RESEARCH ARTICLE

Efficacy of High Dose Radiotherapy in Post-operative Treatment of Glioblastoma Multiform - A Single Institution Report

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Abstract

Background: Glioblastoma multiform (GBM) is a highly aggressive tumor with median survival of approximately 14 months. Management consists of maximal surgical resection followed by post-operative chemoradiation with concurrent then adjuvant temozolamide. The standard radiotherapy dose is 60Gy in 2-Gy fractions recommended by the radiation therapy oncology group (RTOG). With the vast majority of tumor recurrences occurring within the previous irradiation field and the poor outcome associated with standard therapy, regimens designed to deliver higher radiation doses to improve local control and enhance survival are needed. In this study, we report a single institutional experience in treatment of 68 consecutive patients with GBM, treated with resection, and given post-operative radiotherapy followed by concurrent and/or adjuvant chemotherapy. Results: Of the 80 patients who entered this study, 68 completed the treatment course; 45 (66.2%) males and 23 (33.8%) females with a mean age at diagnosis of 49.0±12.9 (21-75) years. At a median follow up of 19 months, 39 (57.3%) patients had evidence of tumor progression and 36 (52.9%) had died. The median over all survival for all patients was 16 months and progression free survival for all patients was 6.02 months. All potential prognostic factors were analyzed to evaluate their effects on overall survival. Age ≤50 year, concurrent and adjuvant chemotherapy and extent of surgery had significant p values. We found lower progression rate among patients who received higher doses of radiotherapy (>60Gy). Higher radiation doses improved progression free survival (p=0.03). Despite increasing overall survival, this elevation was not significant. Conclusions: This study emphasize that higher radiation doses of (>60Gy) can improve local control and potentially survival, so we strongly advise prospective multi centric studies to evaluate the role of higher doses of radiotherapy on GBM patient outcome.

Keywords: GBM surgery - high dose radiotherapy - chemotherapy - outcome

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Introduction

Glioblastoma multiform (GBM), World Health Organization Grade IV Astrocytoma, is usually diagnosed in the 5th and 6th decade of life with an incidence of 0.76 per 100000 in Iranian population, with male to female ratio of 1.8:1 (Jazayeri et al., 2013). The histological features include nuclear atypia, high mitotic activity, vascular proliferation and necrosis. (Kleihues et al., 2000). The prognosis for patients with GBM is poor, with median survival time of approximately 14 months (5-18 months). Age at diagnosis, karnofsky performance status, duration of neurological symptoms are the most important predictors of survival (Curran et al., 1993).

Over the years, management of GBM has progressed from surgery plus radiation to maximal surgery followed by post operative chemoradiation with concurrent then adjuvant temozolamide. (Stupp et al., 2005). The standard radiotherapy dose is 60Gy in 2-Gy fractions recommended by the radiation therapy oncology group (RTOG) (Mac et al., 1990). With the vast majority of tumor recurrences occurring within the previous irradiation filed and the poor outcome associated with standard therapy, regimens designed to deliver higher radiation dose to improve local control and enhance survival. Dose escalation, altered fractionation, using radiosurgery, brachytherapy and proton therapy is some of these attempts.

The goal of this retrospective study is to define the characteristic and treatment out come of 80 adult patients with Glioblastoma Multiform treated and followed up in a referral single institutional review over a 6-year period.

Materials and Methods

Patients

A total of 80 consecutive adult patients with

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histological proven GBM who were treated with radiation therapy at the Mahdieh radiotherapy institute, the pioneer cancer institute in west of Iran, between 2006 and 2012 entered to this study.

All patients had proven histological diagnosis of Glioblastoma Multiform by (gross total resection, partial resection or biopsy), and treated by external beam radiation with Siemens linear accelerator with or without concurrent and adjuvant chemotherapy.

Demographic factors including age, sex, performance status and other factors including extent of resection, tumor location, radiotherapy protocol and dose, chemotherapy regimens, imaging information, time of last follow up and patients status at the time of performing data for this study (alive or expired) were collected.

Treatment plan

All patients were under went surgery. Extent of surgery defined as below; complete resection (defined as resection of more than 95% of the tumor), subtotal resection (defined as resection of 50-94% of the tumor), partial resection (any surgical debulking less than subtotal resection) and biopsy only. 4-6 weeks after surgery, the patients underwent post operative radiation therapy with or without chemotherapy in concurrent and/or in adjuvant setting.

The patient were simulated and treated using a thermoplastic face make for immobilization.

A computerized tomography (CT) Scan of the head was obtained during simulation and images have been transferred to a core plan treatment planning system. With regard to treatment policy in our institute, (RTOG) guideline.

The patients were initially treated with 44-46Gy in 1.8-2Gy fractions for PTV_1 in the first phase and the remaining boost dose up to total 59-64Gy dose delivered to PTV_2 in the second phase.

GTV_1 included contrasting enhancing lesion plus peri tumoral edema and GTV_2 included the contrast enhancing lesion in preoperative magnetic resonance (MR) imaging. PTV_1 consisted of 2-2.5cm margin to GTV_1 and PTV_2 consisted of 2-2.5cm margin to GTV_2. (Colman et al., 2006).

Concurrent chemotherapy regimens was prescribed to some patients.

Most of these patients received adjuvant chemotherapy with temozolamide and some received nitrosourea based regimens.

Follow up

MRI was obtained at 4-6 weeks post-irradiation and every 6 months there fore.

Response was defined using the MacDonald criteria in our institute.

The Mc Donald criteria evaluate responsive disease define as a 30% decrease in largest area also progressive disease as a 25% increase in the largest diameter (Mac Donald et al., 1990).

Early radiological progression defined as any radiology progression from base line to 4-6 weeks post-RT and if the patients showed clinically stable disease for at least 6 months post-RT, pseudo progression mentioned.

Clinical end points included in this study were overall survival, defined as the interval between surgery and death, and progression free survival, defined as the interval between surgery and the date of disease progression at the primary location or other sites of brain.

Statistics

Clinical and pathologic variables were analyzed by Spss-18 statistical soft ware.

Time to event distribution were estimated using the Kaplan-Meier method and proportional hazard ratio and The p value of 0.05 considered significant.

Results

Of the 80 patients who entered the study, 68 patients completed the treatment course and participated in our follow up, 3 of 12 died during radiotherapy or chemotherapy treatment and the 9 patients, lost to follow up.

Informed consent was obtained from all the patients. There was 45 (66.2%) male and 23 (33.8%) female with a mean age at diagnosis of 48.97±12.85 (21-75) years.

Tumor size at diagnosis was 4.8±1.73cm. 8 (11.7%) of Patients presented with multiple lesions.

Patient's characteristics in this study is listed in Table 1.

The mean radiotherapy dose was 59.6±6.8Gy.

Temozolamide was given concurrently with radiation in only 14 patients but adjuvant chemotherapy prescribed for 31 patients (15 Temozolamide and 16 vincristin and nitrousaurea plus procarbazine, PVC regimen).

At a median follow up of 16 months, 39 (57.3%) patients had evidence of tumor progression and 36 (52.9%) patients had died. (The median over all survival for all patients was 16 months and progression free survival for all patients was 6.02 months).

4 of 39 (10.2%) of progressions occurred out of the radiation field and 35 of 39 (89.8%) of progressions occurred within 2cm of the margin of initial tumor bed,

Table 1. All Patient's Characteristics in this Study

		No. (%)
Age	<50	32 (47.1)
	≥50	36 (52.9)
Median (range)	50	(21-75y)
Sex	Female	23 (33.8)
	Male	45 (66.2)
Extent of surgery	Total	0
	Subtotal	9 (13.2)
	Partial	56 (82.4)
	Biopsy only	34 (4.4)
Hemisphere	Right	28 (41.1)
	Left	37 (54.4)
	Both	3 (4.5)
Location	Temporal	4 (5.9)
	Parietal	13 (19.2)
	Frontal	23 (33.8)
	Occipital	3 (4.4)
	Temporoparietal	8 (11.8)
	Frontotemporal	10 (14.7)
	Frontoparietal	7 (10.2)

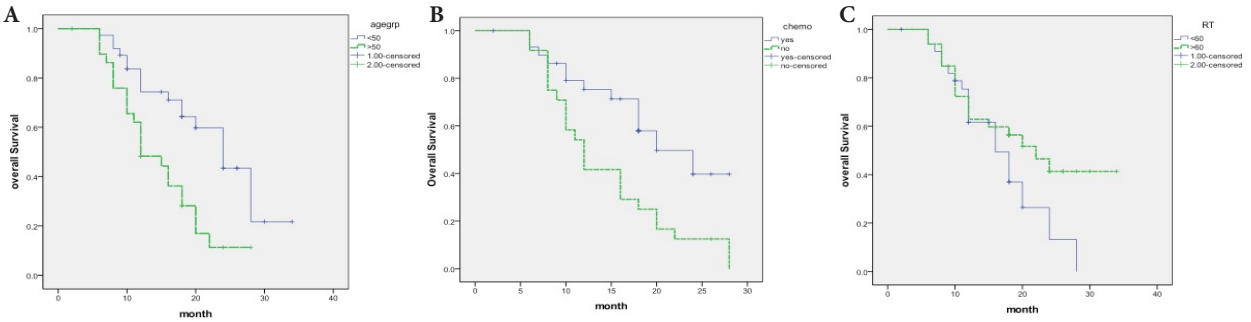

Figure 1. Kaplan Meier Survival Curve of Overall Survival, Categorized According A) Patients Age (p=0.002); B) Chemotherapy Prescription (p=0.005) and C) Radiotherapy Dose Prescription (p=0.06)

Table 2. Treatment Outcome in Standard and Higher Dose of Radiotherapy Groups

RT dose	≤60Gy	> 60Gy(up to 64Gy)	p value
Number		34	34
Age (Y)	48.8±12.7	49.06±13.1	NS
Tumor size(cm)	4.69±2	4.92±1.13	NS
MR responsee			
Partial(%)	52.94	73.5	p=0.05
Stable or Progressive (%)			
	47.06	27.5	
Prgression			
Yes	67.6	47.05	p<0.05
No	32.4	52.95	
OS (month)	14.29±6.28	17.02±7.52	p=0.06
PFS	8±6.43	10.87±9.5	p<0.05

in radiation field.

42 (61.7%) of the patients showed partial response in first MRI imaging after completion of radiotherapy and 26 (38.2%) showed stable or progressive disease. Although only 10 patients strictly met the MacDonald criteria for progression at 1 month.

All potential prognostic factors were analyzed to evaluate their effects on progression free and overall survival. On uni variate analysis of prognostic factors for overall survival, age ≤50 year, concurrent and adjuvant chemotherapy, extent of surgery had significant p values (0.008, 0.05, 0.04) but our study did not show significant effect for sex, tumor location, tumor size on overall survival. (Figure 1-2).

In addition ,we found lower progression rate among patients who received higher doses of radiotherapy (>60 Gy). Higher radiotherapy dose improved progression free survival (p=0.03). Despite increasing overall survival, this elevation was not significant. (p=0.06).

Discussion

In this study, we report a single institutional experience in treatment of 68 consecutive patients with GBM, treated with resection, majority with partial resection, post operative radiotherapy followed by concurrent and/or adjuvant chemotherapy.

It remains obvious that all patients with GBM have not the same prognosis and there is a heterogeneous patients with variable out comes.

In the review of literature, GBM usually occur in the 6th and 7th decade of life, in current study the majority of patients were in 5th and 6th decade of life.

The median age of our patients was 50 years, which is younger than the median age of 7726 patients, reported as 62 years in the review of literature (Ahmadloo et al., 2013).

Maximal safe resection is a basic goal in the management of patients with GBM but there is no consensus regarding the complete brain tumor resection in the literature and total or complete resection define as more than 98% of tumor resection.

The mean rate of complete (total gross) resection is 33% (10-63%) and rate of biopsy only is 20% (1-56%) in reported metanalysis. In our study the rate of complete resection reported zero (0 *vs* 33%) and rate of biopsy only reported significantly lower (4.4 *vs* 20%) (7-10).

Post operative adjuvant radiotherapy is an essential part, in the treatment of GBM.

A benefit for doses >60Gy using conventional treatment has not been demonstrated.

The RTOG and Eastern cooperative oncology group (ECOG) randomized 253 patients to 60Gy whole brain radiotherapy or 60Gy plus 10Gy boost to a limited volume and did not find survival advantage (Nelson et al., 1988).

Tanaka compared 60 and 61 patient with GBM who received conventional 60Gy radiotherapy and 80-90Gy conformal radiotherapy and suggested a survival benefit for patients treated with high dose conformal radiotherapy. (Tanaka et al., 2005).

In our institute, there is a trend to increase radiation dose up to 64Gy in treatment of GBM by some of our colleagues due to their self experiences that induce their believes that treatment with higher doses improve the outcome.

Table 2 shows the characteristics and treatment out come in patients treated with higher doses of radiotherapy in comparison to patients treated with standard or lower doses, as it shows, higher radiotherapy doses decrease progression rate significantly(16 *vs* 23, p<0.05) but could not improve survival significantly (p=0.06).

By using appropriate treatment planning system and conformal radiotherapy techniques higher doses of radiation are tolerable for our patients especially by adding corticosteroids during radiation treatment.

For avoiding the toxicities of higher radiation doses (>60Gy), 32 of 34 patients received concomitant 8-16mg of daily dexamethasone.(Adamson et al., 2010).

Adjuvant chemotherapy plays an important role in treatment of GBM, since 2000 and by adding temozolamide in concurrent and adjuvant setting in combination with post operative radiotherapy modest

improvement in median survival was observed (Jeon et al., 2009; Julka et al., 2013).

In the present study, adjuvant chemotherapy was prescribed for 46% (31 of 68 eligible patients). Due to the expensiveness of temozolamide in our country and very low insurance coverage before 2010, most of our patients could not receive temozolamide, only 15 of 31 patients received concurrent temozolamide.

Initial diagnosis and response assessment is usually determined by measuring gadolinium enhancement of tumor volume with Magnetic Resonance Imaging.

Early radiological progression (ERP), defined as the qualitative interpretation of radiological progression one month post-RT. (Chose et al., 2010).

Patients with ERP were determined to have pseudo progression if clinically stable for ≥5 months. Unfortunately, many GBM treatment modalities, RT and/or chemotherapy, may cause changes in tumor gadolinium absorption that mimic tumor progression (Gladwish et al., 2011).

From 10 patients in our study who met the Mac Donald criteria for progressive tumor in MRI, 5 of them had stable clinical condition for at least 5 months and they were alive up to end of the study, pseudo progression.

Two Canadian studies by Roldan and Sanghera found, pseudo progression rates of 40% and 32% respectively with median survival of 9.1 and 31.2 months. The 50% rate of pseudo progression in our study (5 of 10) is comparable to those studies. (Roldan et al., 2009; Sanghera et al., 2010). In this study, the median overall survival (OS) and progression free survival (PFS) of 16 and 6 months are comparable to the EORTC results showing a median OS and PFS of 14.9 and 6.9 months. (Jalali et al., 2006).

In comparison to a single institute experience from Iran and two other international. Single center experiences have reported OS of 17.9, 18.3 and 16.4 months, our findings are consistent with their findings (Mirimanoff et al., 2007; Jeon et al., 2009).

First limitation of our study is a relatively small sample size of retrospectively recruited GBM patients. Our study must be further validated in a larger prospective study for meaningful interpretation of interesting result that higher radiotherapy dose impact on recurrence rate and PFS. Furthermore low rate of temozolamid prescription among our patients due to socioeconomic problems may effect on our result in comparison to studies reporting standard

In conclusion, GBM is a highly aggressive tumor with early recurrence probability, short overall survival and poor out come associated with standard multimodality therapy. therefore the need for more effective treatment in the treatment of this tumor is strongly prominent. This study emphasize that higher radiation doses (>60Gy) concomitant with chemotherapy improve local control significantly and increase overall survival, however significance did not reached. So we strongly advise prospective multi centric studies to evaluate the impact of higher doses conformal radiation on GBM patient's outcome.

References

Adamson C, Kanu O, Mehta A, et al (2009). Glioblastoma multiform: a review of where we have been and where we are going. *Expert Opin Investing Drugs*, **18**, 1061-83.

Ahmadloo N, Kani A, Mohamadian Panah M (2013). Treatment out come and prognostic factors of adult glioblastoma multiform. *J Egypt Natl Canc Inst*, **25**, 21-30.

Chose A, lim G, Husain S (2010). Treatment for glioblastoma multiform: Current guidelines and Canadian practice. *Current Oncol*, **17**, 52-60.

Colman H, Berkey BA, Maor MH, et al (2006). Phase II radiation therapy oncology group trial of conventional radiation followed by treatment with recombinant interferon for glioblastoma result of RTOG 9710. *Int J Radiat Oncol Biol Phys*, **66**, 818-24.

Curran WJ, Scott CB, Horton J, et al (1993). Recursive petitioning analysis of prognostic factors in three Radiation therapy oncology group malignant glioma trials. *J Nat Cancer Inst*, **85**, 701-10.

Gladwish A, Koh ES, Hoisak J, et al (2011). Evaluation of early imaging response criteria in glioblastoma multiform. *Radiat Oncol*, **6**, 121.

Ho J, Ondo SJ, Ning H (2013). Chemoradiation for glioblastoma multiform: the National cancer institute experience, *Plos ONE*, **8**, 70745.

Jalali R, Basa A, Gupta T, et al (2007). Encouraging experience of concomitant temozalamide with radiotherapy in newly diagnosed glioblastoma multiform: single institutional experience. *Br J Neurosurg*, **21**, 583-7.

Jazayeri B, Movaghar V, shokran F, et al (2013). Epidemiology of primary CNS tumor in Iran: a systemic review. *Asian Pac J Cancer Prev*, **14**, 3979-86.

Jeon HJ, Kong DS, park KB, et al (2009). Clinical out come of concomitant chemoradiotherapy followed by adjuvant temozolamid therapy for glioblastomas: single center experience. *Clin Neural Neurosurg*, **111**, 679-82.

Julka PK, Sharma DN, Mallicks (2013). Post operative treatment of glioblastoma multiform: a mono institutional experience of 215 Patients. *J Cancer Res Ther*, **9**, 381-6.

Kleihues P, Cavanee WK, eds (2000). World Health Organization classification of tumors: pathology and genetics of tumors of the nervous system, Lyon, France: IARC press.

Mac Donald On, Cascino TL, Schold SC, et al (1990). Response criteria for phase II studies of supra tentorial malignant glioma. *J Clin Oncol*, **8**, 1277-80.

Mirimanoff Ro, Gorlia T, Mason W, et al (2006). Radiotherapy and temozolamide for newly diagnosed glioblastoma: recursive partitioning Analysis of the EORTC 26981. *J Clin Oncol*, **24**, 2563-9.

Nelson DF, Diener WM, Horton J, et al (1988). Combined modality approach to malignant gliomas-reevaluation of RTOG7401/ECOG 1374 with long term follow up, *NCI Monogr*, **6**, 279-84.

Roldan GB, Scot JN, Hamilton MG, et al (2009). Population based study of pseudo progression after chemo radiotherapy in GBM, *Can J Neuro Sci*, **36**, 617-22.

Sanghera P, Perry J, Davey P, et al (2010). Pseudoprogression following chemoradiotherapy for glioblastoma multiform. *Can J Neural Sci*, **37**, 36-42.

Stupp R, Mason WP, Vonder ben t MJ, et al (2005). Radiotherapy plus concomitant and adjuvant temozolomide for glioblastom. *New Eng J Med*, **352**, 987-96.

Tanaka M, Ino Y, Nakagava K, et al (2005). High dose conformal radiotherapy for supra tentorial malignant glioma: a historical comparison. *Lancet Oncol*, **6**, 953-60.