

Correlation of Histological Grade and Ki-67 Proliferation Index in Primary Central Nervous System Tumours: A Prospective Study

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ABSTRACT

Background: Histopathological grading of central nervous system (CNS) tumours by World Health Organization (WHO) criteria depends on morphological parameters that are subject to sampling limitations and interobserver variability. Ki-67 (MIB-1), a nuclear proliferation marker, is increasingly used as an adjunct to conventional grading. **Aim:** To study the clinicopathological profile of primary CNS tumours and correlate WHO histological grade with Ki-67 labelling index (LI). **Materials and Methods:** This prospective study was conducted over 18 months in the Department of Pathology, Coimbatore Medical College. Fifty histologically confirmed primary CNS tumours were graded on haematoxylin and eosin sections per WHO criteria, and Ki-67 immunohistochemistry was performed on all specimens by the two-step indirect method. **Results:** CNS tumours constituted 6.4% (50/1530) of all neoplasms diagnosed during the study period. The tumours were most frequent in the 41-50-year age group (32%), with a female preponderance (56%). Meningioma was the commonest tumour (46%), followed by glial tumours (38%). WHO grade I tumours predominated overall (58%). The Ki-67 LI increased progressively with increasing tumour grade in both glial tumours (grade I: 3%; grade II: 1-4%; grade III: 7-10%; grade IV: 24-32%) and meningiomas (grade I: 1-2%; grade II: 7-8%; grade III: 31%). **Conclusion:** Ki-67 LI shows a consistent positive correlation with WHO histological grade across CNS tumour categories and is a useful adjunct to morphology in grading, though it should not replace conventional histopathological assessment.

Keywords: Central nervous system tumours; Ki-67; MIB-1; WHO grading; meningioma; glioma; proliferation index

INTRODUCTION

Tumours of the central nervous system (CNS) form a biologically and morphologically diverse group of neoplasms. Neuroepithelial tumours of glial origin are widely credited with accounting for 40-50% of all intracranial space-occupying lesions (1). Population-based data from the Central Brain Tumor Registry of the United States (CBTRUS) place the overall incidence of primary CNS tumours at approximately 23.4 per 100,000 person-years (2).

Histopathological grading, most widely performed using WHO criteria, remains central to prognostication and treatment planning. Grading depends on morphological parameters - cytological atypia, mitotic activity, microvascular proliferation and necrosis - that can be difficult to assess reliably on small or poorly

preserved biopsy material, and mitotic counting itself is subject to considerable interobserver variability (3). Ki-67 is a non-histone nuclear protein expressed during the active phases of the cell cycle; immunohistochemical labelling with the monoclonal antibody MIB-1 against this antigen readily identifies actively proliferating cells and provides an objective index of proliferative activity (4). Several studies have shown that the Ki-67 labelling index (LI) correlates positively with histological grade and inversely with survival across CNS tumours, although it is recommended for use in combination with, rather than as a substitute for, conventional histopathological criteria (5).

This study was undertaken to determine the clinicopathological profile of primary CNS tumours

diagnosed at a tertiary care centre in South India and to evaluate the correlation between WHO histological grade and Ki-67 proliferation index.

MATERIALS AND METHODS

Study design and setting: Prospective study, Department of Pathology, Coimbatore Medical College, Coimbatore, over 18 months (January 2019 to June 2020).

Study population and sample size: All patients with primary CNS neoplasms attending the neurosurgery ward of the affiliated hospital during the study period were screened; 50 histologically confirmed primary CNS tumour specimens satisfying the selection criteria were enrolled.

Inclusion criteria: Primary CNS tumours, all age groups, both sexes.

Exclusion criteria: Secondary (metastatic) CNS tumours, CNS infections, metabolic disorders, specimens not received in formalin, and inadequate specimens.

Methodology: Specimens, mostly received as aggregate biopsy tissue (0.5-5 cc), were fixed in 10% neutral buffered formalin and processed routinely. Sections of 3-5 micron thickness were stained with haematoxylin and eosin for histopathological evaluation and graded according to WHO criteria. For immunohistochemistry, 3-micron sections on albumin-coated slides were incubated overnight at 60-70°C and Ki-67 (MIB-1) expression was demonstrated by the two-step indirect method. The Ki-67 LI was recorded as the percentage of tumour cells showing nuclear positivity.

Statistical analysis: Data were tabulated and analysed descriptively as frequencies and percentages, and the Ki-67 LI was compared across WHO grades and tumour categories.

RESULTS

During the study period, 5200 general biopsy specimens were received in the department, of which 1530 were confirmed neoplasms; 50 of these (6.4%) were primary CNS tumours.

Demographic profile: CNS tumours were most common in the 41-50-year age group (16 cases, 32%),

followed by the 51-60-year group (13 cases, 26%). The paediatric age groups (0-20 years) together accounted for only 10% of cases. There was an overall female preponderance, with females contributing 56% (28/50) of cases compared with 44% (22/50) males.

Tumour type and site: Meningioma was the single commonest tumour, accounting for 23 cases (46%), followed by diffuse astrocytic and oligodendroglial tumours (17 cases, 34%). Other categories - tumours of cranial and paraspinal nerves (schwannomas, 6%), other astrocytic tumours (4%), and ependymal tumours, other gliomas, choroid plexus tumours, embryonal tumours and sellar-region tumours (2% each) - made up the remainder. The frontoparietal region was the commonest site of occurrence (22%), followed by the frontal lobe (18%) and temporoparietal region (12%).

WHO grade distribution: Grade I tumours were the most frequent overall (58%), followed by grade II (22%), grade IV (14%) and grade III (6%). Females outnumbered males in grade I tumours (34% versus 24%), whereas grade IV tumours were relatively more frequent among males.

Grade and Ki-67 correlation - glial tumours: Among the 19 glial tumours (diffuse astrocytic, oligodendroglial and other astrocytic tumours), grade II tumours were the most frequent (47.5%), followed by grade IV (31.5%), with grade I and grade III each accounting for 10.5%. The Ki-67 LI rose consistently with grade: grade I, 3%; grade II, 1-4%; grade III, 7-10%; and grade IV, 24-32% (Table 1).

Grade and Ki-67 correlation - meningiomas: Among the 23 meningiomas, grade I tumours predominated (20 cases, 87%), with grade II (8.7%) and grade III (4.3%) accounting for the rest; 60.9% occurred in females. The Ki-67 LI likewise increased with grade: grade I, 1-2%; grade II, 7-8%; and grade III, 31% (Table 1).

Grade and Ki-67 correlation - other tumours: The remaining eight tumours (schwannoma, ependymoma, choroid plexus papilloma, craniopharyngioma, angiocentric glioma and one medulloblastoma) were predominantly WHO grade I, with Ki-67 LI ranging from 1-4%. The single medulloblastoma (WHO grade IV, in a seven-year-old boy) showed a Ki-67 LI of 6%.

Table 1: WHO grade distribution and Ki-67 labelling index by tumour category

Tumour category	n (%)	Grade distribution	Ki-67 LI by grade (%)
Glial tumours	19 (38)	I: 2 (10.5%); II: 9 (47.5%); III: 2 (10.5%); IV: 6 (31.5%)	I: 3; II: 1-4; III: 7-10; IV: 24-32
Meningioma	23 (46)	I: 20 (87%); II: 2 (8.7%); III: 1 (4.3%)	I: 1-2; II: 7-8; III: 31
Other CNS tumours*	8 (16)	Predominantly grade I (7); one grade IV	I: 1-4; IV: 6
Total	50 (100)	-	-

*Schwannoma, ependymoma, choroid plexus papilloma, craniopharyngioma, angiocentric glioma, medulloblastoma.

COLOUR PLATES

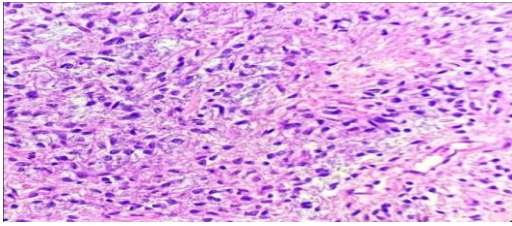


Figure -1: PILOCYTIC ASTROCYTOMA WHO grade I. Dense fibrillary areas in the background composed of long thin processes of bipolar cells.(H&E,40X)

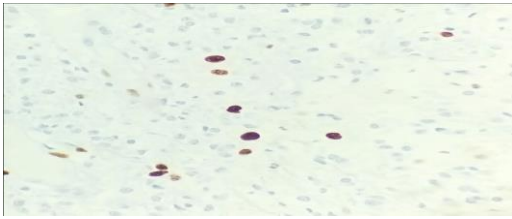


Figure -2: PILOCYTIC ASTROCYTOMA WHO grade I. Ki-67 labelling index-3%. (Ki-67 immunohistochemistry, 40X).

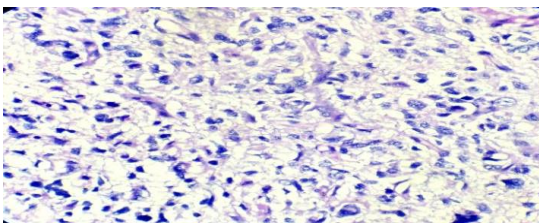


Figure -3: ANAPLASTIC ASTROCYTOMA-WHO grade III. Moderate cellularity, Marked nuclear atypia and mitoses (H&E,40X).

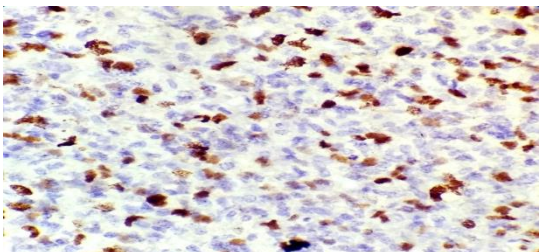


Figure -4: ANAPLASTIC ASTROCYTOMA-WHO grade III. Ki-67 labelling index-30% (Ki-67 immunohistochemistry, 40X).

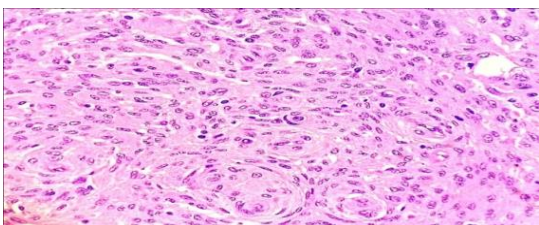


Figure -5: MENINGOTHELIAL MENINGIOMA-WHO grade I. The tumour cells are largely uniform with oval nuclei with delicate chromatin(syncytium like appearance).(H&E,40X).

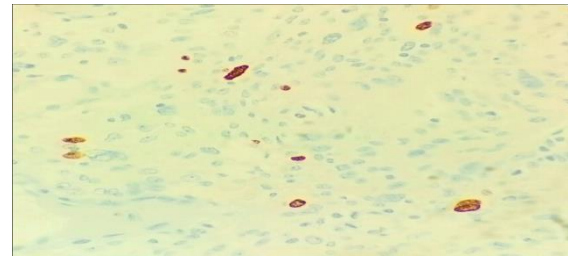


Figure -6: MENINGOTHELIAL MENINGIOMA-WHO grade I. Ki-67 labelling index-2% (Ki-67 immunohistochemistry, 40X).

DISCUSSION

In the present study, primary CNS tumours constituted 6.4% of all neoplasms diagnosed over the study period, lower than the population-based CBTRUS incidence estimate of 23.4 per 100,000 person-years, reflecting the difference between hospital-based proportional data and population-based incidence figures (2). Wide variation in the distribution of CNS tumours by age, sex and geography is well documented (6); in this study, tumours occurred most often in the 41-50-year age group, consistent with reports by Das et al (7), Aryal (8) and Manoharan et al (9) describing an increasing incidence of CNS tumours with age, and with Andrews et al (10) who similarly found CNS tumours to be more common in middle age.

Females were more often affected than males (56% versus 44%) in this study, in keeping with the higher CBTRUS rate reported in females compared with males (25.84 versus 21.28 per 100,000 person-years) (2). Meningioma was the commonest tumour type (46%), followed by glial tumours (38%); CBTRUS data similarly report meningioma as the most common primary CNS tumour, accounting for around one-third of cases, with a female-to-male ratio of nearly 2:1 (11). The site of a CNS tumour carries diagnostic and prognostic significance, since tumour behaviour varies by region of origin (12); the frontoparietal and frontal lobes were the commonest sites in this study, in agreement with Andrews et al (10) and Lee et al (6).

WHO grade I tumours were the most frequent overall (58%), followed by grade II (22%). Counting mitotic figures on haematoxylin and eosin sections can be difficult, particularly when tissue preservation is suboptimal, making it hard to distinguish degenerating cells from mitotic figures (3); the WHO has therefore avoided fixed Ki-67 cut-offs for individual tumour types because of considerable interlaboratory variability in staining and counting methods (13). In this study, the Ki-67 LI nonetheless correlated well with histological grade across tumour categories, in agreement with reports that a Ki-67 LI of 4% or more is an independent prognostic factor for grade II glial tumours, while emphasising that it should be used alongside, and not as a substitute for, other prognostic parameters (14).

Among glial tumours, grade II astrocytic tumours predominated (47.5%), followed by grade IV (31.5%), and the Ki-67 LI rose progressively with grade (grade I, 3%; grade IV, 24-32%), findings comparable to those of Rathie et al (15), Ambroise et al (16) and Ralte et al (17).

Meningiomas showed a similar grade-Ki-67 relationship. Grade I tumours predominated (87%), comparable to the proportions reported by Sakr and Salem (86.5%) (18) and Babu et al (90%) (19); the Ki-67 LI rose from 1-2% in grade I to 31% in grade III meningiomas, broadly consistent with the ranges reported by Bozkurt et al (20), Yang et al (21), Uzum and Ataoglu (22), Smith et al (23) and Roser et al (24), although absolute values vary between studies, likely reflecting interlaboratory differences in antibody clones, staining protocols and counting methods (25,26).

Nerve sheath tumours (schwannomas) accounted for 6% of cases, comparable to the cerebellopontine angle predominance described by Springborg et al (27); the Ki-67 LI in this study (1-4%) was consistent with the low index (under 3%) expected for typical schwannoma reported by Prueter et al (28). The single medulloblastoma occurred in a seven-year-old boy, in keeping with the childhood age peak described by Smoll and Drummond (29), with a Ki-67 LI of 6%, lower than the wider ranges reported by Sengupta et al (4-80%) (30) and Meurer et al (mean 27.5%) (31). Ependymoma and choroid plexus papilloma each showed a low Ki-67 LI (1%), consistent with the low labelling indices reported for these entities (32,33).

The main limitation of this study is its relatively small sample size (n=50), which restricts subgroup analysis, particularly for the less common tumour categories. Differences in antibody clones, background staining, fixation and section age can also contribute to interlaboratory and interobserver variation in Ki-67 assessment, and archived specimens may show reduced antigenicity, giving a falsely low labelling index.

Strengths of the Study

The prospective study design and assessment of Ki-67 across different CNS tumour categories are major strengths. The study also provides clinicopathological data from a tertiary care centre and evaluates Ki-67 as an adjunct to conventional histopathological grading.

Future Research and Recommendations

Larger multicentre studies with standardized Ki-67 assessment, longer follow-up, and integration of molecular markers are recommended to validate its prognostic significance in CNS tumours.

CONCLUSION

Primary CNS tumours were most frequent in the fifth decade of life, with a mild female preponderance. Meningioma was the commonest CNS tumour overall,

followed by glial tumours, with the frontoparietal region being the commonest site. WHO grade I tumours were the most common grade across both sexes; among glial tumours, grade II predominated, and among meningiomas, grade I predominated. The Ki-67 labelling index increased consistently with increasing WHO histological grade across tumour categories, confirming its value as an adjunct to conventional histopathological grading. Ki-67 should be interpreted alongside, and not in isolation from, standard morphological criteria when grading CNS tumours.

Ethical Approval

Ethical approval was obtained from the Institutional Ethics Committee of Coimbatore Medical College prior to commencement of the study.

Consent for Publication

Not applicable, as no identifiable individual patient information or images are presented.

Conflict of Interest

None declared.

Funding

Nil.

Data Availability Statement

The data generated and/or analysed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conception and design of the study, data collection, analysis and interpretation of results, drafting and critical revision of the manuscript, and approved the final version.

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