Diagnosis and management of multiple high-grade gliomas: a retrospective study

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Abstract

**Background:** Multiple high-grade gliomas (M-HGG) are uncommon lesions in the central nervous system. The management is controversial and the prognosis remains unfavorable. The aim of this study is to identify the characteristics of M-HGG and explore more appropriate therapeutic strategies for patients.

**Methods:** A retrospective study was performed on 15 patients who were treated with M-HGG between August 2016 and March 2018 in our hospital. Clinical data including age, sex, Karnofsky Performance Scale (KPS) scores, number and location of lesions, surgical approach, pathology, adjuvant therapy (radio or chemotherapy) and prognosis were collected.

**Results:** The most frequent position of tumors was temporal lobe, followed by frontal and occipital lobe. Patients who underwent surgical removal (gross total resection or subtotal resection) showed longer survival time than that in biopsy group ($p < 0.05$). The index of Ki-67 was higher ($36.11 \pm 1.8$ vs $22.33 \pm 2.1$, $p < 0.05$) and the KPS score was lower ($60.00 \pm 2.7$ vs $82.86 \pm 2.9$, $p < 0.05$) in death group than that in survival group. Two patients presented with different pathological grades: GBM (WHO IV), anaplastic astrocytoma (WHO III). Four patients presenting with methylation of genes of O-6-methylguanine DNA methyltransferase (MGMT) were still alive. No IDH1 mutation was detected in all cases. Eight patients died during follow-up, and the average survival period was 11.2 months. The survival time of living patients was more than 15.9 months.

**Conclusions:** Surgical removal of dominant tumors of M-GBM is recommended, and stereotactic biopsy can achieve pathologic diagnosis if surgical removal is inaccessible. Comprehensive analysis of the clinical features and molecular pathology of multiple gliomas is helpful to find more effective diagnostic and therapeutic strategies.

**Background**

As uncommon lesions, multiple gliomas account for 0.5%-20% of all gliomas and are frequently mistaken as metastatic disease [1]. The most frequent histological subtype found in multiple gliomas is glioblastoma (GBM). The multiple high-grade gliomas (M-HGG) could not be eliminated simply by operation, and it is getting even harder to control if some deep structures, like thalamus and pineal.
region, are involved. Therefore, multiple GBM (M-GBM) patients usually have a poorer prognosis than those with solitary GBM [2]. Several studies have shown that patients with newly diagnosed M-GBM had a lower median survival (2-10 months) than those with solitary GBM [2-4].

Due to its special features such as the invasive nature and resistance to radiotherapy/chemotherapy, the M-HGG patients usually have a poor prognosis [4]. The strategy of surgery followed by concomitant radiotherapy with temozolomide-based chemotherapy has been regarded as the standard treatment of M-HGG. Unfortunately, the therapy is still incapable of inhibiting the disease from deterioration and prolonging patients’ survival time [5]. In addition, it remains unclear whether M-HGG has unique genetic and epigenetic characteristics that could be used as targets for future intervention.

In this study, we systematically analyzed the clinical presentations and molecular pathology in M-HGG patients in order to explore more effective diagnostic and therapeutic strategies.

Methods

Patient population

Retrospective data were collected from 15 patients who suffered from M-HGG at Fudan University Shanghai Cancer Center between August 2016 and March 2018. The clinical details, including age, sex, Karnofsky Performance Scale (KPS) scores, number and location of lesions, surgical approach, pathological identity, adjuvant therapy (radiotherapy or chemotherapy), and prognosis were shown in Tables 1 and 2.

All patients had brain computed tomography (CT) and magnetic resonance imaging/spectrum (MRI/MRS) examinations before surgery (Fig.1). The possibility of cerebral metastases would be excluded by a joint detection of whole-body positron-emission tomography (PET) and/or digestive endoscopic studies. The ultimate diagnosis was based on histological outcomes by stereotactic biopsy or removal of at least one lesion in surgery.

Biopsy procedure
The stereotactic biopsy process was performed as follows. The corresponding images of pre-operative brain MRI (3.0T) were imported into a navigational system (StealthStation S7, MedtronicInc, Minneapolis, MN, USA). The optimum entry point and trajectory to the ideal target was set up on navigational system. Then head immobilization was achieved via a mayfield clamp after anesthesia. The target position was conformed by a passive planar blunt probe. A burr hole was drilled and the navigus instrument holder base was positioned. The target was confirmed again followed by the distance to the target. Then the biopsy needle was inserted into the predefined depth. Multiple biopsies were taken from different orientations and depths along the needle track. Finally, the biopsy needle and the navigus base were removed, and the wound was sutured.

Statistical analysis

Data were analyzed with SPSS 19.0 software (IBM SPSS Inc, Chicago, IL). The outcomes were compared using t-test or Logrank test for trend. Items were considered statistically significant if the probability value was < 0.05.

Results

This research involved 15 patients (nine males and six females). The age of the patients ranged from 39 to 75 years (median 53 years). The pre-operative KPS scores were 50 to 90 (median 70.7). Follow-up period ranged from 6 to 24 months. All tumors were located at supratentorial compartment (ten in the left and five in the right). The most frequent position of the tumors was temporal lobe, followed by frontal and occipital lobe (Table 1).

Patients who underwent surgical removal (gross total resection or subtotal resection) showed longer survival time than those in biopsy group ($p = 0.028$) (Fig.2). All patients received standard radiotherapy combined with temozolomide and the following cyclic treatment with adjuvant temozolomide. Eight patients died during the follow-up, and the average survival period was 11.2 months. The survival time of living patients was more than 15.9 months (Table 1).

Pathologically, all patients were classified as M-GBM, and two patients presented with different
pathological grades: glioblastoma (WHO IV) and anaplastic astrocytoma (WHO III). The index of Ki-67 was higher (36.11 ± 1.8 vs 22.33 ± 2.1, p < 0.05) and the KPS score was lower (60.00 ± 2.7 vs 82.86 ± 2.9, p < 0.05) in death group than that in survival group (Fig.3). Immunohistochemically, four patients with methylation of O-6-methylguanine DNA methyltransferase (MGMT) gene were still alive. All tumor cells showed immunoreactivity toward P53. No IDH1 mutation was observed in all cases (Table 2).

Discussion
The treatment of M-HGG has become a tricky problem due to its character of invasion and migration [6]. Researchers have pointed out that M-HGG may result from tumor growth or dissemination via established pathway [3,6]. M-HGG patients usually have a poor prognosis due to the lack of effective treatment options [7,8]. In order to explore more appropriate therapeutic strategies, we conducted a comprehensive analysis of clinical features and molecular pathology in 15 M-HGG patients.

There was no difference in age between patients with single glioma and multiple gliomas in previous study [9]. In our study, the age of patients with M-HGG ranged from 39 to 75 years. Other researcher suggested no sex difference in M-HGG patients [10]. However, it seems that males have a slightly higher probability of M-GBM than females (9/6) in our study.

M-GBM tumors usually exist in the supratentorial compartment, while infratentorial tumors have also been reported as unusual cases [11,12]. Besides, we found that multiple gliomas could be histologically same or different among multiple intracranial tumors. GBM was the most common histological subtype in multiple gliomas, whereas low-grade gliomas (LGG) may exist in multifocal form sometimes [13,14]. It has been postulated that patients with secondary malignancies or a family history of cancer might have a higher incidence of multifocal gliomas [10], and that might be associated with gene mutations of germline P53 [15]. Herein, seven patients had a family history of cancer, four of them had short survival period and died during the follow-up. Moreover, tumor cells were immunoreactive for P53 in all cases. Of course, this result should be further verified in larger samples.
It has been reported that the status of IDH1 mutation has a correlation with survival improvement and the sign of invasion on MRI [16]. However, patients with multiple gliomas had a relatively low level of IDH1 mutation [17]. In our research, no IDH1 mutation was observed. Hence, the conclusive results about the role of IDH1 mutation in M-HGGs should be further investigated.

Numerous studies have documented that GBM patients with the methylation of MGMT promoter may benefit from the treatment of temozolomide [18,19]. In our study, four patients showed the methylation of MGMT promoter and all of them accepted the treatment of temozolomide combined with radiotherapy after surgery. They are still alive and one patient has achieved a survival time of 20 months. Therefore, M-HGG patients with the methylation of MGMT promoter may benefit from temozolomide treatment.

Other factors such as Ki-67, age, tumor location, and KPS scores were also related to the prognosis of M-GBM patients. According to our research, patients with higher Ki-67 had significantly shorter survival durations, which suggested that Ki-67 could be considered as a potential indicator for M-HGG prognosis. Furthermore, the older patients with lower KPS scores (less than 60) and deeper structures involved on images had poor prognosis.

Multiple gliomas were classified as multicentric or multifocal gliomas based on pathological and radiological characteristics [3,6]. Multicentric gliomas usually occur in different hemispheres or lobes, while multifocal gliomas are defined with the evidence of spread via blood vessels, cerebrospinal channels or commissual pathways [8]. However, Di Carlo et al [20] found that there were no statistically significant differences between multifocal and multicentric HGGs in gender, lesion location, histological type and surgical treatment. And the gliomas (including astrocytic type, oligodendrocytic type and mixed type) have a similar treatment strategy [21, 22]. Thus, the clinical significance of further identifying differences between multicentric and multifocal gliomas is anticipated.
The surgical management of M-GBM is equally controversial. Because of the low risk of hemorrhage or neurologic deficit, the stereotactic biopsy has become a more conservative method than surgery in precise diagnosis of M-GBM [1]. However, other scholars prefer resecting the multifocal/multicentric tumors to improve overall survival [2]. Aggressive resection achieved an overall survival time of 9.7 months for the multifocal/multicentric group [2]. In another study, the average survival time caused by surgical resection and biopsy was 9.5 and 2.8 months respectively [14]. Some researches pointed out that surgical resection (gross total resection or subtotal resection) was an independent predictor of improved outcome [20]. We found the consistent result that the patients who underwent surgical removal (gross total resection or subtotal resection) had longer survival than those in biopsy group (p < 0.05). In our research, eight patients died during follow-up, and the average survival period was 11.2 months. The survival time of living patients was more than 15.9 months.

Radiotherapy is indispensable in the treatment of multiple gliomas. 3D conformal radiotherapy can avoid toxicity in the treatment of multiple gliomas, which has an advantage over whole-brain radiotherapy [7]. Some investigators also approve the therapeutic effect of SRS toward small, inaccessible, residual, or recurrent focuses after whole-brain radiotherapy [23, 24]. However, it must be noted that the option of radiotherapy depends on the clinical manifestation including the number of lesions, overlapping fields and intraventricular or meningeal-subarachnoid spread [19].

Currently there are no effective targeted drugs for M-GBM clinically. Temozolomide, as standard adjuvant chemotherapy, should be applied to various M-HGG. Bevacizumab, an intravenous monoclonal antibody against the vascular endothelial growth factor, has been recommended as an alternative in patients with recurrence GBM [25]. In the present study, three patients who received chemotherapy of temozolomide and bevacizumab had achieved an average survival time of 16.7 months. Although many factors can affect the survival time, the combination of temozolomide and bevacizumab is expected to be a novel treatment for M-GBM.

Conclusions
M-HGG is pathologically rare and presents with a variety of clinical and imaging patterns. Its final
diagnosis depends on the pathology by surgery (resection or biopsy). Surgical removal of dominant tumors of M-HGG is recommended, and if surgical removal is inaccessible, stereotactic biopsy can achieve pathologic diagnosis. Research that comprehensive analysis of clinical features and genetic status of M-HGG is called on at multi-center with larger sample capacity.

Abbreviations
M-HGG: Multiple high-grade gliomas; KPS: Karnofsky Performance Scale; WHO: World Health Organization; GBM: glioblastoma; MGMT: O-6-methylguanine DNA methyltransferase; IDH: isocitrate dehydrogenase; PTEN: phosphatase and tensin homolog; DNA: deoxyribonucleic acid; WHO: World Health Organization; M-GBM: multiple glioblastoma; CT: computed tomography; MRI/MRS: magnetic resonance imaging/spectrum; PET: positron emission tomography; BEV: bevacizumab; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery

Declarations
Ethics approval and consent to participate

The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by the Ethics Committee of Fudan University Shanghai Cancer Center. Because of the retrospective nature of the study, patient consent for inclusion was waived.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

All authors approved the consent for manuscript publication.

Availability of data and materials

The data of this study were available from the corresponding author on reasonable request.

Authors’ Contributions
CYQ carried out conception and performed the operations. GY and ZH carried out acquisition of data, design, analysis and interpretation of data, drafting the article and performed some of the operations. HB was responsible for the data acquisition; data analysis; statistical analysis. CYQ and CX were responsible for critical revision of the draft, and the final approval of the version to be published.

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Tables
Table 1 Clinical features of the patients are summarized.

| Number | Age (ranges) | KPS | Location and number of tumors (numbers) | Surgery | RT | Chemoth | Follow-up | Prognosis |
|--------|--------------|-----|----------------------------------------|---------|----|---------|-----------|-----------|
| 1      | 45-49        | 50  | Left supratentorial: frontal lobe, parietal lobe, occipital lobe (3) | Remove one tumor | WBRT | Temozolomide | 6 months | Death     |
| 2      | 45-49        | 80  | Left supratentorial: temporal lobe, occipital lobe (2) | Gross total resection | WBRT | Temozolomide | 12 months | Alive     |
| 3      | 50-54        | 90  | Left supratentorial: thalamus, occipital lobe (2) | Stereotactic biopsy | WBRT | Temozolomide | 20 months | Alive     |
| 4      | 75-79        | 60  | Left supratentorial: frontal lobe (2) | Remove one tumor | SRS | Temozolomide | 9 months | Death     |
|   | 40-44 | Left supratentorial: thalamus, temporal lobe (2) | Stereotactic biopsy | WBRT | Temozolomide | 6 months | Death |
|---|---|---|---|---|---|---|
| 5 | 60 | Right supratentorial: temporal lobe, callosum (2) | Stereotactic biopsy | WBRT | Temozolomide | 5 months | Death |
| 6 | 50 | Right supratentorial: frontal lobe, parietal-occipital lobe, callosum (3) | Remove two tumors | WBRT | Temozolomide | 10 months | Alive |
| 7 | 70 | Right supratentorial: temporal lobe (2) | Gross total resection | SRS | Temozolomide + BEV | 24 months | Alive |
| 8 | 80 | Left supratentorial: temporal lobe (2) | Gross total resection | SRS | Temozolomide | 12 months | Alive |
| 9 | 90 | Left supratentorial: temporal lobe (2) | Stereotactic biopsy | WBRT | Temozolomide | 6 months | Death |
| 10 | 60 | Left supratentorial: frontal lobe, callosum (2) | Remove one tumor | WBRT | Temozolomide | 9 months | Death |
| 11 | 70 | Left supratentorial: temporal lobe (3) | Gross total resection | SRS | Temozolomide | 15 months | Alive |
| 12 | 90 | Right supratentorial: temporal lobe (2) | Stereotactic biopsy and remove temporal tumor | WBRT | Temozolomide + BEV | 18 months | Alive |
| 13 | 80 | Right supratentorial: thalamus, temporal lobe (2) | Stereotactic biopsy | WBRT | Temozolomide + BEV | 8 months | Death |
| 14 | 70 | Left supratentorial: thalamus, temporal lobe (2) | Stereotactic biopsy | WBRT | Temozolomide | 6 months | Death |
M: male; F: female; KPS: Karnofsky Performance Scale; N: no; RT: radiotherapy; WBRT: whole brain radiotherapy; SRS: stereotactic radiosurgery; BEV: bevacizumab

Table 2 The histopathology of M-GBM was summarized

| Number | Pathology | MGMT-methylated | IDH1-mutated | P53 | PTEN | ATRX | Ki-67 | Gross total resection | WBRT | Temozolomide | RT | Death |
|--------|-----------|-----------------|--------------|-----|------|------|------|----------------------|------|-------------|----|--------|
| 1      | Glioblastoma (WHO IV) | - | - | + | - | - | + | 40% |
| 2      | Glioblastoma (WHO IV) | - | - | + | - | + | 25% |
|        | Glioblastoma (WHO IV) | - | - | + | - | + | 30% |
| 3      | Glioblastoma (WHO IV) | + | - | + | - | + | 20% |
|        | Anaplastic astrocytoma (WHO III) | + | - | + | - | + | 8% |
| 4      | Glioblastoma (WHO IV) | - | - | +/- | - | + | 40% |
| 5      | Glioblastoma (WHO IV) | - | - | +/- | - | + | 25% |
| 6      | Glioblastoma (WHO IV) | - | - | + | - | + | 35% |
|   | Glioblastoma (WHO IV) |   |   |   |   |   |   |
|---|----------------------|---|---|---|---|---|---|
| 7 | +                    | - | +/- | - | + | 20% |
| 8 | -                    | - | +/- | - | + | 25% |
| 9 | +                    | - | +/- | - | + | 30% |
|   | +                    | - | +/- | - | + | 25% |
| 10 | -                    | - | +/- | - | + | 40% |
| 11 | -                    | - | +  | - | + | 35% |
| 12 | -                    | - | +/- | - | + | 20% |
|   | -                    | - | +  | - | + | 30% |
| 13 | -                    | - | +/- | - | + | 25% |
|   | +                    | - | +/- | - | + | 10% |
| 14 | -                    | - | +/- | - | + | 30% |
|   | -                    | - | +/- | - | + | 40% |
| 15 | -                    | - | +  | - | + | 40% |
MGMT: O-6-methylguanine DNA methyltransferase; IDH1: isocitrate dehydrogenase 1; PTEN: phosphatase and tensin homolog

Figures

Figure 1

(A-D) Brain MRI including axial and sagittal images showed M-HGG.

Figure 2

Patients in surgical removal group (gross total resection or subtotal resection) showed longer survival time than that in biopsy group (p < 0.05).

Figure 3

(A) Index of Ki-67 was higher (p < 0.05) and (B) the KPS score was lower (p < 0.05) in death group.