

Original Research Article

Clinico-pathological and radiological correlation of CNS tumors along with role of Ki 67 proliferative index in grading Astrocytoma and Meningiomas

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ABSTRACT

Background: CNS neoplasms are a heterogeneous group contributing to <2% of all the malignant neoplasms. Imaging and histopathology play a great role in diagnosing these lesions. Aim of the study is to correlate radiological findings with that of histopathology and evaluate the role of Ki 67 proliferative index in various grades of Astrocytomas and Meningiomas

Methods: This is an observational study for a period 2 years from July 2015 to June 2017 in Department of Pathology Andhra Medical College. The total number of specimens of CNS tumors received during this period were 126. The specimens were routinely processed and stained with H&E. The tumors were classified based on WHO 2016 classification. In total 71 cases-45 cases of meningiomas and 26 cases of astrocytomas, the expression of Ki 67 labelling index was recorded in various grades of these tumors and results tabulated.

Results: Among 126 cases, tumors predominantly encountered were of meningeal origin accounting to 45 cases (35.71%) followed by tumors of neuroepithelial origin 35 cases (27.78%). Tumors were seen in all age groups, but common was among 41-50 years of age group with metastatic tumors being seen in >60 year group. Tumors were more common in males with male: female ratio being 1.25:1. Ki 67 proliferative index increased as the grade of tumor increased in both astrocytomas and meningiomas.

Conclusions: Grading of meningiomas and astrocytomas are very much essential with reference to prognosis and therapy. Histopathology plays a great role in grading these lesions but Ki 67 proliferative index adds as an adjunct and helps in confirmation and predicting the recurrence of these lesions.

Keywords: Astrocytomas, CNS tumors, Diagnostic accuracy, Ki 67 proliferative index, Meningiomas, Radiology

INTRODUCTION

Brain tumors are heterogeneous as most of them differ in histomorphological features. Though there is availability of advanced imaging techniques, histopathological examination is the gold standard.¹ Sometimes they may

not be straightforward to diagnose creating a diagnostic dilemma in pathologist mind due to overlapping histomorphological features in benign as well as certain non-neoplastic lesion which mimics as brain tumors. Clinical needs are expanding and pathologists role in interpreting the various CNS neoplasms and grading

them is very much essential for effective treatment.² Proliferative potential of the tumor provides important prognostic information that supplements histological grading, Ki 67 index is the simplest and most reliable method of estimating it.^{3,4}

The purpose of this study is to provide current overview of epidemiology of CNS tumor in our hospital setup and study the prevalence of these lesions by using WHO 2016 classification and understand the significance of KI 67 labeling index in grading of tumors. Aim of the study is:

- To study spectrum of CNS tumors in the specimens received for histopathological examination.
- To correlate the radiological diagnosis with that of histopathological diagnosis.

To know the expression of Ki 67 proliferative index in various grades of Astrocytomas and Meningiomas. To assess the relationship of Ki 67 staining with, the histopathological grading of Astrocytomas and Meningiomas.

METHODS

Study design

A hospital based observational study.

Study period

2 years from July 2015 to June 2017 at Department of Pathology, Andhra Medical College, Visakhapatnam.

Inclusion criteria

All the specimens of CNS tumors received in the Department of Pathology for histopathological examination were included in the study

Exclusion criteria

Recurrent CNS tumors and on therapy were excluded

Sample size

126 cases.

Detailed clinical data and radiological findings were recorded. The tissue was fixed in 10% formalin and was subjected to routine paraffin embedded processing, stained with H and E.

The spectrum of CNS tumors was classified based on WHO 2016 classification.

Histomorphological criteria for grading of Meningiomas.

WHO Grade	Criteria
I.	Mitosis <4/10 HPF
II.	Mitosis 4-19/10 HPF
	Or
	3 or more of the following features
	<ul style="list-style-type: none"> • Increased cellularity • Sheet like growth pattern • Small cells with high N/C ratio • Prominent nucleoli • Foci of spontaneous or geographic necrosis.
III.	1. Mitosis >20 /10 HPF
	2. Loss of differentiated features resulting in carcinoma, melanoma or sarcoma like appearance.

Grading of Astrocytomas:

- Pilocytic astrocytoma
- Diffuse astrocytoma
- Anaplastic astrocytoma
- Glioblastoma multiforme

All the cases of astrocytomas and meningiomas were stained with Ki 67 proliferation marker. Three microns thick formalin fixed paraffin embedded sections were obtained for staining with Ki 67 proliferation marker by adopting Dako immunohistochemistry staining procedure. Fields with maximal labeling were chosen for counting. The total number of nuclei taking brown colored stain was counted manually under high power (400 X) magnification. The total number of nuclei counted was 1000 nuclei. The Ki 67 expression was recorded as percentage:

$$\frac{\text{Number of nuclei showing positive staining (brown color)}}{\text{Total number of nuclei counted}} \times 100 \%$$

- Areas free from necrosis and capillary endothelial proliferation were selected.
- Interpretation of Ki 67 for Astrocytomas was done based on David and Louis et al.⁵

Astrocytoma Grade I is <1% Astrocytoma Grade II is <4% Astrocytoma Grade III is 5 to10% Astrocytoma Grade IV is >15 to 20%

- Interpretation of Ki 67 for Meningiomas was done based on Sashidhar babu et al.⁶

Grade I-0-4%, Grade II - 4.1-7%, Grade III - >7%

Statistical analysis

Sensitivity, specificity, positive predictive value, negative predictive value and overall accuracy of radiodiagnosis as

investigative method was evaluated taking histopathology as gold standard.

Data for Ki 67 proliferative index was expressed as mean and statistical significance of Ki 67 expression and histological grade was determined by chi-square test.

RESULTS

A total of 126 cases of CNS neoplasms were analyzed during this period. Male: Female ratio was 1.25:1. The age groups with tumors included a wide range from 3

years to 69 years with the highest number of cases seen within 41-50 years age group, 38 cases (30.15%) and metastatic tumors are common with age group of 60 and above (9 cases, 7.14%) (Table 1). Tumors were tabulated according to the WHO CNS 2016 classification series. Most common presentation of brain tumors in the present study was headache and vomiting (41 cases 32.54%), seizures (40 cases 31.75%), other symptoms were weakness and focal neuro deficits (25 cases 19.84%), visual disturbances (6 cases, 4.76%), hearing loss and tinnitus (12 cases, 9.52%) and gait disturbances (2 cases 1.59%).

Table 1: Age distribution in CNS tumors (n=126).

Category of CNS tumors	0-10 years	11-20 years	21-30 years	31-40 years	41-50 years	51-60 years	>60 years	Total
Neuroepithelial tumors	2	3	6	6	13	5	-	35
Embryonal tumors	3	1	-	-	-	-	-	4
Tumors of cranial and spinal nerves	-	1	7	12	4	1	-	25
Tumors of meningeal origin	-	-	3	13	21	2	6	45
Tumors of sellar region	-	-	2	-	-	-	-	2
Metastatic tumors	-	-	-	-	-	2	7	9
Others	-	2	1	2	-	1	-	6
Total	5	7	19	33	38	11	13	126

In the present study majority of the CNS tumors were meningiothelial tumors (35.71%) followed by neuroepithelial tumors (27.78%) and tumors of cranial and spinal nerves was (19.84%). The tumors were common in the frontal lobe and cerebropontine angle (15.87% each).

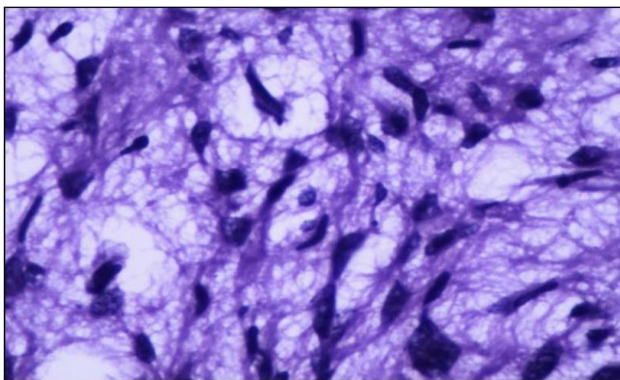


Figure 1: Photomicrograph of Pilocytic astrocytoma (H and E, 400 X).

Astrocytic tumors constituted 26 cases (74.28%) of the neuroepithelial tumors. The common histopathological variants of neuroepithelial tumors were diffuse astrocytomas (28.58%), followed by Pilocytic astrocytomas (17.14%) (Figure 1) and glioblastoma

multiforme (17.14%) Meningiothelial meningioma (Figure 2,3).



Figure 2: Gross photograph of Meningioma with Duramater.

constituted 55.6% of meningeal tumors, followed by transitional meningioma (20%) and 5 cases of psammomatous meningioma, 3 cases of atypical meningioma (figure 4) and a case of angiomatous meningioma.

In the tumors of cranial and spinal nerves schwannoma (figure 6) constituted 84% of the cases and 16% were neurofibroma. (Table 2).

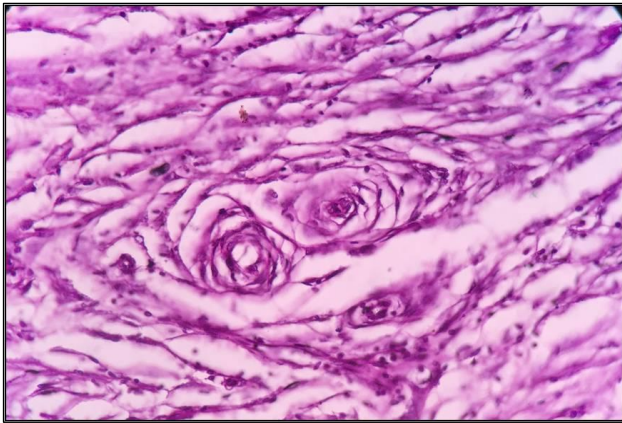


Figure 3: Photomicrograph of Meningiotheliomatous meningioma (H and E, 100 X).

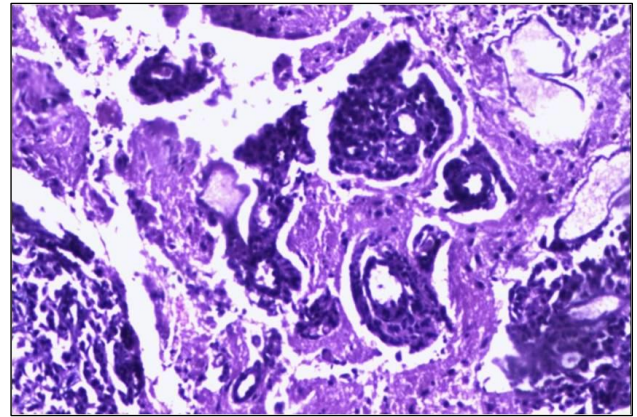


Figure 5: Photomicrograph of Metastatic carcinoma in the brain (H and E, 100 X).

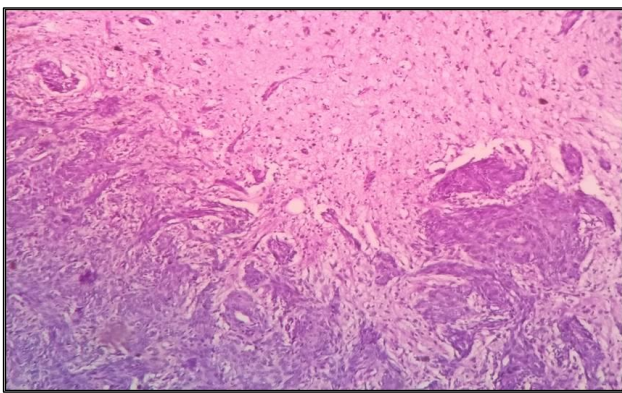


Figure 4: Photomicrograph of Atypical meningioma invading the glial tissue (H and E, 100 X).

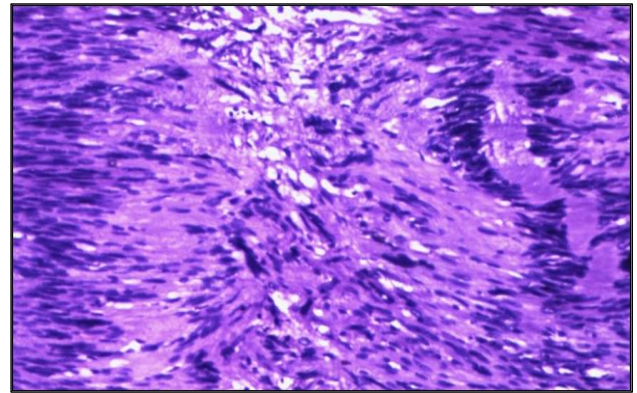


Figure 6: Photomicrograph of Schwannoma with Verocay bodies (H and E, 400 X).

Table 2: Distribution of histopathological variants of CNS tumors in the present study (n=35).

Neuroepithelial tumors	Grade of tumor	Number	Percentage
Pilocytic astrocytoma (nos type)	Grade-i	6	17.14
Diffuse astrocytoma (nos type)	Grade-ii	10	28.58
Anaplastic astrocytoma (nos type)	Grade-iii	4	11.43
Glioblastoma multiforme (nos type)	Grade-iv	6	17.14
Ependymoma	Grade-ii	2	5.71
Oligodendroglioma (nos type)	Grade-ii	2	5.71
Neuronal tumor	Grade-i	5	14.29
Total	-	35	100
Meningeal tumors	Grade of Tumor	Number	Percentage
Meningothelial	Grade-1	25	55.56%
Transitional	Grade-1	9	20.00%
Psammomatous	Grade-1	5	11.11%
Atypical	Grade-ii	3	6.67%
Fibrous	Grade-1	2	4.44%
Angiomatous	Grade-1	1	2.22%
Total	-	45	100 %
Cranial and spinal nerves tumors	Grade of Tumor	Number	Percentage
Schwannoma	Grade-i	21	84%
Neurofibroma	Grade-i	4	16%
Total		25	100%

Tumors from cranial and spinal nerves, tumors of sellar region, metastatic tumors (figure 5) and pituitary adenomas (figure 7) showed hundred percent (100%) correlation between radiology and histopathology, while 88.57% of neuroepithelial tumors and 84.44% of meningeal tumors showed correlation between radiology and histopathology (Table 3). Radiology as a diagnostic test for central nervous tumors: shows sensitivity: 66.67 %, specificity: 97.78 %, positive predictive value: 87.5%, negative predictive value: 92.63% and overall accuracy: 91.89 % (Table 4). Mean KI 67 proliferative index (Fig 8) increased as the grade of tumor increased in astrocytic tumors with P value of 0.0006. Mean KI 67 proliferative index increased as the grade of tumor increased in astrocytic tumors with P value of 0.00001 (Table 5).

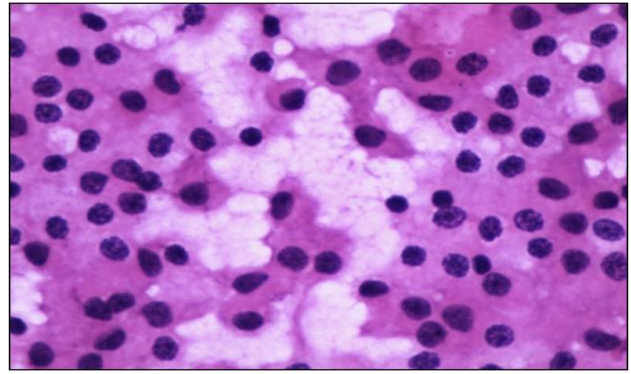


Figure 7: Photomicrograph of Pituitary adenoma (H and E, 400 X).

Table 3: Histo-radiological correlation taking histopathology as gold standard (n=126).

CNS tumors	Number	Correlated with radiology	Did not correlate with Radiology	Overall correlation percentage
Neuroepithelial tumors	35	31	4	88.57%
Embryonal tumors	4	0	4	0%
Tumors of cranial and spinal nerves	25	25	0	100%
Tumors of meningeal origin	45	38	7	84.44%
Tumors of sellar region	2	2	-	100
Metastatic tumors	9	9	-	100
Pituitary adenomas	6	6	-	100
Total	126	111	15	88.09%

Table 4: Histo-radiological correlation showing deferred cases in the present study (n=15).

Radiological Diagnosis	Histopathological diagnosis
Glioma (6 cases)	Fibrous meningioma (2 cases)
	Atypical meningioma (2 cases)
	Medulloblastoma
	Ganglioglioma
Ependymoma (5 cases)	Medulloblastoma
	Meningothelial meningioma (3 cases)
	Anaplastic astrocytoma
Atypical meningioma (1 case)	Pilocytic astrocytoma
Choroid plexus papilloma (1case)	Ependymoma
Chordoma (1 case)	CNS embryonal tumor with rhabdoid features
Malignant peripheral nerve sheath tumor (1 case)	Ewings sarcoma

DISCUSSION

Tamkeen Masoodi et al¹ analysed 106 cases of CNS tumors, the age of the patients ranged from 4 to 82 years with a mean age of 43.29 years. Maximum number of cases (47.1%) were seen in the age group between 31-50 years. Overall males were slightly more frequently

affected than females, the male: female being 1.12:1. Headache was the most common symptom (69.6%) followed by seizures (35.9%). Frontal lobe was the commonest site (20.7%) involved.

In the present study male: female ratio was 1.25:1. The age groups with tumors included a wide range from

3years to 69 years with highest number of cases seen within 41-50 years age group. Most common presentation of brain tumors was headache and vomiting (32.54%) followed by seizures (31.75%). The tumors were common in the frontal lobe and cerebropontine angle (15.87% each). This is in agreement to the findings of Jalali and Datt⁷ and Jamal et al.⁸

The various patterns of CNS tumors in the study by Tamkeen Masoodi et al were astrocytomas (41.50%), meningiomas (19.81%), pituitary adenomas (11.32%), schwannoma (11.32%), oligodendrogliomas (2.84%), ependymoma (4.72%), medulloblastoma (3.78%).¹ In the present study the various patterns were astrocytomas (20.63%) meningiomas (35.71%), pituitary adenomas (4.76%), nerve sheath tumors (19.84%), oligodendrogliomas (1.59%), ependymoma (1.59%), medulloblastoma (1.59%) and metastatic tumors (7.14%). In the present study meningiomas comprised the major group, which was comparable with studies by Das et al, Suh et al¹⁰ and Lee et al.^{9,11}

Lakshmi S analysed 507 CNS tumors, meningiomas comprised 25.25% of cases. The classical meningiothelial variant was the commonest (23.44%).¹² In the present study meningiomas constituted (35.71%) of cases and the commonest variant being meningiothelial meningioma constituting 55.56% of cases, followed by transitional meningioma (20.00%) and 5 cases of psammomatous meningioma, 3 cases of atypical meningioma and a case of angiomatous meningioma. Various studies done by AB Shah et al, Khaled R Zalata, Sangamithra et al, S Babu et al showed similar findings.^{6,13-15}

Tumors from cranial and spinal nerves were compared with various studies. In the study by Lilith and Dastur et al, Schellinger et al, Kaye et al, Cheang et al, Herbet H Engelhard et al, Moein P et al, Nitin M. Gadgil et al the percentage of nerve sheath tumors were 39.92%, 24.4%, 32.3%, 52.2%, 21.2%, 33%, 42.36% respectively.¹⁶⁻²² In the present study all the tumors were nerve sheath tumors constituting 19%, 84% being schwannoma and 16% being neurofibroma.

The diagnostic accuracy of MRI in CNS tumors ,the study by Raj Kumar et al showed sensitivity of 94.5%, specificity of 75%, positive predictive value of 96.29%, and negative predictive value of 66.66%.²³ In the present study the diagnostic accuracy was sensitivity:66.67 %, specificity: 97.78 %, positive predictive value: 87.5%, negative predictive value: 92.63% overall accuracy: 91.89 %.

Thotakura M et al³ evaluated Ki 67 as proliferative index in the grading of astrocytomas in order to predict the biological behavior of the tumor and prognosis of patients. His observations were; mean Ki 67 LI in Grade I astrocytomas was 3.36, 7.05 in Grade II astrocytomas, in Grade III astrocytomas and 38.7 in Grade IV astrocytomas.

p values were significant between all grades of astrocytomas except between Grade I and Grade II tumors which was 0.5076. In the present study mean Ki 67 LI in Grade I astrocytomas was 4.66, 8.07 in Grade II astrocytomas, 13.5 in Grade III astrocytomas and 22.93 in Grade IV astrocytomas.

Sashidhar Babu et al in their study Grade-I meningiomas constituted about 90%, Grade-II about 7% and Grade-III about 2% of the meningiomas. Histopathologic grading is one of the important predictors of recurrence. Ki 67 LI correlates with histological grade and recurrence.⁶ However, all the tumors in each grade do not behave uniformly. The Ki 67 LI increased with the grade of meningiomas and mean Ki 67 LI between Grade I and II and I and III were statistically significant. In the study by Sanghamitra Mukherjee et al Mean Ki 67 LI of Grade I meningiomas was 1.4%, Grade II meningiomas was 4.08% and Grade III meningioma showed Ki 67 LI of 15%. In the present study the Ki 67 LI increased with the grade of meningiomas. Mean Ki 67 LI of Grade I meningiomas varied from 3.1 to 7.3% and Grade II meningiomas was 10.8%.¹⁵

CONCLUSION

In the present study the commonest tumors consisted of meningiomas, followed by neuroepithelial tumors and tumors from cranial and spinal nerves with a radio histopathological over all correlation of 91.89%. Measurement of proliferative activity are important in determining the grade and recurrence of the tumor. Histopathology grading may sometimes overrate or under rate the actual behavior of the tumor especially in Astrocytomas. Ki 67 is a nuclear marker used to demonstrate proliferative phase of cell cycle. Thus immunohistochemical evaluation with Ki 67 may prove to be a vital supplementary tool for diagnostic and prognostic significance. In the present study the expression of Ki 67 increased as the grade of tumor increased in both astrocytomas and meningiomas. In one case with Ki 67 index greater than 7 in case of meningiomas showed recurrence within a period of 1 year. Determination of Ki 67 should constitute a part of routine investigation in patients with astrocytomas and meningiomas.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

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