DOI: https://doi.org/10.2298/SARH220312072S
UDC: 616.62-006.6-074

ORIGINAL ARTICLE / ОРИГИНАЛНИ РАД

Predictive value of GATA3 and Ki-67 expression in biopsy and transurethral resection specimens in patients with urothelial carcinoma of the urinary bladder

Milena Šunjević[1,2], Jovo Bogdanović[3,4], Sandra Trivunić-Dajko[1,2]

[1]University of Novi Sad, Faculty of Medicine, Department of Pathology, Novi Sad, Serbia;
[2]University Clinical Center of Vojvodina, Center for Pathology and Histology, Novi Sad, Serbia;
[3]University of Novi Sad, Faculty of Medicine, Department of Surgery, Novi Sad, Serbia;
[4]University Clinical Center of Vojvodina, Clinic for Urology, Novi Sad, Serbia

SUMMARY

Introduction/Objective Urothelial carcinoma is the most commonly diagnosed malignancy of urinary bladder in clinical and pathohistological practice where various prognostic factors play a significant role. One of the most important pathohistological prognostic factors is the intensity of immunohistochemical staining. Among various immunohistochemical markers that have been proven to influence disease progression and the patient's survival, role of Ki-67 and GATA3 in prediction of disease prognosis has not been completely clarified yet. The aim of this study was to determine the predictive value of GATA3 and Ki-67 mutual expression in urothelial carcinoma.

Methods Eighty patients were included in this study, out of which four groups were formed based on the pathological stage of urothelial carcinoma. After using preferred antibodies, their staining intensity was analyzed semiquantitatively.

Results Results showed that there was statistically significant correlation between the type of urothelial carcinoma, the pathological stage, and invasiveness and different grades of GATA3 expression, as well as statistically significant correlation between the type of urothelial carcinoma and the pathological stage and different grades of Ki-67 expression. The regression model showed low value of GATA3 and Ki-67 mutual expression. There was also statistical significance regarding the pathological stage and invasiveness of the tumor in survival analysis.

Conclusion Predictive value of GATA3 and Ki-67 mutual expression resulted as low from this study, but to our knowledge this was the first study to examine their predictive capability on biopsy and transurethral resection specimens.

Keywords: urothelial carcinoma; biopsy; transurethral resection; GATA3; Ki-67

INTRODUCTION

Urothelial carcinoma is the most commonly diagnosed malignancy of urinary bladder in clinical and pathohistological practice and it closely follows prostatic adenocarcinoma on the epidemiological malignancy scale of genitourinary system. Global data from 2020 showed 573,278 newly diagnosed urinary bladder carcinomas, which makes it the 10th one on the list of the most common malignancies in the general population [1]. In the 2006–2016 decade, annual frequency of urinary bladder carcinoma has declined by 1.3%, while mortality rate has not changed [2, 3]. The disease is more frequently diagnosed among males considering the differences in carcinogenic exposure between the sexes [4, 5]. Age represents a strong and independent risk factor as various demographic studies showed that patients older than 65 have 11-fold higher risk of getting this disease, unrelated to sex [6]. Considering the unchanged mortality rates during the last couple of years, the future burden of bladder cancer will fully depend on the newly formed diagnoses [3–6].

Pathohistological prognostic factors in bladder carcinoma include the histologic type, depth and tumor extension, stromal response and the intensity of inflammatory infiltrate, lymphovascular invasion, necrosis and disease stage, and intensity of immunohistochemical staining [7, 8]. Among various immunohistochemical markers that have been proven to influence disease progression and the patient's survival, Ki-67 and GATA3 have been chosen as the focus of the study, as their role in the disease prognosis has not been completely clarified yet [8, 9, 10].

The aim of this study was to determine the correlation between clinical and pathohistological parameters and urothelial carcinoma, as well as to determine the correlation between Ki-67 proliferation index and GATA3 expression with histological parameters of urothelial carcinoma and their predictive values.

Received • Примљено: March 12, 2022
Revised • Ревизија: June 5, 2022
Accepted • Прихваћено: July 12, 2022
Online first: July 13, 2022

Correspondence to:
Milena ŠUNJEVIĆ
Stevana Hristića 11
21000 Novi Sad, Serbia
milena.sunjevic@mf.uns.ac.rs

METHODS

During a one-year period (from October 1, 2020 to October 31, 2021), this retrospective–prospective study included pathohistological material from 80 patients who had been diagnosed with urinary bladder carcinoma or with a non-cancerous bladder lesion. The material for histological analysis was analyzed at the Center for Pathology and Histology of the University Clinical Center of Vojvodina. The study protocol was approved by the Ethics Committee of this institution (No. 00-400) and the Faculty of Medicine in Novi Sad (No. 01-39/299).

Study group

The cases of 80 patients who underwent biopsy or transurethral resection after clinical suspicion of bladder cancer existence were reviewed in this study, and an adequate tissue specimen was histologically analyzed. The exclusion criteria used in this study referred to patients with inadequate tissue specimens (not enough material suitable for immunohistochemical staining, remarkable exogenous tissue damage, and extensive necrosis present). All clinical data referring to demographic characteristics, type of procedure, pathohistological diagnosis, and stage were obtained from the patients' medical charts.

Urinary bladder tissue specimens for the histological analysis were fixed by 10% neutral formalin, then routinely paraffin-embedded. The specimens were cut at approximately 5 mm-intervals, sliced to 4 µm-thick sections, and stained with hematoxylin and eosin. By examining all tissue specimens, the following diagnoses were made and four numerically equal groups of 20 patients were formed:

- group I (control group) – tissue specimens where regular histological elements of bladder mucosa/wall as well as inflammation were present (in the form of *Cystitis cystica et glandularis, Cystitis polypoides et papillaris*), without any dysplastic epithelium changes or carcinoma *in situ* (CIS);
- group II – tissue specimens where papillary urothelial carcinoma, pTa stage was histologically confirmed and further divided into low grade and high grade (Figures 1A and 1B);
- group III – tissue specimens where infiltrating urothelial carcinoma pT1 stage was histologically confirmed and further divided into pT1m (microinvasive) and pT1e (extensive invasive) urothelial carcinoma (Figures 1C, 1D, and 1E);
- group IV – tissue specimens where infiltrating urothelial carcinoma, pT2 stage was histologically confirmed (Figure 1F).

The immunohistochemical analysis was performed on paraffine blocks with the biggest amount of preserved tissue and by using monoclonal antibody Ki-67 (clone MIB-1, DAKO, Glostrup, Denmark) and monoclonal GATA3 (clone L50-823, Cell Marque, Rocklin, CA, USA).

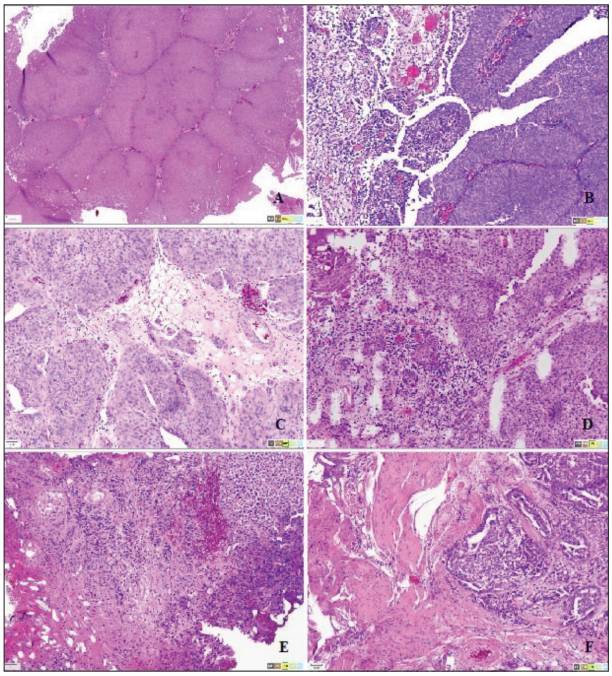

Figure 1. Microscopic appearance of urothelial carcinoma; (A) pTa, low grade, H&E, 2.5 ×; (B) pTa, high grade, H&E, 10 ×; (C) and (D) pT1, microinvasive, H&E, 10 ×; (E) pT1, extensive invasive, H&E, 10 ×; (F) pT2, H&E, 10 ×

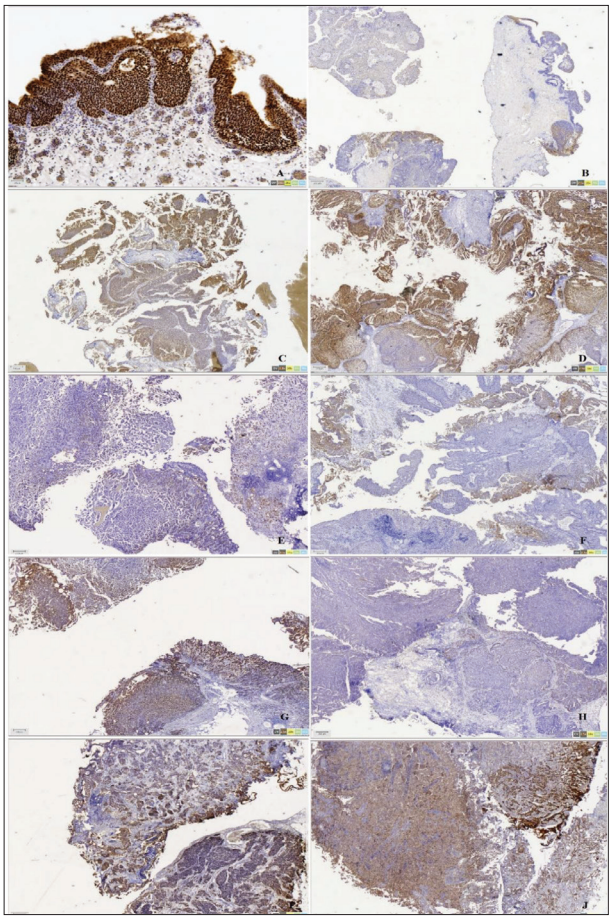

Figure 2. Micrographs showing GATA3 positivity in: (A) control group, 10 ×; (B), (C), and (D) pTa – grades I, II, III, 2.5 ×; (E), (F), and (G) pT1 – grades I, II, III, 2.5 ×; (H), (I), and (J) pT2 – grades I, II, III, 2.5 ×

Evaluation of Ki-67 and GATA3 immunohistochemical expression

The intensity of immunohistochemical staining was determined semiquantitatively, by analyzing areas where marker expression was most strongly presented. Ki-67 and GATA3 expression was evaluated as nuclear staining in tumor cells, while positive cytoplasmic staining was not considered important during the evaluation. Ki-67 proliferation index and GATA3 expression were defined as a percentage of positive tumor cells in regard to total number of tumor cells on histological section.

GATA3 positivity grading was defined as the following (Figure 2):

- grade 0 – no positivity;
- grade 1 – 1–10% positivity;
- grade 2 – 11–50% positivity;
- grade 3 – ≥ 51% positivity.

Ki-67 positivity grading was defined as the following (Figure 3):

- grade 0 – 0–10% positivity;
- grade 1 – 11–25% positivity;
- grade 2 – 26–50% positivity;
- grade 3 – ≥ 51% positivity.

Statistical analysis

The data were processed in the IBM SPSS Statistics, Version 23.0 (IBM Corp., Armonk, NY, USA). Data analysis methods used descriptive and inferential statistics. Numerical variables were presented by arithmetic mean and standard deviation, and the categorized variables through frequencies and percentages. Methods used to test statistical hypotheses were the χ^2 test and Fisher's exact test. The correlation between different parameters was determined with φ and Cramer's V correlation coefficients. Cumulative survival rates were calculated by the Kaplan–Meier method. All differences were considered significant for $p < 0.05$. The results are shown as tables (1–7).

RESULTS

Descriptive statistics and frequency of clinical and pathohistological characteristics

This study included 80 patients, 60 of which had a diagnosis of urothelial carcinoma, and 20 had a diagnosis of cystitis in different forms, without any elements of dysplasia, CIS, or carcinoma *per se*. The study included 54 men (67.5%) and 26 women (32.5%). Table 1 shows descriptive statistics of clinical characteristics and follow-up period of urothelial carcinoma and cystitis.

As patients with urothelial carcinoma were divided into three groups, 10 patients had a histological grade (HG) defined as low (16.7%), while 50 patients had high-grade urothelial carcinoma (83.3%). Twenty patients in each stage had pTa, pT1, and pT2 stages. Within patients with invasive pT1 and pT2 urothelial carcinoma, microinvasive pT1m stage was present in 11 patients (27.5%), while extensive invasive pT1e and invasive pT2 stage were present in 29 patients (72.5%).

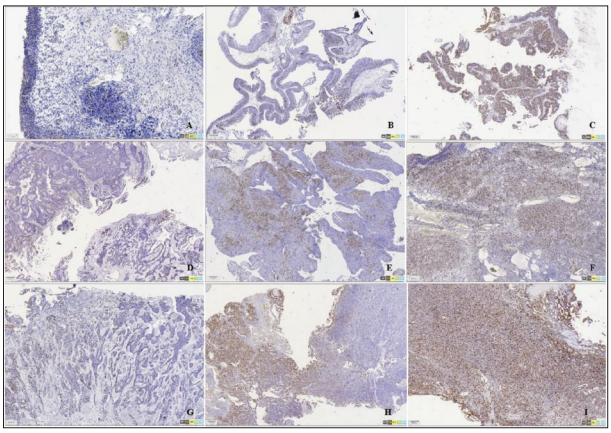

Figure 3. Micrographs showing Ki-67 positivity in: (A) control group, 10 ×; (B) and (C) pTa – grades I and III, 2.5 ×; (D), (E), and (F) pT1 – grades I, II, III, 2.5 ×; (G), (H), and (I) pT2 – grades I, II, III, 2.5 ×

Table 1. Descriptive statistics of clinical characteristics and follow-up period of urothelial carcinoma and cystitis

Age	Mean	68.87
	Median	69
	Standard deviation	10.13
	Minimum	30
	Maximum	88
Follow-up period (months)	Mean	12.71
	Median	12.5
	Standard deviation	7.37
	Minimum	1
	Maximum	27
Period until death outcome (months)	Mean	7.8
	Median	8
	Standard deviation	4.96
	Minimum	1
	Maximum	55

The correlation between urothelial carcinoma and cystitis with clinicopathological parameters

Table 2 shows summarized pathohistological parameters and their correlation with noninvasive and invasive urothelial carcinoma. As the results show, sex was not significantly associated with the presence of urothelial carcinoma, while significant associations were found between age groups, HG, and invasiveness with urothelial carcinoma.

In order to determine the predictive value of different age groups, multinomial logistic regression was used, in which regression model proved to be statistically significant (Table 3). In patients with noninvasive papillary urothelial carcinoma, age groups did not show any prediction value. On the other hand, age between 76 and 90 years was proven to be a good predictor for infiltrating urothelial carcinoma – patients of the aforementioned age had a

Table 2. Noninvasive and invasive urothelial carcinoma in different correlations with clinicopathological parameters

Parameters	Noninvasive papillary urothelial carcinoma (n/%)	Invasive (infiltrating) urothelial carcinoma (n/%)	Cystitis (n/%)	Total (n/%)	p	φ (p)
Sex						
Male	17 (21.3)	23 (28.7)	14 (17.5)	54 (67.5)	0.096*	
Female	3 (3.7)	17 (21.3)	6 (7.5)	26 (32.5)		
Age, years						
< 60	0 (0)	7 (8.8)	6 (7.5)	13 (16.3)	0.017**	
61–75	14 (17.5)	18 (22.5)	12 (15)	44 (55)		
76–90	6 (7.5)	15 (18.7)	2 (2.5)	23 (28.7)		
Histological grade						
Low grade	10 (16.7)	0 (0)		10 (16.7)	< 0.001***	0.632 (< 0.001)
High grade	10 (16.7)	40 (66.6)		50 (83.3)		
Invasiveness						
pT1m		11 (27.5)		11 (27.5)	< 0.001****	0.616 (< 0.001)
pT1e and pT2		29 (72.5)		29 (72.5)		

*χ^2 test = 4.672; **Fisher's test = 11.485; ***Fisher's test = 24.00; ****χ^2 test = 15.172

Table 3. Regression model for predictive values of different age groups

-2 Log	χ^2	p
16.834	14.269	0.006

Table 4. Age as a predictive factor for urothelial carcinoma of urinary bladder

Age groups	Noninvasive papillary urothelial carcinoma		Invasive (infiltrating) urothelial carcinoma	
	95% CI	p	95% CI	p
< 60	1 (reference group)		1 (reference group)	
61–75	1.5 (0.35–345.05)	0.17	0.78 (0.21–2.89)	0.70
76–90	2.57 (0.44–15.19)	0.29	**5 (0.96–25.94)**	**0.04**

five-fold greater chance of being diagnosed with infiltrating urothelial carcinoma than cystitis compared to patients younger than 60 years (Table 4).

The correlation between GATA3 and Ki-67 expression and histological parameters of urothelial carcinoma

Histological parameters of urothelial carcinoma and their association with classified positivity of GATA3 are presented in Table 5. The correlation between the type of urothelial carcinoma, pathological stage and invasiveness, and different grades of GATA3 expression was statistically significant, while the correlation between HG and GATA3 expression was not statistically significant. Table 6 shows histological parameters of urothelial carcinoma and their association with classified positivity of Ki-67. There was statistically important significance between type of urothelial carcinoma and pathological stage and different grades of Ki-67 expression, while correlation between HG, invasiveness and Ki-67 expression was not statistically significant.

Using the multinomial logistic regression, mutual predictive value of GATA3 and Ki-67 expression was examined, as well as separate predictive capability of these two markers. Analyzing mutual predictive capability, the regression model showed low values of GATA3 and Ki-67 mutual expression, thus separate expression of these markers had no statistically significant predictive values in urothelial carcinoma (Table 7).

Survival analysis

From the Kaplan–Meier plots, it can be concluded that the cumulative survival proportions varied between examined parameters. The cumulative survival proportion does not appear to differ remarkably considering HG, GATA3, and Ki-67 expression (Figures 4A, 4D, and 4E). It would appear that there was a statistical significance in regard to pathological stage (log rank (df = 2) = 8.327; p = 0.016, Figure 4B)

Table 5. The correlation between GATA3 expression and histological parameters of urothelial carcinoma

Histological parameters	Grade 0	Grade 1	Grade 2	Grade 3	Total	p	Cramer's V (p)
Urothelial carcinoma							
Noninvasive papillary	1 (1.3)	4 (5)	7 (8.8)	8 (10)	20 (25)	**< 0.001***	0.443 (< 0.001)
Invasive (infiltrating)	1 (1.2)	18 (22.5)	9 (11.3)	12 (15)	40 (50)		
Cystitis	0 (0)	0 (0)	0 (0)	20 (25)	20 (25)		
Pathological stage							
pTa	1 (1.7)	4 (6.7)	7 (11.7)	8 (13.3)	20 (33.3)	**< 0.001****	0.467 (< 0.001)
pT1	0 (0)	16 (26.7)	3 (5)	1 (1.7)	20 (33.3)		
pT2	1 (1.7)	2 (3.3)	6 (10)	11 (18.3)	20 (33.3)		
Histological grade							
Low grade	0 (0)	3 (5)	2 (3.4)	5 (8.3)	10 (16.7)	0.699***	
High grade	2 (3.3)	19 (31.7)	14 (23.3)	15 (25)	50 (83.3)		
Invasiveness							
pT1m	0 (0)	9 (22.5)	2 (5)	0 (0)	11 (27.5)	**0.008****	0.491 (0.012)
pT1e and pT2	1 (2.5)	9 (22.5)	7 (17.5)	12 (30)	29 (72.5)		

*Fisher's test = 32.347; **Fisher's test = 25.935; ***Fisher's test = 1.491; ****Fisher's test = 9.812

Table 6. The correlation between Ki-67 expression and histological parameters of urothelial carcinoma

Histological parameters	Grade 0	Grade 1	Grade 2	Grade 3	Total	p	Cramer's V (p)
Urothelial carcinoma							
Noninvasive papillary	14 (17.5)	5 (6.3)	0 (0)	1 (1.3)	20 (25)	< 0.001*	0.457 (< 0.001)
Invasive (infiltrating)	12 (15)	9 (11.2)	9 (11.3)	10 (12.5)	40 (50)		
Cystitis	20 (25)	0 (0)	0 (0)	0 (0)	20 (25)		
Pathological stage							
pTa	14 (23.4)	5 (8.3)	0 (0)	1 (1.7)	20 (33.4)	0.034**	0.325 (0.047)
pT1	6 (10)	5 (8.3)	4 (6.7)	5 (8.3)	20 (33.3)		
pT2	6 (10)	4 (6.7)	5 (8.3)	5 (8.3)	20 (33.3)		
Histological grade							
Low grade	7 (11.7)	3 (5)	0 (0)	0 (0)	10 (16.7)	0.099***	
High grade	19 (31.7)	11 (18.3)	9 (15)	11 (18.3)	50 (83.3)		
Invasiveness							
pT1m	0 (0)	9 (22.5)	2 (5)	0 (0)	11 (27.5)	0.275****	
pT1e and pT2	1 (2.5)	9 (22.5)	7 (17.5)	12 (30)	29 (72.5)		

*Fisher's test = 32.494; **Fisher's test = 13.08; ***Fisher's test = 5.515; ****Fisher's test = 4.121

Table 7. Regression model for predictive values of mutual GATA3 and Ki-67 expression

-2 Log	χ^2	p
5.589	0.587	0.344

and invasiveness of the tumor (Figure 4C). A log rank test was run to determine if there were differences in the survival distribution for these parameters and the results showed that patients with pT1m have better survival than patients with pT1e urothelial carcinoma [log rank (df = 1) = 2.989; p = 0.048, Figure 4C].

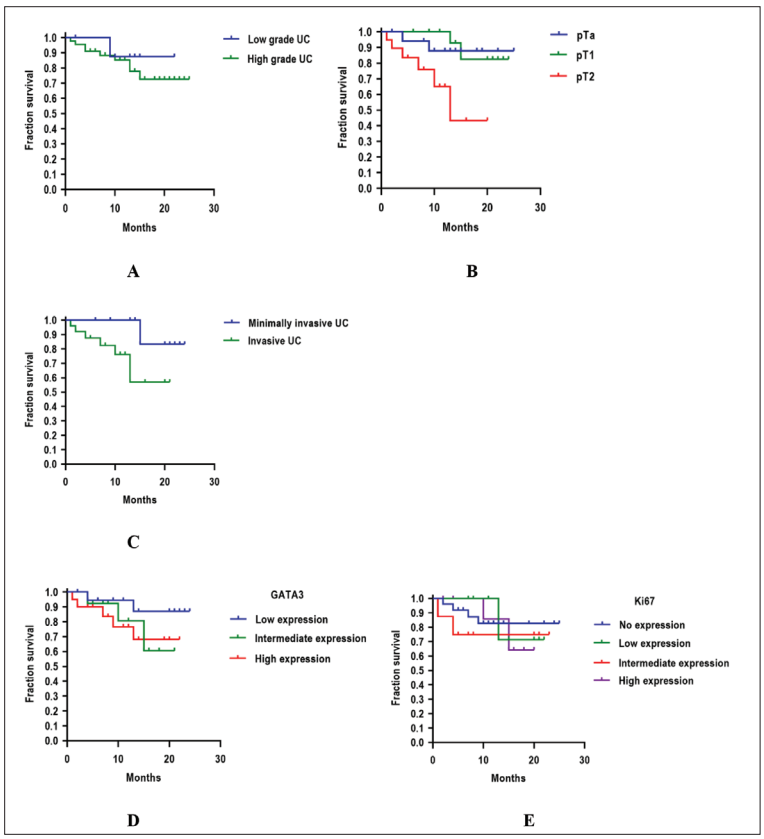

Figure 4. Cumulative overall survival curves stratified by: A) histological grade; B) pathological stage; C) invasiveness; D) GATA3 expression grades; E) Ki-67 expression grades

DISCUSSION

According to the International Agency for Research on Cancer and updated GLOBOCAN data from 2020, urinary bladder carcinoma is at the 10th place of the most commonly diagnosed carcinomas all over the world [1, 2]. This study included 40 men and 20 women with carcinoma, and male domination was compatible with data from larger studies, but with no statistical significance between the groups. Analyzing the sex influence on postoperative outcome from radical cystectomy, various authors showed that sex was an independent predictor; women had a two-fold greater risk of postoperative infection, extravesical extension, shorter disease-free period, and higher rate of relapse [6, 7]. In our study, patients in the 76–90 years age group had a five-fold greater chance of being diagnosed with infiltrating urothelial carcinoma compared to patients younger than 60 years. As a result of carcinogenic exposure, accumulation of somatic mutations and immune system changes, the general risk of urothelial carcinoma rises with age [11]. Autopsy studies frequently show many undetected malignancies, thus delayed detection reflects on lower cancer incidence, which is a result of less intense screening and diagnostic procedures [11, 12].

Numerous studies have also been dedicated to the analysis of the pT1 stage of urothelial carcinoma after radical cystectomy, its biological behavior and the ability for progression and relapse, as well as the possibilities for adequate and effective therapeutic modalities. According to these, the optimal solution for treating pT1 urothelial carcinoma was transurethral resection (TUR), and the most important predictors

are tumor size, multifocality, the presence of lymphovascular invasion, and concomitant CIS [13, 14]. Many studies have made their effort in order to stratify pT1 tumors according to the depth of invasion, and the results are highly variable. The possibility to substage pT1 varies 58–100%, and the percentage of accuracy is dependent on the number of specimens, sample quality, presence of muscularis mucosa, and the pathologist's level of experience [15, 16, 17]. According to one study, invasion depth 0.5–1.5 mm was defined as pT1, pT1b, and pT1c [15]. Based on this one and similar studies, pT1b and pT1c stages are significant predictors of disease progression [15, 16, 17]. pT1a/b/c substaging has not found constant and stable use in daily practice because it is associated with variable diagnostic accuracy 43–100% [16]. Other authors suggested a different pT1 substaging system, namely pT1m (microinvasive) and pT1e (extensive invasive). Studies showed that diagnostic accuracy of this substaging is higher and that patients with pT1e stage of urothelial carcinoma are at higher risk of disease progression [16, 17]. A study from 2018 is one of the rare studies which described a method for determining the depth of invasion within the pT1 stage, by biopsy or TUR specimens. Defining the linear extent of the urothelial carcinoma with optical micrometer and the cut-off value of 2.3 mm after regression analysis made this system 100% accurate for all included specimens, because the system did not require specific specimen orientation and did not depend on the presence of muscularis mucosa, histologic subtypes, lymphovascular invasion, and CIS [18].

There are different attitudes towards the correlation between GATA3 expression and the HG, as well as the pathologic stage. In the study by Agarwal et al. [19], statistically significant correlation between HG and GATA3 expression was present, as 100% of low-grade urothelial carcinoma showed intermediate to strong staining intensity, and more than half of pT2 urothelial carcinoma showed low intensity. Newer studies showed results similar to the study by Miyamoto et al., in which high-grade urothelial carcinoma was showing negative GATA3 expression [20]. On the other hand, Kamel et al. [21] suggested that GATA3 expression in non-muscle invasive urothelial carcinoma did not correlate with tumor stage, but was significantly downregulated in regard to tumor progression. In our study, the lowest intensity of GATA3 expression was associated with infiltrating pT1 stage of the disease. As study included smaller number of patients compared to the mentioned studies, the difference in results could be explained by the number and unpredictable behavior of the tumor in pT1 stage, which represents a therapeutic dilemma at the same time, because it is often difficult for a surgeon to decide whether to apply bacillus Calmette–Guerin immunotherapy or proceed with radical cystectomy, an aggressive and life-quality reducing surgery. Results from some other studies also show that GATA3 demonstrated significant correlation with oncological outcome, where higher expression was associated with longer disease-free period. GATA3-negative tumors had a tendency for an early relapse and the loss of GATA3 expression in invasive urothelial carcinoma increased the risk of death outcome, independent of age, morphology, and nodal status [20, 22]. GATA3 also represents a strong prognostic indicator for urothelial tumors of the upper urinary tract – a study by Inoue et al. [23] showed that GATA3-positive upper urinary tract tumors had a significantly lower risk of disease progression and cancer-specific mortality, in contrast to invasive bladder tumors.

Prognostic significance of Ki-67 reactivity in urothelial carcinoma has been analyzed through meta-analyses and cohort studies, but among patients who underwent radical cystectomy. High staining intensity was proved to be a predictor of significantly higher rate of cancer-specific mortality and shorter disease-free period [24, 25]. Critical values that would define high staining intensity were different between studies because of the non-existing standardized access, which contributes to the heterogeneity while interpreting Ki-67 expression. In most studies, 20%-value has served as a discriminator for poorer clinical outcome and shorter disease-free period [25]. In our study, Ki-67 expression within specimens of pTa urothelial carcinoma was absent or of low intensity. In the pT1 stage, Ki-67 expression varied from low to high intensity, as was the case with the pT2 stage. Similar results were found in the study by Ali Mohamed [26], but it should be mentioned that the study included twice as many patients. As Ki-67 is a cell cycle and proliferation regulative protein, it is probably capable of predicting tumor behavior based on histological grading and staging. Variable expression of Ki-67 in pT1 and pT2 urothelial carcinoma in our study could be explained by increasing bladder carcinoma's clinical, histological, and biological heterogeneity, where one marker is unlikely to predict precise prognosis.

Data showing mortality and five-year survival rate of patients with urothelial carcinoma are yet promising. Cumulative risk of death outcome from bladder carcinoma from birth to age of 74 years was 0.29% among men and 0.09% among women [1]. Data regarding five-year survival rate were obtained from the American Cancer Society for the 2010–2016 period. According to these, five-year survival rate depends on the stage. For example, five-year survival rate in CIS was 96%, 69% in patients with carcinoma confined to urinary bladder, and only 6% in patients with positive M descriptor (distant metastasis). With respect to all analyzed stages, patients' survival was brought down to noteworthy 77% [1, 2, 3].

CONCLUSION

In our study, cumulative probability of death outcome for microinvasive and extensive invasive pT1 urothelial carcinoma was proved to be statistically significant. Also, statistical significance was proved considering the pathological stage and invasiveness of the tumor. Even though this study found low predictive value of GATA3 and Ki-67 mutual expression, it was the first one to examine their predictive capability on biopsy and TUR specimens.

Conflicts of interest: None declared.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin. 2020;72(1):7–33. [DOI: 10.3322/caac.21708] [PMID: 35020204]
2. Fernández MI, Brausi M, Clark PE, Cookson MS, Grossman HB, Khochikar M, et al. Epidemiology, prevention, screening, diagnosis, and evaluation: update of the ICUD–SIU joint consultation on bladder cancer. World J Urol. 2019;37(1):3–13. [DOI: 10.1007/s00345-018-2436-y] [PMID: 30105454]
3. Poirier AE, Ruan Y, Walter SD, Franco EL, Villeneuve PJ, King WD, et al. The future burden of cancer in Canada: Long-term cancer incidence projections 2013–2042. Cancer Epidemiol. 2019;59:199–207. [DOI: 10.1016/j.canep.2019.02.011] [PMID: 30831552]
4. Wong MCS, Fung FDH, Leung C, Cheung WWL, Goggins WB, Ng CF. The global epidemiology of bladder cancer: A joinpoint regression analysis of its incidence and mortality trends and projection. Sci Rep. 2018;8(1):1–12. [DOI: 10.1038/s41598-018-19199-z] [PMID: 29348548]
5. Radkiewicz C, Edgren G, Johansson ALV, Jahnson S, Häggström C, Akre O, et al. Sex Differences in Urothelial Bladder Cancer Survival. Clin Genitourin Cancer. 2020;18(1):26–34. [DOI: 10.1016/j.clgc.2019.10.020] [PMID: 31787542]
6. Uhlig A, Seif Amir Hosseini A, Simon J, Lotz J, Trojan L, Schmid M, et al. Gender Specific Differences in Disease-Free, Cancer Specific and Overall Survival after Radical Cystectomy for Bladder Cancer: A Systematic Review and Meta-Analysis. J Urol. 2018;200(1):48–60. [DOI: 10.1016/j.juro.2017.11.150] [PMID: 29477716]
7. Richters A, Aben KKH, Kiemeney LALM. The global burden of urinary bladder cancer: an update. World J Urol. 2020;38(8):1895–904. [DOI: 10.1007/s00345-019-02984-4] [PMID: 31676912]
8. Akgul M, MacLennan GT, Cheng L. The applicability and utility of immunohistochemical biomarkers in bladder pathology. Hum Pathol. 2020;98:32–55. [DOI: 10.1016/j.humpath.2020.01.004] [PMID: 32035992]
9. Zhang L, Wu B, Zha Z, Qu W, Zhao H, Yuan J. Clinicopathological factors in bladder cancer for cancer-specific survival outcomes following radical cystectomy: A systematic review and meta-analysis. BMC Cancer. 2019;19(1):1–13. [DOI: 10.1186/s12885-019-5924-6] [PMID: 31324162]
10. Ko K, Jeong CW, Kwak C, Kim HH, Ku JH. Significance of Ki-67 in non-muscle invasive bladder cancer patients: A systematic review and meta-analysis. Oncotarget. 2017;8(59):614–30. [DOI: 10.18632/oncotarget.21899] [PMID: 29246006]
11. DeSantis CE, Miller KD, Dale W, Mohile SG, Cohen HJ, Leach CR, et al. Cancer statistics for adults aged 85 years and older. CA Cancer J Clin. 2019;69(6):452–67. [DOI: 10.3322/caac.21577] [PMID: 31390062]
12. Fonteyne V, Ost P, Bellmunt J, Droz JP, Mongiat-Artus P, Inman B, et al. Curative Treatment for Muscle Invasive Bladder Cancer in Elderly Patients: A Systematic Review. Eur Urol. 2018;73(1):40–50. [DOI: 10.1016/j.eururo.2017.03.019] [PMID: 28478043]
13. Kvikstad V, Mangrud OM, Gudlaugsson E, Dalen I, Espeland H, Baak JPA, et al. Prognostic value and reproducibility of different microscopic characteristics in the WHO grading systems for pTa and pT1 urinary bladder urothelial carcinomas. Diagn Pathol. 2019;14(1):1–8. [DOI: 10.1186/s13000-019-0868-3] [PMID: 31412916]
14. Mannas MP, Lee T, Nykopp TK, Batista Da Costa J, Black PC. A risk-stratified approach to the management of high-grade T1 bladder cancer. Curr Opin Urol. 2018;28(6):563–9. [DOI: 10.1097/MOU.0000000000000548] [PMID: 30148753]
15. Sjöström C, Thorstenson A, Ströck V, Hosseini-Aliabad A, Aljabery F, Liedberg F, et al. Treatment according to guidelines may bridge the gender gap in outcome for patients with stage T1 urinary bladder cancer. Scand J Urol. 2018;52(3):186–93. [DOI: 10.1080/21681805.2018.1462254] [PMID: 29676191]
16. Turan T, Efiloğlu Ö, Günaydin B, Özkanli S, Nikerel E, Atis G, et al. Comparative differences between T1a/b and T1e/m as substages in T1 urothelial carcinoma of the bladder. Int Braz J Urol. 2018;44(2):267–72. [DOI: 10.1590/S1677-5538.IBJU.2017.0424] [PMID: 29219283]
17. Gordon PC, Thomas F, Noon AP, Rosario DJ, Catto JWF. Long-term Outcomes from Re-resection for High-risk Non–muscle-invasive Bladder Cancer: A Potential to Rationalize Use. Eur Urol Focus. 2019;5(4):650–7. [DOI: 10.1016/j.euf.2017.10.004] [PMID: 29089252]
18. Leivo MZ, Sahoo D, Hamilton Z, Mirsadraei L, Shabaik A, Parsons JK, et al. Analysis of T1 Bladder Cancer on Biopsy and Transurethral Resection Specimens. Am J Surg Pathol. 2018;42(1):1–10. [DOI: 10.1097/PAS.0000000000000964] [PMID: 29076872]
19. Agarwal H, Babu S, Rana C, Kumar M, Singhai A, Shankhwar SN, et al. Diagnostic utility of GATA3 immunohistochemical expression in urothelial carcinoma. Indian J Pathol Microbiol. 2019;62(2):244–50. [DOI: 10.4103/ijpm.ijpm_228_18] [PMID: 30971548]
20. Wang CC, Tsai YC, Jeng YM. Biological significance of GATA3, cytokeratin 20, cytokeratin 5/6 and p53 expression in muscle-invasive bladder cancer. PLoS One. 2019;14(8):1–14. [DOI: 10.1371/journal.pone.0221785] [PMID: 31469885]
21. Kamel NA, Abdelzaher E, Elgebaly O, Ibrahim SA. Reduced expression of GATA3 predicts progression in non-muscle invasive urothelial carcinoma of the urinary bladder. J Histotechnol. 2020;43(1):21–8. [DOI: 10.1080/01478885.2019.1667126] [PMID: 31551051]
22. Bontoux C, Rialland T, Cussenot O, Compérat E. A four-antibody immunohistochemical panel can distinguish clinico-pathological clusters of urothelial carcinoma and reveals high concordance between primary tumor and lymph node metastases. Virchows Arch. 2021;478(4):637–45. [DOI: 10.1007/s00428-020-02951-0] [PMID: 33128085]
23. Inoue S, Mizushima T, Fujita K, Meliti A, Ide H, Yamaguchi S, et al. GATA3 immunohistochemistry in urothelial carcinoma of the upper urinary tract as an urothelial marker and prognosticator. Hum Pathol. 2017;64:83–90. [DOI: 10.1016/j.humpath.2017.04.003] [PMID: 28428106]
24. El-Gendi S, Abu-Sheasha G. Ki-67 and Cell Cycle Regulators p53, p63 and cyclinD1 as Prognostic Markers for Recurrence/Progression of Bladder Urothelial Carcinoma. Pathol Oncol Res. 2018;24(2):309–22. [DOI: 10.1007/s12253-017-0250-2] [PMID: 28488128]
25. Vetterlein MW, Roschinski J, Gild P, Marks P, Soave A, Doh O, et al. Impact of the Ki-67 labeling index and p53 expression status on disease-free survival in pT1 urothelial carcinoma of the bladder. Transl Androl Urol. 2017;6(6):1018–26. [DOI: 10.21037%2Ftau.2017.11.10] [PMID: 29354488]
26. Ali Mohamed S. The Diagnostic Role of p53 and Ki67 Immunohistochemistry in Evaluation of Urinary Bladder Carcinomas in Egyptian Patients. Int J Chin Med. 2019;3(1):1–6. [DOI: 10.11648/j.ijcm.20190301.11]

Прогностички значај експресије *GATA3* и пролиферативног индекса *Ki*-67 у биоптичким узорцима и узорцима добијеним трансуретралном ресекцијом карцинома мокраћне бешике

Милена Шуњевић[1,2], Јово Богдановић[3,4], Сандра Тривунић-Дајко[1,2]

[1]Универзитет у Новом Саду, Медицински факултет, Катедра за патологију, Нови Сад, Србија;
[2]Универзитетски клинички центар Војводине, Центар за патологију и хистологију, Нови Сад, Србија;
[3]Универзитет у Новом Саду, Медицински факултет, Катедра за хирургију, Нови Сад, Србија;
[4]Универзитетски клинички центар Војводине, Клиника за урологију, Нови Сад, Србија

САЖЕТАК

Увод/Циљ Уротелни карцином је најчешће дијагностикована малигна неоплазма мокраћне бешике у клиничкој и патохистолошкој пракси, где различити прогностички фактори имају значајну улогу. Један од најзначајнијих патохистолошких прогностичких фактора је интензитет имунохистохемијског бојења. Међу различитим имунохистохемијским маркерима за које је доказано да имају утицај на прогресију болести и преживљавање болесника, заједничка улога *Ki-67* и *GATA3* у предикцији прогнозе болести није још потпуно разјашњена.

Циљ ове студије је дефинисање предиктивног значаја заједничке експресије *GATA*3 и *Ki*-67 у уротелном карциному.

Методе Осамдесет болесника је учествовало у студији, при чему су формиране четири групе на основу патолошког стадијума уротелног карцинома. Након употребе наведених антитела интензитет бојења је анализиран семиквантитативно.

Резултати Статистичка значајност је доказана између хистолошког типа, патолошког стадијума и инвазивности и различитих степена експресије *GATA*3, као и између хистолошког типа и патолошког стадијума и различитог степена експресије *Ki*-67. Регресиони модел је показао ниску предиктивну вредност заједничке експресије *GATA*3 и *Ki*-67. Такође је доказана статистичка значајност између патолошког стадијума и инвазивности тумора при анализи преживљавања.

Закључак Анализом предиктивног значаја заједничке експресије *GATA*3 и *Ki*-67 добијена је ниска вредност. Значај истраживања огледа се у његовој јединствености, што за циљ има испитивање успешности предикције наведених антитела у узорцима биопсије и трансуретралне ресекције уротелног карцинома.

Кључне речи: уротелни карцином; биопсија; трансуретрална ресекција; *GATA*3; *Ki*-67