The Clinical Characteristics and Outcomes of Incidentally Discovered Glioblastoma

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Abstract

Objective

With an increase in the number of imaging examinations and the development of imaging technology, a small number of glioblastomas (GBMs) are identified by incidental radiological images. These incidentally discovered glioblastomas (iGBMs) are rare, and their clinical features are not well understood. Here, we investigated the clinical characteristics and outcomes of iGBM.

Methods

Data of newly diagnosed iGBM patients who were treated at our institution between August 2005 and October 2019 were reviewed. An iGBM was defined as a GBM without a focal sign, discovered on radiological images obtained for reasons unrelated to the tumor. Kaplan-Meier analysis was performed to calculate progression-free survival (PFS) and overall survival (OS).

Results

Of 234 patients with newly diagnosed GBM, four (1.7%) were classified as having iGBM. Health screening was the most common reason for tumor discovery (75.0%). The preoperative Karnofsky performance status score was 100 in three patients. Tumors were found on the right side in three cases. The mean volume of preoperative enhanced tumor lesion was 16.8 cm$^3$. The median duration from confirmation of an enhanced lesion to surgery was 13.5 days. In all cases, either total (100%) or subtotal (95–99%) resections were achieved. The median PFS and OS were 11.5 and 20.0 months, respectively.

Conclusions

The iGBMs were often small and in the right non-eloquent area, and the patients had good performance status. We found that timely therapeutic intervention provided iGBM patients with favorable outcomes. This report suggests that early detection of GBM may lead to a better prognosis.

Introduction

With increase in the number of imaging examinations and the development of imaging technology, incidental findings of intracranial neoplastic lesions have become more frequent in clinical situations. According to a systematic review of incidental brain findings on magnetic resonance imaging (MRI), the incidence of incidental neoplastic findings on head MRI, mainly meningioma, pituitary adenoma, and lower-grade glioma, was estimated to be 0.70% [1, 2]. In the past decade, the epidemiology and characteristics of incidental low-grade gliomas have been investigated. Incidental lower-grade gliomas account for 3.8–17.2% of all lower-grade gliomas [3–6]. A lower-grade glioma is reported to grow slowly
but steadily with 3.5 mm/year diametric expansion [3] or 3.9 cm³/year volumetric increase [6]. The prognosis of incidental lower-grade glioma patients is better than that of symptomatic low-grade glioma patients, even when comparing complete resection groups [5]. In contrast to lower-grade gliomas, no study has investigated incidental high-grade glioma or glioblastoma. Therefore, their clinical and biological characteristics are poorly understood.

Glioblastoma (GBM) is the most life-threatening malignant brain tumor and is categorized as WHO grade IV. Even with the best treatment with maximal safe surgical resection following chemoradiotherapy with temozolomide, the median overall survival of GBM patients does not reach two years [7]. The representative prognostic factors of GBM patients include age, Karnofsky performance score (KPS), molecular diagnosis including isocitrate dehydrogenase 1 and 2 (IDH1/2) mutations and O-6-methylguanine deoxyribonucleic acid methyltransferase (MGMT) promoter methylation status, and the extent of initial surgical resection [8–14]. Additionally, a small preoperative contrast-enhanced tumor on imaging is an independent favorable prognostic factor [15]. These results indicate that early diagnosis with younger age, better performance status, and small tumor size may contribute to better outcomes in GBM patients.

This study retrospectively reviewed and investigated incidentally discovered GBM (iGBM) cases to determine their biological characteristics and clinical outcomes.

Methods

Patient Selection

This study was designed as a single-center retrospective analysis of a consecutive series of patients with GBM. First, adult GBM patients (age ≥ 18 years) who were newly diagnosed and treated at our institution between August 2005 and October 2019 were identified. The patients had at least six months of postoperative follow-up. Patient data, including age, sex, clinical history, presurgical physical assessment, radiological images, surgical reports, and postsurgical clinical courses, were reviewed. Second, patients with iGBM were included in the study. The iGBM was defined as GBM, which was discovered by radiological images performed for reasons unrelated to the tumor, such as general clinical check-ups or unspecific headaches, which started to be treated within 6 months from the diagnosis. Patients who initially presented with headaches with any sign of increased intracranial pressure, such as nausea, vomiting, and any cerebral nerve symptoms, were excluded. All patients underwent surgical intervention within six months from the initial tumor discovery when gadolinium-enhanced mass lesions were confirmed on head MRI. The pathological diagnosis of glioblastomas was certified based on the 2007 or 2016 WHO classification of tumors of the central nervous system. The molecular profiles of the tumors, including IDH, telomerase reverse transcriptase (TERT), serine/threonine kinase B-RAF (BRAF), H3 histone, family 3A (H3F3A) mutation status, and MGMT promoter methylation status, were extracted from medical records. The extent of resection was determined based on the surgeon's operative notes and on
postoperative imaging studies, classified as either total if 100% of the enhanced lesion was resected, subtotal if 95–99% was resected, partial if < 94% was resected, or a biopsy.

**Molecular Analysis**

Tumor DNA was extracted from frozen tumor tissues for all cases using a DNeasy Blood & Tissue Kit (Qiagen, Tokyo, Japan). The presence of hotspot mutations in \textit{IDH1} (R132) and \textit{IDH2} (R172) was assessed by pyrosequencing, as previously described [16]. Pyrosequencing assays were designed to detect all known mutations in these codons [16]. The two mutation hotspots in the TERT promoter were analyzed in all tumors by Sanger sequencing and/or pyrosequencing, as previously reported [17]. The mutation hotspots at codons 27 and 34 of \textit{H3F3A} and codon 600 of \textit{BRAF} were analyzed by Sanger sequencing and/or pyrosequencing [18]. The methylation status of the \textit{MGMT} promoter was analyzed using bisulfite modification of the tumor genomic DNA, followed by pyrosequencing, as previously described [17]. Methylation was considered positive when its mean level at the 16 CpG sites examined was greater than 16% [17, 19].

**Statistical Analysis**

Overall survival (OS) was defined as the interval between the date of surgery and death. Progression-free survival (PFS) was defined as the interval between the date of surgery and the detection of progression. These times were calculated using the Kaplan-Meier method using GraphPad Prism 9 (GraphPad Software Inc., La Jolla, California, USA).

**Ethics Approval**

This study was conducted retrospectively using data obtained for clinical purposes. This study was approved by the Internal Review Board of the National Cancer Center (approval number: 2004-066).

**Result**

**Patient Demographics**

A total of 234 newly diagnosed GBM patients were treated at our institution between August 2005 and October 2019. Among them, four (1.7%) were classified as having iGBM. The clinical characteristics of the four patients with iGBM are summarized in Table 1. The selected patients included three men and one woman, and their median age at the time of tumor discovery was 59.5 years old (range, 38–66 years). Health screening was the most common reason for tumor discovery (75.0%, n=3), followed by nonspecific headaches (25.0%, n=1). The tumors were first detected as enhanced lesions in patients 1, 2,
and 3 and non-enhanced lesions in patient 4 (Fig. 1). Patient 4 was tightly followed by MRI and underwent surgical intervention when the tumor emerged as an enhanced lesion. The median duration from confirmation of an enhanced lesion to surgery was 13.5 days (range, 4–19 days). The preoperative KPS score was 100 in three patients (75.0%) and 90 in one patient (25.0%). Before surgery, patient 1 experienced minor left hemiparesis.

### Table 1
Characteristics of patients with iGBM

| Patient No. | Age (yrs), sex | Mode of discovery | Diagnosis                        | Duration from confirmed enhanced lesion to surgery | Preop KPS |
|-------------|----------------|-------------------|----------------------------------|---------------------------------------------------|-----------|
| 1           | 62, F          | Health check-up   | Glioblastoma, IDH-wild           | 4 days                                            | 90        |
| 2           | 57, M          | Health check-up   | Glioblastoma, IDH-wild           | 19 days                                           | 100       |
| 3           | 38, M          | Health check-up   | Glioblastoma, IDH-wild           | 9 days                                            | 100       |
| 4           | 66, M          | Headache screening| Glioblastoma, IDH-wild           | 18 days                                           | 100       |

KPS = Karnofsky performance score

### Tumor Characteristics

The tumor characteristics and representative images are summarized in Table 2 and Figure 1. All tumors showed ring-enhanced lesions. The most common tumor location was the temporal lobe (50.0%, n=2), followed by the parietal lobe (25.0%, n=1) and frontal lobe (25.0%, n=1). Tumors were found on the right side in three cases (75.0%). The mean volume of preoperative enhanced tumor lesion was 16.8 cm$^3$ (range, 2.2–23.6 cm$^3$).
### Table 2
Characteristics of iGBM and the clinical outcomes

| Patient | Side | Tumor location | Preop tumor volume | Extent of resection | Postop KPS | PFS from surgery | OS from surgery | Survival |
|---------|------|----------------|--------------------|---------------------|------------|------------------|----------------|----------|
| 1       | Right | Parietal lobe  | 22.6 cm³           | 100%, total resection | 90         | 3 months        | 17 months       | Dead     |
| 2       | Right | Temporal lobe  | 23.6 cm³           | 100%, total resection | 90         | 13 months       | 23 months       | Dead     |
| 3       | Right | Temporal lobe  | 19.0 cm³           | 95%, Subtotal total resection | 90         | 21 months       | 34 months       | Alive    |
| 4       | Left  | Frontal lobe   | 2.2 cm³            | 95%, Subtotal total resection | 90         | 10 months       | 16 months       | Dead     |

KPS = Karnofsky performance score, PFS = Progression-free survival, OS = Overall survival

### Surgical Results, Molecular Diagnoses, and Adjuvant Therapies

Three patients underwent surgery under general anesthesia, and one underwent awake surgery. Total resection of an enhancing lesion was achieved in two cases (50.0%) and subtotal resection (95–99% removal) in two cases (50.0%). No postoperative mortality was observed. The median postoperative hospital stay was 18.0 days (range, 8–58 days). All patients were discharged with a KPS score of 90. Histopathological diagnosis of GBM was confirmed in all cases. Molecular genetic examination revealed that no tumor had IDH1/2 mutation, two tumors (50.0%) had TERT promoter mutation, one tumor (25.0%) had BRAF mutation, and no tumor had H3F3A mutation; all tumors had low MGMT promoter methylation status. Following tumor resection, temozolomide (75 mg/m² for seven days per week during radiotherapy, followed by 150–200 mg/m² during six cycles of adjuvant therapy) was the most selected adjuvant chemotherapeutic agent and was used in three patients (75.0%), and nimustine hydrochloride (100 mg/body) was used in one patient (25.0%). Local brain radiotherapy (60 Gy in 30 fractions) was performed in all patients. No severe adverse effects were documented due to chemoradiotherapy.

### Outcomes
All patients in this study had disease progression, and three patients died at the last follow-up. The median PFS and OS were 11.5 and 20.0 months, respectively (Fig. 2A and B).

**Discussion**

In this study, we demonstrate the clinical and genetic features of iGBMs. They are frequently located in the right hemisphere and in non-eloquent areas and received total or subtotal resection. Although iGBM exhibits unfavorable molecular characteristics, such as IDH-wildtype and MGMT promoter hypomethylation status, it demonstrated favorable clinical outcomes.

The initial signs and symptoms of glioblastoma depend on the location and size of the tumor. Headache (57.3%) was the most common presenting symptom, followed by cognitive changes (38.8%), language deficits (36.2%), and motor deficits (35.9%) [20]. Because there have been no reports of asymptomatic GBM patients, the proportion of asymptomatic patients at the initial presentation in the entire GBM population is still unknown.

This study revealed that iGBM accounted for 1.7% of patients with GBM during the examined period. The incidence may vary among countries and regions depending on the prevalence, resolution, and number of brain imaging performed annually. The brain screening system, familiarly named the “Brain Dock” system, is commercially and commonly available in Japan. This system was first established in 1988 to salvage non-symptomatic intracranial vascular diseases, including ischemic diseases and unruptured cerebral aneurysms [21], which costs approximately 500 US dollars. This system also contributes to the detection of asymptomatic brain tumors, including meningiomas, pituitary adenomas, and lower-grade gliomas. Based on these social and medical backgrounds, the incidence of iGBM in Japan is higher than the world average.

The laterality and size of the iGBM were unique. The iGBM is exceptionally lean on the right side. Generally, the laterality of GBM is symmetrical as 46–47% of them are right-sided, 42–48% are left-sided, and 6–12% are bilateral or at the central neuroaxis [20, 22]. The tendency of right-sided iGBM is attributed to a functional difference in the left and right brain hemisphere; in 95–99% of right-handed individuals and 70% of left-handed individuals, the left cerebral hemisphere is the dominant hemisphere that controls language [23]. Therefore, tumors in the right hemisphere were less likely to be symptomatic than those on the left side. In addition, the small volume (16.8 cm$^3$) of iGBM, compared to the mean GBM volume of 33.2 cm$^3$ in a previous study [24], must contribute to the asymptomatic character of iGBM. On the other hand, the tumor location of iGBMs was similar to that of the GBM population; iGBM were found in the temporal, frontal, and parietal lobes, and according to past research, GBM is located at the frontal lobe in 43%, and the temporal lobe in 28% [25]. Furthermore, the gender and age of iGBM are similar to those of general GBM; the incidence of GBM is 1.3–1.6 higher in males than in females [22, 26–28] and the median age of diagnosis is 63–64 years old [22, 26, 27]. The molecular status of iGBM (100% of IDH wild
type and 50.0% of TERT promoter mutation) almost agrees with the previous report of 10% IDH1/2 mutations and 74.2% TERT promoter mutation in GBM [28].

In this study, all iGBMs were removed via either total or subtotal resection. In general, gross or 100% total resection of GBM is only achieved in 20–43% of cases [20, 22]. This favorable result might be due to the surgically optimal characteristics of iGBM, such as small volume and non-dominant hemisphere. Moreover, good perioperative physical and neurological conditions of iGBM patients contribute to tolerance to general anesthesia and complete chemoradiation therapy. As a result, the median PFS and OS of iGBM patients (11.5 and 20.0 months, respectively) were better than previous reports (6.3–7.1 months and 10.1–15.2 months) [9, 10, 13, 15, 27]. It is worth noting that the general patient demographics and molecular features of iGBM were not different from those of general GBM. In summary, iGBM patients have a great advantage in receiving timely therapeutic intervention when they are asymptomatic or before developing severe neurological deterioration.

The main limitation of this study is the small sample size due to the rarity of iGBM; therefore, our results need to be carefully interpreted. The majority of iGBM cases were identified by health screening. Patients who can afford to undergo health screening are considerably wealthy and health-conscious, thus having better physical conditions and broader treatment options. These factors may affect the clinical outcome of iGBMs.

**Conclusion**

We present a series of iGBM features, including clinical, radiological, molecular, and outcome data. The unique characteristics of iGBM provide a greater chance of tumor resection and consecutive chemoradiation therapy, which leads to a better prognosis.

The pathophysiology of GBM involves the rapid growth of the tumor and progression of neurological symptoms. Although finding a tumor by health screening is economically challenging, this report suggests that the prognosis of GBM may improve if it is diagnosed when the tumor is small and the symptoms are mild. Patients must consult a neurosurgeon or neurologist immediately when they become aware of neurological symptoms such as paralysis and aphasia.

**Declarations**

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Author Contribution:

Conceptualization: Yoshitaka Narita; Methodology: Daisuke Kawauchi, Makoto Ohno, Yoshitaka Narita; Formal analysis and investigation: Daisuke Kawauchi, Makoto Ohno, Mai Honda-Kitahara, Koichi Ichimura; Writing - original draft preparation: Daisuke Kawauchi; Writing - review and editing: Makoto Ohno, Yoshitaka Narita; Funding acquisition: Yoshitaka Narita; Resources: Yoshitaka Narita; Supervision:
Makoto Ohno, Yasuji Miyakita, Masamichi Takahashi, Shunsuke Yanagisawa, Yukie Tamura, Miyu Kikuchi, Koichi Ichimura, Yoshitaka Narita.

Data Availability: The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

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Previous Presentations: Any portion of the paper has not been presented previously.

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Figures

**Figure 1**

Axial gadolinium-enhanced T1-weighted MR images obtained in iGBM patients.
Figure 2

Kaplan-Meier curves for PFS (A) and OS (B) in patients with incidental GBM.