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# Patient-specific risk of undetected malignant disease after investigation for haematuria, based on a 4-year follow-up

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Study Type – Diagnostic (exploratory cohort)
Level of Evidence 2b

**What's known on the subject? and What does the study add?**
When a standardized set of investigations are applied in a 'one-stop' haematuria clinic setting, the detection rates of malignancy in a given population are predictable and have been defined. The detection rates are known to vary according to the extent of haematuria as well as the patient age and sex.

The current study attempts to understand the 'true' incidence of disease in the investigated population by re-analysing the records of an early cohort of patients four years after their initial investigations. The actual risk of missing disease in higher-risk groups appears to be greater than previously documented.

## OBJECTIVES

- To estimate the diagnostic accuracy of a guidelines-based haematuria clinic protocol by measuring the incidence of undetected malignancy during a follow-up period.
- To estimate an individual's post-test risk of having undetected malignancy using the protocol likelihood ratio and the population prevalence of disease.

## METHODS

- Data were collected prospectively on a cohort of 4020 consecutive patients who were referred to a 'one-stop' haematuria clinic between 1998 and 2003.
- All patients had a plain radiograph taken and underwent ultrasonography and flexible cystoscopy as a part of 'first-line' investigation.
- Intravenous urography was performed where indicated after abnormal first-line tests or in patients with persistent haematuria where no abnormality had been detected.
- Records of the initial 687 participants from the first year of the study were reviewed 4 years after the original consultation. Missed diagnoses of urinary tract malignancy were recorded and sensitivities, likelihood ratios and the post-test probability of missing all disease and upper tract malignancy were calculated.

## RESULTS

- As previously reported, the overall prevalence of malignant disease was 12.1% (18.9% for macroscopic haematuria compared with 4.8% for microscopic haematuria).
- The records of the first year's cohort of patients ($N = 687$) were analysed 4 years after their original consultation and 10 potentially 'missed' tumours were identified.
- The sensitivity of the protocol was 90.9% for the detection of all urinary tract malignancy (95% CI, 82.4 to 95.5) and 71% for upper tract tumours alone (95% CI, 45.4–88.3). The latter improves to 78.6% (95% CI, 52.4–92.4) with the addition of further upper tract testing.
- The probability of missing malignant disease overall was 1.7% (95% CI, 0.95–3.04) but this rose sharply to >4% for males over 60 with macroscopic haematuria.
- For those with non-visible haematuria, the percentage probability of missed malignant disease was less than 1%.

## CONCLUSIONS

- The haematuria clinic protocol described is robust but it is not infallible.
- The risk of missing malignant disease in the higher risk groups identified in the study is much greater than previous studies would suggest.
- If additional upper tract testing or interval follow-up were to be recommended, it could be rationally targeted at these groups, given the measurable risk shown here.

## KEYWORDS

haematuria, diagnosis, likelihood functions, neoplasm

## INTRODUCTION

The patient who returns a normal set of test results after the investigation of haematuria poses a further set of questions. Namely, what is the chance that malignant disease has been missed, are more tests needed, and do they need follow-up? There is a lack of high quality data available to estimate the probability of having missed malignant disease and, hence, there is a lack of consensus regarding the further management of patients who have been investigated but in whom no malignant disease has been found [1]. There is debate regarding the value of further investigations aimed at detecting upper renal tract malignancy and follow-up is not currently recommended in the majority of protocols [2,3].Evidence-based estimates of the probability of having missed malignant disease would rationalize practice.

The probability of missing malignant disease is determined by two factors: the test protocol and the prevalence of disease within the population. This is the Bayesian principle [4]. Edwards *et al.* [5] have previously published the diagnostic yield from the largest series of patients investigated in a protocol-driven haematuria clinic. This confirmed previous estimates of disease prevalence in patients undergoing out-patient investigation for haematuria [6]. The scope of the study allowed estimates of prevalence in smaller subgroups based on the pre-existing risk factors, age, sex and the presence of visible or non-visible haematuria.

By following up this previously investigated cohort of haematuria patients, the present study aimed to estimate how reliably the clinic protocol had excluded disease and then to use this estimate to derive the probability of having missed malignant disease for a given individual based on their pre-existing risk of disease. Accurate estimates of the latter will begin to provide answers regarding the value of additional testing and follow-up/re-referral.

## METHODS

Local research ethics committee approval was secured. The study was conducted in accordance with the Standards for the Reporting of Diagnostic Studies (STARD) guidelines for reporting the accuracy of diagnostic tests [7]. It was conducted in three phases, comprising two separate phases of data collection then the analysis. Phase 1 entailed the auditing of the test outcomes from a cohort of haematuria patients, phase 2 was the follow-up of a sample of these patients after a 4-year interval, and in phase 3 these data were used to produce estimates of accuracy.

### PHASE 1 THE TEST PROTOCOL

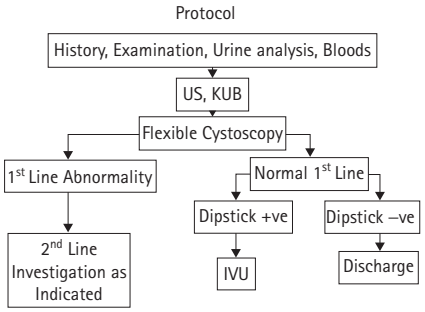
The methodology and outcomes from the first phase have been previously reported [5]. The outcomes of all investigations undertaken on consecutive patients attending a protocol-driven, 'one-stop' haematuria clinic in a large teaching hospital, between October 1998 and August 2003, were recorded (catchment population: 400 000). Patients with macro- or microscopic haematuria were referred from primary care once UTI had been excluded. Whether co-existing symptoms influenced the decision to refer is unknown. Investigations were conducted according to a local protocol encompassing recognized guidelines (Fig. 1).

Notably, testing was divided into first and second line. Initially, all patients underwent a flexible cystoscopy performed by a urologist. Upper tract imaging comprised a plain abdominal radiograph and ultrasonography performed and interpreted by two dedicated uro-radiologists. Those with abnormalities on these first-line tests underwent further investigation appropriate to their provisional diagnosis. In particular, the protocol dictated IVU after diagnosis of TCC of the bladder or upper tract calculus disease. In the case of suspected upper tract malignancies, computed axial tomography was performed in addition to IVU, as directed by the radiologist.

In patients with normal first-line tests, subsequent follow-up was determined by the outcome of repeat urine analysis on the day of the clinic attendance. Those patients found to have persistent microscopic haematuria were selected to undergo IVU in addition to their first-line tests, whilst the remaining patients were discharged. The exceptions to this algorithm were patients of ≤40 years, or those with indicators of renal disease, who were referred for a nephrological opinion.

All patient and outcome data were recorded prospectively on a source data pro-forma by one of three urological nurse specialists and entered into a central database by the investigators. With the exception of non-operatively managed tumours, all diagnoses of malignancy were confirmed histologically after resection.

*FIG. 1. Haematuria clinic protocol. US, ultrasonography; KUB, plain abdominal film of kidney, ureter and bladder.*




### PHASE 2 FOLLOW-UP

Four years on from their original attendance at the haematuria clinic, a consecutive sample of the original cohort of patients was followed up. The sample began with the first attendee recruited to the original audit.

The follow-up took the form of an electronic review of the local radiological and histological databases and also looked for duplicate attendances via the haematuria clinic. All appropriate radiological investigation reports occurring during the follow-up period were reviewed, as were reports on all histology samples obtained. Whether a patient had died was also determined. All incidences of previously undiagnosed urological malignancy were recorded as missed malignant disease after the original testing.

### ANALYSIS

True and false negative rates for the original haematuria clinic protocol were determined by comparing them with a 'gold standard' which was based on the results of the follow-up period. These were also determined for first-line tests alone. In this case, both the additional contribution of the second-line tests and the results of the follow-up period were used as the 'gold standard'. Only the results relating to the follow-up cohort were used in the estimation of the test efficacy. Sensitivity and specificity were calculated for detecting all malignancy and upper tract

*TABLE 1 Prevalence of malignant disease within age groups of each gender and further division into macro- and microscopic haematuria*

| Age sub-groups, years | Patients, *n* | Malignant disease (% prev.)* | Macroscopic (% prev.)* | Microscopic (% prev.)* |
|---|---|---|---|---|
| Males | | | | |
| 10–19 | 13 | 0 (0) | 0 (0) | 0 (0) |
| 20–29 | 67 | 1 (1.5) | 1 (1.5) | 0 (0) |
| 30–39 | 134 | 8 (6.0) | 7 (5.2) | 1 (0.7) |
| 40–49 | 274 | 14 (5.1) | 13 (4.7) | 1 (0.4) |
| 50–59 | 467 | 51 (10.9) | 38 (8.1) | 13 (2.8) |
| 60–69 | 626 | 87 (13.9) | 77 (12.3) | 10 (1.6) |
| 70–79 | 732 | 121 (16.5) | 94 (12.8) | 27 (3.7) |
| 80–89 | 284 | 67 (23.6) | 59 (20.8) | 8 (2.8) |
| 90–99 | 31 | 9 (29.0) | 6 (19.4) | 3 (9.7) |
| Total males | 2628 | 358 | 295 | 63 |
| Females | | | | |
| 10–19 | 4 | 0 (0) | 0 (0) | 0 (0) |
| 20–29 | 19 | 0 (0) | 0 (0) | 0 (0) |
| 30–39 | 91 | 2 (2.2) | 1 (1.1) | 1 (1.1) |
| 40–49 | 181 | 2 (1.1) | 2 (1.1.) | 0 (0) |
| 50–59 | 365 | 15 (4.1) | 11 (3.0) | 4 (1.1) |
| 60–69 | 302 | 34 (11.3) | 25 (8.3) | 9 (3.0) |
| 70–79 | 282 | 43 (15.2) | 34 (12.1) | 9 (3.2) |
| 80–89 | 123 | 22 (17.9) | 17 (13.8) | 5 (4.1) |
| 90–99 | 25 | 9 (36.0) | 6 (24.0) | 3 (12.0) |
| Total females | 1392 | 127 | 96 | 31 |
| Total overall | 4020 | 485 | 391 | 94 |

**Numbers in parentheses are the percentage prevalence of disease within various subgroups.*

malignancy in isolation, with and without second-line tests.

Likelihood ratios for ascertaining the absence of disease were determined using the equation:

$$\frac{\text{Probability of a false negative}}{\text{Probability of a true negative}} = \text{Likelihood ratio for a negative result}$$

This can also be expressed as:

$$\frac{1/\text{Sensitivity}}{\text{Specificity}} = \text{Likelihood ratio for a negative result}$$

Using the equation below, the post-test probability of having disease (despite negative tests) was then calculated for the test population as a whole and then for all subgroups based on their pre-existing risk factors for malignant disease: age, sex and presentation with macro- or microscopic haematuria.

Post-test odds of having disease
= Pre-test odds of having disease
× likelihood ratio for negative result

The pre-test odds of having malignant disease were derived from the disease prevalence identified in the population originally tested. All estimates of diagnostic accuracy were expressed with a 95% CI.

## RESULTS

In total, 4020 patients were investigated initially between 1998 and 2003. Of these, a consecutive series of 687 patients were followed up at a median of 48 (42–54) months.

The results of the original testing phase have been previously published [5]. In summary, the overall prevalence of urinary tract malignancy was 12.1% (95% CI, 11.2–13.2). The overall prevalence of upper tract malignancy was 1.8% (95% CI, 1.4–2.3). The age, sex and presentation with macro- or microscopic haematuria individually determined probability of disease (Table 1).

Of the 687 patients that were followed up, 677 had no new diagnosis made. Of the 10 new cases of malignancy, three were upper tract tumours, with two of these being upper tract TCCs. There were seven new diagnoses of bladder tumours. Seven of the new cancers occurred in men, seven in those over 60 and seven in those whose original presentation had been with non-visible haematuria. In all, 78 had died at the time of follow-up (three of whom were in the 'missed' diagnosis group). Both of the missed upper tract TCCs had received full protocol assessment with a normal IVU at original testing. Half of the new cases were identified within eighteen months of the original testing.

The sensitivity of the whole protocol for all urinary tract malignancy was 87.5% (95% CI, 78.5–93.1) and for upper tract malignancy was 78.6% (95% CI, 52.4–92.4). The sensitivity of first-line testing alone for upper tract malignancy was 71% (95% CI, 45.4–88.3). The likelihood ratio for a negative result was 0.125 (95% CI, 0.070–0.224) for all urinary tract malignancy, 0.025 (95% CI, 0.107–0.585) for upper tract malignancy for the whole testing protocol, and 0.313 (95% CI, 0.151–0.647) for upper tract malignancy if only first-line tests were employed.

Figure 2 shows the percentage probability of having missed any urological malignancy for specific population subgroups if no disease was found on completion of the original testing protocol. For those with non-visible haematuria, the percentage probability is ≤1% (except for the small subgroup >90 years old). For those presenting with macroscopic haematuria, the risk rises from 1% to 3% between 40 and 60 years of age, with the rise in men's risk pre-dating that of women's by 10 years but reaching similar levels by the age of 60. For both men and women, the risk continues to rise by 1% per decade so that by the ninth decade of life, the risk of missing malignant disease is 5%.

Figure 3 shows the percentage probability of missing upper tract malignancy if the whole protocol or first-line tests alone are used. The risk increases in an approximately linear fashion with age. It does not exceed 0.6% for those under the age of 70. The overall relative risk of missing malignant disease of the full testing protocol, including the selective use of

*FIG. 2. Percentage probability of missing urological malignant disease by population subgroup.*

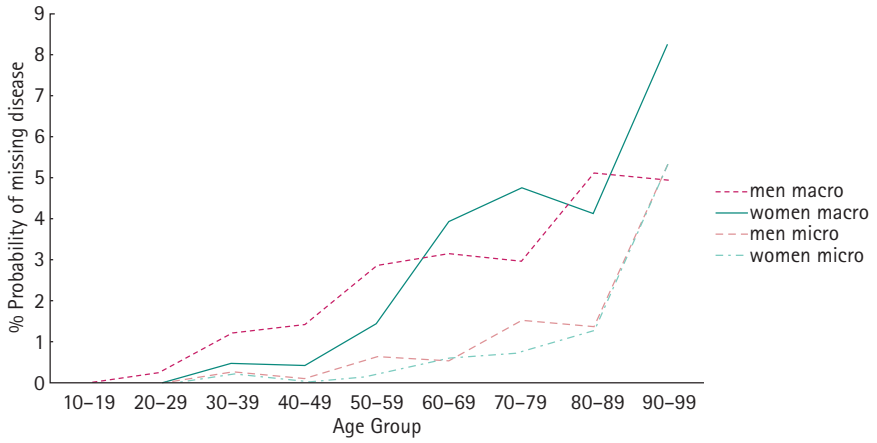



*FIG. 3. Percentage probability of missing upper tract malignant disease by population subgroup. Micro, microscopic haematuria; macro, macroscopic haematuria.*

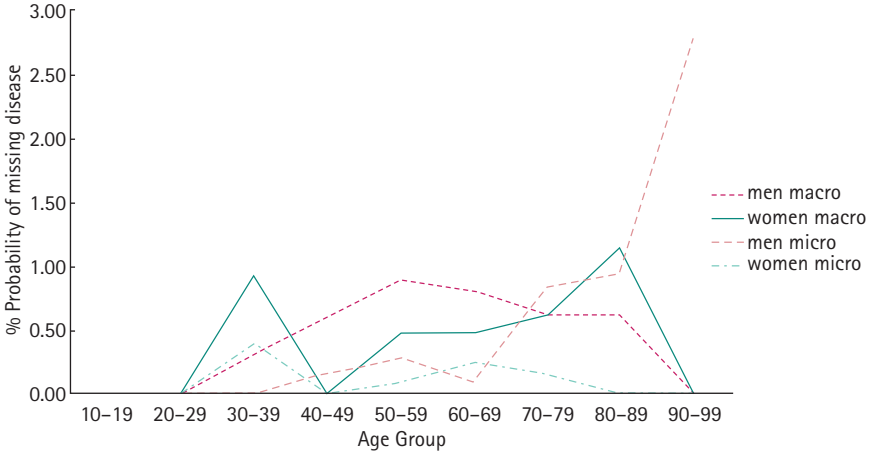
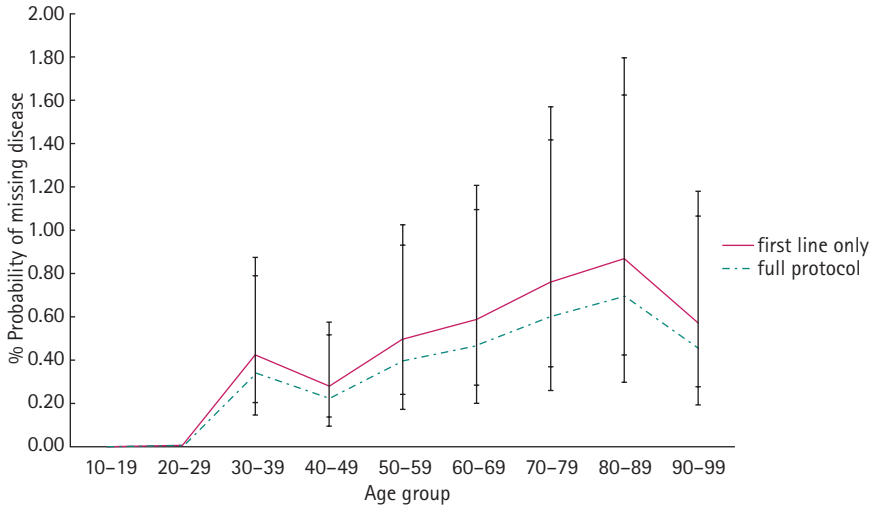



*FIG. 4. Percentage probability of missing upper tract malignant disease by age group for full protocol or first-line tests only (Y error bars = 95% CI).*




IVU, vs the first-line tests alone is 0.750 (95% CI 0.168–3.339). The difference in the probability of missing malignant disease remains consistent throughout the age subgroups. The difference is not significant (Fig. 4).

## DISCUSSION

As anticipated, the haematuria clinic protocol described is robust but not infallible. It leaves an overall post-test probability of missing malignancy of 1.7% (95% CI, 0.95–3.04). The risk of missing malignant upper tract disease is 0.6% (95%CI 0.28 to 1.19), reducing to 0.5% (95% CI, 0.20–1.07) if IVU is included as per protocol. The relative risk reduction afforded by the addition of second-line testing in addition to first-line investigations is 0.750 (95% 0.168–3.339).

The probability of missing any disease for both men and women with microscopic haematuria is <1%, and this remains consistent through all age groups (only rising above 1% for those greater than 90 years of age). In contrast, for those patients presenting with macroscopic haematuria, the overall risk of missing malignant disease for men >30 years and for women >50 years is closer to 2%. This rises to 3% by age 60 years, 4% by 70 years and in excess of 5% for both sexes >80 years.

Recently published long term follow-ups of patients originally assessed for non-visible (microscopic) haematuria confirm that the risk of new or missed malignant disease in this group is no higher than the background incidence of disease. Our findings support the predicted low risk of missed malignant disease within this group [8,9]. A study of interval testing and repeat investigation of patients within 1 year of their original presentation concluded that the small number of tumours identified subsequent to the original testing represented new disease [10]. Other authors have identified very few, if any, individuals who, having previously tested negative, subsequently develop a urinary tract malignancy regardless of their original risk of disease [6,11,12].

Previous estimates of the additional benefit of performing an IVU (in terms of increasing the sensitivity of the protocol) are in keeping with the predicted risks described herein for missing upper tract malignancy [1,6,13,14].

This is the first study to provide estimates of test sensitivity and the risk of missing malignant disease for the individual presenting to a protocol-driven haematuria service. Quantifying the risk of missed malignant disease in an individual, based on patient-level characteristics, allows informed decision-making to occur with regard to the provision of additional investigations or interval testing. The risk is linearly proportional to the prevalence of the disease within a specific population subgroup – those at high risk of disease are also at high risk of it remaining undetected after the testing process. Of course, the derived values are an '*a priori*' estimate of the risk. Because of the low frequency of missed malignant disease, actual demonstration of this risk would require post-test follow-up of an unfeasibly large sample population.

The effect of low disease prevalence on the risk of missing malignant disease is most marked in the upper urinary tracts. It was previously accepted that this risk was low; nevertheless, European and North American Guidelines have included additional testing for upper tract malignancy in high-risk groups over and above ultrasonography alone [15,16]. This will invariably involve an absorbed dose of ionizing radiation (IVU = 21 mGy; CT = 25 mGy) with its own theoretical risk of inducing malignancy as well as considerable economic cost [17–19].

## WEAKNESS

The accuracy of any estimate is predominantly determined by the sample size and the frequency of the event in question. In limiting the sample size of the follow-up group to 687 cases, the CIs are correspondingly wider than if a larger cohort had been followed. This issue becomes more pressing when considering rarely occurring events such as upper tract tumours.

Furthermore, in counting all malignancies that arise during the follow-up period as a false negative result of the original tests, no allowance is made for the possibility of an interval cancer arising *de novo*. This may have resulted in an over-inflated estimate of the false negative rate. In addition, no mention is made of false positive rates. In the majority of cases, the result was confirmed by histological analysis. A nominal value of 1 was given for the number of false positives, without which the calculation of likelihood ratios would not have been possible.

The use of hospital database records to identify previously unrecorded malignancies during the follow-up period, rather than face-to-face review of each individual or re-submission to the testing protocol raises questions about the validity of the results. Specifically, patients moving out of the catchment area will be lost to follow-up, although the population of this area of South West Devon is noted for its migratory stability [personal communication, L Bryant *et al.*]. In addition, the low rates of post-mortem examination in the UK and the failure to include such data in this study means that those patients who died during the follow-up period represent a significant unknown if not diagnosed with urothelial disease pre-mortem.

Weaknesses aside, the pick-up rate of missed or new malignant disease far exceeds any previously published similar post-test cohort follow-up data, which allows for some confidence in the completeness of this method.

In conclusion, these data allow informed decision-making regarding the counselling and subsequent management of the patient who, after referral and testing for haematuria, has not been found to have malignancy. Men and women of any age with microscopic haematuria can be reassured and discharged on the basis of a low probability of missed malignant disease. The management of those presenting with macroscopic haematuria will depend on the level of risk that one is prepared to accept. This will be a decision for professional bodies or healthcare policy makers. The data now allow an accurate representation of this level of risk. For the authors' part, a 3% risk of missing malignant disease in those >60 years seems significant. This risk increases by approximately 1% per decade thereafter. No provision currently exists for any sensible further monitoring of this group and, at present, we do not know the effect of more contemporary second-line investigation such as CT or urinary biomarkers on the risk of missed malignant disease.

The current data throw into question the unselected use of additional upper tract testing where all first-line tests have been normal. Ultrasonography remains safe in all patients, does not use ionizing radiation and, if negative, results in a very low risk of missed malignant disease. It is conceivable that further unselected testing may confer no additional survival benefit. If further tests were to be employed, targeting them at those >50 years presenting with macroscopic haematuria may be a more rational use of the data. The potential for missed malignant disease may remain even with additional upper tract investigations. Therefore, an alternative strategy could be discontinuation of further imaging at initial presentation with deferred interval follow-up and repeat imaging for the known high-risk groups.

## ETHICAL APPROVAL

This work has been granted full ethical approval from the Local Research Ethics Committee.

## CONFLICT OF INTEREST

None declared.

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