Journal of Radiotherapy in Practice

cambridge.org/jrp

Hypofractioned radiotherapy versus conventional radiotherapy for the treatment of multiform glioblastoma in adults over 70 years old

Adriana Jiménez Cantero, Jessica Chávez Nogueda, Fabiola Flores Vázquez, José Pablo Castillo de la Garza, Raymundo Hernández Montes de Oca and Alejandro Olmos Guzmán

National Hospital XXI Century, Radiation Oncology Service, Instituto Mexicano del Seguro Social, Ciudad de México, México

Technical Note

Cite this article: Jiménez Cantero A, Chávez Nogueda J, Flores Vázquez F, Castillo de la Garza JP, Hernández Montes de Oca R, and Olmos Guzmán A. (2020) Hypofractioned radiotherapy versus conventional radiotherapy for the treatment of multiform glioblastoma in adults over 70 years old. *Journal of Radiotherapy in Practice* **19**: 193–196.
doi: 10.1017/S146039691900044X

Received: 3 April 2019
Revised: 21 May 2019
Accepted: 2 June 2019
First published online: 18 July 2019

Key words:
conventional radiotherapy; glioblastoma multiform; glioblastoma multiform elderly; hypofractionated radiotherapy

Author for correspondence:
Alejandro Olmos Guzmán, National Hospital XXI Century, Radiation Oncology Service, Instituto Mexicano del Seguro Social, Ciudad de México, México. E-mail: alex_olmos13@hotmail.com

Abstract

Aim: Multiform glioblastoma (MG) represents 70% of all gliomas, with half of patients older than 65 years with median survival of 12–18 months, hypofractionation seeks to reduce the intensity and duration of treatment without impacting on survival rates. The objective was to determine the global survival and recurrence-free survival of adults over 70 years old with MG treated with hypofractionated radiotherapy and standard scheme. The review of patients older than 70 years treated with radiotherapy from 2013 to 2016 was performed.
Results: Twenty-four patients were analysed, with a median follow-up of 239 days, and there is no difference in overall survival 12·3 versus 10·5 months ($p = 0{\cdot}55$) and recurrence-free survival 8·3 versus 3·4 months ($p = 0{\cdot}48$) between both schemes, conventional versus hypofractioanted, respectively.
Conclusion: The results in this study show that hypofractionated scheme could be comparable in overall survival and recurrence-free survival to conventional fractionation, but a longer patients' trial should be done.

Introduction

Multiform glioblastoma (MG) is the most frequent primary intracranial tumour in adults,[1] representing 60–70% of all gliomas.[2] The incidence of these neoplasms has increased especially in elderly patients, with half of the patients older than 65 years and 20% older than 75 years.[3,4] These patients generally present with a poor prognosis and a mean overall survival (OS) rate of 12–18·2 months[1,2,5,6] for which an aggressive multimodal approach is required, encompassing maximum resection and concomitant radiotherapy with temozolomide. Older adults have means survival from 4 to 9 months[7] and present with multiple co-morbidities and a low physiological reserve, which increases the surgical risk and they are less likely to receive aggressive treatment.

There is also the added concern regarding the toxicity of the temozolomide, so shorter courses of radiotherapy has been adopted to reduce the dose and duration of treatment to lower the possible combined toxic effects of treatment. This also reduces the number of hospital visits, when compared with the standard treatment, providing an improved quality of life in the elderly without an impact on OS rates, or disease-free survival (DFS).

Currently among the hypofractioned regimens adopted, one is tested in the Nordic study by Malmstrom et al., in which a comparison of 34 Gy in 10 fractions versus temozolomide monotherapy versus conventional radiotherapy of 60 Gy in 30 fractions, in patients older than 65 years. The findings reported an increase in survival in the hypofractionated arm and temozolomide alone with higher treatment interruption rates in the standard radiotherapy scheme.[8] In contrast the NOA-08 study by Roa et al. found survival means of 5·1 months versus 5·6 months with doses of 60 Gy in 30 fractions and 40 Gy in 15 fractions, respectively, as well as a greater possibility of completing radiotherapy treatment.[9]

Another study that promotes the use of hypofractionation is that of the International Atomic Energy Agency (IAEA) in 2015; this study compared 25 Gy in 5 fractions versus 40 Gy in 15 fractions and concluded that there is no difference in survival (average global survival of 7·9 months and 6·4 months, respectively, $p = 0{\cdot}988$) or in progression-free survival with a mean of 4·2 months in both arms.[10] This is corroborated by a phase III study by de Castro et al., in 2017, that compared the same regimens as in the IAEA study, and found no difference in the mean of overall survival (6·8 months and 6·2 months, $p = 0{\cdot}936$) or in the average

progression-free survival (4·3 and 3·2 months, $p = 0·706$) concluding that the shortened regimen is not inferior and is a good alternative, particularly in elderly patients, or for those with poor functional status or contra-indications for systemic management.[11]

In this retrospective study, we sought to describe OS and DFS in adults over 70 years of age with a diagnosis of MG who received radiotherapy, both conventional and hypofractionated in our hospital.

Materials and Methods

The study received endorsement from the research and bioethics committee of the unit. A retrospective review of the records of all patients older than 70 years diagnosed with the MG and treated in the period from 2013 to 2016 was performed. The inclusion criteria were: patients with confirmed diagnosis of MG by a histopathological report or conclusive image study, age over 70 years, patients who had received treatment with radiotherapy. Patients were assessed for functional status, according to the scale of Eastern Cooperative Oncology Group (ECOG).[12]

The OS and DFS of patients treated with the 60 Gy scheme in 30 fractions and the hypofractioned scheme 45 Gy in 15 fractions were compared. For the analysis of results, descriptive statistics were applied; using measures of central tendency, for qualitative variables frequencies and percentages were used. In the survival analysis we used the Mann–Whitney U method and Student's *t*-test according to the distribution of the sample and the respective Kaplan–Meier curves; for the analysis of qualitative variables the Chi square test was applied.

Results

From January 2013 to December 2016 there were 24 patients who met the inclusion criteria (Table 1), of whom 62·5% were women and 37·5% men; the median age was 72 years (range 70–81 years). The main comorbidity found in the sample was systemic hypertension in 37·5% of the population, followed by type 2 diabetes mellitus in 25% of the population; benign prostatic hypertrophy was found in 12·5% of the population.

The most frequent clinical manifestations in the population were headache in seven patients, hemiparesis in seven patients, memory alterations in five patients and nonspecific alterations in muscle strength in five patients. The locations of tumour presentation were the temporal lobe in 46% of the patients, followed by the frontal lobe in 29% and the parietal lobe in 21%.

A total of 83% of patients underwent subtotal resection; about 12·5% of patients were candidates only for biopsy, while one of the patients underwent macroscopically complete resection. Regardless of the extent of the resection, 71% of patients older than 70 years received standard radiotherapy treatment of 60 Gy in 30 fractions and 29% received a hypofractionated scheme of 40 Gy in 15 fractions.

In the relationship between functional status and type of treatment selected, there was a tendency to use the standard regimen in patients with ECOG equal to or less than 1 (88·2%), and only 11·6% of patients in the 60 Gy in 30 fraction regimen had a higher ECOG or equal to 2, while in the hypofractionated treatment group all patients were found to have functional status of 2 and 3 in 57 and 43%, respectively.

The median OS in the 24 patients in this study was 344 days; in patients who received hypofractionated treatment the median overall survival was 317 days; and the median OS was 370 days in those who received a standard regimen without being statistically significant ($p = 0·55$) as presented in Figure 1.

Table 1. Demographic characteristics of the population

Demographic characteristics	n(%)
Gender	
Male	15 (62·5)
Female	9 (37·5)
Age	
	Median 72 years (70–81 years)
Symptoms	
Headache	7 (29)
Hemiparesis	7 (29)
Alterations of muscle strength	5 (20·8)
Alterations in memory	5 (20·8)
Aphasia	2 (8·3)
Dysarthria	4 (16·6)
Size of the tumour	
>3 cm	24 (100)
Location	
Frontal	7 (29·2)
Temporary	11 (45·8)
Parietal	5 (20·8)
Occipital	1 (4·16)
Type of resection	
Total	1 (4·16)
Subtotal	19 (83·32)
Biopsy	3 (12·5)
Treatment scheme	
Standard scheme	17 (70·8)
Hypofractioned scheme	7 (29·2)
Adyuvant treatment	17 (70·8)
Yes	6 (25)
No	1 (4·2)

The DFS in patients who received the standard regimen was 250 days and 104 days in the hypofractionated arm. As shown in Figure 2, no statistically significant difference was found between standard and hypofractioned treatment ($p = 0·48$).

After radiotherapy treatment, it was observed that regarding the ECOG, the patients who received treatment with the hypofractioned scheme, the ECOG was maintained or improved in 42·5% of the patients and deteriorated the ECOG in 57·3%, without having statistical significance ($p = 0·147$), while in the standard fractionation 17·6% of patients maintained their ECOG and 82·3% showed deterioration of their general conditions, being statistically significant ($p = 0·002$); however, when comparing the final functional status of both radiotherapy schemes, there was no statistical significance ($p = 0·272$).

https://doi.org/10.1017/S146039691900044X Published online by Cambridge University Press

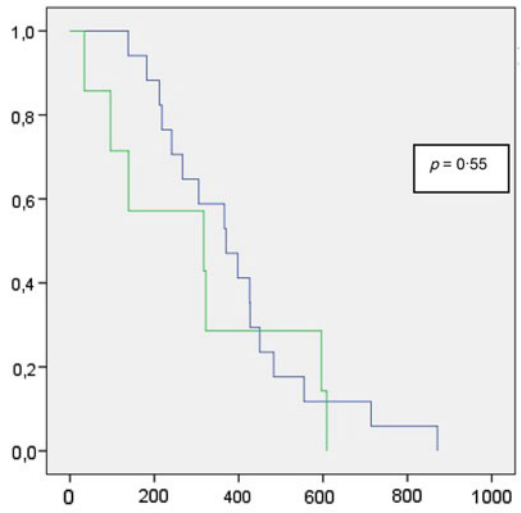

Figure 1. Kaplan–Meier curve OS for the standard scheme and the hypofractioned one.

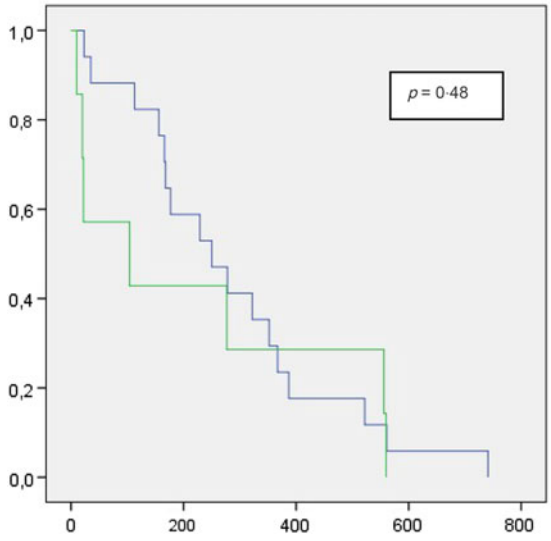

Figure 2. Kaplan–Meier curve DFS for the standard scheme and the hypofractioned one.

Discussion

In the analysed sample, the number of patients undergoing subtotal resection was 83% and 12% for biopsy, with percentages significantly higher than reported in several international studies where the percentage of subtotal resection is 23–52 and 42% and 66% for biopsy.[9,13] Currently shortened fractionations are comparable in disease control and survival to conventional schemes. In the present study, it was observed that patients with functional status higher than 2 on the ECOG scale were included in the hypofractionated treatment and those with ECOG less than 2 were chosen to the conventional scheme.

During the follow-up of the patients, it was found that in the arm of the standard fractionation they present greater deterioration using the ECOG and quality of life scale, found in 82·3% of the patients (p = 0·002); therefore, the longer treatment worsens the quality of the life of the patient.

One of the objectives of this study was to report on OS in elderly population of 70 years treated with both radiotherapy regimens, finding a median survival of 10·42 months for hypofractionation and 12·16 months for the standard scheme (p = 0·55), which agrees with what is reported worldwide.[8–17]

The median DFS in the hypofraction arm was of 3·41 months and 8·21 months for the standard treatment fractionation (p = 0·48); these results agree with the different studies published. In a range of 4·2–6·3 months and 4·2–8·2 months, respectively.[14,16,18]

Although this was a retrospective study and included a relatively small sample of patients, it opens the door to new research questions. Authors suggest prospective studies to research the effects of adding temozolomide to the hypofractioned regimen, in order to determine its impact on survival and adverse effects in patients older than 70 years, using a detailed analysis of their functional status during and after treatment.

Conclusions

In this study we found that the use of hypofractionation radiotherapy had been prescribed in 29% of patients with MG over the age of 70 years, treated in our radiotherapy unit from 2013 to 2016.

We found no significant statistical difference in OS and DFS in the conventional or hypofractionated radiotherapy treatment.

The therapeutic decision must be considered and made by a multidisciplinary team because there is the opportunity to adopt the hypofractionated regimen in order to reduce hospital visits and treatment time, benefiting both the patient and the health service.

Author ORCIDs. Alejandro Olmos Guzmán 0000-0002-8237-4166

Acknowledgements. To the Radiotherapy service of the National Medical Center XXI Century, to the Radiotherapy service of the National Medical Center Bajio of the Mexican Social Security Institute.

References

1. Almeida J P, Chaichana K L, Rincon-Torroella J, Quiñones-Hinojosa A. The value of extent of glioblastoma: clinical evidence and current approach. Curr Neurol Neurosci Rep 2015; 517 (15): 1–13.
2. Wen P Y, Kesari S. Malignant gliomas in adults. N Engl J Med 2008; 359: 492–505.
3. Sulman E P, Ismaila N, Armstrong T S et al. Radiation therapy for glioblastoma: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Guideline. J Clin Oncol 2016; 34: 1–8.
4. Huang J, Samson P, Perkins S M et al. Impact of concurrent chemotherapy with radiation therapy for elderly patients with newly diagnosed glioblastoma: a review of the National Cancer Data Base. J Neurooncol 2017; 131 (3): 593–601.
5. Stupp R, Mason W P, van den Bent K J et al. Radiotherapy plus concomitant and adyuvant temozolamide for glioblastoma. N Engl J Med 2005; 352: 987–996.
6. Alifieris C, Trafalis T D. Glioblastoma multiforme: pathogenesis and treatment. Pharmacol Ther 2015; 152: 63–82.
7. Babu R, Komisarow J M, Agarwal V J, et. al. Glioblastoma in the elderly: the effect of aggressive and modern therapies on survival. J Neurosurg 2016; 124: 998–1006.
8. Malmstrom A, Gronberg B H, Marosi C et al. Temozolamide versus standard 6-week radiotherapy versus hypofractionated radiotherapy in patients older than 60 years with glioblastoma: the Nordic randomised, phase 3 trial. Lancet Oncol 2012; 13: 916–926.

https://doi.org/10.1017/S146039691900044X Published online by Cambridge University Press

9. Roa W, Brasher P M A, Bauman G et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: a prospective randomized clinical trial. J Clin Oncol 2003; 22: 1583–1588.
10. Roa W, Kepka L, Kumar N et al. 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 2015; 33: 4145–4159.
11. de Castro D G, Matiello J, Roa W et al. Survival outcomes with short course radiotherapy in elderly patients with glioblastoma: data from a randomized phase III trial. Int J Radiat Oncol Biol Phys 2017; 98 (4): 931–938.
12. Oken M M, Creech R H, Tormey D C et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5: 649–655.
13. Bracci S, Laigle-Donadey F, Hitchcock K et al. Role of irradiation for patients over 80 years old with glioblastoma: a retrospective cohort study. J Neurooncol 2016; 129: 347–353.
14. Keime-Guibert F, Chinot O, Taillandier L et al. Radiotherapy for glioblastoma in the elderly. N Engl J Med 2007; 356: 1527–1535.
15. Roa W, Xing J, Small C et al. Current developments in the radiotherapy approach to elderly and frail patients with glioblastoma multiforme. Expert Rev Anticancer Ther 2009; 9 (11): 1643–1650.
16. Minniti G, DeSanctis V, Muni R et al. Hypofractioned radiotherapy followed by adjuvant chemotherapy with temozolomide in elderly patients with glioblastoma. J Neurooncol 2009; 91 (1): 95–100.
17. Arvold N D, Tanguturi S K, Aizer A A et al. Hypofractionated versus standard radiation therapy with or without temozolomide for older glioblastoma patients. Int J Radiation Oncol Biol Phys 2015; 92 (2): 384–389.
18. Minniti G, Scaringi C, Lanzetta G et al. Standard (60 Gy) or short-course (40 Gy) irradiation plus concomitant and adjuvant temozolomide for elderly patients with glioblastoma: a propensity-matched analysis. Int J Radiation Oncol Biol Phys 2015; 91 (1): 109–115.

https://doi.org/10.1017/S146039691900044X Published online by Cambridge University Press