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Recurrent Malignant Gliomas

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Abstract

In almost all patients, malignant glioma recurs following initial treatment with maximal safe resection, conformal radiotherapy, and temozolomide. This review describes the many options for treatment of recurrent malignant gliomas, including reoperation, alternating electric field therapy, chemotherapy, stereotactic radiotherapy or radiosurgery, or some combination of these modalities, presenting the evidence for each approach. No standard of care has been established, though the antiangiogenic agent, bevacizumab; stereotactic radiotherapy or radiosurgery; and, perhaps, combined treatment with these 2 modalities appear to offer modest benefits over other approaches. Clearly, randomized trials of these options would be advantageous, and novel, more efficacious approaches are urgently needed.

Introduction

Malignant gliomas almost inevitably recur following initial treatment. For patients with glioblastoma (GBM) treated with the current standard of care (maximal safe resection, fractionated external beam radiotherapy, and concurrent and adjuvant temozolomide) in the European Organisation for Research and Treatment of Cancer–National Cancer Institute of Canada randomized trial,[1] 2- and 5-year progression-free survivals (PFSs) of only 11% and 4%, respectively, were observed with less than 10% of patients surviving more than 5 years from diagnosis.

Today, most patients with malignant glioma and the clinicians caring for them face the challenge of managing recurrent disease following multimodality treatment. A variety of approaches for treatment of recurrent disease exists, and this article describes these options, the evidence supporting their use, and their relative risks, efficacy, and logistics.

Diagnosis of Recurrence

Historically, the predominant site of initial recurrence following radiotherapy alone has been within a few centimeters of the tumor bed and resection site.[2–5] Despite the addition of temozolomide to radiotherapy for GBM, local failure remains the most common site of initial recurrence.[6–9] Nonetheless, it is essential to remember that malignant gliomas are

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infiltrative in nature, as the brain offers minimal barriers to spread within its confines, and that distant failures (in the brain) are likely to occur.

Immediately following primary concurrent chemoradiation, many patients with GBM develop pseudoprogression, that is, the false radiographic appearance of progressive disease. This phenomenon has been estimated to occur in approximately 20% of patients with recurrent malignant glioma[10] and typically appears within 6 months of completion of radiotherapy. Conversely, the use of antiangiogenic therapies (vide infra) can produce "pseudoresponses," in which the disease is disproportionately less apparent radiographically though the change in tumor burden may be minimal. Although a great deal of progress has been made in establishing the radiographic criteria for disease progression in treated malignant glioma,[11–13] the interpretation of magnetic resonance (MR) imaging studies is complicated by radiotherapeutic effects and concomitant biochemotherapies. Although a variety of other imaging modalities, including single photon emission computed tomography and positron emission tomography with various biomarkers, exist, no method has emerged as providing an unambiguous method of ruling in recurrence or progression and ruling out purely radiation-induced changes.[14]

The gold standard for diagnosis of recurrent disease is, of course, a definitive histologic confirmation. However, before performing a biopsy to establish or deny gross recurrence, it is essential to ask whether the value of making the diagnosis outweighs the risk of the procedure. Inherent in this judgment is the upfront probability that an apparent lesion represents recurrent disease. During the first 6 months following treatment of the primary disease with radiotherapy, there is a substantial probability that radiographic changes represent pseudoprogression and many practitioners may elect to follow up the patient with closely spaced MR imaging examinations in the absence of clinically significant new symptoms. At longer times, the probability that there is recurrent disease, often in admixture with local radiotherapeutic effects, is very high. In addition, biopsy can be complicated by impaired wound healing from previous radiation therapy or ongoing chemotherapy, particularly bevacizumab (BVZ).[15] Thus, the appearance of a new, distinct lesion on MR images may be sufficient to initiate further interventions without histologic confirmation of recurrence, especially when the lesion is outside the high-dose area of initial radiotherapy or appears more than 6–12 months after completion of radiotherapy or both.

Surgery

Surgical resection of recurrent lesions has the advantage of being potentially diagnostic and therapeutic. In particular, surgery tends to be most beneficial when there is a well-demarcated lesion involving noneloquent brain, producing a symptomatic mass effect on normal brain structures. However, reoperation may be complicated by several factors. First, the site of recurrence is at or near the resection bed, and this volume has typically received a full dose of radiation during the initial course of treatment, potentially impairing wound healing. Second, the goal of the initial glioma surgery is to achieve maximal safe resection and, consequently, surgical margins may often abut eloquent areas. Thus, for recurrences near the resection cavity, the extent of reoperation may be severely constrained. Third, the

use of salvage chemotherapy, particularly antiangiogenic agents, can also increase the rate and severity of wound-healing complications.[15]

Notwithstanding these potential limitations, reoperation *can* often be safely performed by an experienced neurosurgeon, as described in several recent reports.[16–18] However, this is not equivalent to stating that reoperation *should* be performed on most patients.[19] Studies on reoperation of recurrent glioma,[17,18,20–28] summarized in Table 1, do not show a consistent benefit to surgical resection as compared with no reoperation, particularly when the typically more favorable attributes of surgical candidates are considered. In reviewing these reports, higher Karnofsky performance status, lower age, and smaller, more readily resectable recurrent tumors tend to be associated with more favorable outcomes. In addition, several small studies[19,23,26] suggest that superior survival may be associated with a combination of resection (an effective "local" therapy) and systemic adjuvant therapy (ie, "global" brain therapy).

Alternating Electric Field Therapy

In preclinical studies, low voltage, intermediate-frequency alternating electric fields (AEFs) have been shown to kill a variety of tumor cells.[29,30] Purportedly, the application of an AEF kills rapidly growing cells by preventing the mitotic spindle from properly aligning during cell division.[30] A phase I study of AEFs in recurrent GBM[29] showed that the treatment was well tolerated with a median time to progression of 26 weeks and a median overall survival (OS) of 62 weeks.

A subsequent phase III trial in 337 adult patients with recurrent GBM randomized these patients to the use of a portable AEF device alone vs "active" chemotherapy.[31] In this trial, chemotherapy was chosen at the discretion of the physician, with 31%, 31%, 25%, 15%, 11%, or 5% of the regimens containing BVZ, irinotecan, nitrosoureas, carboplatin, temozolomide, or other agents, respectively. Although all patients received radiation therapy during their initial treatment, it is not clear how frequently salvage radiotherapy was attempted. The portable AEF device was applied to the bare scalp essentially continuously for several months, though brief breaks were permitted for 1–2 h/d for hygiene and 2–3 d/mo. In this trial, 78% of the 116 patients starting AEF therapy completed at least 1 month of therapy.

No significant difference in median OS was observed (6.6 months for the AEF group vs 6.0months for the chemotherapy arm, hazard ratio for death 0.86 in favor of AEF, $P = 0.27$). Median PFS was similar in the 2 groups (2.2 vs 2.1 months). While systemic side effects were more common in the chemotherapy arm, central nervous system toxicity appeared similar in both arms. Serious adverse events were less AEF (6% vs 16%), with the chief non–central nervous system concern in the AEF arm being mild-to-moderate scalp dermatitis. Sufficient quality-of-life (QoL) data were available for analysis in 27%of patients. The QoL results in the domain of cognitive and emotional functioning and role functioning appear to favor AEF, physical functioning seemed better in the chemotherapy arm, and no differences in global health or social functioning were apparent. Treatment-

related symptoms, pain, and fatigue were judged worse in the chemotherapy group. The statistical significance of these QoL differences is unclear.

In April 2011, the Food and Drug Administration subsequently granted approval to market a portable AEF device (NovoTTF-100A, Haifa, Israel), indicated for the treatment of recurrent GBM. Preclinical studies suggest that AEFs may enhance the efficacy of chemotherapy,[32] and a trial of this device and temozolomide in GBM is underway.[31] To assess the efficacy of AEF therapy vs biochemotherapy, radiotherapy or both, several questions must be addressed. The phase III trial did not test AEF vs necessarily the best therapy, “only” the physician's choice of chemotherapy. It would be interesting to evaluate AEFs (± chemotherapy?) against anti-angiogenic agents, radiosurgery, and combination regimens, discussed later.

Chemotherapy

Given the infiltrative nature of gliomas, it seems logical to use agents that treat the entire neuraxis (ie, “global” brain treatments) to address gross and diffuse disease. By contrast, surgery and focal radiotherapy (discussed later) represent “local” treatments and by design do not directly address subclinical disease. A broad range of chemotherapy and biochemotherapy agents have been and are being evaluated for the treatment of recurrent gliomas, and a detailed discussion of the many trials is beyond the scope of this article. However, the major developments and obstacles are presented later. It is important to note that since 2005, virtually all patients with recurrent malignant glioma would have undergone initial treatment with radiotherapy and concurrent or adjuvant temozolomide, most following at least subtotal resection.

Table 2 summarizes selected studies[33–57] of chemotherapeutic agents in the treatment of recurrent glioma. The initial studies on cytotoxic chemotherapeutic agents showed short OS and PFS following recurrence, approximately 3–4 and 6–7 months, respectively. For example, Wong performed a meta-analysis of 8 consecutive phase II chemotherapy trials in recurrent malignant glioma conducted at M.D. Anderson Cancer Center between 1986 and 1995. For all histologies, the median PFS and OS were 2.4 and 7.0 months, respectively, with 1-year OS of 47% and 21% in anaplastic astrocytoma and GBM, respectively. Similarly, Gorlia analyzed the outcome of 8 phase I–II trails in 300 patients with recurrent GBM performed through the European Organisation for Research and Treatment of Cancer between 1999 and 2010. The median PFS and OS were 1.8 and 6.2 months, respectively, and the 1-year OS was 22%. Although better performance status and unifocal and smaller lesions were associated with improved survival, there was no significant difference in outcome in the patients who had received temozolomide and radiotherapy vs radiotherapy alone at initial presentation.

Human malignant gliomas highly express vascular endothelial growth factor (VEGF), and anti-VEGF agents exhibit activity against GBM in preclinical models.[58] BVZ, a recombinant humanized antibody against VEGF, appears to offer improved survival in recurrent gliomas when compared with that by other agents alone.[34,36,38,41,46,50,54,57–60] In a trial of 35 patients with recurrent GBM treated with BVZ and irinotecan, Vredenburgh et

al[54] found 6-month PFS and OS of 46% and 77%, respectively. In a separate study, Kreisl et al[41] administered BVZ to 48 patients with recurrent GBM and obtained 6-month PFS and OS of 29% and 57%, respectively. A multi-institutional trial[36] of 177 patients with recurrent GBM revealed a median OS in patients treated with BVZ alone vs BVZ plus irinotecan of 9.2 vs 8.7 months, respectively (difference not significant).

On May 5, 2009, the Food and Drug Administration approved a single-agent BVZ for the treatment of recurrent GBM after the "standard" therapy. It is important to recognize that BVZ may be associated with severe, potentially life-threatening side effects, including gastrointestinal perforation, wound-healing complications, hemorrhage, and blood clots. Given the conflicting preliminary results from phase III studies on the efficacy of BVZ in the initial treatment of GBM, BVZ should be employed judiciously in the recurrent setting. In addition, patients receiving BVZ for treatment of recurrent disease have been observed to exhibit fulminant progression, whereas discontinuation of BVZ at the progression of disease may be associated with adverse outcomes. It is unclear whether BVZ is unique among other antiangiogenic agents in its role in the treatment of recurrent malignant gliomas, as well as the optimum combination of BVZ and agents having other mechanisms of action.[37,42–45,47,52] Finally, the combination of BVZ and radiosurgery may afford some benefits, as described later, though this remains an area of active investigation and controversy.[61]

Radiation Therapy

Monomodality Therapy

Essentially all recurrent primary malignant gliomas would have been treated with partial-brain irradiation to a dose of approximately 60 Gy in total, in 1.8–12.0 Gy fractions, as discussed elsewhere in this issue. Transformed or secondary malignant gliomas should be considered for radiation using conventional regimens if not previously irradiated. In the setting of previous partial-brain irradiation and recurrence within the volume of the brain receiving an initial high dose of radiation (the most common scenario), it is difficult to administer another "conventional" course of irradiation to the recurrent lesion and margin without risking adverse toxicity. Thus, hypofractionated stereotactic radiotherapy (HFSRT) or stereotactic radiosurgery (SRS) to a limited volume is often employed, as discussed later. Alternatively, Marples et al have proposed a novel approach to improve the therapeutic ratio and permit effective re-treatment of large volumes, based on the principle of low-dose hypersensitivity and the application of pulsed irradiation.[62–64]

Conceptually, SRS and HFSRT have some attractive features. First, the area requiring re-treatment is close to or within the area that has been manipulated during the initial surgery and treated to a high dose of irradiation. Radiation Therapy Oncology Group (RTOG) 9005 demonstrated that SRS of recurrent primary brain tumors could be performed with minimal morbidity and established the maximum-tolerated dose for single-fraction SRS in this setting.[65] Second, a short course of radiation has obvious logistic advantages over the much longer courses of radiation typically employed in primary treatment. Third, application of a high dose of radiation over a short period may evoke different mechanisms of tumor response and enhance tumor control,[66,67] though this last point is controversial.[68]

However, the concept of SRS or HFSRT in the treatment of recurrent malignant gliomas also presents logical inconsistencies. First, as most patients with recurrent disease initially received a high-dose radiation to the area of recurrence, it is not clear why a second treatment should be any more effective than the first. At the very least, one would expect a "narrower" therapeutic window due to the effects of the initial irradiation. Second, an SRS boost as part of the initial treatment of malignant gliomas showed no benefit over conventional radiotherapy alone in RTOG 9305.[69] Third, as malignant gliomas have a diffuse, broadly infiltrative component in addition to discrete nodular disease, it is unclear why a strictly "local" treatment of the nodules alone should substantially alter the outcome.

Despite these apparent limitations, SRS, SRT, and even conventionally fractionated SRT appear to provide reasonable OS in comparison with that by chemotherapy alone for the treatment of recurrent glioma, with median OS ranging from 5–13 months (typically 8–10 months) as shown in Table 3. It is noteworthy that several of the early studies involving single-fraction SRS reported fairly high rates of late complications (20%–40%) requiring reoperation and that this problem is often viewed as a substantial limitation of SRS.[70–73] The use of HFSRT appears to mitigate the rate of adverse radiation events, as shown in the study by Fogh et al,[74] who reported worsened symptoms in only 1 patient (of 147 patients) at 6 weeks follow-up.

Combined Modality Therapy With BVZ

Apart from the potential, direct antitumor effect of BVZ in the treatment of gliomas, as discussed earlier, it may offer some specific additional benefits when used in combination with radiotherapy. As described by Moeller et al,[75–77] a paradoxical effect of radiotherapy is the upregulation of hypoxia factor–mediated angiogenesis, an unwanted effect that could be potentially blocked by antiangiogenic agents. In addition, adverse radiation events following SRS appear to be substantially reduced by the use of BVZ.[78–80]

The combination of BVZ and SRS or HFSRT may provide superior outcomes when compared with that by either modality alone.[81–86] A prospective trial of HFSRT and BVZ from Memorial Sloan-Kettering Cancer Center[83] showed that the combination was well tolerated and demonstrated an OS of 12 months after HFSRT. In a follow-up study, the predominant pattern of failure continued to be at or near the site of HFSRT.[87] Cabrera et al[81] assessed the toxicity of concurrent BVZ and SRS in a cohort of 15 patients with recurrent malignant gliomas. Only 1 grade 3 and no grade 4–5 toxicities were observed, and QoL and neurocognition were well preserved following SRS; the median OS was 14 months in this group of 8 grade IV and 7 grade III gliomas.

In a retrospective study from Duke University,[82] OS in heavily pretreated patients with recurrent GBM who received BVZ at approximately the time of SRS was significantly higher than in those who did not receive it (11 vs 4 months, $P = 0.014$ on univariate analysis, respectively). On multivariate analysis, survival after SRS was statistically more favorable for patients who received BVZ, had a Karnofsky performance status >70, or were younger than 50 years. It is noteworthy that most of these patients received a variety of chemotherapies after SRS, and the authors of the Duke study emphasize that ongoing, continual chemotherapy is an integral component of their approach to recurrent gliomas. A

case-control study from the University of Pittsburgh[85] revealed a significantly higher OS (18 vs 12 months, $P = 0.005$) in patients who were treated with SRS and BVZ vs controls who were receiving SRS alone.

Although the median OS with SRS and BVZ in Table 3 appears higher than that of BVZ alone (Table 2), this is not a direct comparison of the 2 approaches. A small retrospective analysis from Henry Ford Hospital[88] found a substantially higher median OS in patients treated with SRS or HFSRT and BVZ than that in those receiving only BVZ (7 vs 3 months, respectively). Several studies have reported low rates of radionecrosis and adverse radiation events in patients treated with SRS or HFSRT and BVZ. For example, in the retrospective study from Duke University,[82] 4 of 21 (19%) patients treated with SRS alone exhibited symptomatic radionecrosis vs only 2 of 42 (5%) patients receiving both SRS and BVZ. Similarly, in the studies from Memorial Sloan-Kettering Cancer Center,[83] Ludwig Maximilian University of Munich,[89] and the University of Cincinnati,[90] 0%, 7%, and 9% rates of radionecrosis were observed in patients receiving SRS and BVZ, respectively.

Selection bias undoubtedly influences the outcome, but the magnitude and direction of that influence in recurrent glioma therapy are unclear. For example, the fact that focal radiotherapy requires a discrete target would exclude those patients with diffuse brain disease from treatment with radiosurgery but not necessarily from treatment with systemic chemotherapy. RTOG 1205 is currently enrolling BVZ-naïve patients with recurrent glioma for a randomized trial of BVZ alone vs HFSRT and BVZ (Fig.). The targeted accrual for this study is 178 patients with a primary end point of OS.

Radiotherapy Technique

A variety of stereotactic systems, target volumes, and dosing schemes have been used in the treatment of recurrent malignant gliomas. The optimum technique has not been established, and the following regimens are presented to illustrate potential advantages and disadvantages of each system.

- In the Memorial Sloan-Kettering approach,[83] the target volume is the contrast-enhancing lesion on T1-weighted MR images uniformly expanded by 5 mm. The regimen is delivered as five 6 Gy daily fractions.
- In the Duke approach,[81,82] the planning target volume (PTV) is the contrast-enhancing lesion on T1-weighted fine-cut MR images uniformly expanded by 1 mm. For PTV < 2 cm or ≥2 and <3 cm in maximum dimension, doses of 20–24 or 18 Gy are delivered in a single fraction. PTV 3–5 cm in greatest dimension is treated with five 5 Gy daily fractions (25 Gy total).
- In the Jefferson approach,[74] the PTV is the contrast-enhancing lesion on T1-weighted MR images (no additional expansion). Treatment consists of ten 3.5 Gy daily fractions (35 Gy total).
- In the RTOG 1205 protocol, the PTV is the contrast-enhancing lesion or resection cavity on T1-weighted MR images, expanded by 5–10 mm at the discretion of the treating physician. Treatment consists of ten 3.5 Gy daily fractions (35 Gy total).

In these studies, the PTV is smallest in the Duke and the Jefferson approaches and largest in the RTOG protocol. Assuming an alpha-beta ratio of 10 Gy and disregarding repopulation effects, the biological equivalent dose[91] is lowest in the 5 Gy × 5 regimen (37.5 Gy_{10}); intermediate in the RTOG, Jefferson, Memorial Sloan-Kettering, and 18-Gy single-fraction approaches (47.5–50.4 Gy_{10}); and highest in the single-fraction treatments of 20–24 Gy (60–81.6 Gy_{10}). Logistically, the single-fraction regimen is obviously advantaged, though it is important to factor in the time required for planning when comparing the overall length of these courses.

Observations on Management

The optimum management for recurrent glioma has not been identified. A variety of treatments—radiation therapy or radiosurgery, surgery, chemotherapy, or some combination of these options— as well as supportive care alone are available. Clearly, decisions on care should be made in the setting of a multidisciplinary team representing radiation oncology, surgery, and neuro-oncology, attentive to the specific patient's situation and wishes. Nevertheless, we offer some general observations on therapy for patients with recurrent disease following initial maximum safe resection, partial-brain irradiation, and concurrent or adjuvant temozolomide.

In general, younger patients with less disease burden who have a better performance status tend to derive the most benefit from salvage therapies. However, survival is highly variable on an individual basis. Surgery may be appropriate in patients with a symptomatic lesion located in a noneloquent site or for which resection would relieve the mass effect. The role of AEF therapy is intriguing but requires further evaluation. Although BVZ may offer survival advantages over other biochemotherapy approaches, the benefit is modest. SRS and HFSRT are associated with median OS of approximately 8–12 months, and the addition of BVZ may improve outcomes and reduce adverse radiation effects. However, the efficacy of this approach is not proven.

Combination therapy with multiple biochemotherapies and SRT may provide superior outcomes than that by monomodality treatment, but improving the current limited efficacy of salvage therapy requires novel approaches and robust enrollment on clinical trials. Ultimately, research in malignant gliomas needs to address prevention of this disease and the development of first-line treatments such that the incidence of recurrence is substantially reduced.

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Targeted Accrual: 178 Bevacizumab-Naïve Adult Recurrent GBM Patients

STRATIFY	Age 1. <50 2. ≥50 Karnofsky performance status 1. 70-80 2. 90-100 Recent resection 1.Yes 2. No/biopsy only	**RANDOMIZE**	Arm 1: Bevacizumab alone q 2 weeks (control arm) Arm 2: Hypofractionated radiotherapy 35 Gy in 10 fractions with concurrent Bevacizumab q 2 weeks (experimental arm)

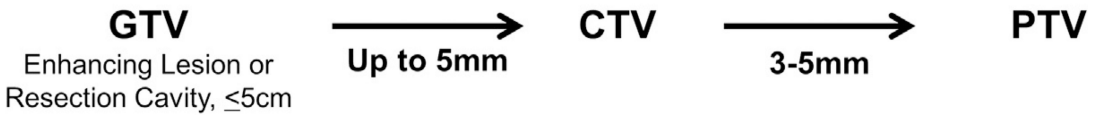

Figure.

Radiation Therapy Oncology Group (RTOG) protocol 1205, a randomized trial of bevacizum (BVZ) vs radiotherapy + BVZ in BVZ-naïve patients with recurrent glioma. In this trial, 3D conformal radiotherapy, intensity-modulated radiotherapy, proton therapy, and stereotactic radiosurgery (SRS) techniques are permitted. However, SRS is *not* required.

Table 1

Surgery for Recurrent Malignant Gliomas

Institution	Number of Patients GBM/Total	Reoperation Period	Median OS for GBM After Reoperation (mo)	Factors Associated With Improved OS	Factors *Not* Associated With Improved OS
Memorial Sloan-Kettering[20]	38/55	1972–1983	8.3	KPS ≥ 70, gross total resection, and AA	
Miami[25]	12/33	1986–1992	8	Younger age and higher KPS	
Munich[28]	38/38	1993–1998	5.3	Age < 50 y, KPS ≥ 90, and gross total resection	
VU[26]	32/32*	1999–2005	3 (S only), 7 (CT or SRS), and 8 (S + CT or SRS)	S + CT or SRS	
NIH[27]	34/34	Not stated	7.4	Noneloquent site, KPS < 80, and tumor volume <50 mL	–
North American Brain Tumor Consortium[22]	593/593	1998–2008	7.3 (S) and 6.4 (no S)	–	S
North American Brain Tumor Consortium[21]	224/333†	1995–2002	7.0 (All)	Younger age, higher KPS, non-GBM histology, no CS, and frontal lobe location	S
EORTC[24]	300/300‡	1999–2010	6.2	Higher KPS, 1 lesion and tumor diameter <42 mm	Age, sex, and S
Catholic University (Rome)[23]	76/76	2002–2008	7	S + AT and KPS ≥ 70	S and gross total resection
Mayo (Rochester)[18]	62§/131	1995–2010	12§	–	–
Johns Hopkins[17]	224/224‖	1997–2007	Not stated	Increased number of reoperations	

Abbreviations: AA, anaplastic astrocytoma; AT, adjuvant therapy; CS, corticosteroid use; CT, chemotherapy; EORTC, European Organisation for Research and Treatment of Cancer; KPS, Karnofsky performance status; NIH, National Institutes of Health; S, surgery at reoperation.

*9 Patients with S only at recurrence, 11 with S + CT/SRS, and 12 with CT/SRS only.

†181 Patients underwent S at recurrence.

‡130 Patients enrolled on an S protocol.

§46 Patients with primary and 16 patients with secondary WHO grade IV tumors who underwent one or more reoperations.

‖Overall, 168, 41, and 15 patients with GBM underwent 1, 2, or 3 reoperations, respectively.

Table 2

Selected Studies of Chemotherapy or Biochemotherapy Agents in Recurrent Malignant Gliomas

Institution	Agent	Number of Patients GBM/ Total	Median OS After Recurrence (mo)	Median 6-mo PFS After Recurrence (%)	Comments
M.D. Anderson[55]	Multiple*	225/375	4.9 (GBM)	15 (GBM)	
EORTC[24]	Multiple†	300/300	6.2	14.7	None showed clinically relevant activity
NIH[41]	BVZ	48/48	7.2	29	Phase II
Duke[54]	BVZ + IRT	23/23	9.6	30	Phase II
Rigshospitalet[46]	BVZ + IRT	32/85	7.9 (GBM)	29	Phase II
GEINO[38]	BVZ + IRT	92/130	8.8 (GBM)	42	Retrospective
UCLA[50]	BVZ + IRT	44/44	9	41	Retrospective
ASMO[34]	BVZ + IRT	92/115	8 (GBM)	46 (All)	Retrospective
Henry Ford[57]	BVZ + IRT	37/51	11.5 (GBM)	64 (GBM)	Retrospective
Multileft[36]	BVZ ± IRT	177/177	9.2 (BVZ alone) and 8.7 (BVZ + IRT)	43 (BVZ alone) and 50(BVZ + IRT)	Phase II
University of Washington[47]	BVZ + CBP	14/19	10 (GBM)	40 (GBM)	
Duke[52]	BVZ + CBP + IRT	40/40	8.3	47	
North Central Cancer Group[37]	BVZ + SOR	54/54	5.6	20	
Rigshospitalet[44]	BVZ + TEM	13/13	3.5	Not stated	Judged not effective
EORTC[35]	CCNU + DAS	26/26	6.4	8	
UCLA[49]	ERL + SIR	14/19	Not stated	Median PFS 1 mo	
Cedars-Sinai[39]	Gimatecan	29/29	Not stated	12	Judged not effective
Dana Farber[53]	LAP + PAZ	41/41	Not stated	0 (Biomarker +) vs 15 (biomarker −)	Judged not effective
Aristotle[40]	LAP + TMZ	14/16	5	~20	Judged not effective
M.D. Anderson[56]	LON + TMZ	36/36	14.9‡	42‡	
Rigshospitalet[48]	Nintedanib	25/25	6	4	Judged not effective
North American Brain Tumor Consortium[45]	SOR + TEM	31/31	Not stated	0	Judged not effective
NIH[43]	Sunitinib	63/63	9.4	0 (BVZ resistant) 10 (BVZ naïve)	
Columbia[33]	TMZ	68/120	8.8	35	Only TMZ-naïve pts
MSK[51]	TMZ	32/47	7	19	49% Had failed BVZ

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Institution	Agent	Number of Patients GBM/ Total	Median OS After Recurrence (mo)	Median 6-mo PFS After Recurrence (%)	Comments
NIH[42]	Vandetanib	32/64	6.3	7	Judged not effective

Abbreviations: ASMO, Anatolian Society of Medical Oncology; CBP, carboplatin; CCNU, lomustine; DAS, dasatinib; EORTC, European Organisation for Research and Treatment of Cancer; ERL, erlotinib; GEINO, El Grupo Español de Investigación en Neurooncología; IRT, irinotecan; LAP, lapatinib; LON, lonafarnib; MSK, Memorial Sloan-Kettering; NIH, National Institutes of Health; PAZ, pazopanib; PFS, progression-free survival; SIR, sirolimus; SOR, sorafenib; TEM, temsirolimus; TMZ, temozolomide; UCLA, University of California, Los Angeles.

*Pooled analysis of 8 phase II trials (IFNβ, IFNβ + *cis*-retinoic acid, menogaril, CBP, CBP + 5FU + procarbazine, and difluoromethylomithine) conducted between 1986 and 1995.

†Pooled analysis of 2 phase I (LON and enzastaurin) and 6 phase II (DACA, glufosfamide, imatinib, erlotinib, and sagopilone) trials conducted between 1999 and 2010.

‡Disease-specific survival (not OS) and 6-month PFS for 26 patients receiving maximum-tolerated dose of LON.

Table 3

Studies of Stereotactic Radiosurgery (SRS) and Conventionally and Hypofractionated Stereotactic Radiotherapy (FSRT and HFSRT, Respectively) for Recurrent Malignant Gliomas

Institution	Technique, Median Dose Regimen(s)	Number of Patients GBM/Total	BVZ at SRS	Median OS After Recurrence, GBM (mo)	Toxicity
Minnesota[71]	SRS, 20 Gy × 1	26/35	No	8	31% With reoperation
Harvard[73]	SRS, 13 Gy × 1	86/86	No	10	48% Risk of reoperation at 2 y
Minnesota[70]	FSRT, 2.5 Gy × 15	15/25	No	7.1	30% vs 8% late complications with SRS vs FSRT
	SRS, 17 Gy × 1	27/46			
Heidelberg[92]	FSRT, 2 Gy × 18	59/172	No	8	RN in 1 pt
Heidelberg[93]	SRS, 15 Gy × 1	32/32	No	10	No RN
Rochester[94]	SRS, 15 Gy × 1	18/18	No	5.3	RN in 1 pt
Jefferson[74]	HFSRT, 3.5 Gy × 10	105/147	Yes (2%)	10	1 Gr 3 toxicity
Sungkyunkwan[72]	SRS, 16 Gy × 1	65/114	No	13	RN in 22%
Henry Ford[88]	SRS, 18 Gy × 1 or	26/26	No concurrent	8.4	2 And 1 pts in SRS and FSRT groups with RN
	HFSRT, 6 Gy × 6	10/10		7.5	
Gulhane[95]	SRS, 16 Gy × 1	19/19	No	9.3	No Gr ≥ 3 toxicity
NYU[96]	SRS, 15 Gy × 1	16/26	No	12.9	RN in 2 pts
Haukeland[97]	SRS, 12.2 Gy × 1	51/51	No	12	9.8% Complication rate vs 25.2% in reoperation
Hoag[98]	HFSRT, 5 Gy × 5	4/8	No	7.6 (All pts)	RN in 1 pt
Staten Island[99]	SRS, 6 Gy × 4	88/88	No*	7.0	12% With reoperation
UCSF[100]	SRS, 15 Gy × 1	14/26	No†	8.8	Not stated
Sant'Andrea[101]	HFSRT, 6 Gy × 5	38/54	No‡	12.4 (All)	Gr 3 CNS toxicity in 7%
MSK[83]	HFSRT, 6 Gy × 5	20	Yes (all)	13	Gr 3 CNS toxicity in 3 pts
Duke[82] (retrospective)	SRS, 18 Gy × 1 or 5 Gy × 5	49/63	No (16)	4	Crude rate of RN 19% vs 5% (− BVZ vs + BVZ)
			Yes (33)	11	
Henry Ford[86]	SRS, 18 Gy × 1 (7) or HFSRT, 6 Gy × 6	18/23	Yes	7 RT + BVZ vs 3.3 BVZ alone	Not stated
Ludwig-Maximilians[89]	FSRT, 2 Gy × 18	22/30	No (10)	5.8 (All)	One each Gr 3 and 4 in BVZ group
			Yes (20)	Not reached (all)	
Pittsburgh[85]	SRS, 16 Gy × 1	11/11	No (44§)	12	9% vs 46% ARE (+ BVZ vs −BVZ)

Institution	Technique, Median Dose Regimen(s)	Number of Patients GBM/Total	BVZ at SRS	Median OS After Recurrence, GBM (mo)	Toxicity
			Yes (11)	18	
St. Gallen[84]	FSRT, 2.67 Gy × 15	8/14	No (4)	9 (All)	RN in 1 non-BVZ patient
			Yes (10)		
Cincinnati[90]	HFSRT, 6 Gy × 5	30/35	Yes (30)	8.6 (All)	RN in 3 pts (all non-BVZ)
Duke (prospective)[81]	SRS, 18 Gy × 1	8/15	Yes (all)	14.4 (All)	1 Grade 3 (headache)

Abbreviations: ARE, adverse radiation event; CNS, central nervous system; Gr, grade; MSK, Memorial Sloan-Kettering; RN, radionecrosis; RT, radiation therapy; UCSF, University of California, San Francisco.

*All patients received concurrent paclitaxel.

†All patients received marimastat after SRS.

‡All patients received concurrent low-dose temozolomide.

§Matched case-controls undergoing SRS but not receiving BVZ.