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Can renal and bladder ultrasound replace CT urogram in patients investigated for microscopic hematuria?

Running head: Can ultrasound replace CT for microscopic hematuria

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Abstract

Purpose

Computed tomography urogram (CTU) is recommended when investigating patients with hematuria. We determine the incidence of urinary tract cancer and compare the diagnostic accuracy of CTU and renal and bladder ultrasound (RBUS) at identifying urinary tract cancer.

Methods

The DETECT I study (clinicaltrials.gov NCT02676180) is a prospective observational study recruiting patients ≥18 years following a presentation of macroscopic or microscopic haematuria at 40 hospitals. All patients had cystoscopy and upper tract imaging (CTU, RBUS or both).

Results

3,556 patients with a median age of 68 years were recruited, of which 2166 had RBUS and 1692 had CTU in addition to cystoscopy. The incidence of bladder, renal and upper tract urothelial cancer (UTUC) were 11.0%, 1.4% and 0.8% respectively in macroscopic hematuria patients. Patients with microscopic hematuria had a 2.7%, 0.4% and 0% incidence of bladder, renal and UTUC respectively. The sensitivity and negative predictive value (NPV) of RBUS for the detection of renal cancer was 85.7% and 99.9% respectively but 14.3% and 99.7% for the detection of UTUC. RBUS was poor at identifying renal calculi. Sensitivity of RBUS was lower than CTU for the detection of bladder cancer (both <85%). Cystoscopy has a specificity and PPV of 98.3% and 83.9% respectively.

Conclusion

CTU can be safely replaced with RBUS in patients with microscopic hematuria. The incidence of UTUC is 0.8% in patients with macroscopic hematuria and CTU is recommended. Patients with suspected renal calculi will require non-contrast renal tract CT. Imaging cannot replace cystoscopy to diagnose bladder cancer.

Introduction

Hematuria is a cardinal clinical symptom with an associated risk for urinary tract cancer. The risk of malignancy with patients presenting with macroscopic hematuria is 20.4% and by comparison, the risk of malignancy is 5.2% for patients presenting with microscopic hematuria.[1] Bladder cancer is the most common cancer detected in patients with microscopic hematuria accounting for 4.8% of cases investigated whereas renal cancers and UTUC are less common with an incidence of 0.3% and 0.1% respectively.[1]

Recommendations on who should be investigated for microscopic hematuria differ across guideline bodies.[2] While there is a resounding consensus that cystoscopy remains the investigation of choice to visualise the bladder, there is a lack of consensus for the optimal upper tract imaging. RBUS and CTU are the most commonly used imaging modalities. The AUA recommends using CTU for both macroscopic and microscopic hematuria while the UK NICE and the American College of Physicians do not specify a recommended imaging modality.[3-5] Similarly, the role of upper tract imaging in newly diagnosed bladder cancer patients also differ between guidelines.[6]

CTU has the highest diagnostic performance to identifying upper tract disease. Meta-analysis suggest CTU achieves a sensitivity of 93% and specificity of 99% for UTUC.[7] However, the diagnostic performance of CTU should be balanced against the risk attributed by intravenous contrast. Intravenous contrast administration is associated with a 3% risk of contrast induced nephropathy in high risk patients (eGFR: 30-59 ml/min/1.73m^2) and prophylaxis hydration has been shown to be ineffective.[8, 9] In addition, exposure to ionising radiation itself is carcinogenic and although rare, there is a risk of anaphylactic reaction.[10, 11]

The DETECT I study (ClinicalTrials.gov: NCT02676180) represents a prospective multi-centre observational study prospectively recruiting patients referred from primary care physicians to urology departments for investigation following a presentation of hematuria.[12] We report the incidence of upper tract disease and bladder cancer in patients with macroscopic and microscopic hematuria as well as the diagnostic ability of CTU and RBUS to identify upper tract cancer to determine if

CTU can be safely replaced with RBUS in patients presenting with microscopic hematuria.

Patient and Methods

Between March 2016 and June 2017, DETECT I recruited patients from 40 hospitals throughout the UK with one stop hematuria investigation clinics. All patients were referred to secondary care following a presentation of hematuria. Macroscopic hematuria was defined as a visible hematuria reported by patient or primary care physician. Microscopic hematuria was defined as ≥1+ on urine dipstick on ≥2 occasions.[13] Study inclusion criteria was male or female patients ≥18 years old and willing to provide consent. All patients underwent cystoscopy and upper tract imaging within 12 weeks from study registration. Determining the diagnostic accuracy of RBUS and CTU represents a post hoc analysis.

The study protocol was approved by Health Research Authority: North West Liverpool Central Research Ethics Committee on March 2016 (IRAS project ID: 179245, REC reference: 16/NW/0150). Full study protocol has been previously described.[12]

A medical history and physical examination were performed on all patients. Patient demographics including age, gender, occupation, ethnicity and smoking history were collected. Patients with a suspicion of bladder cancer had a TURBT or bladder biopsy under general anaesthesia. The reference standard for bladder cancer was histopathological examination and classified according to TNM WHO tumour classification.[14] Risk stratification of bladder cancer was performed based on clinical-pathological features according to the EAU risk classification.[15] Upper tract imaging comprised of one of more radiological imaging modality: CTU, RBUS or both.

DETECT I is a pragmatic observational design study and choice of upper tract imaging and the decision to perform more than one imaging modality was according to local hospital guidelines. Renal cancer and UTUC were confirmed by histopathological examination where nephrectomy or renal biopsy were performed with the exception of a small number of renal cancers which had active surveillance without biopsy. Renal calculi diagnosed on CTU was used as the reference standard.

Continuous data such as mean, median, interquartile range and 95% confidence interval were reported using descriptive statistics. Categorical variables were compared using Chi-square test. T-test was used to compare continuous variables.

Normal distribution was assumed. Sensitivity, specificity, PPV and NPV were calculated for correct identification of bladder cancer or upper tract cancers. SPSS v22 (IBM Corp, Armonk, New York, USA) was used to perform all statistical analysis. Statistical significance was set at p value <0.05. This report adhered to the STROBE guidelines. This study was registered with ClinicalTrials.gov, number NCT02676180.

Results

Patient demographics

Flow diagram of patients recruited into the study is shown in Figure 1. Patient demographics were shown in Table 1. 3,556 patients with a median age of 68 years (IQR: 57, 76) were recruited. The overall incidence of urinary tract cancer was 10.0% (bladder cancer 8.1%, renal cancer 1.0%, UTUC 0.5%). RBUS was performed on 2,166 patients (60.9%) and CTU on 1,693 patients (47.6%), 470 patients (13.2%) had both URT and CTU.

Incidence of urinary tract disease

Table 1 shows the incidence of urinary tract cancer and renal stones stratified according presentation of microscopic and macroscopic hematuria. Overall, 2.7% (n=33) of patients investigated for microscopic hematuria had a diagnosis of bladder cancer, 0.4% (n=5) of patients had a renal cancer and 4.4% (n=55) of patients had renal calculi. No patients with NVH had a diagnosis of UTUC.

By comparison, patients with macroscopic hematuria had a higher incidence of urinary tract disease compared to microscopic hematuria. 11.0% (n=255) patients investigated for macroscopic hematuria had bladder cancer, 1.4% (n=32) had renal cancer and 0.8% (n=18) had a diagnosis of UTUC. A diagnosis of renal calculi was confirmed in 9.3% (n=215) of patients.

Diagnostic performance of RBUS and CTU for the detection of upper tract disease.

Of the 2166 patient who had RBUS, the incidence of RCC and UTUC were 0.6% (n=14) and 0.3% (n=7) respectively. CTU was performed in 1692 patients with a RCC and UTUC incidence of 2.1 (n=35) and 1.1% (n=18) respectively. Table 2 shows the diagnostic ability of RBUS and CTU at detecting upper tract disease.

RBUS identified 12 of 14 renal cancers (85.7%) and misclassified one renal cancer as a UTUC increasing the sensitivity of detecting cancer to 92.9% with a NPV of 99.9%. The sensitivity of RBUS for the detection of UTUC was poor (14.3%). Three patients were misclassified as renal cancer and one UTUC diagnosed on RBUS was

renal cancer on histology suggesting a sensitivity of 62.5% to detect cancer with a NPV of 99.9%.

Given that a suspicious CTU for renal cancer or UTUC was a trigger for nephrectomy or renal biopsy, the sensitivity and NPV for CTU cannot be determined. The PPV of CTU to diagnose renal cancer was 94.6% where two lesions were benign. CTU had a PPV of 72.0% for the diagnosis of UTUC with 19 suspected UTUC cases were correctly identified. Three suspected UTUC were histologically confirmed renal cancer suggesting a PPV of cancer of 88.0%. Ureteroscopy with/ without biopsy did not confirm cancer in 3 cases. Diagnostic performance of RBUS at identifying renal calculi was poor using CT as a reference standard with a sensitivity, specificity, PPV and NPV of 34.0%, 97.9%, 65.4% and 92.7% respectively.

Diagnostic ability of RBUS, CTU and cystoscopy at identifying bladder cancer

Table 2 reports the diagnostic ability of RBUS, CTU and cystoscopy at detecting bladder cancer. The diagnostic accuracy for RBUS to identify bladder cancer was sensitivity: 50.7%, specificity 99.3%, PPV 84.3% and NPV 96.5%. CTU was better than RBUS at identifying bladder cancer. The sensitivity, specificity, PPV and NPV of CTU to identify bladder cancer was 80.8%, 97.0%, 78.9% and 97.3%. Excluding suboptimal scans, the diagnostic ability of RBUS and CTU to detect bladder cancer improved.

The sensitivity and NPV of cystoscopy cannot be determined as patients with a normal flexible cystoscopy were discharged without follow-up cystoscopy. Using histopathological confirmation of tumour as reference, the specificity of flexible cystoscopy was high at 98.3% with a PPV of 84.0%.

Discussion

We report that the incidence of upper tract cancer in patients presenting with hematuria is low. Upper tract cancer was identified in 2.2% (n=50) of patients presenting with macroscopic hematuria (1.4% renal cancer, 0.8% UTUC) and 0.4% (n=5) of patients presenting with microscopic hematuria (0.4% renal cancer, 0% UTUC). RBUS can identify suspicious renal cancer and one cancer misclassified as UTUC with a sensitivity of 92.9%. However, RBUS only has a sensitivity of 62.5% to identify a suspected UTUC (including 3 cancers diagnosed as renal cancer and one UTUC which was renal cancer on histology) missing three of 8 UTUC. The fact that no UTUC was identified following a presentation of microscopic hematuria suggest that RBUS should be used to assess the upper urinary tract in patients presenting with microscopic hematuria.

The role of cystoscopy to diagnose bladder cancer remains the gold standard. Cystoscopy has a specificity of 98.3% with a PPV of 83.9%.[16] Conventional imaging modalities cannot replace cystoscopy. Even after excluding suboptimum scans, the accuracy of RBUS to detect bladder cancer was poor, with a sensitivity of 63.6% and specificity of 99.3%. CTU had a higher diagnostic accuracy to identify bladder cancer but not sufficient to replace cystoscopy (sensitivity 83.6%, specificity 97.0%).

It is estimated that the incidence of microscopic hematuria is as high as 2.5% of the population and rises to as high as 18% in male patients ≥70 years.[17, 18] However, majority of these cases do not have a sinister identifiable cause for microscopic hematuria. CTU has been shown to be superior at identifying UTUC compared to RBUS.[1, 7] RBUS may miss small ureteric tumours, which are too small to cause luminal occlusion. This in turn results in a false negative because no hydronephrosis is identified which would otherwise prompt further imaging. The operator dependent nature of RBUS may also miss small renal pelvis UTUC. While CTU is superior at identifying UTUC, the risk of UTUC in patients presenting with microscopic hematuria is rare suggesting that there is no benefit for CTU over RBUS.[7]

RBUS has been shown to detect renal cancer with a high sensitivity although a small number of cases are false positive (n=14). These false positive cases would have a second scan typically a renal protocol CT which will better characterise the renal mass. Hence, the approach of perform cystoscopy with RBUS instead of CTU to

investigate the upper tracts of patients presenting with microscopic hematuria should be the preferred upper tract imaging of choice. We acknowledge that RBUS has a poor sensitivity at identifying renal calculi. Hence, we proposed that patients presenting with symptoms suggestive of renal colic such as flank pain would benefit from RBUS with non-contrast CTKUB or CTU. We acknowledge that replacing CTU with RBUS for patients with microscopic hematuria would potentially miss asymptomatic renal calculi with no hydronephrosis presenting with microscopic hematuria. We believe such patient would be uncommon and identifying such a patient will be at the expense of subjecting a high number of patients to CTU which would yield negative results.

In an ideal world, all patients should be investigated with the best diagnostic test available. However, risk of adverse events, low incidence of disease in the specific patient cohort as well as the high cost of diagnostic test suggest that this may not be warranted. In the case of microscopic hematuria, where the disease specific incidence of UTUC is low (0%) and below the 3% threshold for diagnostic investigation used by NICE and the 1% suggested by the AUA.[3, 4] Additionally, the risk of adverse reaction to iodinated contrast while low, can be life threatening.[11] Ionising radiation from CTU is 4 mSv with is 200 times that of a standard chest X-ray.[19] And the cumulative exposure to ionising radiation has been shown to account for 0.6-0.9% of cancer diagnosed.[10]

Further, cost-effectiveness analysis recommends using RBUS instead of CTU for the evaluation of microscopic hematuria patients.[20] A comparison of four diagnostic approaches comprising of CT alone, cystoscopy alone, CT with cystoscopy and RBUS with cystoscopy suggest that the RBUS with cystoscopy combination represents the most cost-effective combination at $53,810 per cancer detected. Replacing RBUS with CTU will cost $6,480,484 per cancer identified. It is estimated that using RBUS instead of CTU will result in cost savings of $390 million which is much needed in an era of escalating healthcare cost.[21]

The role of cystoscopy to visualise the bladder remains the gold standard. Even after excluding suboptimal scans, a patient with a normal CTU or RBUS will still require cystoscopy due to a high risk of false negative. This is similar to the diagnostic ability of FDA approved urinary biomarkers for the detection of bladder cancer with a

reported sensitivity of 57-82% and specificity of 74-88%.[22] While larger tumours would be easily identifiable, smaller tumours might be missed. It is likely that an optimised CTU, where the urinary bladder is well distended, and contrast has fully opacified the bladder lumen, will improve the diagnostic accuracy. However, such scans may be difficult to achieve in clinical practice.

While majority of bladder lesions are considered cancer until proven otherwise, we report that a visual diagnosis of malignancy has a PPV of 83.9% following white light cystoscopy. In the setting of surveillance cystoscopy, low grade bladder cancer was identifiable from high grade cancers by urologists 99% of the time.[23] Cystoscopy is operator dependent and the specificity for a more experienced cystoscopist will be higher. Hence, it is essential that suspicious bladder lesions be biopsied due to a high likelihood of malignancy. Bladder biopsy can be performed at the point of initial diagnosis with flexible cystoscopy and this can reduce the need for a general anaesthetic.

There are several limitations to this study. While we did not identify any UTUC presenting with microscopic hematuria, it is plausible that these patients might have initially presented with microscopic hematuria if screening for microscopic hematuria was performed although this is not recommended by any consensus. While sonographers normally will visualise the renal tract with the bladder distended to adequately visualise the bladder, this was not performed in all cases. Similarly, assessment of the urinary bladder was limited in some CTU scans where contrast did not opacify the bladder or where the was artefact due to metal work in the pelvis. To account for these suboptimal scans, we exclude these scans to determine the diagnostic accuracy of imaging to identify bladder cancer. Additionally, we cannot determine the sensitivity of cystoscopy as we are unable to determine if tumours were missed due as patients with a normal cystoscopy were discharged and did not have a repeat test.

Conclusions

Our results suggest that CTU can safely be replaced with RBUS to image the upper tracts in conjunction with cystoscopy as part of investigations following a presentation of microscopic hematuria. The risk of UTUC in patients with microscopic hematuria is extremely low and RBUS can identify renal parenchymal cancers with a high sensitivity. Where renal calculi is suspected, a non-contrast CTKUB with RBUS or CTU is necessary. Cystoscopy remains the diagnostic test of choice to detect bladder cancer.

DETECT I collaborators

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Ethical approval of studies and informed consent

The study protocol was approved by Health Research Authority: North West Liverpool Central Research Ethics Committee on March 2016 (IRAS project ID: 179245, REC reference: 16/NW/0150).

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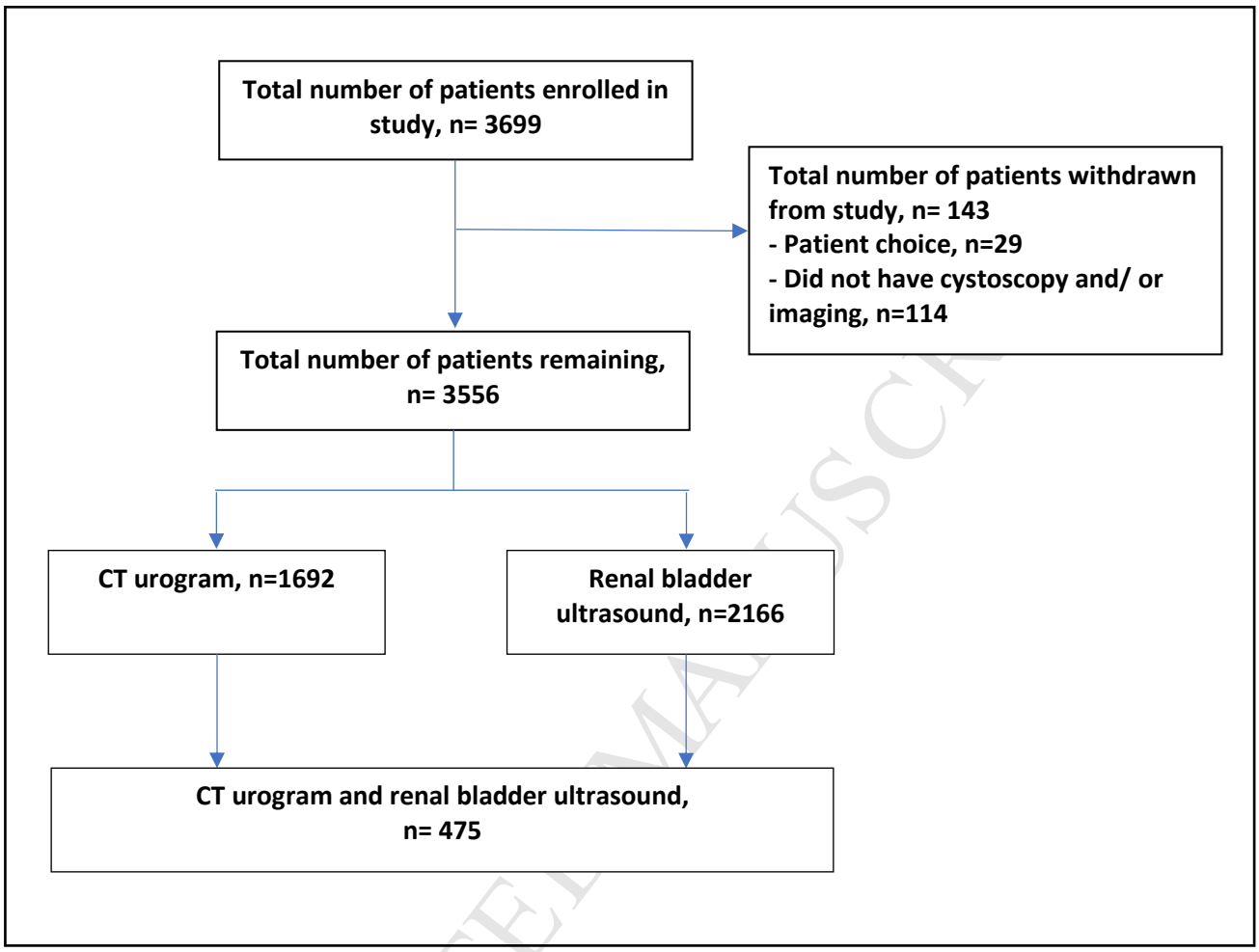
Table 1: Patient demographics according to type of hematuria

	All patients (n=3556)	Macroscopic hematuria (n=2311)	Microscopic hematuria (n=1245)	p value
Age (median, IQR)	67.7 (57, 76)	68.1 (56.4, 76.2)	67.0 (56.9, 75.0)	0.568
Gender, n (%):				<0.001
Male	2112 (59.4)	1607 (69.5)	505 (40.6)	
Female	1444 (40.6)	704 (30.5)	740 (59.4)	
Ethnicity, n (%):				0.235
Afro-Caribbean	51 (1.4)	36 (1.6)	15 (1.2)	
South Asian	86 (2.4)	57 (2.5)	29 (2.3)	
East Asian	15 (0.4)	8 (0.3)	7 (0.6)	
White	3080 (86.6)	2013 (87.1)	1067 (85.7)	
Mix	31 (0.9)	20 (0.9)	11 (0.9)	
Other	23 (0.6)	18 (0.8)	5 (0.4)	
Not known	271 (7.6)	159 (6.9)	111 (8.9)	
Smoking history, n (%):				0.739
Non-smoker	1528 (42.9)	991 (42.9)	537 (43.1)	
Current/ ex-smoker	1896 (53.2)	1240 (53.7)	656 (52.7)	
Not known	137 (3.8)	80 (3.4)	52 (4.2)	
Any urinary tract cancer, n (%)	354 (10.0)	315 (13.6)	39 (3.1)	<0.001
Bladder cancer, n (%)	288 (8.1)	255 (11.0)	33 (2.7)	<0.001
Renal cancer, n (%)	37 (1.0)	32 (1.4)	5 (0.4)	0.006
UTUC, n (%)	18 (0.5)	18 (0.8)	(0)	0.002
Renal calculi, n (%)	270 (7.6)	215 (9.3)	55 (4.4)	<0.001

Table 2: Comparison of RBUS, CTU and cystoscopy to diagnose bladder cancer, renal cancer and UTUC

Diagnostic test	Reference standard	Diagnostic accuracy				
		sensitivity	specificity	PPV	NPV	Area under the curve
RBUS (n=2166)	Histopathological confirmation of UTUC	14.3 (0.9-49.4)	100 (99.8-100.0)	50.0 (3.8-96.2)	99.7 (99.4-99.9)	0.571
CTU (n=1692)	Histopathological confirmation of UTUC		99.6 (99.2-99.8)	72.0 (52.8-86.9)		
RBUS (n=2166)	Histopathological confirmation of renal cancer	85.7 (62.1-97.5)	99.2 (98.8-99.5)	41.4 (24.8-59.5)	99.9 (99.7-100.0)	0.925
CTU (n=1692)	Histopathological confirmation of renal cancer		99.9 (99.6-100.0)	94.6 (84.2-99.1)		
RBUS (n=475)	CTU to diagnose renal calculi	34 (21.9-47.7)	97.9 (96.2-99.0)	65.4 (46.3-81.6)	92.7 (90.0-94.8)	0.659
RBUS (n=2166)	Histopathological confirmation of bladder cancer	50.7 (42.7-58.7)	99.3 (98.9-99.6)	84.3 (75.8-90.8)	96.5 (95.6-97.2)	0.750
Unoptimized RBUS excluded (2090)		63.6 (54.7-71.9)	99.3 (98.9-99.6)	84.3 (75.8-90.8)	97.9 (97.2-98.4)	0.814
CTU (1692)	Histopathological confirmation of bladder cancer	80.5 (74.8-85.4)	97.0 (96.1-97.8)	79.3 (73.6-84.4)	97.2 (96.3-98.0)	0.887
Unoptimized CTU excluded (1615)		83.6 (78.1-88.3)	97.0 (96.1-97.8)	80.0 (74.2-85.0)	97.7 (96.8-98.4)	0.903
Cystoscopy (n=3556)	Histopathological confirmation of bladder cancer		98.3 (97.9-98.7)	84.0 (79.7-87.5)		

Figure 1: Flow diagram of patients recruited into study



Abbreviations and Acronyms:

AUA (American Urological Association), CT (Computed tomography), CTKUB (Computed tomography kidney, ureters, bladder), CTU (Computed tomography urogram), EAU (European Association of Urology), IRAS (Intergrated Research Application System), NICE (National Institute for Health and Care Excellence), NPV (negative predictive value), PPV (positive predictive value), REC (Research Ethics Committee), RBUS (renal and bladder ultrasound), STROBE (STrengthening the Reporting of OBservational studies in Epidemiology), TURBT (transurethral resection of bladder cancer), UK (United Kingdom), UTUC (upper tract urothelial carcinoma), WHO (World Health Organisation)