Non-visible haematuria: would discontinuing urgent investigation have a visible impact?

Abstract

National guidance in the UK continues to recommend urgent referral of selected patients with non-visible haematuria for urological assessment. The positive predictive value of non-visible haematuria for urological cancer is low, so it is uncertain whether this is an effective and equitable use of healthcare resources. This article considers rationales for and against continuing this practice, and outlines alternative investigative strategies for patients presenting with non-visible haematuria based on current knowledge and modern technology.

Key words: Bladder cancer; Cystoscopy; Guidance; Haematuria; Screening; Uro-oncology

Submitted: 31 January 2020; accepted after double-blind peer review: 12 February 2020

Joseph B John[1]

Alberto Coscione[2]

Peter Acher[2]

Mark Speakman[3]

Author details can be found at the end of this article

Correspondence to: Joseph B John; joseph.john3@nhs.net

Introduction

Non-visible haematuria has remained a contentious criterion for suspected cancer referral since the urgent '2-week wait' initiative was introduced (Department of Health, 2000). The validity of its inclusion has been questioned in numerous studies (Allen et al, 2004; Edwards et al, 2006).

In 2015, the National Institute for Health and Care Excellence guidance for non-visible haematuria changed. The previous 2005 guidance recommended urgent referral of all patients aged over 50 years with non-visible haematuria on two of three urine dipstick tests, including those who were asymptomatic (National Institute for Health and Care Excellence, 2005). The updated 2015 guidance increased the threshold age to 60 years and now only recommends referral of patients with non-visible haematuria if this is accompanied by dysuria or an elevated white cell count on blood testing (National Institute for Health and Care Excellence, 2015). There remains doubt as to whether this modified guideline is appropriately selective. This article examines the evidence for and against the ongoing inclusion of non-visible haematuria in the urgent suspected cancer referral guidelines, and considers possible strategies for improving the effectiveness of bladder cancer investigation.

There are compelling arguments for and against the ongoing inclusion of non-visible haematuria in the urgent referral pathway. When the urgent suspected cancer referral initiative was introduced, it was projected that the cancer detection rate among all patients referred with haematuria would be around 17% (Allen et al, 2004). While studies indicate that referrals of patients with visible haematuria have exceeded this projection, with positive predictive values of 19–26% reported in UK literature (Edwards et al, 2006; Mathew and Desai, 2009), non-visible haematuria has delivered less impressive yields of between 0.5% (Hiatt and Ordonez, 1994) and 4.9% (Carel et al, 1987; Edwards et al, 2006; Price et al, 2014; Tan et al, 2018b). On the whole, services have evolved to match the excess demand placed by referral of patients with non-visible haematuria – a great testament to how NHS services can adapt to meet requirements.

It is right to question the appropriateness of urgently investigating patients who have non-visible haematuria (typically with cystoscopy and ultrasound) in the context of these low cancer detection rates. Given the background of persistently poor outcomes for patients diagnosed with muscle-invasive bladder cancer (National Cancer Intelligence Network, 2013) resources might be used differently to achieve better outcomes for these patients.

How to cite this article: John JB, Coscione A, Acher P, Speakman M. Non-visible haematuria: would discontinuing urgent investigation have a visible impact? Br J Hosp Med. 2020. https://doi.org/10.12968/hmed.2020.0035

The case for keeping non-visible haematuria in the urgent referral pathway

The National Institute for Health and Care Excellence (2015) guidance modified the non-visible haematuria urgent referral criteria on the basis of a case-control study indicating that the positive predictive values of non-visible haematuria with a raised white cell count on blood testing and non-visible haematuria with dysuria were 3.9% and 4.5% respectively (Price et al, 2014). A positive predictive value of greater than 3% was deemed to be sufficiently high to warrant urgent referral. Despite the availability of cytology and urinary biomarkers, no tests to date have matched the sensitivity and specificity of cystoscopy in detecting bladder cancer (van Rhijn et al, 2009). No less invasive and less resource-intensive alternatives have been validated for definitively ruling out cancer in these patients.

The fact that urological services generally manage to assess all urgent haematuria referrals in a timely manner suggests that practice may not need to change with any haste. Many hospitals have established one-stop clinics, staffed by highly experienced and efficient specialist nurses whose expertise might not be easily transferred to other activities. One could argue that these services should not be taken for granted, nor should an inherent opportunity cost be assumed associated with their ongoing use in investigating suspected bladder cancer.

An uncharacterised factor in the referral pathway should also be considered – the clinical acumen of referring clinicians. No guidance exists advising GPs on when to perform a urine dipstick test for suspected bladder cancer, therefore little is understood about their initial clinical reasoning for doing the test. To completely remove the non-visible haematuria referral pathway might close an avenue through which experienced GPs can urgently refer patients who they are rightly worried about for reasons beyond the scope of referral criteria. Likewise, little is understood about the potentially large cohort of patients who GPs rationally never test or do not refer owing to a low perceived cancer risk, despite the presence of non-visible haematuria.

Evidence indicates that bladder cancer diagnosed following visible haematuria tends to present at a more advanced stage (Ramirez et al, 2016). If one presumes non-visible haematuria to be a prelude to visible haematuria in bladder cancer then one could strongly argue against avoiding complacency when presented with a patient with unexplained non-visible haematuria.

A Dutch population-based study showed that delay to bladder cancer diagnosis resulted in worse outcomes, independent of tumour grade or stage (Hollenbeck et al, 2010). Furthermore, a UK study of over 3500 patients found an overall cancer detection rate of less than 3% in non-visible haematuria referrals but, of those cancers, 59% were classified as high grade and 31% were muscle invasive (Tan et al, 2018a). This adds weight to the idea that clinicians should remain attentive to any clinical data suggesting possible bladder cancer, including non-visible haematuria.

Clinicians should consider the risks associated with altogether removing non-visible haematuria from the urgent referral pathway. Unfortunately, strain on hospital resources is such that there is commonly a stark contrast between elective and suspected cancer referral timelines. It is hard to imagine that a compromise of referral on a semi-urgent basis could be established for patients with non-visible haematuria. If non-visible haematuria is removed from the guideline, a proportion of patients who would have been found to have bladder cancer may wait many months to be assessed. In this time, the cancer could have advanced, if not by stage progression then by enlarging to the extent that surgery becomes more challenging with subsequent increased morbidity.

The association of haematuria with bladder cancer is deeply ingrained into the population psyche. It would be difficult for an individual with un-investigated non-visible haematuria to understand a subsequent delay in diagnosis.

The case for removing non-visible haematuria from the urgent pathway

Asymptomatic non-visible haematuria occurs in 2.6% of men and 8.1% of women of working age (Carel et al, 1987). This figure rises significantly in both sexes with increasing age.

Non-visible haematuria can essentially be considered a normal population variant (Tomson and Porter, 2002), demonstrating a need to be highly prescriptive in advising when to test urine for blood, and to be shrewd in interpreting the significance of incidental non-visible haematuria. Clinicians should consider ways to improve the positive predictive value of testing beyond the modest 3.9–4.5% expected from the evidence informing the National Institute for Health and Care Excellence guidance (Price et al, 2014). This might take the form of additional pre-cystoscopy urine biomarker testing, or factoring in additional risk factors such as smoking history.

In the UK, the 'Blood in Your Pee' media campaign was part of the government's 2013 'Be Clear on Cancer' health drive to raise awareness of urological cancers. Analysis of the impact of this campaign on referral practices to a large London hospital with a catchment area of over 2 million people found a 79% increase in non-visible haematuria referrals in the initial 4 months of the campaign, but no statistically significant increase in diagnosis of any target urological cancers (Hughes-Hallett et al, 2016).

As discussed above, there are no evidence-based data indicating the typical processes leading to a patient's referral with non-visible haematuria. It might be that urine is generally only dipped in association with concerning symptoms and patient risk factors. Alternatively, urine might be tested in a less discriminate and more routine manner by, for example, practice nurses. It is possible that benign urological disease with incidental non-visible haematuria is frequently referred as suspected cancer, when the patient would be better served in a general urology clinic. Urine dipstick testing forms a part of 'well man' and female health checks in the NHS and private sector (NHS, 2019; BUPA, 2020). This is another means of detecting incidental non-visible haematuria, potentially leading to urgent urology referral.

It is worth remembering that diagnosis is only one aspect of the management of bladder cancer. There is an opportunity cost associated with allocating disproportionate resource to diagnosis, and diagnosis in itself is relatively meaningless if similarly prompt and appropriate treatment cannot be delivered to patients with bladder cancer. This is pertinent when considering the low detection rate of bladder cancer in patients with non-visible haematuria. While urology departments are increasingly well staffed with specialist nurses who are adept in diagnostic procedures and able to run clinics, it is worth noting that urology cancer nurse specialists have the highest patient to nurse ratio and the highest vacancy rate of any cancer specialty in England in the most recent figures (Macmillan Cancer Support, 2017). Given the key role these professionals play in coordinating patient care, it is vital that this deficit is addressed.

It is well established that inordinate delays to definitive treatment are commonplace in bladder cancer (Varughese et al, 2019). Time to first treatment according to the 62-day national performance target is considered the time to transurethral resection of a bladder tumour. Transurethral resection of bladder tumour is rarely curative in muscle-invasive bladder cancer – definitive treatment typically takes the form of neoadjuvant chemotherapy with either radical cystectomy or radical radiotherapy. Without this treatment being performance assessed in the same way as for other cancers, patients with muscle-invasive bladder cancer commonly wait much longer for potentially curative treatment. In an aggressive disease recognised as having a short latent period (Wijkstrom et al, 2000) it is astonishing that time to curative treatment can be so long. Meanwhile, significant resource is still allocated to promptly ruling out cancer in a relatively low risk patient group referred with non-visible haematuria. This opportunity cost should therefore be borne in mind. Contemporary transitional cell carcinoma detection rates in studies of UK patients referred with non-visible haematuria are less than 3% (Khadhouri et al, 2019; John et al, 2020). This is lower than the threshold set by the National Institute for Health and Care Excellence (2015) to justify urgent investigation for possible cancer.

Bladder cancer screening: considering advances in colorectal cancer detection

Bladder cancer typically progresses rapidly, before becoming advanced and potentially incurable. It is rarely identified incidentally at postmortem. This represents a major challenge to producing

an effective bladder cancer screening programme. UK experiences in public health campaigns have not shown conclusive benefits, as discussed above (Hughes-Hallett et al, 2016).

Despite colorectal cancer typically advancing at a slower rate than bladder cancer, it is worth considering an interesting advance in colorectal cancer screening – quantitative faecal immunochemical testing. Quantitative faecal immunochemical testing measures the concentration of blood present in faeces using antibodies that bind specifically to compounds found in blood. At appropriate threshold concentrations, quantitative faecal immunochemical testing exhibits high sensitivity (92.1%) and specificity (85.8%) in patients presenting with non-specific symptoms and low risk for bowel cancer (0.1–3%). In this patient group, the test has an estimated 8.9% positive predictive value and 99.8% negative predictive value (National Institute for Health and Care Excellence, 2017). For non-visible haematuria, similar quantitative methods to faecal immunochemical testing should be sought to significantly improve the positive predictive value, before considering referral for cystoscopy.

A range of urine tests has already been compared against the standard of care (cystoscopy and upper tract imaging) in diagnosis of bladder cancer. Urine cytology is long-established, but its poor sensitivity (17% for low-grade disease and 58% for high-grade disease) and moderate specificity (94%) limits its utility (van Rhijn et al, 2009). More modern urine tests include the qualitative point of care bladder tumour antigen stat test and the quantitative nuclear matrix protein 22 test. The uCyt+/immunocyt test uses fluorescent monoclonal antibodies to detect cancer cell antigens, DNA microsatellite analysis detects common genetic mutations seen in bladder cancer, and fluorescence in situ hybridisation detects chromosomal abnormalities. All of these tests have higher sensitivity (58–77%) but lower specificity (73–86%) than cytology, but none match cystoscopy. A systematic review of urine biomarkers found that testing certain biomarker panels rather than individual markers improved sensitivity and specificity to greater than 90% (Tan et al, 2018c). However, the studies assessed were limited by an absence of prospective trial designs and a lack of validation in independent patient cohorts. For the tests where validation in independent cohorts was sought, poorer test performances were observed.

Further studies could nonetheless be developed to test a combination of risk factors and non-invasive testing results. Negative urine biomarker tests in patients referred with non-visible haematuria could help to circumvent unnecessary cystoscopies by indicating an even lower likelihood of finding bladder cancer, were cystoscopy to be performed. In the future, targeted screening of high-risk patients could be effectively conducted to avoid the potentially inequitable allocation of diagnostic investigations that is currently seen with the non-visible haematuria pathway.

A different strategy could be to offer quality community-based ultrasound scanning to patients with non-visible haematuria. This would detect larger bladder tumours (greater than 3 mm) as well as a proportion of other diagnoses, such as renal masses and stones. The risk of bladder cancer in patients with normal ultrasound scans would likely be similar to that of patients without non-visible haematuria. This approach would allow better use of specialist services.

Patient perception

Investigations for non-visible haematuria can have a significant burden on patients. A Dutch study of 220 participants revealed that 39% of patients found cystoscopy uncomfortable and 35% found it painful. Post-cystoscopy patient-reported rates of dysuria, haematuria and fever were 30%, 7% and 2% respectively (Van der Aa et al, 2008). Clinicians could argue that in the setting of non-visible haematuria, this significant burden is not justified against a very low probability of detecting cancer. On the other hand, a study assessing patient preference for testing in the setting of cancer risk showed that 85% of patients would prefer referral for a symptom with a potential cancer risk of as low as 1%, even if it entailed invasive investigations such as a colonoscopy (Banks et al, 2014).

Consideration of patients' preferences and their perceptions of the burdens of investigations are important to explore and balance against clinical evidence and public health data. This allows for a balanced discourse regarding whether patients with non-visible haematuria should be investigated, and how.

Further research

The single study that informed the referral of patients over 60 years of age with non-visible haematuria was a retrospective case-control study reviewing coded and un-coded electronic GP records (Price et al, 2014). The study recognised that non-visible haematuria was probably underestimated because typographical errors and omission of urinalysis results from records will have resulted in some relevant records not being retrieved. As a result, the calculated positive predictive values in the study may have been overestimated.

Furthermore, the statistical significance of the positive predictive value of non-visible haematuria with dysuria or non-visible haematuria with raised white cell count was not actually calculated in the study. Therefore the exact positive predictive value of the non-visible haematuria referral criteria is not known, but it is already very low and probably overestimated. A range of scenarios could be selected, based on patient demographic and risk factors, where clinical equipoise with the current non-visible haematuria pathway could be established, with a view to conducting randomised controlled trials aimed at improving the bladder cancer referral pathway.

An alternative to formal randomised controlled trials could be to use machine learning. The non-visible haematuria pathway represents an ideal scenario in which computer science could be applied. By feeding various patient factors into a computer model, and later inputting diagnoses, over time computers could feasibly provide vastly more informative pre-test probabilities of finding bladder cancer. Predictions would become increasingly accurate with time, as patient data and outcomes are input iteratively. Clinicians could undertake increasingly more informed discussion regarding risks and benefits of cystoscopic investigation, and more patients might appropriately decline investigation after having a more personalised estimate of their cancer risk. Machine learning could offer future opportunities to elicit previously unknown factors associated with an increased bladder cancer probability, for example dietary factors. However, this approach would be contingent on obtaining high-quality and accessible electronic patient information.

Testing in other countries

Observing outcomes in countries with similar healthcare systems can inform decisions in the UK. In 2011, Sweden discontinued fast-track referral of patients with non-visible haematuria. Despite this, there was no subsequent decline in bladder cancer outcomes and the proportion of patients with muscle-invasive bladder cancer at diagnosis fell (Jahnson et al, 2016).

There is certainly more to learn from large retrospective studies, to inform future decisions in the UK. The international collaborative IDENTIFY study, having collected a large volume of data on haematuria referrals, might provide necessary insight. The full results from the IDENTIFY study are due to be published later in 2020. If uncertainty over how to manage non-visible haematuria remains, then a randomised controlled trial might be necessary to clarify whether non-visible haematuria warrants urgent investigation.

Conclusions

The inclusion of referral of patients with non-visible haematuria in the urgent suspected cancer pathway remains contentious and its ongoing presence arguably has a high associated opportunity cost. A stronger evidence base is needed to justify the ongoing urgent referral of any patient with non-visible haematuria. The diagnostic yield of the 2015 National Institute for Health and Care Excellence non-visible haematuria referral criteria should be audited and compared directly against the National Institute for Health and Care Excellence (2005) non-visible haematuria criteria, to determine whether an improvement has been realised. Given the low positive predictive value of non-visible haematuria, ethics committees should consider permitting large-scale randomised controlled trials. These trials could include the use of established but infrequently used urinary biomarker assays, in combination with patient risk factors. It would also be useful to understand the rationale leading to GPs testing urine for non-visible haematuria. A database of all non-visible haematuria referrals should be established and machine learning used to refine the referral pathway and inform pre-cystoscopy clinician–patient discussions.

Key points

- Evidence indicates that non-visible haematuria has a relatively low positive predictive value for bladder cancer, between 0.5 and 4.9%.
- Further evidence is required to understand whether the urgent referral for urology assessment of patients with non-visible haematuria constitutes an effective use of healthcare resources.
- Using current technology, including urinary biomarkers and ultrasound scanning, could avoid unnecessary cystoscopy for selected patients with non-visible haematuria.
- Machine learning, using electronic patient records, could develop increasingly accurate predictions of whether patients are likely to have bladder cancer.

Author details

[1]Department of Urology, Royal Devon and Exeter NHS Foundation Trust, Exeter, UK

[2]Department of Urology, Southend University Hospital NHS Foundation Trust, Southend-on-Sea, UK

[3]Department of Urology, Taunton and Somerset NHS Foundation Trust, Taunton, UK

Conflicts of interest

The authors declare no conflicts of interest.

References

Allen D, Popert R, O'Brien T. The two-week-wait cancer initiative in urology: useful modernization? J R Soc Med. 2004;97(6):279–281. https://doi.org/10.1258/jrsm.97.6.279

Banks J, Hollinghurst S, Bigwood L et al. Preferences for cancer investigation: a vignette-based study of primary-care attendees. Lancet Oncol. 2014;15(2):232–240. https://doi.org/10.1016/S1470-2045(13)70588-6

BUPA. Female health check. 2020. https://www.bupa.co.uk/health/health-assessments/female-health (accessed 22 February 2020)

Carel RS, Silverberg DS, Kaminsky R, Aviram A. Routine urinalysis (dipstick) findings in mass screening of healthy adults. Clin Chem. 1987;33(11):2106–2108. https://doi.org/10.1093/clinchem/33.11.2106

Department of Health. The NHS cancer plan: a plan for investment, a plan for reform. London: DoH. 2000;1–98. https://doi.org/10.1145/2463209.2488949

Edwards T, Dickinson AJ, Natale S, Gosling J, Mcgrath JS. A prospective analysis of the diagnostic yield resulting from the attendance of 4020 patients at a protocol-driven haematuria clinic. BJU Int. 2006;97(2):301–305. https://doi.org/10.1111/j.1464-410X.2006.05976.x

Hiatt RA, Ordonez JD. Dipstick urinalysis screening, asymptomatic microhematuria, and subsequent urological cancers in a population-based sample. Cancer Epidemiol Biomarkers Prev. 1994;3(5):439–443

Hollenbeck BK, Dunn RL, Ye Z et al. Delays in diagnosis and bladder cancer mortality. Cancer. 2010;116(22):5235–5242. https://doi.org/10.1002/cncr.25310

Hughes-Hallett A, Browne D, Mensah E, Vale J, Mayer E. Assessing the impact of mass media public health campaigns. Be Clear on Cancer 'blood in pee': a case in point. BJU Int. 2016;117(4):570–575. https://doi.org/10.1111/bju.13205

Jahnson S, Hosseini Aliabad A, Holmäng S et al. Swedish National Registry of Urinary Bladder Cancer: no difference in relative survival over time despite more aggressive treatment. Scand J Urol. 2016;50(1):14–20. https://doi.org/10.3109/21681805.2015.1085089

John J, Wijeyaratne S, Speakman M. Impact of the 2015 NICE guidance for urgent assessment of patients with non-visible haematuria. J Clin Urol. 2020;13(1):56–61. https://doi.org/10.1177/2051415819872910

Khadhouri S, Gallagher KM, Mackenzie KR et al; The IDENTIFY Study Group. P2-1 IDENTIFY: The Investigation and DEtection of urological Neoplasia in paTIents reFerred with suspected urinarY tract cancer: A multicentre analysis. J Clin Urol. 2019;12(1s):9–89. https://doi.org/10.1177/2051415819846081

Macmillan Cancer Support. A census of cancer, palliative and chemotherapy speciality nurses and support workers in England in 2017. 2017. https://www.macmillan.org.uk/_images/cancer-workforce-in-england-census-of-cancer-palliative-and-chemotheraphy-speciality-nurses-and-support-workers-2017_tcm9-325727.pdf (accessed 22 February 2020)

Mathew A, Desai KM. An audit of urology two-week wait referrals in a large teaching hospital in England. Ann R Coll Surg Engl. 2009;91(4):310–312. https://doi.org/10.1308/003588409X391767

National Cancer Intelligence Network. Renal pelvis and ureter cancer incidence, mortality and survival rates in the United Kingdom. 2013. http://www.ncin.org.uk/view?rid=1006 (accessed 22 February 2020)

National Institute for Health and Care Excellence. Referral guidelines for suspected cancer. NICE guideline CG27. 2005. London: National Institute for Health and Care Excellence

National Institute for Health and Care Excellence. Suspected cancer: recognition and referral. NICE guideline NG12. 2015. www.nice.org.uk/guidance/ng12 (accessed 22 February 2020)

National Institute for Health and Care Excellence. Quantitative faecal immunochemical tests to guide referral for colorectal cancer in primary care: guidance and guidelines. DG30. 2017. https://www.nice.org.uk/guidance/dg30 (accessed 12 March 2020)

NHS. What are well man clinics? 2019. https://www.nhs.uk/common-health-questions/mens-health/what-are-well-man-clinics/ (accessed 22 February 2020)

Price SJ, Shephard EA, Stapley SA, Barraclough K, Hamilton WT. Non-visible hematuria. Br J Gen Pract. 2014;64(626):e584–e589. https://doi.org/10.3399/bjgp14X681409

Ramirez D, Gupta A, Canter D et al. Microscopic haematuria at time of diagnosis is associated with lower disease stage in patients with newly diagnosed bladder cancer. BJU Int. 2016;117(5):783–786. https://doi.org/10.1111/bju.13345

Tan WS, Feber A, Sarpong R et al. Who should be investigated for haematuria? Results of a contemporary prospective observational study of 3556 patients. Eur Urol. 2018a;74(1):10–14. https://doi.org/10.1016/j.eururo.2018.03.008

Tan WS, Sarpong R, Khetrapal P et al. Can renal and bladder ultrasound replace computerized tomography urogram in patients investigated for microscopic hematuria? J Urol. 2018b;200(5):973–980. https://doi.org/10.1016/j.juro.2018.04.065

Tan WS, Tan WP, Tan M-Y et al. Novel urinary biomarkers for the detection of bladder cancer: a systematic review. Cancer Treat Rev. 2018c;69:39–52. https://doi.org/10.1016/j.ctrv.2018.05.012

Tomson C, Porter T. Asymptomatic microscopic or dipstick haematuria in adults: which investigations for which patients? A review of the evidence. BJU Int. 2002;90(3):185–198. https://doi.org/10.1046/j.1464-410x.2002.02841.x

Van der Aa MNM, Steyerberg EW, Sen EF et al. Patients' perceived burden of cystoscopic and urinary surveillance of bladder cancer: a randomized comparison. BJU Int. 2008;101(9):1106–1110. https://doi.org/10.1111/j.1464-410X.2007.07224.x

van Rhijn BWG, van der Poel HG, van der Kwast TH. Cytology and urinary markers for the diagnosis of bladder cancer. Eur Urol Suppl. 2009;8(7):536–541. https://doi.org/10.1016/j.eursup.2009.06.008

Varughese M, Treece S, Drinkwater KJ. Radiotherapy management of muscle invasive bladder cancer: evaluation of a national cohort. Clin Oncol. 2019;31(9):637–645. https://doi.org/10.1016/j.clon.2019.04.009

Wijkstrom H, Cohen SM, Gardiner RA et al. Prevention and treatment of urothelial premalignant and malignant lesions. Scand J Urol Nephrol Suppl. 2000;34(205):116–135. https://doi.org/10.1080/00365590050509878