# The diagnostic value of macroscopic haematuria for the diagnosis of urological cancer in general practice

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*SUMMARY*

***Background:*** *The diagnostic value and the impact of some signs and symptoms in most diseases in primary care have only been studied incompletely.*

***Aim****: To assess the diagnostic value of macroscopic haematuria for the diagnosis of urological cancer (bladder, kidney) in a general practice setting, as well the influence of age, sex, and some additional signs and symptoms.*

***Design of study****: Diagnostic study.*

***Setting****: The study was performed in a sentinel station network of general practices in Belgium, covering almost 1% of the population.*

***Subjects****: All patients attending their general practitioner and complaining of haematuria during 1993 and 1994 were included for the prospective part of the study. Every patient diagnosed with a urological cancer in this period was registered for the retrospective part.*

***Method:*** *Mean outcome measures of sensitivity, specificity, positive and negative predictive value, and positive and negative likelihood ratio were used to assess diagnostic value.*

***Results:*** *Within the registration year 1993–1994, patient–doctor encounters, related to 83 890 patient-years, were registered. The positive predictive value (PPV) for urological cancer was 10.3% (95% CI = 7.6% to 13.7%). Sensitivity was 59.5% (95% CI = 50.4% to 60.1%). The PPV of patients aged over 60 years was 22.1% (95% CI = 15.8% to 30.1%) for men and 8.3% (95% CI = 3.4% to 17.9%) for women. In the age group 40 to 59 years, the PPV was 3.6% (95% CI = 0.6% to 13.4%) for men and 6.4% (95% CI = 1.7% to 18.6%) for women. In the prospective part of the study, no urological cancer was found in the age group under 40 years.*

***Conclusion****: Men older than 60 years of age with macroscopic haematuria have a high positive predictive value for urological cancer. In these patients, a thorough investigation is indicated. In patients over 40 years of age of either sex, referral or watchful waiting can be justified.*

***Keywords:*** *symptoms and signs; diagnostic value; haematuria; urological cancer.*

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## Introduction

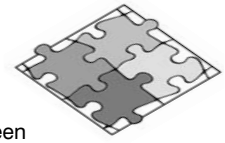
PRIOR odds of most diseases in primary care are well known from a number of general practice-based morbidity registries. Signs and symptoms significantly alter these prior odds; for example, haematuria for urological cancer. Some of these signs and symptoms are believed to indicate a high likelihood of a disease for which early diagnosis may have important consequences (key symptoms). The diagnostic value and the impact of some of these signs and symptoms have only been studied incompletely.[1] Although most cases of urological bleeding are owing to infections and lithiasis,[2] macroscopic haematuria is considered to be one of the early key symptoms for urological cancer, particularly in older patients. It is also a frequent sign in general practice. Lamberts reported an incidence rate of microscopic and macroscopic haematuria in general practice of four per 1000 patients (all ages) per year.[2] There is little research available to support the general practitioner's (GP's) decision of whether to refer a patient with macroscopic haematuria for further evaluation, or not. The study of Summerton *et al*[3] involving patients with new onset haematuria, gives some information on individual variables, such as sex, age, hesitancy, and the possibility of urological cancer, although in this study some degree of selection by referral may have taken place. All other studies examining the diagnostic value of macroscopic haematuria for the diagnosis of urological cancer have been carried out on referred patients or in a cancer registry setting. However, reports from study populations selected by referral to hospital are seldom useful for supporting decision making in general practice. To obtain results that are applicable in general practice, which is a low prevalence setting, it is therefore relevant to study the diagnostic value of macroscopic haematuria in patients who present their symptoms to their GP. Therefore, our aim was to study the diagnostic value (sensitivity, specificity, likelihood ratios (LR+, LR–), and positive and negative predictive value (PPV, NPV) of macroscopic haematuria in relation to a subsequent diagnosis of urological cancer in a general practice setting. We also tested the influence of some additional signs and symptoms (age, sex, fatigue, weight loss, pain, nocturia, dysuria, or frequency of micturition).

## Method

### *Setting*

The Belgian health care system is based on unrestricted access to any physician, including specialists. No patient lists or registers are routinely available. During the last 20 years a network of sentinel practices has been developed, in which GPs voluntarily and constantly register

**HOW THIS FITS IN**



*What do we know?*

The diagnostic value and impact of macroscopic haematuria has largely been studied in a hospital setting, with little research carried out in primary care.

*What does this paper add?*

Men older than 60 years of age with macroscopic haematuria have a high positive predictive value for urological cancer. In these patients, a thorough investigation is indicated. In patients over 40 years of age of either sex, referral or watchful waiting can be justified.

epidemiological data.[4] This Belgian network is representative of all Belgian GPs with respect to sex and age.[4-6] It is equally spread over all the regions of the country. A detailed report of the method used to estimate the denominator in patient-years, has already been published.[5] The registration for this study was performed in the network during the years 1993 and 1994 and the average of the estimated populations of 1993 and 1994 was used. During the registration period, the network covered around 1% of the Belgian population. Only regular registrars in the network who registered both in 1993 and 1994 participated in the study. Participation rate of GPs was about 90% ($n$ = 83).

### *Basic design*

For the study of sensitivity (retrospective part), all patients with urological cancer diagnosed in 1993–1994, were included. Background data (age, sex), as well as information about the presence of signs and symptoms leading to the diagnosis of a urological cancer, were registered. In particular, patients were asked if macroscopic haematuria was a reason for their seeking medical care before the diagnosis was made.

For the study of the PPV (prospective part), all patients complaining to their GP of macroscopic haematuria in 1993–1994 were included with background data, as well as information about the presence of some additional signs and symptoms. Patients complaining repeatedly of haematuria were included only once. No efforts were made to systematically perform a predefined list of technical investigations in all patients. After inclusion, recall letters were sent to the practices every six months, to check the included cases again upon the emergence of a diagnosis of any urological cancer. To ensure that all cases of urological cancer diagnosed within the follow-up period were identified, at the end of the period each of the GPs was sent a list of all their patients with macroscopic haematuria who were included in the study, in order to check for any 'hidden' urological cancer diagnosis.

### *Definitions*

Haematuria was registered if a patient complained to the GP of any blood of urological origin that had not necessarily been checked by the GP during the registration period, irrespective of the duration of the complaint and irrespective of the existence or absence of other signs or symptoms.

Urological cancer was defined as any malignancy of the urological tract that was confirmed histologically or by cystoscopy, intravenous pyelogram, or ultrasound scan. Registered associated signs and symptoms were fatigue, weight loss, pain, nocturia, dysuria or frequency of micturition.

### *Outcome measures*

For the study of sensitivity of macroscopic haematuria the occurrence of haematuria as reason for encounter, previous to the diagnosis of urological cancer, was used as the main outcome measure.

For the study of the PPV of macroscopic haematuria, diagnosis of urological cancer during a clinical follow-up of at least 18 months was registered as the reference standard.

The PPV of macroscopic haematuria in combination with other associated signs and symptoms was also calculated.

### *Analysis*

Because the data had arrived in different ways and the numbers were different between the two parts of the study, we constructed two 2 x 2 tables to present sensitivity and PPV, with missing data in each case (Tables 1 and 2). Incidence of cancer and macroscopic haematuria, sensitivity, and PPV were calculated directly from the retrospective and prospective data of the study, respectively. NPV and specificity were estimated from the 2 x 2 table based on the initial study results. The effect of age, sex, or additional signs and symptoms on these indicators was estimated by comparing the indicators in patients with and without the study characteristic. Confidence intervals (95% CI) were calculated for all indicators. Epi-Info version 6.04 software was used for statistical analysis.[7]

## Results

### *Patients*

During the inclusion period, 83 890 patient-years were registered. One-hundred and twenty-six patients (150/100 000 patient-years, 104 for men and 46 for women) were

*Table 1. Sensitivity of haematuria as a diagnostic tool for urological cancer. Numbers are derived from the retrospective part of the study.*

| Haematuria | Urological cancer | | |
|---|---|---|---|
| | Present | Absent | Total |
| Present | 75 | – | – |
| Absent | 51 | – | – |
| Total | 126 | – | 83 890 |

*Table 2. Positive predictive value for urological cancer. Numbers are derived from the prospective part of the study.*

| Haematuria | Urological cancer | | |
|---|---|---|---|
| | Present | Absent | Total |
| Present | 42 | 367 | 409 |
| Absent | | – | – |
| Total | | – | 83 890 |

diagnosed with urological cancer. Four hundred and nine patients (488/100 000 patients-years) were registered with macroscopic haematuria.

The mean age of patients with macroscopic haematuria but without cancer was 57 years (SD = 20) and the mean age of patients with cancer was 72 years (SD = 10). Thirteen per cent of those with haematuria were younger than 40 years and 53% were older than 60 years. The main study results are presented in Tables 1 and 2.

### *Sensitivity*

In 87 patients (male = 70, female = 17) a bladder cancer and in 39 patients (male = 23, female = 15, and one of unknown sex) other urological cancers were detected during the registration period. Seventy-five of those 126 patients reported macroscopic haematuria in the weeks previous to the diagnosis, resulting in a sensitivity of diagnosis of any urological cancer of 59.5 % (95% CI = 50.4 to 68.1). The sensitivity of diagnosis of bladder cancer was 70.1% (95% CI = 59.2 to 79.2) and the sensitivity for other urological cancers was 35.9% (95% CI = 21.7 to 52.8). Results according to age groups and sex are shown in Table 3. There was no case of urological cancer in this group below age 36 years; only 12 patients were aged under 60 years.

### *Positive predictive value*

Within the registration period, 409 patients (male = 232, female = 176, sex unknown = 1) complained to their GP of macroscopic haematuria. During follow-up, urological cancer was found in 42 of these patients (Table 2).

The PPV of macroscopic haematuria for the diagnosis of urological cancer was 10.3% (95% CI = 7.6 to 13.7). The PPV of bladder cancer was 8.3% (95% CI = 5.9 to 11.5) and of other urological cancers 2.0% (95% CI = 0.9 to 4.0). The indicators of diagnostic value of macroscopic haematuria for urological cancer according to sex and age groups are presented in Table 3. In males aged over 60 years, the PPV was 22.1% (95% CI = 15.8% to 30.1%) and in females in the same age group 8.3% (95% CI = 3.4% to 17.9%). In patients below 60 years the PPV was 2.6% (95% CI = 0.9 to 6.2). Adding additional signs and symptoms to the macroscopic haematuria did not change the general picture (Table 4). The PPV of haematuria with other symptoms was 6.4% (95% CI = 4.3% to 9.3%) while the PPV of haematuria without any additional sign or symptom was 3.9% (95% CI = 2.3% to 6.4%).

### *Other indicators*

The NPV of macroscopic haematuria for the diagnosis of urological cancer was estimated to be 99.9%. The specificity was 99.5%. The likelihood ratio was 98.9% (95% CI = 77.3% to 126.5%) for the presence of macroscopic haematuria and 0.55% (95% CI = 0.46% to 0.66%) for its absence.

## Discussion

With the exception of the study of Summerton *et al*,[3] this is to our knowledge the first study examining the diagnostic value of macroscopic haematuria for the diagnosis of urological cancer in a general practice setting.[8] It is the second of a series of similar studies, in which patients with anal blood loss,[9] long periods of coughing, a breast lump, or digital rectal examination abnormalities[10] are also included.

In this study the presence of macroscopic haematuria increased the probability of urological cancer from 0.15% to 10.3%, and for men over 60 years to 22.1%. This is an important increase. The overall PPV of 10.3% is very high and is certainly influenced by the distribution of the patients; only 12.8% of the contacts were in patients under 40 years and 47.5% were under 60 years. Younger female patients with urinary tract infection increased the macroscopic haematuria rate and decreased the PPV of urological cancer. The overall sensitivity of diagnosis was 59.5%. Relating this number to a specificity of 99.5% resulted in a positive likelihood ratio of 98.9.

Association of haematuria with other signs and symptoms, like pain, frequency of micturition, dysuria, nocturia, weight loss, or fatigue did not influence the PPV significantly. In this respect, it should be emphasised that, according to this study, the co-occurrence of haematuria with dysuria or increased frequency of micturition does not change the likelihood of urological cancer in any relevant way. This finding is in agreement with previous results of Mommsen *et al*.[11] In their study, 70% of patients with bladder cancer had cystitis-like symptoms.

In most diagnostic studies in general practice, the gold standard is problematic. Performing invasive tests (e.g. histological diagnosis, radiology or cystoscopy) in all patients, including those without specific signs or symptoms, is impossible for ethical as well as practical and financial reasons. Therefore, some years ago a final diagnosis after normal clinical follow-up during a suitable period was proposed and widely used as the next best solution. We adhered to this method. We are aware that in doing so, some degree of verification bias may have been produced but it was not possible to avoid this. All our patients were followed for at least 18 months up to a maximum of 30 months. This was considered acceptable, as urological cancer is not self-limiting and without treatment would probably progress to a more elaborate clinical picture within this period. Because of the relatively long follow-up period, 10.3% may be a slight overestimation of the real PPV, but this will not affect the order of magnitude.

The negative likelihood ratio was estimated to be 0.55. This means that absence of haematuria is not very predictive for the presence or absence of urological cancer. It relates to a rather low sensitivity. It also is an example of the very asymmetric diagnostic power of a test: macroscopic haematuria has a strong power to indicate the presence of urological cancer; but it is weak in excluding urological cancers.

The healthcare system in Belgium allows patients to see a urologist without referral from their GP. This could cause bias if a GP is not informed about the condition of his/her patient. Specialists, however, tend to inform the GP if a serious condition, such as cancer, is diagnosed. The completeness of our data is supported by the finding that our incidence rate for urological cancer (150/100 000 patient-years) is even higher than the incidence rate found by the Limburg cancer registry (LIKAR).[12] The LIKAR study, however, only reported invasive cancers.

*Table 3. Indicators of the diagnostic value of macroscopic haematuria for urological cancer, according to sex and age groups. The specificity was between 99.2% and 99.9%, the NPV was between 99.9% and 100% , and in the prospective part of the study no cancers were found in patients aged under 40 years.*

| | % Sensitivity (95% CI) | % PPV (95% CI) | LR+ (95% CI) | LR– (95% CI) |
|---|---|---|---|---|
| All patients | 59.5 (50.4–68.1) | 10.3 (7.6–13.7) | 98.9 (77.3–126.5) | 0.55 (0.46–0.66) |
| Men (age in years) | 63.8 (53.2–73.3) | 14.2 (10.1–19.5) | 99.5 (75.2–131.6) | 0.51 (0.40–0.65) |
| <40 | 50.0 (2.7–9.3) | 0 (0–12.0) | –[a] | –[a] |
| 40–59 | 42.9 (11.8–79.8) | 3.6 (0.6–13.4) | 62.1 (19.4–198.5) | 0.67 (0.38–1.18) |
| >59 | 65.9 (54.7–75.6) | 22.1 (15.8–30.1) | 47.9 (35.2–65.2) | 0.49 (0.38–0.63) |
| Women (age in years) | 46.9 (29.5–65.0) | 5.1 (2.5–9.8) | 83.3 (48.1–144.2) | 0.66 (0.50–0.87) |
| <40 | –[b] | 0 | –[a] | –[a] |
| 40–59 | 50.0 (13.9–86.1) | 6.4 (1.7–18.6) | 114.1 (48.7–267.8) | 0.50 (0.23–1.12) |
| >59 | 46.2 (27.1–66.3) | 8.3 (3.4–17.9) | 45.8 (22.5–93.2) | 0.70 (0.53–0.94) |

[a]No results because the number of false negatives is 0. [b]No results because the number of true positives and false negatives is 0.

*Table 4. Probability (expressed as a percentage) of prior urological cancer for macroscopic haematuria and additional signs and symptoms.*

| Sign | Haematuria and sign present | | Haematuria and sign absent | |
|---|---|---|---|---|
| | All ages | Men aged >60 years | All ages | Men aged >60 years |
| Pain | 5.3 (2.7–9.8) | 17.8 (8.5–32.6) | 10.9 (7.3–16.0) | 18.9 (11.9–28.6) |
| Increased frequency of micturition | 7.2 (3.8–12.8) | 22.6 (10.3–41.5) | 13.4 (9.4–18.7) | 22.0 (14.9–31.2) |
| Dysuria | 5.6 (2.6–11.0) | 24.1 (11–43.9) | 23.6 (17.1–31.5) | 21.6 (14.6–30.6) |
| Nocturia | 6.3 (2.4–14.8) | 12.5 (3.3–33.5) | 11.2 (8.1–15.2) | 23.3 (16.3–32.1) |
| Weight loss | 10.0 (0.5–45.9) | 33.3 (1.8–87.5) | 8.3 (5.8–11.5) | 18.2 (12.4–26.0) |
| Fatigue | 20.8 (11.0–35.4) | 30.0 (12.8–54.3) | 8.9 (6.2–12.4) | 20.8 (14.2–29.4) |

The sensitivity of diagnosis was calculated as the quotient of 75 cancer patients reporting haematuria and 126 patients with urological cancer. It is noteworthy that in the prospective part of the study, only 42 cancer patients were found in the same population and the same period of registration, and 33 were not registered. This may have been as a result of having free access to a urologist without referral from their GP: the haematuria would then not be registered by the GP in the prospective part of the study. Other reasons might be patient recall bias, the time shift in the registration of the urological cancers in the two different parts of the study, some registration error, or a combination of these. If we were to use 75 as the number in the upper left-hand cell of the 2 x 2 table, then the predictive value would be 17.0% (95% CI = 13.7% to 20.9%) overall and 34.3% (95% CI = 27.3% to 42.2%) for men aged over 60 years. The LR+ would be 135.9 (95% CI = 113.8 to 162.1), and the LR– would be 0.41 (95% CI = 0.33 to 0.50). This would not change the general picture of our results. Specificity and NPV are very high, as would be expected for a low-prevalence disease.

Although most cases of macroscopic haematuria are owing to a self-limiting disease, such as an infection, there is some evidence that over the age of 60 years, the prior probability of urological cancer, according to our data, increases significantly (22.1% in males, 8.3% in females).

In this age group, macroscopic haematuria is a warning sign, particularly for men. Over the age of 40 years, either referral or watchful waiting can be justified for both sexes. We did not find any case of urological cancer in patients under 40 years, but at least some watchful waiting is indicated. Under the age 40, however, urological cancers are exceptional and there is no need to systematically refer.

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