The investigation of haematuria and bladder cancer

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Although there has been a decline in the incidence and mortality attributed to bladder cancer over the last two decades the disease is still a relatively common cause of cancer-related death worldwide. Here the authors argue that, in contrast to national guidelines, patients of any age presenting with visible haematuria or non-visible haematuria at >40 years of age should be referred to a urologist for further evaluation.

Bladder cancer is the ninth most common malignant disease and the 13th most common cause of cancer-related death worldwide. Over the last 20 years, there has been a gradual decline in the incidence and mortality attributed to bladder cancer in the developed world. This is reflected by the decline in incidence of smoking and occupational risk factors. Although the incidence is consistently lower in women, it is rising due to the increasing prevalence of smoking among women. However, despite medical advancements, 50% of patients diagnosed with muscle-invasive bladder cancer (MIBC) succumb to the disease within five years.

Patient-specific risk factors for bladder cancer include increasing age and male gender. There remains no known genetic alteration that can be clinically used to predict the risk of bladder cancer. Environmental risk factors are predominantly exposure to tobacco smoking and specific occupational carcinogens. It is estimated that cigarette smoking is responsible for half of all cases of diagnosed bladder cancer.

Occupational risk factors include workers exposed to aromatic amines (tobacco, dye, rubber workers, hairdressers, printers, leather workers) and polycyclic aromatic hydrocarbons (chimney sweeps, waiters, aluminium workers, seamen, petroleum workers). Other factors include the use of drugs such as cyclophosphamide and possibly pioglitazone; history of previous pelvic radiotherapy as well as chronic irritation to urothelium due to long-term catheter use; bladder stones or Schistosoma haematobium infection.

Who should be investigated?
As with other cancers, the early and prompt diagnosis of bladder cancer is crucial to improve patient survival. Screening asymptomatic patients for bladder cancer is currently not recommended due to the relatively low incidence in the general population. Haematuria, particularly visible haematuria (VH), is a cardinal sign to suspect urinary tract cancer. The risk of cancer is considerably lower in patients presenting with non-visible haematuria (NVH).

In the UK, the use of urine dipstick to test for haematuria is recommended and urine microscopy is not a requirement. NHS England has recently restated the ‘Blood in pee’ campaign as part of the ‘Be Clear on Cancer’ programme. Contemporary data suggest that patients with VH and NVH have a 13.5% and 3.1% risk of urinary tract cancer, respectively (see Table 1).

Bladder cancers account for 82% of all urinary tract cancers. NICE guidance recommends that patients ≥45 years old with unexplained VH without urinary tract infection (UTI)
Investigations

Nevertheless, prophylactic antibiotics following cystoscopy. Patients may develop UTI requiring treatment – as well as patients ≥60 years old with recurrent or persistent unexplained UTI. We recently reported that using age thresholds VH in patients ≥45 years, and NVH in patients ≥60 years, will result in a small but significant risk of cancer. Of the 2312 patients with visible haematuria, seven cases of urinary tract cancers were identified in patients aged <45 years, with an incidence rate of 3.5%. The risk of cancer in patients presenting with NVH between 40–59 years of age was 1.4%, with five cases of bladder cancer detected among the 358 patients investigated. However, no cancers were identified in patients <40 years old presenting with NVH.

Given the risk of clinically significant cancer in the age thresholds outside NICE guidelines, we would recommend that patients with VH aged <45 years, and patients with NVH between 40–59 years old, would benefit from non-urgent referral for investigation of haematuria; in addition to the current two-week suspected cancer pathway recommendations.

Investigating haematuria

The investigation of haematuria includes both cystoscopy and upper tract imaging. Flexible cystoscopy, which comprises an 18Fr fibre optic scope, is typically performed following instillation of local anaesthetic, infused with lubricating jelly, into the urethra. This is performed as an outpatient procedure and patients leave the hospital after voiding. It is worth acknowledging that up to 5% of patients may develop UTI requiring antibiotics following cystoscopy. Nevertheless, prophylactic antibiotics are not recommended in low-risk patients, defined as those with sterile urine, no history of UTI and not immunocompromised.

Upper tract imaging is crucial to rule out upper tract cancers, specifically renal cell carcinoma and upper tract urothelial carcinoma. Contemporary UK data suggest an overall incidence of upper tract cancer of 1.5% (renal cell carcinoma, 1.0%; upper tract urothelial carcinoma, 0.5%). We have shown recently that ultrasound of the kidneys is sufficient in patients presenting with NVH and CT urogram is not necessary.

Ultrasound of the kidneys has a high sensitivity for the detection of renal cell carcinoma and though it cannot identify upper tract urothelial carcinoma well, the risk of such cancer is rare (0% in a series of 3556 patients). Recent evidence has suggested that the use of CT for the imaging of the upper tracts in patients presenting with NVH may contribute to the development of more urinary tract cancers (due to excess ionising radiation) than cancers missed on ultrasound but picked up on CT.

Urine cytology should not be performed as part of the routine evaluation of haematuria. We recently reported that the sensitivity of cytology is poor and is more likely to result in false positives – subjecting patients to unnecessary further invasive procedures. Similarly, the role of other commercially available urine biomarkers – such as BTA stat, BTA TRACK, NMP22, ImmunoCyt and UroVysion (FISH) – remains limited as they have a sensitivity of 57–82% and should not be used as a replacement for cystoscopy due to the risk of missing cancers. Although they seem promising, novel urine biomarkers currently lack external validation. Instead, cystoscopy currently remains the gold standard for bladder visualisation with a sensitivity of ≥98%.

Management

Abnormal finding on cystoscopy such as a reddish flat, papillary or solid lesion requires a pathological evaluation (Figure 1). This is typically performed in a separate appointment under general anaesthetic, where histology is obtained via a transurethral bladder biopsy or a resection of the entire area. This procedure is both therapeutic and diagnostic. Following complete endoscopic tumour resection, a review of bladder cancer histology is essential to determine further management. The presence of cancer involvement of the detrusor is key in determining treatment.

Patients with non-muscle invasive bladder cancer (NMIBC) (Ta, T1, carcinoma in situ) may require adjuvant treatment, depending on disease risk, in a form of intravesical chemotherapy and bacillus Calmette-Guerin (BCG) immunotherapy to reduce the risk of disease recurrence and progression. These patients go on to have regular surveillance cystoscopy to ensure prompt treatment can be administered when recurrence is identified.

Patients with MIBC (T2–4) should be considered for radical cystectomy. This can be performed in the conventional open approach or using a minimally invasive approach with robotic assistance. There is still not a strong body of evidence to support robotic cystectomy, although anecdotal evidence suggests that a totally minimal invasive approach (including where urinary diversion is performed robotically) may promote an early return to normal activity, and may be better tolerated by less-healthy patients.

Patients who are fit and with good renal function should be considered for neoadjuvant cisplatin-based chemotherapy, which has been shown to have an absolute survival advantage. The recent developments in immunotherapy in the form of check point inhibitors is exciting and has shown great efficacy in the metastatic setting, with numerous ongoing trials.
Investigations

to test them in the neoadjuvant and adjuvant setting.

Conclusion

Patients of any age presenting with VH or NVH at ≥40 years of age should be referred to a urologist for further evaluation. Patients who are male, smokers and those with occupational risk factors are at an increased risk of bladder cancer. The evaluation of haematuria should be with cystoscopy and a form of upper tract imaging. Ultrasound of the kidneys can be used instead of CT urogram in patients with NVH. The role of urine cytology in the haematuria setting is limited and should be avoided.

Declaration of interests: none declared

References


Key points

- Patients of any age presenting with visible haematuria, or non-visible haematuria, at ≥40 years old, should be referred to a urologist
- The evaluation of haematuria should be with cystoscopy and a form of upper tract imaging
- Ultrasound of the kidneys can be used instead of CT urogram in patients with non-visible haematuria
- The role of urine cytology in the haematuria setting is limited and should be avoided

Figure 1. Endoscopic view of bladder cancer