

Overall Survival in Patients With Resected Glioblastoma Treated With Adjuvant Therapy: A Retrospective Study in a Public Hospital in Chile

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Abstract

Glioblastoma (GB) is the most frequent and aggressive primary tumor of the central nervous system (CNS) in adults. Standard treatment is complete tumor resection followed by concomitant radiochemotherapy (RCT) and subsequent adjuvant temozolomide (TMZ). Information about brain tumors statistics in Latin American countries is scarce, so we aimed to measure the overall survival (OS) of patients with resected GB in a single institution in Chile.

This is a retrospective report of 67 patients treated between 2012 and 2019 with resected GB and who received adjuvant treatment with radiotherapy (RT) with and without TMZ during 2012-2019 in this center (Chilean NCI). Most of them were men (72%), ages > 50 years old (57%), with Karnofsky performance status (KPS) scale \geq 70% (94%) and recursive partitioning analysis-IV (RPA-IV) (60%). Some 54% received concomitant TMZ and RT. Median OS was 11.4 months, with 1-, 2-, and 5-year OS of 48%, 15%, and 3% respectively.

In conclusion, in patients with GB treated with RCT at the NCI, OS was the same as expected from international articles.

Adjuvant RCT therefore is considered the standard of care at NCI.

Categories: Neurology, Radiation Oncology, Oncology

Keywords: glioblastoma, radiotherapy, temozolomide, adjuvant treatment, survival, chile

Introduction

Glioblastoma (GB) is the most frequent and aggressive primary tumor of the central nervous system (CNS) in adults [1]. Its average age of diagnosis is 64 years old and men have a higher incidence [1-2]. Brain MRI is the preferred imaging study in suspected cases [3]. Histologic diagnosis confirms the GB diagnosis [4], so surgical management has a diagnostic and therapeutic role, with possible neurologic symptom, outcome, and quality of life improvement [5-8].

Standard treatment is complete tumor resection if possible, confirmed with early 24-72 hours after surgery imaging with an MRI with gadolinium [9], followed by concomitant radiochemotherapy (RCT) and subsequent chemotherapy (CT) with temozolomide (TMZ) [10-11]. With this treatment, the median survival is 14.6-21.1 months [11-13]. In addition, poor prognostic factors have been identified, including age, functional status, and the extent of resection, among others [14-15].

In Chile, approximately 80% of the population has public health insurance (FONASA) [16] and this does not ensure TMZ access, mMGMT or other molecular markers in GB. The complete TMZ treatment in Chile exceeds 14,000 dollars [17], so it is a significant barrier for candidates for this therapy, and as a consequence they receive exclusive radiotherapy (RT).

In Chile, this issue has not been published so far and there are scant reports in Latin America [18]. The main objective of this study is to determine the overall survival (OS) of patients with resected GB who received adjuvant therapy with RT (with or without TMZ) at the main Chilean tertiary level of care Oncologic Public Hospital (Chilean NCI) during years 2012-2019.

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Materials And Methods

A retrospective cohort study was performed in patients with resected GB and who received adjuvant treatment with RT at the National Cancer Institute (NCI) between 2012 and 2019. The inclusion criteria were: patients with resected GB with histological confirmation based on the CNS WHO tumor classification, aged 18 years of age or more at diagnosis, ECOG Performance status ≤ 2 at the time of RT planning. Patients with another concomitant malignant neoplasia, who had received systemic treatment for another tumor, who did not complete planned adjuvant RT, who received RT with other than conventional (1.8-2 Gy / fraction) fractionation or those who were treated with palliative intention were excluded.

Data of these patients were obtained from the statistical record service of the NCI. Date of death was acquired from the death records of the Chilean Civil registration. Analyzed variables were: age and sex, performance status (PS) at the beginning of treatment according to the Karnofsky performance status (KPS) scale, recursive partitioning analysis (RPA), date of tumor resection, definitive surgery, the extent of resection, date of initiation of adjuvant treatment with RT, type of adjuvant treatment received (with or without concomitant and/or adjuvant TMD, dose of TMD), and death date or last clinical control. OS was defined as time between start of RT and death. Methylation of the MGMT gene promoter (MGMT) methylation and isocitrate dehydrogenase (IDH) mutation are not reported and unavailable.

The RT technique consisted of 3D conformational RT with a high energy linear accelerator (6-18 MV). Contouring in the first 34 patients was defined as per The Radiation Therapy Oncology Group (RTOG): clinical target volume 1 (CTV1): tumor bed including the T2 FLAIR MRI sequence edema area + 2 cm margin. CTV2: tumor bed + 2 cm margin based on T1 gadolinium MRI. The following 33 patients were treated with a single CTV including the operative bed + residual tumor and a margin of 2.5-3 cm. For the planning target volume (PTV) a margin of 5 mm was added to the CTV. In the first 34 patients, PTV1 prescribed dose was 46 Gy in 23 fractions and a boost to PTV2 up to 60 Gy in fractions of 2 Gy/day. The remaining patient's PTV received 60 Gy in 30 fractions. Concomitant CT with TMD was administered according to the Stupp trial [10].

For data presentation, descriptive statistics were performed. The groups were compared using Fisher's test for categorical variables and for quantitative variables according to Student's t-test or Wilcoxon-Mann-Whitney test. Kaplan Meier survival analysis was used, with exploratory comparison using the Log rank method and the Cox proportional hazard regression (HR) model to obtain the ratio of risk in univariate and multivariate analysis, considering an α of 5%. Stata / IC®16 (Stata Corp LLC, College station, TX, USA) for Mac software was used.

We use RPA classes in GB (based on four patient variables: age, Karnofsky score, extent of resection, and neurologic function) within the statistical analysis as prognostic classes.

Results

A total of 358 files with the diagnosis of CNS tumor were reviewed, identifying 82 patients with a diagnosis of GB. Of these, 15 patients were excluded because they did not meet the inclusion criteria and / or consider exclusion (5 did not receive RT, 2 suspended treatment, 4 had palliative intention, 3 had nonconventional 2 Gy per fraction RT fractionation, and 1 was under 18 years old). Finally, a total of 67 patients were included in the analysis. The basal characteristics are detailed in Table 1.

Overall survival	Median (months)	95% IC (months)
Whole cohort	11.4	9.7–14.6
Without TMZ concomitant	9.7	6.1–10.4
With TMZ concomitant	14.6	11.8–20.7
		HR 0.39, (p < 0.001)

TABLE 1: Overall survival.

TMZ, temozolomide; HR, hazard regression

Most patients were men (72%), > 50 years (57%), KPS $\geq 70\%$ (94%), and RPA IV (60%).

Regarding surgery, 45% had macroscopic total resection (GTR) and median time from surgery to the start of RT was 50 days.

Globally 54% had concomitant RT TMZ; these patients received 100% of the prescribed standard

concomitant dose, but the number of patients receiving TMZ consolidation adjuvant TMZ after RT TMZ is unknown due to lack of data in our clinical records, as many of them received their adjuvant CT outside our institution. The group with exclusive RT included patients with worse prognosis: RPA IV 77% vs 50% ($p < 0.05$) and GTR 41% vs 67% ($p < 0.04$) compared to the RT TMZ group.

For the entire cohort, with a median follow-up of 10.3 (4-70) months, the median OS was 11.4 months, with an OS at 1, 2, and 5 years of 48%, 15%, and 3%, respectively (Table 2).

Variables	Cases	%
Total patients	67	100
Age		
> 50 years old (%)	38	57
< 50 years old (%)	29	43
Years [median (range)]	50 (range 20-76)	
Gender		
Female (%)	19	28
Masculine (%)	48	72
KPS before RT		
≥ 70 (%)	63	94
< 70 (%)	4	6
Extent of resection		
GTR	30	45
STR	37	55
RPA		
III	25	37
IV	40	60
V	2	3
Time from surgery to RT		
Days [median (range)]	50 (range 31-156)	
TMZ concomitant with RT		
Yes	36	54
No	31	46

TABLE 2: Patients and treatment characteristics.

TMZ, temozolomide; KPS, Karnofsky score scale; GTR, gross total resection; STR, subtotal resection; RPA, recursive partitioning analysis; RT, radiotherapy

Differences in OS were identified when patients were stratified according to RT treatment with concomitant TMZ vs without TMZ, presenting a median OS of 14.6 months vs 9.7 months, a 2-year OS of 26% vs 4%, and 5-year OS of 10% vs 2%, respectively (Figure 1). A significant better survival was observed on univariate analysis (Table 2) with concomitant TMD (HR 0.48, $p < 0.001$), but this lost significance in the multivariate analysis (Table 3).

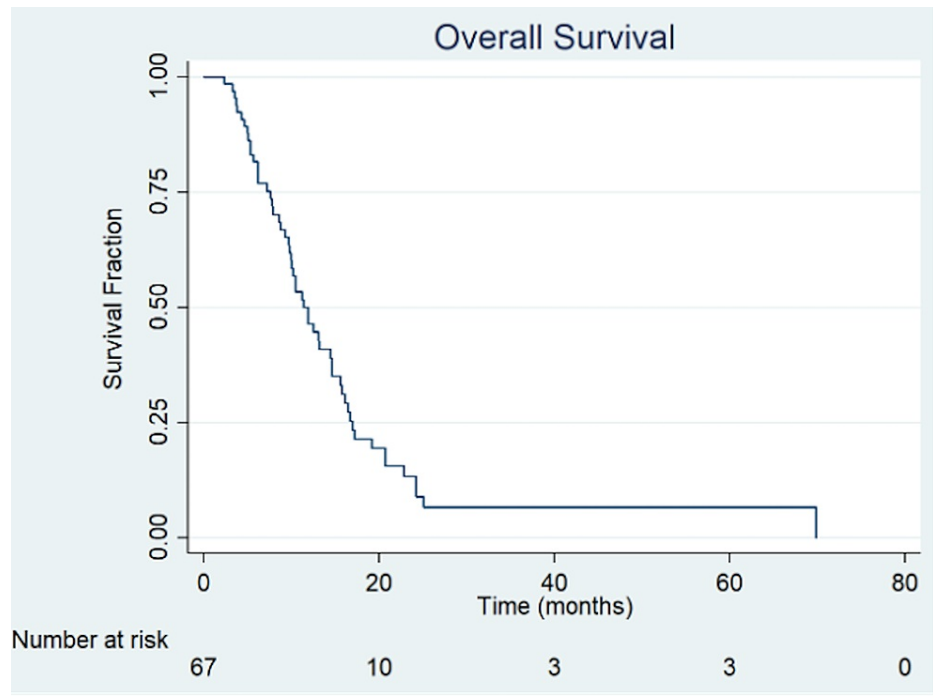


FIGURE 1: Overall survival of the cohort.

Variable	P Univariate	HR	P Multivariate	HR
Age (≥ 50 vs < 50 years old)	0,01	2,1	0,03	3,8
Gender	0,8	1,1		
KPS (< 70 vs ≥ 70)	0,2	1,9		
RPA ($\geq IV$ vs III)	0,02	2	0,6	0,7
Resection (GTR vs STR)	0,01	0,4	0,001	0,3
Concomitant TMZ	0,001	0,4	0,09	0,6
Time from surgery to RT (≥ 2 vs < 2 months)	0,06	0,5		

TABLE 3: Multivariate analysis.

HR, hazard regression; KPS, Karnofsky performance status; RPA, recursive partitioning analysis; GTR, gross total resection; STR, subtotal resection

Of the entire sample, 18 patients had RPA 1 and TMZ. In this subgroup, the median OS was 14.6 months with OS at 1, 2, and 5 years of 80%, 39%, and 15%, respectively. Patients with RPA-III, IV, and V had a median survival of 14.1 vs 10.1 vs 7.4 months respectively ($p < 0.02$) (Figure 2). Considering the other variables, patients with GTR had better survival than STR ($p < 0.001$) and those < 50 years better than ≥ 50 years ($p < 0.009$). The rest of the variables did not show significant differences.

After multivariate analysis, the extent of resection and the age of the patient remained significant, while for concomitance there was only a trend (HR 0.6 95% CI 0.33-1.09).

Discussion

This is the first published analysis with Chilean data of survival in GB patients. Ours results are consistent with international experiences.

Several studies have been carried out to obtain better oncological results in this pathology. The pivotal

study, which defines the current standard of treatment, is a randomized Phase III clinical trial conducted by the EORTC Group [10], in which RT alone was compared to concomitant TMZ for seven weeks followed by adjuvant for six cycles. Some 573 GBM patients were included in which 82% underwent surgery, 85% completed the concomitant scheme, but only 47% completed the adjuvant cycles. The RCT has a HR of death of 0.63 (95% CI 0.52-0.75, $p = 0.001$) vs RT alone. The two-year survival was 27.2% (95% CI 22.2%-32.5%) with combined therapy vs 10.9% (95% CI 7.6%-14.8%) with RT alone. At five years, the OS is 9.8% vs 1.9%, respectively. Progression-free survival (PFS) was 6.9 months (95% CI 5.8-8.2) vs 5 months (95% CI 4.2-5.5). Among the adverse effects, severe myelosuppression occurred in 16% of patients, but only 5% discontinued therapy [10-11].

A Cochrane systematic review demonstrated that the use of TMZ concomitant to RT vs RT alone in patients with high-grade gliomas was associated with better OS (HR 0.60, 95% CI 0.46-0.79, $p = 0.0003$) and better PFS (HR: 0.63, 95% CI 0.43-0.92, $p = 0.02$). The benefit was greater for the concomitant and adjuvant therapy regimens, without demonstrating benefit in the concomitant regimen without adjuvant treatment. The risk of infections, fatigue, and hematological complications was higher with TMZ [19].

We can observe that the two-year and five-year OS in patients who received concomitant TMZ in our cohort is similar to that published by Stupp et al. [10]. However, the median OS in the group with exclusive RT was lower than the control group of that study, which can be explained by selection bias, since group with exclusive RT in our cohort included patients with worse prognostic factors. Univariate analysis showed higher survival in patients with concomitant RT TMZ, but significance was lost in multivariate analysis, probably accounting for bias.

Regarding the extent of tumor resection, we observed that those who were treated with GTR had a 70% survival benefit compared to those with STR. These results are consistent with what has been published internationally. A recent meta-analysis showed a 35% lower risk of mortality in patients treated with GTR vs STR [20]. This could be related to the significant delay in the start of adjuvant treatment that we observed, with a median of close to two months between surgery and RT. In this context, the absence of tumor residue during this interval could be important. A study based on the NCDB data showed that even in patients with GTR, OS decreases if RT is started with a delay greater than eight weeks (HR 1.23, $p = 0.007$), therefore reducing this interval to 4-8 weeks could be considered optimal [21]. Finally, we observed better survival in patients under 50 years of age, similar to previously published articles [22].

Chilean public system has economic limitations so glioblastoma tumor patients do not have full diagnostic characterization with molecular markers, or access to TMZ, so response to therapy and prognosis in our series is not accurately described as in other publications [23-24]. It would have been interesting to report toxicity, but this information was not readily and reliably available.

Although the design of our study does not allow conclusions other than consistent results with previously published international phase III trials, it has the value of reporting the results of a single institution with limited access to TMZ.

Conclusions

Despite the limitations faced by resected GB patients in our public health system, those who received RT with concomitant TMZ, OS is representative of the phase III Stupp trial. It is important to achieve a GTR, optimize the interval from surgery to initiation of RT TMZ adjuvant therapy, and there is a need to emphasize an improved access to TMZ for patients with public health insurance.

Additional Information

Disclosures

Human subjects: Consent was obtained or waived by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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