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Ureteroscopic Management of Large ≥ 2 cm Upper Tract Urothelial Carcinoma: A Comprehensive Twenty-three Year Experience

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Title: Ureteroscopic Management of Large ≥ 2 cm Upper Tract Urothelial Carcinoma: A Comprehensive Twenty-three Year Experience

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ABSTRACT

Objectives: To evaluate the effectiveness of ureteroscopy (URS) with laser ablation as an alternative treatment for UTUC lesions larger than 2 cm. Traditionally, patients with large upper tract urothelial carcinoma (UTUC) are treated with radical nephroureterectomy (RNU). However, in patients with pre-existing renal disease, a solitary kidney, or those who decline RNU, management of UTUC may prove challenging.

Methods: An institutional database review identified 80 patients with biopsy proven low grade UTUC who had at least one lesion larger than 2 cm. We collected clinical data including demographics, operative parameters and pathologic features. Follow-up for all patients was standardized and included cystoscopy and ureteroscopy every 3 months until clear, every 6 months through the fifth year and yearly thereafter. We calculated rates of recurrence, progression and overall survival.

Results: 86 unique lesions ≥ 2cm were identified in the 80 qualifying patients; mean tumor size was 3.04 cm. Median follow-up was 43.6 months. During follow-up of patients treated curatively, 90.5% of tumors had ipsilateral recurrence and 31.7% progressed in grade at a median of 26.3 months. RNU was performed in 16 patients (20%); mean time to surgery was 23.2 months. Overall survival was 75% and cancer specific survival was 84% at five year follow-up.
Conclusions: Under strict surveillance, ureteroscopic management of large (≥ 2cm) UTUC lesions is a viable treatment alternative to RNU. While recurrence is common, ureteroscopy can potentially preserve renal units in patients with large lesions.

Introduction

Upper tract urothelial carcinoma (UTUC) accounts for 5-7% of renal tumors and 5% of all urothelial tumors.\textsuperscript{1} It is a relatively rare disease with the number of newly diagnosed cases in 2017 in the United States estimated to be between 6830 and 8100.\textsuperscript{2} Radical nephroureterectomy (RNU) has been considered the standard treatment for UTUC. However, the risk of developing chronic kidney disease has raised the need for techniques for renal preservation. Nephron sparing surgeries in patients with renal cell carcinoma have been shown to decrease the risk for chronic kidney disease,\textsuperscript{3} which may prevent the development of cardiovascular morbidity and improve overall survival.\textsuperscript{3,4} Ureteroscopic management of UTUC has achieved favorable treatment outcomes and renal preservation rates in patients with solitary kidneys and renal insufficiency. It has also been applied in carefully selected patients with a normal contralateral kidney.\textsuperscript{5,6}

Ureteroscopic biopsy is important to guide treatment.\textsuperscript{7} Grade can be determined in the majority of cases but staging is unreliable. Other factors may indicate staging and several
reports have presented prediction models considering both preoperative imaging and grade to guide the optimal treatment of UTUC. None of these models accounts for tumor size.\textsuperscript{8,9}

Recently published guidelines from NCCN and EAU recommend extirpative surgery for UTUC lesions which are high-grade, "large" or two cm in diameter independent of tumor grade.\textsuperscript{10,11}

This study reviews our experience and evaluates the effectiveness of ureteroscopic resection and laser ablation with a strict surveillance protocol as an alternative treatment for UTUC lesions two cm or larger.

\textbf{Materials and Methods}

In an institutional review board approved study, a retrospective review was performed to assess the clinical outcome of endoscopic treatment of large UTUC tumors. Electronic and paper records were evaluated to identify patients treated ureteroscopically for large upper tract urothelial carcinomas from January 1994 to August 2011. Follow-up information was evaluated to July 2017.

We defined large UTUC as at least one tumor measuring 2cm or larger. Tumor size was determined based on largest diameter. Tumor size was typically stated in the operative note based on CT-urogram or retrograde pyelography. When the tumor size was not specifically noted but described qualitatively as "large" or "extensive", it was assumed to be 40 mm (see Discussion).

A total of 109 consecutive patients were identified. Patients were excluded from the statistical evaluation if the index tumor had been initially managed at another institution or they underwent RNU immediately subsequent to initial diagnostic ureteroscopy with biopsy, if they
returned to their primary urologist after initial ureteroscopy or underwent percutaneous intervention. Following these exclusions, the records of 80 patients were deemed appropriate for evaluation (Supplemental Figure). They were further divided into palliative and intent to cure patient groups (Supplemental Figure).

Patient and disease predictors including age, gender, laterality and presence of bladder tumor were assessed via comprehensive patient and operative chart review. Renal function was assessed using creatinine levels and estimate glomerular filtration rate (eGFR). Pathological grade was expressed.

Figure 1A demonstrates a large UTUC. Retrograde pyelogram was undertaken using 8 French (Fr) cone-tip catheters (Fig. 1C, D). Ureteroscopy was performed using a "no touch technique", whereby the urinary tract is visualized prior to insertion of guide wires, to avoid trauma or bleeding. One of two biopsy devices was used to obtain tissue: 3Fr cup biopsy forceps or 2.4Fr flat wire basket (Fig. 1B). When forceps were used, multiple biopsies were taken from the same lesion until grossly visible tumor was noted in the sample container. The basket was used to remove the specimen by avulsing a piece of tumor. Specimens were promptly delivered to the cytopathology laboratory and processed with the Cytospin technique. A cell block was also prepared from any visible tissue in the sample.

In order to express the pathology results both in the old (1973) and new (2004) systems, a reclassification of the grade two slides as either high or low grade was done where possible.

Specimen was unavailable for reclassification in 32 cases.

Tumors were treated with Neodymium: YAG, Holmium: YAG or a combination of the two lasers.

Electro-fulguration with a 2Fr Bugbee electrode was used in selected cases where laser fibers
limited ureteroscopic deflection. The surveillance protocol consisted of ureteroscopy within six weeks then cystoscopy and ureteroscopy every 3 months until clear, every 6 months through the fifth year and yearly thereafter. The endoscopic surveillance at six weeks was added later in the series. Tumor recurrence dictated resetting of the protocol.

Cox regression analysis was used to analyze patient outcomes including time to recurrence, progression (defined as increase in tumor grade), overall survival and cancer specific survival. Kaplan-Meier curves were utilized for data presentation. Subgroup analysis was performed for those patients ureteroscopically treated with curative intent.

Results

This study evaluates 80 patients who underwent ureteroscopy for large (≥ 2 cm) UTUC tumors (Figure 1). Reasons for choosing this method of treatment include patient preference in 25 patients (31.3%), solitary kidney/chronic kidney disease in 21 patients (26.3%) and high risk in 11 patients (13.8%). The remainder of patients did not have well-documented reasons for choosing ureteroscopy. Of the 80 patients in this study, 17 (21.3%) were treated palliatively for high grade disease, or for tumor burden that was not amenable to curative ureteroscopic treatment. Sixty-three (78.8%) patients with low grade disease were treated with curative intent. Patient and tumor demographics of this sub-group are summarized in Table 1. Mean tumor size was 30.7 mm (20-60). Tumors were located in the kidney (60.9%), ureter (33.3%) or both (5.8%). Mean follow up was 44.3 months (2.7-177).

Eradication of the initial tumor was achieved after a mean of 1.69 ureteroscopies. Of these, initial tumor clearance was achieved in one or two sessions for all 63 curative patients. Tumor
observed at the first surveillance study was considered persistent; 45 patients had persistent tumor. Forty patients (63.5%) were free of tumor at some point during the surveillance period. Fifty-seven patients (90.5%) had tumor recurrence during follow-up. Mean time to first recurrence was 4.9 months. Twenty (31.7%) showed disease progression with 11 (17.4%) progressing to high grade disease. Mean time to grade progression was 26.3 months. Metastatic disease developed in seven patients (11.1%) at a mean time of 49.6 months. Of those seven patients, six died of metastasis-related causes. Sixteen patients eventually underwent RNU (Supplemental Table) with mean time to procedure 23.2 months. Bladder tumors were diagnosed prior to, concomitant with, or after the diagnosis of UTUC in 19 (30.2%), five (7.9%) and 19 (30.2%) patients, respectively. The remaining 30% had no bladder tumors. Mean serum creatinine levels for this cohort prior to the first procedure and after the last follow-up were 1.31 (0.5-4.7) and 1.89 (0.5-6.6) respectively. Mean eGFR prior to the first procedure and after last follow-up was 49.6 and 40.3, respectively.

In the palliative group, mean tumor size was 29.4 mm (20-60). Location included: 10 kidney (58.8%) and seven (41.2%) ureteral tumors. No patients had tumor in both locations. Mean follow-up was 43.1 months. All patients had tumor recurrence during the surveillance period. Four of the 17 (23.5%) patients developed metastatic disease at a mean time of 14.3 months. Bladder tumors were diagnosed before, during, or after the diagnosis of UTUC in nine (52.9%), three (17.6%) and one (5.9%) patient, respectively.

Seventeen (21.3%) patients had a solitary kidney: 8 patients (47.1%) in the intent to cure group and 9 patients (52.9%) in the palliative group. Patient and tumor characteristics of this group are summarized in Table 2.
Neodymium: YAG laser energy was primarily used for laser ablation with mean energy for the entire patient cohort of 14.9 kJ. Holmium: YAG was also utilized with mean energy level of 4.58 kJ. Overall mean tumor size was 30.4mm.

We demonstrated 10% recurrence free survival at 5 years (Fig. 2 A) but 65% progression free survival (Fig. 2B). Metastasis- free survival was 82% at five years of follow-up (Fig. 2C). Overall survival was 75% at five years and 39% at 10- year follow-up (Fig. 2D) while cancer specific survival was 84% at five and 65% at 10 years (Fig. 2E).
Comment

Ureteroscopic treatment of UTUC was initially limited to patients with solitary kidney or impaired renal function, and reserved solely for distal ureteral and renal pelvis tumors. The advent of small-caliber semi-rigid and flexible ureteroscopes extended their use from the distal ureter to the entire collecting system. Endoscopy was performed in patients with bilateral functioning kidneys, based on successful treatment of patients with imperative indications. Multiple series have demonstrated the utility of ureteroscopic treatment.

Patients were chosen for ureteroscopic management by baseline renal function, concurrent comorbidities and patient preference. Patients presenting with a solitary kidney underwent ureteroscopy. Others with severe comorbidities, such as CKD and cardiovascular disease, were deemed better fit for ureteroscopy as well. The 17 palliative patients were those with advanced disease or those with other terminal illnesses or comorbidities precluding major surgery. Three of these patients died of verified metastatic UTUC. The remainder died of other illnesses or official cause of death was not known. Around half of patients diagnosed with UTUC have a baseline GFR less than 60mL/min/1.73m before initiation of any treatment. Those patients can potentially benefit from nephron-sparing treatment. After RNU, patients are left with a solitary kidney, which may in some cases eventually lead to chronic dialysis, cardiovascular morbidity and overall mortality. Other curative patients simply preferred endoscopic management when presented with the option of RNU and its potential complications. Around 35-38% of patients undergoing either minimally invasive or open RNU experience significant post-operative complications. In contrast, we have found that complication rates post-URS
are generally minor and rates are low, typically below 13%. Despite the fact that an RNU is a single procedure, some patients preferred the decreased risk associated with ureteroscopy.

Current EAU guidelines limit the use of endoscopic treatment to UTUC tumors smaller than two cm, whereas tumors > two cm are referred to RNU; NCCN guidelines state that "large" tumors should be referred to RNU. However, technological improvements in ureteroscopes have allowed effective treatment of large tumors. Ablative devices in use today include small electrodes, Holmium: YAG, Neodymium: YAG or a combination of these lasers. Neodymium is first used to coagulate the tissue which kills the cells resulting in a bloodless field. This allows for uncomplicated subsequent resection with Holmium: YAG even with large tumors. Some authors have advocated for the percutaneous treatment of large volume intrarenal tumors, with comparable results to extirpative surgery. Additional reports have included limited numbers of patients with large tumors in their series, but did not specifically study this unique group. Thus the relationship between tumor size and treatment efficacy is difficult to determine based on available data. In this study, 63 patients with at least one index tumor of size at least two cm (average diameter 3.07cm) were treated ureteroscopically with intent to cure. Despite tumor volume, this approach was shown to clear the entire tumor with a mean of 1.69 procedures.

As reported previously, patients exhibited a high recurrence rate, demanding a strict surveillance protocol and patient compliance. This is also necessary for identification of strictures and is crucial for the detection of grade progression and development of locally advanced or metastatic disease. Most recurrences were small low-grade lesions which are...
easily treated. For patient follow up, we used a bladder cancer surveillance protocol which was modified according to our experience. Initially, every three months cystoscopy and ureteroscopy were performed until the upper tract was determined to be clear. However, we noted the high rate of persistent tumor at the initial three-month follow-up procedure which likely represented incompletely treated large tumor rather than a true newly recurrent lesion. Therefore, the surveillance protocol was modified to add an initial ureteroscopy at six weeks follow-up. We continued to perform endoscopy every three months, with eventual extension to six months if negative at two years follow-up. After five years, surveillance was performed on a yearly basis.

Initially, surveillance of the contralateral collecting system was performed yearly using retrograde ureteropyelography. After detecting neoplasms at shorter intervals, bilateral retrograde pyelography is now performed with every endoscopic procedure. Surveillance has been expanded to include yearly cross-sectional imaging, usually with a CT scan.

Sixteen patients were referred for RNU during the course of surveillance, largely for progression to high grade disease or high tumor burden (Supplemental Table). None of the patients in this series developed locally advanced disease. Other studies have also compared extirpative treatment versus RNU, demonstrating similar outcomes. In a long-term 15-year study by Grasso, they compared cohorts undergoing RNU versus URS for treatment of the UTUC. They also had several patients with large tumors > 3 cm, and 32 patients with 1-3 cm lesions.\textsuperscript{23} When comparing URS to RNU in patients with low-grade disease, they found cancer specific survival (CSS) rates at 5 and 10 years were 87% and 81% respectively, which were not significantly
different than patients treated with RNU. Separately, Gadzinski and colleagues compared RNU to endoscopic management and found a 5-year metastasis free survival of 88% and 94%, respectively. Overall survival in their study was 72% and 75% for RNU and ureteroscopy.

When specifically evaluating patients with low grade UTUC, they found no significant difference in five-year CSS, metastasis-free survival and overall survival. Simhan and colleagues used a large population-based dataset to compare outcomes of patients with low to moderate grade UTUC after undergoing RNU versus nephron-sparing procedures including URS. They also found no significant difference in cancer specific mortality. We have demonstrated a CSS of 84% and overall survival of 75% at five years despite the large tumor burden of our cohort, suggesting nephron sparing management of UTUC does not adversely affect survival. Our results indicate that patients with UTUC larger than two cm managed ureteroscopically have generally favorable survival outcomes.

Previous reports have shown that grading of the primary tumor has significant prognostic value. During the period of this study, the grading system for UTUC was changed. The 1973 system graded tumors on a scale of one to three; this was modified in 2004 to high-grade versus low-grade, wherein grade one and three lesions of the 1973 system correlate with low and high grade disease, respectively. Grade two lesions were classified as either low or high grade. Re-classification of all grade two lesions in this series according to the 2004 system was attempted. Unfortunately, several specimens were absent, thus precluding repeat evaluation. For those specimens able to be reclassified, five of the seven curative patients who developed metastasis were originally diagnosed with grade two disease. Four of these were revealed to
have had high grade disease (data not shown). Had these patients been diagnosed according to the 2004 system, they would have been referred to extirpative surgery, resulting in only three patients with metastatic disease in this series. We propose that the changes to the grading system have allowed for increased confidence in the decision to undertake endoscopic management of UTUC such that only appropriate patients would undergo ureteroscopy. Mean tumor size for patients in the curative arm was 30.7 mm (20-60). A total of 15 patients had tumor size described as “large”. On evaluating the intraoperative retrograde pyelogram for three random such patients (see Materials and Methods), all three were noted to have tumors larger than 40 mm (40, 46 and 43).

Bladder tumors were diagnosed prior to, concomitant with, and subsequent to the diagnosis of UTUC. Almost one-third of curative patients (30.2%) had a history of bladder cancer prior to presenting with UTUC, consistent with previous reports.²⁷ Five of the patients who subsequently developed bladder tumors had grade progression. Four of those did not develop metastases; the fifth was lost to follow-up.

There are little data regarding renal function prior to and after RNU. A recently published meta-analysis analyzed 36 studies with a total of 41,010 patients who underwent either partial or radical nephrectomy. The study showed a 61% reduction in risk of developing severe CKD in the partial nephrectomy compared to the radical nephrectomy group.²⁸ We advocate for nephron sparing surgeries when possible in the UTUC patient population given their baseline kidney function (creatinine and eGFR in this series). There was a relatively small decrease in these numbers -0.58 and 9.3, respectively- subsequent to endoscopic management at long-term
follow-up. This represents a change from CKD 3A to 3B over the course of follow-up. Another important factor to consider in treating UTUC is the overall cost incurred to patients and the medical system. Pak et. al examined costs to patients in a worst-case scenario model of patients undergoing RNU with subsequent dialysis to URS with tumor recurrence at 5 year follow up. The overall savings at 5 years was close to 250,000 dollars in favor of ureteroscopy. While a progression to dialysis may not be a challenge faced by all of the patients who are potential candidates for URS, it is important to consider the cost of care. These data may inform the decision making process.

One limitation of the study is that it is retrospective. The relative rarity of UTUC has made large prospective studies challenging. This is a single surgeon single site study, allowing for comparisons over time.

**Conclusions**

Under a strict surveillance protocol, ureteroscopic management of large UTUC lesions ≥ 2cm is an acceptable alternative to the current standard of RNU in well selected patients. Patients with low grade UTUC lesions larger than two cm may be offered ureteroscopic treatment with good oncologic outcome. While recurrence is common, this approach can potentially preserve renal function, avoid complicated surgical procedures and lessen tumor burden in patients with large lesions. Further multi-institutional prospective studies are needed in order to better define the role of endoscopic treatment for UTUC tumors.
Figure 1: Visualization of large upper tract urothelial carcinomas. 

A. Ureteroscopically visualized large UTUC. 
B. Biopsy of UTUC. 
C. Retrograde pyelogram demonstrating a large upper pole and renal pelvis filling defect. 
D. Renal pelvis status post laser ablation of mass.
Figure 2. Survival statistics  A. Recurrence free survival  B. Progression free survival  
C. Metastasis free survival  D. Overall survival  E. Cancer specific survival.
### Table 1: Patient and Tumor Demographics

<table>
<thead>
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<th>Curative Group (n=63)</th>
<th>Palliative Group (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean age (years)</strong></td>
<td>72.7 (53-90)</td>
<td>75.2 (47-93)</td>
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<tr>
<td><strong>Gender</strong></td>
<td></td>
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<tr>
<td>Male</td>
<td>42 (66.7%)</td>
<td>10 (58.8%)</td>
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<tr>
<td>Female</td>
<td>21 (33.3%)</td>
<td>7 (41.2%)</td>
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<tr>
<td><strong>Side</strong></td>
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<td>Right</td>
<td>31 (44.9%)</td>
<td>11 (64.7%)</td>
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<tr>
<td>Left</td>
<td>38 (55.1%)</td>
<td>6 (35.3%)</td>
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<tr>
<td><strong>Location</strong></td>
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<td></td>
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<tr>
<td>Kidney</td>
<td>42 (60.9%)</td>
<td>10 (58.8%)</td>
</tr>
<tr>
<td>Ureter</td>
<td>23 (33.3%)</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Kidney &amp; Ureter</td>
<td>4 (5.8%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Size (mm)</strong></td>
<td>30.7 (20-60)</td>
<td>29.4 (20-60)</td>
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<tr>
<td>Initial highest tumor grade (1973 system)</td>
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<td>25 (36.2%)</td>
</tr>
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<td>-----------------------------------------</td>
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<tr>
<td>2</td>
<td>28 (40.6%)</td>
<td>4 (23.5%)</td>
</tr>
<tr>
<td>3</td>
<td>3** (4.3%)</td>
<td>6 (35.3%)</td>
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<tr>
<td>Non-classified***</td>
<td>13 (18.8%)</td>
<td>4 (23.5%)</td>
</tr>
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</table>

* Note multiple index tumors identified in 5 patients. N=69

** Note these patients decided to attempt curative treatment

***Atypical, suspicious, free floating transitional cells

Table 2: Patient and Tumor Demographics of Patients with Solitary Kidney
<table>
<thead>
<tr>
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<th>Solitary Kidney (n=17)</th>
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<tbody>
<tr>
<td>Mean age (years)</td>
<td>69.7 (53-85)</td>
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<td>Gender</td>
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<tr>
<td>Male</td>
<td>11 (64.7%)</td>
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<tr>
<td>Female</td>
<td>6 (35.3%)</td>
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<tr>
<td>Side</td>
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<tr>
<td>Right</td>
<td>9 (52.9%)</td>
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<td>8 (47.1%)</td>
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<tr>
<td>Location</td>
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<tr>
<td>Kidney</td>
<td>9 (52.9%)</td>
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<tr>
<td>Ureter</td>
<td>7 (41.2%)</td>
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<td>Kidney &amp; Ureter</td>
<td>0 (0%)</td>
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<td>Size (mm)</td>
<td>34.4 (20-60)</td>
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<td>Initial tumor grade (1973 system)</td>
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*Atypical, suspicious, free floating transitional cells*
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