SPANDIDOS PUBLICATIONS

# Long-term results and management of ureteral transitional cell carcinoma using the holmium: YAG laser via rigid-ureteroscopy

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**Abstract.** The standard operative procedure for ureteral transitional cell carcinoma is nephrouterectomy with partial cystectomy at the affected ureteral orifice. However, nephron-sparing surgery and endoscopic surgery and management have become common practice for low-grade and low-stage cases. We investigated the follow-up results of patients who underwent endoscopic surgery using the holmium:YAG laser, and evaluated its treatment effect. The patients were 4 men and 3 women aged from 68 to 87 years (mean: 74.7 years). Two were imperative cases and 5 were elective cases. The tumor size ranged from 8 to 25 mm (mean: 15.4 mm). Hydronephrosis was not found in any case, and urinary cytology was negative in all cases. Biopsy revealed 5 cases of grade 1, and 2 of grade 2. A Versa Pulse Select 80 laser generator, a 365-$\mu$m slim line laser fiber, and a rigid ureteroscope with 8F-point diameter were used. A 6F double J catheter was placed postoperatively for 3 weeks. Pulse energy was set at 0.5-1.0 J (mean: 0.8 J) with a frequency of 10 Hz. The total amount of energy was 0.9-11.22 KJ (mean: 2.89 KJ) and the operation time including ureteral stent placement was 20-97 min (mean: 66 min). Neither urinary tract perforation nor ureteral stricture associated with laser irradiation was observed. The postoperative follow-up period ranged from 23-88 months (mean: 67.8 months). Patients underwent urinary cytological examination once a month, and cystoscopy, retrograde pyelography and urethroscopy once every 3 months for 2 years, then once every 6 months thereafter. One patient developed tumor recurrence 23 months after surgery and received another laser treatment, but no recurrence has been observed in the other 6 patients (85.7%). Transurethral endoscopic surgery and management using the holmium:YAG laser is safe and effective nephron-sparing surgery for ureteral transitional cell carcinoma, and good long-term treatment results can be expected even in elective cases if the indications are carefully selected.

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## Introduction

The development of both flexible and rigid ureteroscopes has enabled surgeons to easily and less invasively approach all parts of the upper urinary tract by means of the transurethral endoscope (1,2). This has made endoscopic observation of upper urinary tract tumors routine practice, and endoscopic treatment such as for superficial bladder cancer is now possible even in the upper urinary tract. We previously reported the indications and safety of the holmium:YAG laser for endoscopic resection of ureteral transitional cell carcinoma (3). Herein, we report a retrospective examination of the long-term treatment effect in patients who we were able to follow-up for ~5 years.

## Patients and methods

*Patients*. We evaluated 7 patients diagnosed with ureteral transitional cell carcinoma and treated with the holmium:YAG laser in the Department of Urology, Aichi Medical University Hospital from November 2000 to October 2003. The last observation date was set at December 2007. The patients were 4 men and 3 women aged 68-87 years (mean: 74.7 years). Four had disease on the left side and 3 on the right side.

Hydronephrosis was not found in any case, and urinary cytology was negative in all cases. Biopsy revealed 5 cases of grade 1 and 2 of grade 2. One patient had a tumor in the middle of the ureter while 6 had a tumor at the lower end of the ureters. Two had a papillary pedunculated solitary tumor and 5 had papillary pedunculated multiple tumors. There were 2 imperative cases (1 solitary kidney case and 1 high-risk

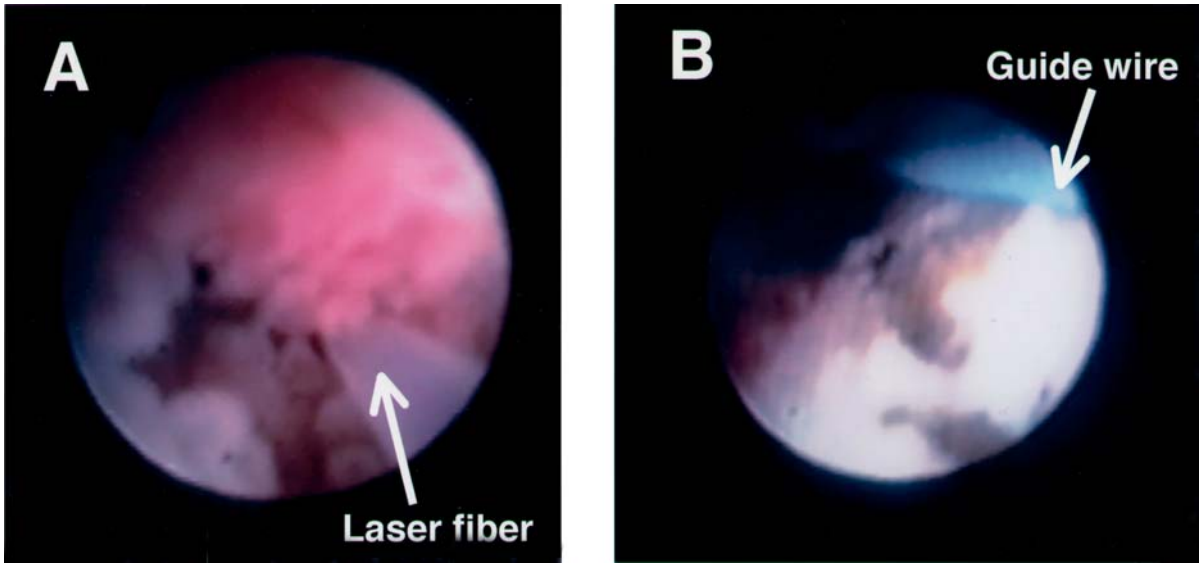


Figure 1. Case 5: Findings of operation. (A) A 365-$\mu$m laser fiber was used under direct rigid ureteroscopic visualization to resect a tumor by evaporation of surrounding tissue without touching it. (B) Irradiation stopped after sufficient coagulation of the tumor base and mucosal membrane surrounding it was obtained. No damage to the guide wire was observed.

Table I. Characteristics of seven patients.

| Pt. No. | Age | Sex | Side | Site | Biopsy | Tumor size (mm) | Growth pattern | Preoperative urine cytology | Hydronephrosis | Prior therapy | Past history |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 87 | F | Rt | Lower ureter | TCC, G1 | 20x5 | Papillary, multiple pedunculated | Negative | None | TUR-Bt | Heart failure |
| 2 | 68 | M | Lt | Lower ureter | TCC, G1 | 8x4 | Papillary, multiple pedunculated | Negative | None | TUR-Bt | Diabetes mellitus |
| 3 | 80 | M | Lt | Upper ureter | TCC, G1 | 15x5 | Papillary, solitaly pedunculated | Negative | None | Rt-nephroure-terectomy | None |
| 4 | 71 | M | Rt | Lower ureter | TCC, G2 | 25x3 | Papillary, multiple pedunculated | Negative | None | TUR-Bt | Hypertension |
| 5 | 74 | M | Lt | Lower ureter | TCC, G1 | 20x7 | Papillary, multiple pedunculated | Negative | None | TUR-Bt | Enone |
| 6 | 72 | F | Lt | Lower ureter | TCC, G1 | 10x4 | Papillary, solitaly pedunculated | Negative | None | TUR-Bt | Diabetes mellitus |
| 7 | 71 | F | Rt | Lower ureter | TCC, G2 | 10x3 | Papillary, multiple Pedunculated | Negative | None | None | None |

case) and 5 elective cases. The tumor size ranged from 8 to 25 mm (mean: 15.4 mm) (Table I). The World Health Organization classification (4) was used for histopathological grading.

*Instruments*. A Versa Pulse Select 80 holmium:YAG laser generator, a slim line laser fiber with a core diameter of 365 $\mu$m and a rigid ureteroscope with 8F-point diameter were used.

*Operation method*. Surgery was conducted after each patient was confirmed to have low grade (grade 1 or 2) histology on preoperative biopsy. First, the bladder was confirmed to be tumor-free, and then a 0.035 inch safety-guide wire was placed from the ureteral orifice. Then an 8F-rigid ureteroscope was inserted from the ureteral orifice under direct visualization. Saline was used for perfusion by gravity at a height of 100 cm. Normal ureter above the tumor was confirmed, and a 365-$\mu$m laser fiber was used carefully, so as not to touch the guide wire, to resect tumor by evaporation of surrounding tissue without touching it. Irradiation was stopped after sufficient coagulation of the tumor base and the mucosal membrane surrounding it was obtained (Fig. 1). A 6F double J catheter was placed for 3 weeks after the operation.

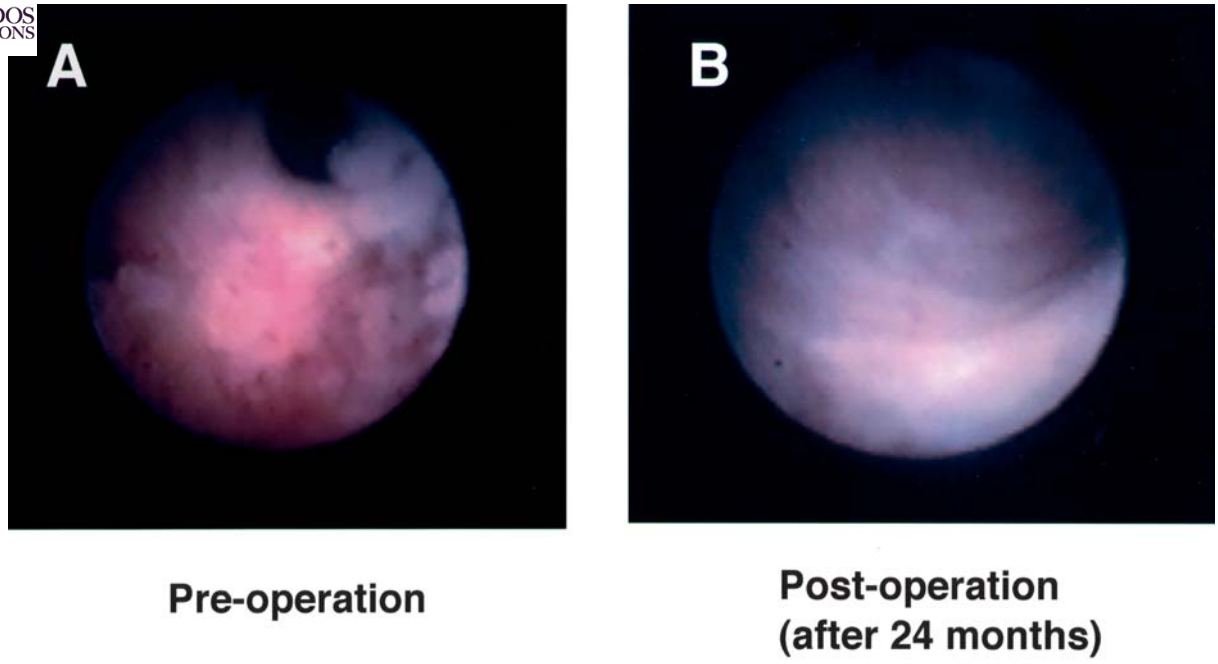


Figure 2. Case 5: Urereroscopic findings. (A) Initial ureteroscopy revealed multiple pedunculated papillary tumors. (B) Ureteroscopy performed 24 months postoperatively showed no recurrence of cancer.

Table II. Results.

| Pt. No. | Indication | Energy output, rate | Total energy (KJ) | Operation time (min) | Follow-up period (months) | Reccurence | Outcome |
|---|---|---|---|---|---|---|---|
| 1 | Imperative | 0.5J, 10 Hz | 1.3 | 60 | 23 | Yes | Died of cerebral infarction |
| 2 | Elective | 0.5J, 10 Hz | 1.02 | 20 | 88 | None | No evidence of disease |
| 3 | Imperative | 1.0J, 10 Hz | 2.53 | 45 | 84 | None | No evidence of disease |
| 4 | Elective | 0.5J, 10 Hz | 1.74 | 32 | 78 | None | No evidence of disease |
| 5 | Elective | 1.0J, 10 Hz | 11.22 | 97 | 78 | None | No evidence of disease |
| 6 | Elective | 1.0J, 10 Hz | 1.49 | 30 | 67 | None | No evidence of disease |
| 7 | Elective | 1.0J, 10 Hz | 0.9 | 29 | 56 | None | No evidence of disease |

## Results

*Laser irradiation and operation time*. Pulse energy of the holmium:YAG laser was set at 0.5-1.0 J (mean: 0.8 J) and the frequency was 10 Hz. The total amount of energy was 0.9-11.22 KJ (mean: 2.89 KJ) and the operation time including ureteral stent placement was 20-97 min (mean: 66 min).

*Postoperative course*. No patient received postoperative adjuvant therapy. One patient experienced tumor recurrence 23 months after the operation and underwent another laser treatment. The patient died of cerebral infarction 3 years after the operation. The observation period including this case was 23-88 months (mean: 67.8 months). Patients underwent examination of urinary cytology once a month, and cystoscopy, retrograde pyelography and urethroscopy once every 3 months for 2 years. From then, the patients have been followed every 6 months and no recurrence has been observed in the other 6 patients (85.7%) (Table II) (Fig. 2).

*Complications*. No urinary tract perforation associated with laser irradiation occurred. No ureteral stricture has been observed during the follow-up period.

## Discussion

Since upper urinary tract tumors tend to be multifocal, the standard operative procedure is nephrouterectomy with partial cystectomy at the affected ureteral orifice. In addition, since diagnosis and determination of the depth of upper urinary tract tumors are not clear, this procedure has been selected even for small tumors as well as large ones. However,

recurrence is rare in low-grade and low-stage cancer, and therefore, conservative surgery represented by partial ureterectomy is now commonly performed, especially for small tumors in the lower urinary tract (5,6).

Recently, endoscopy is commonly used to diagnose upper urinary tract tumors, and our group also actively uses endoscopic observation. In our experience, we often encounter cases that could possibly be treated endoscopically such as transurethral resection of bladder cancer.

We have reported the safety and effectiveness of the use of the holmium:YAG laser for endoscopic treatment of ureteral stenosis (7-9). Herein, we used the holmium:YAG laser to resect ureteral cancers and examined 7 patients who we were able to follow-up for a long period of time.

Initially, the tools used for endoscopic resection of upper urinary tract tumors were mainly electric coagulators or ureteroscopes for resection (10,11), but the energy needed for resection was high and they could cause postoperative stricture or perforation due to thermal degeneration of the ureter's thin wall. On the other hand, the laser has a narrow light guide and flexibility, and is suited for both rigid and flexible ureteroscopes with small diameter. Recently, the holmium:YAG laser, which can evaporate, coagulate and resect tumors, has attracted much attention (5,12). The holmium:YAG laser can be used safely since its irradiation affects only the surface. The problem, however, is that postoperative histological diagnosis from resected samples is difficult. In addition, since the holmium:YAG laser is a pulse wave, tumor cells may be scattered in cases of upper tract tumors, and the risk of dissemination cannot be eliminated. However, we are not aware of such a report to date.

Sufficient perfusion is required to smoothly conduct endoscopy. However, if perfusion pressure is increased to secure a sufficient amount of perfusion, the perfusion fluid is absorbed by the vascular system, risking dissemination of tumor cells (13). Therefore, we used saline perfusion by gravity at a height of 100 cm instead of using a roller pump for perfusion, based on the study that pressure <75 mmHg does not affect the kidney (14). However, since the pressure was low, we often lost the visual field soon after laser irradiation started and had to stop irradiation to drain the fluid and irradiate again while reinfusing the fluid.

Smith *et al* (15) considered that the indication for endoscopic treatment is solitary, local, low-grade, non-invasive papillary pedunculated tumor without the complication of other transitional carcinoma, since their recurrence rate is low. Matsuoka *et al* (16) designated solitary kidney, bilateral disease and high risk cases as imperative cases and low-grade small papillary pedunculated tumors as elective cases. In our study, though some had multiple tumors, all had negative urine cytology and low grade disease at biopsy. However, the most important aspect in deciding to perform endoscopy for upper urinary tract tumors may be the depth of invasion. Imaging such as IVP, RP, CT and MRI are used in urology, but it is difficult to accurately judge the depth with these images. Therefore, the depth of invasion is currently estimated from the diagnosed grade. In addition, since it is difficult to make postoperative histopathological diagnosis with laser ablation, reliable tissue sampling and diagnosis by biopsy are considered crucial. Intraureteral ultrasonography using a 20 MHz small-diameter ultrasound probe has been developed and its effectiveness is currently under review. Small-diameter ultrasonography is expected to play an important role in urological endoscopy in the future (17-19).

Keeley *et al* (5) reported that they performed nephron-sparing surgery for upper urinary tract tumors in 41 kidneys (all had laser ablation) and observed recurrence in 8 (28.5%) of 28 kidneys that were evaluable. Matsuoka *et al* (16) reported that 3 (16.7%) of 18 cases (all with holmium:YAG laser ablation) experienced recurrence. The treatment results of 59 upper tract urothelial carcinomas previous studies by Martinez-Pineiro *et al* (20) revealed the recurrence rate of endoscopic treatment (including electric coagulation and laser ablation) to be 9.5-45%. The mechanism of recurrence has not been elucidated, but multifocal recurrence, where the source of tumor development remains, is believed to be the cause. They also noted that high grade (including grade 3) or preoperative urinary cytology-positive cases are more likely to have recurrence. Some reported good treatment results in elective cases (21,22), but we consider the indication for endoscopy treatment is the selection criteria of Matsuoka *et al* (16) as well as urinary cytology-positive cases.

In all our cases, a ureteral stent catheter was placed for 3 weeks for postoperative management, but catheter placement may not be needed for short-term procedures in the lower ureter. The indication for stent catheter placement should be reconsidered. Furthermore, unlike bladder cancer, there is no established standard therapy to prevent recurrence. Some studies reported that postoperative adjuvant therapy with mitomycin-C or BCG is effective (5,20,23,24), but since they were conducted under various kinds of protocols, the effectiveness is not clear at this point and further research involving more cases is needed.

For postoperative follow-up, Bagley (25) recommended cystoscopy and urinary cytology once every 3 months, urethroscopy once every 6 months and pyelography every 12 months. Chen *et al* (26) recommended cystoscopy once every 3 months and urethroscopy once every 6 months for 2 years after surgery, and cystoscopy once every 6 months and urethroscopy once a year thereafter. However, considering the detection rate of endoscopy, we think that endoscopic follow-up of the upper urinary tract with cystoscopy is necessary in cases of bladder cancer. Therefore, we observe the renal pelvis and renal calyx with a flexible cystoscope once every 3 months, even though it is an invasive method, in the routine follow-up.

Transurethral endoscopy with the holmium:YAG laser, as nephron-sparing surgery for ureteral transitional cell carcinoma, was safe and effective during a long period of observation. Good long-term results can be expected in elective cases if the indications are carefully selected.

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