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AN OBSERVATIONAL STUDY TO EVALUATE THE ADVERSE EFFECTS OF HYPOFRACTIONATION RADIOTHERAPY IN PATIENTS OF 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 (one). 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 adverse effects of hypofractionated radiotherapy post treatment in patients of malignant glioma of brain 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 early and late toxicities. **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. In our study among acute toxicities group we found that 63.3% of cases had grade 2 toxicity followed by grade 1 toxicity in 16.6% cases, grade 3 toxicity was observed in 16.6% and grade 5 toxicity in 3.3%, most of the cases belong to grade 2 toxicity group due to symptoms of fatigue ,headache and nausea .While in late toxicities group we observed that 66.6% of cases had grade 2 toxicity followed by grade 3 toxicity in 16.6% patients and grade 1 toxicity in 13.3% grade 2 toxicity was seen higher compared to others due to moderate headache and lethargy. **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 acute and late toxicities upto 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 was found to be mostly affected. Among acute toxicities grade 2 toxicity was observed in most of the cases due to symptoms of fatigue, headache and nausea. And in late toxicities grade 2 toxicity was seen higher compared to others due to moderate headache and lethargy.

KEYWORDS : Glioblastoma , Hypofractionation, Radiobiology, Immobilization

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 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. We have found that Rapid Arc is a feasible and practical treatment delivery technique for everyday use.

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. This study was designed to measure the acute and late toxicity of patients treated with a hypofractionated, high biologic dose of conformal radiation delivered via Rapid Arc, response of GBM to this treatment, overall survival after therapy completion, and the time to disease progression after completion. 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 adverse effects of hypofractionated radiotherapy post treatment in patients of malignant glioma of brain 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 histoligically 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) Adverse effects profile.

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 brain were 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 their adverse effects profile.

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, haematological 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.

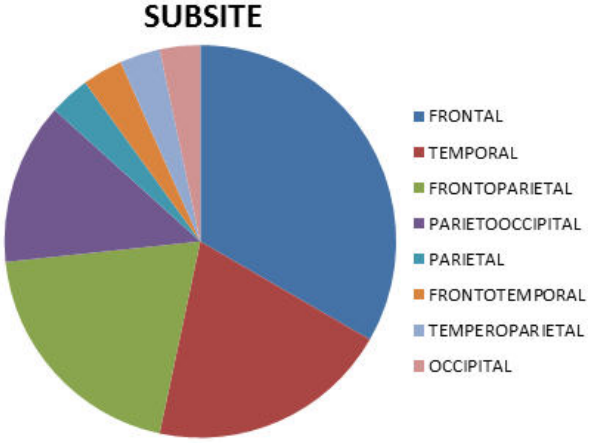
Table 2:

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:

Acute Hematologic Toxicity
In our study we observed that neutropenia of grade 1 and grade 2 was seen in among 6.6% of patients, leucopenia of grade 1 and 2 among 6.6% of patients, anaemia of grade 1 and 3 among 6.6% of patients, thrombocytopenia of grade 2 and 3 among 6.6% of patients.

Table 4:

Grade	Neutropenia	Leukopenia	Anemia	Thrombocytopenia
Grade 1	1	1	1	0
Grade 2	1	1	0	1
Grade 3	0	0	1	1
Grade 4	0	0	0	0

Late Hematologic Toxicity
In our study we found that neutropenia of grade 1, 2 and 3 was seen among 10% of patients, leucopenia of grade 1, 2 and 3 was there among 10% of patients, anaemia of grade 1 and 2 was in among 10% of patients, thrombocytopenia of grade 1 and 2 among 10% of patients.

Table 5:

Grade	Neutropenia	Leukopenia	Anemia	Thrombocytopenia
Grade 1	1	1	2	2

Grade 2	1	1	1	1
Grade 3	1	1	0	0
Grade 4	0	0	0	0

RTOG Acute Radiation Scoring Criteria

0	1	2	3	4	5
No change	Fully functional status (i.e. able to work) with minor neurologic findings, no medications needed.	Neurologic findings present sufficient to require home care, nursing assistants may be required, medications including steroids, antiseizure agents may be required.	Neurologic finding requiring hospitalization for initial management.	Serious neurologic impairment that includes paralysis, coma or seizures more than 3/week despite medication, hospitalization required	Death

Toxicity At First Week V/s Second Week Of RT

This table shows that 73.3% of patients had grade 2 neurotoxicity followed by 13.3% of patients had grade 1 neurotoxicity at the end of 1st week of RT no significant difference seen in adverse effects at the end of 2nd week of RT.

Table 6:

GRADES	1st WEEK	2nd WEEK	PERCENTAGE
GRADE 0	1	1	3.3
GRADE 1	4	4	13.3
GRADE 2	22	22	73.3
GRADE 3	2	2	6.6
GRADE 4	1	1	3.3
GRADE 5	0	0	0

Toxicity At Third Week Of RT

In our study 70% of patients had grade 2 neurotoxicity followed by 16.6% of patients had grade 1 neurotoxicity at the end of 3rd week of RT and at the end of 4th week only grade 2 neurotoxicity increases rest remains same.

Table 7:

GRADES	3rd week	4TH week	% 3rd week	% 4TH week
GRADE 0	0	0	0	0
GRADE 1	5	5	16.6	16.6
GRADE 2	21	22	70	73.3
GRADE 3	4	3	13.3	10
GRADE 4	0	0	0	0
GRADE 5	0	0	0	0

Toxicity At Fifth Week Vs Sixth Week Of RT

73.3% of patients had grade 2 neurotoxicity followed by 16.6% of patients had grade 1 neurotoxicity at the end of 5th week of RT. and this remains same at the end of 6th week RT also.

Table 8:

GRADES	5th WEEK	6th WEEK	%
GRADE 0	0	0	0
GRADE 1	5	5	16.6
GRADE 2	22	22	73.3
GRADE 3	3	3	10
GRADE 4	0	0	0
GRADE 5	0	0	0

Rtog Late Radiation Scoring Criteria

0	1	2	3	4	5
None	Mild headache, slight lethargy	Moderate headache, great lethargy	Severe headache, severe CNS dysfunction (partial lose of power or dyskinesia)	Seizure or paralysis, coma	Death

Neurotoxicity At Third Month And Sixth Month Of Follow Up

In our study 63.33% of patients had grade 2 neurotoxicity followed by 17.24% of patients had grade 1 neurotoxicity at the 3rd month of follow up post RT while 63.33% of patients had grade 2 neurotoxicity followed by 17.24% of patients had grade 1 neurotoxicity at the 6th month of follow up post RT.

Table 9:

GRADES	3rd MONTH	6th MONTH	PERCENTAGE
GRADE 0	0	0	0
GRADE 1	5	5	17.24
GRADE 2	19	19	63.33
GRADE 3	5	5	16.66
GRADE 4	0	0	0
GRADE 5	1	1	3.33

Acute Toxicity V/s Late Toxicity

In our study among acute toxicities profile we found that 63.3% of cases belonged to grade 2 toxicity followed by grade 1 toxicity (16.6%), grade 3 toxicity (16.6%) and grade 5 toxicity (3.3%) and in among late toxicities profile that 66.6% of patients had grade 2 toxicity followed by grade 3 toxicity (16.6%) and grade 1 toxicity (13.3%).

Table 10:

GRADES	ACUTE TOXICITY	LATE TOXICITY
GRADE 0	0	0
GRADE 1	5	4
GRADE 2	19	20
GRADE 3	5	5
GRADE 4	0	0
GRADE 5	1	0

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. **NPS SCORE-**In our study ,we observed that most cases belong to 0-1 score (60%) followed by 3-

4 score (30%) and 2 score (10%) we also concluded that the most of the cases belonged to 0-1 score that means most patient has no neurological deficit or having minimal neurological deficit but function is adequate for useful work. In the study by Maarten CCM et al they found that most cases belonged to 0-1 score (39.3%) followed by 3-4 score (37.3%) and 2 score (26.6%). [11]Among late toxicities profile we observed in our study that 66.6% of cases were having grade 2 toxicity followed by grade 3 toxicity was seen among16.6% and grade 1 toxicity in 13.3%.This inference was found similar to the study by Nathan S. Floyd et al where they found that most cases belonged to grade 0 toxicity 67% group, grade 2 were found in 13% cases and grade 4 in 20% of cases.[12]

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 early and late toxicities profile 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. These cases were observed till sixth months post treatment for follow up. In our study ,we observed that most cases belong to 0-1 score (60%) followed by 3-4 score (30%) and 2 score (10%) we also concluded that the most of the cases belonged to 0-1 score that means most patient has no neurological deficit or having minimal neurological deficit but function is adequate for useful work. Among late toxicities profile we observed in our study that 66.6% of cases were having grade 2 toxicity followed by grade 3 toxicity was seen among16.6% and grade 1 toxicity in 13.3%.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.*
11. Maarten C.C.M. Hulshofa, Erik C. Schimmela, D. Andries Boschb, Dionisio Gonzalez research article: *Hypofractionation in glioblastoma multiforme (1999).*
12. Nathan S Floyd, Shiao Y Woo, Bin S Teh, Charlotte Prado, Wei-Yuan Mai, Todd Trask, Philip L Gildenberg, Paul Holoye, Mark E Augspurger, L.Steven Carpenter, Hsin H Lu, J.Kam Chiu, Walter H, E.Brian Butler research article: *Hypofractionated intensity-modulated radiotherapy for primary glioblastoma multiforme (2004).*