TITLE:

Second surgery for recurrent glioblastoma. A concise overview of the current literature.

ABSTRACT

Optimal treatment for recurrent glioblastoma continues to evolve. Currently, however, there is no consensus in the literature on the role of reoperation in the management of these patients, as several studies provide evidence for a longer overall survival in selected patients with recurrent glioblastoma who underwent second surgery and other studies report a limited impact of second surgery in the clinical course. In this paper, a review of the current literature was performed to analyze the role of reoperation in patients with recurrent glioblastoma and to report the overall survival from diagnosis, progression-free survival and quality of life. Using PubMed and Ovid Medline databases, we performed a review of the literature of the last seven years, finding a total of 28 studies and 2279 patients who underwent second surgery, that were included in the final analysis. The median overall survival from diagnosis and the median survival from second surgery were 18.5 months and 9.7 months, respectively. Extent of resection at reoperation improves overall survival, even in patients with subtotal resection at initial operation. Preoperative performance status and age are important predictors of a longer survival, reason why younger patients with a good preoperative performance status could benefit from reoperation.

KEY WORDS: recurrent glioblastoma, glioblastoma, reoperation, overall survival, progression-free survival.

1. Introduction

With a peak incidence between 50 and 70 years of age, glioblastoma multiforme (GBM) (WHO grade IV) is the most common primary intrinsic brain tumor of adulthood and the most malignant glioma subtype [7]. Despite advances in diagnostic technology, surgical techniques and adjuvant treatments, the prognosis remains poor and the median overall survival (OS) of patients has increased only 3.3 months (from 11.3 months to 14.6 months) over the past 25 years [33]. In order to prolong survival, treatment strategies have become more aggressive, with an increasing number of patients who underwent second surgery and salvage chemotherapy or radiotherapy for recurrent GBM over the past 10 years. Surgery for recurrent GBM is possible with potential surgical and systemic complications and accepted morbidity [20,30,37].

As nowadays quality of life at the time of tumor recurrence is higher than in the past in a great number of patients, second surgery is increasingly considered a valid option [8]. The analysis of recent studies dealing with OS and progression-free survival (PFS) in patient who underwent second surgery could help to identify yet poorly appreciated clinical factors that are associated with a more favorable prognosis.

2. Materials and methods

A MEDLINE search was performed for the key words “recurrent glioblastoma”, “glioblastoma”, “survival” and “glioblastoma reoperation” from 2007 to present. Only reports in English were used and articles referenced in other articles were also included. The search was limited to articles reporting survival from diagnosis or from second surgery and PFS in patients who underwent reoperation for recurrent GBM. Using these search methods, a total of 218 records were identified (Fig. 1). In addition, the abstracts of the identified studies were screened for relevancy and duplicate patient databases. Studies were excluded if 1) patients had malignant gliomas but not GBM; 2) the outcomes did not include survival analysis; 3) patients did not perform second surgery; 4) patients received locoregional chemotherapy after second surgery; 5) patients received gamma knife surgery before second surgery. Accordingly 190 records were excluded, leaving 28 records (Fig. 1). Collected data were used for the final analysis, whose endpoints were to evaluate the median OS (defined as the time from first diagnosis until death from any

cause), the median survival from reoperation (SFR) (defined as the time from second surgery until death from any cause) and PFS (defined as the time from first diagnosis until recurrence). All studies, according to Macdonald criteria, evaluated tumor progression as the appearance of new lesions, an increase in tumor extension by 25% on computed tomography (CT) or magnetic resonance imaging (MRI), a worsening in the clinical/neurological condition or a stable or increased use of corticosteroids [25]. Arithmetic was performed for survival and tumor recurrence analysis.

3. Results

A total of 28 studies with significant data were identified using PubMed and Ovid Medline databases and included in our analysis, accounting for 5736 patients who underwent surgery for GBM [2-4,8,10,11,14,15,19,23,24,26-29,31-35,37,38,41-43,46-48]. Of these patients only 2279 (39.7%) underwent a second or more than two reoperations for recurrent GBM. Twenty-four of the 28 papers included in the analysis demonstrated a survival benefit from a second surgery [2-4,8,10,11,19,24,26-29,31-35,38,41-43,46-48]. Table 1 showed all details. Twenty-three studies provided details about OS, accounting for 1643 patients (Fig. 2). Survival data after second surgery were obtained from 19 studies, including 1433 patients. The median SFR and the median OS resulted 9.7 months and 18.5 months, respectively. Similarly, 13 studies, including 1017 patients, reported data regarding PFS, which was 9.2 months.

4. Discussion

Recurrence is a hallmark of GBM that eventually occurring in all patients, despite every kind of known therapy. Median OS of patients with GMB is still poor and this is largely the result of the recurrence of tumor after initial treatment with maximal safe surgical resection, radiotherapy and chemotherapy [33]. Radiation therapy in addition to surgery and chemotherapy showed to prolong survival from 3-4 months to 7-12 months in patients with GBM compared with surgery alone [40]. Treatment of recurrent GBM should be individualized, depending on patient's clinical condition and performance status, age and quality of life. In our review 24 of the 28 studies included showed a survival benefit or improved functional status

after reoperation followed by adjuvant treatments for recurrent GBM [2-4,8,10,11,19,24,26-29,31-35,38,41-43,46-48]. In contrast to these studies, Filippini et al. [14] found no benefit of reoperation on survival, as instead, chemotherapy did. Similarly, Franceschi et al. [15] showed, through a multivariate analysis, that second surgery did not affect survival and had a limited impact in the clinical course of patients with recurrent GBM patients. Skeie et al. [37] reported that median survival after treatment for patients who underwent reoperation alone was lower compared with patients treated with Gamma Knife surgery (GKS) alone (6 months Vs 12 months), whereas the combination of both led to higher median survival (15 months). Kim et al. [23] reported that a salvage treatment (GKS + temozolomide) provided a longer OS than reoperation at the time of recurrence of GBM, after standard first-line treatment. Despite modern treatment strategies, reoperation remains, for Oppenlander et al. [31], still the most important factor determining the length of survival in recurrent GBM, even if surgery itself must be balanced against the risk of neurological morbidity, that can increase with a more aggressive cytoreduction. Helseth et al. [19] demonstrated a higher OS (18.4 months) in patients who underwent second surgery than patients who didn't attend it (8.6 months). Similarly Ma et al. [24] and Rusthoven et al. [35] that reported a median OS from diagnosis of 16 months (Vs 10.7 months without reoperation) and 22.2 months (Vs 14.2 if no reoperation), respectively. Park et al. [32], introducing a 3-tier scale (scoring range, 0–2 points), depending on Karnofsky Performance Scale (KPS), (0 for KPS $\geq$ 70 and 1 for KPS < 70) and ependymal involvement (0 for no enhancement and 1 for enhancement of the ventricle wall in the MRI), identified 3 groups (0 points, 1 point, 2 points), finding different median OS (18, 10 and 4 months, respectively).

Recently, Sughrue et al. [41] emphasized the relevant role of reoperation in improving the OS in selected patients.

Several studies reported that a higher preoperative performance score (KPS $\geq$ 70) is strongly correlated with a longer OS [20,33,38,43]. Chang et al. [9] in 2003 and recent studies [11,33] reported that KPS at tumor recurrence represents the most important factor associated with a better OS. Accordingly, Michaelsen et al. [29] reported that the Eastern Cooperative Oncology Group Performance Status (ECOG

PS) has a significant impact on survival following therapy. Quick et al. [34] found that there is a good statistical association between KPS score and OS in their series.

Although some studies suggested that age does not represent a contraindication to reoperation [27], age at the time of diagnosis represents the most important prognostic factor in most of recent studies, where OS from diagnosis is significantly higher in younger patients [15,29,34,38,43]. Although authors usually do not emphasize gender as a prognostic factor, Tugcu et al. [43] reported that male gender is a good prognostic factor.

Although previous studies [12,22] reported that a short interval time between the first and second operations was significantly related to a higher survival from reoperation, Filippini et al. [14] showed no statistically significant difference in survival in patients who underwent second surgery before or after 9 months from first surgery. Similarly, Park et al. [33] reported that time interval between initial diagnosis and reoperation doesn't effect the survival.

Several studies investigated the effect of extent of tumor resection in OS [8,16,33,34,36,41]. Surgical resection of the tumor is still the most effective therapy in GBM, as surgical resection improves the efficacy of radiotherapy. In 2005 Stupp et al. [40] demonstrated that gross total resection (GTR), achieved with fluoroscopic 5-aminolevulinic acid guidance [39], and second surgery (in 23% of patients) at the time of progression, in combination with temozolomide and radiotherapy improve average survival to more than 14 months. In patients candidate to second surgery, maximal tumor volume resection should be the surgical goal. There is evidence in the literature that involvement of eloquent brain is associated with shorter duration of survival [9, 36]. Interestingly, Sanai et al. [36] reported that when GTR cannot be achieved because of tumor location in eloquent areas, subtotal resection (STR) as low as 78% of the enhancing portion of the tumor corresponds to a statistically significant survival benefit. Bloch et al. [3] reported that tumor volume resection in recurrent tumor is associated with a longer OS. In 2004, Keles et al. [21] reported that there is a statistically significant difference in OS between patients with tumors ≤ 10 cm^3 and those > 10 cm^3. However, more recent studies [34,38,42] concluded that survival is not correlated with tumor volume resection. On the other hand, Quick et al. [34] concluded that the removal of at least

95% of the tumor volume led to a survival benefit of 5.5 months and that there is no statistically significant difference between patients bearing tumors smaller or greater than 5 cm^3. Recently published studies showed the importance of extent of resection as also the numbers of reoperations at the time of recurrence to prolong survival in patients with recurrent GBM [3,8,41]. Chaichana et al. [8] reported 578 patients with primary GBM who underwent 1 time surgery (354 patients), 2 times surgery (168 patients), 3 times resection (41 cases), 4 times resections (15 patients) with a median survival of 6.8, 15.5, 22.4 and 26.6 months, respectively. However Surghrue et al. [41] reported patients who underwent surgery more than two times, showing that the median OS after reoperation were 7.8, 6.0, and 4.8 months following the second, third, and fourth–sixth craniotomies, respectively.

The significance of O6-methylguanine-DNA methyltransferase (MGMT) promoter methylation and others molecular markers, such as the 1p/19q chromosomal codeletion and the mutations of isocitrate dehydrogenase (IDH) 1 and 2, in recurrent GBM is controversial. Previous studies showed a significant correlation between lack of MGMT expression and survival of GBM patients [13,16,18]. However Michaelsen et al. [29] reported that none of the molecular markers, such as MGMT, p53 and epidermal growth factor receptor (EGFR) is significantly correlated with patient survival when the GBM recur. Franceschi et al. [15] found that MGMT methylation status at diagnosis is not significantly correlated to post-progression survival (PPS), although the OS and the PFS are significantly correlated with MGMT methylation status in univariate analysis. Quick et al. [34] showed that although SFR in patients with a methylated MGMT promotor is longer than in those not exhibiting this methylation, this difference is not statistically significant. Similarly, Brandes et al. [5] reported that MGMT methylation status determined at first surgery seems to be of prognostic value although is not predictive of outcome following second surgery. MGMT status at the time of second surgery in patients with GBM is neither prognostic for OS nor for SFR [5,6]. Recent studies suggested that 1p/19q codeletions in GBM are rare and of unknown biological significance [45] and that IDH1/2 mutations are prognostically favorable and suggestive of secondary GBM [44,45]. Hartmann et al. [17] reported that patients with IDH mutations had a longer OS

than those with IDH wild-type tumors, whereas Amelot et al. [1] showed similar long-term survival in both groups with and without IDH1/2 mutation.

5. Conclusion

This concise overview of the current literature suggests evidence of a higher OS in selected patients who underwent reoperation at the time of GBM recurrence. Repeat surgery leads to a longer OS and should be considered in patients with a favorable KPS score at the time of recurrence, favorable preoperative clinical and radiological characteristics. The decision of a second surgery for a recurrent GBM should be individualized. Careful analysis of the current literature shows that age and preoperative performance status are the most important prognosis factors, as in patients younger than 60-year-old and with KPS ≥70, reoperation could increase OS. Preserving eloquent brain areas in order to avoid worsening of the neurological status, second surgery should be a GTR or NTR. The treatment of recurrent GBM remains multimodal. Regularly scheduled imaging and clinical evaluations, in patients who completed first-line therapy, must be performed to allow an earlier detection of tumor recurrence. This review showed how the role of second surgery in the treatment of recurrent GBM remains unclear; the understanding of underlying tumor biology is essential in developing more effective strategies.

Conflicts of interest

The authors declare that there are no conflicts of interest.

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Figures

Figure 1 – Flow diagram of study selection

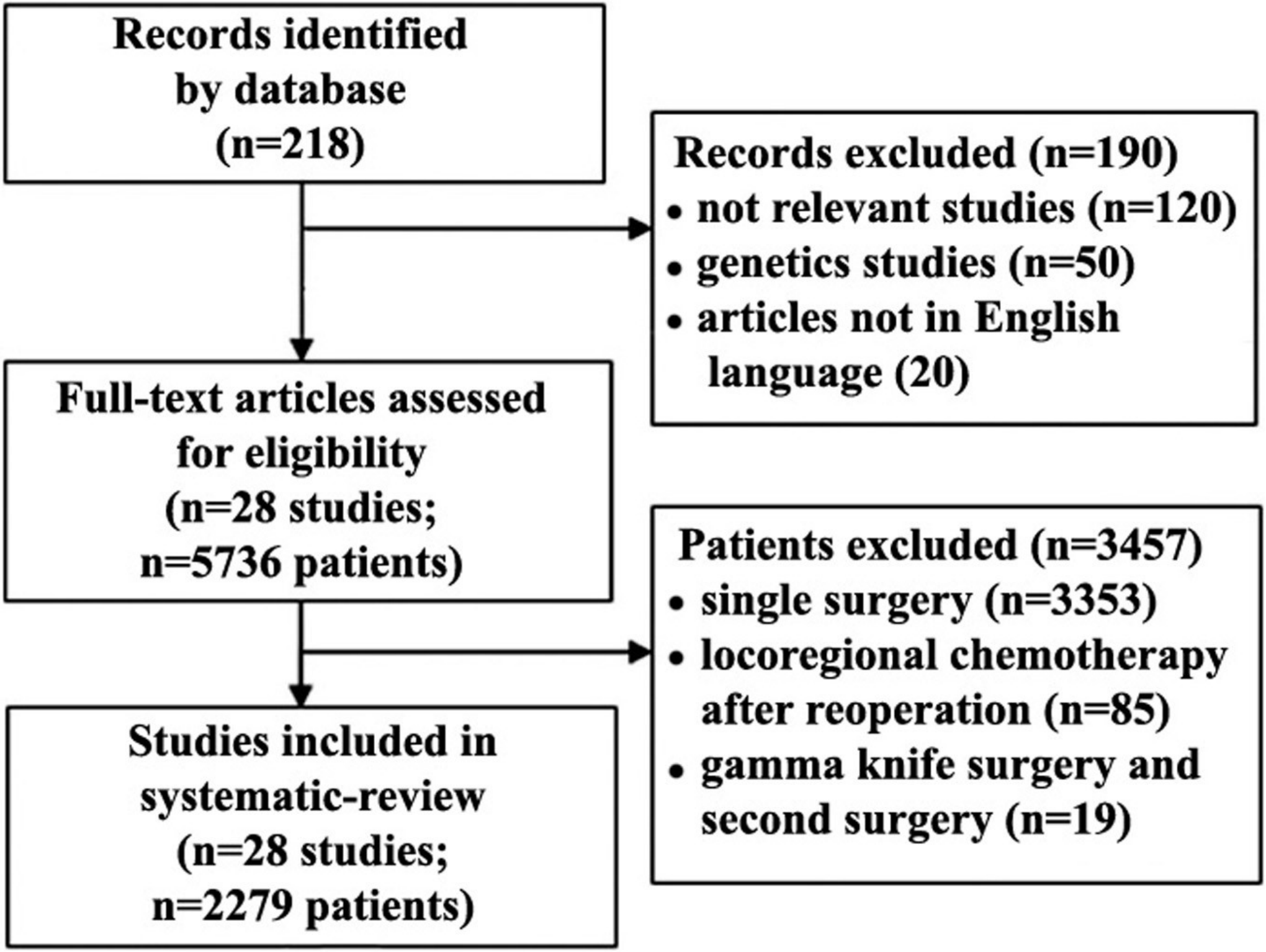
Figure 2 – Overall survival data from diagnosis of glioblastoma multiforme in patients who underwent second surgery, associated with adjuvant treatment, collected from the literature of the last seven years.

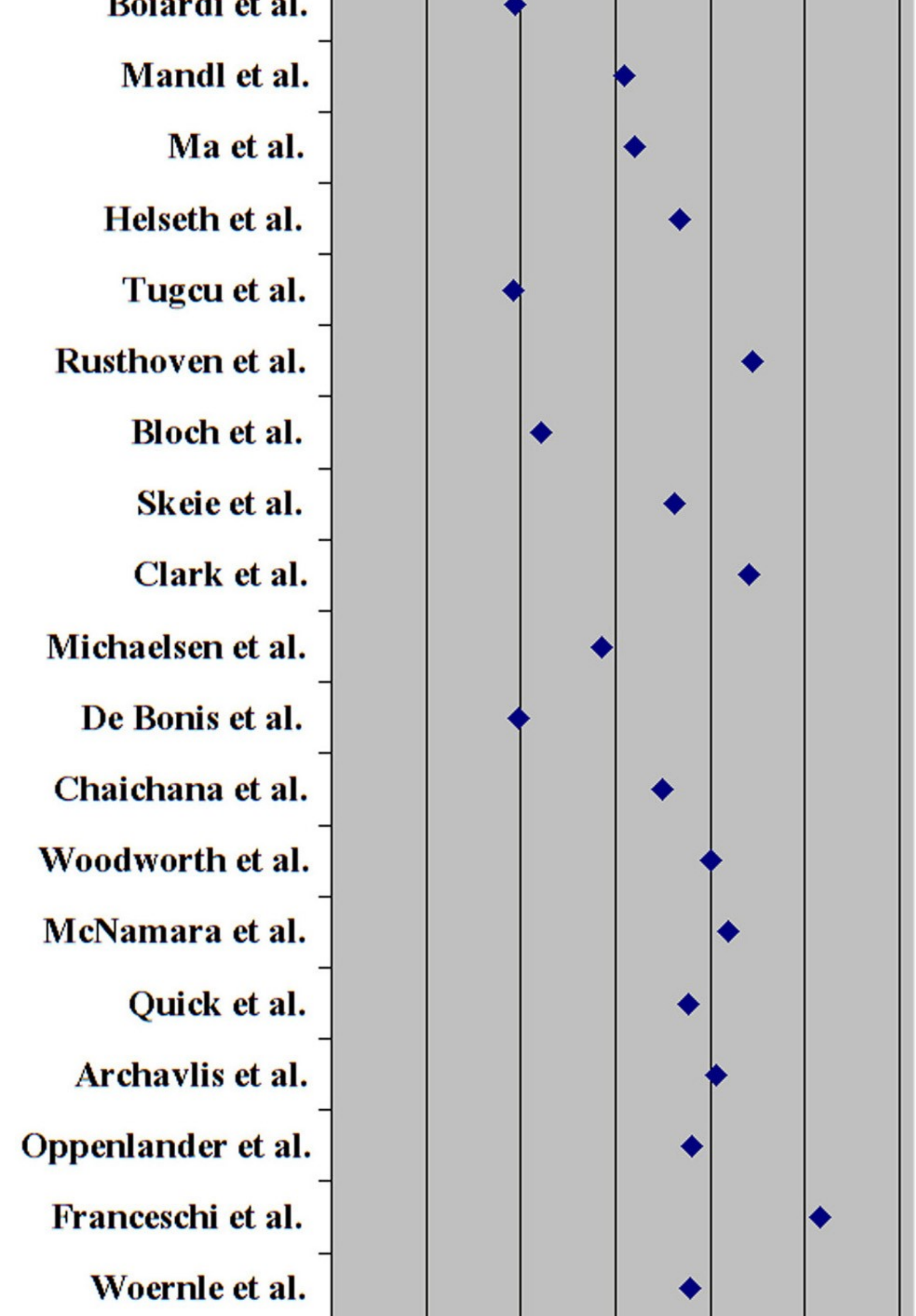
Table 1 – Studies reporting overall survival and progression-free survival for recurrent glioblastoma.

Authors	Year	GBM patients underwent surgery	Patients underwent additional surgery (%)	PFS	Survival from reoperation (mo)	OS from diagnosis (mo)
Terasaki et al. (42)	2007	35	7 (20%)	6.9	9	15,1
Stark et al. (38)	2007	345	107 (31%)	-	12	15
Filippini et al. (14)	2008	676	173 (25.6%)	6	-	-
Boiardi et al. (4)	2008	276	50 (18.1%)	-	-	8 (reoperation + TMZ)
Mandl et al. (26)	2008	126	20 (15.9%)	-	3.2 (2 resection); 8.5 (2 resection + CT or SRS); 7 (CT or SRS)	15.5
McGirt et al. (27)	2009	451	294 (65.2%)	-	11 (GTR), 9 (NTR), 5 (STR)	-
Ma et al. (24)	2009	205	52 (25.3%)	-	-	16 (Vs 10.7 if no reoperation)
Helseth et al. (19)	2010	516	65 (12.6%)	7	-	18.4 (Vs 8.6 if no reoperation)
Park et al. (33)	2010	34	34 (100%)	11.1	tot. Media 7.4 --> 10.8 (NIH score 0), 4.5 (NIH score 1), 4.4 (NIH score 1), 1 (NIH score 3)	-
Tugcu et al. (43)	2010	50	11 (22%)	-	6.9	9.6 (Vs 6,7 if no reoperation)
Rusthoven et al. (35)	2011	34	34 (100%)	6.7	9.3 (Vs 4.9 if no reoperation)	22.2 (Vs 14.2 if no reoperation)
Bloch et al. (3)	2012	107	107 (100%)	11.1 (GTR/GTR), 11.8 (GTR/STR), 6.1 (STR/GTR), 7.3 (STR/STR)	-	11.5 (GTR/GTR), 8.5 (GTR/STR), 16.7 (STR/GTR), 7.4 (STR/STR)
Skeie et al. (37)	2012	77	26 (33.7%)	2 months (after second surgery)	6 (Vs 15 with GKS+reoperation)	16 (Vs 21 with GKS+reoperation)
Clark et al. (10)	2012	174	174 (100%)	12.5	9.8 (no BV), 5 (preoperative BV), 13 (postoperative BV)	21.8 (no BV), 23.3 (preoperative BV), 21.3 (postoperative BV)
Michaelsen et al. (29)	2013	225	74 (32.8 %)	5.9	6.3	14.3
De Bonis et al. (11)	2013	76	33 (43.4%)	-	-	14 (reoperation + CT); 6 (surgery alone); 5 (no treatment); 8 (chemotherapy alone)
Park et al. (32)	2013	55	55 (100%)	12	10	13
Chaichana et al. (8)	2013	578	224 (63.3%)	-	-	6.8 (1 operation), 15.5 (2 operations), 22.4 (3 operations), 26.6 (4 operations)
Woodworth et al. (47)	2013	59	21 (35.6%)	-	9	20
McNamara et al. (28)	2014	584	107 (18.3%)	11.5	7	20.9 (Vs 9.9 if no reoperation)
Yong et al. (48)	2014	97	97 (100%)	-	12.4	-
Quick et al. (34)	2014	40	40 (100%)	10.2	13.5	18.8

Archavlis et al. (2)	2014	90	20 (22.2%)	-	8 (reoperation + TMZ)	20.5 (reoperation + TMZ)
Oppenlander et al. (31)	2014	170	170 (100%)	-	5.2	19.0
Kim et al. (23)	2015	222	38 (17.1%)	-	13.2 (reoperation); 9.2 (GKS); 5.6 (TMZ alone); 15.5 (GKS+TMZ)	-
Franceschi et al. (15)	2015	232	102 (44%)	13.1	-	25.8 (Vs 18.6 if no reoperation)
Woernle et al. (46)	2015	98	40 (40.8%)	-	-	18.9 (Vs 14.81 if no reoperation)
Sughrue et al. (41)	2015	104	104 (100%)		7.8 (2 operations), 6.0 (3 operations), 4.8 (4-6 operations)	17.8 (2 operations), 13.9 (3 operations), 12.5 (4-6 operations)

BV, bevacizumab; **CT**, chemotherapy; **GBM**, glioblastoma; **GKS**, gamma knife surgery; **GTR**, gross-total resection; **NIH**, national institutes of health; **NTR**, near-total resection; **OS**, overall survival; **PFS**, progression-free survival; **SRS**, stereotactic radiosurgery; **STR**, subtotal resection; **TMZ**, temozolomide.


Records identified by database (n=218)
Records excluded (n=190)
• not relevant studies (n=120)
• genetics studies (n=50)
• articles not in English language (20)
Full-text articles assessed for eligibility (n=28 studies; n=5736 patients)
Patients excluded (n=3457)
• single surgery (n=3353)
• locoregional chemotherapy after reoperation (n=85)
• gamma knife surgery and second surgery (n=19)
Studies included in systematic-review (n=28 studies; n=2279 patients)


Bolardi et al.
Mandl et al.
Ma et al.
Helseth et al.
Tugcu et al.
Rusthoven et al.
Bloch et al.
Skeie et al.
Clark et al.
Michaelsen et al.
De Bonis et al.
Chaichana et al.
Woodworth et al.
McNamara et al.
Quick et al.
Archavlis et al.
Oppenlander et al.
Franceschi et al.
Woernle et al.