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Decisional and prognostic impact of diagnostic ureteroscopy in high-risk upper tract urothelial carcinoma: A multi-institutional collaborative analysis (ROBUUST collaborative group)

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Abstract

Background: Diagnostic ureteroscopy (URS) with or without biopsy remains a subject of contention in the management of upper tract urothelial carcinoma (UTUC), with varying recommendations across different guidelines. The study aims to analyse the decision-making and prognostic role of diagnostic ureteroscopy (URS) in high-risk UTUC patients undergoing curative surgery.

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Materials and methods: In this retrospective multi-institutional analysis of high-risk UTUC patients from the ROBUUST dataset, a comparison between patients who received or not preoperative URS and biopsy before curative surgery was carried out. Logistic regression analysis evaluated differences between patients receiving URS and its impact on treatment strategy. Survival analysis included 5-year recurrence-free survival (RFS), metastasis-free survival (MFS), cancer-specific survival (CSS) and overall survival (OS). After adjusting for high-risk prognostic group features, Cox proportional hazard model estimated significant predictors of time-to-event outcomes.

Results: Overall, 1,912 patients were included, 1,035 with preoperative URS and biopsy and 877 without. Median follow-up: 24 months. Robot-assisted radical nephroureterectomy was the most common procedure (55.1%), in both subgroups. The 5-year OS ($P = 0.04$) and CSS ($P < 0.001$) were significantly higher for patients undergoing URS. The 5-year RFS ($P = 0.6$), and MFS ($P = 0.3$) were comparable between the 2 groups. Preoperative URS and biopsy were neither a significant predictor of worse oncological outcomes nor of a specific treatment modality.

Conclusions: The advantage in terms of OS and CSS in patients undergoing preoperative URS could derive from a better selection of candidates for curative treatment. The treatment strategy is likely more influenced by tumor features than by URS findings. © 2024 The Author(s). Published by Elsevier Inc. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/)

Keywords: Diagnostic ureteroscopy; Kidney-sparing surgery; Nephroureterectomy; Upper tract urothelial carcinoma

1. Introduction

The use of diagnostic ureteroscopy (URS) with/or without biopsy remains a topic of debate in the management of UTUC. While AUA and NCCN guidelines suggest its adoption in patients suspected of UTUC [1] for any lesion identified on imaging [2], EAU guidelines recommend employing diagnostic URS only when imaging and/or voided urine cytology do not provide diriment data for diagnosis and risk stratification [3]. These discrepancies stem from uncertainty about an increased risk of intravesical recurrence of urothelial carcinoma after URS for suspected UTUC. Indeed, 2 recent meta-analyses yielded opposing results regarding the effect of URS before definitive surgical treatment of UTUC [4,5]. URS with concurrent biopsy may play a pivotal role, as a potential decision-making tool of the most appropriate treatment strategy between radical nephroureterectomy (RNU) and kidney-sparing surgery (KSS), the latter usually reserved for low-risk UTUC patients. However, the role of KSS is evolving in patients with high-risk UTUC, given the relative comparability of oncological outcomes with RNU as suggested in previous studies [6,7]. Hence, the broadening of indications for KSS underscores the importance of accurate preoperative localization and staging, emphasizing the valuable role of diagnostic URS. Given the dynamic evolution of management strategies in UTUC patients, a comprehensive assessment of the use of diagnostic URS is imperative. Additionally, an exploration of its prognostic significance is particularly noteworthy due to its potential impact on oncological outcomes. The present study aims to evaluate the decision-making and prognostic role of diagnostic URS in high-risk UTUC patients undergoing either RNU or KSS definitive surgery.

2. Methods

2.1. Study population

The ROBUUST (RObotic surgery for Upper tract Urothelial cancer STudy) dataset comprises data from an international, multicentre registry involving institutions worldwide. It includes information on patients who underwent RNU or KSS for UTUC at participating centres between 2015 and 2022. According to the study protocol, patients were followed up with quarterly urinary cytology and cystoscopy for the first 2 years, and quarterly CT scans for the first year, and annually thereafter [8]. Institutional review board approval was obtained at all centres (IRB 22111001). The database was queried to retrieve data about high-risk patients, according to EAU prognostic stratification criteria, who underwent treatment for UTUC with or without prior URS with subsequent biopsy. Exclusion criteria were: preoperative metastatic diseases; URS without biopsy; patients with solitary kidney; patients with bilateral tumors; missing data in potential predictor data fields.

2.2. Study variables and outcomes

Baseline features included patient age, gender, BMI, American Society of Anaesthesiologists (ASA) score, history of bladder cancer, history and type of surgery for bladder cancer, preoperative serum creatinine (SCr) recorded most recently prior to the surgical procedure and estimated glomerular filtration rate (eGFR) (calculated by the Chronic Kidney Disease Epidemiology Collaboration formula [9]), and execution of URS. Tumor characteristics included biopsy tumor grade, tumor size, cT stage on preoperative imaging, multifocality, and presence of ipsilateral hydronephrosis. Surgical (operative time [OT]; estimated blood loss [EBL], type and grade of intraoperative and postoperative complications, length of stay [LOS], SCr, and eGFR at discharge) and pathological (pT and grade; tumor dimension; margin status; pN-stage; lymph node yield and number of positive nodes) variables were collected. Oncological time-to-event outcomes were calculated with the primary endpoint of recurrence-free survival (RFS), and secondary endpoints metastasis-free survival (MFS), cancer-specific survival (CSS) and overall survival (OS).

2.3. Statistical analysis

Statistical analysis was conducted according to published guidelines [10]. The cohort was stratified into two groups based on whether diagnostic URS was performed or not. Median and interquartile range (IQR) were used to report continuous variables, while proportions and frequencies for categorical variables. The Mann-Whitney U test for continuous and the chi^2 test for categorical variables were adopted to compare the difference between the 2 groups. After adjusting for sex, ASA score, presence of hydronephrosis, multifocality, history of previous radical cystectomy, clinical stage, tumor size, and preoperative renal function, a logistic regression analysis was performed to evaluate the association between URS and patients' features and based on their URS status, to determine their likelihood of receiving neoadjuvant therapy, and the type of curative surgery. Sensibility, specificity, positive predictive value (PPV), and negative predictive value (NPV) of preoperative biopsy was calculated using final pathology as a reference. Cohen's kappa coefficient was used to assess the concordance between tumor grade at preoperative biopsy and surgical specimen [11]. A survival analysis of time-to-event outcomes was performed, with a 5-year cut-off, to estimate RFS, MFS, CSS, and OS according to the Kaplan-Meier method. The follow-up duration for censored patients was determined from the treatment to recurrence or metastasis at the last follow-up, for RFS and MFS respectively, and until death or last follow-up visit for OS. Log-rank test was used to evaluate statistical differences between cohorts. After adjusting for clinical features of the high-risk prognostic group, Cox proportional hazard model was used to evaluate significant predictors of each oncological outcome. Stata® 17.0 (StataCorp LLC, College Station, TX, USA) was used for statistical analysis with statistical significance set at $P < 0.05$.

Table 1
Baseline features.

	Ureteroscopy (1,035)	No ureteroscopy (877)	*P*-value
Age	71 (64−78)	72 (65−78)	0.9
Sex			
Male, n (%)	600 (58%)	553 (63%)	**0.02**
BMI	25 (22.9−27.8)	26.1 (23.5−29.7)	**<0.001**
ASA			
≥3	593 (57.8%)	349 (39.8%)	**<0.001**
History of BC			0.4
No	529/824 (64.2%)	342/539 (63.4%)	
LG	119/824 (14.4%)	90/539 (16.7%)	
HG	176/824 (21.4%)	107/539 (19.9%)	
Preop Cr	1.07 (0.88−1.36)	1.13 (0.92−1.4)	**<0.01**
Preop eGFR	61.4 (49−79)	60 (47.3−76.3)	**0.01**
Tumor size	2.5 (1.5−3.5)	3.7 (2.5−5)	**<0.001**
≥2 cm	422/637 (66.2%)	490/557 (88%)	**<0.001**
Multifocal			
Yes	207/1017 (20.3%)	187/867 (21.6%)	0.5
Hydronephrosis			0.07
Yes	539/1,031 (52.3%)	492/873 (56.4%)	
cT			**<0.001**
>2	138/984 (14%)	197/851 (23.1%)	

ASA, American Society of Anesthesiologists; BC, bladder cancer; BMI, body mass index; Cr, Serum creatinine; eGFR, estimated glomerular filtration rate; Preop, preoperative.
Continuous variables as median (IQR) compared with Mann-Whitney U test.
Categorical variables as number (%) compared with chi^2.

3. Results

3.1. Baseline features and risk stratification

Overall, 1,912 patients with high-risk UTUC were analysed. Among them, 1,035 underwent diagnostic URS and concurrent ureteroscopic biopsy, while 877 did not receive a definitive preoperative endoscopic diagnosis. The median (IQR) follow-up length was 24 (9−44) months. Patients in the URS cohort had mainly high-grade tumors (726/1,035, 70.1%), and 4.5% (47/1,035) of the biopsies were non-diagnostic (Table 1). At multivariable logistic regression analysis, a diagnostic URS was performed significantly less likely in patients with tumor size ≥2 cm (OR 0.33, 95%CI 0.23-0.46), and clinical suspect of locally-advanced disease (≥cT2) (OR 0.49, 95%CI 0.35-0.68) (Supplementary table 1).

3.2. Concordance between biopsy and final pathology

The most common procedure was RNU, irrespective of the URS status, followed by segmental ureterectomy and endoscopic ablation ($P < 0.001$). Respectively, 820 (79.2%) patients in the URS group and 642 (80.1%) in the no URS group were diagnosed with a high-grade tumor in the surgical sample, with no difference between the 2 groups ($P = 0.8$) (Table 2). Preoperative biopsy showed a sensitivity of 81.3%, a specificity of 75.3%, a PPV of 93%, and a NPV of 50%, respectively. A concordance of 80.1% was observed between preoperative biopsy and final histology in terms of tumor grade (k = 0.47, $P < 0.001$).

3.3. Survival analysis

After excluding patients with missing values about oncological follow-up, 1,690 patients with data of at least one oncological outcome were available for survival analysis.

Local recurrence was observed in 542 (34.3%) patients, of which 365 (41.3%) did and 177 (25.3%) did not undergo URS before treatment. The 5-year RFS was 7 months (4−13) in the URS group, and 8 months (4−15); in the no URS group, with no significant differences between the cohorts ($P = 0.6$) (Fig. 1A). Metastatic disease occurred in 299 patients (20.3%), 178 (20.9%) in the URS group, and 121 (19.5%) in the non-URS group. Comparable 5-year MFS was observed between the two groups (URS: 8 months [4-20]; no URS: 8 months [3-17], $P = 0.4$) (Fig. 1B). A cancer-related death was experienced by 218

Table 2
Surgical and pathological features.

	Ureteroscopy (1,035)	No ureteroscopy (877)	*P*-value
Surgery type			**<.001**
Ablation	32 (3.1%)	1 (0.1%)	
Ureterectomy	44 (4.3%)	12 (1.4%)	
RNU	959 (92.6%)	862 (98.3%)	
Approach			**0.01**
Transperitoneal	851/986 (86.3%)	716/871 (82.2%)	
Technique			**<0.01**
Robotic	581/997 (58.3%)	449/872 (51.5%)	
Laparoscopic	315/997 (31.6%)	335/872 (38.4%)	
Open	101/997 (10.1%)	88/872 (10.1%)	
OT (min)	222 (167−291)	190 (140−250)	**<.001**
EBL (mL)	100 (50−200)	100 (100−200)	**<.001**
Postop compl (CD)			
Yes	191 (18.5%)	135 (15.4%)	0.07
≥3	37 (20.3%)	40 (30.3%)	0.3
LOS (days)	4(2−7)	5(3−7)	**<0.001**
Cr at discharge	1.38 (1.1−1.72)	1.33 (1.1−1.66)	0.2
eGFR at discharge	48 (37.9−60)	50 (38−61.1)	0.1
pT			0.7
≥T2	519/980 (52.9%)	476/801 (54.3%)	
Other/Unknown	11/980 (1.1%)	9/801 (1.1%)	
Grade			0.8
HG	755/980 (77%)	642/801 (80.1%)	
Margins			0.06
Positive	60/980 (6.1%)	35/801 (4.4%)	
pN			**<0.001**
pN0	357/980 (36.4%)	213/801 (26.6%)	
≥pN1	96/980 (9.8%)	83/801 (10.4%)	
pNx	485/980 (49.5%)	521/801 (65%)	
LN yeld	1 (0-6)	1 (0-6)	0.8

CD, Clavien-Dindo; compl, complications; Cr, Serum creatinine; EBL, estimated blood loss; eGFR, estimated glomerular filtration rate; HG, high grade; LN, lymph node; LOS, length of stay; OT, operative time; Postop, postoperative; RNU, radical nephrureterectomy.

Continuous variables as median (IQR) compared with Mann-Whitney U test.

Categorical variables as number (%) compared with chi^2.

(16.4%) patients, 93 (7%) with and 125 (9.4%) without preoperative URS. The 5-year CSS was 37 months (18-60) in patients undergoing URS, significantly higher than patients without URS (20 months [10-41], P < 0.001) (Fig. 1C). Overall, 361 (21.4%) patients died, 180 (19.6%) from the URS group, and 181 (23.4%) with no prior URS. The 5-year OS was significantly higher in the former group (19 months [7-37]), compared to the latter (13 months [6-26], P = 0.04) (Fig. 1D).

3.3.1. Multivariable Cox proportional hazard model

At multivariable Cox proportional hazard model, the adoption of preoperative URS and biopsy was not a significant predictor of worse oncological outcomes. The Cox proportional hazard model for each time-to-event outcome is reported in Supplementary table 2.

3.4. Decisional role of ureteroscopy

At logistic regression analysis, URS was not associated to a higher likelihood of receiving neoadjuvant therapy (OR 1.08, 95%CI 0.54-2.17). Similarly, the preoperative diagnostic workup did not affect either the choice of the surgical treatment (KSS: OR 0.87, 95%CI 0.63-2.45), or the surgical approach (Robotic: OR 0.74, 95%CI 0.41-1.32; Laparoscopic: OR 1.23, 95%CI 0.51-4.19) (Table 3).

4. Discussion

The evolution of KSS and the integration of neoadjuvant chemotherapy in the management of UTUC underscore the crucial role of URS in the diagnosis, follow-up, and decision-making pathway for this condition [12]. The present study highlights several aspects that could prompt a reassessment of the role of diagnostic URS in the planning of appropriate therapeutic management. We reported a low rate of non-diagnostic biopsies (4.5%), consistent with previous findings. According to a meta-analysis by Subiela et al., the rate of non-diagnostic biopsies varied between 3% (95% CI 0-4) and 8% (95% CI 1-19) on per-patient and per-biopsy specimen analysis, respectively [13]. It could be argued that the low incidence of inconclusive biopsies in the present study may stem from procedures performed by experienced surgeons at high-volume centres. However, it has been observed that biopsy volume does not directly impact its diagnostic performance [14]. Therefore, the standardization of the procedure and strict adherence to protocols for sampling and specimen collection may be of greater importance than the gross pathological features of the specimen itself [15].

The relevance of implementing URS in the diagnostic work-up of UTUC is highlighted by the enhanced diagnostic accuracy of a stage- and grade-based predictive model, compared to the EAU and NCCN risk stratification models, in predicting the presence of localized UTUC and identifying a higher proportion of patients potentially eligible for KSS [16]. Despite this, our results reveal significant differences between the 2 cohorts in terms of the characteristics of candidates for diagnostic URS. The association between a higher ASA score and increased odds of undergoing URS (OR 2.07, 95% CI 1.56-2.75) might be attributed to the pursuit of a more precise diagnosis, aiming to spare more fragile individuals from invasive procedures. On the contrary, patients with tumor ≥2 cm (OR 0.49, 95%CI 0.35-0.68) and ≥cT2 stage (OR 0.33, 95%CI 0.23-0.46) were significantly less likely to undergo diagnostic URS before treatment, and therefore recommended directly for RNU. Indeed, these features impose a more radical surgical treatment in these patients, given the worse prognosis [3]. Nevertheless, emerging evidence on comparable outcomes between RNU and KSS in selected high-risk patients is accruing [17,18], and the actual role of tumor dimensions as a predictor of more aggressive disease remains uncertain.

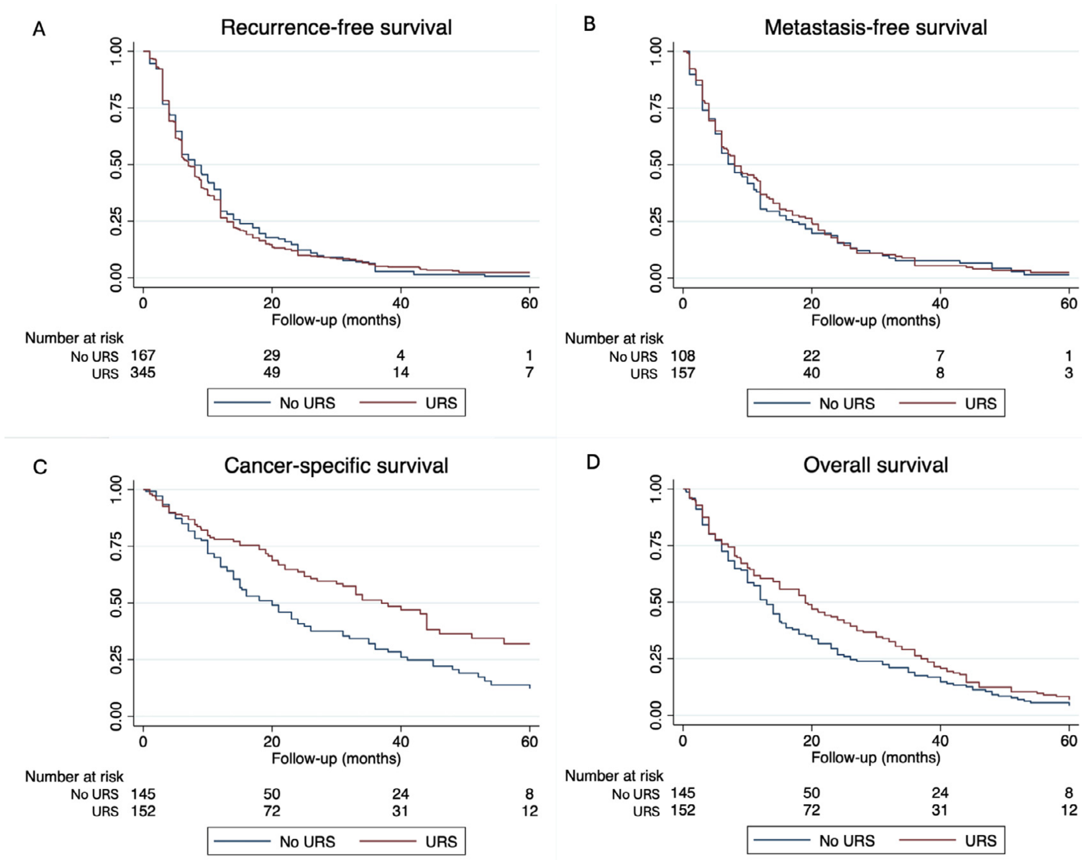

Fig. 1. Kaplan-Meier analysis comparing URS and no URS groups for survival outcomes. A, RFS. B, MFS. C, CSS. D, OS.
Abbreviations: CSS, cancer-specific survival; MFS, metastasis-free survival; OS, overall survival; RFS, recurrence-free survival; URS, ureteroscopy.

In a single-centre retrospective study on 92 patients with UTUC receiving conservative endoscopic treatment, tumor size did not increase the risk of disease progression, in contrast to high tumor grade which decreased progression-free survival [19]. Moreover, the predictive role of tumor size in terms of muscle invasion at RNU final pathology has been contradicted in different studies [20,21]. For determining clinical staging, CT scan has the highest accuracy, compared to other imaging techniques, although some concerns remain, especially regarding the discrimination between non-muscle and muscle-invasive disease [22]. Indeed, while CT is not always able to distinguish between invasive and non-invasive tumors [23], the combination of imaging and URS parameters was effective in predicting a muscle-invasive and non-organ-confined disease in most cases [24]. Therefore, use of both CT and URS with concurrent ureteroscopic biopsy should be included in the preoperative assessment to enhance diagnostic accuracy and patient-centric operative planning.

Table 3
Logistic regression analysis of the decisional role of diagnostic ureteroscopy.

	Ureteroscopy (OR, 95%CI)	*P* value
Type of surgery		
RNU	(ref)	
KSS	0.87 (0.63−.45)	0.2
Surgical technique		
Open	(ref)	
Robotic	0.74 (0.41−1.32)	0.3
Laparoscopic	01.23 (0.51−4.19)	0.2
Neoadjuvant		
No	(ref)	
Yes	1.08 (.54−2.17)	0.8

CI, confidence interval; KSS, kidney-sparing surgery; OR, odds ratio; RNU, radical nephrureterectomy.

We observed no differences in the clinical decision-making process between patients undergoing preoperative URS and those who did not, in terms of use of neoadjuvant therapy and type of definitive extirpative surgery performed. This could be attributed to the high incidence of high-risk UTUC patients in the dataset, resulting in a straightforward treatment pathway leading to RNU in the majority. Yet, Marcq et al. showed that sessile architecture and high-grade histology in preoperative biopsies are independent predictors of more advanced disease. Moreover, Douglawi et al. reported the negative impact of variant histology on oncological outcomes of patients undergoing RNU [25]. Therefore, these factors, accessible only through a biopsy, can enhance the selection of patients eligible for KSS [21]. The primary limitation attributed to diagnostic URS is accurate clinical staging and grading [26]. We observed a concordance of 80.1% in terms of tumor grade between biopsy and final surgical pathology. The evaluation of staging performance and concordance of histologic reports was not possible due to the absence of data on clinical staging at the time of preoperative biopsy. However, it has been observed how clinical staging after biopsy has little value in ruling out invasive disease [26], while the most important predictor is tumor biopsy grade and architecture [27]. Therefore, even if concordance between biopsy and final histology can range from 54.2% to 97%, depending on the reports [13,28], and preoperative biopsy may not represent the entire tumor histology, this procedure can still provide valuable elements that allow to rule out more advanced staged disease.

Indeed, the survival analysis revealed a significantly prolonged OS and CSS among patients who underwent preoperative URS and biopsy. This finding may suggest a more effective treatment selection following the acquisition of biopsy-related information in UTUC patients. On the contrary, we did not observe any difference in terms of RFS, the main drawback attributed to diagnostic URS. However, the literature does not consistently support this aspect, and numerous studies have contradicted the higher risk of local or distant recurrence [29,30]. In a retrospective, multi-institutional study on a cohort of 208 patients undergoing open or minimally invasive RNU, the 2-year bladder RFS rate was 60.0% and 58.7% in patients with and without diagnostic URS, with no significant difference between the 2 groups [31]. Moreover, it has been suggested that the implementation of immediate chemotherapy instillation following URS may reduce intravesical recurrence [32].

The focus of the discussion could be redirected towards the technical aspects of the procedure. Adequate sampling of the lesion is warranted to obtain sufficient tissue for an adequate diagnosis. Indeed, nitinol baskets and backloading biopsy forceps may be more effective in obtaining a truthful diagnosis when compared to other tools with potentially smaller biopsy tissue sampling [33,34]. The accurate diagnostic performance observed in the present study may arise from the experience at the tertiary referral centres in which biopsies were performed. Consequently, it could be speculated, as previously suggested for other urological surgeries [35], that centralizing these procedures within high-volume centres could enhance oncological outcomes.

The present study is not devoid of limitations. First, its retrospective nature carries inherent bias. Discrepancies in diagnostic and surgical techniques may exist given the multi-institutional nature of the dataset and the absence of pre-emptive workflow. Nonetheless, procedures were performed by experienced surgeons at tertiary referral centres, following standardized procedures [36,37], partially mitigating the degree of this potential source of disparity. Given the inclusion of both U.S. and European centres in the study, the recommendation for diagnostic URS may not be uniform due to adherence to different guidelines. The absence of centralized reviews for pathological assessments represents an additional limitation, despite the presence of dedicated uropathologists at each institution involved in this consortium. Tumor stage assessment at preoperative biopsy was not possible due to dataset limitations. Moreover, the inclusion of diverse treatment modalities (RNU and KSS) may introduce selection bias. Nonetheless, the use of multivariable models and a large number of observations enabled us to account for numerous confounding factors, thereby reducing this potential bias to some extent. Indeed, the study benefits from a large sample size of consecutive patients with adequate follow-up. Moreover, it relies on a comprehensive data collection process specifically targeting high-risk UTUC patients, a subgroup of patients at the centre of the current debate in optimizing preoperative risk-stratification and treatment decision-making.

5. Conclusions

Diagnostic URS is a valuable tool in the management of UTUC, aiding in diagnosis and treatment decision-making. The low rate of non-diagnostic biopsies and the high concordance with final pathology support the effectiveness of URS, especially when performed at high-volume centres. An advantage in terms of OS and CSS has been observed in patients undergoing preoperative URS, possibly related to a better selection of candidates for curative surgical treatment with this preoperative workup.

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics Statement

This study was conducted in accordance with the principles of the Declaration of Helsinki. All participants provided informed consent before participating in the study.

Author Contributions

Conception or design of the work: Ditonno, Antonelli, Veccia, Autorino. Acquisition, analysis, or interpretation of data: Antonelli, Autorino, Wu, Abdollah, Simone, Correa, Ferro, De Cobelli, Porpiglia, Perdonà, Margulis, Singla, Derweesh, Gonzalgo, Mehrazin, Rais-Bahrami, Sundaram, Djaladat, Ditonno, Franco, Veccia, Bertolo, Wang, Finati, Tuderti, Helstrom, Amparore, Tufano, Bhanvadia, Broenimann, Puri, Mendiola, Ben-David, Moon, Yong, Moghaddam, Ghoreifi. Drafting of the manuscript: Ditonno. Revising the work critically for important intellectual content: Antonelli, Autorino, Wu, Abdollah, Simone, Correa, Ferro, De Cobelli, Porpiglia, Perdonà, Margulis, Singla, Derweesh, Gonzalgo, Mehrazin, Rais- Bahrami, Sundaram, Djaladat, Ditonno, Franco, Veccia, Bertolo, Wang, Finati, Tuderti, Helstrom, Amparore, Tufano, Bhanvadia, Brönimann, Puri, Mendiola, Ben-David, Moon, Yong, Moghaddam, Ghoreifi. Supervision: Autorino, Antonelli. Final approval of the version to be published: Antonelli, Autorino, Wu, Abdollah, Simone, Correa, Ferro, De Cobelli, Porpiglia, Perdonà, Margulis, Singla, Derweesh, Gonzalgo, Mehrazin, Rais- Bahrami, Sundaram, Djaladat, Ditonno, Franco, Veccia, Bertolo, Wang, Finati, Tuderti, Helstrom, Amparore, Tufano, Bhanvadia, Broenimann, Puri, Mendiola, Ben-David, Moon, Yong, Moghaddam, Ghoreifi. Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved: Antonelli, Autorino, Wu, Abdollah, Simone, Correa, Ferro, De Cobelli, Porpiglia, Perdonà, Margulis, Singla, Derweesh, Gonzalgo, Mehrazin, Rais-Bahrami, Sundaram, Djaladat, Ditonno, Franco, Veccia, Bertolo, Wang, Finati, Tuderti, Helstrom, Amparore, Tufano, Bhanvadia, Broenimann, Puri, Mendiola, Ben-David, Moon, Yong, Moghaddam, Ghoreifi. All authors read and approved the final version of the manuscript.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

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Supplementary materials

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