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Investigating Upper Urinary Tract Urothelial Carcinomas: A single centre 10-year experience

--Manuscript Draft--

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Abstract:	OBJECTIVES Evidence of the accuracy of predictive tests in confirming the presence and grade of upper urinary tract urothelial carcinomas (UUTUC) is limited. We present the largest series evaluating the diagnostic value of pre- and intraoperative parameters in the detection of UUTUC. MATERIALS AND METHODS We retrospectively analysed records of patients who underwent diagnostic ureteroscopy between 2005 and 2014 for suspected UUTUC. Preoperative workup included voided urine cytology and CT imaging. Intra-operative assessments involved ureteroscopy to directly visualise suspicious lesions, and where possible selective cytology and biopsy. Primary outcomes were the visualisation of UUTUC and histopathological confirmation of tumour. RESULTS 100/160 (63%) of patients presenting with suspected upper tract malignancy had UUTUC. Voided and selective urine cytology and CT individually predicted UUTUC with a sensitivity/specificity of 63%/67%, 76%/73% and 95%/26% respectively. 40/48 (83%) of patients who had abnormal CT and abnormal voided urine cytology had UUTUC, while 100% of those with normal CT and normal voided cytology (investigated for ongoing symptoms) were normal. Comparing endoscopic biopsy to nephrouretectomy specimen grade, 19 (46%), 18 (44%), and 4 (10%) were identical, upgraded and downgraded respectively. CONCLUSIONS

	Pre-operative investigations can predict UUTUCs. When these investigations were normal, the risk of UUTUC is negligible. In selective patients with abnormal investigations, ureteroscopy should be performed to confirm and predict the grade of UUTUC, in order to guide future management. Selective cytology is unlikely to signfiicantly contribute to the diagnostic workup of UUTUC.
Response to Reviewers:	Dear Editor, We are grateful to you and the reviewers for your comments on our manuscript, and have addressed all the issues that were raised. We believe the manuscript has been improved as a result, and would like to thank you all for your efforts. Please find attached a file with your comments along with our corresponding reply in blue. We hope that our amendments are found to be satisfactory and look forward to your decision as to whether this manuscript is now ready for publication in the World Journal of Urology. Yours Sincerely, Harveer Dev On behalf of all the authors.

Dear Editor,

We are grateful to you and the reviewers for your comments on our manuscript, and have addressed all the issues that were raised. We believe the manuscript has been improved as a result, and would like to thank you all for your efforts.

Please find attached to each comment below our corresponding reply in blue.

We hope that our amendments are found to be satisfactory and look forward to your decision as to whether this manuscript is now ready for publication in the *World Journal of Urology*.

Yours Sincerely,

Harveer Dev

On behalf of all the authors.

COMMENTS FOR THE AUTHOR:

Reviewer #1: How was chosen group of 186 patients indicated for cytology/ureteroscopy?

We thank the reviewer for their feedback. The study population consisted of 186 consecutive patients who underwent ureteroscopy at our centre between 2005 and 2014. We have clarified the methods to highlight how these patients suspected of malignancy were selected:

"Patients were referred to our urology service with a suspicion of malignancy based on urinary tract symptoms (including haematuria, loin pain, recurrent urinary tract infections). Following initial evaluation with flexible cystoscopy and upper tract imaging, patients were counseled and offered further upper tract assessment with rigid and/or flexible URS if they had abnormal cytology [(n=59, 51%)], abnormal CT [(n=135, 85%)], ongoing haematuria [(n=3, 2%)], or abnormality from ureteric orifice at flexible cystoscopy [(n=2, 1%].

What does mean „for suspected UUUTC"?

Those patients who met the above criteria, as now clarified in the manuscript.

Abnormal CT?

An abnormal CT was defined as one which demonstrated a filling defect in the excretory phase, a visible mass in the region of the pelvis or ureter, a thickening of the ureteric wall, peri-ureteric stranding, hydroureter/hydronephrosis or a ureteric stricture. This has been clarified in the methods.

Why it was indicated?

CT is a routine investigation at our institute with suspected UUTUC; this has been highlighted in the amended manuscript. A non-contrast CT may have been chosen on occasions where renal impairment or contrast allergy restricted the use of a CT

urogram.

Why 26 cases were excluded?
The reasons for the 26 patients excluded has been reiterated in the amended manuscript, and remains in Figure 1.

26 patients were excluded in this study. 3 patients were found to have peri-ureteric deposits which were investigated by upper tract imaging and ureteroscopy, but which actually resulted from a secondary pancreatic metastasis, local invasion from a large bowel malignancy, and a renal cell carcinoma. As these were not transitional cell upper urinary tract malignancies we did not seek to skew our data by including their findings as part of our evaluation.

To clarify, the remaining 23 patients have been described as unclear or unknown ureteroscopy reports, in which the findings of the ureteroscopy and intraoperative diagnosis could not be confidently ascertained from the clinical notes. We have highlighted the limitations of such retrospective analysis and hence reiterate the need for future prospective studies which can further improve the confidence of our results.

What type of ureteroscopy - semirigid, flexible?
We have access to semirigid and flexible ureteroscopes. We usually start with semirigid URS to inspect the distal and mid ureter. The flexible URS can then be used to check the proximal ureter, renal pelvis and collecting system.

Page 3 paragraph the last but tow: (2) hydronephrosis - megaureter is probably better term, because no only pelvis is dilated, but mostly ureter as well
We agree and have amended the description to “hydronephrosis/hydroureter”.

Can we really express specificity, if you include to the study only cases with any abnormal finding?
The reviewer highlights an important consideration, which is the need to clarify the population to which the sensitivity and specificity figures refer. While the specificity often describes the proportion of non-diseased individuals correctly identified within the entire population, the findings of our study are of far greater clinical utility to urological practitioners. In fact the goal was to check if clinical or radiological suspicion is enough to subject a patient to a major surgery in the form of radical nephroureterectomy
The patient population that we have studied and obtained specificities and sensitivities for are precisely those at-risk patients who we will be considering to evaluate further. While the statistics would not be applicable to the general population at large, they should be relevant to any patient in whom UUTUC is clinically and/or radiologically suspected (based on the criteria described above). In this way we feel the statistics are more relevant and practicably applicable to the urological community.

Conclusion: It is very difficult to follow study step-by-step. There are too many questions to scheme of study. I don't find clear understandable conclusion important for clinical practise.

This is an exploratory study evaluating the investigations needed to confirm or exclude UUTUC, hence we have looked at several variables in order to evaluate this important and complex topic. In addressing the points raised by the reviewer, and amending the manuscript, we hope we have further clarified our comprehensive evaluation for investigating suspected UUTUC.

Reviewer #2: Authors have done retrospective analysis of 160 cases of suspected upper urinary tract urothelial carcinoma (UUTUC) at a single center. 100/160 (63%) patient had UUTUC; diagnoses was based on cytology and CT scan findings. Those patients neither had abnormality in cytology in voiding urine specimen and also in CT evaluation did not have UUTUC.
I have few questions.
1. Title is "Can we predict the presence and grade of upper urinary tract urothelial carcinoma ?" Authors have not taken etiological factors in account (e.g. history of analgesic abuse).
We thank the reviewer for the feedback. The reviewer is correct that we were unable to include a comprehensive list of associated risk factors into our analysis, with the important exception of previous bladder TCC. While we establish exposure to smoking, pelvic irradiation, excess analgesics, cyclophophasmides certain chemicals/dyes as part of the patient's general risk assessment, it was not possible to include all of these parameters in this evaluation. The use of larger scale epidemiological studies would have the necessary power to draw the conclusions of these associations with the presence of UUTUC. We feel that their exclusion from this study would not impact upon the results of detection rates of UUTUC by CT and URS. However we have nevertheless reiterated this limitation in the discussion. We also feel that the reviewer has highlighted an important improvement in the title of our study, and would therefore suggest the amendment which has been made in the manuscript.

2. Table-1 shows associated history of bladder TCC in 28%, 45% and 39% of benign, malignant and total number of patients respectively. It is important to know the grade of bladder tumor and associated carcinoma in situ. Was the high grade bladder tumor associated with UUTUC? In other words, is high grade bladder urothelial tumor predictive of UUTUC?
We do have some data (below) which supports the general conclusion that higher grade bladder TCCs are associated with UUTUCs. There is a general trend towards differing distributions within the categories of bladder TCC ($\chi 2=10.53$, $p=0.062$): 18% and 33% of patients with an absence or presence of a UUTUC respectively, having a history of CIS, Grade 2 or Grade 3 TCC of the bladder. Furthermore multinomial logistic regression analysis for bladder TCC (relative to the absence of any such history), revealed, as expected, a significantly lower incidence of Grade 2 disease in patients without a UUTUC compared to those with identified UUTUC ($Exp(B)=0.256$, $p=0.040$).

However given the *post-hoc* nature of this subgroup analysis which on balance is underpowered to reveal the true extent of this relationship, we are more confident in describing the general trend of a higher proportion of bladder TCC in our UUTUC cohort, and have as such only described and included this first table of data.

			UUTUC investigation findings		
			Benign	Malignant	Total
Bladder TCC	No previous Bladder TCC	Count	43	55	98
		% within UUTUC	71.7%	55.0%	61.3%
	G1	Count	4	6	10
		% within UUTUC	6.7%	6.0%	6.3%
	G2	Count	3	15	18
		% within UUTUC	5.0%	15.0%	11.3%
	G3	Count	6	18	24
		% within UUTUC	10.0%	18.0%	15.0%
	CIS	Count	2	0	2
		% within UUTUC	3.3%	0.0%	1.3%
	Unknown	Count	2	6	8
		% within UUTUC	3.3%	6.0%	5.0%
Total		Count	60	100	160
		% within UUTUC	100.0%	100.0%	100.0%

Multinomial Logistic Regression analysis parameter estimates

Bladder TCC[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
G1	Intercept	-2.216	.430	26.556	1	.000			
	Ben vs. Mal	-.159	.677	.055	1	.814	.853	.226	3.213
G2	Intercept	-1.299	.291	19.896	1	.000			
	Ben vs. Mal	-1.363	.664	4.210	1	.040	.256	.070	.941
G3	Intercept	-1.117	.272	16.920	1	.000			
	Ben vs. Mal	-.852	.513	2.756	1	.097	.426	.156	1.166

a. The reference category is: No bladder TCC.

3. What definition was accepted to diagnose "Thickening" of ureteric wall?
The radiologists typically identified an increase in the size of the ureter as being a relative finding to the contralateral ureter, although no precise threshold has been established.

4. Table-4 shows two different value of negative biopsy of ureteroscopy (10

out of 75 and 11/75). It needs correction.
This has been amended.

5. Did you use narrow band imaging or other methodology during cystoscopy and ureteroscopy? Do you think it would have improve further the diagnostic yield over combined use of cytology and radiology only?
Narrow-band imaging is becoming of increasing interest, as an active area of research in the diagnosis bladder TCCs, although its general utility has not been widely adopted and applicability to upper tract TCCs is less well documented. We did not employ the technique for our patients included in this study, although we have highlighted the technique as an important additional consideration for future studies which seek to address this issue.

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Contributions:

Protocol/project development:	Wisman, Hayek
Data collection or management	Dev, Poo, Armitage, Wiseman, Hayek
Data analysis	Dev, Poo
Manuscript writing/editing.	Dev, Poo, Armitage, Wiseman, Hayek

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INTRODUCTION

Upper urinary tract urothelial carcinoma (UUTUC) is a rare malignancy, accounting for 5% of all urothelial cancers (Siegel et al 2014). Few useful prognostic factors have been established, and the 5-year specific survival remains low, at less than 50% for pT2 and pT3 disease, and less than 10% for pT4 disease (Jeldres et al 2010).

Radical nephroureterectomy (RNU) with excision of a bladder cuff remains the gold standard treatment for UUTUC, regardless of the location of the tumour in the upper urinary tract (Margulis et al 2009); however improvements in endoscopic techniques have led to increasing number of patients being managed endoscopically.

The natural history of UUTUC is still poorly understood, and accurate risk stratification remains elusive. Attempts have been made to incorporate clinical and pre-operative parameters into risk stratification tools (Chitale et al 2008; Williams et al 2008), which included urine cytology and imaging studies such as Multi-Detector Computed Tomography Urography (MDCTU or CT) (Dillman et al 2008). This is in addition to ureteroscopic findings, which have shown to be important in identifying and predicting the progression of UUTUC (Chen et al 2000). Early diagnosis is crucial to tailor individualised management plans and improve outcomes, and delays between diagnosis and surgery have shown to have negative implications on disease recurrence and cancer-specific mortality (J N Lee et al 2014).

Our study evaluates the diagnostic and prognostic value of the pre-operative and intra-operative parameters utilised in the investigation of UUTUC.

PATIENTS AND METHODS

Study Population: We retrospectively analysed consecutive patients who underwent ureteroscopy (URS) at a single centre between January 2005 and March 2014. Patients were referred to our urology service with a suspicion of malignancy based on urinary tract symptoms (including haematuria, loin pain, recurrent urinary tract infections). Following initial evaluation with flexible cystoscopy and upper tract imaging, patients were counselled and offered further upper tract assessment with rigid and/or flexible URS if they had abnormal cytology, abnormal CT, ongoing haematuria, or abnormality from ureteric orifice at flexible cystoscopy. The diagnosis of UUTUC was based on the presence of distinct papillary or solid tumours observed on URS, and where available, histopathology results from ureteroscopic biopsies and nephroureterectomy specimens. The medical charts, radiological, cytological and pathological reports for all patients were independently reviewed by two authors (HD and SP). The clinico-pathological parameters collected were: gender; age and clinical presentations at diagnosis; previous history of bladder cancer; and patient treatment (endoscopic, radical surgery or palliation). 26 patients were excluded due to other malignancies or incomplete information (Figure 1).

Pre-operative investigations: Both pre-operative ‘voided’ and intra-operative ‘selective’ cytology reports were assessed. Selective cytology was obtained during ureteroscopic washings of the renal pelvis and/or ureters. Cytology samples were classified as negative, atypical, and positive. Positive cytology was used when a high proportion of cells carried a high index of suspicion for malignant UUTUC, possessing exceedingly abnormal morphology. Atypical cytology was defined by the presence of a few abnormal cells, insufficient to exclude malignancy. CT reports were obtained prior to URS and three main outcomes were evaluated: the presence or absence of (1) a filling defect or a soft tissue mass; (2) hydronephrosis/hydroureter; and (3) thickening of the ureteric wall. As such, an abnormal CT was defined as one which demonstrated a filling defect in the excretory phase, a visible mass in the region of the pelvis or ureter; hydroureter/hydronephrosis or a ureteric stricture; a thickening of the ureteric wall with or without peri-ureteric stranding.

For each of these variables, the sensitivities and specificities were calculated, with respect to the presence of UUTUC, and for nephroureterectomy specimens with respect to tumour invasiveness.

Histopathological assessment: All biopsies and histopathological specimens were reviewed by our institution's histopathologists, based on 2004 World Health Organisation's (WHO) and International Society of Uropathologists (ISUP) grading system (Jones and Cheng 2006, J.N. Eble et al 2004). PUNLMP, grade 1 and 2 were defined as low-grade, while Grade 3 was classified as high-grade disease. Pathology stage was used as a marker of tumour invasiveness, with invasive tumours defined as pT1 and above.

Statistical Analysis: We performed Pearson's Chi-squared tests to evaluate the relationship between pre-operative variables, and intra-operative variables, and calculated the sensitivities and specificities. We also conducted two separate multivariable regression analyses and calculated the corresponding Area Under the Curve. All results were two-sided and deemed statistically significant if the p value < 0.05. Statistical analyses were performed using IBM SPSS Statistics for Windows®, Version 22.0. Armonk, NY: IBM Corp.

RESULTS

Patients: Out of 186 patients who underwent diagnostic URS, 160 patients were included in the analysis (Figure 1). The patient characteristics, demographics and presenting symptoms were outlined in Table 1. Patients underwent diagnostic URS (rigid +/- flexible) if they had abnormal cytology (n=59, 51%), abnormal CT (n=135, 85%), ongoing haematuria (n=3, 2%), or abnormality from ureteric orifice at flexible cystoscopy (n=2, 1%). The proportion of patients who underwent each diagnostic investigation is shown in Supplemental Figure 1.

100 (63%) patients had UUTUC confirmed at URS and/or after nephroureterectomy (Figure 1). Malignancy was defined by the presence of UUTUC when directly visualised, and where available, from biopsies taken endoscopically and/or confirmed after nephroureterectomy.

There was a general trend towards differing rates of previous bladder TCC between the benign cohort and those found to have an UUTUC ($\chi2=10.53$, $p=0.062$). 33% and 18% of patients with or without an UUTUC had a prior history of CIS, Grade 2 or Grade 3 TCC of the bladder (see Supplemental Table 1).

Pre-operative investigations: Voided urine cytology was obtained in 116 (73%) patients; of which, 57 (49%) were negative, 31 (27%) were atypical and 28 (24%) were positive (Supplemental Figure 2a). Abnormal (i.e. atypical or positive) voided urine cytology predicted the presence of UUTUC ($\chi2=10.165$, $p=0.006$) with a sensitivity and specificity of 63% and 67% respectively, and predicted tumour invasiveness ($\chi2=6.67$, $p=0.048$). Figure 2 shows the proportions of each voided cytology parameter relative to the final histopathological grade. Voided urine cytology was able to predict G2 and G3 disease on final histopathological specimens at 43% and 80% sensitivities respectively. In addition, voided urine cytology was also able to significantly predict selective cytology obtained endoscopically (Supplemental Figure 2c), with only 10 extra malignancies being identified by selective ureteroscopic washings. Of note, all of these 10 additional patients also had abnormalities on CT (8 with filling defects or mass, 1 with ureteric thickening and 1 with hydronephrosis/hydroureter).

All 160 patients who underwent a URS had a CT, which identified a filling defect or mass in 100 (63%) cases. The proportions of each parameter identified on CT imaging, and their respective ability to predict UUTUC is summarised in Table 2. Abnormal CT predicted UUTUC with a sensitivity of 95% and specificity of 26% (Table 2), however CT findings were unable to predict tumour invasiveness (data not shown). Of the three CT parameters (filling defect or mass, ureteric thickening or hydronephrosis/hydroureter) evaluated individually, a filling defect or soft tissue mass detected on CT was the only significant predictor of malignant status ($\chi2=15.213$, $p<0.001$). Five (25%) patients with normal CTs had UUTUC identified on URS, while 15 (75%) with normal CTs were correctly confirmed after URS; 42 (31%) patients with abnormalities on CT had a normal URS.

UUTUC was detected in 33/39 (85%) patients who had filling defects or mass reported on CT together with abnormal voided urine cytology (17/20 with positive cytology, and 16/19 with atypical cytology) (Table 3). Similarly 47/55 (85%) patients were identified with UUTUC having had filling defects or mass on CT and abnormal selective cytology.

Eight (17%) patients with positive voided cytology and abnormality on CT demonstrated a benign histology; six (75%) of these had an identifiable filling defect or mass on CT.

Selective Cytology: Selective cytology was obtained during URS in 126 (79%) patients; where 55 (44%), 27 (21%), and 44 (35%) were reported as negative, atypical and positive respectively. Selective cytology predicted UUTUC ($\chi2=30.866$, $p<0.001$) with a sensitivity and specificity of 76% and 73% respectively, in addition to predicting tumour invasiveness ($\chi2=8.608$, $p=0.197$) (Supplemental Figure 2b). Figure 2 shows the proportions of each selective cytology outcome relative to the final grade from nephroureterectomy specimens. The prognostic ability of selective cytology was only marginally better than pre-operative voided cytology. In G2 and G3 nephroureterectomy specimens, the respective sensitivities for selective cytology, was 65% and 96% compared with 43% and 80% for voided urine cytology (data not shown).

Of those with available selective cytology results and subtle CT findings (hydronephrosis/hydroureter or ureteric thickening only) (Table 2): 8 had a benign outcome (with 2 abnormal and 6 negative selective cytology results); 8 had a malignant outcome (4 abnormal and 4 negative selective cytology results).

Ureteroscopic biopsy: Table 4 shows the histopathology from ureteroscopic biopsies and post-nephroureterectomy specimens, stratified according to grade and stage. Of 75 ureteroscopic biopsies that were taken, 65 (87%) had UUTUC present. Of 59 gradable specimens, 38 (64%) were low grade, while 21 (36%) were high grade disease; 34 (64%) tumours were invasive, and 19 (36%) were non-invasive. 55 out of 57 (96%) nephroureterectomy specimens were identified as malignant; 2 (3%) final cases had previously identified malignancy on URS, where the tumour was likely sufficiently removed by biopsy or diathermy rendering the final post-nephrouretectomy histopathological diagnosis as benign.

Ureteroscopic biopsy positively correlated with nephrouretectomy specimen in terms of grade ($\chi2 = 19.793$, $p=0.071$) and stage ($\chi2=19.950$, $p=0.336$) (Figure 3). Nineteen (43%) and 12 (32%) biopsies matched the grade and stage of nephroureterectomy specimens. As expected, the proportion of biopsies that were up-graded and up-staged was higher than those down-graded and down-staged (Figure 3). 7 cases of 41 cases which could be analysed, were upgraded to G2 or G3 disease (data not shown).

Multivariable analysis of pre-operative and Intra-operative variables: Pre-operatively, male gender, age, voided urine cytology, and the presence of filling defect or mass on CT imaging were shown to be robust independent predictive factors of UUTUC, with the latter demonstrating the highest hazard ratios of 11.7 (Table 5); AUC 0.816 (95% CI: 0.73-0.90). Ureteric thickening and hydronephrosis/hydroureter on CT were not significant independent predictors of UUTUC.

DISCUSSION

Our results confirm that, pre-operatively, voided urine cytology and the presence of filling defect or mass on CT are important positive finginds in the investigation of suspected UUTUC. In addition to gender and age, they were able to independently predict the presence of UUTUC.

There were high false positive rates particularly from CT investigations and non-specific findings of hydronephrosis/hydroureter and ureteric thickening. Specifically, these findings on CT were not able to significantly predict the presence of tumour compared to the conclusions of another study (Brien et al 2010). The combined sensitivity of voided urine cytology and CT of 85% demands the use of URS to correctly identify patients with UUTUC. In contrast, since 100% of those with both a normal CT and normal voided cytology had

benign findings on URS (Table 3), we would propose that with clinical judgment such patients, individually risk-stratified, would not require URS in the presence of persisting symptoms. Clearly equivocal results in either modality may necessitate further investigation.

A limited analysis of 6/39 (15%) benign cases after URS, had demonstrated measurable mass or filling defects on CT. While the presence of a measurable mass is more indicative of malignancy (approximately 2:1 incidence rates in malignant and benign pathology respectively – data not shown), we were unable to identify a cut-off size of a mass on CT that would be able to discern between benign and malignant findings.

As expected, voided urine cytology correlated well with selective cytology, although multivariate analysis suggests that selective cytology has statistically superior predictive capability. However, in terms of clinical utility, when directly compared to selective cytology this only identified 10 additional malignant cases over voided cytology. We found 85% of patients with both abnormal CT and abnormal voided cytology had an UUTUC. The same proportion (85%) was identified in those with abnormal CT and abnormal selective cytology. Indeed, our results suggest that the addition of selective cytology provides only marginal additional value. Furthermore, the combination of an abnormal selective cytology with subtle CT findings (thickening or hydronephrosis/hydroureter alone) was not sufficient to predict the presence of UUTUC, and direct visual observation and/or confirmation with biopsy was critical in determining clinical need for nephrouretectomy in these cases.

Previous descriptions have been made correlating histology of ureteroscopic biopsies with nephroureterectomy specimens but these have been limited by small case numbers (Chitale et al 2008). We present the largest such series, and demonstrate that biopsies do correlate with high grade disease, and relatively few cases require upgrading, which may reflect more systematic technical approaches to the biopsying of tumours.

In the absence of sufficient staging data, we attempted to identify the predictive capacity of a high grade biopsy to predict UUTUC invasiveness; however after multivariate analysis a high grade biopsy was unable to predict UUTUC invasiveness in our series. Smith and colleagues (Smith et al 2011) suggested that biopsy grade may still be subject to a non-negligible rate of sampling error, particularly with larger tumours, which may in part, explain these results. It is possible that employing narrow-band imaging technology, better characterized for the diagnosis of bladder TCC, may still further improve the identification and biopsy of suspected UUTUC, and this will be an important variable to consider in future studies as these ureteroscopes become more widely available.

The study is limited by variations between reporting radiologist and histopathologists, although all followed standard protocols employed at our institution, and undergo robust quality control measures. Visualisation of lesions was used to define the presence of malignancy in some cases, and although this was restricted to clear papillary lesions, there is an inherent limitation when a biopsy is not taken. The study data is also from a single institution, with retrospective data collection, and lacked a comprehensive account of potential aetiological risk factors for each patient. Future work could benefit from prospective data collection, standardised reporting on URS and pathological specimens, and multi-institutional data collection, to further improve statistical power and clinical applicability.

CONCLUSION

Our study represents the largest series in the UK to evaluate and quantify the predictive capabilities of the pre-operative and intra-operative parameters in the diagnosis of UUTUC. We support the strategy whereby voided urine cytology and CT are useful as screening tools to identify at-risk patients. When abnormalities were detected in both preoperative voided cytology and CT, malignancy was confirmed in 85% cases. URS is imperative in identifying benign cases, particularly when the CT findings represent the only abnormal

preoperative investigation. In the presence of a normal CT and voided urine cytology, we propose that a clinical judgment can be made for not performing a URS, provided that individual patient risk factors are also taken into account.

Selective urine cytology does not appear to clinically improve the prediction of UUTUC. However, URS and biopsy remains a valuable confirmatory tool for diagnosis, therapy and guiding surgical management. Our results provide quantitation of the current diagnostic tools utilized in clinical practice, and in combination with multi-institutional datasets could contribute towards more robust tools of risk stratification.

The ethical responsibilities from the World Journal of Urology website have been fulfilled.

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Contributions:

Protocol/project development: Wiseman, Hayek

Data collection or management: Dev, Poo, Armitage, Wiseman, Hayek

Data analysis: Dev, Poo

Manuscript writing/editing: Dev, Poo, Armitage, Wiseman, Hayek

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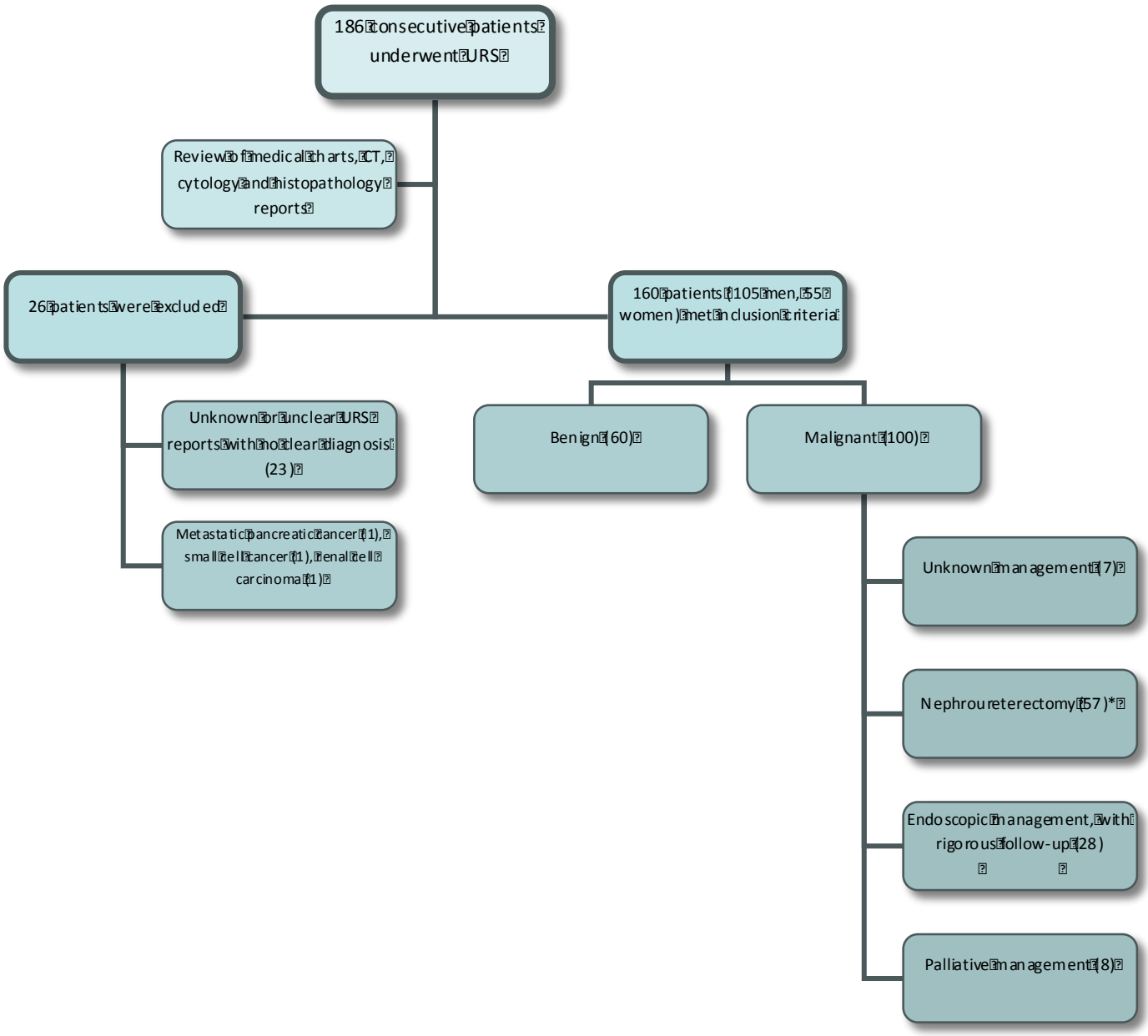
Tables and Figures

Figure 1: **Patient selection criteria**



*2 of which were later confirmed to be benign on final histopathological analysis of nephroureterectomy specimens.

Table 1: Patient demographics and characteristics

Variable	**Benign** (%)	**Malignant** (%)	**Total** (%)
Total	**60** (100)	**100** (100)	**160** (100)
Male	**33** (55)	**72** (72)*	**105** (66)
Female	**27** (45)*	**28** (28)	**55** (34)
Median Age at presentation (IQR)	**66** (50-76)	**73** (66-81)	**71** (61-78)
Presenting Symptoms			
Haematuria	**36** (60)	**56** (56)	**92** (58)
UTI/loin pain	**14** (23)	**12** (12)	**26** (16)
Associated History of Bladder TCC	**17** (28)	**45** (45)*	**62** (39)
Affected Side			
Right	**20** (33)	**38** (37)	**58** (36)
Left	**27** (45)	**55** (55)	**82** (51)
Bilateral	**13** (22)	**7** (7)	**20** (13)

Key: (*) denotes statistical significance (p <0.05)

Figure 2: **Distribution of voided and selective urine cytology results according to nephroureterectomy specimen grade**

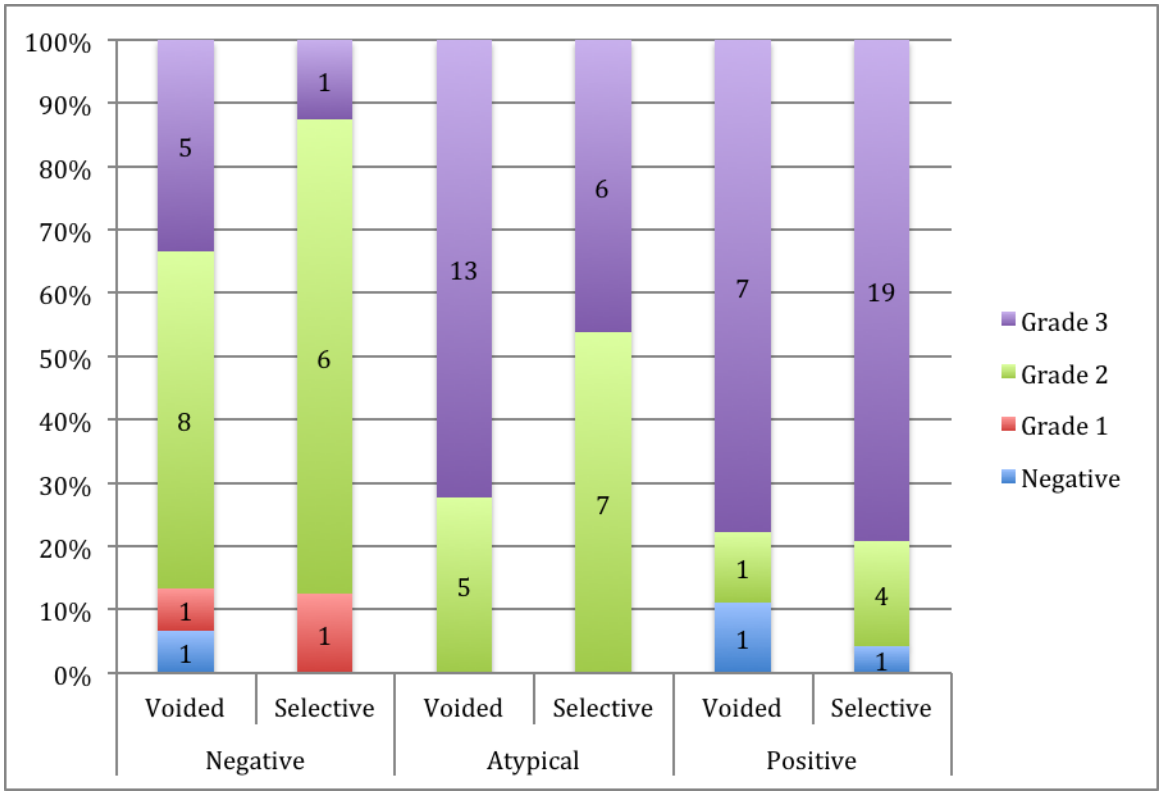


Table 2: **CT findings and prediction of UUTUC.**

CT	**Malignant status (%)**		
	Benign	Malignant	Total
Normal	**15 (75)***	**5 (25)***	**20**
Abnormal	**42 (31)***	**93 (69)***	**135**
• Hydronephrosis/hydroureter	16 (29)	39 (71)	55
• Ureteric thickening	12 (35)	22 (65)	34
• Filling Defect or Soft Tissue Mass	28 (28)*	72 (72)*	100
Total			**155**
Single findings on CT urogram:	Benign	Malignant	Total
Hydronephrosis	8 (47)	9 (53)	**17**
Thickening	5 (56)	4 (44)	**9**
Filling Defect or Soft Tissue Mass	12 (24)*	37 (76)*	**49**

Key: Malignant status is determined by the presence of UUTUC observed on URS, and/or histologically defined from biopsies taken endoscopically or following nephroureterectomy. CT reports were available in 155 out of 160 patients. The term "abnormal" refers to the detection of filling defect or soft tissue mass, hydronephrosis/hydroureter or ureteric thickening on CT. Percentages of row totals are denoted in brackets. (*) denotes a statistically significant difference between columns.

Table 3: Correlations between CT imaging and cytological findings

	Voided Urine Cytology (%)				**Selective Urine Cytology (%)**			
	Negative		**Atypical or Positive**		**Negative**		**Atypical or Positive**	
CT	Benign	Malignant	Benign	Malignant	Benign	Malignant	Benign	Malignant
Normal	5 (100)	0 (0)	5 (71)	2 (29)	10 (100)	0 (0)	4 (80)	1 (20)
Relevant Pathology	9 (56)	7 (44)	2 (22)	7 (78)	6 (50)	6 (50)	2 (20)	8 (80)
Filling Defect/Mass	19 (53)	17 (47)	6 (15)	33 (85)	19 (61)	12 (39)	8 (15)	47 (85)

Table 4: Distribution of ureteroscopic biopsy and post-nephroureterectomy specimen histopathology, stratified according to tumour grade and stage

Variable		Ureteroscopic biopsies (%)	Nephroureterectomy specimens (%)
Total		**75**	**57**
	Negative	10 (12)	2 (4)
	UUTUC	65 (87)	55 (96)
Grade			
Total		**75**	**57**
	Negative	11 (15)	2 (4)
	UUTUC NOS[+]	5 (7)	4 (7)
	G1	8 (11)	1 (2)
	G2	30 (40)	19 (33)
	G3	21 (28)	31 (54)
Stage			
Total		**67**	**55**
	Negative	11 (16)	-
	UUTUC NOS[+]	2 (3)	2 (4)
	pTa	45 (67)	15 (27)
	pTis	-	4 (7)
	pT1	6 (9)	9 (16)
	pT2	3 (4)	5 (9)
	pT3	-	17 (31)
	pT4	-	3 (6)

Key: [+]UUTUC NOS denotes malignant UUTUC not otherwise specified.

Figure 3: Comparison of ureteroscopic biopsy and post-operative nephroureterectomy specimen grade (left) and stage (right)

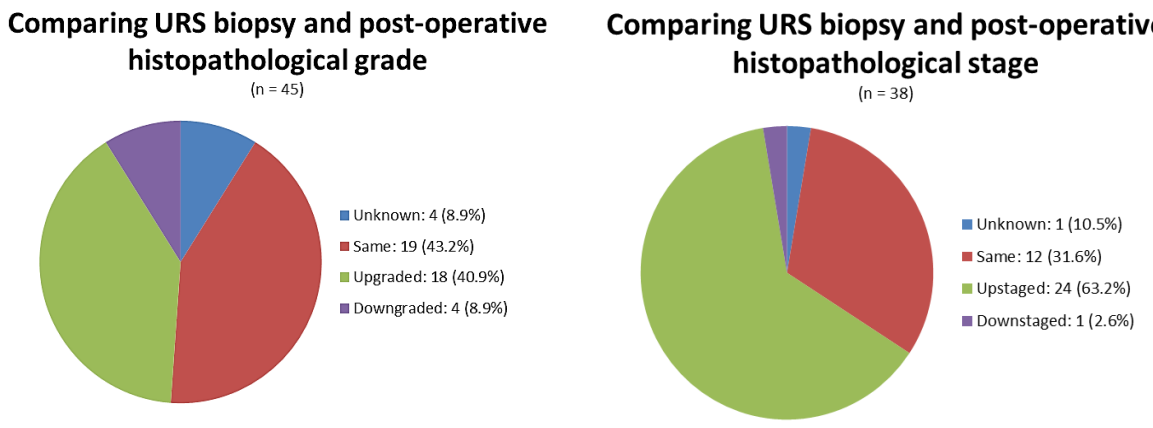


Table 5: Multivariable regression analysis of pre-operative variables predicting the presence of UUTUC

Variable	Exp(B)	95% CI	p-value
Preoperative factors			
Male vs. Female (Ref)	3.025	1.080-8.474	0.035
Age	1.060	1.019-1.102	0.004
Preoperative Urine Cytology			
Negative (Ref)			0.018
Atypical	4.980	1.518-16.331	0.008
Positive	2.557	0.843-10.663	0.090
CT			
Normal (Ref)			0.014
Hydronephrosis/hydroureter or ureteric thickening	6.643	0.890-49.571	0.065
Filling defect/soft tissue mass	11.675	1.819-71.817	0.009

Amended Supplementary Material