Doctoral Thesis Summary

MODERN MANAGEMENT IN THE SURGICAL TREATMENT OF THE MALIGNANT GLIOMAS

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The doctoral thesis is illustrated through 36 tables, 143 figures and 142 pages. The summary reproduces selectively the iconography and bibliography of the text respecting the numbering and the contents of the thesis in extenso. The bibliographical references present are identical with the existent ones in the doctoral thesis.

Key-words: Glioblastoma, Acid 5- aminolevulinic (5-ALA), Gliolan, Neurosurgery, Neuronavigation
INTRODUCTION

Malignant brain gliomas

Malignant brain gliomas are tumors with invasive character, which lead inevitably to death in 1-2 years after diagnosis (Kleihues P., 1999). These tumors are associated with a weak prognostic, despite the maximal, surgical treatment completed with radiotherapy and chemotherapy. The resection grade of the tumor is accepted as essential for the optimal surgical treatment, and recent studies offers level II evidence in favor of a cytological maximal reduction in the management of the new diagnosed malign glioma. (Mc Girt et al., 2009; Stummer at al., 2008; Stummer at al., 2009). The first case of cerebral glioma in which surgical resection was performed belongs to Rickman Godlee in 1884. (Godlee at al., 1884).

The malignant glioma treatment is not representing just from the surgical resection, but nowadays it’s existing like gold standard the multimodal treatment (radiotherapy, chemotherapy), taking into consideration the fact that the best treatment option is the resection as extent as possible of tumor volume, keeping in this way the morbidity minimum level. In the literature existing a lot of evidences which lead to the fact that a maximal surgical cytoreductive technique (over 98% of the initial mass of the tumor) is an important prognostic factor for the patient’s survival (Kleihues P., 1999). Due to the infiltrative character of these tumors this thing is not easy to count and to accomplish.

The target of this chosen theme for study in this doctoral preparation it is a pathological surgical issue frequently met in the medical practice, represented by the modern management neurosurgical techniques of the malignant glioblastomas.

In Stummers’s et al. in the paper “Counterbalancing risks and gains from extended resections in malignant glioma surgery: a supplemental analysis from the randomized 5-aminolevulinic acid glioma resection study”, published in 2011 (Stummer W T. J., 2011) realized a prospective randomised phase III trial where he found out the same results which are trying to follow in this doctoral thesis. In this way, he showed that the surgical treatment guided by fluorescence induced by 5-aminolevulinic acid (5-ALA) reach achieve easier a maximal resection, than using the conventional microsurgical treatment with the white light. In the same time, the studies published by the international literature obtain the same results (Stummer et al., 2006; Díez Valle et al., 2013; Hefí et al., 2008; Wen et al., 2008;). Maximal resection of malignant glioma using 5-ALA was proved to be the best technique in nowadays, which has a longer free time without relapse and a longer survival rate.

The targets of this doctoral study

The investigations followed in the surgical treatment will be structured in the next directions of researching:

The principal targets:

The principal targets of this doctoral study were linked to the effectiveness of applicability of interventional methods at Clinical Emergency Hospital „Prof. Dr. N. Oblu” Iasi at the Neurosurgery Department in the brain malign gliomas area, for evaluate the improvements in the survival rate through a maximal resection.

Another main objective is that one who is linked by effectiveness study of the administration multimodal treatment at the patients who were undergone the resection with
conventional method versus those one who had undergone resection guided by fluorescence induced by 5-aminolevulinic acid (5-ALA). One the other hand, here were highlighted the specificity and the sensitivity the variety of guided methods. All of these providing supports to the feasibility of the proposed study.

Another principal target is represented by statistical analyzed of the results, for clinical-imagistic correlations with a high accuracy. After all, we will adapt in this way the surgical protocols through obtaining positive results for the patients.

The secondary targets:

Improvement of the patients’ tracking protocol from an imagistic point of view (imagistic controls performed according to an established schedule), who are imagistic diagnosed with cerebral malignant gliomas, operated in the hospital and its implementation in the neurosurgery department. The clinical investigations of the efficiency of this protocol was performed on short time (3 days) and long time (1 year) and included applied interventional methods (the neurological, imagistic and functional evaluation of the patients).

It will be study the following:

- The protocols and therapeutic algorithms used till in this moment in the resection of malignant gliomas, and the obtained data will be compared with those which are published in the literature;
- The asymptomatic arterial cerebrovascular complications and the symptomatic ones which are associated with the tumor pathology in preoperative and postoperative time;
- The role of the prevention of the postoperative cerebral edema and the pulmonary embolism, like a possible complication which can be associated with the surgical intervention or the anesthesia;
- The secondary side-effects on short term and long term of the 5-ALA administration and its influence on the patient’s neurological status;
- The association between the postinterventional neurological deficit and the patient’s quality life;
- The neuromotor recovery to those patients who were undergone microsurgical resection, showed through by international Karnofsky Score;
- The establishing of correlations between the early imagistic diagnostic and on the long term of the patients and their survival rate. One the other hand, we can adding to follow the post operator complications (local and distance).

Material and method

1. Inclusion Criteria

At the Neurosurgery Hospital “Prof. Dr. N. Oblu” Iasi, based-image malign glioma diagnosed patients were included in study and explored both in the neuroimaging department of the hospital and externally.

We mention some of the inclusion criteria:
- Patients to whom the image-based malign glioma suspicion was raised, who also have surgical indication, lending to 5-ALA resection
• Young patients with a history of recurrent malignant glioma, with a favorable neurological status;
• Based-image diagnosed malign glioma patients, which lies in the functional area with surgical indication and with the use of 5-ALA, associated with modern intraoperator techniques (neuronavigation, intraoperative ultrasound, intraoperative monitorization);

The conditions under which the present subjects fit in the selection criteria and agree to take part at the clinical trial, they sign their consent regarding both the surgical intervention and the 5-ALA administration and their logging will be done in the database.

2. Exclusion criteria

Out of the exclusion criteria we mention:
• the refusal of subjects with malignant glioma or their families to be included in the clinical trial after having been informed of the procedure and the risks involved;
• patients with a history of allergy to any of the 5-ALA compounds, after detailed anamnesis;
• patients with porphyria or history of porphyria in the family;
• patients with acute or chronic hepatopathy, after studying the biological profile;
• patients who have been diagnosed with psychological illness or psychiatric illness as a result of the psychological examination at the clinic;
• non-cooperative patients who have cerebral functional areas affected by tumors and have not been accompanied by compliant families able to understand and assume the exposed technique;
• people without stable residence;

Although there are patients who meet all the requirements of the inclusion criteria, the presence of a single exclusion criterion determines the impossibility of belonging to the presented study.

3. Studied lots

The present thesis study was based in the Clinical Emergency Hospital „Prof. Dr. N. Oblu” in Iași, in the I, II and III neurosurgical clinics, in the period 1 January 2013 to 1 May 2015.

The first study of the thesis was retrospective and was performed on a total of 110 selected patients from the hospital archive, diagnosed with high-grade glioma that were operated by the classical interventional method during January 2009 - December 2011. The second study is one prospectively conducted on a lower batch of 17 patients from the clinics mentioned above between 2013 and 2015, in which imaging of glioblastoma suspected and surgical maximum resection was performed following administration of 5-aminolevulinic (Gliolan®). The 17 surgical interventions used modern hospital equipment and advanced neurosurgical techniques (intraoperative ultrasound, neuronavigation and intraoperative monitoring).
Fig. 6.1. Intraoperative microscope integrated into the complex neuronavigation system (hospital equipment)

Fig. 6.2, 6.3 Intraoperative images of resection in blue light. Fluorescence of tumor infiltrated brain tissue is observed.
Results and discussions

In the database created for this study, data were entered about patients such as: name, sex, age distribution (20-30 years, 31-40 years, 41-50 years, 51-60 years old, 61-70 years, 71-80 years), tumor localization by dominant hemisphere, onset symptom, interval from first symptom to doctor presentation, anatomical location of the tumor (frontal, parietal, temporal, insular, occipital), structure (Biopsy, subtotal resection, total resection), use of ultrasound for total resection - echocardiography, macroscopic aspect of tissues, the number of lobes affected, localization in functional areas, invasion of basal nuclei, invasion of vascular structures, Microscopic tissue appearance, histopathological diagnosis, postoperative complications, postoperative status, control data, radiotherapy, radio and chemotherapy treatment, chemotherapy treatment C, reintervention data, recidivism data (no. Months), imaging aspect - tumor aggression (correlation), free time of symptoms, survival rate. All of these data and not only were taken into consideration to analyze the 5-ALA effects on the health of the patients who were treated in our surgical center.

The statistical study was performed on a retrospective group of 110 patients diagnosed with glioblastoma and operated, respectively on a prospective group of 17 patients with the same diagnosis of resection and administration of Gliolan®. Statistical analysis was performed in SPSS 20.0.

For the statistical analysis of the relevant data on the treatment of the patients included in the study, classical and new data processing and statistical analysis methods were used to obtain relevant results on the achieved objectives.

The study confirms the data from the literature on the age distribution of malignant gliomas, a peak between 51-60 years, and only 4.5% at the young ages of 20-30 years. Malignant gliomas have been found to be most commonly located in the frontal and temporal-frontal region of 46.4%. All patients were subjected to surgical treatment and maximum microscopic resection was performed in the 17 patients receiving Gliolan®. The study found a good quality of life, prolonging the non-relapse survival rate to 1.7 years. The survival rate at 12 months was 100%, at 16 months 2 patients were lost, the study continues.

The first group, consisting of 110 patients, consisted of 61 men (55.5%) and 49 women (44.5%) - Fig. 7.1, aged between 20 and 80 years - Fig. 7.2. The largest proportion of patients with glioblastoma was enrolled in the age range of 51-60 years, the lowest (5 patients and 4.5%) aged between 20 and 30 years.

![Fig. 7.1. Batch structure by gender](image1)

![Fig. 7.2. Batch structure by age range](image2)
Regarding the comparative distribution of patients by age and gender (Figure 7.3), it can be seen that in men the most cases were also recorded in the age range of 51-60 years, while in women, in addition to this age range, an equal percentage of patients aged 61-70 years is added. It can also be noted the high percentage (19.7%) of older men (between 71-80 years), a phenomenon whose presence has not been identified in women as well.

We also studied the nature and severity of onset symptoms (Figure 7.70). The most common onset symptoms were paresis and motor deficit, identified in 40 patients (36.4%), followed by various types of seizures, identified in 38 patients (34.5%), HIC or headache (30 patients, 27.3%). Confusional syndrome was identified in 21 patients (19.1%), anamnestic disorders in 14 patients (12.7%), and dysphasia or aphasia in 13 patients (11.8%).

Patients were subjected to more detailed monitoring by periodic MRI examinations (Figure 7.71) - 3 weeks (1 case), 3 months (6 cases), 6 months (3 cases) and 9 months (2 cases).
In 4 patients (22.2%) the tumor was located frontally and temporally; The most frequent localization was parietal, present in 5 patients (27.8%), there was also a patient with localized and occipital localization (Figure 7.74). Two patients (11.1%) were diagnosed with location on the median line (CC), and also 2 patients had 2 affected lobes, and 2 were affected by one single lobe.

All patients were operated between 2013 and 2015, with most (66.7%) operating in 2014; In 2013, 22.2% of the patients were operated and 11.2% in 2015.

After surgery, biopsy of extirpated specimens was performed. In 8 cases (44.4%) of the 17 resection was performed (Figure 7.79).
Conclusions

1. A challenge in today's modern neurosurgery is to establish protocols for the management of patients diagnosed with cerebral malignant glioma and their correct implementation at hospital level. The surgical resection of malignant gliomas using 5-ALA (Gliolan®) is a new, successful technique introduced for the first time in Romania at the Emergency Clinical Hospital “Prof. Dr. N. Oblu " Iasi.

2. From our experience, 5-ALA is a well-tolerated substance by patients, and fluorescence-guided tumor resection procedures if well implemented will in the future provide a current glioblastoma operative technique and inclusion in the binding protocol of the hospital.

3. According to our findings, 5-ALA is an intraoperative tumor marker that reliably guides us towards an effective cost-benefit innovation, being well above classical resection.

4. Neuronavigation was used in over two thirds of patients, being useful for the minimal invasive surgery and the choice of the pathway.

5. In the researched cases it was found that the resection of malignant gliomas with localization near the cerebral functional areas, when accompanied by intraoperative imaging (ultrasound, neuronavigation), we obtained better neuro functional results.

6. Intraoperative neurophysiological monitoring was used on a case-by-case basis, postoperative patients did not show worsening of neurological deficit or Karnofsky score decrease.

7. These techniques, combined, constitute a new therapeutic strategy to achieve positive outcomes in the diagnosis and survival rate of patients with malignant brain tumors.

Selective Bibliography


ANNEX. LIST OF PUBLISHED WORKS


**SCIENTIFIC PAPERS PRESENTED**


**Munteanu R.**, Eva L., Dobrin N., Chiriac A., Managementul modern al stroke-ul ischemic. Zilele Spitalului Clinic de Urgență „, Prof.Dr. N.Oblu “,Iași ,24-26 Octombrie 2013

Eva L. **Munteanu R** ,Poeată I., The resection of malignant gliomas using 5-Aminolevulinic Acid( 5-ALA, Gliolan), Conferința de neuroștiințe cu participare internațională, 20-22 Octombrie 2016

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Eva L.Bișoc O.,Turliuc D., **Munteanu R.**. Tratamentul neurochirurgical al Bolii Parkinson, Simpozion de Neuroștiințe , Iași 29-31 Octombrie, 2015
