Preoperative pyuria predicts the presence of high-grade bladder carcinoma in patients with bladder tumors

Sławomir Poletajew¹, Dominika Gajewska², Krystian Kaczmarek³, Wojciech Krajewski³, Marcin Łykowski¹, Joanna Sondka-Migdalska¹, Michał Borowik³, Paweł Buraczyński⁶, Mateusz Dzięgala³, Maciej Przudzik³, Marcin Słojewski², Piotr Kryst¹

¹Second Department of Urology, Centre of Postgraduate Medical Education, Warsaw, Poland
²Department of Urology and Urological Oncology, Pomeranian Medical University, Szczecin, Poland
³Department of Urology and Oncological Urology, Wrocław Medical University, Wrocław, Poland
⁴Department of Urology, Medical University in Łódź, Łódź, Poland
⁵Department of Urology, University of Warmia and Mazury, Olsztyn, Poland
⁶Department of Urology and Urologic Oncology, Medical University of Lublin, Lublin, Poland

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Introduction Preoperative identification of high-grade bladder cancer presence can optimize patient management. The aim of this study was to assess the association between preoperative pyuria and the pathological features of bladder cancer.

Material and methods This retrospective analysis enrolled 943 patients undergoing transurethral resection of a bladder tumor. Patients were divided into two study groups based on the presence of pyuria in preoperative urine analysis, defined as the presence of >5 leukocytes in the high power field. Pyuria status as a potential predictive factor was then confronted with pathological features based on standard microscopic examination of the surgical specimen.

Results Among 943 recruited patients, 294 (31.2%) presented with pyuria. Patients with pyuria were older (71 vs. 68 years, p <0.05), had higher rates of large (≥3 cm) tumors (37% vs. 26%, p <0.05), and more frequently presented concomitant hematuria (58% vs. 24%, p <0.05). In case of recurrent tumors patients with pyuria more often received intravesical chemotherapy in the past (4.8% vs. 1.4%, p <0.05). Regarding oncological data, patients with pyuria had significantly higher tumor stage and grade. On multivariable analysis pyuria was independently associated with high-grade tumors (OR 1.97, 95% CI 1.45–2.67). Specificity and negative predictive value of pyuria as a biomarker of high-grade tumors were 76% and 68%, respectively.

Conclusions Preoperative pyuria can be regarded as a predictor of the presence of high-grade bladder carcinoma in patients with bladder tumors.

Key Words: bladder cancer, pyuria, transurethral resection

INTRODUCTION

Pathological data, including cancer stage and grade, plays a key role in making clinical decisions in patients with bladder cancer [1]. However, pathological data cannot be given before transurethral resection of the bladder tumor (TURT), a standard diagnostic as well as potentially therapeutic procedure. For this reason, TURT is a schematic surgery. There are several proposed options to preoperatively predict stage and/or grade of bladder cancer, including imaging studies, urine cytology or endoscopic appearance. However, none of them is widely recommended for the use in clinical practice. Identification
of preoperative predictors of advanced and/or high-grade cases is still needed to shorten time to radical cystectomy, avoid unnecessary intravesical instillations or reduce number of restaging TURTs. This seems to be a particularly urgent need in Poland, where >50% of non-muscle invasive bladder cancer cases are at high-risk of progression as defined by the European Association of Urology criteria [2]. The aim of this study was to define the association between preoperative pyuria and pathological characteristics in patients with bladder tumors undergoing TURT.

MATERIAL AND METHODS

Patients

This is a retrospective post-hoc analysis of the prospectively collected data from a multicentre study on predictive factors for complications of TURT [3]. The study protocol was registered within ClinicalTrials.gov (NCT03029663) and was approved by the Institutional Review Board.

Nine hundred forty-three patients undergoing TURT were enrolled in this study. Mean age of the cohort was 68.9 years (range 18–98), male to female ratio was 3:1. Inclusion criteria were as follows: age ≥18 years, resection of bladder tumor, sterile urine preoperatively or ongoing directed antibiotic therapy at the time of surgery, signed informed consent. Study recruited patients with both primary and recurrent bladder tumors. Patients undergoing restaging resection, cold-cup biopsy, fulguration only or cystoscopy only were not enrolled.

Methods

Recruited patients were divided into two study groups based on the presence of pyuria in preoperative urine analysis, defined as the presence of >5 leukocytes in high power field. Pyuria status as a potential predictive factor was then confronted with the results of pathological staging based on microscopic examination of surgical specimen.

Statistical analysis

For the comparison of study groups, unpaired t-test and Pearson test were used for continuous and qualitative variables, respectively. A multivariable analysis was used to assess the association of preoperative factors with final tumor stage and grade. On the multivariable analysis, all effect method was implemented. The receiver operating characteristic curve was used to estimate predictive parameters. All tests were performed with Statistica software, version 13.3 (StatSoft, Inc., Tulsa, OK).

RESULTS

Among 943 recruited patients, 294 presented with pyuria. Patients with pyuria were older, had a higher rate of large tumors and a history of intravesical chemotherapy (Table 1). Regarding oncological data, patients with pyuria had significantly higher rate of invasive tumors (including stage T1 and T2 or higher) and higher rate of high-grade tumors. On the multivariable analysis pyuria was independently associated with high-grade tumors; OR was 1.97 (95%CI 1.45–2.67) (Table 2). Sensitivity, specificity, positive predictive value and negative predictive value for pyuria as a biomarker of high-grade tumors were 43%, 76%, 52% and 68%, respectively. The area under a curve was 0.63.

DISCUSSION

Bladder cancer is the most common malignancy within the urinary tract. The initial step in the treatment is a diagnostic and therapeutic surgical procedure, namely TURT. It is a universal, well described surgery [4]. However, the extent of the surgery and immediate postoperative management could be personalized and optimized if pathological cancer features were known preoperatively. Here we present results of our retrospective analysis of the clinical significance of preoperative pyuria in patients undergoing TURT due to bladder cancer. We found that this finding is an independent prognostic factor of high-grade
carcinoma presence. We believe that it can be regarded as a simple and universally available urine-based biomarker. Together with clinical staging based on imaging [5], endoscopic appearance of the tumor [6, 7, 8] and urine cytology [9], it can help to adequately plan the surgery and postoperative management. In case high-grade tumor is suspected, one can consider multiple site mucosa biopsies to increase a chance for proper diagnosis of concomitant carcinoma in situ [10, 11], while single postoperative intravesical instillation of chemotherapy could be omitted in favor of intravesical Bacillus Calmette-Guérin (BCG) therapy or radical cystectomy [12]. Of note, all patients in our study had negative urine culture, while the exclusion of urinary tract infection is one of the most significant goals when facing a patient scheduled for TURT who presents with pyuria. Pyuria in bladder cancer is regarded as a sign of local inflammatory process related to the malignancy [13]. The significance of pyuria in bladder cancer was already described by Satake et al. and Azuma et al. Both research groups found that recurrence-free survival was lower in patients with preoperative pyuria [14, 15]. Recently, Sazuka et al. confirmed this finding [16]. Interestingly, also postoperative pyuria was described as a negative prognostic factor in patients with bladder cancer [17, 18]. Regarding upper urinary tract urothelial carcinoma, the impact of preoperative pyuria on the risk of bladder recurrence is uncertain due to conflicting results of published studies [19, 20, 21]. The mechanism by which pyuria can impact patients’ prognosis is not clear. According to our findings and previously published data on the role of granulocyte-colony stimulating factor in progression of bladder cancer [22], we suggest that poor cancer differentiation plays a key role in patients with pyuria. Another inflammatory markers were also shown to be associated with prognosis of bladder cancer patients, including neutrophil-lymphocyte ratio or C-reactive protein [23–28].

CONCLUSIONS

Preoperative pyuria can be regarded as a predictor of the presence of high-grade bladder carcinoma in patients with bladder tumors.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

Table 2. The impact of pyuria on oncological outcomes in patients with bladder tumours

| Outcome                              | Incidence in patients with pyuria | Incidence in patients without pyuria | Odds ratio (OR) | Univariate analysis | Multivariate analysis |
|--------------------------------------|-----------------------------------|--------------------------------------|-----------------|---------------------|----------------------|
| No malignancy (stage pT0)            | 11.2%                             | 14.0%                                | 0.80            | 0.23                | –                    |
| Invasive bladder cancer (stage pT1 or higher) | 43.9%                             | 31.1%                                | 1.41            | 0.0001              | 0.58                 |
| Muscle-invasive bladder cancer (stage pT2 or higher) | 19.0%                             | 10.9%                                | 1.74            | 0.0007              | 0.41                 |
| Concomitant carcinoma in situ        | 2.0%                              | 0.8%                                 | 2.50            | 0.09                | –                    |
| High-grade cancer (any stage)        | 52.4%                             | 31.7%                                | 1.65            | 0.0000              | 0.0000               |

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