

Research Article
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Glioma Image Analysis to Accurately Classify Mgmt and Predict Drug Effectiveness

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ABSTRACT

Glioblastoma multiforme is a deadly brain cancer with a median patient survival time of 18-24 months. A single biopsy cannot provide complete assessment of the tumor's microenvironment, making personalized care limited. 50% of the patients do not respond to the anti-cancer drug Temozolomide(TMZ) because of the over-expression of MGMT gene. Epigenetic silencing of the MGMT gene by methylation results in decreased MGMT expression, resulting in increased sensitivity to TMZ, and longer survival. The purpose of this research is to use artificial intelligence (AI) to design a low cost methodology to determine the MGMT's methylation status and suggest non- invasive treatment plan.

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Introduction

Glioblastoma multiforme is a very lethal form of brain cancer with no known cure. The prognosis remains poor with a 5% average survival rate, despite aggressive treatments. For high grade gliomas, treatment combines surgical resection, postoperative radiation, and chemotherapy using temozolomide (TMZ), an alkylating agent [1]. Although radiation therapy and chemotherapy with TMZ contribute to lengthen the survival and improve quality of life, the survival advantages are still palliative due to TMZ resistance as primary reason for GBM treatment failure as 50% of TMZ treated patients don't respond to TMZ [2].

The methylation status of the O6-methylguanine-DNA methyltransferase (MGMT) gene promoter region impacts sensitivity to temozolomide by repairing the main cytotoxic lethal base pairs, which are composed of the alkylating agent TMZ, and hence, is linked to reliably predicting effectiveness of TMZ.

MGMT is an enzyme involved in DNA dealkylation and mediation of DNA damage, and is overexpressed in 60% of glioblastomas [1]. MGMT encodes for a DNA repair enzyme that provides resistance to alkylating chemotherapies such as temozolomide (TMZ). Because MGMT transcription can be silenced by promoter methylation in tumor cells, MGMT promoter methylation in patient tumors causes decreased MGMT protein expression, thereby abrogating the DNA repair activity necessary for TMZ resistance (mechanism explained in the Figure 1(a) below) [3]. Thus, patients with a methylated MGMT promoter have improved survival and better response to radiation with concurrent temozolomide-based therapy. Hence, methylation of the O-6-methylguanine-DNA methyltransferase (MGMT) gene promoter has Emerged as a strong prognostic factor for newly diagnosed glioblastoma [3].

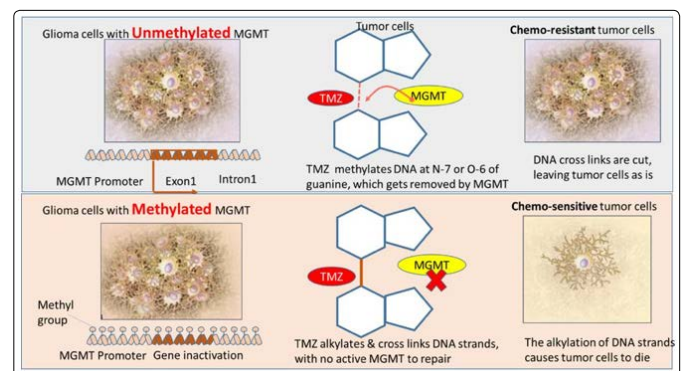


Figure 1(a): Chemosensitivity of MGMT: Enhanced due to epigenetic silencing of the DNA-repair gene MGMT [10].

The picture below shows survival rate for low risk and high risk patients in 4 cases: (1): The survival improvement for patients with radio therapy (RT) using temozolomide (2); standard radiotherapy without temozolomide

(3) impact of RT+TMZ in case of unmethylated MGMT

(4) Impact of RT+TMZ in case of methylated MGMT (4) on the survival rate for low-risk and high-risk patients is shown below in Figure 2. Radiotherapy and TMZ combined confers a clear overall survival benefit to patients with methylated MGMT relative to standard radiotherapy. Ref: Novel predictive epigenetic signature for TMZ in glioblastomas Additionally, MGMT can be epigenetically repressed in multiple ways, most commonly due to methylation of its promoter region, or by over-expression of several microRNAs [4].

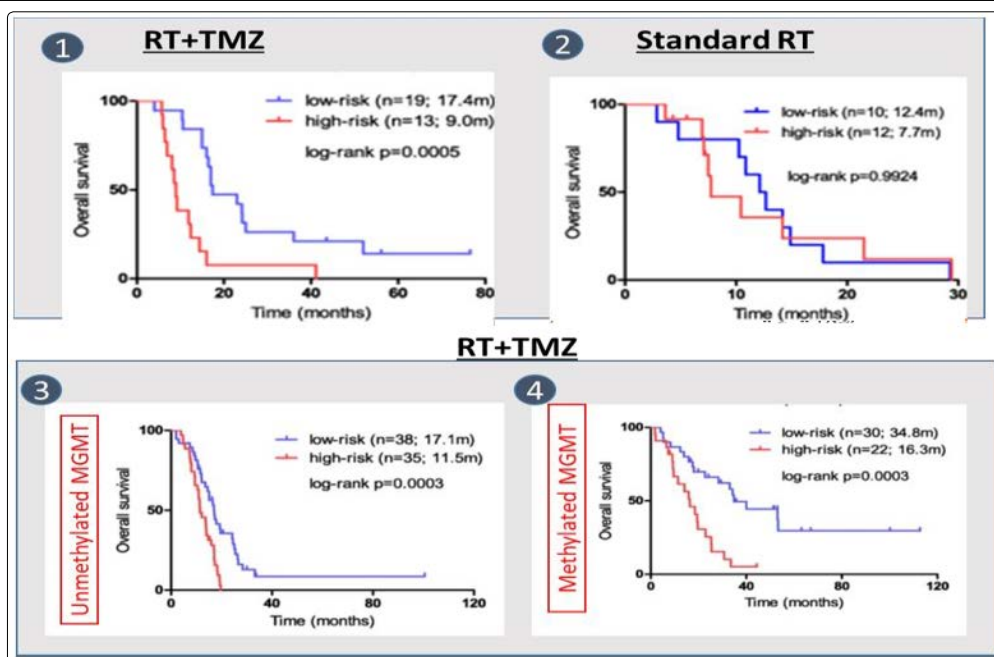


Figure 2: MGMT and Overall survival

MicroRNAs are small noncoding RNAs that target specific sequences of mRNAs, thereby regulating gene expression, causing translational repression or mRNA degradation [4].

This is summarized in the following table:

Problem Statement

Current methods for tumor detection and MGMT gene methylation identification in order to recommend effective TMZ dosages to glioblastoma patients are extremely invasive and time- and cost-intensive. Current methods use invasive biopsies and expensive procedures like genetic testing that add to the financial burden and unnecessary time lag between patient testing and therapy recommendation.

Proposal

Train a convolutional neural networks and the combined TCGA and TCIA data to predict MGMT methylation status and overall survival for patients with methylated and unmethylated MGMT. Perform computation modeling using miRNA databases and MGMT interaction to find miRNAs that can regulate MGMT expression, leading to improved TMZ sensitivity for patients with unmethylated MGMT.

Methods and Materials

Tools and framework used: Python 3, OpenCV, TensorFlow

Tumor segmentation using the Convolutional Neural Network Architecture

Neural network on the TCIA dataset provides evaluation of state-of-the-art methods for the segmentation of intrinsically heterogeneous (in appearance, shape, and histology) brain tumors, namely gliomas. A CNN was trained on the BraTS dataset to create a pixel-wise segmentation map that would predict the tumor region in a brain MRI scan. The Convolutional Neural Network contains an encoder path, which reduces image dimensionality to capture the context of the image, and a decoder path, which enables precise localization using transposed convolutions and up-sampling.

It uses a binary mask to classify each pixel in the image as either containing or not containing a tumor region. The CNN architecture uses convolutional layers and pooling layers. The number of channels is shown on top of each box. The white boxes represent feature maps and arrows indicate different operations (concatenation, convolution, pooling etc).

The Sorenson-Dice coefficient was used to predict accuracy: the Sorensen–Dice coefficient is a statistic used for comparing the similarity of two samples, defined as

$$\text{Dice}(P, T) = \frac{2|P \cap T|}{|P| + |T|}$$

where P is algorithmic predictions $\in \{0,1\}$ and T is consensus truth $\in \{0, 1\}$

CNN model applied to TCIA patient dataset for tumor segmentation

CNN (Convolutional Neural Network) model trained on BraTS dataset above resulted in high accuracy. The trained CNN was then applied (run) on the TCIA dataset to detect tumor areas.

Genomics (methylation data) was retrieved from the TCGA website and filtered by TCGA- GBM, DNA methylation, and methylation β value [5]. Methylation values for these 3 mentioned sites were taken, and a patient was considered to have a positive MGMT methylation status if the maximum of the three was greater than a specific threshold. In general, the methylation value for each site is expressed as a β value, representing a continuous measurement from 0 (completely unmethylated) to 1 (completely methylated). Following the merge of the preprocessed T1 modality MRIs from the TCIA dataset with the methylation label, the resulting methylation data was mapped to patient IDs and T1 images. The data was then used to train a second CNN to predict a patient's methylation status.

Results

1) Overall survival: Kaplan Meier curve, drawn using Xenabrowser, demonstrates higher survival for patients with methylated MGMT vs unmethylated MGMT (drawn for a subset of the total dataset of patients). Ref: xenabrowser.net
 2) miRNA-MGMT mRNA analysis: In reference to Table 2, high absolute values of Minimum Free Energy and GSC (Geometric Share Complementarity Score) demonstrate the stability of the miR181d and miR603 binding. Thus, miR603 and miR181d can silence MGMT and improve glioma cell sensitivity to TMZ.

The regression analysis between miRNA and MGMT mRNA from the TCGA dataset indicated that miR-603 and miR-181d are consistently inversely related with MGMT mRNA in the TCGA dataset (p value of 0.005 and 0.006 respectively).

Table 3: Correlation between MGMT mRNA (TCGA database) and miRNAs

	miR-181d-5p	miR-603	miR-409-3p	miR-124-3p
r	-0.218	-0.211	0.073	-0.011
p-value	0.006	0.005	0.363	0.882

Discussion

The first CNN model used for tumor segmentation was a fully convolutional model with an encoder-decoder architecture. The CNN consists of 4 down-sampling blocks, in which the input image is scaled down using convolutional layers, followed by 4 up-sampling blocks in which the input image is scaled up using transpose convolution blocks.

$$\text{Mathematically: } DL = \frac{2TP}{2TP+FP+FN} = \frac{2|X \cap Y|}{|X|+|Y|}$$

The second CNN, a classification model uses two fully connected layers at the end to classify each image into one of two categories, methylated or unmethylated. The CNN has residual connections that enable an easier propagation of the error into the lower layers of the network. Additionally, the loss used was a categorical cross entropy loss with acategorical cross entropy accuracy for evaluation.

Categorical cross-entropy loss is defined as

$$CCE = -\sum_{i=1}^2 t_i * \log(f(s_i)) = -t_1 * \log(f(s_1)) - (1 - t_1) * \log(1 - f(s_1))$$

Where i=1 if methylation is false, i=2 if methylation is true, f(s_i): probability output for class i
 t_i: 1 for true ground truth class, 0 otherwise. Simply put, it is the (negative) log of the probability output for the ground truth class.

Conclusion

Gene methylation is a control mechanism that regulates gene expression. MGMT is a DNA repair enzyme that causes resistance to the effect of alkylating chemotherapy. Aberrant methylation deactivates the gene, leading to loss of MGMT protein expression and reduced proficiency to repair DNA damage induced by alkylating chemotherapeutic agents, thereby increasing tumor susceptibility to alkylating agent-based chemotherapy [6-8].

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