UNRAVELLING PSEUDOPROGRESSION IN GLIOMA

A Study on MRS Data Analysis in Patients Treated with Concomitant Therapy

Universitat Autònoma de Barcelona

Jordi Martín Pérez
Bachelor's Degree in Biochemistry

May 2023

Introduction

The standard course of treatment for glioblastoma (De Stupp protocol) consists of tumor resection followed by radiation with contemporaneous and adjuvant temozolomide administration. During their initial post-radiation magnetic resonance imaging (MRI), 20–30% of patients manifest enhanced contrast that gradually goes away without modifying treatment. This condition, known as pseudoprogression (PP) or therapy-induced necrosis makes difficult to determine tumor advancement non-invasively right away once radiotherapy is finished [1].

Magnetic resonance spectroscopy (MRS) has proved to be able to distinguish between active tumor regions and tumor recurrence before changes in contrast enhancement become obvious. To do so, it measures non-invasively the content or ratios of metabolites in the brain in vivo. Improvements in MRS technology, such as multivoxel MRS (acquiring spectra from multiple smaller volumes of interest within a larger imaging matrix), allows for better assessment of regional abnormalities. Moreover, O(6)-methylguanine-DNA methyltransferase (MGMT) promoter methylation in glioblastoma has been shown to predict a successful outcome in patients who receive concomitant radiochemotherapy treatment [2].

Objectives and Hypothesis

OBJECTIVES

- To **analyze MRS multivoxel data** from 20 glioblastoma patients one month after concomitant therapy **using TARQUIN** (Totally Automatic Robust Quantitation in NMR) to find out if there exists a **correlation between the possible evolution of the disease and changes in MRS data for the selected metabolites**: Choline (Cho), N-acetylaspartate (NAA), Creatine (Cr), Lactate (Lac), Glx (Glutamate + glutamine combination), Myo-inositol (Ins), lipids and macromolecules (LM).
- To evaluate the **association between MGMT promoter methylation and glioma progression**.

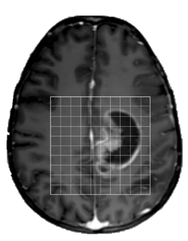
HYPOTHESIS

It may exist a **difference in MRS metabolite concentration and ratios between or True Progression (TP) and PP** post-surgery and treated glioma patients, as well as **a pattern in MGMT promoter methylation**.

Materials and Methods

MATERIALS

MR explorations of glioma patients were acquired at 3T with a Philips Ingenia scanner



Radiologist **labelled the voxels of interest**. Two months after concomitant therapy, **PP or TP** of the glioma was determined. **MGMT promoter methylation** status of each patient was also provided

Obtaining of the **DICOM** (Digital Imaging and Communication in Medicine) files of the 20 patients

METHODS

1. Data processing was performed using **TARQUIN**.

Inputs: the DICOM files of the patients

Outputs: concentration values for all metabolites and voxels exported in text file format (.txt)

2. Data filtering output using a **custom R script**.

Filtering by voxels of interest, informative metabolite, group (TP or PP) and statistical criteria (%SD ≤ 50) were extracted from the TARQUIN output.

Ratios for each patients and **plots** of the results were obtained with this script.

3. Statistical tests were performed using statistical analysis software **Jamovi**:

- Saphiro-Wilk
- Student's t
- Mann–Whitney
- Chi-square
- Fisher's exact test

Results and Discussion

METABOLITE CONCENTRATIONS

Ins, TCr and TNAA concentration values exhibit a significant increase in the PP subgroup when compared to the TP:

- **Ins:** TP patients' lower Ins value when compared to PP could be due to a progress to a higher-grade glioma over-time, which is known as malignant transformation [3,4].
- **TCr:** creatine signal is often reduced in brain tumors as a result of altered energy metabolism. Therefore, TP patients showing lower TCr values agrees with the variations that this metabolite frequently exhibits in patients with gliomas [3].
- **TNAA:** reduction in NAA is interpreted as the disruption of normal neural tissue. Thus, PP higher NAA concentration could indicate a positive evolution of the patient [3].

The other metabolites did not show significant differences according to T-student or Mann-Whitney test. Quality control exercised on the data caused an important loss of values.

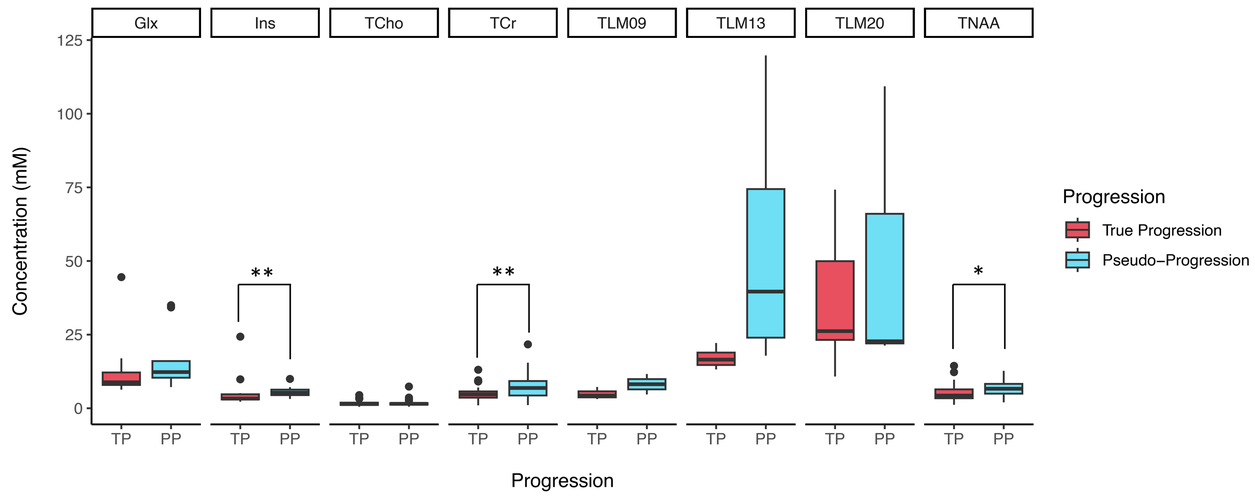


***Figure 1**: Boxplot of each metabolite is displayed for the two subgroups. Asteriscs (*) indicate significance, if p< 0,01 (* *) and if p< 0,05 (*)*

METABOLITE RATIOS

For both ratios **a dawnward trend** is observed **for the PP subgroup.**

However, none of the calculated ratios presented **any significant difference between the PP and the TP patients** according to Students't or Mann Whitney test. As a result of the statistical filtering by the SD provided by TARQUIN of the metabolites, some patients did not have enough data to calculate the ratios, resulting in a more **limited sample size**.

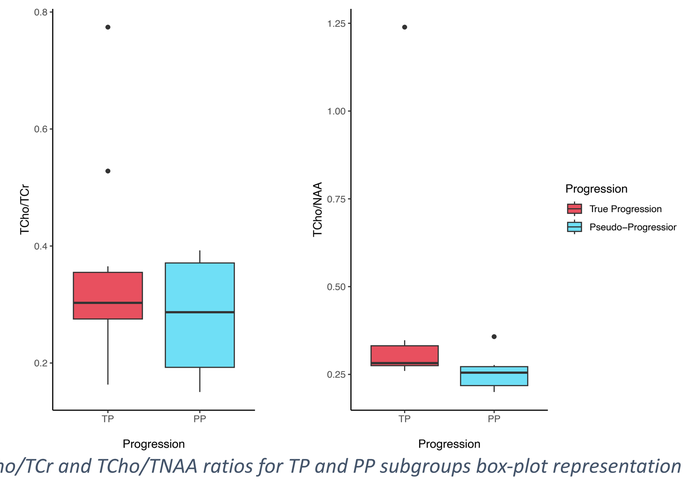


***Figure 2**: TCho/TCr and TCho/TNAA ratios for TP and PP subgroups box-plot representation*

MGMT METHYLATION

Chi-square and Fisher's exact tests indicate that there is **no significant association between the variables TP/PP and the presence of methylation in the MGMT promoter**.

MGMT promoter methylation status has been shown to potentially predict the incidence of PP, but it is **not the only determinant** [2]. Also, the **sample size** of the study is limited, a fact which would help to omit the relationship between methylation of the MGMT promoter and PP.

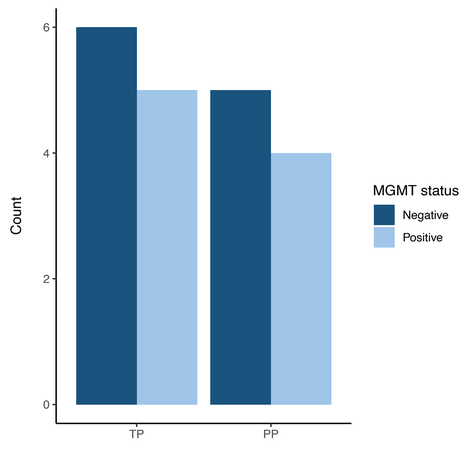


***Figure 3:** Bar plot displaying MGMT methylation counts for both TP and PP patients*

Conclusions and Future work

- As a non-invasive method for glioma prognosis, MRS has demonstrated to be quite promising. MRS could assists medical professionals to forecast patient outcomes and direct additional therapeutic measures by offering crucial metabolic information about the tumor.
- It would be interesting to include MRS into standard clinical practice for glioma patients. A decision support system for the prognosis of glioma using in vivo MRS could offer a more effective and easy manner to incorporate this practice in the clinics.
- When data on MGMT promotor methylation were included in MRS studies, diagnostic performance improved [2]. Thus, the evaluation of angiogenetic pathways and connections with MGMT status in glioblastoma could serve as the basis for subsequent research.
- Future research should concentrate on massive data patients' analysis, establishing a rigorous evaluation criterion. Moreover, improvements in MRS equipment and technique could provide enhanced capabilities for diagnosing gliomas and accurately, assessing pseudoprogression.

References

[1] Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. New England Journal of Medicine. 2005 Mar 10;352(10):987–96.

[2] Sidibe I, Tensaouti F, Roques M, Cohen-Jonathan-Moyal E, Laprie A. Pseudoprogression in Glioblastoma: Role of Metabolic and Functional MRI-Systematic Review. Biomedicines. 2022 Jan 26;10(2):285.

[3] Van der Graaf M. In vivo magnetic resonance spectroscopy: basic methodology and clinical applications. European Biophysics Journal. 2010 Mar 13;39(4):527–40.

[4] Czernicki T, Szeszkowski W, Marchel A, Gołebiowski M. Spectral changes in postoperative MRS in high-grade gliomas and their effect on patient prognosis. Folia Neuropathol. 2009;47(1):43–9.