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Survival and prediction of distant recurrence in glioblastoma

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ABSTRACT

Introduction. Glioblastoma is the most prevalent and aggressive primary tumor of the nervous system. The condition manifests with a high rate of recurrence, predominantly in a localized pattern. The impact of distant recurrence on survival and the associated factors are a controversial subject. This study aims to determine whether the pattern of distant recurrence exerts any influence on progression-free survival, survival after first progression, and overall survival in patients with *de novo* glioblastoma and low residual tumor volume (RTV) < 5 cc. It also aims to identify which factors predict distant recurrence.

Material and methods: A retrospective single-center cohort study included patients aged 18 years or over with *de novo* glioblastoma and RTV < 5 cc after histological diagnosis, who were treated between 2017 and 2023 in our center. Kaplan–Meier curves were utilized for time-to-event analyses. Risk factors were assessed by univariable analysis and logistic regression.

Results: The analysis encompassed 102 patients with a median survival period of 12.9 months. Distant recurrence was associated with a more extended progression-free survival (11.9 months; p = 0.003) and overall survival (21.5 months; p = 0.021) compared with the remaining patterns (6.1 and 12.7 months, respectively), with no significant impact on survival after the first progression. Epidermal growth factor receptor (EGFR) amplification (odds ratio [OR] = 3.42, 95% confidence interval [CI]: 1.14–10.60; p = 0.029) and Ki-67 < 30% (OR = 6.15, 95% CI: 1.12–33.67; p = 0.036) were identified as independent risk factors for distant recurrence.

Conclusions: Distant recurrence in glioblastomas with low tumor burden after diagnosis is associated with superior progression-free survival and overall survival compared with other recurrence patterns. The EGFR amplification and Ki-67 < 30% were identified as independent risk factors for distant progression.

Clinical implications: The study underscores the significance of incorporating molecular profiling into decision-making processes for patients with glioblastoma. Furthermore, stratification by recurrence patterns has the potential to enhance the efficacy of future clinical trials.

Keywords: distant, glioblastoma, progression-free survival, recurrence, risk factors, survival

Introduction

Glioblastoma is the most common and aggressive primary malignant tumor of the nervous system. The most effective treatment to date is the 'Stupp protocol'. It involves maximal surgical resection, followed by treatment with concomitant chemotherapy (CT) and radiotherapy (RT), and then adjuvant chemotherapy with temozolomide [1]. The median overall survival is 16 months [2], but in cases of recurrence or progression, survival varies between three and nine months from detection [1]. Therefore, it is a highly aggressive disease with a high relapse rate and limited response to second-line therapies.

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Seventy per cent of patients with glioblastoma experience tumor recurrence or progression within the first year of diagnosis [1]. In most cases, it is localized to the surgical site or within 2–3 cm of the initial tumor [3, 4]. Conversely, multicentric or distant recurrence is more frequent in later stages of the disease [5], while leptomeningeal dissemination is even rarer (2–6%) and usually appears in the final stage [6].

Different patterns of progression imply clinical differences that may affect salvage treatments. Local recurrence usually offers more options for salvage surgery and improves prognosis compared to multicentric recurrence [7]. Additionally, distant, multicentric, and leptomeningeal recurrences have been associated with poorer survival in patients receiving bevacizumab at recurrence [8]. However, other studies have found that distant recurrence may be associated with a longer progression-free survival, although it is unclear whether this affects overall survival [4, 9, 10]. Therefore, the importance of the recurrence pattern lies in its possible relationship with survival.

Among the factors associated with the pattern of recurrence or progression and overall survival, residual tumor volume (RTV) emerges as a critical variable. This is not only because it reflects the extent of resection (EOR) but also because it may modulate residual tumor dynamics independently of treatment beyond the standard chemoradiotherapy (CT-RT) protocol [11]. Supramarginal surgical resection appears to reduce the risk of local recurrence while increasing the rate of distant recurrence. Conversely, partial resection appears to increase the risk of local recurrence while reducing the number of new distant lesions [12]. Quantitatively, it has been estimated that in tumors with the potential for complete macroscopic resection, a RTV under 2 cc is associated with a greater reduction in the risk of death and recurrence than larger volumes [13]. However, when considering the heterogeneity of glioblastoma, which often presents unfavorable locations due to the risk of postoperative deficit or multicentricity at diagnosis, the threshold with the most significant impact on survival and recurrence risk is estimated to be 5 cc [14].

The tumor's location may also influence the patterns of progression or recurrence. For example, infiltration of the subventricular zone (SVZ) has been associated with greater distant and multifocal recurrence, possibly due to its proximity to the ventricles, which favors subependymal dissemination [2, 15]. Additionally, this location has been linked to a higher rate of incomplete resection and a greater likelihood of ventricular entry during the procedure [16, 17]. This last technical detail has been associated with an increased risk of leptomeningeal dissemination [18], although no direct link has been established with distant recurrence risk or survival differences [15, 17, 19]. Conversely, several studies have reported a higher risk of recurrence in patients with cortical tumors at diagnosis [16, 20]. Therefore, a direct relationship between SVZ infiltration and distant recurrence has not been conclusively established.

Different molecular profiles have also been linked to recurrence patterns. *MGMT* gene promoter methylation, which prevents gene expression and is associated with a better response to temozolomide, has been associated with a higher rate of distant recurrence and a better response to retreatment with CT after progression. However, other studies have observed an opposite association, finding a higher risk of distant metastasis in the absence of *MGMT* gene methylation [21, 22]. Meanwhile, Rapp et al. [4] found no relationship.

Epidermal growth factor receptor (EGFR) amplification has been associated with distant recurrence as it increases cell proliferation and trophism [21], although it has no clear impact on survival [23]. Other factors, such as overexpression of the surface marker CD133, have been linked to earlier distant recurrences, which are even more prevalent in glioblastomas located in the SVZ [20]. A high Ki-67 proliferation index (> 20%) is associated with greater aggressiveness and poorer survival [24]. Meanwhile, mutation of the *TP53* gene, which encodes the p53 protein, has been related to increased intratumoral heterogeneity and progression. However, it is unclear whether there is a relationship between the Ki-67 index, p53 pathway mutations, and the pattern of distant recurrence.

Considering the role of the administered treatments, beyond the previously mentioned impact of surgery, initial local control of the disease could influence a higher probability of distant dissemination. Complete surgical resection [9], CT-RT protocols with dose intensification [25], and CT [26] have been described as protective factors against local dissemination. However, evidence regarding second-line drugs is limited.

It is important to consider the substantial changes introduced by successive modifications to the World Health Organization (WHO) classification of nervous system tumors. The 2021 edition identifies *IDH*-mutated grade 4 astrocytomas as distinct from glioblastoma, which currently includes any non-mutated *IDH* astrocytoma. This distinction is based on observed differences in prognosis between the two groups [27]. Most research conducted prior to this modification includes mutated *IDH* grade 4 astrocytomas [10, 17, 20]. Consequently, few studies analyze risk factors, specifically in patients with glioblastoma, according to the latest classification [2, 16]. In some cases, patients who have undergone surgery followed by CT-RT are selected [4, 10, 12], while in others, patients who have received some but not necessarily all these therapies are selected [15, 19]. Another controversial element is the variability in the definition of distant recurrence. Some authors use the term "non-local" recurrence, which includes multifocal and/or distant recurrence [20]; others include distant and leptomeningeal recurrence in the same group [4]; and others consider distant recurrence to be any recurrence at a variable distance from the primary focus [2, 9, 17].

Despite growing interest in understanding the impact of glioblastoma distant recurrence on overall survival and the factors involved in its development, available evidence remains heterogeneous. It is often based on cohorts that do not fully conform to the current definition of glioblastoma. There are also significant discrepancies in the definitions of distant

recurrence and inclusion criteria, making it difficult to draw solid conclusions. Additionally, the possible interaction between clinical, surgical, and molecular variables in predicting these recurrence patterns is not well established and requires further investigation.

In this context, the selection of glioblastoma patients according to the most recent classification with lower tumor burden, and therefore lower recurrence risk, has not yet been evaluated. This approach may help identify recurrence patterns in a more homogeneous group. Identifying possible factors associated with each recurrence pattern could contribute to better risk stratification and the development of personalized therapeutic strategies.

This study aims to determine the impact of the distant recurrence pattern on progression-free survival, survival after the diagnosis of the first progression, and overall survival in patients with *de novo* glioblastoma and a low tumor burden, compared to other patterns. The secondary purpose is to identify predictive factors of distant recurrence in this patient subgroup.

Material and methods

The study employed a single-center, retrospective observational design. It was approved by the Ethics Committee of the center (reference PI 99/24) and was conducted in accordance with the 1964 Declaration of Helsinki and its subsequent modifications or comparable ethical standards.

Setting and patient selection

Data were obtained from the tumor registry of the Puerta de Hierro University Hospital. All patients who met the following inclusion criteria were retrospectively analyzed: over 18 years of age; with a codified diagnosis of glioma or diffuse astrocytoma; treated at the Puerta de Hierro University Hospital between January 1st, 2017, and December 31st, 2023.

Patients were excluded from the study if they met any of the following criteria: diagnosis of oligodendroglioma; lack of histological confirmation of the diagnosis (only radiological suspicion); presence of *IDH* mutation or unknown *IDH*; incomplete information due to lack of imaging tests or loss of follow-up (transfer to another center or city); subjects who did not receive any treatment at the center (second opinion consultation); RTV equal to or greater than 5 cc.

Independent variables

The patient's electronic medical record was reviewed, and, when deemed pertinent, reports and imaging tests from other centers were obtained. The following variables were systematically collected during this process: age; gender; preoperative and postoperative functional status assessed by the "Karnofsky performance status" (KPS) scale; presence of preoperative and/or postoperative seizures; tumor volume at diagnosis (measured in cc in magnetic resonance imaging [MRI] considering the area of contrast enhancement); location (frontal, temporal, parietal, occipital lobes and deep region, which includes insula, basal ganglia and corpus callosum); invasion of the SVZ (defined as a maximum distance of 2 mm from the ventricular ependyma); invasion of eloquent areas according to the classification of Chang et al. [28]; multicentric tumor at diagnosis; RVT after diagnostic surgery (measured in cc in the postoperative MRI); date of surgery; EOR (considering complete resection as the removal of 100% of the contrast enhanced zone, subtotal resection as 95–99%, partial resection as less than 95%, and biopsy as only sampling for histological diagnosis without removal intent); fenestration of the ventricular wall during the procedure; use of intraoperative tools (intraoperative MRI, fluorescence, neurophysiological monitoring, intraoperative ultrasound); RT protocol, CT protocol; administration of the Stupp protocol after histological diagnosis (concomitance of RT and CT followed by at least 3 adjuvant cycles of temozolomide); *MGMT* gene promoter methylation, *ATRX* mutation, p53 overexpression, proliferative index assessed by Ki-67 percentage, and EGFR amplification.

Endpoint

The recurrence date was defined as the date of the MRI that indicated recurrence or progression of the disease. Recurrence or progression of the disease was classified as follows: local (surgical site), distant (more than 1.5 cm from the original focus, with intervening healthy parenchyma), or multicentric (coincident local and distant recurrence). In cases where clinical progression was suspected due to the deterioration of the patient's condition but no confirmatory imaging test was obtained prior to death, it was classified as clinical progression. These patients were included solely to calculate recurrence and survival rates, not to analyze the radiological pattern.

Survival was calculated as the time from the date of diagnostic surgery to the date of death or the end of the follow-up period (February 2025). According to the report of a neuroradiologist and the treating specialist, progression-free survival was calculated as the time from diagnostic surgery to the first radiological tumor recurrence or progression.

Statistical analysis

The data set was processed and analyzed using R statistical software version 4.3.3. Descriptive analyses were performed for categorical variables using absolute and relative frequencies, and for numerical variables using the mean and standard deviation (SD) as well as the median and 25th and 75th percentiles (P25; P75). For time-to-event analyses (death or progression), Kaplan–Meier curves were used, and groups were compared using the log-rank test.

To determine the association between different variables and the probability of distant recurrence, the chi-square test ($\chi 2$) or Fisher's exact test were used for categorical variables and the Mann–Whitney U test for continuous variables. The significance level was set at 0.05. For statistically significant

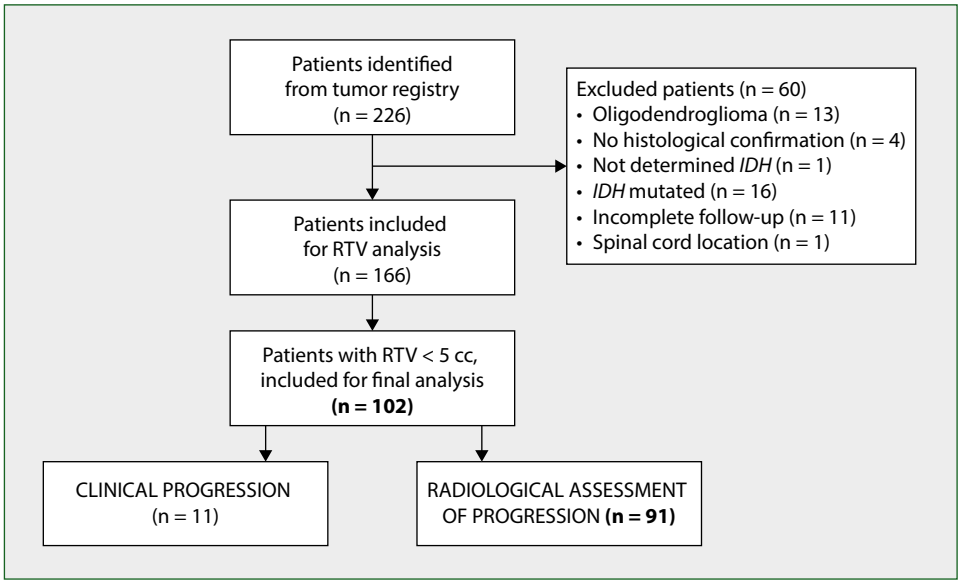

Figure 1. Flowchart illustrating patient selection; RTV — residual tumor volume

candidates and those with marginal value ($p < 0.1$), logistic regression was performed. Odds ratios (OR) and their corresponding 95% confidence intervals (95% CI) were estimated for all analyses. Therefore, all statistical hypotheses were subjected to a two-tailed test, and the null hypothesis was rejected in all hypothesis contrasts with type I error or α error inferior to 0.05.

Results

Sample description

Initially, 226 patients were identified, of whom 60 were excluded (Fig. 1). Therefore, the RTV after surgery was analyzed for the remaining 166 patients. The 102 patients with a RTV under 5 cc after histological diagnosis were selected for the final analysis. Eleven of these cases were classified as clinical progression (in the absence of radiological confirmation), which ultimately resulted in death.

The mean age of the sample was 61.1 years (SD 10.01), with a predominance of men (53.0%). Preoperatively, 32.0% of the patients presented with a seizure, and 83.5% of the patients were treated with levetiracetam for therapeutic or prophylactic purposes. An additional 6.6% of patients received a different antiseizure drug. The median preoperative KPS score was 100 (90; 100). In descending order of frequency, the tumor locations were the frontal lobe (34.0%), temporal lobe (32.0%), parietal lobe (23.0%), deep region (6.9%), and occipital lobe (2.9%). A total of 63.0% of the tumors were in an eloquent area, and 36.0% presented a multicentric pattern at diagnosis. Additionally, 35.0% of the subjects exhibited tumor invasion in the SVZ. The mean tumor volume at diagnosis was 22.3 cc (SD 20.92).

The surgical procedure was a biopsy in 9.8% of the cases, achieving complete resection in 24.0% of the patients. The median EOR was 97.9% (87.3; 99.8), and the median RTV was 0.37 cc (0.05; 1.15). Different surgical tools were used in 42.8% of the procedures that recorded this information, in addition to the navigation used in all cases. In 12.0% of the procedures, ventricular entry was confirmed.

The molecular study confirmed the presence of *MGMT* gene promoter methylation in 41.0% of the patients for whom this information was available. It also confirmed an *ATRX* mutation in 4.0% of the patients, an EGFR amplification in 67.0%, as well as p53 overexpression in 69.0% of the patients. Finally, the Ki-67 index was less than 30% in 47.0% of patients who registered this information.

Following the intervention, 58.0% of patients completed the Stupp protocol. The median progression-free survival from diagnosis was 6.57 months. Clinical progression occurred in 10.8% (11 out of 102) of cases, resulting in death. Only 2.0% (2/102) of the patients did not present any progression or recurrence in their evolution, while the rate of distant progression was 25.3% (23/91). After the diagnosis of recurrence, 15.0% underwent salvage surgery, 13.0% received RT, and 54.0% received CT. The median overall survival was 12.9 months (Suppl. Tab. 1).

Recurrence pattern and progression-free survival

The likelihood of progression-free survival was 53.9% (95% CI: 45.1–64.5) at 6 months after diagnosis, 26.3% (95% CI: 19.0–36.5) at 1 year, and 6.8% at 2 years (95% CI: 3.3–14.3). When analyzing the probability of progression according to the radiological pattern of recurrence (local, multicentric, and

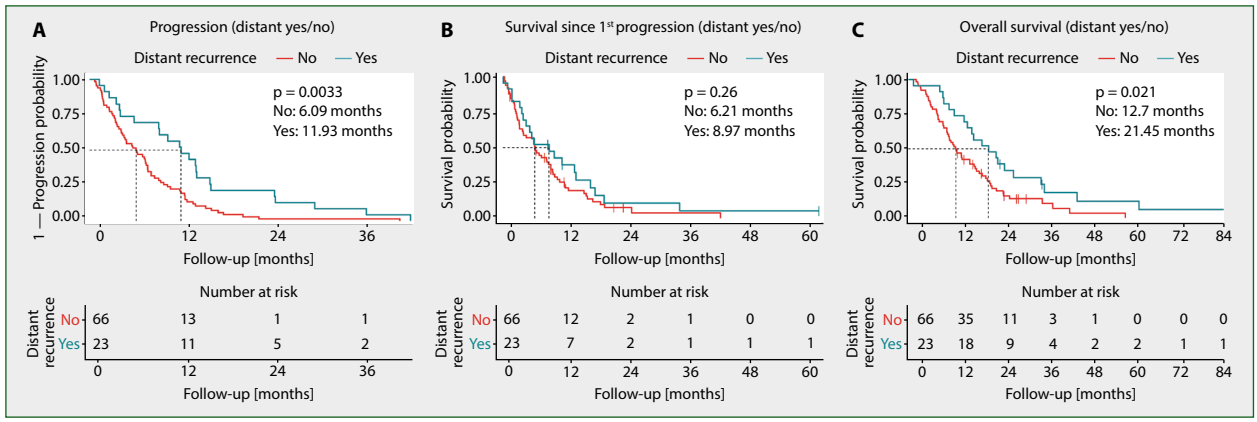

Figure 2. Kaplan–Meier curves. **A.** Progression-free survival as a function of distant recurrence pattern; log-rank test p = 0.003; median progression-free time as a function of each pattern is added; **B.** Survival following first progression as a function of distant recurrence pattern; log-rank test p = 0.260; median survival after first progression as a function of each pattern is added; **C.** Overall survival as a function of distant recurrence pattern; log-rank test p = 0.021; median survival as a function of each pattern is added

distant), it was observed that the progression-free survival was significantly more prolonged when the recurrence was distant (Suppl. Fig. 1; p = 0.013).

When comparing distant recurrences to the rest of the patterns (local and multicentric), distant recurrences occurred later (median 11.9 months; Fig. 2A; Suppl. Tab. 2). Additionally, the progression-free survival was significantly shorter when the recurrence was of another type (median 6.1 months; p = 0.003).

Survival following first recurrence

The probability of survival was 50.6% (95% CI: 41.7–61.5) at 6 months from the first progression, 24.5% (95% CI: 17.7–35.0) at 1 year, and 7.7% (95% CI: 3.6–16.4) at 2 years. The median survival after the first progression was 6.0 months.

No statistically significant difference in survival after the first progression was observed between a distant pattern and the rest (p = 0.260; Fig. 2B; Suppl. Tab. 3).

Overall survival

The overall survival probability was 79.4% (95% CI: 71.9–87.7) at 6 months from diagnosis, 54.9% (95% CI: 46.0–65.4) at 1 year, 22.1% (95% CI: 15.1–32.2) at 2 years, and 3.6% (95% CI: 1.0–13.3) at 3 years. The median overall survival was 12.9 months.

The distant survival pattern was associated with significantly longer overall survival (median 21.5 months) compared to the other patterns (median 12.7 months; p = 0.021; Fig. 2C, Suppl. Tab. 4).

Risk factors for distant progression

Univariate analysis revealed a significant association between the rate of distant progression and the presence of EGFR amplification, a Ki-67 proliferative index less than 30%, and tumor location in an eloquent area (Tab. 1).

Logistic regression analyses were then used to calculate the magnitude of the association (Tab. 2). The presence of EGFR amplification was associated with a 3.42-fold higher likelihood of distant progression compared to patients without amplification. Furthermore, a low proliferative index — defined as less than 30% — was found to be associated with a 6.25-fold higher risk of distant progression compared to tumors exhibiting elevated Ki-67 levels. Tumor location in an eloquent area was found to have a protective effect on distant progression, although this effect was only marginally significant. Conversely, ventricular entry and adjuvant therapy following the Stupp protocol were associated with an increased risk of distant progression, but this association did not reach statistical significance.

Conclusions and discussion

This study confirms that the pattern of distant tumor progression was associated with longer progression-free survival and more prolonged overall survival in patients with glioblastoma and low tumor burden. However, survival after the first progression showed no significant differences. EGFR amplification and proliferative index Ki-67 < 30% were identified as independent risk factors for distant progression.

The recurrence rate of 98% observed in this series was local in most glioblastoma patients, although this rate was lower (52%) compared to other studies (70–90%) [2, 4, 10]. The percentage of patients with distant and multifocal recurrences varies, ranging from 10–50% [4, 12] to 10–40% [4, 15]. In our experience, these patterns reached 25% and 21%, respectively. It is essential to consider the selection of patients with low RTV to elucidate the disparities in comparison to other studies.

The median distant progression-free survival was almost 12 months, a result that is significantly higher than that

Table 1. Univariate analysis of factors associated with the pattern of distant progression

Variable	Local or multicentric progression (n = 66)[1]	Distant progression (n = 23)	P-value
Age at diagnosis [years]	60.82 (10.87)	59.22 (6.45)	0.388
Gender [male]	39 (59%)	11 (48%)	0.384
Preop KPS	100 (90; 100)	100 (90; 100)	0.846
Location			0.284
Frontal	24 (36%)	7 (30%)	
Temporal	17 (26%)	11 (48%)	
Parietal	17 (26%)	5 (22%)	
Occipital	2 (3%)	0 (0%)	
Deep	6 (9.1%)	0 (0%)	
Eloquence	44 (67%)	10 (43%)	**0.050**
Multicentric	24 (36,5%)	8 (35%)	1.000
SVZ	21 (32%)	8 (35%)	0.794
EOR			0.359
Complete	14 (21%)	8 (35%)	
Subtotal	28 (42%)	10 (43%)	
Partial	18 (27%)	5 (22%)	
Biopsy	6 (9.1%)	0 (0%)	
RTV [cc]	0.33 (0.08; 1.10)	0.20 (0.00; 0.68)	0.260
Ventricular entry	4/66 (6.1)	4/21 (19.0)	**0.073**
MGMT methylation	22 (35%)	10 (45%)	0.380
ATRX mutation	2 (3,3%)	2 (11%)	0.238
EGFR amplification	15 (27%)	10 (56%)	**0.025**
p53 overexpression	21 (75%)	4 (50%)	0.214
Ki-67 ≥ 30%	20 (61%)	2 (20%)	**0.034**
Postop KPS	90 (80; 100)	100 (90; 100)	0.151
Adjuvant Stupp protocol	38 (58%)	18 (78%)	0.077
Progression-free survival [months]	6.09 (3.12; 10.20)	11.93 (4.97; 16.01)	**0.003**
Survival following 1st recurrence [months]	6.21 (2.52; 10.17)	8.97 (3.87; 14.33)	0.260
Overall survival [months]	12.90 (7.93; 20.77)	21.77 (13.77; 32.23)	**0.006**

[1]Mean [standard deviation (SD)]/median (P25; P75); n (%); EGFR — epidermal growth factor receptor; EOR — extent of resection; KPS — Karnofsky Performance Scale; N — absolute value; RTV — residual tumor volume; SVZ — subventricular zone

observed for local (less than 6 months) and multicentric (approximately 7 months) recurrences. These findings align with other studies that have also reported an association between distant recurrence and a more delayed recurrence time vs. other patterns [4, 9, 10, 25, 29]. Tejada et al. [10] observed a difference of 13.8 months in the non-local pattern vs. 6.4 months in local recurrence, while Rapp et al. [4] found differences along the same lines but without reaching statistical significance (13 months in distant recurrence and 7 months in local recurrence). In contrast, other authors found a non-significant difference of opposite sign, with local progression being later (median 8.5 months) compared to other patterns (7 months for distant progression, 6 months for subependymal and leptomeningeal dissemination) [2]. However, we did not observe differences in survival after the first recurrence attributable to the pattern, as other authors have found [2]. Finally,

Table 2. Logistic regression analyses for distant recurrence. Each row represents an independent model

	Distant recurrence		
Factor	OR	95% CI	P-value
EGFR amplification	3.42	1.14–10.60	**0.029**
Ki-67 < 30%	6.15	1.12–33.67	**0.036**
Eloquence	0.38	0.14–1.01	0.054
Ventricular entry	3.65	0.83–16.12	0.088
Adjuvant Stupp protocol	2.65	0.88–8.01	0.083

CI — confidence interval; EGFR — epidermal growth factor receptor; OR — odds ratio

some authors have reported lower survival rates in cases of multifocal and distant progression [10, 29].

The overall survival of glioblastoma varies considerably between series, with estimates ranging from 14.6 months

in the study by Stupp et al. [1] to 21 months in the study by Tejada et al. [10]. In our study, the median survival was 12.9 months, considering the selection of patients with low RTV and non-mutated *IDH*. This discrepancy could be attributed to differences in the clinical, surgical, or molecular characteristics of the cohorts, as well as to different inclusion criteria (such as the inclusion of *IDH*-mutated astrocytomas in the analysis, only patients with complete surgical resection, or treatment with Stupp protocol in all cases) [5, 9, 10]. Although the evidence is limited, studies have shown significant differences in overall survival based on the recurrence pattern. For example, Tsuchiya et al. [3] (23 months for the local pattern, 17 for distant recurrence, 14 for leptomeningeal dissemination, and 13 for subependymal dissemination), Rapp et al. [4] (overall survival of 21, 20, and 14 months in cases of local, distant, and multifocal recurrence, respectively), or Jiang et al. [2] (23 months of survival in cases of local recurrence and 17 months in cases of distant recurrence).

In all cases, the results are contrary to those described by Tejada et al. [10] and De Bonis et al. [9], as well as to our own experience, which also suggests that longer progression-free survival contributes to prolonged overall survival when the recurrence pattern is distant. However, once progression has occurred, the pattern does not appear to influence subsequent evolution.

Previous studies have identified risk factors for distant recurrence, including SVZ involvement, *MGMT* gene promoter methylation [2, 3], male sex [2], and preoperative tumor volume [10]. However, these factors have not been confirmed in our series, nor have they been confirmed in other analyses [17]. However, our experience indicates that EGFR amplification is associated with a 3.42-fold higher probability of distant progression compared to cases in which amplification is absent. This finding aligns with the observations reported in the only two studies published to date that analyze this relationship [21, 22]. Conversely, while prior studies have identified Ki-67 expression levels above 20% and p53 expression as indicators of poor survival [24, 30], this study reveals a novel association: low Ki-67 proliferative index (< 30%) significantly increases the risk of distant progression by a factor of 6.15 compared to other patterns. Notably, no discernible relationship was observed between recurrence patterns and p53 expression. Additional factors, including ventricular fenestration during surgery (increasing the risk of subependymal dissemination) and adherence to the Stupp protocol (which may involve greater local control of the disease), tended to elevate the risk of distant progression. Conversely, infiltration of eloquent areas was observed to act as a protective factor (a possible explanation may be a lower rate of complete tumor removal that increases the risk of local progression). However, none of these three factors reached statistical significance, and previous experience is inconclusive [3, 18, 21].

Multimodality radiological techniques, such as diffusion tensor imaging-based tractography, show promise in identifying brain regions at risk for distant recurrence, even before it is visible on conventional imaging [31]. This technique is not routinely used at our center, so it was not considered in the analysis. However, this is a field that must be further explored because the technique could be used to plan treatment for patients at high risk and detect recurrence in earlier stages.

From a biological standpoint, the increased survival observed in distant recurrences is associated with an extended progression-free period. This could be indicative of more infiltrative, less proliferative, and ultimately less aggressive tumor behavior in the early stages. However, once progression occurs, the remote location of the tumor could interfere with new therapeutic interventions, limiting survival beyond that point.

It is essential to underscore the limitations of this study, including the selection bias resulting from the inclusion of only patients treated at our center, which restricts the generalizability of the results. Additionally, the retrospective design introduces incomplete information and variability in data collection, which can compromise the reliability of the results. Finally, the smaller sample size limits the ability to detect significant associations, given the lower statistical power. Additionally, the limited number of events necessitates the implementation of multivariate analysis to assess performance. Notably, the study highlights a substantial correlation between recurrence patterns and survival, underscoring the significance of factors such as EGFR amplification and Ki-67 in this context.

Clinical implications

This study confirms that the pattern of distant recurrence in patients with glioblastoma and low tumor burden after diagnosis was associated with longer progression-free time and more prolonged survival compared to other recurrence patterns. This study also reveals a novel association: EGFR amplification and low Ki-67 proliferative index (< 30%), considered "low aggressiveness" factors, were independently associated with an increased likelihood of distant progression.

These findings underscore the significance of incorporating molecular profiling into decision-making processes for patients with glioblastoma. Furthermore, stratification by recurrence patterns has the potential to enhance the efficacy of future clinical trials.

Article information

Data availability statement: *The dataset generated and analyzed during the current study is available at Zenodo, https://doi.org/10.5281/zenodo.15824899.*

Ethics statement: *This study was performed in line with the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of Puerta de Hierro University Hospital (reference 99/24). No informed consent to participate in the study was collected since the design was retrospective (the need for consent was waived by the Ethics Committee of Puerta de Hierro University Hospital).*

Authors' contributions: *R.G.G. conceived the study, participated in its design, carried out data collection, and drafted the manuscript; Z.H. participated in the design, carried out data collection, and drafted the manuscript; E.R.B. participated in the design of the study and performed statistical analysis, he also revised the manuscript for intellectual content; A.Z. carried out data collection and critical review of the manuscript for intellectual content. All authors read and approved the final manuscript. All authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.*
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