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REVIEW

Assessing the efficacy of repeat resections in recurrent glioblastoma: a systematic review

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Abstract

Background The inevitable recurrence of glioblastoma (GBM) results in patients often undergoing multiple resections with questionable benefit to overall survival (OS).

Objective To systematically review and analyze prior studies examining the potential added benefit of repeat resection (RR) in recurrent GBM.

Methods We performed a PRISMA-compliant systematic review of literature published between 1969 to 2019 involving patients undergoing RR at GBM recurrence.

Results The search yielded 3994 non-duplicate citations. Final abstraction included 43 articles, with 2 level II and 41 level III studies. The earliest paper we included was published in 1987 [1], and 35 identified papers (81.4%) were published within the last 10 years. The survival data of 9236 patients (55% male) were analyzed, with a median age of 56; 3726 patients underwent RR. In 31 studies with a comparable single-surgery-only cohort, 20 articles reported a statistically significant increase in OS with RR, 7 reported nonsignificant trends toward increased OS with RR, and 4 reported no significant increase in OS with RR. Twenty-two articles with multivariate analyses of Karnofsky performance scores and 17 articles with extent-of-resection reported these as significant prognostic factors of OS. In 26 studies, median OS among all patients was 17.85 months inclusive of median OS following RR totaling 9.6 months. Notably, in 10 studies with data on subsequent progressions (2+ recurrences), 6 studies reported significant increases in OS with subsequent repeat resection (sRR) compared to those not undergoing sRR.

Conclusions Recurrent GBM presents a treatment challenge. There appears to be an OS benefit for RR upon first recurrence as well as sRR. Such findings warrant further investigation of the potential benefits of continued surgical intervention after subsequent progressions of GBM.

Keywords Glioblastoma (GBM) · Karnofsky performance score (KPS) · Overall survival (OS) · Progression-free survival (PFS) · Repeat resections (RR)

Introduction

Glioblastoma (GBM) carries a rapidly fatal and devastating prognosis. Unfortunately, GBMs are also among the most common central nervous system (CNS) neoplasms, constituting roughly 80% of all malignant astrocytomas and 15% of all CNS tumors [2]. With an incidence of 2–3 per 100,000 persons, GBMs remain a rare yet incurable disease [3]. Notwithstanding recent advances in molecular targeting and immunotherapy, GBM treatment primarily revolves around maximal safe resection (MSR), chemotherapy, and radiotherapy, with spread of the Stupp protocol for adjuvant chemoradiation in 2005 demonstrating an improvement in GBM overall survival (OS) from 12.1 to 14.6 months [4].

Despite these advancements, patients inevitably face recurrence. The aforementioned standardization of GBM treatment, unfortunately, does not extend beyond its primary treatment, leaving patients and clinicians with varying treatment plans upon tumor recurrence. An emerging trend for treating recurrent GBM looks toward repeat resections (RRs) for possible

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extension of OS through tumor cytoreduction rather than curative intent. Patients receiving RRs may undergo multiple surgeries before ultimately succumbing to the disease. These repeat surgeries, while potentially increasing OS, may also lead to unintended sequelae. Previous reports on surgical complications in patients with malignant gliomas highlight the increased risk of iatrogenic stroke and subsequent new neurological deficits upon repeat resection [5, 6]. Currently, institutions rely on metrics such as preoperative Karnofsky performance score (KPS) to determine patients' fitness for RR and to help predict the likelihood of poor sequelae [7]. Furthermore, the relative sparsity of quality of life (QoL) data in GBM patients presents a dilemma when considering the overall benefits of a repeat resection strategy.

In this systematic review, we sought to discern whether RRs are associated with increased OS and progression-free survival (PFS) in patients with recurrent GBM. In addition, we investigated the utility of KPS and extent of resection (EOR) as prognostic markers of OS in this patient population.

Methods

This systematic review was carried out using Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) formatting and guidelines.

Search strategy

A comprehensive literature search was conducted using PubMed, Embase, Cochrane Library, Web of Science, Scopus, and ClinicalTrials.gov for articles published between March 1, 1969, and February 28, 2019. The complete search terms used for each database are listed in Supplemental Digital Content.

Initial screen using eligibility criteria

All studies identified from the databases were reviewed manually to determine relevance, and duplicate articles were consolidated. Two reviewers (D.B. and H.D.) reviewed article titles and then article abstracts to determine which manuscripts were eligible for full-text review. A subset of these manuscripts were then selected for data extraction based upon inclusion and exclusion criteria.

Inclusion criteria

The study inclusion criteria included the following: (1) reported on adult (18+ years old), human subjects; (2) mentioned recurrent glioblastoma patient population; and (3) included data on survival and complications.

Exclusion criteria

Editorials, review articles, and articles lacking primary data were excluded, as were studies addressing primarily pediatric populations, written in a non-English language, or including less than five patients. Articles mainly discussing adjuvant therapy, chemotherapy, and radiation-based therapeutics, as opposed to focusing on the impact of RR on survival, were also excluded. We excluded studies reporting data on secondary (i.e., progressing from lower-grade gliomas) rather than primary de novo GBM due to the dramatic difference in reported OS between these patient subtypes [8].

Data extraction and analysis

Once selected, the studies were screened for publication year, number of patients treated within each cohort, level of evidence, study design, and significant findings. These findings centered chiefly on OS (time of histological diagnosis until death), PFS (time of diagnosis until progression/recurrence) following initial surgery, and survival following subsequent surgeries. Where appropriate, we noted where data on OS, as defined above, was not included. Two reviewers (D.B. and H.D.) independently reviewed articles to determine eligibility for data extraction and subsequently extracted data into a standard evidence data table (Microsoft Excel version 16.32). A third reviewer (D.M.) independently assessed this table for accuracy and completeness.

Levels of evidence

Levels of evidence were assigned according to guidelines from the 2011 Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence Working Group [9]. Level III was defined as comparative retrospective analyses, and level II studies were defined as prospective analyses. In our literature search, we did not identify any level I studies investigating repeat resections in recurrent GBM.

Qualitative analysis

Qualitative synthesis Our review included a narrative synthesis in which we identified pertinent clinical characteristics and methodologies of included studies, examined strengths and limitations of the studies both individually and collectively, described how study designs may have introduced bias, explored the relationship between study characteristics and subsequent reported findings, and contextualized individual studies relative to overall populations, settings, and outcomes of interest.

Assessment of heterogeneity We qualitatively assessed heterogeneity of included studies in clinical (patient

populations and exposure categories, namely, single versus repeat resection), methodological (study type), and statistical domains. Heterogeneity was significant across these three domains partly due to inherent temporal heterogeneity when sampling GBM patients pre- and post-advent of the Stupp protocol; therefore, we did not combine these results into a meta-analysis. With variation in results and direction of effects, a Cochrane Q statistic could not be calculated in this review.

Results

Search results

Through our search strategy, we identified 1278 citations from PubMed, 1418 from Embase, 1199 from Scopus, 2423 from Web of Science, 111 from ClinicalTrials.gov, and 111 from the Cochrane Library. After eliminating duplicates, 3951 unique articles were identified and analyzed for review. Thereafter, 3616 articles were excluded for failing to meet inclusion criteria in review of titles and abstracts. The full text of 335 articles was analyzed, with 43 ultimately selected for inclusion in this systematic review. Of the excluded articles, 77 were excluded for addressing secondary (low-grade glioma progression) GBM, 26 for containing a primarily pediatric population, 86 for lacking primary data, 46 for lack of data on repeat resections, 21 for being editorials, 18 for including less than five patients, 8 for text in a non-English language, and 10 for inappropriate study design. Inappropriate study design included studies with primary outcomes on efficacy of chemotherapeutic agents in the setting of resection, neuroimaging predictiveness, and formulation of statistical decision-making models rather than survival. A visual of this search process is depicted in Fig. 1.

Characteristics of the included studies are presented in Table 1. Two level II studies and 41 level III studies were included. The two level II studies included secondary analyses on prospectively collected data at two different medical centers [15, 28]. In the reviewed studies, the number of included patients ranged from 7 to 949 subjects. Across all 43 studies, 9236 patients were examined. Of those, 5685 patients were analyzed for recurrent disease. Publication date ranged from November 1987 [1] to November 2018 [49, 50]. Similarly, there was significant heterogeneity in location of treatment centers as well as reported outcomes. Single-center study locations included the USA (13 studies), Germany (7), Italy (5), Australia (5), Turkey (2), Norway (2), France (2), South Korea (1), the Netherlands (1), Switzerland (1), Singapore (1), Spain (1), and Japan (1). Only one international study was included, which gathered patients from Germany, Switzerland, and Austria [41].

Outcomes

OS was considered to be our primary outcome; however, studies differed in this definition. Some analyses of recurrent patients considered OS from the time of repeat surgery [11, 19, 28, 32, 46–48], while others considered OS from the time of initial surgery [1, 10, 12, 14, 15, 17, 18, 20–22, 24–27, 29–31, 33, 35–45, 49–51]. Among these two definitions, all 43 studies included some mention of OS, and 21 included some mention of PFS following initial surgery [1, 10, 11, 14, 15, 18, 21, 24, 26, 27, 29, 31, 32, 34, 35, 37, 41, 42, 45, 48, 51].

Overall, median OS values ranged from 9.9 to 27.6 months (median: 17.85 months). In studies with a measured PFS after initial surgery, median PFS ranged from 4.9 to 10.8 months (mean: 8.3 months). Among studies published in the pre-Stupp era (1969–2005), median OS was 14.25 months (IQR: 12.35–21.1 months) versus post-Stupp era (2005–2018) which was 18.7 months (IQR: 14–21 months).

For patients receiving RR at 1st recurrence, 20 studies reported survival benefits with 19 reporting significant increase in OS [12, 14, 17, 19–24, 26, 30, 38, 41, 42, 45–49, 51]. Seven studies did not reach significance but saw similar trends [11, 13, 25, 32, 33, 36, 43], and four studies did not see an increase in OS or PFS following second surgery [31, 35, 40, 50]. Of these four, the study by Goldman et al. is unique both in methodology and result as the authors demonstrate a negative correlation between RR and survival when using a time–dependent model not employed by other papers. Such findings provide compelling evidence to suggest that the purported merits of RR could, in reality, be confounded largely by individual tumor characteristics and selection bias [50]. Twelve studies lacked a comparison group to the RR group, rendering direct OS comparisons between groups impossible [1, 10, 15, 18, 27–29, 34, 37, 39, 44, 52].

Beyond the second surgery

Among 10 studies where patients underwent 3 or more total surgeries, Azizi [13] and Ortega et al. [35] failed to report a survival benefit beyond the second surgery, while 4 studies displayed significant OS increases with continued reoperations [17, 22, 23, 41]. Similarly, Sughrue [34] and Coburger et al. [44] saw extended survival with continued reoperation but lacked a direct comparison group.

Additional factors

Secondarily, we also examined documented associations of EOR and KPS on OS and PFS. The effect of EOR on OS appeared in 35 articles, with 27 documenting a significant increase in OS for patients with a higher EOR at 1st surgery and with 9 demonstrating a similar association with greater

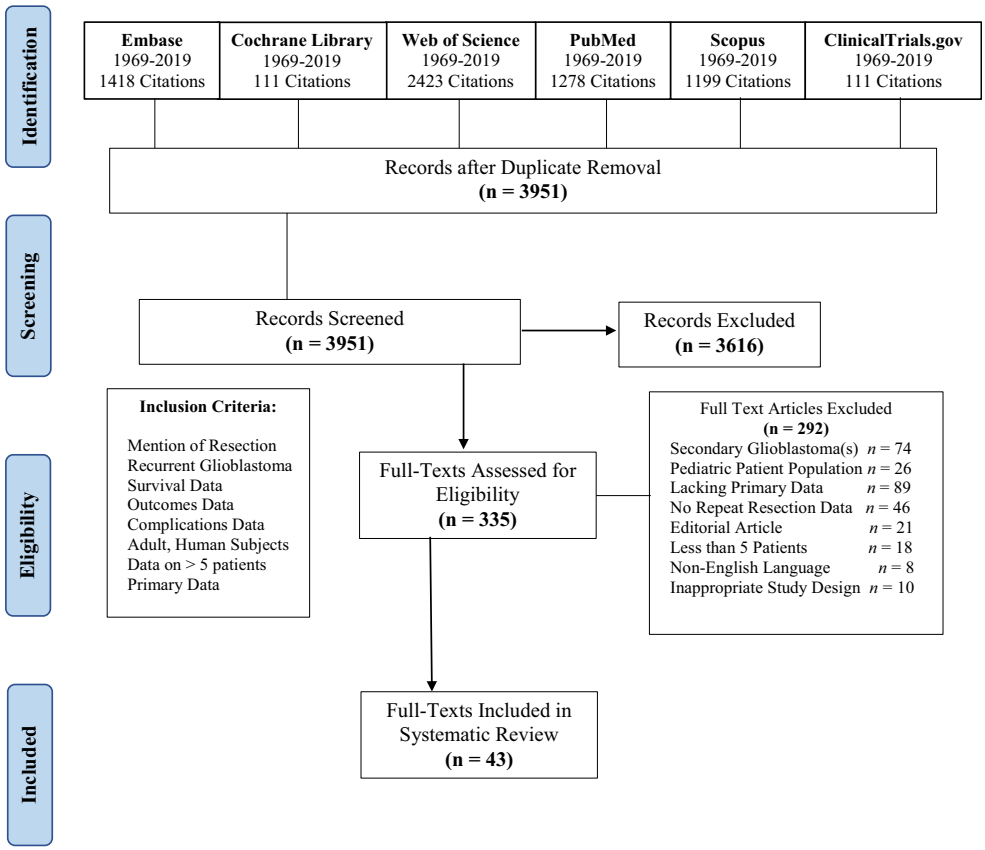

Fig. 1 Flowchart depicting the review process, adhering to the PRISMA guidelines (adult patients: ≥ 18 years old; secondary glioblastoma indicates glioblastoma which progressed from lower-grade gliomas)

OS and higher EOR at RR [14, 18, 27, 29, 37, 39, 41, 44, 52]. Thirty-five articles discussed the strength of KPS as a prognostic factor in recurrent GBM (rGBM), and 27 reported an association between higher preoperative KPS and longer OS; however, 8 studies did not find this association [15, 19, 32, 33, 36, 38, 42, 47]. A more complete quantitative summary can be found in Table 2.

Risk of biases of included studies

Selection bias

All but one of the included reports was a single-center study [46]. Therefore, the generalizability of each result remains unknown as these cohorts may not represent the broader, diverse GBM patient population. Retrospective studies are often subject to unavoidable bias resulting from a lack of uniformity in patient selection. In the case of recurrent GBM studies, patients undergoing repeat resection may be identified as having potential for good post-RR survival through higher functional status [26], having received GTR initially [38], or being of younger age [35, 43]. Patients receiving repeat surgery also generally benefit from having reasonable survival rates following their initial resection. Thus, the RR cohort as a whole is comprised of individuals who are generally younger, of higher functional status, with better prognoses, and less aggressive tumors. These trends represent real-world considerations made by physicians in recommending RR for rGBM patients and may contribute heavily to positive outcomes in RR patients compared to non-RR counterparts. Given that retrospective studies constitute 41 of the 43 papers in this review, consideration of such bias is crucial in drawing conclusions about rGBM outcomes.

Selection bias can also be imposed at the level of patient inclusion and exclusion in retrospective analysis, as we identified 21 papers with criteria that could potentially shift results of RR toward better outcomes. Specifically, 8 papers excluded patients with deep, eloquent, or multifocal tumors (or initial biopsy, presumably as a result of infiltrative tumors) [22, 28, 35, 37, 42, 45, 52, 53], 3 papers excluded patients without initial GTR or with tumors not amenable to GTR [19, 29, 34], 2 papers excluded patients on the basis of poor prognostic age or functional status [12, 24], and 8 papers excluded patients that might have died or been unable to follow-up due to presumed poor outcomes after the first resection [31–33, 38, 39, 46–48]. By selecting patients with less infiltrative tumors, better prognostic factors, and greater EOR at initial operation, authors potentially bias RR outcomes by excluding patients with shorter OS. More explicitly, suppression of worse outcomes occurred in studies such as Franceschi et al. [31] and Brandes et al. [39], which excluded patients demonstrating

Table 1 Included study characteristics and demographics

Study	Country	Study period	Level of evidence	Overall			Patients with RR, *n* (% of overall)	Patients at first recurrence, size (*n*)	Second recurrence, size (*n*)
				Size (*n*)	Age (years)	Males, *n* (%)			
Ammirati et al. 1987 [1]	USA	1972–1983	3	35	NR*	NR	NR	35	0
Daneyemez et al. 1998 [10]	Turkey	1985–1995	3	72	NR	NR	14 (19)	NR	0
Barker et al. 1998 [11]	USA	1988–1993	3	223	54*	140 (62)	46 (20.6)	223	0
Boiardi et al. 1999 [12]	Italy	1991–1993	3	87	55*	NR	15 (17.2)	54	0
Azizi et al. 2001 [13]	USA	1998–2000	3	109	54*	64 (59)	33 (30.3)	33	0
Pinsker et al. 2002 [14]	Germany	1993–1998	3	38	54*	25 (66)	38 (100)	38	0
Terasaki et al. 2007 [15]	Japan	2002–2005	2	7	52*	3 (42)	7 (100)	7	0
McGirt et al. 2009 [16]	USA	1996–2006	3	949	51*	564 (59)	400 (42.1)	400	0
Helseth et al. 2010 [17]	Norway	2003–2008	3	516	63.7*	304 (58)	65 (12.6)	65	10
Bloch et al. 2012 [18]	USA	2005–2009	3	107	53.7*	51 (47)	107 (100)	107	0
De Bonis et al. 2012 [19]	Italy	2002–2008	3	76	59*	43 (56)	33 (43.4)	33	0
Bekar et al. 2012 [20]	Turkey	2001–2010	3	161	54.8*	88 (54)	50 (31.1)	161	0
Skeie et al. 2012 [21]	Norway	1996–2007	3	77	55.3*	49 (63)	45 (58.4)	77	0
Chaichana et al. 2013 [22]	USA	1997–2007	3	578	55*	347 (60)	224 (38.8)	168	41
Hong et al. 2013 [23]	Germany	2006–2010	3	42	57.5*	19 (45)	42 (100)	42	10
Archavlis et al. 2013 [24]	Germany	2005–2010	3	111	55.8*	62 (55)	36 (32.4)	111	0
De Cock et al. 2014 [25]	France	2008–2011	3	207	NR	NR	16 (8)	158	NR
McNamara et al. 2014 [26]	USA	2004–2011	3	584	59*	363 (62)	107 (18.3)	107	0
Oppenlander et al. 2014 [27]	USA	2001–2011	3	170	55.2*	105 (61)	170 (100)	170	0
Yong et al. 2014 [28]	USA	2002–2012	2	97	49*	28 (28)	97 (100)	97	NR
Quick et al. 2014 [29]	Germany	2007–2010	3	40	58*	18 (45)	40 (100)	40	0
Ening et al. 2015 [30]	Germany	2006–2011	3	141	60.6*	76 (53)	53 (37.6)	53	0
Franceschi et al. 2015 [31]	Italy	2005–2010	3	232	52*	NR	102 (44)	232	0
Kim et al. 2015 [32]	Korea	2002–2011	3	144	51*	81 (56)	38 (26.4)	144	0
Amini et al. 2015 [33]	USA	2007–2014	3	60	57.5*	35 (58)	9 (15)	60	0
Sughrue et al. 2015 [34]	Australia	1995–2009	3	104	NR	NR	104 (100)	59	24
Ortega et al. 2015 [35]	USA	2001–2011	3	202	58*	121 (59)	202 (100)	83	94
Woernle et al. 2015 [36]	Switzerland	2007–2011	3	98	55*	64 (65)	40 (40.8)	98	0
Perrini et al. 2016 [37]	Italy	2001–2015	3	48	59.2*	29 (60)	48 (100)	48	0
Chen et al. 2016 [38]	Singapore	2004–2014	3	65	56.2*	43 (66)	20 (30.8)	65	NR
Brandes et al. 2016 [39]	Italy	2005–2014	3	270	50.7*	178 (65)	270 (100)	270	0
Parakh et al. 2016 [40]	Australia	2006–2008	3	194	61.7*	129 (66)	95 (49)	194	95
Ringel et al. 2016 [41]	Multiple	2006–2010	3	503	58*	313 (62)	503 (100)	421	71

Table 1 (continued)

Study	Country	Study period	Level of evidence	Overall			Patients with RR, *n* (% of overall)	Patients at first recurrence, size (*n*)	Second recurrence, size (*n*)
				Size (*n*)	Age (years)	Males, *n* (%)			
Tully et al. 2016 [42]	Australia	2010–2013	3	204	66*	125 (61)	49 (24.0)	49	32
Gately et al. 2017 [43]	Australia	2006–2015	3	776	63*	456 (58)	51 (6.6)	111	72
Coburger et al. 2017 [44]	Germany	2008–2014	3	170	60*	107 (62)	46 (27.1)	43	3
Delgado-Ferndandez et al. 2017 [45]	Spain	2010–2015	3	121	62.21*	71 (58)	31 (25.6)	31	0
Azoulay et al. 2017 [46]	USA	2005–2012	3	180	58	109 (60)	69 (38.3)	180	0
van Linde et al. 2017 [47]	Netherlands	2005–2014	3	299	56*	202 (67)	56 (18.7)	299	0
Zanello et al. 2017 [48]	France	2005–2015	3	777	58*	504 (64)	179 (23.0)	777	0
Hager et al. 2018 [49]	Germany	NR	3	59	71*	NR	27 (45.8)	59	0
Goldman et al. 2018 [50]	USA	2005–2014	3	163	62	111 (68)	89 (54.6)	163	0
Wann et al. 2018 [51]	Australia	2009–2015	3	120	56*	65 (54)	60 (50)	120	0

Age (*) = mean age; (**) = range; otherwise, median

time to first progression less than 6 or 3 months, respectively; Amini et al. [33]., which required patients demonstrate follow-up of at least 3 months post-recurrence; and Kim et al. [32], which excluded patients forgoing further salvage therapy beyond first recurrence due to poor performance status.

Comparability

All but two studies were observational, with only two level II studies gathering prospectively collected data [15, 28]. Patient selection was not randomized, and studies did not match for demographics between cohorts. These study designs allow potential differences in age, ethnicity, and comorbidities between cohorts. Wann and Chaichana et al., however, stand as exceptions where patients were case controlled for age and EOR at initial surgery, as well as by socioeconomic and performance status [22, 51]. Wann and Chaicahana et al. demonstrated improved OS and PFS with RR. Generally, case-control studies generate strong evidence when randomized clinical trials are not available. In the absence of internal controls, some studies contextualized survival outcomes using historical controls. This practice may detract from the significance of outcome comparisons with current GBM cohorts due to the previously mentioned heterogeneity in GBM treatment. Such heterogeneity of treatment is obvious when comparing data acquired from patients treated before and after implementation of Stupp protocol for primary adjuvant treatment. Nevertheless, qualitative analysis for risk of treatment bias revealed that heterogeneity of primary adjuvant treatment was prevalent in papers both pre- and post-Stupp. Overall, twenty-one studies (48.8%) demonstrated treatment bias either through incomplete adherence to Stupp protocol or inadequate reporting of primary adjuvant therapies encountered by patients [1, 10–15, 17, 21, 22, 26, 30, 38, 40, 42–45, 49–51]. Additionally, potential initial treatment heterogeneity made conclusions about RR efficacy less robust considering the impactful nature of initial treatment on overall GBM survival.

Lack of randomization, variability in individual patient factors, and different institutional practices were all factors that contributed to weakened direct comparisons between studies.

Outcomes

We evaluated risk of bias in the overall assessment of outcomes. All included studies did address OS, but discordant definitions of survival made comparison difficult. Many studies reported survival statistics following each resection, but three of the 20 studies demonstrating RR benefits described OS only from recurrence, rather than from initial operation [19, 46, 47]. Seven studies described OS from recurrence, whereas 36 studies described OS from initiation diagnosis or initial operation; the proportion of studies demonstrating

Table 2 Study clinical features and survival data

Study	RR Significant effect on survival?	Extent of resection at IS			% of Patients receiving Stupp protocol	RR Cohort			Non-RR Cohort		KPS at RR
		GTR, n	STR, n	Significant effect on survival?		Median OS	Median PFS from IS	Median SSS	Median OS	Median PFS from IS	Significant effect on survival?
Ammirati et al. 1987 [1]	-	NA	NR	Y	0	19.1	NR	7.25	-	-	Y
Daneyemez et al. 1998 [10]	-	32	30	Y	0	17	9.5	-	-	-	Y
Barker et al. 1998 [11]	I	26	168	Y	0	-	6.6	9	-	-	Y
Boiardi et al. 1999 [12]	Y	NR	NR	NR	0	27.6	-	18	-	-	NR
Azizi et al. 2001 [13]	I	NR	NR	NR	0	18.3	-	-	12.7	-	Y
Pinsker et al. 2002 [14]	Y	21	17	Y	0	14.25	10.5	5.75	10.25	-	Y
Terasaki et al. 2007 [15]	-	4	3	N	0	15.1	6.9	9	-	-	NR
McGirt et al. 2009 [16]	-	333	231	Y	100	-	-	11	-	-	Y
Helseth et al. 2010 [17]	Y	NR	NR	Y	100	18.4	7	-	8.6	-	Y
Bloch et al. 2012 [18]	-	52	55	Y	100	20.4**	11.1**	11.5**	-	-	Y
De Bonis et al. 2012 [19]	Y	76	0	N	100	-	-	14	8*	-	Y
Bekar et al. 2012 [20]	Y	101	60	Y	100	26.7	-	-	12.2	-	Y
Skeie et al. 2012 [21]	Y	77	0	NR	37	16	9.3	8	18	-	N
Chaichana et al. 2013 [22]	Y	102	252	Y	100	15.5	-	-	6.8	-	Y
Hong et al. 2013 [23]	Y	28	14	Y	100	19	-	-	-	-	Y
Archavlis et al. 2013 [24]	Y	81	30	Y	0	16	5.25	7.5	12	3.75	Y
De Cock et al. 2014 [25]	I	NR	NR	NR	100	29.7	-	10.8	-	-	NR
McNamara et al. 2014 [26]	Y	NR	NR	Y	100	20.9	7.8	7.1	9.9	-	Y
Oppenlander et al. 2014 [27]	-	NR	NR	Y	100	19	8.9	-	-	-	Y
Yong et al. 2014 [28]	-	NR	NR	Y	100	-	-	12.4	-	-	Y
Quick et al. 2014 [29]	-	23	17	Y	100	21.7	10.2	13	-	-	Y
Ening et al. 2015 [30]	Y	NR	NR	NR	100	19	9	11	13	-	Y
Francheschi et al. 2015 [31]	N	NR	NR	Y	100	25.8	13.1	9.6	18.6	-	Y
Kim et al. 2015 [32]	I	NR	NR	N	100	-	7.2	13.2	-	-	Y
Amini et al. 2015 [33]	I	35	25	N	100	-	-	-	-	-	Y
Sughrue et al. 2015 [34]	-	NR	104	Y	100	-	7.8*	-	-	-	Y
Ortega et al. 2015 [35]	N	124	52	Y	100	25.5	8.5	-	21.1	5.7	Y
Woernle et al. 2015 [36]	I	69	24	N	85	18.86	-	-	14.82	-	N
Perrini et al. 2016 [37]	-	27	21	Y	100	21	-	7	-	-	N
Chen et al. 2016 [38]	Y	29	36	N	100	25.4	-	13.5	11.6	-	N

Table 2 (continued)

Study	RR Significant effect on survival?	Extent of resection at IS			% of Patients receiving Stupp protocol	RR Cohort			Non-RR Cohort		KPS at RR
		GTR, n	STR, n	Significant effect on survival?		Median OS	Median PFS from IS	Median SSS	Median OS	Median PFS from IS	Significant effect on survival?
Brandes et al. 2016 [39]	-	NR	NR	Y	100	27.6	-	11.4	-	-	N
Parakh et al. 2016 [40]	N	NR	NR	NR	56	14	-	8	10	-	NR
Ringel et al. 2016 [41]	Y	238	170	Y	93	25	9.1	11.9	-	-	Y
Tully et al. 2016 [42]	Y	60	184	N	46	20.1	8.3	7.6	9	6.7	N
Gately et al. 2017 [43]	I	519	261	NR	100	-	-	14.27	9.37*	-	NR
Coburger et al. 2017 [44]	-	164	135	Y	100	31	5	16	-	6	Y
Delgado-Ferndandez et al. 2017 [45]	Y	59	62	Y	100	24.2	7.9	-	8.4	5.2	Y
Azoulay et al. 2017 [46]	Y	NR	NR	Y	0	-	10.3	9.6	5.3*	7	Y
van Linde et al. 2017 [47]	Y	74	NR	N	66	-	9*	11	7.3*	4.3*	N
Zanello et al. 2017 [48]	Y	458	319	Y	46	-	-	-	-	-	Y
Hager et al. 2018 [49]	Y	NR	NR	NR	100	22.64	10.89	-	-	-	NR
Goldman et al. 2018 [50]	N	NR	NR	Y	87	20	-	9	18	-	Y
Wann et al. 2018 [51]	Y	26	76	Y	100	22	-	9.6	14	-	Y

Survival: (*) indicates post-repeat resection/recurrence survival; OS, overall survival; PFS, progression-free survival; EOR, extent of resection; IS, initial surgery; RR, repeat resection; NR, not reported; GTR, gross total resection; STR, subtotal resection; I, nonsignificant increase. Survival (**) – Bloch et al. data from patients with GTR at IS and RR

significant OS benefits with RR was approximately similar between both study types (3/7 [43%] vs. 17/36 [47%]) [11, 19, 28, 32, 46–48]. Additional variability in OS determination saw some use time of radiographic diagnosis rather than time of operation as a starting point, posing the risk of arbitrarily increasing reported OS depending on time delay between diagnosis and first operation. This was deemed to constitute lead-time bias, as was the case in 17 studies (39.5%) [11, 18, 21–23, 25, 26, 31–33, 38, 40, 42, 44, 47, 49, 51]. Such a significant proportion of studies with risk of lead-time bias suggests that the collective OS data may overestimate. Nine studies reporting significant correlation between RR and OS also showed lead-time bias, meaning that nearly half of the twenty articles demonstrating increased survival with RR may have done so using overstated OS data [21, 22, 26, 38, 42, 46, 47, 49, 51].

Twenty-one of 43 studies reported PFS data [1, 10, 11, 14, 15, 18, 21, 24, 26, 27, 29, 31, 32, 34, 35, 37, 41, 42, 45, 48, 51]. However, EOR and KPS were extensively reported, and 32 studies found associations between EOR/KPS and OS/PFS [1, 10, 11, 13, 14, 17–20, 22–24, 26–35, 37, 39, 41, 44–46, 48, 50–52]. Absence of internal controls and reliance on historical survival data diminished the generalizability of findings for or against the value of RR. Importantly, with regard to follow-up adequacy, mortality was clearly defined and well-reported in all studies.

Assessment of heterogeneity

Clinical and methodological heterogeneity

Our systematic review had significant clinical and methodological heterogeneity. Evidence of this is seen from geographically far-flung study locations to substantial variation in number of patients (ranging from 7 to 949) and types of adjuvant therapies utilized. Earlier studies treated patients with nitrosureas and procarbazine [1]; meanwhile, post-Stupp era studies followed the temozolomide regimen. Length of follow-up varied widely from 15.1 [15] to 40 months [44], as did PFS and OS data. In fact, median OS ranged from 9.9 to 27.6 months and PFS ranged from 4.9 to 10.8 months. Control for confounding factors was addressed via multivariate regression models, but covariates included in these models varied widely. Furthermore, complete prognostic data was not consistently available—whereas some studies considered only KPS (n = 22) and age (n = 26), others accounted for prior intervention (n = 2), tumor eloquence/location (n = 7), volumetric data (n = 5), interval between operations (n = 8), or adjuvant therapy (n = 17). Although characteristics such as MGMT methylation and IDH-1 mutation status have demonstrated independent correlation with survival and response to treatment, this data was inconsistently reported, thus potentially minimizing the generalizability of our findings [39, 44, 46]. The inherent limitations of retrospective studies must also be considered in 41 of 43 included studies.

Statistical heterogeneity

Statistical heterogeneity was minimal due to the uniform use of multivariate analyses in determining the relationship of RR and OS. KPS and EOR were included in multivariate analyses in 37 and 35 studies, respectively. Twenty-seven studies presented associations between RR and OS using Kaplan Meier survival analysis [1, 13–15, 18–24, 28, 30, 32, 34, 35, 41, 42, 45–52]. Finally, Goldman et al. presented a time-dependent analysis by including time to recurrence (TTR) following initial surgery in a multivariate model which was not repeated elsewhere [50].

Discussion

Effect of repeat resection on survival

The use of RR in rGBM management has been the subject of much discourse dating back at least as early as 1987. Early reports, such as those by Ammirati et al., showed remarkable survival benefits totaling approximately 7.3 months in those receiving RRs [1]. In contrast, a similarly timed publication by Harsh et al. understated the observed lack of a survival benefit with RR, choosing instead to focus on reported increase in quality of life (QoL) among these patients [54]. With an infiltrative condition where nearly all patients succumb to disease progression, Harsh suggested a role for surgery in maximizing the quality of post-progression survival through addressing associated symptoms via RR. While this report by Harsh et al. was excluded from our review due to its inclusion of secondary GBM patients, it maintains its relevance to existing literature regarding rGBM treatment in its illustration of the need for maximizing QoL, serving as impetus for further study of this important clinical outcome in future GBM patients.

The recent trend toward increasingly aggressive resection requires careful assessment, especially with reported complications that detract from an already-limited post-progression survival. Lu et al. (2018) recently conducted a meta-analysis and systematic review of the role of RR in rGBM to generate a pooled hazard ratio (HR) of death from prior studies [55]. They included 8 studies, 6 of which failed to find a significant increase in survival between RR and non-RR patients. Despite this finding, the authors achieved a statistically significant decreased pooled hazard ratio for death in rGBM patients undergoing RR (0.722, $p < 0.001$). The selected studies for this meta-analysis reflected current trends in GBM practice with nearly all patients treated in the post-Stupp protocol era

(2003-2015); 6 of these studies were also included in our review [35, 36, 45, 46, 48, 51]. The remaining two studies were excluded for including pediatric patients or using progression as the primary outcome. Of these two, Nava et al. did not find an increase in survival with repeat surgery, and Suchorska et al. saw survival benefits only if GTR was achieved at the time of RR [56, 57]. Moreover, if only STR was achieved at RR, survival was less than in non-reoperated counterparts.

Building upon the work by Lu et al., we conducted the most extensive systematic review to date on the value of RR in rGBM, assessing 43 papers, spanning 13 countries, and representing 50 years (1969–2019) of survival data. While this broad timespan introduces potential heterogeneity, the increase in reported median OS between pre- and post-Stupp era studies may be, in part, attributable to advances in chemotherapy or other broad improvements in management of GBM patients over time, including advancements in surgical technique over the past three decades. Additionally, increased uniformity in histopathological diagnoses, in concert with updated WHO central nervous system tumor definitions [58], may have additionally contributed to better isolation of true GBMs without inclusion of lower-grade gliomas, as discussed by Scheithauer et al. [59]. Despite this variability, 20 of the included studies noted a significant increase in OS for patients receiving RR compared to non-RR counterparts, with only four studies finding no benefit with RR. Of those four, the study by Goldman et al. [50] reported a distinctly negative association between survival and RR. The authors used an extended Cox model of OS where RR is treated as a time-dependent variable (rather than fixed), and in doing so, they demonstrated that RR held a greater than twofold increased risk of death (HR, 2.19; $p < 0.001$) compared to the fixed CHD model. This contribution by Goldman et al. posits that the apparent benefit of RR might have less to do with reoperation and more to do with individual risk factors, such as tumor biology and selection bias. Goldman's clever analysis is an example of available methodology to assess the efficacy of RR while controlling for intrinsic differences between patients with longer PFS but similar OS. Future analyses utilizing this time-dependent model may further elucidate the true effect of RR on survival in rGBM patients.

Additionally, 7 studies reported trends toward OS increase with RR, though these studies ultimately failed to demonstrate statistical significance, and an additional 12 studies lacked a comparison group [1, 10, 15, 18, 27–29, 34, 37, 39, 44, 52]. Notably, the 7 studies without significant OS increases did not suffer from low sample sizes (median: 109 patients). Specifically, a 776-patient study by Gately et al., which stands as one of the largest studies in our review, failed to show a significant increase in OS for RR patients [43]. Among the 12 single-arm studies focusing on patients undergoing RR, median OS ranged from 15.1 to 27.6 months, demonstrating equal-to-longer survival than existing comparable literature on GBM patients only undergoing a single resection.

Beyond the second resection, data is more sparse on the role of surgery at further recurrence. We only found 10 studies which reported on multiple recurrences [13, 17, 21–23, 34, 35, 41, 42, 44]. Six studies found continued reoperation to be beneficial; however, the low sample size among these cohorts must be noted. Within all 10 studies, the mean number of patients at second recurrence was 28.5. GBM's poor prognosis often results in patients succumbing to their disease before reaching a second recurrence. The benefit of RR beyond first recurrence, therefore, remains elusive. The dearth of current evidence calls for a thorough patient-physician discussion on the potential positive and negative sequelae of RR individualized to the needs of each patient.

Extent of resection and its strength of survival prediction

Evaluation of patient prognosis is often tied to extent of surgical resection, with increasing resection associated with survival advantage in prior GBM literature. Previous work by Lacroix et al. established the role of ≥ 98% removal of the contrast enhancing portion of GBMs in extending OS following first resection [60]. Similarly, 27 studies in our review confirmed this finding at first resection, with 9 studies supporting this finding at RR. For example, Ortega et al. found that only EOR at first surgery carried an effect on OS [35]. Furthermore, patients who received an STR at first surgery but a GTR at subsequent surgeries did not see similar survival benefits as those who received an initial GTR [35]. Few articles relied on volumetric data to determine GTR [18, 21, 24, 28, 36] and, instead, utilized existing radiology reports or non-blinded assessments that varied across institutions. Furthermore, McGirt et al. [52] added a near-total resection classification alongside GTR and STR which further increased EOR heterogeneity among these reviewed articles. Eight studies could not establish a statistically significant association between EOR and survival following any surgery [15, 19, 32, 33, 36, 38, 42, 47], and 8 studies did not report data on EOR [12, 13, 21, 25, 30, 40, 43, 49].

KPS and age analysis in RR

Beyond EOR, a provider's decision to recommend RR also considers the patient's functional status, often measured by Karnofsky performance status (KPS). KPS is recorded in 10-point increments (100, 90, 80, etc.) with a maximum score of 100 and each score correlating to the patient's disease burden upon activities of daily living (ADLs) [61]. Thirty out of 43 studies found that higher KPS conferred a survival advantage; seven studies showed no OS advantage for patients with higher preoperative KPS [21, 36–39, 42, 47]. Due to the

subjectivity of KPS assignment, its discordance among providers may explain, in part, the variability of outcomes. In fact, a 1984 study of KPS inter-rater reliability by Schag et al. demonstrated a kappa statistic of 0.53 (where 1.0 is complete agreement) between multidisciplinary teams and oncologists with regard to KPS reliability [62]. Despite this possible subjectivity, the inclusion of the KPS metric in 37 of 43 studies reflects its prevalence in the field and its importance in clinical decision-making among GBM patients considering RR.

Alongside KPS, age was also studied as a prognostic factor for OS, and a potential bias in patient selection became apparent. Younger reoperation cohorts were widespread among the included studies, with some studies positing patient age as a central factor in recommending RR for recurrent GBM patients [14, 35, 36, 63]. However, this practice may unfairly preclude surgically fit patients from benefiting from RR, as studies by Hager and Zanello et al. have shown equal survival gains for all age groups with equivalent KPS [48, 49]. Viewing age outside the context of KPS may inappropriately exclude otherwise fit, older rGBM patients from the potential benefits of a repeat resection.

Limitations

The nearly uniform retrospective nature of the included studies presents obvious barriers in attaining unbiased individual patient data. Also, the temporal and spatial heterogeneity in the included studies presented difficulties in directly comparing studies, especially those in the pre- vs. post-Stupp protocol era. Additionally, the plethora of single-center studies introduced high risk of bias in data reporting. Lastly, the poor availability of molecular data in the majority of studies limited our conclusions. Thus, our review describes a heterogenous population of tumors differing in focality, eloquence, and molecular characteristics to draw general conclusions in the recurrent GBM population.

Conclusion

Questions surrounding the optimal management of patients with rGBM have been long-standing. In our report of 43 studies, 20 found a significant survival benefit for RR at first recurrence, whereas four studies failed to show survival benefits with repeat surgery, with one citing decreased survival in RR patients [50]. Beyond the first recurrence, 6 of 10 studies showed increased OS for continued reoperations, albeit with few patients in these cohorts. Furthermore, we found that EOR played a pivotal role in predicting survival in 27 of 35 studies and that KPS played a significant role in predicting survival in 30 of 37 studies, reporting significant increases in OS with maximization of both measures. However, such findings must be interpreted with caution due to the risk of significant selection bias. Such bias is a consequence of retrospective studies in general and is reflected in our categorization of all 43 papers to be at some risk of bias. For instance, construction of cohorts preferentially reporting on patients with better outcomes was witnessed in 8 papers excluding highly infiltrative tumors [22, 28, 35, 37, 42, 45, 50, 52], 3 papers including only patients with initial GTR [19, 29, 34], 2 papers excluding patients with less favorable functional status or advanced age [12, 24], and 8 papers excluding patients with potentially poor outcomes following initial resection [31–33, 38, 39, 46–48].

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Only published studies were used for our analysis, and no patient medical records were accessed in completing this article. Thus, patients' consent was not required

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