Chapter

Stereotactic Radiosurgery for Recurrent Glioblastoma Multiforme

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Abstract

Glioblastoma multiforme (GBM) is the most aggressive intracranial tumor that primarily affects adults. Since the introduction of temozolomide in 2005, maximal resection surgery with concurrent chemoradiation has become the standard treatment method for patients with newly diagnosed GBM. Although newly discovered chemoagents have been demonstrated to improve the median survival time, GBM still recurs in most patients. Recurrent GBM is still a therapeutic challenge for clinical physicians. Surgical intervention and other conventional chemoagents have been applied to manage recurrent GBM. Stereotactic radiosurgery (SRS) provides a highly precise radiation dose to the tumor lesion and reduces the dose to the adjacent normal brain tissue. After standard treatment for newly diagnosed GBM is completed, conventional re-irradiation therapy is not suitable for patients with recurrent GBMs. Therefore, SRS may become an alternative option in the treatment of recurrent GBMs. In this review, we discuss the relevant literature regarding SRS for recurrent GBMs and provide treatment advice for clinical physicians.

Keywords: stereotactic radiosurgery, recurrent glioblastoma multiforme, re-irradiation, survival time, prognosis

1. Introduction

Glioblastoma multiforme (GBM) is the most common primary brain neoplasm in adults [1, 2]. There are 1.6 times more males than females who develop a GBM [1]. According to the latest statistical report of the Central Brain Tumor Registry of the USA, the annual incidence of GBM has been estimated at approximately 3.22 cases per 100,000 people, and the median age is 65 years [3]. The current standard treatment of patients with a newly diagnosed GBM was established in 2005, and it consists of maximal surgical resection of the tumor followed by chemotherapy and conventional radiotherapy [4, 5]. Despite this therapy, the median overall survival time is approximately 15–17 months [2].

GBM is a refractory malignant and infiltrating tumor that may recur any time after initial multimodal treatments are completed [6]. Managing recurrent GBM has always been challenging, and a balance has to be achieved between significant treatment toxicity and associated morbidities and mortalities [6, 7]. Reoperation with maximal resection at recurrence remains as an independent predictor to improve overall survival [8, 9]. However, repeat gross-total resection may not be

easily achieved when recurrent GBM involves important eloquent brain structures, such as the brainstem or motor area. Extensive bevacizumab and temozolomide are the two main FDA-approved chemoagents used to treat patients with recurrent GBMs, but the prognosis remains poor [10].

Re-irradiation is an alternative option for managing recurrent GBMs [11]. The majority of recurrent tumors occur at the initial or adjacent regional sites [12]. Because a total dose of 60 Gy in 30 fractions has been prescribed for initial radiation therapy, re-irradiation with further dose escalation appears to produce more significant toxicity [10, 11]. Stereotactic radiosurgery (SRS) is a noninvasive treatment that provides a highly precise, targeted additional radiation boost to the tumor lesion, and it maintains an acceptable rate of adverse radiation effects while reducing the dose to adjacent normal brain tissues [13]. In this review, we searched the relevant literature and investigated the role of SRS in the management of recurrent GBMs. Our results may provide treatment information for clinical treatment.

2. Search methodology

In this study, different combinations of the keywords "recurrent glioblastoma multiple," "high-grade glioma," "stereotactic radiosurgery," and "re-irradiation" were used to search the published literature in the PubMed database until October 31, 2019. The inclusion criteria of the study were (1) patients with recurrent GBMs, (2) treatment with stereotactic radiosurgery (SRS) or a fractionated radiosurgery (less than 5 fractions), and (3) outcomes with overall survival time. Tumor progression was also accepted as a recurrent disease. Potentially relevant studies were identified from the reference lists of the studies obtained from the database search. Articles excluded from the review were those written in languages other than English and those that lacked survival response data. Finally, a total of 49 studies were included in this review.

3. The summary of patients with recurrent GBMs treated with SRS

A total of 49 studies published from 1994 to 2019 were enrolled in this review, as summarized in **Table 1** [13–61]. There were 6 prospective studies and 43 retrospective studies. About 2066 patients with recurrent glioblastomas treated with SRS, including linear accelerator (LINAC) radiosurgery, Gamma Knife radiosurgery, and Cyberknife radiosurgery, are reported. In all studies, the median age of the patients who received SRS treatment for recurrent GBM ranged from 34 to 62 years. The majority of patients were males. The median prescribed dose of SRS ranged from 6 to 30 Gy. The median targeted volume for treatment ranged from 1.35 to 21.3 cc. The overall survival time from treatment for SRS ranged from 3.9 to 17.9 months, where the progression-free survival time from the treatment of SRS ranged from 2.1 to 14.9 months. In the prognostic analysis of survival time in patients with recurrent GBMs treated with SRS, a small tumor volume, younger age, higher Karnofsky performance scale (KPS) score, lower recursive partitioning analysis (RPA) class, adjuvant bevacizumab, methylated O6-methylguanine-DNA-methyltransferase (MGMT) promoter, and longer interval between the original surgery and SRS were significantly associated with patients' survival outcomes.

3.1 The effect of LINAC radiosurgery in patients with recurrent GBMs

From 1994 to 2018, a total of 501 patients with recurrent GBMs treated with LINAC SRS were enrolled in 22 studies, including 3 prospective trials and 17

Year	Author	Study type	Enrolled year	All patients	Numbers of patients with rGBM	Gender	Age (years)			Treatment Modality of SRS	Radiation dose (Gy)			Adjuvant chemo agents	Target volume (cm3)			Median overall survival after SRS (months)	Median progressive-free survival after SRS(months)	Factors associated with favorable outcome	
						Male: Female	Mean	Median	Range		Median marginal dose	Mean marginal dose	Range		Median	Mean	Range			Univariate analysis	Multivariate analysis
1994	Chamerlain et al.[14]	Prospective phase II	NR	20	5			34[a]	8-62a	LINAC	13.4[a]		12-15.7[a]		17[a]		3-53.5[a]	8[a]	4[a]		
1995	Shrieve et al.[16]	Retrospective	1985-1993	118	72			46[a]	9-77[a]	LINAC	13[a]		6-20[a]		10.1[a]		2.2-83[a]	10.2		age<46 years, tumor volume < 10.1 cm^3,	younger age, small tumor volume
1995	Hall et al.[15]	Retrospective	1991-1994	35	26			48[a]	18-72[a]	LINAC	21[a]	20[a]	7.5-40[a]		28[a]	35[a]	2.4-98[a]	8		younger age, higher KPS	younger age
1996	Larson et al.[17]	Retrospective	1987-1994	189	66			45[a]	2-70[a]	GK	16[a]		5-37.5[a]		6.5[a]		0.3-96[a]	10			younger age, increased KPS, smaller tumor volume, and unifocal tumor
1997	Kondziolka et al.[18]	Retrospective	1987-	107	19		51[b]		3-72[b]	GK(since 1991)		15.5[b]	12-25[b]			6.5[b]	0.88-31.2[b]	30			younger age, smaller tumor volume, and KPS ≥ 70
1999	Cho et al.[19]	Retrospective	1991-1998	71	27			48[a]	16-74[a]	LINAC	17[a]		9-40[a]		10[a]		1-54[a]	7.1			younger age, higher KPS, smaller tumor volume
1999	Sanghavi et al.[60]	Retrospective	1989-1997	30	22			52[a]	13-68[a]	LINAC		12			7.2[a]		0.42-35.1[a]	8[a]	3		
2000	Park et al.[61]	Retrospective	1990-1999	23	22			53[a]	36-80[a]	LINAC (n=13)/GK (n=10)	15[a]		12-20[a]		9.9[a]		0.8-37.9[a]	10.3[a]		NS	
2002	Larson et al.[20]	Prospective phase II	1996-1999	80	14	9:5		53	22-74	GK	15		12-17.5	Marimastat	8		1.6-29.7	8.7	3.8[c]		
2002	Larson et al.[20]	Prospective phase II	1996-1999	80	39	26:13		50	21-77	GK	16		10-20		9.1		0.3-29.1	10.1	3.8[c]		
2005	Mahajan et al.[23]	Retrospective	1998-2003	41	38			54[a]	17-69[a]	LINAC	NR		NR		4.7[a]		0.15-16.3[a]	11[a]			
2005	Hsieh et al.[22]	Retrospective	1998-2003	51	26		58.2	59[b]	17-81[b]	GK	12[b]		15-32[b]		13.6[b]		0.6-64.4[b]	10			age < 50 years, KPS > 90, the use of chemotherapy
2005	Combs et al.[21]	Retrospective	1993-2001	32	32	19:13		56	33-76	LINAC	15		10-20		10		1.2-59.2	10	5	NS	
2008	Schwer et al.[25]	Prospective Phase I	2004-2006	15	11			47[a]	23-65[a]	LINAC			18-36(3 fx)[a]	Gefitinib	41.3[a]		8.4-150.9	10[a]	7[a]		
2008	Kong et al.[24]	Retrospective	2000-2006	114	65			49[a]	5-75[a]	LINAC (n=5)/GK (n=109)	16[a]		12-50[a]		10.6[a]		0.09-79.6[a]	13	4.6	tumor volume < 10cc	NS
2009	Pouratian et al.[29]	Retrospective	1991-2007	48	26			60.7	12.9-76.9	GK	6		3-15		21.3		0.3-110	9.4	7.1	the use of steroid, time to SRS	the use of steroid
2009	Patel et al.[28]	Retrospective	2001-2006	36	26			53	25-70	LINAC	18		12-20		10.4		0.3-60.1	8.4			
2009	Biswas et al.[26]	Retrospective	2000-2007	33	18			57.8[b]	33-81b	LINAC	15		9-20		8.4		0.2-32.2	5.3	3.4	NS	
2009	Kida et al.[27]	Retrospective	-	172	54[b]		52.4		11-80	GK		14.7	8-25			29	7-48.3	14			
2009	Villavicencio et al.[30]	Retrospective	2002-2005	46	26	18:8	56.4		36-82	CK		20	8-25			7	0.4-48.5	7		NS	NS

2011	Elliott et al.[31]	Retrospective	2004-2009	26	16		60	36.5-70.6[a]	GK	15		12-18		1.35		0.27-11.9[a]	12.9		age at diagnosis, age after SRS for recurrence, interval between surgery and recurrence, KPS ≥ 90, RPA class, tumor volume	interval between surgery and recurrence, KPS ≥ 90, tumor volume
2011	Marazano et al.[32]	Retrospective	2001-2008	22	13		55[d]	27-81[d]	LINAC	17		14-22		5.3		0.6-14	11	4[d]		
2011	Sirin et al.[33]	Retrospective	1998-2010	19	19	13:6	47	23-65	LINAC	16		10-19		13		2-59	9.3	5.7		
2012	Cuneo et al.[35]	Retrospective	2002-2010	63	33		47[a]		LINAC	15[a]		12.5-25[a]	BEV	4.5[a]			11.2[a]	5.2[a]		KPS > 70, age < 50
2012	Cuneo et al.[35]	Retrospective	2002-2010	63	16		48[a]		LINAC	15[a]		12.5-25[a]		5.6[a]			3.9[a]	2.1[a]		KPS > 70, age < 50
2012	Skeie et al.[38]	Retrospective	1996-2007	77	32	12:20	51	27-73[a]	GK	12.2		8-20			12.4		9			tumor volume, RPA class, neurological deficits, time to recurrence, adjuvant therapy, tumor location
2012	Skeie et al.[38]	Retrospective	1996-2007	77	19	7:12	50	27-73[a]	GK+re-operation	12.2		8-20			13.9		15			tumor volume, RPA class, neurological deficits, time to recurrence, adjuvant therapy, tumor location
2012	Park et al.[37]	Retrospective	1987-2010	11	11	8:3	62	46-72	GK	16		13-18	BEV + irinotecan/ TMZ	13.6		1.2-45.1	17.9	14.9		
2012	Koga et al.[36]	Retrospective	1990-2007	9	8	5:3	43[a]	17-64[a]	GK		>20			15[a]		3-47[a]	10.5			
2012	Koga et al.[36]	Retrospective	2007-2010	9	7	4:3	53[a]	27-79[a]	GK		20			13.6[a]		6-19[a]	9			
2012	Conti et al.[34]	Retrospective	2007-2010	23	11		58[c]		CK		20	NR			15.1	NR	7	4		
2012	Conti et al.[34]	Retrospective	2007-2010	23	12		58[c]		CK		20	NR	TMZ		13.8	NR	12	7		
2013	Cabrera et al.[39]	Prospective trial	2010-2011	15	8		53[a]	25-66[a]	LINAC		18	NR	BEV				14.4[a]	3.9[a]		
2014	Clark et al.[40]	Retrospective	2010-2013	21	18		54.1[a]	30-82[a]	LINAC	30 (5-fractions)			BEV	20[a]		3.6-85.6[a]	12.5[a]	11[a]		
2014	Greenspoon et al.[42]	Prospective cohort	2011-2012	31	31		53	36-75	CK	NR		25-35 (5-fractions)	TMZ	12.1		4.9-19.7	9	7	small tumor volume (<3 cm)	
2014	Dodoo et al.[41]	Retrospective	2001-2007	55	35		51.1a	17-81.1a	GK	20		14-22		4.8		0.03-38.1	11.3			
2014	Martinez-Carrillo et al.[43]	Retrospective	1997-2010	87	46	27:19	49.5	26-78	LINAC		18	14-20			4	0.05-34.1	7.5		age, tumor and treatment volume, RPA class, KPS, margin to the planning target volume	KPS > 80, RPA class, margin to the planning target volume
2014	Yazici et al.[44]	Retrospective	2009-2011	37	37	18:19	37	22-69	CK	30		14-32	BEV	24		2-81	10.6	7.9	tumor volume < 24cc	

2015	Bir et al.[45]	Retrospective	2000-2013	36	36[b]	20:16	53	16-82	GK	14	10-20			11.4		7.9		KPS > 70, age ≤ 50, initial post-operative treatment with EBRT, adjuvant SRS for recurrence	
2015	Niranjan et al.[13]	Retrospective	1987-2008	297	153[b]		58	23-89	GK	15	9-25		14		0.26-84.2	10.2	4.3	age < 60 years, KPS ≥ 80, marginal dose ≥ 15Gy, tumor volume ≤ 14cc	age < 60 years, tumor volume ≤ 14cc
2015	Kim et al.[47]	Retrospective	2002-2011	144	29	13:16	61	35-87	GK	15	9-30		11		0.5-40	9.2	3.6		
2015	Kim et al.[47]	Retrospective	2002-2011	144	28	16:12	53	28-73	GK	15	5-20	TMZ	9.8		0.6-49	15.5	6		
2015	Pinzi et al.[48]	Retrospective	2004-2011	128	88		51[a]	18-79[a]	CK	15 (23 for m-SRS group)[a]	6-22 (12-28 for m-SRS group)[a]		2 (10 for m-SRS group)[a]		0.14-83 (0.63-120 for m-SRS group)[a]	10		age<40 years, RPA class 1-2, other therapy after SRS, Radiotherapy=60Gy	other post-SRS therapies (second-line chemotherapy and/or surgery)
2015	Hasan et al.[46]	Retrospective	2007-2014	19	19	13:6	55	28-78	CK	25 (3-5 fractions)	18-35 (3-5 fractions)	BEV/TMZ/anti-epidermal factor receptor (125)I-mAB 425/combina-tion		35	0.9-151.7	5.3		frontal lobe tumor, adjuvant therapy with BEV or TMZ, time to first recurrence > 16 months, tumor volume < 36 cc, RPA class < 5, ECOG < 2	
2016	Frischer et al.[50]	Retrospective	NR	42	42	24:18	57.2	15.7-81.9	GK	10	6-16		5.1		0.6-15	9.6	4.4	MGMT methylation	
2016	Holt et al.[51]	Retrospective	2004-2012	34	34	20:14	59.9	29.7-79.4	CK (n=39)/LINAC(n=2)	23.4 (1-3 fractions)	12-30 (1-3 fractions)		9.2		1-100	10.9		tumor volume	prior TMZ therapy
2016	Bokstein et al.[49]	Retrospective	2004-2013	47	33		53.3[a]	24-86[a]	LINAC	18	14-24	BEV/TMZ/Carbopl[a]tin	2.2[a]		0.2-9.5[a]	12.6	4.8	Adjuvant BEV therapy	
2017	Imber et al.[52]	Retrospective	1991-2013	174	174	102:72	54.1	21.8-85.3	GK	16	10-22		7		0.3-39	10.6			younger age at SRS, higher prescription dose, longer interval between original surgery and SRS

2017	Kim et al.[53]	Retrospective	2004-2015	61	61	34:27		58	27-79	GK	16	9-25		7	0.033-35.1	14 (in methylated group)/ 9 (in unmethylated group)	8.9 (in methylated group)/ 4.6 (in unmethylated group)		MGMT methylation
2017	Sutera et al.[54]	Retrospective	2002-2012	65	55			56[a]	30-87[a]	CK (96.1%)/ LINAC(3.9 %)[a]	21[a]	9-30[a]		8.7[a]	0.3-100[a]	10.25[a]	6.6[a]	prior TMZ therapy	prior TMZ therapy
2018	Guseynova et al.[57]	Retrospective	1992-2014	126	126	69:57		56	17-80	GK	12	10-25		3.75	0.04-37.1	7		age < 50 years	
2018	Sharma et al.[58]	Retrospective	1997-2016	53	53	36:17		58	19-82	GK	18	12-24		3.8	0.01-29.7	11	4.4	KPS ≥ 80; tumor volume < 15 cc, homogeneity index > 1.75	KPS ≥ 80; tumor volume < 15cc, homogeneity index > 1.75
2018	Abbassy et al.[55]	Prospective Phase I		9	9	7:2	52.7		28-71	GK	20	18-22	BEV	4.72	2.1-8.8	13	7.5		
2018	Gigliotti et al.[56]	Retrospective	2000-2017	25	20			54[a]	23-74[a]	LINAC	25[a]	27.5[a]		9.83[a]	0.55-92.78[a]	9		Receiving SRS since 2014	
2019	Morris et al.[59]	Retrospective	2009-2015	45	45	21:24		57	20-78	GK	17	13-24	BEV	2.2	0.1-25.2	13.3	5.2		KPS ≤ 70, SRS dose < 18 Gy, use of <2 chemoagents prior to SRS

[a]Including patients with other malignant glioma.

[b]Including patients with upfront adjuvant SRS for residual tumor.

[c]Represented with all study groups.

[d]Including the patients with fractionated stereotactic radiotherapy.

Abbreviations: rGBM, recurrent glioblastoma multiforme; SRS, stereotactic radiosurgery; NR, not reported; NS, not significant; KPS, Karnofsky performance scale; RPA, recursive partitioning analysis; EBRT, external beam radiation therapy; BEV, bevacizumab; TMZ, temozolomide; ECOG, eastern cooperative oncology group performance status; MGMT, O6-methylguanine-DNA-methyltransferase promoter.

Table 1.
Summary of the published literature on stereotactic radiosurgery in patients with recurrent glioblastoma multiforme.

retrospective studies [14–16, 19, 21, 23–26, 28, 32, 33, 35, 39, 40, 43, 49, 51, 54, 56, 60, 61]. The median age ranged from 34 to 54 years. The median prescribed dose ranged from 13 to 30 Gy. The median targeted tumor volume was 4.5 to 41.3 cc. The median overall survival time from the treatment of SRS ranged from 3.9 to 14.4 months, whereas the median progression-free survival time was 2.1 to 11 months.

The first study about LINAC radiosurgery for recurrent GBMs was described by Chamerian et al. [14]. The median prescribed dose was 13.4 Gy, and the median treated tumor volume was 17 cc. The median overall survival time was only 8 months, whereas the median progression-free survival time was 4 months. After that, only one retrospective study of more than 100 patients with recurrent high-grade gliomas treated with LINAC SRS has been reported [16]. Shrieve et al. showed that the median survival time of 72 recurrent GBM patients was 10.2 months [16]. Younger age (less than 46 years) and small tumor volume (less than 10.1 cc) were the significant prognostic factors associated with survival time. There were two studies that enrolled patients with only recurrent GBMs [21, 33]. In 2005, Combs et al. reported 32 patients, including 19 males and 13 females with recurrent GBMs treated with LINAC SRS [21]. The median age was 56 years, ranging from 33 to 76 years. The median prescribed radiation dose was 15 Gy, ranging from 10 to 20 Gy. The median targeted tumor volume was 10 cc with a range of 1.2 to 59.2 cc. The median overall survival time and progression-free survival time were 10 and 5 months, respectively. However, no prognostic factor was significant enough to influence the survival time. In a retrospective study of 19 patients with recurrent GBMs, Sirin et al. also showed that the median overall survival time and progression-free survival time were only 9.3 and 5.7 months, respectively [33]. In the bevacizumab era, three studies reported the combination of LINAC SRS, and bevacizumab improved the overall survival time ranging from 11.2 to 14.4 months [35, 39, 40]. In a retrospective study of 48 patients with recurrent GBMs, Cuneo et al. reported that the median progression-free survival time in recurrent patients who received adjuvant bevacizumab and LINAC SRS was 5.2 months vs. 2.1 months for patients who received LINAC SRS alone. The median overall survival times for patients who received a combination of adjuvant bevacizumab/LINAC SRS and LINAC SRS alone were 11.2 and 3.9 months, respectively. The authors concluded that the combination of salvage radiosurgery and bevacizumab to treat recurrent malignant gliomas seemed to be associated with improved outcomes. Younger age and higher KPS were still significant prognostic factors associated with overall survival time in patients with recurrent GBMs.

3.2 The effect of gamma knife radiosurgery in patients with recurrent GBMs

From 1996 to 2019, a total of 1247 patients with recurrent GBMs in 23 published studies were treated with Gamma Knife SRS [13, 17, 18, 20, 22, 24, 27, 29, 31, 36–38, 41, 45, 47, 50, 52, 53, 55, 57–59, 61]. The median age ranged from 43 to 61 years. The median prescribed marginal dose varied from 6 to 20 Gy. The median targeted tumor volume ranged from 1.35 to 21.4 cc. The median overall survival time ranged from 7 to 30 months, whereas the median progression-free survival time ranged from 3.8 to 14.9 months.

In a retrospective study of 189 patients with recurrent high-grade gliomas treated with Gamma Knife SRS, Larson et al. first reported that the median overall survival time in 66 patients with recurrent GBMs was 10 months [17]. Younger age, smaller tumor volume, higher KPS, and unifocal tumors were significant prognostic factors associated with patients' overall survival times. Several studies reported the impact of a combination of Gamma Knife SRS and adjuvant chemoagents on overall

survival times [17, 37, 47, 55, 59]. In 2002, Larson et al. reported a prospective phase II study on patients who received a combination of Gamma Knife SRS, and marimastat had a median overall survival of 8.7 months, whereas the median survival time in patients who received only Gamma Knife SRS alone was 10.1 months. Marimastat did not offer an advantage for patients with recurrent GBMs. However, in a retrospective study of 57 patients with recurrent GBMs, Kim et al. showed that the combination of adjuvant temozolomide and Gamma Knife SRS significantly improved the medium overall survival time from 9.2 to 15.5 months [47]. In the bevacizumab era, two studies reported that the median survival time was approximately 13 months after the combined treatment of Gamma Knife SRS and adjuvant bevacizumab [55, 59].

3.3 The effect of Cyberknife radiosurgery in patients with recurrent GBMs

From 2009 to 2017, a total of 318 patients with recurrent GBMs in eight published studies were treated with Cyberknife SRS [30, 34, 42, 44, 46, 48, 51, 54]. The median age ranged from 37 to 59.9 years. The median prescribed marginal dose ranged from 15 to 30 Gy. The median targeted tumor volume ranged from 2 to 24 cc. The median overall survival time after Cyberknife SRS ranged from 5.3 to 12 months, whereas the median progression-free survival time ranged from 4 to 7.9 months.

The first report on Cyberknife SRS for patients with recurrent GBMs was published by Villavicencio et al. [30]. The median overall survival time in a total of 26 patients with recurrent GBMs was 7 months. No prognostic factor associated with the overall survival time was identified. In 2015, Pinzi et al. reported a retrospective study of more than 100 patients who had recurrent high-grade glioma treated with Cyberknife SRS [48]. Among 88 patients with recurrent GBMs, the median survival time was 10 months after treatment with Cyberknife SRS. Adjuvant second-line chemotherapy and/or surgery were the significant prognostic factors associated with overall survival times. The effect of adjuvant chemoagents, including bevacizumab, temozolomide, and anti-epidermal factor (125)-mAB 425, on the overall survival times was evaluated in four studies [34, 42, 44, 46]. In 2012, Conti et al. compared the effect of a combination of temozolomide and Cyberknife SRS with that of Cyberknife SRS alone on the overall survival times of patients with recurrent GBMs [34]. The progression-free survival time and median survival time in patients who received the adjuvant temozolomide and Cyberknife SRS were 7 and 12 months, respectively. The patients who received Cyberknife SRS alone had a progression-free survival time and median survival time of only 4 and 7 months, respectively. In the bevacizumab era, Yazici et al. revealed that the median survival time in 37 patients with recurrent GBMs was 10.6 months, whereas the median progression-free survival time was 7.9 months [44]. A tumor volume less than 24 cc was the only significant prognostic factor associated with overall survival times.

4. Discussion

4.1 The role of SRS for recurrent GBMs

GBM is an incurable disease with local progression in the majority of patients. The management of recurrent GBMs is a clinically challenging problem, and treatment options are limited [7, 10]. Although reoperation with gross-total removal of the tumor has been shown to improve the overall survival time in patients with recurrent GBMs, surgery may not be preferred for patients with tumors in the eloquent area, older age, or lower performance status [8]. Re-irradiation offers an

alternative option for treating recurrent GBMs. In a systematic review and meta-analysis of re-irradiation with external beam radiotherapy for recurrent GBMs, Kazmi et al. showed that the 6- and 12-month overall survival times from the time of re-irradiation were 70 and 34%, respectively, whereas the 6- and 12-month progression-free survival times were 40 and 16%, respectively [11]. The overall toxicity rate was low, ranging from 4 to 10%.

SRS has the ability to combine surgical and radio-oncological treatments to deliver a high dose of focused radiation on the focal tumor lesion and spare the adjacent normal anatomical structures. For recurrent GBMs, the majority of tumors tend to grow within 2 cm of the contrast-enhancing lesion border, and SRS seems to be a reasonable tool to add radiation boost for the focal lesion followed by the standard treatment of initial radiation with 60 Gy in 30 fractions [4, 13]. In our present review, despite the different SRS modalities with the median prescribed dose ranging from 6 to 30 Gy, the overall survival time from the treatment of SRS ranged from 3.9 to 17.9 months, where the progression-free survival time from the treatment of SRS ranged from 2.1 to 14.9 months. Severe prognostic factors, such as small tumor volume, younger age, higher KPS score, and lower RPA class, were mostly suggested to be significantly associated with the overall survival time in patients with recurrent GBMs treated with SRS. These results showed that re-irradiation with the SRS modality are an alternative and feasible method to manage patients with recurrent GBMs.

4.2 The impact of SRS and adjuvant temozolomide for recurrent GBMs

Since 2005, temozolomide, which is an alkylating agent, is the most important FDA-approved chemoagent for the standard treatment of patients with newly diagnosed GBMs [1, 4]. The median overall survival time significantly improved from 12.1 to 14.6 months after the patients with newly diagnosed GBMs received combined treatments with radiotherapy and adjuvant temozolomide. However, the disease frequently progresses within 6–9 months, and the 2-year survival rate is less than 25% [62]. The failure of temozolomide treatment has been found to be associated with the expression of MGMT protein [63–65]. Among the GBM patients with a methylated MGMT promoter, the median overall survival time was 21.7 months after treatment with radiotherapy and temozolomide, whereas the median survival time was 15.3 months in the unmethylated group treated with radiotherapy alone [64].

Due to the blood-brain barrier, temozolomide rechallenge is considered to be a reasonable option in patients with recurrent GBMs. In this review, the combination of SRS and temozolomide was employed in three studies [34, 42, 47]. Cyberknife SRS was performed in two studies, and the other study used the Gamma Knife SRS. The median overall survival time ranged from 9 to 15.5 months, and the median progression-free survival time was approximately 7 months after the time of SRS treatment. In 2012, Conti et al. analyzed the effect of adjuvant temozolomide in recurrent GBM patients treated with Cyberknife SRS [34]. The median overall survival time significantly improved from 7 to 12 months, whereas the median progression-free survival time improved from 4 to 7 months. Based on 57 recurrent GBM patients, Kim et al. also showed that the improved median overall survival time and progression-free survival time were 15.5 and 6 months, respectively [47]. Otherwise, in a retrospective review of 61 patients who received Gamma Knife SRS as a salvage treatment at the time of the first progression, Kim et al. showed that the median overall survival time was 14 months in the methylated MGMT promoter group and 9 months in the unmethylated group [53]. Methylation of the MGMT promoter was significantly corrected with better overall survival times and progression-free survival times. The results mentioned above indicated that the

combination of salvage SRS and adjuvant temozolomide may offer an important treatment option to improve the overall survival times in patients with recurrent GBMs.

4.3 The impact of SRS and adjuvant bevacizumab for recurrent GBMs

Bevacizumab is a recombinant human monoclonal antibody that acts against the vascular endothelial growth factor to prevent the growth and maintenance of tumor blood vessels. In 2009, bevacizumab was approved by the USFDA for the treatment of patients with recurrent GBMs [66, 67]. The use of bevacizumab demonstrated a radiological response of up to 40% [68]. However, in a large prospective phase III trial, the use of adjuvant bevacizumab revealed only improvement in the progression-free survival times from 1.5 to 4.2 months but not in the overall survival times [69]. In a systematic review and meta-analysis, Diaz et al. showed that the survival advantage of bevacizumab at recurrence was limited to 4 months [70]. Although bevacizumab may reduce steroid requirements, there was no additional benefit in the health-related quality of life. The role of bevacizumab in combination with other cytotoxic chemoagents remains unclear.

The role of adjuvant bevacizumab in patients with recurrent GBMs treated with SRS has been reported in nine studies, which were included in our review [35, 37, 39, 40, 44, 46, 49, 55, 59]. The median overall survival time ranged from 5.3 to 17.9 months, whereas the median progression-free survival time ranged from 3.9 to 14.9 months. The comparison of SRA with or without adjuvant bevacizumab was investigated in two studies [35, 37]. Among 49 patients with recurrent GBMs, Cuneo et al. showed that the median overall survival time was 11.2 months in patients receiving SRS and adjuvant bevacizumab and 3.9 months in patients receiving SRS therapy alone [35]. The progression-free survival time also improved from 2.1 to 5.2 months. In a case-controlled study of patients with recurrent GBMs treated with SRS and adjuvant bevacizumab plus temozolomide or irinotecan, Park et al. also showed that the median overall survival time and progression-free survival time improved from 12.2 to 17.9 months and 6.7 to 14.9 months, respectively [37]. In a retrospective study and review of the literature, Morris et al. reported that the dual role of bevacizumab and radiosurgery had a benefit in the overall survival times (11.2–17.9 months) and progression-free survival times (3.9–14.9 months). These results showed the potential therapeutic effect of adjuvant bevacizumab in combination with other treatment modalities, such as cytotoxic chemoagents or salvage SRS, in patients with recurrent GBMs.

4.4 The future of SRS for recurrent GBMs

With the advance of molecular diagnostic techniques, newly diagnosed GBMs should be classified based on the mutant status of isocitrate dehydrogenase 1 defined by the updated guidelines of the World Health Organization in 2016 [71]. These molecular profiles influence the overall survival time and the possible therapeutic effects of chemoagents. Similar to the recurrent GBMs, several main molecules, such as MLH1 [72], CASP8 [73], MSH2 [74], and P53 [74], were found to be different from primary GBMs [75]. The molecular features, intra-tumor heterogeneity, immunogenicity, and microenvironment around the tumor contribute to the clinical prognostic outcomes in patients with recurrent GBMs [7, 10]. Reoperation, re-chemotherapy, and re-irradiation currently remain as the standard treatments for most patients with recurrent GBMs [2, 7, 10, 11]. A growing body of literature, including our current review, demonstrates the tolerability and efficacy of salvage SRS for recurrent GBMs, which did not inhibit re-irradiation, followed by a total of

60 Gy typically applied in the first-line treatment [59]. Although younger age is commonly considered as an important independent prognostic factor that is associated with survival, the selected criteria of salvage SRS for better outcomes need to be investigated in further large prospective studies. In the future, individualized precise multi-modality treatment will play an important role in patients with recurrent GBMs, including the combination of cytotoxic chemotherapy, angiogenesis inhibitors, or immunotherapy [76]. Salvage SRS with a combination of other treatment modalities may offer an alternative therapeutic method to manage patients with recurrent GBMs.

5. Conclusion

Our review suggests that salvage SRS is an important treatment protocol for managing patients with recurrent GBMs. The irradiation doses provided by SRS may improve the clinical outcome of patients with recurrent GBMs, which is not hampered by the standard case of 60 Gy prescribed for newly diagnosed GBMs. The dual role of salvage SRS and other cytotoxic chemoagents, such as temozolomide and bevacizumab, also seems to be effective in the management of recurrent GBMs. Further application of salvage SRS combined with other chemoagents or a new treatment modality needs to be investigated.

Conflict of interest

The authors declare no conflict of interest.

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