A Radiomics-Based Signature for Identifying Successful Response to TMZ Treatment in Murine GL261 Glioblastoma: leveraging the peritumoral zone

Benito Farina[1,2], Juan E. Ortuño[2,1], Andrés Santos[1,2], Ana Paula Candiota[2,3], María J. Ledesma-Carbayo[1,2]*

[1]Biomedical Image Technologies, ETSI Telecomunicación, Universidad Politécnica de Madrid, Madrid, Spain; [2]CIBER-BBN, Instituto de Salud Carlos III, Madrid, Spain; [3]Departament. de Bioquímica i Biología Molecular (Unitat Biociències), Universitat Autònoma de Barcelona, Cerdanyola del Vallès, Spain. *mj.ledesma@upm.es

Abstract

INTRODUCTION: Glioblastoma (GB) is the most aggressive primary brain tumor in adults, characterized by high invasiveness and poor prognosis [1]. Magnetic Resonance Imaging (MRI) is crucial for characterizing GBM, but distinguishing early treatment effects from tumor progression remains challenging. Temozolomide (TMZ) is the standard chemotherapy for GB, yet its effectiveness varies, underscoring the need for advanced biomarkers to assess treatment response, allowing for an early switch to a second line treatment [2]. This study evaluates the potential of T2-weighted MRI-derived radiomic features to identify local tissue changes in TMZ-treated GL261 GB-bearing mice showing transient response, from untreated controls in which tumors are showing uncontrolled proliferation, regardless of tumor volumes. **METHODS:** GL261 tumors were generated through intracranial injection as described by us [3]. TMZ was administered (60mg/kg) to treated groups starting at day 11 post-implantation, with protocols described in [3] and [4]. T2w MRI studies were performed at 7T with a RARE sequence (TR/TEeff = 4200/36ms). T2-weighted MRI data were collected from 60 mice (31 TMZ-treated, 29 controls), and radiomic features (51 features/case) were extracted from three regions: tumor core, dilated peritumoral borders (3.5 mm radius), and combined tumor regions (Figure 1). Image intensities were normalized (0–250 range), and feature discretization was tested with bin widths of 2, 4, and 6. A training set (30 mice: 17 treated, 13 controls) was used to develop supervised machine learning models (Random Forest, SVM, Logistic Regression) with ANOVA-based feature selection and hyperparameter optimization (GridSearchCV, 5-fold cross-validation). The other 30 mice were used as an independent test set. **RESULTS & DISCUSSION:** Models relying solely on tumor core or tumor edge features showed poor classification (low AUC/accuracy), while combined tumor-peritumor features enabled robust discrimination. The optimized Random Forest classifier achieved an AUC of 0.92 and accuracy of 0.93 on the test set (30 mice: 14 treated, 16 controls), with texture-based features dominating the predictive signature. These findings support the idea that the peritumoral zone contains molecular/cellular alterations involved in proliferation, invasion, and recurrence [5]. Moreover, microglial cells have been described in peritumoral zones, and depending on their phenotype, they can have different impact on tumor response to therapy. The changes in molecular characteristics and cell populations, as well as local effects on tumors, can be potentially spotted with advanced imaging approaches [6] which are not currently considered in standard pipelines. TMZ-treated mice that were followed-up until endpoint presented prolonged survival time (43±10 days, n=11), and some mice (n=4) showed total tumor remission, compared with the standard survival of untreated mice (ca. 21 days, UAB data, n>100), confirming the treatment efficacy. It is worth mentioning that in most cases, the study was not conducted to endpoint since euthanasia was done for validation purposes. However, data were obtained during a clear response (TMZ-treated) or exponential tumor growth (control mice). Although control mice do not fully represent a “tumor progression after treatment” group, this approach could pave the way for future studies in this direction. **CONCLUSION:** These results suggest that radiomic heterogeneity within the tumor and its peritumoral area is critical for distinguishing treatment effects triggered in TMZ-treated mice, which presented, as expected, relevant differences from control animals. The model’s predictive potential arises from its ability to capture microenvironmental heterogeneity reflective of TMZ-induced biological changes, which are linked to treatment response.

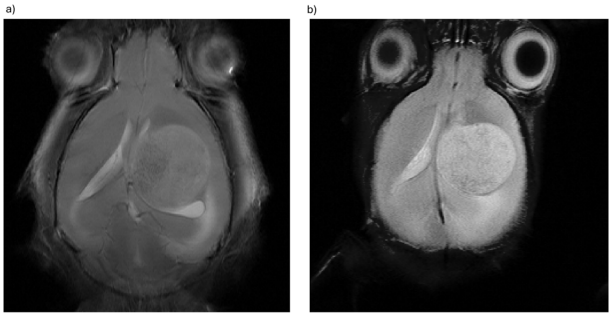

Figure 1 – MRI images at day 16: (a) Control case, (b) Treated case.

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