BRAINLAB

STEREOTACTIC RADIOTHERAPY OF RECURRENT MALIGNANT GLIOMAS

Clinical White Paper

Tumors of the central nervous system (CNS) represent approximately 176,000 newly diagnosed cases worldwide per year, with an estimated annual mortality of 128,000[1,2]. Malignant gliomas comprise 30% of all primary CNS tumors and remain one of the greatest challenges in oncology today, despite access to state-of-the-art surgery, imaging, radiotherapy and chemotherapy[3].

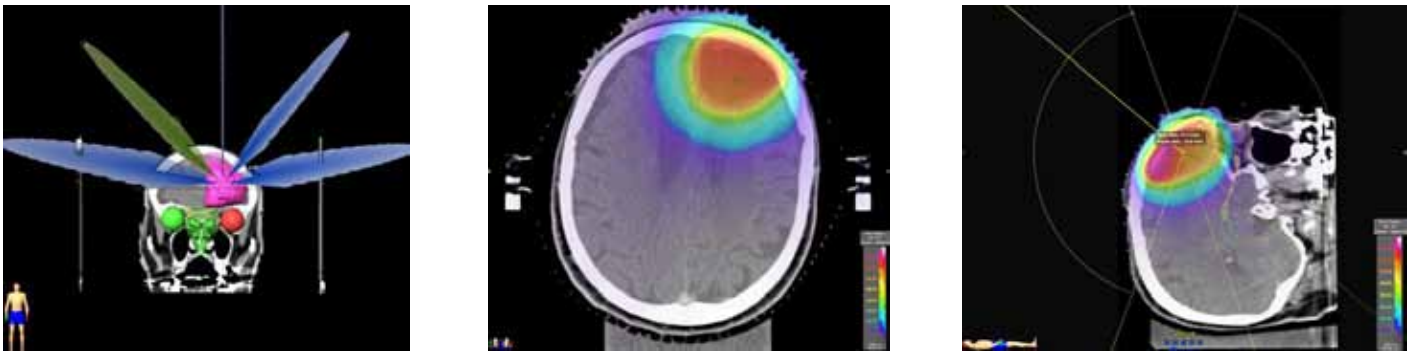

Figure: Details of a typical malignant glioma treatment plan

Signs and symptoms of malignant gliomas depend on the location, size and growth of the tumor and may include headaches, seizures, focal neurologic deficits and changes in mental status[4]. Both the tumor and its treatment often result in profound quality of life changes. Early failure of local treatment is common with this disease and relapse occurs in form of continuous growth close to the margin of the original lesion in approximately 80% of all cases[5].

The World Health Organization classification system is predominantly used for naming and grading malignant gliomas; within this system, grade III astrocytomas and grade IV glioblastoma multiforme (GBM) are the most prevalent types with grim prognoses[6]. For neoplasms, median survival time is limited to approximately 10 – 17 months[7].

Although malignant gliomas are incurable in the vast majority of patients, surgery and radiotherapy are the traditional cornerstones of initial therapy protocols and provide palliative survival benefit[8,9]. Surgical techniques remain an important tool for glioma management, with complete surgical resection as the goal[10].

Regardless of the degree of resection, adjuvant radiotherapy is administered after surgery. In early randomized studies, significant increases in survival were achieved in patients with high-grade gliomas with the administration of 50 – 60 Gy of whole brain radiotherapy following surgery[4,8,11]. Adjuvant chemotherapy is also used in the initial treatment of high-grade gliomas, with increased survival recently demonstrated in clinical trials[4,10,12].

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The vast majority of gliomas recur within or adjacent to the original tumor bed[13]. Treatment options for recurrent gliomas are limited because most therapeutic alternatives have already been performed, including neurosurgery and a full course of radiotherapy and chemotherapy. Optimal surgical resection might be possible in a subgroup of patients; however, it is accompanied by a high risk of morbidity because of the infiltrative nature of the tumor[14]. Conventional radiotherapy alternatives are often limited with respect to dose prescription because radiotherapy is already a component of first-line therapy in most patients.

Stereotactic radiosurgery (SRS) is appealing because of its ability to precisely deliver high doses of irradiation to a defined target volume in a single fraction with less treatment-associated morbidity compared with surgery[15]. However, SRS is limited to smaller lesions and low doses, as the risk of radiation-induced side effects rises with increasing treatment volume and dose[16]. Fractionated stereotactic radiotherapy (SRT) enables the precise application of radiotherapy to a defined target volume, while exploiting the radiobiologic advantage of fractionation and minimizing the risk for severe radiation-induced side effects[17-21].

Combining SRT with chemotherapy further increases high-grade recurrent glioma treatment efficiency. For recurrent GBM, temozolomide has been shown to improve quality of life and progression-free survival[22].

An overview of the recent literature on hypofractionated SRT treatments for recurrent malignant gliomas is presented in the table below.

In each of these studies, all patients had the initial tumor surgically resected followed by a full course of conventional radiotherapy with a median dose of 60 Gy. At the time of recurrence, a typical dose of 3 to 5 Gy was delivered in a limited number of fractions, independent of the tumor grade or volume.

The resulting overall survival, expressed in the number of months following stereotactic re-irradiation, ranges from 20 months for low-grade to approximately 10 months for high-grade recurrent malignant gliomas.

Comparing the reported radiation-induced toxicity rates suggests a correlation to the delivered dose per fraction, independent of the tumor grade[18]. The observed toxicity is about 1% for a typical dose of 3 Gy per fraction and increases to about 10 % for doses of 5 Gy per fraction.

In the absence of any randomized trial data, these individual results suggest that SRT is a reasonable treatment option for recurrent malignant gliomas. Because of its non-invasive nature and low toxicity rates, SRT can provide symptom palliation while assuring a patient´s quality of life.

Overview of the recent clinical literature on SRT for recurrent malignant gliomas

Author	Institution	Year	# Lesions	WHO Grade	Time from RT to SRT (months)	Mean Vol (cm^3)	Mean Dose (Gy)	# Fractions	% IDL covering PTV	Overall Survival (months)	% Toxicity
Combs[17]	University of Heidelberg	2005	71	II	48	42	36	12	90	22	0
Wurm[18]	Charité University Hospital, Berlin	2006	5	III	22	17	25	5	80	21	12
Fogh[19]	John Hopkins University, Baltimore	2010	42	III	11	22	35	10	90	10	1
Combs[17]	University of Heidelberg	2005	42	III	32	56	36	12	90	16	0
Ernst-Stecken[20]	University Hospital, Erlangen	2007	15	III & IV	10	22	35	5	90	12	20
Grosu[21]	Klinikum Rechts der Isar, Munich	2005	44	III & IV	16	20	30	6	100	13	14
Wurm[18]	Charité University Hospital, Berlin	2006	20	IV	12	17	25	5	80	8	12
Fogh[19]	John Hopkins Universiy, Baltimore	2010	105	IV	8	22	35	10	90	11	1
Combs[17]	University of Heidelberg	2005	59	IV	10	48	36	12	90	8	0

Overall survival is expressed in the number of months following stereotactic re-irradiation.

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