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# Early Diagnosis and Surgical Intervention Within 3 Weeks From Symptom Onset Are Associated With Prolonged Survival of Patients With Glioblastoma

**Daisuke Kawauchi, MD, PhD***
**Makoto Ohno, MD, PhD***
**Yasuji Miyakita, MD, PhD***
**Masamichi Takahashi, MD, PhD***
**Shunsuke Yanagisawa, MD, PhD***
**Takaki Omura, MD***
**Akihiko Yoshida, MD, PhD‡**
**Yuko Kubo, MD, PhD§**
**Hiroshi Igaki, MD, PhD‖**
**Koichi Ichimura, MD, PhD¶**
**Yoshitaka Narita, MD, PhD***

*Department of Neurosurgery and Neuro-Oncology, National Cancer Center Hospital, Tokyo, Japan; ‡Department of Pathology, National Cancer Center Hospital, Tokyo, Japan; §Department of Diagnostic Radiology, National Cancer Center Hospital, Tokyo, Japan; ‖Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan; ¶Department of Brain Disease Translational Research, Juntendo University Faculty of Medicine, Tokyo, Japan

**Correspondence:**
Yoshitaka Narita, MD, PhD,
Department of Neurosurgery and Neuro-Oncology,
National Cancer Center Hospital,
5-1-1, Tsukiji, Chuo-ku,
Tokyo, 104-0045, Japan.
Email: yonarita@ncc.go.jp

**Received,** April 7, 2022.
**Accepted,** June 5, 2022.
**Published Online,** August 15, 2022.

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**BACKGROUND:** Glioblastoma (GBM) is a rapidly growing and most life-threatening malignant brain tumor. The significance of early treatment to the clinical outcomes of patients with GBM is unclear.

**OBJECTIVE:** To determine whether early diagnosis and surgery improve the preoperative and postoperative Karnofsky performance status (KPS) and prognosis of patients with GBM.

**METHODS:** Data of isocitrate dehydrogenase-wildtype patients with GBM treated at our institution between January 2010 and December 2019 were reviewed. Patients were classified into early or late diagnosis groups with a threshold of 14 days from initial symptoms. In addition, patients were divided into early, intermediate, and late surgery groups with thresholds of 21 and 35 days. Representative symptoms and patient prognoses were examined.

**RESULTS:** Of 153 patients, 72 and 81 were classified into the early and late diagnosis groups. The median tumor volume was significantly smaller in the former group. The proportion of patients with preoperative KPS scores ≥ 90 was 48.6% and 29.6% in the early and late diagnosis groups ($P$ = .016). The early, intermediate, and late surgery groups included 43, 24, and 86 patients. The median overall survival was significantly longer in the early surgery group than in the late surgery group (28.4 vs 18.7 months, $P$ = .006). Multivariate analysis demonstrated that significant predictors of shorter survival included extent of tumor resection (partial or biopsy), preoperative and postoperative KPS ≤ 60, and O6-methylguanine-DNA-methyltransferase promoter status (unmethylated).

**CONCLUSION:** Early diagnosis within 2 weeks and surgical interventions within 3 weeks from the symptom onset are associated with prolonged patient survival. Early GBM treatment will benefit patients with GBM.

**KEY WORDS:** Diagnosis, Glioblastoma, Karnofsky performance status, Prognosis

*Neurosurgery 00:1–8, 2022* https://doi.org/10.1227/neu.0000000000002096

Glioblastoma (GBM) is the most common and life-threatening adult malignant brain tumor categorized as a World Health Organization (WHO) grade 4. Recurrence is inevitable in most patients, even with the best treatment and maximal safe surgical resection after chemoradiotherapy with temozolomide (TMZ). The median survival of patients with GBM is <2 years.[1,2] Various factors contribute to this poor prognosis, such as older patient population, rapid tumor growth, tumor heterogeneity, difficulty in total resection, frequent complications, and limited chemotherapeutic options. Poor Karnofsky performance status (KPS) is also an essential factor associated with poor prognosis of patients with GBM.

Preoperative and postoperative KPS scores of <80 are associated with poor prognosis in patients with GBM.[3,4] In addition, recursive partitioning analysis classification for GBM splits the younger patient group (age 49 years or younger) by KPS 90 and the older patient group (age

**ABBREVIATIONS: BEV,** bevacizumab; **HR,** hazard ratio; **IDH,** isocitrate dehydrogenase; **KPS,** Karnofsky performance status; **OS,** overall survival; **TERT,** telomerase reverse transcriptase; **TMZ,** temozolomide; **WHO,** World Health Organization.

Supplemental digital content is available for this article at neurosurgery-online.com.

50 years or older) by KPS 70.[5] These data indicate a strong association between KPS and prognosis.

GBM is one of the most rapidly growing tumors with an expected doubling time of 49.6 days.[6] Therefore, even a short delay in diagnosis and surgical intervention is attributed to an increase in tumor volume and decrease in preoperative and postoperative KPS. We hypothesized that early diagnosis and surgery will improve the preoperative and postoperative KPS scores and consequently improve the prognosis of patients with GBM. This study aimed to establish an effective time course for patients with GBM, from the development of symptoms to the diagnosis and the surgical intervention.

## METHODS

### Patient Characteristics

This study was a single-center retrospective analysis of a consecutive series of patients with isocitrate dehydrogenase (IDH)-wildtype GBM. We identified adult patients with GBM (age 20-80 years) who were newly diagnosed and treated at our institution between January 2010 and December 2019. Patients had at least 6 months of postoperative follow-up. We collected patient data, including age, sex, clinical history, radiological images, surgical reports, perioperative KPS, and postsurgical clinical courses. The onset of initial symptoms was determined based on clinical records. If the clinical record described that patients recognized their clinical symptoms at the beginning, middle, end, or around the month, we determined the onset dates as 1, 11, 30, and 15, respectively. Diagnosis of GBM was histologically certified based on the WHO classification 2007/2016. In this study, we included only IDH-wildtype GBM cases, conforming to the WHO classification 2021.[7] We defined progression-free survival (PFS) as the interval between initial surgery date and the detection of any progression and overall survival (OS) as the interval between initial surgery and death. Patients with unknown survival were censored at the last follow-up date. The data sets used and/or analyzed during this study are available from the corresponding author on reasonable request.

We extracted molecular profiles of the tumors from medical records, including IDH and O6-methylguanine-DNA-methyltransferase promoter methylation status. We classified the extent of resection of the tumor as total (100%) resection, subtotal (95%-99%) resection, partial (<94%) resection, or biopsy, based on the surgeon's operative notes and postoperative imaging studies. KPS scores were classified as low (60 or below), middle (70 or 80), or high (90 or 100).

### Molecular Analysis

Details of molecular analysis are described in the **Supplemental Digital Content 1**, **Methods and Materials**, http://links.lww.com/NEU/D257.

### Statistical Analysis

Comparison of tumor volumes between 2 groups was evaluated using the Mann-Whitney test. OS and PFS were calculated using the Kaplan-Meier method and compared using the log-rank test. In addition, Mantel-Haenszel method was used to calculate hazard ratios of 2 groups. The $\chi^2$ test was used to evaluate the distribution of KPS between 2 arbitrary groups. Cox proportional hazards regression was used to identify significant predictors of shorter survival. Statistical analyses were performed using GraphPad Prism 9 (GraphPad Software, Inc). Statistical significance was defined as a $P$ value of <.05.

**TABLE 1. Durations From the Symptom Onset to the Specific Event**

| Days | Patients |
|---|---|
| Duration from the symptom onset to the first hospital visit | |
| 0-7 | 76 (49.7%) |
| 8-14 | 10 (6.5%) |
| 15-21 | 11 (7.2%) |
| 22-30 | 11 (7.2%) |
| 31-60 | 22 (14.4%) |
| 61-90 | 7 (4.6%) |
| 91-120 | 9 (5.9%) |
| 120- | 7 (4.6%) |
| Duration from the symptom onset to the radiological diagnosis of a tumor | |
| 0-7 | 62 (40.5%) |
| 8-14 | 10 (6.5%) |
| 15-21 | 13 (8.5%) |
| 22-30 | 13 (8.5%) |
| 31-60 | 26 (17.0%) |
| 61-90 | 8 (5.2%) |
| 91-120 | 12 (7.8%) |
| 120- | 9 (5.9%) |
| Duration from the symptom onset to the first surgical intervention | |
| 0-7 | 5 (3.3%) |
| 8-14 | 15 (9.8%) |
| 15-21 | 23 (15.0%) |
| 22-30 | 10 (6.5%) |
| 31-60 | 43 (28.1%) |
| 61-90 | 21 (13.7%) |
| 91-120 | 11 (7.2%) |
| 120- | 25 (16.3%) |

### Ethics Approval

This retrospective study used data obtained for clinical purposes. This study was approved by the internal review board of the National Cancer Center (approval number: 2004-066). Written informed consent was obtained from all individual participants.

## RESULTS

### Patient Demographics

A total of 153 patients newly diagnosed with IDH-wildtype GBM were treated at our institution between January 2010 and December 2019. The median duration from the symptom onset to the hospital visit, the radiological diagnosis of a tumor, and the first surgery was 8, 17, and 40 days, respectively (Table 1). Of the patients with GBM, within 14 days of symptom onset, 56.2% visited the clinic or hospital and 47.1% obtained a radiological

**TABLE 2. Characteristics of Early and Late Diagnosis Groups**

| Days from the initial symptoms to the radiological diagnosis | Early diagnosis group 0-14 d | Late diagnosis group 15 d or later | *P* value |
|---|---|---|---|
| Patient number | 72 | 81 | |
| Male:female | 49:23 (68%) | 47:34 (58%) | |
| Multiple tumor | 6 (8.3%) | 7 (8.6%) | |
| Multilobe tumor | 5 (6.9%) | 9 (11.1%) | |
| Tumor volume (median) $cm^3$ | 12.0 | 29.0 | .0004 |
| Main tumor location | | | |
| Frontal lobe | 27 (37.5%) | 23 (28.4%) | |
| Temporal lobe | 14 (19.4%) | 14 (17.3%) | |
| Parietal lobe | 18 (25.0%) | 17 (21.0%) | |
| Occipital lobes | 2 (2.8%) | 0 | |
| Preoperative KPS | | | |
| 100 or 90 | 35 (48.6%) | 24 (29.6%) | |
| 80 | 23 (31.9%) | 29 (35.8%) | |
| 70 | 10 (13.9%) | 14 (17.3%) | |
| 60 or below | 4 (5.6%) | 14 (17.3%) | |
| Initial symptoms | | | |
| Headache | 12 (16.7%) | 20 (27.8%) | |
| Paralysis | 10 (13.9%) | 18 (25.0%) | |
| Seizure | 16 (22.2%) | 2 (2.8%) | |
| Aphasia | 10 (13.9%) | 9 (12.5%) | |
| Disorder of consciousness | 7 (9.7%) | 9 (12.5%) | |
| Memory disturbance | 4 (5.6%) | 9 (12.5%) | |
| Sensory disturbance | 5 (6.9%) | 6 (8.3%) | |
| Anopsia | 1 (1.6%) | 3 (4.2%) | |
| Incidental | 5 (6.9%) | 0 | |
| Other | 0 | 4 (5.6%) | |
| Unknown | 2 (2.8%) | 1 (1.4%) | |

KPS, Karnofsky performance status.

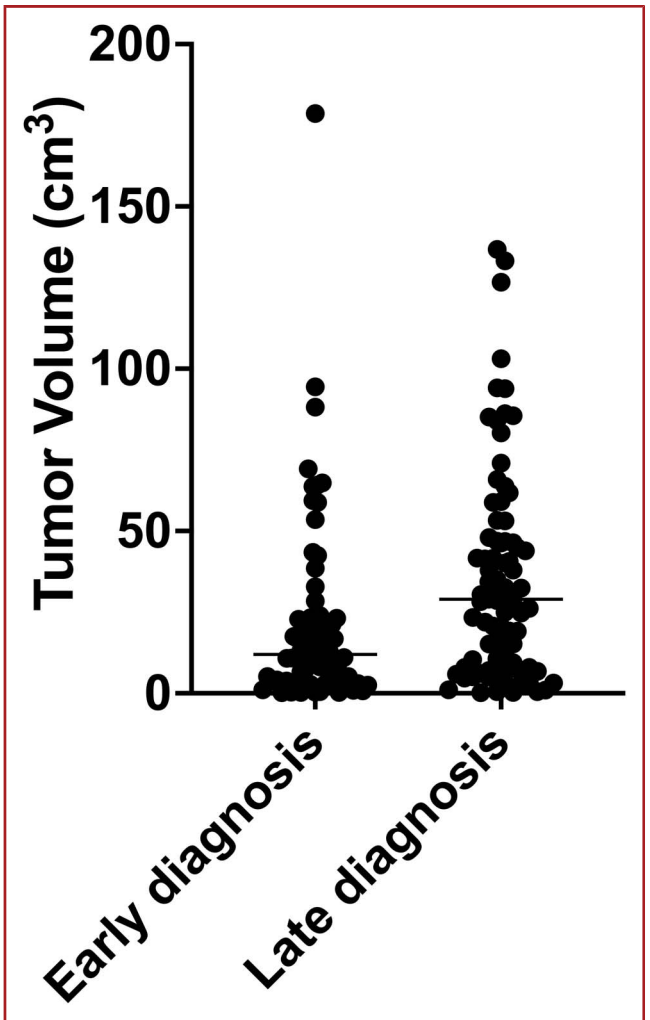


**FIGURE 1.** *Tumor volume in the early diagnosis group (tumors were radiologically diagnosed within 14 days from the initial symptoms) and late diagnosis group (tumors were found 15 days or later from symptom development). The median tumor volumes of the early diagnosis group and the late diagnosis group are 12.0 and 29.0 $cm^3$ (P = .0004).*

diagnosis of brain tumors. Only 28.1% of the patients received their first surgery within 21 days. After the initial surgery, 147 underwent radiotherapy with concomitant and adjuvant TMZ, 5 received radiotherapy alone, and 1 received no adjuvant therapy. In addition to TMZ, 31 patients received adjuvant chemotherapy with bevacizumab (BEV) as a first-line treatment.

## Tumor Characteristics

We divided patients with GBM into 2 groups: early diagnosis group (n = 72) and late diagnosis group (n = 81), whose tumors were radiologically diagnosed within 14 days and 15 days or later from initial symptom development. The tumor characteristics of the early and late diagnosis groups are summarized in Table 2. Sex distribution was similar between the groups. Although multiple tumors were found equally (8.3% and 8.6%), multilobe tumors were less frequently found in the early diagnosis group (6.9% vs 11.1%). The median tumor volume was significantly smaller in the early diagnosis group than in the late diagnosis group (12.0 vs 29.0 $cm^3$, $P = .0004$, Figure 1). The mean tumor volume of entire patients was 29.1 ± 31.5 $cm^3$. The anatomic distributions of the tumors were similar between the groups.

## Initial Symptoms and KPS

The initial symptoms of the patients with GBM are summarized in Table 2. Headache, paralysis, and memory disturbance were more common symptoms in the late diagnosis group (27.8%, 25.0%, and 12.5%, respectively) than in the early diagnosis group (16.7%, 13.9%, and 5.6%, respectively). By contrast, seizure was more frequent symptom in the early diagnosis group (22.2%) than in the late diagnosis group (2.8%).

Significantly more patients with preoperative KPS ≥70 (94.4%) and ≥90 (48.6%) were observed in the early diagnosis group than

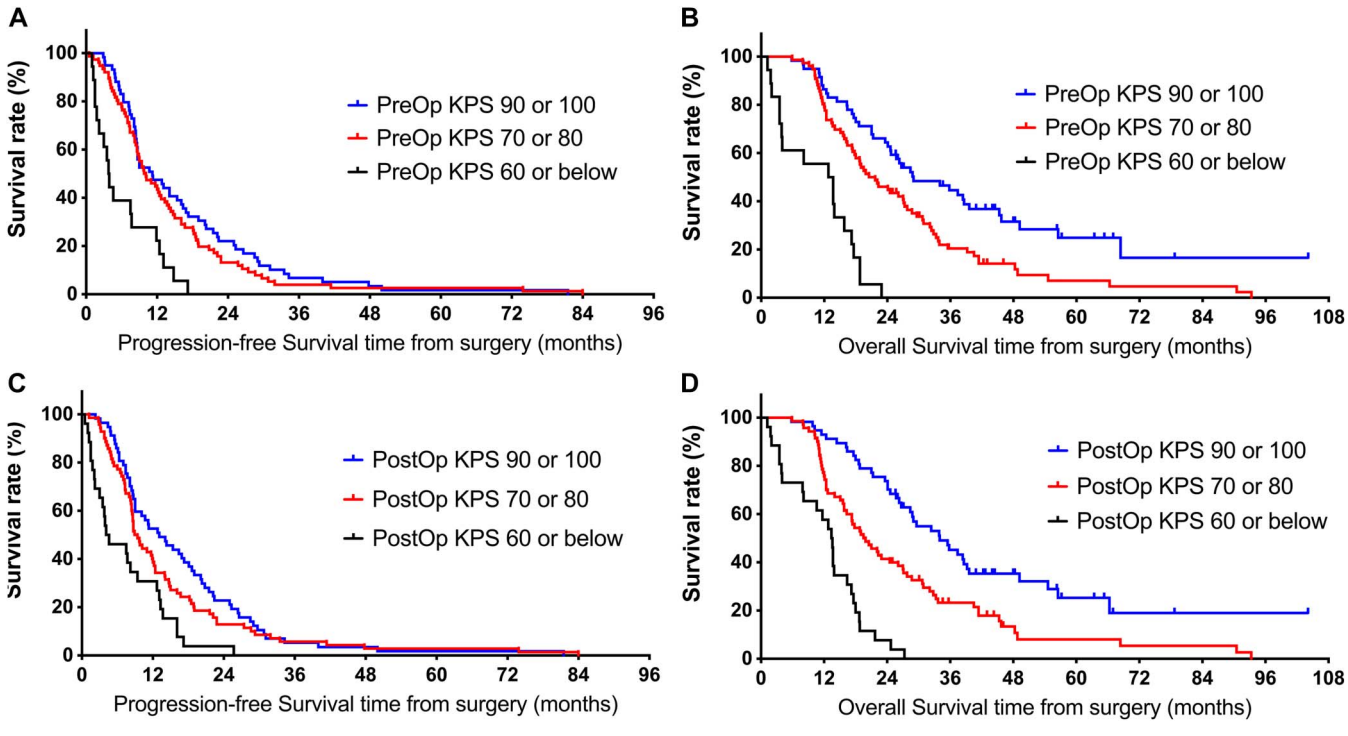


**FIGURE 2.** *Kaplan-Meier curves of PFS and OS.* **A**, *The median PFS of patients with low (60 or below), middle (70 or 80), and high (90 or 100) preoperative KPS scores is 3.9, 10.0, and 11.2 months (P < .0001).* **B**, *The median OS of patients with low, middle, and high preoperative KPS scores is 13.3, 20.5, and 29.0 months (P < .0001).* **C**, *The median PFS of patients with low, middle, and high postoperative KPS scores is 4.4, 9.2, and 13.1 months (P = .0002).* **D**, *The median OS of patients with low, middle, and high postoperative KPS scores is 13.5, 19.7, and 34.0 months (P < .0001). KPS, Karnofsky performance status; OS, overall survival; PFS, progression-free survival.*

in the late diagnosis group (82.7% and 29.6%, respectively) ($P$ = .025 and .016, respectively, **Supplemental Digital Content 2**, http://links.lww.com/NEU/D258, and **Supplemental Digital Content 3**, http://links.lww.com/NEU/D259).

## Clinical Outcomes

The median PFS and OS of patients with low, middle, and high preoperative KPS scores were 3.9, 10.0, and 11.2 months ($P$ < .0001, Figure 2A) and 13.3, 20.5, and 29.0 months ($P$ < .0001, Figure 2B), respectively. The median PFS and OS of patients with low, middle, and high postoperative KPS scores were 4.4, 9.2, and 13.1 months ($P$ = .0002, Figure 2C) and 13.5, 19.7, and 34.0 months ($P$ < .0001, Figure 2D), respectively. Higher preoperative and postoperative KPS scores were associated with significantly better patient survival rates.

We analyzed the association between the timing of surgery and patient performance status. We divided the patients with GBM into 3 groups: early surgery group (n = 43), intermediate surgery group (n = 24), and late surgery group (n = 86), who received surgical intervention from the initial symptoms within 21 days (0-3 weeks), between 22 and 35 days (4-5 weeks), and after 36 days (after 6 weeks) (Table 3). Among the 72 patients with an early diagnosis, 42 (58.3%) underwent early surgery. The number of patients with high preoperative and postoperative KPS score in the early, intermediate, and late surgery groups was 21 (48.8%), 10 (41.7%), and 28 (32.6%) and 22 (51.2%), 9 (37.5%), and 26 (30.1%), respectively (Figure 3). In addition, significantly more patients with postoperative KPS scores ≥70 and ≥90 were found in the early surgery group (95.3% and 51.2%) than in the late surgery group (77.9% and 30.2%) ($P$ = .011 and .020, respectively, **Supplemental Digital Content 2**, http://links.lww.com/NEU/D258, and **Supplemental Digital Content 3**, http://links.lww.com/NEU/D259).

Next, we examined the efficacy of early diagnosis and surgery on the patients' clinical outcomes. Although we observed no difference in median PFS between the early and late diagnosis groups (9.0 vs 10.2 months, $P$ = .098, Figure 4A), the median OS was significantly extended in the early diagnosis group than in the late diagnosis group (24.7 vs 19.5 months, $P$ = .023, Figure 4B). The median PFS and OS of the early, intermediate, and late surgery groups were 9.0, 12.8, and 8.9 months ($P$ = .22, Figure 5A) and 28.4, 22.7, and 18.8 months ($P$ = .017, Figure 5B), respectively. There was no difference in median PFS between the early and late surgery groups ($P$ = .15). However, the median OS of the early surgery group was significantly longer than that of the late surgery group (hazard ratio [HR] 0.59, 95% CI 0.40-0.86, $P$ = .006). In addition, a higher

**TABLE 3. Characteristics of Early and Late Surgery Groups**

| Days from initial symptoms to the first surgical intervention | Early surgery group 0-21 d | Intermediate surgery group 22-35 d | Late surgery group 36 d or more |
|---|---|---|---|
| Patient number | 43 | 24 | 86 |
| Male:female | 30:13 (69.8%) | 10:14 (41.7%) | 56:30 (65.1%) |
| Multiple tumor | 4 (9.3%) | 1 (4.2%) | 8 (9.3%) |
| Multilobe tumor | 4 (9.3%) | 2 (8.3%) | 8 (9.3%) |
| Tumor volume (median), $cm^3$ | 17.5 | 18.4 | 19.3 |
| Main tumor location | | | |
| Frontal lobe | 18 (41.9%) | 7 (29.2%) | 25 (29.1%) |
| Temporal lobe | 9 (20.9%) | 5 (20.8%) | 14 (16.3%) |
| Parietal lobe | 9 (20.9%) | 7 (29.2%) | 19 (22.1%) |
| Occipital lobes | 0 | 0 | 2 (2.3%) |
| Preoperative KPS | | | |
| 100 or 90 | 21 (48.8%) | 10 (41.7%) | 28 (32.6%) |
| 80 | 13 (30.2%) | 8 (33.3%) | 31 (36.0%) |
| 70 | 8 (18.6%) | 3 (12.5%) | 13 (15.1%) |
| 60 or below | 1 (2.3%) | 3 (12.5%) | 14 (16.3%) |
| Postoperative KPS | | | |
| 100 or 90 | 22 (51.2%) | 9 (37.5%) | 26 (30.2%) |
| 80 | 14 (32.6%) | 7 (29.2%) | 27 (31.4%) |
| 70 | 5 (11.6%) | 3 (12.5%) | 14 (16.3%) |
| 60 or below | 2 (4.7%) | 5 (20.8%) | 26 (22.1%) |
| Median days from initial symptom to the first hospital visit | 0 | 2.5 | 31.5 |
| Median days from initial symptom to radiological tumor diagnosis | 0 | 3.5 | 44.0 |
| Median days from the first hospital visit to surgery | 15 | 31.5 | 80 |

KPS, Karnofsky performance status.

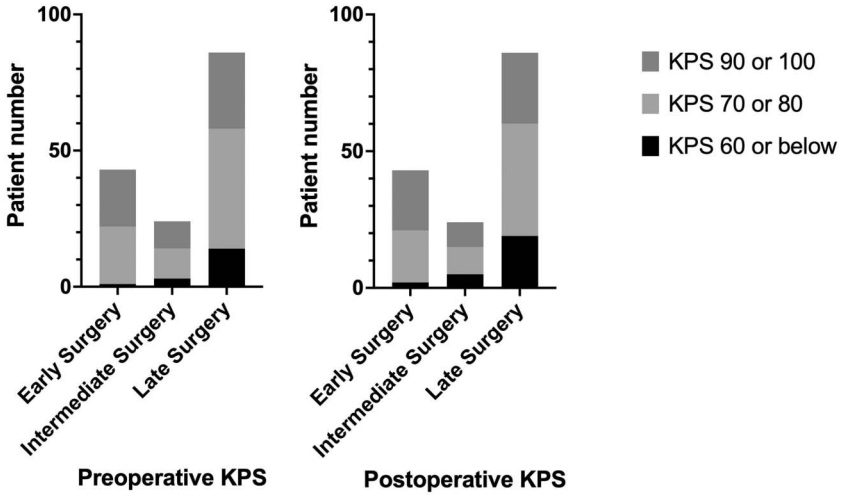


**FIGURE 3.** *Patient number of preoperative and postoperative KPS in the early, intermediate, and late surgery groups. The patients in the early, intermediate, or late surgery groups received surgical intervention within 21 days (0-3 weeks), between 22 and 35 days (4-5 weeks), or after 36 days (after 6 weeks) from the initial symptom development. The number of patients with preoperative KPS scores below 60, 70 or 80, and 90 or 100 was 1 (2.3%), 21 (48.8%), and 21 (48.8%) in the early surgery group; 3 (12.5%), 11 (45.8%), and 10 (41.7%) in the intermediate surgery group; and 14 (16.3%), 44 (51.1%), and 28 (32.6%) in the late surgery group. The number of patients with postoperative KPS scores below 60, 70 or 80, and 90 or 100 was 2 (4.7%), 19 (44.2%) and 22 (51.2%) in the early surgery group; 5 (20.8%), 10 (41.7%), and 9 (37.5%) in the intermediate surgery group; and 19 (22.1%), 41 (47.7%), 26 (30.2%) in the late surgery group. KPS, Karnofsky performance status.*

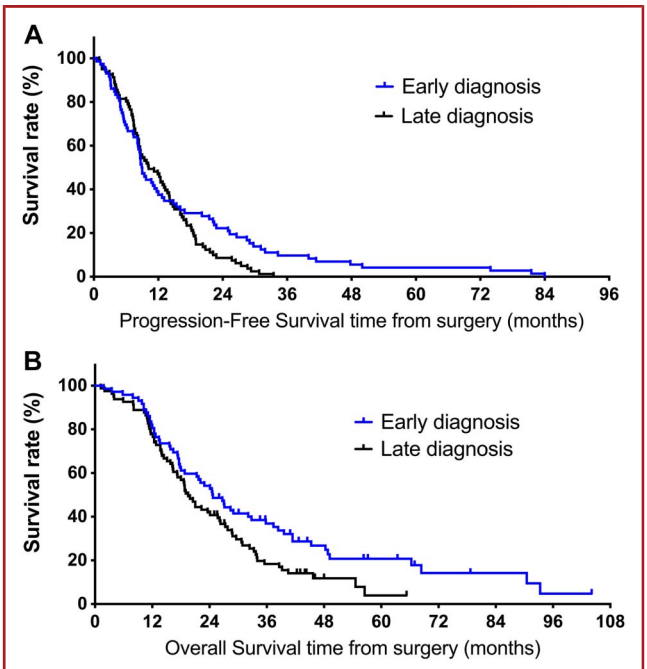


**FIGURE 4.** *Kaplan-Meier curves of PFS and OS. Patients in the early and late diagnosis groups obtained radiological diagnoses of brain tumors within 14 and 15 days or later from the initial symptom development.* **A**, *The median PFS of the early diagnosed group and late diagnosed group was 9.0 and 10.2 months (P = .098).* **B**, *The median OS of the early and late diagnosis group was 24.7 and 19.5 months (P = .023). OS, overall survival; PFS, progression-free survival.*

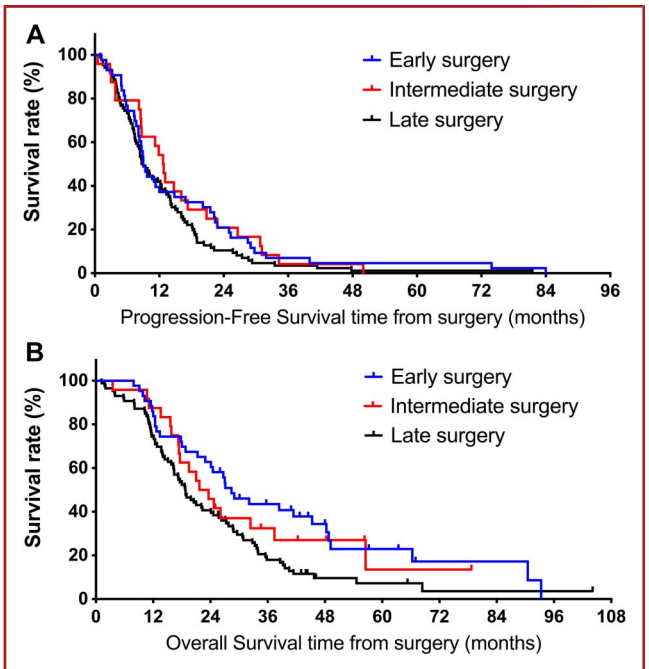


**FIGURE 5.** *Kaplan-Meier curves of PFS and OS. The patients in the early, intermediate, and late surgery groups received surgical intervention within 21 days (0-3 weeks), between 22 and 35 days (4-5 weeks), or after 36 days (after 6 weeks) from the initial symptom development.* **A**, *The median PFS of the early, intermediate, and late surgery group was 9.0, 12.8, and 8.9 months (P = .22).* **B**, *The median OS of the early, intermediate, and late surgery group was 28.4, 22.7, and 18.8 months (P = .017). OS, overall survival; PFS, progression-free survival.*

extent of tumor resection (95% or more) significantly prolonged patient prognosis regarding PFS (8.4 vs 12.2 months, $P = .0028$) and OS (16.8 vs 28.8 months, $P < .0001$, **Supplemental Digital Content 4**, http://links.lww.com/NEU/D260).

Multivariate analysis demonstrated that the significant predictors of shorter survival included the extent of tumor resection (partial or biopsy), poor preoperative and postoperative KPS (≤60), and O6-methylguanine-DNA-methyltransferase promoter methylation status (unmethylated) (Table 4).

Finally, considering adjuvant chemotherapy with BEV might have extended patient PFS, we selectively calculated the PFS of patients who have not received adjuvant chemotherapy with BEV as a first-line treatment (n = 122). As a result, the PFS of early, intermediate, and late surgery groups were 9.7, 12.8, and 8.2 months, respectively ($P = .069$, **Supplemental Digital Content 5**, http://links.lww.com/NEU/D261). Patients in early surgery group demonstrated significantly extended PFS than those in the late surgery group ($P = .05$).

## DISCUSSION

In this study, 56.2% of patients with GBM visited a doctor and 47.0% of them obtained a radiological diagnosis of a brain tumor within 2 weeks from symptom onset. Japan was ranked 12th in 195 countries worldwide in the Health Care Access and Quality[8] Index and recorded the smallest range of subnational Health Care Access and Quality performance. In addition, Japan owns the highest number of diagnostic imaging devices, including computed tomography and MRI, per population in the world.[9] Japanese patients have freer access to medical facilities and diagnostic imaging devices than the global population. Thus, the number of patients who obtained a tumor diagnosis within 2 weeks of symptom onset was presumed to be higher than the global average. Another finding was that 28.1% of patients with GBM received surgical intervention within 3 weeks from symptom onset. Because we could not find any previous literature to compare, it is difficult to interpret whether this number is high.

The average tumor volume in this study was 29.1 $cm^3$. This result corresponds to an average tumor volume of 33.2 $cm^3$ in a previous study.[10] By contrast, a significant difference in tumor volume was observed between the early and late diagnosis groups. GBM grows rapidly with an expected volume doubling time of 49.6 days.[6] The doubling time of GBM is shorter than that of other cancers, such as small-cell lung cancer (86.3 days),[11] breast cancer (103-127 days for triple-negative),[12,13] cutaneous melanoma (144 days),[14] or colon cancer (146.5-398.5 days).[15] The rapid growth of

**TABLE 4. Significant Multivariate Predictors of Survival in 153 Patients With Glioblastoma**

| Variable | Patients | HR estimate | 95% CI |
|---|---|---|---|
| Age (y) | | | |
| 49 y or younger | 38 | 1 | |
| 50 y or older | 115 | 0.44 | −0.037 to 0.94 |
| Symptom to diagnosis | | | |
| Early diagnosis group | 72 | 1 | |
| Late diagnosis group | 81 | −0.079 | −0.58 to 0.44 |
| Symptom to Surgery | | | |
| Early surgery group | 43 | 1 | |
| Intermediate surgery group | 24 | 0.23 | −0.41 to 0.85 |
| Late surgery group | 86 | 0.37 | −0.22 to 0.95 |
| Extent of resection | | | |
| Total or Subtotal | 79 | 1 | |
| Partial or biopsy | 74 | 0.48 | 0.085 to 0.87 |
| Preoperative KPS | | | |
| 90 or 100 | 59 | 1 | |
| 70 or 80 | 76 | 0.27 | −0.22 to 0.77 |
| 60 or below | 18 | 0.85 | 0.061 to 1.63 |
| Postoperative KPS | | | |
| 90 or 100 | 57 | 1 | |
| 70 or 80 | 70 | 0.50 | −0.0030 to 1.01 |
| 60 or below | 26 | 1.42 | 0.68 to 2.14 |
| MGMT promoter | | | |
| Methylated | 62 | 1 | |
| Unmethylated | 91 | 0.97 | 0.56 to 1.38 |

HR, hazard ratio; KPS, Karnofsky performance status; MGMT, O6-methylguanine-DNA-methyltransferase.

GBM emphasizes the importance of early diagnosis before the development of devastating neurological dysfunction.

According to the Brain Tumor Registry of Japan 2005 to 2008, 14% of patients with GBM experience seizures during initial symptoms.[16] Seizure is a discriminative symptom, with a higher incidence in the early diagnosis group (22.2%) than in the late diagnosis group (2.8%). By contrast, more than a quarter of the patients in the late diagnosis group experienced headache or paralysis as initial symptoms. These results indicate that while a seizure becomes a stronger incentive for patients to visit a health institute, headaches and paralysis have a weaker influence on patient behaviors. Headache is the presenting symptom in 30.1% of all patients with GBM[17] and is the most common symptom. Considering that more than a quarter of the patients presented with headache as an initial symptom in the late diagnosis group, we learned 2 lessons. First, we need to advocate earlier hospital visits to people, especially to those with progressive severity, unilateral localization, and new-onset headaches >50 years.[18] Second, we need to determine more tumor-specific headaches to distinguish them from benign headaches. In addition, other modalities, such as serum microRNA,[19] to screen brain tumors may be helpful for regions where radiological imaging techniques are limited in the future.

Previous reports have indicated an association between the perioperative KPS and clinical outcomes. For example, KPS scores of 70 and 90 are essential bifurcations in the recursive partitioning analysis classification for predicting the prognosis of patients with GBM.[5] Bette et al[4] also reported that a low postoperative KPS score (≤70) was a poor prognostic marker in multivariate analysis. Our results entirely corresponded to these previous results and confirmed the significance of postoperative KPS, as 70 and 90 demonstrated evident splits in clinical outcomes.

This study demonstrated that early diagnosis within 2 weeks and surgical intervention within 3 weeks after symptom onset are associated with the prolonged survival of patients with GBM. We presume that their improved outcomes by early treatment are attributed to a smaller tumor volume and better postoperative KPS. First, we observed a smaller tumor volume in the early diagnosis group than that from the late diagnosis group. A previous study reported that a larger preoperative tumor volume was associated with worse clinical outcome.[4] In addition, a smaller residual tumor volume (<2 $cm^3$) was beneficial for survival.[20] Thus, early diagnosis of GBM when the tumor size is small is beneficial for patient prognosis. Second, more patients with higher postoperative KPS scores were observed in the early diagnosis and surgery groups. Postoperative KPS scores demonstrated a strong correlation with survival in patients with GBM[4] and metastatic tumor.[21] Early surgical intervention supposedly averted patients' performance status from deteriorating further and maintaining a high postoperative KPS score.

We observed that patient PFS was prolonged when ≥95% tumor resection was performed. In addition, the PFS of the early surgery group was extended when patients who had not received adjuvant chemotherapy with BEV were selectively examined. In Japan, adjuvant chemotherapy with BEV is approved for the treatment of malignant glioma, including newly diagnosed GBM, in combination with radiotherapy and TMZ, and patients with a poor KPS tended to receive BEV from the initial treatment. Our result emphasized the efficacy of BEV in extending PFS and the significance of early surgery in countries where BEV is not approved for newly diagnosed GBM.

## Limitations

A limitation of this study is selection bias. Because this was a single-center study, the patients studied may be selected from a biased population and may not reflect the general population. In addition, we specified the nearest date of symptom onset based on patients' self-report complaints on our clinical records. Therefore, the dates of initial symptoms might not be precise in some patients. In addition, this was a retrospective study that examined patients treated between 2010 and 2019. Meanwhile, many advances in therapeutic strategies have been made, including generalization of awake surgery, assistance with intraoperative MRI or fluorescence guidance using 5-aminolevulinic acid, the introduction of BEV, and the development of novel therapeutic modalities such as tumor-treating fields.[2] These advances in treatment options can diminish or expand the advantages of early surgical intervention.

## CONCLUSION

Early diagnosis within 2 weeks and early surgical intervention within 3 weeks from the initial symptom are associated with improved patient survival. We believe that constructing social and medical networks to facilitate early GBM treatment will be beneficial for patients with GBM.

### Funding

This study did not receive any funding or financial support.

### Disclosures

The authors have no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article. Dr Ichimura reports grants from Chugai Pharmaceutical Co., Ltd., Eisai Co., Ltd., and Daiichi Sankyo Co., Ltd., outside the submitted work. Dr Narita reports grants from Japan Agency for Medical Research and Development, Chugai Pharmaceutical Co., MSD, Eisai, Toshiba, SBI pharma, Glaxo, Abbive, Ono, Stella-pharma, Ohtuka, Meiji-seika, and Daiichi-Sankyo, outside the submitted work. Dr Igaki has research grants from Elekta, CICS, and HekaBio.

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***Supplemental digital content*** *is available for this article at neurosurgery-online.com.*

**Supplemental Digital Content 1. Materials and Methods.** Details of materials and methods used for molecular analysis.

**Supplemental Digital Content 2. Figure.** Number of patients with perioperative KPS ≤ 60 and ≥ 70 in the early and late diagnosis/surgery groups. The patients in the early or late diagnosis groups received radiological diagnoses of brain tumors within 14 or 15 days after the initial symptom development. Patients in the early or late surgery groups received surgical intervention within 21 or 36 days after the initial symptom development.

**Supplemental Digital Content 3. Figure.** Number of patients with perioperative KPS ≤ 80 and ≥ 90 in the early and late diagnosis/surgery groups. The patients in the early or late diagnosis groups received radiological diagnoses of brain tumors within 14 or 15 days after the initial symptom development. Patients in the early or late surgery groups received surgical intervention within 21 or 36 days after the initial symptom development.

**Supplemental Digital Content 4. Figure.** Kaplan-Meier curves of progression-free survival (PFS) and overall survival (OS). The extent of tumor resection (EOR) was classified as high (total or subtotal) or low (partial or biopsy). The median PFS of the patients with high and low EOR was 8.4 and 12.2 months ($P = .0015$). The median OS of the patients with high and low EOR was 16.8 and 28.8 months ($P < .0001$).

**Supplemental Digital Content 5. Figure.** Kaplan-Meier curve of progression-free survival (PFS) in patients who have not received adjuvant chemotherapy with bevacizumab as a first line treatment (n = 122). The patients in the early, intermediate, and late surgery groups received surgical intervention within 21 days (0-3 weeks), between 22 and 35 days (4-5 weeks), or after 36 days (after 6 weeks) from the initial symptom development. The median PFS of the early, intermediate, and late surgery group was 9.7, 12.8, and 8.2 months, respectively ($P = .069$).

## COMMENT

The authors present a study in which they determined that early diagnosis within 2 weeks and surgical intervention within 3 weeks from symptom onset are associated with improved patient survival in glioblastoma. The authors are to be commended for this important finding that underscores the significance of early treatment to the clinical outcomes of GBM patients. Our health care system needs to do everything it can to facilitate the early diagnosis and treatment of GBM patients.

**Manish Aghi**
*San Francisco, California, USA*