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Research Article

AN OBSERVATIONAL STUDY TO EVALUATE THE RESPONSE OF HYPOFRACTIONATION RADIOTHERAPY IN MALIGNANT GLIOMA OF BRAIN

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ABSTRACT

Background: Glioblastoma multiforme (GBM) is a poorly differentiated, highly aggressive malignancy of the central nervous system (CNS). Although it carries a uniformly fatal prognosis, postoperative radiotherapy (RT) has been shown to increase the median survival compared with that for patients treated with surgery alone. Consequently, surgical resection followed by 6 weeks of RT has become the standard of care for the management of these tumors. The standard dose of radiation given after surgical resection is 60 Gy delivered in 1.8–2.0-Gy fractions. Hyperfractionation (giving a smaller fraction size twice daily) to a total dose of 72 Gy has shown no specific benefit for GBM. Although the methods of these trials varied in terms of fraction size, total dose, and overall treatment time, all were shown to have acceptable toxicity and encouraging results. From a radiobiologic standpoint, late-responding tissues such as neural tissue should be more responsive to fewer, but larger, dose fractions of radiation. Therefore, to control CNS tumors such as GBM adequately, it is likely that the radiation dose given must exceed the tolerance of the surrounding brain, resulting in an unacceptable side effect profile. If a greater biologic radiation dose can be delivered to tumor while selectively sparing normal brain through a specialized treatment technique such as Rapid Arc, it may be possible to increase patient survival without increasing toxicity. **Objective:** To evaluate the outcome using hypofractionated radiotherapy for treatment of all the stages of malignant glioma of brain in terms of locoregional control by clinical and radiological assessment. **Method:** This prospective observational study involves 30 histological proven, hematological stable cases of malignant glioma of brain was conducted during March 2018 - March 2019 in the department of Radiotherapy, Pt. JNM medical college and Regional cancer center (RCC) of Dr. BRAM Hospital Raipur. Informed written consent, detail history and complete Physical examination were performed in every patient. Patients were simulated with appropriate immobilization technique then planned with IMRT. Treatment planning was performed using VARIAN (eclipse V.S 13.6.23) treatment planning system. Dose to PTV and OARs were calculated. Follow up was done for 6 months. Patients were evaluated for local response. **Result:** In this study the majority of patients (33.3%) were of 50-60 years age group. 66.6% of participants were males and rests were females. There was equal tumor distribution noted in both halves of brain i.e. 50%. Frontal lobes (33.3%) followed by fronto -parietal were found to be most affected areas in brain. Complete response (CR) was seen in 33%,partial response (PR) was in 43.3% and progressive disease was observed in 20% of patients. Death occurred in 3.3% patients. In this study, patients group who belonged to 0-1cm (pre radiotherapy tumor size) showed complete response in 20%. In 4-5 cm group CR was observed in 10%. **Conclusion:** Glioma of brain is a very fatal disease and carries a poor prognosis overall. The mainstay of treatment in this disease is surgery followed by radiotherapy. The response post radiotherapy depends mainly on dose fractionation schedule and type and technique used for radiotherapy. In this study 30 patients were treated with rapid arc (RA) technique with fraction regimen of 2.3 Gy per fraction 5 days a week for 5-6 weeks along with Tab. Temozolamide 75mg/ m2 once a day daily concurrently. Follow up was done to assess the response and local control up to 6 months. This study reveals that high grade glioma mostly occurs at old age group and majority among men. Glioma of brain can involve any areas of brain, our study reveals that Frontal followed by fronto -parietal were found to be mostly affected. Complete response was observed in most patients who completed radiotherapy in some patients progressive disease was observed.

INTRODUCTION

Glioblastoma multiforme (GBM) is a poorly differentiated, highly aggressive malignancy of the central nervous system (CNS). Although it carries a uniformly fatal prognosis, postoperative radiotherapy (RT) has been shown to increase the median survival compared with that for patients treated with surgery alone.[1] Consequently, surgical resection followed by 6 weeks of RT has become the standard of care for the management of these tumors. Unfortunately, the median survival remains only 9–12 months, with a 5-year survival rate of 5%. The standard dose of radiation given after surgical resection is 60 Gy delivered in 1.8–2.0-Gy fractions. Dose escalation through standard fractionation to 70–90 Gy has recently been attempted with conformal techniques, and, although changes in the pattern of failure have been observed, survival improvement has not been achieved.[2] Hyperfractionation (giving a smaller fraction size twice daily) to a total dose of 72 Gy has shown no specific benefit for GBM.[3] Brachytherapy in addition to external beam RT is effective in delivering a higher dose of radiation to a small target volume, resulting in a survival benefit at the cost of a greater incidence of radiation necrosis. [4]The purpose of this study was to evaluate the safety and efficacy of a novel regimen of adjuvant hypofractionated RT for patients with GBM using Rapid Arc (RA). From a radiobiologic standpoint, late-responding tissues such as neural tissue should be more responsive to fewer, but larger, dose fractions of radiation. Therefore, to control CNS tumors such as GBM adequately, it is likely that the radiation dose given must exceed the tolerance of the surrounding brain, resulting in an unacceptable side effect profile. [5] If a greater biologic radiation dose can be

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delivered to tumor while selectively sparing normal brain through a specialized treatment technique such as Rapid Arc, it may be possible to increase patient survival without increasing toxicity. The biologically effective dose (BED) of radiation increases with either the increasing total radiation dose or an increasing fractional radiation dose, with the total dose held constant (hypofractionation). In addition to the possible advantages compared with conventional fractionation in terms of the increased BED, hypofractionation can also be more convenient for the patient, because the overall treatment time is decreased.

Objective: To evaluate the outcome using hypofractionated radiotherapy for treatment of all the stages of malignant glioma of brain in terms of loco regional control by clinical and radiological assessment.

MATERIAL AND METHOD

Method: This prospective observational study involves 30 histological proven, hematological stable cases of malignant glioma of brain was conducted during March 2018 - March 2019 in the Department Of Radiotherapy, Pt. JNM Medical College and Regional Cancer Center (RCC) Of Dr. BRAM Hospital Raipur.

Patient Inclusion Criteria

1. Patient was histologically proven malignant glioma of brain.
2. Blood reports were under normal range.

Patient Exclusion Criteria

1. Pregnant and lactating mothers with malignant glioma of brain.
2. Patient with any other malignancy.
3. Patient with co-morbidities.

Major Variables

1. Age
2. Sex
3. Histopathology
4. Target volumes (Gtv, Ptv, Ctv)
5. Dose (objective organs and OAR)

Outcome Variables

1) Treatment response

METHODOLOGY

- This study was performed in the Department of Radiotherapy, Regional Cancer Centre, Pt. J.N.M. Memorial Medical College &Dr BRAM Hospital Raipur, C.G.
- Total 30 post operated patients of malignant glioma of brainwere taken for this study.
- Informed written consent was taken from every patient.
- Detail history was recorded from each patient pertaining to the onset and duration of present complaint.
- Physical examination was done on all patients including general, local and systemic examination.
- All the routine investigations including CBC, RFT, LFT, X-ray chest, ECG, MRI of brain were done on all the cases.
- Patients were simulated with appropriate immobilization technique then planned with IMRT. Evaluation of the plan for dose to primary site and dose to organ at risk was done and best better plan was executed.
- Treatment planning was performed using VARIAN (eclipse V.S 13.6.23) treatment planning system.
- Dose to PTV and OARs was calculated.
- Follow up was done for 6 month. Patients were evaluated for local response.

RESULTS

This prospective observational study involves 30 histological proven, hematological stable cases of malignant glioma of brain was conducted during March 2018 - March 2019 in the Department Of Radiotherapy, Pt. JNM Medical College and Regional Cancer Center (RCC) Of Dr. BRAM Hospital Raipur. All patients were evaluated with a detailed history, clinical examinations, hematological and radiological investigations. All patients were treated with rapid arc (RA) technique with fraction regimen of 2.3 Gy per fraction 5 days a week for 5-6 weeks along with Tab. Temozolamide 75mg/ m2 once a day daily concurrently.

Age

10 out of 30 patients (33.3%) were in age group of 50-60 yrs. followed by 8 (26.6%) in 40 -50 years age group. Glioma of brain is most common among adults.

Table 1

Age Group	Patient No.	Percentage %
10-20	2	6.6
20-30	5	16.6
30-40	4	13.3
40-50	8	26.6
50-60	10	33.3
60-70	1	3.33

Gender

20 out of 30 (66.6%) patients were male rest 33.3% were female. According to our study male patients were more prone to glioma of brain as compared to female.

Table 2

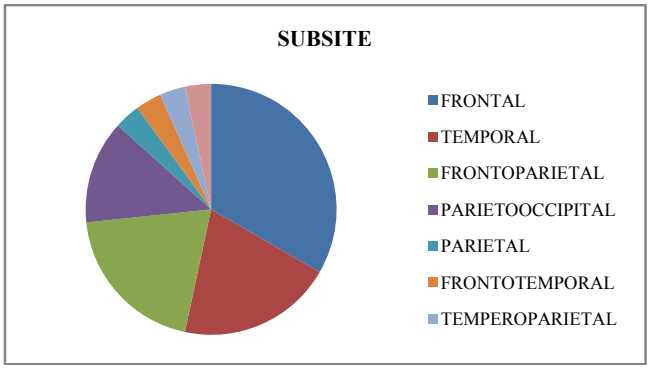
Gender	Patient no.	Percentage %
Male	20	66.6
Female	10	33.3

Subsite Wise Disease Distribution

10 out of 30 patients (33.3%) had disease in frontal lobe. Temporal lobe and frontoparietal lobe were found to be involved in 6 patients i.e. (20%) each followed by parietal, frontotemporal and occipital.

Table 3

Subsite	Patient no.	Percentage %
Frontal	10	33.3
Temporal	6	20
Frontoparietal	6	20
Parietooccipital	4	13.3
Parietal	1	3.3
Frontotemporal	1	3.3
Temperoparietal	1	3.3
Occipital	1	3.3



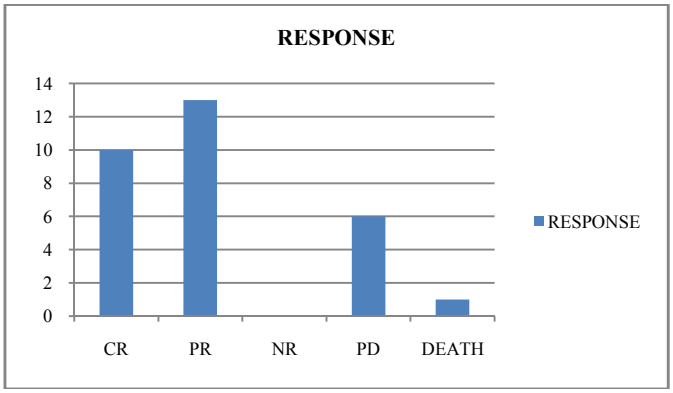
Graph 1

Disease Response to Treatment

10 out of 30 patients (33.3%) showed complete response(CR) to treatment, 13 patients (43.3%) had partial response , 6 out of 30 (20%) had progression in disease and 1 patient died during the course of treatment.

Table 4

Response	Patient no.	Percentage %
CR	10	33.3
PR	13	43.3
NR	0	0
PD	6	20
DEATH	1	3.3



Graph 2

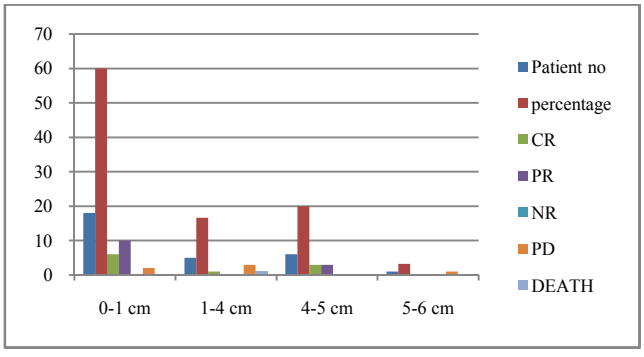
Response wise percentage of patients

Pre RT Tumour Size Response

In this study complete response was seen among patients (20%) who belonged to 0 – 1 cm size group followed by (3.3%) belonged to 1 – 4 cm size group and 10% of patients who belonged to 4 – 5 cm.

Table 5

Tumor size	Patient no	percentage	CR	PR	NR	PD	DEATH
0-1 cm	18	60	6	10	0	2	0
1-4 cm	5	16.6	1	0	0	3	1
4-5 cm	6	20	3	3	0	0	0
5-6 cm	1	3.3	0	0	0	1	0



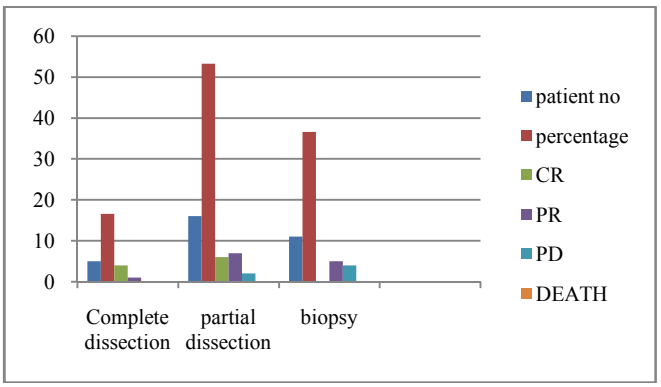
Graph 3

Surgical Dissection Wise Response

This study showed that 80% of patients had complete response who had undergone complete dissection and 37.5% of patients undergone partial dissection had complete response.

Table 6

	patient no	percentage	CR	PR	PD	DEATH
Complete dissection	5	16.6	4	1	0	0
partial dissection	16	53.3	6	7	2	1
biopsy	9	30	0	5	4	0



Graph 4

DISCUSSION

A glioma is a brain tumor made up of astrocytes, which are glial cells that support the neurons of the brain. Gliomas are the most common type of primary brain tumors originating from brain tissue. There are approximately 12,000 new cases of glioma every year.[6] Even the most aggressive gliomas almost never spread throughout the blood and lymphatic systems into other parts of the body, and in this sense they differ from cancers in that they typically remain confined to the central nervous system. Among three types of glioma, most common are Astrocytomas which are defined by their histological grade from low grade to high grade. The most common type of glioma is the high grade glioblastoma multiforme (GBM)[7] which is rapidly growing and generally carries a poorer prognosis. Lower-grade astrocytomas (grades 1 and 2 and pilocyticastrocytomas) are generally slow-growing and carry a better prognosis others are Ependymomas and Oligodendrogliomas. Among gliomas, there is a spectrum of how malignant or aggressive a tumor can be. The World Health Organization (WHO) grades gliomas from I-IV, with IV being the most aggressive and infiltrative glioma called glioblastoma multiforme (GBM). Grade 3 Gliomas are also known as anaplastic glioma (also called anaplastic astrocytomas, AA).Grade II gliomas are also known as low grade, or diffuse glioma. Grade I tumors comprise a separate entity, consisting of various (often benign) tumors usually seen in pediatric populations. The most common of these are pilocytic gliomas, which usually have a very good prognosis following complete surgical removal.[8] Although they do not metastasize like malignant cancers, gliomas are not "benign" because they may infiltrate or invade the brain tissue, even beyond the areas they are visualized on imaging studies such as MRI. Cells from the tumor may spread into and mix themselves among normal brain cells. With the naked eye, or even under an operating microscope, it is often not possible to differentiate normal from infiltrated brain. It is only with the neuropathologists' high-power microscope magnifying 25 to 40 times that abnormal tumor cells can be seen as they mix in

with normal brain tissue. The cause of a glioma is unknown. Although the initial cause is thought to be related to mutations in the DNA of the tumor cells, there are currently no clear-cut environmental or behavioral risk factors (such as air pollution or smoking) that are known to cause gliomas.[9] Treatment for brain gliomas depends on the location, the cell type, and the grade of malignancy. Often, treatment is a combined approach, using surgery, radiation therapy and chemotherapy. The radiation therapy is in the form of external beam radiation or the stereotactic approach using radio surgery. Spinal cord tumours can be treated by surgery and radiation. [10] Temozolomide is a chemotherapy drug which can be administered easily in an outpatient setting and is able to cross the blood–brain barrier effectively. Treatment via immunotherapy may help some gliomas.

A 2017 meta-analysis compared surgical resection versus biopsy as the initial surgical management option for a person with a low-grade glioma. Results show the evidence is insufficient to make a reliable decision. The relative effectiveness of surgical resection compared to biopsy for people with malignant glioma (high-grade) is unknown. For high-grade gliomas, a 2003 meta-analysis compared radiotherapy with radiotherapy and chemotherapy. It showed a small but clear improvement from using chemotherapy with radiotherapy. A 2019 meta-analysis suggested that for people with less aggressive gliomas, radiotherapy may increase the risk of long term neurocognitive side effects. Whilst, evidence is uncertain on whether there are long term neurocognitive side effects associated with chemo radiotherapy. Temozolomide is effective for treating Glioblastoma Multiforme (GBM) compared to radiotherapy alone. A 2013 meta-analysis showed that Temozolomide prolongs survival and delays progression, but is associated with an increase in side effects such as blood complications, fatigue, and infection. For people with recurrent GBM, when comparing temozolomide with chemotherapy, there may be an improvement in the time-to-progressionand the person's quality of life, but no improvement in overall survival, with temozolomide treatment. Evidence suggests that for people with recurrent high-grade gliomas who have not had chemotherapy before, there is similar survival and time-to-progression outcomes between treatments with temozolomide or the chemotherapy multidrug known as PCV (procarbazine, lomustine and vincristine).

CONCLUSION

This study was performed in department of radiotherapy Pt. J N M Medical College & Dr. BRAM Hospital Raipur (C.G.) 30 patients were treated with rapid arc technique (RA) with fraction regimen of 2.3 Gy per fraction 5 days a week for 5-6 weeks along with Tab.temozolamide 75mg/ m2 concurrently with radiotherapy. Follow up was done to assess response and local control in the duration of 6 months post treatment. 33.3% patients belonged to 50 to 60 age groups which revealed that high grade glioma mostly occurs at old age group. 66.6% patients were male rest were female which showed that males are more prone to high grade glioma. In this study we observed that high grade glioma mostly occurred at frontal lobe followed by temporal lobe.

According to our study 65% of patient's neurological performance score was 0-1 which revealed that most patients came with no neurological deficit or having some neurological deficit but functioning adequate for useful work. We observed in our study that 33.3% cases had complete response, 43.3% cases had partial response and 20% cases had progression of disease. These cases were observed till sixth months post treatment for follow up. Our study concluded that judicious and prompt use of hypofractination radiotherapy along with concurrent tab. Temozolamide have good response and less neurological deficit in high grade glioma of brain post treatment.

References

1. Walker MD, Green SB, Byar DP *et al*. Randomized comparisons of radiotherapy and nitrosoureas for the treatment of malignant glioma after surgery. *BTSG 72-01 Eng J Med 1980; 303*: 1323-1327.
2. Nakagawa K, AOKI Y, Fujimaki T *et al*. High dose conformal radiotherapy influenced the pattern of failure but did not improve survival in glioblastoma multiforme*. Int J RadiatOncol Bio Phys 1998; 40:1141-*1149.
3. Nelson DF, Curran WJ, Scott C, et al. Hyper fractionated radiation therapy and bis-chloroethylnitrosourea in the treatment of malignant glioma – Possible advantage observed at 72 Gy on 1.2 BID fractions: Report of the RTOG protocol 8302. *Int J RadiatOncol Bio Phys 1993; 25:193-*207.
4. Gutin PH, Prados MD , Phillips TL, et al. External irradiation followed by an interstitial high activity iodine 0125 implant "boost" in the initial treatment of malignant gliomas. NCOG study 6G-82-2.*Int J RadiatOncol Bio Phys 1991; 21:601-*606.
5. Perez and Brady's radiation principle and practice of oncology 7th edition.
6. Young RM, Jamshidi A, Davis G, Sherman JH et al. Current trends in the surgical management and treatment of adult glioblstoma. *Annals of Translational Medicine.3 (9): 121*:2305-5839.
7. BleekerFE, Molenaar RJ *et al.* Recent advances in the molecular understanding of glioblastoma. *Journal of Neuro-Oncology.108 (1):* 11-27
8. Ostrom QT, Cioffi G *et al*. Primary brain and other central nervous system tumour diagnosed in the United States. *Neuro- Oncology.21 (Supplement 5): v1-v100*.
9. World Cancer Report 2014. World Health Organisation.2014.*ISBN 978-9283204299*.
10. Lacroix M, Fourney DR, Shi W *et al.* A multivariate analysis of 416 patients with glioblastoma multiforme: prognosis, extent of resection, and survival. *Journal of Neurosurgery 95 (2):190-98.*

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