International Journal of Advances in Medicine
Ulrich J et al. Int J Adv Med. 2021 Dec;8(12):1792-1798
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20214513

Original Research Article

From 65 to 70 years old: what is the best approach in the treatment of glioblastoma?

João Ulrich*, Diogo Delgado, André Figueiredo, Miguel Simas, Maria Eduarda Neves, Joana Pisco, Manuel Carmo da Silva, André Abrunhosa-Branquinho, Ana Amado, Maria Filomena de Pina

Department of Radiotherapy, Centro Hospitalar Universitário Lisboa Norte, Lisbon, Portugal

Received: 04 November 2021
Accepted: 20 November 2021

***Correspondence:**
Dr. João Ulrich,
E-mail: joaohvulrich@gmail.com

ABSTRACT

Background: Glioblastoma (GBM) is the most common primary CNS tumor in adults. Between 65-70 years of age, treatment involves the best possible surgical removal followed by radiotherapy (RT), with or without temozolomide (TMZ). After assessing whether patients can tolerate TMZ, doubts regarding RT regimens persist in this age group. This study aimed to compare the overall survival (OS) in GBM patients aged 65-70 years, in two RT regimens with TMZ: Stupp (RT 60 Gy/30 fractions (fx)+TMZ) versus mini-Stupp (RT 40.05 Gy/15 fx+TMZ) and 2 regimens of RT without TMZ: 40 Gy/15 fx versus 25 Gy/5 fx.
Methods: All GBM patients, 65-70 years, undergoing RT from 1 January 2014 to 31 December 2020 were retrieved and retrospectively evaluated. Patients were divided into 4 groups: group 1 was Stupp; group 2 was mini-Stupp; group 3 was 40,05 Gy/15 fx without TMZ; and group4 was 25 Gy/5 fx without TMZ.
Results: Sixty patients were retrieved with median follow up of 12 months. In the analysis of groups 1 and 2, all variables were comparable ($0.21<p<0.6$). Median OS was 18 and 15 months, respectively, with no statistically significant difference ($p=0.13$). The OS at 2 years was 26% and 21% respectively, decreasing to 13% and 0% at 3 years. Analyzing groups 3 and 4, all variables were comparable ($0.06<p<0.88$). OS had no difference ($p=0.5$) with 7 months of median OS for both groups.
Conclusions: From 65-70 years, if CHT is not viable, the 25 Gy/5 fx should be the standard. When CHT is possible, mini-Stupp appears to be equivalent to Stupp.

Keywords: Glioblastoma, Radiotherapy, Elderly, Stupp, Temozolomide

INTRODUCTION

GBM is the most common primary CNS tumor in adults.[1] Survival is inversely associated with age: 5% of all patients diagnosed with GBM are alive after 5 years and this measure decreases to 2% among patients aged 65 years or older.[2] Glioblastoma accounts for 82% of cases of all malignant glioma.[1]

Most gliomas occur in the frontal (25.8%), temporal (19.7%) and parietal (12.2%) lobes, whereas occipital-lobe (3.2%) and cerebellar (2.9%) gliomas are more rare.[1] Brainstem gliomas are also rare in adults.[3] Survival of patients with frontal-lobe GBMs was longer compared to patients with temporal or parietal lobe GBM median overall survival, 11.4 versus 9.1 versus 9.6 months, log rank ($p=0.01$) in a COHORT of 645 adults who were treated within three consecutive trials of the radiation therapy oncology group (RTOG) in the pre-TMZ era.[4]

Headaches are relatively frequent, present in about 50% of patients at diagnosis, but usually with a nonspecific pain

pattern.[5] Cognitive difficulties and personality changes may develop. Gait imbalance and incontinence may be present. Focal signs such as hemiparesis, sensory loss or visual field disturbances are common and reflect tumor location. Language difficulties may be mistaken for confusion or delirium. Seizures are the presenting manifestation in about 20% to 40% of patients and usually a focal onset is reported.[6]

Treatment involves symptomatic control and the best possible surgical removal followed by RT, with or without TMZ.[7] TMZ alone is a noninferior option compared to standard RT in elderly patients and may be preferred over standard RT alone in patients with MGMT promoter methylation.[8] Use of TMZ alone or hypo fractionated RT should be considered standard in the elderly population, especially if over age 70.[9] Since patients with ECOG-PS performance status (ECOG-PS-PS) for treatment with TMZ can also comply with RT, combined adjuvant therapy is the preferred option leaving TMZ in monotherapy as an alternative only for patients who refuse RT.[7]

Therapeutic paradigm

Surgery-improved OS with ≥98% resection in better prognostic patients (young, good ECOG-PS, no MRI evidence of necrosis). It also limited chance of cerebral edema during RT.[10]

Chemotherapy-improved OS in the adjuvant setting but due to its toxicity it was limited to selected patients and was especially effective in patients with MGMT promoter methylation.[11]

Radiotherapy-adjuvant RT improved OS versus observation or CHT alone after surgery and was indicated to all patients with sufficient functional status to tolerate treatment. Dose escalation was beneficial to 60 Gy/30 fx but there was no benefit to escalating even further.[12-14]

Before the TMZ era, Roa et al demonstrated no difference in survival between patients ≥60 years receiving standard RT (60 Gy/30 fx) or short-course (SC)-RT (40,05 Gy/15 fx). The short-course showed even less use of corticosteroid therapy and fewer treatment interruptions demonstrating to be a reasonable treatment option for older and frail patients with GBM.[15]

In 2015, after the role of TMZ was established, the same author compared 40,05 Gy/15 fx versus 25 Gy/5 fx in elderly and/or frail patients unable to tolerate CHT. There were no differences in OS, progression-free survival and quality of life between patients receiving the two radiotherapy regimens.[16] Despite the results of this study, in patients not undergoing chemotherapy, longer regimens were still used than the 25 Gy/5 fx.

The Stupp protocol published in 2005, established RT 60 Gy/30 fx+concomitant and adjuvant TMZ as gold standard in patients ≤70 years and ECOG-PS ≤2.[17] In 2017, Perry et al confirmed that adding TMZ to SC-RT (40,05 Gy/15 fx) in patients ≥65 years translated into increased OS and progression-free survival (PFS).[18]

The two studies above left us with the dilemma of which was the best approach for patients in the intermediate age group (65-70 years) when administering TMZ, Stupp or mini-Stupp as we authors referred to the SC-RT+TMZ (Figure 1). After assessing whether patients can tolerate TMZ, doubts regarding RT regimens persist in patients from 65-70 years old.

This study aimed to compare the OS in two RT regimens with TMZ: Stupp (RT 60 Gy/30 fx+TMZ) versus mini-Stupp (RT 40.05 Gy/15 fx+TMZ) and 2 regimens of RT without TMZ: 40 Gy/15 fx versus 25 Gy/5 fx in GBM patients aged 65-70 years.

METHODS

This was a single centre retrospective non interventional study, carried out in Centro Hospitalar Universitário Lisboa Norte, in Lisbon, Portugal. Clinical charts of all the GBM patients, 65-70 years old, undergoing RT from 1 January 2014 to 31 December 2020 were selected and retrospectively evaluated.

The variables collected in a database were year of birth; gender (male/female); location of tumor; therapeutic intervention for each patient; ECOG-PS; age; tumor resection extension, date of diagnosis, date of ending of RT, date of death (if applicable).

Patients were divided into 4 groups: group 1 was Stupp (RT 60 Gy/30 fx+TMZ according to Stupp et al; group 2 was mini-Stupp (RT 40.05 Gy/15 fx+TMZ according to Perry et al; group 3 was 40,05 Gy/15 fx without TMZ; and group 4 was 25 Gy/5 fx without TMZ.[17,18]

RT was delivered to the gross tumor volume with a 2 cm margin for the clinical target volume. RT was planned with dedicated computed tomography and the techniques used were 3D conformal radiation therapy or intensity-modulated radiation therapy.

Data was analysed using IBM SPSS Statistics 23®. Comparisons were made using Chi square, Fisher´s exact test and cox regression. Kaplan-Meier curves were used to calculate survival.

RESULTS

Between 1 January 2014 and 31 December 2020 sixty patients were selected and all were considered for statistical analysis. The median follow up was 12 months. Demographic and clinical characteristics of the study population are shown in Table 1.

Median age at diagnosis was 67.3 years old. The majority of patients were male (n=37, 61.7%). The majority of patients had an ECOG-PS ≤1 (n=45, 75%). The average duration of treatment until the end of RT was 80.3 days (51-96 days). The most common location of tumors was in the temporal lobe (17, 28%), followed by the frontal (14, 23%), parietal (8, 13%), occipital (7, 12%) and other locations (14, 23%). In the other locations, tumors occupying ≥2 brain lobes were included. The distribution of the number of patients by groups was: group 1, 31 (52%) patients; group 2, 13 (22%) patients; group 3, 9 (14%) patients; group 4, 7 (12%) patients. Four (6.7%) patients had performed MGMT methylation analysis.

Figure 2 shows the Kaplan-Meier curves for overall survival for patients with tumors in the location of a single brain lobe. Median OS ranged from 11 to 20 months, corresponding to the occipital and temporal lobe respectively, with no statistically significant difference (Log-Rank p=0.051).

When evaluating patients receiving TMZ versus patients that did not (groups 1 and 2 versus groups 3 and 4), these groups were not comparable in ECOG-PS, age or tumor resection extension (p=0.01, p=0.01 and p≤0.003, respectively) and the groups not subject to TMZ had the worst values in these 3 variables.

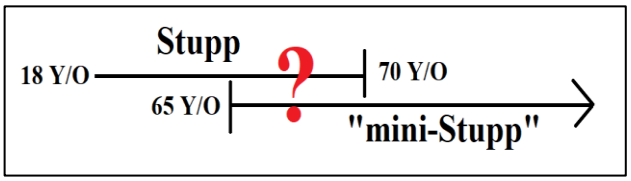

Figure 1: Graphical representation of the dilemma.

Table 1: Clinical variables of patients included.

Variables	Group 1	Group 2	P value	Group 3	Group 4	P value	Total
Sex							
Female	9	5		7	2		23
Male	22	8	0.54	2	5	0.06	37
Total	31	13		9	7		60
ECOG-PS							
0	17	3		1	1		22
1	8	7	0.21	5	3	0.88	23
2	3	2		3	3		11
Total	28	12		9	7		56
Tumor resection extension							
No histology*	1	2		1	1		5
Biopsy	5	3	0.26	5	3	0.88	16
Total resection	25	8		3	3		39
Total	31	13		9	7		60
Average time from diagnosis to the end of RT	51 days	75 days	P=0, 21	64 days	96 days	P=0, 38	
Location of the tumor							
Frontal	6	3		3	2		14
Fronto-temporal	1	-		1	2		4
Occipital	4	2		-	1		7
Parietal	5	3		-	-		8
Parieto-occipital	1	-		1	-		2
Temporal	10	5	0.21	1	1	0.38	17
Temporo-occipital	-	-		2	-		2
Temporo-parietal	1	-		-	-		2
Cerebellum	1	-		-	-		1
Multifocal	-	-		-	1		1
Septum pellucidum	-	-		1			1
Total	31	13		9	7		60

*Imaging diagnosis.

OS was compared between patients treated with Stupp protocol (group 1) and patients diagnosed treated with mini-Stupp protocol (group 2). These groups were comparable for gender, ECOG-PS, tumor resection extension and time of treatment (p=0.54, p=0.21, p=0.26

and p=0.21, respectively). Figure 3 shows the Kaplan-Meier curves for overall survival in these two groups. Median OS was 18 and 15 months, respectively, with no statistically significant difference (Log-Rank p=0.13). The OS at 2 years was 26% and 21% respectively, decreasing to 13% and 0% at 3 years.

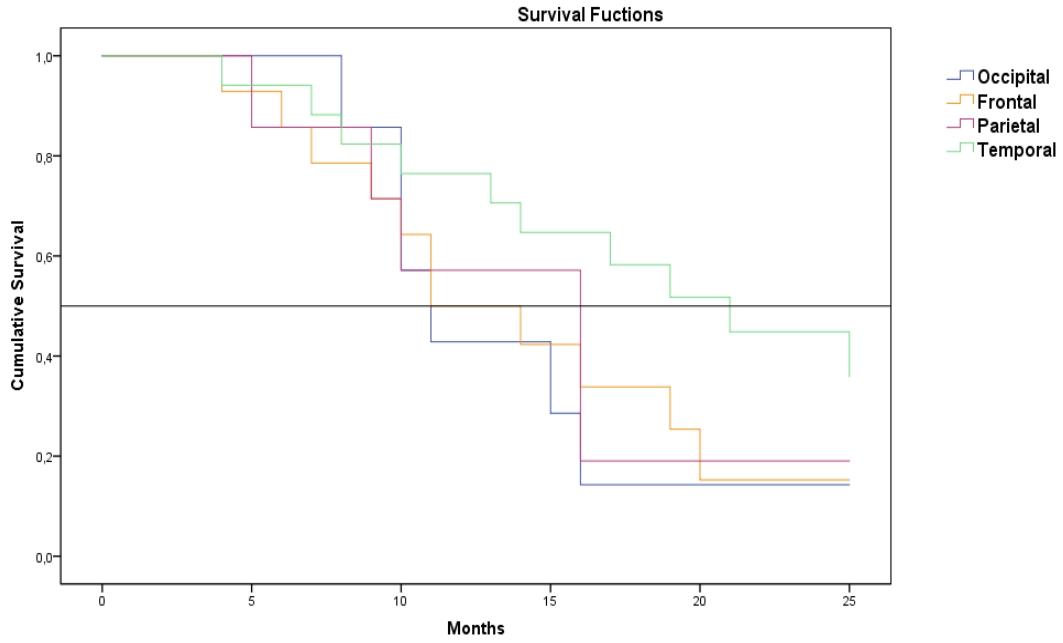

Figure 2: Kaplan-Meier curves for overall survival for patients with GBM in different locations.

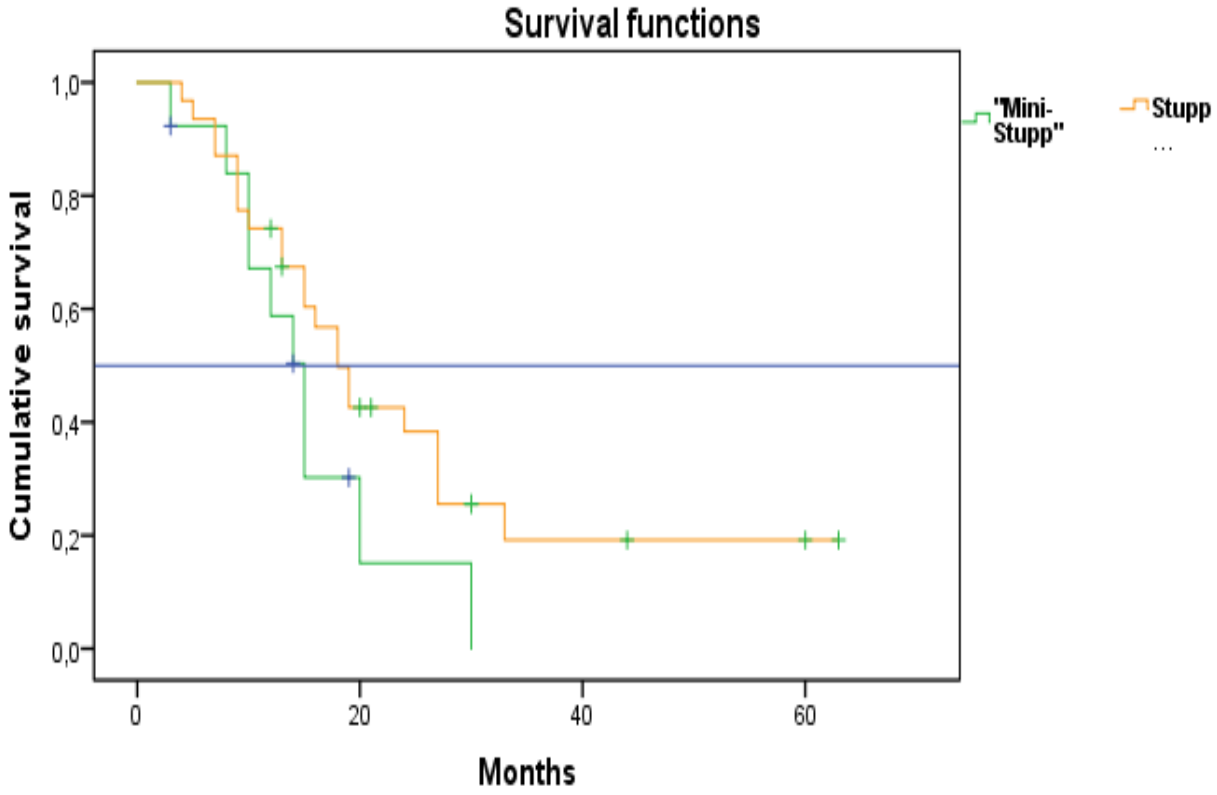

Figure 3: Kaplan-Meier curves for overall survival for patients with TMZ treatment.

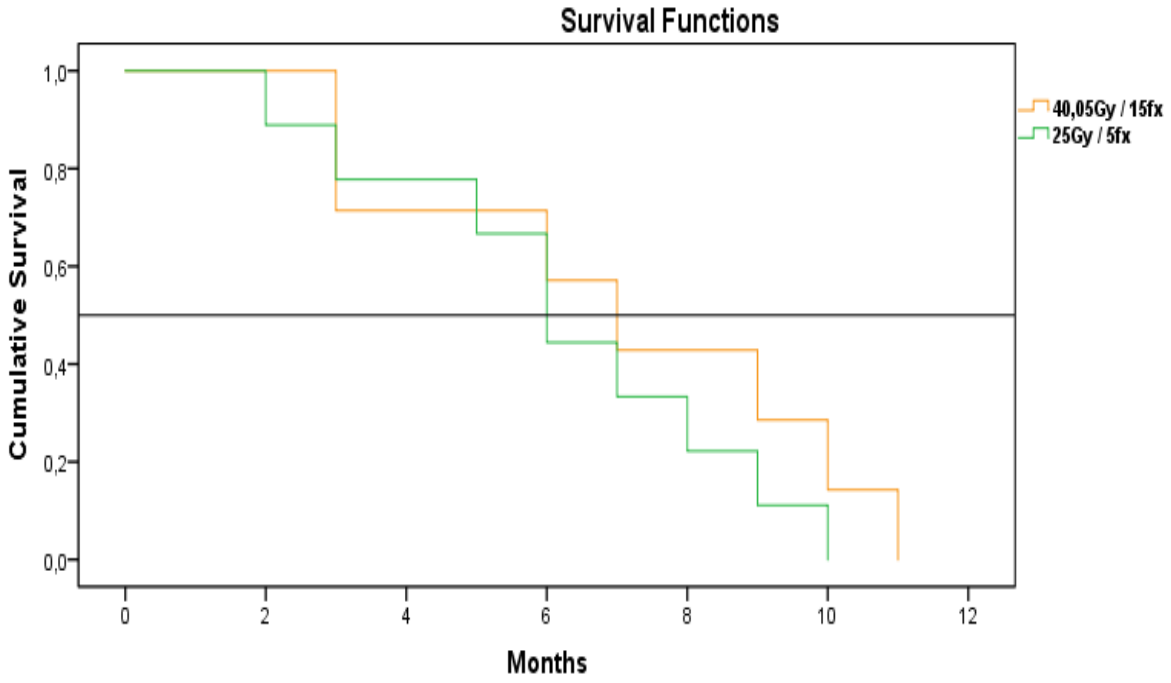

Figure 4: Kaplan-Meier curves for overall survival for patients without TMZ treatment.

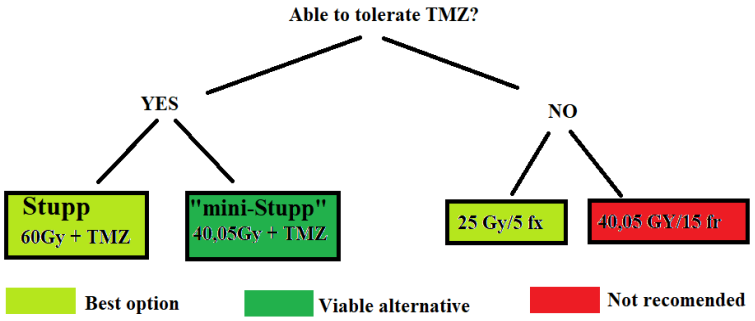

Figure 5: Conclusion's diagram.

Patients treated without TMZ were also analysed. Overall survival was compared between patients treated with 40.05 Gy/15 fx without TMZ (group 3) and patients diagnosed treated with 25 Gy/5 fx without TMZ (group 4). These groups were comparable for gender, ECOG-PS, tumor resection extension and time of treatment (p=0.06, p=0.88, p=0.88 and p=0.38, respectively). Figure 4 shows the Kaplan-Meier curves for overall survival for this two groups. Median OS was 7 months, for both groups, with no statistically significant difference (Log-Rank p=0.5).

Cox regression showed an increased risk of death associated with a worse ECOG PS, Hazard ratio of 3.03 (p=0.003) and a decreased risk of death associated with a best tumor resection extension, Hazard ratio of 0.514 (p=0.028). There was a direct correlation between the tumor resection extension and the ECOG-PS (p=0.04).

DISCUSSION

Contrary to what was found in the literature, most patients had GBM in the temporal lobe and there were no statistically significant differences in OS for the different locations.[1,4] A trend towards higher OS in the temporal location and lower in the occipital location was noted.

As expected, ECOG-PS and the tumor resection extension were prognostic factors for OS in GBM patients aged between 65 and 70 years.[2] At our center, a correlation between ECOG-PS and the tumor resection extension was highlighted, which translated into a proportional surgical

investment dependent on ECOG-PS, leaving in doubt which was the main prognostic factor in this case, ECOG-PS or tumor resection extension.

Patients with worse ECOG-PS and a lower tumor resection extension were not candidates for TMZ, which demonstrated these factors as decisive for the choice of treatment.

Patients who were not candidates for CHT, 25 Gy/5 fx should be the standard, as had already been shown by the study by Roa et al so the 40.05 Gy/15 fx scheme in monotherapy should not be used.[16]

In CHT candidates aged between 65-70 years, mini-Stupp can be seen as a therapeutic option and the decision regarding the Stupp versus mini-Stupp must be made in a multidisciplinary meeting. The Stupp protocol must remain the gold standard, not forgetting that although there was no statistically significant difference, there was an OS trend favouring it.

The Stupp protocol was made standard with an OS difference of 2.5 months, which was statistically significant in favor of adding TMZ to RT.[17] Our study, with the limitation of being a retrospective study and having a small population, showed a 3 month survival difference between the two treatment groups. Those limitations may explain the non-statistical significance in the 3 month difference between the two arms. Another significant limitation was the absence of MGMT methylation status in most of our patients.

More studies were needed in this age group, with a larger number of patients, especially comparing the two available radiotherapy schemes in order to define with one was the best. Currently, it was essential to evaluate MGMT methylation, which had already been proven to be prognostic and predict response to TMZ therapy.[19] However, of the 60 patients evaluated, only 4 had this research, which made a statistical analysis impossible.

CONCLUSION

With the findings of our study, we proposed a treatment protocol recommendation for patients between the ages of 65 and 70 (Figure 5). In conclusion, for patients with no indication for adjuvant CHT, shorter fractionation appears to be equivalent to longer radiotherapy treatment. As for patients able to tolerate TMZ we propose that both radiotherapy regimens appear to be equivalent, making the mini-Stupp a viable alternative with advantages in terms of convenience for the patient and for the radiotherapy department.

ACKNOWLEDGEMENTS

The authors would like to thank the support that was given by all of the staff from the radiotherapy department.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Dolecek TA, Propp JM, Stroup NE, Kruchko C. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2005-2009. Neuro Oncol. 2012;14(5):1-49.
2. Ostrom QT, Bauchet L, Davis FG, Deltour I, Fisher JL, Langer CE, et al. The epidemiology of glioma in adults: a “state of the science” review. Neuro Oncol. 2014;16(7):896-913.
3. Ostrom QT, Gittleman H, Fulop J, Liu M, Blanda R, Kromer C, et al. CBTRUS statistical report: primary brain and central nervous system tumors diagnosed in the United States in 2008-2012. Neuro Oncol. 2015;17(4):1-62.
4. Simpson JR, Horton J, Scott C, Curran WJ, Rubin P, Fischbach J, et al. Influence of location and extent of surgical resection on survival of patients with glioblastoma multiforme: results of three consecutive radiation therapy oncology group (RTOG) clinical trials. Int J Radiat Oncol Biol Phys. 1993;26(2):239-44.
5. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. Neurology. 1993;43(9):1678-83.
6. Glantz MJ, Cole BF, Forsyth PA, Recht LD, Wen PY, Chamberlain MC, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the quality standards subcommittee of the American academy of neurology. Neurology. 2000;54(10):1886-93.
7. National Comprehensive Cancer Network. Fact sheet: Central nervous system cancer NCCN guidelines. Available at: https://www.google.com/search?q=central+nervous+system+cancer+nccn+guidelines&rlz=1C1CHBD_pt-PTPT864PT864&oq=central+nervous+system+cancer+nccn+guidelines&aqs=chrome..69i57j0i512l4j0i22i30l5.11118j0j7&sourceid=chrome&ie=UTF-8. Accessed on 17 September 2021.
8. Wick W, Platten M, Meisner C, Felsberg J, Tabatabai G, Simon M, et al. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol. 2012;13(7):707-15.
9. Malmström A, Grønberg BH, Marosi C, Stupp R, Frappaz D, Schultz H, et al. Temozolomide 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(9):916-26.
10. Lacroix M, Abi-Said D, Fourney DR, Gokaslan ZL, Shi W, DeMonte F, et al. A multivariate analysis of 416 patients with glioblastoma multiforme:

prognosis, extent of resection, and survival. J Neurosurg. 2001;95(2):190-8.
11. Ward MC, Tendulkar RD, Videtic GMM. Essentials of clinical radiation oncology. 1st ed. Springer Publishing Co.; 2017.
12. Walker MD, Alexander E, Hunt WE, MacCarty CS, Mahaley MS, Mealey J, et al. Evaluation of BCNU and/or radiotherapy in the treatment of anaplastic gliomas: a cooperative clinical trial. J Neurosurg. 1978;49(3):333-43.
13. Kristiansen K, Hagen S, Kollevold T, Torvik A, Holme I, Stat M, et al. Combined modality therapy of operated astrocytomas grade 111 and iv. confirmation of the value of postoperative irradiation and lack of potentiation of bleomycin on survival time: a prospective multicenter trial of the Scandinavian glioblastoma study group. Cancer. 1981;47(4):649-52.
14. Chan JL, Lee SW, Fraass BA, Normolle DP, Greenberg HS, Junck LR, et al. Survival and failure patterns of high-grade gliomas after three-dimensional conformal radiotherapy. J Clin Oncol. 2002;20(6):1635-42.
15. Roa W, Brasher PMA, Bauman G, Anthes M, Bruera E, Chan A, et al. Abbreviated course of radiation therapy in older patients with glioblastoma multiforme: A prospective randomized clinical trial. J Clin Oncol. 2004;22(9):1583-8.
16. Roa W, Kepka L, Kumar N, Sinaika V, Matiello J, Lomidze D, 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(35):4145-50.
17. Stupp R, Mason WP, Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med. 2005;352(10):987-96.
18. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-course radiation plus temozolomide in elderly patients with glioblastoma. N Engl J Med. 2017;376(11):1027-37.
19. Hegi ME, Diserens AC, Gorlia T, Hamou F, de Tribolet N, Weller M, et al. MGMT gene silencing and benefit from temozolomide in glioblastoma . N Engl J Med. 2005;352(10):997-1003.

Cite this article as: Ulrich J, Delgado D, Figueiredo A, Simas M, Neves ME, Pisco J, et al. From 65 to 70 years old: what is the best approach in the treatment of glioblastoma? Int J Adv Med 2021;8:1792-8.