**2025**
**UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA", BUCURESTI**
**DOCTORAL SCHOOL**
**MEDICINE**

# CURRENT DEVELOPMENTS IN CEREBRAL GLIOBLASTOMA DELIMITATION, HISTOPATHOLOGICAL, NEUROIMAGING, THERAPEUTIC AND PROGNOSTIC CORRELATIONS

## PHD THESIS ABSTRACT

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2025

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# A. General Part

## Chapter 1 - General considerations about glioblastoma

### 1.1 Definition

Glioblastoma (GB), according to the WHO 2021 classification, is a diffuse astrocytic tumor of grade IV, IDH-wildtype, recognized for its biological aggressiveness and extremely reserved prognosis. The diagnosis can be established by histopathologic criteria (palisading necrosis and microvascular proliferation) or by the presence of defining molecular alterations such as EGFR amplification, TERT promoter mutation and chromosomal signature +7/-10. The lack of IDH mutation differentiates these tumors from IDH-mutant grade 4 astrocytomas, previously classified as secondary glioblastomas. Histopathologically, GB is marked by hypercellularity, nuclear atypia, frequent mitoses and central necrosis, being the most common and aggressive brain tumors in adults, with a median survival of less than 15 months despite multimodal treatment.(1)

### 1.2 Brief history

The first descriptions of gliomas belong to Virchow (1863), followed by Byrom Bramwell (1888), who noted their infiltrative character and lack of demarcation from normal brain tissue. The term "glioblastoma multiforme" was introduced in 1914 by Mallory, and popularized by Bailey and Cushing. In 1940, Scherer described "secondary structures" (perivascular, perineuronal, subpial infiltrative patterns) and the theory of progression from tumors of low malignancy, a theory subsequently confirmed by genetic confirmation.(2)

### 1.3 WHO classification

WHO Classification 2021 uses a stratified system:

- Integrated diagnosis (molecular + histologic)

- Histologic diagnosis

- WHO grade

- Additional molecular information

This classification drops the terms "anaplastic" and "IDH mutant glioblastoma", redefining the entities by genetic profile. Tumors with IDH mutation are classified as astrocytomas grade 2-4 and those without mutation - as IDH-wildtype glioblastoma. Genetic abnormalities (EGFR,

TERT, +7/-10) may classify an apparently low-grade tumor as grade IV. The histological subtypes of glioblastoma include: giant cell form, gliosarcoma and epithelioid form.(3)

### 1.4 Incidence

GB accounts for 12-20% of all intracranial tumors and 50-60% of astrocytic tumors. Incidence is 2-4 cases per 100,000 population/year, relatively uniform globally, with discrepancies influenced by the quality of the health care system(4).

### 1.5 Etiologic Factors

The etiology remains unclear, but the only confirmed factor is cerebral radiotherapy, especially at a young age. Viral infections (CMV, SV40) and exposure to polyvinyl chloride are also suspected. Risk factors include age >50 years, male sex, Caucasian race, history of astrocytoma and genetic syndromes such as Li-Fraumeni (TP53), Von Hippel-Lindau (VHL gene), Turcot (association with colonic polyposis).(5)

### 1.6 Grading

The most used grading systems are WHO and St. Anne-Mayo, based on histological criteria: nuclear atypia, mitoses, necrosis, vascular proliferation. In the WHO system, grade IV (glioblastoma) is defined by the presence of ≥3 criteria, with emphasis on molecular data. WHO 2021 reaffirms that glioblastoma is exclusively grade 4, IDH-wildtype.(6)

## Chapter 2 - Clinical, histopathologic and diagnostic aspects

### 2.1 Clinical aspects

Symptomatology is dominated by intracranial hypertension (headache, nausea, vomiting) and focal neurologic deficits depending on localization. Onset may be acute, mimicking stroke, or subacute with epileptic seizures, behavioral disturbances, pareses. Progressive hemiparesis is the most common sign. In patients with slow progression, signs of cognitive dysfunction and brain syndromes intensify.(7)

Performance scores:

- Karnofsky (KPS): grading of functionality between 100 (normal) and 0 (death).

- ECOG/WHO/Zubrod: score 0-5, equivalent to Karnofsky, used to assess general condition.

### 2.2 Pathological anatomy

Macroscopically:

The tumor appears infiltrative, with extensive areas of necrosis (80-90%) and hemorrhage, contrasting with a grayish-lucinous peripheral portion. It frequently localizes frontal, sometimes in the brain stem or cerebellum. The large size generates mass effect, midline deviation and CSF blockage.(8)

Microscopically:

Histologically, the glioblastoma is highly pleomorphic, with anaplastic, multinucleated astrocytes with mitotic activity and central necrosis. The presence of necrosis surrounded by tumor pseudopalisades and microvascular proliferation is essential. Immunohistochemistry reveals positivity for GFAP. Pathogenic mechanisms include hypoxia, VEGF secretion, and prothrombotic states with local thrombosis.(9)

Relapse:

Tumor cells infiltrate remotely, subpial, perineuronal and perivascular, creating Scherer structures. "Guerilla" cells are identified >3 cm from the main focus, with a tendency to hypoxia-induced migration.(10)

### 2.3 Neuroimaging diagnosis

Computed tomography (CT):

Presents a hypodense image with annular contrast uptake and extensive peritumoral edema. Difficult to differentiate from abscess, AVCh or demyelinating lesions.

Nuclear Magnetic Resonance Imaging (MRI):

Gold standard in diagnosis, gives details of necrosis, contrast uptake (tumor ring), vasogenic edema and infiltration through corpus callosum. MRI spectroscopy helps differentiate between low vs high-grade tumors. T1-weighted images highlight the tumor ring, and T2-weighted images enlarge the signal area in edema.(11)

## Chapter 3 - Treatment of glioblastoma

### 3.1 Treatment goals

Treatment of glioblastoma is multimodal, including surgery, radiotherapy and chemotherapy, with the primary goal of prolonging survival and improving quality of life. Due to the infiltrative nature of the tumor and resistance to treatments, the therapeutic approach is difficult. The aim is to reduce mass effect, relieve symptoms, eliminate resistant tumor cells and sensitize to adjuvant therapies. Psychological support, functional recovery and patient involvement in the therapeutic process are essential(12).

### 3.2 Neurosurgical aspects

Surgery has a key role in diagnosis and cytoreduction. Extensive surgical resection correlates with increased survival but is rarely complete due to tumor localization in eloquent areas. Pre-operative imaging (MRI, tractography, PET) and modern technologies (neuronavigation, intraoperative ultrasound, fluorescent 5-ALA) help to maximize resection and minimize risks. In some cases, stereotactic craniotomies or functionally guided resections are practiced.(13)

Pros: decrease in intracranial pressure, reversibility of neurologic deficit, increased efficacy of adjuvant therapies.

Cons: impossibility of total resection, risk of complications or new neurological deficits, potential tumor spread.

## 3.3 Radiotherapy

Postoperative radiotherapy increases survival from 3-4 to 7-12 months. It affects cellular DNA by ionizing radiation, destroying residual tumor cells. Modern techniques such as IMRT and conformal radiotherapy are used to limit irradiation of sensitive structures. The standard dose is 60 Gy in 30 fractions, 5 days a week. Response is assessed imaging, but effectiveness is limited by the radioresistance induced by tumor hypoxia.(14)

## 3.4 Chemotherapy

Temozolomide (TMZ), introduced in 2005, is the standard treatment in combination with radiotherapy and subsequently as monotherapy. Studies have shown a significant increase in survival (14.6 months vs 12.1 months) and quality of life. TMZ crosses the blood-brain barrier and has good tolerability, but its efficacy is influenced by MGMT gene status. Other options include: nitrosoureas (BCNU), PCV protocol, carboplatin, etoposide, etoposide, irinotecan and adjunctive agents (tamoxifen, celecoxib). Novel therapies such as nanotechnology vectors are being explored.(15)

## 3.5 Prognosis

Glioblastoma has a poor prognosis, with a median survival of less than one year despite intensive therapy. Without treatment, the median duration is 3 months. Only <2% of patients become long-term survivors (>3 years). The prognosis depends on: age, Karnofsky score, resection grade, MGMT methylation, response to chemo/radiotherapy and tumor localization(7,16).(7,16)

Favorable prognostic factors:

- Age <50 years

- KPS score >70

- Quvasitotal resection

- MGMT metastases

- Tumors in non-eloquent areas

- Long interval to recurrence

Poor prognostic factors:

- Tumors with severe anaplasia, extensive necrosis

- Old age

- Exclusive biopsy or limited resection

- Rapid recurrence

- Localization in eloquent areas

# Chapter 4: Retrospective analysis of clinical course and survival in patients with glioblastoma in the Romanian oncologic context

## 4.1 Introduction

4.1.1.1 General background and importance of the topic

Glioblastoma (GBM) is one of the most aggressive malignant brain tumors, with a median post-diagnosis survival of about 15 months, even with standard multimodality treatment (surgery, radiotherapy, chemotherapy). According to WHO 2021, IDH-wildtype is considered the canonical form of glioblastoma. The incidence is higher in males and in Caucasian patients.(17)

Risk factors involved include exposure to ionizing radiation, toxic compounds (vinyl chloride), and possibly oncogenic viral infections. Treatment costs are high, and the standard protocol (Stupp) involves surgical resection followed by fractionated radiotherapy and administration of temozolomide (TMZ).(12)

4.1.1.2 Obstacles and limitations in the application of treatment

The fundamental limitations include:

- Diffuse tumor infiltration making complete resection impossible;

- Molecular heterogeneity with variable response to treatment;

- Lack of access to molecular testing and advanced therapies;

- Resistance to alkylating agents (e.g. unmethylated MGMT).

4.1.1.3 Need for personalization and multidisciplinary integration

Management of GBM requires personalization and interdisciplinary collaboration. Planning of interventions, selection of patients for adjuvant therapies, and integration of new molecular tests need to be carried out by mixed teams (neurosurgeons, oncologists, radiotherapists, geneticists, etc.).

4.1.2 Limitations and particularities of the national context

In Romania, adjuvant treatment is frequently delayed due to:

- Fragmentation of the patient circuit between hospitals;

- Overcrowding of oncology centers;

- Lack of infrastructure and personnel;

This delay transforms adjuvant therapy into "rescue" therapy with suboptimal effect on survival. Mean OS in the study cohort was 9 months and PFS was 5.3 months, considerably lower compared to other systems.

4.1.3 Working hypothesis

Extensive surgical resection combined with prompt initiation of adjuvant therapy (according to the Stupp protocol) may significantly improve survival. The integration of molecular markers (MGMT, EGFR) allows treatment personalization and patient stratification.

4.1.4 Specific objectives

1. Demographic and clinical characterization of patients;
2. Assess the impact of MGMT and EGFR on OS and PFS;
3. Correlation of KPS score with postoperative outcome;
4. Analysis of the role of repeated interventions on survival;
5. Identification of systemic barriers to treatment initiation;
6. Comparison with relevant international data.

## 4.2. Patients and methods

Study design and selection criteria

The retrospective study was conducted between 2012-2024 in the Department of Neurosurgery of the University Emergency Hospital of Bucharest, with a single-center character. The main aim was to evaluate the influence of clinical, surgical and molecular factors on overall (OS) and progression-free survival (PFS) in patients diagnosed with IDH-wildtype glioblastoma.

Inclusion criteria:

- Age ≥ 20 years;
- Histopathologic confirmation of IDH-wildtype glioblastoma;
- History of curative or palliative neurosurgical intervention;
- Presence of complete postoperative follow-up data.

After applying these criteria, the final cohort included 144 patients. Cases with astrocytomas or other glial neoplasms were excluded.

Clinical-demographic data collected

For each patient, variables such as:

- Sex and age;
- Tumor location and laterality;
- Pre-operative Karnofsky score;
- Molecular status: MGMT (methylated/methylated), EGFR (amplified/normal);
- Primary and secondary surgical interventions;
- Administration of adjuvant therapy (chemo/radiotherapy);

- Overall and progression-free survival.

Pre-operative evaluations included imaging investigations (contrast-enhanced MRI), paraclinical analysis and interdisciplinary consultation. The operating microscope and neuronavigation were used for surgical planning. For financial reasons, 5-ALA fluorescence and neurophysiologic monitoring were not used.

Surgical technique and postoperative management

Interventions were performed by minimal craniotomies with piecemeal resection under microscopic control. The objective was to achieve complete gross resection (GTR) where feasible without compromising neurologic function.

Postoperatively, each patient was:

- Monitored in the ICU;

- Re-evaluated imaging (CT at 48h);

- Referred to the oncology service for initiation of adjuvant treatment (according to the Stupp protocol, where feasible).

## 4.3. Results

General characteristics of the cohorts studied

Out of an initial total of 157 patients treated surgically for suspected glioblastoma between 2012-2024, only 144 cases (91.7%) were confirmed as IDH-wildtype glioblastoma. The remaining 13 (8.2%) were excluded and diagnosed as astrocytomas.

Type of surgery

Of the 144 patients included, 135 (93.7%) underwent gross total resection and 9 underwent surgical biopsy only, probably due to tumor location or clinical status.

Sex and age distribution

The male/female ratio was 0.8:1 (64 males vs. 80 females), contrary to international data. Age ranged from 30-82 years, with a mean of 60.7 years and a median of 61, with the most common ages being in decades 6 and 7.

Localization of tumors

The frontal lobe was most frequently affected (31.9%), followed by multilobar localizations (26.3%) and other areas (temporal, parietal, occipital lobes).

Laterality of tumors

The lesions were predominantly located in the right hemisphere (51.3%), followed by the left (43.7%) and only 4.8% had bilateral involvement.

Molecular status: MGMT methylation

The MGMT promoter was methylated in 31.9% of cases, indicating a potential favorable response to temozolomide treatment.

Molecular status: amplification of EGFR

EGFR amplification was present in 52.7% of patients and was associated with a more aggressive course and a more guarded prognosis.

Administration of chemotherapy

A total of 105 patients (72.9%) received temozolomide treatment, while the remaining 39 (27.1%) did not receive chemotherapy.

Administration of radiotherapy

Standard radiotherapy was administered to 116 patients (80.5%), while 28 patients did not receive this treatment, most likely due to limited access to specialized services.

Impact of combined treatment

Combined treatment (chemotherapy + radiotherapy) resulted in significantly higher overall survival according to Kaplan-Meier and log-rank test analyses, supporting the effectiveness of the multimodality approach.

Correlation of MGMT status with survival

Patients with methylated MGMT promoter had a superior OS regardless of the type of adjuvant treatment ($p < 0.005$), confirming the predictive value of this marker.

Correlation of EGFR amplification with survival

EGFR amplification correlated negatively with survival. Patients without this genetic alteration had a better OS ($p < 0.005$) regardless of treatment.

Survival by treatment type

Combination treatment provided the best results ($p < 0.005$). Single treatments (chemotherapy or radiotherapy) also had a significant positive impact on OS compared to no treatment.

Karnofsky Performance Status (KPS) score distribution

The majority of patients had KPS scores in the 80-100 range (34%) or below 70 (65%). This variability significantly influenced prognosis and selection for adjuvant treatments.

Tumor recurrence and repeat surgery

15 patients (10.4%) required reoperation, with a mean PFS of 5.87 months and OS of 10.8 months. These data suggest the value of salvage surgery in selected cases.

Progression-free survival (PFS)

The mean PFS was 5.3 months, with a median of 5 months, and most patients progressed within less than 6 months of treatment.

Overall survival (OS)

OS had a mean of 9 months and a median of 8.5 months, significantly lower than the international average (~15 months).

Comparison with international literature

Decreased overall survival is attributed to delays in initiating treatments, absence of effective postoperative integration, and systemic limitations in local oncologic infrastructure.

## 4.4 Discussion

The study highlights a significant discrepancy between the results obtained locally and those reported in the international literature, particularly in terms of overall survival (OS) and progression-free survival (PFS). The mean OS of 9 months in the analyzed cohort is below the international average, commonly estimated at 15 months in case of correct implementation of the Stupp protocol. The causes of these differences are not only therapeutic, but reflect delays in initiating adjuvant treatment, lack of interdisciplinary integration and systemic deficiencies. The atypical gender distribution (female predominance) compared to the global average (1.6:1 in favor of men) adds another contextual dimension, possibly explained by social, cultural or access to health care factors.(5,16,18)

4.4.1. Influence of age and KPS score

The median age of 61 years is in line with international data. The importance of this parameter remains of major prognostic importance, as advanced age implies low tolerance to treatments. Likewise, the Karnofsky score (KPS) has been shown to be a strong predictor: patients with KPS $\geq$ 80 had better survival, supporting the need for rigorous preoperative assessment and differentiated therapeutic selection(19).

4.4.2. Peculiarities of the Romanian context

Among the most relevant observations was the average delay of 4-5 months in the initiation of adjuvant treatment, which transforms postoperative therapy from a prophylactic to a "salvage" approach, applied on tumors that have already relapsed. This lack of coordination between neurosurgery and oncology directly contributes to the decrease in OS and PFS, marking a systemic limitation of the local healthcare system.

4.4.3. The importance of MGMT promoter methylation

Methylated MGMT status has been correlated with significantly better therapeutic response in both OS and PFS. However, the proportion of methylated cases (31.9%) is lower than in Western studies (where it reaches 45-50%). This difference may negatively influence prognosis. In addition, MGMT testing should become standard practice in Romania to personalize treatment, in line with European and American protocols.(20)

4.4.4. Role of EGFR amplification

EGFR amplification (observed in 52.7% of patients) was associated with significantly poorer overall survival, confirming its aggressive profile. The lack of access to targeted anti-EGFR therapies in Romania limits therapeutic options. In other healthcare systems, EGFR inhibitors, combined with TMZ or immunotherapy, are in advanced stages of testing, with promise of improving prognosis for this subset of patients(21).

4.4.5. The need for comprehensive molecular assessment

Given the biological heterogeneity of glioblastoma, comprehensive molecular assessment (MGMT, EGFR, IDH, TERT, ATRX, etc.) is essential for accurate risk stratification and treatment tailoring. This approach allows the integration of patients in clinical trials and the application of personalized experimental therapies, an aspect lacking in current practice in many Romanian centers.(22)

4.4.6. Salvage surgery

Reinterventional surgery brought clear benefits in our study: Mean OS of 10.8 months and PFS of 5.87 months in reoperated patients. This strategy should be applied selectively based on KPS, tumor location and molecular profile. Although risky, salvage surgery may provide an important survival advantage, also confirmed in the international literature.(23)

4.4.7. Future perspectives: biomarkers and emerging therapies

The use of extracellular vesicles (EVs) as minimally invasive biomarkers promises to revolutionize glioblastoma monitoring. They may allow real-time treatment adjustment based on tumor molecular profile and reduce the need for biopsies. Integrating EVs into clinical practice would mark an essential step towards personalized medicine(24).

4.4.8. Experimental therapies and treatment innovations

Innovative strategies include:

- Stereotactic Radiation Therapy (SRT): high-targeted local treatment for recurrence.

- Apatinib + TMZ: combination with antiangiogenic effect and good tolerability.

- Checkpoint inhibitors, CAR-T, tumor vaccines: in advanced stages of testing, these therapies may open new avenues for patients with aggressive molecular profile.

They all converge towards a personalized, multimodal, dynamically adaptable and biomarker-guided personalized therapeutic paradigm.(25,26)

4.4.9 Limitations of our study

Among the major limitations of the study are:

1. Small cohort size (144 patients).
2. Lack of access to extensive genetic analysis.
3. Lack of postoperative KPS assessment.

4. System deficiencies: lack of neurosurgery-oncology integration.

5. Impact of the COVID-19 pandemic on access to treatment.

All these emphasize the urgency of developing an integrated model of oncology care in Romania, based on:

- Interdisciplinary coordination.

- Rapid access to molecular testing.

- Introduction of modern therapies and salvage surgery.

## 4.5. Conclusions

Retrospective analysis of 144 patients with glioblastoma (GBM) treated for 12 years at the University Emergency Hospital in Bucharest has revealed a number of critical factors involved in the prognosis and survival of these patients. Among the major findings is the importance of the preoperative functional score (KPS) as a predictive indicator of the ability to tolerate and complete multimodal treatment. The study also emphasizes the crucial role of early application of combined treatment (surgery + radiochemotherapy according to the Stupp protocol), as well as the major impact of molecular status - in particular MGMT promoter methylation and EGFR amplification - on therapeutic response.

The median overall survival (OS) of 9 months and PFS of 5.3 months are lower than international values, a discrepancy mainly attributed to delays in initiating adjuvant treatment and poor local infrastructure. Another significant aspect was the confirmation of the value of repeat surgery, especially in carefully selected patients, where salvage surgery was associated with prolonged survival.

The study convincingly argues the need to integrate systematic molecular testing into routine practice, not only for MGMT and EGFR, but also for other emerging biomarkers. Tailoring treatment to the patient's genetic and clinical profile can transform the therapeutic trajectory of an otherwise devastating disease. To this end, urgent measures are recommended: the creation of an integrated neurosurgery-oncology medical circuit, the formation of multidisciplinary teams (tumor boards), expanding access to routine molecular testing and facilitating participation in clinical trials.

At the same time, the potential of promising innovations - such as liquid biopsy, extracellular vesicle monitoring and experimental therapies (SRT, apatinib, immunotherapy) - that could completely reshape the management of glioblastoma in the future is highlighted. Systemic health care reforms, supported by dedicated public policies, are essential to ensure equitable access to modern treatments and to increase survival in this highly severe disease. Thus, the study not only contributes to the understanding of the disease, but also provides a clear direction for optimizing oncology management in Romania.

# Chapter 5. Predicting overall survival in glioblastoma patients using machine learning algorithms: correlations between therapeutic efficacy and clinical prognosis

## 5.1. Introduction

Glioblastoma (GBM), the most aggressive brain tumor in adults, has a poor prognosis, with a median survival of about 15 months. High biological variability and therapeutic resistance limit the accuracy of traditional predictive methods. In this context, machine learning (ML) algorithms offer an advanced alternative capable of integrating clinical, molecular and imaging data for personalized survival estimates. Radiomics - by extracting MRI features - and molecular markers such as MGMT and EGFR play a key role in refining these models. Ensemble algorithms such as XGBoost and Random Forest efficiently handle heterogeneous data, providing robust predictions. Current challenges include data imbalance and poor interpretability of complex models, addressed in this study by techniques such as SMOTE, SHAP and LIME to ensure clinical validity and decision transparency(27).(27)

## 5.2. Working hypothesis

The central hypothesis argues that ML models, especially ensemble models, can outperform traditional statistical methods in predicting survival in GBM patients. The main objectives of the study include: (1) construction of a balanced dataset with clinico-molecularly relevant variables, (2) rigorous data preprocessing, (3) training and optimization of six ML models (XGBoost, RF, ETR, SVM, ANN, KNN), (4) performance evaluation by ROC-AUC and accuracy, (5) interpretation of predictions by SHAP for transparency and clinical relevance, and (6) identification of major prognostic factors (KPS, MGMT) in order to personalize therapeutic decisions. This approach integrates modern analytical methods to support decision support in neuro-oncology.

## 5.3. Patients and methods

The study included 135 patients diagnosed with glioblastoma, rigorously selected from an extensive clinical database to include only surgically treated cases who subsequently received at least one adjuvant therapy. Variables analyzed were grouped into four categories: demographic (age, sex), clinical (KPS, OS), therapeutic (radiotherapy, chemotherapy, resection) and molecular (MGMT, EGFR). Overall survival was discretized into five classes to allow multi-class classification.

In the preprocessing stage, categorical variables were transformed numerically by label encoding, and continuous variables were normalized with the MinMax scaling method. The dataset was divided into training and testing subsets, preserving an unbalanced distribution - with underrepresentation in the upper survival classes - which is why balancing methods such as SMOTE were applied.

Six machine learning models were trained and optimized: XGBoost, Extra Trees, Random Forest, SVM, Neural Networks (ANN) and KNN. Their performance was evaluated by accuracy and ROC-AUC on each class with repeated validation. XGBoost provided the best

results, followed by Extra Trees and Random Forest. The interpretability of the models was investigated by SHAP, which confirmed the importance of KPS score, radiotherapy treatment, age and MGMT methylation in predicting survival. KNN, in contrast, had reduced predictive performance and interpretative clarity.

## 5.4 Results

Overall performance of machine learning models

To evaluate the ability of ML algorithms to predict overall survival in glioblastoma patients, two main metrics were used: ROC-AUC and accuracy on the test set. Of the six models tested, XGBoost demonstrated the highest performance, with a mean ROC-AUC of 0.90 and accuracy of 78%. Extra Trees Regressor showed the same level of accuracy, but with a higher ROC-AUC score variance (0.82 ± 0.19). Other models, such as SVM and Random Forest, provided moderate results, while KNN and ANN performed significantly worse, emphasizing their difficulty in handling the complexity of the data. This hierarchy is supported by the distribution of ROC-AUC scores.

XGBoost performance by survival classes

Stratified analysis of the XGBoost model showed excellent discrimination ability for frequently represented classes. Class 0 (0-2 months) was perfectly classified (AUC = 1.00), indicating maximum sensitivity for patients with severe prognosis. Classes 1 (3-8 months) and 2 (9-18 months) also had high ROC-AUC scores (above 0.85). In contrast, for classes 3 and 4, AUC scores were lower, reflecting the difficulties inherent in data imbalance. The model nevertheless managed to maintain a robust and stable performance in identifying cases with variable prognosis.

Performance of other models by class

Random Forest confirmed efficiency in the lower classes, with AUC = 1.00 for class 0 and above 0.80 for classes 1-2, but showed poor performance in classes 3 and 4. Surprisingly, KNN recorded AUC = 0.94 for class 4, but due to the small sample size, the results cannot be considered stable. The KNN also suffered from general inconsistency in the classification of the intermediate classes, indicating lack of adaptability to the complexity of the GBM data.

Comparison of overall accuracy

Figure 5.3.5 revealed the superiority of ensemble models: XGBoost and Extra Trees achieved the best accuracies (78%), ANN and Random Forest were intermediate (68% and 66%), and KNN had the lowest score (54%). These data confirm that ensemble models offer not only high accuracy but also increased generalizability, essential for implementation in practice.

Confusion matrices and behavior on training and testing ensembles

Confusion matrices revealed the tendency of the models to classify patients into core classes (1 and 2), these being better represented in the data. The XGBoost and Extra Trees models demonstrated the highest accuracy in these classes, but all models, including the high performers, had difficulty correctly classifying classes 3 and 4. KNN showed numerous

confounds between neighboring classes, suggesting a lack of accuracy and clinical applicability.

Model interpretability - SHAP analysis

SHAP analysis was applied to understand the importance of each variable on model decisions. For KNN, the influence of KPS was noted, but without a clear differentiation of the other variables. In contrast, for XGBoost (Figure 5.3.9), SHAP showed a clear hierarchy of importance: KPS > radiotherapy > age > MGMT. Extra Trees reflected a similar distribution, confirming the robust interpretability of ensemble models.

Performance Synthesis and Recommendations

The results of the study demonstrate the clear superiority of ensemble models, in particular XGBoost, which obtained the best scores both numerically and explanatorily. Extra Trees, although slightly more variable, remains a solid option. KNN and ANN proved unsatisfactory in the face of the predictive requirements of a complex pathology such as GBM. High-performing, interpretable and stable models such as XGBoost are best suited for clinical applications, especially when decisions need to be transparently justified.

Limitations and future directions

Classification of long-surviving patients (classes 3 and 4) has been hampered by underrepresentation and heterogeneity. Solutions such as SMOTE, cohort expansion and integration of imaging data could improve outcomes. Also, approaches such as recurrent neural networks (RNN) or transfer learning could add value in the future.

Clinical implications

The application of ML in survival prediction has the potential to optimize treatment and resource allocation. XGBoost, with its performance and interpretability, is an ideal candidate for integration into clinical decision support systems. Expanding collaborations and external validation of models are necessary steps for sustainable implementation in precision oncology.

## 5.5. Discussion

### 5.5.1 Integration of results

Study results confirm the superiority of ensemble models, in particular XGBoost, in predicting overall survival in glioblastoma patients. With an accuracy of 78% and a ROC-AUC score of 0.90, XGBoost demonstrated robustness and flexibility, outperforming classical algorithms and efficiently adapting to heterogeneous data. The algorithm excelled in discriminating patients with severe prognosis (class 0), providing real opportunities for treatment optimization or palliative care orientation.

At the same time, the model maintained solid performance for the middle classes (classes 1 and 2), but had difficulties in classifying long-term survivors (classes 3 and 4) due to numerical imbalance. Future integration of methods such as SMOTE or GANs is recommended to correct these imbalances.

The SHAP analysis confirmed the ability of XGBoost and Extra Trees to identify clinical and molecular variables essential for prognosis, in particular KPS score, radiotherapy, age and MGMT methylation. These convergences between algorithmic predictions and clinical knowledge validate the models from a medical and biological perspective.(27,28)

5.5.2. Karnofsky score - clinical rationale

The KPS score was identified as the main predictor of survival, replicated in all models analyzed. It reflects the overall functional status of the patient and influences eligibility for intensive therapies. ML models autonomously recognized the importance of this score without human intervention, suggesting a learning of causal and biologically valid relationships(7).

5.5.3. Radiotherapy and MGMT - key factors

Postoperative radiotherapy was the second most important predictor in the models analyzed. All models associated it with increased survival. In parallel, methylated MGMT was a strong marker of positive response to temozolomide. The models automatically recognized the significance of these variables, reinforcing the idea that they can support already validated clinical hypotheses.(29)

5.5.4. Integrating interpretability

Validation of predictive decisions by SHAP ensures not only performance but also decision transparency. The models thus become acceptable tools in the clinical setting, providing detailed and intuitive explanations for individual predictions - an essential criterion for the integration of AI in personalized oncology.(30)

5.5.5. Interpretability of algorithmic decisions

SHAP provides not only global but also individualized - per patient - explanations, allowing the clinician to understand concretely why a patient is classified in a certain category. This granularity supports effective communication with the patient and the medical team and allows for an ethical and responsible approach to AI-supported decisions(31).

5.5.6. Convergences and differences with other studies

The XGBoost model confirms current trends in neuro-oncology, being powerful, stable and interpretable. In contrast to deep learning models, it works efficiently on tabulated, readily available data and offers superior transparency. The use of SHAP in this context becomes a major methodological advantage, facilitating interdisciplinary collaboration and clinical application in multidisciplinary teams.(32,33)

5.4.7 Methodological limitations

The small cohort (n=135) and class imbalance limit the generalizability of the results. Also, the single-center nature reduces external validity and the lack of imaging and multi-omics data limits the depth of biological analysis. In addition, the retrospective design exposes the study to methodological risks such as selection bias and lack of confounder control.

5.5.8 Future strategic directions

Four major directions emerge:

1. Cohort expansion through multicenter consortia;
2. Integration of radiomics and multi-omics data for more accurate multimodel models;
3. Development of sequential models for longitudinal predictions;
4. Practical implementation in the form of a clinical decision support system (CDSS), with intuitive interface, EHR connection and integrated SHAP explanations - turning models into active tools for treatment personalization.

## 5.6 Conclusions

The study demonstrated that machine learning models, in particular XGBoost and Extra Trees, provide robust and interpretable predictions of survival in glioblastoma patients, outperforming classical algorithms in accuracy (up to 78%) and high ROC-AUC scores (up to 0.90). XGBoost excelled in classifying patients with severe prognosis, with a perfect AUC for class 0 (0-2 months), and the SHAP analysis validated the clinical relevance of algorithmic decisions, identifying Karnofsky score (KPS), radiotherapy and methylated MGMT as the most important predictors of survival. The models reflected the learning of real causal relationships, not just statistical ones, providing a medically coherent decision hierarchy. Radiotherapy and MGMT were automatically recognized as essential prognostic factors, confirming the effectiveness of automatic prediction even in the absence of imaging or multi-omics variables. SHAP provided both global and patient-level interpretability, allowing the clinician to understand and justify the algorithm's predictions, an essential criterion for the integration of these tools into precision medicine. Compared to deep learning approaches, XGBoost offers similar performance on tabular data, with the advantage of a simpler and more explainable implementation. However, the study has important methodological limitations, such as small sample size (n=135), class imbalance and single-center character, which affect external validity. Also, the lack of radiomic and omics data reduces the ability for advanced customization. In this context, four strategic directions of development are outlined: cohort expansion through multicenter consortia, integration of complex imaging and molecular data, use of sequential models for longitudinal predictions, and practical implementation of a clinical decision support system (CDSS), connected to the hospital infrastructure and able to provide real-time SHAP explanations. These developments can transform ML models from mere algorithmic tools into ethical, transparent and directly applicable predictive mechanisms in personalized oncology practice.

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