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Psychiatric Manifestations in the Context of Brain Tumors: Study and Findings

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Abstract: *The increase in the frequency of psychiatric disorders is increasingly observed in patients diagnosed with cancer. Brain tumors are often associated with psychiatric symptoms such as mood symptoms, psychosis, memory problems, personality changes, anxiety, or depression. This study investigates what types of manifestations are present in patients with brain tumors, highlighting the connection with the location of the tumor. We conducted a clinical study on a sample of 91 patients diagnosed with primary brain tumors, hospitalized at the "Prof. Dr. Nicolae Oblu Emergency Clinical Hospital," Iași, Romania, between 2011 and 2023. Demographic data, type, and location of tumors were collected from the patients' medical records. Patients underwent detailed neuropsychological evaluations to identify psychiatric manifestations. Statistical analyses were performed to determine the prevalence of these manifestations and the correlations between tumor location and the severity of psychiatric symptoms. Our results show a significant prevalence of psychiatric disorders among patients with brain tumors, with notable differences between genders and types of manifestations. Organic personality disorders and mixed anxiety and depression disorders were among the most common. Additionally, a correlation was observed between the location of tumors in the frontal lobe and the severity of psychiatric symptoms. Conclusions: The research highlights the increased frequency of psychiatric symptoms in patients with brain tumors, especially when the tumor is located in the frontal lobe. These observations emphasize the relevance of a multidisciplinary approach in the management and treatment of these patients, including both cancer therapy and psychiatric support services.*

Keywords: *brain tumor; astrocytic tumors; psychiatric manifestations; frontal lobe.*

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1. Introduction

Brain tumors called gliomas are a variety of neoplasms that are predominantly sporadic and develop from glial cells. They constitute approximately 40-45% of all brain tumors and are the most common tumors among those that develop primarily in the central nervous system (Russell & Rubinstein, 1989). Gliomas are classified into various subgroups based on morphological appearance and presumed histogenesis, including astrocytic tumors (including glioblastoma), oligodendroglial tumors, mixed gliomas (oligoastrocytomas), and ependymal tumors (Alvarez & Bredel 2013).

Astrocytes are the most prevalent type of glial cells among the three found in the central nervous system, displaying high adaptability and being classified into protoplasmic and fibrous categories. Astrocytes work together with vascular endothelial cells to preserve the blood-brain barrier's integrity and safeguard a balanced environment for the brain (Campisi et al., 2018). Astrocytoma is a broad classification used for the invasive spread of tumors made up of well-developed cancerous astrocytes (Kleihues, Burger, & Scheithauer, 1993). Astrogliosis occurs when astrocytes are activated and proliferate following an injury or illness (Vrapciu et al., 2023).

Astrocytoma is the most prevalent type of brain tumor, making up more than 50% of all primary central nervous system cancers (Fernandez et al., 2003). Astrocytoma originates from astrocytic neuroglia derived from neuroectoderm and is classified into four groups according to malignancy level (Niculescu, Stănescu, & Popescu, 2010).

Psychiatric signs may serve as early indicators of primary brain tumors. Research indicates that certain brain tumors, such as glioblastomas and meningiomas, are found up to ten times more frequently in patients with pre-existing psychiatric disorders, particularly in specific demographics such as older adults or those with a history of psychiatric hospitalisations. However, this correlation may vary based on tumor type and patient characteristics, necessitating further investigation. Supporting evidence can be found in population-based and retrospective clinical studies exploring the prevalence of brain tumors in psychiatric populations (Kocher, Linder, & Stula, 1984; Madhusoodanan, Danan, & Moise, 2004). The frequency of psychiatric symptoms reported in the case of brain tumors ranges from 50% to 78% (Madhusoodanan, Danan, & Moise, 2004). Metastatic brain tumors can cause more intense psychiatric symptoms than primary brain tumors, probably due to their diffuse distribution in the brain tissue (Madhusoodanan et al., 2006). A retrospective analysis of benign brain tumors showed that psychiatric symptoms can be the first manifestation of meningiomas in 21% of cases, which occur around the age of 50 (Gupta & Kumar, 2004).

Although efforts are being made to improve the treatment of gliomas, they remain incurable. Patients with low-grade glioma (grade II) have an average survival of 5-15 years (Van den Bent et al., 2005), while patients with a grade III tumor have an average survival of 2-3 years (Ohgaki & Kleihues, 2005). For patients with grade IV tumors, the median survival duration is around 12-14 months (Stupp et al., 2005). Low-grade astrocytomas are more common in younger people, while high-grade astrocytomas primarily affect elderly individuals (Starkweather et al., 2011).

2. Aim

The purpose of the research is to contribute to neuro-oncology and psychiatry by encouraging a better understanding of the complex connection between brain cancer and psychiatric symptoms.

3. Astrocytic tumors

Astrocytoma, or astrocytic glioma, can be divided into two primary groups. The first category comprises tumors that spread widely, including astrocytoma, anaplastic astrocytoma, and glioblastoma. The second category includes less common tumors with more confined growth, like pilocytic astrocytoma, pleomorphic xanthoastrocytoma, and subependymal giant cell astrocytoma associated with tuberous sclerosis (Alvarez & Bredel 2013).

Astrocytic tumors make up 65%- 70% of all gliomas and are categorised into grades I-IV based on histological traits (Kleihues et al., 1995). Pilocytic astrocytic tumors, a type of grade I malignancy, are typically less aggressive cancers seen primarily in children. They rarely advance to more serious forms and usually have a positive prognosis (Jennings & Iyengar, 2001). Slow growth is observed, with a minor percentage (10%) found in the cerebral hemispheres (Jemal et al., 2007).

Diffuse astrocytomas, including fibrillar astrocytoma, gemistocytic astrocytoma, and protoplasmic astrocytoma (Starkweather et al., 2011) tend to invade the adjacent brain tissue. Thus, despite their slow growth, even well-differentiated astrocytomas (corresponding to histological grade II) tend to recur (Arabestanino, Ai, & Jalali, 2022). They primarily affect young adults and tend to evolve malignantly (Starkweather et al., 2011). These formations mainly occur in the brain and represent 35% of all astrocytic brain tumors.

Anaplastic astrocytomas that are malignant are characterised by diffuse anaplasia, such as cell growth, pleomorphism, nuclear atypia, and mitotic activity. Histologically, they are classified as grade III (Arabestanino, Ai, & Jalali, 2022). They are commonly found in the cerebral hemispheres and have a high probability of progressing to grade IV glioblastoma multiforme (Starkweather et al., 2011).

Glioblastoma is a form of anaplastic brain tumor, formed of poorly differentiated cells, in spindle, round, or pleomorphic shapes, and sometimes including multi-cellular giant cells (Arabestanino, Ai, & Jalali, 2022). It is the most common form encountered, constituting 15% of total brain tumors and 60% of total astrocytic tumors. The highest frequency occurs between 45 and 70 years old, and these malignant formations are mainly located in the cerebral hemispheres (Starkweather et al., 2011). Prominent vascular proliferation or necrosis is essential for histological diagnosis. Histologically speaking, glioblastomas are considered as grade IV. Approximately 17% of primary brain tumors in adults are astrocytomas and glioblastomas, compared to only 4% in children (Kleihues, Burger, & Scheithauer, 1993; Arabestanino, Ai, & Jalali, 2022). Glioblastoma is classified as the most aggressive type of glioma by the World Health Organization (Sukheeja et al., 2015).

Astrocytomas are recognised as a broad and varied group of tumors, distinguished by notable differences in clinical occurrence, visible and microscopic features, and biological behavior. Despite the significant advancements in radiological imaging and surgical procedures, the histopathological examination of a substantial tissue sample continues to be the standard method (Sukheeja et al., 2015).

4. Histological determination of astrocytic tumors

Atypia, anaplasia, microscopic proliferation, and necrosis are histological signs used to distinguish low-grade tumors from high-grade tumors. Highly differentiated glia with a high cell density, presenting nuclear atypia and rare mitotic activities, are the histological characteristic elements of low-grade tumors. Differentiation of tumor type can be done based on cell morphology, such as „fried egg” cells and pleomorphic giant cells found in oligodendrogliomas and astrocytomas (Aiman, Gasalberti, & Rayi, 2023).

Pilocytic astrocytoma is histologically defined by the presence of bipolar, spindle-shaped, or densely fibrillar cells. A remarkable pattern involves pilocytic areas closely associated with a poorly structured microcystic component (Arabestanino, Ai, & Jalali, 2022). Nuclei with intensely colored chromatin, a Byzantine appearance, vascular growth at the level of glomeruli, and invasion of the leptomeninges are commonly encountered but do not indicate malignancy. Eosinophilic elongated forms, in the form of Rosenthal fibers, and eosinophilic proteinaceous intracytoplasmic inclusions (called "granular bodies") are distinctive histopathological features of this tumor (Collins, Jones, & Giannini, 2015).

In the case of diffuse astrocytomas, morphological diversity involves an increase in the number of gemistocytic and protoplasmic astrocytes. Gemistocytes have a globular acidophilic cytoplasm, highlighting a distinct membrane, as well as irregular eccentric nuclei and thick

cytoplasmic processes. On the other hand, protoplasmic astrocytes have multipolar cytoplasmic processes and develop on a mixoid background, creating microcysts (Gupta, Djalilvand, & Brat, 2005). From a histological point of view, anaplasia is characterised by an increase in the number of cells, an increase in structural variety, and an increase in their division rate (Takei et al., 2007).

As its name indicates, glioblastoma "multiforme" is distinguished by the presence of a variety of cells, including giant fibrillary, gemistocytic, and disseminated tumor cells (Al-Hussaini, 2013). In order to diagnose glioblastoma, it is important to identify microvascular proliferation and/or necrosis, regardless of whether they are palisading or not. Microvascular proliferation is vaguely described as including endothelial hypertrophy, endothelial hyperplasia, and glomeruloid vessels, characterised by multiple clusters of proliferative endothelium accompanied by smooth muscle and pericytes (Miller & Perry, 2007). Glioblastoma can either appear as an aggressive evolution of a preexisting lower-grade astrocytoma (generally in 10% of cases) or develop directly as a grade 4 tumor (in 90% of cases). The first scenario is most commonly seen in younger patients, while the second is more common after the age of 60.

5. Associated neuropsychiatric manifestations

As the tumor advances, the symptoms it produces typically grow more noticeable. Because of how the disease and its treatment directly affect brain function, patients typically show symptoms related to neurological, cognitive, and psychiatric issues (Mukand et al., 2001). Neurobehavioral symptoms can influence the patient's involvement in clinical decisions and can affect survival, but they can also affect social relationships, such as those with spouses, family members, and close friends (Sherwood et al., 2008).

Approximately 80% of patients with tumors who exhibit psychiatric symptoms have tumors located in the frontal lobes or the limbic system. Individuals with these types of tumors are more likely to experience changes in behavior, which are usually consistent and very different from the individual's previous behavior (Arifin et al., 2014). The character transformations observed in individuals affected by brain tumors are generally represented by aggressive manifestations, lack of impulse control, lack of interest, and paranoia (Lupton et al., 2020). Typical changes can include lack of emotional control and difficulties in understanding social behaviors, as well as the development of anxiety, depression, or adjustment disorders. Additionally, symptoms such as social withdrawal, sadness, indifference, and lack of initiative may appear (Boele et al., 2015).

Usually, individuals are not aware of the changes in personality and symptoms they are experiencing, which can lead to increased confusion, frustration, and aggressive behavior. The changes can occur from localised lesions caused by the tumor itself or can take place as a result of surgery, chemotherapy, radiotherapy, or medications administered to treat tumors (Arifin et al., 2014). Tumors such as those in the tonsils and temporal lobe have been observed to be associated with aggression in behavior (Lupton et al., 2020). Symptoms such as anger, loss of emotional control, indifference, and changes in behavior are frequently reported (Andrewes et al., 2003; Cavers et al., 2012; Janda et al., 2008; Lucas, 2010). Personality changes can affect the recognition and interpretation of social behavior, influencing family life and social relationships. In patients with brain tumors, personality changes can cause exhaustion, anxiety, and social withdrawal (Lucas, 2010). Depression is a common issue associated with brain glioma (Litofsky & Resnick, 2009; Weitzner, 1999). Among all cancer patients, those with glioma present the highest risk of significant psychiatric complications around the time of their diagnosis (Dalton et al., 2009; Benros et al., 2009).

In addition to higher levels of aggressiveness, individuals with brain tumors also have a high risk of suicidality. In the study conducted by Shah et al. (2015), the potential link between brain cancer and the long-term psychological consequences of therapies used in the treatment of pediatric brain tumors was investigated, and it was found that brain tumor survivors were 2.6 times more likely to develop depression compared to the healthy population.

6. Materials and methods

Study design

This retrospective descriptive observational study was conducted on patients who were hospitalised, respecting the principles of institutional ethics. The study was conducted within the Pathology Department of the Emergency Clinical Hospital "Prof. Dr. "N. Oblu", located in Iasi, Romania, and is recognised as the main center for neurological and neurosurgical medical care in the northeastern region of Romania.

Patient Selection

This retrospective study included 91 patients monitored at the "Prof. Dr. Nicolae Oblu Emergency Clinical Hospital" in Iaşi, Romania, between February 17, 2011, and May 8, 2023, for whom an anatomopathological examination was performed on the resected fragment during surgery. In the Biopsy Ledger of the Pathology Department of the hospital, the identification data of each operated patient (name, surname, sex, and age), the location, type of tumor, and the dyes used were noted. All individuals who underwent surgery were informed about the importance of performing special histopathological tests for diagnosis. All patients agreed to use biological material for diagnosis and research.

Sample Selection

Only patients with an astrocytoma tumor or metastasis localised in the frontal, parietal, or temporal lobes of the brain, with psychiatric symptoms appearing before the diagnosis of a brain tumor and located in different anatomical regions, were selected for the current study. Based on the information provided by the pathologist in the biopsy records, information about the deceased person (name, surname, sex, age) and information about the physical aspects of the tumors, including tumor types and characteristics, were collected. Tumors with a benign appearance on anatomopathological diagnosis were excluded from the research.

Our research involved analysing the following aspects: age at diagnosis and patient sex, pathological characteristics of tumors, and characteristics of neuropsychiatric disease manifestations associated with them.

7. Results

There were a total of 91 patients, with an average age of 56 years, who met the inclusion criteria and were enrolled. Among them, 41 were men (45%) and 50 were women (55%), 35 from rural areas, including 20 men and 15 women, and 56 from urban areas, including 22 men and 28 women.

To further investigate the relationship between the location of brain tumors and associated psychotic manifestations, we conducted a detailed analysis of the data regarding these manifestations. Within this analysis, we focused on identifying correlations between the specific location of tumors and the types of psychotic manifestations observed in patients. The results of this analysis are presented in Table 1, which highlights the relationship between the location of brain tumors and the frequency of associated psychotic manifestations.

Table 1. Psychiatric manifestations and localisation of brain tumors

Psychotic manifestations	Tumor Location	Number of cases	Gender distribution
Organic personality disorder, moderate depressive episode	Left frontal lobe	3	W=1, M=2
	Right frontal lobe	3	W=1 M=2
	Right fronto-temporal lobe	1	W=1
	Left fronto-temporo-insular lobe	1	W=1
	Left fronto-temporal lobe	1	M=1
	Left parietal lobe	1	W=1
Organic personality disorder	Left frontal lobe	10	W=5, M=5
	Right frontal lobe	6	W= 2, M=4
	Right fronto-temporal lobe	1	W=1
	Left fronto-parieto-temporal lobe	2	W=2
	Left fronto-parietal frontal lobe	2	W=1, M=1
	Right fronto-parietal lobe	2	W=2

	Fronto-parieto-temporal lobe	1	W=1
	Parieto-temporal lobe	1	M=1
	Frontal lobes	1	M=1
Mixed anxiety and depressive disorder	Left frontal lobe	4	W=2, M=2
	Right frontal lobe	4	W=1 M=3
	Frontal lobes	1	M=1
	Right fronto-temporal lobe	1	W=1
	Left fronto-insular lobe	1	W=1
	Right fronto-parieto-temporal lobe	1	M=1
Organic mild cognitive disorder	Right frontal lobe	5	W=2 M=3
	Right fronto-insular lobe	1	W=1
	Right fronto-parietal lobe	1	M=1
Unspecified recurrent depressive disorder	Right frontal lobe	4	W=1 M=3
	Left frontal lobe	4	W=1 M=3
	Right fronto-insular lobe	1	W=1
Organic personality disorder, panic disorder (panic attacks)	Frontal lobes	1	M=1
	Left frontal lobe	1	M=1
	Right frontal lobe	1	M=1
	Right fronto-temporal lobe	1	W=1
	Left fronto-parietal lobe	1	W=1
Unspecified organic personality and behavioral disorder caused by disease dysfunction and brain damage	Left frontal lobe	4	W=2, M=2
	Right frontal lobe	3	W=2, M=1
Unspecified anxiety disorder	Right frontal lobe	1	W=1
	Left frontal lobe	1	W=1
Postencephalitic syndrome, moderate depressive episode	Right fronto-parietal frontal lobe	1	M=1
Postencephalytic syndrome, severe depressive episode with psychotic symptoms	Left frontal lobe	1	W=1
Organic personality disorder, severe depressive episode with psychotic symptoms	Right fronto-parieto-temporal lobe	1	W=1
	Right frontal lobe	1	W=1
Postencephalitic syndrome	Right fronto-parietal frontal lobe	1	W=1
Recurrent depressive episode, mild current episode	Right frontal lobe	1	W=1
	Left frontal lobe	1	W=1
Organic personality disorder, mixed anxiety and depressive disorder	Left frontal lobe	1	M=1
Panic disorder (panic attacks), postencephalitic syndrome	Frontal lobes	1	M=1
	Left frontal lobe	1	W=1
Other recurrent depressive disorders	Right frontal lobe	1	W=1
W- woman, M- man			

Regarding the left frontal lobe, the most frequent manifestations are organic personality disorders and recurrent depressive disorders. Chi-square tests were applied to evaluate categorical data to determine the statistical significance of the correlation between specific tumor locations and psychiatric symptoms. In contrast, correlation coefficients (e.g., Pearson or Spearman, as appropriate) were used to assess the strength of relationships. Organic personality disorders are the most common, appearing in multiple forms, including moderate depressive episodes and mixed anxiety and depressive disorder. The patients' sex is fairly balanced, with a slight predominance of men in some cases. Similar to the left frontal lobe, the right lobe is frequently associated with organic personality disorders and unspecified recurrent depressive disorders. There is a diversity in psychiatric manifestations, including mild organic cognitive disorders and recurrent depressive episodes. Patient gender is also balanced here but with a slight predominance of males in some disorders.

Organic personality disorders are the most commonly reported and are associated with multiple locations of tumors, especially in the frontal lobes (both left and right). Depressive episodes (moderate, severe, with psychotic symptoms) are frequently associated with tumors in the frontal and fronto-parietal lobes. Anxious and mixed disorders are more commonly found in tumors located in the frontal and fronto-temporal lobes.

Specific locations of brain tumors, such as the fronto-parietal and fronto-insular lobes, seem to be associated with more complex psychotic manifestations, including mixed anxiety and depression disorders, and personality disorders with severe depressive episodes. This indicates a complex interdependence between the location of the tumor and the type of psychotic manifestation. These data highlight the fact that there is a significant association between the location of brain tumors and specific psychotic manifestations. Tumors located in the frontal lobes, in particular, seem to be linked to a variety of mental disorders, including organic personality disorders, anxiety and depression disorders, and cognitive disorders.

Although immunohistochemical analysis was applied to all 91 patients included in the study, detailed images of the results were only available for 30 of them. This subset of images allowed for a more thorough visual examination and provided additional data for interpreting the results. Among them, 40% were men and 60% were women. The average age of the patients was 53 years, with a range between 25 and 81 years. The distribution by sex and age is presented in Figure 1.

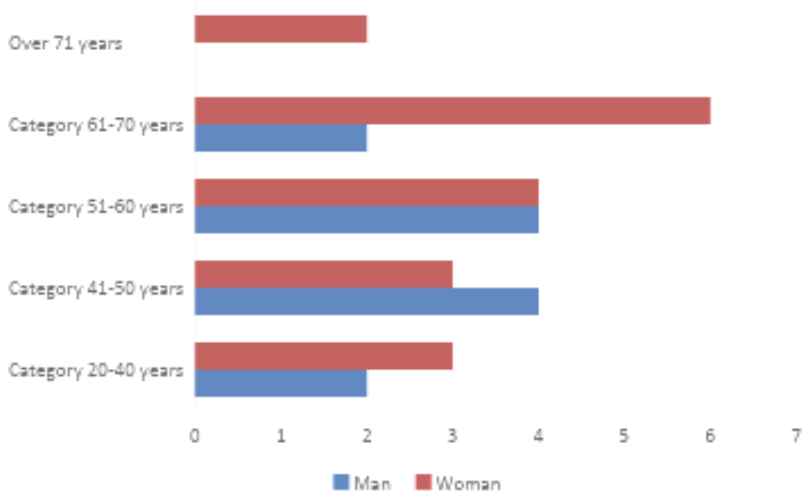

Figure 1. The distribution by gender and age of the subset.

In our study, we analysed data from 30 patients diagnosed with various types of brain tumors, distributed as follows: grade 0 tumors - astrocytoma (diffuse, gemistocytic, and fibrillar) and meningioma (meningoepithelial and atypical), grade I tumors - oligodendroglioma and gliosarcoma, and grade II tumors - glioblastoma. In addition to these primary tumors, our study also includes cases of brain metastases, such as carcinoma, poorly differentiated anaplastic carcinoma, adenocarcinoma, and invasive breast carcinoma. This diversity of tumor types and grades allows us to evaluate the variability of histological and immunohistochemical characteristics specific to each type of tumor, thus contributing to a deeper understanding of the complexity and heterogeneity of brain tumors and associated metastases.

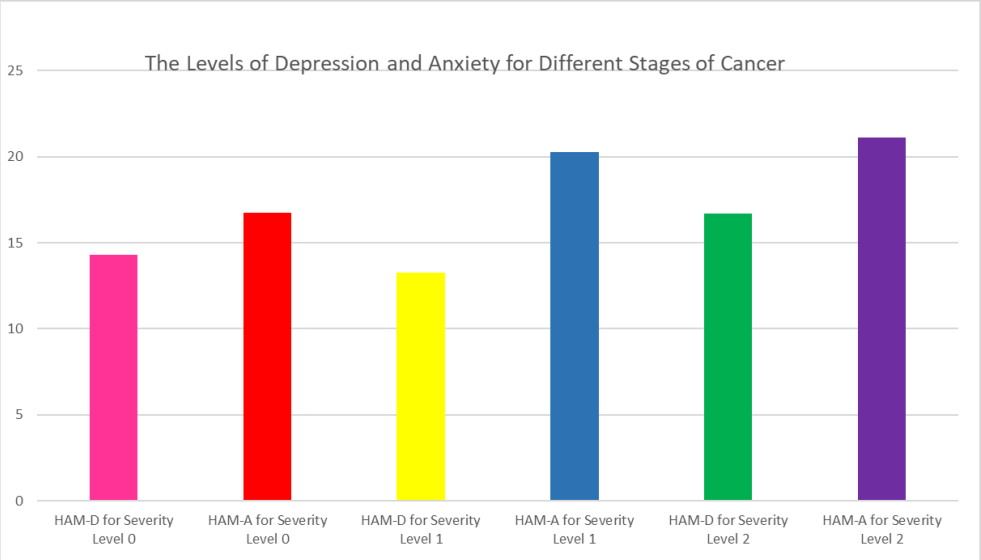

Figure 2. This figure illustrates different levels of anxiety and depression measured across the stages of cancer. The data is represented using bar graphs, with one set of bars corresponding to anxiety levels (measured by Hamilton Anxiety Rating Scale - HAM-A) and the other to depression levels (measured by the Hamilton Depression Rating Scale - HAM-D). The figure highlights significant differences in psychological impact as the disease progresses, showing the need for customised mental health interventions at each stage.

We conducted a comprehensive statistical evaluation of the levels of depression and anxiety associated with various stages of cancer. Our analysis aimed to identify significant differences and correlations between the psychological impact and the progression of the disease, providing valuable insights for patient care and support (Figure 2).

The scales used for this evaluation were the Hamilton Depression Rating Scale (HAM-D) and the Hamilton Anxiety Rating Scale (HAM-A).

To evaluate the impact of severity level on depression and anxiety, one-way ANOVA analyses were conducted using HAM-D (depression) and HAM-A (anxiety) scores as dependent variables.

Depression (HAM-D) and Severity Level

The results of the ANOVA analysis (Figure 3) did not indicate a statistically significant difference between severity levels in terms of depression scores ($F(2,8) = 0.36$, $P = 0.706$). The coefficient of determination, R-Sq = 8.33%, suggests that only a small portion of the variability in HAM-D scores can be attributed to the severity level. Additionally, the adjusted R-Sq value (0.00%) indicates a total lack of adjustment for model complexity, suggesting that severity level does not significantly contribute to the variability in depression scores in this sample. These findings are also supported by the analysis of the individual 95% confidence intervals for means, which show substantial overlap between the severity levels, further emphasising the lack of relevant differences between the groups.

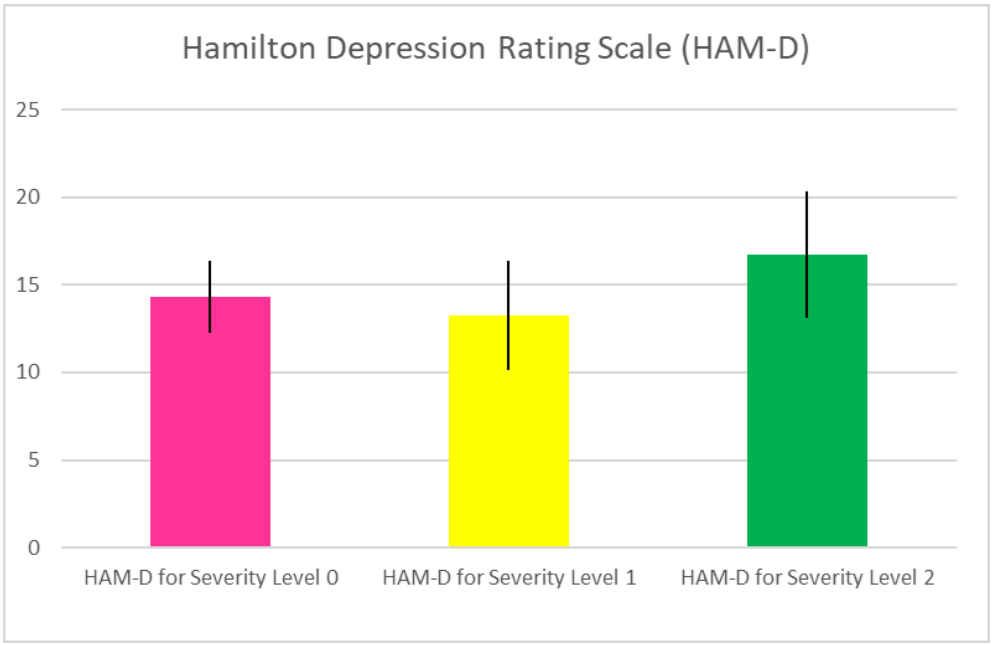

Figure 3. The graph shows that there is no statistically significant difference in HAM-D depression scores across different severity levels. The R-Sq value of 8.33% indicates minimal variability explained by severity level, and the 95% confidence intervals for the means overlap significantly, suggesting no meaningful differences between the groups.

The correlation coefficient r = 0.111 indicates a very weak and positive correlation between severity level and depression. This means that there is a very weak linear relationship between the two variables, but it is so weak that it practically does not suggest a meaningful association between them. The p-value = 0.746 is much larger than the conventional significance level (usually 0.05). This indicates that there is insufficient statistical evidence to reject the null hypothesis. The null hypothesis, in this case, would be that there is no significant linear relationship between severity level and depression in the studied population. Given the very low correlation coefficient (r = 0.111) and the very high p-value (p = 0.746), we can conclude that there is no significant linear relationship between severity level and depression in this sample of 91 participants. In other words, the severity level does not appear to be significantly associated with depression levels in this study (Figure 4).

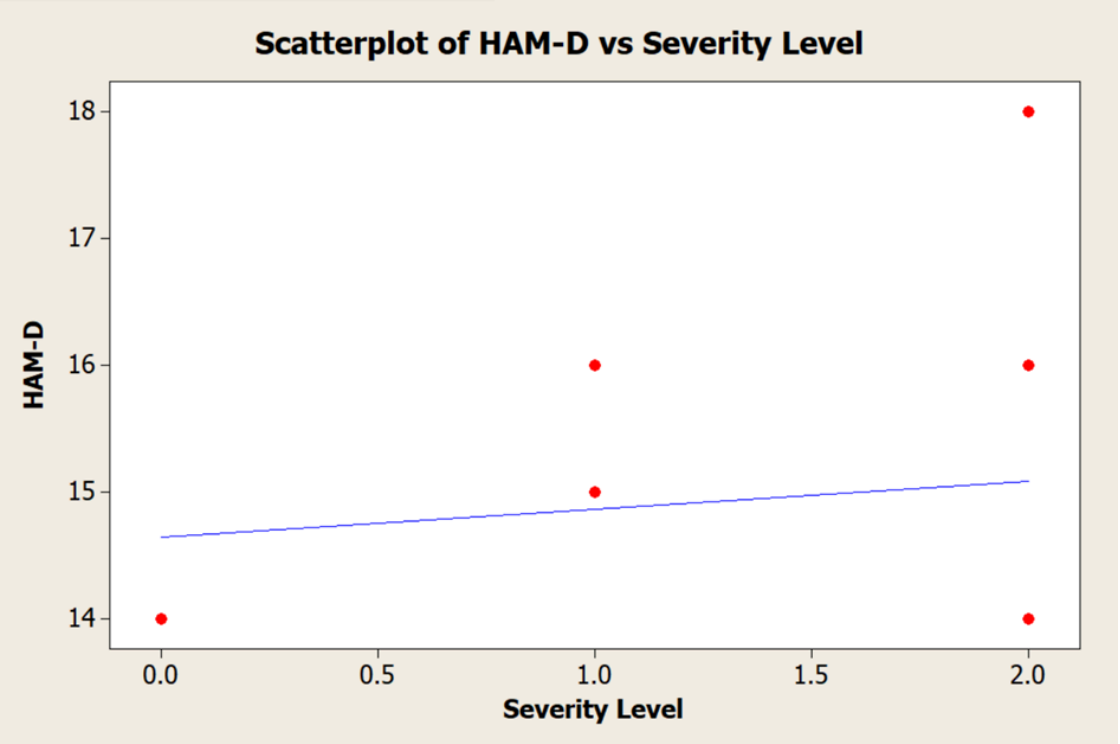

Figure 4. The scatterplot shows a very weak and positive correlation between severity level and depression (r = 0.111). The data points are widely dispersed, indicating that there is no meaningful linear relationship between severity level and depression. The high p-value (0.746) further confirms the lack of significant association between the two variables in this sample.

Anxiety (HAM-A) and Severity Level

Regarding anxiety scores (HAM-A) (Figure 5), the ANOVA analysis showed an $F(2,8) = 2.52$ and a $P = 0.142$. Although this P-value does not reach the conventional significance threshold (0.05), the results indicate a trend towards significance, suggesting that there might be a relationship between severity level and anxiety, but it is not strong enough to be considered significant in this sample. The R-Sq of 38.64% suggests that nearly 39% of the variability in anxiety scores can be explained by the severity level, a much more robust result compared to the depression analysis. This indicates a stronger relationship between anxiety and severity level, although the adjusted R-Sq (23.30%) suggests that some of these results might be due to internal group variations rather than real differences between severity levels. The confidence intervals show a slight overlap between the severity levels, highlighting that there may be a possible difference between groups that require further investigation with a larger sample size to achieve statistical significance.

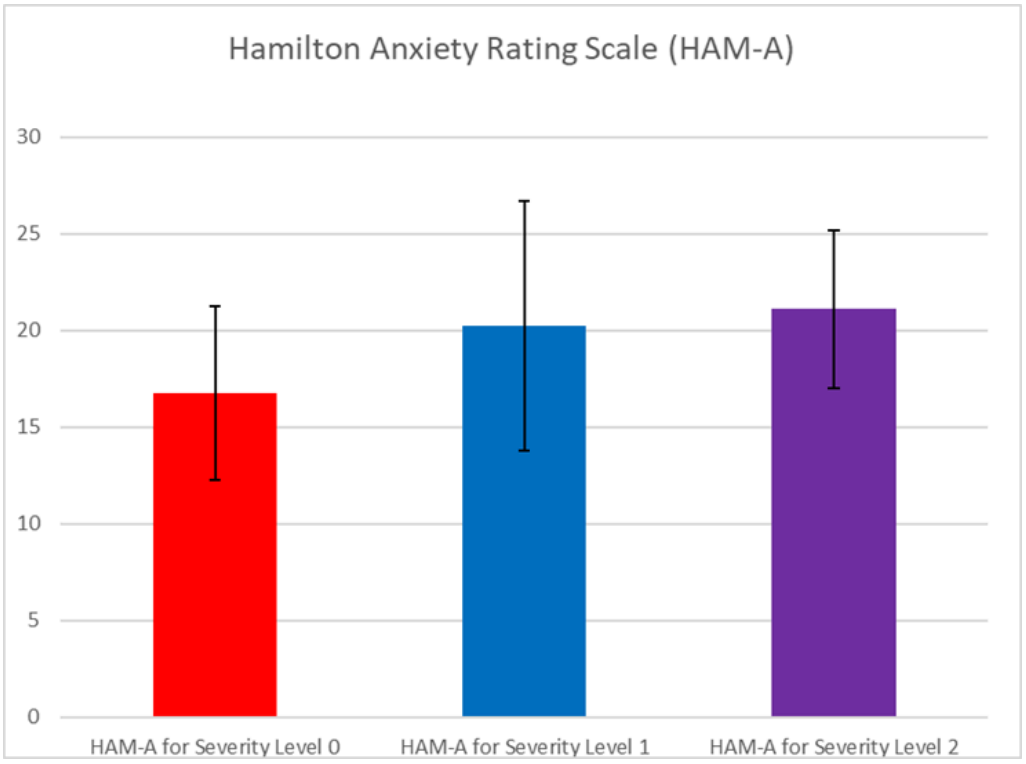

Figure 5. The graph shows a trend towards a relationship between severity level and HAM-A anxiety scores (F(2,8) = 2.52, P = 0.142), though not statistically significant. The R-Sq value of 38.64% suggests a notable relationship, but the adjusted R-Sq of 23.30% indicates some variability might be due to internal group differences. The confidence intervals show slight overlap, suggesting potential differences that require further investigation with a larger sample.

The correlation coefficient r = -0.529 indicates a moderate negative correlation between severity level and anxiety (Figure 6). This means that as the severity level increases, anxiety levels tend to decrease moderately. In other words, there is a moderate inverse relationship between the two variables. The p-value = 0.094 is higher than the conventional significance threshold of 0.05, but relatively close to it. This suggests that although there is a trend toward statistical significance, it is not strong enough to reject the null hypothesis at a 0.05 significance level. In other words, there is insufficient evidence to assert with certainty that the observed negative relationship in the sample exists in the general population. The moderate negative correlation (r = -0.529) indicates a moderate inverse relationship between severity level and anxiety, where an increase in severity is associated with a decrease in anxiety. However, the p-value = 0.094 suggests that this relationship is not statistically significant at the conventional 0.05 level. Therefore, we cannot conclusively state that this relationship exists in the general population, but there is an indication that such a relationship might exist, which could become significant with a larger sample or a higher significance threshold.

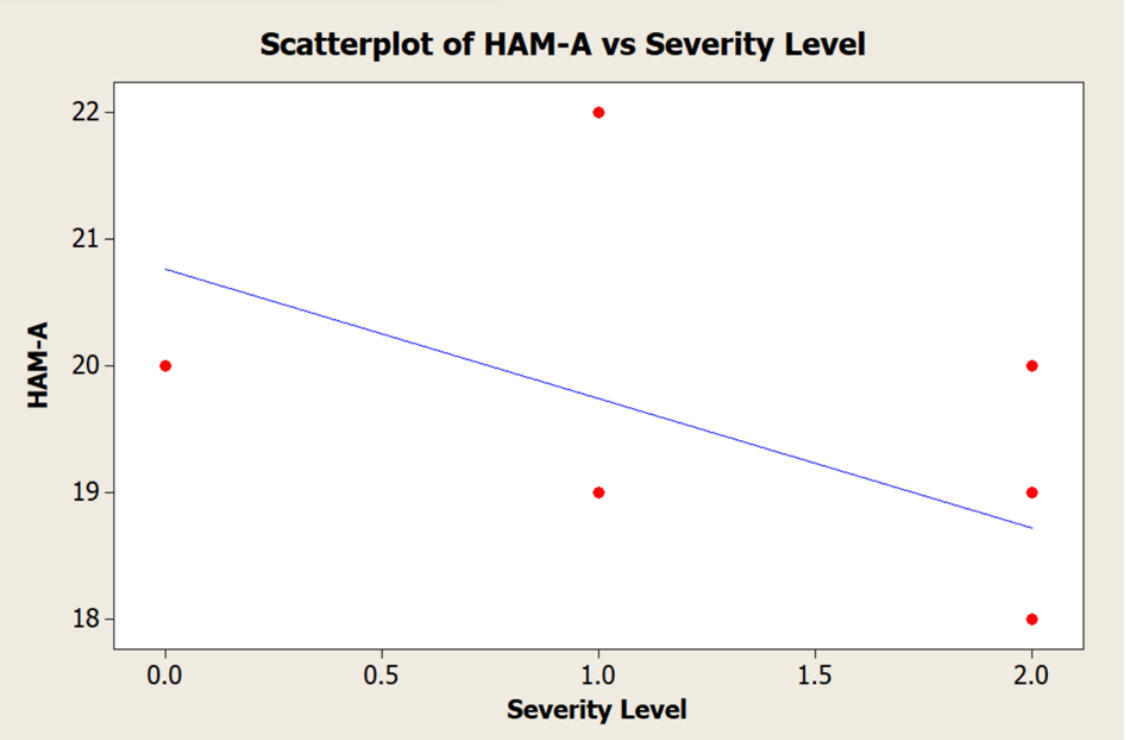

Figure 6. The scatterplot reveals a moderate negative correlation between severity level and anxiety (r = -0.529). As the severity level increases, anxiety levels tend to decrease moderately. The data points show a general downward trend, suggesting an inverse relationship between the two variables. Although the p-value (0.094) is close to the conventional significance threshold of 0.05, it does not reach it, indicating that while there is a trend toward significance, the relationship is not statistically significant at this level.

The range of tumor types and grades enables us to assess the variability in histological features unique to each type, deepening our understanding of the complexity and diversity of brain tumors and their associated metastases.

Glioblastomas are characterised by their densely cellular nature, with medium-sized tumor cells that have indistinct cell borders, irregular nuclei, and coarse chromatin. High mitotic activity is evident, with up to 14 mitoses per mm². The tumor also displays numerous intratumoral vessels that show endothelial-pericytic proliferation, often with a glomeruloid appearance. Additionally, extensive areas of necrosis are frequently observed. Immunohistochemically, they show intense GFAP and vimentin positivity, IDH1 negativity, and 100% ATRX positivity in tumor nuclei. p53 is positive in less than 80% of nuclei. These characteristics are critical for accurate diagnosis and understanding of glioblastoma pathology.

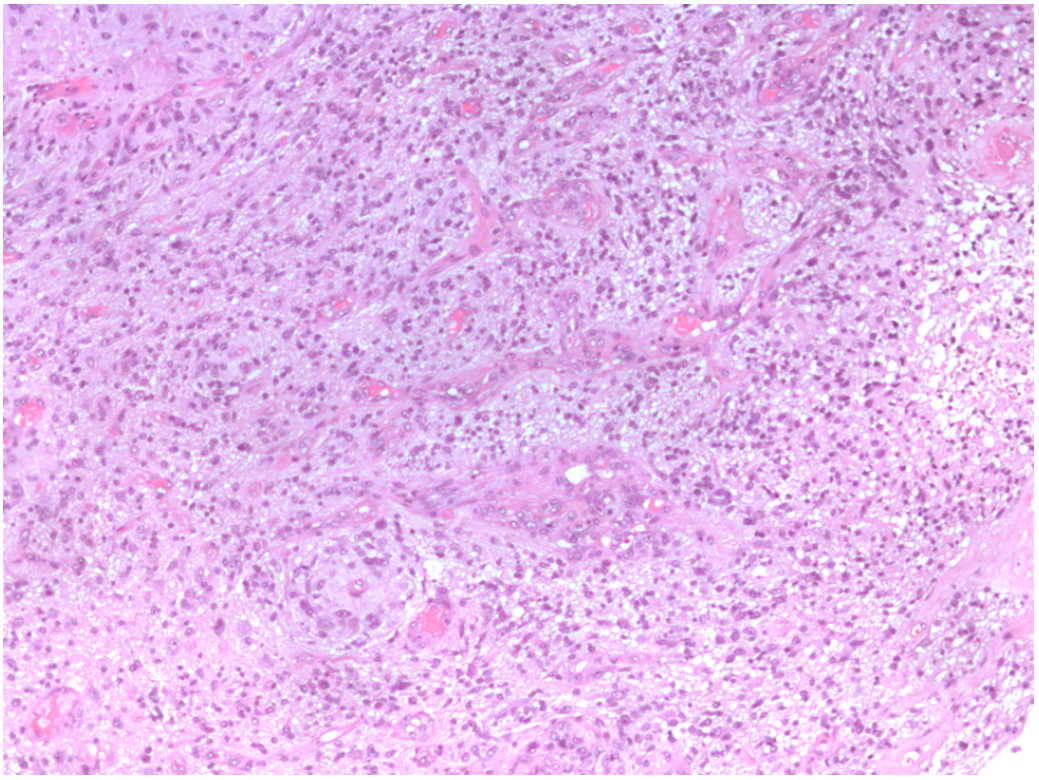

Figure 7. Glioblastoma - Microscopic features: a densely cellular tumor composed of pleomorphic astrocytes diffusely arranged on a fibrillar background. The intratumoral vessels are numerous and exhibit endothelial-pericytic proliferation, often with a glomeruloid appearance. Extensive areas of necrosis are also observed within the tumor (HE, x100).

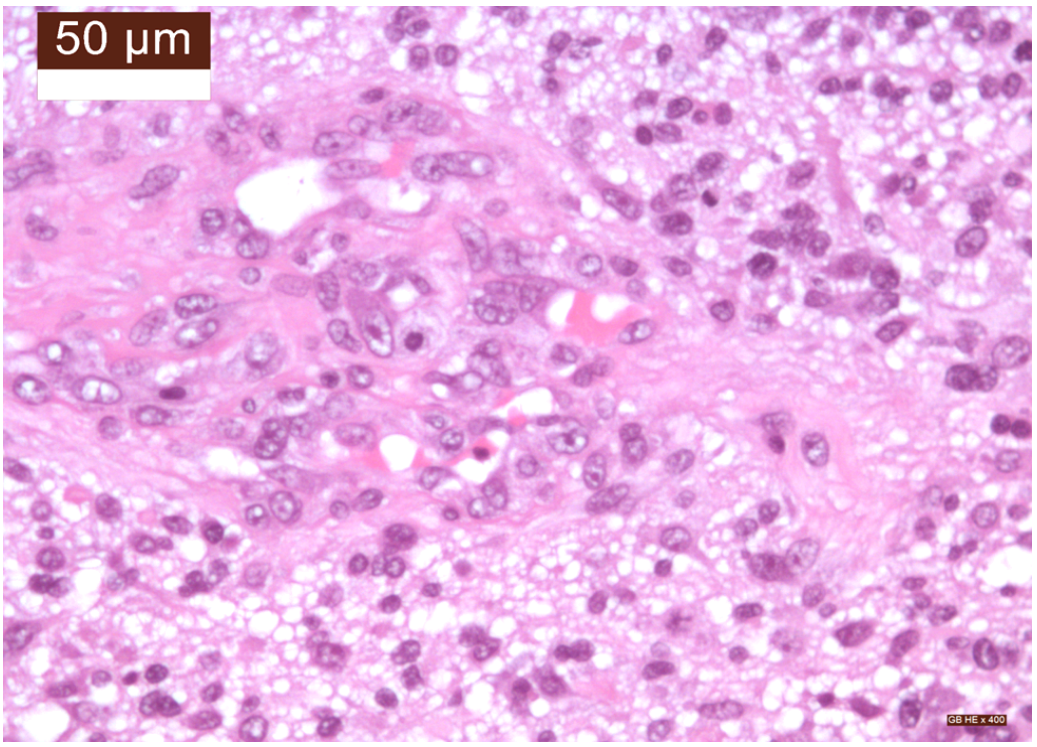

Figure 8. Glioblastoma - Microscopic features: The intratumoral vessels exhibit endothelial-pericytic proliferation, often with a glomeruloid appearance. Mitotic activity is present both in the proliferating endothelial cells and in the tumor glial cells (HE, x100).

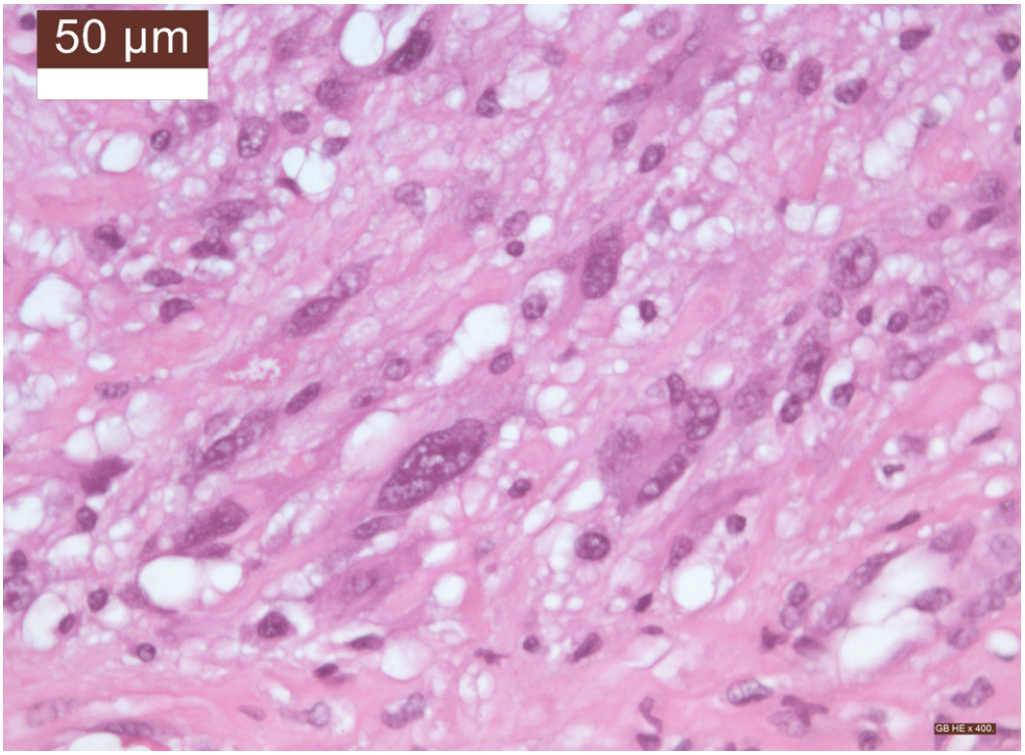

Figure 9. Glioblastoma - Microscopic features: The tumor cells are of medium size, with indistinct cell borders, irregular nuclei, coarse chromatin, and increased mitotic activity (14 mitoses/mm²) (HE, x400).

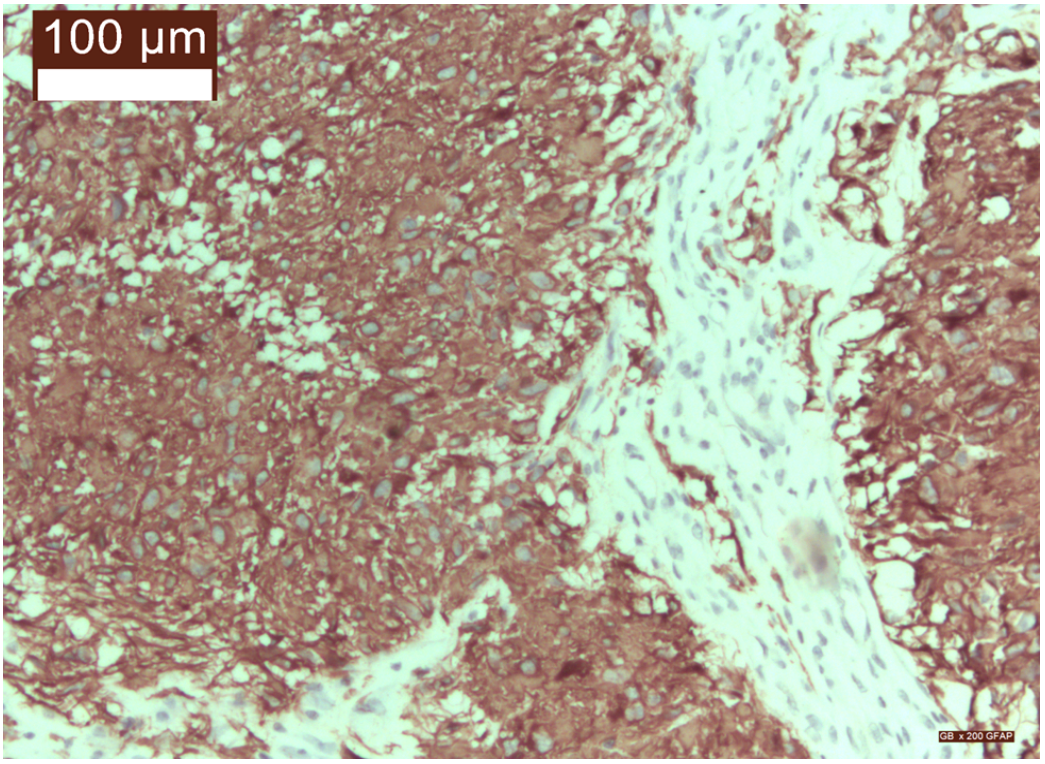

Figure 10. Glioblastoma - Immunohistochemical features: GFAP is intensely positive in the cytoplasm of tumor cells (anti-GFAP antibody, x200).

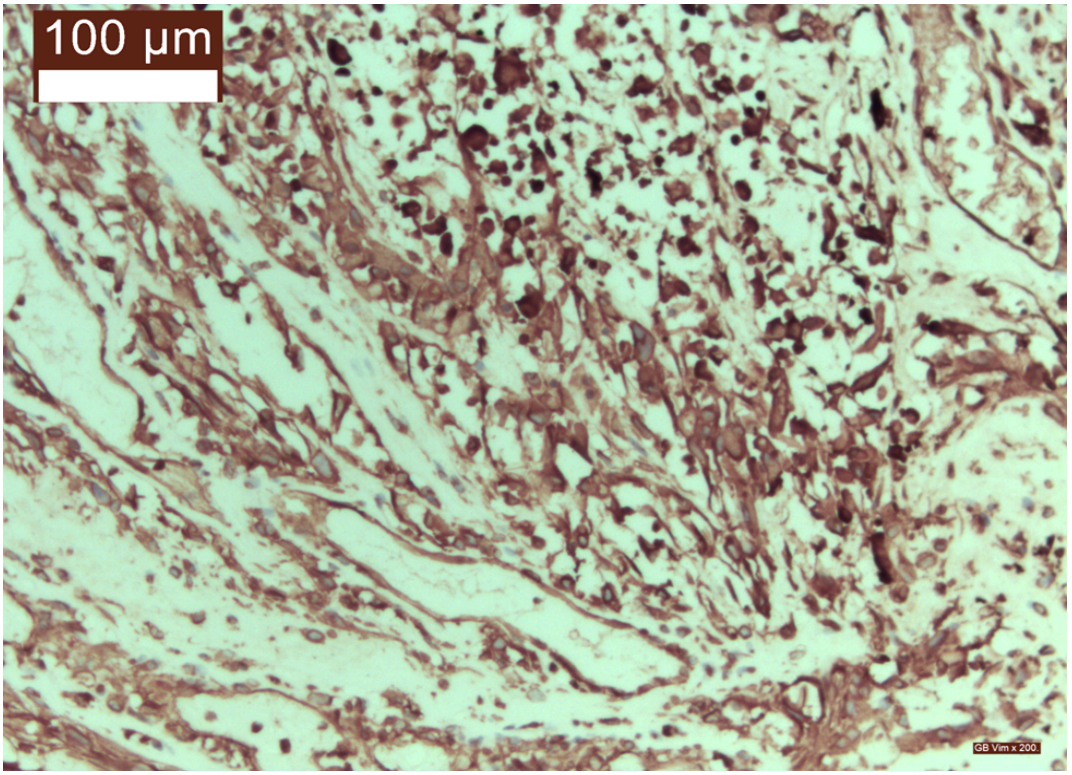

Figure 11. Glioblastoma - Immunohistochemical features: Vimentin is intensely positive in the cytoplasm of tumor cells (anti-Vimentin antibody, x200).

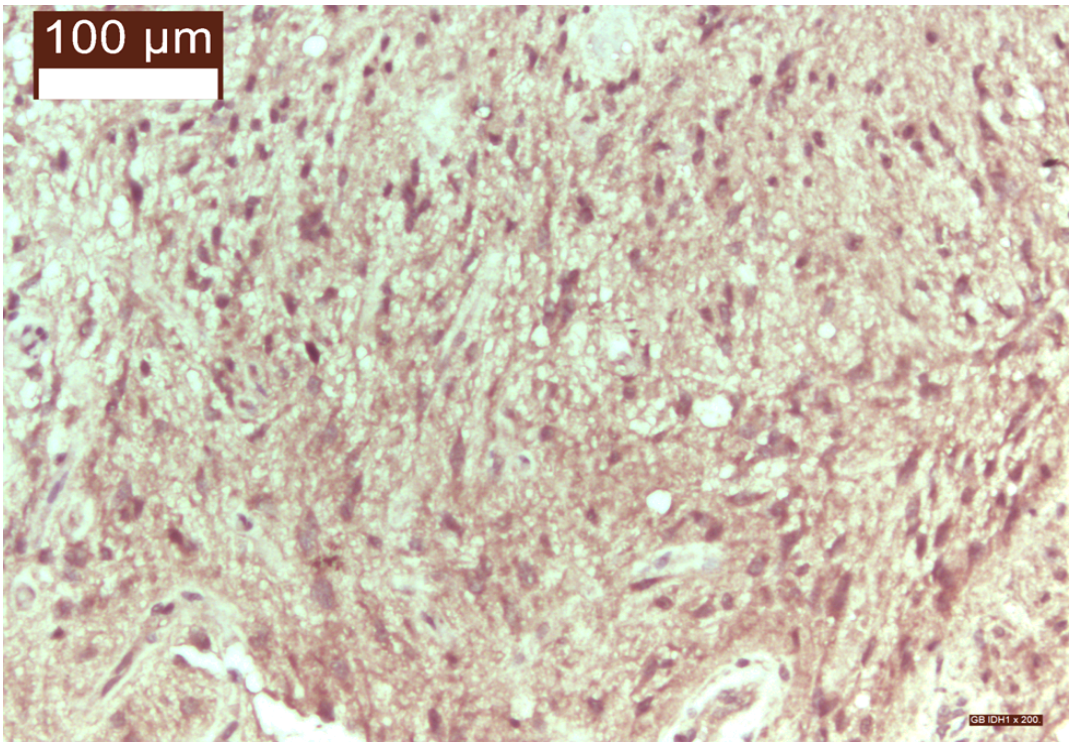

Figure 12. Glioblastoma - Immunohistochemical features: IDH1 is negative (anti-IDH1 antibody, x200).

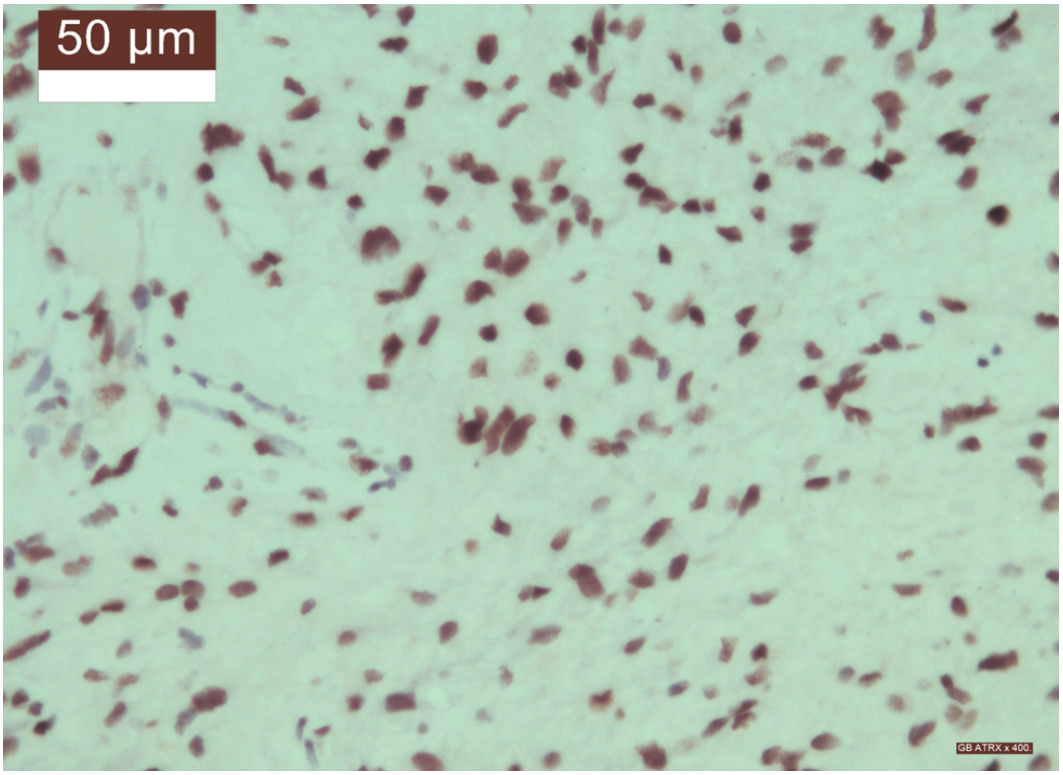

Figure 13. Glioblastoma - Immunohistochemical features: ATRX is intensely positive in 100% of the tumor cell nuclei (anti-ATRX antibody, x400).

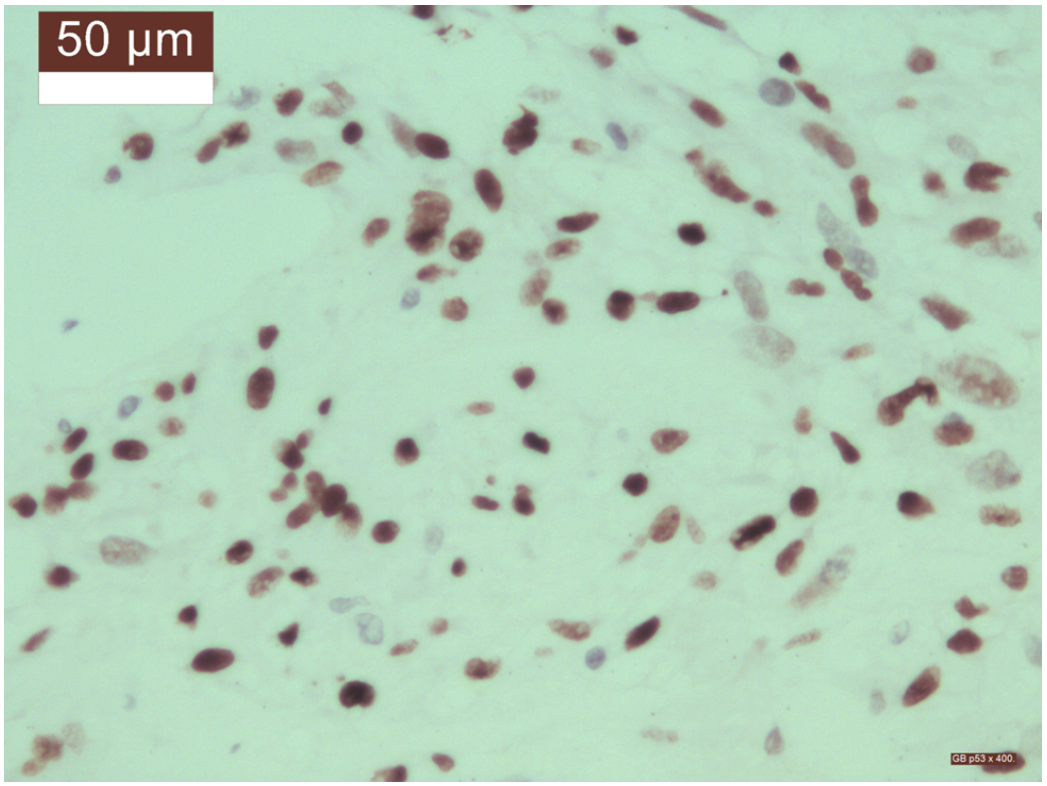

Figure 14. Glioblastoma - Immunohistochemical features: p53 is positive in less than 80% of the tumor cell nuclei (anti-p53 antibody, x400).

8. Discussions

This study explored in detail the psychiatric manifestations in patients diagnosed with primary brain tumors, trying to identify patterns and the prevalence of these symptoms in the context of the oncological disease. Our analysis focused on evaluating the frequency and types of psychiatric disorders among patients of both sexes.

Common psychological and emotional reactions to cancer are the result of realising the life-threatening diagnosis, uncertainty about prognosis, and fears of death. Psychological issues such as symptoms of anxiety, symptoms of depression, psychological distress, and fear of cancer recurrence are frequently reported in cancer patients (Krebber et al., 2014; Simard et al., 2013; Mitchell et al., 2013). Even though most cancer patients and their families have established normal psychological functioning (Kornblith, 1998), psychological suffering states are common in individuals with cancer. The frequency of mental suffering varies depending on the type of cancer, the moment when it is diagnosed, the severity involved in physical and role impairment, the level of pain, prognosis, and other factors. The prevalence of psychiatric symptoms in primary brain tumors is between 50 and 78%, including various disorders such as mania, psychosis, anxiety, and personality changes (Madhusoodanan et al., 2010). In our study, we observed that the three most common psychiatric manifestations associated with primary brain tumors are "Organic personality disorder", found in 29% of men and 32% of women. The next most common disorder is "Mixed anxiety and depression disorder", present in 12% of women and 17% of men. In third place is "Organic personality disorder, moderate depressive episode", which occurs in 12% of men and 14% of women.

Tumors located in the frontal or limbic regions are more likely to present personality changes (Lloyd & Guthrie, 2007; Moise & Madhusoodanan, 2006). Personality changes are constant, showing significant differences compared to previous personality patterns. Anxiety disorders are particularly prevalent in tumors located in the left frontal lobe, which may be explained by the functional specialisation of this brain region. The left frontal lobe plays a critical role in regulating mood, decision-making, and emotional responses, with dysfunctions often leading to heightened anxiety and difficulty managing stress. Our findings align with those reported by Madhusoodanan et al. (2004), who highlighted the left frontal lobe’s involvement in emotional regulation and its vulnerability to psychiatric disruptions in brain tumor patients. Additionally, studies such as those by Cummings (1993) emphasise the frontal lobe's role in integrating higher-order cognitive and emotional functions, which may explain the observed correlation. By comparing these results, it becomes evident that tumor-induced damage to this region exacerbates anxiety symptoms, underscoring the need for targeted psychiatric interventions in such cases. The patient presents an unstable affect, lack of inhibition in controlling impulses, aggressive behavior, apathy, paranoia, or a combination of symptoms. These changes are characteristic of frontal lobe syndrome, which includes slowing of the thinking process, judgment problems, lack of curiosity, social isolation, and high levels of aggression (Sarkhel, 2009). These patients seem to lack energy and knowledge, but they could become suddenly aggressive due to loss of impulsive control. As supported by specialised literature, organic personality disorders are frequently encountered in the context of brain tumors. In our study, 29% of men exhibited this type of manifestation, while women had an even higher incidence, at 32%. These data support specializâsed literature, demonstrating that psychiatric disorders are often associated with brain tumors located in the frontal lobe. Regarding statistics for women, the highest proportion of tumor localisation is in the left frontal lobe, representing 36% of cases, followed by the right frontal lobe with 15%. Regarding the statistics for men, the largest proportion of tumor localisation is in the left frontal lobe, with 38%, followed by the right frontal lobe with 31%. These findings highlight the importance of tumor localisation in determining psychiatric symptoms and are consistent with observations reported in the specialised literature.

High levels of long-term mental suffering in cancer patients can cause anxiety, depression, or both (Linden et al., 2012). Two-thirds of cancer patients suffering from depression also have

clinically significant levels of anxiety, which is a common manifestation in this situation (Brintzenhofe-Szoc et al., 2009). According to Mainio et al. (2011), 44% of total brain tumor patients, primary and metastatic, have been diagnosed with depression, which is associated with functional impairment, cognitive dysfunction, decreased quality of life, and reduced survival rate (Rooney, Carson, & Grant, 2011). It has also been noticed that depression was more frequently encountered in frontal lobe tumors (Filley & Kleinschmidt-DeMasters, 1995; Cummings, 1993). In our study, it was found that depression was more frequently encountered in frontal lobe tumors. In the case of women, 8% suffer from mixed anxiety and depression disorder, with 40% of tumors showing this manifestation being located in the left frontal lobe, while 20% are located in the right frontal lobe. In the case of men, the percentage of mixed anxiety and depression disorder is 17%, with the highest percentage of brain tumors causing this disorder being in the left and right frontal lobes, with 33% in the left frontal lobe and 50% in the right frontal lobe.

According to the information provided by the Central Brain Tumor Registry in the United States, glioblastomas represent 51%, anaplastic astrocytomas 8%, and oligodendrogliomas 10% of the total primary brain and central nervous system gliomas (Larjavaara et al., 2007). Similarly, in our study, glioblastomas were predominant, representing 50% of cases, followed by anaplastic astrocytomas, with a proportion of 9%. Both the disease and its therapy directly affect brain function in glioblastoma. Patients tend to have neurological, cognitive, or psychiatric problems while being diagnosed and treated (Lucas, 2010).

Brain metastases are a common complication of cancer and the most frequent type of brain tumor. Between 10% and 26% of patients develop brain metastases (Smedby et al., 2009). Primary cancers such as lung, breast, and melanoma are most likely to metastasize to the brain. It is rare for other types of malignancies, such as prostate or head and neck cancer, to spread to the brain (Amsbaugh & Kim, 2023). Out of the 91 patients studied, approximately 16% were identified with brain metastases. This percentage indicates that there are fewer metastatic tumors compared to non-metastatic tumors in this study group. There are various forms of metastases, all of which are represented by a small percentage in the sample, reflecting the diversity of the origin of metastatic tumors. The metastases are distributed in various areas of the brain, including the frontal, parietal, and temporal lobes, both on the right and left side. As mentioned in the literature and our study, among the observed metastases, the most common were metastases from invasive breast carcinoma and papillary bronchopulmonary carcinoma.

9. Conclusion

Considering the high prevalence of psychiatric manifestations in patients with brain tumors, a detailed neuropsychiatric evaluation is essential for the correct diagnosis and proper management of these disorders. Clinicians must be attentive to possible psychotic symptoms in patients with brain tumors, especially in the case of frontal tumors.

Immunohistochemical identification is very important in understanding how brain tumors develop and their molecular characteristics, having a major impact on treatment plans and patient prognosis. This method of analysis facilitates a more detailed evaluation of the types of cancer cells and specific markers, influencing the development of more precise and effective treatments.

The differences in the distribution by the stages of cancer and the specific location of tumors suggest that therapeutic approaches should be personalised. To implement personalised treatments in clinical settings, multidisciplinary teams should integrate neuropsychological assessments and advanced imaging techniques to map tumor locations and their potential impact on psychiatric symptoms. For example, patients with left frontal lobe tumors exhibiting severe anxiety or personality changes may benefit from early psychiatric intervention combined with tailored neuro-oncological therapies. Furthermore, incorporating biomarkers such as immunohistochemical profiles (e.g., GFAP, IDH1, ATRX) could refine prognostic predictions and guide treatment decisions.

Future studies should explore the relationship between less commonly studied tumor locations, such as the parieto-occipital lobes, and psychiatric symptoms. Investigations into the effects of emerging therapies, including targeted molecular treatments or immunotherapy, on the neuropsychiatric outcomes of brain tumor patients, could provide critical insights. Additionally, longitudinal studies tracking changes in psychiatric symptoms pre- and post-treatment across various tumor types and locations would be invaluable for developing more effective, individualised care plans. Treatment should take into consideration both the anatomical location of the tumor and the demographic factors of the patients in order to optimise clinical outcomes. Future studies should explore in depth the interactions between tumor location, psychiatric manifestations, and immunohistochemical profiles in order to develop more efficient and personalised treatment strategies.

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