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Original Article

Pathology Section

Immunohistochemical Study of Ki-67 Labelling Index in Neoplasms of Central Nervous System

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ABSTRACT

Introduction: The central nervous system tumours show a varied histopathological spectrum. The cell proliferation index may provide an objective method for assessing tumour biology. The Ki-67 is considered to be the most reliable proliferative marker predicting the tumour behaviour of various systemic and intracranial neoplasms. As it reflects tumour proliferating potential, it helps in determining the grade and hence the likelihood of recurrence. This study was carried out considering that very few studies of Ki-67 Labelling Index (LI) is seen in Central Nervous System (CNS) neoplasms collectively.

Aim: To study the Ki-67 LI in CNS neoplasms and the association of Ki-67 LI with different parameters like age, sex, World Health Organisation (WHO) grading and histological types.

Materials and Methods: The present descriptive analytical study was conducted at Department of Pathology, Mahadevappa Rampure Medical College, Karnataka, India, attached to a tertiary care hospital, Kalaburagi, for a period of five years between 1st Aug 2013 to 31st July 2018 after approval from the Institutional Ethics Committee. The formalin-fixed and paraffin-embedded tissue sections were stained with haematoxylin and eosin. Immunohistochemistry (IHC) was carried out with Ki-67 antibody using standard protocol. The data was analysed using IBM SPSS software version 19.0. The descriptive statistics frequency and percentages were calculated. The morphological grading of CNS tumours was done and the distribution of Ki-67 LI values were analysed.

Results: A total of 102 histopathologically diagnosed primary CNS tumours were included in the study. High incidence of CNS neoplasms was seen in 3rd to 4th decade with slight male preponderance. This study included 40 meningioma cases. Mean percentages of Ki-67 LI for grade I and grade II meningiomas were 3.3% and 4%, respectively. The Ki-67 mean value for Astrocytomas grade I was 5.6% and grade II was 8.7%. Grade IV Glioblastoma and Gliosarcoma showed mean value of 18% and 18.8%, respectively. It was observed that LI increased with increase in grade of the tumour. Schwannoma and Dysembryoplastic Neuroepethelial Tumour (DNET) showed Ki-67 LI of 2.9% and 2.6%, respectively. Mean value of Ki-67 LI of other primary CNS neoplasms were as follows: Medulloblastoma 53%, Atypical Teratoid/Rhabdoid Tumour (ATRT) 32%, Haemangiopericytoma 8%, Neurocytoma 4%, Malignant Peripheral Nerve Sheath Tumour (MPNST) 3%, Ganglioglioma 4% and Haemangioblastoma 4%.

Conclusion: The Ki-67 LI is the simplest and the most reliable method for evaluating the cell proliferation. It has a great value in designating the exact grade of the tumour when used in combination with histopathological features. It can also be used for planning of adjuvant therapy in primary CNS neoplasms.

Keywords: Brain tumours, Immunolabelling, Proliferative marker, Self proliferative index

INTRODUCTION

Primary CNS tumours are a complex heterogeneous group of benign and malignant tumours, with more than 100 histologic subtypes of tumours [1]. The primary CNS tumours account for less than 2% of all cancers but they causes a disproportionate burden of cancer related morbidity and mortality [2]. In India, the tumours of CNS constitute about 1.9% of all tumours [3]. The WHO histological grading for CNS tumours is well accepted for evaluation of the prognosis of patients [4]. However, this is not always accurate and hence there is an increasing need to develop better prognostic markers. One such complimentary method is assessment of proliferative index of tumours [5].

The cell proliferative index is done by evaluating mitotic activity in routine slides, but only those cells in the M phase of the cell cycle can be detected by this method. Ki-67 protein is a non histone protein that expresses in active phases of cell cycle (G1, S, G2 and M phase). Hence, Ki-67 is considered to be the most reliable proliferative marker for predicting the tumour behaviour [6]. Previous studies conducted on Ki-67 LI have shown that it has excellent sensitivity and specificity in placing patients correctly into survivor and non survivor groups and it is important in determining the grade and likelihood of recurrence [7-9].

There are studies in literature on Ki-67 LI in individual tumours like gliomas, astrocytomas, meningiomas, ependymomas, etc., [6,9-11]. Hence, this study was carried out considering all CNS neoplasms collectively for Ki-67 LI.

MATERIALS AND METHODS

The present study was a hospital based, descriptive analytical study conducted at Department of Pathology, Mahadevappa Rampure Medical College, Karnataka, India, attached to a tertiary care hospital, Kalaburagi, for a period of five years between 1st August 2013 to 31st July 2018. Institutional Ethics Committee clearance was obtained to carry out the study (IEC no: HKES/MRMCK/IEC/181003). Sample size was achieved by convenient sampling technique. All the 102 cases of primary CNS tumours received for histopathological examination during the five years period were included in this study.

Inclusion criteria: Those cases for which a diagnosis of primary CNS neoplasm (both benign and malignant) was made with definitive grading on histopathology were included in the study.

Exclusion criteria: All cases of non neoplastic, inflammatory lesions and metastatic neoplasms of CNS were excluded from the study. The samples where there was extensive tumour necrosis without sufficient viable tumour cells for accurate evaluation of the immunohistochemical results and cases who had received radiotherapy/chemotherapy were excluded from this study.

Study Procedure

Patient's case records were obtained and details of age, gender, clinical presentation and location were noted. The histological sections were reviewed and all the tumours were graded histopathologically into four grades (I to IV) according to 2016 WHO classification of CNS tumours [4]. All the specimens were fixed in 10% buffered formalin, were grossed and processed manually. The tissues were embedded in paraffin wax. Sections of 3-5 µm thickness were cut using a microtome and then were stained with routine Haematoxylin and Eosin (H&E).

For IHC, 3-4 µm thick sections were cut and taken on Poly-L-lysine coated slides which were incubated at 60°C overnight followed by three changes in xylene and alcohol. Antigen retrieval was performed in Tris buffer in microwave oven, twice at 95°C for 12 minutes at pH 7.4. The slides were exposed to blocking reagent hydrogen peroxide for 20 minutes and were then subjected to IHC by employing Ki-67 antibody, ready to use dilution, supplied by Biogenex. Sections were incubated with secondary antibody conjugated to Polymer-Horse Raddish Peroxidase (HRP) reagent for 30 minutes. Reaction products were revealed with Chromogen-Diamino-Benzidine (DAB) and were counterstained with haematoxylin. Positive controls (tonsil and lymphoma, LN) and negative controls (without adding primary antibody) provided with staining kit, were used in each staining run [5].

Every brown stained nucleus was considered positive irrespective of intensity. Ki-67 was recorded as percentage of positively stained tumour nuclei per 1000 tumour cells. The cells were counted in regions of maximum immunoreactivity under high power (40x) objective.

STATISTICAL ANALYSIS

Statistical analysis was done using IBM Statistical Package For The Social Sciences (SPSS) software version 19.0. The descriptive statistics frequency and percentages were calculated. The morphological grading of CNS tumours, Ki-67 LI for each neoplasm, the mean Ki-67 LI for each group of neoplasm were determined and the distribution of Ki-67 LI values were analysed.

RESULTS

In present study, the age of the patients ranged from 4-80 years with mean±SD age of 54.4±15.34 years. Majority of cases were seen in 31-40 years age group. There were 56 (54.9%) cases of males and 46 (45.1%) cases of females showing male preponderance. Highest mean Ki-67 LI was seen in 0-10 year age group [Table/Fig-1].

Age wise distribution	No. of cases	Sex distribution		Percentage of cases	Mean Ki-67 (%)
		Male	Female		
0-10 years	10	4	6	9.8%	15.1%
11-20 years	11	7	4	10.7%	4.1%
21-30 years	12	7	5	11.7%	6.2%
31-40 years	26	15	11	25.4%	9.5%
41-50 years	14	7	7	13.7%	7.2%
51-60 years	22	12	10	21.6%	11%
61-70 years	4	2	2	3.9%	9.1%
71-80 years	3	2	1	2.9%	5.2%
Total	102	56 (54.9%)	46 (45.1%)	100%	

[Table/Fig-1]: Incidence of age, sex and mean Ki-67 Labelling Index (LI) in primary CNS neoplasm.

The most common clinical presentation in this study was headache 52 (50.9%) followed by weakness of limbs 25 (24.6%). Other complaints included combination of blurring of vision, seizures, giddiness and vomiting. The most common location of primary CNS neoplasm in the present study was frontal lobe (27.4%), followed by the parietal lobe (23.5%) [Table/Fig-2]. It was seen that grade I tumours were most common (65.7%) followed by grade II tumours (18.62%). Grade III tumours were not observed in the present study. Out of 102 cases, maximum number of cases were of meningioma grade I (37.2%), followed by 14.7% cases of astrocytoma grade II. Maximum percentage of Ki-67 LI was found in two cases of medulloblastoma (53%) [Table/Fig-3]. There were 40 cases of meningiomas (grade I 37.2% and grade II 1.8%). Mean value of Ki-67 LI in meningioma grade I was 3.3% and grade II was 4% [Table/Fig-3]. The age ranged from 4-78 years with mean age ±SD being 44.3±16.31 years.

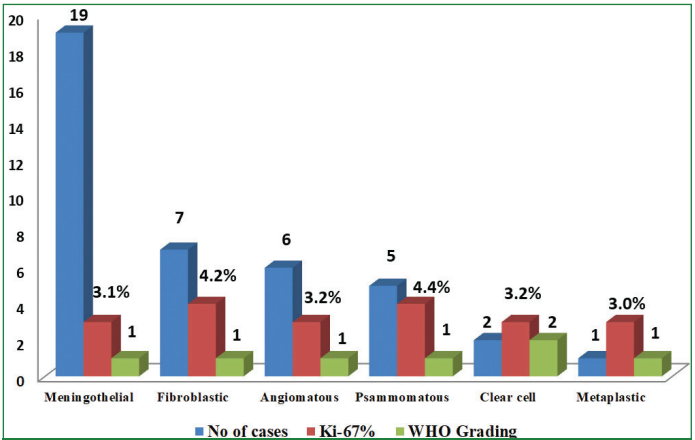
Tumour location	Number of cases	Percentage
Frontal	28	27.4%
Parietal	24	23.5%
Cerebropontine angle	22	21.5%
Occipital	20	19.8%
Cerebellum	08	7.8%
Total	102	100%

[Table/Fig-2]: Locations of primary CNS neoplasms.

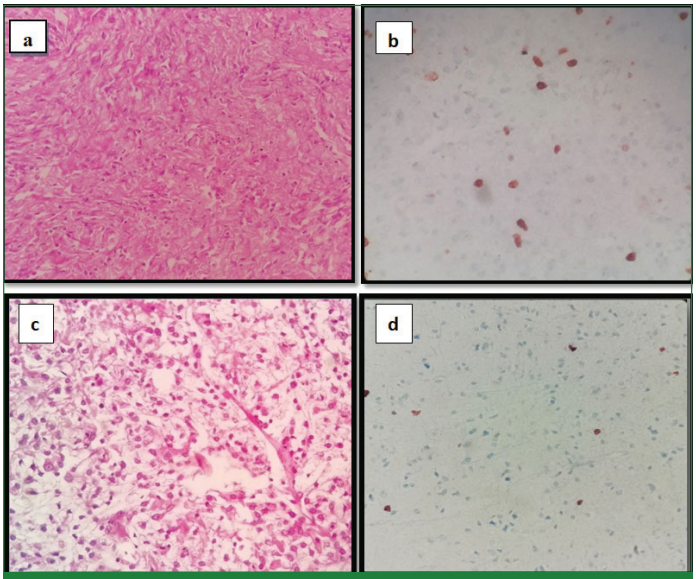
Diagnosis	Total no cases	Percentage of cases	WHO grade	Mean Ki-67 (%)
Meningioma grade I	38	37.2%	I	3.3%
Meningioma grade II	2	1.9%	II	4%
Astrocytoma grade I	3	2.9%	I	5.6%
Astrocytoma grade II	15	14.7%	II	8.7%
Glioblastoma	6	5.8%	IV	18%
Gliosarcoma	7	6.8%	IV	18.8%
Schwannoma	17	16.6%	I	2.9%
Dysembryoplastic neuroepethelial tumour	6	5.8%	I	2.6%
Medulloblastoma	2	1.9%	IV	53%
Malignant peripheral nerve sheath tumour	1	0.9%	I	3%
Ganglioglioma	1	0.9%	I	4%
Atypical Teratoid/Rhabdoid tumour	1	0.9%	IV	32%
Haemangioblastoma	1	0.9%	I	4%
Haemangiopericytoma	1	0.9%	II	8%
Neurocytoma	1	0.9%	II	4%
Total	102	100%		

[Table/Fig-3]: Variant of tumours with WHO grade and mean Ki-67% in primary tumours of CNS.

The most common histological variant among meningioma was meningothelial meningioma (n=19) [Table/Fig-4]. The [Table/Fig-5] shows Ki-67 LI of fibroblastic and clear cell variants of meningioma.

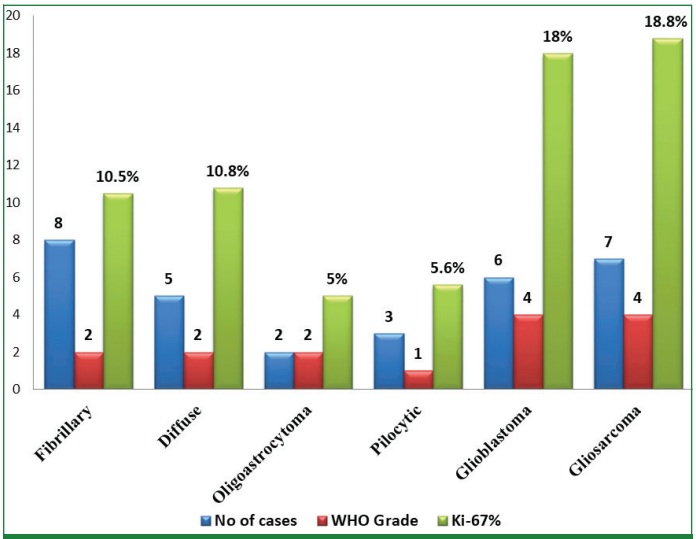


[Table/Fig-4]: Number of cases, histopathological variants, WHO grading with Ki-67 distribution in meningioma.



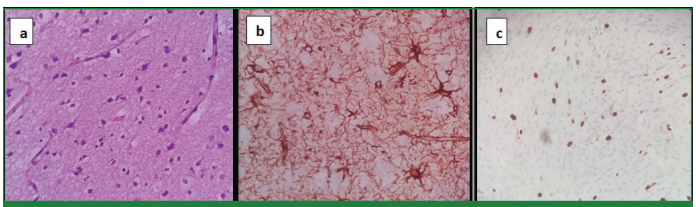
[Table/Fig-5]: Photomicrographs showing grade I and grade II meningiomas with Ki-67 LI: a) Grade I fibroblastic meningioma showing bland looking spindle cells (H&E, 40x); b) 6% Ki-67 LI in fibroblastic meningioma (IHC, 40x); c) Grade II Clear cell meningioma showing clear cells in patternless arrangement (H&E, 40x); d) 4% Ki67 LI in clear cell meningioma (IHC, 10x).

The present study included 31 cases of tumours with astrocytic differentiation [Table/Fig-6]. The age ranged from 8-65 years with mean age being 39.64±16.48 years. Male to female ratio was 1.2:1.



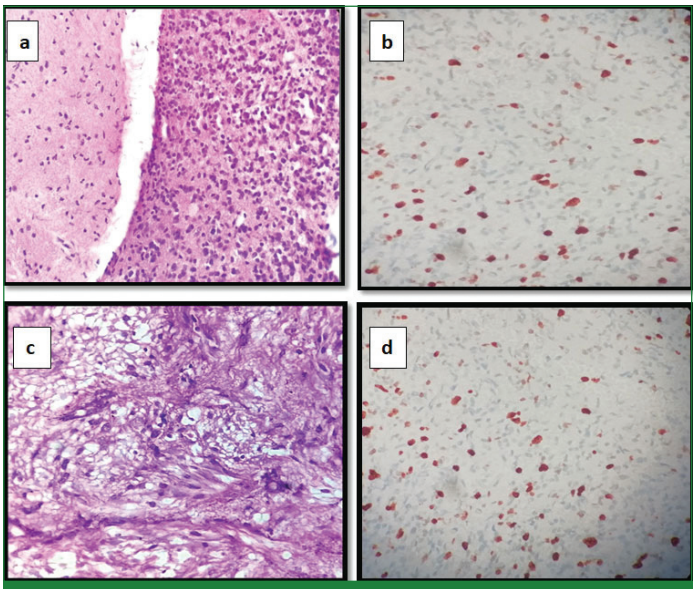
[Table/Fig-6]: Number of cases, histopathological variant, WHO grading and Ki-67 LI in tumours of astrocytic differentiation.

Most common histological variant of astrocytic tumour in the present study was grade II fibrillary astrocytoma (n=8) [Table/Fig-7]. Mean Ki-67 LI of grade I, grade II and grade IV tumours of astrocytic differentiation were 5.6%, 8.7% and 18.4%, respectively and the Ki-67 LI increased with the grade of the tumour. The [Table/Fig-8] shows mean Ki-67 LI in grade IV astrocytic tumour.

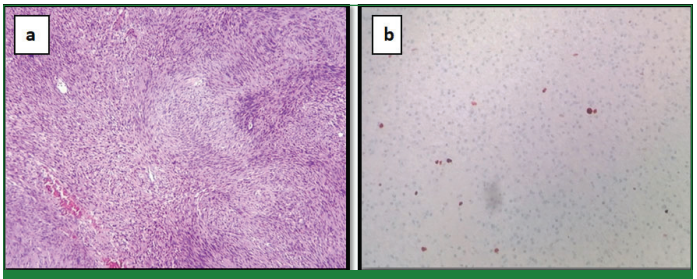


[Table/Fig-7]: Photomicrograph showing grade II astrocytomas with Ki-67 LI: a) Diffuse fibrillary astrocytoma showing increase in glial cells with mild pleomorphism in fibrillary background (H&E, 40x); b) Glial Fibrillary Acid Protein (GFAP) positivity in diffuse fibrillary astrocytoma (IHC, 10x); c) 8.7% Ki-67 LI in diffuse fibrillary astrocytoma (IHC, 10x).

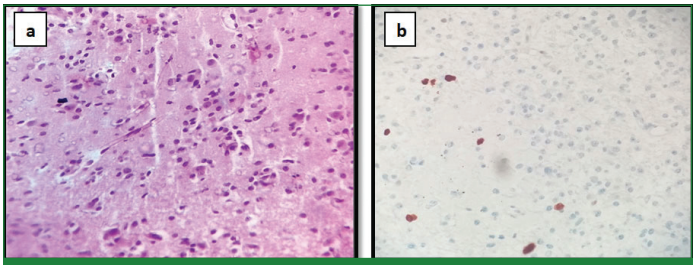
A total of 17 cases of schwannoma and six cases of DNET were included in this study with mean Ki-67 LI of 2.9% and 2.6%, respectively [Table/Fig-9,10]. Out of total eight miscellaneous primary CNS neoplasms, three were grade IV of which two were medulloblastoma and one was (ATRT) [Table/Fig-11,12]. Mean Ki-67 LI of medulloblastoma was 53% and that of ATRT was 32%.



[Table/Fig-8]: Photomicrograph of grade IV astrocytic tumours with Ki-67 LI: a) GBM with normal brain tissue (H&E, 40x); b) Ki-67 LI in GBM is 18% (IHC, 40x); c) Gliosarcoma showing both glial and sarcomatous components (H&E, 40x); d) Ki-67 LI is 20% in gliosarcoma (IHC, 40x).



[Table/Fig-9]: Photomicrograph of Schwannoma with its Ki-67 LI: a) Schwannoma showing Verocay bodies (H&E, 10x); b) Ki-67 LI is 3% in schwannoma (IHC, 10x).



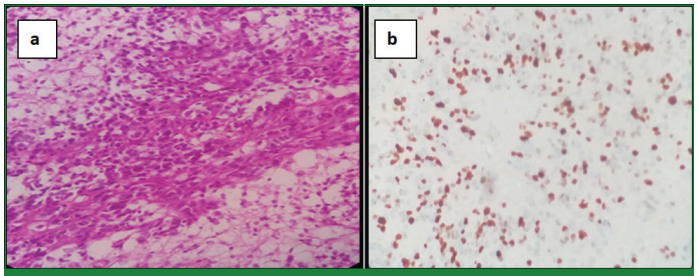
[Table/Fig-10]: Photomicrograph of Dysembryoplastic Neuroepithelial Tumour (DNET) with Ki-67 LI: a) DNET showing oligodendroglioma-like cells in mucin-rich background (H&E, 40x); b) Ki-67 LI is 4% in DNET (IHC, 40x).

Age	Sex	Diagnosis	WHO grade	Ki 67 (%)
3 years	F	Atypical teratoid/rhabdoid tumour	IV	32%
53 years	M	Haemangipericytoma	II	8%
10 years	M	Medulloblastoma	IV	52%
9 years	F	Medulloblastoma	IV	54%
6 years	F	Malignant peripheral nerve sheath tumour MPNST	I	3%
9 years	M	Neurocytoma	II	4%
15 years	M	Ganglioglioma	I	4%
35 years	F	Haemangioblastoma	I	4%

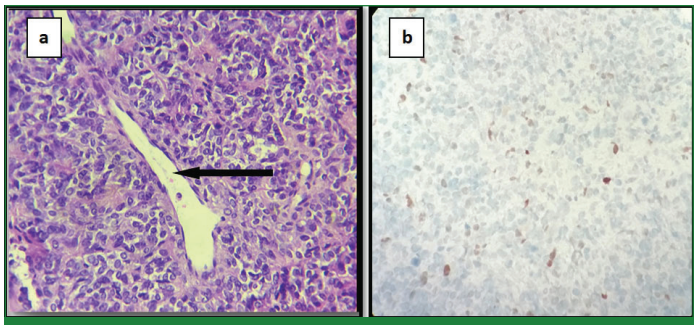
[Table/Fig-11]: Age, sex, histopathological variants and Ki-67 LI in miscellaneous primary CNS neoplasms.

Grade II tumours in miscellaneous category were Haemangiopericytoma [Table/Fig-13] and Neurocytoma with Ki-67 LI 8% and 4%, respectively. Other three tumours were of grade I including Malignant Peripheral Nerve Sheath Tumour (MPNST),

Ganglioglioma and Haemangioblastoma with Ki-67 LI of 3%, 4% and 4%, respectively.



[Table/Fig-12]: Photomicrograph of desmoplastic medulloblastoma: a) Desmoplastic medulloblastoma showing densely packed round to oval cells with hyperchromatic and pleomorphic nuclei. (H&E, 40x); b) Ki-67 LI is 54% in desmoplastic medulloblastoma (IHC, 40x).



[Table/Fig-13]: Photomicrograph of Haemangiopericytoma with its Ki-67 LI: a) Haemangiopericytoma with a staghorn vessel (black arrow) (H&E, 40x); b) Ki-67 LI is 8% (IHC, 10x).

DISCUSSION

The CNS tumours are the most widely classified tumours [12]. The incidence and pattern of CNS neoplasms are subject to considerable geographic and racial variation [13]. The Ki-67 LI for evaluating the proliferation rate of the tumours is one of the best and well known IHC methods [14].

In this present study, a total of 102 primary brain neoplasms were examined histopathologically and the proliferation of tumour cells was assessed by Ki-67 LI. Majority of the CNS tumours occurred in the age group of 31-40 years (25.6%). Studies by Hema NA et al., and Kinkhede DS et al., also showed maximum cases in the age group of 31-40 years [15,16]. Male preponderance (54.8%) was observed in present study which was similar to other studies shown in [Table/Fig-14] [15-18].

Gender	Butt ME et al., [17] (2005)	Mahmoud MZ [18] (2013)	Hema NA et al., [15] (2016)	Kinkhede DS et al., [16] (2021)	Present study (2018)
Male	54 (54%)	64 (64%)	29 (58%)	169 (56%)	56 (54.9%)
Female	46 (46%)	36 (36%)	21 (42%)	131 (44%)	46 (45.1%)
Total	100	100	50	300	102

[Table/Fig-14]: Comparison of sex-wise distribution [15-18].

The distribution of various CNS tumours in the present study showed that meningiomas were the top on the list constituting 40 (39.2%) cases. Similar findings were seen in other studies of Kakshapati T et al., and Kanthikar SN et al., where meningiomas constituted 30.3% and 39.4% respectively [19,20]. Out of the 40 meningioma cases in present study, grade I tumours were maximum comprising 38 (95%) cases which was in concordance with other studies conducted by Babu S et al., and Telugu RB et al., [21,22].

Mean Ki-67 LI in meningioma grade I was 3.3% and in grade II was 4% in present study. This was similar to the observations made in other studies [Table/Fig-15] [21-23]. Astrocytomas were the second most common neoplasm in present study. There was an increase in incidence in males in all the grades of astrocytomas in the present study giving a male to female ratio of 1.2:1. This was in concordance with the studies conducted by Das B et al., and Shivaprasad NV et al., where male to female ratio was 2.07:1 and 1.72:1, showing male preponderance [11,24]. The most common histological grade of astrocytic neoplasms in the present study was grade II (n=15), followed by grade IV (n=13). The mean Ki-67 LI of present study for grade I, II and IV were 5.6%, 8.7% and 18.4%, respectively. It was observed that as the tumour grade increases, the value of Ki-67 LI also increased. This was seen in concordance with the study conducted by Thotakura M et al., and Das B et al., [Table/Fig-16] [5,11].

Meningiomas	Roser F et al., [23] (2004) 57 cases	Babu S et al., [21] (2011) 300 cases	Telugu RB et al., [22] (2016) 224	Present study (2018) 40 cases
Grade I	3.88%	4.07%	3.1%	3.3 %
Grade II	9.95%	9.5%	7%	4 %

[Table/Fig-15]: Comparison of Ki-67 LI of meningioma [21-23].

Tumour grade	Thotakura M et al., [5] (2014)	Das B et al., [11] (2018)	Present study (2018)
Grade I	3.36%	4.66%	3 (5.6%) cases
Grade II	7.05%	8.07%	15 (8.7%) cases
Grade III	28.24%	13.5%	-
Grade IV	38.7%	22.93%	13 (18.4%) cases

[Table/Fig-16]: Comparison of Ki-67 LI in various grades of astrocytic tumours [5,11].

The schwannomas were the third most common tumour in the present study constituting 16.6% of cases. Mean Ki-67 LI was 2.9%. This result was similar to the observations done by Rai P et al., and Mani U et al., who gave a mean Ki-67 LI as 2.97% and 5.3% respectively [7,8]. Total six cases of DNET were found in present study with age ranging from 15-30 years. Mean Ki-67 LI was 2.6%. Thom M et al., examined 101 cases of DNET and found Ki-67 LI is 1-5% (mean=3.2%) which was similar to present study [25]. Among eight cases of miscellaneous tumours, one case was of Ganglioglioma which was reported in a 15-year-old male constituting 0.9% of all CNS neoplasms. The Ki-67 LI of this tumour was 4%. Mani U et al., in their study showed mean Ki-67 LI of 0.72% and Lukyen C et al., reported Ki-67 LI of 1.1-2.7% [8,26].

Two cases of pediatric Medulloblastoma showed 53% Ki-67 LI. This was similar to the study conducted by Senugupta S et al., where Ki-67 LI ranged from 4-80% (mean=43.2%) [2]. The Ki-67 expression was 4% in one case of Haemangioblastoma and this value was close to the study of Mani U et al., who showed a mean expression of 2.85% [8]. In the present study, we evaluated the expression of Ki-67 in various primary CNS tumours collectively. The expression of Ki-67 varied widely in each study done and there were no specific cut-off levels to grade any CNS tumour. The variation in immune reactivity may be due to different expression during the cell cycle, or differences in techniques and the interpretations [8].

Limitation(s)

Statistical analysis of intra or interobserver variability was not done. As the study included retrospective cases, the archived specimens would have lost their antigenicity over time giving a false or low LI.

CONCLUSION(S)

To conclude, Ki-67 LI is a valuable tool for assessing the proliferative index of the tumour. This can be used as an adjunct to the histopathological grading in CNS neoplasms with suspicious histopathological features or when there is lack of clinicomorphological correlation, for designating the grade of tumour. Grading of tumours with malignant potential is of utmost important for planning appropriate management.

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