Diagnostic evaluation of upper tract urothelial carcinoma

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Diagnostic evaluation of upper tract urothelial carcinoma: can we safely omit diagnostic ureteroscopy?

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Abstract

Objective

To identify clinicopathological or radiological factors that may predict a diagnosis of upper urinary tract urothelial cell carcinoma (UTUC) to inform which patients can proceed directly to radical nephroureterectomy (RNU) without the delay for diagnostic ureteroscopy (URS).

Patients and Methods

All consecutive patients investigated for suspected UTUC in a high-volume UK centre between 2011 and 2017 were identified through retrospective analysis of surgical logbooks and a prospectively-maintained pathology database. Details on clinical presentation, radiological findings, and URS/RNU histopathology results were evaluated. Multivariate regression analysis was performed to evaluate predictors of a final diagnosis of UTUC.

Results

In all, 260 patients were investigated of whom 230 (89.2%) underwent URS. RNU was performed in 131 (50.4%) patients, of whom 25 (9.6%) proceeded directly without URS – all of whom had a final histopathological diagnosis of UTUC - and 15 (11.5%) underwent RNU after URS despite no conclusive histopathological confirmation of UTUC. Major surgery was avoided in 77 patients (33.5%) where a benign or alternative diagnosis was made on URS, and 14 (6.1%) patients underwent nephron-sparing surgery.

Overall, 178 (68.5%) patients had a final diagnosis of UTUC confirmed on URS/RNU histopathology. On multivariate logistic regression analysis, a presenting complaint of visible haematuria (Hazard Ratio (HR) 5.17, Confidence Interval (CI)=1.91-14.0, p=0.001), a solid lesion reported on imaging (HR 37.8, CI=11.7-122.1, p=<0.001) and a history of smoking (HR

3.07, CI=1.35-6.97, p=0.007), were predictive of a final diagnosis of UTUC. From this cohort, 51 (96.2%) of 53 smokers who presented with visible haematuria and who had a solid lesion on CTU had UTUC on final histopathology.

Conclusion

We identified specific factors which may assist clinicians in selecting which patients may reliably proceed to RNU without the delay of diagnostic URS. These findings may inform a prospective multicentre analysis including additional variables such as urinary cytology.

Introduction

Upper urinary tract urothelial cell carcinoma (UTUC) accounts for around 5% of urothelial malignancies and carries an estimated incidence of two per 100 000 inhabitants in Western populations [1]. Patients may present symptomatically with visible haematuria (VH) or loin pain or loin pain; however, the rate of asymptomatic incidental radiological detection has risen in recent years with advances in diagnostic technology [2].

In contrast to the streamlined pathways utilised in the management of muscle-invasive bladder cancer (MIBC), when it is accepted that a delay in radical treatment which exceeds twelve weeks from initial diagnosis is associated with higher mortality [3], the diagnostic pathway in UTUC is often more convoluted. This may involve numerous multidisciplinary team (MDT) discussions and, in some cases, diagnostic ureteroscopy (URS) to confirm or exclude the diagnosis after suspicion on initial imaging. Each step in the diagnostic pathway has potential to cause delay and runs the potential risk of tumour upstaging. Furthermore, in the COVID-19 era, access to hospital services is more limited and, thus, any measures which preclude the need for further procedures are very valuable. To optimise oncological outcomes, it is imperative for patients with suspected UTUC to progress efficiently through the diagnostic pathway to facilitate early definitive surgical management. Radical nephroureterectomy (RNU) remains the gold-standard radical treatment for high-risk (high grade or ≥pT1) organ-confined UTUC; however, nephron-sparing surgery (NSS) has a role in patients with low-risk disease and those with solitary kidneys or renal impairment [4]. The disease is considered more aggressive than bladder cancer [5] and tumour stage and grade are the primary prognostic predictors, in addition to patient performance status.

Approximately two thirds of cases present with muscle-invasive disease, and this carries a poor prognosis with a 5-year disease-specific survival (DSS) of <50% [6].

The European Association of Urology (EAU) [4] recommends that all patients with suspected UTUC undergo a comprehensive diagnostic workup including CT urography (CTU) and cystoscopy as 17% of patients have a concomitant bladder tumour [7] and up to 47% will develop bladder cancer [8]. Cytology may aid diagnosis in selected cases of high grade UTUC although it is less sensitive for detection of UTUC than bladder cancer [4,9]. Diagnostic URS, which permits thorough visualisation of the upper urinary tract, is recommended when diagnostic uncertainty exists or when patients are candidates for NSS [4]. It is considered a safe procedure [10]; however, it may be associated with intravesical recurrence [11,12] and can potentially contribute to significant delay in the diagnostic pathway that may negatively impact overall survival (OS) [13,14,15]. Thus, it has been suggested that diagnostic URS should not be performed in all patients [16].

We aimed to identify specific clinicopathological or radiological factors that are reliably predictive of a final diagnosis of UTUC, to select which patients can safely proceed to primary radical surgery without the need for prior diagnostic URS.

Patients and Methods

Study population

A retrospective analysis of a prospectively-collected histopathology database at the Western General Hospital, Edinburgh was undertaken to identify all consecutive patients who underwent diagnostic URS with biopsy or RNU for suspected UTUC between July 2011 and August 2017. To identify patients in whom diagnostic URS was performed without tissue

biopsy, operation notes for all patients who underwent diagnostic URS, after radiological imaging which raised suspicion of UTUC, were also reviewed retrospectively. We included only patients with a suspected primary diagnosis of UTUC and so patients with a history of endoscopic management of UTUC (surveillance imaging or therapeutic URS for known UTUC) were excluded from the analysis.

Data acquisition

Baseline patient demographics and details on clinical presentation, risk factors and the initial radiological report were identified through retrospective review of electronic patient records and paper case files.

Statistical analysis

Differences in baseline characteristics and the various patient-specific clinicopathological or radiological variables between those with a final diagnosis of UTUC, and those with alternative diagnoses or negative investigations, were made using the independent samples t-test and χ^2 tests as appropriate. Association between CT description and tumour stage and grade on final RNU specimen was evaluated using the Pearson correlation coefficient. Univariate and multivariate logistic regression analysis were performed to identify if patient demographic, clinicopathological or radiological covariates that were independently predictive of a definitive histological diagnosis of UTUC. With all tests, a two-sided p-value of <0.05 was considered statistically significant. All statistical analyses were performed using the software Statistical Package for the Social Sciences (SPSS) for Windows (IBM Corp, Armonk, NY, USA).

Results

Between July 2011 and August 2017, 260 patients were investigated following radiological imaging which raised suspicion of UTUC. All radiological imaging had been reviewed by a specialist Uro-Radiologist in a MDT meeting, prior to diagnostic URS biopsy or RNU. All subsequent biopsies were double-reported by specialist Uro-Pathologists and all RNU specimens reviewed prior to further MDT discussion. The varying outcomes for these patients are illustrated in Figure 1. Following URS biopsy or RNU, 178 patients (68.5%) had a final histopathological diagnosis of UTUC. There was a significant difference in time from diagnosis to nephroureterectomy in those patients who underwent diagnostic ureteroscopy compared to those who did not (median 135 days and 90 days respectively, $p<0.001$).

Diagnostic URS was undertaken in 230 patients (88.5%). From this cohort, major surgery was avoided in 77 patients (33.5%) when a benign or alternative diagnosis was made, for example ureteric endometriosis or a metastatic prostate cancer or breast cancer lesion, and 14 patients (6.1%) underwent NSS.

In all, RNU was performed in 131 patients (50.4%), of whom 25 (19.1%) proceeded directly to RNU without diagnostic URS – all 25 of whom had UTUC on final histopathology. Furthermore, 15 patients (11.5%) proceeded to RNU after URS despite no conclusive histopathological confirmation of UTUC. Of these patients, 10 (66.7%) had a high clinical suspicion of UTUC but a failed URS due to ureteric stricture and 5 (33.3%) had indeterminate biopsy histopathology following macroscopic suspicion of a tumour at URS. Overall, 11 (4.8%) patients who underwent ureteroscopy had an indeterminate biopsy result. The reasons for equivocal biopsy results are often multifactorial. Whilst it may be a consequence of suboptimal tissue quality due to small size or crush/diathermy artefact, atypia of the epithelium or an

undulating or papillary appearance can also make it challenging for pathologists to interpret the architecture.

Of the 131 patients who underwent RNU, all except five patients (126/131, 96.2%), had UTUC in the RNU specimen. Of the five patients (5/131, 3.8%) who did not have UTUC, all had undergone diagnostic URS. Four of these patients had a macroscopic lesion on URS with low grade UTUC on biopsy but no residual UTUC on RNU (including one patient with an incidental finding of pT1a (7mm) papillary renal cell carcinoma on RNU histopathology). The other patient had a CTU suggesting a solid ureteric lesion, and URS which reported a malignant-appearing stricture, with ureteroscopic biopsy which was non diagnostic and retroperitoneal fibrosis on RNU specimen.

Associations between demographics and clinicopathological/radiological variables with final diagnoses are described in Table 1. Of the 49 patients who had undergone previous surgery, 22 had been treated for benign disease while 27 patients for malignant disease (10 colon cancer, 8 bladder cancer, 4 endometrial cancer, 3 prostate cancer and 2 cervical cancer). Numbers were too small to allow comparisons for each cancer type but a history of bowel of endometrial cancer had a significantly greater rate of UTUC on final diagnosis compared with those with surgery for other pathologies (100%; 66.7%p=0.09). Patients with a history of smoking were more likely to have a final diagnosis of UTUC (104/137 (75.9%) vs 33/137 (24.1%), p=0.002), as were those who presented with VH (120/152 (78.9%) vs 32/152 (21.1%), p=<0.001). The report of a solid lesion on CT was more common in patients with a final diagnosis of UTUC compared with those with benign or alternative diagnoses (126/136 (92.6%) vs 10/136 (7.4%), p=<0.001). The same was true for the identification of a filling defect (39/74 (52.7%) UTUC diagnosis vs 35/74 (47.3%) non-UTUC diagnosis, p=<0.001).

Other non-specific findings such as ureteric thickening or hydronephrosis were more common in patients who subsequently had negative investigations or an alternative diagnosis (13/50 (26.0%) UTUC diagnosis vs 37/50 (74.0%) non-UTUC diagnosis, p=<0.001).

CTU was the primary imaging modality for 194 patients (74.6%), whilst 43 patients (16.5%) had a contrast-enhanced CT abdomen and pelvis, without a urographic phase, and 20 patients (7.7%) underwent a non-contrast CT scan of the kidneys, ureters and bladder. The remaining three patients (1.2%) had either an MRI abdomen, X-ray intravenous urogram (IVU) and an emergency inpatient retrograde pyelogram (RPG) following an abnormal ultrasound. CTU was more likely to report a filling defect and less likely to report other non-specific changes compared to the other imaging modalities (CTU findings: filling defect 68 (35.1%), solid lesion 105 (54.1%) and non-specific changes 21 (10.8%); Non-CTU findings: filling defect 6 (9.1%), solid lesion 31 (47.0%) and non-specific changes 29 (43.9%); p<0.001). When imaging reported either a solid lesion or filling defect, the positive predictive value (PPV) for a final diagnosis of UTUC was 78.6% overall and, notably, 92.6% when confined to scans reporting a solid lesion. There was a correlation between CT description and tumour invasion on final pathology (pTa vs pT$\geq$ 1; r=0.197, p=0.034) but not final tumour grade (low grade vs high grade; r=-0.045, p=0.633) after RNU. The report of a solid tumour on CT was associated with a greater proportion of muscle-invasive disease (at least pT2) compared to the report of a filling defect (43.3% and 18.5% respectively, p=0.02).

Univariate logistic regression analysis demonstrated that age (HR 1.05 [95% CI 1.03-1.08], p<0.001), smoking history (HR 2.49 [95% CI 1.37-4.57], p=0.003), previous abdominal surgery (HR 2.77 [95% CI 1.23-6.24], p=0.014), presenting complaint of VH (HR 3.02 [95% CI 1.71-5.31], p<0.001), CTU as the modality of imaging (HR 2.28 [95% CI 1.28-4.06], p=0.005) and CT

finding of a filling defect (HR 3.17 [HR1.45-6.92], p=0.004) or solid lesion (HR 35.86 [95% CI 14.5-88.4], p<0.001) were associated with a diagnosis of UTUC on final histology (Table 2). On multivariate logistic regression analysis, patient age (HR 1.07 [95% CI 1.03-1.11], p=0.001), history of smoking (HR 3.07 [95%CI 1.35-6.97], p=0.007), previous abdominal surgery (HR 4.10 [95% CI 1.27-13.3], p<0.001), presentation with visible haematuria (HR 5.17 [95% CI 1.91-14.0], p=0.001) and a report of a solid lesion on imaging (HR 37.8 [95% CI 11.7-122.1], p<0.001) remained predictive of a final diagnosis of UTUC (Table 2). In all, 53 patients (20.4%) fulfilled three independent categorical predictors– smoking history, presentation with visible haematuria and report of a solid lesion on imaging – of whom 51/53 (96.2%) had a final diagnosis of UTUC. From the two patients who did not have UTUC on final histopathology, one had a diagnosis of ureteric endometriosis on URS biopsy and the other was one of the patients who had low grade TCC on URS biopsy with no residual disease identified in the RNU specimen. Of the 79 patients with a filling defect or solid lesion on imaging with a history of smoking and visible haematuria, 70 (88.6%) had a confirmed diagnosis of UTUC.

Discussion

Diagnostic URS continues to have an axiomatic role in the assessment and management of patients with suspected UTUC, and its use meant approximately one third (77/230) of our patients avoided unnecessary RNU. However, we observed that amongst patients who are smokers and presented with both visible haematuria and with a solid lesion reported on imaging, there was a 96.2% (51/53) probability of UTUC on RNU histopathology. Importantly, these patients, with a solid lesion on CTU, are also more likely to have more advanced (muscle invasive) disease. With appropriate counselling, it may be considered judicious for such patients to undergo RNU without the requirement for prior diagnostic URS, thereby

potentially reducing their delay to definitive treatment. While many units may have methods to stratify which patients should proceed directly to nephroureterectomy, to our knowledge, this is the first study to objectively identify clinical and radiological factors that can be used to select patients who may avoid prior diagnostic URS.

We found that the overall positive predictive value of a filling defect or solid lesion on imaging for the diagnosis of UTUC was 78.6% overall and 92.8% when confined to scans reporting a solid lesion. This is consistent with existing data [**Error! Bookmark not defined.**]. The addition of the two clinical parameters, visible haematuria and smoking, improved the PPV for a filling or solid lesion on imaging for UTUC diagnosis to 88.6% and 96.3% for solid lesions alone. We acknowledge that the diagnostic reliability of imaging is dependent on the availability of specialist Uro-Radiologist, which may vary between institutions, and the imaging report must be considered within the context of each patient's presentation at a specialist Uro-Oncology MDT meeting.

Given the risk of ureteric strictures with previous surgery or radiotherapy, or the potential secondary malignancies from radiotherapy, we felt it necessary to include these variables in our analysis. Radiotherapy was not predictive of final diagnosis of UTUC although the small numbers may prevent any valid conclusion. Interestingly, a history of previous abdominal surgery was associated with a diagnosis of UTUC on univariate and multivariate logistic regression analysis. Crucially, all patients with a history of colon or endometrial cancer, associated with Lynch syndrome, a genetic risk factor for UTUC [17], had UTUC on final pathology therefore we hypothesise that the history of previous surgery may indeed be a surrogate for other genetic or environmental risk factors for UTUC, independent of previous

surgery. This requires further study and we would therefore not advocate the use of this factor alone in predicting risk of UTUC.

We found that there was a significant lag between initial diagnosis and definitive RNU in all patients in our cohort, but this was greatest for those who underwent URS during their diagnostic pathway. It has previously been reported that a delay within the UTUC management pathway may negatively impact prognosis. Xia et al [13] evaluated national registry data encompassing 3581 patients with UTUC and observed inferior OS in patients who waited longer than 120 days from initial diagnosis. Two smaller single-centre series have supported these findings [14,15]; however, this has been challenged in other published literature. Nison et al [18] performed a multicentre retrospective analysis of 512 patients with UTUC and found no difference in oncological outcome between patients who underwent diagnostic URS and those who proceeded directly to RNU, although the median delay was only 35 days. Similarly, Sundi et al [19] evaluated outcomes of 240 patients and found no difference in 5-year DSS when RNU was delayed although 50% of patients in the delayed group had neo-adjuvant chemotherapy, which may well have confounded the results given our recent understanding of the benefits of adjuvant chemotherapy from the POUT trial [20].

Diagnostic URS is only one potential source of delay within the pathway [21] and we acknowledge that delays associated with initial imaging, radiological reporting, MDT discussion and theatre scheduling may also be significant contributing factors. However, undue delay should be avoided whenever possible and if there are patients who can safely undergo immediate RNU without the need for prior diagnostic URS, then this should be strongly considered. In some centres, the management pathway has been revised to include dedicated diagnostic URS operating lists and expedited MDT discussion to prioritise patients

with suspected UTUC on imaging [21], measures which we have also subsequently implemented in our own department along with the expansion of services for upper tract surgery. Such policies can minimise delays within a patient's treatment pathway. As well as potential delay in definitive treatment, the oncological impact of diagnostic URS must also be considered. Diagnostic URS in patients with UTUC has been reported to increase the risk of tumour seeding, extravasation and intravesical recurrence [11,12] although this remains a controversial topic [22]. Furthermore, ureteroscopic biopsies are small and can be very difficult to interpret - especially if there has been a history of ureteric stenting, urolithiasis or inflammation as this can result in disorder and atypia in the urothelium sampled. In addition, there has been recent recognition of lesions of the upper tract with an inverted growth pattern, akin to papillary urothelial neoplasm of low malignant potential (PUNLMP) in the bladder, which are particularly difficult to interpret on biopsy [23].

We continue to advocate diagnostic URS in patients with solitary kidneys, bilateral UTUC or advanced renal impairment, when NSS may have a profound benefit on quality of life [24,25]. For such patients, data suggests that endoscopic management is a feasible primary treatment option for low-risk disease and has equivalent DSS to RNU [26,27,28]. Diagnostic URS is also imperative when there is diagnostic uncertainty. From our cohort, one third of patients (77/230; 33.5%) avoided major surgery by undergoing diagnostic URS, and it permitted a further small cohort of patients (6.1%) to undergo NSS.

Ultimately, in any case whereby a patient undergoes RNU without diagnostic URS, there is a risk that UTUC is not present, and patients must be appropriately counselled of the possibility of an unnecessary nephroureterectomy. Hong et al [29] evaluated outcomes from a series of 244 patients who underwent RNU at a single institution and reported a 2.9% rate of benign

final histopathology - with none of these patients having undergone diagnostic URS. Another series identified a much higher rate (10.3%) rate of benign disease on RNU [30]. Although a small proportion of cases in our series had no evidence of UTUC in the RNU specimen (5/131, 3.8%), all these patients had undergone diagnostic URS and all except one patient had evidence of low grade UTUC confirmed on ureteroscopic biopsy. The 25 cases in our series which proceeded to RNU without diagnostic URS, all had UTUC confirmed on definitive RNU histopathology - demonstrating that, through consideration of all clinical and radiological findings with robust MDT review, this pathway is judicious and reproducible in carefully selected cases.

Limitations

The inherent limitations associated with retrospective cohort studies must be considered in the interpretation of our observations; however, this was minimised by a robust data collection system including review of both electronic and paper patient records to minimise selection bias. We do, however, recognise that our methodological protocol of identifying patients will have missed a subset of patients who underwent imaging but were then deemed too unfit for further investigation with URS or to proceed directly to RNU. While we accept this may alter the overall PPV of the parameters for detection of UTUC, we believe that the number of patients not included are likely to be small and the results presented are valid as they remain applicable to patients deemed fit for further investigation and management. Missing data did prevent some analyses. Only 58% of patients with a reported 'solid lesion' on imaging had dimensions specified in the report, our model was not sufficiently powered to evaluate any correlation between reported lesion size and either likelihood of an UTUC diagnosis or final histopathological stage/grade in patients with confirmed UTUC. It should

also me noted that there is no standardised reporting matrix for CTU for the identification of UTUC akin to PI-RADS for prostate cancer on multiparametric MRI. This is likely to result in inter-observer variability and further work to reduce this is warranted. In the absence of a robust evidence-based protocol for reporting of CTU and stratification of UTUC risk on CTU alone, expert review by an experienced uro-radiologist in the multidisciplinary team meeting within high volume centres is important, as is the case in this study, to ensure quality control and confidence when discussing the CTU results with patients.

We recognise that routine assessment of urinary cytology was inconsistent in our institution. Urinary cytology may be a useful adjunct to diagnosis and risk stratification in UTUC potentially reducing the need for diagnostic URS. However, there remains concern about the reliability, inter-observer and intra-observer variability and nonconclusive results produced with cytology [9]. Indeed, only two of ten centres treating UTUC in Scotland described their use of urine cytology in the diagnostic assessment of UTUC as 'mostly' while eight of ten describe their use as 'rarely' or 'occasionally' (personal correspondence via email), suggesting that our practice is broadly similar to other units. These concerns about urinary cytology reliability are reflected in the recent change in the 2022 EAU guidelines which no longer recommends the use of cytology routinely in the diagnostic pathway of patients with suspected UTUC but in selected cases only [4]. Interestingly there was no correlation between radiological findings (solid lesion) and tumour grade on final histology and therefore clinical and radiological predictors of UTUC may be independent of a positive cytology result. Our results offer a high PPV for a diagnosis of UTUC even in the absence of cytology although a further study to assess whether cytology adds to the PPV of smoking, haematuria and solid

lesion on CTU for the detection of UTUC is warranted to determine whether it can be omitted in this group and also assess the likely additional benefit in the patient cohort without the three risk factors. Finally, while our study focussed on the diagnostic workup of patients, we did not include an analysis of the impact of delay within the pathway or the undertaking of diagnostic URS on DSS or OS and the financial implications of omitting diagnostic URS. These outcomes may be of value for analysis in a prospective multicentre cohort.

Conclusions

Diagnostic URS plays an integral role in the diagnostic evaluation of UTUC; however, in some patients it may be unnecessary and potentially cause delays prior to definitive cancer treatment. We observed patients with a smoking history who presented with visible haematuria and had a reported solid abnormality on imaging, to have a higher likelihood of an UTUC diagnosis. These patients may reliably proceed to primary nephroureterectomy from the outset. These observations may form the basis for a multicentre prospective study to establish a risk stratification algorithm including additional variables, for example urine cytology, to allow clinicians to select which patients can safely proceed to RNU without prior diagnostic URS.

Conflicts of Interest

None declared

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Table 1: Descriptive characteristics of patients investigated for upper tract urothelial cell carcinoma (UTUC) with comparisons between those with and without a final diagnosis of UTUC.

		Final Diagnosis		*p-value*
Variable (data available)	**n (% of data available)**	**UTUC [n (%)]**	**Non-UTUC [n (%)]**	
				Demographics
Median age [range] (y)	72.5 [24-93]	74 [39-93]	68 [24-89]	<0.001*
Male gender	165 (63.5)	118 (71.5%)	47 (28.5%)	0.16
				Risk Factors
Smoking history (n=214)	137 (64.0)	104 (75.9%)	33 (24.1%)	0.002*
Bladder cancer history (n=256)	58 (22.7)	45 (77.6%)	13 (22.4%)	0.09
Abdominal/pelvic radiotherapy (n=255)	20 (7.8)	12 (60%)	8 (40%)	0.41
				Surgical History
Abdominal surgery (n=254)	49 (19.3)	41(83.7%)	8 (16.3%)	0.01*
				Presenting Complaint
Visible haematuria	152 (58.5)	120 (78.9%)	32 (21.1%)	<0.001*
Loin pain without haematuria	16 (6.2)	7 (43.8%)	9 (56.3%)	
Incidental	92 (35.4)	51 (55.4%)	41 (44.6%)	
				Radiological Finding
Filling defect	74 (28.5)	39 (52.7%)	35 (47.3%)	<0.001*
Solid lesion	136 (53.1)	126 (92.6%)	10 (7.4%)	
Other (e.g. ureteric thickening/hydronephrosis)	50 (19.2)	13 (26.0%)	37 (74.0%)	

RNU = radical nephroureterectomy; UTUC = upper tract urothelial carcinoma

*Denominator noted when there was incomplete data for assessment of all patients. *denotes statistically significant result*

Table 2: Logistic regression analysis of clinical and radiological factors predictive of a histological diagnosis of UTUC on URS or RN U

Variable (n)		Univariate			Multivariate		
		HR	**95% CI**	**p-value**	**HR**	**95% CI**	**p-value**
Male gender (165)		1.47	0.86-2.51	0.16			
Age (260)		1.05	1.03-1.08	<0.001*	1.07	1.03-1.11	<0.001*
Smoking history (137)		2.49	1.37-4.52	0.003*	3.07	1.35-6.97	0.007*
History of bladder cancer (58)		1.81	0.91-3.59	0.089			
History of abdominal/pelvic radiotherapy (20)		0.68	0.27-1.72	0.41			
History of abdominal surgery		2.77	1.23-6.24	0.014*	4.10	1.27-13.3	0.018*
Presenting complaint	*Incidental (92)*	1.0			1.0		
	Visible haematuria (152)	3.02	1.71-5.31	<0.001*	5.17	1.91-14.0	0.001*
	Loin pain without haematuria (16)	0.63	0.22-1.82	0.390	0.70	0.12-4.02	0.69
CTU as primary imaging modality (193)		2.28	1.28-4.06	0.005*	1.10	0.36-3.36	0.87
Radiological finding	*Other (50)*	1.0			1.0		
	Filling defect (74)	3.17	1.45-6.92	0.004*	2.00	0.66-6.04	0.221
	Solid lesion (138)	35.86	14.5-88.4	<0.001*	37.8	11.7-122.1	<0.001*
Location of abnormality	Pelvicalyceal system (109)	1.0					
	Ureteric (131)	0.66	0.38-1.59	0.147			
	Multifocal (13)	1.15	0.30-4.49	0.838			

*UTUC = upper tract urothelial carcinoma; URS = ureterorenoscopy; RNU = radical nephroureterectomy; CTU = CT Urogram; HR = Hazard radio; CI = confidence interval. *denotes statistically significant result*

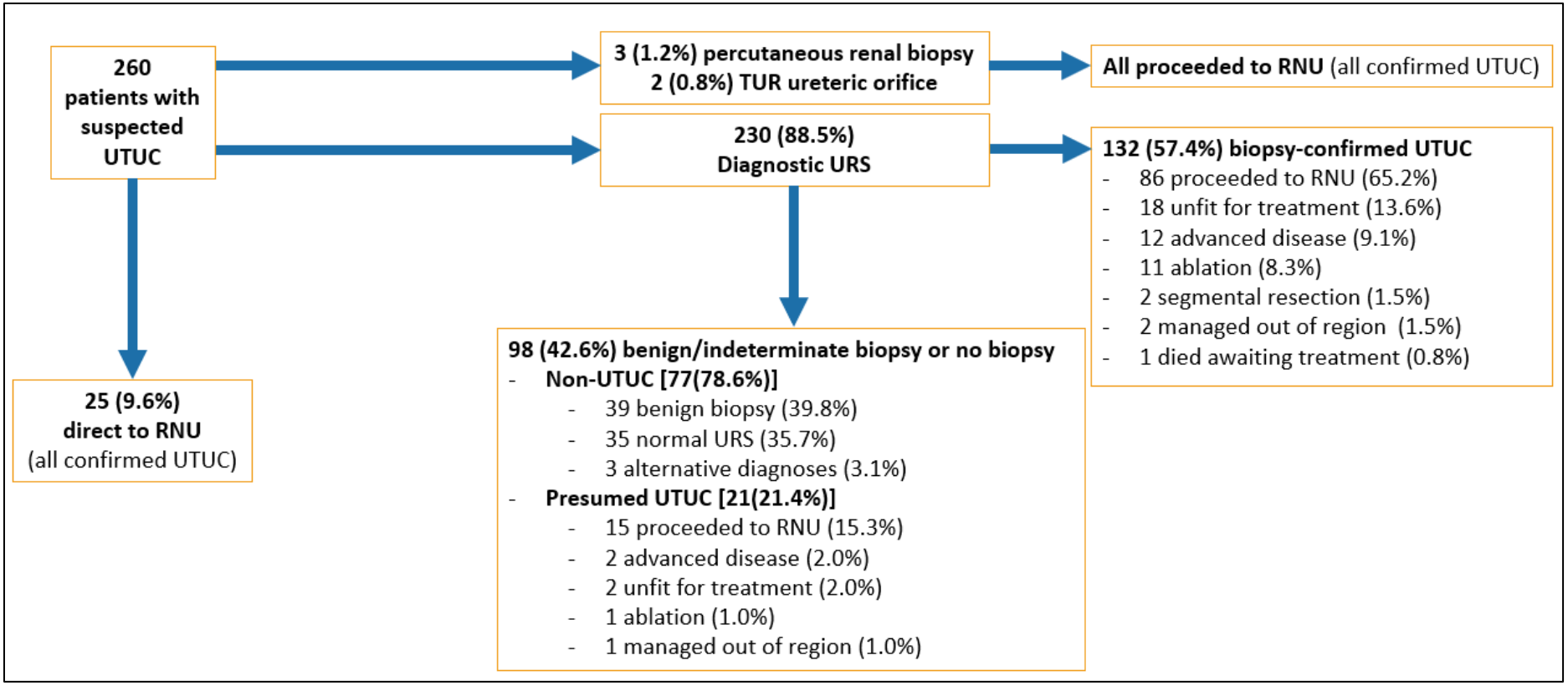

Figure 1: Outcomes of patients investigated for upper tract urothelial cell carcinoma (UTUC) during the study period.
260 Patients were included with suspected UTUC with 235 (90.4%) undergoing additional investigations after initial CT and 25 (9.4%) proceeding directly to surgery. For those with further investigation details of biopsy results and subsequent management are detailed. Of the 21 patients with no biopsy confirming UTUC but presumed UTUC, 10 patients had ureteroscopic findings suspicious of UTUC but no biopsy was taken due to technical reasons (eg stricture or bleeding) and 11 patients had inconclusive biopsies.
UTUC = upper urinary tract urothelial carcinoma; URS = ureteroscopy; TUR = transurethral resection; RNU = radical nephroureterectomy