

Author's Accepted Manuscript

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

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PII: S0022-5347(18)43045-5
DOI: [10.1016/j.juro.2018.04.065](https://doi.org/10.1016/j.juro.2018.04.065)
Reference: JURO 15571

To appear in: *The Journal of Urology*

Please cite this article as: Tan WS, Sarpong R, Khetrpal P, Rodney S, Mostafid H, Cresswell J, Hicks J, Rane A, Henderson A, Watson D, Cherian J, Williams N, Brew-Graves C, Feber A, Kelly JD, on behalf of DETECT I trial collaborators, Can renal and bladder ultrasound replace CT urogram in patients investigated for microscopic hematuria?, *The Journal of Urology*® (2018), doi: 10.1016/j.juro.2018.04.065.

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3 Running head: Can ultrasound replace CT for microscopic hematuria

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32 Keywords: Bladder cancer, hematuria, imaging, kidney cancer, ultrasound

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34 Word count: 2,494

35 Abstract

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37 Purpose

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

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43 Methods

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

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49 Results

50 3,556 patients with a median age of 68 years were recruited, of which 2166 had
51 RBUS and 1692 had CTU in addition to cystoscopy. The incidence of bladder, renal
52 and upper tract urothelial cancer (UTUC) were 11.0%, 1.4% and 0.8% respectively in
53 macroscopic hematuria patients. Patients with microscopic hematuria had a 2.7%,
54 0.4% and 0% incidence of bladder, renal and UTUC respectively. The sensitivity and
55 negative predictive value (NPV) of RBUS for the detection of renal cancer was
56 85.7% and 99.9% respectively but 14.3% and 99.7% for the detection of UTUC.
57 RBUS was poor at identifying renal calculi. Sensitivity of RBUS was lower than CTU
58 for the detection of bladder cancer (both $< 85\%$). Cystoscopy has a specificity and
59 PPV of 98.3% and 83.9% respectively.

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61 Conclusion

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

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69 Introduction

70 Hematuria is a cardinal clinical symptom with an associated risk for urinary tract
71 cancer. The risk of malignancy with patients presenting with macroscopic hematuria
72 is 20.4% and by comparison, the risk of malignancy is 5.2% for patients presenting
73 with microscopic hematuria.¹ Bladder cancer is the most common cancer detected in
74 patients with microscopic hematuria accounting for 4.8% of cases investigated
75 whereas renal cancers and UTUC are less common with an incidence of 0.3% and
76 0.1% respectively.¹

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

86 CTU has the highest diagnostic performance to identifying upper tract disease. Meta-
87 analysis suggest CTU achieves a sensitivity of 93% and specificity of 99% for
88 UTUC.⁷ However, the diagnostic performance of CTU should be balanced against
89 the risk attributed by intravenous contrast. Intravenous contrast administration is
90 associated with a 3% risk of contrast induced nephropathy in high risk patients
91 (eGFR: 30-59 ml/min/1.73m²) and prophylaxis hydration has been shown to be
92 ineffective.^{8, 9} In addition, exposure to ionising radiation itself is carcinogenic and
93 although rare, there is a risk of anaphylactic reaction.^{10, 11}

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

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

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125 Patient and Methods

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

135 The study protocol was approved by Health Research Authority: North West
136 Liverpool Central Research Ethics Committee on March 2016 (IRAS project ID:
137 179245, REC reference: 16/NW/0150). Full study protocol has been previously
138 described.¹²

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

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

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

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

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182 Results

183 Patient demographics

184 Flow diagram of patients recruited into the study is shown in Figure 1. Patient
185 demographics were shown in Table 1. 3,556 patients with a median age of 68 years
186 (IQR: 57, 76) were recruited. The overall incidence of urinary tract cancer was 10.0%
187 (bladder cancer 8.1%, renal cancer 1.0%, UTUC 0.5%). RBUS was performed on
188 2,166 patients (60.9%) and CTU on 1,693 patients (47.6%), 470 patients (13.2%)
189 had both URT and CTU.

190

191 Incidence of urinary tract disease

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

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

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

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

208 RBUS identified 12 of 14 renal cancers (85.7%) and misclassified one renal cancer
209 as a UTUC increasing the sensitivity of detecting cancer to 92.9% with a NPV of
210 99.9%. The sensitivity of RBUS for the detection of UTUC was poor (14.3%). Three
211 patients were misclassified as renal cancer and one UTUC diagnosed on RBUS was

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

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

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

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

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

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243 Discussion

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

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

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

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

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

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

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

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

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

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

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

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340 Conclusions

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

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424

425 Funding

426 DETECT I was funded by the Medical Research Council (MRC). Additional funding
427 was by the Urology Foundation and the UCLH Biomedical Research Centre. It was
428 supported both in the delivery and development by the UCL Surgical Interventional
429 Trials Unit (SITU). NHS associated cost supported all standard of care investigations
430 and procedures.

431

432 Declaration of intent and financial disclosures

433 No direct or indirect commercial incentive associated with publishing this article.

434 The corresponding author certifies that, when applicable, a statement(s) has been
435 included in the manuscript documenting institutional review board, ethics committee
436 or ethical review board study approval; principles of Helsinki Declaration were
437 followed in lieu of formal ethics committee approval; institutional animal care and use
438 committee approval; all human subjects provided written informed consent with
439 guarantees of confidentiality; IRB approved protocol number; animal approved
440 project number.

441

442 Ethical approval of studies and informed consent

443 The study protocol was approved by Health Research Authority: North West
444 Liverpool Central Research Ethics Committee on March 2016 (IRAS project ID:
445 179245, REC reference: 16/NW/0150).

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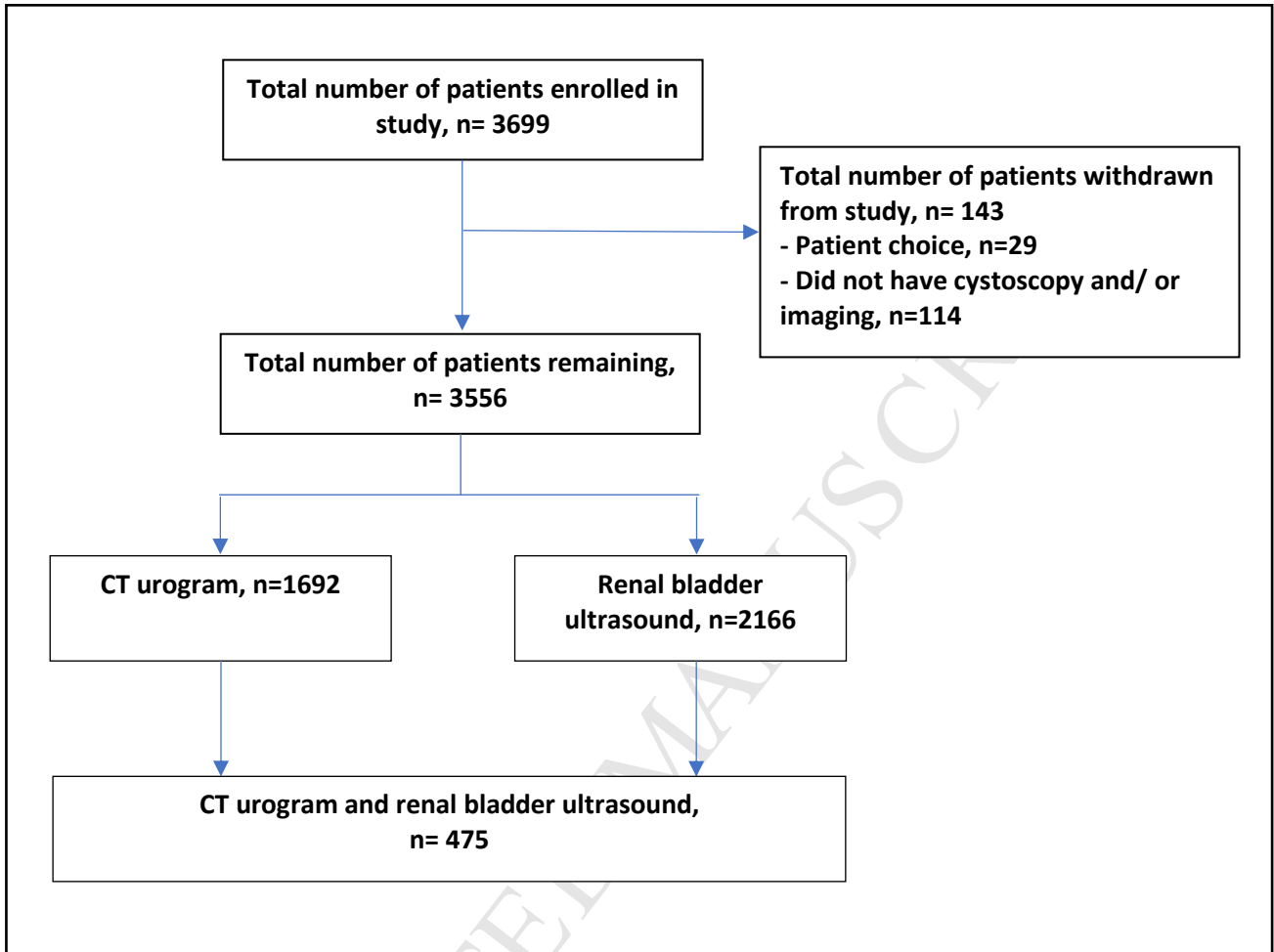
Table 1: Patient demographics according to type of hematuria

	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)