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Immunohistochemical Expression in Gliomas - CD117 in a Prognostic and Theranostic Vision

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Abstract: ***Gliomas are a varied group of infiltrative neoplasms, They are mostly high grade, with a short survival time and less amenable for surgical treatment. Hence there is a dire need for chemotherapy. CD117 is a protooncogene encoded tyrosine kinase receptor. It is expressed in some normal tissues and in neoplasms like gastrointestinal stromal tumours (GIST), where treatment with inhibitors of tyrosine kinase receptor namely imatinib was proved successful. Likewise this study evaluates the expression of CD117 in gliomas and its role as a as diagnostic and theranostic tool. Materials and methods: This is a retrospective two year study. A total of 836 cases of neuro biopsies were received out of which 263 cases were gliomas.Among them 50 representative cases were selected grade wise and evaluated immunohistochemically for CD117 expression. Results: Incidence of gliomas was 31.4% (263 cases) in our study. Glioblastoma multiforme, WHO GRADE IV tumour was the most common type. Pilocytic astrocytoma was the most common GRADE Itumour. Anaplastic astrocytoma was the most common Grade III tumour.CD117 was expressed in 54% of total cases and was expressed maximum in high grade tumours (66.8%) compared to low grade tumours. Significant CD117 expression was seen in cases with high cellularity and marked nuclear pleomorphism. Conclusion: Our study shows CD117 is expressed remarkably in high grade gliomas than low grade. Hence CD117 can be used as a perfect tool to differentiate high grade tumours and subject them to chemotherapy with tyrosine kinase inhibitors, namely imatinib..Hence our study opens the vision on targeted therapy in high grade gliomas.***

Keywords: CD117, Gliomas, High Grade Tumours, GIST, Imatinib

1. Introduction

Central nervous system tumours consist of less than 2 % of all malignancies worldwide ([1]). The major group of brain tumours are derived from glial cells, collectively called gliomas Gliomas are histologically classified by WHO [2] and graded and typed. Gliomas are infiltrative neoplasms and are deep within the brain substance and less amenable for complete surgical resection.They pose a major challenge to neurosurgeons due to their site. Thus surgical morbidity is very high and lethal rather than the tumour by itself. Prognosis depends on extent of surgery [3] Some of them are inaccessible for surgery. Hence prognosis depends not only on tumour type, and grade but also on the site of the tumour and the type of treatment**.** Hence alternative modalities of therapy namely chemotherapy play a better role in reducing morbidity and mortality of gliomas.

CD117, is a 145KD, transmembrane glycoprotein from type iii sub family of tyrosine kinase receptors. The protooncogene C-KIT found to be located in chromosome 4 in its long arm encodes the tyrosine kinase receptor namely CD117 [4]. It is expressed usually in some normal tissues and.in some neoplasms [5].It has been demonstrated that CD117 expression is necessary for the normal development of mast cells, melanocytes, some hematopoietic cells, and germ cells. CD117 has found its place in immunohistochemistry after the successful treatment of CD117 positive gastrointestinal stromal tumours [6, 7] with tyrosine kinase inhibitors, namely imatinib as a part of chemotherapy [8, 9] Hence in this concept, evaluation of this receptor, its distribution, function and its coding gene in many tumours of CNS is very useful. As the fact that only very little data is available on immunohistochemical expression of CD117 in glial tumours, this study is aimed at determining CD117 expression in all histopathological tumour types and grades. The percentage of stained cells (CD117 SCORE) and intensity of staining were considered as useful parameters in making distinction between low grade and high grade gliomas when determination of grade is not straight forward.

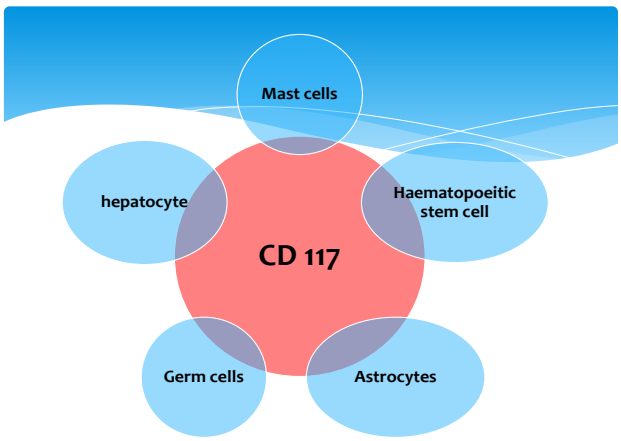

Figure 1: Expression of CD117 in the normal cells

It has been demonstrated that CD117 expression is necessary for the normal development of mast cells, melanocytes, some hematopoietic cells, and germ cells and hepatocytes

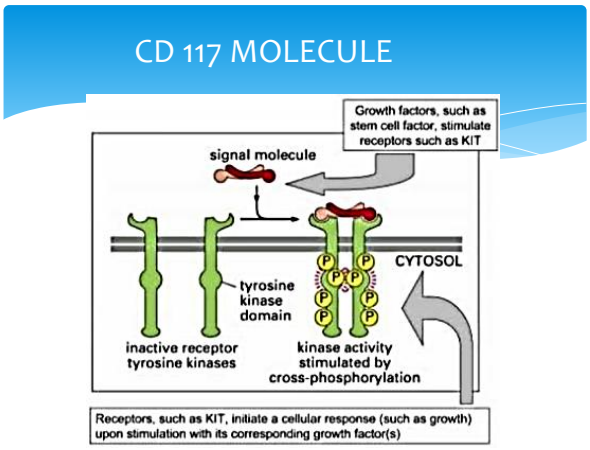

Fig 2: Schematic Diagram of CD117 Molecule

2. Materials and Methods

This is a retrospective descriptive immunohistochemical analysis of gliomas in the Department of Neuropathology, Madras Medical College and Rajiv Gandhi Government General hospital, Chennai during the period of jan 2014 to dec 2015

2.1 Source of data

A total 836 specimens where received during this study period, out of this 263 cases were gliomas31.4%. (Table-1) Out of these glioma cases, a total of 50 cases which were representative of the Whole sample was selected. with grade-I (9 cases) 15%, grade II (15 cases) 37%, grade III (7cases) 13%, grade IV (19 cases) 35%. (Table -2) Corresponding paraffin blocks were collected and histopathological sections were prepared and subjected to H&E staining and immunohistochemical analysis by primary marker CD117. The results were tabulated in a master chart and also recorded with photographs..

2.2 Inclusion Criteria

Patients diagnosed as glial tumours astrocytoma, oligod endroglioma, oligoastrocytoma, glioblastoma multiforme ependymoma, their subtypes and combinations.

2.3 Exclusion criteria

Nonneoplastic lesions of CNS, benign lesions of CNS, meningiomas, lymphoid neoplasms and all other neoplasms excluding gliomas.

2.4 Immunohistochemical evaluation

Immuno histochemistry is a molecular technique which was first described by Dr. Albert Coons in 1941. Immuno histochemical analysis using CD 117 were done in paraffin embedded tissue samples using poly Excel detection system protocol. Due to economic constraints, immuno-histochemistry were done only for 50 cases. 4 micron thickness of paraffin embedded sections are taken and transferred to gelatin coated slides. Antigen retrieval is done using EDTA buffer, as antigen retrieval solution. And heat retrieval methodology is used for antigen retrieval.

Sections with a thickness of 4 µ from selected formalin fixed paraffin embedded tissue samples were transferred on to gelatin coated slides. Heat induced antigen retrieval was done. The antigen is bound with rabbit monoclonal antibody CD117 receptor and then detected by the addition of secondary antibody conjugated with horse radish Peroxidase-polymer and Diaminobenzidine substrate.

Table 1: Antibodies in Immunohistochemistry

Antigen	Vendor	Clone	Species	Dilution	Positivity	Positive Control
CD117-C-terminus	Path n Situ	EP 10	Rabbit IgG	1:50 To 1:100	Cyto plas m & mem brane	Gastro intestinal stromal tumour

2.4.1. Interpretation & Scoring System:

The CD117 immunohistochemically stained slides were analyzed under the microscope for the presence of reaction which was detected by the brown colour of DAB chromogen and following various parameters are analysed.

1) Cellular localization - both cytoplasmic and membrane positivity
2) Among the neoplastic cells the percentage of CD117 stained cells were graded by a semiquantutative scale which ranges from
   score 0 - No immunoreactive cells
   score 1+ - 1-10%
   score 2+ - 11-50%
   score3+ - 51-75%
   score4+ - more than 75% ([10])
3) The intensity of staining reaction was graded as Weak, moderate and strong.

2.5 Statistical analysis:

The statistical analysis was performed using statistical package for social science software version IBM SPSS 20. For analysis for category variables we have used chi square test.

3. Observation And Results

Among the total cases received in our neuropathology department 31.4% (263) were glioma. All the 263 cases of gliomas, were grouped according to WHO classification into four grades namely grade I - IV. WHO Grade I and II are grouped together as low grade and Grade III and IV are grouped under high grade in this study.

Table 2: Distribution of cases in neuropathology department

	No of cases	*Percentage*
Non neoplastic	274	32.8
Gliomas	263	31.4
Meningiomas	137	16.4
Other neoplasms	162	19.4
Total	836	100

The expression of CD117 was studied and analysed in different grades of gliomas.

Table 3: List of cases studied for CD117 expression

Grade	*Diagnosis*	*No of cases*	*Total cases 263*
I	Pilocytic Astrocytoma	9	40 (15%)
II 14 cases	Diffuse Fibrillary Astrocytoma	4	97 (37%)
	Oligo Astrocytoma	2	
	Pleomorphic Xanthoastrocytoma	1	
	Oligodendroglioma	4	
	Ependymoma	3	
III	Anaplastic Astrocytoma	8	33 (13%)
IV	GBM	19	93 (35%)
Four Grades	8 Types	50	263

3. 1 CD117 Expression

CD117 was positive in 54% (27) of total cases studied. (Chart-1)

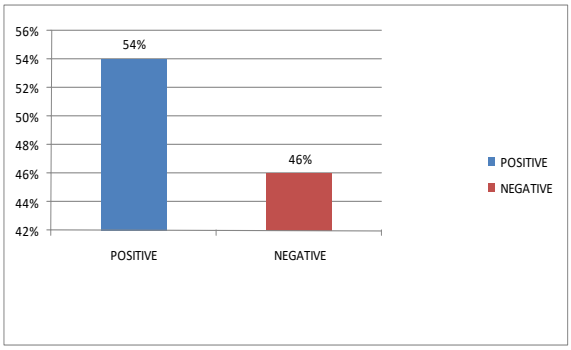

Chart 1: Distribution of CD117 expression in Gliomas

3.2.1 CD117 and Grade Correlation

CD117 was expressed in 39.13% of low grade tumours and 66.87% 0f high grade tumours, inferring that maximum expression was seen in high grade tumours. This correlation was found to be statistically significant. P <0.05. (Chart-2)

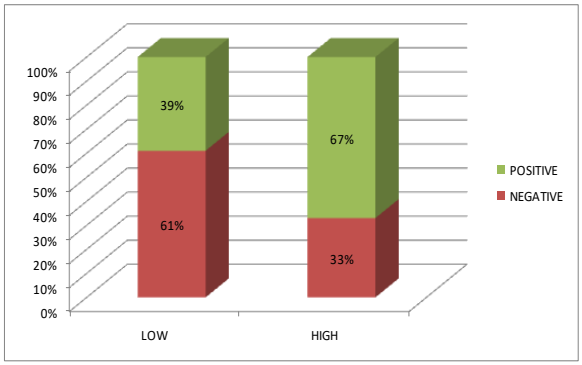

Chart 2: Correlation of CD117 expression with low grade (I & II) and high grades (III & IV) glioma

3.2.2 CD117 Expression in individual Grades

CDII7 expression was 56% expression in WHO grade I gliomas. In case of grade II, grade III, and grade IV gliomas the percentage of expression was 29%, 75%, and 63% respectively. The maximum expression was seen in grade III & IV gliomas. (Chart 3)

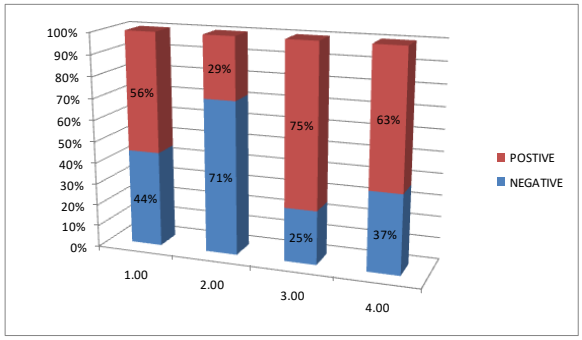

Chart 3: Correlation of CD117 expression in individual grades

3.2.3 Distribution of cd117 expression in various subtypes of glioma (% of cases positive expression in subtypes)

Anaplastic astrocytoma showed highest expression percentage (75%), second highest expression was seen in glioblastoma multiforme (63.2) % pilocytic astrocytoma showed 55%, oligodendroglioma showed 50% positivity. Diffuse fibrillary astrocytoma and pleomorphic xanthoastrocytoma was 100% negative. (Chart 4)

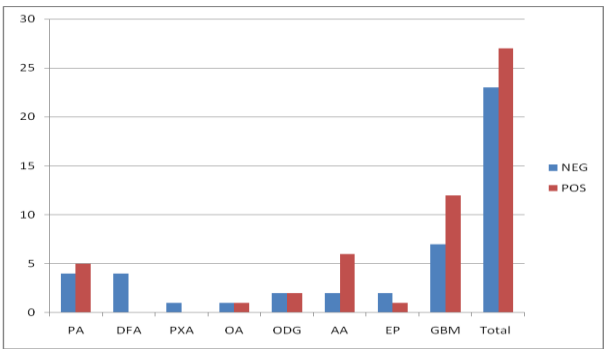

Chart 4: Distribution of cd117 expression in various subtypes of glioma

AA- Anaplastic astrocytoma, PA-pilocytic astrocytoma, DFA-Diffuse fibrillary astrocytoma, PXA-pleomorphic xanthoastrocytoma, OA-oligoastrocytoma, ODG oligodendroglioma, E-ependymoma, GBM-glioblastoma multiforme.

3.3 CD117 Score (Percentage of CD117 Stained Cells)

The percentage of stained cells

- In WHO grade I gliomas 44.4 % were 0+, and 2+, 3+, 4+ positivity was found with percent of 22.2%, 11.1%, 22.2% respectively.
- In WHO grade II gliomas 71.4% were 0+, and 3+ positivity (21.4%) and 4+ positivity (7.1%)
- In WHO grade III gliomas 25% are 0+, and 2+ positivity, 3+ positivity (37.5%), 4+ positivity in (12.5%).
- In WHO grade IV gliomas, 36.8 % were 0+, 21.1% were 1+ and 42.1% were 2+

More number of cases with highest scores of 3+ and 4+ was seen in WHO grade III Tumours. So inferring that there is statistical correlation between CD117 score and grade of the tumour. (P=0.011*) (Table 4)

Table 4: Correlation of CD117 Score (% of stained cells) with grade

GRADE		*SCORE*					*Total*
		0+	*1+*	*2+*	*3+*	*4+*	
I	Count	4	0	2	1	2	9
	% within GRADE	44.4 %	0.0%	22.2 %	11.1 %	22.2 %	100.0 %
II	Count	10	0	0	3	1	14
	% within GRADE	71.4 %	0.0%	0.0%	21.4 %	7.1%	100.0 %
III	Count	2	0	2	3	1	8
	% within GRADE	25.0 %	0.0%	25.0 %	37.5 %	12.5 %	100.0 %
IV	Count	7	4	8	0	0	19
	% within GRADE	36.8 %	21.1 %	42.1 %	0.0%	0.0%	100.0 %
Total	Count	23	4	12	7	4	50
	% within GRADE	46.0 %	8.0%	24.0 %	14.0 %	8.0%	100.0 %

P=0.011*

0=negative, 1+=0-10% stained cells, 2+ 11-50% stained cells, 3+=51-75% stained cells 4+=>75% stained cells.

3.4 CD117 Staining Intensity

WHO Grade I tumours show both moderate and strong staining intensity in equal percentage (22.2%) two cases each.

WHO Grade II tumours show more moderate staining intensity (14.3%) in two cases, weak in one case (7%).and strong in one case (7%)

WHO Grade III tumours, three cases show strong staining intensity (37.5%), 2 cases moderate (25%), and one case (12.5%) showed weak staining intensity.

WHO Grade IV tumours (31.6%) show more strong staining intensity, 10.5%moderate and 21.1% showed weak positivity. This study shows significant statistical correlation between staining intensity and grade of the tumour .

Table 5: Correlation of grade with cd117 staining intensity

	Neg	***Weak***	***Moderate***	***Strong***	***Total***
I	(4 44.4%	(1) 11.1%	(2) 22.2%	(2) 22.2%	9
II	(10) 71.4%	(1) 7.1%	(2) 14.3%	(1) 7.1%	14
III	(2 25.0%	(1) 1 2.5%	(2) 25%	(3) 37.5. %	8
IV	(7) 36. 8%	(2) 10.5%	(4) 21.1%	(6) 31.6%	19

3.5 Correlation of individual HPE diagnoses with pattern of CD117 expression including, Score and Intensity of staining

Anaplastic astrocytoma

Out of the eight cases, 6 cases were positive, 2 cases showed strong positivity, one moderate and 3 weak positivity. more than 25% cells were stained in all cases, one case showed more than 75% cells with strong positivity, CD117 SCORE OF 4+

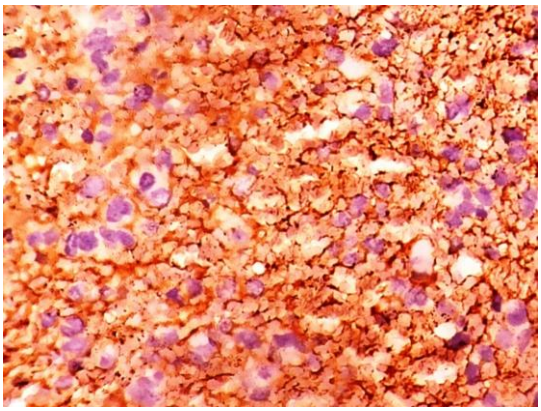

Figure 3 (a): CD117 Positive in Anaplastic Astrocytoma

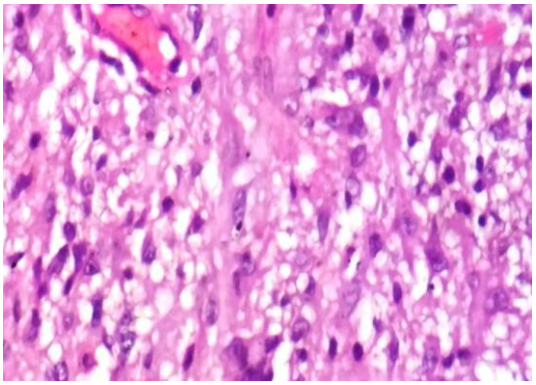

Figure 3 (b): H&E of Anaplastic Astrocytoma

Glioblastoma multiforme

12 cases showed positivity out of 19 cases.6 cases weak positive, four moderate, and two strong positive.50% cells were stained in all cases.cd117 score 2+.

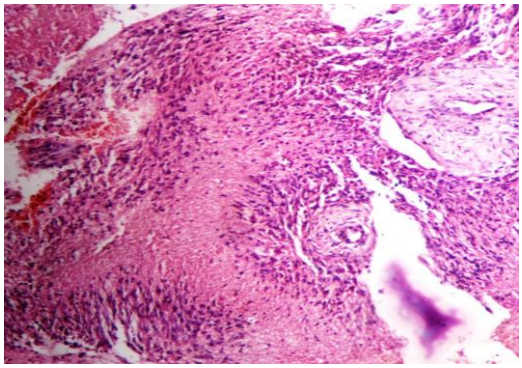

Figure 4 (a):H&E Glioblastoma Multiforme

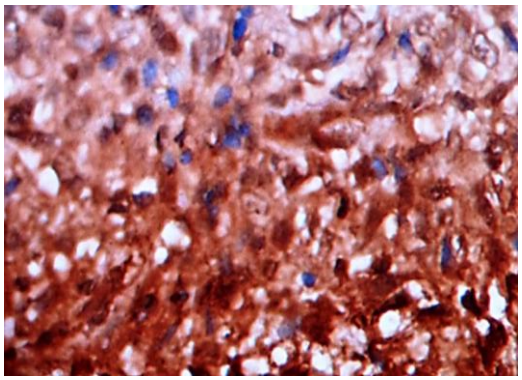

Figure 4 (b):CD117 positive in glioblastoma multiforme

Pilocytic astrocytoma
Out of the 9 cases studied 5 were CD117 positive, 2 cases were strong positive, 2 moderate, 1 weak. positive. they had strong and weak positive of equal incidence, and more than 25% cells were stained in all cases.cd117 score of 2+

Oligodendroglioma
Out of 4 cases, two showed positivity one was moderate and one strong positive in > 50% of cells, cd117 score of 3+

Ependymoma
Out of the three cases studied one case was positive for CD117 which showed moderate staining intensity in > 50% cells. Score 3+

Oligoastrocytoma
Out of the two cases studied one case was positive forCD117showing moderate staining intensity in > 50% of cells.

Diffuse Fibrillary Astrocytoma
All four cases studied were negative

Pleomorphic Xanthoastrocytoma
One case studied was negative for CD117

3.6 Correlation of CD117 with other histological parameters (TABLE NO 5)

3.6.1 Cellularity
Correlation of CD117 expression with cellularity shows that those cases with high cellularity had highest percentage of expression (69.6%).The cases with low cellularity showed nil positivity. This study was statistically significant. P < 0.041

3.6.2 Nuclear Pleomorphism
Correlation between nuclear pleomorphism and CD117 expression showed cells with marked nuclear pleomorphism had increased CD117 expression.The study was statistical significant. (P< 0.042.)

3.6.3 Mitoses, Vascular Proliferation and Necroses
Correlation of CD117 with mitoses, vascular proliferation and necroses showed no statsitical significance.

3.7 Age, Sex& Side

Comparison of CD117 with age shows highest CD117 positivity in age group of 61-80 years age., in females was high (56.2 %) when compared to males (52.9%) .

Comparison of CD117 with side of gliomas shows highest percentage of CD117 positivity in left hemisphere (64.7%) Right hemisphere show 50% positivity. Deep seated midline structures show 44.4% positivity.

Table 5: Correlation of CD117 with other Histological Parameters

Tumour characteristics		*CD117 Expression*		*Chi – Square Test*
Description		*Negative*	*Positive*	
Cellularity	1 Low	3	0	P= 0.041*
	2 moderate	13	11	
	3 high	7	16	
Nuclear pleomorphism	1+	16	11	P= 0.042*
	2+	7	16	
Mitoses	Absent	3	2	P= 0.508
	Present	20	25	
Vascular proliferation	Absent	9	7	P= 0.318
	Present	14	20	
Necroses	Absent	15	16	P= 0.665
	Present	8	11	

4. Discussion

In our study the peak incidence of gliomas was 41 -60 years. The maximum age observed was 85 years. This is similar to study of Gurney et al [(10)] and Vovoras et al[11]

The expression of CD117 was studied in different grades of glioma. A subset of 50 cases constituting of all four grades of glioma as representative of sample of 263 cases was analysed immunehistochemically. The formalin fixed paraffin embedded section was subjected to immunohistochemical analysis with CD117.

4.1 CD117 Expression

Among the 50 Cases CD117 expression was seen in 54% of tumours.

Table 6: Comparison of CD117 positivity with world statistics

Cetin et al	75%
Parvin et al	76%
arash degan et al.	42%
Current study	54%

CD117 expression was lower than the studies of parvin et al[13], and cetin et al[14], higher than studies of arash degan et al[12].

4.2 CD117 and Grade

Table 7: Comparison of CD117 positivity with grade as low and high grade

	Current Study	*Parvin et al*	*Arash deghan et al*
Low	39.13	68%	21.2%
High	66.67	84%	61.1%

CD117 was positive in 39.13 % of low grade tumours and 67% of high grade tumours inferring that maximum expression was seen in high grade tumours. This correlation was found to be statistically significant with P value of 0.05*.The study correlated with study of parvin et al[11], arash devgan et al [12]

4.3 CD117 Score

CD117 expression score when individual grades were analysed, maximum expression score of 3+ and 4+ was seen in WHO grade III tumours. This correlation was statistically significant with a P value of <0.011 which correlates with the study of parvin et al.[13]

4.4 Comparison of the intensity of stained cells with grade of the tumour-CD117 Staining Intensity

When all low and high grades were considered strong staining intensity was seen in high grade tumours similar to study of parvinet al.[13]

Table 8: Comparision of staining intensity and grade with other studies

	Parvin et al		*Current study*	
	LOW-25	*HIGH-25*	*LOW-23*	*HIGH-27*
NO	32%	16%	60.8%	30.9%
Weak	36%	32%	17.39%	11.05%
Moderate	24%	32%	8.69%	23.05%
Strong	8%	20%	13.04%	34.55%

4.5 Comparision of CD117 expression score (% of stained cells) in glioma subtypes with other studies

In cases of pilocytic astrocytoma, diffuse astrocytoma and oligodendroglioma, our study did not correlate with study of arash devgan et al [12].In cases of ependymoma, and glioblastoma multiforme., although It did not accurately match with study of arash deygan et al [12] had more or less similar results.In our study Anaplastic astrocytoma shows more than 75% of cases positive. With one case 4+ score and 3 cases 3+, which did not correlate with arash devgan et al.

Table 9: Comparision of CD117 expression score in glioma subtypes with other studies

DIAGNOSIS		*0+*	*1+*	*2+*	*3+*	*4+*
Pilocytic astrocytoma	Arash devgan et al	4	0	0	0	0
		100%				
	Current Study %	4	0	2	1	2
		44.4 %	0.0 %	22.2 %	11.1 %	22.2 %
Diffuse astrocytoma	Arash devgan et al	17	1	3		
		81%	5%	14%		
	Current study %	4	0	0		
		100%	0	0		
Oligoden dr	Arash devgan et al	4	1	0		
		80%	20%	0		
Oglio ma	Current study %	2	0	0	1	1
		50 %	0.0 %	0.0%	25.0 %	25.0 %
Ependymoma	Arash devgan et al %	1	2			
		33.3 %	66.6 %			
	Current study %	2	0	0	1	
		66.66 %	0	0	33.33%	
Anaplastic astrocytom	Arash devgan et al %	3	3	1		
		43%	43%	14%		
	Current study %	2	0	2	3	1
		25.0 %	0.0 %	25.0 %	37.5 %	12.5%
GBM	Arash devgan et al %	8	7	1	1	0
		47%	41%	.05%	.05%	0
	Current study %	7	4	8	0	0
		36.8 %	21.1 %	42.1 %	0.0%	0.0%

4.6 Comparision of histopathological parameters (Cellularity, Nuclear pleomorphism, Mitosis, Vascular proliferation and necrosis) with CD117 expression.

In our study there was statistically significant correlation between cellularity, nuclear pleomorphism and Cd117 expression. Cases with high cellularity and marked nuclear pleomorphism had highest expression percentage.

Correlation of CD117 with mitoses, vascular proliferation and necroses showed no statsitical significance.

There are no studies in literature to compare the Histological parameters with CD117 expression in literature.

4.7 Comparison of CD117 with Age, Sex and Side

Comparison of CD117 with age shows maximum CD117 expression in age group of 61-80 years age.

On Comparing CD117 with sex, among the CD117 positive cases percentage positivity in females was high (56.2 %) when compared to males.

Comparison of CD117 with side of gliomas shows maximum percentage of CD117 positivity in left hemisphere (64.7%).Deep seated midline structures show 44.4% positivity.

There are no studies in literature to correlate CD117 positivity with age, sex and side of the lesion.

Hence from our study we see a statistically significant percentage expression of CD117 in high grade glial tumours when compared to low grade tumours, especially in WHO grade III tumours. This a significant correlation with studies of parvin et al[13], arash degan et al [12]and cetin et al[14]. It proves that high grade glial tumours are immunoreactive to CD117, a transmembrane receptor, encoded by C-KIT a proto-oncogene. There is a considerable statistically significant difference in the CD117 expression score between low and high grade tuomurs Anaplastic astrocytoma shows a significant expression score and strong staining intensity, showing that they are remarkably immunoreactive to CD117..Thus this study throws light on the concept that, this study when coupled with molecularpathology of C-KIT Analysis, paves a way for targeted therapy with tyrosine kinase inhibitors, namely the drug imatinib, as discussed earlier.

5. Conclusion

Brain tumours are different from other tumours. They are mostly high grade, with a short survival time, and less amenable for surgical treatment. Prognosis depends on the site of the tumour and extent of surgery. Hence there is a dire need for chemotherapy. Our study reveals that CD117 is remarkably expressed in high grade tumours than low grade, with significantly high percentage of stained cells and strong staining intensity in high grade tumours. Especially anaplastic astrocytoma needs special mention with strong staining intensity and more than 75% of cells stained. Hence CD117 can be used as a perfect tool to identify these tumours and thus make them amenable to chemo therapy with tyrosine kinase inhibitors like Imatinib, which is already proven and in vogue in gastrointestinal stromal tumour.

This study opens the vision for targeted therapy in high grade gliomas.

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