Mutation Of *p53* And Its Clinical Significance In Muscle-Invasive Bladder Tumor

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Research

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Abstract

Background: Previous studies have shown that *p53* gene is expressed in muscle invasive bladder cancer (MIBC) , but the relationship between *p53* gene and prognosis of muscle invasive bladder tumor is controversial.

Methods: Download *p53* gene expression profiles and clinical data of 412 cases bladder cancer from the Cancer Genome Atlas (TCGA) database on c-BioPortal website, and analyze their relationship. Carrying on mutation and survival analysis with c-BioPortal tools.

Results: Among 412 cases, 207 cases had mutations, including 161 cases missense mutations and 68 cases truncation mutations. Among them, 22 cases had both missense and truncation mutations, and 1 case had frameshift mutation, with high incidence of mutations. Expression of *p53* was negatively correlated with TNM stage, distant metastasis, lymph node metastasis and clinical stage for studying objects ($P < 0.05$) , and positively correlated with lymphatic infiltration and pathological stage ($P < 0.05$) . There was no correlation between *p53* expression and mutation ($P > 0.05$) . There was no significant difference between expression and mutation of *p53* and total survival and disease-free survival of bladder cancer patients ($P > 0.05$) . Cox multivariate analysis of *p53* expression and prognosis of bladder cancer indicated, lymph node metastasis and infiltration of bladder cancer, distant metastasis of bladder cancer was independent adverse factors of bladder cancer prognosis ($P < 0.05$) , and *p53* expression and mutation in bladder cancer was not independent factors affecting prognosis of bladder cancer.

Conclusion: Although *p53* has a high mutation rate in myometrial invasive bladder cancer, there is no clear difference in survival and disease-free survival period, and it can not be considered that *p53* mutation can affect the prognosis of myometrial invasive bladder cancer.

Background

Bladder cancer (BCa) is the 8th most common cancer and ranks 13th in terms of cancer mortality worldwide¹. About 45,000 men and 17,000 women in the United States suffer from bladder cancer each year, thus deducing that more patients are diagnosed with bladder cancer every year in the world. Bladder cancer can be divided into non muscle invasive bladder cancer (NMIBC) and muscle invasive bladder cancer (MIBC) according to the depth of tumor invasion. About a quarter of patients are diagnosed as muscle invasive bladder cancer². Perhaps for this reason, although the incidence of bladder cancer is increasing year by year, bladder tumor literature mainly studies non-muscular-invasive bladder cancer, while muscular-invasive bladder cancer is rarely studied. MIBC is considered a life-threatening disease, and it has a high degree of malignancy, easy to relapse and distant metastasis, and has a poor prognosis. Without any treatment, the 2-year mortality rate is about 85%. There are some theories about the underlying pathogenesis and mechanisms of MIBC³⁻⁵. Some scholars have proposed that bladder cancer is closely related to gene mutations⁶⁻⁸. In view of the low survival rate of MIBC⁹, it is urgent to find

markers to study the mechanism of MIBC occurrence and development, so as to improve the survival rate of patients with MIBC.

Among the genes involved in urothelial tumors, *p53* mutation is one of the most common genetic events¹⁰. *P53* is a well-characterized tumor suppressor gene, encoded by the *p53* gene located on chromosome 17p13.1. Mutations in the *p53* gene are thought to be associated with tumor progression and prognosis¹¹. In this study, we selected research data from the American Cancer Gene Atlas (TCGA) database, which provides a large sample size and complete clinical data, which can make our study more convincing.

Materials And Methods

Collection Of Data Materials

We used the website (<http://www.cBioPortal.org/>) to obtain the 412 bladder cancer research data we needed, which were provided by the TCGA database¹². The data we selected included the clinical data of bladder cancer and the RNASeq V2 data of *p53* gene. We used these data to analyze the expression and mutation of *p53* gene in bladder cancer, and combined the clinical data to analyze the prognosis of bladder cancer patients.

Data Set Screening And Clinical Parameter Data Research

Integrate the information of the screened data set into excel table, delete missing data and incomplete data, rank them from high to low according to *p53* expression value, take the median as the cut-off point, divide them into low expression group 206 cases, high expression group 201 cases, and analyze the correlation between *p53* expression and clinical.

Prognostic Value Of *p53* In Patients With Invasive Bladder Cancer

IBM SPSS Statistics V25.0 software was used to process the data. The measurement data is expressed by $\bar{x} \pm s$. T test was used to compare the measurement data. The count data were expressed by rate (%), and the comparison was made by chi square test. The statistical significance was indicated by $P < 0.05$. Spearman correlation analysis was used to analyze the correlation between *p53* gene expression and clinical stage, pathological grade, myometrial invasion, lymph node metastasis, lymph node invasion, metastasis, TNM stage (according to the American Joint Committee on Cancer), and mutation. Cox model was used to analyze the statistically significant indexes.

Results

The Mutation Of *P53* Gene In This Study

Among the 412 bladder cancer samples, 207 cases (50%) had *p53* gene mutation. Among 207 cases of *p53* gene mutation, 161 cases (77.8%) were missense mutation, 68 cases (32.9%) had truncated mutation, 22 cases had both missense mutation and truncated mutation, and 1 case had a frame shift mutation. The results are shown in Fig. 1.

Correlation Of *P53* Expression With Clinical Data And Pathological Indexes

The expression of *p53* was negatively correlated with TNM stage, distant metastasis, lymph node metastasis and clinical stage in Spearman correlation analysis ($P < 0.05$), but positively correlated with lymphatic invasion and pathological grade ($P < 0.05$). There was no correlation between *p53* expression and mutation. T test showed that the expression of *p53* was different between low grade (2510.44 ± 960.50) and high grade (1669.41 ± 968.28) ($P < 0.05$), but there was no difference in the expression of *p53* in other TNM stages, clinical stages and mutated *p53* ($P > 0.05$). According to the high and low expression group of *p53* expression, chi square test was performed. The detailed data are shown in Table 1.

Table 1

Correlation analysis of *p53* gene expression with clinical and pathological parameters of bladder cancer [n (%)]. (Note: There are less than 412 cases of T stage and pathological grade in the table, because some cases have partial data missing. For example, the tumor metastasis data of a certain patient is missing, but the staging data is complete. Therefore, the total number of cases with T stage and pathological grade is different, and there are less than 412 cases with some indicators) .

	Classification index	Low expression group	High expression group	P value
Age	≤ 60 (n = 107)	52 (48.6)	55 (51.4)	0.00
	> 60 (n = 300)	151 (50.3)	149 (49.7)	
Gender type	male (n = 300)	114 (38.0)	156 (52.0)	0.248
	female (n = 107)	59 (55.1)	48 (44.6)	
Tumor	T0 (n = 0)	0	0	0.074
	T1 (n = 4)	1 (25.0)	3 (75.0)	
	T2 (n = 119)	50 (42.0)	69 (58.0)	
	T3 (n = 193)	104 (53.9)	89 (46.1)	
	T4 (n = 83)	59 (71.9)	24 (28.9)	
	TX (n = 1)	0	1	
Lymph node	N0 (n = 237)	107 (45.1)	130 (54.9)	0.088
	N1 (n = 45)	25 (55.6)	20 (44.6)	
	N2 (n = 75)	47 (62.7)	28 (37.3)	
	N3 (n = 8)	3 (37.5)	5 (62.5)	
	NX (n = 36)	18 (50.0)	18 (50.0)	
Lymph node infiltration	yes (n = 151)	91 (60.3)	60 (39.7)	0.000
	no (n = 129)	50 (38.8)	79 (61.2)	
Metastasis	M0 (n = 195)	83 (42.6)	112 (57.4)	0.001
	M1 (n = 11)	2 (18.2)	9 (81.8)	
	MX (n = 198)	116 (58.6)	82 (41.4)	
Staging	I (n = 2)+	I (50.0) +	1 (50.0) +	0.017
	II (n = 130)	52 (40.0)	78 (60.0)	
	III (n = 140)	73 (52.1)	67 (47.9)	

	Classification index	Low expression group	High expression group	P value
	IV (n = 133)	76 (57.1)	57 (42.9)	
Grading	high (n = 383)	199 (50.9)	184 (48.0)	0.010
	low (n = 21)	3 (14.3)	18 (85.7)	
Mutation	yes (n = 193)	94 (48.7)	99 (51.3)	0.726
	no (n = 214)	109 (50.9)	105 (49.1)	
Myometrial infiltration	yes (n = 408)	201 (49.3)	207 (50.7)	/
	no	0	0	
<i>P53</i> Expression And Prognosis Of Bladder Cancer				

There was no significant difference between the expression of *p53* and the overall survival and disease-free survival of patients with bladder cancer by Kaplan Meier test ($P > 0.05$), suggesting that the expression of *p53* may not be related to the prognosis of bladder cancer. This analysis result is consistent with that of c-BioPortal tools, as shown in Fig. 2.

Cox Multivariate Analysis Of The Relationship Between *P53* Gene Expression And Prognosis Of Bladder Cancer Patients

The results showed that lymph node metastasis, lymph node invasion and distant metastasis were the independent adverse factors affecting the prognosis of bladder cancer ($P < 0.05$), while the expression and mutation of *p53* gene in bladder cancer were not independent factors affecting the prognosis of bladder cancer.

Discussion

Most bladder cancer comes from urothelial cells. About 75% of the patients are non muscle invasive bladder cancer (NMIBC), and 25% of the patients are muscle invasive bladder cancer (MIBC). With the development of medical technology, the treatment and survival prognosis of bladder cancer patients have not changed. The human *p53* gene is composed of 11 exons and 10 introns, which is located in the 31 band 17 p13.1 of the short arm 1 region of chromosome 17. The full length of its cDNA is 2074 BP. It has a single open reading frame. The first exon does not encode. There is a promoter P1 at the upstream 400 BP and a promoter P2 at the downstream 1 KB. The two exons encode 5, respectively These domains are highly conserved in evolution. *P53* gene can be divided into wild type and mutant type. For mutant *p53*, there are deletion mutation, point mutation, frameshift mutation and gene rearrangement. However, wild-

type *p53* is a normal gene and its half-life is very short, so it is difficult to detect it by immunohistochemistry. The spatial conformation of the mutant *p53* protein was changed, the half-life was prolonged, and it was easy to be detected by immunohistochemistry.

P53 can be used as a powerful transcription factor in cells. When DNA damage occurs, *p53* can be activated by different signal pathways and remain stable. It can enhance the transcription of downstream genes and cause cell cycle arrest, apoptosis or senescence, so as to maintain the integrity of cell genome and remove damaged cells. These biological effects depend on different stress signals and cell types.

It has been reported that *p53* plays a role in many cancers such as cholangiocarcinoma, liver cancer and gastric cancer. However, there are few studies on the prognosis of muscle invasive bladder cancer based on large sample data. In this study, about half of the samples had *p53* gene mutations, missense mutations and truncated mutations. A small number of samples had missense mutations and truncated mutations at the same time, and the mutation rate was high. The expression of *p53* was negatively correlated with TNM stage, distant metastasis, lymph node metastasis and clinical stage ($P < 0.05$), but positively correlated with lymphatic invasion and pathological grade ($P < 0.05$), but not with mutation ($P > 0.05$). Survival analysis showed that *p53* gene mutation had no effect on disease-free survival and overall survival of bladder cancer patients ($P > 0.05$). The above results are similar to those of P. gontro and other scholars. Our study agreed that *p53* mutation has little effect on predicting the recurrence of early bladder cancer. However, more research results are not consistent with the results of this study, such as thorstenh et al. They believe that *p53* mutation can be used as a prognostic indicator of bladder cancer, which is inconsistent with the results of this study. The reason for this difference may be that most of the samples in this study have muscle layer infiltration, and the clinical stage of the patients is mainly in the late stage. The difference of samples leads to the inconsistency of results. And the related mechanism is worthy of our in-depth study.

P53 is a classic tumor suppressor gene. In many kinds of cancer research, it has been shown that *p53* gene is related to the prognosis of patients. In the study of bladder cancer, its correlation is controversial. J. G. Lorenzo Romero and his team studied 115 patients with bladder cancer. Their results showed that *p53* gene mutation can be used as a prognostic and therapeutic decision-making factor. In this study, the survival analysis of patients with *p53* mutation and patients without *p53* mutation showed that there was no difference in overall survival and disease-free survival ($P > 0.05$). So far, there is no sufficient evidence that *p53* can be used as an independent prognostic factor for bladder cancer. In this study, multivariate Cox analysis showed that lymph node metastasis and invasion and distant metastasis were independent adverse factors affecting the prognosis of bladder cancer ($P < 0.05$), which was consistent with the results of many literatures.

Conclusions

In this study, despite the high mutation rate of *p53* in muscle invasive bladder cancer, there is no clear correlation between *p53* gene and patient survival and disease-free survival. It is not considered that *p53*

mutation can affect the prognosis of muscle invasive bladder cancer.

Declarations

Consent for publication - I am the first author and corresponding author of this article and agree to publish it in BioData Mining.

Availability of data and material - The original data of this paper can be obtained by the corresponding author. The database materials in this paper are correctly referenced without any modification or editing. See the link: <https://www.cbiportal.org/>. The data that support the findings of this study are available from the corresponding author but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of the corresponding author.

Competing interests - The author declares that there is no competitive interest in this article.

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Figures

Figure 1

Mutation types of p53 gene in bladder cancer.

Figure 2

Relationship between p53 gene mutation and survival of bladder cancer patients. (A) Comparison of overall survival between patients with p53 mutation and those without p53 mutation. (B) Comparison of disease-free survival between patients with p53 mutation and those without p53 mutation.