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Risk Stratification in Low Grade Glioma: A Single Institutional Experience

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Abstract

Background: Low grade gliomas (LGG) are most often noted with the unpredictable overall survival and progression to higher grades. Objective: In the present study, we analyze the clinicopathological features influencing the prognostic outcomes and compared the features with criteria developed by EORTC. **Materials and Methods:** We observed the 130 LGG clinical cases in single institute and maintained the follow-up for more than 5 years. In addition, the molecular details were confirmed with markers as IDH, 1p/19q codeletion, p53 and ATRX mutations. **Results:** The mean age of patients as 37.67 years and male population contributing to 70%. We observed biased incidence among the male population with dominating occurrence at frontal and parietal lobes in the brain. 40.8% patients had oligodendroglioma, 33.8% astrocytoma, 19.2% oligoastrocytoma and 2.3% gemistocytic astrocytoma pathology. Patients who were subjected to chemotherapy and radiotherapy were noted with average survival of 29 months. Oligodendroglial tumors were found with progression free survival (PFS) of 25 months, oligoastrocytoma cases with 32 months, diffuse astrocytoma cases with 23 months while the gemistocytic astrocytoma cases had 22 months. The PFS for LGG cases was 4.7 years while the overall survival was 4.9 years. Mean survival of patients with KPS score <70 and >70 was 1.5 & 4.9 years respectively. 64 patients were observed with the tumor size >5 cm. In total, 72.3% of the patients were underwent GTR, 23.3% STR and 3.8% underwent biopsy. **Conclusion:** Taken together, the clinical symptoms, expression of molecular markers and the prognosis details provided by our results can help for better management of LGG cases. We further propose to use following five factors to accurately describe the prognosis and tumor recurrence: 1) Age >50 years, 2) tumor size >5 cm, 3) MIB index >5%, 4) KPS score < 70 and 5) gemistocytic pathology.

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Full Text

The group low grade gliomas (LGG) includes the WHO 2007 classified grade I and grade II glial tumors. The diagnosis was then based on histopathological features as nuclear polymorphism, mitotic index, and cellular proliferation.[1] We have previously reported that the low grade tumors contributed to 46% of all astrocytomas in our tertiary observation. We also reported median age of diagnosis of 15 years for pilocytic astrocytoma and 54 years for diffuse astrocytoma with predominance of male population.[2] Histological subtypes of LGGs include oligodendrogliomas, diffuse astrocytoma and mixed oligoastrocytoma. These are reported to be highly infiltrative and exhibit the property of malignant transformation.[3] Recent WHO 2016 classification takes into account the expression of molecular markers as IDH1, 1p/19q codeletion and EGFR amplification to assertion the prognostic outcomes on account of expression of the markers. Diffuse astrocytoma with IDH1/2 mutations are slow in growth and detected with moderate polymorphism. In addition to these molecular markers, usually the TP53 and ATRX mutations are also reported. Additionally, for the low grade tumors, the revised classification system has introduced a term called 'not otherwise specified' (NOS) for those low grade tumors where the molecular details are not available. Gemistocytic astrocytoma accounts for nearly 10% of the WHO II astrocytomas and are reported to progress to high grade tumors more frequently.[4]

The factors influencing the prognosis of the low grade astrocytoma patients includes age of patients, histology of tumors, post treatment response, seizures and tumor diameter.[3],[5],[6],[7] The older patients are usually reported with reduced prognosis with 5 year overall survival rate up to 40%. However, the patients who survives more than 2 years on initial diagnosis exhibits the prolonged progression free survival.[8],[9] The location of the tumor is known to impact the well-being of patients. LGG patients with tumor located at right hemisphere have reported with greater physical well score as compared with the left hemisphere as location.[10] Irrespective of the survival rate, most of the patients are noted to exhibit the cognitive deficits post-surgery.[11]

In past, the 'wait and watch' approach was generally preferred for treatment of LGG[12] however the present practice involves comprehensive approaches as surgery, chemotherapy and radiotherapy.[13] The choice of approach is usually influenced by the age and physiology of patients, tumor location and the KPS index.[14] Temozolomide is the widely used chemotherapeutic agent on account of its toxicity profile, ability to cross the blood brain barrier and overall efficacy against glioma when compared with the procarbazine, lomustine, and vincristine (PCV).[15],[16]

The EORTC (European Organization for Research and Treatment of Cancer) developed a prognostic scoring system based on 2 large, randomized, multicenter trials with more than 600 patients. The chief factors influencing the prognosis includes, age >40 years, astrocytic tumor type, tumor size >6 cm, tumor location, and neurological deficit at diagnosis. Combined appearance of less than 2 of these adverse factors and was associated with a median survival of 7.7 years, while a median survival of 3.2 years (95% CI 3.0-4.0 years) was noted in the presence of 3-5 prognostic factors[6] while the UCSF criteria relies on four factors as: 1) location of tumor in presumed eloquent cortex, 2) KPS score ≤80, 3) age >50 years, and 4) maximum tumor diameter >4 cm.

There are very few clear evidences on the management and clinical features of LGG in Indian population. Ethnic and genetic diversity may account for the differences in the incidence rates and the prognostic outcomes. Our study represents the subpart of Indian population. Together, we describe the surgical management, prognostic outcome, factors affecting prognosis, clinical and molecular features of patients with LGG operated at a single institution.

Methods

Patients' information, survival details and clinical characteristics

The cases were reported during 2011-2017 at Krishna Institute of Medical Sciences (KIMS), Secunderabad, India.

A registry of patients was maintained and each patient was assigned with a unique ID and basic information as age, previous history of any malignancy, gender and the symptoms were noted. Initially, MRI imaging was used to designate the location and density of tumor [Figure 1]. Briefly, the location and side of tumor was determined. Side was sub-categorized as in left or right part of the brain. The location was categorized as frontal, parietal, temporal, occipital or mixed. Patients were subjected to surgical removal of the tumor. Type of surgical removal was categorized as gross total resection, subtotal resection, biopsy, etc., The type of surgery was defined by the tumor location, intensity of the lesions and the health of the patients. The informed consent was obtained from the patients or their close relatives. Each participant in the study was completely anonymized. Present study was approved by institutional ethical committee.{Figure 1}

Histopathological diagnosis and molecular profiling

The surgically resected tissue was subjected to histopathological diagnosis as per the WHO 2007 classification.[1] Pathological information as the cellular proliferation, nuclear polymorphism, and mitotic index was used to assign the pathological grades [Figure 2]. MIB1 was used to determine the proliferative index. Each slide was observed by two independent pathologists for the conformation. The patients reported after 2016 were subjected to profiling of molecular markers as IDH mutations, p53, 1p/19q codeletion as per the revised WHO classification [Figure 3].[4] For histopathological diagnosis, the paraffin blocks of the surgically resected tissues were prepared. The sections were made by Leica microtome of 5 mm thickness. The histopathological procedures were followed as described previously.[17] Briefly, the tissues were deparaffinized by heating at slide warmer at 100°C for 10 minutes, followed by the gradient washes in xylene and series of alcohol for rehydration. Antigen retrieval was performed in sodium citrate buffer. Further steps were followed as given in the instruction manual of the Invitrogen IHC kit.{Figure 2}{Figure 3}

Karnofsky performance index (KPS) index

KPS index was calculated to observe the functional impairment in patients. The patients who can carry out their activities normally without assistance and those are with some disease symptom are assigned KPS score in the range of 80-100. Those patients who are unable to work independently and need personal help with varying degree are given the KPS score in the range of 50-70. While those, who need personal assistance, hospital or institutional help indicate that the possibility of disease progression is relatively fast and are assigned with the KPS index in the range of 0-40.[17]

Statistical analysis

Univariate and multivariate analysis was performed to determine association of survival of patients with factors as type of surgery, location of tumor, side of tumor in brain. Kaplan-Meier (Mantel-Cox) survival statistics was used to extrapolate the statistical significance in survival of patients. P 0.05 was considered as statistically significant.

Results

Patients' characteristics, symptoms and KPS score

We observed pathology, clinical characteristics, and symptoms for the 130 patients. Overall, male population was more as compared with females. The age group was divided in 3 categories as <20, 20-50 and >50. Among these, the middle age population was found to be dominant (n = 95) and males with more frequency (M: 66, F: 29). [Table 1]. The symptoms were categorized as vomiting, seizures, headache, motor weakness, etc., Among these, seizures (94) were found in most of the cases followed by headache (46) and vomiting (24) [Table 1]. Out of the total 130, in 127 cases the KPS index was found ≥70 [Table 1]C. Mean PFS in patients with pre-operative KPS score <70 was 2.2 years (95% C.I. 1.9-2.6) which was significantly less than in the patients with KPS score > = 70 (4.7 years, 95% C.I. 4.5-5.0).{Table 1}

Pathology of LGG

The surgically resected tumor tissue was processed for the histological diagnosis. The H and E staining was used to confirm the cellularity, mitotic index, presence of gemistocytic and oligodendroglial component [Figure 1]. The molecular markers as IDH, p53, were visualized by the Immunohistochemical staining [Figure 2].

Anatomic location of tumor and association of the symptoms

We observed nearly equal localization of tumor in left and right part of the brain [Table 2]. Among the total 130 cases, in 74 cases, the tumor was found to be located at frontal lobe; in 22 cases, at the parietal lobe. While in 19 cases, the location was observed to be mixed [Table 2]. Among the age groups, frontal lobe was observed more frequently in middle age groups of 20-50 years of age followed by the parietal one [Table 2]. Seizures were most commonly found when the tumor location was at frontal lobe. Among 74 cases where tumor was reported at the frontal lobe, the seizures were observed in 58 cases. Of 22 cases where the tumor was observed at parietal lobe, seizures were observed in 17 cases [Table 2].{Table 2}

Mortality rate was higher in patients who underwent near total resection (NTR) (7.1%), STR (5.8%), biopsy (20%) as compared to patients who underwent GTR (3.19%). The mean OS for patients undergoing GTR was 4.9 years (95% C.I.4.7-5.1) which was clinically significantly higher than those who underwent STR (3.9 years, 95% C.I.3.6-5.3) and biopsy (3.1 years 95% C.I.2.0-4.1). 5-year OS rate for patients with GTR, STR and biopsy was 94.4%, 88.7% and 80%, respectively.

Tumor recurrence and the associated clinical features

Among the total cases reported, recurrence was observed in 9 cases. Among these, in 6 cases, the tumor was found in right part of the brain [Table 3]. All the cases were reported in the middle age group of 20-50 [Table 3]. Frontal lobe was found to be more prone among the other lobes. In 4 cases, the recurrent tumor was observed at frontal lobe [Table 3]. In all the cases, the tumor was surgically resected. In 6 cases, gross total resection was practiced while near total resection in 3 cases [Table 3]. Among the LGG subtypes, recurrent diffuse astrocytoma was observed in 3 cases, oligoastrocytoma in 3 cases, and oligodendroglioma in 2 cases. Among the 3 gemistocytic astrocytoma cases, one was found to be recurrent [Table 3]. We also observe the impact of surgical resection method (Gross total resection-GTR, near total resection-NTR, biopsy and subtotal resection-STR) on occurrence of the postoperative seizures. Least chances of seizures were observed when the patients underwent GTR. Among the 94 cases operated by GTR, postoperative seizures were observed in 11 (11.7%) of the cases. Of 14 cases operated by NTR, seizures were observed in 7 (50%) of the cases. Biopsy and NTR cases were observed with 40% and 23% of post-operative seizures. The seizures were significantly higher in other ways of resection as compared with the GTR ($P = 0.003$).{Table 3}

Mortality rate was highest in elderly age group of >50 years (8.3%) followed by young age group of 20-50 years (3.15%). Mean OS in male was (4.9 years, 95%C.I. 4.7-5.1) higher than that of female group (4.5 years 95% C.I. 3.9-5.0). Mean survival was least for parietal tumors [3.0 years (95% C.I.3.4-3.6)] whereas for frontal and temporal tumors was 4.8 (95% C.I.4.6-5.2) and 4.7 years respectively. Mean OS time was more for tumors with size <5 cm [4.9 years (95% C.I 4.7-5.2)] than tumor with size >5 cm -4.7 years (95% C.I. 4.5-5.0).

Profile of molecular markers in LGGs

The LGG cases reported after 2016 were subjected for the profile of molecular markers as p53, IDH, 1p/19q codeletion and ATRX mutation. IDH mutation was found to be prevalent in oligodendroglial tumors followed by the diffuse astrocytoma cases. Out of 14 cases of oligodendroglioma, IDH was found to be mutated in 12. P53 mutations were more common in diffuse astrocytoma (DA) cases. 10 DA cases and 2 oligodendroglioma cases were found harbor mutant p53. P53 and IDH mutations were mutually found in 9 cases of diffuse astrocytoma. 1p/19q codeletions were more frequent in oligodendroglioma (5/14). ATRX was found to be mutated in one case

of diffuse astrocytoma and oligodendroglial tumors [Table 4]. In total 36 cases, 27 were found to be positive with IDH mutation. 38 among the 61 cases were found to express the mutant p53 while the ATRX mutations was confined to 13 of total 15 cases. The 1p/19q codeletion was observed in 5 of total 9 cases [Table 4]. The MIB1 staining was done in 126 cases. Among these, in 88 cases the staining index was found to be less than 5% while in 35 cases it was greater than the 5% [Table 4]. In cases observed for the IDH mutation, one was found to be recurrent [Table 4] Mean OS for patients with mib index > = 5% was less [4.6 years (95% C.I. 4.2-5.1)] compared to patients with mib index <5% which was 5.0 years (95% C.I. 4.8-5.1). Mean survival for patients KPS score > = 70 was 4.9 years (95% C.I.4.7-5.1), whereas in patients with KPS score <70 was 1.5 years (95% C.I.0.0-3.6).{Table 4}

Survival pattern of patients with LGG

We have observed the survival pattern of patients with pilocytic astrocytoma and diffuse astrocytoma as well as seen the cumulative survival of patients with LGG [Figure 4]a and [Figure 4]b. The median progression free survival noted was 4.7 years while the overall survival as 4.9 years. The survival of patients was plotted on the basis of histopathological appearance and location of tumor (frontal, parietal, temporal or occipital lobe). The progression free survival (PFS) was significantly different between oligoastrocytoma patients, oligodendroglioma patients ($P = 0.01$) and oligoastrocytoma vs diffuse astrocytoma patients ($P < 0.05$). Gemistocytic astrocytoma had the highest mortality rate (33.3%) followed by astrocytoma (4.5%), oligoastrocytoma (4.1%) and least for oligodendroglioma (1.9%). Mean OS for oligodendroglioma patients was 4.98 years (95% C.I. 4.8-5.1), for astrocytoma patients 4.7 years (95% C.I. 4.4-5.0), for oligoastrocytoma patients 4.9 years (95% C.I. 4.5-5.3) and least for gemistocytic astrocytoma patients (3.0 years) (P value = 0.036) [Figure 5]a. However, the tumor location was not significantly associated with the prognosis [Figure 5]b. Further, we also observed the survival of patients when given chemotherapy and/or radiotherapy [Figure 6]. The patients with no adjuvant therapy were noted with the mean survival of 26 months. The patients when subjected to RT alone were found to have the average survival of 25 months while the patients with combined RT and CT were observed with average survival of 29 months. In total, 39 patients were given no adjuvant therapy, 61 patients were given only radiotherapy and 29 patients were given chemo and radiotherapy. The type of surgery also had no influence on the survival of LGG patients [Figure 7]a and b]. We also observe the significant difference in the progression free and overall survival pattern when tumor size was categorized as less and more than 5 cm [Figure 8]a and [Figure 8]b.{Figure 4}{Figure 5}{Figure 6}{Figure 7}{Figure 8}

Discussion

In current study, we present the significance of clinicopathological management of low grade glioma patients from a single hospital in India. We collected the patient information and the associated pathological details and extrapolated its importance for the clinical survival. The patients were followed for the tumor recurrence, overall survival and observed over the prognostic value of various risk factors.

Low grade glioma constitutes a heterogeneous group of brain tumors consisting of pathological variants as diffuse astrocytoma, oligodendroglioma, oligoastrocytoma, gemistocytic astrocytoma and pilocytic astrocytoma. The existing reports claims homogenous prognosis for the LGG patients.[18],[19] We observed nearly 70% of male population in our group was predominantly of middle age (20-50 years). The previous reports[18],[20] claims for nearly 60% of the male population (unclear). In total, we predominantly observed 38.8% of cases (n = 44) of diffuse astrocytoma, 40.8% (n = 53) of oligodendroglioma and 19.2% (n = 25) of oligoastrocytoma cases. Previously, oligodendroglioma cases were noted with 11% while the oligoastrocytoma for 31%.[18] Our observation notes >70% of LGG patients from seizures followed by headache (35%) and vomiting (18%). Existing literature also reports most common presenting symptom in the form of seizures. These symptoms are often correlated with the positive prognosis.[5],[21] When viewed with the anatomic location, we observe it was dominated by the frontal (56.9%) and parietal (16.9%) lobe and among middle age group. Seizures were also most commonly observed at these anatomic locations [Table 2]. All the recurrent cases were observed in the

middle age group. Tumor located at the temporal lobe was more prone for recurrence (recurrence at temporal lobe was noted in 20% of the cases) as compared with the frontal and parietal location. In all recurrent cases, the tumor was removed by the surgical resection (mostly by gross total resection). The frequency of recurrence was more with the gemistocytic astrocytoma cases [Table 3]. We also observe other factors influencing the recurrence as tumor size, MIB index and KPS score. Higher MIB index (>5%, 18.1, HR-26.7, 95% CI of HR: 1.3 to 246.9), tumor size (>5 cm- HR: 1.73, 95% CI of HR: 0.43-6.8) and lower KPS score (<70, HR: 18.1, 95% CI of HR: 2.0-162.7) were associated with higher chances of recurrence. Patents with tumor size >5 cm were noticed to have poorer prognosis as compared with the patients [Figure 8]. Patients with KPS score >50 were found to have mean survival of 4.9 years, while for patients with KPS <50 were observed with the mean survival of 1.5 years. Previous reports however have mixed evidences, some claiming the less frequent involvement of frontal and parietal lobes while the others observing frontal lobe to contribute to >70% of cases in LGG and harbor no prognostic importance.[9],[20],[22] IDH mutations were seen most prevalent among oligodendroglioma and diffuse astrocytoma cases. Diffuse astrocytoma cases were found with the p53 mutations.

Overall, IDH mutations were detected in 75% of the cases, p53 mutations in 62% of the cases, ATRX mutations in 86% of the cases while the 1p/19q codeletions in 55% of the cases [Table 4]. A study has shown that the type and frequency of IDH mutations are related to oligodendroglial and astrocytic differentiation. In oligodendroglioma, this study reports IDH1 mutations contributes to nearly 70% of the cases.[23] Otherwise, the IDH mutations are most commonly noted in secondary glioblastoma which progresses from the previous low grade symptoms but not in primary glioblastoma.[24] We observed nearly 25% of LGG cases without IDH mutations and warrant the meticulous follow-up. IDH mutations are viewed as an important favorable prognostic marker.[24],[25] Our follow-up study reveals only one mortality among the 27 IDH positive cases and is in agreement with the existing evidences. The P53 mutations are reported with more frequency in diffuse astrocytoma and the oligoastrocytoma cases and is supported by the previous report.[5] For prognosis, however there are no consistent evidences on importance of p53 mutations in the prognosis or progression free survival of LGG.[26],[27] Among the total 61 cases, we observed the p53 mutations were confined to 35 cases. Follow-up details report three death events in the p53 mutation group while no death was noted in patients with wild type p53. Similarly, we do not find any death in patients harboring the 1p/19q codeletion and the ATRX mutation. Presence of 1p/19q codeletions has been portrayed as measures of better prognosis, give better response to chemotherapy in LGG and occur frequently in oligodendroglial tumors.[5],[15],[28]

We report median progression free survival of 4.7 years in LGG group of 130 patients [Figure 4]. There was a significant difference in the survival pattern among the LGG subgroups ($P < 0.05$) however, was not ascertained with the anatomic location of the tumor [Figure 5]. Standard care for the LGG patients included surgical resection, chemo and radiotherapy. We observed that the group of patients receiving combined chemotherapy and radiotherapy yielded average survival of 29 months [Figure 6]. Overall, the patients receiving both radiotherapy and chemotherapy yielded better prognosis. Reports in existing literature suggests chemotherapy as a mode of promising treatment. Use of radiotherapy on other hand is generally not given in children, on account of the possible neurocognitive deficits inducted by the radiation.[20],[29],[30],[31] The 5-year survival rate was found to be 92.3%. Previous study however notes this rate to be 55.6%[32] and 57%.[33]

Of the total 130 cases, in 94 (72%) cases, the tumor was resected by gross total resection, in 14 (10%) cases by near total resection, in 5 (3.8%) cases by biopsy and in 17 (13%) by subtotal resection. The highest percentage of deaths were reported in cases operated by biopsy (20%) with overall survival of 3.1 years (95% CI: 2-4.2). The lowest percentage of deaths (3.2%) were reported in gross total resection with overall survival of 5 years (95% CI: 4.8-5.2) [Figure 7]. Existing literature also documents the benefits of extensive surgical resection.[18],[21],[34] Gross total resection was found to enhance the overall survival in patients as compared with the subtotal resection.[35] We report highest median survival in patients operated by gross total resection (59 months) as compared with biopsy (37 months), near total resection (47 months) and the subtotal resection (58 months). Age of patients was also found to be not significantly associated with the prognosis. Maximum deaths were noted in the patients middle age group (20-50) but not in younger (<20) or older (>50) patients.

Several of the predictors of outcome in this study have been identified in other series. Patient age, for example,

has been the most well-established predictor of survival in several multivariate analyses. Whereas many have shown a linear relationship between patient age and survival, we observed that patients >50 years old had a specifically increased risk of death as compared to age >40 years included in risk stratification by EORTC.[6] The cause of this association is unclear but may involve a more malignant underlying biology related to an advanced age as well as natural life expectancy, higher incidence of other diseases, and general vulnerability to illness. Previous study by EORTC group proposed risk criteria scoring system which score of ≤80 had a distinctly worse rate of survival.[6]

Tumor size has been identified as an important predictor in several studies. Tumor size appeared to predict survival in the present series of patients. Tumors with size more than 5 cm appeared to have more recurrence and poor survival. Gross-total resection is more difficult to achieve with larger infiltrative tumors, and these lesions reflect a more extensive disease burden.

In this series, patients with oligodendrogliomas or mixed oligoastrocytic tumors had a more favorable prognosis than patients with pure astrocytoma and gemistocytic astrocytoma. Gemistocytic histology subtype was statistically significantly associated with poor prognosis. Survival in pure astrocytic tumors was less than that of oligodendroglioma but that was not statistically significant. In other series, both on low- and high-grade glioma, tumors with oligodendroglial elements also had a better prognosis, however astrocytic subtype was included in EORTC prognostic factor.

In the present study, we noticed that: 1) Age >50 years, 2) tumor size >5 cm, 3) MIB index >5%, 4) KPS score <50 and 5) gemistocytic pathology were associated with higher recurrence and decreased overall survival. We propose "RULE OF 5" (including these 5 factors) for predicting prognosis. Longer follow-up would be needed to validate the above mentioned factors into a prognostic scoring system.

Several advantages in this study included the following: 1) all patients underwent imaging studies after the widespread adoption of MR imaging; 2) a uniform histological diagnosis was conducted by an independent in-hospital centralized pathology review; 3) telephone interviews and MR imaging reviews were conducted to ensure the best follow-up data possible. 4) Prognostic factors included in the study do not have any inter-observer variability.

Longer follow up would be needed to validate the above mentioned factors into a prognostic scoring system and also this risk factor rule should be validated at other institutions. We will attempt to validate the findings of this study by having other institutions apply the same system to patients with LGGs.

In conclusion, the present study provides the reliable basis for clinicopathological management of low grade glioma. The results show LGGs have biased origin in male population. Radio and chemotherapy alone is found to yield the reduced prognosis. Headache and seizures were the most common symptoms with fronto-parietal dominance, however, the underlying molecular mechanisms seems unclear. Our observations confirm the prognostic benefit of gross total resection on biopsy. In one way, present single institute study surveys the possible management of LGGs and demands further investigations.

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Conflicts of interest

There are no conflicts of interest.

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Figure 1: Representative pre (a) and post-operative (b- taken after two years of surgery) MRI images of a oligoastrocytoma patient. The lesion has been marked by an arrow

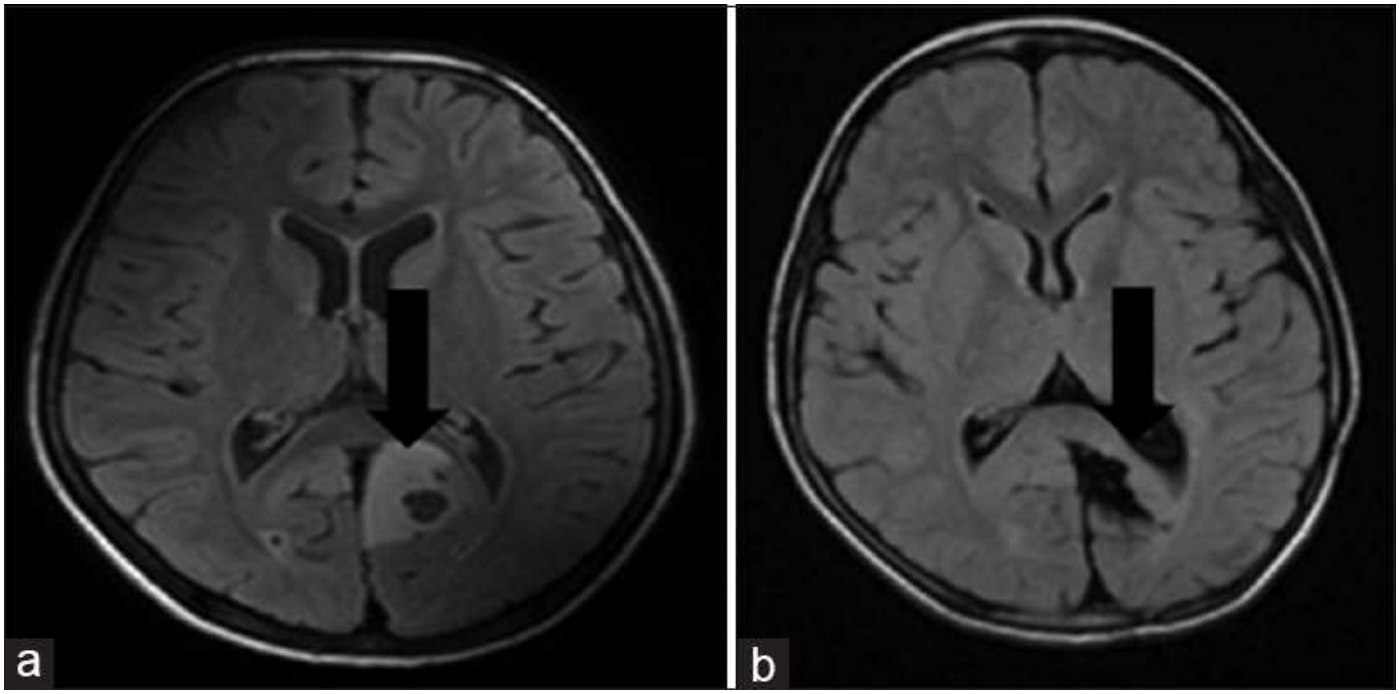

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Figure 2: Representative H and E images of (a): Oligoastrocytoma with gemistocytic component and (b): with purely astrocytic component, (c): Egg fried appearance of oligodendroglioma, (d and e): Both oligo and astrocytic component. All images were taken at 40× magnification

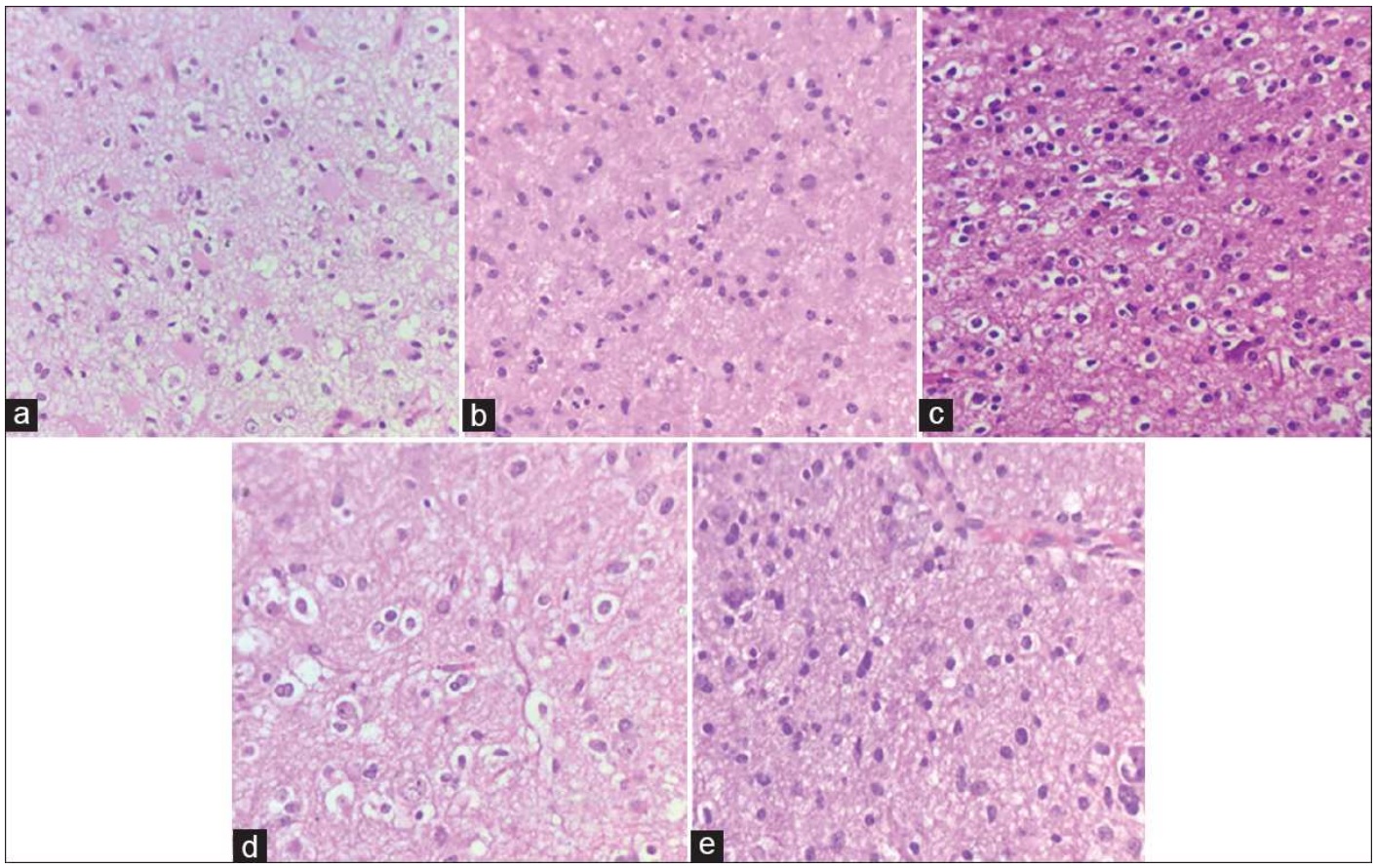

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Figure 3: Representative IHC images of (a): IDH (b): ATRX (c): p53 protein is LGG. Intense Panel A shows the intense staining for the mutated IDH. Panel C shows the 4 × magnification view of p53 staining in one of the LGG case

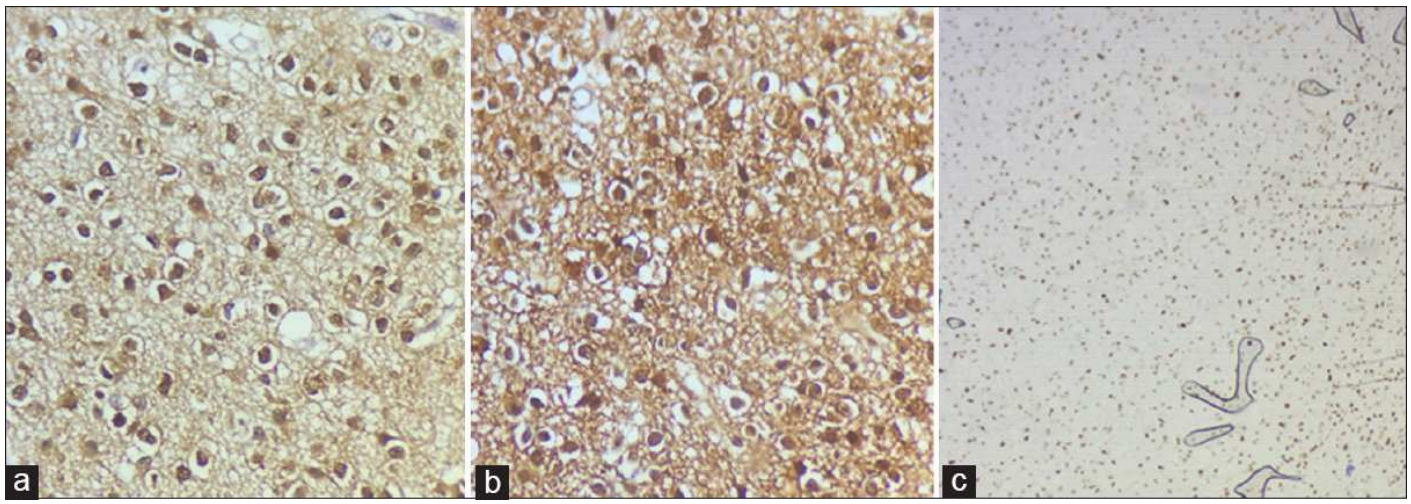

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Figure 4: Comparison between the survival pattern of patients of pilocytic and diffuse astrocytoma patients (a) and the cumulative survival of diffuse astrocytoma patients (b). Tumor recurrence was observed in 9 patients. Median PFS was 4.7 years. The 1-, 3-, and 5-year PFS rates were 98.2%, 88.0%, and 81.3%, respectively

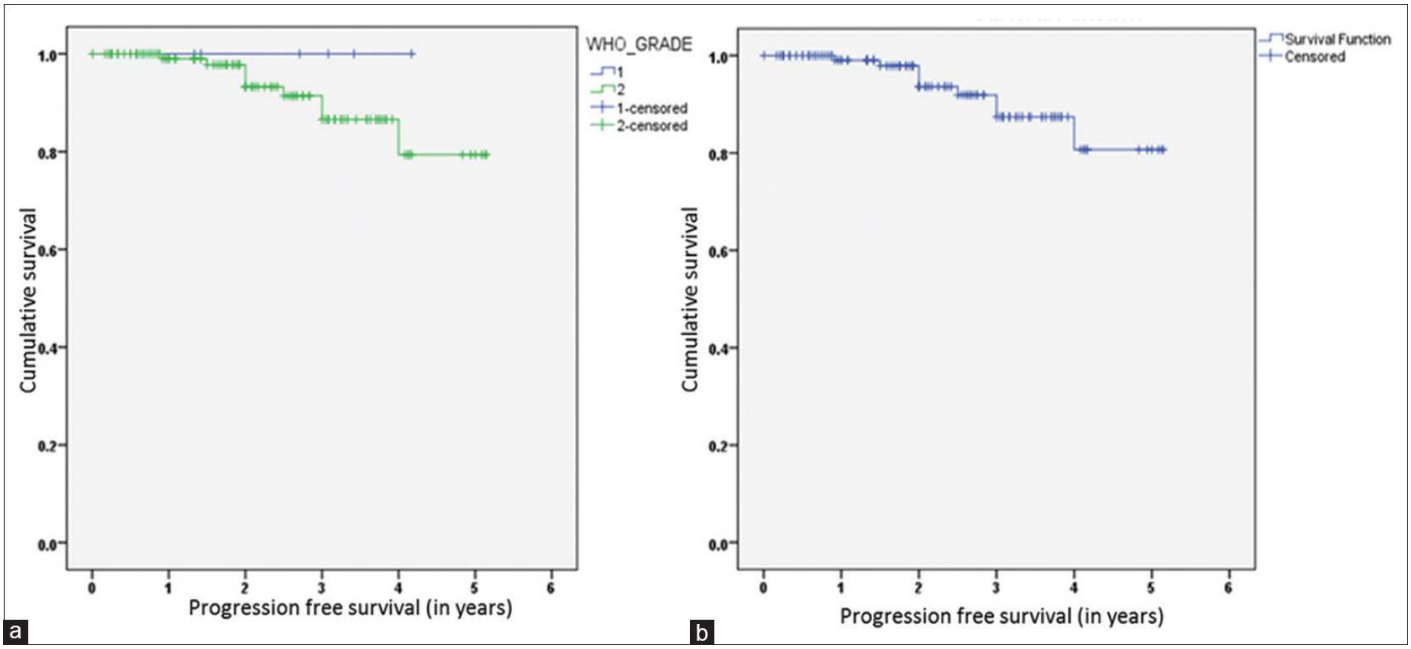

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Figure 5: Survival pattern of patients on the basis of histopathological (HPE) diagnosis (a) and tumor location (b). PFS is significantly different between Oligoastrocytoma vs ODG (*P* = 0.018) and Oligoastrocytoma vs diffuse astrocytoma (*P* = 0.005). However, the tumor location was not significantly associated with the survival (*P* = 0.21)

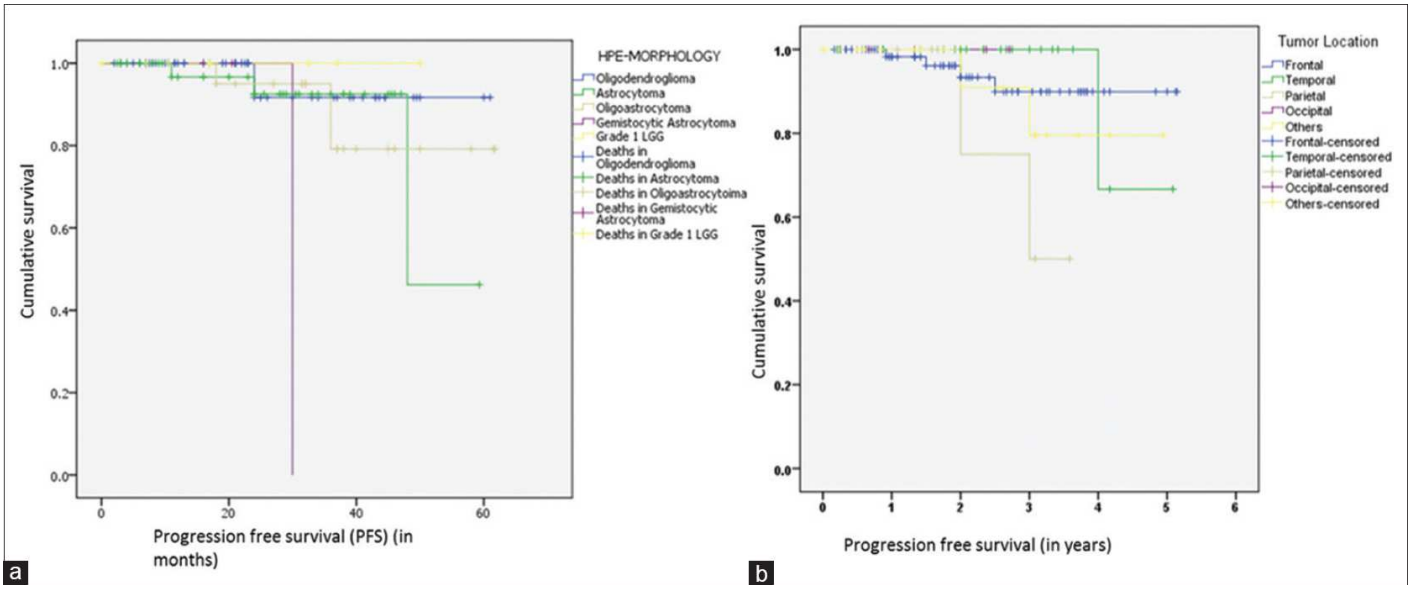

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Figure 6: Survival details of the patients when subjected to no adjuvant therapy, only radiation therapy (RT) and when with RT and chemotherapy (CT)

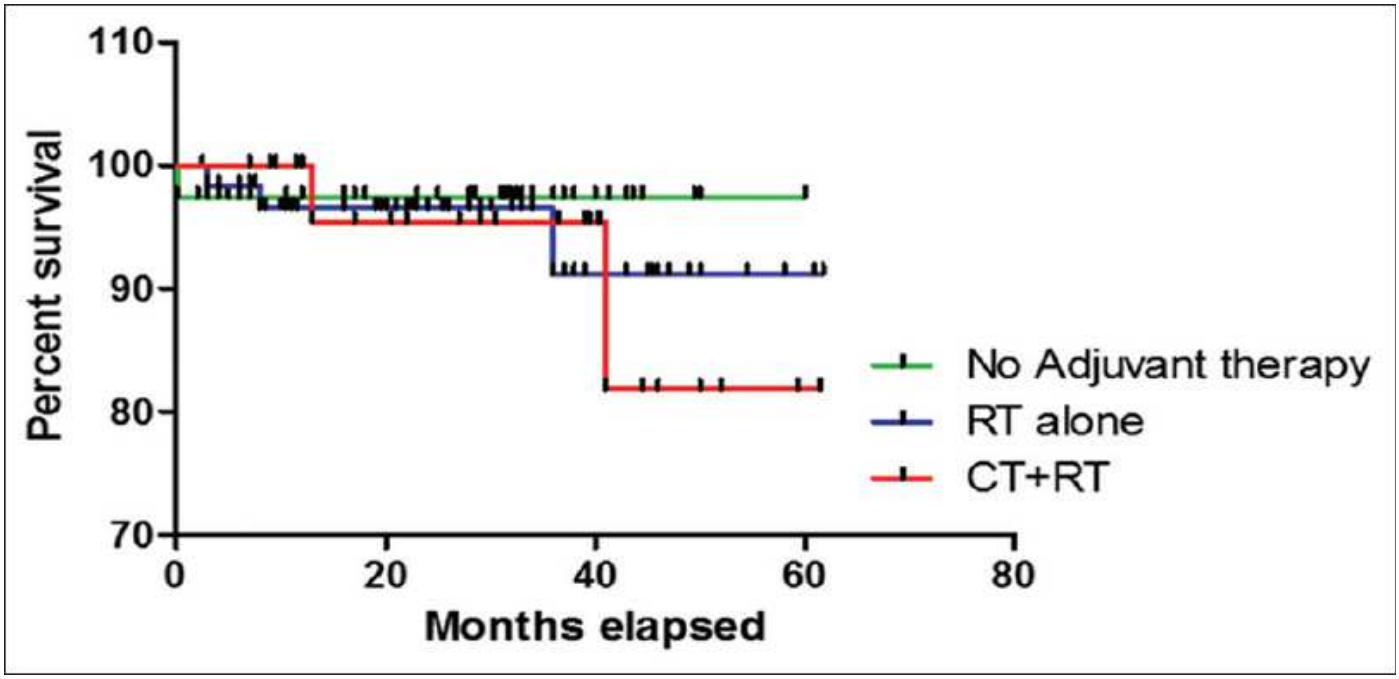

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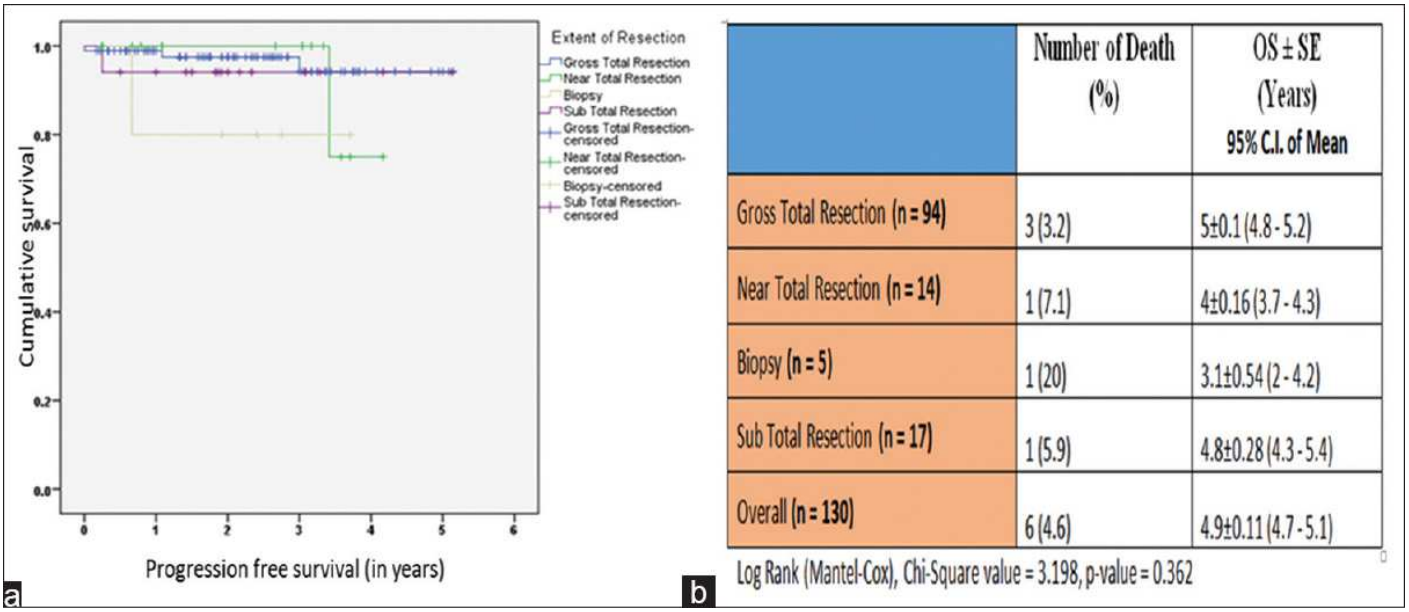
Figure 7: Progression free survival in patients when operated with gross total resection, near total resection, biopsy or subtotal resection (a). There was no statistical significant difference in the survival of patents (b)



	Number of Death (%)	OS ± SE (Years) 95% C.I. of Mean
Gross Total Resection (n = 94)	3 (3.2)	5±0.1 (4.8 - 5.2)
Near Total Resection (n = 14)	1 (7.1)	4±0.16 (3.7 - 4.3)
Biopsy (n = 5)	1 (20)	3.1±0.54 (2 - 4.2)
Sub Total Resection (n = 17)	1 (5.9)	4.8±0.28 (4.3 - 5.4)
Overall (n = 130)	6 (4.6)	4.9±0.11 (4.7 - 5.1)

b Log Rank (Mantel-Cox), Chi-Square value = 3.198, p-value = 0.362

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Figure 8: Progression free survival (a) and overall survival (b) of the low grade glioma (LGG) patients with tumor size >5 cm and <5 cm. ($P < 0.05$)

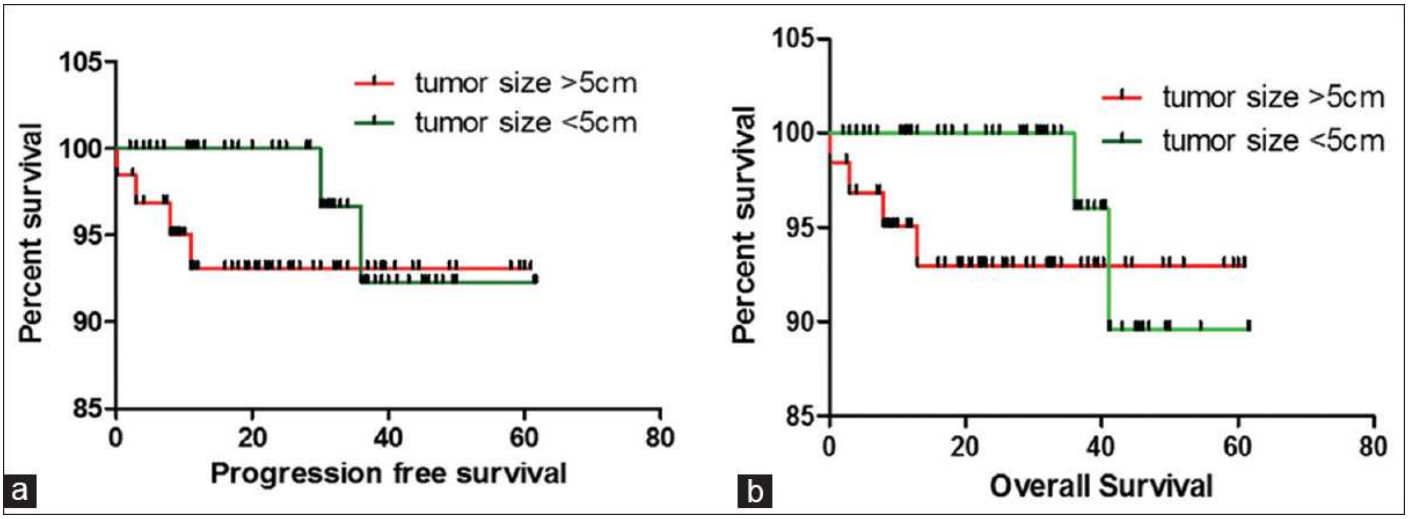

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Table 1: Characteristics of the patients diagnosed with low grade glioma (LGG) A: Among the total diagnosed cases, 91 were male and 39 females with middle age peoples more prone. B: Seizures were observed most prominently followed by headache. C: KPS score for the patients

Age / Gender	<20 (n=11)	20-50 (n=95)	>50 (n=24)	Total
Male	8 (8.7%)	66 (72.5%)	17 (18.6%)	91(69.4%)
Female	3 (7.6%)	29 (74.3%)	7 (17.9%)	39(30%)

Symptoms	Total no. of patients (n= 130)	Percentage (%)
Headache	46	35.3
Seizures	94	72.3
Vomiting	24	18.5
Visual defects	5	3.8
Motor weakness	17	13.1
Sensory symptoms	6	4.6

KPS index	Total no of patients (n=130)	Percentage (%)
Pre KPS		
<70	3	2.3
≥70	127	97.7
Post KPS		
<70	2	1.5
≥70	128	98.5

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Table 2: Anatomic location based tumor distribution and presence of seizures. A: overall there was uniform laterality of distribution. B: Among the lobes, the location was dominated by frontal and the parietal lobes C: middle age group was found with frontal and temporal dominance. D: patients with fronto-parietal dominance were found to be mostly suffering from seizures

Tumor laterality	Total no. (n=130)	Percentage (%)
Left	65	50
Right	64	49.2
Bilateral	1	0.8

Tumor location	Total no. of patients (n=130)	Percentage (%)
Frontal	74	56.9
Parietal	22	16.9
Temporal	10	7.7
Occipital	4	3.1
Multi lobar	19	14.6

Age gr. / Tumor location	<20 (n=11)	20-50 (n=95)	>50 (n=34)	Total (n=130)
Frontal	2 (2.7%)	52 (70.2%)	20 (27%)	74 (56.9%)
Parietal	6 (27.2%)	16 (72.7%)	0 (0%)	22 (16.9%)
Temporal	0 (0%)	8 (80%)	2 (20%)	10 (7.7%)
Occipital	1 (25%)	2 (50%)	1 (25%)	4 (3.1%)
Multi lobar	2 (10%)	17 (85%)	1 (5%)	20 (15.4%)

Tumor location	Presence of seizures		Total no of cases (n= 129)
	Yes	No	
Frontal	58 (78.3%)	16 (21.6%)	74 (57.3%)
Parietal	17 (77.2%)	05 (22.7%)	22 (17%)
Temporal	05 (50%)	05 (50%)	10 (7.7%)
Occipital	02 (50%)	02 (50%)	04 (3.1%)
Multi lobar	12 (63.1%)	07 (36.8%)	19 (14.7%)

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Table 3: Details of recurrent cases of LGG. A: Laterality of cases, B: age distribution of the recurrent LGG, C: Lobe distribution of the recurrent LGG, D: Type of surgical resection followed, E: Histopathological distribution of the cases among LGGs

Tumor side	Recurrence		Total (n=130)
	Yes (n=09)	No (n=121)	
Left	03 (4.6%)	61 (95.3%)	64 (49.2%)
Right	06 (9.2%)	59 (90.7%)	65 (50%)
Bilateral	0 (0%)	01 (100%)	01 (0.76%)

Extent of resection	Recurrence		Total (n=130)
	Yes (n=09)	No (n=121)	
Gross total resection	06	88	94
Near total resection	02	12	14
Biopsy	01	04	05
Near total resection	00	17	17

Age group	Recurrence		Total (n=130)
	Yes (n=09)	No (n=121)	
<20	0 (0%)	11 (100%)	11 (8.4%)
20-50	9 (9.4%)	86 (90.5%)	95 (73%)
>50	0 (0%)	27 (100%)	24 (18.4%)

Histopathological morphology	Recurrence		Total (n=130)
	Yes (n=09)	No (n=121)	
Diffuse astrocytoma	03	41	44
Gemistocytic astrocytoma	01	02	03
Oligoastrocytoma	03	22	25
Oligodendroglioma	02	51	53
Pilocytic astrocytoma	00	05	05

Tumor location	Recurrence		Total (n=130)
	Yes (n=09)	No (n=121)	
Frontal	4 (5.4%)	70 (94.5%)	74 (56.9%)
Parietal	1 (4.5%)	21 (95.4)	22 (16.9%)
Temporal	2 (20%)	08 (80%)	10 (7.6%)
Occipital	0 (0 %)	04 (100%)	04 (3%)
Mixed	2 (10.5%)	17 (89.4%)	19 (14.6%)

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Table 4: Molecular marker profile of LGG. Among the total cases, the cases which were detected after 2016 were followed for the presence of molecular mutations. A: LGGs observed with the presence of molecular markers B: ATRX and the IDH mutations were frequently observed. C: MIB1 staining pattern in all cases. D: IDH mutations in the recurrent cases

GENETIC ALTERATION	DIFFUSE ASTROCYTOMA (n=11)	OLIGODENDROGLIOMA (n=14)	OLIGOASTRO (n=5)	GEMISTOCYTIC ASTRO (n=2)
IDH mutation	9	12	5	1
P53 mutation	10	2	3	2
1p/19q codeleted	1	5	0	0
ATRX	MUTATED-1 RETAINED-5	MUTATED- 1 REST – retained.	-	-
P53+ 1DH mutation	9	1	3	1

Molecular markers	Positive counts / Total no of cases	Percent (positive cases)
IDH mutation	27/36	75%
P53 mutation	38/61	62%
ATRX mutation	13/15	86%
1p/19q codeletion	05/09	55%

MIB1	Total cases studied	Percentage
<5	88	69.8%
≥5	38	30.1%
Not done	04	

IDH	Recurrence		Total (n=36)
	Yes (n=01)	No (n=35)	
Mutated	0	9	9
Non-mutated	1	26	27