Laser Therapy for Upper Urinary Tract Transitional Cell Carcinoma: Indications and Management

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Abstract

Context: Ureteroscopically guided laser techniques are commonly used in the treatment of upper urinary tract transitional cell carcinoma (UUTT); however, there is an ongoing debate with regard to indication and management.

Objective: To review the indication, feasibility, and treatment outcome of laser application for definitive endoscopic treatment of UUTT, focusing on technical aspects of different laser devices and their impact on tissue.

Evidence acquisition: PubMed and Medline were searched for reports on laser therapy in UUTT from 1980 to 2008, with particular focus on the technical background of various laser systems.

Evidence synthesis: For decades, nephroureterectomy has been considered the gold standard for treating UUTT. With the intent to preserve functioning renal parenchyma, minimally invasive approaches, initially advocated for patients requiring a nephron-sparing approach (ie, single functioning kidney, renal insufficiency or significant comorbidities), have gained widespread acceptance due to advances in ureteroscopy, percutaneous renal surgery, and laparoscopy. Ureteroscopically guided laser ablation has been used successfully, resulting in recurrence rates ranging from 31% to 65% and disease-free rates of 35% to 86%, depending on stage and grade at diagnosis.

Conclusions: To obtain the highest treatment success, the initial staging and grading of the tumour is crucial. Because low-grade tumours rarely if ever progress in stage or grade, the success rate of ureteroscopic therapy parallels that of endoscopic resection of identical bladder tumours. In the treatment of higher grade, advanced tumours, ureteroscopic therapy is less likely to be curative, and thus, endoscopic manoeuvres can only be palliative. Due to the relatively low prevalence of this tumour and the lack of comparable randomised, multicentre trials, the indications for an endoscopic laser treatment option has to be defined based on the patient’s individual situation.

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1. Introduction

Nephroureterectomy with bladder-cuff removal still is the standard treatment for upper urinary tract transitional cell carcinoma (UUTT) because of the high recurrence rates in the remaining distal ureter, the multicentricity on the same side, and the low incidence of bilateral tumours [1,2]. In order to preserve renal function, therapeutic approaches have evolved from complex open surgery to minimally invasive ureterorenoscopic therapy in selected cases.

Minimally invasive procedures for the treatment of upper urinary tract urothelial malignancies were first utilised in the 1980s. The first patients treated ureterorenoscopically had comorbidities that prohibited open surgical therapy (eg, solitary kidney, renal insufficiency, significant comorbidities).

Due to the success rates of ureteroscopic treatment for low-grade and low-stage disease, the indications were expanded to patients with upper urinary tract urothelial tumours and normal contralateral kidney function [1–3].

With the development of smaller and more durable, rigid, and flexible ureterorenoscopes, retrograde endoscopic procedures have become more practical and efficacious. Flexible-scope ureterorenoscopy has improved the treatment of tumours in the proximal ureter and in the renal collecting system. These instruments have evolved from passive deflection endoscopes used primarily for diagnosis into actively deflectable instruments useful for both diagnostic and therapeutic purposes [4]. Another reason for the increased acceptance of retrograde endoscopic tumour treatment has been the advance of neodymium: yttrium aluminium garnet (Nd:YAG) lasers. Over the last few years, several high-volume centres have reported the outcomes with endoscopic laser treatment [2,3,5–9].

With miniature laser fibres, energy can be employed without prohibiting the deflection of the ureterorenoscope, and it can be utilised to ablate and coagulate tissue in a therapeutic manner throughout the whole upper urinary tract [2,3]. Other currently available technologies such as diode laser systems and thulium (Tm) laser systems show promising initial results, but their clinical value in comparison to existing laser systems that are used clinically in urology practice will depend upon upcoming studies and their outcomes [10].

2. Evidence acquisition

PubMed and Medline were searched for reports on laser therapy in UUTT from 1980 to 2008, with particular focus on the technical background of various laser systems.

3. Evidence synthesis

UUTT is an uncommon disease, accounting for 5–6% of all urothelial tumours and for 5–10% of all renal cancers. Ureteral tumours occur in about 25% of UUTT cases; of these, most occur in the distal ureter (70%) followed by the middle ureter (25%), and the remainder occur in the proximal ureter [1,3,11].

Bilateral disease is rare and occurs in 2–4% of cases. A bladder lesion that may be a result of tumour multifocality, of unstable urothelium field effect, or of tumour seeding will eventually develop in 30–75% of patients with UUTT [1,12–14].

Transitional-cell carcinoma of the bladder occurs in approximately 1–4% of UUTT patients, but the risk of its occurrence can increase up to 20% in patients with high-grade (G3) superficial bladder tumours, with concurrent carcinoma in situ, or with recurrence after bacillus Calmette-Guérin (BCG) therapy [1,15–17].

3.1. Laser specifications

The endoscopic treatment of UUTT with a laser requires a light-energy transport via flexible quartz fibres introduced through the working channel of the endoscope. Depending on the laser source and the laser parameters (ie, output power, fluence, fluence rate), the induced effects on soft tissue vary among coagulation, ablation, vaporisation, and incision.

The Nd:YAG and the Ho:YAG lasers are well-established laser systems. Their use in urology is already widespread, including their use in the treatment of UUTT [4–6,10,18]. Forthcoming laser technologies like the Tm laser have shown promising initial results in hard- and soft-tissue ablation including accuracy, energy efficiency, and minimal collateral damage under experimental conditions, but clinical studies and long-term data are needed to define their role in the treatment of UUTT [10].

Laser impact on tissue can be differentiated by optical parameters such as scattering and absorption coefficient. While scattering is relevant for laser distribution within the tissue, the absorption of laser energy is required for therapeutic interaction resulting in coagulation, vaporisation and ablation of soft tissue, or in fragmentation of stones. In Fig. 1, the absorption coefficients of water, haemoglobin, and melanin are depicted from the ultraviolet to the near-infrared spectral range. The number of absorption events per centimetre (in water) of the Ho:YAG laser is about 100 times larger compared with that of the Nd:YAG laser, while the absorption of diode laser light at 980 nm is in the same range as the Nd:YAG laser. Furthermore Ho:YAG laser energy is solely absorbed by the water in the tissue. Laser wavelengths of Nd:YAG lasers as well as the different diode lasers can be absorbed by water and also by haemoglobin in different amounts. Each wavelength results in a slightly different interaction with the target tissue due to the difference in its tissue composition (eg, water–haemoglobin content). In Fig. 1, the optical penetration depth resulting from calculation (using the Lambert–Beer law) due to the absorption coefficient is shown. The optical penetration depth differs by a factor of 10–30 for the laser systems discussed in this paper and is the lowest with Ho:YAG lasers. Optical penetration is not the maximum tissue depth at which an effect of the laser can be achieved. The effect depth differs from tissue to tissue and depends on the laser's
parameter adjustments to the thermal and optical properties of the tissue [19–21].

Depending on the amount of absorption of light, the temperature within the tissue increases. Due to the increase in the internal temperature, different superficial tissue effects can be observed that must be judged by the laser surgeon: whitening, shrinkage, and colour darkening. Tissue removal must also be assessed and achieved. In the case of whitening, the temperature reaches about 60–65 °C, inducing denaturing of tissue proteins and resulting in coagulation and necrosis of tissue. The shrinkage of tissue follows from water vaporisation near 100 °C, thus reducing the thermal conductivity of the tissue. Darkening of the tissue surface results from further increase in temperature (150–250 °C) that results in carbonisation of tissue. In case of a black tissue surface, all laser-light energy is absorbed by the dark surface, and the thermal conductivity of the tissue leads to a temperature increase deeper into the tissue. Tissue removal can be achieved either by burning the surface of the tissue with high temperatures or with pulsed-light energy depositions. In the latter case the applied energy creates instantaneous explosive vaporisation of the water within a small tissue volume, resulting in an explosive eruption, taking all the energy out of the tissue [19–21].

This dynamic change, a result of laser–tissue interaction, depends on the laser fluence rate. This critical parameter can be regulated or adjusted by the surgeon with respect to the distance of the distal fibre end to the tissue, resulting in different sizes of the laser spot (illumination area). The high fluence rates of the contact mode induce the vaporisation needed for incisions. Using a noncontact mode results in lower fluence rates that induce coagulation and a continuous temperature increase that, in turn, induces deep-tissue coagulation [19].

The physicotechnical basics of laser application are listed in Table 1. Laser energy from diode systems is absorbed by different cell composites, and the main diode-laser applications are for coagulation in noncontact mode, while vaporisation as well as incision can be achieved in contact mode. Water in the tissue is the main absorber of the energy of the Nd:YAG laser, the Ho:YAG laser, and the Tm laser. In contact mode, all three systems can be used for vaporisation and incision. The Nd:YAG laser, used in noncontact mode, induces coagulation and, to some extent, vaporisation; the Ho:YAG-laser shows, in addition to superficial coagulation, a sufficient vaporisation and incision capability. The Tm laser shows a high cutting efficiency in soft tissue and haemostasis and, thus, can be applied in all of the applications for which the Ho:YAG laser is used [10].

Retrograde ureteroscopic treatment can be performed using semirigid or flexible ureterorenoscopes. Selection is based on tumour size, location, and anatomic considerations. In the majority of cases, tumours located in the distal and middle parts of the ureter are treated with semirigid ureterorenoscopes. The new generation of flexible ureterorenoscopes provides full access to tumour findings in the proximal ureter and throughout the whole intrarenal collecting system [5,18].

The additional use of ureteral access sheets allows easy introduction and reintroduction of flexible ureterorenoscopes with low-pressure, continuous-flow irrigation for excellent intraoperative visualisation [18].

The Ho:YAG and Nd:YAG lasers are utilised most frequently ureteroscopic treatment of UUTT. Ho:YAG laser energy is delivered via small quartz fibres (core diameter: 200 μm, 365 μm, or 600 μm).

The currently available flexible ureterorenoscopes can accommodate 220-μm and 365-μm laser fibres; however, the amount of active and passive deflection and the amount of the available rinse flow are least affected when using 220-μm fibres.

Because there are no small fibres available for diode-laser devices, potential ureteroscopic treatment is limited to the range of application of semirigid ureterorenoscopes (ie, the ureter and parts of the renal pelvis).

Attention must always be paid to the scope tip, which should be straightened while advancing the laser fibre in the work channel. Therefore, the laser tip should always be visualised a few millimetres beyond the tip of the scope [5,18].

The Ho:YAG laser energy is highly absorbed by water and water-containing tissues, resulting in rapid dispersion of heat, resulting in minimal thermal damage to the surrounding tissue. The Ho:YAG laser fibre must be used in contact with the tissue to achieve tumour ablation. For debulking and clearing papillary urothelial tumours, the Ho:YAG laser parameters should be set in the range of 0.6–1.0 J per laser pulse at a repetition rate between 5 Hz and 10 Hz. In case of vascular and bulky tumours, successive ablation with the Ho:YAG laser at the same setting or in a staged fashion can be performed [3,8,22,23].
Due to the need to operate the Ho:YAG laser in contact mode, tissue adherence to the fibre tip during ablation can occur, resulting in decreased visibility and decreased ablation capacity. Interruption of laser application and cleaning of the fibre, which results in extended operation times, may become necessary.

Vascular and bulky tumours should be coagulated with Nd:YAG laser energy primarily. The Nd:YAG laser, with its greater depth of penetration (4–6 mm), provides a deeper coagulation and ablative effect on the tumour. Devitalised tissue can subsequently be cleared with forceps or baskets to explore the deeper portions. Most authors suggest Nd:YAG laser parameter settings of 20–30 W for 2–3 s, using fibre diameters that range from 200 μm to 600 μm. During laser application, the distal fibre tip should be directed tangentially in noncontact mode until the tumour whitens [3,5,6,8,22–24]. When using the Nd:YAG laser, the risk of subsequent ureteral stricture is significantly higher due to its deep tissue penetration, and therefore Nd:YAG laser energy should never be employed circumferentially in the ureter [6].

The shallow depth of penetration with the Ho:YAG laser allows focused tissue ablation under direct visualisation. However, Ho:YAG laser energy will not coagulate larger tumour vessels [4,6,24]. With the very low level of tissue penetration noted with Ho:YAG laser application, there is more freedom to treat lesions that are circumferential [7,8,25]. Patients with bulky, low-grade, upper-tract tumours frequently require staged ureteroscopic therapy. Incomplete tumour resection may be a problem when treating large tumours (<1.5 cm) or tumours in the lower pole. The tumour is ablated at the first sitting, a ureteral stent is placed, and the patient returns after an interval of healing (eg, 1–2 wk up to 4–8 wk for large tumours) for an additional treatment after the devitalised tissue is allowed to slough [3,18,24]. Staged therapy is also employed when extensive or multifocal tumour resection is required and when visualisation is compromised because of bleeding during the primary endoscopic resection [3,8,26]. Postoperatively, most patients who undergo ureteropyeloscopic laser therapy require ureteral stents for 1–6 wk thereafter. This allows the ureteral and intrarenal urothelia to heal [18,3,24]. In cases in which the ureter is dilated and endoscopic therapy is used to remove only small volume tumours, no ureteral stent is required [8].

### 3.2. Treatment outcomes

Ureterorenoscopy following laser treatment has been reported in a relatively small but increasing number of published studies. A common theme in all of the reported trials is the lack of progression in grade and stage of low-grade, upper-tract, urothelial tumours. The rate of disease-specific mortality for low-grade tumours is zero in the majority of the series [3]. Initial studies were limited to case reports only. In 1993, Gerber and Lyon reviewed the literature and noted that, in endourologically treated cases, local recurrence rates were as low as 13.7%; however, disease progression and disease-specific mortality rates were difficult to ascertain due to the limited number of patients [26]. Tawfik and Bagley [27] reviewed the treatment results in 205 renal units. The local recurrence rate was 33% for renal pelvic tumours, and it was 31.2% for ureteral tumours. Bladder recurrences were found in 43% of patients treated ureteroscopically, emphasising the importance of lower- and upper-tract surveillance [27].

The success rate of ureteroscopic therapy for grade 1 and grade 2 UUTT is similar to that of lesions managed transurethrally in the bladder.

Martínez-Piñeiro found no deep tumour invasion in all patients with low-grade lesions that were treated ureteroscopically [28]. Grasso stratified patients based on the initial presentation grade of the tumour. Patients with grade 1 and 2 tumours treated ureteroscopically did not progress in grade or stage during close endoscopic follow-up [8]. Keeley found that the recurrence rate ranged from 25.7% to 44.4%, depending on the grade of the primary tumour and that tumours >1.5 cm (requiring subsequent treatment) had a significantly higher rate of local recurrence [29]. To determine the current practice patterns in the management of UUTT among a large group of urologists, Razdan pooled data from multiple ureteroscopic series. With an overall
Some 17 (81%) of the 21 renal units were treated endoscopically. The overall recurrence rate was 33% (7 of 21 patients) with a time to recurrence of 1.7 to 9 yr. None of the four patients who underwent nephroureterectomy had invasive disease [9].

In their series of the 315 patients with UUTT, 271 patients (86%) were treated with nephroureterectomy, and 44 patients (14%) were treated endoscopically. Some 21 patients (6.6%) during an 11-yr period matched the study criteria and were treated endoscopically. The overall recurrence rate was 33% (7 of 21 patients) with a time range of 2–24 mo. Some 17 (81%) of the 21 renal units were able to be preserved, with a mean follow-up of >6 yr. None of the four patients who underwent nephroureterectomy had invasive disease [9].

High-grade tumours have been treated with ureteroscopic therapy in situations when palliation is needed, but as expected, the rate of tumour progression is high [34]. Local control can often be accomplished by patients presenting with high-grade tumours, but all of these patients eventually present with metastasis [8,34]. Individuals with high-grade lesions are best served with nephroureterectomy that is most often performed laparoscopically [3,8,24,30].

### 3.3. Complications

The rate of complication associated with retrograde endoscopic therapy has decreased with the advances in instrumentation and technique. With this procedure, there is a 2% risk of ureteral or pelvic perforation from technical errors with endoscopes, guide wires, baskets, and/or laser fibres; these occurrences are usually managed with a ureteral stent or a nephrostomy tube. Perforation while using the Ho:YAG or Nd:YAG laser can occur if the power settings are too high and the laser is directed onto the ureteral or pelvic wall rather than onto the tumour. The penetration depth of Ho:YAG laser is 0.5 mm; the Nd:YAG laser penetrates to a depth of 5–6 mm. The laser-fibre tip should always be visualised a few millimetres beyond the tip of the ureteroscope and directed onto the tumour under direct vision control [3,5,6,24]. There is a risk of scarring and of subsequent stricture formation after laser ablation in the ureter [3,5,6]. The risk is greatest in patients with large tumours, particularly following circumferential lesions of the ureter [5,6]. After ureteroscopic management of UUTT, the reported stricture rate in large series has ranged from 5% to 14%. These strictures can be treated by prolonged ureteral stenting, endoscopic incision, or balloon dilation followed by short-term stenting [5].

In endoscopic treatment of UUTT, ureteral stricture is not always caused by technical factors, but may represent recurrent disease. Daneshmand et al showed that 40% of patients with stricture after ureteroscopic treatment had recurrent UUTT [16].

Increased intrarenal pressure during ureteroscopic saline irrigation and laser-induced tumour ablation has a theoretical potential for tumour cell migration; Hendin has demonstrated that diagnostic ureteroscopy for UUTT induced no significant differences in recurrence rates, time to recurrence, or mortality rates between the groups of patients who had and who did not have ureteroscopic treatment before nephroureterectomy [32].

Some authors recommended the percutaneous approach to treating tumours in the renal pelvis because it provides a better working environment and the possibility of using more and larger tools through the nephroscope in patients with bulky (>1 cm) tumours or lower calyx tumours [35–37]. Percutaneous treatment has risks associated with significantly higher rates of blood transfusion, and overall complication rates in percutaneous treatment compare with those of ureteroscopic treatment. Nephrostomy tract tumour seeding associated with the antegrade percutaneous approach was documented in several reports,
whereas tumour seeding via ureteroscopic therapy is also a theoretical risk [22,23,38].

Newly developed bladder tumours after endoscopic treatment of UUTT are found in 30% of patients, a percentage similar to that of open surgical resection series. Bladder-tumour recurrences have been reported in 25–30% of patients after nephroureterectomy or partial ureterectomy [29,39,40]. Kang et al found multiplicity to be a significant and independent factor for recurrent bladder tumours in patients with primary UUTT [39]. There appears to be a high incidence of bladder tumours, regardless of treatment, indicating the need for mandatory long-term follow-up of the bladder [29,33,39].

3.4. Postoperative surveillance and follow-up

Careful, lifelong follow-up is mandatory after endoscopic treatment of all upper-tract urothelial lesions.

A surveillance schedule similar to that performed after transurethral resection of bladder tumours has to be established individually for each patient.

Surveillance should be lifelong and should be aimed at detecting local recurrence of tumours (in all cases) in the upper and lower urinary tracts because of the risk of developing metachronous bladder tumours (which is about 30%) and distant metastases (in case of invasive tumours) [1,40–42]. Minimally invasive procedures are frequently needed, and white-light cystoscopy is best performed under additional photodynamic diagnostic (PDD) conditions [43].

Ureteroscopy and cytology should be performed with respect to the patient’s tumour grade and stage.

A well-established surveillance schedule was presented by Ho and Chow, consisting of cystoscopy and cystology every 3 mo alternating with cystoscopy, retrograde pyelogram, cytology, and flexible ureteroscopy every 6 mo for the first 2 yr, then cystoscopy every 6 mo, and ureteroscopy annually [40].

Oosterlinck suggests that intravenous pyelography (IVP) in addition to urinary cytology performed at 1–3 mo be repeated after 6 mo and then repeated annually for 5 yr, in combination with cystoscopy, ureteroscopy, and urinary cytology and upper-tract cystoscopy performed at 3 mo and 12 mo, postoperatively, then annually thereafter, alternating with IVP between these controls for 5 yr [1].

A special follow-up in case of a conservative approach with carcinoma in situ consists of cystoscopy, ureteroscopy, and bladder and upper-tract cytology performed every 3 mo for 2 yr, then repeated every 6 mo for 5 yr [1].

It is mandatory to continue endoscopic surveillance because isolated recurrences have been noted > 5 yr after primary ureteroscopic resection [1,24,38,41,42]. In their review, Johnson and Grasso underscore the necessity of endoscopic surveillance because 75% of tumours identified by ureteroscopy are being missed radiographically [21].

There is an urgent need to inform appropriately selected patients about conservative laser treatment. Because the potential for disease progression must be clearly recognised, patients have to be actively involved in the decision about endoscopic laser treatment of UUTT [6].

4. Conclusions

Diagnostic ureteroscopy is the standard in defining upper tract urothelial lesions. With miniature instrumentation and refined techniques, the indications for ureteroscopic treatment of UUTT have broadened significantly. Ureteroscopic laser treatment of malignant urothelial lesions in the upper urinary tract, however, should be reserved for a selected patient population only. The initial stage and grade of the tumour is the key to defining the ultimate success of treatment. Because low-grade tumours rarely, if ever, progress in stage or grade irrespective of size and location, the success rate of ureteroscopic therapy parallels that of endoscopic resection of identical bladder tumours. In the treatment of high-grade lesions, especially grade 3 lesions, ureteroscopic therapy is less likely to be curative, and thus, endoscopic manoeuvres are palliative. Absolute conclusions about the outcomes of endoscopically managed UUTT cannot be drawn because of the relatively low frequency of this tumour and the lack of comparable randomised, multicentre trails. Patients who undergo ureteroscopic therapy require lifelong, vigilant ureteroscopic surveillance because recurrences are common. Whereas the roles of the diode laser and other newly evolved laser devices like the Tm laser have yet to be defined, Nd:YAG and Ho:YAG laser systems are well established in the treatment of UUTT.

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