EUROPEAN UROLOGY OPEN SCIENCE 46 (2022) 99–104

available at www.sciencedirect.com
journal homepage: www.eu-openscience.europeanurology.com

European Association of Urology

Endo-urology

Effectiveness and Safety of Thulium Fiber Laser in the Conservative Management of Patients with Upper Tract Urothelial Carcinoma

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Article info

Article history:
Accepted October 14, 2022

Associate Editor:
M. Carmen Mir

Keywords:
Upper urinary tract urothelial carcinoma
Thulium fiber laser
Conservative treatment
Laser

Abstract

Background: Few clinical data are available on thulium fiber laser (TFL) and conservative treatment of upper urinary tract urothelial carcinoma (UTUC).
Objective: To assess the effectiveness and safety of TFL in the conservative treatment of UTUC in terms of both tumor ablation and complication rates in a short-term follow-up.
Design, setting, and participants: Retrospective data were collected from all patients who underwent endoscopic management of UTUC between January 2021 and April 2022. All patients with nonmetastatic UTUC who were deemed suitable candidates (low- and high-grade disease) for conservative treatment were reviewed.
Intervention: All patients underwent ureteroscopy with biopsy and at 2, 6, and 12 mo after the first surgery. UTUC ablation was achieved using TFL.
Outcome measurements and statistical analysis: Clinical data were collected in a dedicated database. Intra- and postoperative outcomes were assessed. A descriptive statistical analysis was performed.
Results and limitations: In total, 28 patients were evaluated. Thirteen patients (46.4%) were included in the low-risk UTUC treatment group and 15 (53.6%) in the high-risk group. The mean tumor size was 15.3 ± 5.7 mm. Biopsy showed low- and high-grade UTUCs in 19 and eight patients, respectively. Only one biopsy was inconclusive for achieving a diagnosis. At the second procedure biopsy, no tumor was found in 19 cases (70.4%), whereas seven had tumors confirmed (25.9%). To date, 23 and 17 out of 26 patients completed the 6- and 12-mo follow-up, respectively. UTUC recurrence was detected in five of 23 patients (21.7%) and in three of 17 patients (17.7%) at 6 and 12 mo, respectively. A total of 95 procedures were performed. No intraoperative complications were observed. In ten of the 95 procedures (10.5%), Clavien-Dindo grade I–II postoperative complications were experienced. Only one grade IIIB postoperative complication was noted.
Conclusions: TFL is a safe and effective technique for conservative treatment of UTUC in a short-term follow-up. Optimal tumor ablation and fine hemostatic control were achieved without major complications.

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https://doi.org/10.1016/j.euros.2022.10.010

Patient summary: In this study, we looked at the outcomes of upper urinary tract tumors conservatively treated with the new thulium fiber laser (TFL). We conclude that TFL represents a safe and effective technique for the treatment of this kind of tumors in a short-term follow-up.

1. Introduction

Upper urinary tract urothelial carcinoma (UTUC) accounts for 5–10% of all urothelial carcinomas, with a peak incidence in patients aged 70–90 yr [1,2].

Historically, radical nephroureterectomy was considered the standard of care for UTUC, but over the past two decades, largely due to improvements in endoscopic instrumentation and laser technologies, endoscopic conservative management of UTUC has gained popularity in the urological community [3,4].

The European Association of Urology (EAU) guidelines recommend consideration of "kidney-sparing management" in low-risk UTUC patients and in selected high-risk patients with a serious renal insufficiency or having a solitary kidney [5].

Laser technology has several applications in endourology, such as in the treatment of urinary stones, benign prostatic hyperplasia (BPH), bladder cancer, and upper urinary tract carcinoma [6,7].

Over the past few decades, several clinical studies have shown the effectiveness and safety profile of holmium-YAG (Ho:YAG) and thulium-YAG (Tm:YAG) lasers for the treatment of prostate cancer and UTUC [7–9]. Recently, thulium fiber laser (TFL) has been introduced in the endourological field [10], with early laboratory studies identifying it as a potential alternative to conventional lasers in the treatment of soft tissue [11,12]. To date, only one retrospective study has analyzed the results of the first-generation TFL with the quasicontinuous wave (QCW) emission mode on UTUC ablation [13], and one retrospective study of four cases has analyzed the results with SuperPulsed TFL [14].

The aim of this study was to assess the effectiveness and safety of the TFL SuperPulsed version in the conservative treatment of UTUC in terms of both tumor ablation and complication rates in a short-term follow-up.

2. Patients and methods

Retrospective data were collected from all patients who had undergone endoscopic management of UTUC between January 2021 and April 2022. Preoperatively, all patients were informed of the benefits and risks of conservative management of UTUC, even in the presence of high-risk disease, and the need for stringent and lifelong follow-up. All patients with nonmetastatic UTUC who were deemed suitable candidates (low- and high-grade disease) for conservative treatment were reviewed. The "low-risk" UTUC group included patients with tumor size up to 2 cm, negative for high-grade cytology, with no invasive aspect on imaging and low-grade biopsy. The "high-risk" UTUC group included patients with a solitary kidney or severe renal insufficiency with high-grade biopsy, high-grade cytology, and tumor size >2 cm.

Multifocality did not represent a strict criterion for being excluded from the low-risk group.

The exclusion criteria were as follows: patients who refused, at the beginning, endoscopic management of UTUC and/or refused to accept our stringent surveillance protocol.

All patients underwent a second-look procedure 2 mo after the primary surgery. After that, they underwent endoscopic evaluation at 6- and 12-mo follow-up.

Preoperative data collection, included history, physical examination, urinalysis, urine culture, blood test, urine cytology, computed tomography (CT) scan, or magnetic resonance imaging (MRI). Peri/postoperative complications were reported according to the Clavien-Dindo classification system [15].

2.1. Surgical technique

All procedures were performed by two experienced surgeons at a single tertiary care referral center. Under general anesthesia, semirigid ureteroscopy (URS) was performed to treat only distal ureteric carcinoma, whereas flexible digital URS was performed to treat the proximal ureter and renal carcinoma. All procedures included the visualization of all parts of the upper urinary tract by using a digital flexible ureteroscope, even in the presence of only a distal ureteric tumor. The flexible ureteroscope used was Olympus URF-V3 (Olympus Medical Systems, Tokyo, Japan). Whenever possible, an initial "no touch technique" was always attempted to avoid any traumatic lesion of the upper urinary tract mucosa and/or bleeding secondary to the guidewire placement [16]. For the proximal ureter and renal urothelial carcinoma, a 10–12 Fr ureteral access sheath (Biflex Evo; Rocamed, Monaco, Monaco) was placed to facilitate repeated access to the collecting system during specimen acquisition and to ensure adequate intrarenal flow while maintaining low intrarenal pressures. The irrigation system used was the T-Flow (Rocamed, Monaco, Monaco); passive irrigation was obtained by gravity keeping the saline bag at 40 cmH20 above the operating bed. Only when needed, extra pressure was delivered by the assistant by gently squeezing the antireflux chamber.

Intraoperative selective urine samples were collected for cytological evaluation. Biopsies were performed using biopsy forceps (Pirahna Forcep; Boston Scientific, Marlborough, Massachusetts, US) for flat lesions and baskets (N-Gage; Cook Medical, Bloomington, Indiana, US, or 0-tip; Boston Scientific, Marlborough, Massachusetts, US) for exophytic lesions.

During the second-look procedure, a biopsy was taken at the site of the previous tumor if no visible tumor was observed.

Laser ablation of the tumor was performed using TFL (Fiber Dust; Quanta System, Samarate, Italy).

The UTUC ablation was achieved using the SuperPulsed mode (1 J, 10 Hz, short pulse using a 200 μm laser fiber).

At the end of the procedure, a single-J ureteric stent and bladder catheter were placed.

3. Results

A total of 28 patients (21 males and seven females) met the inclusion criteria and were included in the study (Table 1).

Table 1 – Patient demographics, UTUC characteristics (*n* = 28), and intra/postoperative outcomes (1° procedure)

Gender, *n* (%)	
Male	21/28 (75)
Female	7/28 (25)
Age (yr), mean ± SD	73 ± 6.2
Low-risk UTUC treatment group, *n* (%)	13/28 (46.4)
High-risk UTUC treatment group, *n* (%)	15/28 (53.6)
Number of lesions, *n* (%)	
Single	16/28(57.1)
Multiple	12/28 (42.9)
2	5/12 (41.7)
>2	7/12 (58.3)
Tumor location, *n* (%)	
Renal pelvis	6/28 (21.4)
Calyces	5/28 (17.9)
Upper ureteral tract	1/28 (3.6)
Lower ureteral tract	4/28 (14.2)
Multifocal	12/28 (42.9)
Tumor size (mm), mean ± SD	15.3 ± 5.7
Selective urinary cytology, *n* (%)	
Positive	6/28 (21.4)
Negative	22/28 (78.6)
Biopsy tumor grade, *n* (%)	
Low grade	19/28 (67.8)
High grade	8/28 (28.6)
Inconclusive for a diagnosis	1/28 (3.6)
Complications by Clavien-Dindo grade, *n* (%)	
Grade 0	24/28 (85.8)
Grade I	2/28 (7.1)
Grade II	2/28 (7.1)
Grade III/IV/V	0 (0)

SD = standard deviation; UTUC = upper urinary tract urothelial carcinoma.

At the time of diagnosis, the mean age of the patients was 73 ± 6.2 yr.

Thirteen patients were included in the low-risk UTUC conservative treatment group (46.4%), whereas 15 patients were in the high-risk group (53.6%).

A single lesion was found in 16 patients (57.1%), and multiple lesions were detected in 19 patients (42.9%). The mean tumor size was 15.3 ± 5.7 mm. Biopsy confirmed low- and high-grade UTUCs in 19 and eight patients, respectively. Only one biopsy was inconclusive for achieving a diagnosis. Selective urinary cytology was positive in five out of 28 samples (17.9%). One patient did not undergo a second procedure because he failed to survive a heart attack 1 mo after the first procedure. TFL was used in all cases.

At the second-look procedure biopsy, no tumors were found in 19 cases (70.4%), whereas seven had tumors confirmed (25.9%). Notably, five patients with confirmed tumors were included in the “high-risk” conservative treatment group and two in the “low-risk” group; one patient of the latter group showed multiple lesions at the second-look procedure and was therefore a candidate for nephroureterectomy. One biopsy was inconclusive. To date, 23 and 17 out of 26 patients completed the 6- and 12-mo follow-up, respectively. UTUC recurrence was detected in five of 23 patients (21.7%) and in three of 17 patients (17.7%) at 6 and 12 mo, respectively.

None of these 26 patients was lost to follow-up or refused to continue with the endoscopic UTUC management (Table 2).

A total of 95 procedures were performed. No intraoperative complications were observed. In ten of the 95 procedures (10.5%), Clavien-Dindo grade I–II postoperative complications were experienced. Only one major complication (grade IIIB) was noted: one patient with a solitary kidney, after postoperative single-J stent removal, experienced acute obstructive renal failure and consequently underwent a double-J stent placement. No ureteric strictures were observed at each endoscopic follow-up. None of the patients required preoperative stenting or staged procedures because of narrow ureters.

Table 2 – UTUC patients’ follow-up

	Follow-up		
	2 mo	6 mo	12 mo
Patients, *n*	27	23	17
Biopsy, *n* (%)			
Absence of tumor	19/27 (70.4)	18/23 (78.3)	13/17 (76.5)
Presence of tumor	7/27 (25.9)	5/23 (21.7)	3/17 (17.7)
Inconclusive for a diagnosis	1/27 (3.7)	0/23 (0)	1/17 (5.8)
Complications by Clavien-Dindo grade, *n* (%)			
Grade 0	24/27 (88.9)	21/23 (91.4)	15/17 (88.2)
Grade I	2/27 (7.4)	1/23 (4.3)	0/17 (0)
Grade II	1/27 (3.7)	1/23 (4.3)	1/17 (5.9)
Grade III/IV/V	0 (0)	0 (0)	1/17 (5.9) (IIIb)

UTUC = upper urinary tract urothelial carcinoma.

4. Discussion

The EAU guidelines recommend kidney-sparing management as a primary treatment option for patients with low-risk tumors, solitary kidney, bilateral UTUC, and pre-existing chronic kidney disease with both low- and high-risk tumors [5].

However, no guidance has been provided regarding the optimum laser technology for tumor ablation.

Currently, Ho:YAG laser is assumed to be the gold standard [17] as it has been the most utilized laser source rather than there being robust scientific evidence comparing it with other available laser systems. Urologists use Ho:YAG laser regularly for conservative treatment of UTUC, as it is the most available laser technology in hospitals for the management of stones rather than it being the most effective technology for soft tissue ablation.

In fact, as indications for conservative treatment of UTUC have broadened, especially regarding tumor dimension, the search for a laser with a better coagulation profile led some experts to investigate the use of continuous wave (CW) Tm:YAG laser for the management of UTUC after observing good performance in the treatment of BPH. These studies reported good oncological outcomes for UTUC [9], which could be attributed to the CW nature of Tm:YAG laser and better water absorption, which translates into a longer pulse length and therefore decreases the pulse peak power. This, in addition to the ubiquity of the target chromophore (water molecules), provides continuous conditions to maintain the tissue heated by the laser beam up to its boiling point. Consequently, the residual tissue after each laser pass is covered by a coagulated layer of tissue, which guarantees optimal hemostasis [18]. In contrast, the drawback of CW emission is the high degree of carbonization, which may impair intraoperative navigation or affect cutting precision [19].

For these reasons, we started using TFL to determine whether this innovative technology could represent a good middle ground between the explosive operational mode of Ho:YAG laser and the CW behavior of Tm:YAG laser.

Whiles et al [14] reported a preliminary study of four patients with UTUC treated with SuperPulsed TFL showing promising results in terms of ablation, hemostasis, and intraoperative safety.

This study reports the outcomes of 28 patients using the TFL SuperPulsed mode in the conservative treatment of UTUC.

The effectiveness of TFL in terms of tumor ablation was satisfactory, with 19 out of 27 biopsy specimens (70.4%) being negative for tumor detection at the second-look procedure.

Five patients with confirmed tumors were included in the "high-risk" conservative treatment group and two in the "low-risk" group; one patient of the latter group showed multiple lesions at the second-look procedure and was therefore a candidate for nephroureterectomy.

This could suggest that a residual tumor is related more to disease extension and grading, rather than pointing to a potential deficiency of TFL. Villa et al. [20] suggested performing an early flexible URS second-look procedure at 6–8 wk after the first procedure. This is of paramount importance not only to rapidly detect any tumor recurrence/persistence, but also to identify the aggressiveness of the disease and correctly stratify UTUC patients who are potential candidates for conservative treatment.

Based on this study, the EAU guidelines recommend an early second-look URS and advocate complete tumor resection or ablation.

This approach was therefore adhered to in this study and also helped assess the tumor ablation rate of TFL.

Villa et al. [17,20] reported a tumor recurrence rate of 51.2% for UTUC treated with Ho:YAG laser ablation. The fact that in our TFL series this rate was reduced by half (25.9% vs 51, 2%) may suggest better ablation performance by TFL, but additional randomized controlled studies would be required to prove this hypothesis.

In addition, the following endoscopic follow-up showed satisfactory tumor ablation, with presence of UTUC found in five of 23 patients (21.7%) and three of 17 patients (17.7%) at 6 and 12 mo, respectively.

In 2018, Wen et al. [13] performed a retrospective comparison study on 32 UTUC patients conservatively treated by TFL versus nephroureterectomy. They reported that the loss of renal function was lower in the conservative treatment, but the tumor recurrence rate was higher (21.9% vs 7.8%).

The authors defined tumor recurrence as being either in the ureter or in the bladder, making it hard to draw firm conclusions on the effectiveness of TFL ablation for UTUC. In addition, this study used TFL in the QCW mode (PPmax 120 W), which differs from our series in which a TFL machine with a SuperPulsed mode was used (PPmax 500 W).

It is essential to understand the differences between the laser technologies currently available for urological soft tissue treatment as these have different properties that could potentially impact reported clinical outcomes. This is particularly important for thulium lasers (TLs).

TL operates within a wavelength range of 1.94–2.0 μm; three main TL machines are available for UTUC treatment: the TFL QCW mode (Pmax 120 W, 1.94 μm), Tm:YAG CW mode (Pmax 200 W, 2.0 μm), and TFL SuperPulsed mode (Pmax 500 W, 1.94 μm).

The 1.94 μm wavelength almost matches the peak of the absorption curve of water, whereas the 2.0 μm wavelength has a lower coefficient but is still higher than that of Ho:YAG laser.

Ho:YAG laser works in the pulsed mode with a wavelength of 2.09 μm.

One advantage of TFL is its higher water absorption than that of Ho:YAG laser, which improves tumor ablation due to more energy being absorbed by cells if one assumes water absorption as a model of cell absorption [21]. In contrast to Ho:YAG laser, the laser fiber tip should always be in contact with the tissue being ablated.

Tm:YAG laser, with its continuous emission, induces smooth incision and vaporization of soft tissue with excellent hemostasis [22].

In an ex vivo study, Proietti et al. [23] reported several advantages of Tm:YAG laser over Ho:YAG laser for the treatment of UTUC, namely, a shallower incision depth, greater coagulation area, and greater total laser surface area.

However, the drawback of CW emission due to low peak power and the absence of thermal relaxation is the high degree of carbonization [19].

Comparing the soft tissue effects of TFL and Ho:YAG laser, Taratkin et al. [12] demonstrated that SuperPulsed TFL produces a Ho:YAG laser–like incision but with better coagulation and almost zero carbonization, while QCW TFL allows for fast, deep, and precise cutting with increased coagulation, but with some associated carbonization. The advantage of TFL is its lower peak power and longer pulse duration, which allows for equal laser distribution on the tissue, providing efficient vaporization and coagulation while maintaining carbonization within reasonable limits.

In another ex vivo study, Doizi et al. [11] showed no statistical differences between Ho:YAG laser and SuperPulsed TFL regarding the incision widths, whereas incision depths and areas of coagulation were statistically greater with Ho:YAG laser than with TFL. Carbonization zones were consistently found with TFL and never with Ho:YAG laser.

Therefore, TFL seems to be a good compromise between the excellent hemostasis of Tm:YAG laser and the tissue cutting of Ho:YAG laser with an acceptable degree of carbonization.

Musi et al. [8] reported the outcomes of 42 patients with UTUC conservatively treated with Tm:YAG laser. The mean tumor size was 14.3 mm (2–30 mm), with a median follow-up of 26.3 mo (2–54 mo). Only five of 42 patients (12%) underwent the second-look procedure for residual tumor persistence. Tumor persistence was found in 25% of cases in this study; however, all our patients underwent a second-look procedure as the probability of finding tumor persistence/recurrence was higher than expected [20].

Moreover, Musi et al. [8] recorded 38%, 35.7%, and 2.4% of grade I, II, and III complications, respectively. We report only minor complications in 10.5% of cases, except one grade IIIb complication in a solitary kidney patient with obstructive acute renal failure.

Musi et al. [8] concluded that Tm:YAG laser is a good alternative for UTUC treatment aimed at optimal tumor ablation and fine hemostatic control.

Defidio et al. [24] reported their experience of 178 UTUC patients treated by using a combination of dual wavelengths of Tm:YAG and Ho:YAG lasers. The authors initially performed tumor ablation and coagulation with Tm:YAG laser, and the removal and dislodgement of the necrotic tumor tissue with Ho:YAG laser. This combined laser technique benefits from optimal tumor ablation and coagulation by Tm:YAG laser and improved access to the tumor base by Ho:YAG laser, which better cuts and removes the necrotic tissue. One drawback of Tm:YAG laser alone is that the laser fiber tip coating adheres to the coagulated necrotic tissue and generates a layer of coagulative necrosis at the tumor base, which prevents complete tumor ablation, especially in the case of larger lesions.

Defidio et al. [24] reported only 10% grade I complications over a 13-yr period, concluding that Tm-Ho:YAG duo laser was safe and oncologically noninferior to the alternative laser energy technology for conservative UTUC treatment.

This laser combination was also described by Sanguedolce et al. [25], who emphasized the advantages of switching from one laser mode to another during a procedure to perform better tumor ablation without compromising safety.

From these studies, it is therefore reasonable to postulate that TFL exhibits the beneficial qualities from both Ho:YAG and Tm:YAG laser, leading to improved tumor ablation and hemostasis. We therefore performed UTUC ablation using the TFL SuperPulsed mode (1 J, 10 Hz, short pulse), reducing the carbonization effect and avoiding the sticking of the laser tip to the necrotic tissue typical of Tm:YAG laser, as well as taking advantage of the lower mechanical impact on the tissue and shallower tissue penetration than Ho:YAG laser [26].

To date, there is no standardization of the laser settings for the conservative treatment of UTUC, especially regarding TFL laser technology. Since this technology is clearly in its infancy, we are still figuring out the ideal setting: we are sure that we do not need to use the higher frequency and the extremely low power that the machine is able to deliver. Conversely, we have identified as ideal a setting of 1 J, 10 Hz, basically replicating what we have been using with Ho:YAG laser. This setting provides optimal hemostasis without generating the excessive carbonization typical of Tm:YAG laser, which may sometimes hinder the radicality of the tumor extirpation.

The study limitations include its retrospective design, small sample size in a single center, and the lack of mid- to long-term follow-up, which limit the reliability of our results and the possibility of reaching substantial conclusions.

However, this is the first study that explores the use of SuperPulsed TFL in clinical settings in 28 patients with short-term follow-up.

Prospective randomized studies in larger populations with longer-term follow-up using different laser sources are required to confirm the effectiveness and safety of TFL in conservative UTUC treatment.

5. Conclusions

TFL is a safe and effective laser technique for conservative treatment of UTUC in a short-term follow-up. Effective tumor ablation and hemostasis were achieved without any major complications.

Author contributions: Silvia Proietti had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Proietti, Giusti.
Acquisition of data: Proietti, Rico, Pupulin, Di Pietro, Spagna, Lucianò.
Analysis and interpretation of data: Proietti, Rico, Pupulin, Di Pietro, Spagna.
Drafting of the manuscript: Proietti.
Critical revision of the manuscript for important intellectual content: Proietti, Johnston, Giusti.
Statistical analysis: Proietti, Rico.
Obtaining funding: None.
Administrative, technical, or material support: None.
Supervision: Proietti, Johnston, Giusti, Ventimiglia, Villa, Gaboardi.
Other: None.

Financial disclosures: Silvia Proietti certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: G. Giusti: consultant for Coloplast, Rocamed, Olympus, Boston Scientific, BD-Bard, Cook Medical, and Quanta System. S. Proietti: consultant for Quanta System and Boston Scientific. The other authors have no conflicts of interest to declare.

Funding/Support and role of the sponsor: None.

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