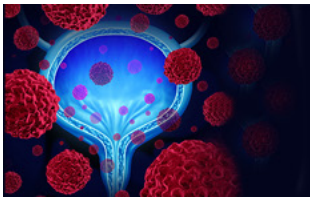


Addressing Challenges in Diagnosis and Treatment of Low-Grade Upper Tract Urothelial Carcinoma

OVERVIEW

Upper tract urothelial carcinoma (UTUC) has many similarities to bladder carcinoma, but also some important differences. Join Dr. Seth Lerner, as he contrasts these 2 diseases, as well as important differences between low-grade and high-grade UTUC. Dr. Lerner highlights important considerations in the instruments, imaging, and biopsy techniques for diagnosing low-grade UTUC. Surgical options are considered, with a focus on patient selection for endoscopic nephron-sparing surgery. The safety and efficacy of intracavitary therapy are discussed, with an emphasis on mitomycin for pyelocalyceal solution.

TARGET AUDIENCE

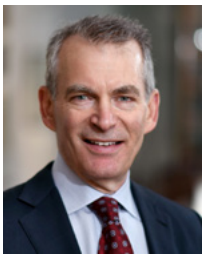
This activity is intended for urologists, oncologists, advanced practitioners, oncology nurses and other healthcare providers involved in the care of patients with low-grade upper tract urothelial carcinoma.

LEARNING OBJECTIVES

At the conclusion of this activity, participants should be better able to:

- Identify techniques to directly view and biopsy malignant abnormalities in the upper urinary tract
- Distinguish between low- and high-risk UTUC according to the latest guidelines
- Employ kidney-sparing endoscopic options in treating patients with low-risk, LG-UTUC
- Describe the safety, efficacy, and patient benefits of mitomycin for pyelocalyceal solution as therapy for LG-UTUC patients in whom tumor ablation with surgery is not feasible
- Employ upper tract imaging, ureteroscopy, and urine biomarkers to monitor patients for recurrent disease after kidney-sparing treatment for UTUC

FACULTY



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INTRODUCTION

Upper tract urothelial carcinoma, or UTUC, has an annual incidence of 1-2 patients per 100,000 population (Table 1). While not quite a rare disease, UTUC is not a disease that a general urologist is going to see frequently over the course of the year. UTUC constitutes about 7% of all renal tumors and it constitutes up to 10% of urothelial carcinomas. The bladder and urinary tract are far and away the most common, being about 2 cases per 100,000 population in western countries. Interestingly, renal pelvic tumors occur about twice as frequently as ureteral tumors, but they can be multifocal in 10% to 20%.[1,2]

Table 1. Upper tract urothelial carcinoma

Annual incidence	1-2/100,000 population
Male:Female	2:1
Mean age at diagnosis	73 years

Similar to bladder cancer, there's a male preponderance, but the ratio is a little bit different. The ratio is about 2:1 for the upper tract, whereas in bladder it's at least 3:1 and maybe 3 or 4:1. UTUC is a disease of older patients, with a mean age at diagnosis of 73 years. About one-quarter of patients will have concurrent asynchronous bladder cancer and 22% to 47% metachronous bladder cancer, meaning separated in time, with most of those occurring within 2 years. So, when we get to talking about surveillance, that time frame really is critical.[1,2]

The risk of a contralateral UTUC, which is a second primary tumor of the upper urinary tract, is actually quite low, about 2% to 5%. Patients with Lynch syndrome would be at much higher risk for a contralateral tumor or bilateral tumors, whether they're synchronous or metachronous.

The risk factors and etiology are quite similar to bladder cancer. Cigarette smoking is the most common risk factor. Other risk factors include occupational risks such as diesel exhaust and aromatic amines. Another risk factor is the DNA adduct producer aristolochic acid, which is present in Chinese herbs. It's a fascinating story to learn about as these patients have a very high risk of upper tract urothelial carcinoma as well as renal failure. Lynch syndrome should always be considered in these patients. Although many patients are asymptomatic, hematuria is the most common symptom by far. Flank pain is also common, particularly if there's any component of obstruction.

DIAGNOSTIC EVALUATION

Amsterdam II Criteria

The Amsterdam II Criteria are used to identify patients with Lynch syndrome, which is due to alterations in a set of genes called mismatch repair. The Amsterdam II Criteria require at least 3 relatives with any Lynch syndrome-associated cancer, with one of those being a first degree relative of the other 2.[3] One should be diagnosed before the age of 50 years. Two successive generations should be affected. In addition, familial adenomatous polyposis should be excluded in patients with colorectal cancer. Patients with Lynch syndrome have a 22-fold increased risk of UTUC compared with the general population. Lynch syndrome is relatively easy to identify using immunohistochemistry testing of ureteral or renopelvic tumor tissue to detect the presence of mismatch repair gene alterations in the tumor. Immunohistochemistry tests are MLH1, PMS2, MSH2, and MSH6. Germline mismatch repair gene alterations are seen in about 9% of patients with upper tract tumors compared with 1% of bladder cancers.

Visualization and Biopsy

The CT urogram is the benchmark to make the diagnosis of UTUC. A filling defect, often in the lower pole infundibulum, is the classic finding. The CT urogram is useful to assess tumor size, number, and whether or not there's evidence of infiltration which would suggest a more locally advanced high-grade cancer. The CT urogram can also provide information related to the ipsilateral draining lymph nodes. The anatomy of the draining lymph nodes is essentially identical to that observed in testicular cancer.

MRI urography also can be used, especially in patients with contrast allergy. Revised contrast guidelines enables both MRI and CT scans to be used in patients with lower kidney function than in the past and can be used in patients with an estimated glomerular filtration rate >30 mL/min/1.73 m^2.

Patient Journey

"I have 4 sons and a coworker and we go bowling every Tuesday night. On May the 14th of 2019, I slipped and almost fell, and, in the process, I had a sharp pain shoot up my left side. When I got up that next morning and went to the bathroom, there was a lot of blood in my urine. So, I had an appointment later in the week with the urologist who found some unusual cells and he referred me to the oncologist with whom I had an MRI. And it revealed that I had a 3 cm tumor."

The ureteropyeloscope is the instrument used most commonly for diagnosis. Compared to the large, rigid instruments that were previously used, ureteropyeloscopy is now undertaken with a very small, thin caliber instrument with a high-definition camera that easily traverses to the upper urinary tract and allows for visualization of the entire collecting system. If there is difficulty passing the ureteroscope, a stent can be placed, with scoping easily accomplished in 2 weeks or so. It is important that the ureteroscope is never forced since this may cause avoidable tissue damage or destruction. Stents and nephrostomy tubes are also useful to relieve obstruction and optimize renal function, which is especially important when cisplatin-based neoadjuvant chemotherapy is being considered.

In conducting the ureteroscopy, it is important to obtain a good quality tissue sample as this enables stratification of low-grade or high-grade.[4,5] Among the tools available for obtaining a biopsy, the Piranha biopsy forceps are the most commonly used, in my experience. However, because they sometimes malfunction, it is important to use them carefully.

Another biopsy device is the BIGopsy device, which enables the obtaining of a good biopsy specimen. A limitation is that it has to be backloaded, so that it has to be used in an access sheath. Access sheaths can be used quite safely and are particularly useful if there is a need to go in and out frequently, as is often the case if tumor ablation is attempted. Endourologists often use a basket such as the nitinol basket as it is very flexible and pliable, thereby allowing collection of a larger biopsy specimen,

especially if using a push-pull technique. This technique involves grasping the tumor at its base, then pushing it forward (rather than backward) into the lumen of the ureter to avoid perforation, thereby shearing off the entire grasped tissue.[6] Resected tumor is then retrieved. This technique can be repeated several times until the tumor is detached at its base and a significant portion is separated from the wall.

Biopsy is preferable to visual inspection for determination of disease grade

Biopsy is preferable for determination of grade because a low-grade appearance visually is not as accurate for determining grade. In fact, upgrading the tumor occurs in about 20% of patients where the grade has been established visually. However, visual appearance can provide useful information about the tumor, such as whether it is sessile or papillary, large or small.

Another option is a brush biopsy. This is particularly helpful when carcinoma in situ (CIS) is suspected, since trying to get biopsy forceps on spots with urothelium in order to obtain a sample can be difficult. The brush biopsy enables collection of ample cells and is done by brushing on the abnormal area, followed by irrigation.

Risk Stratification

Once a diagnosis of UTUC is made, the next step is to risk stratify based on clinical findings. Low-risk UTUC requires the presence of all of the features listed in Table 2.1 Essentially anything that doesn't meet the criteria for low-risk disease would fall into a high-risk category. High-risk doesn't necessarily mean high-grade. For example, large volume renal pelvic disease is generally not going to be amenable to intercavitary chemoablation. Consequently, a nephrectomy is the appropriate treatment even though it may not be high-grade disease. The analogy would be the unresectable, large-volume, low-grade disease in the bladder where a cystectomy may be preferred.

Table 2. Risk stratification of non-metastatic UTUC

Low-risk	**All of the following:** • Unifocal disease • Tumor size <2 cm • Negative for high-grade cytology • Low-grade ureteroscopy biopsy • No invasive aspect on computed tomography
High-risk	**Any of the following:** • Multifocal disease • Tumor size ≥2 cm • High-grade cytology • High-grade ureteroscopy biopsy • Local invasion on computed tomography • Hydronephrosis • Previous radical cystectomy for high-grade bladder cancer • Variant histology

From a histopathologic perspective, UTUC is almost exclusively pure urothelial in nature, although variant histology may be seen, similar to what is observed in the lower urinary tract. The most common variant is squamous cell, generally indicating high-grade UTUC.[1]

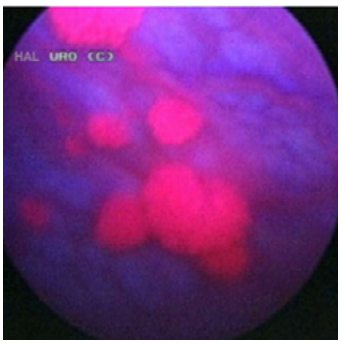
In terms of cytology, a wash or barbotage sample is better than a voided sample, since false-negatives are common with a voided sample. Recall that a brush biopsy with post-brush irrigation increases the sensitivity.

Imaging

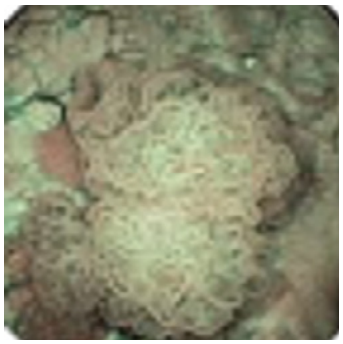
There have been a lot of innovations and enhanced endoscopic imaging, but these have been developed for the lower urinary tract. Some are approved for that use. These are not approved for the upper urinary tract, so they should not be considered standard of care at this point (Figure).

Figure. Imaging techniques

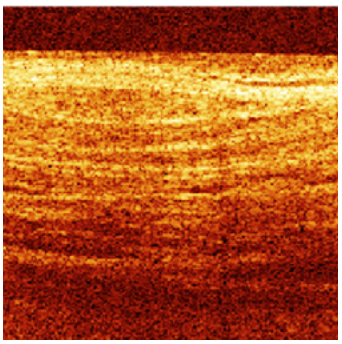
Fluorescence Cystoscopy



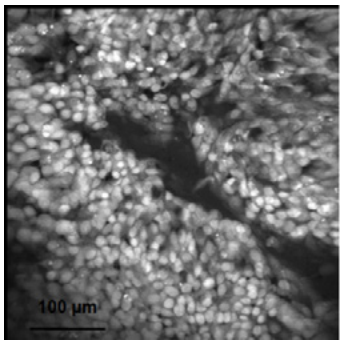
Narrow Band Imaging



Optical Coherence Tomography



Confocal Microscopy



An emerging imaging technique is fluorescence cystoscopy or so-called blue light cystoscopy. This technique requires scopes that are specially fit for blue light cystoscopy. Narrow band imaging uses only blue and green light, thereby accentuating blood vessels, depending upon if they're on the surface or in the submucosa. Although false-positives appear to be more common in my experience, narrow band imaging provides a more complete assessment of visible papillary disease. To date, there has only been a small case series of upper tract imaging. Another imaging technique is optical coherence tomography, which uses near infrared light. Accordingly, it is more like an ultrasound. Confocal microscopy is a standard technique used for upper endoscopies when Barrett's esophagus is suspected. It is being investigated for application to the lower and upper urinary tracts. These and other techniques will continue to evolve, so it is important for urologists to keep abreast of this information.

With respect to prognosis, outcomes are driven by depth of invasion and stratified by low-grade and high-grade. Findings by Margulis et al from 2009 showed that the 3-year recurrence-free survival (RFS)

was 92% for low-grade UTUC and 60% for high-grade UTUC following radical nephroureterectomy.[7] Five-year RFS rates were 88% and 57%, respectively.

Nomograms

Nomograms are available to guide decision-making prior to radical nephroureterectomy. One was developed by Petros et al for non-organ-confined (NOC) UTUC.[8] Multivariate analysis of 566 patients showed that clinical stage, biopsy tumor grade, tumor architecture, and hemoglobin level were independently associated with NOC. The nomogram has 82% accuracy, 48% sensitivity, and 95% specificity. Another was developed by Freifeld et al in patients with high-grade UTUC and is based on age, ECOG performance status, hydronephrosis, architecture, eGFR, cT3 status, and hemoglobin level.[9] The nomogram has an accuracy of 71%.

Faculty Summary

In summary, there's really no reason to not utilize direct visualization with ureteroscopy and to be facile in the techniques to get a good biopsy and cytology, so that after ureteroscopy, the diagnosis and treatment plan are clear. A variety of techniques are available for biopsy using forceps, baskets, and brush, that enable an accurate diagnosis to be made. One of the reasons to rule in or rule out Lynch syndrome is that pembrolizumab is approved for these patients, independent of tumor type. In my experience, and that of others, pembrolizumab is very effective in patients who have large volume disease and solitary kidneys because these mismatch repair gene alterations prime the tumor for response to immunotherapy.

For high-grade tumors that meet the criteria, neoadjuvant chemotherapy should be considered as it results in reduction in eGFR that may obviate the use of platinum-based chemotherapy postoperatively. In the case of a low-grade tumor, consider maximal chemoablation even in 2 or more settings. If there's residual papillary disease, consider intracavitary therapy or adjuvant therapy.

SURGICAL TREATMENT

Conventional treatment for UTUC is surgical, specifically radical nephroureterectomy, with complete removal of the intramural ureter. It's certainly the standard of care for high-grade disease in the proximal ureter in the pelvis. Lymphadenectomy should be performed in these patients as well, and can be done laparoscopically, with or without robotic assistance. If the lymphadenectomy is done in open fashion, one must be prepared to do a dissection, with verification of a 1 cm cuff around the ureter orifice, and complete removal of the intramural ureter. Surgical treatment has an impact on long-term renal function and overall survival as the risk of renal insufficiency increases with age and obvious comorbidities. For example, Xylinas et al showed that 5-year overall survival was 76% in patients with preoperative eGFR <60 mL/min/1.73 m^2 compared with 73% in patients with preoperative eGFR <45 mL/min/1.73 m^2.[10] Moreover, patients age <70 years were more likely than older patients to maintain an eGFR ≥60 mL/min/1.73 m^2 (21% vs 11%) and ≥45 mL/min/1.73 m^2 (61% vs 43%).

Nephron-Sparing Surgery

Nephron-sparing surgery is an important treatment option, particularly for patients who are likely to have diminished eGFR. Nephron-sparing surgery can be approached endoscopically, either through a retrograde or a percutaneous approach. Determination of partial or subtotal ureterectomies is determined by tumor location. A complete ureterectomy with reconstruction with an ileal ureter up to the renal pelvis may be appropriate when there is an a priori need to preserve kidney function or if positive nodes are discovered, indicating the need for postoperative chemotherapy. A distal ureterectomy and Psoas hitch reimplanter, reconstruction with a Boari flap, or ileal ureter are all options for reconstruction when renal preservation is indicated, such as for low-grade disease in the distal ureter. Instead of nephrectomy, a distal ureterectomy would be appropriate for patients with high-grade disease in the distal ureter where proper reconstruction is achievable, provided that the mid and proximal ureter and renal pelvis are free of disease as determined by ureteroscopy. However, it must be realized that these patients are at higher risk for developing proximal disease and ultimately may require a nephrectomy.

A meta-analysis from 2014 investigated the impact on overall survival with radical nephroureterectomy compared with endoscopic surgery.[11] The analysis included 8 retrospective or nonrandomized comparative studies; one-third of patients had high-grade disease. The analysis showed no difference between radical nephroureterectomy and endoscopic surgery in overall survival or cancer-specific survival. The analysis also showed that local recurrence rates and bladder recurrence rates with the 2 techniques were quite similar. These findings must be interpreted cautiously since the level of evidence was low (3b).

The 2021 guidelines developed by the European Association of Urology recommend nephron-sparing management[1]:

- as primary treatment option for patients with low-risk UTUC
- specifically distal ureterectomy, for patients with high risk UTUC limited to the distal ureter
- for patients with solitary kidney and/or renal function, providing that it will not compromise survival, as determined through consultation with the patient

Imperative indications for nephron-sparing surgery include patients with low-risk UTUC, solitary kidney, impaired renal function such as chronic kidney disease, bilateral disease, or comorbidities that pose a high surgical risk. Elective indications include low-grade UTUC, small volume, high-grade distal ureter disease, complete response to neoadjuvant systemic chemotherapy, or where there is a risk of upstaging by delaying radical nephroureterectomy.

Faculty Summary

In summary, it's really important to understand the relative and absolute indication for nephron-sparing surgery, particularly because many patients can be appropriately treated endoscopically or percutaneously. For example, percutaneous resections through an established nephrostomy tract can be done successfully when there is a need to spare the kidney. Enhanced imaging should be used whenever possible as it can provide a more complete understanding of the extent of disease. Distal ureterectomy should be considered in selected patients with high-grade disease since adjuvant platinum-based chemotherapy is now standard of care. However, this requires preserving the kidney.

Post-Operative Treatment

In terms of postoperative treatment, there is level 1 evidence from 2 randomized trials supporting single-dosage intravesical chemotherapy after radical nephrouterectomy.[12,13] One trial utilized mitomycin[12] and the other pirarubicin (investigational).[13] More recently, single-dose gemcitabine showed a clear benefit in reducing the risk of recurrence as a single dose for patients with low-grade bladder cancer.[14] This has prompted some clinicians to switch to gemcitabine to avoid potential toxicities with mitomycin such as necrosis of perivesical tissues if leakage occurs.

An important consideration regarding single-dose intravesical chemotherapy is timing of the instillation. In the gemcitabine study, it was given any time up to the point when the catheter came out. Depending on the extent of surgery and the ability to achieve a watertight closure, catheter removal generally occurs from 7-10 days postoperatively. Prior to instillation, a cystogram is helpful to verify that there is no leak. Gemcitabine is generally retained for about an hour and is followed by catheter removal. Intravesical chemotherapy can also be instilled in the surgical suite, which makes sense since the whole purpose is to kill circulating tumor cells in the bladder.

Recommendations regarding postoperative surveillance were included in the 2021 European Association of Urology Guidelines.[1] Since all of the recommendations were supported by a weak level of evidence, common sense may be the best guide. Since the risk of bladder recurrence may be as high as 40% at 2 years, my practice is to scope patients at 4, 8, and 12 months, then twice a year in year 2, and then annually for a little while longer depending on the individual patient.

Imaging the upper tract is important, particularly the ipsilateral kidney in patients who have undergone nephron-sparing surgery. Monitoring the contralateral kidney is especially important in patients with Lynch syndrome.

INTRACAVITARY THERAPY

Intracavitary therapy for UTUC was first used more than 30 years ago.[15] It can be delivered through a nephrostomy tube or a ureteral catheter, but must be delivered directly into the upper urinary tract. A variety of drugs have been used investigationally for intracavitary therapy, including mitomycin C, epirubicin, thiotepa, and Bacillus Calmette-Guerin vaccine (BCG) either alone or with interferon.[16] While BCG can be used safety in the upper urinary tract, it is imperative to ensure that you're not in a high-pressure system as this can lead to death due to intravascular dissemination of BCG.

Prior to irrigation of the upper urinary tract, it is important to verify that the urine is sterile. The instillation is run in over an hour with appropriate monitoring. Instead of using a manometer to ensure that the pelvic pressure is kept below 20 cm H_2O, the patient can be monitored for any pain or discomfort. This simplifies the procedure so that it can be easily done in the office.

The safety and efficacy of intracavitary therapy for non-muscle-invasive urothelial carcinoma of the upper urinary tract have been investigated in several clinical trials. In one, Giannarini et al observed a recurrence rate of 47% over a median of 42 months of follow-up after BCG therapy.[17] Recurrence was less frequent in patients with carcinoma in situ (40%) where treatment was for curative intent compared with patients with Ta/T1 tumors (59%) where it was used as adjuvant therapy. Similarly, progression-free survival was significantly better in patients treated for curative intent. A review of 12 series of upper urinary tract instillation with BCG yielded similar results showing better outcomes with curative vs adjuvant therapy.[16]

A more contemporary meta-analysis concluded that there was no difference in outcomes with or without treatment, regardless of drug, stage/grade, delivery (percutaneous vs retrograde).18 Thus, there isn't a lot of high-level evidence to support intracavitary therapy with these treatment options. However, intracavitary therapy may be considered in patients with high-grade disease since they are not eligible for treatment with mitomycin for pyelocaliceal solution, which was recently approved by the US Food and Drug Administration for patients with low-grade UTUC.

Patient Journey

"So, we scheduled for surgery and during the surgery, he ablated the tumor and one of the kidney stones. Then, a month later, we went back and got the second kidney stone. Then, 6 months later, we repeated the process and he found that the tumor had grown back to 2 mm that he ablated and I went home with a catheter in again and had to be hospitalized overnight for an infection that they did by IV."

Mitomycin for Pyelocalyceal Solution

Mitomycin for pyelocalyceal solution is formulated with reverse thermal properties that appears as a viscous liquid for instillation. It must be prepared and administered under chilled conditions. It is administered via ureteral catheter or nephrostomy tube using a technique similar to what is used for balloon insufflation for dilation of ureters and percutaneous tracts.

The safety and efficacy of mitomycin for pyelocalyceal solution were investigated in the OLYMPUS trial.[19] OLYMPUS was a prospective, phase 3, single-arm, open-label trial involving patients with biopsy-proven, low-grade UTUC and no cytologic evidence of high-grade disease. Patients were required to have a target tumor 5 mm to 15 mm in size. Patients were treated once a week for 6 weeks followed by ureteroscopy 4-6 weeks later. Patients with no visible evidence of disease were evaluated by cytology, while patients with any abnormality were biopsied. At the follow-up evaluation, 59% of patients had a complete response, defined as a negative uteroscopic evaluation, negative cytology, and negative for-cause biopsy (Table 3). Ongoing follow-up has demonstrated the complete response is durable with 82% maintaining a complete response at 12 months after the 4-6-week follow-up evaluation.

Table 3. Intention-to-treat analysis; N=71

Response	N (%)
Complete response	42 (59)
Partial response	8 (11)
No response	12 (17)
High grade	6 (9)
Indeterminate	3 (4)
Unresectable at baseline	20 (59)

Among adverse events, the most important one was ureteral stenosis, which occurred in 44%. Other common adverse events included urinary tract infection (32%), hematuria (31%), flank pain (30%), and nausea (24%). The finding of ureteral stenosis is not surprising since these patients undergo frequent instrumentation. Moreover, if mitomycin C penetrates into the submucosa, it can cause edema, inflammation, and narrowing of the ureter. Many of these were managed with placement of a stent. Twenty-four patients (50%) required a transient stent and 23% a long-term stent, while 2 patients underwent radical nephroureterectomy due to stenosis and the inability to access the upper urinary tract.

Patient Journey

"I still do not lift anything beyond 15 pounds unless I happen to forget bringing the groceries in for the wife. But I'm doing my normal activities, things that I want to do, just don't do any strenuous stuff but other than that, it's like nothing ever happened."

Faculty Summary

In summary, a 5F to 7F ureteral catheter was used to access the upper urinary tract in the OLYMPUS trial. A pressure interrupter was particularly helpful when using the 5F ureteral catheter. A percutaneous nephrostomy tube can be used as well. Fluoroscopy with contrast is used to confirm placement of the catheter tip in the remote renal pelvis. Determination of the volume of the renopelvis is probably best done during ureteroscopy since this will need to be known prior to injecting the mitomycin for pyelocaliceal solution. Instillation of the mitomycin for pyelocalyceal solution is best done cephalad to caudad because of how the gel forms.

Thank you very much for listening and good luck with taking care of your patients.

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