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Genetic Profile of Primary Brain Tumours and the Degree of Their Resection Versus Survival of Patients Undergoing Surgery and Complementary Oncological Treatment

Profil genetyczny pierwotnych guzów mózgu oraz stopień ich resekcji a przeżywalność pacjentów poddanych zabiegom operacyjnym i onkologicznemu leczeniu uzupełniającemu

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Abstract

Introduction. Recently, the incidence of brain glial tumours has increased significantly worldwide. Gliomas are among the most malignant types of tumours of the central nervous system. Patients diagnosed with glial tumours have a very unfavourable prognosis leading to death, and the course of the disease itself has a negative impact on their physical, mental and social condition.
Aim. The aim of this study was to determine the effect of the results of histological and genetic tests as well as the degree of resection of primary CNS tumours on the survival of patients undergoing neurosurgery and complementary oncological treatment — pharmacology and radiotherapy.
Material and Methods. The research was carried out on the basis of an analysis of medical records (2019–2021) of 63 adult patients from the Department of Neurosurgery of the Specialist Municipal Hospital of Nicolaus Copernicus in Toruń. The study group included patients who had been diagnosed with a primary brain tumour and had undergone neurosurgery and complementary oncological treatment. The analysis of medical documentation consisted in comparing the results of histopathological tests with the results of specialized molecular tests and correlating them with the survival time of patients. The statistical analysis was carried out using the Pearson correlation, statistical inference was made at the significance level of $p=0.05$.
Results. Based on the obtained results, it was found that the presence of MGMT gene promoter methylation ($r=0.30$, $p=0.018$) and IDH mutation ($r=0.38$, $p=0.002$) correlated positively with survival. The extent of resection also had a significant impact on patient survival ($r=0.55$, $p<0.001$). Patients who underwent complete tumour resection survived an average of 19.34 months, while those who underwent biopsy survived for 7.94 months.
Conclusions. The data collected during the conducted analyses may be important for the prognosis perspective and the selection of the optimal treatment strategy for both current and future patients. **(JNNN 2022;11(4):162–166)**
Key Words: brain tumours, gliomas, IDH mutation, MGMT methylation, survival

Streszczenie

Wstęp. W ostatnim czasie na całym świecie częstość występowania nowotworów glejowych mózgu znacznie wzrosła. Glejaki zaliczane są do jednych z najbardziej złośliwych typów guzów ośrodkowego układu nerwowego. Pacjenci, u których zdiagnozowano guzy glejowe mają bardzo niekorzystne rokowanie prowadzące do śmierci, a sam przebieg choroby ma negatywny wpływ zarówno na ich stan fizyczny, psychiczny i społeczny.

Cel. Celem niniejszej pracy było określenie wpływu wyników badań histologicznych i genetycznych oraz stopnia resekcji pierwotnych nowotworów OUN na przeżywalność pacjentów poddanych zabiegom neurochirurgicznym i uzupełniającemu leczeniu onkologicznemu — farmakologicznemu oraz radioterapii.
Materiał i metody. Badania zostały przeprowadzone na podstawie analizy dokumentacji medycznej (2019–2021) 63 pełnoletnich pacjentów z Oddziału Neurochirurgii Specjalistycznego Miejskiego Szpitala im. Mikołaja Kopernika w Toruniu. W badanej grupie znaleźli się pacjenci, u których zdiagnozowano pierwotnego guza mózgu, a także wykonano zabieg neurochirurgiczny oraz wprowadzono uzupełniające leczenie onkologiczne. Analiza dokumentacji medycznej polegała na porównaniu wyników badań histopatologicznych z wynikami specjalistycznych badań molekularnych oraz ich skorelowaniu z czasem przeżycia pacjentów. Analizę statystyczną przeprowadzono z wykorzystaniem korelacji Pearsona, wnioskowanie statystyczne dokonano na poziomie istotności p=0,05.
Wyniki. Na podstawie uzyskanych wyników stwierdzono, że obecność metylacji promotora genu MGMT (r=0,30, p=0,018) oraz mutacji IDH (r=0,38, p=0,002) koreluje dodatnio z długością przeżycia. Zakres resekcji, również miał duży wpływ na przeżywalność pacjentów (r=0,55, p<0,001). Chorzy poddani całkowitej resekcji guza przeżywali średnio 19,34 miesiąca, natomiast poddani biopsji 7,94 miesiąca.
Wnioski. Dane zebrane w czasie przeprowadzonych analiz mogą mieć istotne znaczenie dla perspektywy rokowania i doboru optymalnej strategii leczenia zarówno obecnych, jak i przyszłych pacjentów. **(PNN 2022;11(4):162–166)**
Słowa kluczowe: guzy mózgu, glejaki, mutacja IDH, metyzacja MGMT, przeżywalność

Introduction

Glial cell tumours (gliomas) are the most common primary malignant tumours of the human central nervous system. They account for about 65% of primary intracranial tumours [1]. Most gliomas develop supratentorially — in the frontal, temporal, parietal and occipital lobes, much less often infratentorially — in the cerebellum, brainstem, and the spinal cord. Although their incidence is lower compared to other cancers, such as lung, breast, prostate or colorectal cancer, they are a significant health problem due to high mortality [2].

In recent years, the incidence of brain glial tumours has increased worldwide [1]. Most patients with glial tumours have an unfavourable prognosis, the disease leads to death, and its course has a negative impact on the physical, mental and social condition not only of the patients themselves, but also of their families [3]. The clinical course of the disease is related to the histological type and genetic profile of the tumour, which is related to its degree of local invasiveness, ability to suppress the immune system response, angiogenesis and resistance to chemo- and radiotherapy [1].

The management of glioblastoma begins with surgical treatment, preceded by a possible stereotactic biopsy in the event of diagnostic doubts. The goal of surgical treatment is to perform the maximum safe resection of the tumour. Although there are no randomized clinical trials to determine the extent of surgery, complete resection (GTR) is recommended if feasible. Retrospective analyses have shown that GTR can prolong the survival of patients even in old age, regardless of the molecular status of the cancer, but it will not reduce mortality [4]. In situations where surgery or microsurgical resection is not possible (e.g.: patient refusal, medical contraindications, or location of the lesion that does not allow for safe resection), biopsy, preferably stereotactic, remains an option. This method allows to obtain material for histological and molecular diagnostics and to determine the strategy of further therapeutic management [5]. In patients diagnosed with glioblastoma, radiotherapy, chemotherapy, immunotherapy and targeted therapies may also be implemented. Throughout the course of the disease, patients with glioblastoma experience significant and progressive symptoms, both general and neurological, which deteriorate the quality of life, independence and increase the sense of illness. Symptoms result from the nature of the disease itself and from the toxicity of the therapy used. As a consequence, patients often require greater medical and social support and supportive treatment [6].

The aim of our study is to determine the impact of the genetic profile and the degree of resection of primary brain tumours on the prognosis of patients undergoing neurosurgery, as well as complementary oncological treatment — pharmacology and radiotherapy.

Material and Methods

The study was conducted on the basis of the analysis of medical records of 63 adult patients of both sexes from the Department of Neurosurgery of the Specialist Municipal Hospital of Nicolaus Copernicus in Toruń. The study group included patients who in the last 3 years (2019–2021) were diagnosed with a primary brain tumour, and underwent neurosurgery and complementary oncological treatment. The analysis of medical documentation consisted in comparing the results of histopathological tests with the results of specialized molecular tests and correlating them with the survival time of patients.

The result of the molecular test was analysed on the basis of MGMT methylation status, 1p/19q deletion and mutations in the IDH1 (R132C), IDH1 (R132H), IDH2 (R172K) and IDH2 (R172M) genes. The study was approved by the Bioethics Committee of Collegium Medicum of LudwikRydygier in Bydgoszcz, Nicolaus Copernicus University in Toruń (KB 215/21).

The statistical analysis was carried out using a Microsoft Excel 2016 spreadsheet. Statistical inference was made at the significance level of p=0.05. Categorical variables are represented by counts and percentages. Pearson's correlation analysis was also used in the work.

Results

The study was conducted among 63 adults who underwent neurosurgical surgery: complete resection (50.8%), partial resection (22.2%) or biopsy (27%), and complementary treatment: pharmacological and/or radiotherapy. All patients underwent histopathological examinations of the tumour (LGG — 14.3%, HGG — 23.8%, GBM — 62%), as well as specialized molecular tests for MGMT methylation status (68.3%), 1p/19q deletion (1.6%) and mutations in IDH1 and IDH2 genes (17.5%). The average age of the respondents was 59.84 years, while the average survival was about 7 months. The characteristics of the study group are presented in Table 1.

Table 1. Characteristics of the test sample

Variable	Women (N=29, 46%)	Men (N=34, 54%)	Total (N=63)
Mean age	61.34 (Me=62)	58.56 (Me=58)	59.84 (Me=61)
Total surgery (%):			
Total resection (GTR)	25.4	25.4	50.8
Partial resection	11.1	11.1	22.2
Biopsy	9.5	17.5	27
Histopathological diagnosis (%):			
LGG (WHO grade II)	7.9	6.4	14.3
HGG (WHO grade III)	7.9	15.9	23.8
GBM (WHO grade IV)	30.2	31.8	62
Mutations (N):			
MGMT gene promoter methylation	21	22	43 (68.3%)
IDH mutation	5	6	11 (17.5%)
1p/19q deletion	0	1	1 (1.6%)
Survival mean	7.11 (Me=5.5)	7.55 (Me=5.5)	7.34 (Me=5.5)

N — number of observations; Me — median

Table 2. Average survival of the study population due to the surgery performed

Variable	N	Mean survival for women (months)	Mean survival for men (months)	Mean overall survival (months)	r	p
Surgery performed:						
Biopsy	17	4.33	9.91	7.94		
Partial resection	14	6.43	6.29	6.36	0.55	<0.001
Total resection	32	18.63	20.06	19.34		
MGMT gene promoter methylation:						
MGMT methylation present	43	13.71	16.86	15.33	0.30	0.018
No MGMT methylation	20	10.125	8.58	9.2		
IDH mutation:						
IDH1/IDH2 mutation presence	11	20.4	22.17	21.36	0.38	0.002
No IDH1/IDH2 mutation	52	11.13	12.18	11.69		

N — number of observations; r — Spearman's rank correlation coefficient; p — test probability

Patients who underwent complete tumour resection survived an average of 19.34 months, while those who underwent biopsy survived for 7.94 months. It is also worth noting that the lowest median survival time is in the group that underwent partial tumour resection. It was shown that the extent of resection correlates with the length of survival (r=0.55), which means a high correlation according to Guilford. This is a statistically significant correlation (p<0.001). Moreover, patients with MGMT promoter methylation lived longer (on average 15.33 months) than patients without methylation (on average 9.2 months). This is probably related to a better response to systemic treatment. The presence of MGMT methylation correlates positively with the length of survival (r=0.298), which means a weak correlation according to Guilford, but at a statistically significant level (p=0.018). It was also observed that patients with the IDH mutation lived almost twice as long (on average 21.36 months) compared to patients with the negative variant (on average 11.69 months). The presence of the IDH mutation positively correlates with the length of survival (r=0.383), which is an average correlation according to Guilford. This is a statistically significant correlation (p=0.002) (Table 2).

Discussion

Malignant brain tumours are associated with high morbidity and mortality, and the course of the disease itself has a negative impact on the physical, mental and social condition of not only the patients themselves, but also their families. The most common primary malignant tumours of the human central nervous system are gliomas, which account for approximately 65% of primary intracranial tumours. The most aggressive form is considered to be glioblastoma multiforme, with an annual incidence rate of 0.6 to 3.7 per 100,000 people and an OS median of patients is. The main factor related to the survival of patients with high-grade glioma include: histopathological diagnosis, patient's age, Karnofsky performance status (KPS), extent of resection, use of postoperative adjuvant therapy, and for several years also the molecular status of the tumour [7]. The study conducted by Shaw et al. showed that the gender and diameter of the tumour are not related to the prognosis, which is consistent with other publications [8]. Multivariate regression analysis showed that advanced age (>60 years), advanced tumour stage, partial surgical resection, low preoperative KPS index (<70), and lack of radiotherapy and chemotherapy were independent risk factors for prognosis in patients with gliomas [8,9].

Traditionally, the classification of CNS tumours was based solely on histological features, but recently molecular parameters have also been added to more accurately classify them and further estimate the prognosis of many types of cancer. Molecular markers for the classification of gliomas were first used in the WHO CNS classification in 2016, and in 2021 even more emphasis was placed on them [10]. In the current classification system, the primary genetic markers for gliomas are: IDH mutation status, codeletion of chromosomal arms 1p and 19q (1p/19q codeletion), H3F3A changes, nuclear alpha-thalassemia/mental retardation syndrome X (ATRX) gene mutation, O6-methylguanine-DNA (MGMT) promoter methylation, loss of cyclin-dependent kinase 2A (CDKN2A) inhibitor, epidermal growth factor receptor (EGFR) amplification, combined enhancement of chromosome 7 and loss of chromosome 10 (7+/10–) and telomerase reverse transcriptase (TERT) promoter mutation. A large number of biomarkers not only indicates a change in the classification paradigm, but also has an impact on the clinical management of patients with these tumours [11]. IDH1 or IDH2 mutations are considered positive prognostic factors.

Many meta-analyses have shown that IDH mutations are associated with both longer OS (overall survival) and PFS (progression-free survival), regardless of the severity of the disease. The presence of the IDH1/2 mutation increases the average survival time (31 months vs 15 months) regardless of other prognostic factors [12]. The most favourable clinical results were observed in LGG gliomas with IDH mutations and 1p/19q codeletion [11]. In addition, in malignant gliomas, the combination of an IDH1 mutation and MGMT methylation status is a greater predictor of survival than a single IDH1 or MGMT mutation alone. The polygenic mechanism behind this prognostic value is very consistent with current observations made in mechanistic cancer research [12].

Conclusions

Our study showed that the extent of brain tumour resection correlates with the length of survival. Patients who underwent complete resection had the longest survival among the study population. The lowest median survival time was noted in the group that underwent partial tumour resection. It was also observed that the presence of the MGMT gene promoter methylation or the presence of the IDH mutation contributed to the prolongation of patients' survival.

Implications for Nursing Practice

Clinical symptoms associated with brain glial tumours can be divided into general ones, which are related to the mass of the tumour and increased intracranial pressure

caused by its growth. The most common of these include persistent headaches, drowsiness, nausea, vomiting, apathy, loss of appetite and visual disturbances. In turn, symptoms related to the location of the tumour cause epileptic seizures, increasing paresis, as well as subtly appearing personality disorders, changes in behaviour or depression in patients. Recognizing symptoms earlier often leads to a faster diagnosis, which speeds up treatment and can increase patient survival. However, the recognition of discreet and gradually developing symptoms of a brain tumour is difficult for both patients, their relatives and healthcare professionals, because they are usually non-specific and do not indicate a specific disease **[13,14]**. That is why it is so important to know the symptoms of a brain tumour among nursing staff.

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