Precision medicine and quantitative imaging in glioblastoma

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https://github.com/MMIV-ML/ELMED219-2022

Team #3

1 Research plan

1.1 A brief background to the field

About 80% of adult tumors of the brain parenchyma fall into the category of astrocytomas, originating in astrocytes in the brain. Glioblastomas are grade 4 astrocytomas. Grading is done through histological findings and a higher grade represents higher malignancy and worse prognosis [1]. Glioblastomas are the most common type of malignant primary brain tumors, and a highly aggressive type of cancer. After diagnosis of glioblastoma, the prognosis is very poor and survival time averages only about 15 months with treatment [1]. These tumors are difficult to both diagnose and treat, as they are located in one of the most crucial and highly protected organs in the body. Diagnosis based on histology requires biopsy, which may not always be safe to perform in the brain tissue due to accessibility and potential post-surgical complications. Any form of local or general treatment of brain tumors is also problematic due to poor access to the site through the blood-brain-barrier and risk of damaging the rest of the brain in the attempt to kill cancer cells. Collaboration between different areas of medicine is necessary to develop effective methods for early diagnosis and safe treatments.

Effective classification of these tumors is significant with regards to prognosis, and plays an important role in treatment. The cancer cells often contain certain mutations in their genome. Discovering a mutation in the genes encoding the enzyme Isocitrate Dehydrogenase (IDH) can play a vital role in prognosis of glioblastomas, with a likelihood of prolonged survival where the mutation is present [2]. The mutation is typically identified through immunohistochemical analysis (IHC) and genome sequencing, although both of these methods have their flaws. The methods still require biopsy of the tumor through invasive surgical procedures [3] and the heterogeneity of the tumors and the scarce amount of tumor tissue available makes classification difficult. Almost 15% of IDH-mutated glioblastomas remain undetected through IHC analysis [4] and the cost, time and volume of tissue required by genome sequencing, alongside with high rates of false negatives, makes this a less than ideal test. This proves that there is a need for other tests to efficiently

and correctly classify these tumors without the need for invasive surgical procedures on the brain. Advanced imaging techniques such as MRI has proven itself useful and shows great promise [5] [3].

Magnetic resonance imaging (MRI) is useful for depicting soft tissue inside the body, such as the brain. MRI uses magnetic fields to produce an image based on the magnetic properties of the different atoms in different organs and structures in the body. Different MRI imaging techniques have different indications; when depicting cancerous tumors, diffusion weighted MRI (dfMRI) is recommended as an imaging biomarker [6]. However, also T1 weighted, T2 weighted, fluid-attenuated inversion recovery (FLAIR) and T1 weighted with gandolinium contrast enhancement add additional information useful when diagnosing brain tumors [3] [7].

Diagnostics from MRI images is a big field of research where machine learning is especially popular. Using machine learning means to let the program learn from a data set according to a specified algorithm [8]. The data set contains features for several individuals and a target value that the program should be able to predict from the other features. The algorithm is the tactic used to learn from the data.

In recent years, deep learning has also emerged as an important field of research for diagnosing patient from MRI images, and has proved to have even better performance than machine learning. A study on how well different machine learning models predict survival in glioblastoma with texture analysis from T1 weighted MRI images, found that neural networks has the best performance [9]. In deep learning neural networks are used to build the model. A neural network can be seen as an an simplified simulation of the functionality and interactions between neurons in our human brains during a learning process [10].

In this paper, we will discuss the use of machine learning to diagnose, classify and, predict prognosis and treatment of glioblastoma based on imaging techniques through MRI images.

1.2 Objectives and expected impact

Our goal is to explore imaging derived biomarkers trough deep learning. More specifically we propose a study that aims to develop a MRI-based, voxelwise deep-learning IDH classification network using T2-weighted (T2w) MRI images and compare it to other networks developed for the same task, for example the network described by Bangalore et al [3].

We want to see if the method described by Eitel et al. [11] can be used for the same purpose as described by Bangalore et al. [3]. Bangalore et al. proposed usage of deep-learning for classification of IDH-mutation in glioblastomas [3], whereas Eitel et al. proposed a method based on patch individual filter (PIF) layers in convoluted neural networks and the usage of this in disease detection [11]. Eitel et al's method has shown promising results for diagnosing Alzheimer's, and we believe it can play a significant role in diagnosing glioblastomas. Our proposed model should be able to derive biomarkers for glioblastomas by focusing on the localization of the tumor. With PIF, the rest of the image will also be of some importance, but marked for a lower level.

1.3 Material and methods

1.3.1 Building the model

We want to use deep learning to find biomarkers in MRI images. When the input is an image, a type of neural network called convolutional neural network (CNN), is often preferred. The role of CNN is to make

the images easier to process, while keeping the important features that are used to make predictions [12].

Convolutional neural networks uses several layers, the usual layers are convolution, pooling and rectified linear units. In addition to these layers we want to apply patch individual filters (PIF). This type of layer has shown to improve the ability to recognise special features in images [11]. With patch individual filters we will be able to mark certain parts of the images of higher importance.

PIF is a path based approach where the input set is divided into patches, each patch is then weighted before being sent further down the model [11]. The main advantage of using PIF is that it is well suited for small data sets with a lot of homogeneous entries, like brain scans.

A point to be taken into consideration when using PIF layers is how much each patch needs to overlap to reduce the risk of disagreement between two neighbouring patches. In Eitel et al.'s article about the PIF technique, he describes a 50% overlap, but other percentages might yield a better runtimes and results [11]. In this paper the suggested 50% overlap will be used in constructing the model, this is to better build a baseline model and then improve it for later generations.

1.3.2 Data set

The data set will consist of multiple T2w MR images with associated labels specifying whether the tumor is caused by IDH mutation or a wild type. T2w images are used mainly due to short examination time as well as T2w relative resistance to patient motion. T2w images are almost universally required in order to evaluate brain tumors [3]. Table 1 shows what we will include in our data set. Fig. 1 shows two T2w MRI images with glioblastomas. Red highlights a IDH mutation, while green highlights IDH wild type.

To get enough data we will also use some data for other brain tumors. The IDH enzyme also plays a similar role in other tumor types and so the mutation of the gene encoding for this enzyme will be equally useful for training and testing our neural network[2].

In addition to using data of different tumor types, further generalization can be achieved by image transformations. Yogananda et al. used a technique involving mirroring the images vertically and horizontally, and by applying rotational transformation to increase the amount of training data[14]. Such augmentations will increase the amount of training and test data. Resulting in m

Category	Features
Patient information	Age Gender Tumor type Tumor position
Target	IDH-mutation/wildtype
MRI	T2w

Table 1: Summary of data set used to create model.

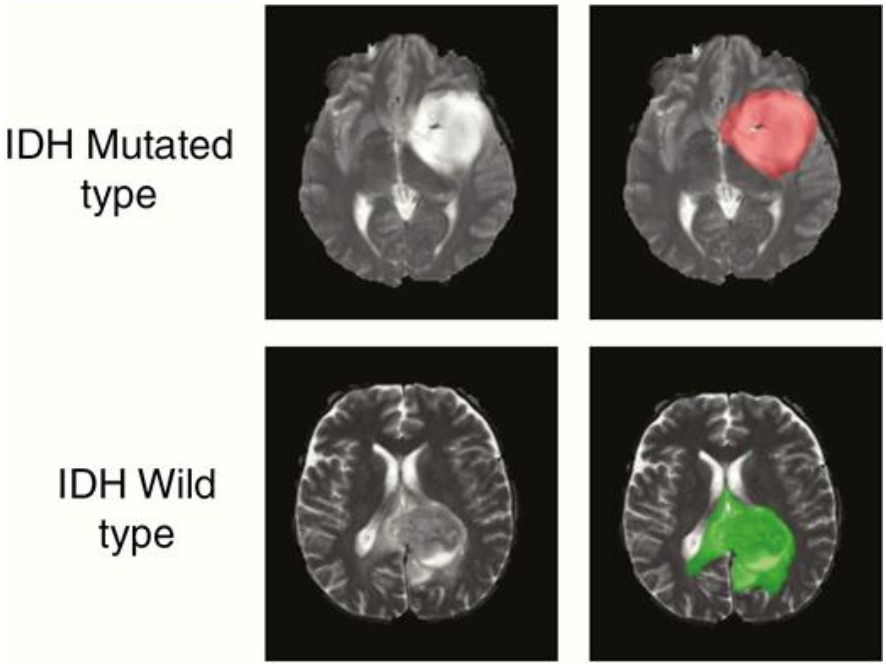

Figure 1: Neuro Oncol, Volume 22, Issue 3, March 2020, Pages 402–411, https://doi.org/10.1093/neuonc/noz199. ©[13]

1.4 Evaluation

The goal outlined by this paper is the same as Bangalore et al. described [3], to develop a highly accurate, MRI-based deep learning IDH classification network, using T2w MRI images. Their method lead to a ”mean cross validation accuracy of (97,14 ± 0,04)%” [3]. We hope to be able to discover a similar pattern with our convolutional neural networks including PIF layers. Our method will most probably use other biomarkers for classification of the IDH gene mutation status in brain glioblastoma, and this may result in even better accuracy. To create a neural network with high performance rate it has to be trained with a large amount of test data. Consequently, our idea is very dependent on accessing enough data with the different glioblastomas, which can be difficult to obtain.

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2 Data management plan and ethical considerations

2.1 Description of generated data and code

We will obtain data from various bio banks, and the data will be filtered, so that we only take the essential data and discard the rest. The essential data will solely consist of the patients age and gender, tumor type and position, whether it's an IDH mutation or a wild type, and the relevant T2w MRI images displaying the tumor. An overview of the information we plan to keep was given in table 1.

There is no generalized test data set for glioblastomas specifically for studies such as this to verify and compare research results on the same data set. To test our data and get an accuracy score comparable to other models we will be splitting the obtained data into a training set and a test set, by doing this we can predict accuracy/precision for our model, given that we have enough initial data. We suggest splitting the data set so that we use 80% of the data to train our model and 20% of the data to test the model afterwords. The mean cross validation accuracy of the study done by Bangalore et al [1] was 97.1% and our goal is to match or exceed this number.

It is important that we have enough initial data to represent the diversity of the population we wish to apply the final model to, whether that be national or international. The model will only produce reliable results within the population used for learning.

2.2 Sharing of data and code

The concept of sharing research is an important part of science for understanding of how nature and everything in the world around us works. By sharing research others can build upon that research [2]. That research should then be shared to be built upon by others. This way every bit of progress made becomes the new foundation to create further progress. This is the foundation on which human advancement in technology and other sciences has developed and is the basis for further such advancements. Our proposed study is to further develop the study by Bangalore et al. [1] and to publish our study for others to further build upon.

The model and results will be made public on GitHub, so that other researchers can validate and/or make further research based on this model and results. Due to the filtration of data described above, the data, that helps build this model, can be published while maintaining patient anonymity. This contributes to the possibility that the diagnosis of glioblastoma, can be made by a deep learning model with a very high accuracy.

2.3 Ethical considerations

Given the nature of the data that will be used in this project, a strict privacy policy is to be enacted to maintain the patients privacy and anonymity during the lifetime of the project. The patients and/or relatives must be informed of the usage, and for how long the data will be kept. In the event that the data is to be published, proper information will be given and consent to publication will be required before publishing. However, since the data will be filtered as described above, this will contribute to maintain the privacy and anonymity of the patients.

Anonymous data and the coding we use for the machine learning, can and should be published. It is important that the experiment we conduct can be peer reviewed and reproduced.

Vollmer et al. has proposed 20 critical questions that should be satisfactory answered in order to meet concerns regarding transparency, reproducibility, ethics and effectiveness [3]. And we wish to use these as a basis for evaluating the ethics of our study. We will also strive to uphold the four principles of clinical ethics: beneficence, non-maleficence, autonomy, and justice [4]. We will also send our study to a third party, such as a committee of Medical research, for ethical consideration and approval.

We believe this study and studies like it can be an important direction for development in the approach of glioblastomas to the benefit of patients. It can reduce complications from the current diagnostic procedures by replacing invasive biopsy through brain surgery with non-invasive MRI scans. It will also make it possible to correctly diagnose and make better prognostic assumptions for patients with glioblastomas that are impossible to biopsy. We believe our method can be a safer and more cost effective alternative to today's methods as it requires less personnel and requires no new equipment.

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