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Clinical effectiveness of sodium fluorescein-guided microsurgery in patients with high-grade gliomas

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Abstract. – OBJECTIVE: The aim of this study was to assess the clinical effectiveness of sodium fluorescein-guided microsurgery in patients with high-grade gliomas.

PATIENTS AND METHODS: 120 patients with high-grade gliomas who were hospitalized in our Neurosurgery Department from January 2018 to January 2021 were selected and then divided into a control and a study group using the random number table method, with 60 cases in each group. To compare the clinical efficacy of patients in both groups, neuronavigation microsurgery was used in the control group and neuronavigation microsurgery combined with sodium fluorescein-guided microsurgery was used in the study group.

RESULTS: The Gross Total Resection Rate (GTRR) of the study group was significantly higher than that of the control group. There was no significant difference in intraoperative bleeding loss or hospital stay between the two groups, and the study group had a much shorter operation time than the control group. The Karnofsky Performance Score (KPS) and the National Institutes of Health Stroke Scale (NIHSS) scores did not significantly differ between the two groups prior to surgery but declined significantly in the study group compared to the control group following treatment. In terms of adverse effects, there was no significant difference between the two groups. In the control group, the median progression-free survival (PFS) was 7.5 months, and the median overall survival (OS) was 9.6 months, whereas in the study group, the median PFS was 9.5 months, and the median OS was 11.5 months. PFS did not significantly differ between the two groups (HR=1.389, 95% CI=0.926-2.085, *p*=0.079); however, OS was significantly higher in the study group compared to the control group (HR=1.758, 95% CI=1.119-2.762, *p*=0.013).

CONCLUSIONS: Fluorescein-guided microsurgery can dramatically improve total resection rate, postoperative neurological functional status, and overall survival with higher efficacy and safety in patients with high-grade gliomas.

Key Words:

Sodium fluorescein-guided, Microsurgery, High-grade gliomas, Primary malignant craniocerebral tumors, MRI.

Introduction

Gliomas are the most common primary malignant craniocerebral tumors that arise from the carcinogenesis of glial cells in the brain and spinal cord[1]. Glioma originates in glioblasts. It accounts for around 35.2% to 61.0% of intracranial tumors, with a high incidence, high recurrence rate, high mortality rate, and low cure rate[2]. Standard treatment for gliomas is surgical resection followed by radiotherapy and temozolomide chemotherapy, but the prognosis is poor, with a median overall survival of 15 months and a 5-year survival rate lower than 7%[3]. One of the independent prognostic factors for high-grade glioma is the degree of tumor resection, and total tumor resection prolongs postoperative tumor recurrence and patient survival[4]. When compared to biopsy alone, removing as much tumor as possible improves the prognosis of patients with high-grade gliomas, but achieving pathologically complete resection of the tumor is often difficult due to the diffuse infiltrative growth pattern of high-grade glioma, which can invade the adjacent brain parenchyma along the white matter fiber tracts[5]. Magnetic resonance imaging (MRI) is a common method for determining the extent of a tumor, with T2 weighting being used

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for non-enhanced gliomas. Although extended resection is a common surgical strategy, there is a risk that it will impair brain function[6]. A significant surgical challenge is striking a balance between optimizing tumor resection and avoiding serious complications owing to loss of brain function. Many novel surgical adjunct techniques, such as conventional neuroimaging navigation, functional neuroimaging navigation, intraoperative neurophysiological monitoring techniques, and intraoperative MRI-based real-time neuroimaging navigation, are now being used to achieve maximum safe resection of high-grade gliomas[7].

Fluorescence-guided microsurgery can assist clinicians in depicting tumor shape and determining the location and extent of tumor tissues in order to lead them through tumor tissue resection[8]. Yellow fluorescence can complete tumor resection safely and reliably to the greatest extent for tumors with ambiguous boundaries, such as gliomas, or involving essential functional brain areas. Several investigations[9,10] in recent years have demonstrated the efficacy of fluorescein-guided microsurgery in high-grade gliomas, but randomized controlled trials comparing fluorescein-guided microsurgery to conventional microsurgery are lacking.

Patients with high-grade gliomas who were admitted to our hospital were included in this study and were treated with conventional microsurgery and sodium fluorescein-guided microsurgery, respectively. The findings are listed below.

Patients and Methods

Study Design

The study was a prospective randomized controlled trial (Clinical Trials Registration Number: ChiCTR.2300069911) with the Gross Total Resection Rate (GTRR) as the primary outcome measure. According to the literature, the expected GTRR for the study group was 81% and for the control group was 55%, with a significance level of 0.05 and a power (1-) of 80%. According to the 1:1 grouping, the sample size was calculated to be a minimum of 47 cases per group. Given the shedding of the sample, each group contained 60 patients. 120 Patients with high-grade gliomas who were hospitalized in the Department of Neurosurgery between January 2018 and January 2021 were selected and randomized into control and study groups using the random number table method, with 60 cases in each group. Our Ethics Committee approved the experimental study protocol, and all processes followed the Declaration of Helsinki's ethical criteria for clinical research[11].

Inclusion Criteria

(1) Patients between the ages of 18 and 75, regardless of gender; (2) Patients who had high-grade gliomas on imaging and were eligible for surgery; (3) Patients being diagnosed for the first time and without receiving particular oncologic treatment; (4) electrocorticography (ECoG) score[12] $\leq$2.

Exclusion Criteria

(1) patients with tumors involving the basal ganglia or brain stem as examined by MRI; (2) patients with allergies to experimental drugs such as sodium fluorescein; (3) patients who were pregnant or gestational; (4) patients with uncontrolled complications, including but not limited to chronic or active infections, symptomatic congestive heart failure, unstable angina pectoris, and arrhythmias; (5) patients with additional tumors in combination; (6) patients who were unable to complete follow-up.

Surgical Method

Glioma was removed by neuronavigation microsurgery alone in the control group. However, in the study group, tumor tissue was stained by intravenous injection of sodium fluorescein injection (5 mL: 500 mg, Alcon Laboratories, Fort Worth, TX, USA) during neuronavigation microsurgery, and tumor resection was performed to determine the tumor's boundaries based on the degree of fluorescence staining. Postoperatively, all patients had concurrent radiation as well as six courses of standard chemotherapy.

Observation Indexes

Tumor resection rate

The remaining tumor volume was calculated 72 hours after surgery using the enhanced tumor volume based on T1-weighted MRI imaging. The degree of tumor resection was classified as follows: total resection was defined as 100% resection or enlarged resection; subtotal resection was defined as more than 90% resection; majority resection was defined as 60% to 90% resection, and partial resection was defined as less than 60% resection.

Perioperative status

Perioperative indications such as operative time, intraoperative bleeding loss, and hospitalization time were gathered from both groups.

Scores of quality of life and neurological function

Karnofsky Performance Score (KPS) scores were used to assess patients' quality of life[13], while NIHSS scores were used to assess neurological function[14]. The poorer the quality of life, the higher the KPS score; the worse the neurological function, the higher the NIHSS score.

Long-term efficacy

All patients were followed postoperatively until June 1, 2022, with MRI plain scans and enhancement scans of the head conducted at regular intervals or at the onset of symptoms to assess progression-free survival (PFS) and overall survival (OS). The period from the date of surgery to tumor recurrence was defined as PFS, and the time from the date of surgery to the last follow-up or death was defined as OS.

Adverse reactions

The occurrence of adverse reactions during the follow-up period was recorded for all patients, and the severity was graded from I to V according to the 4th edition of Common Terminology Criteria for Adverse Events (CTCAE)[15].

Statistical Analysis

SPSS 23.0 software (IBM Corp., Armonk, NY, USA) was used to organize and statistically analyze the data, and GraphPad Prism 8.0 software (GraphPad Software, San Diego, CA, USA) was used to draw the pictures in the text. The count data were expressed as rates, and the Chi-square test was used to compare whether there was a statistical difference between groups, while the measurement data were expressed as mean ± standard deviation ($\bar{x}\pm s$), and the *t*-test was used to compare whether there was a statistical difference between groups. Survival data were analyzed using Kaplan-Meier analysis, and survival curves were plotted using the R survival package (available at: https://www.r-project.org). Differences were considered statistically significant at $p<0.05$.

Results

Comparison of General Information

In this study, each group had 60 patients. Age, gender, body mass index (BMI), disease duration, maximum lesion diameter, lesion site, pathological type, and whether the functional region was invaded were detected in the two groups, and the comparison revealed no difference for any of the aforementioned variables that were comparable (all $p>0.05$) (Table I).

Comparison on GTRR

MRI T1-weighted imaging was used to assess tumor volume and calculate tumor resection rate before and 72 hours after surgery. Statistically, the control group had 42 cases of complete tumor resection with a GTRR of 70.00%, whereas the

Table I. Comparison of general information.

N	Control group 60	Study group 60	t/χ^2	*p*
Age (years old)	54.25±6.58	52.11±7.05	1.719	0.088
Gender (Male/Female)	38/22	31/29	1.671	0.834
BMI	24.12±3.45	22.95±3.61	1.815	0.072
Duration (months)	6.29±1.42	6.44±1.56	0.551	0.583
Lesion diameter (cm)	5.14±1.12	5.42±1.34	1.242	0.217
Location			0.834	0.639
Left	33	28		
Right	27	32		
Pathological type			0.586	0.556
Astrocyte glioma	37	41		
Polymorphic glioblastoma	23	19		
Violation of the Ribbon			0.862	0.647
Yes	22	27		
No	38	33		
WHO grade			1.292	0.744
III	41	35		
IV	19	25		

Table II. Comparison of resection rates.

	N	Total resection	Subtotal resection	Majority resection	Partial resection	Total resection rate
Control group	60	42	11	5	2	70.00%
Study group	60	52	6	2	0	86.67%
χ^2						4.910
p						0.027

Table III. Comparison of operative time, intraoperative bleeding and hospital stay.

	N	Operating time	Intraoperative blood loss	Hospital stays
Control group	60	285.13±55.12	441.02±62.35	11.25±3.11
Study group	60	229.11±49.28	458.21±59.74	10.98±4.06
t		5.869	1.542	0.409
p		<0.001	0.126	0.683

study group had 52 cases of complete tumor resection with a GTRR of 86.67%, and the GTRR of the study group was significantly higher than that of the control group (p=0.027) (Table II).

Comparison of Perioperative Indicators

Operative time, intraoperative bleeding loss, and hospital stay were used to assess surgical quality in this study, and there was no significant difference between the two groups in terms of intraoperative bleeding loss and hospital stay, but the operative time was significantly shorter in the study group than in the control group (p<0.001) (Table III).

Comparison of KPS and NIHSS Scores

KPS and NIHSS scores are indicators of neurological functional status, and there was no significant difference in KPS and NIHSS scores between the two groups before surgery; both groups' scores decreased significantly after treatment, and the study group's scores were significantly lower than the control group's (all p<0.05) (Figure 1).

Comparison of Adverse Reactions

Complications such as electrolyte abnormalities, upper gastrointestinal bleeding, intracranial infection, and postoperative seizures are used to assess the safety of surgery. There were no grade III or higher adverse reactions in any of the patients in this trial, and the incidence of postoperative adverse reactions was 8.33% (5/60) in the control group and 13.33% (8/60) in the study group. There was no statistically significant difference in adverse reactions between the two groups (p=0.378) (Table IV).

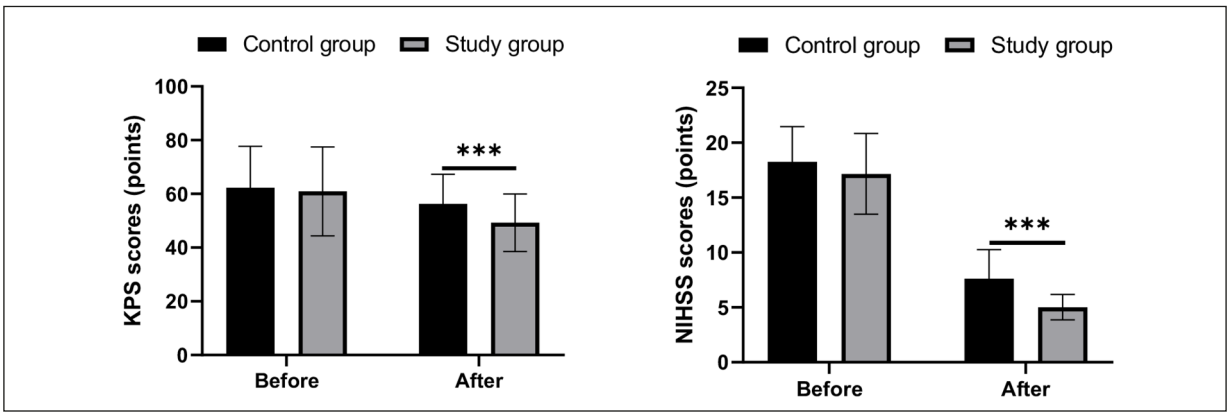

Figure 1. Comparison of KPS and NIHSS scores, ***indicates p < 0.001.

Table IV. Comparison of complications.

	N	Electrolyte abnormalities	Upper gastrointestinal bleeding	Intracranial infection	Postoperative seizures	Total rate
Control group	60	2	1	2	0	5 (8.33%)
Study group	60	4	2	1	1	8 (13.33%)
χ^2						0.776
p						0.378

Comparison of Long-Term Efficacy

To assess the long-term efficacy of the two treatment methods, all patients were followed-up for 12 months. As demonstrated in Table V, the control group's median PFS was 7.5 months, and its median OS was 9.6 months; the study group's median PFS was 9.5 months, and its median OS was 11.5 months. PFS did not significantly change across groups (HR=1.389, 95% CI=0.926-2.085, p=0.079); OS was considerably better in the study group than in the control group (HR=1.758, 95% CI=1.119-2.762, p=0.013). The PFS curves of the two groups are depicted in Figure 2 and the OS curves are depicted in Figure 3.

Table V. Comparison of long-term efficacy.

	N	PFS		OSI	
		Median	95% CI	Median	95% CI
Control group	60	7.5	6.6-9.0	9.5	8.6-10.6
Study group	60	9.6	8.1-10.5	11.5	9.3-NA
HR		1.389	0.926-2.085	1.758	1.118-2.762

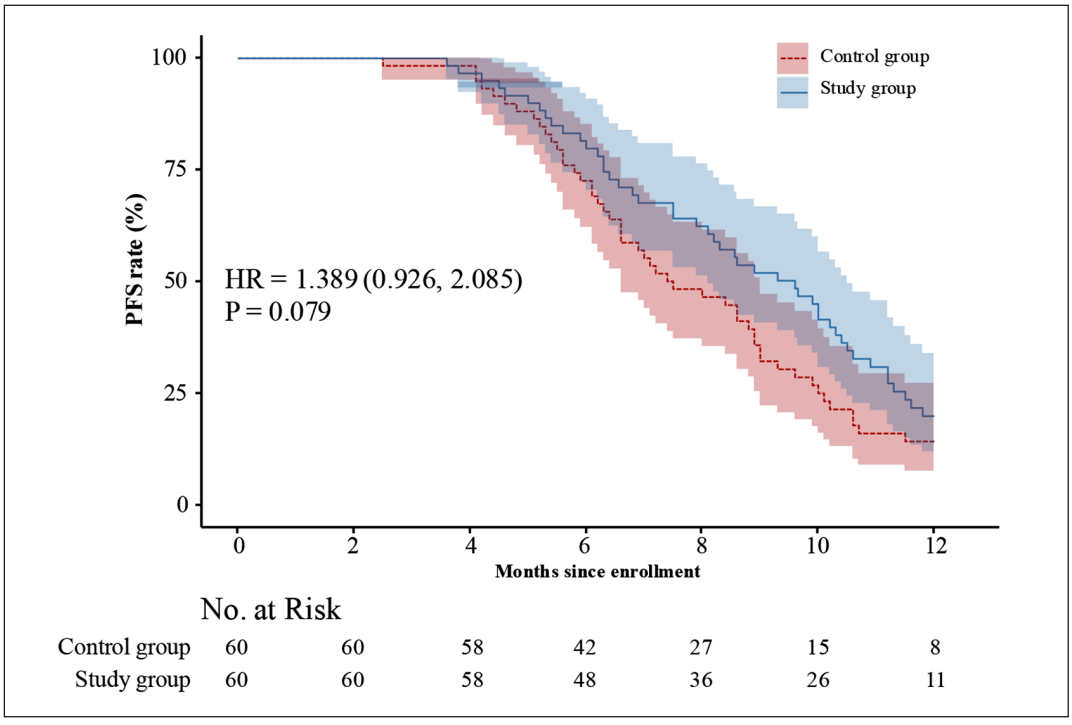

Figure 2. Comparison of PFS curves.

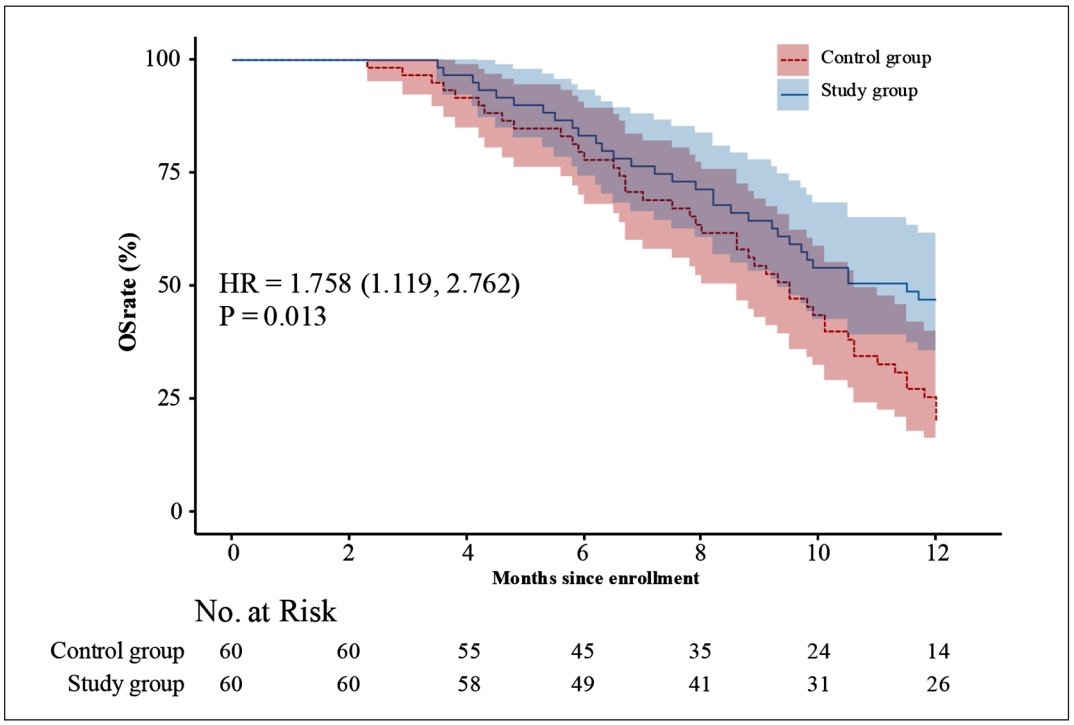

Figure 3. Comparison of OS curves.

Discussion

Gliomas are tumors of the central nervous system that permeate the surrounding brain parenchyma, and there is growing evidence that the degree of resection is an important predictor of outcome in patients with high-grade gliomas. Because of tumor heterogeneity and the presence of cellular infiltration far from the site of contrast enhancement on preoperative MRI, preoperative imaging and intraoperative observation are less effective in determining tumor boundaries[16]. Fluorescence-guided microsurgery opens up new possibilities for visualizing and removing brain tumors and infiltrative margins. The criteria[17] for diagnosis and treatment of glioma recommend that in surgical resection of high-grade gliomas, in addition to imaging-guided tumor resection, which can help determine the extent of resection, fluoroscopy-guided microsurgery can also help to maximize the extent of tumor resection. Several fluorescent substances, including 5-aminolevulinic acid, sodium fluorescein, and indocyanine green, have been explored for fluorescence-guided surgery[18]. Because of the presence of the blood-brain barrier, sodium fluorescein does not normally enter normal brain tissue. The blood-brain barrier permeability is increased around brain metastases. Gliomas, due to disruption of the tightly connected ultrastructure of the vascular endothelium, enables sodium fluorescein to enter and accumulate in tumor tissue *via* the disrupted blood-brain barrier, and fluorescence at 560 nm is readily observed. For fluorescence-guided surgery of high-grade gliomas, sodium fluorescein was administered during anesthesia, followed by craniotomy[19].

There was no significant difference in intraoperative bleeding loss or hospital stay between the two groups in this trial, and the operative time in the study group was much shorter than in the control group. Sodium fluorescein enters the cerebral vascular system immediately after systemic administration and accumulates in tumor areas with blood-brain barrier disruption. The fluorescence of sodium fluorescein can be seen for up to 4 hours after treatment[20]. As a result, real-time surveillance and brain shift reduction are possible. Furthermore, the ability to easily transition between normal light source mode and fluorescence mode saves time spent on operation navigation and considerably reduces operation time. The GTRR of sodium fluorescein-guided microsurgery was as high as 86.67% in this study,

while the GTRR of conventional surgery was 70.00%. A meta-analysis[21] of 21 studies showed that sodium fluorescein-guided microsurgery had an 81% GTRR in high-grade gliomas, with a 29.5% increase in the GTRR rate in the fluorescein group compared to non-fluorescein-guided surgery, consistent with the findings of this study. The major goals of glioma surgery are to preserve neurological function and increase the quality of life, and KPS and NIHSS are essential indices for assessing quality of life and neurological function. In this study, the postoperative KPS and NIHSS scores in the study group were significantly lower than in the control group, indicating the efficacy of sodium fluorescein-guided microsurgery[22]. The median OS in the study group was significantly higher than in the control group, according to the Kaplan-Meier survival curves. Neira et al[23] discovered that fluorescein staining beyond contrast-enhanced areas into non-enhancing infiltrative tumor margins could improve long-term outcomes by extending the extent of surgical resection, including those infiltrative tumor margins that play an important role in disease recurrence.

Conclusions

Fluorescein-guided microsurgery can dramatically improve total resection rate, postoperative neurological functional status, and overall survival with higher efficacy and safety in patients with high-grade gliomas.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

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Informed Consent

All subjects enrolled in the study signed an informed consent form and were informed of the purpose, content, and use of the study.

Ethics Approval

This clinical study protocol has been approved by the Ethics Committee of Renmin Hospital, Hubei University of Medicine (Approval No. 20210203), Clinical Trials Registration Number: ChiCTR.2300069911.

Authors' Contribution

Conceived and designed the analysis: G.-B. Wang. Collected the data: W.-X. Wang. Contributed data or analysis tools: J.-J. Luo. Performed the analysis: J.-J. Luo. Wrote the paper: G.-B. Wang,W.-X. Wang.

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