Temozolamide as an adjuvant in glioblastoma. How long?

The experience of a cancer center in Colombia

CARLOS RAÚL VILLEGAS-MEJÍA, MANUEL VILLEGAS-JARAMILLO, PEDRO VILLEGAS-JARAMILLO
• MANIZALES (COLOMBIA)

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Abstract

Introduction: glioblastoma multiforme is considered to be highly lethal, for which the optimal duration of adjuvant temozolamide chemotherapy has not been determined.

Objective: to evaluate survival according to the length of adjuvant chemotherapy based on the standard Stupp platform protocol.

Materials and methods: a retrospective cohort analysis of 299 high-grade central nervous system tumors seen at Oncólogos del Occidente, focused solely on glioblastoma multiforme, according to clinical, treatment and outcome variables.

Results: one hundred ninety-three patients with glioblastoma; 84 (44%) received standard Stupp platform treatment; mean age 54 years; 55% males; mean tumor size 28,793 mm^2; 48% right hemisphere; 21% crossed the midline; 33% had seizures and 42% neurological deficit; 55% Karnofsky less than 70% and 66% RPA IV classification; 77% received radiation with 60.00 Gy or more; 19% had complications; 79% partial resection and 12% total resection; 77% relapsed; at closure, 57% were alive, global survival of 26% and mean of 26 months, with a difference of 31 months for adjuvance of <or> 6 months and 30 months for adjuvance of <or> 12 months, without reaching a median in the 18 and 24 month groups, all of them favoring the group with the longest time.

Conclusion: a clear increase in survival is shown with adjuvant temozolamide for periods longer than six months, as well as a tendency towards better results with increased duration of adjuvance. **(Acta Med Colomb 2020; 45. DOI: https://doi.org/10.36104/amc.2020.1325).**

Key words: *central nervous system, tumor, glioblastoma, treatment, adjuvant chemotherapy, concomitance, survival.*

Dr. Carlos Raúl Villegas-Mejía: Oncólogo Clínico y Radioterapeuta. Servicio de Oncología y GrupLAC "Oncólogos del Occidente SAS"; Manuel Villegas-Jaramillo y Pedro Villegas-Jaramillo: Estudiantes de Medicina Universidad de Manizales, Facultad de Salud, Escuela de Medicina. Manizales (Colombia).
Correspondencia: Dr. Carlos Raúl Villegas-Mejía. Manizales (Colombia).
E- mail: caravim@hotmail.com
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Introduction

Central nervous system (CNS) tumors are a rare group of lesions which are on the rise. In 2016, the World Health Organization (WHO) published an updated classification of CNS tumors, integrating the phenotype with the genotype according to the IDH gene mutation and 1p/19q deletion to define malignant tumors as grade III anaplastic astrocytomas (AA) and oligodendrogliomas (OligoDA) or anaplastic oligoastrocytomas (OligoAA), and, finally, grade IV glioblastoma multiforme or glioblastoma (GBM) astrocytomas, with the latter being the most common form, which is rapidly progressive and has a low probability of cure, with rates close to 12 months (1).

Historically, the treatment of brain tumors has been based on the previous classification, and, specifically for GBM, has consisted in surgery (Sx), attempting to resect the greatest percentage of tumor possible, while at the same time preserving the best functional status. Later, work was begun with a combination of Sx, radiation therapy (RT) and chemotherapy (CT), seeking to improve outcomes, as shown by Stewart et al. in 2002, with their meta-analysis of 12 randomized studies suggesting a small survival benefit in the CT and RT group compared to RT alone (5% improvement at two years) (2).

Subsequently, and specifically in the last few years, treatment has been based on Sx and concomitant chemotherapy/radiation therapy (CT/RT) using temozolamide, an alkylating agent with antitumor activity for the treatment of gliomas, ultimately tailoring the treatment to regimens based on adjuvancy with temozolamide (Sx+CT/RT+CT) (3). This has shown improved median survival and two-year survival (4-8), although randomized studies have not yet been able to clearly determine the length of adjuvant treatment which produces the best long-term results, both in global survival and disease-free survival without detrimental effects on the

patients' general condition, as well as without secondary complications over time.

In the Eje Cafetero [coffee growing] region of Colombia (Caldas, Risaralda and Quindío), the treatment regimen known as the Stupp platform has been used, based on the current recommendations in the literature (4), without having ascertained the impact (in terms of efficacy and improved survival and relapse-free periods) of longer temozolamide adjuvancy compared to the initial and standard adjuvant treatment of six months.

This leads us to propose the main objective: to first determine the therapeutic result of glioblastoma treatment using the standard multimodal Stupp platform based on temozolamide (Sx+CT/RT+CT), in our area of influence; and, with these results, to determine the ideal length of adjuvancy to ensure the greatest survival compared to the national and international Stupp standard of six months.

Materials and methods

Through an analysis of the database of patients seen at Oncólogos del Occidente in the departments of Caldas, Risaralda, Quindío and Norte del Valle, 386 patients with CNS tumors were found from January 2001 to December 2016. Eight patients with a histological diagnosis prior to 2001 were excluded; of the remaining 378 patients, 79 (21%) had low grade tumors. Of the 299 high-grade patients, 271 (91%) had GBM + AA and 9% had OligoAA +OligoDA. Of these 271 patients, 71% (n=193) had GBM, 44% (84 patients) of whom received the standard treatment of Sx+CT/RT+adjuvant CT, known as the Stupp platform (4), thus making up our main analysis group. The remaining 56% received other treatments based on monotherapy or combinations of Sx, CT or RT.

The variables were grouped according to clinical and epidemiological characteristics, interventions performed, and results obtained. Age was grouped according to the, beginning with groups under 45 years of age and continuing by decades up to those over the age of 85. A second grouping was made of those under and over 65 years of age, and a third grouping from 18 to 44 years, 45 to 59 years, 60 to 74 years, and over 75 years (7).

Demographic (age, sex, occupation, geographic zone, city of origin), clinical (convulsions at onset, duration of the symptoms, neurological deficit on admission, prior symptoms and Karnofsky status), anatomical (tumor size, location and side of the brain) and treatment (type of treatment, length of RT and dose of RT) variables were gathered. Additionally, the Recursive Partitioning Analysis (RPA) classification of the Radiation Therapy Oncology Group was used, which employs clinical, anatomical, demographic and functional parameters such as the Mini-Mental State Examination (MMSE); *along with the O6-methylguanine-methyltransferase (MGMT) promoter methylation status (4, 9).*

Treatment was administered using the Stupp platform of Sx+CT/RT+adjuvant CT, based on which all of the control variables were analyzed. The surgical component was described by the neurosurgeon and corroborated by postsurgical radiological studies as unoperated, biopsy, partial resection or complete resection, and, in this last category, as defined by the neurosurgeon or radiological studies, according to the SEER and DeAngelis classifications

Recurrence was documented by clinical, imaging or pathology data, also recording whether there were histological changes or a migration towards more aggressive forms. Persistence was defined as a recurrence within the 12 months following the first treatment.

Follow up was taken to be the time elapsed in months between the treatment and the last follow-up appointment recorded in the patient's chart, or the study´s close. Survival was defined as the time elapsed between the date of diagnosis and the final follow-up appointment, with data collection completed and the study closed on December 31, 2016.

Qualitative variables were analyzed using proportions, and quantitative variables using averages and standard deviation. The Kaplan-Meier method and log-rank test were used for survival. EpiInfo™ and SPSS version 14.5 programs were employed.

Ethical aspects

The project was approved by the medical director and research department of Oncólogos del Occidente, and permission was given for the institution's name to appear in the publication of results. Since there is no therapeutic intervention other than the accepted treatment for these patients, nor specific external patient information, it is considered to be a no-risk study according to Article 11 of Resolution 8430 of 1993 emitted by the Health Ministry of Colombia. We also adhered to the International Conference on Harmonisation (ICH) harmonized tripartite Good Clinical Practice (GCP) guideline, the Declaration of Helsinki (64th General Assembly, Fortaleza, Brazil, October 2013), and the current regulations on health research (Resolution 8430 of 1993).

Results

Eighty-four patients were treated with the standard multimodal regimen of Sx+CT/RT+adjuvant CT (Stupp platform). The mean age was 54.8 years, 83% were under the age of 65, 55% were males, 41% were homemakers, and 93% were urban. The mean tumor size was 28.79 mm^2, with 23 located in the parietal lobe and 36% having anatomical combinations, 36% of which were temporal-parietal; 48% were on the right side, and 21% crossed the midline. Thirty-three percent of the patients had had prior convulsions with a mean duration of symptoms of 3.45 months; 45% had a Karnofsky greater than 80%; 42% had a prior neurological deficit; 79% received a partial resection; 45% had post-surgical radiological follow up; 76% had tumor recurrences, 65% of which were classified as persistence, with 36% being treated with temozolamide-based CT; 27% had RPA V-VI; 24% were from Manizales and 23% from Pereira, and, in general, temozolamide was used for an average of 10.643 months (Table 1).

From a surgical standpoint, the standard treatment (Sx+CT/RT+CT) was performed with partial resection (PRes) and biopsy (Bx) in 88%. Radiation therapy was given in 55% of cases before eight weeks, with a total mean dose of 59.22 Gys and a mean of 29.2 sessions, with 94% receiving 2.00 Gys/day five times per week; there was a mean of 3.23 fields with 23% receiving a dose less than 60.00 Gys.

Table 1. *Demographic and clinical characteristics.*

Variable	Type	Frequency	%	p
Age	Mean: 54.810 / Range (years): 9 - 84 years / SD[1]: 17.963			
I. Age groups	<45	17	20	0.1924
	45-55	18	21	
	55-65	35	42	
	65-75	11	13	
	75-84	3	4	
II. Age groups	18 - 44	15	18	0.0286
	45 - 59	37	44	
	60 - 74	29	35	
	> 75	3	3	
III. Age groups	< 65	70	83	0.2063
	> 65	14	17	
Sex	Male	46	55	0.0586
	Female	38	45	
Zone	Urban	78	93	0.9163
	Rural	6	7	
Tumor size	Mean: 28.792 / Range (mm^2): 7 - 81.2 mm2 / SD[1]: 17.963			
Anatomical location	Combinations	31	36	0.5398
	Parietal	19	23	
	Frontal	16	19	
	Temporal	10	12	
	Occipital	8	9	
Type of combinations	Temporal-parietal	11	36	0.3221
	Parietooccipital	8	25	
	Frontoparietal	7	23	
	Frontotemporal	4	13	
	Bifrontal	1	3	
Anatomical side	Right	40	48	0.0525
	Left	36	43	
	Medial	6	7	
	Mixed	2	2	

1- SD: standard deviation 2- RPA: *Recursive Partitioning Analysis*

Altogether, 19% had complications which were principally digestive, followed by infectious, hematologic and, to a lesser extent, cutaneous, all generally grade I-II. In patients with recurrence, the five-year survival was 17%, with a difference of 55% and a median of 21 months compared to those without recurrence (p=0.0185) (Table 2).

Discussion

Despite the recent therapeutic outcomes, the global outcome in patients with high-grade central nervous system tumors, especially in AA, with a mean survival of 24-36 months, and GBM continues to be unsatisfactory, with a mean

Variable	Type	Frequency	%	p
Crossing the midline	No	66	79	0.951
	Yes	18	21	
Epilepsy-convulsion	No	56	67	0.8155
	Yes	28	33	
Duration of symptoms	Mean: 3.45 / Range (months): 1 - 48 / SD[1]: 5.163			
Karnofsky	50% - 70%	46	55%	0.8219
	80% or more	38	45	
Neurological deficit	No	49	58	0.2318
	Yes	35	42	
RPA[2] classification	III	6	7	0.2981
	IV	55	66	
	V	18	21	
	VI	5	6	
Occupation	Homemaker	34	41	0.0000
	Employee	11	13	
	Retired	7	8	
	Farmer	6	7	
	Freelance worker	3	4	
	Others	23	27	
Branch	Caldas	24	29	0.9715
	Risaralda	34	41	
	Quindío	22	26	
	Norte de Valle	4	5	
Township	Manizales	20	24	0.0000
	Pereira	19	23	
	Armenia	15	18	
	Dosquebradas	11	13	
	Calarcá	5	6	
	Others	14	16	

1- SD: standard deviation 2- RPA: *Recursive Partitioning Analysis*

global survival of 12-15 months (Figure 1). In general, the prognosis is highly variable, depending on various negative prognostic factors such as age, initial functional status and the degree of surgical resection, which help explain the variable outcomes. Other studies consider the *Radiation Therapy Oncology Group (RTOG) classification as a prognostic factor that encompasses other subcategories, known as Recursive Partitioning Analysis (RPA) (11).*

The analysis by decades shows better outcomes for the under 45 and 45-55 year-old groups, who were the only ones to achieve five-year survival rates of 61% and 22%, respectively, with no statistical difference (p=0.1924).

There was a 66% difference between those under the age of 65 and those over the age of 65 with respect to receiving or not receiving any treatment, which is similar to other researchers and other cancers in which, as patient age increases, the number of patients receiving radical treatment decreases; this is no different in gliomas, being similar to what Amsbaugh (12) reported. There was a four-month median survival difference, 6% in our results at 24 months and 4% at 36 months for those under the age of 65 compared to those over this age, respectively, as well as marked differences at five years, although they were not statistically significant (p=0.2063).

The median age at onset was 54 years, similar to the SEER results, but with differences in those over the age of 65, as we only had 17% in our results compared to the SEER database. These results are similar to those of studies with a greater number of patients, as shown in CBTRUS (6, 7, 13), which confirms what is generally suggested, that the higher the age, the higher the presentation of high-grade gliomas (1) (Figure 2).

The demographic characteristics such as origin, area of residence, race, and profession show no differences from other studies that indicate that the incidence in industrialized countries is increasing, which seems to be related to the behavior of the population pyramid. There was no differentiation regarding each of these characteristics or the clinical signs and symptoms, which have a widely variable presentation as described by most studies that depend mainly on the histology, functional status and topographic location as the principal determinant of symptoms, with a mean duration of symptoms prior to consult of 3.45 months (14, 15). For overall survival outcomes, by sex, females doubled the results both in the median (40 vs. 21 months) and five-year survival (36 vs. 18%); an urban origin was 13% greater (38 vs. 25%); in terms of location, the left hemisphere was 25% greater

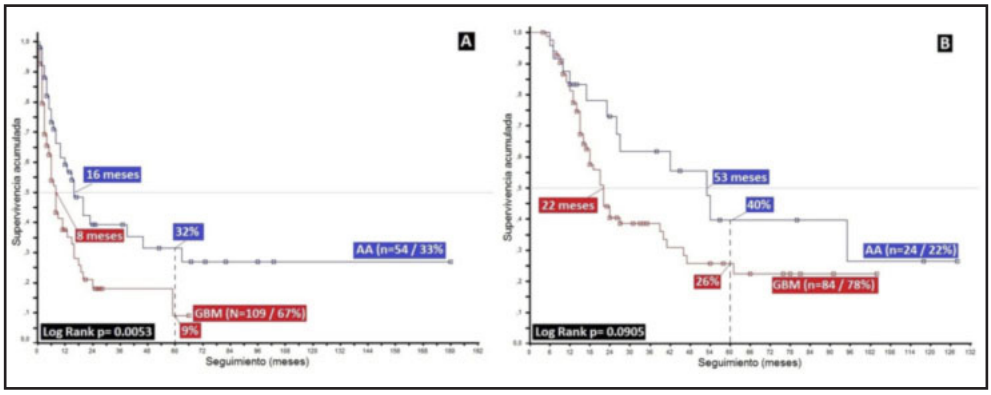

Figure 1. *Global survival of high-grade tumors according to histology (AA and GBM) and treatment received. A. Survival by high-grade histology in patients receiving treatment other than the Stupp platform. B. Survival by high-grade histology in patients with Stupp platform treatment.*

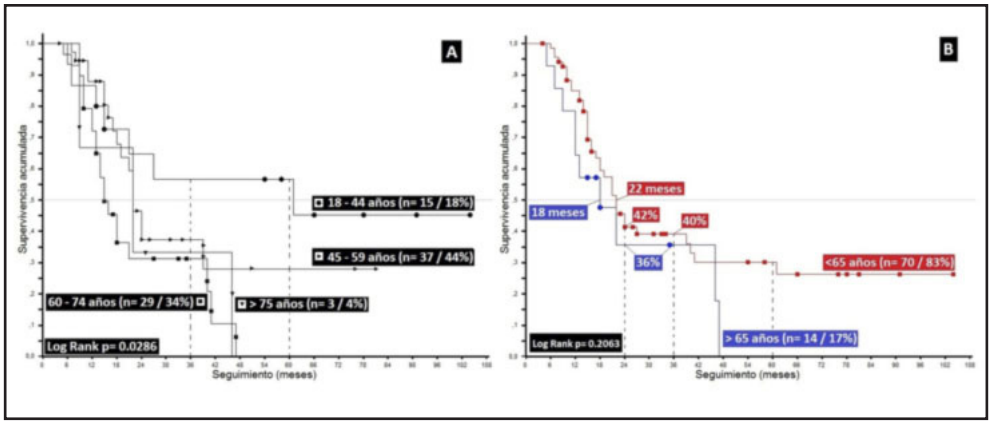

Figure 2. *Global GBM survival by age. A. Survival by different age groups. B. Survival in those under and over the age of 65..*

Table 2. *Internvention characteristics*.

Variable	Type	Frequency	%	p
Surgical treatment	Biopsy	8	9	0.7305
	Partial resection	66	79	
	Total resection by MD[1]	4	5	
	Total resection by Rx[2]	6	7	
Postsurgical imaging	No	46	55	0.2213
	Yes	38	45	
Timing of RT treatment[3]	Immediate (< 8 weeks)	46	55	0.6826
	> 2 months and < 6 months	38	45	
Total RT[3] dose	< 54.00 Gys	16	18	0.3134
	54.00 - 59.90 Gys	3	4	
	60.00 - 64.00 Gys	55	66	
	> 64.00 Gys	10	12	
Total RT[3] dose	Mean: 59.224 Gys / Range (Gys): 30-82 / SD[4]: 6.66 Gys			
RT[3] sessions	Mean: 29.25 / Range (# of sessions): 10-41 / SD[4]: 4.531			
Daily RT[3] dose	1.80 Gys	1	1%	0.3145
	2.00 Gys	79	94	
	3.00 Gys	1	1	
	Other	3	4	
RT[3] fields	Mean: 3.23 / Range (#): 1 - 9 / SD[4]: 1.557			
Complications	No	68	81	0.7179
	Yes	16	19	
Type of Complications	Digestive	9	45	0.1201
	Infectious	7	35	
	Hematological	3	15	
	Skin	1	5	
Recurrence	No	20	24	0.009
	Persistence	55	65	
	Yes	9	11	
Treatement for recurrence	CT[5]	29	45	0.2528
	Sx[6]	10	16	
	Sx[6] + CT[5]	8	13	
	None	11	17	
	Other - mixed	26	9	
CT[5] for recurrence	Temozolamide	30	36	0.1959
	Temozolamide/avastin	7	8	
	Avastin / irinotecam	3	4	
	None	44	52	

1- MD: physician **2- Rx**: radiation **3- RT:** radiation therapy **4- SD:** standard deviation **5- CT**: chemotherapy **6- Sx:** surgery

than the right (37 vs. 12%). Regarding anatomical area, the temporal location had the greatest survival (50%) followed by the occipital (31%) and frontal (30%), and the combinations had the poorest survival outcomes with 20% at five years, possibly explained by the tumor size, although none of these comparisons reached statistically significant differences.

According to the RPA classification, there is an inverse relationship between survival and RPA, with a 14% difference at five years between the group with a good prognosis (III-IV) and the groups with greater adverse factors (V-VI) (p=0.6827), similar to what has been reported by other researchers, showing the importance of this classification for future research projects (4, 9, 16). There were better survivals than those of Wang Li J (2011), who reported 70, 46 and 28% at 12 months, compared to 84, 80 and 65% in the current study in the same period analyzed for Groups III, IV and V, respectively, without statistically significant differences (Figure 3).

There are three overall objectives in surgical treatment: taking a sample for histological diagnosis, decreasing or relieving symptoms, and improving survival. Our results have an uncertain interpretation, since 79% underwent partial resection (PRes), and 9% had a biopsy (Bx), with non-statistically significant treatment outcomes (p=0.2902), but with differences in median survival of 7 and 32 months comparing Bxs to greater resections (17) (Figure 4).

Finally, when PRes is analyzed against TRes alone, there is a 25-month difference in median survival in favor of TRes, but only a 1% difference at five years, without reaching statistical significance (p=0.2902), possibly due to the group distribution with regard to types of resection. Thus, this supports the results that indicate that the initial treatment in accessible locations is maximal resection, always weighing the extent of surgical resection against neurological function preservation (18-20).

However, as with many topics, other studies do not provide a consensus on the efficacy of the extent of surgical resection, especially comparing Bx with PRes, similar to our findings, which makes the analysis difficult. On the other hand, various groups suggest that greater surgical resection is associated with greater survival for gliomas. These resections have currently progressed with the help of NMR, intraoperative ultrasound, and modern surgical techniques which allow broader resections even in tumors which are near or within eloquent areas of the brain, which may be radically resected in surgeries on awake patients and using intraoperative cortical stimulation (21-24).

As has been stated, the standard GBM treatment is based on Sx+CT/RT+adjuvant CT with temozolamide, termed the "Stupp platform", which currently shows a 14-month median and 17% five-year survival difference when compared to other treatments without specific therapeutic considerations, and is similar to most of the published studies (25, 26). The result is survival differences of 45, 23, 21, 9 and 17%, from the first to the fifth year, respectively, in favor of the Stupp group, suggesting improved outcomes vis-à-vis different lengths of adjuvancy in the study. This reinforces the initial proposed hypothesis of finding survival differences and strengthening

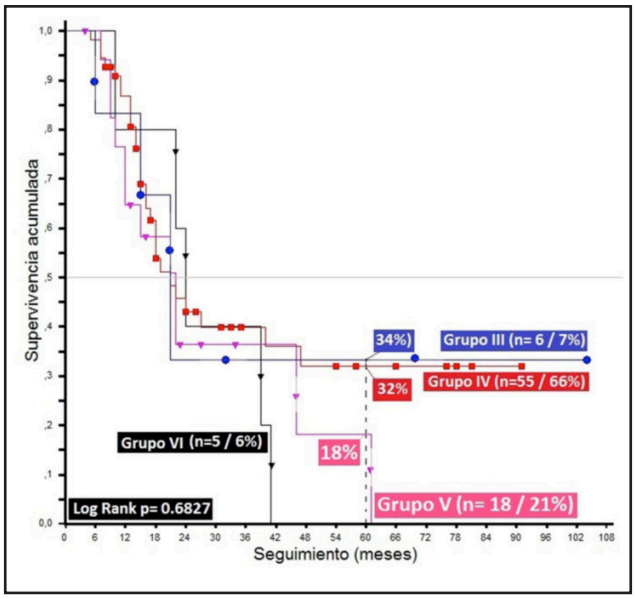

Figure 3. *Global GBM survival according to the Recursive Partitioning Analysis (RPA) classification of the Radiation Therapy Oncology Group.*

the bases for continuing the analysis of various lengths of medication use, seeking the best focus on both concomitance as well as adjuvance based on radiosensitization, spatial collaboration and cellular arrest in RT sensitive phases. This is why the Stupp platform has been applied since 2005 (3) and, based on this therapeutic development, oncology units have adjusted their protocols, producing statistically significant differences both in median survival as well as five-year survival between the various treatment methods of 14 months and 17% in favor of the Stupp platform (p=0.0000), similar to our results (Figure 5).

With regard to treatment with RT, it should be noted that this modality has contributed greatly to final patient outcomes, with an increase in median survival of 2, 9 and 6 months for

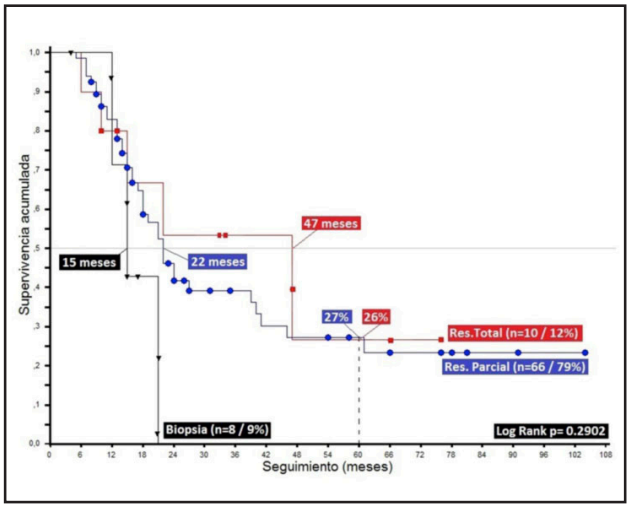

Figure 4. *Global GBM survival according to the magnitude and type of surgical treatment.*

patients treated comparatively with Sx, Sx+RT, Sx+CT/RT and Stupp, respectively (p=0.0000), similar to other studies (4, 17). A four-month improvement was also shown in the median (18 vs. 22 months) and 16% (14 vs. 30%) in five-year survival in favor of doses greater than 60.00 Gys (p=0.0712), with even greater differences when analyzed by total dose less than 54.00 / 54.00-59.00 / 60.00-64.00 and greater than 64.00 Gys, with 60.0 Gys being established as the standard minimum dose for this disease, with similar results to others and survival differences which increase as the dose increases (p=0.3134) (27, 28) (Figure 6).

Similar to this analysis of RT with regard to dose, and based on the few and varied reports on the effect of the time elapsed between Sx and the beginning of CT/RT on the survival of GBM patients, and despite a poorly defined optimal timeframe in the literature due to a lack of consensus. Thus, some research groups show a survival relationship favoring the use of RT with a time lapse between Sx and the beginning of RT of less than 30 days or up to six weeks, even considered as an independent variable (29-31), while in other groups the outcome is due to other general aspects and not just this time interval; therefore, they consider it to have no active effect on survival. In our study, there were no statistical differences between the various intervals whether in number of days (fewer than 30, 30-45, 45-60, 60-90 or >90 días, [mean:66.7 - range:15-283 and p=0.0467) or weeks (<4, 4-6, 6-8, 8-12 or >12 weeks (mean:9.58 – range:2-40 and p=0.0682), with a median survival grouped between 15-20 weeks, with no difference between them (32, 33).

As a consequence of the standard treatment, 19% had some type of complication, with 45% being digestive (grade I-II) and 18% hematological, mainly thrombocytopenia and leukopenia. These complications occurred at similar rates to those described in the literature (10-20%), with grade I-II thrombocytopenia presenting most frequently (34).

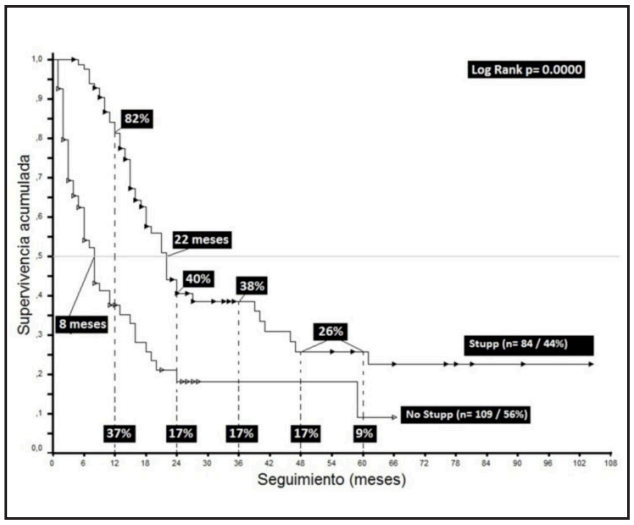

Figure 5. *Global GBM survival according to the type of treatment used. **A**. GBM with treatment other than the Stupp platform (n=109). B. GBM with Stupp platform treatment (n=84).*

With regard to recurrence, it presented as persistence in 66% and as recurrence in 11%, with a five-year survival difference of 55% in favor of those who did not have it, and not reaching the median in this group (p=0.0185). Rescue treatment with CT was given to 45% and, of these, 71% used temozolamide and 29% a combination of bevacizumab and others (temozolamide, irinotecan, carmustine), which is similar to other studies (35, 36).

As described above, global survival for GBM improved by 14 months for the median and 17% for five-year survival using the Stupp platform, with very similar figures to those reported by others (37). In addition, these differences are seen as a function of the length of time over which the medication was used as an adjuvant, demonstrated by comparing groups with less than and more than six months, with an improve-

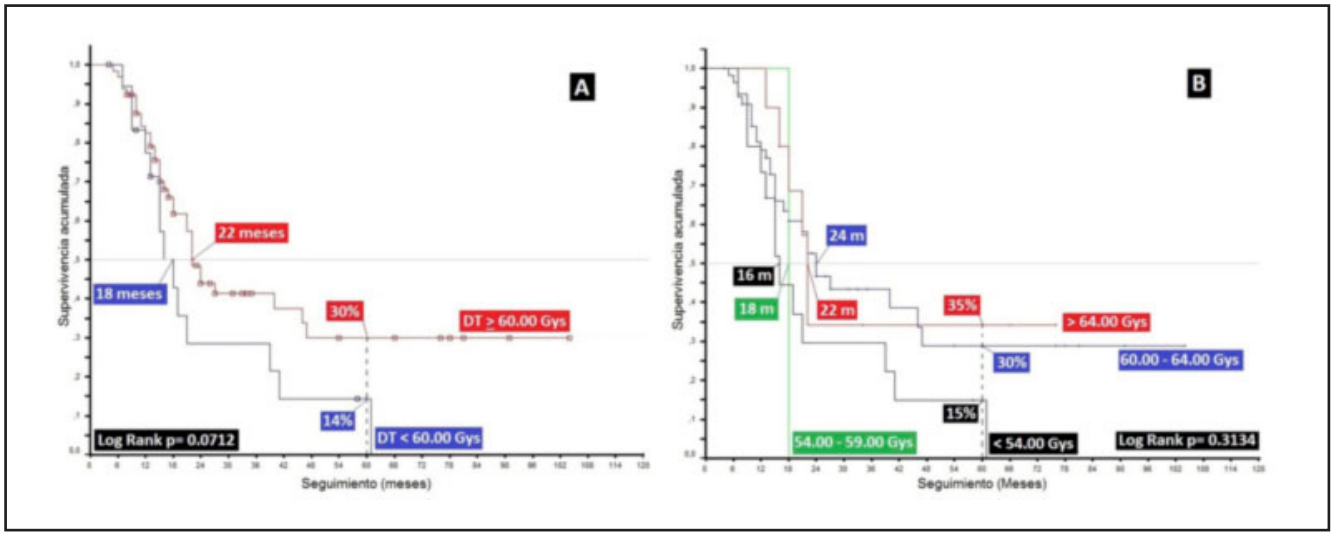

Figure 6. *Global GBM survival according to the total radiation therapy dose. A. With a total RT dose less than or greater than 60.00 Gys. B. According to different RT doses from less than 54.00 Gys to more than 64.00 Gys.*

ment of 31 months and 42% in median and five-year survival in favor of use over a longer time period (p=0.0000). After obtaining this result, groups of less than and more than 12 months of medication use were analyzed, finding differences of 30 months and 29% in five-year survival favoring the longer time period (p=0.0006). There were similar results for less than or greater than 18 months, with 62% in favor of the longer time period, without reaching the median (p=0.0011) in the greater group; and, finally, the analysis for 24 months had the same tendency in favor of more than 24 months at 53%, without reaching the median (p=0.0328). The general global results favored the group with longer adjuvance compared to the shorter period, with our results being similar to others who already venture to extend adjuvant treatment beyond the standard treatment to date (38, 39) (Figure 7).

An analysis of the data from less than six months, 6-12, 12-18 and 18-24 months, and greater than 24 months shows the same tendency, with each of the periods favoring the group with a greater length of adjuvancy, with the following differences beginning at less than or equal to six months: 27% compared to 6-12 months, 92% compared to 18-24 months and 67% compared to more than 24 months. This was also true for median survivals in the same analysis, beginning with differences between the group with the shortest period and its subsequent seven-month (≤6 vs 6-12 months) and five-month (12 vs. 18 months) analysis, without being able to establish the difference vis-à-vis 18 months on as the median survival had not been reached, with all the data being statistically significant (p=0.0000) (Figure 8).

An analysis of the group with less than or more than 24 months showed a 67% difference in five-year survival, with medians which could not be assessed as they had not yet been reached, but with only 5% of all patients belonging to this group, which only shows a positive tendency in favor of using adjuvancy for more than 24 months. Despite statistical significance, sufficient power was not reached due to the small numerical representativity of this group. It does, however, pose a big question regarding a longer period of adjuvancy with temozolamide, as has been suggested by other authors (38, 39) and locally in our group; once a greater volume of patients with a longer follow-up period is maintained, the results of a prior analysis with only 24 patients could be corroborated and reinforced, results which now coincide with a similar positive tendency in favor of a longer use of adjuvancy in a group almost four times larger and with greater follow-up. The above can only be corroborated with more studies,

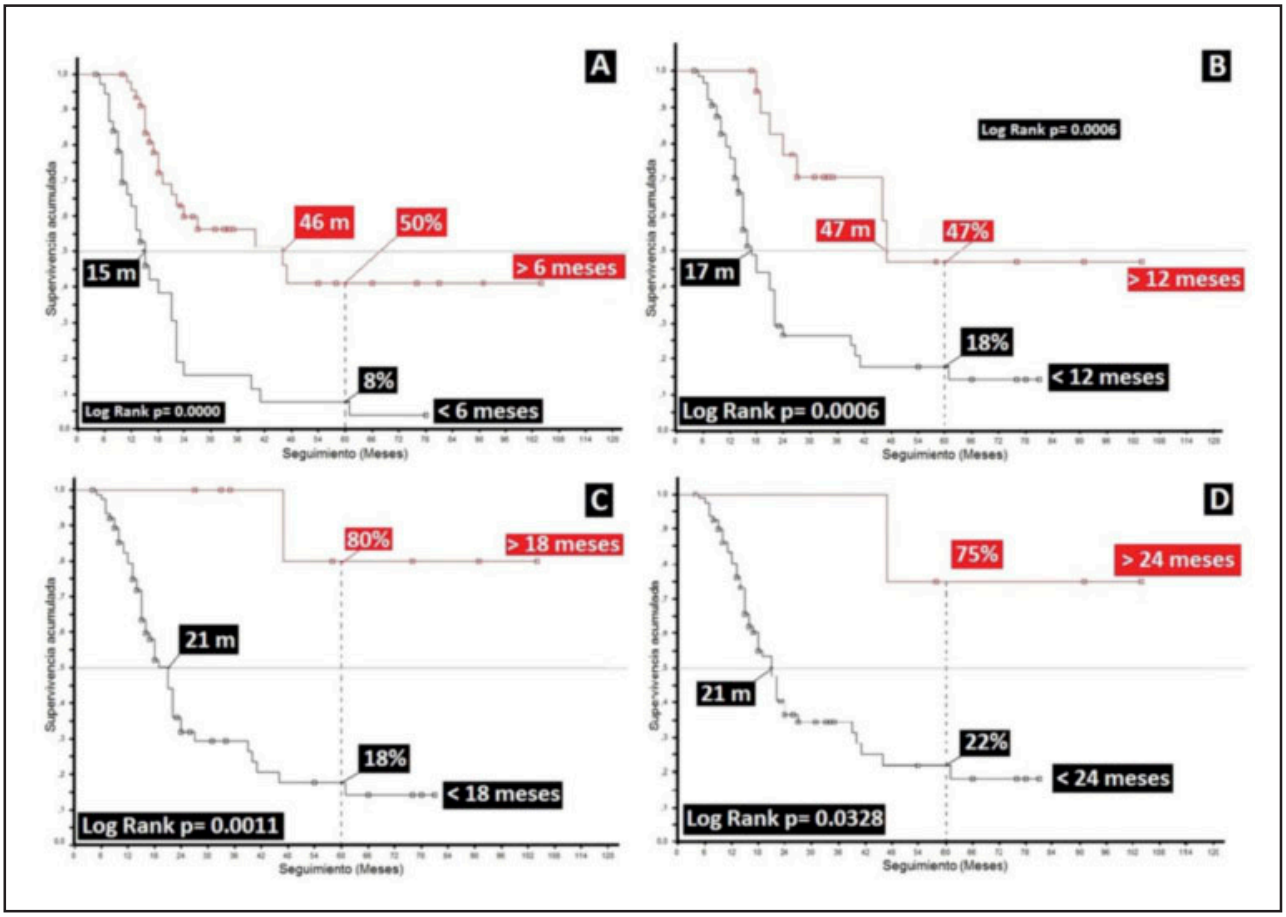

Figure 7. *Global GBM survival according to the length of temozolamide adjuvancy, by semesters. A. Survival in </> six months. B. Survival in </> 12 months. C. Survival in </> 18 months. D. Survival in </> 24 months.*

more follow up, and, especially, with other teams, since there have been no randomized studies thus far researching this aspect, and most of the studies only offer adjuvant therapy for a maximum of 12 months to determine if temozolamide is beneficial or risky for patients after six cycles, as the few existing studies show conflicting results (40, 41) (Figure 8).

In conclusion, these results support the importance of a period of temozolamide adjuvancy longer than six months, as was initially proposed in the original treatment regimen of the Stupp platform and reported by Stuart A (42), proving with the results obtained that the use of temozolamide adjuvant chemotherapy for longer than six months produces significant improvement and impacts global survival without detriment to the general functional state and with minimal, easily treated, adverse effects which do not affect the patients' quality of life. At the same time, we recognize that this is a retrospective study with a significant number of patients for a single institution, especially for Colombia, but still comparatively low compared to other external groups (Table 3).

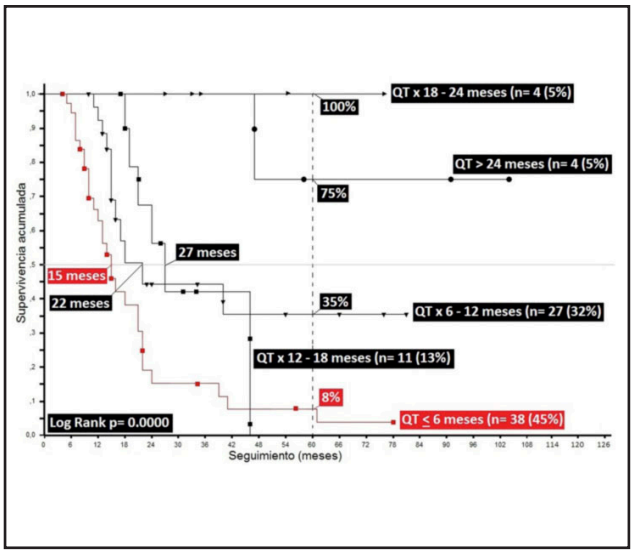

Figure 8. *GBM survival according to the length of temozolamide adjuvancy in Stupp platform regimens.*

Table 3. *Intervention outcomes.*

Variable	Type months	Frequency	%	SV[1]5y[2] %	Median months	P
Duration of adjuvant CT[3]	< 6	38	45	8	15	0.0000
	> 6	46	55	50	46	
	< 12	65	77	18	17	0.0006
	> 12	19	23	47	47	
	< 18	76	90	18	21	0.0011
	> 18	8	10	80	NR	
	< 24	80	95	22	21	0.0328
	> 24	4	5	75	NR	
	< 6	38	45	8	15	0.0000
	6 - 12	27	32	35	22	
	12 - 18	11	13	(-)	27	
	18 - 24	4	5	100	NR[4]	
	> 24	4	5	75	NR[4]	
Duration of use of temozolamide: mean: 10.64 months **/range** (months): 0 - 99 **/SD[5]** : 14.32						
Length of follow up: mean: 24.42 months **/ range** (months): 4 - 104 **/ SD[5]**: 21.20						
	Period years	**General Non-Stupp SV[1] %**			**Stupp SV[1] %**	**Median**
Global survival	1°		37		82	General:
	2°		17		40	8 months
	3°		17		38	
	4°		17		26	Stupp:
	5°		9		26	22 months
1- SV: survival **2- 5y:** 5 years **3- CT**: chemotherapy **(-):** no data **4- NR:** not reached **5- SD**: standard deviation						

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