Section: Neurosurgery

Original Research Article

PROSPECTIVE OBSERVATIONAL STUDY OF INTRACRANIAL AND SPINAL EPENDYMOMAS WITH SPECIAL REFERENCE TO IMMUNOHISTOCHEMICAL MARKERS IN RELATION TO SHORT TERM PROGNOSIS

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ABSTRACT

Background: An ependymal tumor usually begins in cells that line the fluid filled spaces in the brain and around the spinal cord. An ependymal tumor may also be called an ependymoma (Grade I, II or III). The aim is to analyse the intracranial and spinal ependymomas with special reference to immunohistochemical markers in relation to short term prognosis. **Materials and Methods:** The present prospective study was conducted in the Department of Neurosurgery, Bangur Institute of Neurosciences & SSKM Hospital, IPGME & R, Kolkata from April 2020 to December 2021 in the Neurosurgery ward. 30 cases admitted in the department operated for suspected cases of intracranial and spinal ependymomas irrespective of any age groups and histologically confirmed thereafter by Pathology Department of SSKM hospital, IPGMER were included in the study. Age, sex, mode of presentation, clinical symptomatology, clinical findings, clinical, radiological investigations, surgical details, outcome data was recorded. The clinical follow-up observation was carried out by outpatient review. The patients were regularly followed up at 3-, 6- and 12-months operation. **Result:** Intracranial and spinal location was reported among 21 (70%) and 9 (30%) subjects respectively. During surgery, complete resection was achieved in 80% of the subjects. Out of 30 subjects, 90% of the subjects survived whereas mortality happened in 10% of the subjects. Most common complication was cranial nerve palsy (33.33%). The mean Ki-67 and p53 proliferative indices were significantly higher in grade III tumors as compared to grade II and grade I tumors. EMA was found to be positive in 70% of the subjects. **Conclusion:** The results concluded that p53 and Ki 67 indices when performed in routine diagnostic cases can supplement the histological diagnosis and at the same time these values could predict the relative difference in prognosis of various subtypes.

INTRODUCTION

An ependymal tumor usually begins in cells that line the fluid filled spaces in the brain and around the spinal cord. An ependymal tumor may also be called an ependymoma (Grade I, II or III).[1] Ependymal tumors (ependymomas, EPNs), a common type of malignant neoplasms of the central nervous system (CNS), constitute about 10% of all intracranial tumors and about 20% of spinal cord tumors.[2,3] Median age of presentation of ependymoma is 2.4 years, and there is a slight male preponderance. Most pediatric ependymomas are intracranial with 80% of them occurring in the posterior fossa (PF). In adults, about 66% occur in the spinal cord and > 50% of the intracranial ependymomas are supratentorial (ST).[4,5] The molecular subgroups can be categorized based on their location – ST, PF and spine. The new consensus on management of intracranial ependymoma recognizes that the treatment decisions for ependymoma should not be based on histopathological characteristics alone and that the molecular classification should be a component of any future clinical trial. Meanwhile, the 2016 update for the WHO classification of central nervous system

tumors has accepted one genetically defined subtype: ependymoma, v-rel reticuloendotheliosis viral oncogene homolog A(RELA) fusion-positive.[6]

More recently her2 neu, p53 and Ki -67 have been widely used as markers to predict outcome in various malignancies.[7-9] The p53 gene is a tumour suppressor gene located on the 17p13.1 and is the single most common target for genetic alterations in human cancer. Ki -67 is an established marker for proliferative index in cycling cells.[10] Its presence in large proportion of cells suggests an aggressive neoplasm. Investigation into role of these antigens in neuroectodermal tumors have concentrated primarily on astrocytic tumors. Recently some authors have advocated that her2 neu, Ki 67 and p53 immunolabelling are important prognostic markers in ependymomas.[11-14]

However, data regarding the same is very scarce in this part of the country. Hence the present study was conducted to analyse the intracranial and spinal ependymomas with special reference to immunohistochemical markers in relation to short term prognosis.

MATERIALS AND METHODS

The present prospective study was conducted in the Department of Neurosurgery, Bangur Institute of Neurosciences & SSKM Hospital, IPGME & R, Kolkata from April 2020 to December 2021 in the Neurosurgery ward of IPGMER, Kolkata. 30 cases admitted in the department operated for suspected cases of intracranial and spinal ependymomas irrespective of any age groups and histologically confirmed thereafter by Pathology Department of SSKM hospital, IPGMER were included in the study. Patient those who are not willing to participate in the study, relapsing cases of ependymoma (Intracranial or spinal), extraneural metastatic ependymoma and extreme of ages and not fit for surgery were excluded from the study.

Parameters to be studied:

a. Details of the patient in terms of clinical history taking, a thorough physical examination with special focus on central nervous system and spine with relevant radiological investigations were recorded.

b. To look for frozen section or squash cytology positive cases of suspected ependymomas across all CNS compartments.

c. Study tools:

(A) Clinical: History taking and clinical examination with help of predesigned and pre-tested proforma.

(B) Investigation:

[1] Routine hematological and biochemical tests

[2] Radiological

a. NCCT head

b. MRI of brain plain plus contrast with spectroscopy.

1. Size of tumour.
2. Intensity in T1W1 and T2W2.
3. Enhancement
4. Cyst
5. Calcification
6. Peritumoral edema
7. Intratumoral hmg

c. MRI of spinal cord plain plus contrast.

[3] Histological

a. Frozen section or squash cytology

b. Immunohistochemical markers staining like ki67, Her2 neu, RELA fusion protein etc.

Data collection:

1. Age, sex, mode of presentation, clinical symptomatology, clinical findings, clinical, radiological investigations, surgical details, outcome data was recorded.
2. The clinical follow-up observation was carried out by outpatient review. The patients were regularly followed up at 3-, 6- and 12-months operation.

Statistical analysis: Data so collected was tabulated in an excel sheet, under the guidance of statistician. The means and standard deviations of the measurements per group were used for statistical analysis (SPSS 22.00 for windows; SPSS inc, Chicago, USA). For each assessment point, data were statistically analyzed using one way ANOVA and the level of significance was set at $p < 0.05$.

RESULTS

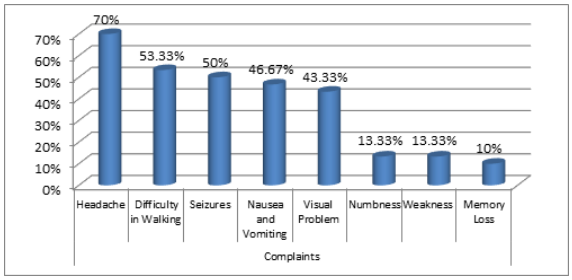

Figure 1: Clinical presentation among the study subjects

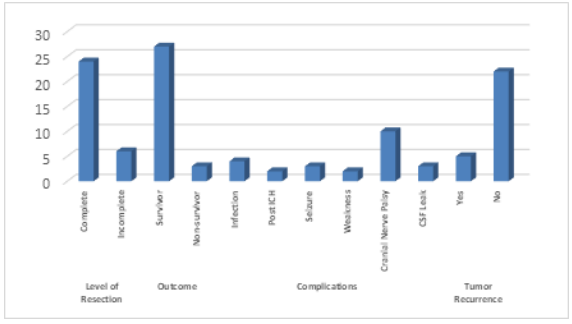

Figure 2: Level of resection, surgical outcome, complications and Tumor Recurrence among the study subjects

Out of 30 subjects, 63.33% of the subjects were male and 36.67% were female. Mean age among the study subjects was 28.73±31.36 years (range 1-59). Intracranial and spinal location was reported among 21 (70%) and 9 (30%) subjects respectively. Most common location was ventricle (46.67%) followed by cerebral hemisphere and dorsal spine (13.33% each). Least common location was lateral ventricle

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(3.33%) followed by CP angle and cervical (6.67% each). Grade I, II and III ependymoma was revealed in 2 (6.67%), 23 (76.67%) and 5 (16.67%). Hence most common grading was grade II. Classical variety (3.33%) was the most common subtype. Myxopapillary ependymoma, Subependymoma and Ependymoblastoma was reported in one subject each. Headache, difficulty in walking, seizures, nausea and vomiting, visual problem, numbness, weakness and memory loss was reported among 70%, 53.33%, 50%, 46.67%, 43.33%, 13.33%, 13.33% and 10% of the subjects respectively. During surgery, complete resection was achieved in 80% of the subjects. Out of 30 subjects, 90% of the subjects survived whereas mortality happened in 10% of the subjects. Most common complication was cranial nerve palsy (33.33%) followed by infection (13.335). Seizure and CSF leak was reported in 3 (10%) subjects each. Tumor recurrence was found among 71.33% of the subjects. 3 cases excluded due to mortality

The mean Ki-67 proliferative indices were significantly higher in grade III tumors (4.78) as compared to grade II (1.63) and grade I tumors (0.81). The mean p53 proliferative indices were significantly higher in grade III tumors (4.28) as compared to grade II (1.39) and grade I tumors (0.77). When Ki-67 and p53was compared according to grading of ependymomas using anova test, significant difference was found as $p<0.01$. EMA was found to be positive in 70% of the subjects. Her-2-neu 1+, 2+ and 3+ was found in 46.67%, 36.67% and 16.67% of the subjects respectively. NANO scale after surgery kept on improving among the study subjects as compared to baseline. NANO scale at pre-operative and immediate post-operative interval was 3.23 and 3.58 respectively. After 12 months, NANO scale increased to 3.97. When NANO scale was compared at different intervals using anova test, significant difference was found.

Table 1: Location and grading of ependymomas

		Parameter	N	%
Location	Intracranial [21 (70%)]	Cerebral hemisphere	4	13.33
		Lateral Ventricle	1	3.33
		Ventricle	14	46.67
		CP Angle	2	6.67
	Spinal [9(30%)]	Dorsal Spine	4	13.33
		Cervical	2	6.67
		Lumbar Region	3	10
Grading	Grade I [2 (6.67%)]	Myxopapillary ependymoma	1	3.33
		Sub ependymoma	1	3.33
	Grade II [23(76.67%)]	Classical Variety	16	53.33
		Clear Cell Ependymoma	5	16.67
		Papillary Ependymoma	2	6.67
	Grade III [5(16.67%)	Anaplastic Ependymoma	4	13.33
		Ependymoblastoma	1	3.33

Table 2: Level of resection, surgical outcome, complications and Tumor Recurrence among the study subjects

	Parameter	N	%
Level of Resection	Complete	24	80
	Incomplete	6	20
Outcome	Survivor	27	90
	Non-survivor	3	10
Complications	Infection	4	13.33
	Post ICH	2	6.67
	Seizure	3	10
	Weakness	2	6.67
	Cranial Nerve Palsy	10	33.33
	CSF Leak	3	10
Tumor Recurrence	Yes	5	16.67
	No	22	71.33

Table 3: Ki67 and p53 according to grading of ependymomas

Grading	Ki67		p53	
	Mean	SD	Mean	SD
Grade I	0.81	0.1	0.77	0.2
Grade II	1.63	0.48	1.39	0.41
Grade III	4.78	1.02	4.28	1.12
Anova Test	11.41		10.09	
p value	<0.001		<0.001	

Table 4: EMA and Her-2-neu distribution among the study subjects

	Parameter	N	%
EMA	Positive	21	70
	Negative	9	30
Her-2-neu	1+	14	46.67

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	2+	11	36.67
	3+	5	16.67

Table 5: Comparison of NANO scale after surgery (brain tumor) at different intervals

Time Interval	Nano Scale		Anova Test	p value
	Mean	SD		
Pre-operative	3.23	2.11	3.04	0.037
Immediate post-operative	3.58	2.37		
3 Month	3.84	2.48		
6 Month	3.89	2.41		
12 Month	3.97	2.23		

DISCUSSION

The ependymoma grade is based on histopathologic criteria and the World Health Organization based grading system (range, 1-3). Several publications discuss the difficulty of the existing criteria, which use morphologic features to determine the grade of an ependymoma; this has led to an ongoing debate regarding the significance of the grade in predicting the prognosis. More recently, molecular markers have been reported for subclassifying ependymomas within anatomic compartments (supratentorial, infratentorial, and spinal cord) and thereby identifying differences in the underlying tumor biology and clinical course, including the prognosis.[15] However, despite the increasing recognition of the importance of these molecular markers, they currently are not routinely determined in clinical practice.[16]

There was male dominancy in our study. Similar male dominance was reported by Suri S. Vaishali et al,[17] and Soheir Mahfouz et al,[18] in their studies. Mean age among the study subjects was 28.73±31.36 years (range 1-59) in this study. According to Suri S. Vaishali et al,[17] the age group of patients varied from 1-61 years.

Intracranial and spinal location was reported among 21 (70%) and 9 (30%) subjects respectively. Most common location was ventricle (46.67%) followed by cerebral hemisphere and dorsal spine (13.33% each). Least common location was lateral ventricle (3.33%) followed by CP angle and cervical (6.67% each) in our study. In a study by Soheir Mahfouz et al,[18] of the 29 classic ependymomas studied, 24 (82.76%) cases were intracranially located, whereas 14 of them (58.3%) were in the posterior fossa and 5 (17.24%) were located within the spinal region. Spinal location was detected in 1 tanycytic ependymoma case (1 of 3), 1 anaplastic ependymoma case (1 of 3), and in all myxopapillary ependymomas (3 of 3). These findings are approximately similar to our study. Suri S. Vaishali et al,[17] in their study found that there were 58 cases of intracranial ependymomas. These were located in cerebral hemisphere (16), lateral ventricle (3). Pineal (1), 4th ventricle (37) and CP angle (1). There were 12 cases of spinal ependymoma. 7 of these were intramedullary and 6 were intradural extramedullary. A majority of these (42%) were located in the dorsal spine followed by cervical (33%), filum (17%) and lumbar regions.

In the present study; grade I, II and III ependymoma was revealed in 2 (6.67%), 23 (76.67%) and 5 (16.67%). Hence most common grading was grade II. Classical variety (3.33%) was the most common subtype. Myxopapillary ependymoma, Subependymoma and Ependymoblastoma was reported in one subject each. Ependymomas are rare tumors with a relatively long survival, therefore creation of the universal grading system for these neoplasm's appear to be difficult. As a result, numerous two-, three- and four-tiered grading systems exist, therefore the rate of high-grade ependymomas broadly varied from 4 to 94% in different reports.[19] Suri S. Vaishali et al,[17] in their study showed that there were 3 cases (4.2%) of Grade I ependymoma (2 cases of myxopapillary ependymoma and 1 case of subependymoma); 57 cases (81.5%) of ependymoma grade II (43 of these were of classical variety, 11 of clear cell ependymoma, 2 of papillary and 1 case of cellular ependymoma).

In the present study, complete resection was achieved in 80% of the subjects during surgery. Out of 30 subjects, 90% of the subjects survived whereas mortality happened in 10% of the subjects. According to Andrey Korshunov et al,[19] at the end point of follow-up analysis 42 patients (48%) were found to be free of disease within the period from 26 to 101 months after the operation (median – 58 months). Local tumor regrowth had developed in the other 46 cases and progression free survival time (PFS) varied from 4 to 54 months (median – 26 months).

In the present study; the mean Ki-67 proliferative indices were significantly higher in grade III tumors (4.78) as compared to grade II (1.63) and grade I tumors (0.81). When Ki-67 was compared according to grading of ependymomas using anova test, significant difference was found as $p<0.01$. Andrey Korshunov et al,[19] in their study similarly revealed that the mean Ki level was significantly prominent for high-grade tumors (12.4 vs 2.6%). Similarly, Suri S. Vaishali et al,[17] in their study reported that the mean Ki-67 proliferative indices were significantly higher in grade III tumors as compared to grade I and grade II tumors with statistically significant difference. Many authors have studied the expression of Ki 67 and Ki si in various Grades of in various Grades of ependymomas and in recurrent tumors.[20-22] These authors have indicated that the Ki- 6 7 labelling index is confirmed as a very

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important prognostic marker for ependymaomas. These findings are similar to our study.

In the present study; the mean p53 proliferative indices were significantly higher in grade III tumors (4.28) as compared to grade II (1.39) and grade I tumors (0.77). When p53 was compared according to grading of ependymomas using anova test, significant difference was found as $p<0.01$. Andrey Korshunov et al,[19] in their study showed that all low-grade ependymomas were found to be p53 negative. On the other hand, 24 high-grade ependymomas contained evenly distributed p53 immunostained nuclei. The overall incidence of p53 positivity in their series was 27%, but previously published data cannot be compared due to the small number of examined cases. Similarly, Suri S. Vaishali et al,[17] in their study reported that the mean p53 proliferative indices were significantly higher in grade III tumors as compared to grade I and grade II tumors with statistically significant difference. Suzuki et al in 2001 in their study on 29 patients of ependymoma advocated that the clinical course was worst in clear cell ependymoma which had significantly higher expression of p53 than the other subtypes.[23] Our results too indicated that aberrant p53 is closely associated with high-grade ependymomas center and poor prognosis.

In the present study; EMA was found to be positive in 70% of the subjects. The above results were close to those found by Hasselblatt and Paulus who studied the pattern and extent of EMA expression in 54 ependymomas (33 classic, 2 tanycytic, 6 myxopapillary, and 13 anaplastic ependymomas). Distinct punctate intracytoplasmic EMA immunoreactivity was observed in 48 of 54 ependymomas (80%), whereas ringlike EMA staining was observed in 17 of 54 (31%) cases. Apart from the absence of EMA expression in most myxopapillary ependymomas (only 1 positive case), neither staining intensity nor pattern was related to tumor type. Moreover, EMA immunoreactivity did not reveal any differences between grade 2 and grade 3 ependymomas, so EMA could not differentiate between different grades of ependymoma.[18] According to Soheir Mahfouz et al,[18] completely negative EMA staining was detected in 8 of 29 cases while positive EMA staining was reported in 21 cases.

The correlation between tumor grade and EMA immunoreactivity was made in previous studies, and controversial results were reached. Uematsu and colleagues studied EMA expression in 20 ependymomas (13 differentiated grades 1 and 2) and 7 anaplastic ependymomas; they found that EMA was ex- pressed in 11 of 13 differentiated cases, whereas no immunoreactivity was detected in anaplastic cases. Their results indicated that EMA is highly selective for differentiated ependymomas. A similar conclusion was also reached by Vege and colleagues, who concluded that EMA is more expressed in differentiated especially cellular ependymomas. On the other hand, EMA expression was found to be more prominent in anaplastic ependymomas in the study done by Kaneko and colleagues.

In all of the above studies, monoclonal antibody E29 was employed; however, this controversy between different studies may be due to differences in methodology and techniques of staining.

NANO scale after surgery kept on improving among the study subjects as compared to baseline. NANO scale at pre-operative and immediate post-operative interval was 3.23 and 3.58 respectively. After 12 months, NANO scale increased to 3.97. When NANO scale was compared at different intervals using anova test, significant difference was found. Johannes Kasper et al,[24] in their study revealed similar results too. Monitoring neurological performance via the NANO scale might provide prognostic information independently from other well established clinical, radiological, or pathological factors. Special attention should be paid when worsened neurological performance occurs at the first outpatient appointment after radiochemotherapy and neurorehabilitation.

Our study highlights that p53 and Ki 67 indices when performed in routine diagnostic cases can supplement the histological diagnosis and at the same time these values could predict the relative difference in prognosis of various subtypes. But for this more studies have to be done with long term follow up of these patients.

CONCLUSION

Immunohistochemical variables viz. Ki-67 and p53 was found to be strongest predictors with grading of ependymoma and they seem to be useful for assessing individual tumor prognosis in routinely processed biopsy specimen. EMA expression and pattern of distribution, on the other hand, cannot be employed to determine the type of variant or the degree of tumor aggressiveness, and hence cannot predict the behavior of ependymal neoplasms. Identification and optimization of immunohistochemical (IHC) markers for ependymoma allowed validation of our findings, using a human ependymoma tissue microarray, and provides a tool for prospective prognostication and stratification of PF ependymoma patients.

More studies of this type along with long term follow up are required to establish definite and uniform criteria and cut off values to inculcate these antibodies as markers of prognosis and survival prediction in ependymomas.

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