Abstract. Aim: To evaluate the role of repeated urological evaluation after negative initial diagnostic work-up of asymptomatic microhematuria (AMH) in low-risk patients. Patients and Methods: Criteria for patient inclusion were a complete negative initial diagnostic assessment including ultrasound (US), cystoscopy, upper urinary tract (UUT) imaging using intravenous urography (IVU) or multiphasic computed tomography (CT), absence of risk factors and a follow-up period of at least three years. Based on our institutional practice, urinalysis was repeated yearly; cystoscopy with US was repeated three years after initial work-up. The oncological outcome was evaluated across a mean follow-up of 8 (range: 3.7-10.2) years. Results: A case series of 87 (32.2% of 270) low-risk patients, 56 women and 31 men, with a mean age of 52.4 (range: 19-87) years was studied. Three years after initial work-up, cystoscopy confirmed no bladder carcinoma in any of these 87 patients. Prostate cancer was diagnosed in one (1.1%) patient. In five (5.6%) patients, nephrological evaluation due to concomitant proteinuria on follow-up demonstrated chronic renal insufficiency (n=3), IgA nephropathy (n=1) and papillary necrosis of the kidney (n=1). Conclusion: Low-risk patients with persistent AMH after negative urological work-up have a neglectable risk of developing bladder cancer on follow-up. Newly-discovered proteinuria on follow-up should be clarified by a nephrologist, as proteinuria could be a sign of significant glomerular disease.

The prevalence of microhematuria in the general population ranges from 0.19% to 38% (1, 2). According to Grossfeld et al., microhematuria is defined by three or more red blood cells (RBCs) per high-powered field (HPF) on microscopic evaluation of urinary sediment gathered from two or three urinalysis specimen with no evidence of infection (1). In contrast to macrohematuria, asymptomatic microscopic hematuria is often an incidental finding during a routine check-up (1). Microhematuria may occur just once, but more frequently, it is a recurrent occurrence persisting for a lifetime. Due to the possible intermittent nature of microhematuria (1, 3, 4), detection, screening and, in particular, follow-up of microscopic hematuria is more difficult than it may appear (1). Regarding the American Association of Urology (AUA) guidelines of 2012 on diagnosis, evaluation and follow-up of asymptomatic microhematuria (AMH) in adults, complete initial diagnostic evaluation with cystoscopy and radiological evaluation of the upper urinary tract (multi-phasic computed tomography urography, with and without contrast and excretory phase) should be performed for all patients with AMH (5). In cases of persistent microscopic hematuria after negative urological work-up, yearly urinalysis should be conducted (as “recommendation grade C”) and repeat evaluation within three to five years in case of persistent AMH should be considered (“expert opinion”) (5). Focusing on the “optimal strategy” of follow-up protocol after negative initial work-up of AMH, insufficient and inhomogenous data (frequency of re-testing, description of repeat and initial evaluation methods) are described in the literature to date, lacking stratification of risk factors (6-10). Therefore, we performed a retrospective analysis among patients with persistent AMH and no risk factors for urothelial cancer, followed-up at our Department for at least three years after complete negative initial work-up, with repeated urinalysis once every year and re-evaluation with cystoscopy and ultrasound three years later as an institutional practice.

Patients and Methods

After approval from the local Ethical Committee (study number UN4000:280/4.22) we retrospectively investigated clinical records of 270 patients with AMH diagnosed at our Department between...
July 1999 and March 2001. Additionally, the initial assessment of microhematuria included a careful record of medical history of risk factors (tobacco smoking, exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, exposure to ionizing radiation or treatment with cyclophosphamide and pioglitazone) as described by EAU Guidelines on Non-Muscle-Invasive Urothelial Carcinoma of the Bladder 2013 (11), physical and laboratory examination to rule out other causes (infections, pyelonephritis, cystitis, prostatitis, trauma, viral infections, microhematuria after exercise or menstruation) (5).

Criteria for study inclusion were a complete initial diagnostic urological assessment of microhematuria [according to the AUA guidelines 2012 of asymptomatic microhematuria (5)] including ultrasound, cystoscopy and upper urinary tract (UUT) imaging (intravenous urography or computed tomography) in combination with a follow-up period of at least three years after negative diagnostic microhematuria work-up. A total of 64 (23.7%) patients were excluded from the study population due to a follow-up of less than three years, 113 (41.9%) patients were excluded due to missing results of diagnostic examinations, or risk factors and two (0.7%) patients noticed gross hematuria due to urinary tract infection during the diagnostic work-up. The initial detection of malignancy (urothelial cancer of the bladder) was a further exclusion criterion in four (1.5%) patients. AMH (one or recurrent episodes) with complete negative work-up (ultrasound, cystoscopy and UUT imaging) and available follow-up of at least three years was determined in 87 (32.2%) low-risk patients (study population) with no risk factors for urothelial cancer (11), (Figure 1). Based on our institutional follow-up protocol at that time, urine analysis (yearly) and cystoscopy with sonography (three years later) was repeated after negative work-up for all patients on follow-up.

Variables such as age, gender, maximum available follow-up after initial diagnostic negative work-up of microhematuria, incidence of genitourinary carcinoma and other diseases resulting in chronic renal insufficiency on follow-up were evaluated. Statistically, descriptive analysis (frequency distribution, mean, median and range) was used and all statistical analyses were performed with SPSS version 20 (IBM, Armonk, New York, USA).

Results

Fulfilling the inclusion criteria, 87 (32.2%) out of 270 patients with AMH and a mean age of 52.4 (range: 19-87) years were retrospectively identified. Risk factors such as tobacco smoking, exposure to aromatic amines, polycyclic aromatic hydrocarbons and chlorinated hydrocarbons, exposure to ionizing radiation, schistosomiasis or treatment with cyclophosphamide and pioglitazone (11) were confirmed in no patient and they were therefore defined as 'low-risk' patients. The study population consisted of 56 (64.4%) women and 31 (35.6%) men. The mean available follow-up was 8 (range: 3.7-10.2) years after the initial negative work-up of AMH. Figure 1 represents an overview of patients’ characteristics by inclusion and exclusion criteria. On follow-up, yearly urinalysis confirmed persistent AMH in all 87 patients, with concomitant proteinuria in five (5.6%) patients. Nephrological evaluation was necessary in patients with proteinuria and confirmed IgA nephritis (n=1), papillary necrosis (n=1) and chronic renal insufficiency (n=3). Out of these five patients, two (2.3%) had to start dialysis because of chronic renal insufficiency (vascular nephropathy due to arteriosclerosis) 2.5 and 4 years after diagnostic microhematuria assessment. Unilateral nephrectomy due to infected renal cysts (initial urosepsis) was necessary in one patient (1.1%) with known polycystic kidney disease 5.4 years after diagnostic work-up of microhematuria. This woman developed renal insufficiency postoperatively and dialysis was also initiated. Additionally, the main attention was drawn to the incidence of malignancies of the urinary tract, which occurred after negative diagnostic evaluation. Therefore, cystoscopy and sonography was repeated three years after initial work-up in all patients. No bladder carcinoma was found in any of the 87 patients. No abnormality was detected on ultrasound. In one patient (1.1%), adenocarcinoma of the prostate was diagnosed 6.4 years after evaluation of AMH. At the time of diagnosis, the patient was 71.7 years old and was treated with radical prostatectomy (Gleason score 6 (3+3), pT2a NX MX R0).

Discussion

Microscopic hematuria is a common finding in approximately 21% of the population of the United States of America (12). As urothelial cancer is the most frequently occurring malignancy in patients on microhematuria screening (13, 14) with an overall detection rate up to 5% (15, 16) (in our study: 1.5%) and a positive predictive value (PPV) of 1.7% for bladder cancer in case of AMH (17), precise urological evaluation, including cystoscopy and multi-phasic CT urography as imaging procedure, is always mandatory in every patient with recurrent or persistent microhematuria, especially in those with known risk factors such as male gender, age >35 years, past or current smoking, analgesic abuse, exposure to chemicals or carcinogenic agents, history of gross hematuria, pelvic irradiation, chronic urinary tract infection, irritative voiding symptoms (5). Variables such as malignant cytology, advanced age and smoking history seem to be the strongest predictors of bladder cancer in patients with AMH (18, 19). Since the prevalence of bladder cancer was found to be higher (15.7%) using a newly developed normogram in patients with AMH (20), a stratification of risk factors seems to be advantageous for screening, as well as for follow-up after negative work-up. Therefore, we evaluated the significance of repeated urological evaluation after negative initial work-up in cases of persistent AMH in low-risk patients. Currently, insufficient oncological data are available on long-term follow up of patients with persistent AMH regarding the risk of subsequent urothelial malignancy (6-10). Searching through the literature, we found a total of five studies with varied oncological follow-up results after (different) initial
diagnostic protocols of microscopic hematuria. For example, Mishriki et al. followed-up 213 patients after negative full AMH work-up (US, cystoscopy and intravenous urography) for 13 years. Follow-up was performed by medical and hospital records; in 15 (7%) patients, a full urological re-evaluation was carried out: 84.5% had negative urinalyses on follow-up and no urological malignancy was detected (8). Additionally, Madeb et al. evaluated 234 patients with complete urological (negative) assessments of AMH (IVU or CT scan, cystoscopy and cytology). During the 14-year follow-up, two patients (0.85%) developed bladder cancer at 6.7 and 11.4 years after their negative evaluations and one died of bladder cancer 7.6 years after his last screening (6). Murakami et al. followed-up 563 patients (after performing US, IVU, cytology and cystoscopy initially) during a mean follow-up of 3.8 years. Bladder cancer was confirmed in three (1.59%) patients. The follow-up protocol included repeated full evaluation every six months for at least three years (10). In our study, all patients (n=87) also underwent complete initial work-up (including cystoscopy and IVU or multiphasic CT). On a follow-up of 3 years, no case of bladder cancer was verified. With performing no initial urological evaluation, Wakui et al. confirmed no association between microcytic hematuria and risk of urothelial malignancy (incidence rate 0%) in 869 patients after a follow-up of three years (telephone interview, questionnaire) (7). Finally, Emamian et al. followed-up 30 patients with microscopic hematuria after negative initial assessment with sonography, one (3.3%) patient developed bladder cancer after 1.5 years of follow-up (hospital case records) (9). In summary, it can be stated that the incidence rate of urothelial cancer on follow-up after incomplete initial work-up (7, 9) was more than twice as high as in the patient group after full (6, 8, 10) initial evaluation. The risk that a patient with AMH after normal urological investigations will subsequently have urological malignancy is dependent on the accuracy of the initial work-up, and may therefore vary with time and among centers. However, after a thorough initial urological investigation of AMH, the majority of patients will remain cancer-free during follow-up (5). As published data on the literature (Table I) are not conclusive regarding patients’ selection, frequency of re-testing, follow-up protocols and the description of repeat and initial evaluation methods, it is impossible to draw any conclusion about the “optimal” strategy of follow-up protocol in cases of persistent microscopic hematuria. Ideally, the development of a homogeneous normogram for the prediction of bladder cancer (screening and follow-up) considering risk factors (11) seems to be indicated to help optimizing referral patterns (timing and prioritization) of patients with AMH.

![Flow chart](https://example.com/flowchart.png)
As the detection rate of urinary tract cancer during diagnostic work-up was increased in the ‘high-risk’ versus the ‘low-risk’ population (11.1% vs. 0.2%) (21), regular evaluations in the high-risk group are recommended in literature (22, 23). Therefore, we agree with the statement that patients at high risk for urinary tract malignancies in particular need complete upper and lower urinary tract evaluation as an initial diagnostic tool (1, 14), with repeated evaluation in cases of persistent or recurrent AMH after negative urological work-up. This is especially true in patients with changes of clinical scenario, such as a substantial increase in the degree of AMH, gross hematuria, pain or other new symptoms (5). Edwards et al. showed that the probability of missing malignant disease (using the protocol likelihood ratio) was 1% in cases of microscopic hematuria based on a 4-year follow-up, but this rose to >4% in patients with the presence of risk factors (macroscopic hematuria, male, age >60 years), (24). On the contrary, in ‘low-risk’ patients we did not identify any case of bladder cancer on cystoscopy three years after negative urological evaluation of AMH and therefore, in the absence of risk factors or symptoms, it is difficult to justify repeated urological evaluations in our opinion. Yearly urinalyses should also be conducted on follow-up to detect patients at risk for other non-malignant diseases such as glomerular nephropathy, proteinuria, renal disease (5). Regarding the risk of developing renal insufficiency or end-stage renal disease (ESRD) in patients with persistent isolated microhematuria, Vivante et al. confirmed an incidence rate of 34.0/100,000 person-years and 26 (0.70%) of 3,690 young adults developed ESRD after a mean follow-up of 21.8 years (5). An association between isolated hematuria and renal insufficiency was not confirmed, but we should keep in mind that 10.6% of patients with asymptomatic hematuria manifested concomitant proteinuria after a mean follow-up period of 5.80±4.42 years. The highest rate of renal insufficiency was noticed in patients with hematuria and concomitant proteinuria (14.9%). Renal biopsy (performed in patients who had a moderate degree of proteinuria) revealed IgA nephropathy (68.2%), non-IgA mesangial proliferative glomerulonephritis (GN) (12.6%), membranous nephropathy (6%), minimal change nephritis (5.3%) and focal and segmental glomerular sclerosis (2.6%) (26). Yamagata et al. reported an incidence of concomitant proteinuria in 9.5% of 404 patients with microscopic hematuria with a mean follow-up of 6.3 years. The highest risk of developing renal insufficiency was confirmed in patients with hematuria and proteinuria developed over 40 years (27). In our study, 5.6% (n=5) out of 87 patients manifested concomitant proteinuria during long-term follow-up. Careful observation and management of this selective patient cohort seems to be useful on follow-up of persistent microscopic hematuria (26). Hall et al. recommended renal biopsy in patients with persistent asymptomatic microscopic hematuria and low-grade proteinuria; 4 (40%) of these patients underwent renal biopsy and were diagnosed with IgA nephropathy (8). Early detection of concomitant proteinuria may have significant impact on a patient’s life because of three facts: firstly, proteinuria in patients with IgA nephropathy during follow-up is the single most important risk factor for renal failure (36% within 20 years) (29); secondly, the degree of proteinuria is widely recognized as a marker of the severity of chronic kidney disease and as a predictor of future decline in glomerular filtration rate (30) and thirdly, an additional relationship between proteinuria levels and cardiovascular risk seems to exist (30).
Conclusion

In summary, ‘low-risk’ patients with persistent AMH after complete negative urological evaluation have a negligible risk of developing bladder cancer on follow-up. Therefore, in the absence of risk factors or symptoms (irritative voiding, flank pain, new developed gross hematuria), it is difficult to justify repeated urological evaluations. Prospective and multi-institutional randomized trials with homogeneous and long-term follow-up protocols are necessary, firstly to demonstrate in detail the subsequent incidence of genitourinary cancer after negative work-up in cases of persistent microscopic hematuria, comparing ‘low-risk’ to ‘high-risk’ patients; secondly, to verify the risk of ESRD/nephropathy in patients with persistent asymptomatic hematuria (with and without proteinuria). The limitation of this study is the small sample size of 87 patients retrospectively evaluated, with subsequent restricted means of interpretation. As the likelihood of finding significant urological diseases on subsequent work-up (particular urological cancer) appears to be related to risk factors, the focus of AMH follow-up should be placed on early detection of patients at higher risk of developing urothelial cancer, affirming the recommended AUA follow-up schedules in cases of persistent microhematuria. Appropriate timing and frequency of re-evaluation should be decided on an individual basis, focusing on symptomatic patients with risk factors.

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