# Prognostic Factors for Survival in Pediatric Diffuse Midline Gliomas: The Importance of T2 FLAIR Missmatch Sign and Nimotuzumab Therapy

## Pediatrik Diffüz Orta Hat Gliomlarında Sağkalım için Prognostik Faktörler: T2 FLAIR Missmatch Sign ve Nimotuzumab Tedavisinin Önemi

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**ABSTRACT**

**Purpose:** The aim of this study is to investigate the clinical and radiological features, especially the importance of the T2-FLAIR mismatch sign and the response to treatment of patients diagnosed with diffuse midline gliomas (DMG) in our center.
**Methods:** Eighteen patients treated with a diagnosis of DMG between January 2008 and January 2021 in Gazi University Medical Faculty, Department of Pediatric Oncology were retrospectively evaluated. The radiologycal evaluation was made as T2-FLAIR mismatch sign positive or negative. After a tumor board review, the diagnosis of DMG was made clinically and radiologically and all patients received local radiotherapy. Nimotuzumab was given as monotherapy or in combination with other medications
**Results:** T2-FLAIR mismatch sign was positive for twelve patients and median OS for patients with T2-FLAIR mismatch positive and negative were 12.5 months and 9.2 months respectively (p=0.77). Median PFS for patients with T2-FLAIR mismatch sign positive and negative were 10.6 months and 4.8 months respectively (p=0.84). After nimotuzumab therapy, there was 4 cases with PR (44.4%), and 1 patient with SD (11.1%). Median OS for patients who were treated with and without nimotuzumab were 16.5 and 6.2 months respectively (p<0.05). Median PFS for patients who were treated with and without nimotuzumab were 13.3 and 3.7 months respectively (p<0.05).
**Conclusion:** In conclusion, DMGs have poor prognosis. In our study patients with T2-FLAIR mismatch sign positive had better prognosis so it can be used as an imaging marker for prognosis. Nimotuzumab therapy may be a promising treatment option for DMG.

**Keywords:** Childhood, diffuse midline gliomas, nimotuzumab

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**ÖZET**

**Amaç:** Bu çalışmanın amacı merkezimizde diffüz orta hat gliomu (DMG) tanısı alan hastaların klinik ve radyolojik özelliklerini, T2-FLAIR mismatch işaretinin önemini ve tedaviye yanıtını incelemektir.
**Yöntem:** Gazi Üniversitesi Tıp Fakültesi Çocuk Onkolojisi Anabilim Dalı'nda Ocak 2008-Ocak 2021 tarihleri arasında DMG tanısı ile tedavi edilen 18 hasta retrospektif olarak değerlendirildi. Radyolojik değerlendirmede T2-FLAIR mismatch işareti pozitif veya negatif olarak sınıflandırıldı. Tümör konseyi incelemesinin ardından klinik ve radyolojik olarak DMG tanısı alan hastalara lokal radyoterapi uygulandı. Nimotuzumab monoterapi olarak veya diğer ilaçlarla kombinasyon halinde verildi
**Bulgular:** T2-FLAIR mismatch işareti 12 hastada pozitifti ve T2-FLAIR mismatch pozitif ve negatif olan hastalar için medyan OS sırasıyla 12.5 ay ve 9.2 aydı (p=0.77). T2-FLAIR mismatch işareti pozitif ve negatif olan hastalarda medyan PFS sırasıyla 10,6 ay ve 4,8 aydı (p=0,84). Nimotuzumab tedavisi sonrası PR (%44,4) olan 4, SD (%11,1) olan 1 hasta vardı. Nimotuzumab tedavi edilen ve edilmeyen hastalarda medyan OS sırasıyla 16.5 ve 6.2 aydı (p<0.05). Nimotuzumab ile tedavi edilen ve edilmeyen hastalarda medyan PFS sırasıyla 13,3 ve 3,7 aydı (p<0,05).
**Sonuç:** Sonuç olarak, DMG'lerin prognozu kötüdür. Çalışmamızda T2-FLAIR mismatch işareti pozitif olan hastalarda prognoz daha iyi olduğundan prognozu öngörmede yardımcı olabilir. Nimotuzumab tedavisi, DMG için umut verici bir tedavi seçeneği olabilir.

**Anahtar Sözcükler:** Çocukluk çağı, diffüz orta hat gliomları, nimotuzumab

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## INTRODUCTION

Gliomas developing from the pons, formerly named diffuse intrinsic pontine gliomas (DIPG), constitute 10 to 15% of childhood brain tumors and 80% of pediatric brain stem tumors (1). In 2021, the World Health Organization (WHO) classification of central nervous system tumors was recently reclassified as diffuse midline gliomas (DMG) (2). Diffuse midline gliomas have been reported in children aged 3 to 10 years and have a median overall survival of 9 to 12 months after diagnosis (3).

Crucial factors in interpreting imaging studies for differential diagnosis include advances in imaging techniques and the extent of difficulty in obtaining adequate biopsy specimens (4). The T2-fluid attenuated inversion recovery (FLAIR) mismatch sign has been reported as a diagnostic imaging biomarker of diffuse astrocytoma. Subsequent studies reported the same findings in diffuse midline gliomas (5). DMGs are frequently observed as homogeneously hyperintense on FLAIR imaging. A recent study reported that a T2-FLAIR mismatch sign in DMG could indicate a higher response to radiation (6).DMGs are naturally resistant to treatment and have a high mortality rate. Recently, advances in our understanding of the underlying molecular mechanisms of DMG tumorigenicity have led to the discovery of novel targets and the development of possible treatment strategies, with several medicines now undergoing clinical trials to assess their therapeutic efficacy (7).

Radiotherapy (RT) is the standard treatment for DMGs; it is known to produce temporary neurological improvement in approximately 70% of patients (8). Although different combinations of chemotherapy, RT, and radiosensitizer agents have been used, the success rates in improving long-term survival are low. Recent studies have demonstrated an amplification or overexpression of the epidermal growth factor receptor (*EGFR*) gene in DIPG, suggesting that EGFR inhibitors could be used as a potential targeted therapy (9).

In this study, we retrospectively investigated the clinical and radiological features, the importance of the T2-FLAIR mismatch marker, and the response to the treatment of patients diagnosed with DMG in our center.

## MATERIALS and METHODS

Eighteen patients with DMG treated between January 2008 and January 2021 in the Department of Pediatric Oncology, Gazi University Medical Faculty, were retrospectively evaluated. Inclusion criteria include children and adolescents with DMG aged between 0 and 18 years. Patients who had their initial treatment at other centers and were referred to us for further management were excluded from the study. The study was performed according to the principles of the Declaration of Helsinki, and informed consent was obtained from all cases.

The study was approved by the institutional review board of the Gazi University Medical Faculty. In addition, we removed all identifiers from our data after the analyses were completed to protect patient privacy. The medical records (gender, age, tumor entity, tumor location, and kind of surgery) of patients, as well as their treatment history and magnetic resonance imaging (MRI) scans, were examined. After a tumor board review, a clinical and radiologic diagnosis of DMG was made, following which all patients received local radiotherapy.

The width, transverse, and length measurements obtained from MRI images were used to evaluate the tumor response criteria. A complete response (CR) was defined as the disappearance of all target lesions, whereas a partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of target lesions. Progressive disease (PD) was defined as a 20% increase in the disease from the baseline, whereas stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD. The term "objective response" (OR) was used to describe all patients who had either a PR or a CR. The disease control rate (DCR) was defined as CR + PR + SD, whereas the response rate (RR) was defined as CR + PR (10).

The most frequently used agents during and after radiotherapy, either alone or in combination, include nimotuzumab, vinorelbine, and temozolomide. Nimotuzumab was administered as monotherapy or in combination with other medications. The treatment regimen was 150 mg/m$^2$/dose intravenous injection based on doses used in earlier studies (11). The progression-free survival (PFS) and overall survival (OS) were determined according to the date of diagnosis. Those with OS shorter than 24 months were referred to as short-term survivors, and those longer than 24 months were named long-term survivors (LTSs).

*Image analysis*

All MRI data were transferred to a workstation (Syngo MR B17 Version, Siemens, Germany) and evaluated independently by one radiologist with 11 years of experience (M.Y.). T2-FLAIR mismatch sign was defined as the presence of complete/near-complete hyperintense signals on the T2-weighted image and broad hypointense signal on FLAIR, except for a hyperintense peripheral rim. The T2-FLAIR mismatch sign was evaluated as either positive or negative. In addition to the T2-FLAIR mismatch sign, tumor location, tumor size, border definition, and changes in the pattern of homogeneity on T1WI, T2WI, contrast enhancement (presence versus absence), and surrounding edema (presence versus absence) were evaluated.

*Statistics*

Calculations were made using the Statistical Package for Social Studies (SPSS, version 18). The Kaplan–Meier method was used for survival analysis, and the log-rank test was used to compare different groups (significance level $p < 0.05$).

## RESULTS

Our study included 18 patients comprising 12 females (%66.6) and 6 males (%33.3) with a mean age of diagnosis of 8.9 (2–17) years. The most common presenting features included headache, diplopia, and seizures. The duration of symptoms had a median value of 1 month (range 10 days–12 months). In our cohort, 13 (72%) of 18 patients had symptoms for less than 3 months. In LTSs, the median value of symptom latency was 7 months.

The diagnosis of DMG was clinically and radiologically made, except for two patients (11.1%) for whom, a histopathological diagnosis was obtained. All patients were treated with local radiotherapy after the diagnosis of DMG. The most common symptoms included headache, diplopia, and strabismus.

The median follow-up time was 8.5 (1 to 110) months after the diagnosis. Following the initiation of treatment with nimotuzumab-containing regimens, patients were followed up for a median of 14 (range, 4 to 107) months. Median OS and PFS values were 12.5 and 9.6 months, respectively.

Of the 18 patients included in the analysis, 4 (22.2%) were LTS. The mean age of LTS was 12.7 (8–15) months. There were four cases with PR (22.2%) and two patients with SD (11.1%). The RR was 22.2% and the DCR was 33.3%. A total of 12 patients (66.6%) experienced PD.

The duration of nimotuzumab therapy ranged from 21 days to 12 months (median 2 months). The mean number of nimotuzumab doses was 18.2 (median 16), from 1 to 32 doses. After the nimotuzumab therapy, there were four cases with PR (44.4%), and one patient with SD (11.1%). The OR and SD were observed in five of the nine patients (55.5%), and other patients progressed. The median OS for patients who were treated with and without nimotuzumab were 16.5 and 6.2 months, respectively ($p < 0.05$) (Figure 1). The median PFS values for patients treated with and without nimotuzumab were 13.3 and 3.7 months, respectively ($p < 0.05$) (Figure 2). No significant adverse effects were reported. No allergic reactions or acneiform rashes were observed. We did not observe any effects of age in terms of efficacy and tolerability.

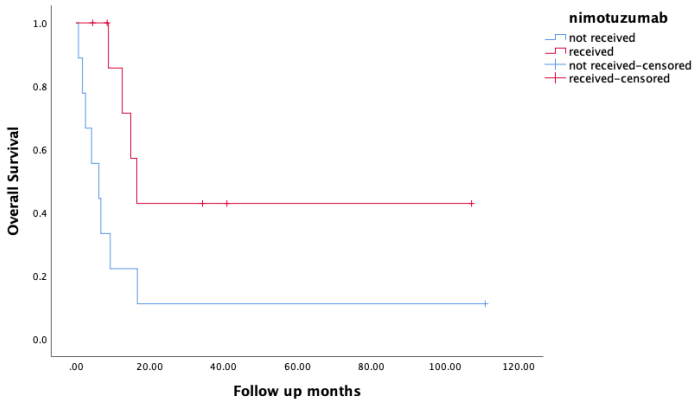


**Figure 1** Kaplan-Meier curve for OS (overall survival) of patients that receive and not received nimotuzumab in the study group (p=0.16).

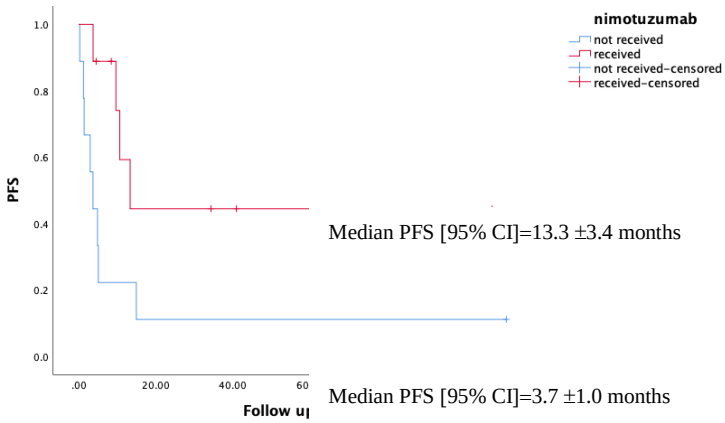


**Figure 2** Kaplan-Meier curve for PFS (Progression free survival) of patients that receive and not received nimotuzumab in the study group (p=0.17)

Patients' symptoms are summarized in Table 1. Imaging characteristics and the response to the treatment of patients are summarized in Table 1 and Table 2. Twelve patients had characteristic T2-FLAIR mismatch, and the ratio was 66.6% (12/18) among all patients.

**Table 1:** Patients' symptoms

| **Presenting symptoms** | **n (%)** |
|---|---|
| Headache | 5 (27.7) |
| Diplopia | 5 (27.7) |
| Stabismus | 5 (27.7) |
| Seizures | 4 (22.2) |
| Dysarthria | 2 (11.1) |
| Lower limb weakness | 3 (16.6) |
| Upper limb weakness | 1 (5.5) |
| Vomiting | 3 (16.6) |
| Gait disturbance | 1 (5.5) |
| Facial weakness | 1 (5.5) |
| Dysphagia | 1 (5.5) |
| Decreased vision | 1 (5.5) |
| Tremor | 1 (5.5) |
| Personality change | 1 (5.5) |

**Table 2.** Summary of radiological findings and therapy responses

| Case No. | Age(year) | Sex | T2W1/FLAIR Mismatch at diagnosis | Irradiation dose | Chemotherapy | Response | OS (month) | Dead/Alive |
|---|---|---|---|---|---|---|---|---|
| 1 | 13 | Female | Negative | 5220 cGy | TMZ | PD | 9 | Dead |
| 2 | 5 | Female | Positive | 5400 cGy | | PD | 4 | Dead |
| 3 | 2 | Male | Positive | 5400 cGy | | PD | 1 | Dead |
| 4 | 6 | Female | Positive | 5040 cGy | NIM,VIN,TMZ | PD | 12 | Dead |
| 5 | 17 | Male | Positive | 5400 cGy | TMZ | PD | 2 | Dead |
| 6 | 8 | Female | Positive | 5400 cGy | NIM,VIN, | PD | 16 | Dead |
| 7 | 6 | Female | Positive | 2340 cGy | | PD | 0 | Dead |
| 8 | 13 | Male | Positive | 5400 cGy | NIM,VIN, | PR | 40 | Alive |
| 9 | 5 | Female | Negative | 5400 cGy | NIM,VIN,TMZ | PD | 8 | Dead |
| 10 | 15 | Male | Positive | 5400 cGy | - | SD | 110 | Alive |
| 11 | 8 | Female | Negative | 5220 cGy | NIM,TMZ | PR | 107 | Alive |
| 12 | 15 | Female | Positive | 5400 cGy | NIM,VIN, | PR | 34 | Alive |
| 13 | 6 | Female | Negative | 5400 cGy | NIM,VIN, | PD | 14 | Dead |
| 14 | 8 | Male | Negative | 5400 cGy | | PD | 6 | Dead |
| 15 | 10 | Male | Negative | 5400 cGy | TMZ | PD | 16 | Dead |
| 16 | 3 | Female | Positive | 5400 cGy | NIM,VIN, | SD | 8 | Alive |
| 17 | 4 | Female | Positive | 5400 cGy | | PD | 6 | Dead |
| 18 | 17 | Female | Positive | 5400 cGy | NIM,VIN, | PR | 4 | Alive |

NIM: nimotuzumab, PD: progressive disease, PR: partial response, SD: stable disease, TMZ: temozolomide, VIN: vinorelbine.

The mean age of patients with T2-FLAIR mismatch positive was 9.2 (2–17) years. The median OS values for patients with T2-FLAIR mismatch positive and negative were 12.5 months and 9.2 months, respectively ($p$ = 0.77) (Figure 3). The median PFS value for patients with T2-FLAIR mismatch positive and negative were 10.6 months and 4.8 months, respectively ($p$ = 0.84) (Figure 4).

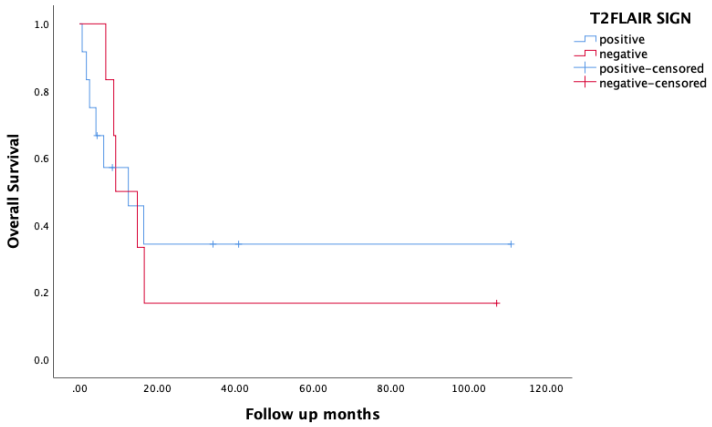


**Figure 3** Kaplan-Meier curve for OS of patients with T2 FLAIR mismatch sign positive and negative (p=0.77)

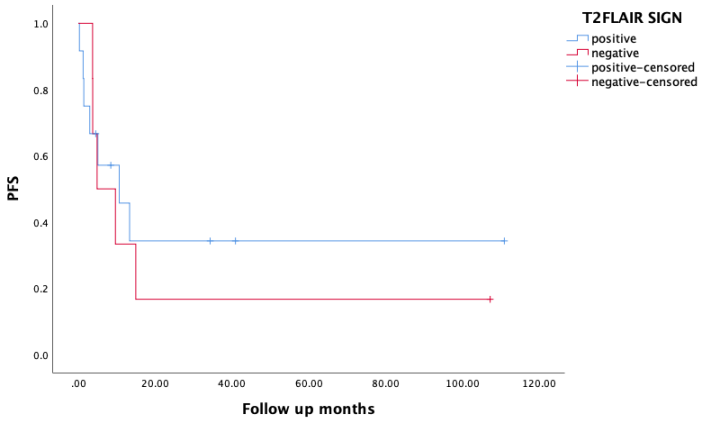


**Figure 4** Kaplan-Meier curve for PFS of patients with T2 FLAIR mismatch sign positive and negative (p=0.84)

## DISCUSSION

Diffuse midline gliomas have been reported to be the most common brainstem tumors of childhood comprising 80% of all childhood brainstem gliomas. Although it has been reported in all age groups, the peak age is 6 to 9 years (12). These tumors are the leading cause of CNS tumor deaths in children, with a median survival < 1 year (11). Long-term survival, which has traditionally been defined as an OS of more than 2 years, has been reported in 10% of patients (12). Longer symptom latency, being under the age of 3 years and above the age of 10 years, and receiving systemic therapy at the time of diagnosis were found to be predictors of LTS (13). Erker et al[14]. reported that patients with DMG ≥ 10-year-old had a median survival of 13 months and over 10% of these patients had a survival of more than 2 years. Older age at diagnosis has been previously linked to a longer OS. Patients who lived more than 24 months had a greater median age at diagnosis (13.6 years, range 9–18) than other DMG patients, according to the authors of a phase II trial that used temozolomide and radiation therapy (15). Patients older than 10 years at the time of diagnosis had a longer median OS (13 months) and were more likely to be LTSs. In a study, all five LTSs reported from 43 patients with radiographically diagnosed DMG were older than 9 years of age (15). In our study, three of the four LTSs were over 10 years old, the remaining patient was 8 years old, and the median survival time for DMGs older than 10 years was 16 months.

The duration of symptoms is generally short, and longer symptom latency is one of the predictors of LTS (11). Univariable and multivariable analyses revealed that the presence of symptoms for more than 24 weeks at diagnosis was highly related to prolonged survival, confirming the results of previous studies. Jackson et al. reported a longer symptom latency in LTSs (12). It has been speculated that a longer duration of symptoms before a diagnosis could reflect a less-aggressive nature of the tumor because most patients do not undergo biopsy. In our study, the duration of symptoms was less than 3 months in 72% of patients and all four LTSs had a symptom duration longer than 3 months.

Although the symptomatology of these tumors depends on the size and degree of infiltration, patients typically present with hydrocephalus, pseudobulbar symptoms (symptoms such as dysphagia, dysarthria), cranial nerve palsies, and headache (4). In patients with DMG, the highly prevalent symptoms were headache, diplopia, and strabismus, with the sixth cranial nerve being the most usually affected (16). In our study, about one-third of patients had headaches, strabismus, and diplopia.

The recent fifth edition of the WHO Classification of Tumors of the CNS (WHO CNS5) divided the “Gliomas, Glioneuronal Tumors, and Neuronal Tumors” entity into six families, including two pediatric types, namely, the “Pediatric-type diffuse low-grade gliomas” (pLGG) and the “Pediatric-type diffuse high-grade gliomas” (pHGG) (17). The WHO Classification of Tumors of the Central Nervous System, Fifth Edition, has identified four hystomolecular subgroups among the specialized pediatric-type high-grade gliomas (pHGG) entity (a) DMG, H3 K27-altered, (b) diffuse hemispheric glioma, (c) H3 G34-mutant H3-wildtype and IDH-wildtype diffuse pediatric-type high-grade glioma, and (d) infant-type hemispheric glioma. The majority of the data was published before the new categorization, which split the pHGG into diffuse intrinsic pontine glioma (DIPG) and non-DIPG tumors based on their location (18).

According to the WHO classification, H3 K27-altered midline gliomas are high-grade gliomas, by definition WHO grade 4, with local infiltration and a poor prognosis. A biopsy of the tumor should be performed to determine the H3K27 status although this is not usually possible in DMGs due to their location.

Because histological sampling is not always possible, clinical and radiological characteristics play a critical role in the diagnosis of DMGs. DMGs appear hyperintense on T2-weighted images and hypointense on T1W1 (19). T2-FLAIR mismatch sign is an imaging marker to predict non-enhancing IDH-mutant, 1p/19q-intact lower-grade glioma (20). Goyal et al[21]. reported the T2-FLAIR mismatch sign as a radio-genomic signature and a highly specific marker of IDH as IDH-mutant astrocytomas. Yamasaki et al[6]. reported that the T2-FLAIR mismatch sign in DMG could indicate a better response to radiotherapy. In this study, T2-FLAIR mismatch sign positivity was observed in pediatric patients, and their better prognosis could be explained by a better prognosis of DMG in the pediatric age group. In our study, patients with T2-FLAIR mismatch signs had a slightly better prognosis, whereas T2-FLAIR mismatch signs did not reach statistical significance as the number of patients was very low ($p > 0.05$).

Nearly half of all juvenile diffuse intrinsic pontine gliomas and around half of all other midline gliomas, such as thalamic and spinal gliomas, primarily affecting young adults, have the H3 K27M heterozygous somatic mutation. The conventional treatment for H3 K27-mutant midline gliomas is fractionated external beam radiation with doses ranging from 54 to 60 Gy. Midline gliomas are difficult to remove surgically because of their positions. Clinical trials have failed to enhance the OS beyond a median of 9 to 11 months and a 2-year survival rate of 10% (22).

Despite improvement in the clinical outcomes with temozolomide observed in adult patients with glioblastoma, a combination of radiation and temozolomide has not been reported to improve outcomes in DIPG over the past 15 years. Hypermethylation of the *MGMT* gene promoter region encoding a DNA repair enzyme related to resistance to alkylating drugs, such as temozolomide (TMZ) in adult glioblastoma, is of special clinical importance. In children, most HGGs, including DMG, have failed to respond to TMZ in several trials because MGMT methylation is less common (23).

When compared with standard RT, chemotherapeutic strategies, including multi-agent neoadjuvant chemotherapy, concurrent chemotherapy with RT, and adjuvant chemotherapy, have not resulted in any consistent survival benefits (24). We used RT in all patients as the standard treatment. The poor prognosis of patients with DMG has led to the development of new therapeutic strategies (25).

In the preclinical stage, progress has been observed for DMG in targeting epigenetic dysregulation, cell cycle, and proliferation processes. While intriguing, these studies have only yielded limited results in terms of effective patient therapy alternatives, which could be related to the complicated chromosomal dysregulation of DMGs and the emergence of resistance mechanisms.

Nimotuzumab is a recombinant humanized monoclonal antibody against the human receptor for an epidermal growth factor (EGF), which contains three domains, including extracellular, transmembrane, and intracellular domains. The extracellular region can recognize and bind to the corresponding ligand, whereas the intracellular part has tyrosine kinase activity (26). EGFR forms homodimers or heterodimers with other members of the ErbB family and then with phosphorylate tyrosine kinases and subsequently activate the downstream signaling pathways such as RAS-RAF-MEK-ERK, JAK-STAT, and PI3K-AKT-mTOR (27). Nimotuzumab recognizes and binds to the extracellular domain of EGFR and blocks the binding of other special ligands to EGFR and indices receptor autophosphorylation, thereby suppressing tumor growth (28). *In vivo* experiments using human brain tumor cell lines xenografted into nude mice have demonstrated that nimotuzumab is effective in reducing the number of CD133+ cancer stem cells when used as monotherapy or in combination with radiotherapy (RT), compared to RT alone (9). A combination of nimotuzumab with radiation could be potentially promising in the treatment of pediatric brain tumors and effective in children with recurrent or relapsed high-grade gliomas (29).

In a report by Massimino et al[30]., the median OS and PFS values were 15 months and 8.5 months in patients with newly diagnosed diffuse intrinsic pontine glioma receiving nimotuzumab and vinorelbine, respectively. In another report by Kebudi et al[31]., the median OS was 11 months in a newly diagnosed group receiving a combination of radiation, temozolomide, and nimotuzumab and 6 months in the PD group. The median PFS for newly diagnosed DIPG and progressive disease DIPG were 4 months and 3 months, respectively, in their study. In addition, patients who received both RT and TMZ had a better OS rate than those who received only RT. In a phase II study by Bartels et al[32]., the median OS and PFS for progressive disease DIPG receiving radiation and nimotuzumab were 3.2 months and 1.7 months, respectively. Similarly, Fleischhack et al[9]. reported a median OS and PFS of 9.4 months and 5.8 months, respectively, for newly diagnosed DIPG receiving radiation and nimotuzumab. In our study, the median OS values for patients treated with and without nimotuzumab were 16 and 6 months, respectively. We found a statistically significant difference between the groups that received and did not receive nimotuzumab ($p < 0.05$). The limitations of our study included its retrospective nature, a limited number of patients, and variations in chemotherapy protocols.

## CONCLUSION

DMGs have a poor prognosis, and the T2-FLAIR mismatch sign could be an imaging marker for prognosis. Patients with positive T2-FLAIR mismatch signs had a better prognosis in our study. Although there are not many agents to be used in addition to radiotherapy in treatment, nimotuzumab therapy could be a promising treatment option for DMG. The efficacy of nimotuzumab remains to be confirmed using prospective clinical trials, including a large number of patients.

**Conflict of interest**

No conflict of interest was declared by the authors.

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