Flexible Ureteroscopy

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Robotic Flexible Ureteroscopy (Robotic fURS)

Nida Zafer Tokatli and Kemal Sarica

Abstract

With the technical advancements in endoscopic procedures and armamentarium, and the increase in surgical skills majority of the practicing urologists began to manage even relatively larger and also multiple upper tract stones with fURS. The suboptimal ergonomic posture and the long-standing position may have a negative impact on the performance of fURS, especially in cases of larger stones that require longer operations, and may add up to increased need of secondary treatment. Moreover, radiation exposure of the surgeon and operating staff is another crucial factor to be kept in mind. Robotic master-slave systems could overcome these limitations; mainly ergonomic restrictions. Robotic-assisted fURS was first reportedly designed for interventional cardiology, using the Sensei-Magellan system in 2008. Avicenna Roboflex (ELMED) was specifically designed for fURS and introduced in clinical practice after CE certification in 2013. This robotic system consists of a robotic manipulator for docking with all commercially available flexible fiber and video ureterorenoscopy and a console for the surgeon. Avicenna Roboflex provides a significant improvement of ergonomics for a suitable and safe platform for robotic fURS.

Keywords

Robotics · Master-slave systems · Urolithiasis · Ureterorenoscopy · Retrograde intrarenal surgery

1 Introduction

Contemporary management of stones faced dramatic alterations in the last decade. On one hand, the popularity of shock wave lithotripsy (SWL) and "standard" percutaneous nephrolithotomy (PNL) began to lose their popularity to some extent (either due to less efficacy with a certain need for repeated procedures or evident invasiveness), and on the other hand relatively less invasive endoscopic procedures namely flexible ureterorenoscopy (fURS) began to gain more acceptance among the endourologists.

Related to this issue, parallel to the significant increase in the acceptance and applications of endourological procedures applied for the removal of stones [1], flexible ureteroscopic stone management (fURS) increased by 86% in the UK [2], use of SWL decreased by 26%. This significant increase in the effective performance of URS has followed the introduction of flexible

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endoscopes which gave rise to these applications in a successful manner. In addition to these advancements, the clinical introduction of the "Holmium YAG laser" for the effective stone disintegration of the calculi with different compositions has led the endourologists to use fURS more commonly than ever [3]. Although the performance of percutaneous nephrolithotomy (PCNL) also increased, considering the total number of treatments, it remained rather stable when compared to the rest of the available treatment options.

Following its clinical introduction in the 1990s, rigid ureteroscopic stone removal has been well performed in all parts of the world with great efficacy and safety. In the light of the huge experience obtained with this technique, flexible ureteroscopy (fURS) applications began to gain more and more popularity by enabling the endourologists to reach every part of the upper urinary tract and treat stones located in different parts of the renal collecting system. Increasing experience after two decades of evolution and obtained successful outcomes (based on rational indications), has clearly shown that fURS is currently, the most preferred endourological stone treatment modality overall. Based on all these achievements and accumulated experience so far, for the first time, fURS began to challenge the highly common worldwide application of PCNL treatment of relatively larger (20–30 mm) renal calculi [4–8].

In summary, as a result of the technical advancements in endoscopic procedures, relevant equipment systems (development of smaller diameter fine scopes, increased scope flexibility, improvement of accessories, and holmium laser technology), and the increase in surgical skills [4, 9, 10], majority of the practicing urologists began to manage even relatively larger and also multiple upper tract stones with fURS. The success rates obtained in terms of stone-free status were found to be acceptable and comparable with PCNL in experienced hands [5, 9, 11].

However, despite its successful outcomes and relatively practical applications, reported data so far has clearly indicated that the learning curve, as well as effective performance of fURS, is somehow longer and more demanding compared to the semirigid approach. Additionally, as the application of fURS gained popularity around the world, in addition to its advantages; certain limitations and mainly ergonomic restrictions, were also clearly demonstrated. Regarding this issue, despite the successful use of ureteral access sheaths (UAS) for easy access and complete laser-fragmentation of the stones in an efficient manner, stone-free status rates after a single session of fURS seemed to be limited depending on the well-established surgeon (experience, physical performance), stone (size, location, hardness, and location) and anatomy (collecting system) related factors. Additionally, the current design of different flexible scopes, management of a moving stone during laser fragmentation were the other limitations observed particularly during the treatment of large as well as multiple stones. These factors coupled with the applications in inadequately experienced hands have resulted in ≥50% secondary procedure rates to reach a completely stone-free rate after this procedure. There are however some other facts which may not let the endourologists perform the fURS procedure in ideal, optimum conditions. Regarding this issue, it is obvious that as the single person operating, the surgeon needs assistance to operate the laser system (open the system and adjust the energy-rate settings), manipulate nitinol baskets, catch the disintegrated fragments, and deal with the irrigation fluid (manipulate, adjust the rate) during all steps of the procedure while holding and keeping the ureterorenoscope tip at the desired position. Additionally, digital endoscopes with "chip-on-the-tip" technology may prove difficult in orienting the renal collecting system in comparison to standard systems with a pendulum camera attached to an eyepiece. Thus, as mentioned above, the surgeon has to deal with and manipulate, activate several accessorial devices by using the foot pedal including fluoroscopy, laser system, or irrigation, and most endourologists do perform all these activities in a "somehow fixed" standing position. This position has been stated to be a suboptimal ergonomic posture which may eventually cause certain orthopedic complaints [12, 13]. Based on these complaints and possible fatigue that may arise during long-lasting procedures for relatively challenging (large, multiple, located in lower calyceal position) stones, such a position may also induce a negative impact on the effective performance of the fURS procedure. Even the presence of an experienced team may overcome some of these problems, the team may be hindered by space limitations in the working field. Prolonged operative times may cause an increased risk of infection, higher secondary treatment rates, and less stone-free rates. However, having a computer and robot functioning as a follower to the urologist's commands, the procedure itself may simply become a matter of advancing or rotating a controller and deciding where to go. Lastly but more importantly exposure of the surgeon and all members of participating staff as well to radiation for a definite period of time (range of 1.7–56 μSv) is another crucial factor to be kept in mind [14–16].

In the light of all the facts mentioned above, it is clear that performing the fURS procedure in a comfortable sitting position (e.g., using a saddle or a chair) may compensate for some of these drawbacks, similar to the use of an ergonomic chair during laparoscopy [17]. This brought the need of developing a robotic device into the agenda of endourologists to improve the performance of the procedure in a successful and effective manner.

Related to this issue, it has been well noted that robotic-assisted surgery has opened a new era in the history of surgery with a very fast acceptance and adoption among surgeons. It has reshaped oncological and reconstructive interventions throughout all surgical specialties. Robotic-assisted surgery has dramatically influenced minimally invasive surgery with the introduction of console-based manipulators, such as the da Vinci robot (Intuitive Surgical, Sunnyvale, CA, USA) or the Hansen device (Hansen Medical, Mountain View, CA, USA) [18–21]. The use of robotic systems has brought many certain advantages for effective and practical applications [22]. (Use of robotics in these fields has rendered practical advantages and effectiveness. And based on the rapid adoption and increasing experience in this field, the use of robotic surgery, especially for oncologic problems like radical prostatectomy and partial nephrectomy became nearly a standard in daily practice [23]. Currently, the use of robotic systems in endourological procedures particularly for stone removal is another rapidly growing area in minimal invasive stone management [24–26]. In other words, despite the common and effective application of robotic-assisted surgery in the field of pelvic urological pathologies and upper tract oncology, a strong desire has been emerged for establishing such a system for stone management of upper tract stones in the last two decades [27, 28].

Additionally, as mentioned above, technical challenges with a flexible ureteroscopy (fURS) were the main factors leading to the development of robotic-assisted flexible ureteroscopes [24].

To accomplish the abovementioned tasks several robotic systems have been developed and clinically used in the management of upper urinary tract stones with some certain theoretical advantages. Regarding the use of robotic systems with this aim, although Desai and colleagues used the Hansen device, designed for cardiovascular interventions, to perform robot-assisted flexible ureterorenoscopy; this project has been discontinued. Following this short-lasting experience, the Sensei-Magellan system flexi fURS was described in 2008 [20]. Desai et al. reported a 94% technical success rate for stone disintegration and a complete stone-clearance rate of 89% in 18 patients undergoing fURS with this system [21]. There was no conversion to manual URS or intraoperative complications in this study. The Sensei-Magellan system project encountered difficulties with scope design development and consequently, the endeavor was abandoned.

Based on this limited experience by Desai M. et al., and as a result of further studies on this issue as well, since 2012, ELMED (Ankara, Turkey) launched the Avicenna Roboflex System in 2011. In 2013 and 2015, new prototypes followed. The first feasibility reports were published in 2014 [24]. After CE certification in 2013, the robot was introduced in clinical practice and tweaked for intraoperative use. As one of the first robots used for ureteroscopy, Avicenna Roboflex

(ELMED) utilized a robotic control and interface that interfaced and docked with all commercially available flexible fiber and video ureteroscopes. The system gained CE approval for use in Europe in 2013 but FDA approval is still pending.

2 The "Avicenna Roboflex" Robotic System

Avicenna Roboflex consists of two main parts. The first is a control console for the surgeon can sit and control all movements and necessary functions. The second is a robotic manipulator for docking with all commercially available flexible fiber and video ureterorenoscopes. The robotic manipulator has the capability of rotation (±220°), advancement (210 mm), deflection (±270°). In addition to the movements of fURS, the irrigation and laser fiber movement operations can be controlled by the surgeon at the console. That robotic system is compatible with a wide range of digital or fiber flexible ureterorenoscopes, access sheaths, laser fibers, and baskets. Saglam R. et al. reported their first experience in 81 patients undergoing robotic-assisted fURS with the Roboflex Avicenna system (prototype 2) [24]. They concluded that the console time and procedure time were within acceptable limits, with only one technical failure requiring manual fURS. The overall success of stone disintegration was recorded at 96% in this study. Geavlete P. et al. published a prospective comparative study between Roboflex Avicenna system (prototype 2) and classical fURS. The study reported similar safety profile and 3-month stone-free rates for the two approaches (89.4% in conventional FURS vs. 92.4% robotic-assisted FURS) [29]. In their prospective multicenter study again Klein E. et al. reported a 97% technical success in stone disintegration and a device failure in only 2 patients (0.7%) for renal stones with an average size of 14 mm [30]. Based on all these preliminary data one may suggest that stone-free rates with robotic-assisted fURS are noninferior to manual fURS.

One of hinderances of fURS performance may be the suboptimal ergonomics resulting in the patients' need for secondary operations and the frequent repair of the endoscopes. Carey et al. [31] reported an 8.1% damage rate at a single tertiary center with 40–48 uses before the initial repair of new flexible ureteroscopes. The main reasons for repair were errant laser firing (36%) and excessive torque (28%). Theoretically, the functions included in Roboflex Avicenna, such as insertion of the laser fiber only in a straight position of the scope using a memory function, stepwise motorized advancement of the laser fiber, and force-controlled deflection of the scope, should contribute to longer life of these precise, smaller, and fine scopes. In their original study, Saglam R. et al. observed one malfunction of the ureterorenoscopes during case 42 (damage of the digital video system); however, the endoscope has been used 25 times or classic fURS. Exact figures can be evaluated only by the planned randomized trial (IDEAL stage 3) [24].

The robotic fURS system has many advantages as stated above but possible limitations of the device may be expressed as the lack of tactile feedback and problems with the use of baskets for extraction of larger stone fragments. Similar to our experiences with the da Vinci robot, lack of tactile feedback did not prove to be a problematic issue during the performance of robotic fURS, mainly due to the superior image quality of the digital endoscope used. Avicenna Roboflex robotic system was found to enable precise movements of the endoscope in deflection, rotation, and advancement which may overcome the lack of tactile feedback well. In addition, displaying the parameters and animated vision of the tip of fURS will help the surgeon for better orientation and control. It is still debatable whether fURS should aim at complete ablation by pulverization of the stone or whether larger fragments should be retrieved using a Dormia basket via the access sheath [32, 33]. One of the arguments in question suggests that, since the robotic fURS requires occasional undocking of the device, aiming and performing these maneuvers may be cumbersome as well as time-consuming if the surgeon in charge is not well accustomed to the device. This issue brings the idea of "pulverization concept" to the fore, and suggests that future robotic fURS studies should focus on overcoming the stated problem. Avicenna Roboflex system is designed to follow up on this argument, by using a combination of high-frequency laser systems, especially Thulium Fiber Lasers (TFL). Last of all, the cost of the device may prove to be an issue of significance, especially regarding the financial restrictions of healthcare systems. Following the IDEAL framework, in order to provide further commentary about the advantages of robot assisted over the classical fURS, a multicenter randomized trial is required. A study as such must include all of the aspects discussed earlier, based on the state-of-the-art definition of primary and secondary outcomes, an example being stone-free rates based on computed tomography rather than on ultrasound and an additional X-ray [34].

3 Current Evidence of the Roboflex

The evidence comparing the Roboflex System to the classical fURS procedure is still limited. (Comparisons of the Roboflex System to the classical fURS system remain insufficient) Geavlete P. et al. [29] reported their first experience in a matched-pair analysis (n = 132) showing no significant difference in terms of clinical parameters and outcome between the two management options. However, they were able to demonstrate a lower retreatment rate and a better stone-free rate at 3 months as well in the robotic treatment group. The study group mentioned some secondary advantages of this approach, mainly ergonomic improvements, for the surgeon as particularly noted in long-lasting surgeries due to difficult stone parameters or a large stone volume to treat [29].

The precision of the system has been investigated by Proietti S. et al. in a K-box Simulator. There was no significant difference between the performance of the robotic fURS group and the manual fURS group, with a slight advantage in the speed for the manual fURS group and a slight significant advantage for the robotic fURS group in terms of stability, centering of the picture, tissue respect, and maneuverability at least in one of the two exercises [35].

In a recent meta-analysis, ample evidence shows serious health risks of prolonged standing, including lower back pain, physical fatigue, muscle pain, tiredness, and body part discomfort. Prolonged standing affects the cardiovascular system as well [24, 36]. The wearing of a protective lead gown can amplify posture-related health problems. Sitting in a personalized position with an armrest at the console reduces physical stress and improves the endurance of the surgeon [24].

4 Future

The robotic systems have no tactile feedback, which is the typical drawback of using master-slave systems. Different companies trying to overcome the limitation of tactile feedback and technical developments show promising early results but a definite solution is not yet on the market [37].

Force sensors could be utilized so that the ureteroscope cannot perforate the renal pelvis by increasing the safety profile. If 3D vision is applied to future ureteroscopy robots, it could also further enhance manipulation and visualization. Furthermore, with the placement of instruments in the kidney, electromagnetic sensors (EM) could be correlated with the preoperative CT images and therefore a 3D GPS-like map could be displayed without using the ionizing radiation with less fluoroscopy time. EM sensing positioning technology used in bronchoscopy systems could be beneficial with this aim. If a real-time ultrasound modality could be added to the robotic systems, this may also help guide surgeons to any remaining stones or fragments that have been displaced during the procedure.

Ultimately, a robot could theoretically control the ureteroscope and synchronize it with respiration during laser lithotripsy to increase the efficiency of fragmentation. Baskets could be controlled by a robotic system and be used to pull the ureteroscope out of the access sheath, drop the stone, and then return to the exact previous spot since it will remember the location in all vectors.

The obvious safety concern with this use is pulling out a stone that does not fit the sheath and avulsing the ureter. The robot could address this in two ways. First, endoscopic measurements of the stone fragments could be made to ensure that the pieces are small enough to fit through the access sheath. Second, force sensors could be incorporated into the system to prevent ureteral avulsion; it would simply stop retracting and the surgeon would be able to further fragment the stone before extraction.

Laser settings could also be programmed into the robot, and instead of the surgeon stopping to alter the settings, the robot could constantly monitor the types of dust or fragment being produced and the amount of retropulsion or stone movement, then alter the settings as lithotripsy is taking place and the stone is decreasing in mass.

Once synchronization of respiratory movements can be accounted for, this may make lithotripsy very fast and efficient. Ultimately, it is conceivable that the surgeon would place a target on the stone in question, hit a "start" button, and then the robot would control the laser, ureteroscope, fluid irrigation, and laser settings to reduce retropulsion and adjust for respiratory movements to break up the stone into dust. This would all take place while the surgeon stands by at the console.

5 Conclusions

Robot-assisted techniques in the minimal invasive management of upper urinary tract stones are still in the early stages of implementation. However, although limited, available data clearly shows that new robotic technologies will provide excellent treatment of renal stones as a result of the improved ability of experts to target stones with better surgeon ergonomics and more importantly reduced ionizing radiation from fluoroscopy. Relatively larger stones and multiple calyceal stones can be successfully treated with robotic systems. The use of robotic technology maintains the performance of the surgeon during long-lasting surgeries due to optimal ergonomic working conditions. However, we believe that further evaluation with long-term follow-up and cost-analysis, multicenter, randomized controlled studies are certainly needed to define the place of robotic surgery in renal tract calculi management. Last but not least, the robotic-assisted fURS procedure could provide some certain potential benefits in the Covid-19 era in the effective minimal invasive management of large as well as multiple renal stones with well-preserved physical distance between the operating room staff and the case.

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Diagnostic Flexible Ureteroscopy

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Abstract

Since its introduction in the 1980s and popularization in the 1990s, flexible ureteroscopy has become an invaluable diagnostic tool for the urologist. Improvements in equipment and technique have enabled urologists to diagnose conditions with efficiency and accuracy. Today, flexible ureteroscopy plays a central role in the evaluation of various upper tract pathologies, ranging from hematuria of unknown origin to upper tract urothelial tumors. In the following chapter, we review the current state of diagnostic flexible ureteroscopy and its role in the diagnosis of various urologic conditions.

Keywords

Diagnostic · Flexible ureteroscopy Ureteroscopy

1 Introduction

Ureteroscopy is a procedure performed by inserting an endoscope through the urethra to visualize the lower or upper urinary tracts [1]. The use of a rigid or semirigid ureteroscope is commonly used to evaluate the distal ureter for both genders and can be advanced as proximal as the upper pole of the kidney in females and the upper ureter/ureteropelvic junction in males. However, with the development of agile flexible ureteroscopes, many clinicians prefer to utilize flexible ureteroscopy (fURS) for the evaluation of the proximal ureter and the intrarenal collecting system. The advantage of fURS is its ability to maneuver through the tortuous path of the upper urinary tract, which is the main limitation of a nonflexible endoscope [2].

There are three main components of a flexible ureteroscope: optical system, deflection mechanism, and working channel [3]. Recent efforts have focused on advancing the optical and illumination system of the flexible ureteroscope, leading to improvements of the early fiber-optic technology and more recently digital flexible ureteroscopes. Historically, fURS has been utilized for the evaluation of benign and malignant upper urinary tract pathologies as well as therapeutic interventions including ablation of upper tract urothelial carcinoma (UTUC) and laser lithotripsy with stone extraction [4]. Over the past several decades, innovations in the design of fURS have transformed the field of urology. In this chapter, we explore the role of fURS in the diagnosis of upper urinary tract pathologies.

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2 Indications

While fURS is utilized for both diagnostic and therapeutic modalities, in this chapter we will primarily focus on the diagnostic indications for fURS. The main indications for diagnostic fURS are unilateral hematuria, positive cytology with normal cystoscopy, radiographic filling defect of the upper urinary tract, obstruction of the upper urinary tract, and follow-up or treatment of low-grade UTUC in the appropriately selected patients. The primary objective during the diagnostic stage is to establish whether the symptomatic lesion is benign or malignant [5]. A complete evaluation of the upper urinary tract can be achieved using fURS in approximately 71–100% of cases, which is dependent on several factors such as anatomical complexity, performance of the flexible ureteroscope used, accessory instruments used for biopsy, visibility, and image quality [6]. With improvements in structural design and maneuverability, fURS has improved accessibility and visualization of the upper urinary tract in a retrograde fashion making it an optimal diagnostic tool. fURS is the first step in the evaluation of the aforementioned upper urinary tract pathologies due to its minimally invasive nature. In a majority of cases, a diagnosis can be achieved by fURS, avoiding more invasive approaches such as percutaneous endoscopy and open, laparoscopic, or robotic surgery.

2.1 Unilateral Hematuria

Patients who present with unilateral hematuria are advised to undergo a diagnostic workup to determine whether the hematuria is a direct symptom caused by a condition such as a neoplasm (benign or malignant) or stone or caused by an isolated event of idiopathic etiology. Furthermore, unilateral essential hematuria, also known as benign essential hematuria or chronic unilateral hematuria, is a diagnosis of exclusion defined as gross unilateral hematuria that is endoscopically demonstrated to lateralize to one upper collecting system. In such cases, patients undergo a diagnostic workup, which includes hematological studies, cytology, and contrast-enhanced imaging of the genitourinary tract (e.g., intravenous pyelography, CT, or MR urography) [7]. Several studies have demonstrated the diagnostic effectiveness of fURS for this condition to vary between 78% and 83% in diagnosing the etiology of unilateral hematuria [6]. Nakada et al. conducted a retrospective review of 17 patients with lateralizing essential hematuria who underwent a diagnostic fURS. Though the study was limited by a small sample size, suggestive lesions were identified in 14 (82%) of 17 patients, specifically 11 (64%) patients with discrete lesions and 3 (18%) patients with diffuse lesions [8]. Similarly, Bagley et al. studied 32 patients undergoing retrograde flexible ureteropyeloscopy for benign essential hematuria. Successful visualization of the entire ureter and pelvicalyceal system was possible in a total of 30 (94%) patients, of which discrete lesions were detected in 16 (50%) patients, diffuse lesions were detected in 9 (28%) patients, and no lesions were detected in 5 (16%) patients [7].

2.2 Upper Tract Urothelial Carcinoma (UTUC)

fURS is the gold standard for establishing the diagnosis of UTUC and is indicated in patients with a positive cytology despite a normal cystoscopy or a “filling defect” suspicious for a neoplastic lesion on CT or MR urography. While urinary cytology can be useful for characterizing the pathological features of urothelial cancer in the bladder, its use is less well-defined for UTUC [9]. Potretzke et al. was the first to perform a meta-analysis along with a pooled analysis of the literature that studied the diagnostic capacity of selective cytology. This study determined that upper urinary tract cytology had an overall sensitivity based on final pathology of 55.3% and specificity based on biopsy pathology of 90.7% when patients with bladder cancer were excluded [10]. Therefore, diagnostic ureteroscopy is recommended in these situations in order to more accurately evaluate the upper urinary tract with direct endoscopic vision and rule out UTUC or other pathologies. Furthermore, cases with an unremarkable CT urography and positive upper urinary tract cytology may require a diagnostic ureteroscopy and subsequent biopsy given the high specificity of selective cytology [10].

A filling defect of the upper urinary tract on radiological imaging is another common indication for diagnostic ureteroscopy. A filling defect may be caused by the presence of UTUCs, calculus, vasculitis, or other tumors—however, CT urography or other imaging modalities will often distinguish the cause of the filling defect as "stone" or "non-stone." fURS is commonly used in the evaluation of upper urinary tract filling defects given its high diagnostic accuracy compared to more historical standard diagnostic regimens, which consists of cystoscopy, retrograde pyelography, urinary cytology, and in some cases ultrasonography or CT [11]. Bagley et al. prospectively studied 59 patients presenting with various symptoms or indications for fURS and successfully diagnosed every patient with a radiological filling defect [12]. In addition, Puppo et al. performed fURS on 23 patients for purely diagnostic indications, radiologic filling defects and/or hematuria, of which 22 (96%) patients were successfully diagnosed [13].

Over the past several decades, ureteroscopic ablation of UTUC and surveillance has played an increasing role in the management of UTUC. While a radical nephroureterectomy (RNU) is the preferred choice for patients with high-risk nonmetastatic or metastatic disease, endoscopic resection via fURS is commonly utilized for low-risk nonmetastatic disease [9]. Endoscopic resection in comparison to RNU is associated with higher tumor recurrence rates ranging from 15% to 90% [14], with additional contributing factors such as tumor size >2 cm, high tumor grade, or history of bladder tumor. Proietti et al. demonstrated that with strict postoperative surveillance, recurrence-free survival (RFS) rates measured between initial treatment and tumor recurrence were 31.7% [15]. In addition, Cutress et al. found that tumor recurrence rate was as high as 52% after ureteroscopic ablation of a UTUC [16]. Given such high recurrence rates, it is recommended that patients who undergo endoscopic ablation comply with a strict surveillance regimen with an earlier second-look URS within 60 days of their first URS [17]. Regardless, the low complication rates, maintenance of a closed-loop system, reduced risk of tumor seeding, and low progression to RNU renders ureteroscopy an acceptable method in managing low-risk UTUC, especially in patients who are poor candidates for RNU.

3 Diagnostic Findings

3.1 Upper Urinary Tract Tumors

UTUC is a relatively uncommon condition, accounting for 5% of urothelial cancers. The incidence of UTUC is difficult to approximate because tumors of the renal pelvis and ureter are reported collectively with renal cell carcinoma, classifying all renal tumors into one category. However, the annual incidence of UTUC in Western countries is about 2 cases per 100,000 patients [18]. Although a rare primary condition, a majority are invasive at the time of diagnosis, 60% for UTUC versus 20–25% for bladder tumors [19]. The most common presenting symptoms of UTUC are gross or microscopic hematuria with or without flank pain. Brant et al. conducted a retrospective study of 168 patients with upper urinary tract tumors and found that hematuria and flank pain were seen in over 70% and 30% patients respectively. Generally, constitutional symptoms such as fever, weight loss, and night sweats indicate worsened prognosis that require further investigation for potential metastases [20].

There are three major steps to definitively diagnose UTUC.

- Imaging.
- Cystoscopy with urinary cytology.
- Diagnostic fURS.

Cross-sectional abdominal imaging is often the first step in the diagnosis of a patient with UTUC. CT urography has the highest diagnostic accuracy of all available imaging techniques and thus remains the gold standard imaging modality [21]. CT urography consists of the intravenous administration of contrast and CT imaging during the excretory phase, approximately 10 min after the injection of contrast, to optimize distension and opacification of the upper and lower urinary tracts [22]. A recent meta-analysis of 1233 patients demonstrated the diagnostic value of multidetector CT urography with a pooled sensitivity and specificity of 92% and 95% respectively. MT urography is utilized for patients with contraindications to radiation or iodinated contrast agents. However, overall, CT urography is superior to MR urography for the diagnosis and staging of UTUC. Prior to curative treatment, a CT scan of the chest, abdomen, and pelvis is required to assess for metastasis [23].

Diagnostic ureteroscopy is recommended for the evaluation of patients who demonstrate a filling defect on CT or MR urography. Evaluation of the bladder can be performed at the time of ureteroscopy or is occasionally performed prior to this as an outpatient office evaluation. The introduction of fURS in the diagnostic workup of UTUC has reduced the misdiagnosis rate from 15.5% to 2.1% compared to multidetector CT urography [24]. Wang et al. conducted a study in which the sensitivity of fURS compared to multidetector CT urography in the diagnosis of upper urinary tract tumors was 78.4% versus 54.5% respectively [25]. Moreover, fURS has demonstrated its multifunctionality in the clinical setting. For example, fURS may guide the sampling of the upper urinary tract for patients referred for selective cytology. In addition, fURS allows for the characterization of tumor size and appearance, biopsy of suspicious tissue, and obtention of information that can aid risk stratification of UTUC.

While fURS has demonstrated adequate results in terms of the presence or absence of tumor and the ability to biopsy a lesion to achieve a definitive diagnosis of UTUC, accurate tumor staging is not always possible [9]. Several studies have questioned whether ureteroscopic biopsy can accurately determine the grade and stage of a UTUC lesion [26]. Roja et al. demonstrated that the histologic grade of the biopsy sample accurately predicted the final histologic grade of the nephroureterectomy specimens at a high concordance rate of 92.6%, even if the biopsy volume was small. While concordance of tumor grade was high between the biopsy and resected specimens, concordance of tumor stage was lower at 43% emphasizing the need for other diagnostic tools to improve tumor staging [27]. Overall, the preoperative evaluation of hydronephrosis with imaging, ureteroscopic biopsy and grade, and urinary cytology can identify patients at risk for advanced UTUC and guide the decision of surgical removal, either by endoscopic resection or RNU [28].

Despite the added diagnostic value fURS provides for the diagnosis of UTUC, concerns about its role in the development of intravesical recurrence exist. Marchioni et al. conducted a pooled analysis of 2372 patients and found a statistically significant association between fURS performed prior to RNU and intravesical tumor recurrence. The rate of intravesical recurrence ranged from 39.2–60.7% versus 16.7–46% in patients who did and did not undergo a diagnostic ureteroscopy respectively [29]. Guo et al. conducted a meta-analysis that similarly conducted a higher risk of intravesical recurrence in the same scenario, regardless of the patient's prior history of bladder tumors [30]. Conversely, Nison et al. found no significant difference of intravesical recurrence rates between patients who did or did not undergo preoperative diagnostic fURS, 27.5% versus 28.3% respectively [31].

3.2 Benign Upper Tract Lesions

Ureteral tumors are a historically uncommon diagnosis that has increased in incidence over the past several years, occurring in about 1 in every 3600–10,000 cases. In a clinical setting, malignant lesions are more common than benign lesions of the ureter [32]. Benign ureteral tumors are classified based on embryological origin with a majority derived from the epithelium. However, approximately 20% are nonepithelial in origin, specifically derived from the mesoderm [33].

The most common benign lesion of the ureter is a fibroepithelial polyp [34]. Fibroepithelial polyps are benign mucosal projections composed of fibrous tissue and lined by a normal layer of surface epithelium [35]. The location varies along the urinary tract, including the urethra, bladder, ureters, and renal pelvis [36]. Historically, fibroepithelial polyps were a rare pathologic diagnosis, that have recently increased in incidence due to improvements in diagnostic endoscopic tools. Preoperative evaluation with various imaging modalities such as contrast-enhanced CT or MR cannot distinguish benign filling defects from UTUC; therefore, the gold standard for diagnosis is retrograde ureteroscopy [34, 37]. One of the benefits of retrograde ureteroscopy is its ability to rule out malignancy as fibroepithelial polyps can clinically mimic malignancy. Georgescu et al. demonstrated that in all 11 patients who underwent an investigative retrograde ureteroscopy for various clinical symptoms, the presumed benign aspects of the lesion identified during semirigid or fURS was confirmed by a final pathologic diagnosis of fibroepithelial polyp. The most common presenting symptom is flank pain, followed by hematuria, suprapubic discomfort, and urinary frequency [34]. An open approach had been historically used for surgical resection of a fibroepithelial polyp, however more recently, endoscopic therapy with a percutaneous or ureteroscopic approach has become more commonly utilized [38].

Hemangiomas are benign vascular tumors that are embryologically derived from unipotent angioblasts that develop in an atypical manner within blood vessels [39]. They generally grow by endothelial hyperplasia. The most common types of hemangiomas are capillary and cavernous, which are classified primarily based on the size of the vascular channel. Capillary hemangiomas have a small diameter, while cavernous hemangiomas have a large vascular channel diameter [40]. Hemangiomas of the genitourinary tract are an extremely rare pathological entity, with only eight cases reported worldwide, and are more commonly found on the liver or skin. Interestingly, almost all cases are diagnosed postoperatively based on pathologic examination. The most common presenting symptom is chronic intermittent unilateral hematuria due to erosion of the urothelial lining, which may be accompanied by lower urinary tract symptoms and colicky flank pain due to ureteral obstruction. However, it is also common for patients to experience no symptoms [41]. Patients undergo a routine diagnostic workup, including imaging, cytology, cystoscopy, and diagnostic fURS, for a malignant etiology such as UTUC given its difficulty to preoperatively identify the pathologic cause. The choice of RNU versus endoscopic management is based on tumor size and location as well as preoperative factors indicating the benign nature of the mass seen with a diagnostic fURS and biopsy margins [41, 42].

There are several other rare benign lesions such as fibromas, leiomyomas, granulomas, endometriomas, and neurofibromas that may occur throughout the urinary tract. The rising incidence of these lesions coincide with the advent of improved endoscopic technique which not only has improved diagnostic capability but also patient mortality through an endoscopic versus open approach to surgical resection [33].

4 Others

There are several other causes for the clinical presentation of hematuria or radiologic filling defects that require the diagnostic efforts of fURS. Bagley et al. conducted a prospective study in which flexible ureteropyeloscopy was performed on 59 patients with various presenting symptoms. An anatomical variant was found in 5 of 23 patients evaluated for a filling defect and/or hematuria. Anatomical variants of the upper urinary tract that may cause a filling defect on imaging or hematuria can include aberrant papillae, compound renal calyces, and renal infundibular septum. Interestingly, in cases where a vascular anatomical variant is located near the renal pelvis causing a filling defect on imaging, diagnostic fURS is able to detect pulsations from blood flowing through the vessel and subsequently diagnose the lesion [12].

Lateralizing hematuria can be distressing for patients, especially when an etiology is not readily identified. As described above, fURS has shown utility in visualizing and determining the source of bleeding. Kumon et al. evaluated 12 patients with unilateral gross hematuria and was able to endoscopically identify the bleeding source in 10 patients. 9 patients had localized bleeding sites: 1 patient with a papillary mass, 4 patients with a hemangioma, and 4 patients with minute venous rupture [43]. A minute venous rupture is ultimately bleeding without a clear abnormality that can appear as a stream of blood from the papillary tip, with an adherent clot at times [12]. Bagley et al. used fURS to diagnose clots within the intrarenal collecting system in 10 of 32 patients who experienced intermittent colic [7]. If bleeding is truly benign, patients may be followed without therapy [44]. However, if the clot induces colic pain, urgent diagnosis and treatment are warranted [7].

5 Guidelines

5.1 Microhematuria

The primary objective during the evaluation of hematuria or a radiologic filling defect is to rule out urologic malignancy. The European Association of Urology 2020 guidelines have updates the recommendations for the diagnostic and treatment modalities for UTUCs. The diagnostic workup for UTUC includes imaging, cystoscopy with urine cytology, and diagnostic ureteroscopy. The initial and preferred imaging technique is CT urography. For patients with contraindications to CT urography, MR urography is often used. The next step in the diagnostic workup of UTUC is cystoscopy and urine cytology, which are important to rule out concomitant bladder cancer. However, urine cytology is less sensitive for UTUC than for bladder tumors, and therefore selective cytology should be performed for patients suspected to have UTUC. Patients with a normal cystoscopy and abnormal cytology results have a greater likelihood of being diagnosed with a high-grade UTUC.

The final approach in the diagnostic workup is fURS to access the upper urinary tract, specifically the ureters and pyelocalyceal and intrarenal collecting systems. In addition to visualization and attainment of tissue biopsy, fURS conveniently allows for the collection of selective cytology samples. However, it is not uncommon for ureteroscopic biopsy to lead to pathologic undergrading and inaccurate assessment of staging. This emphasizes the utility of guiding management with information obtained from both ureteroscopic biopsy and selective cytology and the importance of strict surveillance in patients who elect a conservative treatment approach. Several technical advancements have been made to improve visualization and diagnostic techniques of fURS [9].

The American Urological Association has also published guidelines for the evaluation of microscopic hematuria [45]. While the role of ureteroscopy is less well defined in the investigative workup of microhematuria, for cases with high suspicion of an upper tract malignancy, endoscopic exploration is recommended to better visualize the upper urinary tract and characterize suspicious lesions via biopsy.

6 Novel Technologies and Future Directions

The urologic community has aimed to improve ureteroscopic technique over the past several decades to reliably select patients for a less invasive treatment approach, such as endoscopic therapy. Recent technological advancements have allowed for improved optics when access the upper urinary tract using fURS [46].

6.1 Photodynamic Diagnosis

Traditionally, flexible ureteroscopes utilized white light (WL) to capture endoscopic images. However, the use of WL has posed challenges in obtaining a high-resolution image that provides optimal visualization of upper urinary tract lesions. Photodynamic diagnosis (PDD) is a technique that uses fluorescent contrast agents to better visualize malignant tissue [47]. Both of the commonly used fluorochrome agents, 5-aminolevulinic acid (5-ALA) and hexaminolevulinate hydrochloride (HAL), induce the accumulation of protoporphyrin IX in cells. When tissues are exposed to a blue light at a range of wavelengths between 375 nm to 440 nm, neoplastic cells tend to absorb more light, thus enhancing the excretion of protoporphyrin compared to normal tissue. As such, malignant cells will appear red against normal cells that appear blue, allowing for discrimination between tissues [48].

The role of PDD in the diagnosis of bladder cancer has been well established, but its role in UTUC has only recently been investigated [49]. Several studies demonstrate the added diagnostic value of PDD [49–54]. Recently, Liu et al. conducted a meta-analysis including 289 cases to determine the efficacy of PDD-assisted ureteroscopy in diagnosing UTUCs. Pooled analysis concluded that PDD can differentiate between UTUC and benign upper urinary tract lesions with a high sensitivity of 96% and specificity of 86%. Furthermore, the use of PDD in comparison to WL improves UTUC detection rate [50]. Similarly, Osman et al. conducted a systematic review of 194 patients to determine the sensitivity of 95.8% versus 53.5% respectively and specificity of 96.6% versus 95.2% respectively, leading to the conclusion that PDD is more accurate than WL ureteroscopy for the diagnosis of UTUC [51]. Compared to other novel optical technologies, more studies have been conducted and have demonstrated the additional diagnostic utility that PDD provides with fURS. It is a promising endoscopic technique for the upper urinary tract and requires further studies on larger sample sizes to exemplify its advantages and reduce its limitations.

6.2 Narrow-Band Imaging

Narrow-band imaging (NBI) is an optical enhancement technique that utilizes higher wavelengths such as blue t 415 nm and green at 540 nm to better penetrate the tissue and enhance contrast between mucosa and microvasculature. Both wavelengths of light are strongly absorbed by hemoglobin. On imaging, the vasculature will appear either dark brown or green against the mucosa that appears light pink or white [47].

Several studies have investigated the diagnostic role of NBI-assisted digital fURS. Traxer et al. performed fURS using both WL and NBI to assess whether detection of malignancy was increased. A total of 27 patients underwent examination of the entire renal collecting system first with WL followed by NBI, and images obtained during both were compared to the final pathologic diagnosis. Not only did NBI produce improved endoscopic visualization, but it also detected five additional tumors in 4 patients and three tumors with extended margins in 3 patients. Overall, NBI-assisted fURS improved tumor detection rate by 22.7% [55]. Hao et al. performed a similar study of 54 cases of UTUC. The study demonstrated that NBI-assisted fURS improved tumor diagnosis by 20% and provided better image quality especially in areas near the border between normal tissue and tumor [56]. Iordache et al. also performed a similar prospective analysis of 87 patients with similar results illustrating an improved tumor detection rate for NBI-assisted fURS than standard fURS, 98.4% versus 91.7% respectively. However, interestingly NBI in comparison to WL was associated with a higher false-positive rate, 17.5% versus 10.1% respectively [57]. NBI has demonstrated its value as an addition to a diagnostic modality exploring the upper urinary tract. However, it is important to study its use in larger sample sizes to gain a better understanding of its benefits and limitations.

6.3 Optical Coherence Tomography

Optical coherence tomography (OCT), also referred to as optical biopsy or light ultrasound, is a noninvasive imaging technology that uses signal interference between the tissue sample under observation and a local reference signal to generate a cross-sectional image of tissue while capturing individual layers of the tissue in real time [58, 59]. This diagnostic technique has been widely used in ophthalmology, but only a few studies have explored its use in urology, specifically in diagnostic fURS. OCT has been shown to obtain high resolution images, grade, and stage UTUC as a real-time, intraoperative diagnostic modality. For tumor grading, OCT had a sensitivity of 87% and specificity of 90%. For tumor staging, OCT had a sensitivity of 100% and specificity of 92% [60]. Furthermore, various studies have investigated the optical attenuation coefficient, μ_{OCT}, which measures how quickly light penetrates the medium under investigation, allowing for quantitative analysis of tissue from OCT signals [61]. Bus et al. reported that for low and high-grade lesions, the median μ_{OCT} was 2.1 mm^{-1} and 3.0 mm^{-1} respectively [60]. Similarly, Freund et al. calculated a median μ_{OCT} for low-grade and high-grade UTUC of 3.3 mm^{-1} and 4.9 mm^{-1} respectively. This study also identified an μ_{OCT} cut-off value of 4.0 mm^{-1} to discriminate between high-grade and low-grade papillary UTUC [62]. Further studies are required to accurately extract and optimize the optical attenuation coefficient to be used more extensively in the clinical setting.

6.4 Confocal Laser Endomicroscopy

Confocal laser endomicroscopy (CLE) is a probe-based optical technology that captures real-time images of sectioned tissue and provides a high-resolution dynamic evaluation of tissue microarchitecture and morphology. A confocal microscope is packaged into the small probe utilized in this optical technique, which is compatible with standard endoscopes [63]. Similar to PDD, CLE requires either the topical or intravenous administration of a fluorescent agent, most commonly fluorescein dye [64]. After the tissue is stained with fluorescent dye and molecules of the dye have been excited, the dye emits light that is filtered through a pinhole so that the photodetector measures in-focus light and rejects out-of-focus light. This process ultimately creates optical sectioning of the tissue of interest. Through direct contact between the probe inserted through the endoscope and tissue, images are obtained at a rate of 12 frames per second as a video sequence [63]. CLE was first used to study histopathologic changes in bronchial and colonic tissue [65, 66]. More recently, however, CLE has been utilized during fURS and a few studies have reported favorable experiences. Breda et al. found CLE with fURS to be a reliable real-time histologic characterization of UTUC lesions and the clinical use may be especially useful in patients who are potential candidates for conservative management [67]. Villa et al. demonstrated that CLE was able to recognize distorted microarchitecture and tortuous vasculature more clearly in patients with confirmed high-grade UTUC [68]. Limitations include susceptibility to motion artefact [47] and the inability to determine the sensitivity and specificity of this optical technique [68]. Further studies are required to further determine the diagnostic accuracy of CLE, understand its limitations, and identify its tole in the clinical setting.

7 Conclusion

In conclusion, fURS is a key diagnostic tool in the workup of UTUC and other upper urinary tract pathologies. Several advancements that have been made in diagnostic technique, including optics and image processing, have shown promising results and require further research to better understand their potential use in the clinical setting as well as rectify its shortcomings.

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