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Endoscopic Ablation of Upper Tract Urothelial Carcinoma: A Report of Two Cases with Long Disease Recurrence-Free Periods

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ABSTRACT

Upper tract urothelial carcinoma (UTUC) is a relatively rare disease that accounts for 5% to 10% of all urothelial carcinomas (UCs). Radical nephroureterectomy (RNU) with a bladder cuff is the current gold standard for the management of UTUC; however, endoscopic ablation is also an option for low-risk UTUC to preserve kidney function. Herein, we present two cases of solitary kidney with a right lower ureteral tumor. Both patients underwent left RNU in the past. An 82-year-old man with a right ureteral tumor whose histopathological examination revealed low-grade UC. Laser ablation was performed with ureteroscopy, and there was no recurrence for 7 years after treatment. A 67-year-old woman with a right lower ureteral tumor whose histopathological examination also revealed low-grade UC. Laser ablation was performed, and there was no recurrence for 5 years after the treatment. We closely followed-up our two patients after RNU. This allowed for early detection of tumor recurrence, after which we could perform laser ablation therapy.

Key words kidney-sparing surgery; laser ablation therapy; radical nephroureterectomy; urothelial carcinoma; upper tract urothelial carcinoma

Upper tract urothelial carcinoma (UTUC) is relatively rare. Radical nephroureterectomy (RNU) with a bladder cuff is the current gold standard for the management of UTUC, but endoscopic ablation is also an option for low-risk UTUC to preserve kidney function. The advances in laser technology led to increased acceptance of minimally invasive techniques in the management of UTUC.[1] Endoscopic management of UTUC is characterized by better postoperative renal function, shorter hospitalization, and lower complication rates when compared to RNU.[2, 3] Previously, the indications were limited to patients with a solitary kidney, bilateral tumors, and high-risk patients for surgery; however, kidney-sparing surgery (KSS) such as endoscopic ablation for low-risk UTUC was given a "strong recommendation" grade in the 2020 European Association of Urology (EAU) guidelines.[4] However, there is a risk of tumor recurrence and progression with endoscopic management due to factors, such as the possibility that tumor risk stratification consisting of tumor biopsies and imaging studies, may not be appropriate. Additionally, long-term outcomes after ablation therapy and the appropriate ablation method remain unclear, and protocols for postoperative follow-up have not been established. In this study, we encountered two rare cases of UTUC with asynchronous recurrence in the contralateral ureter after surgery. The two patients with recurrent tumors were treated endoscopically and survived without recurrence. Here, we discuss endoscopic ablation for low-risk UTUCs based on the two cases we have experienced.

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Abbreviations: CT, computed tomography; CTU, CT urography; EAU, European Association of Urology; KSS, kidney-sparing surgery; RNU, radical nephroureterectomy; UC, urothelial carcinoma; UTUC, upper tract urothelial carcinoma

PATIENT REPORT

Case 1

An 82-year-old man was found to have microhematuria. CT urography (CTU) and retrograde pyelography revealed a tumor in the left renal pelvis, and the patient underwent left RNU. Histopathological examination of the resected specimen revealed low-grade urothelial carcinoma (UC), pTaN0M0, Stage0a. Seven years later, a papillary tumor, 5 mm in diameter, was detected in the right intramural ureter. Transurethral resection of the ureteral tumor was performed. The histopathological findings indicated low-grade UC and pTaN0M0, Stage0a. Three months after surgery, a right ureteroscopy was performed to check for recurrence. After confirming that there were no tumors in the bladder, retrograde urography of the right ureter was performed, which showed no defect in the right ureter. The lower ureter was observed using a 6.5 Fr rigid ureteroscope (Richard Wolf GmbH. Knittlingen, Germany) and no neoplastic lesions were observed. We then observed from the middle ureter to the renal pelvis using an 8.4 Fr flexible uretero renoscope URF-V3 (Olympus Corp. Tokyo, Japan), and a 2–3 mm in diameter, was found in

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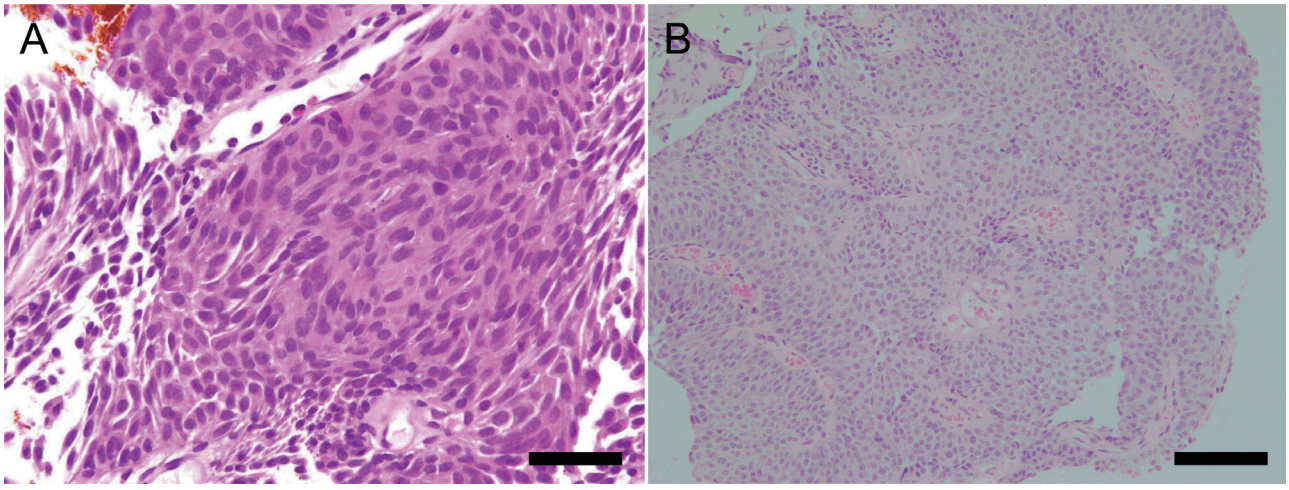

Fig. 1. Pathological findings of urothelial carcinoma. **A**: Pathological finding of ureteroscopic tissue biopsy of a renal pelvic tumor showing no submucosal invasion, diagnosed as low-grade urothelial carcinoma. Bar = 50 μm (Case 1). **B**: Pathological finding of ureteroscopic tissue biopsy of a ureteral tumor showing no submucosal invasion, diagnosed as low-grade urothelial carcinoma. Bar = 100 μm (Case 2).

the renal pelvis. A tumor biopsy was performed, and the histopathological finding indicated low-grade UC (Fig. 1A). We then performed laser ablation with a 200-μm laser fiber connected to VersaPluse (Lumenis, Yokneam Illit, Israel). We used Holmium /yttrium-aluminum-garnet (Ho:YAG) laser for tumor ablation. The laser power was started at a low power and finally set to 0.6 J and 10 Hz. During ablation therapy, the tumor was evaporated from the surface to the base (Figs. 2A and B). After ablation, tissue biopsy of the base of the tumor was performed to confirm that there were no malignant findings. The operation was finally completed with placement of a 6 Fr ureteral stent. Thereafter, we followed up the patient with urine cytology and cystoscopy every 3 months. CTU was performed every 3 months for the first year, every 6 months for the next 3 years, and once a year after the fifth year. We performed ureteroscopy at 3 months and 6 months after surgery, and every 6 months until the fifth year. Seven years after surgery, there was no evidence of recurrence.

Case 2

A 67-year-old woman presented with low back pain, and contrast-enhanced computed tomography indicated a left lower ureteral tumor. She underwent left RNU. The histopathological findings were low-grade UC and pTaN0M0, Stage0a. Two years later, computed tomography (CT) revealed a space-occupying lesion in the right lower ureter. Right ureteroscopy revealed a papillary tumor, 10 mm in diameter, in the right lower ureter. A biopsy of the tumor was performed, and the histopathological results indicated low-grade UC (Fig. 1B). Transurethral laser ablation was then performed. Ablation was performed using the same equipment and laser settings as those in *Case 1*. After ablation, tissue biopsy of the base of the tumor was performed to confirm that there were no malignant findings (Figs. 2C and D). Postoperative follow-up was performed using the same protocol as in Case 1. Five years after surgery, there was no evidence of recurrence.

DISCUSSION

UTUC is a relatively rare disease, accounting for 5% to 10% of all UC cases. The common age range was 50–70 years. It is estimated that UTUC is more than twice as likely to occur in men than women. The incidence of ureteral tumors is estimated to be one-fourth that of renal pelvic tumors.[5] UTUC often occurs unifocal, but multifocal tumors are found in approximately 10–20% of cases.[6] Risk factors for the progression of cancer include smoking, drugs, chronic infections, exposure to chemical carcinogens, and occupational carcinogens.[6, 7]

The standard treatment for UTUC is RNU with bladder cuff. However, there are some reports that endoscopic ablation therapy is comparable to RNU in controlling cancer in low-risk UTUC.[8] The 2020 edition of the EAU guidelines defines low-risk UTUC as one that meets all of the following elements: unifocal disease, tumor size < 2 cm, negative for high-grade cytology, low-grade URS biopsy, and no invasive aspect on CT. The recommended grade for KSS, such as endoscopic ablation of low-risk UTUC, is a strong recommendation in the 2020 EAU guidelines.[4] However, endoscopic ablation is still not a standard treatment in Japan, and

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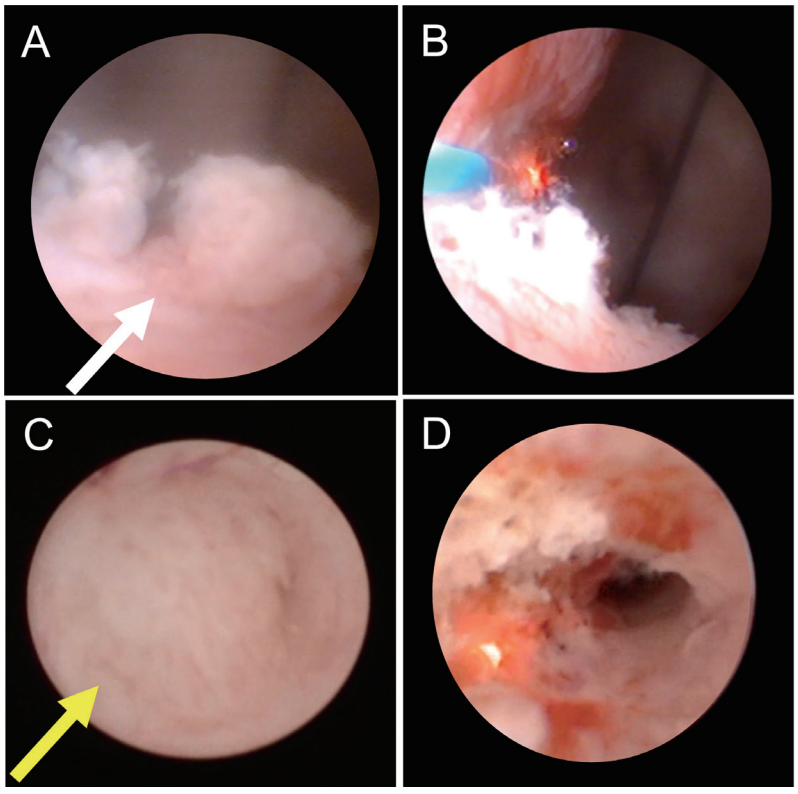

Fig. 2. Ureteroscopic findings. **A**: Ureteroscopic findings showing papillary tumors (white arrows) 2–3 mm in diameter in the renal pelvis (Case 1). **B**: After laser ablation of the tumor under ureteroscopy (Case 1). **C**: Ureteroscopy showing a papillary tumor (yellow arrow) in the lower ureter (Case 2). **D**: After laser ablation of the tumor under ureteroscopy (Case 2).

is currently only used in cases such as solitary kidneys or high risk for RNU. The 2014 edition of the Japanese Urological Association's guidelines gives endoscopic treatment for UTUC a grade C1 recommendation. KSS can preserve renal function, thereby reducing the risk of cardiovascular death caused by chronic kidney disease.[9] Therefore, KSS is an important treatment strategy for UTUC. The main problem with the KSS is local recurrence. Ng Chieng et al. reported a high local recurrence rate of 46% at a mean follow-up time of 4.9 months after endoscopic treatment.[10] The risk of intravesical recurrence after treatment of UTUC is relatively high (30–40%), whereas the recurrence rate in the contralateral upper urinary tract, as observed in our two cases, is rare (2–6%).[11] Moreover, there are still some issues to be discussed. The problems associated with endoscopic ablation are that there is no reliable follow-up protocol after ablation, the appropriate ablation method and long-term outcomes after treatment are still unclear, and it may be difficult to make an accurate preoperative tumor risk diagnosis.

Urine cytology, cystoscopy, and computed tomography are used to diagnose UTUC, and tissue biopsy under ureteroscopy is necessary for pathological diagnosis. Nevertheless, tumor risk stratification, consisting of tumor biopsies and imaging studies, may not be appropriate. The sensitivity of CTU for UTUC was 92% and the specificity was 95%; however, it was difficult to detect small or flat tumors. The sensitivity of urinary cytology for UTUC is approximately 67–76%.[12] The concordance rate between endoscopic biopsy and final pathology of 66% for low-grade cases and 97% for high-grade cases.[13]

Lasers mainly used in endoscopic ablation are Ho: YAG, thulium YAG (Tm: YAG), and neodymium YAG (Nd: YAG). Ho: YAG is characterized by a longer wavelength and less tissue penetration. Tm: YAG has a shallow depth of penetration (about 0.1–0.2 mm) compared to Ho: YAG (approximately 0.3–0.4 mm), showing good coagulation and hemostasis ability. Nd: YAG has deep tissue penetration, which is a good option for tissue coagulation, but may increase its associated complications.[14] Tada et al. reported the appropriate laser selection for ablation for UTUC.[13] They used Nd: YAG for large tumors (> 2 cm) and Ho: YAG for small tumors (< 2 cm), and reported recurrence-free survival (RFS) at 1, 2, and 3 years after the first operation were 80%, 60%, and 60%, respectively.[15] Our endoscopic

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ablation therapy protocol was as follows: First, the superficial layer of the tumor in the ureter or renal pelvis is evaporated with a Ho: YAG laser (energy 0.6 J, rate: 10 Hz). Subsequently, we confirmed that there was no residual tumor and performed biopsy of the tumor base.

Several studies have reported the long-term results of endoscopic ablation therapy for UTUC. Shvero et al. reported 59 patients with low-grade UTUC who underwent endoscopic ablation therapy. They performed the mean number of 5.5 ureteroscopies over a median follow-up of 22 months for the patients, of which 74.1% had recurrence, and the mean time to recurrence was 6.5 months. However, most patients (93.2%) did not experience disease progression. They also reported that tumors located in the renal pelvis and multifocality were significant predictors of the time to local recurrence. Moreover, they also examined the relationship between tumor size and local recurrence rate and found no significant association between them at tumor size cutoffs of 1, 2, and 3 cm. However, larger tumors showed a trend toward a shorter time to recurrence.[16] Scotland et al. reported that after endoscopic treatment of low-grade tumors with a diameter greater than 2 cm, 90.5% of patients had tumor recurrence at a median follow-up of 43 months, 31.7% had an increase in grade, and 20% of patients eventually underwent RNU.[17] In our studies, the close follow-up after RNU allowed for early detection of recurrence, so we could treat the tumors with laser ablation when they were small (Case 1: 2–3 mm, Case 2: 10 mm). This may be the reason why our patients have remained recurrence-free for a long time.

Although there is no reliable protocol for follow-up after endoscopic treatment, several reports recommend follow-up with urine cytology, ureteroscopy, cystoscopy, and CTU every 3 months for 2 years, every 6 months from 3 to 5 years, and every year after 5 years.[18, 19] In particular, ureteroscopy is required every 3 months for the first 2 years after treatment. In_this study, we followed up the patient with urine cytology and cystoscopy every 3 months. CTU was performed every 3 months for the 1st year, every 6 months for the next 3 years, and once a year after the 5th year. We performed ureteroscopy at 3 months and 6 months after surgery, and every 6 months until the 5th year. As Shvero et al. reported that the mean time to recurrence was 6.5 months, our protocol also seems to be appropriate because we have sufficient follow-up for 6 months after surgery.[16]

We report two cases of UTUC treated by endoscopic ablation, which had long-term tumor control. *Cases 1* and *2* were recurrence-free after endoscopic treatment for 7 and 5 years, respectively. A high quality of life (QOL) has been maintained because they can avoid postoperative dialysis, which would deeply impact daily life. Endoscopic ablation therapy can be expected to maintain good outcomes and a high QOL for selected patients, such as those with low-risk UTUC.

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The authors declare no conflict of interest.

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