; BL Rec, bladder recurrence; OS, overall survival; CSS, cancer-specific survival; NUx, patients proceeding to nephroureterectomy; LG, low grade; HG, high grade; NR, not reported.

TABLE 3. Outcomes of series using adjuvant topical therapy for UTUC

Series	No. of patients	No. of RUs	Bx (G1/G2/G3) (n)	Treatment agent	Instillation route	UT Rec, n (%)	Mean FU (mo)
Giannarini et al. [42]	NR	22	NR	BCG	Antegrade	13/22 (59)	42
Rastinehad et al. [25]	NR	89	89 (LG50/HG39)	BCG in 50 RU	Antegrade	18/50 (36)	61
Clark et al. [39]	17	18	18 (6/8/4)	BCG	Antegrade	6/18 (33)	11
Patel and Fuchs [43]	13	17	13 (8/5/-)	BCG	Retrograde	2/17 (12)	15
Cutress et al. [6]	73	NR	59 (34/19/6)	MMC in 18 RU	Retrograde	8/18 (44)	12
Keeley and Bagley [44]	19	21	17 (5/8/4)	MMC in 21 RU	Retrograde	6/11 (54)	30
Martinez-Pineiro et al. [26]	NR	41	34 (21/10/3)	MMC in 14 RU	Ante/retrograde	10/41 (24)	35

UTUC, upper urinary tract urothelial carcinoma; RU, renal unit; Bx, biopsy; UT Rec, upper urinary tract recurrence; FU, follow-up; LG, low grade; HG, high grade; NR, not reported; BCG, Bacillus Calmette-Guerin; MMC, mitomycin C.

tient immediately and four patients during follow-up. Five patients (20.8%) died, and four of those deaths were attributed to disease progression. The authors reported 5-year disease-specific survival rates as 79.5% and tumor-free survival rates as 68%. The tumor grade and stage were predictive of disease-specific survival and recurrence-free survival.

The principal disadvantage of the percutaneous antegrade approach is the increase in morbidity compared with the ureteroscopic retrograde approach. Bleeding is a latent complication of percutaneous management owing to the vascularization of the kidney. Transfusion rates are greater than 20%, while obstruction of the ureteropelvic junction from stricture, adjacent organ injury, and pleural injury are less common [24]. There is a theoretical risk of seeding resulting from tract puncture and perforations that may occur during the procedure [2]. For tract seeding, some authors have suggested placing a large sheath to decrease intrarenal pressures [23]. The reported incidence of seeding of UTUC within the percutaneous tract is extremely rare, being only 0.75% in the most experienced center [25].

Data suggest the percutaneous management of UTUC as a tolerable alternative to radical surgery in patients with low-grade, low-volume tumors. However, the elective indications for the percutaneous management of patients with high-grade tumors are unclear. This approach is being gradually abandoned owing to the development of en-

hanced materials and advances in distal-tip deflection of recent ureteroscopes [2].

ADJUVANT TOPICAL THERAPY

Topical immunotherapy with Bacillus Calmette-Guerin (BCG) and chemotherapy with mitomycin C have been the mainstays of adjuvant topical therapy in bladder cancer. Adjuvant topical therapy has also been used after endoscopic management for UTUC in an attempt to decrease recurrences. Instillation can be performed through a percutaneous nephrostomy tube or via a retrograde ureteral catheter. The aim of therapy is continued exposure of the urothelium to the topical agent while maintaining a low pressure system that is free of infection [12]. Several agents have been used, including thiotepa, interferon, adriamycin, and mitomycin C, but the most commonly used agent is BCG. Adjuvant topical therapy with both mitomycin C and BCG has been the most widely studied, because these agents are considered to provide the best outcomes for reducing the recurrence rates of UTUC [26].

Treatment outcomes from the current literature for adjuvant topical therapy for UTUC are summarized in Table 3. Rastinehad et al. [25] recently analyzed data gathered over 20 years with adjuvant BCG after percutaneous management of UTUC. BCG was instilled as a 6-week course to 50 renal units, and outcomes were compared with 39 con-

TABLE 4. Outcomes of series using adjuvant topical BCG therapy for upper urinary tract CIS

Series	No. of patients	No. of RUs	Positive response, n (%)	Instillation route	UT Rec, n (%)	Follow-up (mo)
Giannarini et al. [42]	NR	42	NR	Antegrade	17/42 (40)	Mean, 42
Hayashida et al. [45]	10	11	11/11 (100)	Ante/retrograde	5/10 (50)	Mean, 51
Miyake et al. [46]	16	16	13/16 (81)	Ante/retrograde	3/16 (19)	Mean, 30
Irie et al. [47]	9	13	13/13 (100)	Retrograde	1/9 (11)	Mean, 36
Thalmann et al. [48]	22	25	22/25 (88)	Antegrade	12/22 (55)	Mean, 42
Okubo et al. [49]	11	14	9/14 (64)	Retrograde	5/11 (45)	Median, 49
Nonomura et al. [50]	9	11	6/11 (82)	Retrograde	2/9 (22)	Mean, 20

BCG, Bacillus Calmette-Guerin; CIS, carcinoma *in situ*; RU, renal unit; UT Rec, upper urinary tract recurrence; FU, follow-up; NR, not reported.

renal units. The two groups had similar underlying grade distributions. In general, there was no statistical difference in recurrence, progression, or time to recurrence between the control and treatment groups when classified by grade and stage. Cutress et al. [6] reported outcomes from 18 patients who underwent adjuvant mitomycin C therapy after endoscopic management. The estimated five-year UTUC recurrence-free survival was 53.8% for patients treated with adjuvant mitomycin C and 54.2% for those without adjuvant treatment. Even with substratification by UTUC grade, adjuvant topical treatment did not show any difference in UTUC recurrence-free survival for grade 1, grade 2, or grade 3 UTUC.

There is no proven efficiency for the administration of adjuvant topical therapy (BCG or mitomycin C) in the management of papillary UTUC. Reports have typically been limited to small, retrospective cohort studies with limited follow-up (typically < 36 months), mainly assessing the use of BCG and with very few assessing mitomycin C [9]. Although adjuvant topical therapy with BCG has not shown proven efficacy for papillary UTUC, several studies have reported positive outcomes for upper urinary tract carcinoma *in situ* (CIS). These studies collectively showed an 85% positive initial response rate and a 37% upper urinary tract recurrence rate, with a follow-up of 20 to 51 months (Table 4). The major limitation of these studies is that the diagnosis of upper urinary tract CIS was made on the basis of the presence of positive selective urine cytology and negative radiologic imaging findings rather than biopsy-proven disease. In addition, the response rates were based on restoration of normal urine cytology rather than more specific criteria, such as biopsy and ureteroscopy. Although the initial positive response rates with adjuvant BCG therapy for upper urinary tract CIS appear encouraging, the disease-specific mortality outcomes varied considerably, between 9% and 40% beyond 3 years, and have not been confirmed in longer terms [9].

The potential side effects of adjuvant BCG therapy include fever, flu-like illness, irritative voiding symptoms, septicemia, and death. It is also important to consider the risk of mitomycin C spillage outside the urinary tract and its tendency to generate inflammation and necrosis, espe-

cially when used in a percutaneous approach [27]. Interestingly, renal function is not impaired after administration of BCG or mitomycin C, thus preserving quality of life owing to the retained kidney [28]. In the majority of cases, complications from the instillation of chemotherapy or immunotherapy can be precluded by sustaining low intracavitary pressures during administration. Additionally, extravasation and obstruction should be systemically controlled by antegrade or retrograde radiographic opacification before the instillation of these adjuvant topical agents [29].

SURVEILLANCE

Long-term endoscopic follow-up of the upper urinary tract and bladder is obligatory. As is seen in other organ-preserving management strategies, surveillance should be stringent. All patients considered candidates for endoscopic management should be counseled and be motivated enough to adhere to a regular evaluation schedule [24]. Most investigators agree that cystoscopy, urine cytology, and ureteroscopy should be performed in declining intensity as is done with bladder cancer surveillance protocols [30]. This surveillance of the upper urinary tract should be tailored to the grade and stage of the UTUC. According to the 2013 European Association of Urology Guidelines, the recommended schedule would be cystoscopy, ureteroscopy, and cytology *in situ* at 3 and 6 months, then every 6 months for the next 2 years, and then yearly if the patient is free from tumor recurrence. Urinary cytology and CT urography are recommended at 3 and 6 months and then yearly. This surveillance after endoscopic management for UTUC should be performed for at least 5 years. Generally, a 3-month interval follow-up protocol for the first year is the most conventional pattern [31]. However, patients should be prepared to follow the schedule and undergo repeated endoscopic surveillance.

CONCLUSIONS

UTUC is a rare disease for which relatively few patients undergo endoscopic management. The definitive purpose

of endoscopic management is oncological control while preserving renal function and diminishing morbidity. The endoscopic management of UTUC has traditionally been utilized only for patients with imperative indications, such as renal insufficiency or a solitary functional kidney, bilateral disease, or a significant comorbidity that precluded radical surgery. More recent studies report that endoscopic treatment can be used even for elective cases (when the contralateral kidney is functional), such as a unifocal tumor, tumor size < 1 cm, low-grade tumor (cytology or biopsies), and no evidence of an infiltrative lesion on CT urography. Patient selection is essential to successful endoscopic management. The evaluation of the overall life expectancy of a patient is a notable consideration for elective cases. Therefore, endoscopic management for UTUC has become a reasonable treatment option in highly selected patients who are expected to adhere to stringent surveillance protocols, because recurrence after endoscopic management is very common and multiple sessions may be necessary.

The current literature supports the use of adjuvant BCG therapy in patients with upper urinary tract CIS. However, the use of adjuvant topical therapy appears to accord little benefit compared with endoscopic management alone.

Definite conclusions about the outcomes of endoscopic management for UTUC cannot be made owing to the relatively low frequency of UTUC and the lack of randomized controlled trials.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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