Ureteroscopic Management of Patients with Upper Tract Transitional Cell Carcinoma

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Abstract

Objectives: This paper reviews the indications, technique, and treatment outcomes for the ureteroscopic management of upper tract transitional cell carcinomas (UTTCCs).

Methods: The author reports on his experience and reviews of the most recent data published in the literature.

Results: The expanding experience with minimally invasive techniques to treat UTTCCs has demonstrated its safety and efficacy in selected patients. Diagnostic accuracy can be enhanced and pathologic confirmation of tumour grade and stage can be regularly obtained. In selected patients with unique, small tumours with low grade and low stage, the results of endoscopic management are encouraging. Patients with a functional solitary kidney, bilateral disease, or renal insufficiency can also be considered for conservative treatment. The patient must be willing to and capable of undergoing vigilant and frequent endoscopies during the follow-up. However, conservative management remains controversial in a patient with low-grade/low-stage disease and a normal contralateral kidney.

Conclusions: Ureteroscopic management of UTTCC is feasible and safe using, preferably, laser fulguration.

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1. Introduction

Advances in the ureteroscopic approach include the development of best optics, small-calibre actively deflecting endoscopes, specific instrumentation, and usable laser technology. With these advances, the treatment of upper tract transitional cell carcinoma (UTTCC) can be considered, particularly when standard nephroureterectomy may leave the patient functionally anephric, that is, with a solitary kidney (anatomically or functionally), bilateral UTTCC, or renal insufficiency. Conservative management of UTTCC can also be considered in case of significant medical disease.

This paper reviews the indications, technique, and treatment outcomes for the ureteroscopic management of UTTCC.
2. Epidemiology, natural history, and pathology

The incidence of UTTCC is highest in the sixth and seventh decades of life and has a 2:1 male-to-female ratio and involves twice as many whites as African Americans [1]. UTTCC is uncommon, accounting for 5% of all urothelial neoplasms and approximately 10% of all renal tumours. Distal ureteral lesions seem to be more common than middle or upper ones (7:2:1), but ureteral tumours occur at a rate one fourth to one half the incidence of tumours in the renal pelvis. UTTCCs are multifocal in 33% of patients, are bilateral simultaneously in 1% of patients, and occur in 2–4% of patients with bladder cancer [1].

The natural history of UTTCC is different from that of the bladder; as many as 60% of UTTCCs are invasive in comparison with 15% of bladder tumours [1].

Risk factors for UTTCC include cigarette smoking, exposure to carcinogens (chemical and petrochemical, coke, asphalt and other aniline exposures), cyclophosphamide treatment, history of urinary tract infections, stones, use of Chinese herbs for weight loss, and inherited tendencies. An association with Balkan nephropathy has also been described [1].

Grading for UTTCC is similar to bladder tumours. Tumour grade and stage represent the most important factors in predicting recurrence and survival for patients with UTTCC. Mufti et al found the survival rate to be >90% for patients with superficial well-differentiated tumours regardless of treatment by radical nephroureterectomy or more conservative resection [2].

Charbit found that 79% of grade 2 or 3 UTTCCs invaded into or beyond the muscle layer. All patients with low-grade tumour in whom lymphadenectomy was performed had negative lymph nodes, whereas 39% of patients with high-grade tumours had positive lymph nodes [3].

3. Symptoms and diagnosis

The most common presenting symptom of UTTCC is gross or microscopic hematuria (70–90% of patients) [1]. Flank pain is the second most common presenting symptom (30% of patients) corresponding to ureteral obstruction by blood clots or tumour. The tumour is found incidentally on an imaging study in 10–15% of patients. A flank mass corresponding to hydronephrosis or tumour mass is found in 10–20% of patients. Constitutional symptoms, such as weight loss, anorexia, or bone pain, are rarely present initially unless there is an advanced disease.

Radiography is the primary diagnostic modality for UTTCC; a filling defect on intravenous pyelography (IVP) is seen in 50–70% of cases (Fig. 1). However, computed tomography (CT) with contrast is actually the best modality to diagnose a UTTCC. This modality is accurate in distinguishing radio-opaque stones (80–250 Hounsfield units [HU]) from soft-tissue masses [10–70 HU]. CT has a sensitivity of 90%, but it does not readily distinguish low-volume Ta, T1, T2, and T3 tumours. It also has a false-negative rate of 59% for the detection of invasiveness and does not predictably identify multifocal lesions [1]. However, its role is essential to determine the stage preoperatively when a decision is needed regarding radical or conservative treatment. It can be helpful in evaluating the local extent of tumour, especially if there is high-volume disease involving renal parenchyma, regional lymph nodes, periureteral soft tissue, renal vein, and adjacent structures (Fig. 1). Metastases to the liver can also be identified. Evaluation of a filling defect seen on CT or IVP includes a voided urine cytology, cystoscopy for bladder evaluation, selective upper tract urine cytology, and sometimes retrograde pyelography. The role of urine cytology is limited for the diagnosis of filling defects, with a sensitivity that ranges from 10% to 71% and a specificity of about 60%. However, urine cytology can be useful in the setting of high-grade UTTCC or carcinoma in situ (CIS). Selective upper tract urine cytology for CIS has a reported accuracy as high as 80%. However, voided urine cytology for low-grade lesions has a false-negative rate as high as 96% [1].

Urine obtained from the collecting system through ureteral catheterisation improves the diagnostic accuracy, but reported sensitivities with this approach are 65–78%. Saline washings of the ureter following catheterisation and brush biopsy seem to improve the diagnosis. The sensitivity and specificity of brush biopsy are estimated to range from 72% to 91% and 88% to 94%, respectively [1,4]. To avoid false-positive results from contamination, it is recommended to removed primarily all bladder tumours before evaluating the upper tract.

Ureteroscopy (URS) to evaluate an upper tract filling defect can greatly enhance diagnostic accuracy.
In addition to visualising the upper tract, it allows biopsies of any lesion. For specific cases, tumour grade and sometimes tumour stage can be determined.

4. Treatment modalities

Radical nephroureterectomy with removal of a bladder cuff surrounding the ipsilateral ureteral orifice en bloc still represents the standard of care for the management of UTTCC. The rationale for this management is based on:

- Relatively low incidence of contralateral disease
- Frequency of multifocality
- Significant rate of ipsilateral recurrence if only an ureteral tract portion is removed

If nephroureterectomy would relegate the patient to dialysis (solitary kidney, renal insufficiency, or bilateral disease), an initial conservative approach with minimally invasive techniques (ureteroscopy or percutaneous approach) could be considered.

Renal-sparing surgery was first proposed by Vest in 1945 for ureteral tumours [6] and by Ferris and Dent in 1948 for renal pelvic malignancies [7]. The rationale for endoscopic treatment in patients who have UTTCC is based on two facts:

- The entire tumour is potentially removable with this technique.
- The results obtained with open surgical resection of distal ureteral tumours and ureteral reimplantation support this concept.

However, results of partial ureteral resection for proximal ureteral tumours have not been as favourable, with a 50% recurrence rate in the ipsilateral ureter or bladder. Continued definitive endoscopic management is usually reserved for patients who do not have high-grade lesions or evidence of muscle-invasive disease in the initially resected specimen. Nephroureterectomy is usually recommended if these factors are present.

5. Indications for endoscopic management

Indications for diagnostic URS include radiographic filling defects or obstruction, unilateral malignant urinary cytology, or gross haematuria and tumour found cystoscopically at the ureteral orifice. Indications for endoscopic management of UTTCC include renal insufficiency, solitary functional kidney,
bilateral tumours, comorbidities that contraindicate open surgery, and patient preference. Ureteroscopic and percutaneous approaches represent the two alternative techniques. The choice is based on lesion size, location, and multifocality. Generally, small (<15 mm) accessible lesions (ureteral, renal pelvis, and upper calices) are treated ureteroscopically because the integrity of the upper tract is maintained. Larger lesions or less accessible calices (lower) can be managed percutaneously in case of a failed ureteroscopic approach. Although nephrostomy tract recurrence is a concern, reported series indicate that the incidence is low [8]. Nevertheless, the retrograde way (ureteroscopy-holmium laser) is actually the preferable technique to use when a conservative approach is used.

Ureteroscopic treatment of UTTCC is not considered adequate therapy for patients with high-grade or invasive lesions or circumferential lesions due to the risk of subsequent ureteral stricture formation [9].

6. Techniques for URS

6.1. Equipment

The essential equipment includes:

- **Cystoscope**: to inspect the bladder, to place wires, and to perform retrograde pyelography
- **Fluoroscopy**: essential for ureteral access, monitoring during ureteroscopy, and stent placement
- **Ureteroscopes**: rigid ureteral resectoscopes with working elements as small as 9F and flexible ureteroscopes as small as 7F are available to allow inspection and treatment of the entire collecting system (Fig. 2)
- **Ancillary instrumentation**: wires, ureteral catheters, biopsy forceps, nitinol basket, JJ stent
- **Energy source**: Holmium/yttrium–aluminum–garnet (Ho/YAG) is the reference energy source due to its localised and efficient coagulation and ablation potential [10] (Fig. 2).

6.2. Operative technique

For diagnostic procedures, intravenous sedation may be used but for therapeutic procedures general anaesthesia is usually required. Depending on the preoperative evaluation, the contralateral collecting system could be evaluated before treatment of the primary lesion. This work-up includes contrast studies and selective ureteral cytology. If either of these is not completely normal, flexible ureteroscopy should be performed.

Cystoscopy is first performed and a first guidewire (working guidewire) is inserted. A safety guidewire could also be inserted. Each guidewire is carefully placed so that urothelial trauma is avoided, which can mask or lead to misdiagnosis of a lesion. The cystoscope is then removed, leaving the guidewires in place. A flexible ureteroscope is passed over the wire. Once the renal pelvis is entered, an urine sample for cytology is collected. Then, a pyelogram is obtained to guide the endoscope for a systematic evaluation of the entire collecting system to exclude synchronous multifocal disease. Contrast can be injected through the working channel of the scope to ensure that the renal collecting system has been entirely inspected. Advances in new endoscopes

Fig. 2 – Holmium/yttrium–aluminum–garnet laser (Dornier™) and flexible ureterorenoscope (ACMI DUR-8 Elite).
allow a complete exploration of the entire collecting system (Fig. 3).

Several methods exist for tissue sampling once a lesion is visualised (Fig. 4A–C). Diagnostic accuracy for UTTCC can be improved with the use of flexible cup biopsy forceps (Piranha™ forceps, Boston Scientific) or baskets [11]. The problem associated with most flexible ureteroscopic biopsy forceps is their limited cup size, usually a 1-mm sample that may be insufficient for accurate pathologic diagnosis. In case of bigger lesions, a basket can be twirled against the lesion under direct vision, closed, and retracted along with the ureteroscope. The specificity of biopsy in detecting the lesion ranges from 75% to 92%. Sometimes flexible instrumentation or the angle required for visualisation precludes direct biopsy. In these situations, the basket can be fluoroscopically positioned adjacent to the tumour and twirled under fluoroscopic control to obtain a tissue sample. The basket or forceps used for biopsies should be removed along with the ureteroscope.
to avoid any loss of tissue within the working channel.

During the procedure, bleeding can obscure visualisation. A variety of irrigation devices are available to obtain better visualisation and the use of a ureteral access sheath significantly improves flow irrigation. Other advantages of the ureteral access sheath include easy introduction and reintroduction of instruments and scopes, removal of large specimens, and low-pressure continuous flow irrigation. Minimising high-pressure irrigation during the procedure is recommended to avoid high intrarenal pressure that promotes pyelovenous or pyelolymphatic migration of malignant cells (to date, not reported) [12].

The Ho/YAG laser also has been advocated for managing UTTCC due to its tissue penetration depth of 0.4 mm. Therefore, the visualised effect represents the maximal depth of tissue penetration. The primary advantages of the Ho/YAG laser are its ability to provide superficial ablation in the thin-walled ureter and the ability to provide coagulation and homeostasis. The laser fibre should be in permanent contact with, or very close to, the tissue to be ablated.

At the end of the procedure, a biopsy of the base of the tumour should be obtained to evaluate the invasion, before laser fulguration. At the same time, cytology may be obtained by aspiration or saline wash before and after tumour ablation. Using these techniques, the accuracy of grading upper tract tumours can be as high as 97%.

An indwelling ureteral stent is left in place and the patient can usually be discharged after an overnight stay if bleeding remains minimal. A second look at 4- to 8-wk intervals is recommended in case of large tumours or if visibility is obscured by bleeding or clots.

7. Treatment outcomes

Multiple series have shown the safety and efficacy of ureteroscopic treatment of UTTCC. The overall recurrence rate for upper tract lesions was 34%. The risk of bladder recurrence was 36%, which is superior to the 25–30% incidence of bladder involvement in patients in whom nephroureterectomy was considered the treatment of choice. Nephroureterectomy was performed in 16% for the management of suspected local recurrence or disease progression.

The inability to treat completely UTTCC, even with multiple URS sessions, may occur in 32% of patients [9]. Patients with low-grade tumours are more likely to be rendered tumour free when compared with patients with high-grade tumours (76% vs. 40%) [9]. Similar favourable outcomes in the endoscopic treatment of low-grade UTTCC have been reported by Martinez-Pineiro [13]. Tumour location does not affect the initial tumour-free or recurrence rate; however, patients with tumours >1.5 cm in diameter have been reported to have a lower likelihood of being rendered tumour free (36%) and a higher recurrence rate (50%) when compared with patients with smaller tumours (91% and 25%, respectively) [9]. Patients with multifocal disease are also more likely to have incomplete resection (50%) in comparison with patients with solitary lesions (19%) [9]. Whether the location of the tumour may have a role in treatment outcomes remains a subject of controversy [13,14]. In a review of major series by Tawfiek and Bagley, the local recurrence rate was essentially the same for renal pelvic tumours (33%) and ureteral tumours (31%) [14].

Data indicate that survival is not compromised by conservative ureteroscopic treatment of UTTCC or local recurrence after such therapy. In a series with long-term follow-up, the 5-yr survival rate was 100% for patients with grade 1 tumours, 80% for patients with grade 2 tumours, and 60% for patients with grade 3 tumours. Of more relevance was the finding that 20 patients who underwent conservative therapy had no associated morbidity precluding radical open surgery. Of these patients, only 3 ultimately required nephroureterectomy, but no patient died of the effects of UTTCC [15].

The greatest theoretical complication associated with URS treatment of UTTCC is the potential for extraluminal spillage. There is at least one report of tumour cells found in the submucosal lymphatic and vascular structures in a nephroureterectomy specimen removed immediately after ureteropyeloscopy [12]. It was advocated that this case represented seeding from the ureteroscopic procedure, in which a pneumatic cuff was used to pressurise saline irrigation up to 200 mm Hg. Another study reported no increased risk of metastatic disease in a group of patients who underwent ureteroscopy before nephroureterectomy in comparison with a group undergoing nephroureterectomy alone [16]. In addition, no adverse effects have been reported in cases of perforation during URS management of UTTCC [9,13,15]. The reported stricture rate in large series has ranged from 5% to 14% in patients treated by prolonged ureteral stent or endoscopically with incision or balloon dilation [9,13,15]. When an ureteral stricture forms, following endoscopic management of UTTCC, it is imperative to obtain a
biopsy of the stricture [17]. If the stricture is malignant, nephroureterectomy is recommended; otherwise, endoscopic incision or dilation may be appropriate.

8. Adjuvant therapy

Topical therapy (bacillus Calmette-Guérin [BCG], mitomycin C, thiotepa, 5-fluorouracil) is often reserved for patients with large, multifocal, or residual tumours. Controversial results have been reported with the use of BCG or mitomycin C after endoscopic treatment of UTTCC. Mitomycin C can be delivered at the time of ureteroscopy or through a ureteral catheter postoperatively. BCG cannot be safely given until the urothelium has completely healed. Although the value of adjuvant topical chemotherapy or immunotherapy with regard to local recurrence and cancer-specific survival has yet to be proved, the therapy is generally safe and well tolerated [1].

Adjuvant topical therapy may be administered by reflux up an indwelling ureteral stent or by instillation through an externalised ureteral stent or percutaneous nephrostomy tube. The ability of instillation by reflux up an indwelling ureteral stent to provide adequate reproducible exposure of the urothelium to the topical agent has not been well established. Issues such as dosage, the frequency of instillation, and indwelling time have not been systematically evaluated [1].

9. Surveillance

Long-term endoscopic surveillance is essential to ensure early detection and treatment of recurrences in the upper tract and bladder. Cystoscopic surveillance is continued because of the relatively high risk for new bladder tumours. Radiographic follow-up of the treated collecting system as the only study is inadequate because as many as 75% of tumour recurrences are identified only endoscopically [18]. Imaging of the contralateral kidney by CT scanning is usually performed annually due to the risk, even low, for contralateral disease.

Ureteroscopy should be done every 3 mo until the upper tract is clear. Following this, the recommended schedule is cystoscopy every 3 mo and flexible URS every 6 mo for the first 2 yr, followed by cystoscopy every 6 mo and annual flexible ureteroscopy [17]. Urinary cytology is also done with a strategy similar to that used for bladder tumours, obtained every 3–6 mo.

10. Conclusions

With the evolution of instrumentation, a primary endoscopic conservative management of UTTCC has become possible with a strategy similar to that used for bladder tumours.

Endoscopic ablation can provide the histologic proof, grade, and stage of the tumour without exposing the patient to additional cancer-related risks. Invasive tumours must be treated by immediate nephroureterectomy. Ureteroscopic management of patients with UTTCC is mainly indicated for those with a solitary kidney, renal insufficiency, or bilateral tumours or severe comorbidities. It is a reasonable approach for patients with a solitary tumour <15 mm and low-grade/low-stage disease. Adjuvant topical therapy with mitomycin C or BCG seems to be safe, efficient, and well tolerated, but prospective studies with long-term results are still necessary.

References


