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# Postoperative intensity-modulated radiotherapy and chemotherapy in patients with high-grade glioma: analysis of efficacy and prognostic factors

**H. Zhu[1,2] and J. Luo[3*]**

[1]*Department of Radiation Oncology, Tongren Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, 200336, China*

[2]*Department of Radiation Oncology, Minhang Branch of Cancer Hospital of Fudan University, Shanghai, 200240, China*

[3]*Department of Radiotherapy, The Affiliated Changzhou Second People's Hospital of Nanjing Medical University, Changzhou Medical Center, Nanjing Medical University, Changzhou, 213003, China*

► ***Original article***

***Corresponding author:***
*Judong, Luo, Ph.D.,*
***E-mail:*** *judongluo@163.com*

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## ABSTRACT

***Background***: To determine the treatment efficacy and prognostic factors for high-grade glioma (HGG) patients treated with postoperative intensity-modulated radiotherapy (IMRT). ***Materials and Methods:*** An analysis of 86 HGG patients who underwent surgery, radiotherapy (total dose: 54-60 Gy), and chemotherapy was performed retrospectively. The primary endpoint was Overall survival (OS), while the secondary endpoint was progression-free survival (PFS). Patient factors, tumor characteristics, and treatments were examined for their prognostic value. ***Results:*** Among the enrolled patients, there were 22 patients of grade III and 64 patients of grade IV. At the end of the study, 48 cases had died, and 66 cases had relapsed. The median OS was 24 months, while the median PFS was just 9 months. The mean OS of patients with grade III and IV glioma was 41 months and 16 months, respectively. Patients had relative survival rates of 73.2%, 46.6%, and 27.0% at 1, 2, and 5 years. The most common type of tumor recurrence was relapse within the radiation field. Univariate analysis indicated that sex, age, Karnofsky Performance Scale score (KPS), Pathological grade, tumor location, surgical approach, and adjuvant chemotherapy cycles were predictive factors for OS ($P< 0.05$). In contrast, sex, age, pathological grade, number of lesions, surgical approach, and adjuvant chemotherapy cycles were predictive factors for PFS ($P < 0.05$). According to multivariate analysis indicated that pathological grade, surgical approach, and adjuvant chemotherapy cycles were associated with longer OS and PFS ($P< 0.05$). ***Conclusions:*** Grade III gliomas, total surgical resection, and adjuvant chemotherapy for more than six cycles were associated with more favorable survival outcomes in this study.

## INTRODUCTION

The World Health Organization (WHO) classifies gliomas into four grades, ranging from low to high malignancy. A high-grade glioma (HGG) is classified as WHO grade III or IV glioma. Glioblastoma (GBM) is adults' most fatal type of primary intracranial tumor. The WHO added molecular typing to histopathological typing for the first time in 2016, establishing a new concept for diagnosing glioma classification in the molecular era [(1)]. Patients with grade III gliomas have an overall survival (OS) time of two to three years, whereas those with grade IV gliomas have an OS time of roughly one year [(2)]. Since the publication by Stupp *et al.*, maximum tumor resection combined with early postoperative radiotherapy and concurrent/adjuvant temozolomide chemotherapy has turned out to be the standard treatment [(3)]. In the past, most large studies used three-dimensional conformal radiotherapy. However, with advancements in radiotherapy technology, intensity-modulated radiotherapy (IMRT) is widely used thanks to its high precision, high-dose delivery, and less damage.

Identifying prognostic factors in neuro-oncology is critical for stratifying patients into relatively homogeneous classes of therapies. Studies have already been conducted on clinical (age, gender, performance status), therapeutic (surgery quality, radiotherapy, chemotherapy), and tumor-specific (location and nature) factors [(4)]. As for patients with GBM, performance status is essential to clinical activity and treatment adherence [(4, 5)]. A study is being conducted to determine the relationship between various age groups and survival in GBM patients. Because of the differences in prognoses



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between age groups, doctors should include age in routine clinical judgments [6, 7]. Gender has been shown in studies to have prognostic value in determining GBM risk [8]. Many studies discuss tumor stage and tumor resection extent as prognostic factors [5, 9].

A meta-analysis looked at the prognostic items for survival in a large, diverse group of patients with gliomas. This study included data from 15 previously published randomized controlled research, totaling 5217 patients. In the multivariable model, women, young, non-glioblastoma type, a better Performance Status, resection, and allocated treatment other than radiotherapy alone were relevant with longer OS and PFS [10].

The precise value of each factor is still debatable. As a result, determining prognosis factors is critical when managing HGG patients to plan and optimize each patient's therapy. Therefore, our retrospective study examined the efficacy and prognostic factors of postoperative IMRT and chemotherapy in patients with HGG in our center.

## MATERIALS AND METHODS

### *Inclusion criteria*

This study retrospectively reviewed the medical database of HGG patients receiving postoperative radiotherapy in the Minhang Branch of Cancer Hospital of Fudan University and Changzhou Second People's Hospital between July 2013 and December 2019. The following were the inclusion requirements: first diagnosis of glioma and pathologically confirmed HGG after surgery; successful completion of postoperative radiotherapy and concurrent chemotherapy; and complete data. Exclusion criteria were failure to complete the course of radiotherapy, diagnosis of other malignant tumors, or missing data. Patient factors (sex, age, Karnofsky Performance Scale [KPS] score, and seizures), tumor characteristics (pathological grade, location, site, diameter, and the number of lesions), and treatments (surgical approach, radiotherapy dose, and adjuvant chemotherapy cycles) were analyzed for their prognostic value for OS and PFS.

### *Surgical treatment*

Most subjects underwent total or partial resection with neuronavigation. A few patients underwent surgical biopsies only. Evaluation of the surgical resection scope was assessed according to surgical records and magnetic resonance imaging (MRI) done before and after brain surgery. Total resection was judged as no residual tumor under the microscope, while partial resection was judged as some residual tumor after the operation.

### *Radiotherapy*

All patients received postoperative radiotherapy with six megavoltage photons (6MV).IMRT technology was implemented by a medical linear accelerator (Varian Clinac iX IGRT, USA). All MRI examinations were conducted by a 3.0 Tesla MRI scanner (Skyra, Siemens, Germany). Based on preoperative and postoperative MRI, the treatment planning system (TPS, Philips pinnacle, Netherlands ) integrated MRI and positioning CT images to delineate the target volume, with reference to the Chinese Guidelines for the Diagnosis and Treatment of Gliomas (2015 version)[2]. The gross tumor volume (GTV) was defined as postoperative visible lesions and areas with abnormal T2/FLAIR signals. We also refer to the postoperative Magnetic Resolution Spectroscopy (MRS) when delineating the GTV. The clinical target volume (CTV) included the GTV plus margin of 1 to 2 cm and was further modified based on anatomy. The planning target volume (PTV-G or PTV-C) involved the modified GTV or CTV plus 0.3 to 0.5 cm margin. The prescribed dose was 54-60 Gy for PTV-G and 50 Gy for PTV-C, and the daily dose was 1.8-2.0 Gy. Radiotherapy was performed once a day, five days a week. Ensure that the isodose line of a minimum of 95% of the prescribed dose covers 100% PTV volume. The total dose was less than 60 Gy in 11 patients due to limited doses to critical organs.

### *Chemotherapy*

We referenced the Stupp protocol and administered oral temozolomide (TMZ, temozolomide Capsules, Tiqing, China) for concurrent chemotherapy (75 mg/m$^2$), followed by adjuvant chemotherapy at an initial dose of 150 mg/m$^2$ and then 200 mg/m$^2$ from the second cycle, for five days in each 28-day cycle [3]. According to the guidelines, patients could receive up to 12 cycles of adjuvant chemotherapy based on patient conditions and tolerance[2]. Therefore, long-term adjuvant chemotherapy was considered in our patients who can tolerate chemotherapy-related side effects and whose conditions continue to improve after temozolomide treatment.

### *Follow-up*

The patients were followed up by reviewing medical records, imaging data, and regular phone calls. Brain MRI was performed 2-3 weeks after the radiotherapy course, then every three months for three years, and at least every half year after that. The primary and secondary endpoint was OS and PFS, respectively. The evaluation criteria of efficacy were response assessment in neuro-oncology (RANO) [11]. Treatment-related toxicities were judged according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). The last follow-up day was May 31, 2021.

### *Statistical analysis*

SPSS statistics software (IBM version 26) was utilized for processing data and generating



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graphs. OS referred to the time from the initial surgery to cancer-related death or last follow-up. PFS was defined as the time from operation until tumor relapse or progression. Patients who died were followed up to obtain complete data, and the data of survivors were censored. A Kaplan-Meier algorithm was utilized for calculating OS and PFS. A univariate analysis was conducted with the log -rank test; a stepwise multivariate analysis was performed using the Cox regression, and the method option was forward logistic regression. Pearson correlation analysis was chosen to evaluate the association between PFS and OS. P-values under 0.05 were deemed statistically significant.

## RESULTS

### *Clinical and Pathological Characteristics*

A total of 86 cases were eligible, including 54 males and 32 females (median age 51 years, 15-73 years); 22 patients had WHO grade Ⅲ HGG, 64 had grade Ⅳ HGG, and 19 patients had seizures before surgery. Before radiotherapy, the KPS score was ≥ 80 for 65 patients and < 80 for 21 patients. Tumors were primarily located in the frontal lobe (n = 32), the temporal and insular lobes (n = 23), the parietal lobe (n = 13), the occipital lobe (n = 7), or other locations (cerebellum and midline structures; n = 11). Other clinical characteristics are shown according to the table (table 1). The midline structures include the corpus callosum, transparent septum, third ventricle, inferior hypothalamus, pineal area, brainstem, fourth ventricle, and cerebellar vermis. In this study, 53 patients received total resection, 30 received partial resection, and 3 underwent biopsy.

### *Survival*

According to the follow-up data, 48 patients died. The median OS was 24.0 months, and the median PFS was 9 months. The median OS was 41 months for patients with grade III HGG and 16 months for those with grade IV HGG. Regarding survival rates for one year, two years, and five years, 73.2%, 46.6%, and 27.0% are recorded.

### *The efficacy and treatment failure*

Sixty-six patients had progressive disease, so the overall relapse rate was 76.7% (66/86). The 1-year relapse rate was 59.3%, and the 2-year relapse rate was 68.6%. In particular, relapse occurred within the radiation field in 56 patients, within the extra-radiation field in 30 patients, and within the radiation field and extra-radiation field in 20 patients. Representation images of one patient with glioblastoma recurrence half a year after radiotherapy were shown in MRI (figure 1).

**Table 1.** Clinical characteristics and univariate analysis of prognostic factors in 86 high-grade glioma patients who underwent postoperative radiotherapy.

| Variables | No | % | Survival Rate (%) | | MST (m) | *P* | MST (m) | *P* |
|---|---|---|---|---|---|---|---|---|
| | | | 12 m | 24 m | OS | | PFS | |
| **Sex** | | | | | | 0.002 | | 0.025 |
| **Male** | 54 | 62.8 | 68.3 | 33.4 | 17 | | 9 | |
| **Female** | 32 | 37.2 | 80.2 | 65.1 | 35 | | 15 | |
| **Age (years)** | | | | | | 0.000 | | 0.000 |
| **≤50** | 42 | 48.8 | 81.2 | 62.1 | 35 | | 15 | |
| **>50** | 44 | 51.2 | 65.0 | 31.8 | 15 | | 8 | |
| **KPS score** | | | | | | 0.004 | | 0.051 |
| **<80** | 21 | 24.4 | 47.2 | 28.3 | 11 | | 4 | |
| **≥80** | 65 | 75.6 | 80.8 | 52.1 | 26 | | 10 | |
| **Seizures** | | | | | | 0.292 | | 0.378 |
| **Yes** | 19 | 22.1 | 82.4 | 54.9 | 26 | | 10 | |
| **No** | 67 | 77.9 | 70.3 | 44.1 | 17 | | 9 | |
| **Pathological grade** | | | | | | 0.004 | | 0.003 |
| **WHO III** | 22 | 25.6 | 90.2 | 73.6 | 41 | | 22 | |
| **WHO IV** | 64 | 74.4 | 66.7 | 35.9 | 16 | | 8 | |
| **Tumor site** | | | | | | 0.756 | | 0.932 |
| **Right** | 45 | 52.3 | 75.9 | 41.9 | 20 | | 10 | |
| **Left** | 32 | 37.2 | 71.8 | 49.8 | 24 | | 9 | |
| **Midline structures** | 9 | 10.5 | 62.5 | 50 | 13 | | 9 | |
| **Tumor diameter (cm)** | | | | | | 0.559 | | 0.519 |
| **≥5 cm** | 52 | 60.5 | 66.2 | 44.2 | 18 | | 10 | |
| **<5 cm** | 34 | 39.5 | 83.3 | 50.7 | 26 | | 9 | |
| **Tumor location** | | | | | | 0.016 | | 0.143 |
| **Frontal lobe** | 32 | 37.2 | 85.9 | 67.9 | 39 | | 13 | |
| **Temporal and insular lobes** | 23 | 26.7 | 74.6 | 19.2 | 16 | | 9 | |
| **Parietal lobe** | 13 | 15.1 | 58.3 | 48.6 | 17 | | 10 | |
| **Occipital lobe** | 7 | 8.1 | 80 | 40 | 14 | | 9 | |
| **Other** | 11 | 12.8 | 50 | 40 | 10 | | 9 | |
| **Number of lesions** | | | | | | 0.068 | | 0.004 |
| **Single** | 73 | 84.9 | 75.1 | 50.0 | 24 | | 10 | |
| **Multiple** | 13 | 15.1 | 61.4 | 24.5 | 14 | | 6 | |
| **Surgical approach** | | | | | | 0.015 | | 0.002 |
| **Total resection** | 53 | 61.6 | 85.3 | 56.6 | 26 | | 12 | |
| **Partial resection** | 30 | 34.9 | 49.6 | 33.5 | 12 | | 6 | |
| **Biopsy operation** | 3 | 3.5 | 66.7 | 0 | 13 | | 4 | |
| **Radiotherapy dose (Gy)** | | | | | | 0.621 | | 0.173 |
| **≥60** | 75 | 87.2 | 72.5 | 47.6 | 22 | | 10 | |
| **54-60** | 11 | 12.8 | 77.8 | 37.0 | 24 | | 9 | |
| **Adjuvant chemotherapy cycles** | | | | | | 0.000 | | 0.001 |
| 0 | 10 | 11.6 | 36.0 | 0 | 11 | | 6 | |
| 1-6 | 48 | 55.8 | 65.2 | 38.9 | 16 | | 9 | |
| >6 | 28 | 32.6 | 92.9 | 73.3 | 41 | | 15 | |

m = month, MST = median survival time

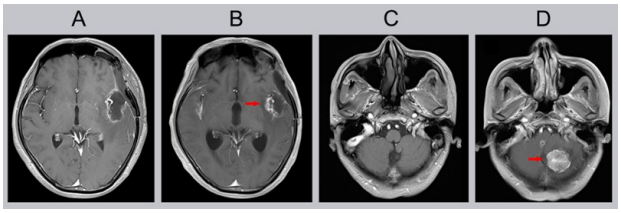


**Figure 1.** Representation of glioblastoma recurrence half a year after radiotherapy. **(A, C)** Contrast-enhanced T1-weighted MR images before postoperative radiotherapy. **(B, D)** Contrast -enhanced T1-weighted MR image showing the relapse within the radiation field and the extra-radiation field.



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### *Clinical toxicity*

The overall adverse reactions for radiotherapy and chemotherapy were mild and mainly hematological toxicity. Three patients had grade I-II leukocyte suppression; two patients had grade II platelet suppression; some patients had fatigue, nausea, vomiting, and rash, as well as varying degrees of headache and head tension; and two patients had seizures. All of these patients improved after symptomatic care during chemoradiotherapy.

### *Prognostic analysis*

Univariate analysis indicated that sex, age, KPS score, pathological grade, tumor location, surgical approach, and adjuvant chemotherapy cycles were prognostic variables of OS ($P < 0.05$) and that sex, age, pathological grade, number of lesions, surgical approach, and adjuvant chemotherapy cycles were prognostic variables for PFS ($P< 0.05$). Multivariate analysis revealed that pathological grade, surgical approach, and adjuvant chemotherapy cycles were associated with good OS and PFS ($P< 0.05$). Details about the prognosis index and its impact on survival are shown as follows (tables 1, 2, 3 and figure 2).

**Table 2.** Multivariate analysis of overall survival in 86 high-grade glioma patients.

| Variables | *β* | *SE* | *Wald* | *P* | *HR* | 95% *CI* |
|---|---|---|---|---|---|---|
| Surgical approach | 0.809 | 0.250 | 10.466 | 0.001 | 2.245 | 1.375-3.664 |
| Pathological grade | 1.046 | 0.384 | 7.413 | 0.006 | 2.846 | 1.340-6.042 |
| Adjuvant chemotherapy cycles | -0.970 | 0.246 | 15.543 | 0.000 | 0.379 | 0.234-0.614 |

CI = confidence interval, Forward logistic regression

**Table 3.** Multivariate analysis of progression-free survival in 86 high-grade glioma patients.

| Variables | *β* | *SE* | *Wald* | *P* | *HR* | 95% *CI* |
|---|---|---|---|---|---|---|
| Surgical approach | 0.897 | 0.227 | 15.575 | 0.000 | 2.453 | 1.571-3.831 |
| Pathological grade | 1.037 | 0.333 | 9.681 | 0.002 | 2.821 | 1.468-5.420 |
| Adjuvant chemotherapy cycles | -0.817 | 0.204 | 15.979 | 0.000 | 0.442 | 0.296-0.659 |

CI = confidence interval, Forward logistic regression

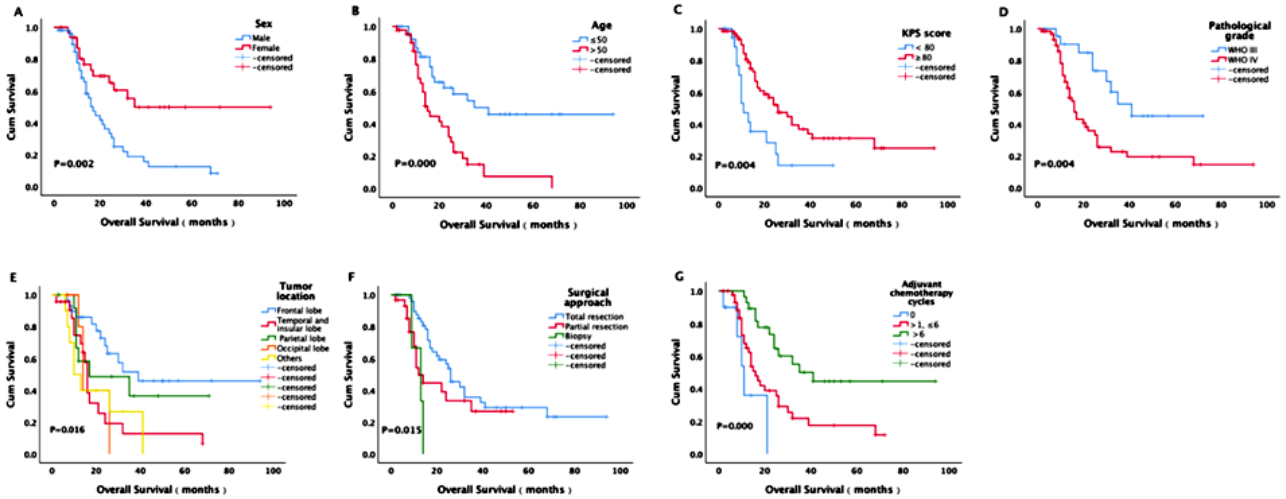


**Figure 2.** Univariate analysis of overall survival times in relation to clinical parameters **(A)** sex; **(B)** age; **(C)** KPSscore; **(D)** pathological grade; **(E)** tumor location; **(F)** surgical approach; **(G)** adjuvant chemotherapy cycles.

### *Correlation analysis of PFS and OS*

The Pearson correlation coefficient (r) was 0.916 ($P = 0.000$), indicating that tumor relapse or progression was closely related to survival and that a local uncontrolled or relapsed tumor was the leading cause of death for patients with gliomas.

## DISCUSSION

Gliomas are mostly incurable because of their aggressive nature and ability to infiltrate adjacent brain tissues, even with a combination of treatment techniques. For HGG, surgery is the basis of treatment. However, local uncontrolled or relapsed glioma is the leading cause of surgical failure. Eighty percent of relapsed cases occur at the primary tumor site or 2-3cm around the initial tumor margin; postoperative radiotherapy is currently the most effective treatment to prevent relapse[12].

Many Studies have shown that specific clinical and tumor characteristics and other treatment factors may affect the prognosis of HGG patients. Clinical factors like age and KPS score are consistently recognized as prognostic survival factors, although the thresholds for age groups vary from study to study[4, 13]. In a survey of 4807 anaplastic astrocytoma patients, Shin *et al.* discovered that patients under 50 had a considerably greater 5-year survival rate than patients over 50 (58.5% vs. 14.0%) [13]. Liang *et al.* discovered that patients under the age of 45 had a better prognosis than those over the age of 45, and patients' prognoses were worse for those with KPS scores below 85 than those with scores above 85 [4].

According to our study, patients with a KPS score of 80 or more had longer OS and PFS than those less than 80. Patients under the age of 50 years also had longer OS and PFS than those over 50. Most previous



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studies did not focus on sex as a potential prognostic factor. Among the 6586 GBM patients enrolled in the research by Tian *et al.*, the 5-year cancer-specific survival rate was 6.8% for men and 8.3% for women. Univariate and multivariate analyses indicated sex as a prognosis indicator [14]. In our study, the univariate analysis revealed that the female sex was a favorable prognostic factor, but the multivariate analysis results did not concur. Liang *et al.* reported that seizures were associated with a more favorable prognosis [4]. The possible reason for this finding is that patients with seizures are more common in secondary GBM or manifest symptoms sooner, facilitating early tumor detection. The frequency of GBM-related seizures is related to age (≤ 60 years), IDH1 mutations, and p53 overexpression [15]. However, epilepsy is not an independent predictor in other studies [16].

For tumor characteristics, the pathological grade is a proven prognostic element. The earlier studies have proved that the average median survival time of patients with Grade III and IV glioma was 2-5 years and less than 2 years, respectively[17]. According to this study, individuals with Grade III and IV gliomas had median overall survival times of 41 and 16 months, respectively. The survival results are comparable to those of previous studies. A study on the relationship between GBM size and prognosis showed that a tumor diameter less than 5cm was associated with a better survival prognosis [18]. Few studies have reported the effect of the number of lesions on survival. Liang *et al.* indicated a less favorable prognosis with multiple lesions (P= 0.026) [4]. In a study by Fekete *et al.* univariate and multivariate analyses indicated more prolonged survival for patients with a single GBM lesion [19]. Our study found no correlation between tumor diameter or the number of lesions and prognosis. Dobran *et al.* showed that for GBM, the OS was eleven months for patients with a frontal tumor, ten months for patients with a temporal tumor, eight months for patients with a parietal tumor, and less than eight months for patients with an occipital tumor and patients with bilateral or multicentric gliomas (P < 0.0001). Multivariate analysis confirmed that tumor location is an important prognostic factor [16]. Some researchers have found that midline tumors were associated with unfavorable survival, significantly if the tumor infiltrated the brainstem, ventricle, or the contralateral side [13]. Survival was worst if the tumor was located in the midline structures or cerebellum. Our research proved that people with frontal tumors live significantly longer than people with malignancies in other lobes.

Surgical resection is the most critical step for glioma treatment. A growing body of evidence emphasizes that complete resection and less residual tumor are linked to a better prognosis [20]. However, partial resection or biopsy may be performed for patients in poor condition or whose tumor is located in a critical functional area to obtain a tumor sample and prepare for subsequent treatment [21]. Researchers stratified by age have analyzed the characteristics of and prognostic factors for HGG and found that the survival rate was lower in partial resection patients than in total resection patients [7]. Ilic *et al.* reviewed the prognosis of 110 GBM patients and demonstrated that the scope of surgical resection was related to OS and PFS. Patients who underwent total resection, subtotal resection, and partial resection had a median OS of 20 months, 13 months, and 11 months, respectively (P = 0.036) [22]. Our study confirmed that the surgical approach was a prognostic element for OS and PFS.

Radiotherapy is necessary for HGG treatment because it further kills tumor cells and delays local relapse. The current standard of care recommends radiotherapy one month after the brain operation, with a total dose of 54 to 60 Gy over 30 to 33 fractions [2, 3]. A study showed that the median OS was 16 months of GBM patients who accepted postoperative radiotherapy, longer than that of patients who did not (by 2.5 months) [23]. Ma *et al.* showed that OS was 15.0 and 8 months each for GBM patients who accepted radiotherapy or not. Multivariate Cox regression indicated that radiotherapy was the most critical prognostic factor [24]. In a prospective, randomized, controlled trial on GBM, the OS was 14.6 months for patients in the three-dimensional conformal radiotherapy plus chemotherapy group and 12.1 months for patients in the radiotherapy alone group [3]. In our study, all enrolled patients received postoperative radiotherapy. The median OS for grade IV patients was 16 months, which is consistent with other reports. These patients received IMRT, which significantly improves target conformity relative to conformal radiotherapy for the treatment of gliomas [25]. The radiotherapy dose (54-60 Gy versus ≥ 60 Gy) did not affect PFS or OS.

This study used postoperative MRS and preoperative and postoperative MRI to define the target volume. MRS is a non-invasive technique for examining biochemistry, quantitative analysis, and substance metabolism in brain tumors and adjacent brain tissue. MRS can clearly show locations with aberrant metabolism, offering a crucial foundation for precision radiotherapy. According to a study that compared in vivo MR spectroscopic imaging parameters with ex vivo histologic characteristics of tissue samples in glioma patients, the regions of raised choline (Cho) and decreased N-Acetylasparticacid (NAA) accurately were related to the parts of increased cellular proliferation. That indicates the active metabolic area of the tumor cells [26]. The ratio of Cho to NAA (also known as the Cho/ NAA index or CNI) was significantly positively correlated with the invasive ability of glioma cells[26]. CNI was applied as a semi-quantitative parameter to gauge the severity of the metabolic abnormalities.



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The CNI anomaly volume is frequently more extensive than the contrast-enhanced area and occasionally extends beyond the T2 FLAIR anomaly boundaries. CNI >2 is a high-risk condition in linked research[26, 27]. When delineating the GTV, we included the region with CNI >2 in the MRS images (figure 3).

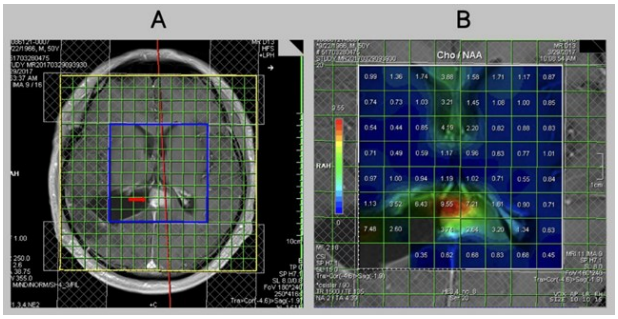


**Figure 3. (A, B)** MRSI map showing abnormalities of Cho/NAA > 2.

We referenced the Stupp protocol and administered TMZ. The anti-tumor effects of TMZ will be "autonomously" enhanced by long-term TMZ therapy since it will lower MGMT levels and impair tumor cell resistance. Compared to standard six-cycle adjuvant chemotherapy, long-term TMZ therapy shows fair tolerability[28]. Some studies comparing six cycles with over six cycles reported that patients with GBM who received long-term adjuvant TMZ had improved PFS and survival rates. [28-30]. The Chinese central nervous system glioma diagnostic and treatment guidelines(2015) recommend 12 cycles then[2]. The American Society of Clinical Oncology reported that for GBM, an additional six cycles of temozolomide did not provide additional survival benefits [31]. However, the related study had a small sample size, with certain confounding factors. What constitutes the ideal number of adjuvant TMZ therapy cycles is still up for debate. Up to 12 cycles of chemotherapy treatment cannot be denied yet. Our study indicated that long-term TMZ therapy was a significant favorable predicting factor relative to adjuvant chemotherapy of fewer than six cycles (P = 0.000). We believe that long-term temozolomide treatment may bring survival benefits to specific patients. Extensive studies are needed to investigate the appropriate patient populations further. Bone marrow suppression is a side effect of concurrent radiotherapy and chemotherapy, but most cases were grade I-II. All other side effects, such as gastrointestinal reactions, improved after symptomatic care.

In recent years, the molecular pathology of glioma has made great progress. In 2016, the WHO incorporated molecular pathology into the pathological diagnosis system of glioma. The pathological diagnosis of brain glioma is deepening to molecular diagnosis, and the evaluation of the prognosis of glioma is increasingly dependent on gene expression characteristics or molecular phenotypes. Patients with gliomas with IDH and ATRX mutations have a better prognosis[32]. Gliomas with MGMT promoter methylation are more sensitive to TMZ[33]. Other genes, chromosome 1p/19q combined deletion, TERT mutation, EGFR amplification, and mutation, are also related to the prognosis [34]. As the patients enrolled in the early stage of our study did not all undergo molecular pathology testing, the data was not complete and statistical analysis could not be performed.

## CONCLUSION

In conclusion, this retrospective study showed that patients with grade III HGG have a more favorable prognosis than those with grade IV HGG. There was a survival benefit with optimal surgical resection plus postoperative concurrent IMRT radiotherapy and adjuvant chemotherapy of more than six cycles of long-term chemotherapy.

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***Authors' Contributions***: Hong Zhu conducted the initial literature search, evaluated the articles, performed the statistical analysis, generated the figures, and drafted the paper. Judong Luo was responsible for the research design and final manuscript revision.

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