ORIGINAL ARTICLE Brain Tumor Res Treat 2025;13(4):140-146 / pISSN 2288-2405 / eISSN 2288-2413
https://doi.org/10.14791/btrt.2025.0022

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Postoperative Seizures Can Predict Overall Survival of Patients With Newly Diagnosed Supratentorial Isocitrate Dehydrogenase-Wild Glioblastoma Treated With Radiotherapy Plus Concomitant and Adjuvant Temozolomide

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Background We aimed to evaluate the correlation between postoperative seizures (POS) and overall survival in patients with newly diagnosed supratentorial isocitrate dehydrogenase (IDH)-wild glioblastoma treated with radiotherapy plus concomitant and adjuvant temozolomide.

Methods This study included 122 patients with newly diagnosed supratentorial IDH-wild glioblastoma who were treated at our hospital between May 2007 and September 2022. Seizures occurring within 7 days after surgery were defined as immediate POS (iPOS). Moreover, seizures from the 8th day after the surgery were defined as delayed POS (dPOS).

Results The median follow-up period and median survival time (MST) from surgery in the entire cohort were 19.3 and 20.4 months, respectively. The rates of iPOS and dPOS in this study were 6.6% (n=8) and 38.5% (n=47), respectively. The MST of patients with iPOS and without iPOS was 27.6 and 20 months, respectively. There was no significant difference between with iPOS and without iPOS. The median time to onset of dPOS was 126 days after surgery. The MST of patients with dPOS and without dPOS was 25.9 and 18.4 months, respectively. Patients with dPOS showed significantly longer survival than those without dPOS (p=0.024). Occurrence of seizures at the initial manifestation of disease was found to be significantly more likely to cause dPOS (p=0.044).

Conclusion Among patients with newly diagnosed supratentorial IDH-wild glioblastoma, the prognosis of patients with seizures in the postoperative course was better than that of patients without dPOS.

Keywords Glioblastoma; Postoperative seizure; Preoperative seizure; Prognostic factors; Isocitrate dehydrogenase.

Received June 28, 2025
Revised August 12, 2025
Accepted August 28, 2025

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INTRODUCTION

Glioblastoma is one of the most common neoplasms among intracranial brain tumors. In patients with glioblastoma, the median survival time (MST) is less than 2 years despite the best treatment approach, i.e., safe maximal resection followed by adjuvant radiotherapy and chemotherapy [1]. Moreover, none of the anticancer agents that followed temozolomide, including bevacizumab and nivolumab, have shown any advantage in clinical trials. Only tumor-treating fields have been shown to contribute to prolonged survival in patients with newly diagnosed glioblastoma [2-4].

Among prognostic factors for glioblastoma, the extent of resection and removal to the fluid-attenuated inversion recovery high-signal region are known to significantly contrib-

ute to a favorable prognosis, while O^6-methylguanine-DNA-methyltransferase (MGMT) methylation is also associated with a favorable prognosis [5-8]. In this regard, previous reports have discussed the prognostic value of preoperative findings in patients with newly diagnosed glioblastoma, including the preoperative Karnofsky Performance Scale (KPS) score, age, tumor contact with the ventricles [9-11], and appearance of seizures as an initial symptom [12,13].

Among patients with high-grade glioma, the incidence of seizures as an initial symptom is 30%–62% [13]. Seizures as an initial symptom have been proven to be a favorable prognostic factor in meta-analyses [12,13], but the prognostic value of postoperative epilepsy remains debatable [14-17]. In this study, we analyzed whether postoperative seizures (POS) can provide prognostic information after surgery for newly diagnosed supratentorial isocitrate dehydrogenase (IDH)-wild glioblastoma.

MATERIALS AND METHODS

Patient characteristics

Clinical data were retrospectively collected to evaluate the preoperative prognostic factors of newly diagnosed supratentorial IDH-wild glioblastoma treated with radiotherapy and chemotherapy at our hospital. The Ethics Committee of Nara Medical University Hospital approved this retrospective study (approval no. 3755). Inclusion criteria were age ≥18 years, supratentorial location, and IDH wild-type tumors. A total of 122 patients with newly diagnosed supratentorial IDH-wild glioblastoma who were treated with radiotherapy and chemotherapy at our hospital between May 2007 and September 2022 were enrolled in this analysis. We collected data regarding patient characteristics, initial symptoms, preoperative seizures (PRS), tumor location, preoperative anti-seizure medications, preoperative KPS scores, and POS. Immediate POS (iPOS) was defined as a documented seizure within 7 days after surgery, and delayed POS (dPOS) was defined as a documented seizure from the 8th day after the surgery to any later time during follow-up [14,18]. Whether or not to administer anti-seizure medications prior to surgery is left to the discretion of the attending physician.

Histological diagnosis of glioblastoma was performed when microvascular proliferation or tumor necrosis was detected. Screening for IDH1 mutations was systematically performed using immunohistochemical analyses targeting the IDH1R132H mutation. Molecular glioblastomas, including IDH1 wild-type astrocytoma, were also excluded. In this study, the extent of resection categories included gross total resection, subtotal resection, partial removal, and biopsy. Gross total removal was defined as ≥95% removal on postoperative MRI scans, subtotal removal as removal ≥90% and <95%, and partial removal as removal <90%.

Statistical analysis

The MST from the date of surgery was calculated using the Kaplan–Meier method by Wilcoxon tests to assess significance for group comparisons. A receiver operating characteristic (ROC) curve was generated, and the area under the curve (AUC) was calculated to evaluate the prognostic power of age for overall survival. We performed t-tests, Fisher's exact tests, and Mann-Whitney U tests comparing all characteristics of the groups with and without dPOS. We analyzed prognostic factors, including sex, age (≥73 vs. <73 years), laterality of tumor location, pretreatment KPS score (≥80 vs. <80), contact with the subventricular zone (SVZ), cortical involvement, temporal lobe involvement, and extent of resection (gross total resection and subtotal resection vs. partial resection and biopsy). All analyses were performed using EZR software (Saitama Medical Center, Jichi Medical University) [19]. A p-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

The cohort consisted of 63 male and 59 female patients (median age: 66±12.3 years; range: 24–91 years). The median follow-up period and MST from surgery in the entire cohort were 19.3 and 20.4 months, respectively (Fig. 1A). An ROC curve was generated, and the AUC was calculated to evaluate the prognostic power of age for overall survival. The cut-off value of age in this cohort was 73 years. In the entire cohort, the MST of patients aged ≥73 years and those aged <73 years was 12.5 and 24.8 months, respectively (p<0.01). Patients with preoperative KPS scores more than 80 showed significantly longer survival after treatment (p=0.031). In MRI assessments of contact with the SVZ, patients showing no contact with the SVZ had a more favorable survival time than those showing contact (p=0.028). On the other hand, assessments of temporal lobe involvement and cortical involvement on MRI showed no significant differences related to these findings.

Eight patients (6.6%) showed iPOS, and 114 patients (93.4%) did not show iPOS. Forty-seven patients (38.5%) showed dPOS, and 75 (61.5%) did not show dPOS. Among cases with dPOS, there were 18 cases of generalized tonic-clonic seizures and 29 cases of partial seizures. Table 1 presents the characteristics of both groups. The two groups showed no significant differences in terms of sex, age, pretreatment KPS score, posttreatment KPS score, tumor laterality, tumor location, temporal lobe involvement, cortical involvement, contact with the SVZ, prophylactic anti-seizure medication, and extent of resection

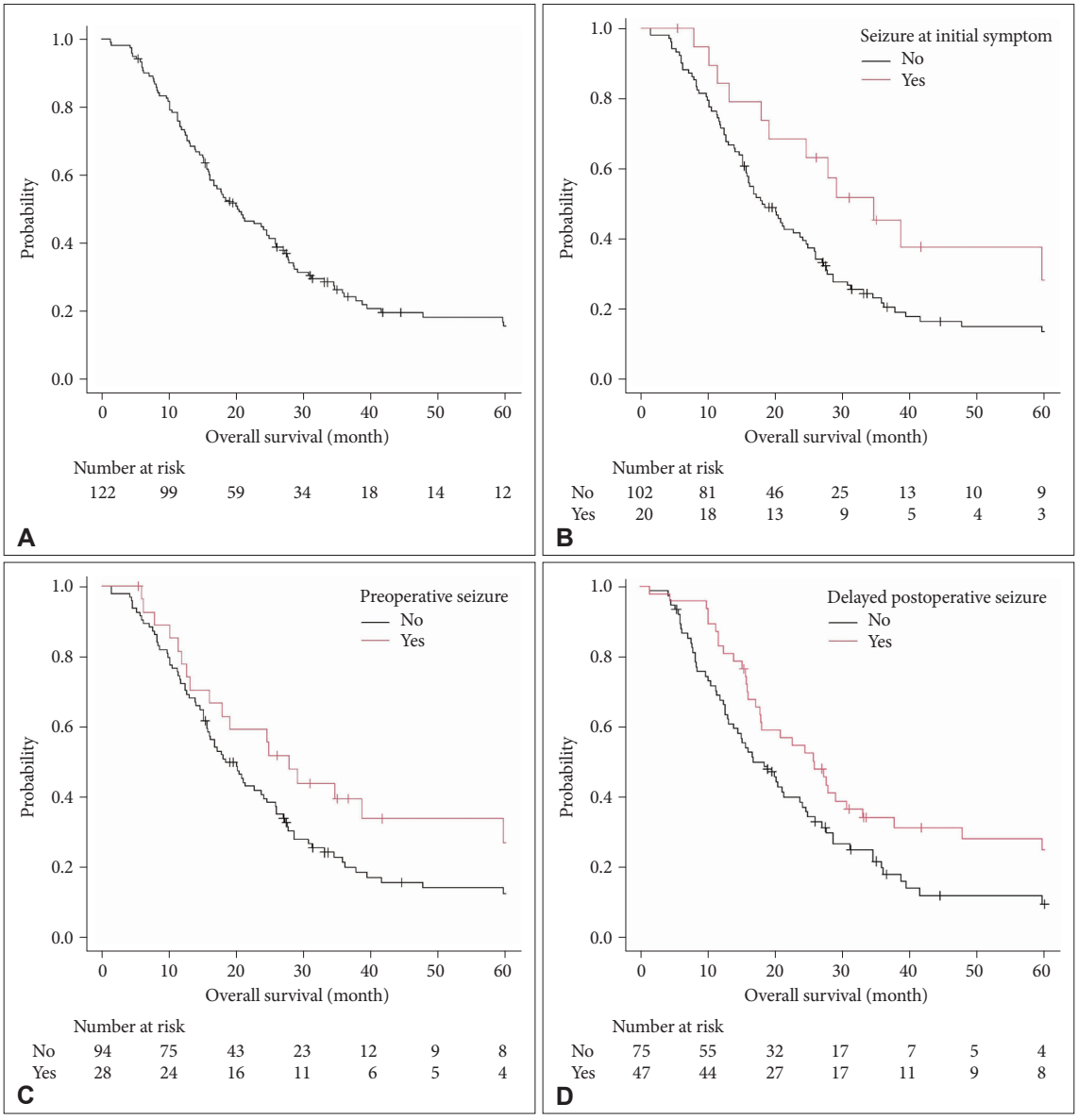

Fig. 1. Survival analysis results estimated using the Kaplan–Meier method. A: Overall survival of the entire cohort. B: Overall survival of patients with seizure as an initial symptom (red line) and no seizures (black line). C: Overall survival of the patients with preoperative seizures (red line) and without preoperative seizures (black line). D: Overall survival of the patients with delayed postoperative seizures (black line) and without postoperative seizures (red line).

(Table 1). The group that had been taking anti-seizure medication prior to surgery was compared with the group that had not been taking anti-seizure medication, but there was no difference in MST between the two groups. Cases with seizure at the initial manifestation showed significantly greater rates of dPOS (p=0.044). MSTs were compared between 12 cases that developed dPOS and 8 cases that did not develop dPOS, but no difference in MST was observed between the two groups.

Seizures appeared as the initial symptoms in 20 patients. The MST of patients with seizure as an initial symptom and the remaining patients was 34.6 and 18 months, respectively. Thus, patients with a seizure as an initial symptom showed significantly longer survival than the remaining patients (p=0.033) (Fig. 1B). A comparison of 28 patients with PRS, including 20 patients with seizures as the initial symptom and 8 patients who showed seizures before surgery, and 94 patients without PRS showed no significant difference in MST (p=0.136) (Fig. 1C). The MST of patients with iPOS and without iPOS was 27.6 and 20 months, respectively. There was no significant difference between with iPOS and without iPOS. The median time of onset of dPOS was 126 days after the initial surgery. The MST of patients with dPOS and without dPOS was 25.9 and 18.4 months, respectively. Patients with dPOS showed significantly longer survival than those without dPOS (p=0.024)

Table 1. The characteristics of patients with dPOS and without dPOS

Characteristic	All cases (n=122)	With dPOS (n=47)	Without dPOS (n=75)	*p* value
Sex				0.711
Female	59	24	35	
Male	63	23	40	
Age (yr)	66.0±12.3	63.7±12.5	67.5±12.0	0.090
Preoperative KPS score	66.8±21.1	67.9±25.1	66.1±18.2	0.650
Postoperative KPS score	70.0±24.2	70.4±26.4	69.7±23.0	0.890
Seizure at initial symptom				0.044
Yes	20	12	8	
No	102	35	67	
Laterality				0.550
Right	52	23	29	
Left	64	22	42	
Bilateral	6	2	4	
Location				0.910
Frontal	39	15	24	
Parietal	23	10	13	
Temporal	40	15	25	
Occipital	6	1	5	
Basal ganglia	11	5	6	
Others	3	1	2	
Temporal involved				0.711
Yes	55	20	35	
No	67	27	40	
Cortical involovement				0.083
Yes	79	35	44	
No	43	12	31	
Contact with subventricular zone				0.158
Yes	85	29	56	
No	37	18	19	
Prophylactic ASM				0.085
Yes	75	24	51	
No	47	23	24	
Extent of resection				0.316
Biopsy	13	3	10	
Partial removal	46	16	30	
Subtotal resection	5	1	4	
Gross total resection	58	27	31	

Values are presented as numbers only or as mean±standard deviation. dPOS, delayed postoperative seizure; KPS, Karnofsky Performance Scale; ASM, anti-seizure medication.

(Fig. 1D). We evaluated whether the administration of anti-seizure medications during the entire treatment period affected overall survival, but there was no difference in overall survival between patients who received anti-seizure medications and those who did not.

DISCUSSION

The median survival of patients with glioblastoma, which has one of the poorest prognoses among malignant brain tumors, is less than 2 years [1]. Among the patients with the newly diagnosed IDH-wild glioblastoma, the proportion of patients who develop seizures at the initial presentation or show PRS is estimated to be approximately 30%−62% [13]. The risk of seizures in patients with glioblastoma has been shown to be lower than that in patients with low-grade gliomas, but is still reported to range from 29% to 49% [20,21]. Thus, neurosurgeons should account for the possibility of seizures while

treating these patients. The prognosis of patients with glioblastoma who show seizures at onset is good, while that of those who develop early POS is poor [22].

In comparison with patients showing IDH-wild gliomas, more patients with IDH mutant-type gliomas have seizures as part of the initial presentation [14,23]. Several mechanisms contribute to this difference. Unlike IDH-wild gliomas, IDH mutant-type gliomas produce D-2-hydroxyglutarate (D2HG) from α-ketoglutarate (αKG). The D2HG produced by IDH mutant-type gliomas increases neuronal excitation, leading to a higher incidence of seizures in IDH mutant-type gliomas [23].

In our cohort, 20 patients (16.4%) presented with seizures as an initial symptom, and overall survival in these patients was significantly longer than that in patients without seizures. In comparisons of patients with and without seizures before surgery, including the initial symptoms, no significant difference was observed, but patients with seizures tended to show a longer overall survival. These results are consistent with the findings of previous reports.

Several reports and meta-analyses have evaluated the relationship between PRS and overall survival in patients with glioblastoma. Ahmadipour et al. [22] analyzed 867 patients with glioblastoma treated at a single center and showed that the overall survival of patients with seizure as an initial symptom was significantly longer than that of patients without seizures, and that seizure as an initial symptom was an independent predictor of overall survival in glioblastoma patients. Other reports have also mentioned the association between PRS and overall survival in patients with glioblastoma [12,24,25]. Dührsen et al. [26] reported that glioblastoma in patients with PRS is smaller and less edematous on MRI scans than glioblastoma in patients without PRS. In addition, the expression of branched-chain amino acid transaminase 1 (BCAT-1), which is involved in the glutamate carrier system, has been shown to be significantly upregulated in glioblastoma in patients with PRS. These findings suggest that tumor size and BCAT-1 expression may affect the survival in glioblastoma patients.

In previous reports, dPOS occurs in approximately 10%–30% of glioblastoma patients [14-17]. In our cohort, dPOS occurred in 38.5% of the patients. In a comparison of groups with and without dPOS, the incidence of PRS (p=0.049) and dPOS (p<0.001) was lower among patients with tumors located in the occipital location [14]. Ahmadipour et al. [22] reported a relationship between seizures occurring within 3 weeks after surgery and overall survival, and they observed that cases with anemia, elevated C-reactive protein levels, and elevated γ-glutamyl transpeptidase levels before surgery showed significantly more seizures immediately after surgery, and that the overall survival was significantly shorter in cases showing seizures immediately after surgery. They stated that the preoperative general condition may be related to the occurrence of seizures immediately after surgery and overall survival. Li et al. [17] also reported a significantly shorter overall survival in cases showing seizures immediately after surgery, and they suggested that these findings may be related to bleeding in the resection cavity due to surgical procedures and increased intracranial pressure.

Several studies have been reported on whether anti-seizure medications have antitumor effects and prolong survival. In basic research, valproic acid, levetiracetam, and perampanel have been shown to have antitumor effects [27-30]. On the other hand, clinical studies have reported that anti-seizure medications do not affect the overall survival of the patients with newly diagnosed glioblastoma in meta-analyses [31]. The only report from a single institution in France indicated that patients with newly diagnosed glioblastoma who took levetiracetam for a long period of time had a longer survival period than patients who took it for a short period of time. Whether anti-seizure medications affect overall survival in patients with newly diagnosed glioblastoma remains a matter of debate.

However, unlike iPOS, dPOS occurring in the postoperative follow-up period may allow detection of recurrence [16]. Other possible factors leading to dPOS include pseudo-progression and neglect of anti-seizure medications. Various reports have described late dPOS and overall survival. In our cohort, overall survival in patients with dPOS was significantly longer than that in patients without dPOS. Toledo et al. [15] reported that dPOS in patients with glioblastoma was an independent prognostic factor for overall survival, although the bias of longer follow-up was evident in patients with recurrent seizures. Prospective clinical trials are needed to determine whether the development of dPOS in patients with glioblastoma influences the prognosis. The primary limitations of the present study are its retrospective design and the small sample of patients with newly diagnosed supratentorial IDH-wild glioblastoma. In addition, this study analyzed data from only one institution, and we could not evaluate the effect of anti-seizure medications.

In conclusion, among patients with newly diagnosed supratentorial IDH-wild glioblastoma, the prognosis of patients with dPOS was better than that of patients without dPOS.

Availability of Data and Material

The datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

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Conflicts of Interest

The authors have no potential conflicts of interest to disclose.

Funding Statement

None

Acknowledgments

None

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