

# Prognostic factors and survival in a prospective cohort of patients with high-grade glioma treated with carmustine wafers or temozolomide on an intention-to-treat basis

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## Abstract

**Background** Patients with high-grade glioma can be treated with carmustine wafers or following the Stupp protocol. As far as we are aware, no scientific evidence has been published comparing the two treatments. The primary objective of this study was to analyse the survival of groups of patients with each of these treatment modalities. The secondary objective was to assess the influence of the usual prognostic factors on the patients in our hospital.

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**Methods** A prospective cohort of 110 patients with single, supratentorial high-grade glioma treated by craniotomy and tumour resection was retrospectively studied. Half of the patients had carmustine wafers placed during this operation while the others (55) did not, the latter group receiving first-line systemic chemotherapy on an intention-to-treat basis.

**Findings** Patients treated with carmustine wafers had a median survival of 13.414 months compared with 11.047 in the group without implants ( $p=0.856$ ). For the overall cohort of patients, the following factors were found to influence survival: age ( $p<0.0001$ ), postoperative KPS score ( $p=0.001$ ), histological grade ( $p=0.004$ ), RPA class ( $p=0.001$ ), extent of resection ( $p=0.002$ ) and salvage surgery ( $p=0.028$ ).

**Conclusions** In this prospective cohort of patients, analysed on the basis of intention-to-treat at the time of the first surgery, no statistically significant differences in survival were found between the two treatment modalities (carmustine wafers vs. first-line systemic chemotherapy). On the other hand, age, preoperative KPS, histological grade, and RPA class were confirmed to be prognostic factors in this cohort. Finally, the extent of resection was also found to influence survival.

**Keywords** Carmustine wafers · Temozolomide · High-grade glioma · Survival · Prognostic factors

## Introduction

Carmustine wafers (Gliadel®) are a combination of a chemotherapeutic agent (carmustine, also known as BCNU) and a polymer wafer (polifeprosan 20, which is poly[1,3-bis

(p-carboxyphenoxy) propane-sebacic acid] in a 20:80 ratio). These wafers are directly placed in the surgical bed following excision of a brain tumour. Later, in contact with the cerebrospinal fluid (CSF), the polymer degrades, releasing the chemotherapeutic agent [17, 19, 22, 67]. After the studies of Brem, Valtonen and Wesphal [12, 62, 65], it was licensed for clinical use both in the United States (by the FDA) and Europe. In addition, following the findings of the EORTC (22981/26981) NCIC CE3 clinical trial, reported by Stupp et al. [61], another chemotherapeutic agent, temozolomide (TMZ), is also considered for the treatment of patients with high-grade glioma. Both have been widely used in daily clinical practice and have become the standard treatments for this condition.

In the case of Gliadel<sup>®</sup>, the aforementioned clinical trials compared carmustine wafers with placebo wafers, while the use of temozolomide (the Stupp protocol) was only compared with radiotherapy treatments. Several authors [2, 25, 26] have highlighted the need to carry out randomised clinical trials that compare the two treatments. To date, however, there have been no studies making this comparison. Indeed, arguably, it is not possible, for both technical (it could not be double-blinded) and ethical reasons, to set up a trial to assess the differences between these two treatments [40].

## Objective

*Primary:* To analyse the survival of a prospective cohort of patients with high-grade glioma who underwent surgery and then received two different treatments. On the one hand, half of the patients received carmustine wafers during surgery and were not later treated with first-line chemotherapy. The other half of the patients did not receive carmustine wafers and were considered candidates to receive first-line chemotherapy on an intention-to-treat basis. The first-line chemotherapy was carried out following either the Stupp protocol [61] or the procarbazine/CCNU/vincristine (PCV) protocol [41].

*Secondary:* To assess the influence on prognosis in the entire cohort of the prognostic factors commonly considered most important [age, preoperative Karnofsky Performance Scale (KPS) score, histological grade and RPA class], and also of other factors: extent of resection, second-line chemotherapy and salvage surgery.

## Material and methods

A prospective cohort of patients was selected with the following inclusion criteria: *Date of surgery:* those who

were operated on between 1 January 2004 and 31 December 2008; *pathology:* only those with histological confirmation of a high-grade tumour according to the WHO criteria, that is, grade III (includes anaplastic astrocytomas and anaplastic oligoastrocytomas) or grade IV (includes glioblastoma multiforme and gliosarcoma); *modality of surgical treatment:* including only patients treated by craniotomy and tumour resection (total/subtotal/partial); *characteristics of the lesion:* contrast-enhanced, single, unilateral, supratentorial lesions, for which, following radiological assessments, it was judged that at least subtotal resection was feasible; *age:* between 18 and 80 years old; *functional status:* good general status prior to surgery (KPS score  $\geq 70$ ); *personal history:* no severe concomitant conditions that contraindicated surgical treatment; *follow-up:* a minimum of at least 12 months from the date of the surgical intervention.

Individuals were excluded from the study if: they had undergone prior cytoreductive surgery or brain radiotherapy; their diagnosis was obtained by stereotactic biopsy/neuro-navigation; or they had multifocal disease (more than one lesion with contrast uptake), known prior hypersensitivity to nitrosoureas, relevant abnormal blood results, tumours in the midline, nucleus basalis, cerebellum or brain stem, or lesions with no uptake or suggestive of low-grade glioma.

Participating patients were treated with dexamethasone at a dose of 4 mg/8 h (orally) from prior to the surgery until 7 days after the intervention. From this point, the dose of this drug was tapered off, continuing provided that there were no neurological signs or disruption of the hypothalamic-pituitary axis. All the patients underwent craniotomy and microsurgical resection, with an attempt to remove as much of the tumour as possible. During the study period, the treatment policy was to place carmustine wafers in all patients after surgical removal of the tumour. However, this did not happen in all cases. The main reasons for this included there being no histological confirmation of the high-grade glioma in the intraoperative biopsies and the wafers not being available in the hospital at the time. The surgical interventions and the subsequent medical management were carried out by the same group of surgeons and following the same procedure.

After the postoperative care, patients were treated by radiotherapy. This was based on the shrinking field technique. Using 3D planning and isocentric fields, compensation with dynamic wedges and multileaf collimators, and varying the energy of the beam (6–10 MV), total 60 Gy doses were achieved, in fractions of 2 Gy/session. The treatment was carried out in 30 sessions in line with the approach used in most protocols [58, 61, 64, 65].

With respect to the oncological treatment, those patients who did NOT receive carmustine wafers were candidates for temozolomide (TMZ) following the Stupp protocol

[61]. On the other hand, patients who received carmustine wafers, were NOT administered the treatment described by Stupp. This approach was based on the fact that, when this study was designed (2003–2004), it was considered that the administration of temozolomide concomitant to radiotherapy in patients treated with carmustine wafers might potentially induce severe haematological toxicity, there not being sufficient evidence to consider this combination as “safe”. For this reason, we opted for the most conservative course, that is, not to administer temozolomide (concomitant or adjuvant) as a first-line treatment to patients who were treated with carmustine wafers. In the event that progression of the disease was detected, patients were considered for active treatment (new surgery or second-line chemotherapy) or, in such cases, given the best possible palliative care.

This study was approved by the Clinical Research Ethics Committee of the Cruces Hospital and complies with the requirements of said committee (CEIC E09/14 and E09/32). All the patients who underwent surgery (prospective cohort) were classified into three groups according to two criteria: first, whether they received carmustine wafers; and second, whether they were treated with first-line chemotherapy.

The study variables are defined as follows:

*Age*: defined as the age of the patients (in years) *on the day of the surgery*.

*Preoperative KPS score*: calculated *the day before surgery*; in all cases the score was  $\geq 70$ .

*Histological grade*: WHO grade of each of the histological findings, glioblastoma multiforme and gliosarcomas being grade IV and anaplastic astrocytomas, oligodendrogliomas, and oligastrocytomas grade III.

*RPA class*: the RPA classes, in line with the original definition of Curran et al. [15]; these are summarised in Table 1.

*Extent of resection*: The extent of the surgical resection of the tumour was determined by means of a cranial CT scan *within 72 h after surgery*. In some patients this was carried out without contrast medium, while in a few cases the imaging test was not performed at all and the extent of resection was estimated, based on the impression of the neurosurgeon (as reflected in the surgical report) (see Table 2). The tumour volumes, both before and after surgery, were calculated using the equation  $(a \times b \times c)/2$ , as has been proposed for the estimation of the volume of intraparenchymatous haematomas [33]. Figure 1 illustrates this method used to calculate the volume of the tumours. In the few patients who did not have preoperative cranial CT scans, the initial tumour volume was calculated using the gadolinium sequence of the preoperative MRI.

This variable was classed into the following categories:

- “*Total resection*”: when in the postoperative CT scan there was no contrast uptake indicating abnormalities nor was there evidence suggesting the existence of tumour remains.
- “*Subtotal resection*”: when the residual tumour volume in the follow-up CT scan was less than 10% of the tumour volume calculated from the preoperative CT scan.
- “*Partial resection*”: when the residual tumour volume in the postoperative CT scan was more than 10% of the tumour volume calculated from the preoperative CT scan.

*Survival*: defined as the time elapsed from the *day of surgery* to *death* in days. In the case of patients who remained alive, the most recent date of *contact* with the patient was used (be it through specialist appointments, emergency room, health centres, palliative care centre, or telephone).

**Table 1** Description of the RPA classes according to the original classification of Curran (GBM, glioblastoma multiforme; AA, anaplastic astrocytomas)

| Class | Characteristics   |
|-------|---|
| I     | Age <50 years, AA; normal mental status   |
| II    | Age $\geq 50$ years, KPS 70–100, AA, symptom >3 m   |
| III   | Age <50 years, AA, abnormal mental status or<br>Age <50 years, GBM, KPS 90–100  |
| IV    | Age <50 years, GBM, KPS <90 or<br>Age $\geq 50$ years, KPS 70–100, AA, symptoms $\leq 3$ m or<br>Age $\geq 50$ years, KPS 70–100, GBM, surgical resection, able to work   |
| V     | Age $\geq 50$ years, KPS 70–100, GBM, surgical resection, unable to work or<br>Age $\geq 50$ years, KPS 70–100, GBM, only biopsy, radiotherapy dose >54.4 Gy or<br>Age $\geq 50$ years, KPS <70, normal mental status |
| VI    | Age $\geq 50$ years, KPS 70–100, GBM, only biopsy, radiotherapy dose $\leq 54.4$ Gy or<br>Age $\geq 50$ years, KPS <70, abnormal mental status  |

**Table 2** Specification of the extent of resection

| Extent of resection | Residual tumour volume Postoperative CT scan | Impression of the neurosurgeon as reflected in the surgical report |
|---------------------|--|--|
| Total               | 0%   | Total removal  |
| Subtotal            | <10%   | Subtotal removal   |
| Partial             | >10%   | Partial removal  |

*Treatment with temozolomide concomitantly to radiotherapy:* those patients, who, during their treatment with radiotherapy received any dose of temozolomide.

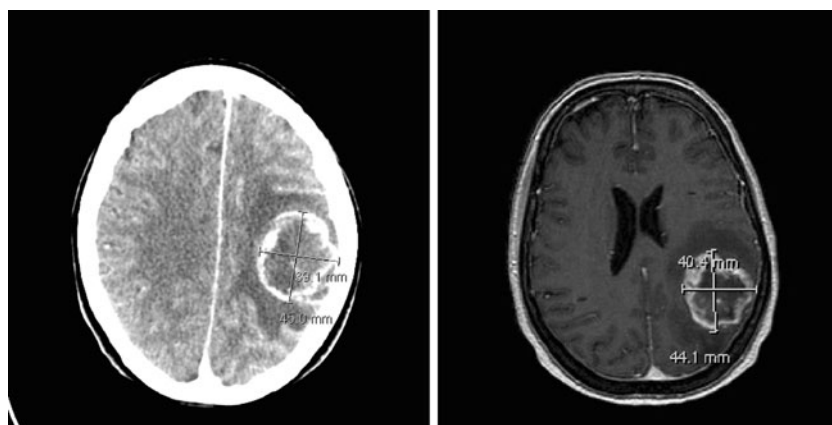
As there might have been a selection bias in the formation of the groups, we analysed whether there were statistically significant differences between the two groups, in terms of the main prognostic factors (age, histological grade, preoperative KPS score, and RPA class). Further, we analysed the differences between the groups with respect to the extent of resection and further treatment (second-line chemotherapy and salvage surgery) in order to rule out other potential confounding factors.

*Statistical analysis* Comparisons were made using the chi square, Student's t and Fisher's exact tests. We used the Kaplan-Meier (log-rank) method to determine the survival of all the patients in the cohort and that of those in each of two groups with different modalities of chemotherapy. This method was also employed to assess, in the entire cohort, the impact of various different prognostic factors on survival. For all the tests, p values < 0.05 were considered to be statistically significant.

## Results

During the study period, 113 patients underwent surgery by supratentorial craniotomy in our hospital, with histological confirmation of high-grade glioma. Of these patients:

**Fig. 1** Examples illustrating the method used for estimating the volume of the tumours



- A total of 55 patients received carmustine wafers, but not first-line chemotherapy; these formed the *Gliadel* group.
- Another 55 patients did not receive carmustine wafers and were considered eligible for first-line chemotherapy, on an intention-to-treat basis; they comprised the *non-Gliadel* group.
- The other three patients received carmustine wafers and were treated with first-line chemotherapy, but were *excluded* from the subsequent analysis due to the small number of cases. (These three patients underwent surgery in our hospital, but the chemotherapy treatment was carried out in other hospitals.)

The primary results of the recognised prognostic factors, as well as the extent of resection and the second-line treatments (chemotherapy and salvage therapy) are summarised for the two groups in Table 3.

As can be observed in Table 3, no statistically significant differences were found between groups with respect to the main prognostic factors (age, KPS score, histological grade, and RPA class), and, accordingly, we can conclude that there was no significant selection bias. Further, we found no differences with respect to other factors that might be sources of bias or confounding variables, such as the extent of resection or second-line treatments (second-line chemotherapy and salvage surgery for recurrence).

*Temozolomide concomitant to radiotherapy* A total of 39 patients (70.9%) in the non-Gliadel group were given TMZ during radiotherapy compared to none in the Gliadel group.

*First-line chemotherapeutic treatment* A total of 36 patients (65.5%) in the non-Gliadel group received first-line chemotherapy on an intention-to-treat basis compared to none in the Gliadel group. In 34 cases (61.8%), the therapy was based on TMZ following the Stupp protocol, while the two other patients (3.6%) were treated following the PCV protocol (4 and 6 cycles). The number of TMZ cycles administered is shown in Fig. 2:

**Table 3** Summary of the results of the prognostic factors (age, KPS score, histological grade, and RPA class), the extent of resection and second-line treatments (chemotherapy and salvage surgery)

| Variable            |          | Results     |             | Statistical test | Significance |
|---------------------|----------|-------------|-------------|------------------|--------------|
|                     |          | Gliadel     | Non Gliadel |                  |              |
| Age                 | Mean     | 59.04 years | 60.32 years | Student's t      | p = 0.519    |
|                     | Median   | 60.71 years | 63.69 years |                  |              |
| KPS score           | Mean     | 85.09       | 82.91       | Mann-Whitney U   | p = 0.220    |
|                     | Median   | 90          | 80          |                  |              |
| Histological grade  | III      | 8 (14.5%)   | 10 (18.1%)  | Chi-square       | p = 0.606    |
|                     | IV       | 47 (85.4%)  | 45 (81.8%)  |                  |              |
| RPA class           | I        | 4 (7.3%)    | 4 (7.3%)    | Chi-square       | p = 0.465    |
|                     | II       | 1 (1.8%)    | 1 (1.8%)    |                  |              |
|                     | III      | 7 (12.7%)   | 2 (3.6%)    | Mann-Whitney U   | p = 0.188    |
|                     | IV       | 23 (41.8%)  | 22 (40.0%)  |                  |              |
|                     | V        | 20 (36.4%)  | 26 (47.3%)  |                  |              |
| Extent of resection | Total    | 31 (56.4%)  | 25 (45.5%)  | Chi-square       | p = 0.515    |
|                     | Subtotal | 18 (32.7%)  | 22 (40%)    | Mann-Whitney U   | p = 0.258    |
|                     | Partial  | 6 (10.9%)   | 8 (14.5%)   |                  |              |
| Second-line chemo.  |          | 12 (21.8%)  | 7 (12.7%)   | Chi-square       | p=0.240      |
| Salvage surgery     |          | 13 (23.6%)  | 12 (21.8%)  | Chi-square       | p=0.820      |

*Systemic chemotherapy due to progression of the disease (second-line and beyond)* The number of patients in each group who were treated with second-line chemotherapy is indicated in Table 3, while Table 4 specifies the regimens (chemotherapeutic agents) administered as a second-line treatment to these patients.

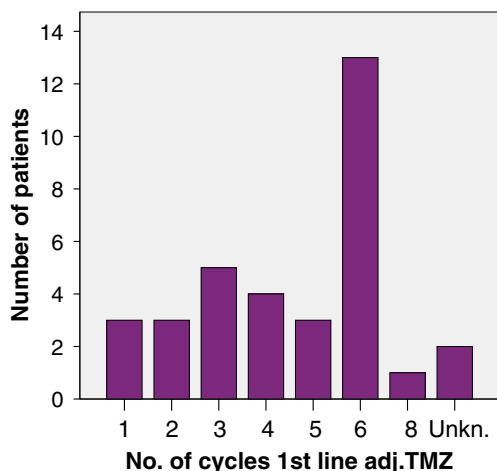
*Salvage surgery as second-line treatment* Table 3 also shows the number of patients in each group that underwent further surgical treatment for tumour resection. With regards to the histological diagnosis obtained after this second-line surgical treatment, it is worth highlighting that

in the group with carmustine wafers, five patients (38.46%) were seen to have necrosis due to the treatment, compared to none (0%) in the non-Gliadel group.

*Follow-up* The median follow-up period for the entire cohort was 43.13 months.

*Survival* The percentage of patients who survived to the different cutoff points are shown in Table 5.

*Death* At the moment when the survival analysis of this cohort was carried out, 91 of the patients (82.7%) had died [42 (76.4%) in the Gliadel and 49 (89.1%) in the non-Gliadel groups, respectively], progression of the brain tumour being the most common cause of death (74.54%).



**Fig. 2** Number of cycles of adjuvant TMZ administered to patients in the non-Gliadel group as first-line chemotherapy

**Table 4** List of the second-line chemotherapy regimens

| Second-line chemotherapy Protocol | Group       |             | Total       |
|-----------------------------------|-------------|-------------|-------------|
|                                   | Gliadel     | Non-Gliadel |             |
| TMZ                               | 11 (20%)    | 2 (3.63%)   | 13 (11.8%)  |
| PCV                               | 1 (1.81%)   | 0           | 1 (0.9%)    |
| BCNU                              | 0           | 4 (7.27%)   | 4 (3.63%)   |
| Bevacizumab+CPT-11                | 0           | 1 (1.81%)   | 1 (0.9%)    |
| Unknown                           | 0           | 2 (3.63%)   | 2 (1.81%)   |
| Total                             | 12 (21.81%) | 9 (16.36%)  | 21 (19.09%) |

**Table 5** Descriptive statistics of survival

| Survival     | Group      |             | Total      |
|--------------|------------|-------------|------------|
|              | Gliadel    | Non-Gliadel |            |
| <12 months   | 27 (49.1%) | 32 (58.2%)  | 59 (53.6%) |
| 12–18 months | 17 (30.9%) | 9 (16.4%)   | 26 (23.6%) |
| 18–24 months | 6 (10.9%)  | 5 (9.1%)    | 11 (10.0%) |
| >24 months   | 5 (9.1%)   | 9 (16.4%)   | 14 (12.7%) |
| Total        | 55 (100%)  | 55 (100%)   | 110 (100%) |

### Influence on survival

#### (1) Influence of the modality of treatment

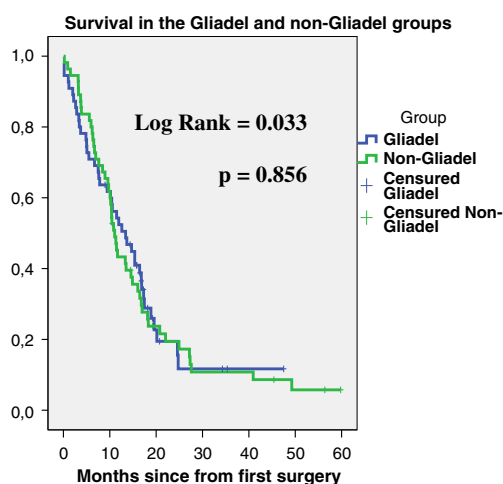
The median survival times of the Gliadel and non-Gliadel groups were 13.414 (8.542–18.826) and 11.047 (9.712–12.381) months, respectively. The details of the results are presented in Fig. 3, in which it can be seen that the differences observed were not statistically significant.

#### (2) Influence of the prognostic factors

Analysing the recognised prognostic factors and the extent of resection of the patients of the entire cohort using Kaplan-Meier curves and the log-rank test, we obtained the results listed in Table 6. As can be observed, age, preoperative KPS, histological grade, and RPA class were confirmed to be prognostic factors in this cohort. In addition, the extent of resection had a significant influence on survival.

#### (3) Influence of first- and second-line treatments

The results we obtained for the first- and second-line treatments, using the same analysis (Kaplan-Meier curves and the log-rank test), are shown in Table 7. Only the variable salvage surgery was found to be of statistical significance.



**Fig. 3** Comparison of survival between the two groups under study (Kaplan-Meier curve)

**Table 6** Summary of the influence of the prognostic variables and the extent of resection on survival on the entire cohort (KPS: Karnofsky Performance Score)

| Variable                                       | Log rank | Significance |
|--|----------|--------------|
| Age (<55, ≥55)                                 | 12.140   | $p < 0.0001$ |
| KPS score (70, 80, 90, 100)                    | 16.758   | $p = 0.001$  |
| Histological grade (III, IV)                   | 8.193    | $p = 0.004$  |
| RPA class (I, II, III, IV, V, VI)              | 19.514   | $p = 0.001$  |
| Extent of resection (total, subtotal, partial) | 12.919   | $p = 0.002$  |

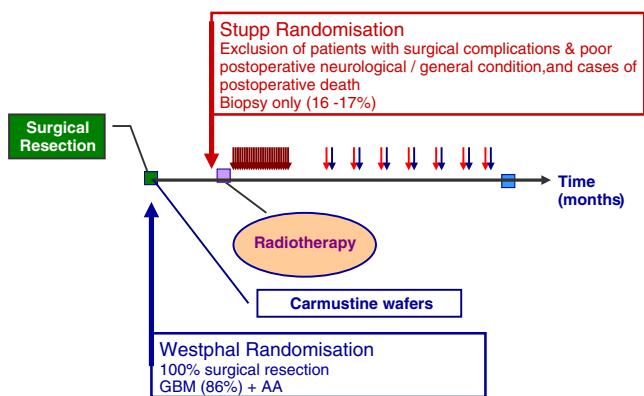
### Discussion

As described in the results, no statistically significant differences were found between the two modalities of treatment (with/without carmustine wafers), and, therefore, we cannot state that either of the modalities of treatment is more effective. It is not possible to make direct comparisons between the survival outcomes of the clinical trials of Westphal [65] and Stupp [61], given differences in the study designs, as shown schematically in Fig. 4. Specifically, the trial reported by Stupp et al. [61], like most clinical trials with first-line chemotherapeutic drugs, did not include patients who, after the initial resection surgery, suffered neurological deterioration, other complications or died, that is those who did not comply with the inclusion criteria at the start radiotherapy [26].

This approach brings down the survival rates of the patients treated in the carmustine wafer clinical trials, meaning that they compare unfavourably with the outcomes of patients treated in the first-line chemotherapy trials [45]. Brada and Yung [8] highlight this issue, indicating that the studies of first-line therapies should include patients on an intention-to-treat basis and not as a function of treatments administered. On the other hand, it should be highlighted that the analysis of Stupp et al. [61] included patients that only underwent biopsies (16.5%), who, as indicated in the literature, have a poorer prognosis than those who have resections [40]. With regards to the histological findings, in the Stupp study, 92% of the samples examined by the central laboratory were glioblastoma multiforme (15% were

**Table 7** Influence of treatment with concomitant TMZ, first- and second-line chemotherapy, and salvage surgery on patient survival in the entire cohort

| Variable                 | Log rank | Significance |
|--------------------------|----------|--------------|
| Concomitant TMZ          | 0.506    | $p = 0.477$  |
| First-line chemotherapy  | 3.349    | $p = 0.067$  |
| Second-line chemotherapy | 0.725    | $p = 0.394$  |
| Salvage surgery          | 7.187    | $p = 0.028$  |



**Fig. 4** Figure showing the differences between the trials of Stupp et al. [61] and Westphal et al. [65] (GBM, glioblastoma multiforme; AA, anaplastic astrocytomas)

not analysed). On the other hand, in the study of Westphal et al. [65], 86% of cases were grade IV tumours. Although there is a difference, it is not possible to ascertain whether it is statistically significant or whether it determines the differences observed in the median survival rates.

In our study, outcomes are analysed on an *intention-to-treat basis* at the moment of the surgical intervention, and only patients who underwent resection are included, so these two issues are resolved. As can be logically expected following this approach, rather than that of Stupp et al. [61], smaller percentages of patients started (85.45%/99%) and finished (81.81%/95%) radiotherapy treatment, received concomitant temozolomide (70.9%/98%), and initiated the phase of adjuvant chemotherapy (65.5%/78%).

If we compare the estimation of *survival* of the group of patients with carmustine wafers obtained in the present study (13.414 months) with that of other studies that include patients treated in the same manner, the results are very similar. For example, Kleinberg et al. [32] reported a figure of 12.8 months, Valtonen et al. [62] 13.37 months, Attenello et al. [6] 13.5 months (although in this study all the cases were glioblastoma multiforme), and Westphal et al. [65] (13.8 months for the group including all the patients who received implants and 13.1 months for the implant subgroup of those with glioblastoma). Affronti et al. [2] achieved survival of 12.78 months in a cohort of patients with glioblastoma who received rotational multi-agent chemotherapy as well as the carmustine wafers.

On the other hand, comparing the outcomes in patients who in our cohort received chemotherapy following the *Stupp* protocol [61], on an *intention-to-treat basis* (non-Gliadel group), with the result obtained by the authors in that trial (estimated median 14.6 months), the median survival in our study was somewhat lower (11.047 months). These differences can probably be attributed, as suggested earlier, to the fact that in the present study outcomes have been analysed on an *intention-to-treat basis* at the moment

of the first surgery and not with respect to the start of the radiotherapy treatment. Notably, Brandes et al. [9] obtained a median survival of 20.7 months in patients under 12-cycle temozolomide treatment, following the *Stupp* protocol, although in this case the patients were selected (by treatment administered) and had a median age of 53 years, slightly lower than those of the patients in the present study. On the other hand, Affronti [1] reported survival of 10.38 months in the group of patients without implants and rotational multi-agent chemotherapy, figures that are closer to those of our study. Further, in a series with an equivalent sample size to that of our study, a median survival of 13.4 months was obtained in the group treated following *Stupp* protocol and also with radiotherapy versus 7.7 months in the group receiving only radiotherapy [5].

As for the use of first-line chemotherapy, in our study, the difference in survival between patients who did and did not receive this treatment was close to significance ( $p=0.067$ ). This may lead us to consider that, in order to improve survival in our patients, it would be advisable to add first-line therapy according to the *Stupp* protocol [61] to patients who receive carmustine wafers, as suggested and tested by some authors [4, 24, 28, 51]. La Rocca et al. [36], in a phase II clinical trial, demonstrated that the combination of *carmustine wafers* followed by chemotherapy concomitant to radiotherapy and adjuvant temozolomide following the *Stupp* protocol [61] does not increase the toxicity with respect to either of the two modalities of treatment separately and increases patient survival (median 18.6 months). This synergy between the treatments may be based on the fact that temozolomide depletes DNA-repair enzymes that are responsible for the resistance to nitrosoureas (carmustine) [37, 40]. Further, this combination may be advantageous because these two modalities of treatment have the peak effect at different times: carmustine wafers start to work as soon as they are implanted and reach their peak effect at 12 months, while temozolomide starts to have an effect 30–40 days after surgery (start of radiotherapy), having a peak effect at 18 months [56]. Moreover, considering that patients with high-grade glioma cannot in general be cured with only one type of treatment, and that in other systemic cancers multimodality therapy (several chemotherapeutic agents) has been shown to be more effective [2, 37, 43], encourages us to think that the combination of carmustine wafers with temozolomide or even with rotational multi-agent therapies may be beneficial for our patients [20, 52]. Probably, the solution will not be only multi-agent chemotherapy, but rather treatment should be based on multimodality and multidisciplinary treatments, that is beyond surgery combining radiotherapy and chemotherapy [39].

In cases where there is progression of the disease, the options are *second-line chemotherapy* protocols different

from those used in the first-line treatment or *salvage surgery*. In this second phase of surgery, carmustine wafers may or may not be placed. In relation to this, Krzeminski et al. [35] indicated that the placement of said implants during surgical resection after tumour progression was safe, while McGirt et al. [42] demonstrated that, in such a re-intervention, total resection of the tumour improves patient survival. It should be taken into account that differences in the therapies for disease progression influence the analysis of the first-line treatments when only survival is analysed, as is the case in our study. However, the statistical tests applied did not detect any significant differences between the groups under study with regards to these second-line therapies, the second-line treatments administered being similar, and therefore, it is believed that they do not introduce significant bias to the analysis of the first-line therapies.

With respect to salvage surgery, Barbagallo et al. [7] state that re-intervention increases median survival by 3 to 5 months with no significant increase in morbidity or mortality. Further, it not only improves the symptoms, but also maintains quality of life and may delay the progression of symptoms and reduce the doses of steroids required. These authors considered age and the Karnofsky Performance Scale score to be most important factors. Similarly, the results of our study demonstrate that salvage surgery has an influence on survival. On the other hand, second-line chemotherapy did not seem to have an influence on prognosis.

The high rate of patients with *necrosis* in the histological analysis after re-intervention is worth particular mention, *all* the patients with this outcome being in the group with carmustine wafers (5 out of 13 re-interventions, that is, 38.46%), while there were no such cases in the group without implants. Similarly, Kleinberg et al. [32] found this histological finding in 5 out of 15 re-interventions (33%), while Attenello et al. [6], according to radiological criteria, found necrosis in 26% of patients who received carmustine wafers. These findings demonstrate good local tumour control, but raise another issue: distinguishing between the cases of necrosis and those of tumour progression, in order to avoid undertaking surgery in patients who may have progressed well with steroid treatment, or stopping treating patients with tumour progression, in the belief that it is necrosis after treatment. This phenomenon, initially described by Hoffman et al. [29] and revisited by Wit et al. [18], has been termed pseudoprogression, treatment-induced necrosis, and radionecrosis [11].

With regards to prognostic factors, we noted earlier that the mean ages are similar in the two groups, and, although the median age is slightly higher in the non-Gliadel group, we did not find statistically significant differences between

the groups. The overall mean and median ages of the patients who underwent surgery (59.68 and 61.69 years, respectively) indicate that ours is a slightly older cohort than those of the clinical trials discussed (53 years [65], 55 years [61], and 60 years [59]), our cohort age being closer to the median age for high-grade glioma described in the CBTRUS report [13].

In the comparison of older and younger groups of patients, it should be taken into account that older age tends to decrease survival. Further, as stated by Sawaya et al. [54], the rate of complications is higher in patients older than 60 years of age.

In terms of histological grade, there were patients with grade III and IV tumours in both of the study groups. Although the current trend, reflected in the most recent studies, is to consider grade III and grade IV patients separately, research conducted around the time when our research project began, in 2004, both randomised clinical trials that analysed the efficacy of carmustine wafers [12, 62, 65] and the trial reported by Stupp et al. [61], combined these two histological grades. In the latter study, while the intention had been to recruit only grade IV patients, histological analysis demonstrated that 4% of patients had grade III tumours. Further, in 15% of patients the histological sample was not analysed in the reference centre for histological analysis. Nevertheless, in order to avoid potential confounding effects due to mixing these two types of patients (grade III and IV), we analysed the groups separately and did not find any significant differences with respect to the proportions of grade III and IV patients in the groups under study (Table 3).

In the present study we observed that the *RPA class* does influence survival, and, accordingly, the classes define groups of patients with a different *prognosis*. This is in line with the reports of some other authors [2, 44, 48] who have identified RPA class as a prognostic factor. The estimation of the overall median survival in this study (including all the patients) is very similar to the figures obtained in Stummer's clinical trial [58] and by Pichlmeier et al. [48]. The rates of 2-year survival are also similar to those reported in this latter publication [48] and in the earlier paper by Curran et al. [15]. The differences found with respect to other results in the literature [2, 44] may be due to the use of more selective inclusion criteria for patients in those studies.

Historically, not much importance has been given to the extent of tumour resection in the treatment of high-grade glioma. Probably, the poor prognosis of this type of cancer and the lack of ways to determine the extent of resection achieved, prior to the use of brain CT imaging, contributed to this. Subsequently, most studies investigating the extent of resection in patients with high-grade glioma have lacked

an objective way of measuring the volume of the tumour removed [3, 38, 57], assessments being based on the impression of the neurosurgeon alone. It has been demonstrated that this does not reliably correlate with the extent of resection as assessed by postoperative neuroimaging [3, 34]. Even in relatively recent research, in which neuroimaging studies have been used to measure the extent of resection, the interpretation and comparison of the results is difficult: various imaging modalities are used, there are several ways of calculating the tumour volume, and the scans have been performed on different numbers of days after the surgery [38]. In part due to all of this, the evidence in this field is not yet conclusive.

Sanai et al. [53] reviewed the scientific evidence with regards to impact of the extent of surgical resection on survival of people with glial tumours and, although there is no grade I evidence, they conclude that “mounting evidence suggests that *more extensive surgical resection* is associated with *longer life expectancy* for both low- and high-grade gliomas”. Further, Proescholdt [50] reported that 72.5% of the papers that analyse the extent of resection in glioma find that total tumour resection is beneficial. On the other hand, a randomised study analysing the extent of tumour resection would raise multiple problems [38], including ethical issues [23, 53], and so it is very difficult to obtain grade I evidence.

With the introduction of postsurgical neuroimaging, it is agreed that the extent of resection should be determined using gadolinium MRI within 72 h after surgical intervention [8, 16, 31, 46, 47]. However, the most precise and objective way to measure the residual tumour volume has not yet been defined [30]. Although in this study we have not performed this type of MRI scan at this point, we have monitored patients using contrast-enhanced cranial CT scans within 72 h after surgery. This non-volumetric technique, though not the gold standard, provides a better estimation of the extent of tumour resection than that used in most studies published to date that base this assessment on the impression of the neurosurgeon, including, for example, the Stupp trial [60, 61]. Proescholdt [50] found that up to 75% of the studies do not estimate the extent of resection or base estimates only on the impression of the neurosurgeon, while 19.2% and 1.6% use postoperative CT and MRI scans, respectively, and only 3.4% of the studies perform volumetric neuroimaging studies (CT or MRI).

Despite these limitations, we found the extent of resection to be a *prognostic factor*. In relation to this, and in agreement with our study, the most important clinical trials carried out concerning the treatment of high-grade glioma [61, 65] have also demonstrated that the subgroups of patients with the most extensive resections had a better prognosis [21, 63, 66].

In the present study, we achieved total resection in as many as 51% of the patients, although we have to recognise that the method for assessing the extent of resection, as already discussed above, is not the gold standard. These figures lie in the range published by Stummer [58] who achieved 65% of total resections in the group of patients in which fluorescence-guided resections (using 5-aminolevulinic acid) were carried out and 36% in the group who underwent conventional surgery using white light. The same author in another study [59] reported 50.2% of total resections. All these data encourage us to try to achieve, as far as possible, the most extensive resections feasible, while maximising the functional status of our patients.

Although this study was not randomised or blinded, and despite the fact that the analysis was *retrospective*, it reports the outcomes of two subgroups of a consecutive prospective cohort of patients treated in the same centre, during the same period of time. Moreover, as has been demonstrated, the *groups are homogenous* with regards to the most relevant prognostic characteristics, such as age, preoperative KPS score, histological grade, and RPA class, and there were no significant differences in the extent of resection or the percentage of patients receiving radiotherapy (see Table 3). Therefore, this work has the validity of an *observational study*, comparable to other studies with similar characteristics [10, 49], as it complies with the requirements for well-carried out *observational studies* as indicated by Concato [14], Hartz [27], and Silverman [55].

## Conclusions

In this prospective cohort of patients, analysing outcomes on an intention-to-treat basis at the moment of the first surgery, we did not find any significant differences between a group of patients receiving carmustine wafers and another group, with no implants placed, considered on an intention-to-treat basis for treatment with first-line systemic chemotherapy (basically in accordance with the Stupp protocol). It was observed that in this cohort, age, preoperative KPS score, histological grade, RPA class, and extent of resection influence survival. We believe that the finding with respect to RPA class is particularly useful. The methods to assess the extent of resection must be standardised, to achieve optimal reproducibility, so that higher quality scientific evidence can be obtained in the field of neurosurgery.

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**Conflicts of interest** None.

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## Comment

This study examined prognostic factors and survival in a prospective cohort of patients with high-grade glioma treated with carmustine wafers or temozolomide on an intention-to-treat basis.

The authors retrospectively analyzed a cohort of 110 patients operated on for a single, supratentorial grade III (n=18) or grade IV glioma (n=92). The 55 patients who did NOT receive carmustine wafers (for one reason or another) were candidates for temozolomide (TMZ), and the 55 patients who likewise received carmustine wafers were NOT candidates for TMZ. Univariate analysis suggested that age, postoperative KPS score, histological grade, RPA class, extent of resection, and salvage surgery were significantly associated with survival.

### Lessons:

1. Do not attempt to publish this kind of data without multivariate analysis, not even in a small cohort like this.
2. These data are not valid in terms of wafers + TMZ - vs. wafers - TMZ +.
3. In future trials of GBMs, the treatment group and the placebo group should be adjusted for several prognostic factors, making GBM trials extremely difficult (almost undoable?).

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