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Diagnostic accuracy of ultrasonography, computed tomography, cystoscopy and cytology to detect urinary tract malignancies in patients with asymptomatic hematuria

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Abstract: **PURPOSE:** To report the incidence of urinary tract malignancies (UTM) and to compare the diagnostic accuracy of cytology with cystoscopy, renal ultrasound (US) and computed tomography (CT) in patients with hematuria. **METHODS:** A retrospective analysis was conducted of patients who underwent cystoscopy, cytology, US and CT for hematuria between 2011 and 2017. Age, gender, BMI, smoking status, and results of further diagnostic interventions including transurethral resection of the bladder (TURB), ureterorenoscopy (URS), renal biopsy and imaging were extracted from medical charts. Logistic regression to identify risk factors for UTM was performed. Discriminatory accuracy of US, CT and cytology was assessed by 2×2 tables. **RESULTS:** Of 847 patients, 432 (51%) presented with non-visible hematuria (NVH) and 415 (49%) with visible hematuria (VH). Of all patients with NVH, seven (1.6%) had bladder cancer (BCA), three ($< 1\%$) had renal cell cancer (RCC) and no single patient had upper tract urothelial cancer (UTUC). Of the patients with VH, 62 (14.9%) were diagnosed with BCA, 7 (1.6%) with RCC and 4 ($< 1\%$) with UTUC. In multivariable analysis VH, higher age, smoking and lower BMI were associated with an increased risk for UTM. The specificity/negative predictive value of US for the detection of RCC or UTUC in patients with NVH and VH were 96%/100% and 95%/99%, respectively. **CONCLUSION:** Due to the low incidence of UTM, the necessity of further diagnostics should be questioned in patients with NVH. In contrast, patients with VH are at considerable risk for BCA, and cystoscopy and upper tract imaging is justified.

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Diagnostic accuracy of ultrasonography, computed tomography, cystoscopy and cytology to detect urinary tract malignancies in patients with asymptomatic hematuria

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Abstract

PURPOSE: To report the incidence of urinary tract malignancies (UTM) and to compare the diagnostic accuracy of cytology with cystoscopy, renal ultrasound (US) and computed tomography (CT) in patients with hematuria.

METHODS: Retrospective analysis of patients who underwent cystoscopy, cytology, US and CT for hematuria between 2011 and 2017. Age, gender, BMI, smoking status, results of further diagnostic interventions including transurethral resection of the bladder (TURB), ureterorenoscopy (URS), renal biopsy and imaging were extracted from medical charts. Logistic regression to identify risk factors for UTM was performed. Discriminatory accuracy of US, CT and cytology was assessed by 2x2 tables.

RESULTS: Of 847 patients, 432 (51%) presented with non-visible hematuria (NVH) and 415 (49%) with visible hematuria (VH). Of all patients with NVH, 7 (1.6%) had bladder cancer (BCA), 3 (<1%) renal cell cancer (RCC) and no single patient upper tract urothelial cancer (UTUC). Of the patients with VH 62 (14.9%) were diagnosed with BCA, 7 (1.6%) with RCC and 4 (<1%) with UTUC. In multivariable analysis VH, higher age, smoking and lower BMI were associated with an increased risk for UTM. The specificity/negative predictive value of US for the detection of RCC or UTUC in patients with NVH and VH were 96% / 100% and 95% / 99%, respectively.

CONCLUSION: Due to the low incidence of UTM, the necessity of further diagnostics should be questioned in patients with NVH. In contrast, patient with VH are at considerable risk for BCA and cystoscopy and upper tract imaging is justified.

Key words: hematuria, bladder cancer, renal cancer, cystoscopy, computerized tomography

Introduction

Hematuria is a prevalent condition and can be a sign of infection, stone disease or malignancy in the urinary tract, but often no etiology can be identified (Hunter et al. 1996). Because early detection and therapy may improve the prognosis of urinary tract malignancies (UTM), it seems reasonable to initiate further diagnostics in patient with hematuria. However, the high prevalence of hematuria which is not associated with malignancy may lead to many unnecessary and potentially harmful investigations.

Investigating NVH started in the 1920's in dye workers as a non-validated opportunistic screening test for bladder cancer (BCA). Later on, investigating asymptomatic NVH was translated into daily clinical routine without being questioned for many years. However, data supporting any diagnostics in patients with hematuria is scarce and the recommendations of many guidelines are based on a low level of evidence. This low evidence is reflected by the diverging recommendations from several guidelines. For example Scandinavian guidelines argue against any investigation in patients with NVH (Skaaheim Haug et al. 2019) whereas the American Urology Association (AUA) recommends cystoscopy and computed tomography (CT) in all patients >35 years and specify that in patients <35 years work-up is recommended "according to the treating physician's discretion" (Davis et al. 2012).

Given the high prevalence and the potential harms and costs of hematuria investigations, it is of utmost importance to improve the level of evidence regarding the value of hematuria investigations. The aim of this study was to provide data on the incidence of UTM including BCA, renal cell cancer (RCC) and upper tract urothelial cancer (UTUC) in a contemporary cohort and to assess and compare the diagnostic accuracy of cytology vs. cystoscopy and renal ultrasound (US) vs. computed tomography (CT) to detect UTM in patients with hematuria.

Methods

We retrospectively identified patients undergoing cystoscopy, cytology, US and CT for asymptomatic, non-infectious, non-traumatic hematuria in a tertiary care academic center between 2011 and 2017. We excluded patients with previous UTM or urinary tract interventions within the last 3 months. Age, gender, body-mass-index (BMI), smoking status, results of further diagnostic interventions including transurethral resection (TUR), ureterorenoscopy (URS), renal biopsy and imaging were extracted from medical charts. Urine cytology retrieved during cystoscopy was scored using a 5-point system: 0 normal; 1 atypical, 2 suspicious, 3 dysplastic, 4 inadequate or no specimen. A score of 0 was classified as negative and 1 – 3 as positive. The local ethics committee approved the study protocol for this investigation (STV KEK-ZH Basec-Nr- 2016-00158).

We performed uni- and multivariate logistic regression analyses to assess the association between clinical risk factors and UTM incidence. Of the significantly associated risk factors, the optimally discriminating cut-off was calculated from receiver operating curve (ROC) analysis using the maximal Youden's index (Sensitivity + Specificity – 1). To calculate sensitivity, specificity, negative predictive value (NPV), positive predictive value (PPV), 2x2 table analyses were performed using R programming language and software environment version 3.1.3 (R Foundation for Statistical Computing, Vienna, Austria) using the package “epiR”. The remaining statistical analyses were performed using SPSS Statistics version 24.0 (IBM Corp., Armonk, New York, USA). The results for continuous normally distributed variables are expressed as means $\pm$ standard deviation (SD) and differences in patient characteristics between two groups were compared using Student's unpaired *t*-test. Continuous non-normally distributed variables are presented as median and interquartile ranges (IQR) and analyzed using the Mann-Whitney U test. The results for categorical variables are presented as percentage analyzed using Fisher's exact test or chi-square test whenever appropriate. All statistical tests were two-sided. All p-values <0.05 were considered statistically significant.

Results

Of 2346 screened patients, 1499 did not fulfill the inclusion criteria (Figure 1). The final cohort consisted of 847 patients of which 432 (51%) had NVH and 415 (49%) had VH (Table 1). Any UTM was diagnosed in 9.8% with 2.3% in patients with NVH and 17.6% with VH. Of all patients with NVH 7 (1.6%, 95% CI <1% to 3%) had BCA, 3 (<1%, 95% CI 1% to 2%) RCC and no single patient UTUC (0%, CI 0% to <1%). Of all patients with VH 62 (14.9%, 95% CI 12% to 19%) were diagnosed with BCA, 7 (1.6%, 95% CI <1% to 3%) with RCC and 4 (<1%, 95% CI <1% to 2%) with UTUC.

Univariable regression analyses revealed that patients with a higher age, male gender and a lower BMI and previous or current smokers had a significantly higher risk of UTM (Table 2). In multivariable regression analysis all variables but gender remained significantly associated with UTM. The odds to be diagnosed with UTM of patients with VH compared to NVH were 8x higher. Similarly, current or previous smokers had 2x higher odds to be diagnosed with UTM than never smokers. Because several guidelines mention certain cut-off values to recommend further investigations, we tried to establish cut-off values for the continuous variables age and number of pack years. For both variables, ROC analyses failed to find a clear cut-off point to discriminate between patients with or without UTM (not shown). A visual overview confirmed age did not clearly discriminate between patients with or without UTM (Figure 2). In patients with NVH, the youngest patients with bladder cancer was 56 years and the youngest patient with renal cell carcinoma was 40 years old. In patients with VH, the youngest patients with bladder cancer was 33 years and the youngest patient with renal cell carcinoma was 34 years old.

In patients with NVH, 23/432 (5%) patients underwent surgery revealing benign histologies in 2/5 renal resections, 3/3 URS and 8/15 TURB. Furthermore 11/432 (3%) patients underwent repeated imaging because of Bosniak IIF cysts. US missed 1 out of 3 patients diagnosed with RCC that were diagnosed on CT scan. No UTUCs were found in patients with NVH. The specificity and NPV for US compared to CT to diagnose an upper urinary tract cancer (UTUC or RCC) were 96% and 99% (Table 3). The PPV of lesions found in the upper urinary tract on CT was 12%. In patients with VH, US compared to CT, failed to diagnose 1 out of 7 patients with RCC and 3 out of 4 patients with UTUC. The PPV to confirm suspicious lesions found in the upper urinary tract on CT was 28%. The specificity/NPV for cytology to diagnose BCA was 99%/99% in patients with NVH and 96%/94% in patients with VH. Negative white light cystoscopy but positive cytology was observed in 12 patients and histological

confirmation of CIS only disease in the bladder was found in 4/12 (33%) patients. In patients with hematuria and negative white light cystoscopy, the PPV of cytology to diagnose CIS only disease in the bladder was 75%.

Discussion

Although there is a compelling argument that all patients with an elevated risk for UTM should be investigated, it is worth balancing the risk of missing a cancer against the risks, costs and side-effects of hematuria investigations. Incidental findings of such investigations may lead to further invasive diagnostic procedures and translate into anxiety and morbidity. In our cohort patients with NVH and VH have substantially different odds to harbor UTM. Thus, the presence of NVH or VH should probably translate into different work-up recommendations.

In patients with NVH the risk for UTM was low and it remains questionable if any further investigations should be recommended at all. Our data reveals that in patients with NVH the incidence of BCA is 1-3%, of RCC 1-2% and of UTUC in 0-1% which is in line with previous reports (Davis et al. 2012; Edwards et al. 2006; Jubber et al. ; Samson et al. 2017; Tan et al. 2018). For the lower urinary tract, cystoscopy represents the diagnostic gold standard but represents an invasive investigation which is associated with a risk of urinary tract infections (Johnson et al. 2007), gross hematuria and patient discomfort. The high NPV and moderate PPV of cystoscopy (68%) leads to further, often unnecessary TURBs (Bromage et al. 2012) as seen in our cohort as well. A compelling solution to improve risk stratification includes risk prediction models as recently proposed by Matulewicz and colleagues who published a prediction model for BCA in patients with NVH (Matulewicz et al. 2020).

To investigate the upper urinary tract in NVH patients, CT offers the highest diagnostic accuracy but is also associated with radiation exposure and adverse reactions to contrast media (Munehika et al. 2003). Two recent modelling analyses suggested that in patients with NVH CT compared to US may cause more harm while being less cost-effective. One study concluded that replacing CT with ultrasound would miss one cancer and would result in cost savings of more than \$6 millions (Halpern et al. 2017). The second study suggested that the most intense CT work-up as suggested by the AUA guidelines might detect 82 more cancers at the expense of up to 467 radiation induced secondary cancers and higher costs (Georgieva et al. 2019). Furthermore the low PPV of CT (22%) leads to further, often unnecessary and potentially harmful invasive diagnostic procedures such as repeated imaging, URS,

renal biopsy or surgery (Bromage et al. 2012). This was also detectable in our cohort. To the best of our knowledge, there are currently no risk prediction tools available to decide whether the upper urinary tract is at risk to harbor malignancy. In conclusion, we argue that in patients with NVH the need for the upper urinary tract should be critically reconsidered in larger cohorts. The current literature suggests that probably US instead of CT has the best risk benefit balance in patients with NVH but further evidence from large prospective studies are necessary (Linder et al. 2017).

In patients with VH we found a considerable proportion of patients with bladder cancer but a low risk of RCC or UTUC and therefore further diagnostics for the lower urinary tract seem reasonable. In our cohort BCA was found in 12-19%, RCC in 1-3% and UTUC in 1-2% which is also in line with the current literature (Edwards et al. 2006; Khadra et al. 2000). In absence of a clear age or smoking history threshold we recommend that all patients with VH should be investigated with cystoscopy and probably upper tract imaging with either US or CT (Tan et al. 2018).

The present analysis is limited by its retrospective design, single center approach and limited sample size. The diagnostic performance of cytology is dependent on the pathologists' and of ultrasonography on the urologists performance and might not be generalizable to other centers as seen previously (Blick et al. 2012). A further limitation of cytology include the fact that urine cytology was collected through the cystoscope, which allows mechanical irrigation prior to collection. However, previous studies showed exactly the same NPV for voided urine samples (Cha et al. 2012). The main strength of our analysis represents the completeness of investigations including contemporary CT protocols and flexible cystoscopy including cytology. The diagnostic yield of lower and upper tract investigations may differ between different countries and ethnicities. Therefore data from different countries are needed to allow evidence-based recommendations regarding hematuria investigations.

Conclusion

Due to the low incidence of UTM, the necessity of further diagnostics should be questioned in patients with NVH. In contrast, patient with VH are at considerable risk for BCA and cystoscopy and upper tract imaging is justified.

Figure legends

Figure 1: Patient selection work flow

Abbreviations: BCA: Bladder cancer; CT: computerized tomography; NoCa: No Cancer; PCA: Prostate Cancer; RCC: Renal Cell Cancer; UTUC: Upper tract urothelial Cancer

Figure 2: Urinary tract cancer incidence stratified by type of hematuria, age and smoking status

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Research involving Human Participants and/or Animals

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent

The authors confirm that an independent ethics committee (STV KEK-ZH Basec-Nr- 2016-00158) approved the study and informed consent for this retrospective study was waived according to Swiss law.

Data availability

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest:

The authors declare that they have no conflict of interest.

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