The Medical Investigation of Macroscopic Hematuria in adults

Cohort presenting delay in investigation and its possible effect on bladder cancer

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THE MEDICAL INVESTIGATION OF MACROSCOPIC HEMATURIA IN ADULTS

Cohort presenting delay in investigation and its possible effect on bladder tumor cancer

Caroline Westblom

Abstract

Introduction and objectives According to Swedish guidelines set up by The National Board of Health and Welfare (2002) macroscopic hematuria (MH) ought to be investigated using urethrocystoscopy and radiological imaging within four weeks’ time. Although a majority of patients with bladder cancer present with MH, multiple studies display a great delay in diagnosing bladder tumors. Thus the aim of this report is to define if a delay in investigating MH exist, and display how a delay (> 28 days) will affect a possible bladder cancer diagnosis regarding tumor stage and recurrence in cancer.

Material and methods: A total of 72 patients were retrospectively reviewed using medical journals, regarding data concerning patient’s characteristics, the investigation of MH and tumor characteristics.

Results: The medical investigation of MH was median 57 days. Only 17 % of the patients did receive an investigation according to guidelines, and 25.5 % did never receive a radiological imaging of urinary tract. No correlation could be seen between delay (≥28 days), and frequency of tumors ≥T1. Patients who sought medical care acute/ or received an acute referral had a greater likelihood of obtaining a short (< 28 days) investigation. Additionally rapid investigation significantly (p=0.002) correlates to lower rate of recurrence in bladder cancer.

Conclusion: Further studies with a larger group of patients are needed, to enable more robust conclusions concerning investigational time of MH, and its effect on bladder cancer tumor stages, bladder cancer survival, as well as its possible consequences on cancer recurrence.

KEY WORDS: Macroscopic hematuria, bladder cancer, delay, investigation
DEN MEDICINSKA UTREDNINGEN AV MAKROSKOPISK HEMATURI HOS VUXNA

Kohort presenterande en fördröjning i utredning och dess möjliga effekt på blåscancer

Caroline Westblom

Sammanfattning

Introduktion och syfte: Synligt blod i urinen, så kallad Makroskopisk hematuri (MH) bör enligt Socialstyrelsen utredas med urethrocystoskopi och röntgen inom fyra veckors tid, för att snabbt kunna utesluta malign orsak. Majoriteten av alla blåscancerfall debuterar med MH. Trots detta har flertalet studier visat att utredningen av blåscancer är tidsmässigt mycket lång. Inga tidigare studier har i detalj visat hur den primära utredningen av MH egentligen fungerar. Således syftar denna studie att kartlägga utredningsgången av MH, samt undersöka om en lång initial utredningstid kan korreleras till högre förekomst av mer avancerade tumörstadijer och/eller återfall i cancer.

Material och metoder: Följande retrospektiva studie omfattar 72 patienter som studerats med hjälp av journalmaterial avseende patient karaktäristika, tidsintervaller för utredning av MH samt tumör karaktäristika.

Resultat: Denna studie uppvisar en utredningstid för MH på 57 dagar (median). 25.5 % av patienterna fick aldrig en radiologisk undersökning av urinvägarna och endast 17.0 % fick en utredning i enlighet med gällande riktlinjer. Inget samband kunde ses mellan lång utredning av MH och högre frekvens av tumörstadium ≥ T1. Däremot återfanns ett signifikant (p=0,002) samband mellan snabb utredning (≤ 28 dagar) och en lägre frekvens av återfall i blåscancer.


NYCKELORD: Makroskopisk hematuri, blåscancer, fördröjning, utredning
Introduction

1. Macroscopic hematuria

1.1 Definitions

Blood in urine (hematuria) is categorized as either non-visible or visible. Non-visible hematuria is only possible to detect by laboratory measurements, either by using a urine dip stick test or a microscope [1]. Macroscopic hematuria (MH), also called gross hematuria or frank hematuria is possible to visualize with the naked eye, which means that the concentration of erythrocytes in the urine has exceeded $5 \times 10^9/L$. Visible hematuria can be subdivided into either asymptomatic or symptomatic depending on the presence of/ or lack of other simultaneous symptoms like pain in lower abdomen, urgency, cystitis-like symptoms etc. [2]

1.2 Epidemiology

The prevalence of macroscopic hematuria in the population is 2.5 % [3], thus making it one of the most common causes of a referral to a urological clinic [1].

1.3 Pathology

Macroscopic hematuria may derive from either nephrological or urological origin [1], of which the latter will be presented in this report. The most common benign urological origin, which accounts for approximately 70 % of all macroscopic hematuria, are urinary tract infections (UTI), urinary tract stone and benign prostate hyperplasia (BPH)[4]. Malignant causes are urinary tract carcinomas, renal cancer and prostate cancer [4], of which bladder cancer is the most common [5], closely followed by renal cancer [1]. More uncommon urinary tract malignancies are renal pelvic cancer and cancer of the ureters [6].

1.4 An importance symptom of urinary tract malignancies

As much as 27 % of all adult cases of asymptomatic macroscopic hematuria derive from bladder cancer [7]. Hence MH is a symptom to take serious, and should be viewed upon as being a sign of urinary tract malignancy until proven otherwise [1]. The risk of having a urinary tract malignancy when presenting with hematuria increases with age, significantly over the age of 50 [8]. MH has a sensitivity of detecting urine tract malignancies of 0.83 for
bladder cancer, 0.66 cancers of the ureters respectively 0.48 for renal carcinoma [5]. The positive predictive value (PPV) of MH detecting a urological cancer in men over the age of 60 is 22.1 %, respectively 8.3 % in women [9].

1.5 Medical investigation and management

According to a State of the Art report (2002) from the National Board of Health and Welfare in Sweden, macroscopic hematuria ought to be completely investigated in four weeks’ time [10]. A complete investigation includes visualization of both lower and upper urinary tract [11]. Optimum diagnostic investigation is by using a combination of flexible/ rigid cystoscopy and computerized tomography (CT) urography [12]. Flexible cystoscopy is quickly performed in a urologist office, and is most often achieved with little discomfort [13]. Cystoscopy enables visualization of macroscopic neoplasms in the bladder, while radiological imaging (CT urography) has a primary role to detect tumors in the upper urinary tract [12]. CT urography has proven to be of use before cystoscopy, in order to obtain an earlier diagnosis [14]. Patients who display a bladder tumor on a CT urography can be referred directly to rigid cystoscopy performed in the operating theatre [12], which reduces the number of flexible cystoscopies [14]. Ultrasonography of urinary tract is not reliable in discovering small bladder tumors, and does neither replace cystoscopy nor CT urography in the investigation of macroscopic hematuria [15].

Patients with hematuria and a positive urine culture have the same likelihood of having a urological malignancy as the ones presenting with negative urine culture [16]. 18 % of all patients with recurrent hematuria will have received a urological cancer diagnosis within five years [17]. Likely Mishriki et al (2009) presented that 9.8 % of patients with recurrent macroscopic hematuria were to be diagnosed with a urological cancer in a near future. Henceforth individuals with recurrent macroscopic hematuria, who has a history of previously being subject to a complete urological examination, should be examined again looking for neoplasms in case of a new episode of macroscopic hematuria [17]. A single episode of macroscopic hematuria is equally as important to investigate as multiple episodes [4].

Correlation between macroscopic hematuria and anticoagulant therapy has been discussed repeatedly [18, 19] and has yet not yielded in consensus. Antoniewicz et al (2012) observed a correlation between the presence of anticoagulant therapy and macroscopic hematuria. The study concluded that urological origins were more often present in patients not receiving
anticoagulant drugs [18]. Avidor et al on the other hand (2000) writes that “the presence of excessive anticoagulation should not impede a full evaluation”. Out of 93 patients with anticoagulant therapy presenting with macroscopic hematuria, 24 % had a previously unknown primary tumor in the urinary tract [19].

Some countries have established so called “hematuria-clinics”[12, 20, 21], in order to offer the patient a quick investigation with flexible cystoscopy and radiological imaging, preferably all in their first visit [21]. Paul et al (1993) displayed that such clinic could reduce time from referral to treatment (TUR-B) from mean of 60 days to 33 days. Unlike cystoscopy and urography, urine cytology has proved to have a low diagnostic significance, and should therefore not be used in “hematuria-clinics” [12].

Scant information in patients’ referrals makes it hard to make a correct priority. Referrals of patients with hematuria contain information about laboratory results such as urine culture in 20 % respectively urine dipstick test in 22% of the cases. [7]

2. Urothelial carcinoma

Urothelial (transitional) cell cancer (UCC respectively TCC) includes bladder carcinoma, renal pelvis cancer and cancer of the ureters [22]. Bladder carcinoma is the most common (90 %) of all urothelial carcinomas [23]. These cancer forms are all closely related to each other. Patients with upper urinary tract UCC (renal pelvis cancer or cancer of the ureter) have a 30-50 % lifetime risk of developing bladder carcinoma, respectively individuals with bladder carcinomas have a 2-3 % lifetime risk of developing cancer of the upper urinary tract. [22]

Risk factors for developing UCC are tobacco smoking, chronic urinary tract inflammation, exposure to toxins (for example organic chemicals, rubber, paint, dye etc), upper urinary tract stones (especially renal pelvis cancer), familial nephropathy and genetic factors. [22]

90-95% of all urinary tract cancers are transitional cell carcinomas. Other less frequently seen histological types are squamous cell cancer and adenocarcinomas. The squamous cell cancer account for 3-7 % of all urinary tract cancers and are more often found in renal pelvis cancer and cancer of the ureters. [22]
This report will henceforth focus on discussing macroscopic hematuria as a symptom of bladder cancer, though it is important not to forget that MH also might be a symptom of upper urinary tract cancer, renal cancer as well as prostate cancer.

2.1 Bladder cancer

Every year 330,000 people worldwide acquire a bladder cancer diagnosis, thus making it the ninth most common cancer in the world [24]. The incidence of bladder cancer increases with age and has its peak between the age of 50 and 70 years old, with three in four patients being male [25].

Bladder cancer is highly correlated to tobacco smoking, which triples the relative risk of obtaining a bladder tumor compared to never smoking. Tobacco smoke serves for 50-65 % of the male bladder cancer, and 20-30 % of the female cases. [26]

The most common symptom of a malignant tumor in the bladder is asymptomatic macroscopic hematuria [25], which is seen in approximately 80 % of all cases of bladder cancer. Other more uncommon symptoms are dysuria, urgency and cystitis-like symptoms [23].

The most important method to identify a tumor in the bladder is by using flexible cystoscopy [23]. The majority (90%) of all bladder tumors are urothelial carcinomas, 5 % squamous cell carcinomas and <2 % adenocarcinomas [25]. Approximately 30 % of all bladder cancer includes involvement of multiple sites of the bladder, most commonly seen in carcinoma in situ (CIS). CIS can be found without macroscopically visualized cancer, and most often means higher disease stages and greater risk of developing muscle-invasive cancer. [22]

25 % of all bladder cancer tumors involving lamina propria, will develop recurrence distant from the primary tumor. There are diverge opinions regarding the origin of bladder tumors, and its common multifocal nature. Two different theories are “field change” and “monoclonal nature”. The theory of “field change” presents that around a primary tumor there are nonvisible in situ formations, which will later on present as recurrent tumors. “Monoclonal nature”-theory on the other hand states that all tumors originate from one monoclonal cell, which spread intravesically or by lateral intraepithelial migration to other sites in the bladder. The monoclonal nature theory is supported by the low risk of contralateral upper urinary tract
UCC in case of pelvic cancer or cancer of the ureter, though having a significant risk (40 %) of developing bladder cancer. [27]

Histologically bladder tumor stage is classified using the TNM-staging system (tumor-node-metastasis), where T is defined by tumor invasion through the bladder muscle wall. All UCC are also histologically graded from 1-3 [25]. Approximately 70-80 % of all bladder cancer is non-muscle-invasive at diagnosis (NMIBC) [28], which includes TNM-stages Tis, Ta and T1 [25]. NMIBC is treated with transurethral resection of the bladder (TUR-B) with or without postoperative intravesical immunomodulation/ or chemotherapy [25]. 33-39 % of all patients with NMIBC develop recurrent bladder cancer after initial TUR-B and following intravesical therapy with bacillus Calmette-Guérin (BCG) [28]. Complete remission is possible in 80 % of all cases of carcinoma in situ (CIS), and > 50 % of the papillary tumors can be long time tumor-free [23]. One third of the superficial bladder tumors progress, despite treatment, and causes death [29]. Low grade (G1-G2) Ta has a progression-free 15-year survival of 95 %, without any cancer specific mortality. High grade (G3) Ta tumors have a progression-free 15-year survival rate of 61 % with a disease specific survival of 74 %. The same numbers for the T1 tumors are 44 % respectively 62 %. Bladder cancer survival is highly determined by whether or not there exists a cell invasion of lamina propria. [25]

Patients with muscle invasive bladder cancer (MIBC) (T2, T3 and T4) should, if possible undergo radical surgery with cystectomy and urine deviation, since it is highly lethal [30]. All patients with MIBC also ought to undergo a metastasis investigation, using computed tomography of chest, abdomen and pelvic area [25]. 5-yearsurvival in MIBC range from 89 % (T2N0M0) to 35 % (T2-T4N1M0) [29]. Factors associated with poor outcome in patients with MIBC are lymph node invasion, surgical margins, lymphovascular invasion and T-substage [31]. A worse outcome has been shown in female patients with T4 tumor than in males within the same tumor stage [31]. Metastasized bladder cancer is often treated with combinations of chemotherapies (most commonly including Cisplatin) [23], and has a median survival of 12-13 months [31], as well as 5-year survival rate of 15 % [29].

2.2 Delay in investigation
Urothelial cancer, of which bladder cancer represent a major part, is the most delayed cancer diagnosis of all. Median time elapsed from symptoms to therapy is 134 days. The same Danish study also showed a patients delay of average 14 days [32]. Another study exhibited a
mean time from onset of symptoms (hematuria) to diagnosis of 53.3 days, and an additional 20.1 days from diagnosis to final treatment (TUR-B) [33]. Wallace et al (2002) showed a mean time from symptom to TUR-B of 110 days [34]. According to Wallace report from 1965 hospital delay represents the major part of the total delay in diagnosing bladder cancer [35]. The most important factor to determine hospital delay is age, with patients under the age of 60 having to wait longer for treatment [36]. Patients with bladder cancer had according to Mommsens (1983) an average time from symptom to treatment of 28 weeks (median 15) [37]. The report also showed that patients with the longest doctor’s delay were the ones presenting with cystitis-like symptoms and women presenting with hematuria [37]. A study by Stower (1988) confirmed Wallace’s data from 1965; namely patients with newly diagnosed bladder cancer are quick at seeking medical care [38]. Three quarters of all patients with asymptomatic hematuria are being referred to a specialist within a month time [38]. The ones who do not get a referral within a month’s time are in higher frequency people under the age of 50 years old [38]. 7 % respectively 4 % of MIBC cases in 1989 and 1993 did not get an upper urinary tract imaging during investigation [39].

2.3 Importance of investigational time
Chang et al (2003) demonstrate that a delay of more than 90 days from diagnosis (TUR-B) to final treatment (cystectomy) in MIBC significantly increases the risk of having a locally advanced tumor, with a majority of the patients presenting cancer spread to lymphatic nodes, and a higher rate of ≥T3 tumors [40]. Age or sex could not be correlated to pathological stage [40]. Tumor stage is a highly significant (p<0.001) prognostic factor when it comes to bladder cancer survival. A delay in investigation, have most adverse effect on bladder cancer survival in case of T1 tumors [34]. For the superficially growing bladder tumors (Ta), a delay in investigation has little effect on the 3-year survival rate. A delay more than four weeks from symptom (MH) to treatment in case of MIBC result in a 3-year survival decrease from 60 % to 25 % [35]. Wallace et al (2002) exhibited an expressively better bladder cancer survival rate in patients who were referred to specialist within 14 days of initial symptoms. There is also a significant difference in survival even within the same tumor stage, seen in pT2a (lymph node negative) respectively pT2b (lymph node positive) bladder cancer [41]. A delay in investigation does not affect the survival rate in T3 or T4 tumors, but there is a significant gain in survival rate for the ones presenting with a T1 or T2 tumors [37]. Contradictory the
ones with the shortest hospital delay have the worst prognosis. Patients with acute referral from a general practitioner showed a worse outcome regarding survival. [42]

3. Present knowledge gap and study purpose

Several studies has presented a delay in the medical investigation of bladder cancer [32-35, 37, 38], of which many also exhibited an impact on bladder cancer survival [34, 37, 40-42]. None has in detail described the potential delay in the investigation of macroscopic hematuria (figure I), its possible inefficacy as well as effect. This study will add an important dimension to the overall description of bladder cancer delay. Hence the aim of this study is to present how current management of MH works, to define it there exist a delay in investigation, give answers to why such delay exist, and finally display how a delay will affect a possible bladder cancer diagnosis.

Figure I. Time from debut of symptom (macroscopic hematuria) to a potential cancer diagnosis.

4. Hypothesis

4.1 Primary hypothesis

There is a higher frequency of more advanced bladder tumor stages (≥T1) in case investigation of macroscopic hematuria is being delayed (> 28 days).

4.2 Secondary hypothesis

- A majority of the patients do not receive a referral to specialist at their first doctor’s visit (at the general practitioners office).
➢ A majority of the patients receive inefficient and unnecessary therapy with antibiotics.

➢ Older patients do more often than young receive a prolonged investigation.

➢ Women do more often than men receive a prolonged investigation.

➢ A majority, of the patients included in this report, do not receive a simultaneous referral to radiological investigation.

➢ Most of the written referrals lack information about:

   a) Smoking habits
   
   b) Serum levels of Prostate specific antigen (PSA)
   
   c) Serum creatinine levels
   
   d) Results of a urine culture
   
   e) Results of a urine dipstick test
   
   f) Diabetes mellitus (type I or II)

**Methods**

This study is a retrospective cohort of all patients who has undergone cystoscopy in operating theatre due to macroscopic hematuria caused by a bladder neoplasm, during 2006-2010, in the region of Gävleborg, Sweden. Patients were selected using Provisio Analysis (2005), which is a local program where all surgeries performed in operating theatre in the region of Gävleborg (Sweden) are being registered. Patients with the following preoperative ICD code (International Code of Diseases) were selected, and reviewed on the basis of inclusions respectively exclusions criteria’s:

- D41.4 (Tumor of uncertain or unknown nature in the urine bladder )
- C67.9 (non-specified localization of malignant tumor in the urine bladder )
- C67.4 (malignant tumor in the back wall of the urine bladder)
- C67.2 (malignant tumor in side wall of the urine bladder)
- C67.1 (malignant tumor in the bladder roof)
- R31.9 (non-specified hematuria)

A total of 72 patients were included and reviewed using medical journals from general practitioners offices, specialists and hospital units within the region. The patients were reviewed upon variables and time intervals listed below. The medical investigation was defined as following (all presented in days):

1. **Patients delay (PD):** Time from onset of symptom (MH) to first medical contact. Date of symptom is based upon journal data. If impossible to obtain precise date, the date is approximated upon time indication such as: “debut of MH one week ago” (=7 days), “debut of symptom one month ago” (=30 days) or “debut of symptom this Christmas” (= number of days passed since 24th of December) etc.

2. **Initial delay (ID):** Time elapsed from the patient’s first medical contact to first doctor’s contact. First medical contact (by telephone or appointment) is most commonly a nurse at a general practitioners office, urologist office or emergency department. Doctor’s contact is defines as either a doctor’s appointment or contact by telephone.

3. **Doctor’s delay (DD):** Number of days passed from first doctor’s contact until date of referral to appropriate specialist (urology). Zero days equals immediate referral. Referral to gynecologist or other medical specialties are not a valid referral.

4. **Cystoscopy delay (CD):** Time from first doctor’s contact until performed cystoscopy (flexible or rigid) at a urological clinic. In case patient refuses initial cystoscopy, date is set to where first cystoscopy has been offered to the patient.

5. **Complete investigational delay (CID= Doctor’s delay+ hospital delay):** Time in days from first doctor’s contact to completed investigation. Complete investigation includes both cystoscopy and adequate radiological imaging (CT urography or conventional urography with contrast). Ultrasound of urine tract is not a valid radiological method, when investigating MH. Investigation is completed at the date of the last investigation (cystoscopy or radiological imaging).
Additional data was collected from medical journals regarding:

- Gender
- Age at time of symptom
- Content of referral: Referral was studied based upon presence of / or lack of following information; smoking habits, serum concentration of prostate specific antigen (only men), serum concentrations of creatinine, results of urine culture, results of urine dip stick test and diabetes mellitus (type I or II).
- Presence of/ or lack of simultaneous referral to radiological imaging
- Results from urine dip stick test, at time of initial doctor’s contact: positive (positive nitrite and/ or leucocytes) or negative (presenting nothing / or only erythrocytes)
- Results from urine culture, at time of initial doctor’s contact: Growth of substantial bacterial colony (positive) or no substantial growth of bacteria (negative) in urine sample.
- ASA classification done by anesthesiologist before medical procedure in operating theatre.
- Anticoagulant therapy at time of symptom: Therapy with warfarin or acetylsalicylic acid
- Presence of/ or lack of recurrence in bladder cancer after initial therapy.
- Choice of initial therapy, as well as therapy in case of recurrent bladder cancer
- Tumor stage and grade at time of diagnosis
- Eventual upgrading of tumor at re TUR-B

**Inclusion criteria’s**

1. Patients over 18 years old at the time of debut (MH).
2. MH investigated during year 2006-2010, which yielded in a bladder cancer diagnosis.
3. Complete medical investigation performed in the region of Gävleborg, Sweden.
Exclusion criteria’s

1. Patients under the age of 18 years old when presenting with MH.

2. Patients with urinary tract tumors without macroscopic hematuria as single/ or part of debut symptoms.

3. Patients with a recurrent bladder neoplasm, detected by routine controls who has presented with MH.

Analytical methods

Descriptive data are being presented in tables and figures as number, percentage, range, median and average number, using Microsoft Office Word and Excel (2010). Correlations analyses are calculated using Pearson’s Chi-Square method in IBM SPSS Statistics (2012).

Ethical approval

Since this study includes personal medical data, as well as aim to be submitted to peer-viewed urological journals, it has undergone ethical examination (DNR 2012/446) approved by a committee 2012-12-05.
Results

Between the years 2006-2010, 345 people underwent cystoscopy in surgery in the region of Gävleborg, Sweden. 74 out of 345 patients had presented with macroscopic hematuria due to a bladder cancer. 2 patients fulfilled the exclusion criteria’s, and were therefore left out. Complete data could be obtained in 47 out of 72 patients. 25 patients had incomplete data regarding certain parts of the initial medical investigation, for example patient’s delay, initial delay and number of visits not yielding in a referral etc. The most common cause to why complete data was impossible be obtained was due to private general practitioners with separate medical journal systems. All statistics are based upon the 47 patients with complete data, and will be presented as fallowing; patients’ baseline characteristics, time intervals regarding the medical investigation of MH, potentially delaying factors in investigation and the effects of such delay on a bladder cancer diagnosis.

1. Baseline characteristics

As displayed in table I, the average age among the patients with complete data was 69 years, and ranged from 48 to 90 years old at debut of symptom (MH). The distribution between men and women was 85.1 % respectively 14.9 %. The most common clinical T-stage was Ta (72.3 %). A great majority (91.5 %) of the patients had NMIBC, whereas 8.5 % had MIBC. Almost half of the patients (48.9 %) had been classified as ASA-class II before surgical intervention.

Table I. Patients’ baseline characteristics.

<table>
<thead>
<tr>
<th></th>
<th>Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
</tr>
<tr>
<td>Average</td>
<td>69</td>
</tr>
<tr>
<td>Median</td>
<td>68</td>
</tr>
<tr>
<td>Range</td>
<td>48-90</td>
</tr>
<tr>
<td><strong>Sex, no (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>Male</td>
<td>40 (85.1)</td>
</tr>
<tr>
<td><strong>Clinical stage, no (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Tis</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Ta</td>
<td>34 (72.3)</td>
</tr>
<tr>
<td>T1</td>
<td>7 (14.9)</td>
</tr>
<tr>
<td>T2</td>
<td>4 (8.5)</td>
</tr>
<tr>
<td>T3</td>
<td>0 (0)</td>
</tr>
<tr>
<td>T4</td>
<td>0 (0)</td>
</tr>
<tr>
<td><strong>ASA-class, no (%)</strong></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>10 (21.3)</td>
</tr>
<tr>
<td>II</td>
<td>23 (48.9)</td>
</tr>
<tr>
<td>III</td>
<td>11 (23.4)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (4.3)</td>
</tr>
<tr>
<td>Unknown</td>
<td>1 (2.1)</td>
</tr>
</tbody>
</table>
2. The medical investigation

2.1 Patients delay

In this report patients delay (PD) was in average 11 days (0-90), and had a median number of 3 days (Table II). Median PD did not differ between the sexes (3 resp. 3 days).

2.2 Instances of initial medical care

Figure II illustrates that a great majority (79%) of the patients with MH due to bladder cancer sought initial medical care at a general practitioner’s office (GP), and are either referred acute or at normal rate. A total of 11% sought medical care at the emergency department (ED) without previous contact with a general practitioner, either once (9%) or multiple times (2%).

![Figure II. Figure illustrating the distribution of initial care instances in this group of patients.](image)

Other less common instances of initial medical care was other hospital units (2%), and direct contact with an urologist office (6%).

2.3 Initial delay

Initial delay was (table II) median 1 day, without any difference between the sexes. A one day initial delay means that the patients did receive a doctor’s appointment within 24 hours from initial contact with medical care.

2.4 Doctor’s delay

Table II presents a doctor’s delay (DD) with a median number of 1.5 days (0-646 days), and average 31 days. Median DD for men was 0 days (referral being done at time of first doctors contact), while the same number for women was 43 days.
Table II. Time intervals from debut of symptom (MH) to completed investigation.

<table>
<thead>
<tr>
<th>Delay (days)</th>
<th>R (M+W)</th>
<th>Md (M+W)</th>
<th>Av (M+W)</th>
<th>R (M)</th>
<th>Md (M)</th>
<th>Av (M)</th>
<th>R (W)</th>
<th>Md (W)</th>
<th>Av (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>(1-90)</td>
<td>3</td>
<td>11</td>
<td>(1-90)</td>
<td>3</td>
<td>12</td>
<td>(1-7)</td>
<td>3</td>
<td>4</td>
</tr>
<tr>
<td>ID</td>
<td>(0-27)</td>
<td>1</td>
<td>2</td>
<td>(0-27)</td>
<td>1</td>
<td>2</td>
<td>(1-1)</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>DD</td>
<td>(0-646)</td>
<td>1.5</td>
<td>31</td>
<td>(0-236)</td>
<td>0</td>
<td>13</td>
<td>(0-646)</td>
<td>43</td>
<td>131</td>
</tr>
<tr>
<td>CD</td>
<td>(0-646)</td>
<td>41</td>
<td>73</td>
<td>(0-384)</td>
<td>40</td>
<td>58</td>
<td>(2-646)</td>
<td>91</td>
<td>156</td>
</tr>
<tr>
<td>DD+HD (N=47)</td>
<td>(0-662)</td>
<td>57</td>
<td>94</td>
<td>(0-427)</td>
<td>57</td>
<td>78</td>
<td>(16-662)</td>
<td>103</td>
<td>171</td>
</tr>
<tr>
<td>Doctor’s contact without referral</td>
<td>(0-6)</td>
<td>0</td>
<td>1</td>
<td>(0-3)</td>
<td>0</td>
<td>1</td>
<td>(0-6)</td>
<td>1</td>
<td>2</td>
</tr>
</tbody>
</table>

Md= Median
Av= Average
MH= Macroscopic hematuria
W= Women
R= Range
PD= Patients delay
ID= Initial delay
CD= Cystoscopy delay
DD= Doctors delay
HD= Hospital delay

The median number of initial doctors’ visits, for the whole group, which did not yield in a referral was 0 (referral being done at time of initial doctors’ contact). Women had a median of 1 (0-6) visit, and an average of 2 visits before referral. Men on the other hand had a median of 0 (0-3), respectively an average number of 1 visits before referral.

2.5 Cystoscopy delay

Table II illustrates a cystoscopy delay (CD) for the whole group of median 41 days, and average 73 days (0-646 days). Median CD for the male patients was 40 days (0-384), respectively 91 days (2-646) for the females.

2.6 Complete investigation

Only 8 patients (22.9 % of the ones with complete investigation and 17.0 % out of the whole group of patients) did acquire a complete investigation according to guidelines (≤ 28 days) set up by The National Board of Health and Welfare (Sweden) (table II). Out of these patients three had received an acute referral from the general practitioner, two sought medical cares at an urologist office, one went through the emergency department, and one through other
hospital units. Only one was referred at normal rate from the GP’s office. The patients (35/47) who had received a complete investigation (table II) had a median time until complete investigation of 57 days (0-662 days) (57 days for men and 103 days for women).

3. Potentially delaying factors in medical investigation

3.1 Radiological investigation

According to table III 47.5 % of the ones who did receive a written referral, also acquired a simultaneous referral to adequate radiological imaging (CT urography or conventional urography with contrast), while 47.5 % did not. The rest (5.0 %) did receive a referral to ultrasound of urinary tract. A third (33.3 %) of the women did get a simultaneous referral, and 50.0 % did not. The same numbers for the men was 50.0 % respectively 47.1 %.

3.2 Content of referral

The most common information (table III) given in a written referral was the results of a urine dip stick test (64.7 % of the obtained referrals contained this information). One fifth (20.6 %) of the referrals did not contain any information about either smoking habits, S-PSA (men), S-creatinine, urine culture, urine dip stick test or diabetes mellitus. Half (50.0 %) of the female referrals did not contain any of the information listed above, while the same number in the male group was 14.3 %. One fourth of the male referrals contained information about s-PSA levels, and one fifth (20.6 %) of all the referrals included data about smoking habits (smoker/non-smoker/previous smoker).

3.3 Differential diagnostics and initial therapy

One third (31.9 %) of the patients (table III) acquired a UTI diagnosis during investigation, and an additional 6.4% obtained multiple UTI diagnoses (≥ 2 times). Other less frequent differential diagnoses were urinary tract stone (4.3 %), BPH (2.1 %) and prostatitis (2.1 %). A majority (57.2 %) of the women received one or multiple UTI diagnoses during investigation, while the same number for men was 35 %. A large part of the patients (57.4 %) did however not obtain another diagnosis during investigation besides macroscopic hematuria. Approximately one third (34.0 %) of the patients (table III) was treated once with antibiotics during the investigation of MH, and another 8.5 % received antibiotics multiple times.
Table III. Radiological investigation, content of referral, differential diagnostics and therapy during the initial medical investigation of macroscopic hematuria.

<table>
<thead>
<tr>
<th></th>
<th>N (M+W)</th>
<th>Percent (M+W)</th>
<th>N (W)</th>
<th>Percent (W)</th>
<th>N (M)</th>
<th>Percent (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients</td>
<td>47</td>
<td>100.0</td>
<td>7</td>
<td>100.0</td>
<td>40</td>
<td>100.0</td>
</tr>
</tbody>
</table>

**Simultaneous radiological referral**

<table>
<thead>
<tr>
<th></th>
<th>N (M+W)</th>
<th>Percent (M+W)</th>
<th>N (W)</th>
<th>Percent (W)</th>
<th>N (M)</th>
<th>Percent (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total numbers of referrals</td>
<td>40</td>
<td>100.0</td>
<td>6</td>
<td>100.0</td>
<td>34</td>
<td>100.0</td>
</tr>
<tr>
<td>Yes</td>
<td>19</td>
<td>47.5</td>
<td>2</td>
<td>33.3</td>
<td>17</td>
<td>50.0</td>
</tr>
<tr>
<td>No</td>
<td>19</td>
<td>47.5</td>
<td>3</td>
<td>50.0</td>
<td>16</td>
<td>47.1</td>
</tr>
<tr>
<td>Only referral for ultrasound Of urinary tract</td>
<td>2</td>
<td>5.0</td>
<td>1</td>
<td>16.7</td>
<td>1</td>
<td>2.9</td>
</tr>
</tbody>
</table>

*Content of referral*

**Total numbers of patients with obtained referrals**

<table>
<thead>
<tr>
<th></th>
<th>N (M+W)</th>
<th>Percent (M+W)</th>
<th>N (W)</th>
<th>Percent (W)</th>
<th>N (M)</th>
<th>Percent (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0. Nothing below (1-6)</td>
<td>7</td>
<td>20.6</td>
<td>3</td>
<td>50.0</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>1. Smoking/ non smoking</td>
<td>7</td>
<td>20.6</td>
<td>2</td>
<td>33.3</td>
<td>5</td>
<td>17.9</td>
</tr>
<tr>
<td>2. S-PSA (men)</td>
<td>7</td>
<td>20.6</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>25.0</td>
</tr>
<tr>
<td>3. S- Creatinin</td>
<td>11</td>
<td>32.4</td>
<td>1</td>
<td>16.7</td>
<td>10</td>
<td>35.7</td>
</tr>
<tr>
<td>4. Urine culture</td>
<td>4</td>
<td>11.8</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>5. Urine dip stick test</td>
<td>22</td>
<td>64.7</td>
<td>3</td>
<td>50.0</td>
<td>19</td>
<td>67.9</td>
</tr>
<tr>
<td>6. Diabetes Mellitus</td>
<td>4</td>
<td>11.8</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>14.3</td>
</tr>
<tr>
<td>(type I or II) referred to gynecologist</td>
<td>2</td>
<td>-</td>
<td>2</td>
<td>28.6</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

*Differential diagnosis during investigation*

<table>
<thead>
<tr>
<th></th>
<th>N (M+W)</th>
<th>Percent (M+W)</th>
<th>N (W)</th>
<th>Percent (W)</th>
<th>N (M)</th>
<th>Percent (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non other than MH</td>
<td>27</td>
<td>57.4</td>
<td>3</td>
<td>42.9</td>
<td>24</td>
<td>60.0</td>
</tr>
<tr>
<td>UTI x 1</td>
<td>15</td>
<td>31.9</td>
<td>2</td>
<td>28.6</td>
<td>13</td>
<td>32.5</td>
</tr>
<tr>
<td>UTI x ≥2</td>
<td>3</td>
<td>6.4</td>
<td>2</td>
<td>28.6</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Urinary tract stone</td>
<td>2</td>
<td>4.3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>BPH</td>
<td>1</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>1</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>

*Initial therapy during Investigation*

<table>
<thead>
<tr>
<th></th>
<th>N (M+W)</th>
<th>Percent (M+W)</th>
<th>N (W)</th>
<th>Percent (W)</th>
<th>N (M)</th>
<th>Percent (M)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No therapy</td>
<td>25</td>
<td>53.2</td>
<td>3</td>
<td>42.9</td>
<td>22</td>
<td>55.0</td>
</tr>
<tr>
<td>Antibiotics x 1</td>
<td>16</td>
<td>34.0</td>
<td>2</td>
<td>28.6</td>
<td>14</td>
<td>35.0</td>
</tr>
<tr>
<td>Antibiotics ≥2</td>
<td>4</td>
<td>8.5</td>
<td>2</td>
<td>28.6</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Fibrinolysis inhibitors</td>
<td>2</td>
<td>4.3</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>5.0</td>
</tr>
<tr>
<td>Alpha-1 receptor inhibitor</td>
<td>1</td>
<td>2.1</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>2.5</td>
</tr>
<tr>
<td>Antimuscarinic drugs (Detrusitol®)</td>
<td>1</td>
<td>2.1</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2.5</td>
</tr>
</tbody>
</table>
**UTI therapy in case of MH**

<table>
<thead>
<tr>
<th>Number of patients receiving AB</th>
<th>20</th>
<th>100.0</th>
<th>4</th>
<th>100.0</th>
<th>16</th>
<th>100.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>AB therapy and verified neg. UC</td>
<td>12</td>
<td>60.0</td>
<td>3</td>
<td>75.0</td>
<td>9</td>
<td>56.3</td>
</tr>
<tr>
<td>AB and verified pos. UC</td>
<td>1</td>
<td>5.0</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>6.3</td>
</tr>
<tr>
<td>AB therapy without UC</td>
<td>4</td>
<td>20.0</td>
<td>1</td>
<td>25.0</td>
<td>3</td>
<td>18.8</td>
</tr>
<tr>
<td>AB therapy with unknown UC</td>
<td>3</td>
<td>15.0</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>18.8</td>
</tr>
<tr>
<td>AB despite neg. UDST</td>
<td>9</td>
<td>45.0</td>
<td>2</td>
<td>50.0</td>
<td>7</td>
<td>43.8</td>
</tr>
</tbody>
</table>

**Definitions:** N= Numbers, M= Men, W= Women, MH= Macroscopic hematuria, AB= Antibiotics, UC= Urine culture, UDST= urine dip stick test

**Acknowledgement:**

* One or more patients have received more than one of the listed criteria’s.

** Patients whom does not need a referral due to direct contact with specialist+ patients with referrals which could not be obtained in computed medical journals are not included.

This gives a total of 20 patients (42.6 %), who did obtain one/ or more treatments with antibiotics during the investigation of macroscopic hematuria. Table III shows that 12 out of 20 patients (60.0 %) with antibiotic therapy did have a verified negative urine culture, and 1 out of 20 (5.0 %) had a positive urine culture. The rest (7 patients) had either no urine culture taken or unknown result of such. Additionally 9 out of 20 (45.0 %) did receive a UTI therapy with antibiotics despite a verified negative urine dip stick test.

### 3.4 Importance of a quick referral and a complete investigation

According to table III 28.6 % (2/7) of the women were incorrectly referred to a specialist in gynecology. Table IV it presents that 44.7 % (17/38) of all patients who sought medical care at a general practitioner’s office were immediately referred to a specialist in urology (acute or at normal rate) at the time of first doctor’s contact. The ones (21 patients) with no immediately referral had a median doctor’s delay of 18.5 (0-646).

Only (table IV) 36.2 % (17/47) underwent adequate radiological investigation before cystoscopy, whereas 63.8 % (30/47) did not, which prolonged the complete investigation with average 32.3 days. One fifth (25.5 %) of the patients (table V) did never acquire a complete investigation with radiological imaging of upper and lower urinary tract, one of whom revealed to have a large tumor of the distal ureter, when radiological investigation was performed several years later.
Tabell IV. Prolongation of overall investigation due to lack of simultaneous radiological imaging and immediate referral.

<table>
<thead>
<tr>
<th></th>
<th>Count (N)</th>
<th>Percentage (%)</th>
<th>Prolongation of complete investigation (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients with radiological imaging prior to cystoscopy</td>
<td>17</td>
<td>36.2</td>
<td>-</td>
</tr>
<tr>
<td>Patients without radiological imaging prior to cystoscopy</td>
<td>30</td>
<td>63.8</td>
<td>32.3 (average)</td>
</tr>
<tr>
<td>Patients receiving referral to specialist at first doctor’s visit (GP)*</td>
<td>17</td>
<td>44.7</td>
<td>-</td>
</tr>
<tr>
<td>Patients who did not receive immediate referral at first doctor’s visit (GP)*</td>
<td>21</td>
<td>55.3</td>
<td>18.5 (median)</td>
</tr>
</tbody>
</table>

*Calculated upon the 38 patients who sought initial care at the general practitioners office (GP)

Table V. Time from first doctor’s visit due to MH until completed investigation.

<table>
<thead>
<tr>
<th>Medical Investigation</th>
<th>N (M+W)</th>
<th>Percentage (M+W)</th>
<th>N (M)</th>
<th>Percentage (M)</th>
<th>N (W)</th>
<th>Percentage (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete investigation</td>
<td>35</td>
<td>74.5</td>
<td>29</td>
<td>72.5</td>
<td>6</td>
<td>85.7</td>
</tr>
<tr>
<td>Incomplete investigation</td>
<td>12</td>
<td>25.5</td>
<td>11</td>
<td>27.5</td>
<td>1</td>
<td>14.3</td>
</tr>
</tbody>
</table>

Patients with complete investigation

<table>
<thead>
<tr>
<th>Time range</th>
<th>N (M)</th>
<th>Percentage (M)</th>
<th>N (W)</th>
<th>Percentage (W)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 28 days</td>
<td>8</td>
<td>22.9</td>
<td>6</td>
<td>20.7</td>
</tr>
<tr>
<td>28-50 days</td>
<td>8</td>
<td>22.9</td>
<td>7</td>
<td>24.1</td>
</tr>
<tr>
<td>51-90 days</td>
<td>9</td>
<td>25.7</td>
<td>9</td>
<td>31.0</td>
</tr>
<tr>
<td>&gt; 90 days</td>
<td>10</td>
<td>28.6</td>
<td>7</td>
<td>24.1</td>
</tr>
<tr>
<td>Total</td>
<td>47</td>
<td>100</td>
<td>40</td>
<td>100</td>
</tr>
</tbody>
</table>

*M= Men

W= Women

N= Numbers

Incomplete investigation= lacks imaging
3. 5 Baseline characteristics and its effect on delay

Crosstabulation and Chi-square tests were also performed to study potential correlation between patients’ characteristics and investigational time (< 28 days or > 28 days). ASA-class, sex and anticoagulant therapy with Warfarin could not be correlated to investigational time (Table VII). Acute management (Acute referral/ or acute contact with medical care in emergency departments) shows a significant (p=0.002) correlation to investigational time (Table VI and VII). Hence an acute management in greater extent yields in a quicker investigation. With an acute management 27.3 % of the patients were delayed > 28 days, in contrast to a normal referral which results in 77.8 % of the patients being delayed > 28 days (Table VII). Regarding age and investigational time this presents a reverse proportional correlation (figure III), with younger patients receiving the longest investigation.

Table VII. Crosstabulations and chi-square tests between acute management and investigational time.

<table>
<thead>
<tr>
<th>Acute management Number, (%)</th>
<th>Investigational time &lt; 28 days</th>
<th>Investigational time &gt; 28 days</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>8 (22.2)</td>
<td>28 (77.8)</td>
<td>36 (100.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (72.7)</td>
<td>3 (27.3)</td>
<td>11 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>16 (34.0)</td>
<td>31 (66.0)</td>
<td>47 (100.0)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Test Type</th>
<th>Value</th>
<th>df</th>
<th>Asymp. Sig (2-sided)</th>
<th>Exact. Sig (2-sided)</th>
<th>Exact. Sig (1-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pearson Chi-Square</td>
<td>9,572</td>
<td>1</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Continuity Correctionb</td>
<td>7,454</td>
<td>1</td>
<td>.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>9,254</td>
<td>1</td>
<td>.002</td>
<td>.004</td>
<td>.004</td>
</tr>
<tr>
<td>Fishers Exact test</td>
<td>9,368</td>
<td>1</td>
<td>.002</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear-by-Linear Association</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of valid cases</td>
<td>47</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
4. The effects of delay on a bladder cancer diagnosis

4.1 Delay and tumor stage
Table VIII displays how a delay of more than 28 days until performed cystoscopy has no effect on tumor stages. The percentage of T1-T2 tumors are virtually the same in both group (with/ or without delay more than 28 days until cystoscopy).

Table VIII. Crosstabulation and chi-square test between cystoscopy delay (> 28 days) and tumor aggressiveness (≥T1).

<table>
<thead>
<tr>
<th>&gt; 28 days until cystoscopy</th>
<th>&lt;T1</th>
<th>T1-T2</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>13 (81.3)</td>
<td>3 (18.8)</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>25 (80.6)</td>
<td>6 (19.4)</td>
<td>31 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (80.9)</td>
<td>9 (19.1)</td>
<td>47 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td>df</td>
<td>Asymp. Sig (2-sided)</td>
</tr>
<tr>
<td>------------------------</td>
<td>---------</td>
<td>----</td>
<td>----------------------</td>
</tr>
<tr>
<td>Pearson Chi-Square</td>
<td>,002a</td>
<td>1</td>
<td>,960</td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>,000</td>
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<td>1,000</td>
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<tr>
<td>Likelihood ratio</td>
<td>,003</td>
<td>1</td>
<td>,960</td>
</tr>
<tr>
<td>Fishers Exact test</td>
<td></td>
<td></td>
<td>1,000</td>
</tr>
<tr>
<td>Linear-by-Linear Ass.</td>
<td>,002</td>
<td>1</td>
<td>,961</td>
</tr>
<tr>
<td>N of valid cases</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. One cell (25 %) have expected count less than 5. The minimum expected count is 3.06
b. Computed only for 2x2 table

4.2 Delay and effect on bladder cancer recurrence

On the other hand there is a significant (p=0.002) correlation (Table IX) between cystoscopy delay (> 28 days) and recurrence in cancer. A majority (90.3 %) of the patients with a cystoscopy delay more than 28 days did recurrence in bladder cancer disease during the investigated period of time, whereas only half (50.0 %) of the patients with less than 28 days until cystoscopy did recurrence during the same period of time.

Table IX. Crosstabulation and chi-square test between cystoscopy delay (> 28 days) and recurrence in bladder cancer

<table>
<thead>
<tr>
<th>&gt;28 days until cystoscopy</th>
<th>No recurrent cancer</th>
<th>Recurrent cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number, (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>8 (50.0)</td>
<td>8 (50.0)</td>
<td>16 (100.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>3 (9.7)</td>
<td>28 (90.3)</td>
<td>31 (100.0)</td>
</tr>
<tr>
<td>Total</td>
<td>11(23.4)</td>
<td>36 (76.6)</td>
<td>47 (100.0)</td>
</tr>
<tr>
<td></td>
<td>Value</td>
<td>df</td>
<td>Asymp. Sig (2-sided)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>---------</td>
<td>----</td>
<td>----------------------</td>
</tr>
<tr>
<td>Pearson Chi-Square</td>
<td>9,572(^a)</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>Continuity Correction</td>
<td>7,454</td>
<td>1</td>
<td>.006</td>
</tr>
<tr>
<td>Likelihood ratio</td>
<td>9,254</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>Fishers Exact test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Linear-by-Linear Associa</td>
<td>9,368</td>
<td>1</td>
<td>.002</td>
</tr>
<tr>
<td>N of valid cases</td>
<td>47</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) One cell (25\%) have expected count less than 5. The minimum expected count is 3.74.
\(^b\) Computed only for 2x2 table

**Discussion**

1. **Present medical investigation and delay**

   Patients delay had a wide range (0-90 days), but the median number was merely 3 days, without any significant difference between the sexes. This confirms the results of previous studies regarding the fact that patients are in general very quick at seeking medical care when presenting with macroscopic hematuria. A short patient’s delay along with the fact that a great majority (80\%) of all bladder cancer presents with MH, should in theory provide an excellent chance to diagnose most cases of bladder cancer quick and efficiently! Still, many studies have shown a reality far from theory, with urothelial cancer being the most delayed cancer of all cancer worldwide!

   Furthermore the results of this study display a short initial delay, with a median time of only one day. In practice this means that most of the patients did receive a doctor’s appointment within 24 hours from their first contact with medical care. Hence neither patients delay nor initial delay plays a greater part in the overall delay in diagnosing bladder cancer. A great majority of the patients sought medical care at the general practitioners (GP) office (79\%), thus illustrating the importance of the general practitioner in the initial care of these patients. Only 44.7\% of the patients seeking medical care at a GP’s office did receive an immediate referral to a specialist in urology. Patients without immediate referral had yet another 18.5 days (median) until implemented referral, which demonstrates the importance of immediate referral to shorten investigational time. Female patients have a tendency to receive a larger
number of doctors’ visits before acquiring a referral, more often than male patients. Median doctor’s delay for the whole group of patients was only 1.5 days, but ranged widely between 0-646 days. Median doctor’s delay among the male patients was 0 days (=immediate referral), while the same number for women was 43 days, thus displaying a great difference in investigational time between the sexes. 28.6 % of the female patients were also incorrectly referred to a gynecologist, potentially prolonging overall investigational time as well making it hard to offer these patients a standardized management.

It is important to acknowledge the complexity behind certain parts of the medical delay concerning the investigation of macroscopic hematuria. For example cystoscopy delay could theoretically depend on factors such as doctor’s delay, priority of referral, the possibility to get an appointment at the urologist office, numbers of urologists working at the department, economics etc. The results of this study presented a median time from patient’s first doctor’s visit due to MH until performed cystoscopy of total 41 days, also with a distinct difference between men (40 days) and women (91 days).

One fourth of the patients (25.5 %) in this study did never receive a radiological imaging during the investigation of macroscopic hematuria, despite the fact that all patients met a specialist in urology at time of cystoscopy. This makes it possible to miss additional tumors in the upper urinary tract, of which one such case was presented in this study. The percentage of patients who never received a radiological imaging is substantially higher than exhibited in prior studies (7 % respectively 4 %), but unlike previous studies, this data includes both NMIBC and MIBC. Since there is a significant correlation between UCC in the bladder and UCC in the upper urinary tract, patients with MH should always receive a complete investigation including radiological imaging of upper urinary tract. A bladder tumor found at cystoscopy does not rule out the possibility of a simultaneous upper urinary tract tumor!

Only 17.0 % (8/ 47) of the patients in this report were investigated according to guidelines (≤ 28 days) set up by The National Board of Health and Welfare (2002). Results presented in this report shows that the best way to obtaining a quick investigation (≤ 28 days) is by seeking acute medical care at the emergency department or to receive an acute referral from the GP’s office. Pearson’s Chi-square tests exhibited that acute management is a highly significant factor (p=0.002) when it comes to investigational time. Hence patients with an acute management are in greater extent investigated within 28 days. Overall median time from first
doctor’s visit to complete investigation was 57 days (57 days for men and 103 days for women), which is far from the national guidelines.

While acute management does correlate to investigational time, Chi-square tests presented no correlation between age, sex or anticoagulant therapy with investigational delay. Age and median time until cystoscopy exhibited a reversed proportional correlation, with younger patients having a greater delay than older patients. This may potentially originate from a general perception in clinical work, of bladder cancer only affecting older patients. The correlation between age and investigation time may appear exaggerated in this report due to the low numbers of very young patients (< 50 years old), and should therefore be interpreted carefully.

2. Factors possibly affecting present medical delay

A significant part of the patients (47.5 %) did not receive a simultaneous referral to radiological imaging, at time of referral to specialist in urology. The issue of whether or not a patient does or do not receive a simultaneous referral to adequate radiological imaging may have partly economical origin, since the referring unit is economically responsible for the intended imaging. This study clearly shows that patients who did not undergo a radiological imaging prior to cystoscopy had a prolonged total investigation (average 32.3 days). Hence a referral to radiological imaging should be done as quickly as possible, in order to shortening total investigational time! Whether or not the responsibility to issue a radiological referral should be assigned the General practitioner (GP) or the specialist is not discussed further. A less percentage of the female patients did obtain simultaneous imaging (33.3 % women respectively 50.0 % of the men), but whether or not any further conclusions could be drawn from this is highly uncertain.

One fifth of the referrals did not contain any information regarding smoking habits, S-PSA (men), S-creatinine, urine dip stick test, urine culture or diabetes mellitus (type I or II), thus making it harder to make a correct priority at an urologist office, especially in differential diagnostic terms. Female referrals did in larger extent have a total lack of information (listed above) than male ones (50.0 % respectively 14.3 %). The most common information given in a referral was the results of a urine dip stick test (64.7%), which displayed a much higher frequency than showed in previous studies. Only one fifth of the total referrals contained
information about smoking habits, though smoking is the most associated risk factor when it comes to bladder cancer.

As much as a third (31.9 %) of the patients did receive a UTI diagnosis once during investigation, and an additional 6.4 % did so multiple times. All in all did 42.5 % (20 patients) received one or multiple therapies with antibiotics, though a great part of the patients did have a verified negative urine culture (60.0 %) and negative urine dip stick test (45.0 %)! Hemorrhagic cystitis is an important differential diagnosis when patients present with MH, but regardless of that- it is highly essential that antibiotics are not used as an “ex juvantebus” therapy for all cases of MH. Not only because the therapy is ineffective in absence of a UTI, but also due to resistant bacteria, drug side effects, delay in investigation and economical cost. On the other hand a positive urine culture should not impede a full investigation of upper and lower urinary tract, since the likelihood of having a urinary tract tumor is the same as in patients presenting with negative urine culture. There is also a tendency for women (57.2 %) more often than men (35.0 %) to receive a UTI diagnosis when presenting with MH, which might originate from the fact that UTI is thought to be more common in women than men.

3. **Problems in present investigation and possible solutions**

Present investigation of macroscopic hematuria is problematic. There are several reasons to why current investigation is far from optimal:

1. **Incomplete investigation:** One fourth of the patients (25.5 %) did never obtain a complete investigation including radiological imaging, which would potentially overlook neoplasms in the upper urinary tract.

2. **Long investigation:** The total delay (median 57 days) presented in this report exceeds the national guidelines (< 28 days) by far. Not only has previous studies showed that a delay in investigation has a great effect on the survival rate in MIBC, but not to forget is the possible frustration and suffering of which these patients may experience during this period of time.

3. **Few receive investigation according to guidelines:** Only 17.0 % (8/47) did receive an investigation according to national guidelines (<28 days), which shows dysfunctionality in present management and investigation of patients with macroscopic hematuria.
4. **Inefficient and unnecessary therapy**: A large part of the patients (42.5 %) did receive therapy with antibiotics despite many verified negative urine cultures and negative urine dip stick tests, resulting in unnecessary therapies with extensive effects on patient, nature, economics and the medical investigation.

5. **Lopsidedness in investigation**: The ones with acute management (acute referral/or acute contact at the emergency department) have in larger extent a short investigational time (< 28 days).

6. **Difference in investigational time between the sexes**: Tendency for women to have a longer investigation, with more doctors’ contacts, more often therapy with antibiotics etc. This may be part of the answer to why there has been shown in prior studies a difference in survival rate in certain bladder tumor stages.

There are several possible solutions to the issue of delay in the investigation of MH, of which establishing “Hematuria-clinics” is one way of doing so. “Hematuria-clinics” has showed promising results in multiple published studies, but such clinics demands both economical means as well as the availability of trained staff. Another possible way to make investigation of MH easier is to improve the contact between the GP’s and the specialists, using for example standardized protocols. A standardized referral sheets for patients presenting with MH could include all variables needed to make a correct priority (PSA, creatinine etc) with additional informational texts for the GP explaining the importance of a quick investigation.

**4. The effect of delay on bladder cancer characteristics**

The result given in the chi-square test does not show a significant correlation between a longer investigation (cystoscopy delay > 28 days) and a higher frequency of T1-T2 tumors. These results differ from previous studies, and could derive from the low the number of patients included in the study as well as a majority being Ta tumors.

Surprisingly this report present a significant (p=0.002) correlation between investigational time and recurrence in bladder cancer. Patients with less than 28 days until performed cystoscopy had a lower frequency (50.0 %) of recurrence in cancer, in contrast with the ones with more than 28 days until cystoscopy (90.3 %). This small cohort makes it difficult to draw widespread conclusions concerning the correlation between short investigational time and low rate of recurrence. But it is none the less highly interesting, and has to the author’s knowledge
newer been shown before. If such correlation was to be shown in a larger group of patients, it could potentially support the “monoclonal theory” regarding the origin of bladder cancer. Meaning that a short investigational time would result in less likelihood of a primary tumor spreading to other loci in the bladder. Bladder cancer origin according to the “field theory”, should in theory have little effect on the recurrence rate, since pathological processes and in situ neoplasms are said to form simultaneously in different sites of the bladder. If the monoclonal theory proved to be true, both diagnostic as well as therapeutic possibilities could open up. One prospect would be to use urine cytology as an early indicator of recurrence, and have it serving as a determinant to whether or not there is a need of additional intravesical therapy alongside TUR-B. An additional possibility would be to develop cancer specific therapy to use prior to/ or after initial TUR-B depending on DNA-specific alterations detected in the primary tumor.

**Limitations**

**Methodical limitations**

Retrospective studies have several great limitations, of which the most important is the lack of randomization. Another essential limitation is the subjective interpretation of data. Journal data is difficult to define, for example the exact date of debut of symptom is often not possible to retrieve in journals. Thus this variable has to be interpreted upon time indications like “symptoms started a week ago” or “debut of visible hematuria a couple of days ago”. To make the interpretation standardized every variable has had its own interpretation protocols. Due to approximation of variables like time intervals, the exact number of days should always be interpreted cautiously. The aim of this study is not to point out the exact number of days of a specific delay, but rather to give a time indication on whether or not a certain part of the investigation is long or short.

When it comes to time intervals presented in this study, the range between lowest number and highest number is very diverge. Therefore mean number rather than the average number of days is used to give an appropriate illustration of reality.

The usage of ICD codes to extract patients, as done in this study, is far from optimal since the coding may differ between clinics and doctors. There is always a risk that small scale local
registering programs, like the one used in this report may be inefficient and incorrect in the way it handles and extracts data.

**Study population**

Out of 72 patients 25 patients fell out due to impossibility to obtain data in medical journals, which is far from optimal when interpreting data. This large fall off will of course affect the results, and diminish the credibility of the results given. The group of patients included in this retrospective cohort, is also too small to be able to draw any widespread conclusions upon.

The baseline characteristics, of the 47 patients with complete data, presented an average age of 69 years old (48-90), with 85.1 % being male and 14.9 % female. According to previous studies there is a 3:1 relationship between men and women in bladder cancer. Observe that this group has further on been selected upon debut of macroscopic hematuria and bladder cancer, of which distribution between sexes has not been presented. The most common T-stage was Ta (72.3 %), and only 8.5 % of the patients had a MIBC at time of diagnosis. Patients included in this study present a lower frequency of MIBC than other studies, which could possibly bias the results to the NMIBC advantage.

**Conclusion**

The main conclusions are following:

- No correlation could be seen between a prolonged (> 28 days) investigation of MH and higher frequency of more aggressive (≥T1) bladder cancer tumors in this small cohort.

- The majority of patients who sought medical care at a general practitioner’s office due to MH did not receive a referral to specialist in their first doctor’s visit.

- A great percentage (42.5%) did receive antibiotics during investigation, though many had presented with both negative urine dip stick test as well as negative urine culture.

- Younger patients tend to receive a longer investigation than older.

- There is a tendency for females to have a longer investigation, multiple doctors’ visits before referral, less likelihood of receiving a simultaneous referral to radiological
imaging, less information given in referrals, more often receiving a UTI diagnosis during investigation as well as more often being treated with antibiotics.

- A great part of the patients (47.5 %) did not receive a simultaneous referral to radiological imaging, which prolongs overall investigation.

- One fifth of the referrals did lack information about smoking habits, PSA (men), creatinine, urine culture, urine dipstick test and diabetes.

- Only 17.0 % of the patients presenting with MH due to bladder cancer did receive investigation according to national guidelines (< 28 days).

- Acute management (acute referral/ or seeking medical care at the emergency department) had significant (p=0,002) correlation to a faster investigation of macroscopic hematuria.

- Patients with less than 28 days until performed cystoscopy had a significantly (p=0.002) lower frequency of recurrence in cancer (50.0 % versus 90.3 %).

Larger scale studies on the subject is needed to be able to conclude how a possible delay in investigation of MH affects bladder cancer tumor aggressiveness, survival in cancer as well as its possible effect on recurrence in cancer.

References


