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Research Article

The relationship between *TP53* Gene Mutation with Treatment Results in High-Grade Gliomas

Relación entre la mutación TP53 con los resultados del tratamiento en glioma de alto grado

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ABSTRACT

Introduction: Determining the relationship between TP53 gene mutation and treatment outcome in high-grade gliomas patients has great significance for disease prognosis and treatment outcome monitoring.

Ojectives: To determine the relationship between TP53 gene mutation rate and some characteristics of treatment outcome in high-grade gliomas patients.

Methods: The study was conducted by descriptive method, on 52 high-grade gliomas patients at Vietnam National Cancer Hospital, from January 2019 to December 2020. Based on statistics of clinical


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symptoms, paraclinical tests and post-operative monitoring results, it was evaluated the relationship between TP53 gene mutation in study patients with response to treatment and patient's survival time.

Results: There was a relationship between TP53 gene mutation and response to treatment according to Response Evaluation Criteria In Solid Tumors (p= 0.004). Progression-free survival was higher in the group with the TP53 mutation than in the group without the TP53 mutation (χ^2= 6.7; p= 0.010). The overall survival in the group with the TP53 mutation was higher than the overall survival in the group without the TP53 mutation (χ^2= 2.6; p= 0.107).

Conclusion: There is a relationship between the occurrence of TP53 gene mutations with treatment response criteria and progression-free survival in patients with high-grade gliomas.

Keywords: genes TP53; mutation; gliomas; treatment outcome.

RESUMEN

Introducción: Determinar la relación entre la mutación del gen TP53 y el resultado del tratamiento, en pacientes con gliomas de alto grado, es importante para el pronóstico de la enfermedad y el seguimiento de los resultados del tratamiento.

Objetivos: Determinar la relación entre la tasa de mutación del gen TP53 y algunas características del resultado del tratamiento en pacientes con gliomas de alto grado.

Métodos: El estudio se realizó mediante un método descriptivo en 52 pacientes con gliomas de alto grado en el Hospital Nacional del Cáncer de Vietnam, de enero de 2019 a diciembre de 2020. Según las estadísticas de los síntomas clínicos, las pruebas paraclínicas y los resultados del seguimiento posoperatorio, se evaluó la relación entre la mutación del gen TP53 en los pacientes del estudio con la respuesta al tratamiento y el tiempo de supervivencia del paciente.

Resultados: Hubo relación entre la mutación del gen TP53 y la respuesta al tratamiento según Response Evaluation Criteria In Solid Tumors (p= 0,004). La supervivencia libre de progresión fue mayor en el grupo con la mutación TP53 que en el grupo sin la mutación TP53 (χ^2= 6,7; p= 0,010). La supervivencia global en el grupo con la mutación TP53 fue mayor que la supervivencia global en el grupo sin la mutación TP53 (χ^2= 2,6; p= 0,107).

Conclusión: Existe una relación entre la aparición de mutaciones en el gen TP53 con los criterios de

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respuesta al tratamiento y la supervivencia libre de progresión en pacientes con gliomas de alto grado.
Palabras clave: genes TP53; mutación; gliomas; resultado del tratamiento.

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INTRODUCTION

Glioblastoma is the most common primary brain tumor of the nervous system, accounting for 74% of central nervous system malignancies, with an increasing incidence of the disease over time and a serious threat to human health.[1] Although only about 2% of cases progress to cancer, the treatment of high-grade glioma (HGG) has become the biggest challenge for oncologists.[2] Despite advances in treatment, these tumors are still associated with higher morbidity and mortality and shorter median survival than other cancers.[2] High-grade glioma has a short survival time, usually less than one year (HGG), of which glioblastoma multiforme (GBM) accounts for about 60-70% malignant glioma, which has the longest median survival, however is still very limited (less than 2 years).[3] The causes of treatment failure, progression, and recurrence of disease stem from the underlying biology of gliomas, which calls for an improved understanding of genetics and cellular mechanisms that regulate tumor activity and provide better diagnostic tools and the development of novel biological therapies in treatment.[4,5,6,7]

Many recent studies have shown the association of *TP53* gene mutations in developing and promoting HGG.[8,9] However, data on the association of *TP53* gene mutations with HGG treatment outcomes are quite limited.[10] Therefore, determining the association between *TP53* gene mutation and treatment outcome in HGG patients have great significance for disease prognosis, relapse prediction, and treatment outcome monitoring. This study had as objective to investigate the association between the *TP53* gene mutation and some characteristics of treatment outcomes in HGG patients.


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METHODS

Design

Descriptive, cross-sectional study of a series of cases.

Subjects

The study was conducted on 52 patients with a confirmed diagnosis of HGG who received chemotherapy and radiation therapy after surgery at Vietnam National Cancer Hospital from January 2019 to December 2020. The inclusion criteria for the included patients were: 1- a confirmed diagnosis of high-grade glioma through histopathological results, examination, and complete record of clinical symptoms; 2- the patient underwent magnetic resonance imaging with magnetic contrast injection, histopathology, gene sequencing to identify *TP53* mutations; 3- the patient underwent surgery to remove the tumor and combined chemotherapy and radiotherapy; 4- the patient does not have life-threatening acute or chronic diseases; have a complete medical record. 5- all patients have explained the study procedure and agreed to participate in the study.

Research process

All medical records had full clinical characteristics, MRI results, pathological results, genetic mutation test results, and treatment results. Patient's function and clinical were evaluated according to the Karnofsky scale,[11] and identification of *TP53* gene mutations by gene sequencing using the ABI 3500 Genetic Analyzer automatic sequencing machine.

The included patients received chemotherapy, and radiation treatment after surgery. The radiotherapy used was a 3-dimensional (3D conformal) technique: the total dose was 60Gy, with fractionation of 2Gy/day administered 5 days/week for 6 weeks after surgery. The chemotherapy was Temozolomide, with a standard dose of 75mg/m^2 of body skin, is administered on days of radiation therapy. Evaluation of treatment response according to the criteria for assessing response to target lesions according to the Response Evaluation Criteria In Solid Tumors (RECIST) classification.[12]

Then, the patient was re-examined 1 month, 6 months after surgery - this was also when the patient received enough chemotherapy and radiation regimen and is in the stage of adjuvant chemotherapy, 12

months, 18 months. Continue to monitor patients to assess progression-free survival and overall survival up to 18 months after surgery. Evaluation of survival according to the Kaplan-Meier method.[13]

Based on statistics of clinical symptoms, paraclinical tests, treatment results, and post-operative monitoring results, the relationship between *TP53* gene mutation in study patients with treatment outcome, response to treatment, and patient's survival time was evaluated.

Variables

Rate of TP53 gene mutation: rate of presence/absence of TP53 gene mutation in patients with grade III and IV.

Relationship between TP53 gene mutation and treatment response (RECIST): Complete response, partial response, stable disease, progressive disease.

The relationship between TP53 gene mutation and progression-free survival.

Relationship between TP53 gene mutation status and overall survival time.

Statistical analysis

All results are presented as mean (SD) or, if biased, as median (interquartile range) for continuous variables and as percentages for categorical variables. Differences between groups were tested by T-test. The Chi-square test or Fisher's exact test was used to assess whether there was a relationship between two categorical variables. Analysis of survival time was performed by Kaplan-Meyer method. Log-rank test was used when comparing survival curves between groups with or without *TP53* gene mutation. P value < 0.05 was considered to be statistically significant. All data were processed using SPSS software version 26 (64-bit) for Windows (SPSS Inc., Chicago, IL).

Ethical considerations

The Ethical Review Committee of Military Medical University, Vietnam approved the protocol of the study. The study was in line with the Declaration of Helsinki. Written informed consent has been signed by all participants after full explanation.


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RESULTS

The rate of p53 gene mutation in all patients was 48.1%. Research results showed that for p53 gene mutation, the positive rate in grade IV patients was lower (44.1%) than this mutation rate in patients with malignancy grade. However, this difference was not significant with p> 0,05 (table 1).

Table 1 - Features of TP53 gene mutation

TP53 mutation	Malignancy		Overall n (%)
	Grade III n (%)	Grade IV n (%)	
Yes	10 (55.6)	15 (44.1)	25 (48.1)
No	8 (44.4)	19 (55.9)	27 (51.9)
Total	18 (100.0)	34 (100.0)	52 (100.0)
p*	0.562		

*Fisher's Exact Test.

Patients with p53 mutation expression had a better RECIST response (100% of patients with complete and partial response) than patients without expression of this gene mutation. This difference was statistically significant with p< 0.05 (table 2).

Table 2 - The relationship between the objective response according to the RECIST classification and the presence or absence of the TP53 mutation

Response according to RECIST	TP53 mutation		Total	p*
	Yes (n, %)	No (n, %)		
Complete response	2 (100.0)	- (0.0)	2 (3.8)	0.004
Partial response	5 (100.0)	- (0.0)	5 (9.6)	
Stable disease	18 (40.9)	26 (59.1)	44 (84.6)	
Progressive disease	- (0.0)	1 (100.0)	1 (1.9)	
Total	25 (48.1)	27 (51.9)	52 (100)	-

*Fisher's Exact Test.

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The rate of progression-free survival was higher in the group with the p53 gene mutation than in the group without the mutation (44.0% vs. 14.8%). Progression-free survival was higher in the group with the p53 mutation than the progression-free survival in the group without the p53 mutation. This difference was statistically significant with $p< 0.05$ (table 3).

Table 3 - Relationship between progression-free survival and the presence or absence of TP53 mutations

TP53 mutation	Numbers of progressed cases	PFS rate (%)	Mean ± SD (months)	95% CI (months)
Yes	14	44.0	14.9 ± 0.7	13.5 – 16.3
No	23	14.8	11.7 ± 0.9	10.0 – 13.5
Total	37	28.8	13.3 ± 0.6	12.1 – 14.5

Test Log Rank $\chi^2 = 6.7$; $p= 0.010$.

The overall survival rate in the group with the p53 gene mutation was higher than in the group without the mutation (80.0% vs. 59.3%). Overall survival was higher in the group with the p53 mutation than in the group without the p53 mutation. However, this difference was not statistically significant with $p> 0.05$ (table 4 and Fig. 1).

Table 4 - Relationship between overall survival and the presence or absence of TP53 mutations

TP53 mutation	Numbers of death	OS rate (%)	Mean ± SD (month)	95% CI (month)
Yes	5	80.0	16.8 ± 0.5	15.8 – 17.8
No	11	59.3	15.4 ± 0.8	13.8 – 16.9
Total	16	69.2	16.1 ± 0.5	15.1 – 17.0

Test Log Rank $\chi^2= 2.6$; $p= 0.107$.

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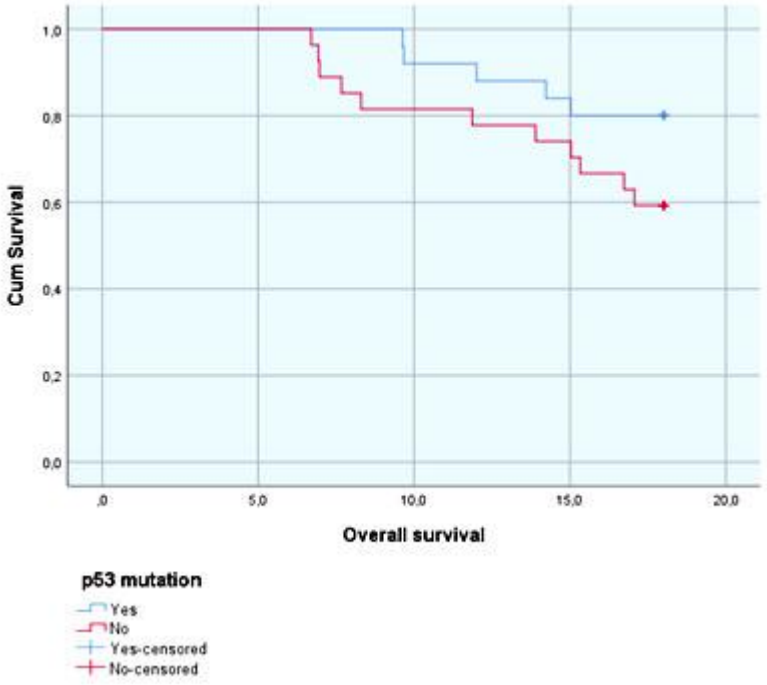

Fig. 1 - Cumulative overall survival curve according to TP53 mutation.

DISCUSSION

The rate of TP53 mutations in HGG patients

The *TP53* gene mutation rate in our study was 48.1%, of which the positive rate in grade IV patients had lower positive rate than with this mutation rate in patients with grade III (table 1). However, this difference was not statistically significant, with p> 0.05. Research results are also consistent with the results of some other studies. One study found the mutation frequency for *TP53* to be 67% in anaplastic astrocytoma (grade III) and 41% in GBM (grade IV).[14] However, the rate of *TP53* mutations in gliomas is still controversial. *Hayes VM* et al.,[15] in an analysis of 20 pediatric astrocytoma cases, 7/20 (35%) had *TP53* mutations in the study patient. Another study in 22 patients with glioma showed a *TP53* mutation rate of 25.7%.[16] Giant cell glioblastoma, a histological variant of GBM, had a high prevalence of *TP53* mutations (90%).[17]


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The relationship between TP53 mutation and response to treatment according to RECIST

In this study, radiotherapy volume followed current standard radiotherapy techniques, including only the tumor and the micro-invasive area surrounding the tumor. After treatment, we found that the disease control rate (including the rate of complete + partial + stable response) was quite high; this rate accounted for 98.1%. Meanwhile, the rate of disease progression after concurrent chemoradiotherapy and postoperative treatment with Temozolomide was low; this rate was only 1.9% (table 2). Results are also consistent with many other studies. According to the study of *Omuro A*,[18] evaluating the effectiveness of chemotherapy and radiation at the same time after surgery for HGG, the results of this study showed that the disease control rate after chemotherapy and radiotherapy was quite high, accounting for 93%, while the rate of disease progression after treatment was low, only 7%. When analyzing the relationship between this mutation feature and the level of response to treatment according to RECIST, the presence of these gene mutations had a positive influence on the level of objective response RECIST. The results of other studies also showed that the occurrence of *TP53* gene mutations was a favorable factor in the response to treatment.[19,20]

The relationship between TP53 mutation and survival time

The results of our study on *TP53* mutations and survival showed that progression-free survival in the group with the *TP53* mutation was higher than in the progression-free survival in the group without the *TP53* mutation. This difference is statistically significant with $p< 0.05$. The overall survival in the group with *TP53* mutation was higher than in the group without the *TP53* mutation; however, this difference was not statistically significant with $p> 0.05$. Results on the prognostic value of *TP53* mutations are unclear for overall survival. Many studies have also confirmed this. Some researchers have suggested that *TP53* mutations have no effect on the survival of patients with astrocytomas.[21] Another group suggested that the prognosis of astrocytomas was relatively poor compared with other types because of the association with a higher frequency of *TP53* mutations.[22] In contrast, another study suggested that the persistence of *TP53* mutations in recurrent HGG may indicate a better prognosis.[19] There was such a difference due to the occurrence of mutations on the *TP53* gene at different locations; the function of each of these gene regions was different, thus leading to different prognoses.[23]


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From a clinical perspective, determining postoperative *TP53* status will be very important and may help establish new therapeutic strategies for astrocytomas. There is still controversy about which treatment regimens should be used in these patients. The role of chemotherapy and radiation therapy remains unclear, both in low-grade and high-grade astrocytomas. Recent studies of human carcinomas, such as colorectal, ovarian, and acute lymphoblastic leukemia, as well as laboratory tests in glioma and lineages of other tumor cells, have shown that *TP53* mutations inactivate the auto-programmed cell pathway and induce resistance to chemotherapy and radiation therapy. Replacing normal *TP53* function or stimulating the apoptotic pathway leads to the re-establishment of chemosensitivity. Therefore, glioblastomas with the *TP53* non-mutant phenotype (wild-type) have a poorer prognosis than those with mutant *TP53*. This may be due to mutations in other genes in the old group that make them more resistant to radiation.[24]

Considering the association between *TP53* mutations and treatments, recent studies[25,26,27] have shown that the status of the *TP53* gene affects the effectiveness of DNA alkylation treatment using temozolomide - most effective chemotherapy for GBM. *Blough* et al.[20] showed that GBM cell lines without functional *TP53* expression were significantly more sensitive to temozolomide than cell lines without functionally intact *TP53* mutations when altered *TP53* expression or function has only a small effect on temozolomide sensitivity in the initiation of cytoskeletal brain tumors and tends to decrease sensitivity to temozolomide.

Thus, for patients with high-grade glioma, the presence of *TP53* mutations may be a beneficial prognostic factor. In addition, thanks to the mutation, the ability to treat with chemotherapy and radiation gives more positive results than patients without this mutation. However, this conclusion still needs to be studied further in the future.

The first limitation of this study is that due to the limited time of the study, it has not been able to track the results of the patient's survival time in the longer term for cancer pathology. The following limitation of this study is that our sample size was not large (52 patients); therefore, the analysis of the relationship between some factors and the rate of *TP53* gene mutation results in some indicators that are not statistically significant.


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In conclusions, in patients with HGG, the presence of *TP53* mutations may be a beneficial prognostic factor. There is an association between the occurrence of *TP53* gene mutations with treatment response according to RECIST criteria and progression-free survival in patients with HGG.

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Conflict of interest

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Data Availability Statement

All data underlying the results are available as part of the article and no additional source data are required.