The Egyptian Journal of Hospital Medicine (October 2017) Vol.69 (2), Page 1918-1922

Hypofractionated Radiotherapy Versus Conventional Radiotherapy in Management of Patients with High Grade Gliomas Older Patients and Poor Performance State

Hesham A. Elghazaly, Dina A. Salem, Nagi S. Gobran, Mariam M. Hussien
Department of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University
Corresponding author: mariam abuzaid ,email:dr.romiaa@gmail.com

ABSTRACT

Background: as guidelines for glioblastoma treatment was based on trial included patients less 70 years old and good performance only. We did a randomised trial to assess the optimum palliative treatment in patients aged 60 years and older and poor performance patients.

Patients and Methods: this study included 50 (elderly and/or frail patients) with high grade glioma who presented to the Clinical Oncology Department, Ain Shams University during the period of November 2013 to march 2016.Theywere categorized in two groups (25 in each group). Group A received standard conventional fractionation of 60 Gy in 30 fractions over 6 weeks. Group B received 45 Gy in 15 fractions over 3 weeks.

Results: progression free survival in conventional RTH group was 4.1 months, while in hypo fractionated group it was 4.2 with no statistically significant difference between the two groups. The median overall survival was 7.2 in the conventional group and 7.4 months in the hypo fractionated group with no statistically significant difference between the two groups. After age analysis patients≥ 70 years old median overall survival was 5.4 month and 6.8 month in patients ≥ 70 years received hypofractionation.it was statistically significant difference (P value = 0.047).

Conclusion: this study showed that short course of radiotherapy has the same efficacy as slandered conventional radiotherapy in older patients and frail patients. And in patients over 70 years short course should be the slandered of care.

Keywords: Hypofractionation, Glioblastoma, Multiform,Elderly patients.

INTRODUCTION

Glioblastoma is the most common primary brain tumor and most aggressive with survival less than one year [1,2]. Chemoradiotherapy with temozolomide became the standard of care in 2004, after a large phase III study, in which patients were aged 70 years or younger; increased age was found to be a negative prognostic factor[3,4]. Elderly and frail patients usually not withstand combined therapy and extensive treatment might not be seen as justify able owing to the short survival [5]. cAlternatives to the standard 6 weeks of radiotherapy that are associated with similar or improved survival and quality of life would be beneficial treatment short treatment times could also lessen demands on medical resources and reduce the risk of treatment being withheld[6].

METHODS

Study design

This phase III prospective study included 50 (elderly and/or frail patients) with high grade glioma who presented to the clinical oncology department, AIN SHAMS University during the period of November 2013 to March 2016 were randomized 1:1 (25 in each arm).

1-Group A: received standard conventional fractionation of 60 Gy in 30 fractions over 6 weeks.

2- Group B: received 45 Gy in 15 fractions over 3 weeks.

ELIGIBILITY CRITERIA

Inclusion Criteria

Patients who diagnosed as high grade glioma by postoperative (debulking surgery) or biopsy or MRI spectroscopy.

Ages eligible for study: 18-60yrs with karnofsky performance state ≥50 - <70, or patients more than 60 years old karnofsky performance state ≥50.

Patients reliable for follow up.

Exclusion Criteria

Prior chemotherapy or radiation for high grade glioma. Or radiotherapy to brain.

Serious concomitant diseases preventing the safe administration of radiotherapy or likely to interfere with the study assessments.

Concomitant administration of any other experimental drug under investigation

Received:21 / 7 /2017
Accepted:30 /7 /2017
DOI : 10.12816/0040623

Pretreatment Evaluation

Complete history, Clinical examination and neurologic examination.

Baseline measurement of the brain lesion with gadolinium enhancement magnetic resonance imaging (MRI) or Computerized Tomography (CT).

Radiotherapy Technique

All patients were received three-dimensional conformal RT planning. All patients were simulated in supine position with immobilization with thermoplastic head mask after being centralized. Radio-opaque markers were placed over the mask along laser beams over both tragus and midline to identify the reference isocenter. All patients underwent CT counter with scan slices thickness of 3 mm. Patients were injected with intravenous contrast, immediately before scanning. CT and postoperative MRI fusion were done when possible. Gross target volume (GTV), clinical target volume (CTV), planning target volume (PTV) and critical structures (lens, optic nerve and chiasm, brain stem, spinal cord) were delineated.

Group A (conventional group): treated with two phases. In the first phase the prescribed dose was 46 Gy in 23 daily fractions. The planning target volume (PTV1) based CT or MRI and included the enhancing tumor plus peritumoral edema with 2 cm margin or 2.5 cm margins if there was no peritumoral edema. In the second phase the prescribed dose was 14 Gy in 7 fractions. PTV2 include enhancing tumor plus 2cm margin.

Group B (short course): 45 Gy in 15 fractions to PTV included the enhancing tumor plus peritumoral edema with 2 cm margin or 2.5 cm margins if there was no peritumoral edema.

In both groups peritumoral edema were sacrificed if the field was large and PTV only included the tumor/surgical cavity plus 2 cm margin in one phase with no expansion beyond anatomic boundaries (eg, skull- contra lateral cerebrum), In order to reduce dose to organs at risk and normal brain tissue.

Multiple fields techniques were used. Dose volume histogram (DVH) was also done where the plan was considered acceptable if 95% of PTV was encompassed by 95% of prescribed tumor dose. And organ at risk (OAR) should not exceed tissue constraints.

Corticosteroid therapy (Dexamethasone) was given at a starting dose of 8 mg/day and the dose was adjusted upward or downward to reach the minimum dose necessary to control neurological symptoms.

Study assessment and follow up:

Patient were assessed by gadolinium-enhanced magnetic resonance imaging (Gd-MRI) 45 days after RT and then performed every 3 months or at time of clinical evidence of neurologic progression.

Tumor response was evaluated according to the basis of World Health Organization. Response criteria: complete response (CR), disappearance of all known brain lesions. Partial response (PR): 50% or greater decrease in measurable brain lesion or an objective improvement in evaluable brain lesion. Stable disease (SD): brain lesion unchanged (< 50% decrease or < 25% increase in the size of measurable lesions). Progressive disease (PD) : >25% increase in size of some or all of brain lesion and/or the appearance of any new brain lesions.

All adverse events were recorded and graded according to the National Cancer Institute Common Terminology. Criteria for adverse events V4 were evaluated weekly during RT, at 4 weeks after RT and every 3 months until tumor progression.

Steroid dependency: was defined as failure to taper steroids after radiotherapy course or increasing the dose.

Progression free survival: is time from start of the randomized treatment till progression of the disease proved by MRI imaging or clinical deterioration and worsened neurologic symptoms (only applies if corticosteroid dose is stable or increased).

Overall survival: was calculated from the date of random assignment to the date of death or lost follow up.

This study was done after approval of ethical board of Ain Shams University and an informed written consent was taken from each participant in the study.

Data Analysis

Statistical Analysis Software (IBM SPSS, version 20) was used for data analysis. First, descriptive analysis for the whole sample was done using counts and percentage for categorical variable and mean + SD for quantitative variables. Univariate frequency analysis was performed using chi square test and fisher exact test for categorical variables and independent t test and paired t test for quantitative variables. Statistical significance was established at a p-value of less than 0.05.

RESULTS

Patients' Characteristics

The study included 50 patients with high grade glioma who presented to the Clinical Oncology Department, Ain Shams University during the period of November 2013 to March 2016 with a median follow up period of 7.98 months.

Table 1: summarized the 50 patient's characteristics in regards to their age, gender, karnofscy scale, clinical presentation, site of tumor, surgery, pathology type, steroid at start and steroid dependence.

variable	Group I (Conventional) (N=25)	Group II (Hypofractionation) (N=25)
Sex		
Male	14 (56.0%)	17 (68.0%)
Female	11 (44.0%)	8 (32.0%)
Age (years)		
Mean±SD	64.76±6.98	65.68±7.10
Range	47-75	42-76
Age (Category)		
<60 years	2 (8.0%)	1 (4.0%)
≥60-69 years	16 (64.0%)	16 (64.0%)
≥70	7 (28.0%)	8 (32.0%)
KFS		
50	3 (12.0%)	5 (20.0%)
60	11 (44.0%)	11 (44.0%)
70	11 (44.0%)	9 (36.0%)
Clinical presentation		
Increase intracranial tension	18 (72.0%)	20 (80.0%)
Neurological deficit	11 (44.0%)	11 (44.0%)
Seizure	6 (24.0%)	5 (20.0%)
Site		
Frontal	4 (16.0%)	5 (20.0%)
Occipital	2 (8.0%)	3 (12.0%)
Parietal	10 (40.0%)	9 (36.0%)
TemproParietal	9 (36.0%)	8 (32.0%)
Surgery	14 (56.0%)	16 (64.0%)
Complete Excision	2 (8%)	3 (12%)
Debulking	12(48%)	13 (52%)
Stertatic biopsy	8 (32%)	7 (28%)
MRS	3 (12%)	2 (8%)
Pathology		
Anaplastic astrocytoma	6 (24.0%)	5 (20.0%)
Glioblastoma multiform	19 (76.0%)	20 (80.0%)
Taking steroid baseline	20 (80.0%)	21 (84.0%)
Time from diagnosis to start radiotherapy		
Mean±SD	20.44±6.21	21.28±5.98
Range	10-35	14-35

This table showed no statistically significant difference between groups according to sex, age, KFS, clinical presentation, tumor site, surgery, pathology, steroid at baseline and time to start radiotherapy.

Progression free survival:

Table 2: showing progression free survival between group I and group II.

	Median progression free survival in month			
	Estimate PFS In months	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Group I	4.1	0.125	3.855	4.345
Group II	4.2	0.061	4.080	4.320
Overall Comparisons		Chi-Square	P value	
Log Rank (Mantel-Cox)		0.144	0.705 NS	

This table showed no statistically significant difference between the two groups.

Overall survival

Table 3: showing overall survival between group I and group II:

	Median overall survival in months			
	Estimate OS In month	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Group I	7.2	0.496	6.227	8.173
Group II	7.4	0.416	6.584	8.216
Overall Comparisons			Chi-Square	P value
Log Rank (Mantel-Cox)			1.059	0.304 NS

This table showed no statistically significant difference between groups in overall.

Table 4: showing overall survival between group I and group II in age ≥70 years:

	Median OS			
	Estimate OS in month	Std. Error	95% Confidence Interval	
			Lower Bound	Upper Bound
Group I	5.40	0.13	5.14	5.66
Group II	6.80	1.34	4.17	9.43
Overall Comparisons			Chi-Square	P value
Log Rank (Mantel-Cox)			3.942	0.047sig

This table showed statistically significant difference between the two groups in overall survival.

Table 5: comparison between the two groups according to acute toxicity:

Acute Toxicity	Group I (Conventional) (N=25)	Group II (Hypofractionation) (N=25)	x2	p-value
Increase cranial tension				
Yes	16 (64.0%)	12 (48.0%)	1.299	0.254
No	9 (36.0%)	13 (52.0%)		
Neurological deficit				
Yes	3 (12.0%)	3 (12.0%)	0.000	1.000
No	22 (88.0%)	22 (88.0%)		
Seizure				
Yes	5 (20.0%)	2 (8.0%)	1.495	0.221
No	20 (80.0%)	23 (92.0%)		

This table showed no statistically significant difference between the two groups according to acute toxicity.

DISCUSSION

Our study showed that short course has the same efficacy as conventional radiotherapy and well tolerated in older and frail patients. Our results are in accordance with previously reported randomized trials in elderly patients with glioblastoma. In a French trial which was carried out by Keime-Guibert *et al.* [7] they used radiotherapy (50 Gy in 28 fractions), compared with best supportive care, It was associated with improved median survival (7 *vs* 4 months) and retained health-related quality of life in patients older than 70 years. A Canadian trial [8] suggested no difference in outcome between patients aged 60 years or older treated with 6 weeks or 3 weeks of radiotherapy.

In our study, after analysis according to age patient ≥ 70 years old who was treated by short course radiotherapy had statistically significant better median overall survival compared to the same age group who were treated by conventional radiotherapy.

This result is in accordance with results of Malmstrom *et al.* [9] trial which proved the benefit of short course radiotherapy for patients older than 70

years and became standard of care for those populations.

Adverse events were reported for all patients in the study, Common adverse events were increased intracranial tension 16 patient in the conventional group 64% and 12 patient in hypo fractionated group 48% ,it was transient early in the course of irradiation which responded to a short term treatment course of corticosteroids. Neurological deficit was 3 patients in each arm and Seizure was 5 in conventional arm and 3 in hypofractionated arm. There is no statistically significant difference between groups according to acute toxicity.

Our result proved that hypo fractionated radiotherapy as tolerable as conventional radiotherapy in elderly and frail patients. And this result is agreed with anther randomized trial showed that short course of radiotherapy is safe in older and poor performance patients [(10).]

CONCLUSION

This study showed short course of radiotherapy has the same efficacy as standered conventional radiotherapy in older patients and frail patients and patients over 70 years short course should be the slandered of care.

REFERENCES

1. Kohler BA, Ward E, McCarthy B J *et al.*(2011): Annual report to the nation on the status of cancer. J. Nat. Cancer Inst., 103: 714–36.
2. Bergenheim T, Malmstrom A, Boland H *et al.* (2007): Registration on regional basis of patients with primary brain tumors. Regional differences disclosed. Lakartidningen, 104: 332–338.
3. Stupp R, Mason WP, van den Bent M J *et al.*(2005): Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N. Engl. J. Med., 352: 987–996.
4. Stupp R, Hegi ME, Mason WP *et al.* (2009): Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study. Lancet Oncol., 10: 459–66.
5. Fiorica F, Berretta M, Colosimo C *et al.*(2010): Glioblastoma in elderly patients: safety and efficacy of adjuvant radiotherapy with concomitant temozolomide. Arch. Gerontol. Geriatr., 51: 31–35.
6. Thomas R, James N, Guerrero D, A shley S, Gregor A and Brada M(1994): Hypofractionated radiotherapy as palliative treatment in poor prognosis patients with high grade glioma. Radiother. Oncol., 33: 113–116.
7. Keime-Guibert F, Chinot O, Taill andier L *et al.*(2007): Radiotherapy for glioblastoma in the elderly. N. Engl. J. Med., 356: 1527–1535.
8. Roa W, Brasher PM, Bauman G *et al.*(2004): Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J. Clin. Oncol., 22: 1583–1588.
9. Malmstrom A, Gronberg BH, Marosi C *et al.*(2012): Temozolomide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma. Lancet Oncol., 13(9):916-926.
10. Roa W, Kepka L, Kumar N *et al.* (2015): An International Atomic Energy Agency randomized phase III study of radiation therapy in elderly and/or frail patients with newly diagnosed glioblastoma multiforme. J. Clin. Oncol., 33:4145-4150.