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Therapeutic and prognostic impact of target volume delineation in postoperative radiotherapy for high-grade glioma patients with subventricular zone involvement

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Abstract

Objective This study aimed to analyze the effect of target volumes for radiotherapy and dose on the prognosis of high-grade glioma (HGG) patients when the tumor involves the subventricular zone (SVZ), and to provide a reference for postoperative target volume delineation in HGG patients with SVZ involvement.

Methods The clinical and pathological data were collected from 50 HGG patients with SVZ involvement were collected in the Department of Neurosurgery of the First Affiliated Hospital of Soochow University during the period from January 1, 2017 to December 31, 2020. The average dose (Dmean) of the whole ipsilateral and contralateral SVZs as well as the V45Gy and V60Gy of the whole ipsilateral SVZs of the tumor were derived from the dose-volume histograms (DVH). The Kaplan-Meier analysis was applied to compare the survival differences between groups under different factors. The Cox proportional risk regression model was used to analyze the influencing factors of progression-free survival (PFS) and overall survival (OS). The correlation between the size of the ipsilateral SVZ target area range and the progression pattern was tested by chi-square test.

Results Univariate analysis revealed that the potential predictors of PFS of HGG patients with tumor involvement in SVZ were as follows: multiple lesions, tumor size > 3.5 cm and total resection; the potential predictors of OS were multiple lesions, surgical approaches to the lateral ventricles and the dose of contralateral SVZ > 37.33 Gy. Multibariate analysis showed that tumor size > 3.5 cm and total resection were the independent prognostic factors of PFS; multiple lesions was the independent prognostic factors of OS. The Kaplan-Meier method showed that the median PFS and OS of HGG patients with V60Gy ≥ 50% was higher than that of patients with V60Gy < 50% but the difference was not statistically significant. Subgroup analysis showed that patients with V60Gy ≥ 50% had significantly higher PFS in the age < 60 years subgroup ($P = 0.006$), WHO IV grade ($P = 0.006$), and surgical penetration of the lateral ventricle subgroup ($P = 0.034$) than in the V60Gy < 50%. Patients with V60Gy ≥ 50% had significantly higher OS in the WHO

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IV grade subgroup ($P=0.035$), surgically penetrated lateral ventricle subgroup ($P=0.008$), IDH1 wild-type subgroup ($P=0.012$), and MGMT unmethylated subgroup ($P=0.047$) than in V60Gy < 50%. A volume of ≥ 50% of the ipsilateral SVZ receiving a 60 Gy irradiation dose improves local control and reduces the risk of local recurrence in patients with SVZ involvement in HGG.

Conclusions For SVZ-involved HGG patients, the whole ipsilateral SVZ receiving 60 Gy irradiation dose in ≥ 50% of the volume prolonged PFS in those with age < 60 years, WHO IV grade and surgically penetrating lateral ventricles and prolonged OS in those with WHO IV grade, surgically penetrating lateral ventricles, IDH1 wild-type and MGMT unmethylated.

Keywords High-grade glioma, Subventricular zone, Radiotherapy, Target volume delineation

Background

High-grade gliomas (HGG), also known as malignant gliomas, are mainly composed of anaplastic astrocytoma (WHO grade III), anaplastic oligodendroglioma (WHO grade III), and glioblastomas (GBM). HGG is highly malignant, characterized by rapid growth and diffuse infiltration, and has a poor prognosis among malignant tumors. Even with comprehensive surgery-based treatment, HGG patients are prone to local recurrence and intracranial metastasis, resulting in a poor prognosis [1].

A series of studies have shown that neural stem cells (NSCs) are likely to be the origin of malignant gliomas [2, 3], and may be an important cause of the occurrence, recurrence and metastasis of HGG [4, 5]. NSCs are a special type of cell subpopulation in normal brain tissues, which have the characteristics of self-renewal, multidirectional differentiation, unlimited reproduction, and are resistant to radiation therapy and chemotherapy [6, 7]. In adult brain tissue, the subventricular zone (SVZ) of the lateral ventricles and the subgranular zone (SGZ) of the hippocampal dentate gyrus are the two main sites for storing NSCs [8]. Among them, the SVZ is defined as an area of 3–5 mm outside the lateral wall of the lateral ventricles and is the largest neural stem cell reservoir in the adult brain [9, 10]. Previous studies have shown a strong association between the SVZ and the development and biological behavior of gliomas. Lee et al. obtained genetic evidence from glioblastoma patients and mouse models, directly demonstrating that glioma cells develop from NSCs at the site of the SVZ [11]. Tumor involvement in the SVZ is associated with poor prognosis in patients with HGG [12]. Radiotherapy is important for local control of residual tumors in HGG patients after surgery, which can effectively reduce the risk of recurrence. However, there is a lack of clear consensus on the target volume delineation for postoperative radiotherapy in HGG patients with SVZ involvement. For example, whether to include the ipsilateral SVZ, what irradiation range is and how much SVZ dose is needed to minimize the recurrence and prolong the progression-free survival (PFS) of the patients have not yet been answered.

An early retrospective study observed a significant prolongation of PFS in HGG patients irradiated bilaterally or ipsilaterally in the SVZ at doses greater than 43 Gy, but no significant improvement in overall survival (OS) [13]. However, studies by Achari et al. and Muracciole's team [14, 15] have found that receiving higher radiotherapy doses to the SVZ site harmed the survival of HGG patients instead. In these studies, different investigators used different cutoff values for the grouping of doses to the ipsilateral SVZ and contralateral SVZ, mainly including the quartile, median, and three-quarter quartile, with the most common division into high-dose and low-dose groups using the median as the boundary. Even when the same statistical cutoff value is used for grouping, such as using the median as the boundary, the doses of the ipsilateral SVZ and the contralateral SVZ in different studies are not the same, or even differ greatly. The reason for this is that there is a lack of uniform consensus on the target volume delineation of the SVZ site [16]. There are also differences in the positional relationship between the tumor lesion and the SVZ in these studies, and the target volume delineation of SVZ can be quite different as different investigators have different understandings of the disease, anatomy and imaging. In addition, the effect of the extent of radiotherapy in the SVZ area on the survival of HGG patients is even less studied.

Therefore, our study analyzed the effect of radiotherapy dose and range of SVZ site on the recurrence in these patients, and then explored the significance of SVZ involvement in the radiotherapy target area outlining, to provide a reference basis for the relevant target area outlining.

Methods

Patient population and data collection

We selected patients with HGG who underwent surgical treatment at the Department of Neurosurgery of the First Affiliated Hospital of Soochow University between January 1, 2017 and December 31, 2020, and who had been confirmed by imaging to have involvement of the SVZ region. Based on preoperative enhanced magnetic resonance imaging (MRI) T1-weighted images of the patients,

SVZ involvement was defined if the distance from the enhancing lesion to the SVZ was 0 cm (the shortest distance between the tumor and the lateral wall of the lateral ventricle ≤ 5 mm). We contoured the area that 5 mm outside the lateral wall of the lateral ventricular as the SVZ region (Fig. 1). Due to the lack of clear consensus on target delineation for postoperative radiotherapy in HGG patients with SVZ involvement, we did not intentionally spare or irradiate the SVZ during radiotherapy treatment planning in this study.

A total of 122 HGGs were collected,4 cases were did not meet the eligibility criteria, 25 cases were unable to undergo treatment or regular follow-up. Finally 50 cases of HGG had SVZ infiltration were included. Clinical, imaging, and target-area planning and dosage information of the patients were collected from the electronic medical record system, imaging system, and treatment planning systems(TPS) system. This included the patient's gender, age, preoperative Karnofsky Performance Status (KPS) score, number of lesions, tumor size, degree of surgical resection, WHO grading classification, whether the surgery penetrated the lateral ventricle, IDH1 mutation status, Ki67 expression status, MGMT methylation status, and the prescribed dose and number of treatments of radiotherapy. In addition, we obtained the mean dose Dmean values of the whole ipsilateral and contralateral SVZ and V45Gy and V60Gy of ipsilateral SVZ by the dose-volume histogram (DVH) of the planning system. The flow chart is shown in Fig. 2.

Progression definition and prognostic follow-up

Patients were followed up every 3 to 6 months after surgery by telephone inquiry or outpatient review. The follow-up included physical examination, imaging and hematology tests, and quality of life assessment. The primary observational endpoints were PFS and OS. PFS was defined as the time interval between the date of surgery and either the patient's first imaging evidence of intracranial lesion progression or recurrence, or the time interval to the pre-surgery MRI prior to pathological confirmation of recurrence at reoperation; and in the absence of progression evidence, the time interval between the date of surgery and either the patient's last follow-up or death. OS was identified as the time interval from the day of the patient's surgery to the last follow-up visit or the patient's death from glioma and its complications.

Imaging recurrence or metastasis was determined according to the diagnostic criteria for response assessment of neuro-oncology proposed by the Response Assessment in Neuro-Oncology (RANO) [17]. Satisfaction of any of the following: (1) An increase of more than 25% in the sum of the perpendicular diameters of all measurable enhancing lesions (compared with baseline if no decrease) on stable or increasing doses of corticosteroids;

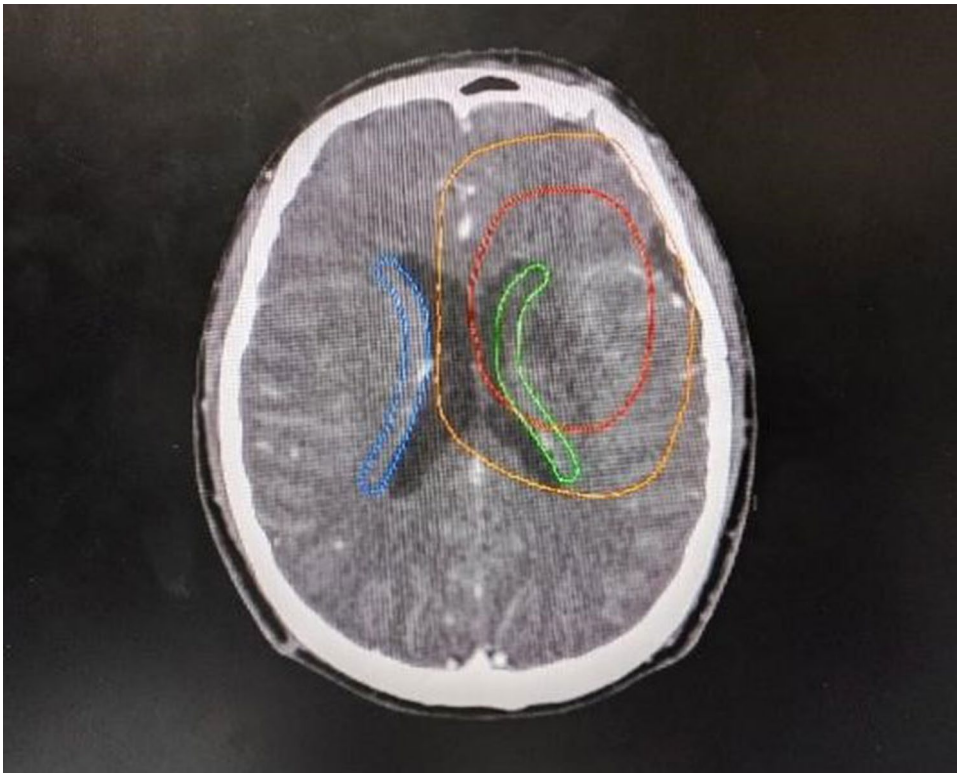

Fig. 1 Ipsilateral SVZ(green line); Contralateral SVZ(blue line)

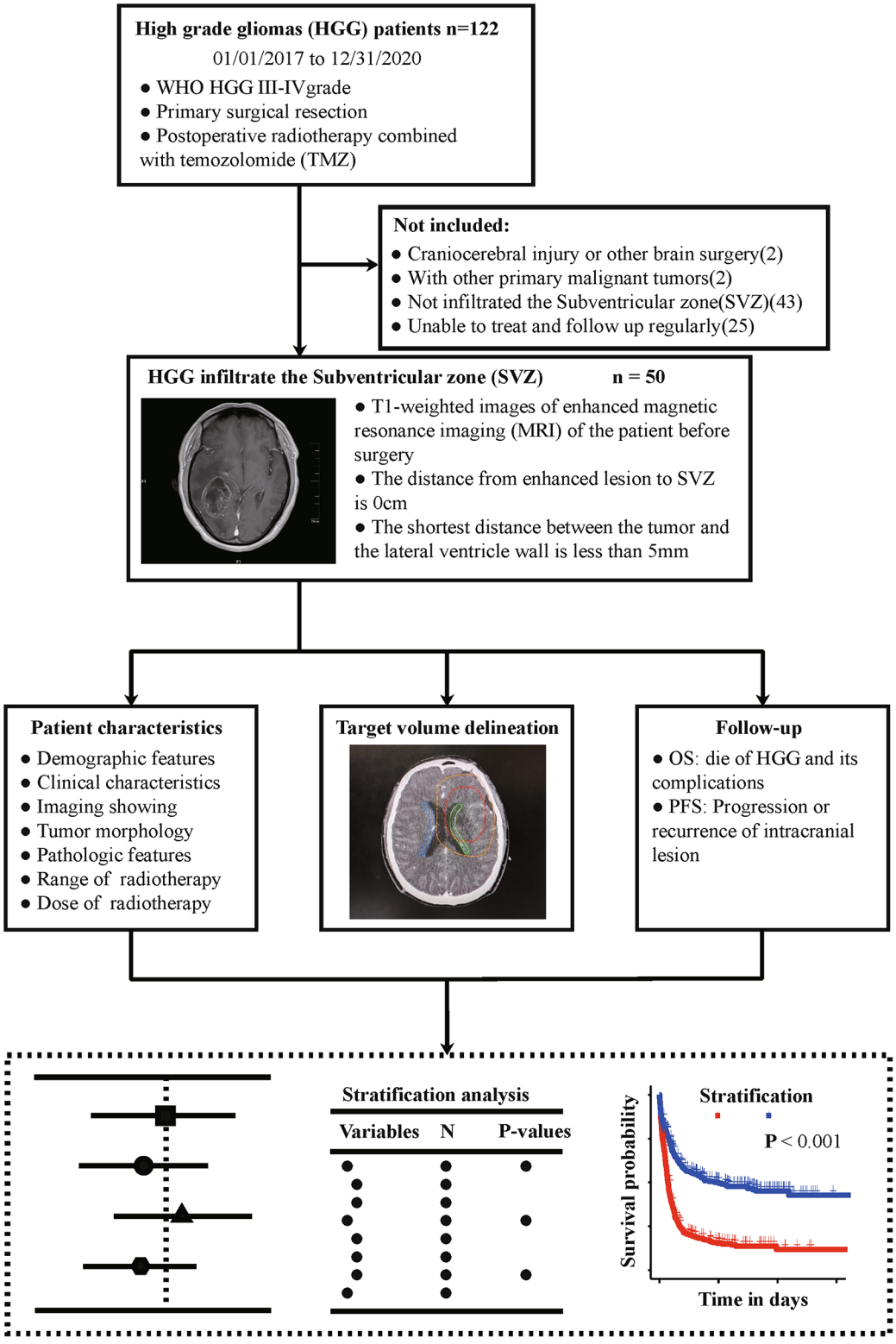

Fig. 2 Study design and procedures

(2) A significant increase in T2/ Fluid-attenuated inversion recovery(FLAIR) nonenhancing lesions, not due to comorbid events (e.g., radiotherapy, demyelination, infection, postoperative changes, ischemic injury, epilepsy, etc.); (3) The appearance of any new lesion; (4) Clear progression of nonmeasurable lesions; (5) Definite clinical deterioration not attributable to other causes apart from the tumor, or to decrease in corticosteroid dose; (6) Failure to return for evaluation due to death or deteriorating condition. Simultaneous diagnosis by at least two senior imaging physicians was required to determine imaging recurrence or metastasis, and in cases of indeterminate imaging recurrence or suspicion of pseudoprogression, the joint judgment of two other experienced associate chief physician and above was required to make the determination.

Outlining of SVZ region and radiotherapy planning

The radiotherapy regimen was based on the Chinese Expert Consensus on Glioma Radiotherapy (2017) and the 2018 National Comprehensive Cancer Network (NCCN) guidelines. According to the principles of target area outlining of the European Society of Radiotherapy Oncology (ESTRO) and the Chinese Expert Consensus on Radiotherapy for Glioma (2017) [18], the scope of target area outlining was determined on localized CT images in TPS concerning the patient's pre- and post-surgical cranial MRIs. These included gross tumor volume (GTV), clinical target volume (CTV), and critical organs (spinal cord, brainstem, optic cross, optic nerve, eyeball, lens, etc.). GTV: Cavity + T1 contrast enhancement, optionally FLAIR alteration clearly visualized as tumour; GTV: 15–20 mm margin from the GTV, include FLAIR-position volume. With the help of the physiatrist, the patient's radiotherapy plan is reverted to the Eclipse or Monaco planning system and finally copied to a new folder. All patients in this study had the ipsilateral SVZ and contralateral SVZ regions outlined separately by the same oncology radiotherapy resident and reviewed by a senior oncology radiotherapist to minimize errors.

The design of the treatment plan was completed using the Monaco treatment system from Elekta, Sweden, and the Eclipse treatment system from Varian, USA, for inverse strength tuning optimization. The plan evaluation required that the planning target volume(PTV) included 95% of the prescribed dose, and the dose distribution within the target area of the PTV was relatively homogeneous, and the error range of the prescribed dose was between − 5% and + 5%. Treatment plans were evaluated by DVH. Positioning errors were controlled within 2–3 mm before radiation therapy was allowed. The planning system used intensity-modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) with an X-ray energy of 6 MV irradiation. Depending on the patient's lesion site and pathological grade, the prescribed dose was designed to be 54 Gy for CTV and 60 Gy for GTV, with a total of 30 irradiations, and the single split dose was 1.8 ~ 2.0 Gy once a day, 5 irradiations per week, for a total of 5 ~ 6 weeks.

Statistical analysis

Data were statistically analyzed using SPSS 26.0 software. Continuous variables was described as median and categorical variables were expressed as counts and percentages. Quartiles were calculated for the median dose of the whole ipsilateral SVZ and contralateral SVZ, respectively. The Kaplan-Meier analysis was applied to calculate median follow up and draw survival curves, and the Cox proportional regression model was used to analyze the risk factors of patients' PFS and OS, and to estimate the hazard ratio (HR) and the corresponding confidence intervals. The correlation between the V60Gy of the ipsilateral SVZ and the recurrence pattern was analyzed using the chi-square test. For all statistical tests, differences were considered statistically significant when the P value was less than 0.05.

Results

Clinical characteristics and prognosis of HGG patients with tumor involvement in SVZ

Based on the screening criteria, a total of 50 patients with SVZ involvement in HGG were selected for our study. The median age of all patients was 54 years old (48.5–62.0), of which 20 cases (40.0%) were female and 30 cases (60.0%) were male. Grade IV tumors, a single lesion and a size greater than 3.5 cm are more common in these patients. Quartile doses of Dmean for the whole ipsilateral SVZ of the tumor were 49.76 Gy for the 25th, 55.56 Gy for the 50th, and 58.75 Gy for the 75th, respectively. The number with V45Gy = 100% for ipsilateral SVZ and < 100% was roughly the same. The number with V60Gy ≥ 50% for ipsilateral SVZ was slightly more numerous than those < 50%. Quartile doses of Dmean for the whole contralateral SVZ were 31.14 Gy for the 25th, 37.33 Gy for the 50th, and 45.02 Gy for the 75th, respectively (Table 1).

Cox regression proportional risk models were used for univariate and multivariable analysis. The results showed that multiple lesions (HR = 2.763, 95% CI = 1.385–5.515; $P = 0.004$), tumor size > 3.5 cm (HR = 3.087, 95% CI: 1.383–6.890; $P = 0.006$), and total resection (HR = 0.378, 95% CI = 0.194–0.737; $P = 0.004$) were significant factors affecting the PFS of HGG patients with tumor involvement in SVZ. Besides, the results for OS showed that multiple lesions (HR = 3.084, 95% CI = 1.279–7.437; $P = 0.012$), surgical approaches to the lateral ventricles (HR = 2.883, 95% CI = 1.200-6.931; $P = 0.018$), and contralateral

Table 1 Clinical characteristics of HGG patients with tumor involvement in SVZ

Variables	Patients ($n=50$)
Age	
Median(Range)	54(48.5–62.0)
Gender	
Male	30(60.0)
Female	20(40.0)
Preoperative KPS	
≤70	24(48.0)
≥80	26(52.0)
Baseline lesion number	
Single lesion	35(70.0)
Multiple lesions	15(30.0)
Tumor size	
≤3.5 cm	8(16.0)
>3.5 cm	42(84.0)
WHO grading	
Grade 3	14(28.0)
Grade 4	36(72.0)
Extent of resection	
Total resection	32(64.0)
Subtotal resection	18(36.0)
Surgical approaches to the lateral ventricles	
Yes	19(38.0)
No	31(62.0)
IDH1	
Mutant type	12(24.0)
Wild type	38(76.0)
Ki67 expression	
≤10%	6(12.0)
>10%	44(88.0)
MGMT	
Methylation	13(26.0)
Unmethylation	32(64.0)
Unknown	5(10.0)
Ipsilateral SVZ	
Dmean (Gy)	
(25th, 50th, 75th)	49.76, 55.56, 58.75
V45(%)	
100%	23(46.0%)
<100%	27(54.0%)
V60(%)	
≥50%	29(58.0%)
<50%	21(42.0%)
Contralateral SVZ	
Dmean (Gy)	31.14, 37.33, 45.02
(25th, 50th, 75th)	

HGG: high-grade glioma; SVZ: the subventricular zone; KPS: Karnofsky performance score; WHO: World Health Organization; IDH1: isocitrate dehydrogenase 1; MGMT: O6-methylguanine-methyltransferase

SVZ irradiated with a dose of greater than 37.33 Gy (HR = 2.545, 95% CI = 1.06–6.252; $P = 0.042$) were the potential predictors that affected the OS of HGG patients with tumor involvement in SVZ (Table 2). The aforementioned variables that are significant for PFS and OS in HGG were selected to for multivariant analysis. Multivariate analysis showed that tumor size > 3.5 cm (HR = 2.666,95% CI = 1.15–6.162; $P = 0.022$) and total resection (HR = 0.466,95% CI = 0.223–0.976; $P = 0.043$) were the independent prognostic factors of PFS of HGG patients with tumor involvement in SVZ; multiple lesions (HR = 2.578,95% CI = 1.050–6.330; $P = 0.039$) was the independent prognostic factors of OS (Table 3).

Table 2 Univariate COX regression analysis of PFS and OS in HGG patients with tumor involvement in SVZ

Clinical characteristics	PFS		OS	
	HR(95% CI)	*P*	HR(95% CI)	*P*
Age ≥ 60y	1.648(0.822–3.303)	0.159	2.172(0.868–5.428)	0.097
Male vs. female	0.784(0.409–1.505)	0.465	1.495(0.602–3.713)	0.386
Preoperative KPS score ≥ 80	0.660(0.347–1.258)	0.207	0.617(0.259–1.471)	0.276
WHO grade 4	1.141(0.552–2.359)	0.722	1.022(0.415–2.518)	0.962
Multiple lesions	2.763(1.385–5.515)	**0.004**	3.084(1.279–7.437)	**0.012**
Tumor size > 3.5 cm	3.087(1.383–6.890)	**0.006**	2.632(0.938–7.381)	0.066
Total resection	0.378(0.194–0.737)	**0.004**	0.466(0.197–1.017)	0.084
Surgical approaches to the lateral ventricles	1.941(0.985–3.828)	0.055	2.883(1.200-6.931)	**0.018**
IDH1 mutant type	0.565(0.248–1.291)	0.176	0.265(0.062–1.136)	0.074
Ki67 expression > 10%	1.326(0.514–3.420)	0.559	2.349(0.542–10.171)	0.253
MGMT methylation	0.849(0.396–1.819)	0.674	1.268(0.475–3.388)	0.635
Ipsilateral dose				
>49.76 Gy	1.362(0.627–2.960)	0.435	1.643(0.549–4.913)	0.374
> 55.56 Gy	1.039(0.542–1.990)	0.908	0.874(0.369–2.069)	0.760
> 58.75 Gy	0.650(0.285–1.480)	0.305	0.385(0.110–1.344)	0.135
Contralateral dose				
> 31.14 Gy	1.017(0.491–2.104)	0.965	1.010(0.369–2.762)	0.985
> 37.33 Gy		0.601	2.545(1.036–6.252)	**0.042**
> 45.02 Gy	1.186(0.626–2.247)	0.722	1.127(0.432–2.938)	0.807
Ipsilateral volume	1.140(0.553–2.350)			
V45 = 100%	0.934(0.486–1.795)	0.838	1.030(0.442–2.399)	0.946
V60 ≥ 50%	0.583(0.306–1.108)	0.100	0.438(0.183–1.050)	0.064

PFS: progression-free survival; OS: overall survival; HGG: high-grade glioma; SVZ: the subventricular zone; KPS: Karnofsky performance score; WHO: World Health Organization; IDH1: isocitrate dehydrogenase 1; MGMT: O6-methylguanine-methyltransferase

Table 3 Multivariate COX regression analysis of PFS and OS in HGG patients with tumor involvement in SVZ

Clinical characteristics	PFS		OS	
	HR(95% CI)	*P*	HR(95% CI)	*P*
Multiple lesions	1.917(0.875-4.200)	0.104	2.578(1.050–6.330)	**0.039**
Tumor size > 3.5 cm	2.666(1.153–6.162)	**0.022**	-	-
Total resection	0.466(0.223–0.976)	**0.043**	-	-
Surgical approaches to the lateral ventricles	-	-	2.446(1.002–5.973)	0.050

PFS: progression-free survival; OS: overall survival

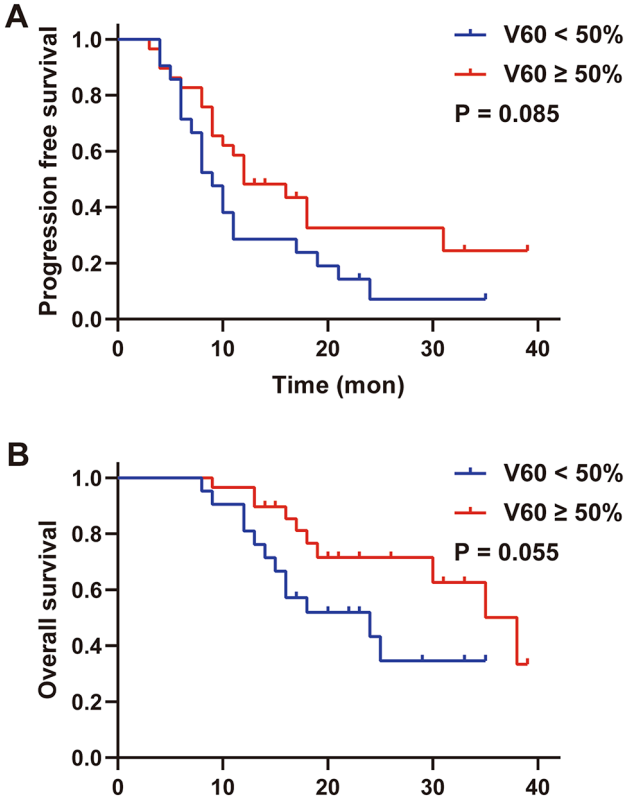

Fig. 3 The Kaplan-Meier survival analysis of progression-free survival (PFS) and overall survival (OS) in HGG patients between V60Gy ≥ 50% and V60Gy < 50%. **A**, PFS. **B**, OS

For different target ranges and doses of the whole SVZ radiotherapy, the Kaplan-Meier method was applied to calculate PFS and OS in different subgroups. And it was found that the median PFS of HGG patients with V60Gy ≥ 50% was higher than that of patients with V60Gy < 50% (12.0 months vs. 9.0 months, $P = 0.085$), but the difference was not statistically significant (Fig. 3A). The median OS of HGG patients with V60Gy ≥ 50% was higher than that of patients with V60Gy < 50% (38.0 months vs. 24.0 months), but the difference was not statistically significant (Fig. 3B). The univariate analysis also indicated that V60Gy ≥ 50% was not the significant predictor for PFS and OS(HR = 0.583, 95% CI: 0.306–1.108, $P = 0.100$; HR = 0.438, 95% CI: 0.183–1.050, $P = 0.064$) (Table 2). This may be related to the small amount of data.

Subgroup analysis in different irradiation ranges with V60 gy

To further explore the population of benefit when ipsilateral SVZ was given with different irradiation ranges with V60 Gy, we performed a subgroup analysis with PFS as the event outcome. The results showed that the target area extent ≥ 50% group significantly prolonged the PFS of HGG patients with involvement of the SVZ region compared with the < 50% group in the age < 60 years subgroup (18.0 months vs. 8.0 months, $P = 0.006$), WHO class IV subgroup (16.0 months vs. 8.0 months, $P = 0.006$), and surgically perforated lateral ventricle subgroup (12.0 months vs. 8.0 months, $P = 0.034$) (Table 4). Subsequently, we explored the survival performance of each of these three subgroups. Kaplan-Meier analysis according to age revealed a total of 36 patients aged < 60 years, 23 patients in the V60Gy ≥ 50% group with a median PFS of 18.0 months, and 13 patients in the V60Gy < 50% group with a median PFS of 8.0 months, with a statistically significant difference ($P = 0.006$, Fig. 4A). Kaplan-Meier analysis based on tumor pathology grade observed a total of 36 patients with WHO grade IV, 20 patients in the V60Gy ≥ 50% group with a median PFS of 16.0 months, and 16 patients in the V60Gy < 50% group with a median PFS of 8.0 months, with a statistically significant difference ($P = 0.006$, Fig. 4B). Kaplan-Meier analysis based on whether or not the lateral ventricle was penetrated by surgery revealed that there were 19 patients with surgical approaches of the lateral ventricle, including 9 patients in the V60 ≥ 50% group with a median PFS of 12.0 months, and 10 patients in the V60 < 50% group with a median PFS of 8.0 months, which was statistically significant ($P = 0.034$, Fig. 4C).

Similarly, we performed a subgroup analysis with OS as the event outcome in the V60Gy ≥ 50% group and V60Gy < 50% group. The results showed that the V60Gy ≥ 50% group significantly prolonged the OS of HGG patients with involvement of the SVZ region compared with the < 50% group in the WHO grade IV subgroup (38.0 months vs. 16.0 months, $P = 0.035$), surgically penetrated lateral ventricle subgroup (30.0 months vs. 16.0 months, $P = 0.008$), IDH1 wild-type subgroup (35.0 months vs. 16.0 months, $P = 0.012$), and MGMT unmethylated subgroup (38.0 months vs. 16.0 months, $P = 0.047$) (Table 5; Fig. 5).

Table 4 Subgroup analysis comparing the PFS of HGG patients with V60 < 50% versus those with V60 ≥ 50% in the ipsilateral SVZ(Kaplan-Meier analysis)

Clinical characteristics	*N*	Median PFS (95% CI)		*P*
		V60Gy < 50%	V60Gy ≥ 50%	
Age				
≥60y	14	10.0(7.2–12.8)	4.0(2.4–5.6)	0.013
< 60y	36	8.0(5.7–10.3)	18.0(10.8–25.2)	**0.006**
Gender				
Male	30	10.0(7.4–12.6)	16.0(10.4–21.6)	0.102
Female	20	7.0(4.2–9.8)	9.0(3.9–14.1)	0.605
Preoperative KPS score				
≥80	26	7.0(4.1–9.9)	18.0(11.9–24.1)	0.074
≤70	24	9.0(5.6–12.4)	9.0(2.2–15.8)	0.685
Lesion number				
Multiple	15	6.0(3.4–8.6)	8.0(2.6–13.4)	0.219
Single	35	11.0(9.2–12.8)	18.0(11.3–24.7)	0.314
Tumor size				
>3.5 cm	42	10.0(7.3–12.7)	16.0(10.1–21.9)	0.094
≤ 3.5 cm	8	6.0(2.1–9.9)	4.0(0.0-8.9)	0.833
WHO grading				
Grade 4	36	8.0(6.7–9.3)	16.0(9.3–22.7)	**0.006**
Grade 3	14	17.0(4.1–29.9)	9.0(0.2–17.8)	0.551
Extent of resection				
Total	32	10.0(6.3–13.7)	18.0(11.5–24.5)	0.148
Subtotal	18	8.0(5.7–10.3)	9.0(6.8–11.2)	0.266
Surgical approaches to the lateral ventricles				
Yes	19	8.0(5.3–10.8)	12.0(7.4–16.6)	**0.034**
No	31	10.0(6.6–13.4)	16.0(7.9–24.1)	0.446
IDH1				
Mutant type	12	10.0(0.0-	18.0(9.0-26.9)	0.839
Wild type	38	28.6)8.0(6.0–10.0)	12.0(9.0–15.0)	0.072
Ki67 expression				
≤10%	6	NA	6.0 (2.1–9.9)	0.819
>10%	44	8.0(5.4–10.6)	16.0(11.4–20.6)	0.097
MGMT				
Methylation	13	17.0(0.0-	11.0(5.7–16.3)	0.999
Unmethylation	32	34.6)9.0(6.4–11.6)	12.0(8.1–15.9)	0.249

PFS: progression-free survival; HGG: high-grade glioma; SVZ: the subventricular zone; KPS: Karnofsky performance score; WHO: World Health Organization; IDH1: isocitrate dehydrogenase 1; NA: Not Available; MGMT: O6-methylguanine-methyltransferase

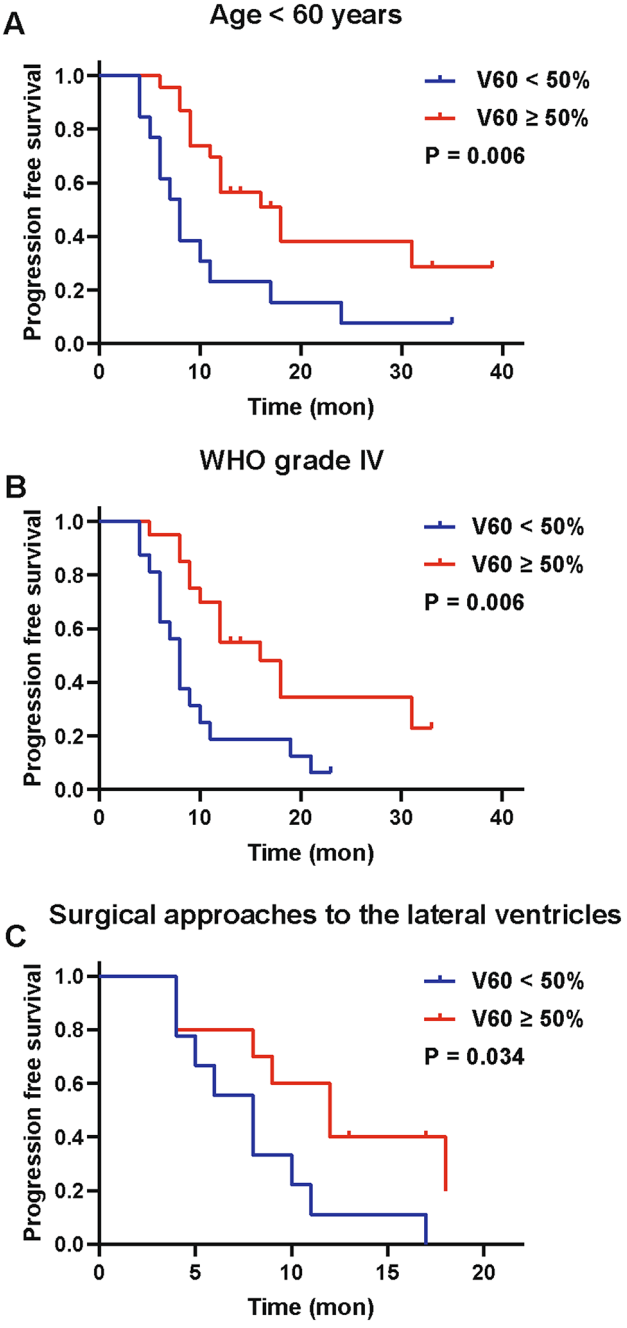

Fig. 4 The Kaplan-Meier survival analysis of progression-free survival (PFS) of HGG patients with V60Gy < 50% versus those with V60Gy ≥ 50% in the ipsilateral SVZ. **A**, Age < 60 years. **B**, WHO grade IV. **C**, Surgical approaches to the lateral ventricles

SVZ target zone outlining and progression patterns

As of December 31, 2021, the median follow-up of 50 patients was 31.0 months (13.0–49.0), and a total of 38 (38/50,76.0%) patients experienced recurrence. Among them, 26 patients (52.0%) had local recurrence and 12 patients (24.0%) had distant metastasis. 13 patients (13/29, 44.8%) had local recurrence, 6 patients (6/29, 20.7%) had distant metastasis, and 10 patients (10/29, 34.5%) had no progression in patients with V60Gy ≥ 50%. In the group with V60Gy < 50%, 13 patients (13/21. 61.9%), 6 cases of distant metastasis (6/21, 28.6%), and 2 cases of non-progression (2/21, 9.5%). The incidence of progression was lower in patients with V60Gy ≥ 50% than in patients with V60Gy < 50% (65.5% vs. 90.5%), and the difference was statistically significant ($P = 0.041$). The incidence of local recurrence was lower in patients with V60Gy ≥ 50% than in patients with V60Gy < 50% (44.8% vs. 61.9%), but the difference was not significant ($P = 0.125$, Table 6).

Table 5 Subgroup analysis comparing the OS of HGG patients with V60 < 50% versus those with V60 ≥ 50% in the ipsilateral SVZ

Clinical characteristics	*N*	Median OS (95% CI)		*P*
		V60Gy < 50%	V60Gy ≥ 50%	
Age				
≥60y	14	24.0(4.7–43.3)	18.0(14.7–21.3)	0.617
< 60y	36	18.0(14.6–21.4)	38.0(32.2–43.9)	0.053
Gender				
Male	30	18.0(12.1–23.9)	35.0(14.6–55.4)	0.149
Female	20	24.4(16.7–32.1)	30.1(25.6–34.6)	0.253
Preoperative KPS score				
≥80	26	27.7(20.8–34.5)	29.2(23.1–35.2)	0.858
≤70	24	15.0(11.6–18.4)	28.0(26.9–43.1)	0.213
Lesion number				
Multiple	15	16.0(13.7–18.3)	19.0(15.7–22.3)	0.410
Single	35	24.7(19.5–29.9)	34.4(30.5–38.3)	0.057
Tumor size				
>3.5 cm	42	24.0(11.1–36.9)	38.0(29.0–47.0)	0.068
≤ 3.5 cm	8	16.0(4.9–27.1)	16.0(5.5–26.5)	0.889
WHO grading				
Grade 4	36	16.0(8.4–23.6)	38.0(26.4–49.6)	**0.035**
Grade 3	14	25.0(10.0–40.0)	35.0(18.8–51.2)	0.982
Extent of resection				
Total	32	25.0(16.4–33.6)	38.0(23.4–52.6)	0.098
Subtotal	18	16.0(13.7–18.3)	35.0(9.3–60.7)	0.204
Surgical approaches to the lateral ventricles				
Yes	19	16.0(14.6–17.4)	30.0(10.7–49.3)	**0.008**
No	31	27.8(22.0-33.5)	33.2(28.1–38.2)	0.562
IDH1				
Mutant type	12	NA	NA	0.371
Wild type	38	16.0(12.2–19.9)	35.0(23.9–46.1)	**0.012**
Ki67 expression				
≤10%	6	NA	NA	0.317
>10%	44	18.0(10.7–25.3)	38.0(18.1–57.9)	0.095
MGMT				
Methylation	13	NA	30.0(13.4–46.6)	0.447
Unmethylation	32	16.0(2.9–29.1)	38.0(32.3–43.7)	**0.047**

OS: overall survival; HGG: high-grade glioma; SVZ: the subventricular zone; KPS: Karnofsky performance score; WHO: World Health Organization; IDH1: isocitrate dehydrogenase 1; NA: Not Available; MGMT: O6-methylguanine-methyltransferase

Table 6 Comparison of progression patterns in HGG patients with V60 < 50% versus those with V60 ≥ 50% in the ipsilateral SVZ

	V60 < 50% (%)	V60 ≥ 50% (%)	χ^2	*P*
Local recurrence	13(61.9%)	13(44.8%)	4.160	0.125
Distant metastasis	6(28.6%)	6(20.7%)		
No progression	2(9.5%)	10(34.5%)		
Total	21(100%)	29(100%)		

HGG: high-grade glioma; SVZ: the subventricular zone

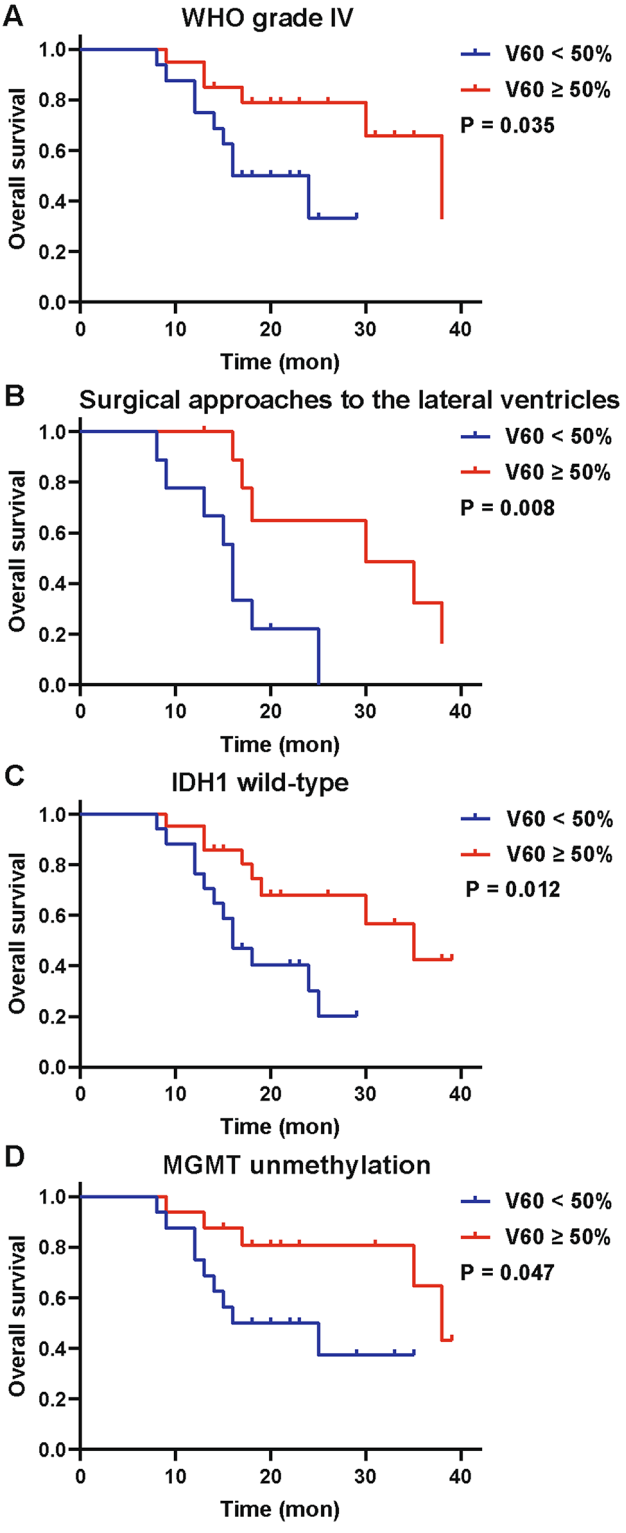

Fig. 5 The Kaplan-Meier survival analysis of overall survival (OS) of HGG patients with V60Gy < 50% versus those with V60Gy ≥ 50% in the ipsilateral SVZ. **A**, WHO grade IV. **B**, Surgical approaches to the lateral ventricles. **D**, IDH1 wild-type. **D**, MGMT unmethylation

Discussion

Our SVZ dosimetry data were high on the ipsilateral side compared to other studies and similar to previous studies on the contralateral side due to the fact that the patients

included in this study were a specific population of HGG with SVZ involvement. Although age, KPS score, and grading were classic prognostic factors in clinical practice, however, due to the small sample size of this study, some confounding factors and the interaction effected among prognostic factors lead to a certain correlation with PFS and OS, but no statistical significant difference. In a univariate analysis, our study found that the irradiated dose of SVZ was not significantly associated with PFS and OS in patients. This is different from the findings of other studies [19], probably because only part of the population of HGG patients included in previous studies had SVZ involvement. However, analyzing the PFS of patients in different irradiated dose and irradiation range groups, it was observed that the median PFS with V60Gy ≥ 50% was significantly higher than that of patients with V60Gy < 50%. The patient's OS showed the same.

We further grouped the patients by whether V60Gy was > 50%, and subgroup analysis revealed that in the subgroup with WHO grade IV, surgical approaches to the lateral ventricles, and age < 60 years, ipsilateral SVZ receiving V60Gy ≥ 50% significantly prolonged the PFS of patients compared with < 50%. From the viewpoint of tumor biology, glioblastoma (WHO grade IV) is the most aggressive and malignant type of glioma, with highly infiltrative growth, difficult to remove cleanly by surgery, and prone to recurrence [20]. Anatomically, the location of the tumor in SVZ-affected HGG patients is closer to the midline, which makes total surgical resection difficult. Therefore, for SVZ-affected glioblastomas, the irradiation range of the therapeutic dose of 60 Gy is conducive to the killing of postoperative residual tumor cells. Meanwhile, for HGG patients with SVZ involvement, surgical penetration of the lateral ventricle increases the risk of cerebrospinal fluid dissemination and distant recurrence, and a large range of the ipsilateral SVZ target area reduces distant metastasis of tumor cells [21]. This would explain why in the WHO grade IV, surgically penetrated lateral ventricle subgroup, ipsilateral SVZ receiving V60Gy ≥ 50% significantly prolonged patients' PFS compared to < 50%. We also observed that patients with age < 60 years benefited from radiotherapy with a radiotherapy extent of V60Gy ≥ 50%, and this population is usually in better general condition and more tolerant to radiotherapy with a larger extent of the target area. Similarly, on OS this group of patients also benefits.

In addition, this study also found that contralateral SVZ dose > 37.33 Gy was a poor prognostic factor in HGG patients with SVZ involvement, probably because the combined factors of tumor invasion of the SVZ on the diseased side, surgery, and radiotherapy made a large number of NSCs in the ipsilateral SVZ region decrease causing impaired neurorestorative function. The high-dose radiotherapy to the contralateral SVZ caused a large number of NSCs necrotic damage in the contralateral SVZ region aggravating the cerebral recovery function damage, which in turn led to neurocognitive toxicity affecting patients' neurocognitive function. Severe neurocognitive decline is closely associated with poor prognosis [22], which may partly explain the shorter survival time of HGG patients treated with higher doses of radiotherapy to the contralateral SVZ in HGG patients with SVZ involvement. In addition, radiotherapy is also highly susceptible to radiation-induced damage to other normal brain tissues, which is closely related to the dose of radiotherapy [23]. The higher the dose of radiotherapy received by normal brain tissue, the more prone to radioactive brain damage [24]. At the same time, the use of chemotherapeutic agents also increases the risk of the occurrence of radioactive brain damage, and the presence of tumor invasion of the SVZ in HGG patients implies a poor prognosis, and clinicians tend to give higher doses and/or longer cycles of adjuvant chemotherapy with temozolomide [25]. In other words, when the contralateral SVZ receives a higher dose of radiotherapy, the other surrounding normal brain tissues are also irradiated at a relatively high dose, and there is a higher risk of brain injury when combined with chemotherapy. Again, there may be a bias in the results arising from OS as a study endpoint.

In this study, we also analyzed the relationship between the extent of radiotherapy at the SVZ site and the pattern of progression and found that the local recurrence rate was lower in patients with an ipsilateral SVZ radiotherapy extent of V60Gy ≥ 50% than in patients with V60Gy < 50%, with a significant trend, but the difference was not statistically significant. The reason may be the bias of the results due to too small sample size, different surgical resection ranges, and so on. That is, a large range of radiotherapy target areas in the SVZ region can to some extent reduce the risk of local recurrence in patients with SVZ-involved HGG patients and improve the rate of local control of the tumor, which is of some clinical significance. In addition, we also observed that the risk of distant metastasis was slightly decreased in HGG patients with radiotherapy range V60Gy ≥ 50%, and more studies are needed to clarify the effect of larger range radiotherapy on the prevention of distant metastasis in this group of patients.

However, there are some shortcomings in this study. Firstly, the study was retrospective and there was recall bias making the information incomplete or inaccurate. Secondly, our sample size was small, which may affect the analysis of the results to some extent. What's more, the study did not analyze the changes in the cognitive function of patients after radiotherapy, and it could not be well-defined whether the SVZ radiotherapy dose and

irradiation range increased the incidence of radiotherapy complications such as radio brain injury. Further information should be accumulated and prospective studies should be conducted to confirm this.

Conclusions

In conclusion, insufficient extent of target zone outlining tends to lead to missed target zone illumination and increase the risk of tumor recurrence. Our results showed that receiving 60 Gy in the ipsilateral SVZ with no less than 50% of the volume was advantageous in prolonging the time to recurrence in HGG patients and could benefit patients aged less than 60 years, WHO grade IV, and those with surgically penetrated lateral ventricles. Moreover, SVZ regional radiotherapy doses of 60 Gy may reduce the risk of local recurrence in HGG patients involved in the SVZ when radiotherapy is more extensive. However, stronger clinical evidence is still needed to validate the clinical significance of target volume delineation in HGG patients with SVZ involvement.

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Author contributions
The research study was designed by Xiaoting Xu; Fei Sun performed the data analysis and interpretation; Guanghui Gan and Yan Zhu performed the target volume delineation; Fei Sun and Yuan Xu performed the statistical analysis; Fei Sun and Xiaoting Xu drafted the manuscript. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The Ethics Committee of the First Affiliated Hospital of Soochow University (the ethics approval number:2021 – 328) approved the study.

Consent for publication
Due to a retrospective study to collect patient clinical data and imaging findings, the patient's informed consent was waived.

Competing interests
The authors declare no competing interests.

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