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Study Of Prognosis And Behavior Of CNS Tumors Based On Ki63 And p53 Index.

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ABSTRACT

Our retrospective study aimed to investigate the prognostic significance of WHO grading, mitotic activity, and the expression of Ki67 and p53 in central nervous system (CNS) tumors. The cohort included 50 patients with histologically confirmed CNS tumors treated at a tertiary healthcare center from January 2020 to June 2021. WHO Grade II tumours were most prevalent (38%), followed by Grade IV (24%). Mitosis was observed in 14% of cases, and necrosis was present in 38%. Ki67 expression varied across tumor types, with the majority (52%) exhibiting less than 5% positivity. Notably, glioblastoma multiforme showed higher Ki67 positivity (36% > 10%). P53(p53) expression correlated with the WHO grade, with astrocytomas showing a notable association with high p53 expression (3+). Ki67 and p53 expression patterns varied across diagnoses, emphasizing the diverse molecular landscape of CNS tumors. This study provides comprehensive insights into the grading and molecular characteristics of CNS tumors, highlighting their heterogeneity. The associations between WHO grading, mitotic activity, and Ki67/p53 expression contribute to a nuanced understanding of tumor behavior. These findings underscore the need for a multimodal approach to tumor assessment for improved prognostication and personalized treatment strategies.

Keywords: Central Nervous System Tumors, WHO Grading, Ki67, p53.

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INTRODUCTION

The study of prognosis and behaviour in central nervous system (CNS) tumors has become increasingly intricate with the advent of molecular markers such as Ki-67 (Ki63) (Ki67) and p53 [1]. These markers play a pivotal role in elucidating the underlying biological mechanisms that govern tumor progression and response to treatment. Ki-67 is a cell proliferation marker, reflecting the growth fraction of tumor cells, while p53 is a tumor suppressor gene involved in cell cycle regulation [2]. Together, they provide valuable insights into the aggressive nature and potential therapeutic responsiveness of CNS tumors [3]. Understanding the correlation between Ki-67 and p53 indices and the clinical outcomes of CNS tumors holds immense significance for tailoring personalized treatment strategies and predicting patient prognosis [4]. Our research work aims to delve into the intricate interplay of these molecular markers, shedding light on their prognostic implications and paving the way for enhanced precision medicine approaches in the management of CNS tumors.

METHODOLOGY

The study, conducted from January 2020 to June 2021 at a tertiary healthcare center, employed a descriptive cross-sectional design to investigate the prognosis and 343ehaviour (behaviour)of central nervous system (CNS) tumors based on Ki-67 and p53 indices. Ethical approval was obtained from the Ethical Committee prior to commencement.

The sample size, calculated using the formula $N=(Z\alpha+Z\beta \text{ error})^2 \times PQ/E^2$, revealed a low prevalence of CNS tumors (10/100,000), leading to a small expected sample size. However, due to the tertiary care nature of the institute and the availability of approximately 100 CNS tumor samples, a sample size of 50 was chosen for the study. Selection criteria included histopathologically confirmed cases of CNS tumors obtained from neurosurgical specimens, while cases with neoadjuvant therapy or inadequate/hemolyzed/autolyzed specimens were excluded.

Tissue samples from primary tumors, obtained between January 2020 and June 2021, were processed by slicing at 5mm thickness and fixing in 10% formalin for 24 hours. Formalin-fixed paraffin-embedded sections, 4-5µm thick, were stained with Hematoxylin and eosin for histopathological evaluation, focusing on assessing histological type and tumor grade according to the WHO classification of CNS tumors 2016. Immunohistochemical examination, using Ki-67 and p53 markers, was conducted on representative tumor paraffin blocks. The slides were examined for nuclear staining, with materials including well-fixed sections, APES/Poly-L-Lysine coated slides, a microwave (EZ-Retriever System), antigen retrieval solution, phosphate buffer saline, primary antibody ready-to-use, polymer detection kit, hematoxylin stain, and mounting media. The examination aimed to elucidate the correlation between these markers and the clinical outcomes of CNS tumors.

RESULTS

Table 1: WHO grading and number of patients:

WHO Grade	Number of patients	Percentage (%)
1	12	24%
2	19	38%
3	7	14%
4	12	24%
Total	50	100%

We graded all the tumors according to the WHO grading system and it was noted that WHO grade II was most commonly found in all the tumors which was followedby WHO grade IV.

Table 2: Mitosis and Necrosis in CNS tumors

	Number of patients	Percentage (%)
Mitosis	7	14.0
Necrosis	19	38.0

IIn the 50 cases studied it was found out that 7 of the cases showed mitosis and 18 cases showed necrosis. The mitosis and necrosis noted in such cases were acknowledge during the grading of the tumors. 3 out of 50 cases showed both mitosis as well as necrosis.

Table 3: Comparison of Ki67 with the diagnosis:

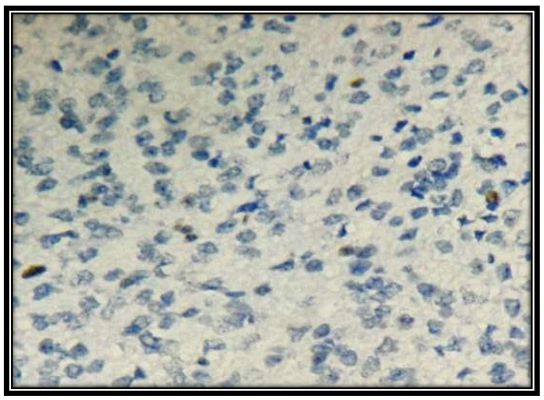
Diagnosis	Ki67			Total
	≤ 5	5.01 - 10.0	> 10	
Astrocytoma	2	7	0	9
Ependymoma	3	0	0	3
Extra ventricular neurocytoma	1	0	0	1
Glioblastoma Multiforme	2	5	4	11
Glioma	3	3	0	6
Gliosarcoma	0	1	0	1
Medulloblastoma	0	1	0	1
Meningioma	8	4	0	12
Oligodendroglioma	1	1	0	2
Papillary Adenocarcinoma	1	0	0	1
Pituitary adenoma	2	0	0	2
Schwanomma of CP Angle	1	0	0	1
Total	24	22	4	50

Ki67 was applied to all the cases of the CNS tumors including meningioma, glioblastoma multiforme, ependymoma, astrocytoma, etc. Maximum cases included were grade II WHO followed by grade IV and grade I.

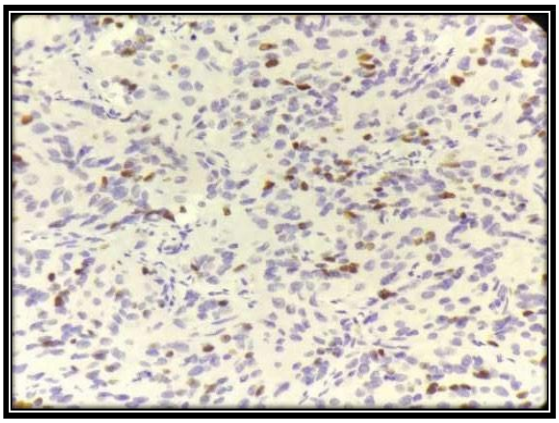
Table 4: p53 scoring with WHO grade of CNS tumors:

Diagnosis	P53				Total
	0(no stain)	1+(<10%)	2+(10-50%)	3+(>51%)	
Astrocytoma	0	0	8	1	9
Ependymoma	2	0	1	0	3
Extra ventricular neurocytoma	1	0	0	0	1
GlioblastomaMultiforme	1	0	6	4	11
Glioma	1	1	2	2	6
Gliosarcoma	0	0	1	0	1
Medulloblastoma	0	0	1	0	1
Meningioma	0	0	9	3	12
Oligodendroglioma	0	0	0	2	2
Papillary Adenocarcinoma	0	0	1	0	1
Pituitary adenoma	1	0	1	0	2
Schwanomma of CPAngle	0	1	0	0	1
Total	6	2	30	12	50

p53 expression in medulloblastoma: p53=60%(p53=+++)



Ki67 expression in oligodendrogliomaKi67=3%)



DISCUSSION

The results of this study provide valuable insights into the grading, mitotic activity, necrosis, and the expression of Ki67 and p53 in various central nervous system (CNS) tumors [5, 6]. The distribution of WHO grades among the studied cases is noteworthy, with Grade II being the most prevalent (38%), followed by Grade IV (24%). This distribution reflects the spectrum of tumor aggressiveness, with higher-grade tumors typically exhibiting more aggressive behavior. The finding of a substantial proportion of Grade II tumors aligns with the clinical observation that CNS tumors often present with varying degrees of malignancy [7].

Mitotic activity and necrosis, essential parameters in tumor grading, were also assessed in the study. The presence of mitosis in 14% of cases and necrosis in 38% further supports the diverse nature of CNS tumors. These features, along with the WHO grading, contribute to a comprehensive understanding of the biological behavior and potential aggressiveness of the tumors. The co-occurrence of mitosis and necrosis in 6% of cases emphasizes the heterogeneity within the studied cohort, suggesting that a subset of tumors may exhibit both proliferative and necrotic features, potentially influencing prognosis [8].

The application of Ki67, a proliferation marker, revealed interesting associations with the diagnosis of CNS tumors. Notably, the majority of cases showed less than 5% Ki67 positivity, indicating a relatively low proliferative index in this cohort. The distribution of Ki67 positivity across different diagnoses provides a nuanced perspective on the proliferative potential of distinct tumor types. For instance, glioblastoma multiforme, known for its aggressive behavior, exhibited higher Ki67 positivity, with 4 cases (36%) showing more than 10% positivity. In contrast, meningiomas, generally considered less aggressive, displayed predominantly low Ki67 expression.

The correlation between p53 expression and the WHO grade of CNS tumors adds another layer of complexity to the study findings. High p53 expression (3+, >51%) was observed in various tumor types, including astrocytoma, glioblastoma multiforme, and meningioma. Interestingly, astrocytomas showed a

notable association with high p53 expression, with 8 out of 9 cases falling into the 2+ and 3+ categories. This underscores the potential role of p53 as a marker of genetic instability and malignant transformation in certain CNS tumors.

Comparing the results of Ki67 and p53 expression across different diagnoses reveals intriguing patterns. While Ki67 primarily reflects proliferative activity, p53 expression may signify underlying genetic alterations. The heterogeneity in Ki67 and p53 expression observed across different tumor types underscores the diverse molecular landscape of CNS tumors. These findings align with the evolving understanding of CNS tumor biology, emphasizing the need for a multimodal approach to tumor characterization.

The study's strengths lie in its comprehensive approach to assessing multiple parameters, including WHO grading, mitotic activity, necrosis, and immunohistochemical markers. However, several limitations warrant consideration. The relatively small sample size may limit of the findings, and the retrospective nature of the study may introduce selection bias. Additionally, the use of a single tertiary healthcare center may not fully capture the diversity of CNS tumors seen in broader populations.

CONCLUSION

In conclusion, this study contributes valuable data on the grading, mitotic activity, necrosis, and molecular markers (Ki67 and p53) in CNS tumors. The findings highlight the heterogeneity within the studied cohort, emphasizing the importance of considering multiple parameters for a comprehensive understanding of tumor behavior. The associations observed between Ki67, p53, and the WHO grade provide valuable insights into the underlying biology of CNS tumors. Future research with larger cohorts and longitudinal follow-up could further elucidate the prognostic significance of these markers and guide personalized treatment strategies for patients with CNS tumors.

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