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Ureteroscopic laser treatment of upper urinary tract neoplasms.

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**“URETEROSCOPIC LASER TREATMENT OF UPPER
URINARY TRACT NEOPLASMS”**

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ABSTRACT

Background: Endoscopic management of upper urinary tract transitional cell carcinoma has assumed an important role in diagnosis and treatment. The introduction of small diameter rigid and flexible ureteroscopes has permitted access to the upper tract. Biopsy techniques have been developed for accurate diagnosis and the addition of lasers has given the urologists an excellent tool for treatment.

Methods: Medical literature available relative to the endoscopic laser treatment of upper tract neoplasms has been reviewed.

Results: Ureteroscopic treatment has been characterized by good success with high recurrence rates, both in the upper tract and the bladder. Bladder recurrence rates are similar to those seen after surgical treatment of upper tract tumors. Surveillance has been ureteroscopic since the other diagnostic options are inadequate. The holmium and neodymium:YAG lasers are the devices most commonly used now for the endoscopic treatment of upper tract tumors.

Conclusion: Ureteroscopic treatment of upper tract neoplasms usually with ablation and resection using the neodymium and holmium:YAG lasers is a current acceptable procedure. This should be reconsidered as one of the options in tumor treatment.

Transitional cell carcinoma of the upper urinary tract is an uncommon lesion but is a potentially lethal tumor requiring treatment. Treatment has traditionally been surgical, either with nephroureterectomy or for low grade distal ureteral tumors, distal ureterectomy, including a wide bladder cuff around the orifice.^{1,2}

The development of small, rigid and flexible ureteroscopes in the early 1980's became possible with the introduction of fiberoptic illumination and imaging. These instruments have permitted routine access to the entire upper collecting system³ and have revolutionized the treatment of calculi and neoplasms. The Holmium:YAG and the Neodymium:YAG lasers are both effective for neoplasms and can be delivered through small flexible fibers.^{4,5}

INSTRUMENTS

Endoscopes

Small rigid endoscopes are available in single and dual channel designs ranging from approximately 5 to 9+French tip diameter (most commonly ~7F with a 3.6F channel).⁶ Dual channel designs allow for simultaneous irrigation and placement of a working device. These endoscopes can be passed easily under direct vision into the distal ureter to inspect that area without any prior instrumentation (i.e. termed the "no touch" inspection technique), but cannot adequately inspect the renal pelvis or intrarenal collecting system.

Actively deflectable, flexible ureteroscopes were developed to access the intrarenal collecting system and proximal ureter atraumatically. They are available in single channel designs from 7.4 to 9+F while a larger endoscope is available with dual channels. The smaller diameter endoscopes can also be placed under direct vision frequently without trauma of guidewire introduction, thus, employing a "no touch" technique. To inspect the lower pole calyx in most kidneys, the ureteroscope must deflect 170° but to compensate for loss of deflection with working instruments in the channel, the active tip deflection has been increased to nearly 300° in most ureteroscopes.

Recently, flexible ureteroscopes have been constructed with digital imaging chips at the tip. These produce an excellent endoscopic image with better resolution but suffer from a larger overall diameter of nearly 10F as well as limited deflectability. Although it has been suggested that these instruments will have greater durability, this remains to be demonstrated.

Lasers

The Holmium and Nd:YAG lasers are effective devices for treating neoplasms throughout the urinary tract. The characteristics of these lasers are listed in Table 1. The Nd:YAG at a wavelength of 1064 nm destroys tissue with coagulation. It has a depth of penetration up to several millimeters (5-10) in tissue or water and therefore, direct contact of the fiber with the neoplasm is not necessary. It is effective in treating tumors up to centimeters in diameter. However, it is difficult to judge the depth of penetration during treatment. It can be combined with techniques to remove the coagulated tissue.

The Holmium YAG laser is a pulsed device with a wavelength of 2100 nm. It can cause coagulation at lower energies and higher pulse durations and can ablate the tissue coagulated either with the holmium or the Nd:YAG laser. The Holmium energy penetrates tissue only <0.4 mm and therefore its effect is relatively superficial and is endoscopically visible.

Fibers of various sizes can be used with either laser. Each fiber consists of a central core and a cladding with resultant diameter and deflection characteristics. The most commonly used fibers are 200 or 365 μ diameter. The smaller fiber is more flexible but is a less efficient ablator of tissue since it has an exponentially smaller spot size, and, with the holmium:YAG, a much smaller vaporization bubble.

Other lasers, like the diode and the thulium, can be delivered with flexible fibers but have not yet been used and/or reported in significant clinical series of patients with upper urinary tract urothelial tumors.

Biopsy Devices

Tissue samples can be taken with several different devices, indwelling baskets, forceps, graspers, snares and brushes. The most effective basket is a stainless steel flat wire design which can be closed to trap the tissue in the angle between the wires.

Several designs of 1 mm diameter cup forceps are available and are useful in sampling flat or solid, nonpapillary lesions with a small sample fully contained within the cup, the device can be withdrawn through the working channel and replaced to obtain multiple tissue fragments. The stiffness of the shaft of the forceps often prohibits endoscope deflection of more than 90 to 100° depending on the endoscope used. The other instruments are relatively ineffective in obtaining tissue and are rarely used.

TECHNIQUES

Suspected upper tract neoplasms are often evaluated with contrast CT scan, (CT urogram, CTU), intravenous pyelogram or retrograde ureteropyelogram. The suspected lesion is then diagnosed endoscopically. The appearance is similar to that of urothelial tumors within the bladder and may be papillary, sessile or flat. In one series, visual inspection alone was only 70% accurate in determining the malignancy or grade of a neoplasm in the upper tract.⁷

It is also important to obtain a sample of tissue for pathologic diagnosis, since the grade of the tumor is important in the decision process for treatment. Papillary lesions can be sampled with a stainless steel flat wire basket which is applied around the tumor and closed snugly but not completely. It is then used to avulse a piece of tissue. The entire unit of tumor, basket and endoscope are removed to preserve the largest piece of tissue available. Samples should not be withdrawn with a basket through the channel since most of the sample would be sheared off and lost.

Alternatively, for smaller, sessile or flat lesions, a cup forceps is used. Multiple samples should be taken. If the entire sample is contained within the cup, it can be withdrawn through

the channel of the ureteroscope. If there is a larger piece extending beyond the extent of the cup, then again the entire unit of tumor, forceps and endoscope should be removed to maintain the largest sample.

The tissue sample is delivered directly into a collection tube with a small aliquot of saline. If there will be a delay in delivering the sample to the cytopathology laboratory, the appropriate amount of cytologic preservative is added. All tissue samples are processed as cytology specimens to avoid loss of tissue in preparation⁸ A cell block can be made for macroscopically visibly evident samples.

After adequate sampling, the tumor can be treated. Very small (1 to 2 mm) lesions can be treated effectively and completely with the holmium laser using few pulses. We commonly prefer to use the holmium laser for all ureteral lesions because of the lower risk of ureteral stricture with this controlled energy source. Localized tissue reaction with subsequent stricture may result from treatment of larger lesions or those encompassing more than one-half circumference of the ureter or from the use of the neodymium:YAG laser which causes a deeper tissue effect. (Table 1)⁹

Specific capabilities of the Ho or Nd:YAG lasers can be utilized to maximize coagulation or ablation of neoplasms throughout the bladder or upper tract. Selection of the laser depends on the size and location of the lesion. The holmium laser alone can coagulate tumors with the maximum coagulative effect given by defocussing the laser beam on the tissue. Close approximation of the tip of the fiber or contact with the tissue gives a more ablative effect and removes tissue. Generally, there is less bleeding with the coagulative technique.

Specific holmium lasers have variable pulse durations which can be employed to obtain unique tissue effects. The longer pulse provides the same energy per pulse giving less intensity and improved coagulation. It retains some ablative properties while the shorter pulse duration maximizes the ablative effect.

The Neodymium YAG laser is a continuous wave device producing a wavelength which penetrates more deeply into tissue. Its major effect is coagulative and is very useful for deeper coagulation of larger tumors. It produces no ablation and the resultant coagulated tissue can be removed mechanically or with a Ho laser. Care must be taken with the Nd:YAG laser to avoid treating the ureteral wall circumferentially since it penetrates deeply and can result in a stricture.

Within the renal pelvis, the energy choice depends mainly upon the size of the lesion. Larger vascular tumors (>1 cm) can be coagulated initially with the neodymium:YAG and then ablated and cleared with the holmium when a combination laser is available. These lesions can also be treated with the holmium laser alone. Lower holmium energy tends to maximize the coagulative effect and minimize the risk of bleeding (e.g. 0.5 to 0.6 joules and 5 hertz). When a laser with a variable pulse duration is available, the longer duration is used to maximize the coagulative effect and minimize bleeding.

Adequate removal of neoplastic tissue without penetration of the pelvis or the ureter is highly technique dependent. The fiber of the holmium laser is applied only where the coagulative or ablative effect is desired. When the tumor partially obscures the ureter or renal pelvis, the laser is moved in an arc along the normal contour at the base of the neoplasm. It is helpful to initiate resection at the more proximal portion of the tissue and then work distally. In this way, it is possible to avoid advancing the fiber into the mucosa or wall of the ureter or renal pelvis.

Some intrarenal locations are inherently difficult to treat with lasers. This occurs most commonly on the medial wall of the lower infundibulum. In these unusual situations, if it is impossible to reach with the 200 micron fiber, the flexible ureteroscope may deflect further with a 2F Bugbee electrode. This device also has the advantage of coagulation from the side of the tip. As opposed to laser fibers, it is not necessary to point the device directly at the tissue.

CLINICAL RESULTS

Several papers have summarized reports of ureteroscopic treatment of upper tract transitional cell carcinoma (UUTTCC).^{10,11,12} Many of these papers have used lasers as one of the endoscopic ablative devices for treatment. The earliest series, before the availability of the holmium laser, used electrocautery or electroresection while some were limited to rigid endoscopes. These reports are characterized by a high success rate for ablation of tumor with preservation of renal units. However, there is a high recurrence rate of the neoplasms. Kidneys have been preserved in approximately 70% of patients, while recurrences have ranged from 20-88%. Therefore, endoscopic surveillance has an essential role in the treatment and follow up process after ureteroscopic treatment of UTTCC.

New or recurrent bladder tumors are also common after the treatment of an upper urinary tract carcinoma (Table 2). New or recurrent bladder tumors were seen after ureteroscopic treatment in 40.5% of patients in series up to 2001.¹³ Among more current series, there is also a wide range of bladder tumors appearing in 20-44% of patients. In comparison, bladder tumors have been reported to occur in from 15 to 45% of patients treated with open surgical nephroureterectomy and from 10 to 55% after laparoscopic nephroureterectomy. It is difficult to make direct comparisons, since the grade and stage of tumors, the intensity of endoscopic follow up and particularly the duration of follow up varies so widely. The rate of bladder tumors from these rough comparisons suggests that the rate of new or recurrent bladder tumors after endoscopic resection is not out of the range seen with nephroureterectomy.

By far the most common complication after ureteroscopic treatment is ureteral stricture. This can occur either at the site of resection of a ureteral tumor or at other sites throughout the ureter. In a combined series a rate of 13.7% was reported in 2001.¹³ It is impossible to separate the strictures occurring in patients treated with lasers since all series include some treated with electrofulguration. The overall stricture rate in the series available is 12.7%, which is

considerably higher than the rate of <1% seen after the ureteroscopic treatment of ureteral stones.³⁰ (Table 3)

DISCUSSION

The standard treatment of upper tract neoplasms has been nephroureterectomy with excision of a bladder cuff. Studies in the 1970's demonstrated the feasibility of distal ureterectomy to treat low grade distal ureteral neoplasms. Therapy was less successful for renal pelvic and proximal ureteral lesions suggesting a "downstream" effect.^{31,32}

The next developmental step was to treat upper urinary tract tumors endoscopically. Based on the established endoscopic treatment of bladder tumors, the application of these techniques became limited only by the instrumentation available. This concept became a reality as appropriate ureteroscopes became available.^{33,34} The refinement of these endoscopes has made it possible to reach the entire intrarenal collecting system in most patients.

Similarly, instruments and techniques were developed to sample and treat upper tract tumors. Accurate diagnosis has improved by using cytologic techniques with cell blocks to identify larger samples.^{35,36} Ureteroscopic biopsies have been shown to have a high, but not perfect accuracy ranging from 80 to 90%.^{37,14}

Endoscopic access to the upper tract presents the opportunity for treatment. The first instruments for ablation and coagulation were 2 or 3F electrodes. In the series cited, patients dating from the early 1980's were treated electrosurgically and often subsequently grouped with and then treated with lasers as they recurred during long term follow up. Both the holmium:YAG and neodymium:YAG lasers can be delivered through small flexible fibers to the vast majority of surfaces within the upper collecting system.

The Neodymium:YAG laser has been demonstrated to be an effective mechanism for the endoscopic treatment of bladder tumors. In a small series, it was shown to coagulate upper tract neoplasms successfully with an open surgical approach.³⁸ The Neodymium:YAG laser can

effectively coagulate tissue, but it may be difficult to determine the depth of coagulation and the treated tissue remains in place and is not cleared. This is a minimal problem in the bladder but in the ureter or the renal pelvis, the coagulated tissue obscures deeper portions of the tumor which may be viable. This treated tissue must be removed mechanically or by ablation with the holmium laser. The holmium:YAG laser can also coagulate tissue primarily, although less efficiently. Lengthening the holmium pulse duration improves the coagulative effect. Combining the Ho and Nd:YAG lasers gives maximal coagulative and ablative effects, delivering a more controlled coagulation and ablation of urothelial tumors than that delivered with a small cautery electrode.

The aim of the conservative management of upper tract neoplasms is to preserve renal function. This may be considered imperative or strongly indicated in patients with a solitary kidney, solitary functioning kidney or limited renal function. The alternative of nephroureterectomy with subsequent dialysis, and even possible later transplantation, must be considered and offered to the patient. There is a high morbidity and also mortality associated with dialysis. In a recent series of 128 hemodialysis patients with a mean age of 61 years, the 3 year survival was only 55%.³⁹ Data from end stage renal disease database shows a decrease in survival in older patients.⁴⁰ Five year survival over the last cited year (2001) was 30.7% for patients ages 65-69, 20.2% for those 70-79 and dropped to 9.6% at ≥ 80 years.

Recently, the risks of chronic renal failure associated with a solitary kidney have become evident.⁴¹ There is interest in for maintaining renal function and avoiding development of an anephric state. Much of this emphasis has been directed toward the development of laparoscopic partial nephrectomy. However, the same arguments can be applied to UUTTCC.

The treatment of upper tract neoplasm with ureteroscopic techniques is quite successful. Low grade tumors carry a low mortality with treatment by many means including ureteroscopy. High grade tumors have a more pessimistic prognosis in general, with lower survival rates after either nephroureterectomy or endoscopic treatment. When high grade tumors are treated

ureteroscopically, often palliatively, most patients maintain renal function with acceptable local control. Overall, ureteroscopic treatment of upper tract tumors has an excellent disease specific survival and results in approximately 70% renal maintenance.⁴²

There are also both recognized and potential risks from ureteroscopic treatment. There remains a very high recurrence rate in most series ranging from 20 to 85%. Generally, the more recent reports have higher recurrence rates. This may be related to the longer follow up in these series. Alternatively, it may be related to the treatment of larger and more proximal neoplasms which in a surgical series have been shown to be more likely to have distal recurrences. The progression of grade is also possible approximating 10% in a large series. Therefore, it is essential that treated patients have endoscopic follow up since the noninvasive modalities of urinalysis, urinary cytology or FISH studies are inadequate to define recurrence.^{43,44,45}

Cost has become an important consideration in guiding treatment. Repetitive treatment or repetitive endoscopic surveillance can be an ongoing expense for health systems. In the US, the high cost associated with transplantation, or the even greater costs of hemodialysis makes endoscopic treatment and surveillance an attractive alternative. In comparison, in the medicare payment system, hemodialysis was the most expensive while successful ureteroscopic treatment with surveillance was the least expensive. There can be expected to be variations in different national health systems.⁴²

There remain many unknown factors involved in the endoscopic therapy of upper tract TCC. For example, it is impossible to determine the exact stage of the neoplasm. Several series have shown that the stage is related to the grade.⁴⁶ The latter can be obtained from ureteroscopic biopsy with a reasonably high accuracy when compared with the grade seen on surgical specimens. Other staging studies, such as CT scanning, can be useful but do not have sufficient resolution for lower stages. Currently, tumor grade remains the best prognosticator.

The sources of urothelial tumor recurrences are unknown. It may be related to the field change in patients with urothelial carcinoma. This is supported from the known 5 to 10%

bilaterality of upper tract neoplasms. Similarly, the high risk of new or recurrent tumors at similar rates after ureteroscopic treatment or open or laparoscopic nephroureterectomy suggests a field change rather than seeding. However, cytologically intact cells can be seen in the irrigant after endoscopic laser treatment.⁴⁷ Their role in recurrence is unknown. Another unknown is the process of treatment itself. It is impossible to determine the adequacy of coagulation and ablation visually. For example, the depth of penetration from the neodymium:YAG laser is never certain except by visual inspection, which is inadequate. Similarly, the extent or presence of invasion of the neoplasm is impossible to determine.

Adjuvant therapy has been considered as a means to reduce recurrence. Agents such as topical Mitomycin, used after endoscopic resection, may have a role in decreasing recurrence in the upper tract as it has in the bladder.⁴⁸ It has been employed in two short series.^{49,50} It has been demonstrated to be tolerated but there are insufficient data to determine its efficacy.

CONCLUSION

Currently, ureteroscopic laser resection of upper tract neoplasms is an acceptable option for treatment. It is an excellent first choice for patients with a solitary kidney, compromised contralateral kidney or impaired renal function. It has been used with very good success electively in patients with small low grade tumors and a normal contralateral kidney in an effort to preserve renal function. All patients must be followed endoscopically and must be willing to agree to endoscopic surveillance because of the high risk of recurrence in the upper tract and bladder. The holmium and neodymium:YAG lasers are presently the most commonly used devices. The laser combining Nd and Holmium:YAG is convenient and effective but the holmium:YAG lasers can be used alone, preferentially with the variable pulse duration.

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Table 1

**Use of Ho and ND:YAG Laser for
Ureteroscopic Treatment of UTTCC***

Laser	Kidney	<u>Site</u> Ureter	Bladder
Ho	8	40	5
Nd	2	--	6
Ho & Nd	34	2	22

Total 77 procedures (some with > 1 site)
Over 1 year (11/08 – 11/09)

*D Bagley unpublished

Table 2

New or Recurrent Bladder Tumors:

After Ureteroscopic Treatment of UUTTCC

Reference	Bladder Tumor	%
Sowter et al ^{16*}	12/35	34.3
Thompson et al ¹⁵	37/83	44.6
Daneshmand et al ¹⁴	6/30	20.0
Chen & Bagley ^{13o}	41/101	40.5
Combined	96/249	38.5

*No history BT

^oreviewed series to 2001

After Laparoscopic or Open Nephroureterectomy for UUTTCC

Reference	%	%
	Laparoscopic	Open
Rassweiler ¹⁷	24.0	24.7
Wolf ¹⁸	55	--
Okegawa ¹⁹	20	17
Tsujihata ²⁰	28	33
Raman ²¹	29	35
Chung ²²	44	36
Manabe ²³	32.8	38.0
Muntener ²⁴	41	--
Roupret ²⁵	10	15
Taweemonkongsap ²⁶	29	45
Waldert ²⁷	26	27

Table 3

**Strictures after Ureteroscopic
Treatment of UUTTCC**

Reference	Patient	Stricture	%
Suh et al ²⁸	16	2	12.5
Daneshmand et al ¹⁴	30	5	16.7
Johnson et al ²⁹	35	3	8.5
Sowter et al ¹⁶	40	4	10.0
Chen et al ^{13*}	139	19	13.7
Overall	260	33	12.7

*combined series to 2001