Radiosurgery and Accelerated Radiotherapy for Patients with Glioblastoma

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ABSTRACT: ***Objective:*** To assess the feasibility, toxicity, and local control of stereotactic radiosurgery followed by accelerated external beam radiotherapy (AEBR) for patients with glioblastoma multiforme. ***Materials and methods:*** Six males and eight females, with a median age of 67.5 years (range 45-78 years), entered the study. Karnofsky performance status was 90 for five, 80 for six, and 60 for three patients. Following surgery, the patients were left with a residual mass 4 cm. Radiosurgery was delivered with a single dose of 20 Gy to the 90% isodose surface corresponding to the contrast-enhancing edge of the tumour. A total AEBR dose of 60 Gy in 30 fractions was delivered using a concomitant boost technique over four weeks. ***Results:*** Median survival time was 40 weeks (range 17-80 weeks). Actuarial survivals at 12 and 18 months were 43% and 14%, respectively. The median time to progression was 25 weeks (range 2-77 weeks). One patient developed a seizure on the day of stereotactic radiosurgery. Two patients experienced somnolence at 47 and 67 days post-radiotherapy. Eight patients remained steroid-dependent. Radiological evidence of leukoencephalopathy was observed in one patient, and brain necrosis in two additional patients at 30 and 63 weeks. One of these two patients with brain necrosis developed complete loss of vision in one eye, and decreased vision in the contralateral eye at 63 weeks. ***Conclusion:*** Stereotactic radiosurgery followed by AEBR was feasible but was associated with late complications. The use of such radiosurgical boost for patients with glioblastoma multiforme should be reserved for those patients entering controlled clinical trials.

RÉSUMÉ: Radiochirurgie et radiothérapie accélérée chez les patients atteints de glioblastome. ***But:*** D'évaluer la praticabilité, la toxicité et le contrôle local de la radiochirurgie stéréotaxique (RS) suivie de radiothérapie externe accélérée (RFEA) chez les patients atteints de glioblastome multiforme (GBM). ***Sujets et méthodes:*** Six hommes et huit femmes, dont l'âge médian était de 67.5 ans (45 à 78 ans), ont été enrôlés dans l'étude. Le score de Karnofsky était de 90 chez 5 patients, de 80 chez 6 patients et de 60 chez 3 patients. Après la chirurgie, les patients avaient une masse résiduelle 4 cm. La radiothérapie était administrée en une seule dose de 20 Gy à la surface isodose de 90% correspondant au bord de la tumeur rehaussant la substance de contraste. Une dose totale de RFEA de 60 Gy a été administrée en 30 fractions étalées sur quatre semaines. ***Résultats:*** La survie médiane a été de 40 semaines (de 17 à 80 semaines). Les survies actuarielles à 12 et 18 mois étaient de 43% et 14% respectivement. Le temps médian jusqu'à la progression a été de 25 semaines (de 2 à 77 semaines). Un patient a présenté des convulsions le jour de la RS. Deux patients ont présenté de la somnolence 47 et 67 jours post-radiothérapie. Huit patients sont demeurés dépendants des stéroïdes. Des indices radiologiques de leucoencéphalopathie ont été observés chez un patient et de nécrose cérébrale chez deux autres patients à 30 et 63 semaines. Un de ces deux patients a présenté une perte totale de la vision d'un oeil et une diminution de la vision de l'autre oeil à 63 semaines. ***Conclusions:*** La radiochirurgie stéréotaxique suivie de RFEA était faisable, mais elle a été associée à des complications tardives. L'utilisation concomitante de ces techniques pour les patients atteints de GBM devrait être limitée à ceux qui sont enrôlés dans des essais cliniques contrôlés.

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The results of surgery alone for the management of high-grade astrocytomas are disappointing. The highly invasive nature of these neoplasms and their location usually preclude radical surgical excision, and the median survival time after tumour resection is approximately 14 weeks.[1] Postoperative irradiation prolongs the median survival time to 37 weeks, however, long-term survival rates are not affected.[2-6]

Conventional postoperative radiotherapy consists of 50 to 60 Gy delivered in 2 Gy daily fractions. Experimental data suggest that the response of malignant gliomas to conventional photon irradiation may be limited by the rapid turnover rate of the clonogenic cells. Since tumour clonogen regeneration reduces the efficacy of treatment if regeneration begins before therapy is completed, it is desirable to deliver the whole radiation course within the shortest practical overall treatment time. Currently, there is a considerable interest in modified radiotherapy schedules based on recent experimental data regarding tumour potential doubling times and radiation tolerance of normal neural tissues.[7-15] Different treatment regimens for high grade astrocytomas have been reported, using accelerated fractionation[16-18] radiotherapy with or without systemic chemotherapy and

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hypoxic cell sensitizer[19-23] and superfractionated radiotherapy.[24,25]

A phase I/II trial evaluating an accelerated external beam radiotherapy (AEBR) schedule was inititated at McGill University for adult patients with high-grade astrocytomas. Accelerated radiotherapy was chosen because of the known biological data regarding high grade astrocytomas cell cycle kinetics, with reported potential doubling times of less than one week,[9,10] the potential advantage of valuable shortening of overall treatment time, and the encouraging results using accelerated fractionation in other sites, namely in head and neck cancers.[26,27] Median survival time was 57 weeks from the date of starting irradiation. Survival was 50% and 28% at one and two years, respectively. To date, the accelerated fractionation schedule appears to be well tolerated and provides a valuable shortening of the overall treatment time.[17]

Most of the patients with glioblastoma multiforme (GBM) recurr at the site of the original tumour.[28] Therefore, in order to increase the total dose while keeping radiation side effects at an acceptable level, we decided to deliver part of the total radiation dose with stereotactic radiosurgery (SR). Radiosurgery has been used in cerebral arterio-venous malformations with excellent results and minimal toxicities.[29,30] By virtue of its highly concentrated dose distribution in tissues, SR delivers radiation to a sharply demarcated target volume of brain tissue with a sharp dose fall-off outside the target volume.

The objectives of this study were to assess the feasibility and to evaluate the toxicity of SR as a boost technique to accelerated external beam radiotherapy in patients with glioblastoma multiforme.

Patients and Methods

Patient selection criteria

Patients included in the study were adults (age 18 years) with a histological diagnosis of GBM with no previous history of brain irradiation or systemic chemotherapy. To be eligible, patients must have a Karnofsky performance status (KPS) of 60, and a maximum residual tumour size of 4 cm as measured on a postoperative contrast-infused brain CT scan. Patients should have no previous history of malignancy within the past five years except for non-melanomatous skin cancer or carcinoma *in-situ* of the uterine cervix. The presence of multifocal lesions, subependymal or extra-cranial spread rendered the patient ineligible. All patients gave written informed consent.

Pretreatment evaluation

All patients had a complete history and physical examination, with special attention to the neurological and KPS evaluation. Complete blood counts, serum biochemistry, pre- and postoperative contrast-infused CT scan, and chest x-ray examination were obtained for all patients.

Patient characteristics

Between August 1991 and July 1993, 14 patients entered the trial. There were six males and eight females with a median age of 67.5 years (range 45-78 years). Karnofsky performance status was 90-100 for five patients, 80 for six, and 60-70 for three. Two patients underwent only stereotactic biopsies, nine had a partial tumour resection, and three had a near complete resection of their brain neoplasms. All patients were left with a maximal residual mass of 4 cm after surgery. The anatomical location of the lesions was as follows: four temporal, three frontal, two parietal, two occipital, one parieto-occipital, one fronto-temporal and one fronto-parietal.

Stereotactic radiosurgery

Stereotactic radiosurgery was started as soon as possible after surgery and was delivered by a 10 MV photon linear accelerator with the dynamic stereotactic technique developed at McGill University.[31] Treatment planning was done with a dedicated three-dimensional planning system that was also developed at McGill University.[32] A single dose of 20 Gy was delivered using a treatment cone covering the CT contrast enhancing lesion. The median cone size was 3 cm with a range of 3 to 4 cm. All patients were treated with a single isocenter. The median interval between surgery and radiosurgery was 12 days (range 1-26 days), with eleven patients starting radiosurgery within two weeks of surgery.

External beam accelerated radiotherapy

The external beam radiotherapy was delivered by megavoltage (4 to 10 MV photons) equipment. CT scan treatment planning for optimal selection of field arrangements, and isodose distribution were obtained in all patients. A total external beam dose of 60 Gy in 30 fractions was delivered using a concomitant boost technique with an overall treatment time of four weeks. The contrast-enhancing mass was encompassed by a 3 cm margin for Plan I, and 2 cm for Plan II fields. Plan I delivered 40 Gy in 20 fractions, and Plan II delivered 20 Gy in 10 fractions given with the last 10 fractions of Plan I as a BID treatment, with an interfraction interval of six hours. The accelerated external beam irradiation treatment started with a median interval of two days after radiosurgery (range 1-12 days); twelve patients (86%) started external beam radiotherapy within seven days from the date of stereotactic radiosurgery. The median overall treatment time for the external beam was 27 days (range 25-28 days). No interruption was necessary because of the onset of acute toxicity.

Follow-up

During treatment, all patients were evaluated on a weekly basis by the treating radiation oncologist. The evaluation consisted of neurological examination, determination of performance status, and assessment for acute radiation-induced toxicity. Both acute and delayed toxicities were assessed according to the Radiation Therapy Oncology Group (RTOG) scoring criteria.

After completion of radiotherapy, the patients were followed on a monthly basis, or more frequently depending on each patient's clinical symptomatology. Contrast-infused CT scans were performed one month after treatment and then every three months, or at time of severe neurological deterioration.

All medications were recorded in the patients' charts. Corticosteroids were discontinued as early as possible after completion of radiotherapy. For patients who developed symptoms upon corticosteroid discontinuation, the medication was reintroduced at the lowest dosage possible depending upon the patient's clinical condition. Anticonvulsive medications and analgesics were used as clinically indicated.

Criteria for evaluation of therapy outcome

Progression of disease was based on clinical and/or radiological evaluation performed at time of the onset of neurological deterioration after completion of protocol therapy. Patterns of failure were categorized as: (i) central when recurrence took place in the high-dose SR region, (ii) peripheral when recurrence occurred within 2 cm of the original tumour edge, and (iii) distant when recurrence was observed > 2 cm from the original tumour edge. Tumour necrosis was determined through a radiological evaluation with contrast-infused CT scan and/or MRI. Radiation necrosis was highly suggested when contrast-infused CT scan and/or MRI showed a progressive edema and increased contrast enhancement without a corresponding increase of the residual tumour dimensions on two consecutive studies done within four to eight weeks apart.

Statistical considerations

Survival time and time to disease progression were calculated from the date of radiosurgery. This decision was based on the fact that the interval between surgery and radiosurgery varied from one to 26 days (median 12 days). Other confounding factors, such as the postoperative clinical course, could have affected the duration of survival, if survival had been calculated from the day of surgery. Survival curves were calculated using the Kaplan-Meier method.[33] The impact of different prognostic factors on survival was assessed using the log-rank test.[34]

Results

Survival analysis and prognostic factors

All patients were followed-up till death with a median follow-up time of 35 weeks (range 17-80 weeks). The actuarial median survival time of all patients was 40 weeks (range 19-89 weeks) calculated from the date of radiosurgery. Survival rates at 12 and 18 months were 43% and 14%, respectively. The median time to disease progression was 25 weeks (range 2 to 77 weeks). Patients younger than 65 years had a median survival time of 40 weeks (range 29-81 weeks), while older (65 years) patients had a median survival time of 35 weeks (range 19-89 weeks) (log-rank test p = 0.8923). Patients with KPS 80 had a median survival time of 40 weeks (range 19-81 weeks) compared to 59 weeks (range 29-89 weeks) for patients with KPS > 80 (log-rank test p = 0.2772). No statistically significant overall survival difference was observed between patients who had biopsy only or partial or complete resection, and whether the external beam treatments were started within 15 days or more from the date of surgery. The results of sub-group analysis in this group of patients should be interpreted with caution, given the small number of patients in each of the subgroups.

Quality of life

Table 1 illustrates the median values as well as the range of KPS, and steroid dose in surviving patients at various times from diagnosis. The median KPS at diagnosis was 80 (range 60-100). This KPS was maintained till 48 weeks when a drop of the median KPS was noted with KPS = 60 (range 40-100). Further deterioration was observed at 72 weeks with KPS = 40 (range 40-100). The need for steroids appears to be present throughout the course of the disease in 57% of the patients.

Table 1: Variation in Karnofsky performance status[1] and steroid dose.[2]

	Time in weeks						
	Dx	4	12	24	36	48	72
KPS	80 (60-100)	70 (60-100)	70 (60-80)	70 (60-80)	80 (50-100)	60 (40-100)	40 (40-100)
Steroid dose	10 (4-16)	4 (4-8)	6 (0.5-24)	10 (0-24)	3 (0-24)	8 (0-16)	6 (0-16)

[1] Karnofsky Performance Status (KPS): median value, range.

[2] Steroid dose expressed in mg/day: median value, range.

Patterns of recurrence

The delineation of disease recurrence versus radiation-induced necrosis in patients with GBM is not possible to make with absolute clarity in each case. Based on clinical criteria of deteriorating KPS, functional neurological status, increasing steroid requirements, and sequential radiological studies, 12 of the 14 patients (86%) were thought to have disease recurrence. The remaining two patients (14%) were considered to have radiation-induced brain necrosis based on clinical deterioration of symptoms and two sequential imaging studies separated by four to eight weeks showing increased brain edema and contrast enhancement with no increase in the size of the residual mass. The pattern of recurrence could be assessed with accuracy only in ten out of the 12 patients with recurrent disease. Central recurrence was observed in five (50%) patients, peripheral in two (20%), distant in one (10%), and both central and peripheral in two (20%).

Treatment at recurrence

Of the 12 patients considered to have disease recurrence, nine patients had supportive care and three received post-recurrence therapy. These three patients were treated with high dose oral tamoxifen and one of them had a second resection. The median survival time of the nine patients who had supportive care at time of recurrence was seven weeks (range 2-60 weeks) from the time of disease progression. The median survival time of the three patients who had post-recurrence therapy was five weeks (range 2-24 weeks).

Two patients were deemed to have radiation-induced necrosis and died from the clinical diagnosis of brain necrosis.

Complications of treatment

Grade I radiation-dermatitis and localized alopecia limited to the treatment portals occurred in all patients. One patient developed a generalized seizure on the day of stereotactic radiosurgery. Two patients experienced somnolence at seven and ten weeks from the start of radiotherapy. Two additional patients developed significant fatigue and one of them had a unilateral serous otitis media. Eight patients (57%) remained steroid dependent. Radiological evidence of leukoencephalopathy was observed in one patient, and brain necrosis was seen in two other patients (14%) at 30 and 63 weeks, respectively. One of these two patients with brain necrosis had loss of vision in one eye on the ipsilateral side of the brain lesion, and decreased vision in the contralateral eye related to optic chiasm radiation damage at 63 weeks from treatment.

Discussion

Despite the ability of surgery, radiotherapy, and chemotherapy to prolong survival in patients with GBM, most patients die

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as a result of local tumour progression. Following conventional radiotherapy, approximately 80% of patients fail within 2 cm of the initial tumour volume.[28] A dose-effect relationship of external beam radiotherapy and survival has been demonstrated.[14] Further attempts at dose escalation using conventional external beam radiotherapy to 70-80 Gy resulted in no survival benefit.[5] At present, conventional fractionated radiotherapy dose is limited to 60 Gy in 30 fractions, to avoid unacceptable risks of brain necrosis.

Stereotactic radiation techniques, including interstitial brachytherapy and radiosurgery, have been used as a boost to full dose external beam radiotherapy in order to focally increase the radiation dose to areas of greatest disease involvement with minimal irradiation to significant volumes of normal brain tissues.

The results of interstitial brachytherapy, as a boost technique following external beam radiotherapy in patients with malignant gliomas, have been published.[35] Prospective non-randomized studies of interstitial brachytherapy boost showed a trend for improved survival with a median survival time ranging between 18 to 22 months for patients with GBM and 39 months for patients with anaplastic astrocytomas (AA).[36,37] Reoperation rates following interstitial brachytherapy boost techniques varied between 38% to 64% in order to remove symptomatic radiation-induced necrosis and/or recurrent disease.[36,37] Interpretation of the results of these studies is limited by the possibility that implant-eligible patients had a more favorable prognosis compared to patients ineligible for brachytherapy based on selection criteria.[38] Further evidence to support the use of brachytherapy in the initial management of patients with malignant glioma was presented by the Brain Tumour Cooperative Group (BTCG). Green et al.[35] reported the preliminary results of the BTCG randomized trial 8701. The median survival time for patients undergoing brachytherapy was 16 months compared to 13 months for those not receiving brachytherapy.

In recent years, the interest in the use of stereotactic radiosurgery techniques for treatment of intracranial malignant neoplasms has increased. Furthermore, because of the encouraging results from interstitial brachytherapy and because of the similarity in dose distribution between brachytherapy and stereotactic radiosurgery, the latter has been considered as an alternative technique for focal dose escalation of malignant glioma following external beam radiotherapy.[39] Stereotactic radiosurgery has a potential advantage over interstitial therapy in that it is a minimally invasive procedure, and may, therefore, result in lower complication rates. Stereotactic radiosurgery boost following external beam radiotherapy has been piloted by many institutions, most notably the Joint Center for Radiation Therapy (JCRT),[40] University of Wisconsin (UW),[41] University of Florida (UF),[42] and University of Arizona (UA).[43] To be selected for such a treatment following external beam radiotherapy, the patients must have a histologically proven AA or GBM; KPS 70; a solitary supratentorial mass measuring less than 4 cm at its maximum diameter, and located more than 5 mm to 10 mm from the optic nerve or chiasm with no evidence of subependymal spread or brain stem involvement. In general only 10% to 20% of patients with newly diagnosed GBM could meet the eligibility criteria for stereotactic radiosurgery. A total of 125 patients were reported from the above-mentioned four centers. Table 2 summarizes the patient characteristics and median survival times from the four series, as well as from our present series.

Table 2: Comparison between stereotactic radiosurgery series for high grade cerebral gliomas.

	UW[1]	JCRT[2]	UF[3]	UA[4]	Present study
Number of patients	31	75	10	30	14
Age < 50 years	30%	55%	30%	47%	14%
KPS					
90-100	3%	66%	90%	0%	36%
70-80	53%	33%	10%	77%	57%
< 70	43%	0%	0%	23%	7%
Histology					
AA	0%	20%	40%	37%	0%
GBM	100%	80%	60%	63%	100%
Surgery					
Biopsy	40%	48%	30%	30%	14%
Partial Res.	53%	51%	70%	60%	64%
Total Res.	7%	1%	0%	10%	22%
RTOG Prognostic Class					
Class 1-3	0%	50%	30%	N/A	7%
Class 4-6	100%	50%	70%	N/A	93%
Median Survival Time					
(Months)	10.5	19.7	N/A	13.9	10

[1]UW: University of Wisconsin[39]
[2]JCRT: Joint Center for Radiation Therapy[38]
[3]UF: University of Florida[40]
[4]UA: University of Arizona[41]

Patients accrued on our study have similar clinical characteristics to patients treated at the UW, mainly regarding the histology with 100% of patients with GBM in both studies. In contrast, the AA histology constituted 20%, 40%, and 37% of the histologies at the JCRT, UF, and UA, respectively. Using the RTOG recursive partitioning analysis,[44] 93% of our patients fall in the poor prognostic class 4 to 6, similar to 100% of patients reported by UW. On the other hand, patients from the JCRT, and those from UF fall into a better RTOG prognostic class with 50% and 30% of the patients in class 1 to 3, respectively. Median survival time of our group of patients is 10 months which is comparable to 10.5 months for patients from the UW. However, considerably longer median survival times are reported from the JCRT (19.7 months) and from the UA (13.9 months).

In both the UW and our study disease progression was reported to be 84% for the UW and 86% for our series. When the results of the UW, JCRT, and UF are compiled, 59% of the patients were reported to die from disease progression. In our group of patients, more central failures (50%) were observed as compared to the compiled results from UW, JCRT, and UF with 36% central recurrences as reported by Sarkaria et al.[45]

The pattern of recurrence following interstitial iridium-192 implantation for malignant brain tumours have been reported by Chun et al.[46] in their series of 37 patients. The pattern of failure was documented by CT scans or by autopsy in 23 patients. Fourteen patients had experienced local failure alone (60%), while six patients had local failure and sub-ependymal spread and two other patients had local failure and multicentric parenchymal disease.

Similar complication rates have been encountered in our series and the one reported by Sarkaria et al.[43] Brain necrosis was observed in 14% of our patients and in 16% of patients as reported by Sarkaria et al. Prolonged steroid dependency was also similar in our study and the one reported by Sarkaria et al., namely 57% and 47%, respectively. The above-mentioned complications were not encountered in the group of patients reported by Gannett et al. from the UA where no significant acute or late toxicity has been observed.[43]

In the present series, the role of accelerated external beam radiotherapy (AEBR) is difficult to define as the results of our previous phase I/II protocol of the AEBR[17] did show a median survival time of 57 weeks in 42 patients with high grade cerebral astrocytomas with no increased toxicity. Both survival and toxicity from our phase I/II protocol of AEBR were similar to other series that have used conventional external beam radiotherapy in the management of a similar group of patients.

In summary, the results obtained from different centers, using stereotactic radiosurgery and external beam radiotherapy for malignant gliomas are encouraging. However, it is important to be cautious in interpreting the results reported so far, as this may represent a selection bias for patients with better prognosis. This issue has been addressed by Curran et al.[47] who demonstrated that stereotactic radiosurgery-eligible patients treated with hyperfractionated external beam radiotherapy on RTOG 8302 had an improved survival compared to stereotactic radiosurgery-ineligible patients.

In order to overcome the compounding effect of patient selection bias inherent in single institution trials, a randomized prospective study RTOG 9305 has been started comparing patients with relatively small volume supratentorial GBM treated with stereotactic radiosurgery followed by external beam radiotherapy and BCNU versus patients receiving external beam radiotherapy and BCNU. Until the results of the ongoing RTOG trial are published, SR must be considered an experimental approach for patients with GBM and its use not recommended outside a protocol setting.

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