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PROGNOSTIC VALUE OF TUMOR MARKERS KI67 AND P53 IN DETECTING RECURRENCE OF BLADDER CANCER

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Abstract. Bladder cancer (BC) remains one of the predominant pathologies in onco-urological practice and poses a significant challenge for global healthcare. Understanding the risk factors and prognosis of this disease can improve prevention, early detection, and treatment of this type of cancer.
Objective of the study. To investigate the expression characteristics of BC biomarkers to predict the likelihood of recurrence.
Materials and methods. In the present study, we adopted a threshold value of 20% nuclear positivity as the cutoff for low and high immunoexpression of p53 and Ki-67, as this discriminative threshold was more predictive in terms of tumor recurrence, progression, and recurrence-free survival in some previous analytical studies.
Results. The results suggest that higher p53 expression may be an indicator of tumor progression and early local therapy failure, as well as for early surgical intervention, particularly in superficial carcinomas. The immunoexpression of p53 and Ki-67 showed a significant association with histological grade and stage individually, as well as in combination.
Conclusion. The combined use of p53 and Ki-67 immunomarkers in bladder carcinomas can provide additional prognostic information alongside histological classification and staging. Overexpression of p53 may be important for stratifying high-risk patients, especially in superficial urothelial carcinomas.
Keywords: bladder cancer, urothelial carcinoma, immunohistochemistry, biomarkers, Ki-67, p53.

Introduction. Transitional cell carcinoma of the bladder (TCCB) is one of the most common onco-urological pathologies of the urinary system and ranks 9th in prevalence among malignant neoplasms worldwide, making it a significant societal problem [1]. In the Republic of Uzbekistan, TCCB ranks 9th in the structure of oncological diseases among men. In 2021, 538 (1.5%) cases of TCCB were detected in the country. The 5-year survival rate is 38.1%. In 2021, 263 patients died from TCCB. The incidence of TCCB in Uzbekistan was 1.5, and the mortality rate was 0.7 per 100,000 population [2].

In the vast majority of cases (62–75%), urothelial TCCB is detected at non-invasive stages (NMIBC). 40–86% of "superficial" tumors recur after comprehensive treatment, and 21–43% progress to invasive forms. The remaining 24–34% of bladder tumors are characterized by invasive growth (MIBC) at the time of diagnosis [3]. Micrometastases at the time of diagnosis are the main reason for the unfavorable prognosis of MIBC [4]. After radical cystectomy (RC), disease progression is observed in the majority of patients within the next 2 years, with a recurrence rate of more than 50% [5]. This group is distinguished by a high aggressive course and high mortality rates [6].

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The choice of treatment method and prognosis of further TCCB progression currently depend on the histological structure of the tumor (G) and the degree of invasion according to the TNM classification. It should be noted that the long-term results of comprehensive treatment of TCCB, belonging to the same classification group, and receiving identical treatment volumes, can vary significantly. Therefore, additional tumor parameters, besides its degree of differentiation, stage, histological type, and individual characteristics, are needed for a complete prognosis of bladder cancer course to determine its clinical progression and biological aggressiveness.

Pathogenesis of TCCB. Risk factors associated with the occurrence and progression of bladder cancer include genetic and molecular abnormalities, environmental factors, as well as chronic infections and inflammatory processes of the urinary tract. In an attempt to better understand the molecular pathways responsible for the heterogeneous and unpredictable progression of this disease, several studies have investigated the molecular components of the cell cycle and identified two distinct and mutually exclusive pathways that play a key role in the molecular pathogenesis of bladder cancer. The FGFR3-RAS-MAPK pathway, associated with low-grade non-invasive tumors, and the p53-RB pathway, associated with highly aggressive tumors [6].

Normal variations in the genomic set may play a significant role in susceptibility to TCCB compared to genomic set mutations. There is evidence that DNA repair gene regions, cytochromes P450, and glutathione-dependent enzymes may be one of the components predisposed to the development of bladder cancer [7]. A high risk of developing bladder cancer may be due to the emergence of specific allelic variants of prooxidant and antioxidant enzyme genes [8]. Increased activity of arylamine-metabolizing enzymes, NAT1, CYP1A2, with insufficient activity of GSTM1, NAT2 genes may be a high-risk factor for bladder cancer development [9].

Under the influence of carcinogens, control mechanisms of cell division are disrupted in the epithelial cells of the bladder. In such cases, the main process contributing to the development of TCCB is considered to be the deletion of the short and long arms of chromosome 9 [10]. Major molecular-genetic aberrations occur when the structure of PTEN, TP53, RB1, which are tumor suppressor genes, is disrupted, leading to genome instability and the development of invasive bladder cancer. A similar situation is observed in the development of severe dysplasia of urothelial cells. Mutation or deletion of 17p may result in disruption of the TP53 gene structure, causing the development of invasive TCCB (see Figure 1) [11].

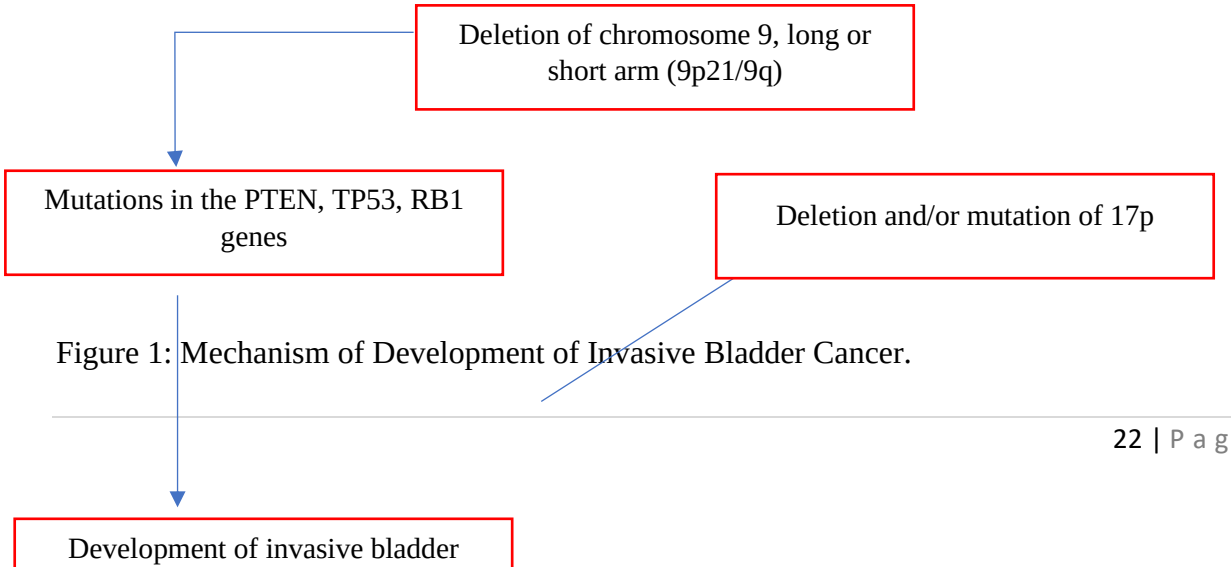

Figure 1: Mechanism of Development of Invasive Bladder Cancer.

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Studying molecular markers will enable predicting the prognosis and characteristics of the disease individually, thus preventing errors during routine histological examination and staging assessment. The immunohistochemical expression of p53 and the proliferation marker Ki-67 can be useful for the accurate classification and staging of bladder carcinomas. This study was conducted to present the clinicopathological features of bladder carcinoma and demonstrate the correlation of p53 and Ki-67 immunoexpression with the grade and stage of primary bladder carcinoma.

Materials and Methods. In the present study, we included a total of 92 cases of bladder carcinoma diagnosed over the past 3 years. Relevant medical histories and clinical-radiological data were recorded on a special form. Tissue samples in 10% buffered formalin were obtained following bladder biopsy. Stained sections, 3–5 µm thick, were analyzed for histopathological diagnosis.

For immunohistochemistry, additional sections 2-4 µm thick were taken on slides coated with poly-L-lysine and subjected to antigen retrieval using microwave heating. Immunohistochemical staining for p53 and Ki-67 was performed using primary antibodies DO7 (cell line key code-CMC45329022; diluted 1:300 in tris-buffered saline) and SP6 (cell line key code-CMC27531021; diluted 1:300 in tris-buffered saline) respectively. The monoclonal mouse antibody DO7 reacts with an epitope at the N-terminus of the p53 protein and recognizes both mutant and wild-type p53 proteins. Sections were incubated with a secondary biotinylated antibody and avidin-biotin-peroxidase complexes for 30 minutes. Reaction products were detected using diaminobenzidine as the chromogen, and sections were counterstained with Harris hematoxylin to enhance nuclear detection. For the negative control, the primary antibody was replaced with phosphate-buffered saline on duplicate sections.

Nuclear positivity was indicated by a dark brown color on a bluish background. The percentage of immunopositive cells was calculated by counting at least 1000 tumor cells in areas of maximal positivity. The results were interpreted considering the 20% threshold value and categorized into three groups as immunonegative, <20% as low, and >20% as high expression for both immunomarkers.
Subsequently, the data were analyzed, tabulated, and compared with the histopathological diagnosis.

Table № 1.

Ki67	Immunonegative	<20%	>20%
Total cases	0	47	45
Histology:			
• Urothelial carcinoma	0	47	42
• Squamous cell carcinoma	0		2
• Adenocarcinoma	0		1
Degree of differentiation:			
• Low	0	40	1
• High	0	5	46

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Stage:			
• Ta	0	21	0
• T1	0	28	20
• T2	0	0	23
p53	Immunonegative	<20%	>20%
Total cases	3	18	71
Histology:			
Urothelial carcinoma	3	16	70
Squamous cell carcinoma		2	
Adenocarcinoma			1
Degree of differentiation:			
Low	2	11	29
High	1	4	45
Stage:			
Ta	2	1	14
T1	1	15	37
T2	0	2	20

Table № 1. Distribution of immunohistochemical staining of p53 and Ki-67 depending on histology, degree, and stage.

Table №2.

Stage	Grade	Quantity	Average ± standard deviation	
			Экспрессия Ki67	Экспрессия p53
Ta	Low	19	6,69±3,61	26,45±8,7
T1	Low + high	48	15,13±7,74	31,77±17,36
T2	High	25	33,48±5,56	35,93±14,79

Table № 2. Correlation of Ki-67 and p53 immunoexpression depending on the stage and grade of bladder tumor.

Results. The majority of patients were males (81 cases, 88.04%), with only 11 cases (11.96%) registered in females, resulting in a male-to-female ratio of 7.36:1 in this study. The average age at admission for males was 55 years, and for females, it was 62 years. The highest number of cases was observed in the age group of 41–60 years (41 cases, 44.56%), followed by the age group of 61–80 years (37 cases, 40.2%). No cases were registered in individuals under 20 years of age. The majority of male patients (48 cases) were in the age group of 41–60 years. However, among females, the highest number (8 cases) was observed in the age group of 61–80 years.

Table №3.

Characteristics	Women	Men
Total number	11	81

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Average age (years)	62	55
Age group:		
• 21-40	0	5
• 41-60	2	39
• 61-80	8	29
• >80	1	8
Histology:		
Urothelial carcinoma	11	78
Squamous cell carcinoma	0	2
Adenocarcinoma	0	1
Degree of differentiation:		
Low	7	34
High	5	46
Stage:		
Ta	4	17
T1	3	45
T2	2	21

Table № 3. Distribution of patients with bladder carcinoma based on age, gender, histological type, grade, and stage of bladder tumor.

In our study, the most common clinical manifestation was macroscopic or microscopic hematuria, observed in 82 cases (89.13%). Hematuria alone was present in 37 cases (40.2%), while its association with symptoms of urinary tract or lower abdominal pain was observed in 29 cases (31.52%) and 17 cases (18.47%), respectively. Seven cases were presented only with microscopic hematuria, and two cases only with lower abdominal pain. Only one patient had asymptomatic disease, diagnosed incidentally.

The most prevalent histological variant was urothelial carcinoma, observed in 89 cases (96.7%), followed by squamous cell carcinoma (2 cases) and adenocarcinoma (1 case). According to the WHO recommendations, all cases were classified as low grade (LG) and high grade (HG). Forty-one cases (44.5%) were registered as LG, while the remaining 51 cases (55.5%) were HG tumors, including squamous cell carcinoma and adenocarcinoma. Staging of all cases was also performed according to the TNM classification of the American Joint Committee on Cancer. In this study, 69 patients (75%) were found to have non-muscle-invasive bladder cancer, of which 21 cases (22.8%) were stage pTa (without lamina propria invasion) and 48 cases (52.1%) were stage pT1 (with lamina propria invasion), while the remaining 23 cases (25.1%) were stage pT2 (detrusor muscle invasion) [Table No. 3]. Patients with stage T1 were further classified as pT1HG (28 cases) and pT1 LG (22 cases) depending on their grade.

It was observed that out of 92 cases of bladder carcinoma, 71 cases (77.1%) showed high expression of p53, 18 cases (19.5%) showed low expression of p53, and 3 cases (3.2%) were immunonegative for p53. High p53 expression was mainly observed in HG tumors (45 cases) compared to 29 cases of LG tumors [Table No. 1]. Low expression was noted in 11 patients with LG tumors and only in 4 patients with HG tumors. This difference in p53 expression was

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statistically significant (p=0.0001) considering the grade. The highest number of patients with high p53 expression (48 cases) was observed at stage pT1 compared to stages pTa (19 cases) and pT2 (25 cases). Only three cases at stages pTa and pT2 showed low immunexpression, whereas 15 cases were identified at stage pT1. From a staging perspective, these results were also statistically significant (p=0.000001). Both cases of squamous cell carcinoma showed low p53 expression, while in one case of adenocarcinoma, high expression was detected [Table No. 1]. Out of the three immunonegative patients, two had stage pTa and one patient had stage pT1, including one case of HG urothelial carcinoma [Table No. 1].

In this study, low Ki-67 immunexpression was observed in 47 cases, while high expression was found in 45 patients. LG tumors predominantly showed low expression (40 cases), whereas HG tumors exhibited high expression (46 cases) [Table No. 1]. All 23 cases of muscle-invasive tumors (pT2) showed high Ki-67 immunexpression, including squamous cell carcinoma and adenocarcinoma [Table No. 1], while all patients with stage pTa had low expression. In carcinomas at stage pT1, low and high expression was observed in 28 and 20 cases, respectively. It was found that the difference was statistically significant in terms of classification (p = 0.01) and stage pT1 (pTa + pT1/pT2, P = 0.000001; pTa/pT1, P = 0.000001; pT1/pT2, P = 0.000002), as highlighted in [Table No. 1].

Discussion. Bladder cancer is a common, multi-stage, progressive malignant neoplasm, ranking 9th in global cancer incidence, with high mortality and morbidity rates. Although the incidence of urothelial carcinomas increases with age, smoking, exposure to petrochemicals, and arylamines, its burden is also rising due to changes in smoking habits, tobacco use, industrialization, and urbanization from developed to developing countries over the past few decades.

In our study, the majority of patients were males and belonged to the middle and older age groups. Similar results have been described in other studies. Additionally, hematuria was the most common symptom, consistent with the findings of other authors. Approximately 10% and 20% of patients with microscopic and macroscopic hematuria, respectively, are subsequently diagnosed with bladder cancer after evaluation. In the present study, the predominant histological variant was urothelial carcinoma. Similar data have been published by other authors. Adenocarcinomas are rare bladder tumors, accounting for approximately 2% of all bladder cancers, consistent with our study. Squamous cell carcinoma was noted in approximately 1.8% of cases. Beltran et al. also described its frequency as 1–3% of all bladder tumors.

A reliable and uniform staging and classification system for bladder carcinoma using histopathological analysis is important for categorizing patients for optimal treatment choices across different institutions, as well as for prognostic stratification into distinct groups. Approximately 80% of patients are diagnosed with superficial non-muscle-invasive carcinoma at initial presentation. In this study, non-muscle-invasive tumors were observed in approximately 75% of cases (stage Ta + T1); similar results were obtained in other studies. Therefore, it is also important to mention the presence of detrusor muscle in the biopsy specimen. We categorized urothelial carcinomas into LG and HG based on cellular atypia, polarity, epithelial thickness, and mitosis (WHO classification system). HG tumors (46 cases)

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were more common in elderly patients over 60 years old, consistent with similar findings reported by Joshi et al. We detected 36.9% of LG carcinoma cases, similar to several other studies. We also observed approximately 48 cases of stage T1, encompassing both non-invasive LG and HG urothelial tumors, while stage Ta identified all patients only with LG tumors.
Since there is a greater risk of tumor recurrence, stage progression, and tumor-related mortality associated with increased tumor grade and infiltrative pattern, histopathological classification and staging of urothelial carcinomas can be important tools in determining disease prognosis. However, these pathological variables demonstrate limited ability to predict treatment response to a greater extent than various treatment approaches and subsequent follow-up schedules. Therefore, there is a clear need for molecular studies that may be useful for accurately predicting the behavior of these cases.

Cell proliferation and mutations in genes regulating the cell cycle are distinguishing features of various tumors, including urothelial carcinomas. In carcinogenesis, p53 is the most common gene mutation observed in lung, breast, colorectal, and bladder carcinomas. The p53 gene is a tumor suppressor gene located on chromosome 17p; it is important for genome stability, response to genotoxic stimuli, and activation of apoptosis. However, its molecular basis influencing cellular functions and oncogenesis remains unclear. In normal tissues, the p53 gene product is a nuclear protein of 393 amino acids with a shorter half-life, whereas the mutated p53 gene product with a longer half-life accumulates, making it easily detectable by immunohistochemistry.

Proliferation abnormalities resulting from cell cycle regulator disruption and abnormal cell proliferation can also be easily detected using immunohistochemistry with the Ki-67 labeling index, which is a measure of cell growth fraction and, therefore, also of the biological aggressiveness of malignant neoplasms. The nuclear antigen Ki-67, encoded by a gene on chromosome 10, is absent in resting cells (G0 phase) and is exclusively positive in the nuclei of proliferating cells. In this study, we adopted 20% nuclear positivity as the threshold for low and high p53 and Ki-67 immunexpression, as this discriminating threshold was more predictive in terms of tumor recurrence, progression, and disease-free survival in some of the previous analytical studies.

A significant association between grade and stage (superficial or muscle-invasive) with positively stained p53 tumor cells was observed when adopting 20% as the threshold value ($p = 0.0001$ and $p = 0.000001$). Similar behavior of this marker has been noted by some other authors depending on grade and/or stage of the tumor or clinical outcome. Serth et al. found disease progression with p53 overexpression (12/14 cases), while only one case out of 55 patients had <20% p53 positivity. From the results, it can be inferred that higher p53 expression may be an indicator of tumor progression and early ineffectiveness of local therapy; it is also for early surgical intervention, especially in superficial carcinomas. Although some researchers have described opposite results.

We also observed p53-negative cases, which may indicate either p53 inactivation or alternative genetic pathways in the molecular pathogenesis of urothelial tumors. Several previous analyses also suggest alternative immune markers. A significant positive correlation of the Ki-67

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labeling index with histological classification and staging of urothelial carcinoma ($p < 0.05$) has been described similarly in other studies. All muscle-invasive carcinomas showed high Ki-67 expression; no immunonegative cases were observed.

In our study, the percentage of p53-positive tumor cells ranged from 0% to 70%, with an overall mean expression of 31.8% (pTa = 26.45%, pT1 = 31.77%, pT2 = 35.93%), while the median value was observed as 37.5%. The mean Ki-67 labeling index was 18.4% (pTa = 6.69%, pT1 = 15.13%, and pT2 = 33.48%), with an overall mean of 22%. We noticed that the mean Ki-67 expression consistently varied more with increasing stage compared to p53 expression. Additionally, there were more differences between the expression of these two markers at stages pTa and pT1 ($p = 0.0001$) compared to pT2.

Conclusion. The obtained results confirm the opinion that the combined use of p53 and Ki-67 immunomarkers in bladder carcinomas may provide additional prognostic information alongside histological classification and staging. Similar results have also been described in several studies. However, p53 overexpression may be important for stratifying patients at high risk, especially in superficial urothelial carcinomas. Nevertheless, further extensive multicenter studies with reliable, reproducible, and standardized immunohistochemical methods, using other biomarkers, are necessary. This could ultimately enable more effective management of malignant bladder neoplasms.

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