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Seminars in
RADIATION
ONCOLOGY

Recurrent Malignant Gliomas

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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.
Semin Radiat Oncol 24:289-298

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 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

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Disclosures: Dr Kirkpatrick has received research funding from Genentech and Varian Medical Systems.
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http://dx.doi.org/10.1016/j.semradonc.2014.06.006
1053-4296/

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

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 $\geq$ 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 $\geq$ 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 $\geq$ 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.