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P53 Over Expression in Bladder Carcinoma

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Author`s Contribution

[1,2,5]Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work, [2]Drafting the work or revising it critically for important intellectual content, [3,4]Final approval of the version to be published, [6]Active participation in active methodology, Literature review

Funding Source: None
Conflict of Interest: None

Received: Feb 10, 2022
Accepted: Aug 26, 2022

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ABSTRACT

Objective: The purpose of this research was to find out how prevalent p53 overexpression is in bladder urothelial cancer.

Methodology: This descriptive, cross-sectional study was conducted in KRL Hospital Islamabad from April 2018 to October 2018. All patients with biopsy-proven urinary bladder cancer, irrespective of gender or age range, were included in the research. Non-probability, consecutive sampling technique was used. The immunohistochemical processing was completed, and the results for p53 expression (positive/negative) were interpreted by the consultant pathologist. SPSS version 22.0 was used for the statistical analysis. Quantitative information, such as the patient's age and length of illness, were displayed using the mean and standard deviation. The P value was less than 0.05, the result was declared significant.

Results: The participants in this study ranged in age from 15 to 70 years old, with a mean age of 47.39 ± 10.26 years. The male to female ratio was 1.6:1 among these 74 patients, with 45 (60.81 percent) being male and 29 (39.19 percent) being female. Overexpression of p53 was found in 31 (41.89 percent) of bladder urothelial carcinoma cases.

Conclusion: This study concluded that the frequency of p53 overexpression in bladder urothelial carcinoma is very high.

Keywords: Urothelial carcinoma, immunohistochemistry, P53 overexpression.

Cite this article as: Afshan S, Zaib L, Sharif S, Faridi J, Habib F, Akbar A. P53 Over Expression in Bladder Carcinoma. Ann Pak Inst Med Sci. 2022; 18(3):261-265. doi. 10.48036/apims.v18i3.596

Introduction

A mutant p53 gene is a frequent genetic defect in bladder urothelial cancer. The p53 gene, when mutated, encodes a metabolically stable protein with a lengthy half-life. It accumulates in large amounts in tumor nuclei and may be identified using standard immunohistochemical procedures. Bladder carcinoma is one of the most frequent malignancies, ranking fourth among males and ninth among females.[1] In 2020, the US is expected to have 1,806,590 new cancer cases and 606,520 deaths from the illness.[2]

Increases in the frequency and lethality of recurrence and mortality, as well as the tumor's development to an invasive stage, are two of the most prevalent UC features.[3] A superficial tumour (stages Ta and CIS) or lamina propria tumour (stages Ta and CIS) is seen in UC patients (T1).[4] More than half of these tumours will recur, and the histological grade or invasion depth will rise in 15% to 20% of patients.[5] Urothelial carcinomas might have diverse clinical outcomes, despite the fact that grade and stage are two of the most significant prognostic variables. The development and clinical prognosis of urothelial carcinoma may be influenced by several genetic processes as a consequence.

There has been an increasing interest in the role of cell cycle proteins, and p53 has been shown to be a common target for mutation in cancer. A number of stresses, including DNA damage, hypoxia, metabolic stress, and oncogene activation, activate the tumour suppressor p53, which plays a crucial role in the stress responses necessary to preserve genomic integrity and prevent tumours. p53's most well-known role is as a transcription factor, which has been extensively researched. Proliferation-inhibiting p53 regulates the expression of genes that control the principal defence mechanisms against tumour

development, including cell cycle arrest and apoptosis, genetic integrity maintenance, as well as angiogenesis suppression and cellular necrosis.[6] Many other cellular proteins, such as those involved in programmed cell death regulation, interact with p53, and these molecular interactions may contribute to p53's tumor-inhibiting activity.[8]

Bladder urothelial carcinoma often has a mutant p53 gene. Mutations in the p53 gene result in a metabolically stable and long-lived protein. It may be identified using traditional immunohistochemical procedures because it accumulates in large amounts in tumour nuclei.[9]

More than one study has shown that overexpression of the p53 gene product is an indicator of progression in urothelial carcinomas at more advanced stages and grades.[10,11] According to a research, 26.0 % of patients tested positive for p53 immunostain.

P53 expression is a strong prognostic marker and predictive tool in the treatment of urinary bladder carcinoma. Previous studies have yielded conflicting results regarding its overexpression in urinary bladder cancer. Our research aims to determine the frequency of p53 over expressions in urothelial carcinoma in the local population.

Methodology

This descriptive, cross-sectional study was conducted at KRL Hospital Islamabad from April 2018 to October 2018. Sample size was 74 by using WHO calculator and taking confidence level as 95%, margin of error as 5% and percentage of overexpression of p53 in urinary bladder cancer as 26.0%.[7] Non-probability, consecutive sampling technique was used.

Our research included all patients with biopsy-proven urinary bladder cancer, ages 15 to 70, of both genders. All patients with benign histology findings, those who had had radiation (as it will impact the expression of p53), and those who had received immunotherapy (as it will affect the expression of p53) were excluded from our research.

A total of 74 biopsy-proven urinary bladder cancer specimens meeting the inclusion criteria were chosen after the approval of the ethics committee. Each patient was given a copy of their informed written permission. After this, the immunohistochemical processing was done, and the results were interpreted by the consultant pathologist (at least 5 years of post-fellowship teaching experience) for p53 expression (positive/negative) as recorded on a pre-designed performance.

SPSS version 22.0 was used for the statistical analysis. The mean and standard deviation were used to display quantitative data, such as the patient's age and the length of time they had been ill. It was reported as a frequency and percentage for qualitative characteristics such as gender, stage of urinary bladder cancer (I/II/III/IV) and expression of p53 (positive / negative). The P value was less than 0.05, the result was declared significant.

Results

Seventy four patients with urothelial carcinoma were included in the study. The age range in this study was from 15 to 70 years, with a mean age of 47.39 ± 10.26 years as shown in Table I.

Table I: Age distribution for both groups (n=74).

Age (in years)	No. of Patients	%age
15-40	17	22.97
41-70	57	77.03
Total	74	100

Among 74 patients, 45 (60.81%) were male and 29 (39.19%) were female. The mean duration of the disease was 5.50 ± 1.06 months, as shown in Table II. The distribution of patients according to stage of carcinoma is shown in Figure I. Most of the patients recruited in our study suffered from stage II (36.49%) or stage IV (27.03%). The frequency of overexpression of p53 in urothelial carcinoma of the bladder was seen in 31 (41.89%) of cases, as shown in Figure II.

Table II: Distribution of patients according to duration of disease.

Duration of disease (months)	**Total (n=74)**	
	No. of patients	%age
≤6 months	58	78.38
>6 months	16	21.62
Mean ± SD	**5.50 ± 1.06 months**	

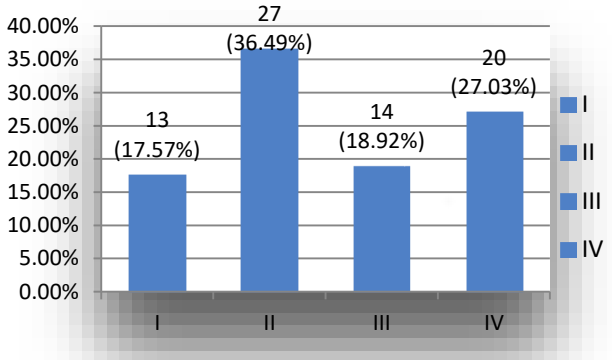

Figure I: Distribution of patients according to stage of carcinoma (n=74)

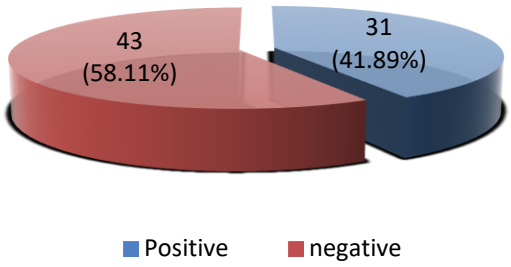

Figure II: Frequency of overexpression of p53 in urothelial carcinoma of bladder (n=74).

Stratification of overexpression of p53 with respect to age groups, gender, duration of disease, & stages of carcinoma is shown in Table III. Among the two age groups, patient within 41-70 years had more expression of p53 when compared to those within 15-40 years of age. (P-value 0.530) Positive results among male and female didn't show any significance difference. (P-value 0.169) Among these patients, those who had carcinoma for <6 months had lower frequency of the p53 mutation (39 out of 58) while those who had carcinoma for >6 months had a higher frequency of the p53 mutation (12 out of 16). In this study, overexpression of p53 had no significance difference among different stages of urothelial carcinoma. P53 overexpression was found in 9.45% of stage I patients, 13.51% of stage II patients, 8.10% of stage III patients, and 10.81% of stage IV patients.

Table III: Stratification of overexpression of p53 with respect to age groups, gender, duration of disease & the stages of carcinoma.

	Overexpression of p53		p-value
Age (years)	Positive	Negative	
15-40	06 (8.10%)	11 (14.86%)	**0.530**
41-70	25 (33.7%)	32 (43.2%)	
Gender			
Male	16 (21.62%)	29 (39.18%)	**0.169**
Female	15 (20.27%)	14 (18.91%)	
Duration of disease (months)			
≤6	19 (25.67%)	39 (52.70%)	**0.002**
>6	12 (16.21%)	04 (5.40%)	
Stage of carcinoma			
I	07 (9.45%)	06 (8.10%)	**0.787**
II	10 (13.51%)	17 (22.97%)	
III	06 (8.10%)	08 (10.81%)	
IV	08 (10.81%)	12 (16.21%)	

Discussion

One of the most prevalent tumors in people in third-world countries, bladder cancer constantly poses a risk of recurrence and disease development. Lack of risk factor education and late presentation in tertiary care hospitals are two variables that may contribute to high morbidity and mortality rates.[12] To determine prognosis in urothelial malignancy, numerous distinct molecular, serological, and immunohistochemical markers are being investigated.[13] Staging and grading, which are traditional characteristics, are insufficient to identify high risk individuals. Recent developments in molecular diagnostics can enhance patient risk categorization and enhance clinical outcomes.[14]

Tumor suppressor gene TP53, widely known as "the custodian of the genome," is frequently altered in cancer patients. Reduced DNA repair and higher genomic instability have been linked to the deactivation of TP53.[15] An aggressive phenotype, tumour development, and metastasis are all related with TP53 inactivation, which may be a helpful genetic biomarker for predicting the progression of bladder cancer and, therefore, a poor prognosis.[16]

Stadler et al. indicated TP53 protein accumulation in nuclei of tumor cells and showed a positive correlation between gene mutation, stage and grade. In this study, the researchers discovered that 64.3% of the bladder cancer patients had nuclear p53 staining that was positive.[17] This is consistent with the research of Bazrafshani and Sidransky, who discovered 60% and 61% of the p53 protein to be mutated, respectively.[18] However, in the current study 48.19% of patients with urothelial bladder cancer were positive for p53 staining and 58.11% had negative p53 staining.

According to a multicenter study done in Poland on 1,360 patients in the years 2012–2013, 39.2% of patients were in stage pTis, 37.9% were in T1, and 21.8% were in stage T2. 8.6% of the patients in this investigation had non-invasive tumors (Tis), 41.4% had muscle invasion (pT1), 41.4% had lamina propria invasion (pT2), 7.1% had microscopic perivesical tissue invasion (pT3a), and 1.4% had macroscopic perivesical tissue invasion (pT3b).[19]

In 2016, a study by Qamar et al showed that 87% of the 70 patients were men and 13% were women. 16% of the 25 low grade lesions and 91% of the 45 high grade lesions had p53 positive patients. Tis positivity was 33% (2/6 instances), T1 positivity was 55% (16/29 cases), T2 positivity was 72% (21/29), and T3a and T3b positive were both 100%. 5.4% of low-grade and 94.6% of high-grade tumors were found to have strong p53 staining. In general, higher grade and stage urothelial carcinomas exhibited stronger and more frequent p53 expression. It can be

utilized as a prognostic indicator to foretell bladder cancer with a more advanced grade and stage.[20]

In contrast, there was no discernible difference in overexpression of p53 between the various stages of urothelial cancer in the current study. P53 overexpression was present in 9.45% of stage I patients, 13.51% of stage II patients, 8.10% of stage III patients, and 10.81% of stage IV patients.

According to Laishram et al, the ratio of men to women was 6:1[21] whereas in the current study prevalence showed no significant difference among gender. In the same study, the median age was found to be 60 years, and the seventh decade saw the highest frequency of tumors.[21] Similarly, in the current study, those between the ages of 41 - 70 exhibited higher levels of p53 expression than patients between the ages of 15-40.

Conclusion

The immunohistochemistry expression of p53 increases and intensifies with increasing grade and stage of urothelial carcinoma. The study's findings support the use of p53 as a predictive marker for bladder cancer. Therefore, the use of p53 immunostaining in urothelial bladder cancer can help in the early and timely management of high risk patients and can help reduce morbidity and mortality.

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