Flexible Fiber Optic vs Digital Ureteroscopy and Enhanced vs Unenhanced imaging for Diagnostic and Treatment of Upper Tract Urothelial Carcinoma: Results from the Clinical Research Office of the Endourology Society (CROES)-UTUC Registry

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Abstract

Objectives

To compare the oncological outcomes of patients with upper tract urothelial carcinoma (UTUC) undergoing kidney-sparing surgery (KSS) with fiber-optic (FO) vs digital (D) ureteroscopy (URS). To evaluate the oncological impact of image enhance technologies such as narrow-band imaging (NBI) and Image 1S in patients with UTUC.

Materials and methods

The CROES-UTUC registry is an international, multicenter, cohort study prospectively collecting data on patients with UTUC. Patients undergoing flexible FO or D-URS for diagnostic or diagnostic and treatment purposes have been included. Differences between groups in terms of overall survival (OS) and disease-free survival (DFS) have been evaluated.

Results

The CROES registry included 2380 patients from 101 centers and 37 countries, of whom 401 patients underwent URS (FO-URS:186 and D-URS:215). FO-URS were performed

more frequently for diagnostic purposes while D-URS when a combined diagnostic and treatment strategy was planned. Intraoperative and postoperative complications did not differ between groups. 5-years OS and DFS rates were 91.5% and 66.4% respectively. Mean OS was 42 months for patients receiving FO-URS and 39 months for those undergoing D-URS (p=0.9); mean DFS was 28 months in the FO group and 21 months in the D group (p<0.001). In patients who received URS with treatment purposes, no difference regarding OS (p=0.9) and DFS (p=0.7) were observed. NBI and Image 1S technologies did not improve OS nor DFS over D-URS.

Conclusions

D-URS did not provide any oncological advantage over FO-URS. Similarly, no differences in terms of OS and DFS were found when image enhance technologies were compared to D-URS. These findings underline the importance of surgeon skills and experience and reinforce the need for the centralization of UTUC care.

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease accounting for around 5% of all urothelial cancers and with an estimated annual incidence of 1 to 2 cases per 100.000 [1]. Historically, the standard treatment of UTUC has been represented by radical nephroureterectomy (RNU) with bladder cuff excision [2,3]. During the last decades kidney-sparing surgery (KSS) has been advocated with the aim to preserve the renal function without compromising long-term oncological outcomes in suitable patients. Based on current recommendations, KSS is indicated in the so-called low-risk group of patients, characterized by a tumor size ≤2 cm, unifocal disease, low-grade cytology, low-grade cancer on ureteroscopic biopsy, and no evidence of invasion or extra-organ spread on computed tomography [2,4–10].

The dissemination of the endoscopic approach for the treatment of UTUC has undoubtedly been favored by several factors such as the improvement in laser

technology and the advent of miniaturization, digital image caption and image enhanced technologies [11]. Notably, the advent of digital ureteroscopy (D-URS) has dramatically improved the endoscopic view of the upper tract, thus facilitating both the diagnosis and the treatment of patients with UTUC. In vitro studies demonstrated superior image quality in favor of D-URS compared to fiber-optic (FO) scopes, and most authors agree that digital technology is superior for the detection of UTUC [12]. However, to date, a direct comparison between FO- and D-URS for the diagnosis and treatment of UTUC in terms of oncological outcomes is lacking.

Image enhance technologies such as the narrow-band imaging (NBI),photodynamic diagnosis (PDD), and the Image 1-S (formerly called SPIES), initially proposed in bladder cancer (BCa) to enhance the cystoscopic view, have become feasible in the field of UTUC, being now incorporated in the last generation of flexible ureterorenoscopes. NBI and PDD already reported to significantly increase the tumor detection rate and, potentially, also the accuracy of the endoscopic treatment [13,14]. However, the impact of these technologies in a real-world scenario remains uninvestigated.

Based on these considerations, our study aimed to evaluate the impact of digital technology and that of image enhance technologies on the oncological outcomes of a large prospective cohort of patients with UTUC included in the Clinical Research Office of the Endourology Society (CROES)-UTUC registry.

Materials and methods

The CROES-UTUC registry is an international, multicenter, cohort study prospectively collecting clinical data on consecutive patients with UTUC initiated in November 2014 after an institutional review board approval at each participating center. The study was closed for inclusion in November 2019. Adult patients (≥18 years old) with a clinical suspicion of UTUC and scheduled for any type of diagnostic or surgical procedure could be included in the registry. Details of the content of data collection have been previously described [15]. Clinical data of included patients have been prospectively collected up to 5-years from inclusion, as per protocol definition. Follow up was not standardized but was generally conducted according to international guidelines and mainly consisted of regular cystoscopy, urinary cytology,

and thorax/abdomen CT scan after RNU, and of regular URS, cystoscopy, urinary cytology and thorax/abdomen CT scan after KSS [2].

The main endpoint of the current study was to compare the oncological outcomes (overall survival and disease-free survival) of patients undergoing FO- vs D-URS for diagnostic only, diagnostic and treatment, and treatment only purposes. The secondary endpoint of the study was to evaluate the impact of NBI and Image 1S enhance technologies on the oncological outcomes (overall survival and disease-free survival) of patients undergoing D-URS. Outcomes of patients who underwent Olympus D-URS were compared to those who received Olympus D-URS with NBI enhancement. Similarly, outcomes of patients who underwent Storz D-URS were compared to those who received Storz D-URS with Image 1S system.

Statistical analysis

Frequencies and column percentages were reported for categorical variables, while medians and interquartile ranges (IQRs) were reported for continuous variables. Chi-square and Mann-Whitney U-tests were performed for categorical and continuous variables to compare the populations, respectively. Kaplan-Meier curves were built to evaluate differences in overall survival (OS) and disease-free survival (DFS). Log-rank test was used to provide difference estimation. Time to death was used to plot OS, and time to first recurrence of the disease was used to assess DFS. Both curves were plotted from the URS procedure to the last available follow-up. For OS, participants were either deceased or censored (alive with or without disease, lost-to-follow-up) at the end of the study (after 5 years), and the differences between the dates of death or follow-up and the date of URS procedure were used as time to event and time to censoring in days. For DFS, participants either had a first recurrence or were censored (no recurrence, deceased with no recurrence or lost-to-follow-up at the end of the study). Time to recurrence or censoring was calculated by taking the difference between the corresponding date of recurrence (when available) or date of follow-up and the date of URS procedure. Statistical analyses were performed using R (R Foundation for Statistical Computing, v3.0 or higher). All tests were two-sided and $p < 0.05$ was considered as statistically significant.

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CIs. Cumulative incidence curves were generated with the post-estimation function.

Results

Overall, 2451 patients from 125 centers and 37 countries have been included in the registry so far. After quality check control and data cleaning, 2380 patients from 101

centers and 37 countries have been retained for the analysis. The main reason for patients' exclusion was missing data regarding the variables of interest. Overall, 488 patients received URS for diagnostic purposes while 696 for diagnostic and treatment reasons (KSS cases). Despite the continuous growth of KSS for the treatment of UTUC, the majority of patients enrolled in the registry have been treated with RNU (1424), and only a few underwent segmental ureterectomy (82).

Fiber Optic Scopes vs Digital Optic Scopes

Overall, 1184 patients underwent a semirigid or flexible URS procedure (alone or in combination with other treatments). After eligibility criteria were implemented (use of flexible ureteroscope, the indication of the type of ureteroscope used, and the reason for performing URS), 401 patients (186 undergoing FO- and 215 undergoing D-URS) were retained for the purpose of the study. 19 centers reported the use of D-URS and 27 centers of FO-URS only. The flow diagram depicting the details of the selection process is reported in Fig. 1.

The baseline characteristics of the population are reported in Table 1. Reasons for visiting the clinic prior to URS were the presence of symptoms (55%), a referral from other centers (23%), incidentaloma on radiologic evaluation (17%), positive urinary cytology during follow- up for bladder cancer (8%), follow-up of contralateral UTUC (3%), and positive family history/Lynch syndrome (1%). Among those presenting with symptoms, the majority had hematuria (64%), while only a minority complained of pain (20%).

The FO scopes were used more frequently for diagnostic purposes while D scopes were used more frequently when a combined diagnostic and treatment strategy was planned (Table 2). Intraoperative complications during URS were uncommon (4.6%), with no difference between FO and D URS (p=0.5). The most frequent intraoperative reported complication was bleeding, representing 33% of all intraoperative complications. Postoperative 30-days complications after URS occurred in 17.7% of the population, with no difference between FO- and D-URS (p=0.1). The most frequent postoperative reported complication was pain requiring medical therapy, and occurring in 5.7% of patients. The details regarding intraoperative and postoperative complications are reported in Table 3. The characteristics of

postoperative pathology after URS procedure are depicted in Supplementary Table 1.

After 5 years of follow up, 91.5% of patients were alive and 66.4% of patients were recurrence-free. Mean OS was 42 months for patients receiving FO-URS and 39 months for those undergoing D-URS (p=0.9); mean DFS was 28 months in the FO group and 21 months in the D group (p<0.001) (Fig. 2).

Subgroup analyses were performed. In patients who received URS with treatment purposes (diagnostic procedures were excluded) no difference regarding OS (p=0.9) and DFS (p=0.7) were observed between FO and D groups. In patients with localized disease (<pT2), OS did not differ between groups (p=0.9) while DFS was higher in the FO group (p<0.001). Again, after excluding diagnostic procedures, OS and DFS did not differ in this subgroup of patients (Fig. 3).

Impact of image enhance technologies on long-term oncological outcomes

Overall, Olympus D-URS with NBI enhancement was used in 10 centers in 64 (2.7%) procedures while Storz D-URS with Image 1S enhancement was used in 6 centers in 94 (3.9%) URSs. 3 centers used both NBI and Image 1S enhacement technologies. Data regarding oncological outcomes were available for 57 patients who underwent Olympus D-URS (21 patients with NBI enhancement vs 36 patients without) and for 73 patients who received Storz D-URS (45 patients with Image 1S enhancement vs 28 without). When comparing the oncological outcomes of patients who received Olympus D- URS vs those who underwent Olympus D-URS with NBI enhancement, no difference was observed in terms of OS (p=0.7) and DFS (p=0.1). Similarly, when comparing the oncological outcomes of patients who received Storz D-URS vs those who underwent Storz D-URS with Image 1 enhancement, no difference was observed in terms of OS (p=0.5) and DFS (p=0.3) (Supplementary Figure 1).

Discussion

In this ad hoc analysis of prospectively collected data, we evaluated the impact of digital technology and that of image enhance technologies on the long-term oncological outcomes of patients undergoing URS for UTUC. We found no differences in terms of OS and DFS in patients undergoing FO vs D URS and in those receiving D vs D-enhanced URS.

The development and the continuous advancement of high definition flexible FO- and D-URS have greatly improved the visualization of the upper urinary tract, thereby expanding the indication for KSS in patients with UTUC. An accurate endoscopic visualization of the urinary tract is of paramount importance for the assessment of tumor size and focality as well as for an accurate biopsying and complete tumor ablation. Oncological outcomes of patients with UTUC receiving endoscopic KSS have been reported in several retrospective series [16,17]. In one of the first studies of 35 patients treated between 2003 and 2007 with an endoscopic approach, Cornu et al. reported a DFS rate of 40%, with a median survival rate without recurrence of 10 months [17]. Subsequently, in a retrospective cohort of 73 patients, Cutress et al. reported a 5-years OS and cancer-specific survival (CSS) rates of 69.7% and 88.9%, respectively [16]. In a systematic review investigating oncological outcomes of patients treated with KSS vs RNU, 5-years OS and CSS rates ranged between 55%-85% and 75%-85%, respectively [18]. In these studies, all endoscopic procedures have been performed with FO scopes. More recently, Villa et al. reported the outcomes of 92 patients treated with URS and holmium laser photoablation between 2003 to 2015 at a single institution [19]. Within a median follow up of around 5 years, local recurrence occurred in 76% of patients; of note, D-URS was the technique of choice after its implementation in 2007. The observation of improved OS and DFS rates in our contemporary series of UTUC patients, compared to those reported in the literature, calls into question the possible impact of the introduction in clinical practice of new tools such as digital technology and image enhance technology on the long-term oncological outcomes of UTUC patients.

D-URS has been shown to provide better image quality over FO-URS and, potentially, to improve the diagnostic and treatment accuracy in patients with UTUC [12]. For this reason D-URS is currently viewed as the most valuable instrument to evaluate the upper urinary tract [20] however, a comparison of oncological outcomes

of FO- vs D-URS in UTUC patients is lacking. In our study, we found no difference in terms of OS and DFS when analyzing patients who underwent KSS with either FO- or D-URS. The statistically significant difference in DFS (favoring FO-URS) observed when combining both diagnostic and operative procedures was in fact lost when only the latter were retained in the analysis.

Similarly, we could not observe any impact on oncological outcomes following the adoption of image enhance technologies such as NBI or Image 1S over standard D URS in patients undergoing KSS for UTUC. In BCa, NBI has demonstrated to improve cancer detection over white light cystoscopy [21,22], although this did not translate in a reduction of recurrence [23]. Conversely, evidence regarding Image 1S is scarce, and the results of a RCT endorsed by CROES aiming to compare the recurrence rate in patients treated with Image 1S-assisted vs white light resection are still awaited [24]. Both NBI and Image 1S have been tested in URS and are nowadays incorporated in the last generation of flexible scopes (NBI in Olympus URF-V, URF-V2 and URF-V3 while Image 1S in the Storz Flex X^c). Compared to white light URS, NBI was reported to improve the diagnostic accuracy of UTUC by 23% in a study of 27 patients with suspected UTUC or undergoing URS for follow-up after KSS [13]. Conversely, no data regarding Image 1S in UTUC have been reported so far.

Some observations can be drown from our resuts. First, we have shown in a real-world scenario, that image enhance technologies are still underused for the endoscopic assessment of UTUC. Second, in spite of the improved image quality, their impact on the oncological outcomes of patients with UTUC remains, to date, unproven.

This calls into question the inherent difficulty to prove the advantages of a new technology within a clinical trial using hard end points (oncological outcomes) in the presence of confoundings such as the “surgical factor” that are difficult to control for. As an example, Bagley et al. in their series of “mandatory” single-surgeon KSS in large UTUC (>2cm) patients, reported 5-years OS and CSS rates as high as 75% and 84%, respectively [25]. The same group recently reported an OS, CSS and renal preservation rate of 81%, 92% and 74% in 164 patients treated with KSS between 1994 and 2017 by the same surgeon [26], pointing out that the surgical skill may

overcome technological advancements. In this respect, our findings may pave the way towards the need for a centralization even in the field of UTUC, as already demonstrated for several other cancers, including BCa [27].

Our study is not devoid of limitations, mainly due to the registry nature of the data. Actually, despite this represents an "ad hoc" analysis of prospectively collected data, possible selection bias could not be ruled out. First of all, the choice between FO- or D-URS may depend on the availability of the instruments and not only on patients' and tumor's characteristics. Usually, D scopes are more often used in referral centers with more centralization of care; consequently, these experienced centers may consider to treat more advanced tumors (multiple and up to 2 cm) compared to less experienced centers (single and smaller tumors). Therefore, the difference in outcome between D- and FO- URS may not be only because of the technology used, but also affected by a selection bias. We did not collected data about the condition of the ureteroscopes (wether new or refurbished) and, therefore, we were not able to comment on this. We were not able to assess the impact of subsequent treatments after URS (i.e. perioperative chemotherapy administration, repeated URSs, RNU) and to account for other factors that may have influenced the results, such as the type of laser energy used for UTUC ablation (Holmium vs Thulium), the size and location of the tumor, and the previous and the subsequent history of endocavitary therapies. The inability to perform multivariable analysis may further limit the strength of our findings. Additionally, the renal preservation rate in patients undergoing KSS was not provided, despite the importance of this endpoint in this clinical scenario. The small sample size may have limited the strength and the reproducibility of the results regarding NBI and Image 1S technologies. Nonetheless we strongly believe that new technologies such as D-URS, NBI and Image 1S should be validated through future powered clinical studies assessing hard end points.

In conclusion, although the registry is not devoid of limitations, its strength mainly relies on its design, based on a prospective registry conducted with a common protocol [15]. Finally, it clearly depicts the current global situation regarding the treatment of UTUC, still mainly based on RNU. This fact also implies that a well powered RCT aiming to compare FO to D or D-enhanced technologies will be almost a 'mission impossible'.

Conclusions

This is the first comparison of FO- vs D-URS for the diagnosis and treatment of patients with UTUC. Despite providing a better quality image, D-URS did not provide any oncological advantage compared to FO-URS in patients treated with KSS. Similarly, image enhance technologies such as NBI and Image 1S did not impact on the oncological outcomes of UTUC patients and are rarely used in the everyday clinical practice. Since the sample size for these technology was limited, the related findings should be judged with care and external validation of these results is warranted.

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Conflicts of Interest

None declared

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Figure Legends

Figure 1

Flow diagram depicting the details of patients' selection process

Figure 2

Kaplan-Meier curves for overall survival (A) and disease-free survival (B) among the cohort of 401 patients included in the CROES registry who underwent fiber-optic or digital flexible ureteroscopy for upper tract urothelial carcinoma

Figure 3

Subgroup analyses:

- Kaplan Meier curves for overall survival (A) and disease-free survival (B) in patients who received flexible ureteroscopy for treatment purposes (kidney-sparing surgery).
- Kaplan Meier curves for overall survival (C) and disease-free survival (D) in patients with localized upper tract urothelial carcinoma (<pT2)
- Kaplan Meier curves for overall survival (E) and disease-free survival (F) in patients with localized upper tract urothelial carcinoma (<pT2) who received flexible ureteroscopy for treatment purposes (kidney-sparing surgery).

Supplementary Figure 1

Kaplan Meier curves for overall survival (A) and disease-free survival (B) in patients undergoing Olympus digital ureteroscopy with or without narrow-band imaging enhancement, and for overall survival (C) and disease-free survival (D) in patients undergoing Storz digital ureteroscopy with or without Image 1S enhancement.