

Flexible fibre optic vs digital ureteroscopy and enhanced vs unenhanced imaging for diagnosis and treatment of upper tract urothelial carcinoma (UTUC): results from the Clinical Research Office of the Endourology Society (CROES)-UTUC registry

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Objectives

To compare the oncological outcomes of patients with upper tract urothelial carcinoma (UTUC) undergoing kidney-sparing surgery (KSS) with fibre-optic (FO) vs digital (D) ureteroscopy (URS). To evaluate the oncological impact of image-enhancement technologies such as narrow-band imaging (NBI) and Image1-S in patients with UTUC.

Patients and Methods

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

Results

The CROES registry included 2380 patients from 101 centres 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 was performed when a combined diagnostic and treatment strategy was planned. Intra- and postoperative complications did not differ between the groups. The 5-year OS and DFS rates were 91.5% and 66.4%, respectively. The mean OS was 42 months for patients receiving FO-URS and 39 months for those undergoing D-URS ($P = 0.9$); the mean DFS was 28 months in the FO-URS group and 21 months in the D-URS group ($P < 0.001$). In patients who received URS with treatment purposes, there were no differences in OS ($P = 0.9$) and DFS ($P = 0.7$). NBI and Image1-S technologies did not improve OS or 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-enhancement technologies were compared to D-URS. These findings underline the importance of surgeon skills and experience, and reinforce the need for the centralisation of UTUC care.

Keywords

upper tract urothelial carcinoma, digital ureteroscopy, fibre-optic ureteroscopy, narrow-band imaging, Image1-S, #utuc

Introduction

Upper tract urothelial carcinoma (UTUC) is a rare disease accounting for ~5% of all UCs and with an estimated annual incidence of one to two cases per 100 000 [1]. Historically, the standard treatment of UTUC has been by radical nephroureterectomy (RNU) with bladder-cuff excision [2,3]. During recent decades, kidney-sparing surgery (KSS) has been advocated with the aim to preserve 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, characterised by a tumour size of ≤ 2 cm, unifocal disease, low-grade cytology, low-grade cancer on ureteroscopic biopsy, and no evidence of invasion or extra-organ spread on CT [2,4–10].

The dissemination of the endoscopic approach for the treatment of UTUC has undoubtedly been favoured by several factors such as the improvement in laser technology and the advent of miniaturisation, digital image caption, and image-enhancement 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 treatment of patients with UTUC. *In vitro* studies showed superior image quality in favour of D-URS compared to fibre-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-enhancement technologies such as the narrow-band imaging (NBI), photodynamic diagnosis (PDD), and the Image1-S (formerly called Storz Professional Image Enhancement System [SPIES]), initially proposed in bladder cancer 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 have already been reported to significantly increase the tumour 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 present study aimed to evaluate the impact of digital technology and that of image-enhancement 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.

Patients and Methods

The CROES-UTUC registry is an international, multicentre, cohort study prospectively collecting clinical data on consecutive patients with UTUC initiated in November 2014 after an Institutional Review Board approval at each

participating centre. The study was closed for inclusion in November 2019. Adult patients (aged ≥ 18 years) 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 standardised, 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 present study was to compare the oncological outcomes (overall survival [OS] and disease-free survival [DFS]) of patients undergoing FO- vs D-URS for diagnostic only, diagnosis and treatment, and treatment only purposes. The secondary endpoint of the study was to evaluate the impact of NBI and Image1-S image-enhancement technologies on the oncological outcomes (OS and DFS) 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 the Image1-S 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 used to evaluate differences in OS and DFS. The 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 the URS procedure. Statistical analyses were performed using R (version 3.0 or higher; R Foundation for Statistical Computing, Vienna,

Austria). All tests were two-sided and a $P < 0.05$ was considered as statistically significant.

Results

Overall, 2451 patients from 125 centres and 37 countries have been included in the registry to date. After quality check control and data cleaning, 2380 patients from 101 centres and 37 countries have been retained for 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).

Fibre-Optic Scopes vs Digital Optic Scopes

Overall, 1184 patients underwent a semi-rigid 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. A total of 19 centres reported the use of D-URS and 27 centres 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 centres (23%), incidentaloma on radiological 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 haematuria (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 frequently reported intraoperative complication was bleeding, representing 33% of all intraoperative complications. Postoperative 30-day complications after URS occurred in 17.7% of the population, with no difference between FO- and D-URS ($P = 0.1$). The most frequently reported postoperative complication was pain requiring medical therapy, and occurring in 5.7% of patients. The details regarding intra- and postoperative complications are reported in Table 3. The characteristics of postoperative pathology after URS procedure are depicted in Table S1.

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

Subgroup analyses were performed. In patients who received URS with treatment purposes (diagnostic procedures were excluded) there were no differences in OS ($P = 0.9$) and DFS ($P = 0.7$) between the FO- and D-URS groups. In patients with localised disease ($< pT2$), OS did not differ between groups ($P = 0.9$), while DFS was longer in the FO-URS 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-Enhancement Technologies on Long-Term Oncological Outcomes

Overall, Olympus D-URS with NBI enhancement was used in 10 centres in 64 (2.7%) procedures, while Storz D-URS with Image1-S enhancement was used in six centres in 94 (3.9%) procedures. Three centres used both NBI and Image1-S image-enhancement 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 Image1-S 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, there was no difference 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 Image1-S enhancement, there was no difference in terms of OS ($P = 0.5$) and DFS ($P = 0.3$; Fig. S1).

Discussion

In the present ad hoc analysis of prospectively collected data, we evaluated the impact of digital technology and that of image-enhancement 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 visualisation of the upper urinary tract, thereby expanding the indication for KSS in patients with UTUC. An accurate endoscopic visualisation of the urinary tract is of paramount importance for the assessment of tumour size and focality, as well as for an accurate biopsying and complete tumour ablation. Oncological outcomes of patients with UTUC

Fig. 1 Flow diagram depicting the details of patients' selection process.

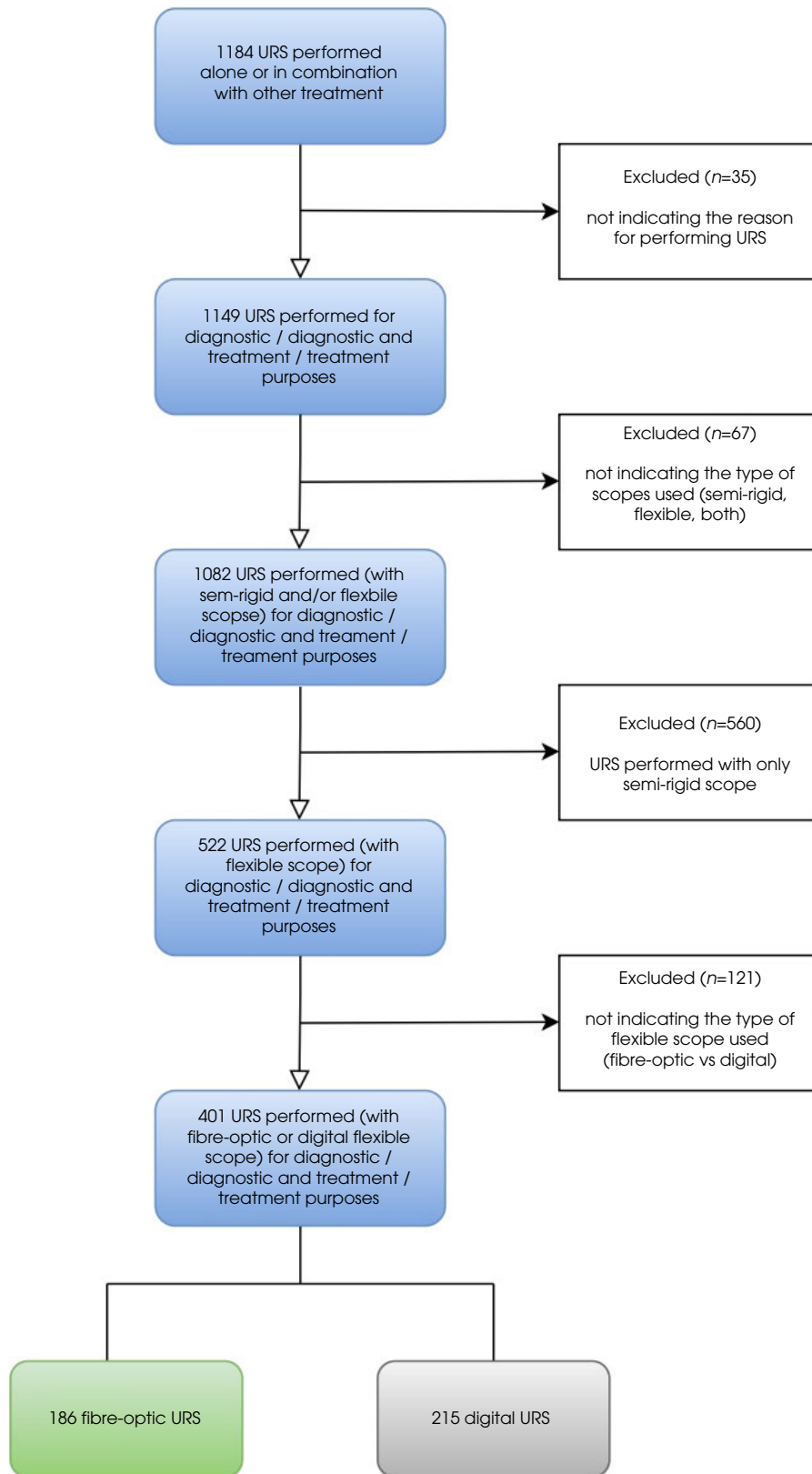


Table 1 Descriptive characteristics of the cohort of 401 patients included in the CROES registry who underwent flexible FO- or D-URS for UTUC.

Variable	Total	Scopes		P
		FO	D	
Number of patients	401	186	215	
Age, years, median (IQR)	70 (63–78)	71 (63–78)	69 (62–78)	0.5
BMI, kg/m ² , median (IQR)	26 (23–28)	26 (24–28)	25 (23–28)	0.4
ASA score, n (%)				
I	59 (15)	20 (11)	39 (19)	0.1
II	193 (50)	91 (49)	102 (49)	
III	125 (32)	66 (36)	59 (29)	
IV	3 (3)	7 (4)	6 (3)	
CCI, n (%)				
0	68 (24)	31 (22)	37 (25)	0.8
1	65 (23)	31 (22)	34 (23)	
2	60 (21)	26 (19)	34 (23)	
3	29 (10)	13 (9)	16 (11)	
4	31 (11)	19 (14)	12 (8)	
5	7 (2)	5 (4)	2 (1)	
6	12 (4)	7 (5)	5 (3)	
Chronic kidney disease ≥2, n (%)	52 (22)	20 (16)	32 (27)	0.056
Diabetes mellitus, n (%)	76 (25)	42 (29)	34 (22)	0.2
Neurological disease, n (%)	33 (12)	6 (4)	27 (19)	<0.001
Cardiovascular disease, n (%)	233 (82)	115 (83)	118 (80)	0.5
Anticoagulation medication, n (%)	139 (35)	69 (37)	70 (33)	<0.001
Haematuria, n (%)	255 (64)	120 (65)	135 (63)	0.8
Pain, n (%)	78 (20)	38 (20)	40 (19)	0.7
Preoperative stent/JJ, n (%)	72 (18)	27 (15)	45 (21)	0.08

ASA, American Society of Anesthesiologists; BMI, body mass index; CCI, Charlson Comorbidity Index.

Table 2 Description of the indication for performing flexible URS in the 401 patients with UTUC included in the CROES registry.

	FO-URS, n (%)	D-URS, n (%)	Total, n (%)	P
Diagnostics only	134 (72.0)	108 (50.2)	242 (60.4)	<0.001
Treatment only	2 (1.1)	4 (1.9)	6 (1.5)	
Both diagnostic and treatment	50 (26.9)	103 (47.9)	153 (38.1)	
Total	186 (100.0)	215 (100.0)	401 (100.0)	

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. [17] reported a DFS rate of 40%, with a median survival rate without recurrence of 10 months. Subsequently, in a retrospective cohort of 73 patients, Cutress et al. [16] reported 5-year OS and cancer-specific survival (CSS) rates of 69.7% and 88.9%, respectively. In a systematic review investigating oncological outcomes of patients treated with KSS vs RNU, the 5-year OS and CSS rates ranged between 55% and 85% and 75–85%, respectively [18]. In these studies, all endoscopic procedures were performed with FO-scopes. More recently, Villa et al. [19] reported the outcomes of 92 patients treated with URS and holmium laser photo-ablation between 2003 and 2015 at a single institution. Within a median follow-up of ~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 patients with UTUC, 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-enhancement technology on the long-term oncological outcomes of patients with UTUC.

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 appropriate instrument to evaluate the upper urinary tract [20] however, a comparison of oncological outcomes of FO- vs D-URS in patients with UTUC is lacking. In our present study, we found no difference in terms of OS and DFS when analysing

Table 3 Description of intraoperative and 30-day postoperative complications after FO- or D-URS among the cohort of 401 patients included in the CROES registry who underwent flexible URS for suspected UTUC.

Postoperative complications by type of scope				
	FO n (%) or n/N	D n (%) or n/N	Total n (%) or n/N	P
Intraoperative complications				
No	173 (96.1)	198 (94.7)	371 (95.4)	0.520
Yes	7 (3.9)	11 (5.3)	18 (4.6)	
Types of intraoperative complications				
Avulsion	0/7	0/12	0 (0.0)	*
Bleeding	3/7	3/12	6 (33.3)	0.494
Bowel lesion	1/7	0/12	1 (5.6)	0.197
Ureter lesion	0/7	1/12	1 (5.6)	0.412
Other	3/7	8/12	11 (61.1)	0.205
Postoperative complications within 30 days				
No	152 (85.4)	164 (79.6)	316 (82.3)	0.139
Yes	26 (14.6)	42 (20.4)	68 (17.7)	
Types of postoperative complications according to Clavien–Dindo distribution				
Clavien–Dindo cardiac				
II	1/1	2/2	3/3	*
Clavien–Dindo infection				
I	0/6	2/9	2 (13.3)	0.287
II	6/6	6/9	12 (80.0)	
III-a	0/6	1/9	1 (6.7)	
Clavien–Dindo haematuria				
I	3/5	4/8	7/13	0.675
II	2/5	2/8	4/13	
III-a	0/5	1/8	1/13	
III-b	0/5	1/8	1/13	
Clavien–Dindo neurological				
I	1/1	0	1/1	*
Clavien–Dindo pain				
II	3/3	19/19	22 (100.0)	*
Clavien–Dindo pulmonale				
I	2/3	1/2	3/5	0.709
IV-a	1/3	1/2	2/5	
Clavien–Dindo other				
I	2/11	2/7	4 (22.2)	0.955
II	4/11	2/7	6 (33.3)	
III-a	3/11	2/7	5 (27.8)	
III-b	2/11	1/7	3 (16.7)	

patients who underwent KSS with either FO- or D-URS. The statistically significant difference in DFS (favouring FO-URS) observed when combining both diagnostic and operative procedures was in fact lost when only the latter were retained in the analysis.

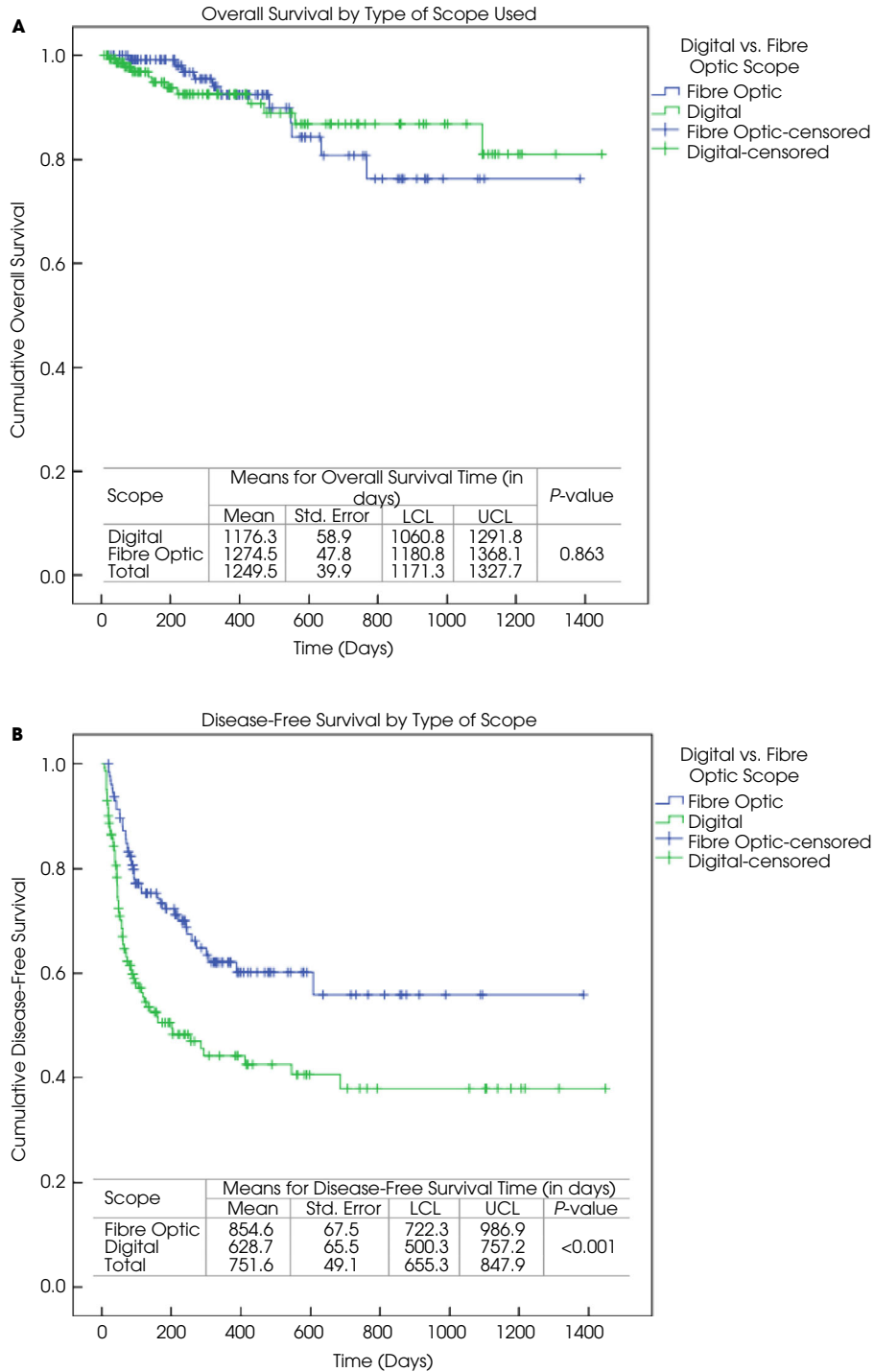
Similarly, we did not observe any impact on oncological outcomes following the adoption of image-enhancement technologies such as NBI or Image1-S over standard D-URS in patients undergoing KSS for UTUC. In bladder cancer, NBI has been shown to improve cancer detection over white-light cystoscopy [21,22], although this did not translate in to a reduction of recurrence [23]. Conversely, evidence regarding Image1-S is scarce and the results of a randomised controlled trial (RCT) endorsed by CROES aiming to compare the recurrence rate in patients treated with Image1-S-assisted vs white-light resection are still awaited [24]. Both NBI and Image1-S 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 Image1-S 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 Image1-S in UTUC have been reported to date.

Some observations can be drawn from our present results. First, we have shown in a real-world scenario, that image-enhancement technologies are still underused for the endoscopic assessment of UTUC. Second, despite 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 in proving the advantages of a new technology within a clinical trial using hard endpoints (oncological outcomes) in the presence of confounders such as the 'surgical factor' that are difficult to

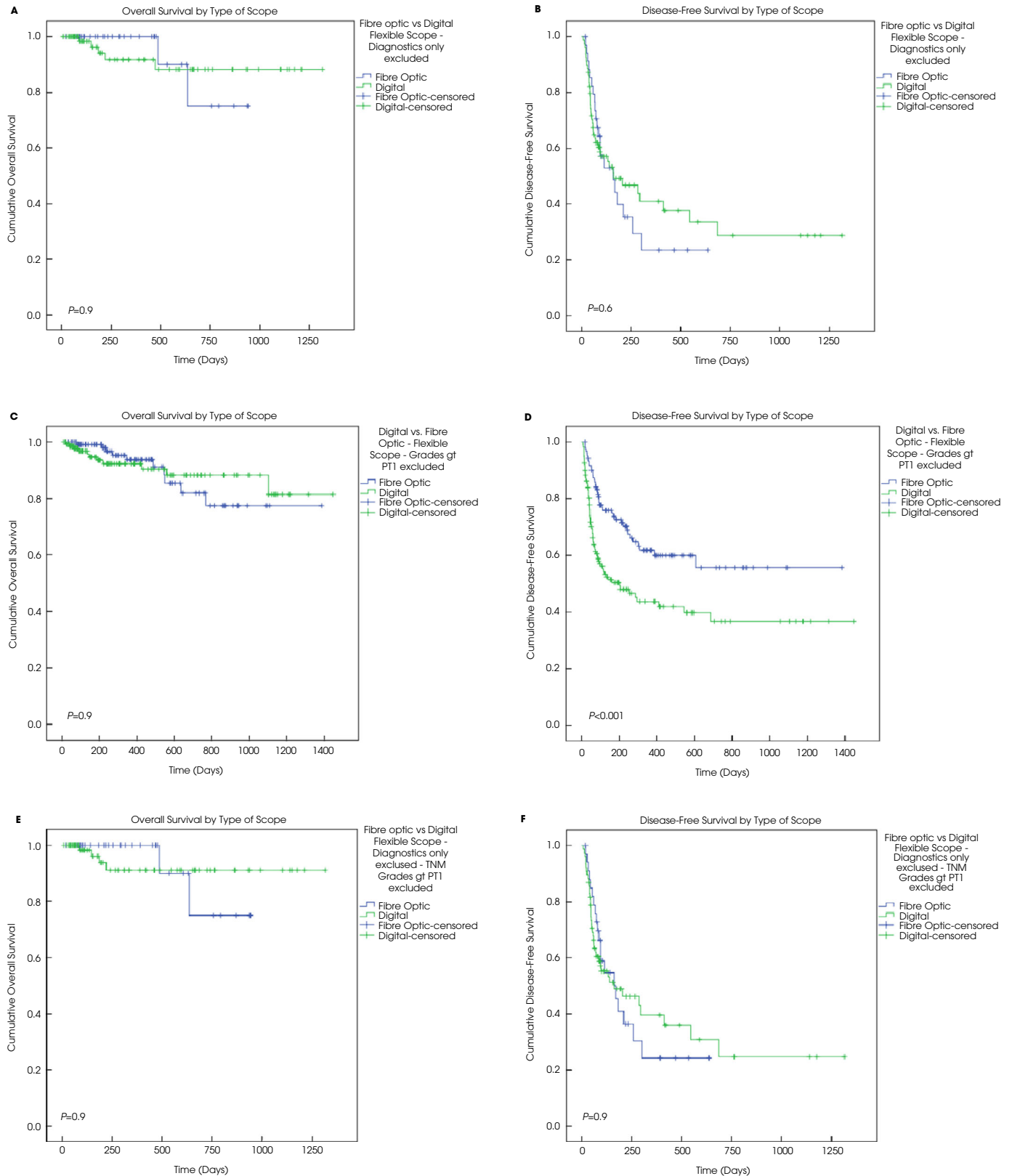
Fig. 2 Kaplan–Meier curves for OS (A) and DFS (B) among the cohort of 401 patients included in the CROES registry who underwent flexible FO- or D-URS for UTUC.



control for. As an example, Scotland *et al.* [25] in their series of ‘mandatory’ single-surgeon KSS in patients with large UTUC (>2 cm) reported 5-year OS and CSS rates as high as 75% and 84%, respectively. The same group recently reported an OS, CSS and renal preservation rate of 81%, 92% and

74%, respectively, in 164 patients treated with KSS between 1994 and 2017 by the same surgeon [26], indicating that surgical skill may overcome technological advances. In this respect, our present findings may pave the way towards the need for a centralisation even in the field of UTUC, as

Fig. 3 Subgroup analyses: Kaplan–Meier curves for OS (A) and DFS (B) in patients who received flexible URS for treatment purposes (KSS). Kaplan–Meier curves for OS (C) and DFS (D) in patients with localised UTUC (<pT2). Kaplan–Meier curves for OS (E) and DFS (F) in patients with localised UTUC (<pT2) who received flexible URS for treatment purposes (KSS).



already demonstrated for several other cancers, including bladder cancer [27].

Our present 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 tumour's characteristics. Usually, D-scopes are more often used in referral centres with more centralisation of care; consequently, these experienced centres may consider treating more advanced tumours (multiple and up to 2 cm) compared to less experienced centres (single and smaller tumours). Therefore, the difference in outcome between FO- and D-URS may not be only because of the technology used, but also affected by a selection bias. We did not collect data about the condition of the ureteroscopes (whether 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 URS, 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 tumour, and the previous and the subsequent history of endocavitary therapies. The inability to perform multivariable analysis may further limit the strength of our present 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 Image1-S technologies. Nonetheless, we strongly believe that new technologies such as D-URS, NBI and Image1-S should be validated through future powered clinical studies assessing hard endpoints.

In summary, 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-enhancement technologies, such as NBI and Image1-S, did not impact on the oncological outcomes of patients with UTUC and are rarely used in everyday clinical

practice. As the sample size for these technologies was limited, the related findings should be judged with care and external validation of these results is warranted.

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Disclosure of Interests

Dr. Ng reports personal fees from Boston Scientific, personal fees from Olympus, outside the submitted work. Dr. Roupret reports personal fees from Astra Zeneca, personal fees from BMS, personal fees from FERRING, personal fees from Janssen, personal fees from Merck-Pfizer, outside the submitted work.

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Abbreviations: CROES, Clinical Research Office of the Endourology Society; CSS, cancer-specific survival; D, digital; DFS, disease-free survival; FO, fibre optic; KSS, kidney-sparing surgery; NBI, narrow-band imaging; OS, overall survival; PDD, photodynamic diagnosis; RCT, randomised controlled trial; RNU, radical nephroureterectomy; URS, ureteroscopy; (UT) UC, (upper tract) urothelial carcinoma.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Fig. S1. Kaplan–Meier curves for OS (A) and DFS (B) in patients undergoing Olympus D-URS with or without NBI enhancement; and for OS (C) and DFS (D) in patients undergoing Storz D-URS with or without Image1-S enhancement.

Table S1. Description of available postoperative pathology after FO- or D-URS among the cohort of 401 patients included in the CROES registry who underwent flexible URS for suspected UTUC.