Half of Visible and Half of Recurrent Visible Hematuria Cases Have Underlying Pathology: Prospective Large Cohort Study With Long-Term Followup

Said Fadel Mishriki,* Ross Vint and Bhaskar K. Somani
From the Urology Department, Aberdeen Royal Infirmary, Grampian NHS Trust, Aberdeen, Scotland, United Kingdom

**Purpose:** Visible hematuria has a cancer yield of up to 24.2%. A large proportion of cases will have no etiology. In this study we determined the incidence of pathology (benign and malignant) in patients with visible hematuria and those with persistent and recurrent visible hematuria, and evaluated the policy for investigations.

**Materials and Methods:** Data were prospectively collected for 1,804 patients with visible hematuria at a United Kingdom teaching hospital from January 1999 to September 2007. In October 2010 the comprehensive hospital electronic database was checked for every individual patient to ensure no urological pathology was missed. All patients underwent standard hematuria investigations, including renal tract ultrasound and excretory urography or contrast enhanced computer tomography urogram, flexible cystoscopy and urine cytology.

**Results:** The male-to-female ratio was 4.8:1. Median age ± SD was 67 ± 17.0 years (range 21 to 109). Median followup was 6.6 ± 2.5 years (range 1.5 to 11.6). No urological pathology was found in 965 (53.5%) patients. Malignant urological disease was found in 386 (21.4%) patients, of whom 329 had bladder tumors. There were 32 patients with persistent visible hematuria and no malignancy. Repeat investigation was performed in 69 patients reporting recurrence. Of these patients 35 received a significant urological diagnosis, including 12 (17.4%) urological malignancies, while 34 (49.3%) still had no diagnosis. Limitations include the possibility of missing pathology.

**Conclusions:** Almost 50% of patients presenting with visible hematuria will have a diagnosis. Therefore, all cases of visible hematuria require full standard investigations. Patients with no diagnosis can be discharged from followup. Recurrent visible hematuria after full initial negative findings requires repeat full standard investigations because 11.6% will have malignant pathology.

**Key Words:** hematuria; carcinoma, transitional cell; prostatic hyperplasia

The incidence of urological cancer in patients presenting with VH is between 18.9% and 24.2%. These cancers are commonly bladder and renal tumors. In addition, benign surgical disease is associated with VH in 21.4%. Less than 6% of malignancy is found in cases of nonvisible hematuria. VH requires urgent referral and swift evaluation. Investigations usually involve U/S, IVU/CTU, cystoscopy and urine cytology. Despite full investigations a significant proportion of patients will receive no etiological diagnosis, and there is uncertainty as to the cause in these patients who are evaluated with no pathology found. The persistence or recurrence of VH requires urgent referral and swift investigation. Further investigations are necessary to identify the cause of VH and guide appropriate management.
may provoke further investigations, but followup for patients with recurrent VH is unclear.

At what stage can patients with no recurrence be safely discharged? What is the likelihood of recurrence and the possibility of a subsequent urological cancer diagnosis? The paucity of information in the literature regarding the natural history of VH after initial negative investigations explains the dearth of guidelines for clinical practice. This has resulted in the lack of a consistent approach. A recent long-term prospective analysis confirmed that patients with nonvisible hematuria and negative investigations were extremely unlikely to have significant urological disease, and that they need repeat investigations only if VH develops subsequently. Does the same apply to patients with visible hematuria? In this study we determined the incidence of pathology (benign and malignant) in patients with new VH and in those with persistent or recurrent VH, and established a policy for investigations.

**PATIENTS AND METHODS**

**Study Period**
This study included all new patients attending a hematuria clinic at a large university teaching hospital between January 1999 and September 2007. Before referral by primary care physicians all patients with VH underwent routine blood tests which included full blood count, renal function, coagulation profile and urinalysis to rule out infection. In October 2010 the comprehensive hospital electronic database (which includes pathology and radiology) was checked for every individual patient to ensure no urological pathology was missed.

**Protocol**
The protocol for investigation of VH was U/S and IVU/CTU to image the upper tracts, flexible cystoscopy and urine cytology. For persistent VH after standard investigations, watchful waiting, medical treatment with 5α-reductase inhibitors and nephrological referral were performed, considering each case on its own merits. CTU replaced IVU for high risk patients (patients older than 50 years, smokers, and those with a family history of bladder cancer and previous pelvic radiotherapy). The policy was to investigate all patients with VH as per the standard hematuria protocol regardless of anticoagulation status (provided it is within therapeutic levels), duration or intensity of hematuria. Patients with recurrent VH (more than 1 year after full standard initial investigation) were reinvestigated with the same protocol as the initial investigation.

**Followup**
After the initial negative investigation, if hematuria settled, patients were discharged. Patients and primary care physicians were informed that after discharge if hematuria recurred, they needed to be re-referred. One year was arbitrarily considered safe before full standard investigations were repeated.

**Database**
Data were prospectively collected on a Microsoft Access database for research and analysis. Data set included age, gender and smoking history. All data were independently maintained, and the results and information were independently checked by 2 authors (RV and BKS).

**Diagnostic Quality**
All first episode and recurrent hematuria referrals were vetted by a consultant urologist. All flexible cystoscopy were performed by a consultant urologist, a senior or supervised junior trainee or an experienced oncology nurse practitioner. The U/S and IVU were done as a part of the hematuria clinic and reported in a standardized fashion by trained radiographers or radiologists. The CTU was reported by an experienced radiologist. When doubt existed, the case was discussed in a multidisciplinary meeting.

**Data Analysis**
The point of last followup (October 2010) was at least 3 years from the end of the study period (1999 to 2007). In October 2010 the records of each individual patient in the comprehensive hospital electronic radiology and pathology database were checked to ensure that no pathology was missed. Final analysis for the full cohort of patients was then completed.

**RESULTS**
A total of 1,804 patients with VH were investigated during the study period. The male-to-female ratio was 4.8:1. Median patient age was 67 ± 17.0 years (range 21 to 109). Median followup was 6.6 ± 2.5 years (range 1.5 to 11.6). No pathology was found in 965 (53.5%) patients. Malignant urological disease was found in 386 (21.4%) patients, of whom 329 had bladder tumors, 39 renal tumors, 10 prostate cancers and 8 upper urinary tract tumors. The remaining patients had benign pathology (table 1).

When patients were grouped according to smoking history, smokers had a higher incidence of bladder cancer and these patients also had a higher stage and grade of cancer (p <0.05, table 2). Ex-smokers were defined as those who had stopped smoking at the time of their investigations. Of the

**Table 1. Urological pathology in patients with VH**

<table>
<thead>
<tr>
<th>No. Pts (%)</th>
<th>No. Pts (%)</th>
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<tbody>
<tr>
<td>No pathology</td>
<td>965 (53.5)</td>
</tr>
<tr>
<td>Bladder tumor</td>
<td>329 (18)</td>
</tr>
<tr>
<td>Renal tumor</td>
<td>39 (2.2)</td>
</tr>
<tr>
<td>Upper tract TCC</td>
<td>8 (0.4)</td>
</tr>
<tr>
<td>Prostate Ca (+ high PSA)</td>
<td>10 (0.6)</td>
</tr>
<tr>
<td>Metastatic disease</td>
<td>3 (0.2)</td>
</tr>
<tr>
<td>Large bleeding prostate</td>
<td>242 (13.4)</td>
</tr>
<tr>
<td>Cystitis/urinary tract infection</td>
<td>36 (2.0)</td>
</tr>
<tr>
<td>Renal/ureteral calculi/hydronephrosis</td>
<td>59 (3.3)</td>
</tr>
<tr>
<td>Bladder stone</td>
<td>36 (2.0)</td>
</tr>
<tr>
<td>Urethral stricture</td>
<td>37 (2.1)</td>
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patients with bladder tumor, complete follow-up data on stage and grade was available on 189 patients, of which 128 (67.7%) were smokers and 61 (32.3%) were nonsmokers. Of the smokers 25% (32) and of the nonsmokers 11.5% (7) had muscle invasive disease. A higher percentage of muscle invasive disease was associated with smoking (p = 0.035). A higher grade of disease was found in 81.8% (104) of smokers and 44.3% (27) of nonsmokers. Thus, higher disease grade was also associated with smoking (p < 0.0001). Urine cytology was beneficial in only 1 patient with upper tract TCC.

There were 32 patients with persistent VH who had no malignancy after full standard investigations. Watchful waiting, medical treatment using 5α-reductase inhibitors and nephrological referral were chosen depending on the circumstances. None of these patients was subsequently diagnosed with a urological malignancy. The 69 patients with recurrent VH during 11.5 years underwent repeat full standard investigation as per local departmental protocol. Of these patients 35 received a significant urological diagnosis including 12 (17.4%) urological malignancies (prostate cancer in 4, bladder cancer in 5, renal cancer in 2 and upper tract TCC in 1). In patients with recurrent VH who underwent repeat investigations, the earliest a pathological diagnosis was made was at 3 years and 9 months. Of these patients with recurrent VH 34 (49.3%) still had no diagnosis (table 3).

**DISCUSSION**

This is the longest cohort prospective followup study to our knowledge for patients with VH. The earliest a pathological diagnosis was made after initial negative investigations was at 3 years and 9 months. This justified the arbitrary 1 year before full standard investigations were repeated in cases with recurrent VH. After a median followup of 6.6 ± 2.5 years (range 1.5 to 11.6) the likelihood of a diagnosis of a urological malignancy if VH recurred and investigations were repeated was 17.4%. When prostate cancer was excluded because it had a different diagnostic pathway, the incidence became 11.6%.

In a previous study 64.4% of patients received no diagnosis on initial presentation, and 48.8% received no diagnosis after recurrence and full investigations. A systematic review of VH and urological cancers advised that all patients with VH should undergo a thorough diagnostic program. Despite full standard urological investigations, in this study a significant proportion of patients (53.5%) received no diagnosis on initial investigations. An important consideration is whether a patient can be discharged with the expectation of no recurrences and no subsequent cancer diagnosis. In the event of recurrence, are reinvestigations appropriate? In a study on VH recurrence in patients with initial negative investigations, Khadra et al found no new diagnosis at 2.5 to 4.2 years in such patients, and concluded that a subsequent urological diagnosis after negative investigations was unlikely. In this study 4 patients with recurrent VH were diagnosed with prostate cancer. PSA was not a standard investigation at the VH clinic. Although this has recently changed there is no reason to believe that prostate cancer was the cause of the VH. PSA testing, in accordance with local guidelines, is being performed by the family practitioner only after full counseling. Despite repeat full investigations for recurrent VH, a significant 49.3% of patients still had no diagnosis.

**Limitations**

In this prospective study with a median followup of 6.6 ± 2.5 years, not every patient with an initial negative evaluation had undergone full urological reinvestigation by the end of the study. Repeat investigations in asymptomatic patients would be considered unethical. Therefore, there is the theoretical possibility that a malignancy could have been missed. However, a comprehensive electronic database search for every patient in the full cohort of all 1,804 patients was completed in October 2010 (a minimum of 3 years after their initial investigation). This search failed to detect any undiagnosed urological malignancy. The length of the followup is sufficient to minimize the possibility of unrecognized underlying urological malignancy with the exception of insignificant renal tumors.

**Implications for Policy and Practices**

Guidelines for the investigation of VH are lacking. One of the most important outcomes in this study is assessing the likelihood of a relevant urological can-

### Table 3. Diagnoses following repeat investigations

<table>
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<tr>
<th>Diagnosis</th>
<th>No. (%)</th>
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<tr>
<td>Calculi/urinary tract infection</td>
<td>14 (20.3)</td>
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<tr>
<td>Benign prostatic enlargement</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Prostate Ca (+ high PSA)</td>
<td>4 (5.8)</td>
</tr>
<tr>
<td>Renal Ca</td>
<td>2 (2.9)</td>
</tr>
<tr>
<td>Upper tract TCC</td>
<td>1 (1.45)</td>
</tr>
<tr>
<td>Bladder Ca</td>
<td>5 (7.3)</td>
</tr>
<tr>
<td>No diagnosis</td>
<td>34 (49.3)</td>
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</table>
cer in a patient presenting with VH in the long term. Of the patients studied 21.4% were diagnosed with urological cancer on initial investigations. The 11.6% probability of finding a urological malignancy in patients with recurrent VH emphasizes the importance of reinvestigating all patients with recurrent VH who had no firm diagnosis on initial investigations. However, despite repeated full re-investigations, approximately half of these patients remained without a diagnosis. Patients and clinicians should be mindful of this. In the study by Edwards et al after a 4-year followup 10 potentially missed tumors were identified. The authors concluded that although the possibility of missed tumors in nonvisible hematuria was less than 1%, it was higher for VH, especially for men older than 60 years (more than 4%). A systematic review of diagnostic tests and algorithms for the investigation of hematuria concluded that there is a lack of sufficient data to formulate evidence-based guidelines.

In this study, consistent with other studies, a patient cleared by initial investigations with no VH recurrence and no urological malignancy diagnosed can be safely discharged from followup. However, after discharge it should be emphasized that in the event of VH recurrence, regardless of time lapse, it is imperative that urgent referral should be made for further expeditious investigations. One year was considered a reasonably safe period for repeat of full standard investigations for recurrent VH.

CONCLUSIONS
In this study, the longest prospective followup study for VH to our knowledge, almost 50% of patients presenting with VH had an underlying pathology. Therefore, all patients with VH require full standard investigations to diagnose malignant or benign pathology that may require treatment. Patients with no diagnoses can be safely discharged from followup provided that they are urgently referred back in case of recurrence. A small percentage of patients will have persistent or recurrent VH. No malignancy was found in patients with persistent VH. As 11.6% of patients with recurrent VH will have a malignant pathology after initial negative findings, it is imperative that they should have full standard investigations repeated. The timing of the repeat investigations is debatable and this study suggests that 1 year is a reasonably safe period.

REFERENCES

EDITORIAL COMMENT
This important study addresses a common problem of determining which patient with a negative evaluation for visible hematuria needs reevaluation. That 11.6% of patients with recurrent VH have new cancers diagnosed indicates that full reevaluation should be undertaken in such individuals. On the other hand, patients with persistent hematuria or those in whom hematuria does not recur do not need urological reevaluation because during a minimum of 3 years (median 6.6) no tumors were reported. A second finding is that cigarette smokers (presumably ex-smokers and current smokers) not only had a higher incidence of bladder cancer, but also had high disease stage and grade. This disagrees with the findings of other groups. Larger numbers and more rigid quantification of smoking history and quit time duration may be needed to clarify this difference.

Edward M. Messing
Department of Urology
University of Rochester
Rochester, New York
REFERENCE


REPLY BY AUTHORS

Nearly 50% of patients with VH had a diagnosis. Patients with no diagnosis were discharged from followup. For recurrent VH, repeat full investigation is recommended as 11.6% of these patients will have a malignant pathology.

The association between smoking and bladder tumor stage and grade has not been well reported in the literature. Some studies did not find significant differences among ex-smokers and current smokers in terms of stage, grade, tumor size or multifocality.1 However, the same studies noted that continued smoking led to worse survival outcomes. In another study smoking not only induced bladder cancer, but once the cancer developed, smoking could increase the tumor grade, resulting in a worse prognosis.2

A systematic review of 15 studies suggested that stopping smoking might favorably alter the course of bladder cancer, but the data were insufficient for clinicians to inform patients that this would improve their prognosis.3 If smokers have a worse prognosis for bladder cancer compared to nonsmokers, the cause could be an association with a higher tumor stage and grade.

REFERENCES

