available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Platinum Priority – Brief Correspondence
Editorial by XXX on pp. x–y of this issue

Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients

Wei Shen Tan [a,b,*], *Andrew Feber* [c], *Rachael Sarpong* [d], *Pramit Khetrapal* [a,b], *Simon Rodney* [a,c], *Rumana Jalil* [d], *Hugh Mostafid* [e], *Joanne Cresswell* [f], *James Hicks* [g], *Abhay Rane* [h], *Alastair Henderson* [i], *Dawn Watson* [f], *Jacob Cherian* [j], *Norman Williams* [d], *Chris Brew-Graves* [d], *John D. Kelly* [a,b], *on behalf of DETECT I trial collaborators*

[a] *Division of Surgery and Interventional Science, University College London, London, UK;* [b] *Department of Urology, University College London Hospital, London, UK;* [c] *UCL Cancer Institute, London, UK;* [d] *Surgical & Interventional Trials Unit, University College London, London, UK;* [e] *Department of Urology, Royal Surrey County Hospital, Guildford, Surrey, UK;* [f] *Department of Urology, James Cook University Hospital, Middlesbrough, UK;* [g] *Department of Urology, Western Sussex Hospitals NHS Foundation Trust, Worthing Hospital, Worthing, West Sussex, UK;* [h] *Department of Urology, East Surrey Hospital, Redhill, UK;* [i] *Department of Urology, Maidstone Hospital, Maidstone, UK;* [j] *Department of Urology, The Pennine Acute Hospitals NHS Trust, North Manchester General Hospital, Crumpsall, UK*

Article info

Article history:
Accepted March 7, 2018

Associate Editor:
Giacomo Novara

Keywords:
Age
Bladder cancer
Haematuria
Incidence
Investigation
Renal cancer

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 nonvisible (NVH) haematuria. The overall incidence of urinary tract cancer was 10.0% (bladder cancer 8.0%, renal parenchymal cancer 1.0%, upper tract transitional cell carcinoma 0.7%, and prostate cancer 0.3%). Patients with VH were more likely to have a diagnosis of urinary tract cancer compared with NVH patients (13.8% vs 3.1%). Older patients, male gender, and smoking history were independently associated with urinary tract cancer diagnosis. Of bladder cancers diagnosed following NVH, 59.4% were high-risk cancers, with 31.3% being muscle invasive. The incidence of cancer in VH patients <45 yr of age was 3.5% ($n = 7$) and 1.0% ($n = 4$) in NVH patients <60 yr old. 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 yr, as recommended in some guidelines, as the investigation of nonvisible 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 that patients will benefit from investigation should be developed.

* Corresponding author. Division of Surgery & Interventional Science, University College London, 3rd Floor Charles Bell House, 43-45 Foley Street, London W1W 7TS, UK. Tel. +4402076799060.
E-mail address: wei.tan@ucl.ac.uk (W.S. Tan).

https://doi.org/10.1016/j.eururo.2018.03.008
0302-2838/

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 yr with visible haematuria (VH) and ≥60 yr with nonvisible 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), aged ≥35 yr, should be investigated [3]. In contrast, the National Board of Health and Welfare of Sweden does not recommend investigating NVH cases [4].

The DETECT I study is a prospective multicentre 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 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 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 previously been reported [5]. The study protocol was approved by Health Research Authority: North West Liverpool Central Research Ethics Committee in March 2016 (IRAS project ID: 179245, REC reference: 16/NW/0150).

Patient demographics according to diagnosis of urinary tract cancer are 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 58.7% (n = 37) of upper tract cancer, and upper tract TCC was detected in the remaining 41.3% (n = 26) of cases (Supplementary Table 1). Exclusively, all upper tract TCC and 83.8% of renal parenchymal cancers presented with

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)	
Nonvisible	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
Nonsmoker	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 work/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)	
Disabled	40 (1.1)	2 (0.6)	38 (1.2)	
Not known	156 (4.4)	14 (3.9)	142 (4.4)	
Occupational risk factor [a], 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)	

IQR = interquartile range.
[a] Defined as gardener, painter, hairdresser/barber, textile worker, or metals factory worker.

Please cite this article in press as: Tan WS, et al. Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.008

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 2 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 and one upper tract TCC). No cancers presented with NVH in patients referred below the AUA threshold of <35 yr. The incidence of cancer was 3.5% (n = 7) in patients with VH who were <45 yr old and 1.0% (n = 4) in patients with NVH who were <60 yr old.

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 having high-risk cancer and 31.3% as having MIBC. Analysis of bladder cancers detected below the NICE age threshold for investigation of VH reported 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 cancers, with a significant number being MIBCs. Application of the NICE-defined age threshold will fail to detect 10.5% of cancers with NVH (incidence: 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 incidence 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 and 59 yr, 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 [8] showed that 85% of patients would want referral for investigation for a symptom attributing a 1% risk of cancer, even if invasive testing such as colonoscopy for colon cancer is required.

An important limitation of the study is that 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 the selection bias based on diagnosis. In this study,

Table 2 – Incidence of malignancy in male and female patients, stratified according to age groups

Age groups	Visible haematuria, n (%)					Nonvisible haematuria, n (%)				
	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
Male patients										
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)
Female patients										
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
NICE-recommended age thresholds for haematuria investigations are shaded.

Please cite this article in press as: Tan WS, et al. Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.008

the incidence of urinary tract cancer in patients with haematuria represents the detection rate in secondary care, and this will be higher than the incidence in 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 Europe-wide guideline would aid in physician decision making and patient selection for referral for investigation of haematuria.

Author contributions: Wei Shen Tan had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Kelly, Feber, Tan, Brew-Graves, Williams.
Acquisition of data: Tan, Mostafid, Cresswell, Khetrapal, Rodney, Hicks, Rane, Henderson, Watson, Cherian, DETECT I trial collaborators.
Analysis and interpretation of data: Tan, Kelly, Williams.
Drafting of the manuscript: Tan, Kelly.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Tan, Williams.
Obtaining funding: Kelly, Feber.
Administrative, technical, or material support: Sarpong, Jalil.
Supervision: Kelly.
Other: None.

Financial disclosures: Wei Shen Tan certifies that all conflicts of interest, including specific financial interests and relationships and affiliations relevant to the subject matter or materials discussed in the manuscript (eg, employment/affiliation, grants or funding, consultancies, honoraria, stock ownership or options, expert testimony, royalties, or patents filed, received, or pending), are the following: None.

Funding/Support and role of the sponsor: DETECT I was funded by the Medical Research Council (MRC). Additional funding was by the UCLH Biomedical Research Centre and the Urology Foundation. It was supported in both delivery and the by the UCL Surgical Interventional Trials Unit (SITU). NHS-associated cost supported all standard of care investigations and procedures. Funding organisations have no role in any part of the study or decision to submit for publication.

Appendix A. DETECT I collaborators

Participating centres and investigators:

W.S. Tan, P. Khetrapal, H. Baker, B.W. Lamb, A. Sridhar, F. Ocampo, H. McBain, J.D. Kelly* (UCLH); K. Baillie, K. Middleton, D. Watson* (James Cook University Hospital); H. Knight, S. Maher, A. Rane* (East Surrey Hospital); S. Pelluri, J. Pati* (Homerton Hospital); A. Cossons, C. Scott, S. Madaan* (Darent Valley Hospital); S. Bradfield, N. Wakeford, H. Mostafid* (Royal Surrey County Hospital); A. Dann, J. Cook, M. Cornwell, R. Mills* (Norfolk & Norwich University Hospital); S. Thomas, S. Reyner, G. Vallejera, P. Adeniran, S. Masood* (Medway Maritime Hospital); B. Pathmanathan, A. Harmathova, G. Hellawell* (London North West University Healthcare); N. Whotton, K. Dent, S. Pearson, J. Hatton, M. Newton, E. Hheeney, K. Green, S. Evans, M. Rogers* (Northern Lincolnshire & Goole NHS Foundation Trust); K. Gupwell, S. Whiteley, A. Brown, J. McGrath* (Royal Devon and Exeter Hospital); N. Lunt, P. Hill, A. Sinclair* (Macclesfield Hospital); A. Paredes-Guerra, B. Holbrook, E. Ong* (North Devon District Hospital); H. Wardle, D. Wilson, A. Bayles* (University Hospital of North Tees); R. Fennelly, M. Tribbeck, K. Ames, M. Davies* (Salisbury District Hospital); J.A. Taylor, E. Edmunds, J. Moore* (East Sussex Healthcare NHS Trust); S. Mckinley, T. Nolan, A. Speed, A. Tunnicliff, G. Fossey, A. Williams, M. George, I. Hutchins, R. Einosas, A. Richards, A. Henderson* (Maidstone Hospital); B. Appleby, L. Kehoe, L. Gladwell, S. Drakeley, J.A. Davies, R. Krishnan* (Kent & Canterbury Hospital); H. Roberts, C. Main, S. Jain* (St James's University Hospital); J. Dumville, N. Wilkinson, J. Taylor, F. Thomas* (Doncaster Royal Infirmary); K. Goulden, C. Vinod, E. Green* (Salford Royal Hospital); C. Waymont, J. Rogers, A. Grant, V. Carter, H. Heap, C. Lomas, P. Cooke* (New Cross Hospital); L. Scarratt, T. Hodgkiss, D. Johnstone, J. Johnson, J. Allsop, J. Rothwell, K. Connolly, J. Cherian* (The Pennine Acute Hospitals NHS Trust); S. Ridgway, M. Coulding, H. Savill, J. Mccormick, M. Clark, G. Collins* (Tameside General Hospital); K. Jewers, S. Keith, G. Bowen, J. Hargreaves, K. Riley, S. Srirangam* (East Lancashire Hospitals NHS Trust); A. Rees, S. Williams, S. Dukes, A. Goffe* (Dorset County Hospital); L. Dawson*, R. Mistry, J. Chadwick, S. Cocks, R. Hull, A. Loftus (Royal Bolton Hospital); Y. Baird, S. Moore, S. Greenslade, J. Margalef, I. Chadbourn, M. Harris, J. Hicks* (Western Sussex Hospitals NHS Foundation Trust); P. Clitheroe, S. Connolly, S. Hodgkinson, H. Haydock, A. Sinclair* (Stepping Hill Hospital); E. Storr, L. Cogley, S. Natale* (Derriford Hospital); W. Lovegrove, K. Slack, D. Nash, K. Smith* (King's Mill Hospital); J. Walsh, A.M. Guerdette, M. Hill, D. Payne* (Kettering General Hospital); B. Taylor, E. Sinclair, M. Perry, M. Debbarma* (Pinderfields Hospital); D. Hewitt, R. Sriram* (University Hospitals Coventry); A. Power, J. Cannon, L. Devereaux, A. Thompson* (Royal Albert Edward Infirmary); K. Atkinson, L. Royle, J. Madine, K. MacLean* (Royal Cornwall Hospital).

* Principal investigators at each centre.

Appendix B. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.eururo.2018.03.008.

References

[1] Linder BJ, Bass EJ, Mostafid H, Boorjian SA. Guideline of guidelines: asymptomatic microscopic haematuria. BJU Int 2017;16:14016.
[2] National Institute for Health and Care Excellence. Suspected cancer: recognition and referral.. 2015.
[3] Davis R, Jones JS, Barocas DA, et al. Diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults: AUA guideline. J Urol 2012;188:2473–81.
[4] Malmstrom PU. Time to abandon testing for microscopic haematuria in adults? BMJ 2003;326:813–5.
[5] Tan WS, Feber A, Dong L, et al. DETECT I & DETECT II: a study protocol for a prospective multicentre observational study to

validate the UroMark assay for the detection of bladder cancer from urinary cells. BMC Cancer 2017;17:767.

[6] Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO classification of tumours of the urinary system and male genital organs—part B: prostate and bladder tumours. Eur Urol 2016;70:106–19.

[7] Babjuk M, Bohle A, Burger M, et al. EAU guidelines on non-muscle-invasive urothelial carcinoma of the bladder: update 2016. Eur Urol 2017;71:447–61.

[8] Banks J, Hollinghurst S, Bigwood L, Peters TJ, Walter FM, Hamilton W. Preferences for cancer investigation: a vignette-based study of primary-care attendees. Lancet Oncol 2014;15:232–40.

Please cite this article in press as: Tan WS, et al. Who Should Be Investigated for Haematuria? Results of a Contemporary Prospective Observational Study of 3556 Patients. Eur Urol (2018), https://doi.org/10.1016/j.eururo.2018.03.008