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COMPARATIVE EXPRESSION OF P53 IN LOW-GRADE AND HIGH-GRADE UROTHELIAL CARCINOMA OF THE URINARY BLADDER: A CROSS-SECTIONAL STUDY

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ABSTRACT

Background: Urothelial carcinoma (UCa) of the urinary bladder is a biologically heterogeneous disease, and histological grade does not necessarily reflect the behavior of the tumor. The tumor suppressor p53 has been identified as a potential biomarker linked to tumor growth and aggressiveness.

Objective: To compare the immunohistochemical expression of p53 in low-grade and high-grade urothelial carcinoma of the urinary bladder and its correlation with clinicopathological features.

Methods: This analytical cross-sectional study conducted at Pak International Medical College analyzed 100 patients with histopathologically confirmed UCa including 50 low-grade and 50 high-grade. Immunohistochemical staining was performed on formalin fixed paraffin embedded tissue sections for p53. The relationships between p53 expression and clinicopathological variables were determined by Chi-square and logistic regression analysis, and a $p<0.05$ was considered statistically significant.

Results: High-grade UCa showed higher expression of p53 (86.0%) than low-grade UCa (48.0%) ($p<0.001$). Smoking history, tumor size, more than one tumor, muscle invasion, lymphovascular invasion, perineural invasion, and pathological stage were significantly associated with positive p53 expression. In multivariable logistic regression, p53 positivity was an independent factor of high-grade UCa (adjusted OR 5.83, 95% CI 2.01–16.89, $p=0.001$).

Conclusions: The high expression of p53 is closely associated with the histological grade and the aggressive pathological characteristics of UCa. Immunohistochemical analysis of p53 could be a valuable biomarker for prognostic evaluation and risk stratification in the common pathological practice.

KEYWORDS: Urothelial carcinoma; Urinary bladder; p53; Immunohistochemistry; Tumor grade

INTRODUCTION

Bladder cancer is one of the most prevalent malignancies of the urinary tract and is an important burden of disease in the world.[1] About 90–95% of bladder cancers are urothelial carcinomas, which develop from the specialized epithelium of the urinary bladder and are formerly called transitional cell carcinomas.[2] UCa are highly biologically heterogeneous and can behave in a variety of ways, from low-grade non-invasive tumours to high-grade cancers with a significant metastatic potential.[3] Histopathological grading is one of the most significant factors for predicting tumor behaviour and remains a key factor for treatment planning, surveillance and prognosis.[4]

Bladder cancer is one of the top 10 most common cancers in the world, with more than 610,000 new cases and more than 220,000 deaths each year.[5] The disease has a marked male predominance, with a 3 to 4-fold greater incidence in men than in women.[6] The incidence of bladder cancer is rising at an accelerating rate in many low- and middle-income countries, in part because of environmental pollution, population ageing, better diagnostic technology, and, of course, tobacco use, although this is most prevalent in developed countries.[7] Bladder cancer is a significant component of genitourinary malignancies in Pakistan and is often diagnosed at a late stage, which leads to high morbidity and healthcare expenses.[8]

The World Health Organization (WHO) classification currently recognizes low-grade and high-grade lesions based on architectural and cytological characteristics of UCa.[9] Low-grade UCa is characterized by relatively well-organized architecture, moderate nuclear atypia, and a relatively good prognosis with frequent recurrence.[10] In contrast, high-grade UCa is characterized by significant cytologic atypia, increased mitotic activity, architectural

disorganization, and a much higher likelihood of invasion of the lamina propria, muscle invasion, metastasis, and disease-specific mortality.[11]

The molecular changes associated with bladder carcinogenesis include abnormalities in the tumor suppressor gene TP53, which have been studied the most.[12] TP53 is located on the short arm of chromosome 17 at position 13.1 and encodes the p53 protein, which is a transcription factor that is essential for maintaining genomic stability through controlling DNA repair, cell-cycle arrest, apoptosis, senescence, and cellular response to genotoxic stress.[13] In physiological conditions, the wild-type p53 is short-lived and exists at low intracellular levels.[13] Mutations in TP53, however, tend to cause the buildup of an abnormal p53 protein in the nucleus, which can be identified by immunohistochemistry (IHC).[14] In various human malignancies, including UCa, aberrant expression of p53 has been linked to tumor progression, genomic instability, a higher proliferation rate, resistance to therapy, recurrence, and poor clinical prognosis.[15]

Two different molecular pathways have been proposed for the development of low-grade and high-grade urothelial carcinoma. Tumors are often low grade, occur with changes in FGFR3, HRAS, and the PI3K signaling pathway, and tend to spread in a papillary pattern where there is a high rate of recurrence but little invasive growth.[16] In contrast, high-grade UCa have more commonly been found to have mutations in TP53, disruption of the RB pathway, chromosomal instability, and multiple genetic abnormalities, leading to more aggressive biological behavior and a greater likelihood for progression.[17] p53 immunohistochemical analysis therefore has become a feasible and relatively inexpensive way of assessing molecular changes, which can be used in addition to traditional histopathological grading. The results will offer insights into the relationship between the expression of p53 and histological grade, and examine whether p53 could be used as an additional prognostic marker for UCa in the local population. Thus, the present study aimed to investigate the immunohistochemical expression of p53 in low-grade and high-grade UCa.

METHODS

An analytical cross-sectional study was carried out in the Department of Histopathology of Pak International Medical College, Peshawar. Histopathology evaluation and immunohistochemistry staining were carried out in the departmental immunohistochemistry laboratory with the supervision of consultant histopathologists. The study was carried out over a period of six months from 1st September 2025 to 28th February 2026.

The sample size was determined with OpenEpi version 3.01 using the study showing p53 overexpression in 54.5% of low-grade urothelial carcinoma and 95.3% of high-grade urothelial carcinoma.[18] Based on a 95% confidence level, 80% study power, and an equal ratio (1:1) of low-grade to high-grade, the sample size was determined to be 100 patients (50 in each grade).

A non-probability consecutive sampling technique was employed. In the present study, patients with histopathologically confirmed urothelial carcinoma of the urinary bladder diagnosed on transurethral resection of bladder tumor (TURBT) or radical cystectomy specimens were included in the study. Eligible were only newly diagnosed cases that had sufficient formalin-fixed paraffin-embedded (FFPE) tissue blocks for immunohistochemical analysis. Urinary tract tumors were low grade or high grade based on the 2022 WHO urinary tract tumor classification. The patients were excluded if they had previously received chemotherapy, radiotherapy, intravesical Bacillus Calmette-Guérin (BCG), or immunotherapy before tissue sampling. Recurrent urothelial carcinoma, non-urothelial histological variants, autolyzed or poorly preserved tissue blocks, inadequate tumor tissue for immunohistochemistry, and missing clinicopathological information were also excluded.

After obtaining approval from the Institutional Research and Ethics Committee, eligible patients were identified from the histopathology records of the Department of Histopathology. Patients' demographic and clinicopathological data (age, gender, smoking history, presenting symptoms, tumour size, tumour multiplicity, anatomical location, pathological grade, depth of invasion, lymphovascular invasion, perineural invasion and pathological stage) were collected from their medical records and histopathology reports on a structured proforma.

FFPE tissue blocks were collected from the archives of the department. New 4 μm sections were cut with a rotary microtome and adhered to poly-L-lysine-coated glass slides. The diagnosis and histological grade (WHO classification) were confirmed independently by two consultant histopathologists on hematoxylin and eosin-stained sections before immunohistochemical staining in order to ensure accuracy.

All p53 immunohistochemical staining was carried out with a commercially available monoclonal anti-p53 antibody, as per the manufacturer's optimized protocol. Higher temperatures were used to retrieve the epitopes (citrate buffer, pH 6.0) before incubation with the primary antibody. A horseradish peroxidase polymer detection system with 3,3′-diaminobenzidine (DAB) chromogen was used for visualization, and the slides were counterstained with hematoxylin. In each staining run, quality assurance was provided by the inclusion of appropriate positive and negative controls.

Tumor cells with nuclear staining were regarded as positive for p53 expression. Representative high-power fields were examined containing at least 500 tumor cells. The percentage of nuclei stained positively in tumor cells was noted, and the intensity of staining was also evaluated. Nuclear staining of ≥10% of tumor cells was considered to be a

positive result for p53 overexpression, while staining of <10% of tumor cells was considered to be a negative result.[19] The slides were independently examined by two skilled histopathologists who were blinded to the clinicopathological features of the patients. If there was any discrepancy, it was settled through a joint review to reach an agreement.

Data collected were imported into Microsoft Excel and analyzed using the IBM Statistical Package for the Social Sciences (SPSS) version 27.0. Continuous variables were presented as mean ± standard deviation or median and interquartile range as per the distribution of data. Categorical variables like gender, smoking status, tumor grade, pathological stage, lymphovascular invasion, perineural invasion, and p53 expression were described as frequencies and percentages. The relationship between p53 expression and histological grade was tested by the Chi-square test or Fisher's exact test as appropriate. Based on data normality, an independent sample t-test or Mann-Whitney U test was used to compare the continuous data among the study groups. A binary logistic regression analysis was used to assess the independent predictive ability of p53 overexpression after controlling for potentially confounding factors such as age, gender, smoking, tumor size, pathological stage, and lymphovascular invasion, for high-grade urothelial carcinoma. Crude odds ratio (OR) and 95% confidence interval (CI) were computed. All analyses used a two-tailed p-value of < 0.05 as statistically significant.

RESULTS

A total of 100 patients with histopathologically confirmed urothelial carcinoma of the urinary bladder were included in the study, with equal representation of low-grade and high-grade tumors. The majority of patients were older men who were current smokers. The most common chief complaint was hematuria, and solitary tumors occurred more commonly than multiple lesions. Most of the tumors were larger than 3cm and more than 50% of the population had p53 overexpression. These detailed demographic and clinicopathological parameters are listed in Table 1.

Patients with high-grade urothelial carcinomas tended to be older and more likely to be smokers, to have larger tumours, multiple tumors, advanced pathological stage, lymphovascular invasion, perineural invasion, and positive p53 expression than patients with low-grade tumors. A number of these clinicopathological differences were statistically significant, reflecting a more aggressive biological profile for the high-grade lesions (Table 2).

Positive p53 expression was significantly associated with adverse clinicopathological features, such as smoking, large tumor size, tumor multiplicity, high-grade tumor, muscle invasion, lymphovascular invasion, and perineural invasion. The expression of p53 did not significantly correlate with patient gender, however (Table 3).

A significant difference in p53 immunohistochemical expression was found between low-grade and high-grade urothelial carcinoma; the high-grade tumors had a markedly increased p53 positivity. This result confirms the correlation between p53 overexpression and the higher grading of tumors (Table 4).

After controlling for potential confounding factors, smoking history, tumor size larger than 3 cm, lymphovascular invasion, and p53 positivity remained independent predictors of high grade urothelial carcinoma on logistic regression analysis. Of these, the strongest independent association with high-grade disease was seen with p53 positivity (Table 5).

Table 1. Baseline demographic and clinicopathological characteristics of the study participants (n=100)

Variable	Total (n=100)
Age (years), Mean ± SD	61.8 ± 11.3
18–49 years	18 (18.0%)
50–59 years	24 (24.0%)
60–69 years	36 (36.0%)
≥70 years	22 (22.0%)
Gender	
Male	79 (79.0%)
Female	21 (21.0%)
Smoking history	
Smoker	64 (64.0%)
Non-smoker	36 (36.0%)
Presenting symptom	
Hematuria	82 (82.0%)
Dysuria	11 (11.0%)
Frequency/Urgency	7 (7.0%)
Tumor multiplicity	
Solitary	58 (58.0%)
Multiple	42 (42.0%)

Tumor location	
Lateral wall	39 (39.0%)
Posterior wall	24 (24.0%)
Trigone	18 (18.0%)
Dome	11 (11.0%)
Neck	8 (8.0%)
Tumor size (cm), Mean ± SD	3.7 ± 1.6
≤3 cm	46 (46.0%)
>3 cm	54 (54.0%)
Histological grade	
Low-grade urothelial carcinoma	50 (50.0%)
High-grade urothelial carcinoma	50 (50.0%)
Pathological stage	
Ta	31 (31.0%)
T1	42 (42.0%)
T2	20 (20.0%)
T3	7 (7.0%)
Lymphovascular invasion	
Present	27 (27.0%)
Absent	73 (73.0%)
Perineural invasion	
Present	14 (14.0%)
Absent	86 (86.0%)
p53 expression	
Positive	67 (67.0%)
Negative	33 (33.0%)

Table 2. Comparison of demographic and clinicopathological characteristics according to tumor grade

Variable	Low-grade (n=50)	High-grade (n=50)	p-value
Age (years), Mean ± SD	58.6 ± 10.4	64.9 ± 11.2	0.004
Male gender	37 (74.0%)	42 (84.0%)	0.218
Smoking history	27 (54.0%)	37 (74.0%)	0.036
Tumor size >3 cm	19 (38.0%)	35 (70.0%)	0.001
Multiple tumors	16 (32.0%)	26 (52.0%)	0.041
Muscle-invasive disease (T2–T3)	5 (10.0%)	22 (44.0%)	<0.001
Lymphovascular invasion	5 (10.0%)	22 (44.0%)	<0.001
Perineural invasion	2 (4.0%)	12 (24.0%)	0.003
p53 positive	24 (48.0%)	43 (86.0%)	<0.001

Table 3. Association of p53 expression with clinicopathological characteristics

Variable	p53 Positive (n=67)	p53 Negative (n=33)	p-value
Mean age (years)	63.4 ± 10.8	58.7 ± 11.7	0.047
Male gender	56 (83.6%)	23 (69.7%)	0.102
Smoking history	49 (73.1%)	15 (45.5%)	0.007
Tumor size >3 cm	44 (65.7%)	10 (30.3%)	0.001
Multiple tumors	35 (52.2%)	7 (21.2%)	0.003
High-grade tumor	43 (64.2%)	7 (21.2%)	<0.001
Muscle-invasive disease	24 (35.8%)	3 (9.1%)	0.005
Lymphovascular invasion	24 (35.8%)	3 (9.1%)	0.005
Perineural invasion	13 (19.4%)	1 (3.0%)	0.024

Table 4. Comparison of p53 expression between low-grade and high-grade urothelial carcinoma

Tumor Grade	p53 Positive	p53 Negative	p-value
Low-grade	24 (48.0%)	26 (52.0%)	<0.001
High-grade	43 (86.0%)	7 (14.0%)	

Total	67 (67.0%)	33 (33.0%)	

Table 5. Binary logistic regression analysis showing predictors of high-grade urothelial carcinoma

Variable	Crude OR (95% CI)	p-value	Adjusted OR (95% CI)	p-value
Age (>60 years)	2.48 (1.08–5.67)	0.031	2.19 (0.96–5.01)	0.062
Male gender	1.84 (0.67–5.03)	0.235	1.52 (0.52–4.45)	0.441
Smoking history	2.43 (1.08–5.45)	0.031	2.11 (1.01–4.87)	0.047
Tumor size >3 cm	3.81 (1.67–8.72)	0.001	3.08 (1.28–7.39)	0.012
Multiple tumors	2.30 (1.03–5.17)	0.043	1.82 (0.77–4.29)	0.172
Lymphovascular invasion	7.07 (2.39–20.88)	<0.001	4.29 (1.36–13.49)	0.013
p53 positivity	6.65 (2.49–17.77)	<0.001	5.83 (2.01–16.89)	0.001

Histopathological examination of low-grade urothelial carcinoma demonstrated delicate papillary fronds lined by urothelial cells with preserved polarity, mild nuclear atypia, and infrequent mitotic figures. In contrast, high-grade urothelial carcinoma exhibited marked nuclear pleomorphism, architectural disorganization, frequent mitotic activity, and loss of cellular polarity. Immunohistochemical analysis showed weak focal nuclear p53 staining in low-grade tumors, whereas high-grade tumors demonstrated strong diffuse nuclear immunoreactivity, supporting the higher frequency of p53 overexpression observed in aggressive lesions (Figure 1).

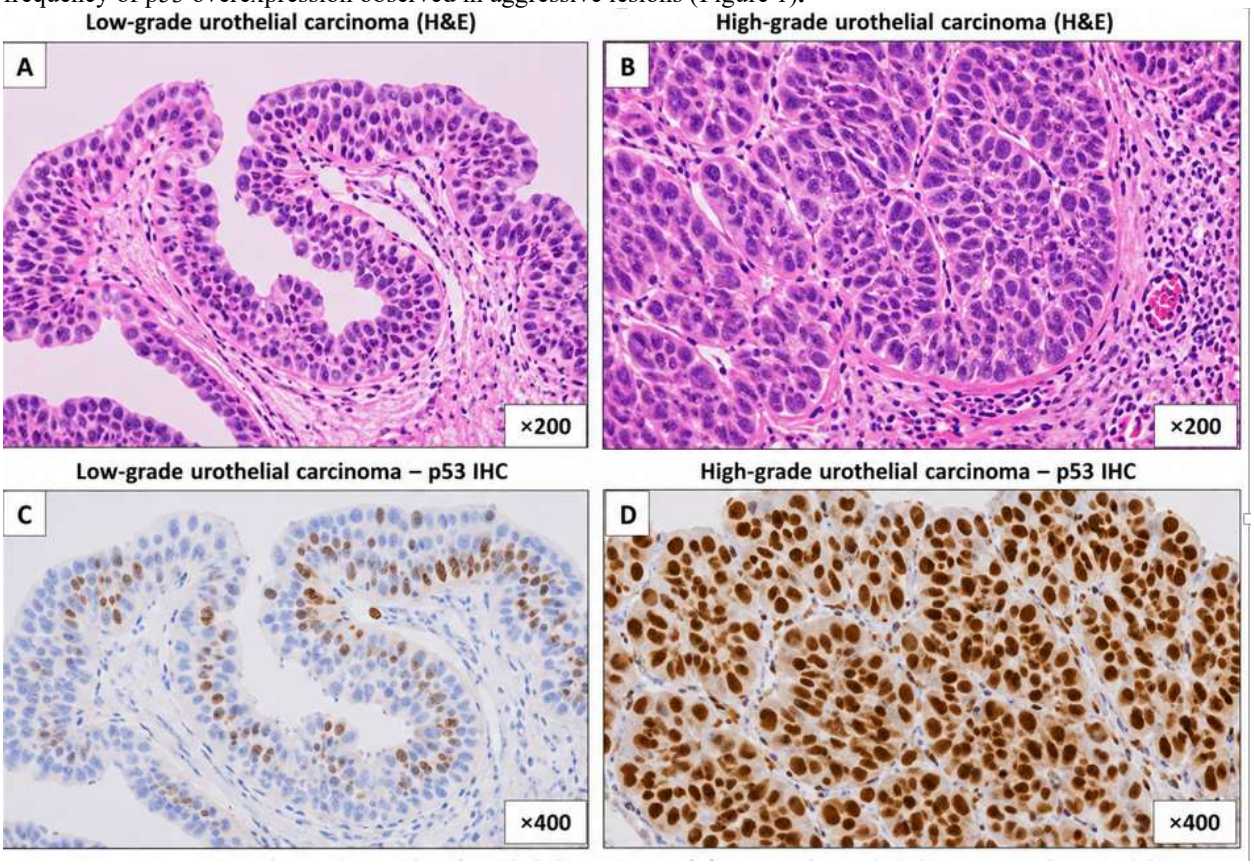

Figure 1. Representative photomicrographs of urothelial carcinoma. (A) Low-grade urothelial carcinoma showing delicate papillary fronds lined by mildly atypical urothelial cells with preserved polarity (H&E, ×200). (B) High-grade urothelial carcinoma demonstrating marked nuclear pleomorphism, architectural disorganization, frequent mitotic figures, and loss of cellular polarity (H&E, ×200). (C) Low-grade urothelial carcinoma showing weak focal nuclear immunoreactivity for p53 (IHC, DAB chromogen, ×400). (D) High-grade urothelial carcinoma demonstrating strong diffuse nuclear p53 immunoreactivity in the majority of tumor cells (IHC, DAB chromogen, ×400).

DISCUSSION

The current study showed that the presence of p53 overexpression was significantly more common in high-grade than low-grade UCa. Furthermore, there were significant correlations between p53 positivity and unfavorable clinicopathological parameters such as larger tumor size, muscle invasion, lymphovascular invasion, perineural invasion, and higher pathological stage. Multivariable logistic regression additionally established that p53

overexpression is an independent risk predictor for HUC. These results validate the ongoing importance of TP53 alterations in bladder carcinogenesis and tumor progression.

Our patient population was similar to the known bladder cancer epidemiology. Most patients were elderly males (mean age 61.8 years), and smoking was the most common risk factor. Alouini S. (2024) also noted in their study that older men were mostly affected by UCa and that smoking was one of the main etiological factors.[20] Similarly, Kumar et al. (2023) reported a higher proportion of men in the group of patients with UCa, due to the increased exposure of males to occupational carcinogens and smoking.[21] The similarities suggest that the demographic profile of our study population is similar to that reported internationally.

The most significant result of the present study was the much higher percentage of high-grade urothelial carcinoma showing p53 overexpression (86% vs. 48% of low-grade). This was very similar to the results obtained by Khurshid et al. (2023), who found that 95.3% of the high-grade tumors were p53 positive while 54.5% of low-grade tumors were p53 positive and concluded that there was a strong association between p53 overexpression and increasing histological grade.[22] The results were similar to our study, albeit with a slightly lower percentage of p53-positive tumors. Minor differences may be due to variations in antibody clones, immunohistochemical protocols, scoring criteria, and sample size.

Our results are also corroborated by those of Angel. (2023), who compared levels of p53 and CK20 expression in patients with UCa, and p53 showed significantly higher immunoreactivity in high-grade lesions than in low-grade lesions. They found that p53 immunohistochemistry would enhance the diagnosis, especially in situations where diagnosis was difficult solely based on morphology. The agreement between their findings and ours strengthens the evidence that p53 is an important adjunct biomarker for distinguishing aggressive urothelial tumors.[23]

In addition to histological grade, p53 overexpression in our study was significantly linked with larger tumor size, muscle invasion, presence of lymphovascular invasion and perineural invasion, suggesting that p53 overexpression is associated with increasing tumor aggressiveness. Asgari et al. (2023) showed similar results, with overexpression of p53 being significantly linked to unfavorable pathological features in UCa. They also found that their cells' combined analysis of p53, CK20, and FGFR3 allowed them to better characterize biologically aggressive tumors and to help predict the behavior of the disease.[24]

After adjusting for potential confounding variables, p53 positivity proved one of the strongest independent predictors of HUC in our logistic regression analysis. The results of the findings are biologically plausible, as TP53 mutation leads to DNA repair failure, failure to undergo apoptosis, chromosomal instability, and uncontrolled proliferation, which could contribute to tumour progression and dedifferentiation. In a similar study, Khurshid et al. (2023) proposed that an evaluation of p53 overexpression along with histological grade and pathological stage better predicts the biological behavior of UCa than morphological assessment alone.[22]

High-grade urothelial carcinoma was also identified as an independent predictor of smoking in the present study. This is backed up by previous data showing that tobacco carcinogens cause DNA damage and raise the frequency of TP53 mutations, thus promoting malignant transformation. The authors also reported that the majority of patients with UCa had known risk factors, again supporting the idea that chronic carcinogen exposure is important in the molecular mechanisms of bladder cancer.[25]

The present study's overall results are well in line with the present evidence that p53 gene overexpression in UCs is significantly associated with the rise of histological grade and the presence of aggressive clinicopathologic parameters. Our results are in good agreement with the studies conducted by Khurshid et al. (2023), and Asgari et al. (2023), which provide further validation of the clinical application of p53 immunohistochemical staining as a supplementary tool for risk classification.[18, 24] The addition of p53 to routine histopathological assessment may enhance the identification of patients at increased risk for disease progression and help implement more tailored treatment and surveillance approaches, especially in resource-limited environments where more advanced molecular testing is not routinely available.

There were a few limitations to this research. First, it is a single-center study with a relatively small number of patients, and the results may not be applicable to the general population. Second, because of the cross-sectional design, long-term clinical outcomes, such as recurrence, progression, disease-free and overall survival, were not assessed. Third, p53 expression was assessed only by immunohistochemistry, and molecular confirmation of TP53 gene mutations was not performed and may not always be associated with p53 protein overexpression. Interobserver variation of immunohistochemical interpretation was minimized by independent review by two histopathologists, but cannot be excluded. Finally, other molecular biomarkers like Ki-67, CK20, FGFR3 and RB1 were not assessed, so their combined prognostic value cannot be determined.

CONCLUSION

The p53 overexpression was significantly more common in high grade than in low-grade UCa of the urinary bladder, and associated with adverse clinic-pathological parameters such as larger tumor size, more advanced pathological stage, having invaded the muscle, presence of lymphovascular invasion, and presence of perineural invasion. In

addition, p53 expression proved to be an independent predictor of high grade UCa on multivariable analysis. The results indicate that p53 IHC could be a useful companion to a standard histological analysis and help risk stratify and predict outcome in UCa patients. The adoption of p53 expression into routine pathological reporting could help the more personalized clinical management of patients, especially in resource-limited areas.

REFERENCES

1. Lenis, A.T., et al., *Bladder cancer: a review.* Jama, 2020. **324**(19): p. 1980-1991.
2. Saginala, K., et al., *Epidemiology of bladder cancer.* Medical Sciences, 2020. **8**(1): p. 15.
3. Amawi, H. et al., *Revisiting strategies to target ABC transporter-mediated drug resistance in CNS cancer.* Cancer Biology & Medicine, 2025. **22**(10): p. 1158-1180.
4. Aljehani, M.R., et al., *The importance of histopathological evaluation in cancer diagnosis and treatment.* International journal of health sciences, 2023. **7**(S1): p. 3614-3623.
5. Ciesielski, A., *Global Patterns of Bladder Cancer Incidence, Mortality, Survival, and Risk Factors: A Comprehensive Epidemiological Analysis.* Mortality, Survival, and Risk Factors: A Comprehensive Epidemiological Analysis (July 03, 2026), 2026.
6. van Hoogstraten, L.M., et al., *Global trends in the epidemiology of bladder cancer: challenges for public health and clinical practice.* Nature reviews Clinical oncology, 2023. **20**(5): p. 287-304.
7. Yashaswini, C., et al., *Epidemiology and risk factors of bladder cancer*, in *Bladder Cancer Breakthroughs*. 2026, Elsevier. p. 1-12.
8. Inayat, M., et al., *Late-Stage Burden and Histopathology of Bladder Cancer in Pakistan: A Retrospective Cohort Study.* Pakistan Journal of Medical & Cardiological Review, 2025. **4**(3): p. 2139-2147.
9. Downes, M.R., et al., *Grading of bladder cancer: updates, controversies and practical solutions.* Histopathology, 2026. **88**(1): p. 86-107.
10. Deshpande, G., S. Menon, and S. Desai, *Pathology and Staging*, in *A Guide to Management of Urological Cancers*. 2023, Springer. p. 125-140.
11. Amin, M.B., et al., *The genitourinary pathology society update on classification and grading of flat and papillary urothelial neoplasia with new reporting recommendations and approach to lesions with mixed and early patterns of neoplasia.* Advances in anatomic pathology, 2021. **28**(4): p. 179-195.
12. Khan, R., B. Pari, and K. Puszynski, *Comprehensive bioinformatic investigation of TP53 dysregulation in diverse cancer landscapes.* Genes, 2024. **15**(5): p. 577.
13. Foroutan, B., *A narrative review of the TP53 and its product the p53 protein.* OBM Genetics, 2023. **7**(3): p. 1-71.
14. Sung, Y.-N., D. Kim, and J. Kim, *p53 immunostaining pattern is a useful surrogate marker for TP53 gene mutations.* Diagnostic Pathology, 2022. **17**(1): p. 92.
15. Chan, T.-C., Y.-L. Shiue, and C.-F. Li, *The biological impacts of CEBPD on urothelial carcinoma development and progression.* Frontiers in oncology, 2023. **13**: p. 1123776.
16. Gahlot, G.P.S., et al., *To evaluate the usefulness of FGFR3, HRAS, KRAS, NRAS, p53, and PIK3CA mutations in urothelial carcinoma cases: A pilot study.* Medical Journal Armed Forces India, 2026.
17. Sriramadasu, K., et al., *Molecular evolution of driver mutations in cancer with microsatellite instability and their impact on tumor progression: Implications for precision medicine in patients with UCEC.* Computers in Biology and Medicine, 2025. **192**: p. 110275.
18. Khurshid, S., et al., *Immunohistochemical expression of p53 in low-grade and high-grade papillary urothelial carcinoma of the bladder.* International Journal of Pathology, 2023: p. 70-70.
19. Han, S.-H., et al., *Expression of HLA class I is associated with immune cell infiltration and patient outcome in breast cancer.* Scientific Reports, 2022. **12**(1): p. 20367.
20. Alouini, S., *Risk factors associated with urothelial bladder cancer.* International Journal of Environmental Research and Public Health, 2024. **21**(7): p. 954.
21. Kumar, R., et al., *Impact of smoking on urologic cancers: a snapshot of current evidence.* World journal of urology, 2023. **41**(6): p. 1473-1479.
22. Khurshid, S., *Immunohistochemical Expression of P53 In Low-Grade and High-Grade Papillary Urothelial Carcinoma of the Bladder.* International Journal of Pathology, 2023: p. 70.
23. Angel, E., *Diagnostic significance of cytokeratin 20 and p53 as adjunct immunocytological markers in urine cytology to detect urothelial carcinomas: a systematic review study.* Iranian Journal of Pathology, 2023. **18**(3): p. 257.
24. Asgari, M., et al., *The association of p53, ck29, and fgfr3 overexpression with the characteristics of urothelial cell carcinoma of the bladder.* Asian Pacific journal of cancer prevention: APJCP, 2023. **24**(9): p. 3125.
25. Chen, X., et al., *Mutant p53 in cancer: from molecular mechanism to therapeutic modulation.* Cell death & disease, 2022. **13**(11): p. 974.