ORIGINAL PAPER

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

Sławomir Poletajew[1], Dominika Gajewska[2], Krystian Kaczmarek[2], Wojciech Krajewski[3], Marcin Łykowski[1], Joanna Sondka-Migdalska[4], Michał Borowik[5], Paweł Buraczyński[6], Mateusz Dzięgała[3], Maciej Przudzik[5], Marcin Słojewski[2], Piotr Kryst[1]

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

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.

Corresponding author
Sławomir Poletajew
II Department of Urology
Centre of Postgraduate
Medical Education
80 Cegłowska Street
00-809 Warsaw, Poland
phone: +48 22 569 01 48
slawomir.poletajew@
cmkp.edu.pl

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 re-staging 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

Table 1. *Baseline characteristics of patients included in the analysis*

	Patients with pyuria (n = 294)	Patients without pyuria (n = 649)	P value
Percentage of women	24.5%	27.1%	0.18
Mean age	70.6 years	68.0 years	0.000
Prior recurrence rate			
Primary tumor	301	128	
≤1/year	276	137	0.50
>1/year	72	29	
Tumor size ≥3 cm	36.1%	26.0%	0.002
Mean number of tumors	2.3	2.2	0.58
Previous intravesical chemotherapy	1.4%	4.8%	0.01
Previous intravesical immunotherapy	14.8%	10.8%	0.14
Mean surgery duration	31.5 minutes	29.1 minutes	0.07

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)	P value	
				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

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-to-lymphocyte ratio or C-reactive protein [23–28].

Strengths of our study is a multicenter patient enrollment and representative population. However, our study is not free from limitations. First, retrospective nature of the study is always associated with the risk of selection bias. Second, direct effect of preoperative pyuria on patients' survival was not reported or analyzed in this study.

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.

References

1. Kluth LA, Black PC, Bochner BH, et al. Prognostic and Prediction Tools in Bladder Cancer: A Comprehensive Review of the Literature. Eur Urol. 2015; 68: 238-253.

2. Poletajew S, Biernacki R, Buraczynski P, et al. Stage of bladder cancer in Central Europe- Polish perspective. Neoplasma. 2016; 63: 642-647.

3. Poletajew S, Krajewski W, Gajewska D, et al. Prediction of the risk of surgical complications in patients undergoing monopolar transurethral resection of bladder tumor - a prospective multicentre observational study. Arch Med Sci. 2019; 16: 863-870.

4. Babjuk M, Burger M, Compérat EM, et al. European Association of Urology Guidelines on Non-muscle-invasive Bladder Cancer (TaT1 and Carcinoma In Situ)- 2019 Update. Eur Urol. 2019; 76: 639-657.

5. Woo S, Panebianco V, Narumi Y, et al. Diagnostic Performance of Vesical Imaging Reporting and Data System for the Prediction of Muscle-invasive Bladder Cancer: A Systematic Review and Meta-analysis. Eur Urol Oncol. 2020; 3: 306-315.

6. Grzegółkowski P, Kaczmarek K, Lemiński A, Soczawa M, Gołąb A, Słojewski M. Assessment of the infiltrative character of bladder cancer at the time of transurethral resection: a single center study. Cent European J Urol. 2017; 70: 22-26.

7. Poletajew S, Radziszewski P. Endoscopic appearance of a tumor can predict the stage of bladder cancer. Cent European J Urol. 2017; 70: 27-28.

8. Skrzypczyk MA, Nyk Ł, Szostek P, Szempliński S, Borówka A, Dobruch J. The role of endoscopic bladder tumor assessment in the management of patients subjected to transurethral bladder tumor resection. Eur J Cancer Care (Engl). 2017; 26.

9. Restrepo-Gonzalez JA, Garcia-Perdomo HA, Varela R. Diagnostic accuracy of preoperative urinary smear test in patients with bladder urothelial carcinoma in a high-volume center. Arch Esp Urol. 2014; 67: 243-248.

10. Gontero P, Sylvester R, Pisano F, et al. Prognostic factors and risk groups in T1G3 non-muscle-invasive bladder cancer patients initially treated with Bacillus Calmette-Guérin: results of a retrospective multicenter study of 2451 patients. Eur Urol. 2015; 67: 74-82.

11. Hara T, Takahashi M, Gondo T, Nagao K, Ohmi C, Sakano S, Naito K, Matsuyama H. Risk of concomitant carcinoma in situ determining biopsy candidates among primary non-muscle-invasive bladder cancer patients: retrospective analysis of 173 Japanese cases. Int J Urol. 2009; 16: 293-298.

12. Sylvester RJ, Oosterlinck W, Holmang S, et al. Systematic Review and Individual Patient Data Meta-analysis of Randomized Trials Comparing a Single Immediate Instillation of Chemotherapy After Transurethral Resection with Transurethral Resection Alone in Patients with Stage pTa-pT1 Urothelial Carcinoma of the Bladder: Which Patients Benefit from the Instillation? Eur Urol. 2016; 69: 231-244.

13. Shindo T. Editorial Comment to Prognostic value of preoperative pyuria in patients with non-muscle-invasive bladder cancer. Int J Urol. 2015; 22: 650.

14. Satake N, Ohno Y, Nakashima J, Ohori M, Tachibana M. Prognostic value of preoperative pyuria in patients with non-muscle-invasive bladder cancer. Int J Urol. 2015; 22: 645-649.

15. Azuma T, Nagase Y, Oshi M. Pyuria predicts poor prognosis in patients with non-muscle-invasive bladder cancer. Clin Genitourin Cancer. 2013; 11: 331-336.

16. Sazuka T, Sakamoto S, Imamura Y, et al. Relationship between post-void residual urine volume, preoperative pyuria and intravesical recurrence after transurethral resection of bladder carcinoma. Int J Urol. 2020; 27: 1024-1030.

17. Kim BS, Tae BS, Ku JH, Kwak C, Kim HH, Jeong CW. Rate and association of lower urinary tract infection with recurrence after transurethral resection of bladder tumor. Investig Clin Urol. 2018; 59: 10-17.

18. Azuma T, Nagase Y, Oshi M. Pyuria predicts poor prognosis in patients with non-muscle-invasive bladder cancer treated with bacillus Calmette-Guérin. Mol Clin Oncol. 2015; 3: 1113-1116.

19. Jeon BJ, Tae BS, Choi H, et al. Preoperative sterile pyuria as a prognostic biomarker for intravesical recurrence in upper urinary tract urothelial carcinoma. Investig Clin Urol. 2020; 61: 51-58.

20. Sato G, Yoshida T, Yanishi M, et al. Preoperative Pyuria Predicts for Intravesical Recurrence in Patients With Urothelial Carcinoma of the Upper Urinary Tract After Radical Nephroureterectomy Without a History of Bladder Cancer. Clin Genitourin Cancer. 2020; 18: e167-173.

21. Milojevic B, Dzamic Z, Bojanic N, et al. Urothelial carcinoma of the upper urinary tract: preoperative pyuria is not correlated with bladder cancer recurrence and survival. Int Urol Nephrol. 2019; 51: 831-838.

22. Tachibana M, Miyakawa A, Tazaki H, et al. Autocrine growth of transitional cell carcinoma of the bladder induced by granulocyte-colony stimulating factor. Cancer Res. 1995; 55: 3438-3443.

23. Cantiello F, Russo GI, Vartolomei MD, et al. Systemic Inflammatory Markers and Oncologic Outcomes in Patients with High-risk Non-muscle-invasive Urothelial Bladder Cancer. Eur Urol Oncol. 2018; 1: 403-410.

24. Racioppi M, Di Gianfrancesco L, Ragonese M, Palermo G, Sacco E, Bassi PF. Can Neutrophil-to-Lymphocyte ratio predict the response to BCG in high-risk non muscle invasive bladder cancer? Int Braz J Urol. 2019; 45: 315-324.

25. Yuk HD, Jeong CW, Kwak C, Kim HH, Ku JH. Elevated Neutrophil to Lymphocyte Ratio Predicts Poor Prognosis in Non-muscle Invasive Bladder Cancer Patients: Initial Intravesical Bacillus Calmette-Guerin Treatment After Transurethral Resection of Bladder Tumor Setting. Front Oncol. 2019; 8: 642.

26. Getzler I, Bahouth Z, Nativ O, Rubinstein J, Halachmi S. Preoperative neutrophil to lymphocyte ratio improves recurrence prediction of non-muscle invasive bladder cancer. BMC Urol. 2018; 18: 90.

27. Vartolomei MD, Porav-Hodade D, Ferro M, et al. Prognostic role of pretreatment neutrophil-to-lymphocyte ratio (NLR) in patients with non-muscle-invasive bladder cancer (NMIBC): A systematic review and meta-analysis. Urol Oncol. 2018; 36: 389-399.

28. Mbeutcha A, Shariat SF, Rieken M, et al. Prognostic significance of markers of systemic inflammatory response in patients with non-muscle-invasive bladder cancer. Urol Oncol. 2016; 34: 483.e17-483.e24. ■