Who should be investigated for haematuria? Results of a contemporary prospective observational study of 3556 patients

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ABSTRACT

There remains a lack of consensus among guideline relating to which patients require investigation for haematuria. We determined the incidence of urinary tract cancer in a prospective observational study of 3556 patients referred for investigation of haematuria across 40 hospitals between March 2016 and June 2017 (DETECT 1; ClinicalTrials.gov: NCT02676180) and the appropriateness of age at presentation in cases with visible (VH) and non-visible haematuria (NVH). The overall incidence of urinary tract cancer was 10.0% (bladder cancer 8.0%, renal parenchymal cancer 1.0%, upper tract transitional cell carcinoma (TCC) 0.7%, prostate cancer 0.3%). Patients with VH were more likely to have a diagnosis of urinary tract cancer compared to NVH patients (13.8% vs 3.1%). Older patients, male gender and smoking history were independently associated with urinary tract cancer diagnosis. 59.4% of bladder cancer diagnosed following NVH were high risk with 31.3% muscle invasive. Incidence of cancer in VH patients <45 years was 3.5% (n=7) and 1.0% (n=4) in NVH patients <60 years. Our results suggest that patients with VH should be investigated regardless of age. Although the risk of urinary tract cancer in NVH patients is low, clinically significant cancers are detected below the age threshold for referral for investigation.

Patient summary

This study highlights the requirement to investigate all patients with visible blood in the urine and an age threshold of ≥60 years, as recommended in some guidelines, for the investigation of non-visible blood in the urine will miss a significant number of urinary tract cancers. Patient preference is important and evidence that patients are willing to submit to investigation should be considered in reaching a consensus recommendation for the investigation of haematuria. International consensus to guide which patients will benefit from investigation should be developed.

Key words: age; bladder cancer; haematuria; incidence; investigation; renal cancer

There remains a lack of consensus among guideline relating to which patients require investigation for haematuria [1]. In 2015, the UK National Institute for Health and Care Excellence (NICE) recommended that patients aged ≥45 years with visible haematuria (VH) and ≥60 years with non-visible haematuria (NVH) with either dysuria or raised white cell count on blood test should be urgently referred on a suspected cancer pathway [2]. The American Urology Association (AUA) recommends that all patients with VH and patients with microscopic haematuria (≥3 red blood cells/ high power field) ≥35 years should be investigated [3]. In contrast, the National Board of Health and Welfare of Sweden do not recommended investigating NVH cases [4].

The DETECT I study is a prospective multi-centre observational study recruiting patients referred for investigation of haematuria [5]. We report the incidence of urinary tract cancer in cases referred for investigation of haematuria and specifically addressing whether age at presentation can be applied as a threshold for referral of haematuria investigation.

Between March 2016 and June 2017, 3556 patients from 40 hospitals were recruited (Supplementary Fig 1). All patients had cystoscopy and upper tract imaging. Patient demographics including age, gender, occupation, ethnicity and smoking history were recorded. Urinary tract cancer comprised of bladder cancer or upper tract cancer (renal parenchymal cancer and upper tract transitional cell carcinoma [TCC]). The reference standard for bladder cancer was histopathological confirmation of tumour according to the TNM WHO tumour classification and European Association of Urology (EAU) risk classification [6, 7]. The reference standard for upper tract cancer diagnosis was based on multidisciplinary team meeting consensus following review of imaging. The full trial protocol has been previously reported [5].

Patient demographics according to diagnosis of urinary tract cancer is described in Table 1. Urinary tract cancer was identified in 10% of all patients referred for investigation for haematuria (13.8% of VH cases and 3.1% of NVH cases). Bladder cancer was detected in 8.0% of patients and accounted for 79.8% of cancers detected whereas the incidence of upper tract cancer was 1.7%, accounting for 17.7% of cancers detected. Renal parenchymal cancer represented 61% (n=37) of upper tract cancer and upper tract TCC was detected in the remaining 49% (n=26) of

cases. Exclusively, all upper tract TCC and 83.8% of renal parenchymal cancers presented with VH. Renal stone disease was diagnosed in 7.5% of patients. Angiomyolipoma and pelvis ureteric junction obstruction were identified in <1% of patients.

Patients were stratified by gender, type of haematuria at presentation and type of cancer diagnosed according to age decile (Table 2A, 2B and Supplementary Table 1). In total, 602 patients (16.9%) were referred below the NICE recommended age threshold for VH (n=199) or NVH (n=403). In this group, a cancer diagnosis was established in 1.8% (n=11) of patients (10 bladder cancer & one upper tract TCC). No cancers presented with NVH in patients referred below the AUA threshold of <35 years. The incidence of cancer in patients with VH <45 years was 3.5% (n=7) and 1.0% (n=4) in patients with NVH <60 years.

High risk cancers accounted for 49.6% of tumours identified following VH; 15.4% were classified as muscle invasive bladder cancer (MIBC) (Supplementary Table 2). In patients with NVH, 59.4% of the cases were classified as high risk cancer and 31.3% were MIBC. Analysis of bladder cancers detected below the NICE age threshold for investigation of VH report that four of the six bladder cancers were high or intermediate risk cancers, one of which was MIBC. Of the four bladder cancers detected following NVH below the NICE age threshold, three were high or intermediate risk cancers, one of which was a G3pT1 cancer.

This study underpins the importance of investigating patients presenting with haematuria. We highlight that an age threshold cannot be assigned in patients with VH and applying an age threshold defined by NICE will fail to detect clinically significant disease. To our knowledge, this study is the first to confirm that cancers detected in patients presenting with NVH are high risk with a significant number of MIBC. Applying the NICE defined age threshold will fail to detect 10.5 % of cancers with NVH (incident: 1.0%) and 2.2% of cancers with VH (incidence: 3.5%). All cancers would be detected using AUA age thresholds.

NICE suggests that a sign or symptom associated with ≥3% risk of cancer should prompt referral for diagnostic tests [2]. Our results suggest a case for the investigation of all patients with VH. The following NVH is less clear with a cancer incident rate of <3%. However, the overall incidence of urinary tract cancer in

females investigated for NVH is actually similar to that of patients aged between 40-59 years, both below the 3% threshold. However, the knowledge that cancers diagnosed following a presentation of NVH are clinically significant highlights the importance of considering patient preference.

The importance of patient preference has recently been highlighted using a vignette study to explore the likelihood that patients would want diagnostic tests if there was a risk of cancer diagnosis [8]. Banks and colleagues showed that 85% of patients would want referral for investigation for a symptom attributing a 1% risk of cancer, even if invasive testing is required such as colonoscopy for colon cancer [8].

An important limitation of the study is accrual of cases was by sampling individual haematuria clinics rather than recruiting all patients during a defined time period. However, patients were recruited before cystoscopy to exclude selection bias based on diagnosis. The incidence of urinary tract cancer in patients with haematuria from this study represents detection rate in secondary care and this will be higher than patients in primary care.

This study suggests that patients with VH should be investigated regardless of age. A decision to investigate NVH should reflect patient choice and public health policy. What is clear is that there is a lack of consensus across guideline bodies and a European wide guideline would aid physician decision making and patient selection for referral for investigation of haematuria.

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Declaration of intent and financial disclosures

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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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Take home message

Visible haematuria should be investigated regardless of age. While the risk of urinary tract cancer in patients <60 years with NVH is low, clinically significant bladder cancers are still diagnosed. European wide consensus for haematuria should be developed.

Table 1: Patient demographics stratified according to presence or absence of urinary tract cancer

	All patients (n=3556)	Urinary tract cancer (n=355)	No urinary tract cancer (n=3201)	Univariate p value
Age (median, IQR)	67.7 (57, 76)	74.2 (67, 81)	66.8 (56, 75)	
Age (mean, range)	65.7 (19-99)	73.0 (28-96)	64.9 (19-99)	<0.001
Haematuria, n (%):				<0.001
Visible	2311 (65.0)	317 (89.3)	1994 (62.3)	
Non-visible	1245 (35.0)	38 (10.7)	1207 (37.7)	
Gender, n (%):				<0.001
Male	2112 (59.4)	273 (76.7)	1839 (57.5)	
Female	1444 (40.6)	82 (23.1)	1362 (42.5)	
Ethnicity, n (%):				0.021
Afro-Caribbean	51 (1.4)	2 (0.6)	49 (1.5)	
South Asian	86 (2.4)	6 (1.8))	80 (2.5)	
Oriental	15 (0.4)	0 (0)	15 (0.5)	
White	3080 (86.6)	330 (93.0)	2750 (85.9)	
Mix	31 (0.9)	2 (0.6)	29 (0.9)	
Other	23 (0.6)	2 (0.6)	21 (0.7)	
Not known	271 (7.6)	13 (3.7)	257 (8.0)	
Smoking history, n (%):				<0.001
Non-smoker	1528 (42.9)	115 (32.6)	1413 (44.0)	
Current/ ex-smoker	1896 (53.2)	230 (64.6)	1666 (52.0)	
Not known	137 (3.8)	11 (2.8)	127 (4.0)	
Employment status, n (%):				<0.001
Full time/ part time work/ study/ home maker	1518 (42.7)	85 (23.9)	1433 (44.8)	
Retired	1764 (49.6)	250 (70.4)	1514 (47.3)	
Unemployed	78 (2.2)	4 (1.1)	74 (2.3)	
Disability	40 (1.1)	2 (0.6)	38 (1.2)	
Not known	156 (4.4)	14 (3.9)	142 (4.4)	
Occupational risk factor*, n (%)				0.708
Yes	531 (14.9)	54 (15.2)	477 (14.9)	
No	2756 (77.5)	278 (78.4)	2478 (77.4)	
Not known	269 (7.6)	23 (6.5)	246 (7.7)	

*defined as gardener, painter, hairdresser/ barber, textile worker or metals factory worker

Table 2: Incidence of malignancy stratified according to age groups. NICE recommended age thresholds for haematuria investigations are shaded. 3A: Male. 3B: Female

A

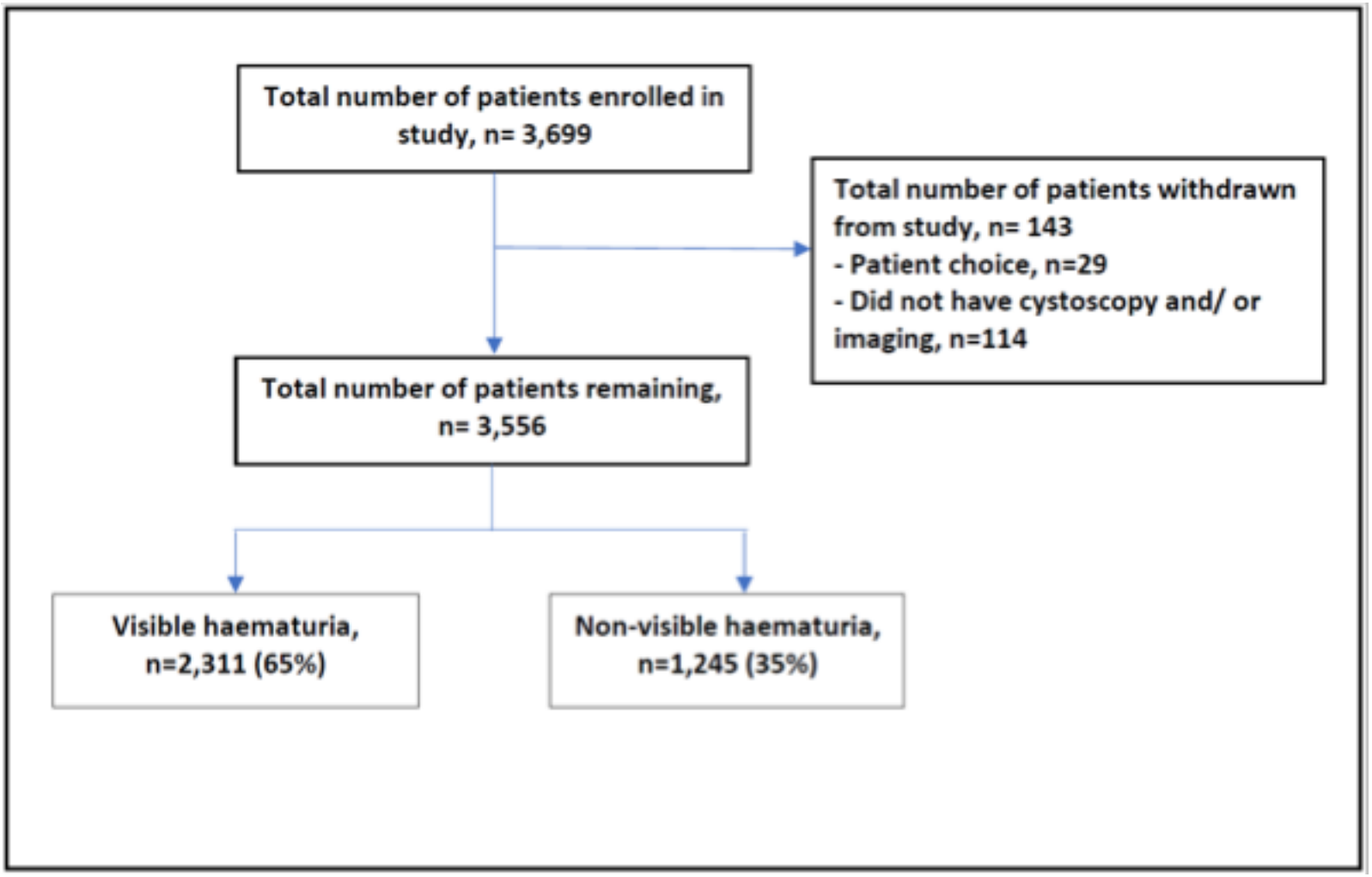
	Visible haematuria, n (%)					Non-visible haematuria, n (%)				
Age groups	Total patients	All urinary tract cancers	Bladder cancer	Renal cancer	Upper tract TCC	Total patients	All urinary tract cancers	Bladder cancer	Renal cancer	Upper tract TCC
10-19	2	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
20-29	19	1 (5.3)	1 (5.3)	0 (0)	0 (0)	2	0 (0)	0 (0)	0 (0)	0 (0)
30-39	44	0 (0)	0 (0)	0 (0)	0 (0)	7	0 (0)	0 (0)	0 (0)	0 (0)
40-44	47	3 (6.4)	2 (4.3)	0 (0)	1 (2.1)	20	1 (5.0)	1 (5.0)	0 (0)	0 (0)
45-49	77	3 (3.9)	2 (2.6)	1 (1.3)	1 (1.3)	33	0 (0)	0 (0)	0 (0)	0 (0)
50-59	280	20 (7.1)	13 (4.6)	4 (1.4)	3 (1.1)	81	1 (1.2)	1 (1.2)	0 (0)	0 (0)
60-69	331	45 (13.6)	37 (11.2)	5 (1.5)	2 (0.6)	126	5 (4.0)	5 (4.0)	0 (0)	0 (0)
70-79	514	108 (21.0)	94 (18.3)	6 (1.2)	6 (1.2)	164	9 (5.5)	9 (5.5)	0 (0)	0 (0)
80-89	261	64 (24.5)	52 (25.2)	2 (0.8)	5 (1.9)	66	7 (10.6)	6 (9.1)	1 (1.5)	0 (0)
90-99	33	5 (15.2)	5 (15.2)	0 (0)	0 (0)	7	1 (14.3)	1 (14.3)	0 (0)	0 (0)
Total	1608	249 (15.5)	206 (12.8)	18 (1.2)	18 (1.1)	506	24 (4.8)	23 (4.6)	1 (0.2)	0 (0)

B

	Visible haematuria, n (%)					Non-visible haematuria, n (%)				
Age groups	Total patients	All urinary tract cancers	Bladder cancer	Renal cancer	Upper tract TCC	Total patients	All urinary tract cancers	Bladder cancer	Renal cancer	Upper tract TCC
10-19	1	0 (0)	0 (0)	0 (0)	0 (0)	0	0 (0)	0 (0)	0 (0)	0 (0)
20-29	20	0 (0)	0 (0)	0 (0)	0 (0)	8	0 (0)	0 (0)	0 (0)	0 (0)
30-39	31	0 (0)	0 (0)	0 (0)	0 (0)	26	0 (0)	0 (0)	0 (0)	0 (0)
40-44	35	3 (8.6)	3 (8.6)	0 (0)	0 (0)	25	0 (0)	0 (0)	0 (0)	0 (0)
45-49	55	1 (1.8)	0 (0)	1 (1.8)	0 (0)	44	1 (2.3)	1 (2.3)	0 (0)	0 (0)
50-59	163	8 (4.9)	1 (0.6)	5 (3.1)	2 (1.2)	157	1 (0.6)	1 (0.6)	0 (0)	0 (0)
60-69	174	17 (9.8)	13 (7.5)	1 (0.6)	3 (1.7)	206	4 (1.9)	3 (1.5)	1 (0.5)	0 (0)
70-79	153	23 (15.0)	18 (11.8)	4 (2.6)	1 (0.7)	191	4 (2.1)	2 (1.0)	2 (1.3)	0 (0)
80-89	58	11 (15.9)	8 (13.8)	2 (3.5)	1 (1.7)	81	4 (4.9)	2 (2.5)	2 (3.4)	0 (0)
90-99	14	5 (35.7)	4 (28.6)	0 (0)	1 (7.1)	5	0 (0)	0 (0)	0 (0)	0 (0)
Total	704	68 (9.7)	47 (6.7)	13 (1.8)	8 (1.1)	743	14 (1.9)	9 (1.2)	5 (0.7)	0 (0)

TCC: transitional cell carcinoma

Supplementary Fig 1: Flow diagram of patients recruited into study



Supplementary Table 1: Diagnosis of patients investigated for haematuria stratified according to haematuria type and gender

	All patients			Male			Female		
	Any haematuria (n=3556)	VH (n=2311)	NVH (n=1245)	Any haematuria (n=2112)	VH (n=1607)	NVH (n=505)	Any haematuria (n=1447)	VH (n=704)	NVH (n=743)
Any urinary tract cancer, n (%)	357 (10.0)	319 (13.8)	38 (3.1)	275 (13.0)	251 (15.6)	24 (4.8)	82 (5.7)	68 (9.7)	14 (1.9)
Bladder cancer, n (%)	285 (8.0)	253 (10.9)	32 (2.5)	229 (10.8)	206 (12.8)	23 (4.6)	56 (3.9)	47 (6.7)	9 (1.2)
Renal parenchymal cancer, n (%)	37 (1.0)	31 (1.4)	6 (0.5)	19 (0.9)	18 (1.2)	1 (0.2)	18 (1.2)	13 (1.8)	5 (0.7)
Upper tract transitional cell carcinoma, n (%)	26 (0.7)	26 (1.1)	(0)	18 (0.9)	18 (1.1)	0 (0)	8 (0.6)	8 (1.1)	0 (0)
Prostate cancer, n (%)	9 (0.3)	9 (0.4)	0 (0)	9 (0.4)	9 (0.6)	0 (0)	0 (0)	0 (0)	0 (0)
Stone disease, n (%)	267 (7.5)	213 (9.2)	54 (4.3)	180 (8.5)	160 (10.0)	20 (4.0)	87 (6.0)	53 (7.5)	34 (4.6)
Angiomyolipoma, n (%)	17 (0.5)	8 (0.3)	9 (0.7)	4 (0.2)	3 (0.2)	1 (0.2)	13 (0.9)	5 (0.7)	8 (1.1)
Pelvic ureteric junction obstruction, n (%)	8 (0.2)	7 (0.3)	1 (<0.1)	5 (0.2)	5 (0.3)	0 (0)	3 (0.2)	2 (0.3)	1 (0.1)

NVH: non-visible haematuria; VH: Visible haematuria; TCC: transitional cell carcinoma

Supplementary Table 2: Histopathological results following transurethral resection of bladder tumour stratified according to type of haematuria.

	Any haematuria (n=299)	Visible haematuria (n=266)	Non-visible haematuria (n=33)
Grade, n (%):			
G1	34 (12.0)	27 (10.8)	7 (21.9)
G2	116 (41.0)	109 (43.4)	7 (21.9)
G3*	133 (47.0)	115 (45.8)	18 (56.3)
TMN stage, n (%):			
CIS*	4 (1.3)	4 (1.6)	0 (0)
pTa	171 (57.4)	155 (61.8)	15 (46.9)
pT1*	58 (19.5)	51 (19.2)	7 (21.9)

≥pT2*	51 (17.1)	41 (15.4)	10 (31.3)
papillary NMIBC + CIS, n (%)	33(14.4)	29(14.1)	4 (18.2)
Number of tumours, n (%):			
1	220 (73.8)	196 (74.0)	24 (75.0)
≥2	46 (15.4)	39 (14.7)	7 (21.9)
Not known	32 (10.7)	30 (11.3)	1 (3.1)
Histology subtype, n (%):			
TCC	276 (92.3)	244 (91.7)	32 (97.0)
Adenocarcinoma	2 (0.7)	2 (0.8)	0 (0)
Squamous cell	4 (1.3)	4 (1.5)	0 (0)
Prostate cancer	9 (3.0)	9 (3.4)	0 (0)
Papilloma	5 (1.7)	4 (1.5)	1 (3.0)
Other**	3 (1.0)	3 (1.1)	0 (0)
Disease risk, n (%):			
Low	33 (11.1)	26 (10.3)	7 (21.9)
Intermediate	107 (35.9)	101 (40.1)	6 (18.8)
High	144 (48.3)	125 (49.6)	19 (59.4)

* signifies high risk disease

**Other tumours comprise of a giant cell cancer, amyloid and non-Hodgkin's lymphoma