Safety and Efficacy of Hypofractionated Stereotactic Radiosurgery for High-Grade Gliomas at First Recurrence: A Single-Center Experience

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Research

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Abstract

Background: The optimal treatment for recurrent high-grade gliomas (rHGG) remains uncertain. This research aimed to investigate the efficacy and safety of CyberKnife radiosurgery as a salvage treatment for high-grade gliomas at first recurrence that within the radiation field.

Methods: Between January 2016 and October 2019, rHGG patients treated with CyberKnife radiosurgery were retrospectively analyzed. The primary endpoint was OS, and secondary endpoints included progression-free survival (PFS) and toxicity. Toxicity was assessed using CTCAE 5.0. The prognostic value of key clinical features (age, performance status, planning target volume, dose, use of bevacizumab) were evaluated.

Results: A total of 70 patients were included in the study. Forty patients were male and 30 were female. Forty-nine had an initial diagnosis Glioblastoma (GBM), and rest (21) were WHO Grade 3 Gliomas. The median planning target volume (PTV) was 16.68 cm^3 (0.81–121.96 cm^3). The median prescribed dose was 24 Gy (12-30 Gy) in 4 fractions (2-6 fractions). Median baseline Karnofsky Performance Status (KPS) is 70 (40-90). With a median follow-up of 12.1 months, the median overall survival after salvage treatment was 17.6 months (19.5 and 14.6 months for grade 3 and 4 gliomas; p = 0.039). No grade 3 or higher toxicities was recorded. Multivariate analysis showed concurrent bevacizumab with radiosurgery and KPS>70 were favorable prognostic factors for grade 4 patients.

Conclusions: Salvage CyberKnife radiosurgery showed a favorable outcome and acceptable toxicity for rHGG. A prospective phase II study (NCT04197492) is ongoing to further investigate the value of HSRS in rHGG.

Introduction

The most frequently diagnosed malignant primary brain tumor in adult is high-grade glioma (HGG). In the United States [1], there are 2.96 newly diagnosed occurrences per 100,000 people per year while the number in China is 5 to 8. Despite definitive primary therapy including surgery, adjuvant chemoradiation and temozolomide based chemotherapy [2], nearly all patients experience tumor recurrence [3] and up to 90% of which is local recurrence [4].

The outcome of recurrent HGG (rHGG) is poor and there is no consensus of optimal treatment. Common approaches include surgery, re-irradiation, systemic therapy, and tumor treating fields (TTF). Surgery has been reported a median overall survival (OS) of 9.7 months in the literature review. However, it can only be administered in less than 30% of patients due to involvement of eloquent areas and infiltrative nature of glioma [5, 6, 7]. The median OS of systemic therapy ranged from 6 to 9 months [8, 9, 10]. The efficacy of salvage systemic therapy is limited because of the cumulative toxicity and resistance of the chemotherapy agents [11]. The median OS of TTF for rHGG patients reported in EF-14 was 6.6 months [12]. Radiotherapy has also been known as an option for rHGG. Several small sample prospective studies

reported a promising outcome and acceptable toxicity with a median OS of 12 to 12.7 months after salvage treatment [13, 14, 15, 16].

HSRS can deliver a high dose of radiation while limiting the toxicity to normal tissues. CyberKnife is a radiosurgery system that allows highly conformal image-guided radiotherapy and shows a promising tumor control effect for central nervous system tumors. This study aims to determine the treatment outcome and toxicity of CyberKnife radiosurgery. To our knowledge, this is the largest cohort of rHGG treated with CyberKnife radiosurgery as first-line salvage treatment.

Methods

Eligibility Criteria and Endpoints

This study was approved by the local ethics committee. Between January 2016 and October 2019, patients with recurrent HGG received salvage HSRS using CyberKnife at HuaShan Hospital were included. All patients had initial histological confirmed World Health Organization (WHO) Grade 3/4 glioma, and received adjuvant external-beam radiation with concomitant temozolomide and adjuvant temozolomide. HGG recurrence was confirmed by RANO criteria and/or stereotactic brain biopsy. All patients were treated at first recurrence that within the radiation field.

The primary endpoint was overall survival from the completion of salvage HSRS (OS-HSRS). The second endpoints included progression-free survival after salvage treatment and toxicity defined by CTCAE 5.0.

Baseline Evaluation and Treatment Delivery

HSRS was performed using the CyberKnife Radiosurgery System (Accuray, Sunnyvale, CA, USA). Patients were immobilized with a custom thermoplastic mask and underwent localizing 1.25 mm thin-slice computed tomography (CT, GE Light speed Ultra 16 Slice, USA) and 2 mm thin-slice MRI including T1 post-contrast and T2 flair images. CT and MRI scans were then fused using the CyberKnife planning system for contouring.

Radiation oncologists, neurosurgeons, and radiation physicists participated in tumor delineation, planning, and dose selection. Gross tumor volume (GTV) was defined as the gadolinium-enhanced tumor on T1 weighted series. The clinical tumor volume (CTV) was considered equal to the GTV. The planning target volume (PTV) was a uniform 2 mm expansion of the CTV, and FLAIR abnormality was not included in the treatment volume. Multiplan (Accuray, Sunnyvale, CA, USA) software was used for inverse planning. The prescribed dose to PTV was determined according to the target volume, site, previous irradiation volume and total dose, and the interval between treatments.

The use of systemic therapy after HSRS was decided by the treating physicians. Thus, the regimens were individualized, most commonly bevacizumab, temozolomide or clinical trials were recommended.

Assessment and Toxicity

All patients underwent clinical and radiological follow-up every three months after HSRS. If any significant deterioration in the patient's performance occurred, an MRI was ordered immediately. The radiological examination included MRI and other necessary examinations, such as MRI-based spectroscopy, perfusion MRI, and methionine positron emission tomography. KPS after treatment, adverse event occurrence, and associated clinical outcomes were recorded. Toxicity was assessed using the CTCAE 5.0.

Statistics

The primary outcome was overall survival after HSRS, defined as survival from the time of the completion of HSRS to death due to any cause. Other measures included progression-free survival after salvage treatment and treatment related toxicities. Survival curves were estimated using the Kaplan-Meier method and compared with the log-rank test.

Multivariate analysis of OS-HSRS in WHO Grade 4 glioma patients was performed using a Cox proportional hazards regression model. Variables included in the multivariate analysis model were those with hypotheses of interest or determined to be clinically related to survival. Age, PTV, biologically effective dose (the median BED was 37.5 Gy, BED was calculated using the LQ model with an alpha/beta ratio of 10, KPS and concurrent bevacizumab regimen (defined as bevacizumab administered during HSRS) were factors included in the multivariate analysis. The multivariable Cox regression model results are reported as hazard ratios with 95% CI and p values. All statistical analyses were performed R version 3.6.1 using the survminer and survival package.

Results

Patient Characteristics

Between January 2016 to October 2019, 70 high-grade glioma patients who had clinical, radiographic and/or stereotactic brain biopsy evidence of recurrence were treated with CyberKinfe (Fig. 1). All patients were initially treated with maximum safe resection, adjuvant radiation treatment with a median dose of 60 Gy in 30 fractions with concurrent and maintenance temozolomide. 40 patients were male and 30 were female. The median age was 53 years (range 20-76 years). The majority of patients (49) had an initial diagnosis Glioblastoma, and rest (21) were WHO Grade 3 Gliomas The median time from the initial diagnosis to salvage HSRS was 13.7 months with a range of 4.2 to 55.3 months.

The median volume of salvage HSRS PTV was 16.68 cm^3 (0.81–121.96 cm^3). The treatment was given daily and the median dose was 24 Gy (12-30 Gy) in 4 fractions (2-6 fractions) with a median iso-dose line of 70% (63-75%). Patient characteristics are listed in Table 1.

Compliance and Toxicities

All patients completed planned HSRS without interruption. There was no significant treatment related acute toxicity (grade ≥ 3). Common nonhematologic grade 2 toxicities included fatigue (9 cases, 12.9%), nausea and vomiting (7 cases, 10.0%) and headache (4 cases, 5.7%). Toxicity details are shown in Table 2. Other toxicities included hypertension, seizure and hematologic toxicities that were considered as chemotherapy related. No operations were related to acute or late toxicity of HSRS.

Treatment Outcomes

By the end of the study, 26 patients died of tumor progression. Median follow-up from the time of HSRS was 12.1 months. The median overall survival after salvage treatment was 17.6 months for the whole cohort (Fig. 2A, 14.5 to 26.1 months, 95% CI), 19.5- and 14.6- months for grade 3 and 4 gliomas, respectively (Fig. 2B, p = 0.039). The overall survival rate following HSRS was 72.8%, 30.1%, and 18.0% at 1, 2, and 3 years, respectively.

All patients were assessed by the RANO criteria, 42 patients had progressive disease. 12 of the patients (28.6%) had new lesions outside the radiation field and 30 patients (71.4%) had local recurrence (LR). The 6-month PFS was 76.3% and 57.1% for grade 3 and 4 patients. The median PFS was 7.0 months (5.9 to 9.2 months, 95% CI), 7.6 and 6.8 months for grade 3 and 4, respectively (p = 0.077). Twenty-four patients received a second-course salvage treatment because of radiographic progression and two of them received surgery [see Additional file 1].

On multivariate analysis, KPS>70 (HR= 0.13, p = 0.0060), bevacizumab concurrently administered with HSRS (defined as bevacizumab administered during HSRS, HR= 0.15, p = 0.0040) were factors that positively affected OS after salvage HSRS for grade 4 patients (Table 3). One-year OS after HSRS in grade 4 patients who had concurrent bevacizumab with HSRS and who did not were 77.3% and 56.0% (Fig. 2C, p = 0.035). Grade 4 patients whose KPS>70 before treatment also showed a longer OS than those whose KPS≤70 (Fig. 2D, p = 0.041).

There was no statistical difference of age, gender, KPS, mutation status, time from the initial diagnosis to HSRS and PTV between these two groups.

Discussion

Salvage Treatment Options for Recurrent high-grade glioma

For rHGG patients, salvage treatment included surgery, re-irradiation, systemic therapy, and TTF. Though the results of prospective trials on these regimens have been published (Table 4), no standard treatment exists [9, 12, 16]. Thus, an individualized option that considered efficacy, quality of life and toxicity is crucial.

The efficacy of systemic therapy in improving OS for rHGG is unclear. Bevacizumab showed the role of improving PFS with a median OS of 9 months in two randomized control trials (RCT) [9, 10]. Programmed death-1 (PD-1) immune checkpoint inhibitor antibody showed a negative result compared with

bevacizumab with a median OS of 9.8 months and median PFS of 1.5 months in the phase III RCT Checkmate 143 trial [8].

HSRS and hypofractionated stereotactic radiotherapy (HSRT) using linear accelerators takes advantage of the stereotactic precision as well as the properties of a standard fractionation schedule. For irradiated recurrent tumors, it allows a high treatment dose to cover the PTV and minimize the normal brain toxicity. Besides, the condensed treatmentschedule could be an important option for rHGG patients with short expected survival and poor KPS. HSRT has been reported a median overall survival for rHGG patients ranged from 12 to 12.7 months. The prospective trial by Wuthrick reported a median survival of 12.7 months in grade 4 glioma patients using HSRT of 30 to 42 Gy in 2.5 to 3.75 Gy fractions with 37.5 daily sunitinib [15]. Fogh et, al reported the largest series

retrospective study of 147 patients using X-Knife with a median dose of 35Gy in 10 fractions. The median survival achieved 11 months [17]. Also, Shi et, al reported a cohort of 36 grade 2 to 4 glioma patients using 30-35 Gy/10fx HSRT with alisertib achieved a median overall survival of 11.1 months [18].

There are limited data addressing the combination of systematic therapy and re-irradiation for rHGG [19]. Several prospective trials examined the safety and efficacy of HSRT with systematic therapy for rHGG exhibiting OS ranging from 12 months to 12.7 months (Table 4). Minniti et, al examined HSRT with TMZ in 54 rHGG patients. With 30 Gy in 5 fractions plus concomitant TMZ up to 12 cycles, the median survival after salvage treatment was 12.4 months. KPS>70 and grade 3 glioma were considered as prognostic factors for survival [16].

Effectiveness of CyberKnife re-irradiation for rHGG

CyberKnife is an image-guided stereotactic radiosurgery system that can deliver accurate treatment dose to the brain lesions. In this study, we showed a median OS after HSRS of 17.6 months (19.5 and 14.6 months for grade 3 and 4 gliomas, respectively; $p = 0.039$). In literature, the survival of grade 4 patients after CyberKnife was reported from 10.6 to 13.7 months [20, 21]. The promising survival in this study due to several reasons. First, radiation was delivered with a relatively low iso-dose line of 63 to 75% and resulted a higher dose delivered to the tumor. It increased the tumor center dose and enhanced the tumor cell killing activity as a direct result. Second, all the enrolled patients received HSRS as first-line salvage treatment. For these patients, survival was expected to be longer. Third, 24 (34.2%) patients underwent a second-course salvage treatment after HSRS including surgery, HSRS, systemic therapy, and TTF. The aggressive multiple salvage treatments may have a positive impact on survival.

Minimizing the radiation injury to the normal brain was considered when increasing the treatment dose. Bevacizumab is an anti-vascular endothelial growth factor (VEGF) monoclonal antibody, which is used in recurrent glioblastoma [9, 10]. Bevacizumab has been hypothesized to protect the normal brain from radiation by reducing brain edema and radiation necrosis. The advantage of adding bevacizumab to HSRS has not been fully illustrated. Philip el al theorized that the additional bevacizumab sensitized the

tumor endothelia of the radiotherapy and induced apoptosis [22]. Also, Kyle et al concluded that the peri-vascular niche and anti-tumor effects could be the reason.

Our data suggest that HSRS with concomitant bevacizumab and good performance status result in improved survival in grade 4 patients. These results are similar to Sharma's research that reported 53 GBM patients achieved a median survival of 11 months after gamma knife radiosurgery and radiosurgery was associated with longer survival in good performance patients [23]. Also, in Cuneo's research, which reported an OS of 11.2 months in patients receiving bevacizumab and stereotactic radiosurgery compared with 3.9 months for patients treated with stereotactic radiosurgery alone [24]. Though the preliminary results of RTOG1205 showed a negative result of HSRT in improving OS [25]. A variety of radiotherapy techniques used in the trial and a relatively larger median PTV may contaminate the result. However, an improved 6-month PFS was achieved in the HSRT+BVZ group compared with the BVZ only group, a longer PFS can increase the quality of life in brain tumor patients. For rHGG patients that have few or other therapeutic options, HSRS or HSRT combined with bevacizumab may represent a reasonable consideration.

Strengths and limitations

To date, this is the largest cohort of CyberKnife as first-line salvage treatment for recurrent high-grade glioma within the radiation field patients. Our study demonstrates a promising survival and mild toxicity using CyberKnife radiosurgery for rHGG patients.

However, the retrospective nature limited this study. The selection bias was created when deciding the eligible patients for salvage treatment, which increased the number of potential good prognosis patients. Also, additional systemic therapy, second-course salvage treatment after HSRS and lack of imaging follow-up for palliative care patients may influence the result. Moreover, both the previous studies and the clinical experience at our center [see Additional file 2] encountered the same dilemma that irradiated brain tumor, the diagnosis of LR and RN was difficult [26, 27].

Despite the limitations, this study presented a promising outcome of salvage HSRS. A prospective phase II study HSCK-002 ClinicalTrials.gov identifier: NCT04197492 is ongoing at our center to further investigate the value of HSRS and anlotinib (an oral novel multi-target tyrosine kinase inhibitor targeting VEGF receptor, fibroblast growth factor receptor and platelet-derived growth factor receptor).

Conclusions

HSRS using CyberKnife radiosurgery system showed a favorable outcome and acceptable toxicity as a salvage treatment for HGG at first recurrence. A prospective phase II trial HSCK-002 (ClinicalTrials.gov identifier: NCT04197492) is ongoing to further evaluate the efficacy of CyberKnife radiosurgery for rHGG.

Abbreviations

rHGG
recurrent high-grade gliomas; PFS:progression-free survival; GBM:Glioblastoma; PTV:Planning target volume; KPS:Karnofsky Performance Status; OS:Overall survival; WHO:World Health Organization; GTV:Gross tumor volume; CTV:Clinical tumor volume; BED:Biologically effective dose; LR:Local recurrence; HSRS:Hypofractionated stereotactic radiosurgery; RCT:Randomized control trials; PD-1:Programmed death-1; HSRT:Hypofractionated stereotactic radiotherapy.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the institutional and the 1964 Helsinki declaration and its later amendments. This retrospective study was approved by the Huashan ethics committee.

Consent for publication

All authors have read and approved the manuscript for publication.

Availability of data and material

Research data are stored in an institutional repository and will be shared upon request to the corresponding author.

Competing interests

All the authors have nothing to disclose.

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Author's contributions

Yun Guan, Ji Xiong and Mingyuan Pan contributed equally to the work. Conception design and interpretation of data: Yun Guan and Xin Wang. Statistical analysis: Yun Guan. Data acquisition: Li Pan, Jiazhong Dai, Ji Xiong, Jing Li, Huaguang Zhu, Xiu Gong, Chao Li, Guanghai Mei and Xiaoxia Liu. Article revising: Mingyuan Pan, Wenyin Shi. Enmin Wang and Xin Wang approved the final version to be published.

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Tables

Table 1
Baseline Characteristics of All Patients (N = 70)

Parameter	N	%
Gender		
Male	40	57
Female	30	43
Age, years		
Median	53	/
Range	20–76	/
Initial histology WHO grade		
3	21	30
4	49	70
Interval between HSRS and initial diagnosis (months)		
Median	13.7	/
Range	1.1–55.3	/
KPS before salvage HSRS		
Median	70	/
Range	40–90	
MGMT		
Unmethylated	25	36
Methylated	9	13
Unknown	36	51
IDH1 Mutation		
Yes	5	7
No	45	64
Unknown	20	29
1p19q codeletion		
Yes	1	1
No	25	36
Unknown	44	63

Parameter	N	%
Planning Tumor Volume (cm^3)		
Median	16.68	/
Range	0.81–121.96	/
Concurrent systemic therapy		
TMZ	14	20
BVZ	28	40
TMZ + BVZ	7	10
BSC	21	30
Total	70	100

Abbreviations: WHO = World Health Organization; HSRS = hypofractionated stereotactic radiosurgery; KPS = Karnofsky performance status; MGMT = O6-methylguanine-DNA methyltransferase; IDH1 = Isocitrate dehydrogenase 1; TMZ = Temozolomide; BVZ = Bevacizumab; BSC = best supportive care.

Table 2
Adverse Events Occurred in rHGG Patients

Adverse Events	Total No. of Patients	No. of Patients		
		Grade 1	Grade 2	Grade 3/4
Hematologic				
Anemia	13	8	5	0
Neutropenia	11	5	6	0
Lymphocytopenia	7	2	5	0
Thrombocytopenia	7	3	4	0
Nonhematologic				
Fatigue	32	23	9	0
Hypertension	21	18	3	0
Headache	21	17	4	0
Nausea and vomiting	13	6	7	0
Seizure	7	7	0	0
AST* increased	5	2	3	0
ALT† increased	4	1	3	0
Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase.				

Table 3
Multivariate Results of Survival after Salvage Treatment in Grade 4 rHGG Patients

Factors	Comparison	HR	95%CI	*P*
Age, years	Continuous	1.03	0.98–1.08	0.250
KPS	> 70 v ≤ 70	0.13	0.03–0.56	0.006
PTV, cm^3	> 10 v ≤ 10	0.44	0.13–1.50	0.187
BED, Gy	> 37.5 v ≤ 37.5	1.50	0.53–4.27	0.446
Concurrent† bevacizumab	Yes v no	0.15	0.04–0.56	0.004

Abbreviations: HR = hazard ratio; CI = confidence interval; KPS = Karnofsky performance status; PTV = planning target volume; BED = biologically effective dose.

*BED was calculated using the LQ model with an alpha/beta ratio of 10.

†Concurrent was defined as bevacizumab administered with HSRS.

Table 4. Recent Prospective Trials of Recurrent High-grade Glioma

Treatment	Author, Year	Regimen	Median Dose（Gy）	Sample Size（N）	MST (Months)
Systemic Therapy	Reardon, 2017 [8]	Nivolumab vs BVZ	N/A	Nivo= 184 BVZ= 185	9.8 vs 10.0
	Wick, 2017 [9]	Lomustine +BVZ vs Lomustine	N/A	L+BVZ= 228 L= 149	9.1 vs 8.6
	Friedman, 2009 [10]	BVZ vs BVZ+CPT11	N/A	BVZ= 85 BVZ+CPT11= 82	9.2 vs 8.7
TTF	Stupp, 2012 [12]	TTField vs Chemotherapy	N/A	TTF=120 Chemotherapy=117	6.6 vs 6
HSRT	Clarke, 2017 [13]	HSRT+BVZ	30	15	12.5
	Miwa, 2014 [14]	HSRT+TMZ	30	21	12.0
	Wuthrick, 2014 [15]	HSRT+Sunitinib	35	11	12.7(GBM)

Abbreviations: TTF = Tumor Treatment Field; HSRT = Hypofractionated stereotactic radiotherapy; BVZ = Bevacizumab; TMZ = Temozolomide; GBM = Glioblastoma Multiforme.

Figures

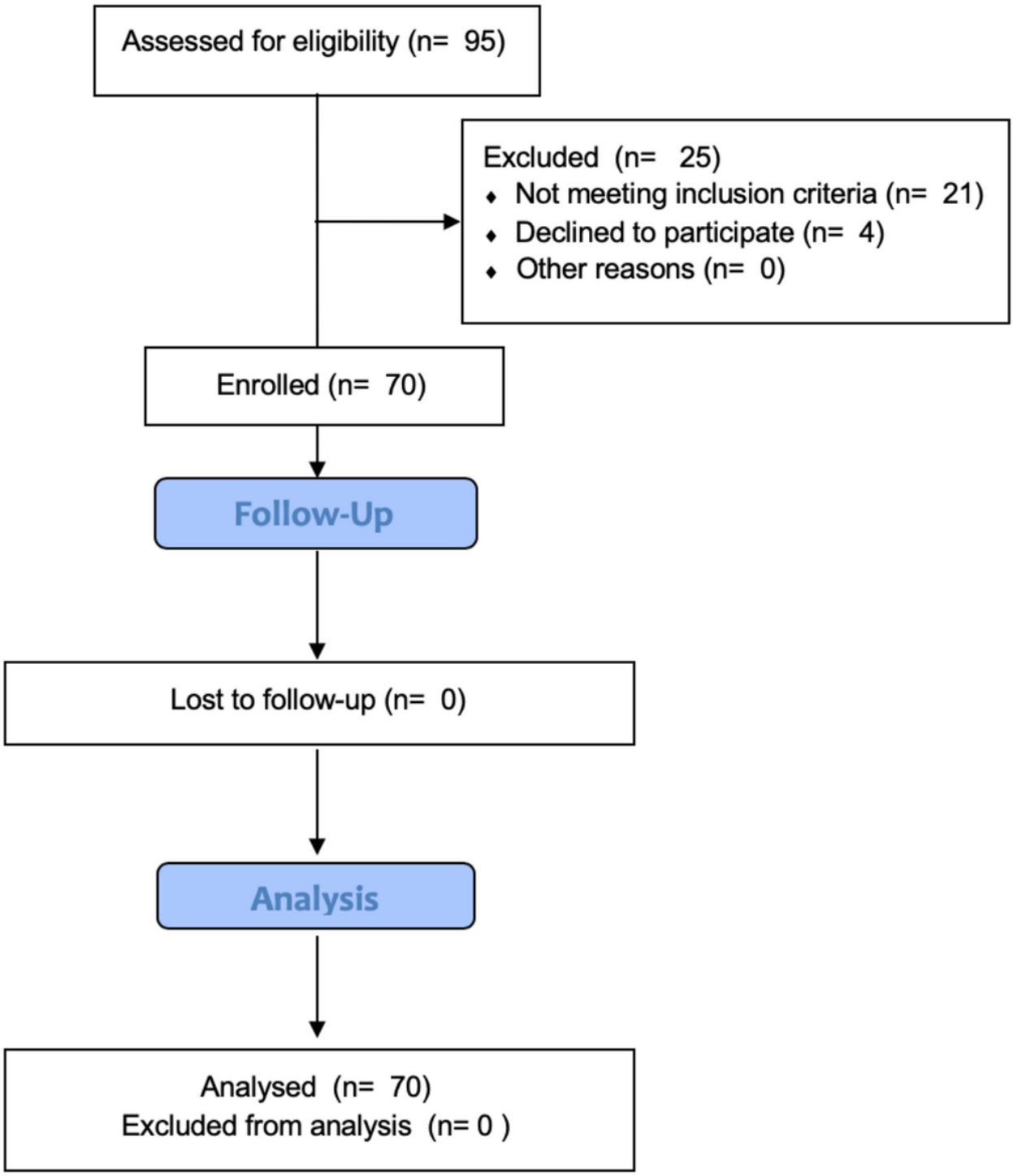

Figure 1

Flow diagram of this retrospective study.

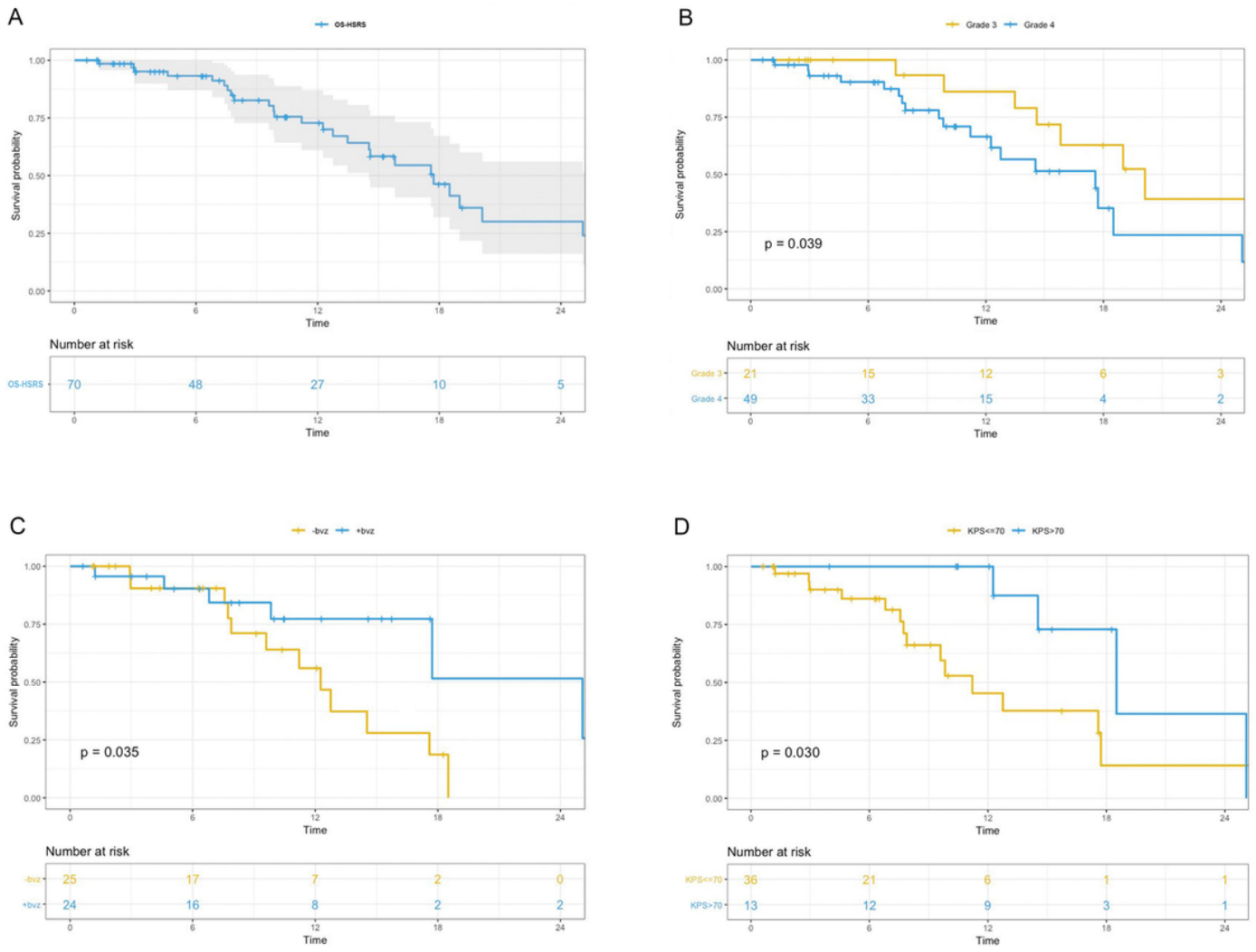

Figure 2

(A) Survival time from salvage HSRS (OS-HSRS) of all rHGG patients; (B) OS-HSRS for WHO Grade 3 and 4 patients; (C) OS-HSRS for WHO Grade 4 patients who underwent concurrent bevacizumab with HSRS; (D) OS-HSRS for WHO Grade 4 patients who had KPS ≤ 70 v >70.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Additionalfile2.pdf
- Additionalfile1.pdf
- AdditionalFiles.docx