Review Article

# Novel laser therapies and new technologies in the endoscopic management of upper tract urothelial carcinoma: a narrative review

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**Background and Objective:** Upper tract urothelial carcinoma (UTUC) is a rare disease. The gold standard treatment is radical nephroureterectomy (RNU). Endoscopic management of UTUC has emerged as an alternative therapy that aims to preserve kidney function while providing effective oncologic control. Over the years, this has become an increasingly important alternative to RNU for treating UTUC in patients with localized disease. Advancements in lasers and endoscopic technology have continued to expand the applications of endoscopic nephron-sparing treatment. This review aims to provide an overview of the available lasers and ureteroscopic technologies used in treating UTUC with a focus on their clinical applications and outcomes.

**Methods:** A comprehensive literature review was completed using PubMed to create this narrative mini review. Publications from peer-reviewed journals written in English between 1987 to 2022 were evaluated by the authors for inclusion.

**Key Content and Findings:** Improvements in ureteroscopic technology have led to improved visualization and tumor detection. Laser ablation using different laser energies including the holmium/yttrium-aluminum-garnet, neodymium/YAG, and thulium/YAG has demonstrated promising oncologic outcomes. However, accurate staging and risk-stratification remain limitations to the role of laser ablation for the treatment of UTUC. This review also highlights appropriate patient selection as a critical component of successful endoscopic management.

**Conclusions:** The continued evolution of endoscopic management will rely on the development of new technologies to improve risk stratification and oncologic outcomes. Overall, this review provides insights into the available laser therapies and ureteroscopic technologies for the endoscopic management of UTUC.

**Keywords:** Upper tract urothelial carcinoma (UTUC); laser therapy; ureteroscopy; nephron-sparing

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## Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease with an incidence of 1–2 cases per 100,000 (1). Radical nephroureterectomy (RNU) with bladder cuff excision continues to be the gold standard treatment (2). A significant disadvantage to RNU is the loss in nephron mass that can accelerate chronic kidney disease (CKD) with an increased risk for cardiovascular morbidity and all-cause mortality (3). To reduce these risks, nephron-sparing treatment options have been developed.

Ureteroscopic management of UTUC was first described by Bagley *et al.* in 1987 (4). Endoscopic management soon after became an attractive management option for patients with imperative indications for renal perseveration, such as those with a solitary kidney or bilateral disease. Renal-sparing UTUC management is thought to effectively reduce end-stage renal disease (ESRD) healthcare expenses in patients with imperative indications (5). Moreover, CKD is a significant risk factor for contralateral upper tract recurrence (6). Contralateral recurrence has been reported in 2–6% of cases of UTUC (7). The growing recognition that hereditary somatic mutations (e.g., Lynch Syndrome) are frequent in this population underscores the increased risk of recurrence and bilateral disease, necessitating nephron-sparing treatment options (8).

Over the last two decades, the application of endoscopic management of UTUC has expanded with the development of novel laser therapies and the clinical implementation of new technologies. Endoscopic treatment aims to preserve kidney function while achieving oncologic control comparable to radical surgery. It cannot be understated that there is a lack of robust level 1 evidence to support endoscopic management due to the low incidence of UTUC. Thus, recommendations have relied on primarily retrospective and pooled data. Nonetheless, endoscopic management of UTUC is well supported by the EAU and AUA guidelines (9). The indications for endoscopic management have continued to expand. In 2018, the EAU guidelines increased the size threshold for endoscopic management from 1.5 to 2.0 cm (10).

Advancements in endourologic technology have allowed urologists to manage UTUC effectively without radical extirpative surgery. Although guidelines support the role of conservative nephron-sparing approaches when oncologically indicated, it still appears to be highly underutilized in practice (11). This review aims to outline advances in technology and laser ablation that have expanded the role of nephron-sparing treatment in the management of UTUC. We present this article in accordance with the Narrative Review reporting checklist (available at https://tau.amegroups.com/article/view/10.21037/tau-23-56/rc).

## Methods

A comprehensive literature review was completed using PubMed to create this narrative mini review. Publications from peer-reviewed journals written in English between 1987 to 2022 were reviewed. The time period reviewed commenced with the year the first article on the endoscopic management of UTUC was published. Search terms included “upper tract urothelial carcinoma”, “UTUC”, “management”, “treatment”, “ablation”, “endoscopic”, “ureteroscopic”, “thulium”, “holmium”, and “neodymium”. The studies were reviewed by two authors (A.A.M. and R.W.P.) for appropriateness of inclusion (*Table 1*).

## Patient selection for endoscopic management

Appropriate patient selection is fundamental to the success of endoscopic management of UTUC. Imperative indications for endoscopic management include solitary kidney, bilateral tumors, chronic renal insufficiency, and hereditary syndromes with an increased risk of UTUC. Criteria for elective endoscopic management for low-risk patients is outlined by the European Association of Urology (EAU) guidelines, defined as low-grade, unifocal tumor, less than 2 cm, with no invasive features on computed tomography (CT) urogram (10). Furthermore, recent studies have demonstrated the feasibility of electively treating carefully selected patients with large volume and multifocal low-grade disease (12). Current guidelines, however, do not support conservative management in high-risk UTUC, although endoscopic management is useful in high-risk patients with imperative indications for nephron-sparing or for palliative therapy.

The EAU guidelines make a grade-A recommendation for performance of cystoscopy, urinary cytology, and CT urogram in the diagnostic evaluation of UTUC (10). CT urogram has a sensitivity of 96% [95% confidence interval (CI): 88–100%] (13). Patients under the age of 60 years, a personal history of lynch-spectrum cancer or those with a first-degree relative less than 50 years old with a Lynch spectrum cancer should undergo screening for Lynch syndrome, which accounts for 10% of UTUC (14,15).

 

**Table 1** The search strategy summary

| Items | Specification |
|---|---|
| Date of search | November 22, 2022 |
| Databases and other sources searched | PubMed |
| Search terms | Search terms included "upper tract urothelial carcinoma", "UTUC", "management", "treatment", "ablation", "endoscopic", "ureteroscopic", "thulium", "holmium", and "neodymium" |
| Timeframe | 1987–2022 |
| Inclusion criteria | English language, peer reviewed publications |
| Selection process | The studies were reviewed by two authors (A.A.M. and R.W.P.) for appropriateness of inclusion |

Additionally, diagnostic ureteroscopy with or without biopsy is recommended when additional information may impact treatment decisions.

Diagnostic ureteroscopy is a fundamental tool in selecting patients for endoscopic management (16). It allows for precise determination of the location, appearance, size and focality of lesions, not readily identifiable on CT urogram (17). A major limitation to UTUC diagnosis is that accurate pathologic staging is not possible with biopsy. Due to the scale of the anatomy, adequate tissue sampling for pathologic assessment is a challenge (18). Subiela *et al.* conducted a meta-analysis in 2020 and found that the rates of undergrading and understaging were 32% (95% CI: 25–38%) and 46% (95% CI: 38–54%), respectively (19). Thus, risk stratification has emerged as a surrogate to pathologic stage using a combination of radiomics and patient characteristics.

The endoscopic management of UTUC requires meticulous and stringent follow-up due to limitations in clinical staging with ureteroscopic biopsies and high recurrence rates. The high rate of recurrence mandates patients' compliance. Repeat ureteroscopic biopsies are obtained at the time of every recurrence as progression from low-grade to high-grade disease occurs in up to 15% of patients (20).

## New technologies in ureteroscopy

Continuous and rapid technologic innovations in the design and optics of ureteroscopy have improved the visualization of the upper urinary tract over the last two decades. As a result, flexible ureteroscopy has evolved from a diagnostic tool to a widely accepted treatment option. Image clarity and accuracy play a critical role in the proper selection of patients and complete ablation of all tumors.

Initial studies on the endoscopic management of UTUC were conducted using fiberoptic ureteroscopes until digital ureteroscopy was introduced to clinical practice in 2008 (21). Digital ureteroscopes achieve better image quality than fiber optic ureteroscopes (22). In the distal tip of digital ureteroscopes, the light source and electronic image sensor are directly incorporated. As they do not require a separate camera head, digital scopes have the added advantage of being lighter and easier to handle. Digital scopes are frequently preferred for diagnosis of UTUC due to the better image quality (23). However, the electronic imaging sensor increases the rigidity of the distal tip, which reduces end-tip deflection compared to fiberoptic scopes (24). Dragos *et al.* performed *in-vitro* study of nine flexible ureteroscopes and found mean difference of 21 degrees in end tip deflection favoring fiberoptic scopes (24). Fiberoptic ureteroscope may be necessary to access a narrow-angled calyx in the lower pole. Furthermore, the digital ureteroscopes tend to be larger due to the distal tip image sensor, limiting access for certain patients with non-accommodating anatomy.

Size reduction in flexible ureteroscopes has improved the ability to access the ureter primarily. Hudson demonstrated in a multi-institutional study of 115 patients that the ability to pass a 7.4 F ureteroscope was 99.1% (25). Compared to a pass rate of 91.5% for 8.6 F and 53% for a 9 F ureteroscope. Additionally, size reduction presents an opportunity for better irrigation outflow by increasing the free space between the ureteroscope and the ureteral wall. Irrigation outflow is the limiting factor in the overall flow rate at constant renal pressure (26). If there is insufficient irrigation flow during tumor ablation, bleeding or debris can quickly obscure the view. Visualization is critical to ensure complete tumor ablation. Furthermore, irrigation flow prevents overheating of fluids that can result in untoward thermal damage during laser ablation (27).

Incremental software-based advancements from the endoscope companies have improved visualization to suggest better detection of UTUC. In 2013, IMAGE1 S (formerly Spies$^{TM}$) Storz Professional Image Enhancement System was introduced to improve endoscopic vision through image enhancement algorithms. Clara enhancement increases the brightness of dark regions in real time. This prevents the need to increase the light intensity and avoids glare. Chroma improves the sharpness of the image by enhancing red color contrast. These modes can be used together as Clara + Chroma. Recently, a multi-center randomized control trial comparing IMAGE1 S to white light was conducted in patients with non-muscle invasive bladder cancer (28). IMAGE1S was associated with significantly reduced recurrence rates in low- and intermediate-risk tumors. Although, there was no difference in overall recurrence rates between the two imaging modalities. The benefit of IMAGE 1S has not been evaluated in UTUC. However, Clara + Chroma is widely considered to produce the best image quality for ureteroscopy (29).

Olympus concurrently developed its own proprietary system called narrow-band imaging (NBI) in 2011. White light filtered by NBI filters into two narrow bands at 415 and 540 nm that are significantly absorbed by hemoglobin. This enhances the visibility of capillaries and urothelial carcinomas due to its vascular nature (30). Traxer and colleagues were the first to describe this new capability for ureteroscopy (31). They demonstrated an increase tumor detection rate of 27% compared to white light in a cohort of 27 patients.

Photodynamic diagnosis (PDD) with oral 5-aminoleveulinic acid is a widely accepted diagnostic modality urothelial carcinoma of the bladder owing to the significantly improved detection rates of carcinoma in situ (CIS) lesions (32). Recent studies have demonstrated the feasibility of applying this technology to the diagnosis and treatment of UTUC. Yoshida *et al.* evaluated detection rates by PDD-ureteroscopy *vs.* white light ureteroscopy in 63 biopsy samples from 20 patients with suspected UTUC based on imaging and urine cytology. PDD had a significantly higher sensitivity to detect UTUC than white light ureteroscopy (93.8% *vs.* 62.5%, P=0.0025) (33).

Furthermore, PDD has demonstrated promise in guiding laser ablation of non-invasive UTUC. In a cohort of 10 patients, PDD was used to confirm tumor ablation was complete and no residual tumor remained (34). Of these 10 patients with a mean tumor size of 23 mm and four patients with high-grade disease, there was a 100% 2-year progression-free survival (PFS) rate. A prospective single-arm trial to evaluate the potential benefit of PDD to reduce recurrence rates is ongoing with completed results expected in 2026 (35). A disadvantage to PDD is that it is not currently compatible with the digital ureteroscope.

Endoscopic visualization is essential to both patient selection and complete tumor ablation. Innovations in flexible ureteroscopy are likely to have a significant impact on the management of UTUC. Technology advancements such as ureteroscopic maneuverability and ergonomics, miniaturization, and enhanced imaging technology are expected to expand the possibilities of nephron-sparing management of UTUC. Despite advances in technology, the skill of the surgeon remains the primary factor determining oncologic treatment outcome (36).

## Laser ablation

Following biopsy, laser energy can be used to achieve hemostasis and for ablation of any remaining tumor. Primarily, three types of laser energy have been studied in the treatment of UTUC—the holmium/yttrium-aluminum-garnet (Ho:YAG), neodymium/YAG (Nd:YAG), and thulium/YAG (Tm:YAG) lasers. The ideal laser to select depends on the size and location of the tumor, but also access to the technology. Each laser studied has unique properties that have individual advantages when used alone or in combination.

The Nd:YAG laser is solid-state laser that at a wavelength of 1,064 nm destroys tissue with coagulation. Direct contact of the fiber with the tumor is unnecessary as the laser has deep penetration of 5–6 mm (37). The affinity of this laser is for hemoglobin (Hgb) thus making it especially useful for hemostasis. This makes the Nd:YAG laser an advantageous choice for larger tumors which require deeper tissue coagulation. The Nd:YAG laser does not have ablative properties and the remaining tissue is removed mechanically or ablated with a holmium laser. Because of the depth of tissue penetration, Nd:YAG is not ideally suited for ureter applications due to the risk of stricture.

The Ho:YAG is a pulsed laser with a 2.1 µm wavelength and a 0.2 to 0.5 mm depth of penetration. It is strongly absorbed by water which minimizes thermal injury to the surrounding tissue but tends to be less hemostatic when heavy bleeding is encountered. For this reason,

 

**Table 2** Laser specifications

| Laser/wavelength | Settings | Tissue penetration | Advantage | Disadvantage |
|---|---|---|---|---|
| Ho:YAG/2,100 nm (holmium) | 0.6–1.0 J/ 10–20 Hz | 0.2–0.5 mm | Minimal tissue penetration ideal for ureteral tumors. Ablative and cutting properties | Prolonged time required for ablation of larger tumors. Minimal hemostatic properties |
| Nd:YAG/1,064 nm (neodymium) | 30–60 watts continuous | 2–5 mm | Ideal for larger tumors in renal pelvis/calyx due to hemostatic capability. Depth of tumor penetration | Not ideal for ureteral tumors due to risk of stricture/perforation |
| Tm:YAG/1,940–2,100 nm (thulium) | 15 watts continuous | 0.2 mm | Minimal tissue penetration. Hemostatic properties | Prolonged time required for ablation of larger tumors. Minimal hemostatic properties |

Ho:YAG, holmium/yttrium-aluminum-garnet; Nd:YAG, neodymium/YAG; Tm:YAG, thulium/YAG.

the holmium laser is the best option for ureteral tumors. Modern holmium lasers are available with variable-pulse durations which can be exploited for desired tissue effects. The longer pulse duration (i.e., 700 ms) improves coagulation by providing the same energy per pulse but with less intensity. The shorter pulse duration (i.e., 350 ms) maximizes the ablative properties of the laser by rapidly delivering the desired pulse energy (38). However, direct contact with the tumor is necessary which is inefficient for ablation of large tumors.

Combining the Ho:YAG and Nd:YAG lasers offers maximal coagulative and ablative effects. Consequently, the Ho:YAG/Nd:YAG laser has been the standard laser used for endoscopic management of UTUC since the 1990's. Treatment starts with coagulation of the tumor with Nd:YAG laser followed by ablation of the necrotic tissue by the holmium laser. The dual foot pedal enables efficient switching between the two lasers. The dual laser energy can be delivered with the 200-, 272-, and 365-micron laser fibers. We most frequently use the 200- or 272-micron laser fibers because the narrow caliber facilitates deflection of the scope and accommodates irrigation for improved visualization compared to the 365-micron laser fiber. The 365-micron fiber is preferred for the larger caliber rigid ureteroscope.

The Tm:YAG laser for laser ablation of UTUC was first described in 2011 by Defidio (39). Tm:YAG laser is a continuous wave solid state laser with a 0.2 mm depth of penetration (40). The Tm:YAG laser operates at a wavelength of 2,013 nm which is closer to the peak absorption point of water than the Ho:YAG laser. Consequently, the thermal damage zone is decreased. Furthermore, the continuous emission produces favorable vaporization and coagulation effects compared to the pulsed Ho:YAG laser (41). A recent advancement is the thulium fiber laser (TFL), a diode pumped laser that allows for operation in continuous or pulsed modes (42). TFL generates a 1,940 nm wavelength. The continuous mode can be used for effective coagulation and hemostasis while the pulsatile mode functions similarly to the Ho:YAG and is preferred for ablation.

The combination of Tm:YAG and Ho:YAG laser has been employed in UTUC tumor ablation. The Tm:YAG laser is first used to coagulate the tumor in a similar role to the Nd:YAG laser. Subsequently, the remaining necrotic tissue is ablated with the Ho:YAG laser. Preliminary studies demonstrate that this treatment approach is successful (43). This option may be of particular value in the ureter or when the Nd:YAG laser is unavailable. In the past, a disadvantage to this approach was the requirement for two separate laser systems and fibers. However, the newly introduced Revolix Duo combines these two lasers into a single machine with a common fiber (44).

The specifications, advantages, and disadvantages of each laser are listed in *Table 2*. Ideally, the laser used would be selected based on the size and location of the tumor. However, in practice, many centers may only have one laser available.

## Clinical experience

There is a lack of level one evidence in support of laser ablation for UTUC due to its low incidence. Therefore, outcomes and efficacy of laser ablation is based on retrospective series and pooled data. Selected observational studies with endoscopic laser ablation using holmium,

**Table 3** Contemporary studies of ureteroscopic management of UTUC

| Laser energy | Author | Year | Patients | Follow up (months), median | Outcomes |
|---|---|---|---|---|---|
| Combined Ho:YAG with Nd:YAG | Grasso *et al.* (20) | 2012 | 66 | 51.5 | RNU: 17% |
| | | | | | 5-year PFS: 75% |
| | Scotland *et al.* (45) | 2018 | 80 | 43.6 | RNU: 20% |
| | | | | | 5-year CSS: 84% |
| | | | | | 5-year OS: 75% |
| | Shvero *et al.* (12) | 2021 | 59 | 22 | RNU: 6% |
| | | | | | PFS: 93% |
| Combined Ho:YAG with Tm:YAG | Defidio *et al.* (43) | 2019 | 101 | 28.7 | RNU: 9% |
| | | | | | Recurrence: 22% |
| | Sanguedolce *et al.* (46) | 2021 | 47 | 24 | RNU: 17% |
| | | | | | Recurrence: 28% |
| | Yoshida *et al.* (34) | 2021 | 10 | 24 | RNU: 0% |
| | | | | | Recurrence: 43% |
| | | | | | PFS: 100% |
| Tm:YAG | Musi *et al.* (47) | 2018 | 42 | 26.3 | RNU: 10% |
| | | | | | Recurrence: 19% |
| | Bozzini *et al.* (48) | 2021 | 47 | 11.7 | Recurrence: 19.2% |
| TFL | Proietti *et al.* (49) | 2022 | 28 | 12 | RNU: 3.5% |
| | | | | | Recurrence at 6 and 12 months: 21.7% and 17.7% |

UTUC, upper tract urothelial carcinoma; Ho:YAG, holmium/yttrium-aluminum-garnet; Nd:YAG, neodymium/YAG; RNU, radical nephroureterectomy; PFS, progression-free survival; CSS, cancer-specific survival; OS, overall survival; Tm:YAG, thulium/YAG; TFL, thulium fiber laser.

neodymium, or thulium energies delivered through retrograde ureteroscopy is summarized in *Table 3*.

Dual Nd-Ho:YAG laser ablation has been the most well-described and utilized with long-term follow-up data. In 2012, Grasso *et al.* published one of the first long-term outcome studies evaluating nephron-sparing treatment of UTUC demonstrating equivalent oncologic outcomes for patients with low-grade disease compared with RNU (20). There were 66 patients with low-grade lesions treated with ureteroscopic laser ablation. The 2-, 5-, and 10-year cancer-specific survival was 97%, 87%, and 78%. There was no statistically significant difference in cancer-specific survival compared to low-grade UTUC patients treated with RNU (P=0.54). In 2018, Scotland *et al.* published a retrospective review of 80 patients with >2 cm biopsy-proven low-grade UTUC with long-term follow-up. During the median 43.6-month follow-up, 16 patients (20%) progressed to RNU with a mean time to surgery of 23 months (45). The cancer-specific survival was 84% at 5-year follow-up. Scotland *et al.* showed that ureteroscopic management can preserve renal function in patients with large (>2 cm) UTUC lesions.

Thulium energy provides excellent hemostatic properties and has been combined with Ho:YAG or used alone. Defidio *et al.* evaluated the long-term outcomes of ureteroscopic Tm-Ho:YAG laser ablation for UTUC in 101 patients with a median follow-up of 28 months (43). Recurrence was managed endoscopically in 22% of patients and a further 9% of patients experienced progression requiring RNU. This study demonstrated that Tm-

 

Ho:YAG laser ablation produced comparable outcomes to the Nd-Ho:YAG laser. When used in combination with PDD technology, the dual Ho-TM:YAG laser ablation demonstrated excellent oncologic outcomes with possible better outcomes based on better patient selection (34). Recently, TFL has been introduced into endourologic practice. Proietti *et al.* reported short-term efficacy and safety of 28 patients treated with the TFL. The recurrence rates at 6 months were 21.7% and no intraoperative complications were observed (49).

## Conclusions

In conclusion, technologic advancements in laser technology and endoscopic optics have improved renal preservation therapy's effectiveness in managing UTUC. Innovations in flexible ureteroscopy have improved the ability to primarily access the ureter and enhanced imaging technology has significantly increased the detection of UTUC. Three types of laser energy have been successful in the treatment of UTUC—the Ho:YAG, Nd:YAG, and Tm:YAG lasers. Laser ablation of UTUC has demonstrated good long term oncologic outcomes compared to radical extirpative surgery minimizing the impact on renal function. However, accurate staging and risk-stratification remain limitations to the role of laser ablation for the treatment of UTUC. Continued evolution of endoscopic management will rely on the development of new technologies to improve risk stratification and oncologic outcomes.

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