TITLE:
Prognostic factors, surgical management and survival of glioblastoma patients: a multicenter prospective study

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CLINICAL TRIAL PROTOCOL

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Brief Background: Glioblastoma remains the most prevalent and aggressive primary tumor of the Central Nervous system (CNS) in adults, with dismal prognosis and median overall survival between 14 to 20 months, despite the current advances in diagnostics and treatment options.

Aim: The aim of this study is to collect data prospectively in all glioblastoma patients treated in centers across Europe and the United States (US). In this data there will be included information regarding demographics, imaging, molecular subtypes, preoperative clinical status, surgical strategy in these patients, and post-operative management, along with any complications. Eventually this data will be assessed in order to distinguish the best surgical approach, according to different groups of

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patients (e.g. age, molecular subtype, tumor locations etc). Furthermore, treatment effect, tumor pseudo-progression, and recurrence management will also be assessed.

Study Design: This project constitutes a prospective, observational, multicenter study. The centers included are staffed with multiple experienced neurooncology surgeons. Patients will undergo a thorough demographic, family and medical history, and clinical examination. The patients' imaging studies will also be assessed. After the surgical management chosen, each patient will be closely monitored postoperatively until discharge. Postoperative imaging, postoperative neurological evaluation, and any complications will be thoroughly documented. Pathology reports, along with information regarding molecular subtypes will be included. The patients will be re-evaluated at one, three, and six months postoperatively, and then every three months or sooner in cases of any suspicion of recurrence or any changes in the patient's clinical status.

Patients: The investigators will include patients fulfilling the following eligibility criteria: Inclusion criteria:

- Adult patients (>18 years of age) with
- Glioblastoma based on radiographic features (Magnetic Resonance Imaging),
- Patients that consent to study participation.

Exclusion criteria:

- Non adult patients (<18 years of age),
- Patients that do not consent for participation in this study,
- Patients with other CNS tumors (primary or secondary).

Intervention: Patients with tumors, compatible with glioblastomas -according to conventional Magnetic Resonance Imaging (MRI)- will fulfil their written consent and will then be included in the study. Each patient will be treated with a different surgical management (e.g biopsy, subtotal resection, gross-total resection, supramaximal resection or lobectomy) according to surgeons' and/or patients' choice. Any adjunct treatment will be documented (such as chemotherapy or/and radiotherapy).

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Outcome: The primary endpoints of the study are: (1) The overall survival (OS) of the patients (2) The progression free survival (PFS) of the patients. OS and PFS will be calculated in months.

The secondary endpoints of the study are: (1) Peri- and post-operative complications, (2) Length of hospital stay counted in days, (3) Preoperative and postoperative Karnofsky Performance Scale (KPS) score (1-100), and (4) Extent of Resection (EoR) (counted as the % percentage of the preoperative tumor).

Co-registration of: (1) Risk factors affecting OS and PFS (patient's age, cerebral dominance, BMI, tumor's molecular subtype),(2) Age (measured in years), (3) Gender (male, female, other), (4) Other demographic information (such as nationality, education level), (5) Anatomic location of the tumor, (6) Size of the tumor before intervention (measured in cm), (7) Intake of mannitol, hypertonic saline or steroids, (8) Dexterity, (9) Symptoms at the time of hospital admission, and (10) Molecular subtype of the tumor.

Timing: Follow up: one month, six months, and then every three months postoperatively. In cases of tumor recurrence or post-discharge complications patients will be reassessed. Enrollment of the first patient will take place after approval by the IRB and Research registration. Indicative time period: 2025 – 2030.

Statistical analysis: Descriptive statistics will be used to summarize count and continuous data. In particular, count data will be presented in absolute numbers and percentages, while continuous data will be given in mean (and standard deviation) or median values (and interquartile ranges) according to the Kolmogorov test. We will also use the chi-square test and logistic regression (or Kruskal-Wallis test), and linear regression to test for between-group differences. Statistical significance will be set at 0.05. All statistical analyses will be carried out in R statistical environment. For count data the results will also be provided in odds ratio along with their 95% confidence interval (CI).

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