The diagnostic value of macroscopic haematuria in diagnosing urological cancers: a meta-analysis
Frank Buntinx and Hans Wauters


**Objective.** To evaluate the diagnostic value of macroscopic haematuria for the diagnosis of urological cancers in primary care as well as referred patients.

**Method.** Systematic review of published reports, identified by a search on *Medline* and *FAMLI* and by screening of reference lists of selected papers. The evaluation of the sensitivity was based on patients with proven cancer of the kidney, ureter, bladder, urethra or prostate. The evaluation of the positive predictive value (PPV) was based on patients complaining to their physicians of macroscopic haematuria.

**Results.** No study executed in a primary care setting was included. In referred patients the pooled sensitivity of macroscopic haematuria for bladder cancer, based on seven remarkably homogeneous studies, was 0.83 (95% CI = 0.80–0.85). For ureteral cancer, this was 0.66 (95% CI = 0.53–0.77) based on four reports and for renal cancer 0.48 (95% CI = 0.36–0.60) based on three studies. The pooled PPV of haematuria for urological cancer was 0.22 (0.17–0.27) in referred patients. Most malignancies detected were bladder cancers (255/317). PPV was highest in patients aged 40 or more at 0.41 (95% CI = 0.10–0.78).

**Conclusions.** The advice that all patients with macroscopic haematuria should receive a thorough diagnostic programme seems justified in a specialized setting, dealing with referred patients. At this moment no data are available to support or discourage a similar policy for GPs. Prospective studies on the diagnostic value of macroscopic haematuria for urological cancer in a primary care setting are urgently needed.

**Keywords.** Cancer, diagnostic studies, meta-analysis, sensitivity and specificity.

Introduction

Many clinicians consider macroscopic haematuria to be a key symptom, suggesting the presence of a neoplasm of the urological tract until this is excluded.1 If the diagnostic value of gross haematuria really is good, referral and further evaluation of these patients should lead to early diagnosis and a higher possibility of cure or improved survival.2 However, if the number of false positive and false negative results is considerable, systematic referral and investigation will lead to both over-use of tests and unnecessary anxiety, and a false feeling of safety.

In this respect, the effect of the setting on the diagnostic value of signs, symptoms and tests also has to be kept in mind.1 What could be a very worthwhile test in one setting (e.g. referred patients in a teaching hospital) may be totally inappropriate in another setting (e.g. primary care) because of different prior odds and a different case-mix, resulting at least partly from the referral process itself. To examine the diagnostic value of gross haematuria in diagnosing urological cancer, a systematic literature review was performed, studying its sensitivity and positive predictive value (PPV) in primary care as well as in referred patients. In the PPV study, only ambulatory patients were included. The impact of age and of pain as a second symptom was also examined. No previous systematic reviews on this topic were available.

Method

**Retrieval of the articles**
A computerized *Medline* search was performed for the period 1966–1995 covering MESH as well as free text
searches and using haematuria, uro-genital cancers and bladder cancer as keywords. Additionally, *FAMLI* was searched for the whole period of its existence (1980–1991) and a number of Dutch-language general practice journals not indexed in *Medline* were searched manually. Reference lists of all selected papers were carefully searched for possible additional papers (ancestry approach).

**Selection**

With respect to the estimation of sensitivity, all papers reporting on consecutive patients with urological cancers (either all cancers or specific types of cancers) and systematically presenting information on the presence or absence of gross haematuria for all patients were selected.

With respect to the estimation of the PPV, all papers were selected that reported on a group of consecutive ambulatory patients presenting with gross haematuria as the reason for encounter and gave information on the possible finding of urological cancers for all of them. Only studies on ambulatory patients were included. To make sure that no patients with microscopic haematuria were included, we only considered reports when the term ‘haematuria’ was used in connection with ‘macroscopic’ or ‘gross’ or when it was formally stated that the patient was ‘complaining’ of haematuria. Sometimes, this resulted in using data for only some of the patients. There were no further exclusion criteria. Information on the presence or absence of pain and on age were registered if available. Results of studies in referred patients and non-referred patients were considered separately.

**Quality scoring**

All studies that fulfilled the inclusion criteria for selection were included in the analysis. To inform the reader about the methodological quality of the studies, a number of quality indicators were systematically scored: type of data collection (prospective registration, chart review), setting, number of patients in the study, age distribution and sex ratio. To estimate the likelihood of indication bias in studies examining the PPV, other diagnostic investigations that were performed systematically were listed.

**Analysis**

Results of individual studies (sensitivity or PPV) were presented with their 95% confidence interval (95% CI). If these data were not presented in the published paper, they were calculated. Homogeneity between studies examining either sensitivity or PPV was tested using the *χ*² test. In the case of heterogeneity, subgroups were identified and also tested for internal homogeneity. Statistical pooling of the results of all individual studies was performed, based upon a random effect model and using FASTPRO version 1.7 for calculations. Results are reported as pooled sensitivity (*Sens*ₚ) or pooled PPV (*PPV*ₚ) and their 95% CI.

**Results**

**Sensitivity and positive predictive value in a primary care setting**

No studies examining the diagnostic value of gross haematuria for a diagnosis of urological cancer and performed in a primary care setting could be identified.

**Sensitivity in referred patients**

Fourteen studies were selected. Thirteen of these were published in specialized medical journals (either cancer or urological journals) and one in a general medical journal. Relevant characteristics of these studies are summarized in Table 1. Most studies are based on chart review (in some cases the files are computerized) in one or two hospital departments. In three cases a regional tumour registry compiled by a larger number of co-operating hospitals was studied. Tumours that were examined separately were located either in the bladder, the ureter or the kidney. The sensitivities reported ranged from 0.79 to 0.91 for bladder tumours, from 0.53 to 0.78 for ureteral tumours and from 0.41 to 0.61 for renal tumours (Table 1). As significant heterogeneity (*P* < 0.01) was detected for the whole of all 14 studies, even after exclusion of studies with fewer than 100 patients, no statistical pooling was performed on this series.

Subgroup analysis was performed examining each localization separately and for bladder cancer, additionally examining those studies restricted to patients aged 40 and less. Results are summarized in Table 2. Sensitivity for bladder cancer was based upon two large prospective studies as well as four small chart review studies and one registry review which show remarkable homogeneity (*P* = 0.62) and result in a high *Sens*ₚ of 0.83 (95% CI = 0.80–0.85).

There was no difference in *Sens* for bladder cancer between the four studies that confined themselves to patients aged 40 or less and the others.

The four studies concerning ureteral cancers were divided into two groups: those recently published and those published in 1970 or earlier. Each group seemed to be internally homogeneous (*P* = 0.52 and 0.35 respectively). Sensitivity was much higher in the older studies (*Sens*ₚ = 0.75; 95% CI = 0.67–0.82) than in the more recent studies (*Sens*ₚ = 0.56; 95% CI = 0.46–0.65). In the case of kidney tumours sensitivity was greater in diagnosing renal pelvic carcinoma (one study; *Sens*ₚ = 0.61) than renal cell carcinoma (two studies; *Sens*ₚ = 0.42, 95% CI = 0.35–0.45). In six studies patients with painless macroscopic haematuria were analysed separately. Two of
<table>
<thead>
<tr>
<th>Study</th>
<th>Data collection</th>
<th>Consecutive cases</th>
<th>No. of cancer patients</th>
<th>Age distribution (years)</th>
<th>Male/female ratio</th>
<th>Localization of the tumour</th>
<th>Sensitivity (95% CI)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erpenbach <em>et al.</em></td>
<td>n.e.</td>
<td>Yes</td>
<td>11/10</td>
<td>20-29</td>
<td>11/0</td>
<td>Bladder</td>
<td>0.91 (0.72-1.00)</td>
<td>Army personnel</td>
</tr>
<tr>
<td>Raabe <em>et al.</em></td>
<td>Chart review</td>
<td>n.e.</td>
<td>64/39</td>
<td>31-87</td>
<td>n.a.</td>
<td>Renal pelvis</td>
<td>0.84 (0.48-0.73)</td>
<td>22 cases included</td>
</tr>
<tr>
<td>Grignon <em>et al.</em></td>
<td>Chart review</td>
<td>Yes</td>
<td>18/16</td>
<td>51-87</td>
<td>n.a.</td>
<td>Bladder</td>
<td>0.89 (0.70-1.00)</td>
<td>Originally information missing in 4 cases</td>
</tr>
<tr>
<td>Anderström <em>et al.</em></td>
<td>Chart review</td>
<td>Yes</td>
<td>49/29</td>
<td>Mean = 65</td>
<td>33/6</td>
<td>Ureter</td>
<td>0.59 (0.44-0.74)</td>
<td>Subsequent development of bladder tumours in 15 patients</td>
</tr>
<tr>
<td>Witjes and Debruyne</td>
<td>Register review</td>
<td>Yes</td>
<td>49/40</td>
<td>&lt;40</td>
<td>30/10</td>
<td>Bladder</td>
<td>0.82 (0.68-0.91)</td>
<td>All transitional cell carcinoma</td>
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<td>Want and Grossman</td>
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<td>Yes</td>
<td>35/28</td>
<td>≤40</td>
<td>Bladder</td>
<td>0.80 (0.63-0.92)</td>
<td></td>
<td>Data of 2 additional patients missing</td>
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<td>Kurz <em>et al.</em></td>
<td>Chart review</td>
<td>Yes</td>
<td>25/21</td>
<td>&lt;40</td>
<td>19/6</td>
<td>Bladder</td>
<td>0.84 (0.64-0.96)</td>
<td>Nephroblastoma and carcinomatous tumour not included</td>
</tr>
<tr>
<td>Sörenson <em>et al.</em></td>
<td>Prospective registration</td>
<td>Yes</td>
<td>746/627</td>
<td>Mean = 66</td>
<td>608/138</td>
<td>Bladder</td>
<td>0.84 (0.81-0.87)</td>
<td>Neoplasm not included</td>
</tr>
<tr>
<td>Mills and Vaughan</td>
<td>Chart review</td>
<td>Yes</td>
<td>53/28</td>
<td>n.a.</td>
<td>Bladder</td>
<td>0.53 (0.38-0.67)</td>
<td></td>
<td>Nephroblastoma not included</td>
</tr>
<tr>
<td>Mønensen <em>et al.</em></td>
<td>Prospective registration</td>
<td>Yes</td>
<td>212/168</td>
<td>42-85</td>
<td>165/47</td>
<td>Bladder</td>
<td>0.79 (0.73-0.84)</td>
<td>Neoplasm not included</td>
</tr>
<tr>
<td>Oehlser <em>et al.</em></td>
<td>Chart review</td>
<td>Yes</td>
<td>103/42</td>
<td>35-77</td>
<td>80/23</td>
<td>Kidney</td>
<td>0.41 (0.31-0.50)</td>
<td>Neoplasm not included</td>
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<tr>
<td>Bloom <em>et al.</em></td>
<td>Register review</td>
<td>Yes</td>
<td>192/59</td>
<td>68-93</td>
<td>77/25</td>
<td>Ureter</td>
<td>0.85 (0.69-0.88)</td>
<td>Neoplasm not included</td>
</tr>
<tr>
<td>Beck <em>et al.</em></td>
<td>Chart review</td>
<td>n.e.</td>
<td>40/26</td>
<td>n.a.</td>
<td>Bladder</td>
<td>0.76 (0.56-0.91)</td>
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<tr>
<td>Gallego <em>et al.</em></td>
<td>Urine review</td>
<td>Yes</td>
<td>11/30</td>
<td>15-90</td>
<td>41/16</td>
<td>Kidney</td>
<td>0.45 (0.39-0.55)</td>
<td>Neoplasm not included</td>
</tr>
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</table>
these studies examined patients with ureteral cancer, while the other studies related to bladder cancer patients. Results for both bladder and ureteral cancer patients were homogeneous ($P = 0.16$ and $P = 0.39$ respectively). Pooled sensitivity of painless gross haematuria for the diagnosis of bladder cancer was $0.74$ (0.66–0.80). For the diagnosis of ureteral cancer it was $0.55$ (0.45–0.65).

Gross haematuria associated with pain had a Sens$_p$ of 0.13 (0.05–0.27) for bladder cancer. The combination was tested in only one study on ureteral cancer (Sens = 0.20 (0.07–0.34)) and one study on renal pelvis cancer (Sens = 0.58 (0.45–0.70)).

**PPV in referred patients**

In six studies, it was possible to calculate the PPV of macroscopic haematuria for cancer of the urological tract (Table 3). In all studies, all consecutive cases during a certain period were included. Cystoscopy was performed on a systematic basis in four studies and on indication only in one study. The policy was not reported in one study.

The predictive value in the different studies ranged from 0.12 to 0.40 (Table 3). The results were heterogeneous ($P < 0.001$). Excluding the study of Gillatt et al., however, results in homogeneity ($P = 0.06$). The pooled PPV for all six studies is 0.22 (0.17–0.27). After exclusion of the study of Gillatt et al., this figure is 0.19 (0.17–0.23). Most malignancies ($n = 255/317$) were bladder cancers.

From none of the papers that were selected was stratification by age, or the information needed to estimate a PPV of the combination of gross haematuria and pain, available. Separate information on age was available from two studies, enabling us to calculate separate PPVs for patients younger or older than 40. The pooled PPV was 0.41 (0.10–0.78) for patients aged $\geq 40$ and 0.12 (0.86–0.21) for younger patients. $\chi^2$ for homogeneity resulted in a $P$ value of $< 0.001$ and 0.12, respectively.

**Discussion**

Most textbooks aimed at both specialized and primary care clinicians consider macroscopic haematuria a key symptom suggesting the presence of urological cancer. The most striking result of this review, therefore, is that no study was found examining the diagnostic value of macroscopic haematuria in non-selected (general practice) patients. As the final diagnosis of a cancer generally is confirmed in a hospital or clinic, sensitivity figures, estimated in a specialized setting, are also highly relevant for GPs. PPV is, however, very sensitive for selection by referral or by previous testing. GPs cannot simply assume that study results gathered in urological services are comparable with those available from their own population. It therefore seems highly advisable for a prospective study examining the diagnostic value of macroscopic haematuria for the diagnosis of urological cancer to be designed and properly executed.

The diagnostic value of tests, signs or symptoms is defined by a combination of five indicators: prior odds, sensitivity, specificity and positive and negative predictive values. In many diagnostic studies concerned with screening or early diagnosis, only sensitivity and positive predictive value are available: in some cases only one of these is given. In such cases, most test-negative patients do not attend for follow-up. On the other hand, for clinicians, the clinical decision to take is how to handle a case of a patient presenting with gross haematuria.

In a referred patient population, pooled sensitivity is high, especially for the rather frequent cancers: bladder cancer (Sens$_p$ = 0.83) and ureteral cancer (Sens$_p$ = 0.66). As has been stated before, most of these cancers would be diagnosed early if all patients with macroscopic haematuria underwent thorough investigation, including IVU and cystoscopy, as soon as possible. However, such policy can only be advocated if the number of superfluous referrals that would result is known.

In view of the seriousness of a cancer diagnosis, a PPV of 0.22 is high enough to advocate a systematic investigation in a referred patient population. Heterogeneity in this analysis was caused by one outlier study with a very high PPV. The reason therefore is mentioned in the paper itself. “General practitioners’ services in the region are ‘extremely good’ and cases
<table>
<thead>
<tr>
<th>Study</th>
<th>Data collection</th>
<th>Age distribution</th>
<th>Male : female ratio</th>
<th>Cytology</th>
<th>IVU</th>
<th>Cystoscopy</th>
<th>Angiography</th>
<th>US</th>
<th>CT</th>
<th>Total no. of patients</th>
<th>PPV (95% CI)</th>
<th>Urethra</th>
<th>Bladder</th>
<th>Ureter</th>
<th>Kidney</th>
<th>Prostate</th>
<th>No final diagnosis</th>
<th>Remarks</th>
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<tr>
<td>Fillatti and O'Reilly</td>
<td>Prospective</td>
<td>25-84</td>
<td>n.a.</td>
<td>S</td>
<td>S</td>
<td>S</td>
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<td>1</td>
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<td>36.90</td>
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<td>(0.30</td>
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<td></td>
<td></td>
<td></td>
<td>28, 3, 4, 1</td>
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<tr>
<td>Lee and Davis</td>
<td>Chart review</td>
<td>5-94</td>
<td>660:334</td>
<td>O</td>
<td>I</td>
<td>S</td>
<td>O</td>
<td>O</td>
<td></td>
<td>2.191000</td>
<td>0.22</td>
<td>(0.19</td>
<td>0.25</td>
<td></td>
<td>3</td>
<td>152, 7, 36, 21</td>
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<tr>
<td>Carter and Rom</td>
<td>Chart review</td>
<td>16-107</td>
<td>61-48</td>
<td>?</td>
<td>?</td>
<td>?</td>
<td>1</td>
<td>?</td>
<td></td>
<td>25.110</td>
<td>0.23</td>
<td>(0.15</td>
<td>0.32</td>
<td></td>
<td>1</td>
<td>10, 0, 7, ?</td>
<td>10</td>
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<tr>
<td>Mariani et al.</td>
<td>Chart review</td>
<td>18-92</td>
<td>n.a.</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>1</td>
<td>I</td>
<td></td>
<td>61-64</td>
<td>0.21</td>
<td>(0.16</td>
<td>0.26</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Lynch et al.</td>
<td>Prospective</td>
<td>19-73</td>
<td>n.a.</td>
<td>S</td>
<td>S</td>
<td>S</td>
<td>?</td>
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<td></td>
<td>35.214</td>
<td>0.16</td>
<td>(0.11</td>
<td>0.22</td>
<td></td>
<td>27***</td>
<td>6</td>
<td>3***</td>
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<td>Paul</td>
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<td>I</td>
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<td>0.20</td>
<td></td>
<td></td>
<td></td>
<td>38</td>
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</tr>
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</table>

O = not done, I = when indicated, S = systematically, ? = no data, n.a. = not available.

* Patients declined cystoscopy.

** The number of life-threatening lesions was presented instead of the number of malignancies. As from the additional information it was clear that both numbers were very similar to each other (the maximal difference can be 3), the presented numbers were used for our analysis. Both the lowest and highest possible figure are presented in the table.

*** Combined bladder + prostate cancer in one case.

Macroscopic haematuria in diagnosing cancer

67
of less serious conditions are probably adequately sifted out and treated without referral*", thus leading to a highly selected study population. PPV's are even higher (PPV, = 0.41) in patients aged ≥ 40 or more, making this an age group at high risk. This was confirmed by the study of Gillatt, in which all cancers were detected in patients aged ≥ 40.

It would be helpful if subgroups with an increased risk for cancer could be defined. The existence of infection seems no argument against a diagnosis of cancer. Indeed, in the study of Momsen 70% of patients with bladder cancer had cystitis-like symptoms. An additional study, not included in our analysis, looked at 112 patients referred because of macroscopic haematuria initially found by the GP, but with no macroscopic haematuria when examined in the haematuria clinic. Ten percent of these patients were diagnosed as having urological cancers. In this study the influence of selection by referral is not known, since this result did not favour a wait-and-see policy after a first episode of macroscopic haematuria, even when haematuria persisted after a short while.

In summary, the advice that a patient with macroscopic haematuria should undergo thorough investigation certainly seems justified in a specialized setting with referred patients. For the time being, the available data neither support nor discourage the same policy in general practice. In view of the possible implications, especially when treatment outcome would be improved, research into the diagnostic value of macroscopic haematuria in a general practice setting is urgently needed. This may result in the definition of subgroups in which referral and further investigation is more frequently needed.

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References


