Classification and Personalized Treatment Strategies Through Multimodal Deep Learning Strategies In GBM Patients

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https://github.com/MMIV-ML/ELMED219-2021

Team #2

1 Introduction and background

1.1 Glioblastoma: Definition, prognosis and current diagnostic tools

Gliomas are tumors stemming from glial cells, the supporting cells of the central nerveous system. Normally tasked with maintaining homeostasis in the brain, the cells, when cancerous, may provide sizable challenges for patients and caretakers alike. The World Health Organizations (WHO) rating of gliomas range from a grade of I to IV, with the latter being the most aggressive. Glioblastoma Multiforme (GBM), a stage IV glioma, is the most common form of malignant brain tumor in adults affecting over 200 Norwegians yearly. [1] There is currently no curative treatment for glioblastoma. Due to quick disease progression and severe burden of disease, despite aggressive multimodal treatment, the median survival of GBM patients is approximately 15 months. [2] Furthermore, GBMs with their heterogeneous disease pattern provide a sizable challenge for researchers seeking to develop new and more effective uniform treatment strategies. [2]

A diagnosis of GBM is currently reached through a series of examinations, usually starting with a clear anamnesis followed by subsequent MRI scans. If positive, a biopsy is likely collected from the patient and analyzed by a pathologist for signs of GMB. This screening sequence then provides the information for a multidisciplinary team of healthcare professionals to diagnose, grade and suggest a prognosis. The decisions made by this team ultimately leads to a decision regarding treatment options. We choose then, to collect data from similar modailites (MRI, and biopsies) as well as genomics data, subsequently feeding this data into a collection of neural networks in hopes of reaching a better understanding of GBM detection, diagnosis and treatment. In order to know which data the deep neural net should receive, an explanation of the modalities used to gather the data, as well as common characteristics of GBM is in order.

1.2 The basics of MRI

MRI is a non invasive imaging modality that uses Magnetic resonance to create images. The MRI system consists of a strong magnetic field, often called B_0, smaller magnetic fields called gradient coils, that are orthogonal to the main field and then a few even smaller controllable fields called shims, to ensure a homogeneous B_0 field. There are also radio transmitters and receiver coils. In addition to this, the system needs a large amount of computer power, to manage the gradients, but also for image reconstruction. The signals used to generate MRI images are quite weak, so the whole system needs to be placed inside a Faraday cage.

[3]

The concept of MRI is using the property of proton spin, and because of this they create a small magnetic field. The human body consists of 70 percent water, and is therefore rich with protons because of all the hydrogen atoms.The magnetic field for a single proton is called a magnetic moment, and while normally oriented randomly, they will align when placed inside a strong magnetic field like B_0. The protons will align parallel and anti parallel with the B_0 field, though more will be parallel. The sum of all these protons will create a "Net Magnetisation Vector". To measure this vector, it needs to be "knocked out" of its alignment with B_0. This is done by adding energy to the system, in the form of an RF pulse. This energy is absorbed and released, and this is what is used to generate images in MRI. This RF pulse needs to have the same frequency as the protons Larmor frequency to achieve excitation. The Larmor frequency is given by the equation: $\omega_0 = \gamma * B_0$ where ω_0 is the Larmor frequency and γ is the gyromagnetic constant for the tissue.[3] [5]

MRI is a very good tool to get images that distinguish between different types of tissue. Since there will be a different amount of protons in different tissues, the signal will be different. MRI also offers the option to get images that highlights different tissues. T1 and T2 are contrast specific values, and will give different images if weighted towards one of them which again will provide more information. It is also possible to use a contrast fluid to get another set of images that will highlight some tissue types even better. In addition to this, MRI offers different ways to acquire images, and by using this in combination with different tissue contrast and/or contrast fluids, it is possible to generate many different images using the same instrument. [3] [5]

MRI is one of the primary tools used to diagnose glioblastoma, usually with several different types of images, including both T1 and T2 weighted images, as well as T1 with contrast. The different contrasts given in MRI images makes it one of the best non-invasive tools to diagnose glioblastoma, and offers a non-invasive way to study and plan for the best course of action for treating it. [4]

Glioblastomas are supratentorial or intra-axial tumors, often located in the frontal or temporal lobe. The tumor is seen as a mass with a heterogeneous growth pattern and diffuse boundaries. The tumor is often observed infiltrating surrounding brain tissue along white matter tracts, often via the Corpus callosum. This crossing through the Corpus callosum creates a pattern called "butterfly glioma". This makes the tumor particularly aggressive, therapy and resection resistant, and therefore carries a poor prognosis. Necrosis in the tumor is also common due to rapid growth. The tumor's angiogenesis, creation of new blood vessels, creates an opening of the blood-brain barrier as these newly generated vessels are not as structurally sound as normal blood vessels in the brain. Leakage from these vessels can therefore produce significant vasogenic edema. This edema can be seen on MRI using gadolinium as a contrast agent. [6]

Negative prognostic factors include: degree of necrosis, size, spread, location, and relationships to other structures such as blood vessels, large white matter tracts, and the brainstem. [7]. However, a radiological diagnosis is still subject to uncertainty, and a histological diagnosis is therefore essential.

1.3 Biopsy and staining

Although somewhat invasive, detection of a brain mass may require a tissue biopsy in order to diagnose and make a prognosis. A neurosurgeon will map the brain in a three dimensional coordinate system in order to decide the appropriate angle of attack and guidance of the needle. The patient is asleep during the procedure, and the tissue sample is analysed by traditional means in real time by a pathologist. Further samples are taken which take three to four days to complete. [11]

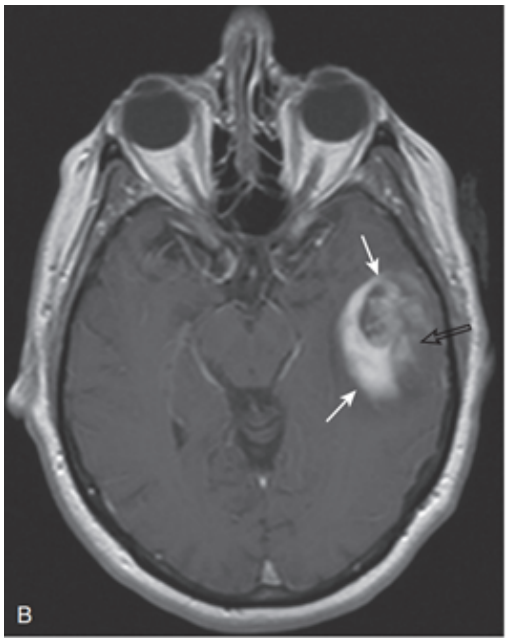

Figure 1: Axial T1 post-gadolinium MRI - mass in left temporal lobe (white arrows), with necrosis (black arrow), and leakage of contrast into the brain parenchyma [6]

There are several artifacts to look for when assessing histology of a possible glioblastoma. The astrocytes are inadequately differentiated and show atypical nuclei, uncontrolled cell division and variation in shape and size. Immunostaining usually shows positive glial fibrillary acidic protein (GFAP). The tumour is necrotic due to faster proliferation than angiogenesis and forms microvascular channels.

Traditional review of a tissue biopsy involves processing the tissue, staining it with Hematoxylin and eosin and the sample being analysed by a pathologist. However, a new form of imaging technology more suited for AI-analysis called SRH imaging has emerged. The device is based on Stimulated Raman Scattering (SRS), which does not require tissue processing, slicing or staining. The original SRS is too large and expensive for an operating room and was refitted with a fiber-laser microscope, making it a portable and high resolution device, the SRH. The SRH-method has proven equally accurate to H&E staining when analysed by pathologists.

Furthermore research teams have applied convolutional neural networks to SRH images of brain tumours. For training the algorithm they used over 2,5 million images from 415 patients. They needed to assess the best size and resolution of the images to train the AI. The algorithm was then used in a clinical trial of 280 patients to assess the accuracy of the SRH-AI method, resulting in an overall 94,6 percent diagnostic accuracy for the algorithm and a 93,9 percent accuracy for conventional analysis by pathologists. [9]

Another interesting finding was that the samples where the algorithm made the incorrect prediction the conventional method proved accurate and vice versa. This points in the direction of an effective collaboration between AI and specialists.

The AI analysis takes less than 3 minutes, making it useful in a variety of ways. It's useful in the initial stages of making a correct diagnosis and prognosis, and more training data will make it even more

accurate. In hospitals where specialists and pathologists are less available the SRH-AI may serve as a useful substitution. The short processing time also allows it to be used during surgery to separate cancerous tissue from healthy tissue. [9]

1.4 Genomics

Primary glioblastomas accounts for approximately 90% of glioblastomas and develop rapidly *de nevo* [13]. Hence, no clinical or histological affirmation of a less malignant precursor lesion is observable before diagnosis. Nevertheless, they evolve as a result of multiple genetic alterations [12]. Genetically, the *classical* neoplasms are characterized by the loss of heterozygosity 10q, *Epidermal growth factor receptor* (EGFR) amplification, p16INK4a deletion, and *Phosphate and Tensin homolog* (PTEN) mutations [12]. Due to next generation sequencing, novel genomic variations have been identified and, accordingly, two additional subtypes declared: Mesenchymal (MSC) and proneural(PN) glioblastoma [13]. MSC is associated with loss of/mutation in p53, neurofibromin (NF1) and CDKN2A, whereas PN is associated with multiple amplifications, mutations in IDH1, PI3K and p53 [14]. Prognostically, the MSC subtype tends to correlate with poorer survival and resistance to therapy compared to the other subtypes [13].

Secondary glioblastomas, on the other hand, progresses from diffuse astrocytoma (grade II glioma) or anaplastic astrocytoma (grade III glioma)[12].Thus, the diagnosis includes analysing neuroimages and biopsies at an early stage. Initially to this development, the presence of detectable TP53 mutations is frequent [12]. During further progression, an accumulation of additional mutations occurs, including the loss of heterozygosity 10q [12]. Mutations in isocitrate dehydrogenase (IDH) have been proven to exist in high numbers during the progression process of secondary glioblastomas [15]. Therefore, IDH status is key in the classification of glioblastomas. While mutations in IDH correspond to secondary glioblastomas, IDH-wildtype (wildtype implicates no mutation) reveals primary glioblastoma [16] . In addition, IDH status indicates prognosis, whereby IDH mutations are associated with better prognosis.

Additionally to the IDH status, O(6)-Methylguanin-DNA transferase (MGMT) promoter methylation status is used as a prognostic indicator. MGMT encodes proteins that repair DNA. However, when methylated, it is inactivated, which in turn suppresses DNA repair activity – including the DNA of the tumour [17]. Methylation of MGMT promoter is acknowledged as being associated with longer survival. The determination of MGMT promoter methylation status is challenged by spatial heterogeneity and temporal evolution [18]. This implies that taking biopsies to assess the MGMT promoter methylation status is an imprecise approach. IDH status, however, seems to be homogenous within a tumour and does not evolve through time [19]. The present approach is therefore adequate. Nonetheless, the process includes immunohistochemistry and/or genetic sequencing to distinguish between IDH mutation and IDH-wt, demanding both precious time and resources [20]. Recent research has used deep learning to make the same distinction from H&E stained histopathological slides, with good accuracy, facilitating the determination of IDH-status [20].

1.5 Treatment options

Current treatment strategies include surgery, radiotherapy and chemotherapy. Patients usually undergo surgery followed by radiotherapy and chemotherapy. Complete surgical resection of a tumor has shown to increase overall survival (OS) in GBM patients, however, radiotherapy does not seem to increase OS. [21] Recently chemotherapeutics has been at the forefront of GBM research. Currently, several chemotherapeutics are available to GBM patients. As an example, results from randomized clinical studies in 573 patients demonstrate that the addition of TMZ to radiotherapy significantly increases OS (27.2% vs. 10.9% in radiotherapy alone at 2 years). [22] Several other treatment options are in development encompassing

various angles of attack based on established pathogenic GMB pathways. These include but are not limited to: IDH mutations, the Notch pathway, Ceramide signaling, the Vascular endothelial Growth Factor (VEGF) signaling pathway, the Platelet Derived Growth Factor (PDGF) signaling pathway, the Epidermal Growth Factor Receptor (EGFR) pathway, the PI3k/AKT/mTOR Pathway, Phosphate and Tensin Homolog (PTEN) Signaling, and Sonic Hedgehog Signaling (SHH). (Figure 2) A thorough understanding of these pathways is integral to future drug development, as well as an AI model's ability to suggest treatment options for GBM patients of the future.

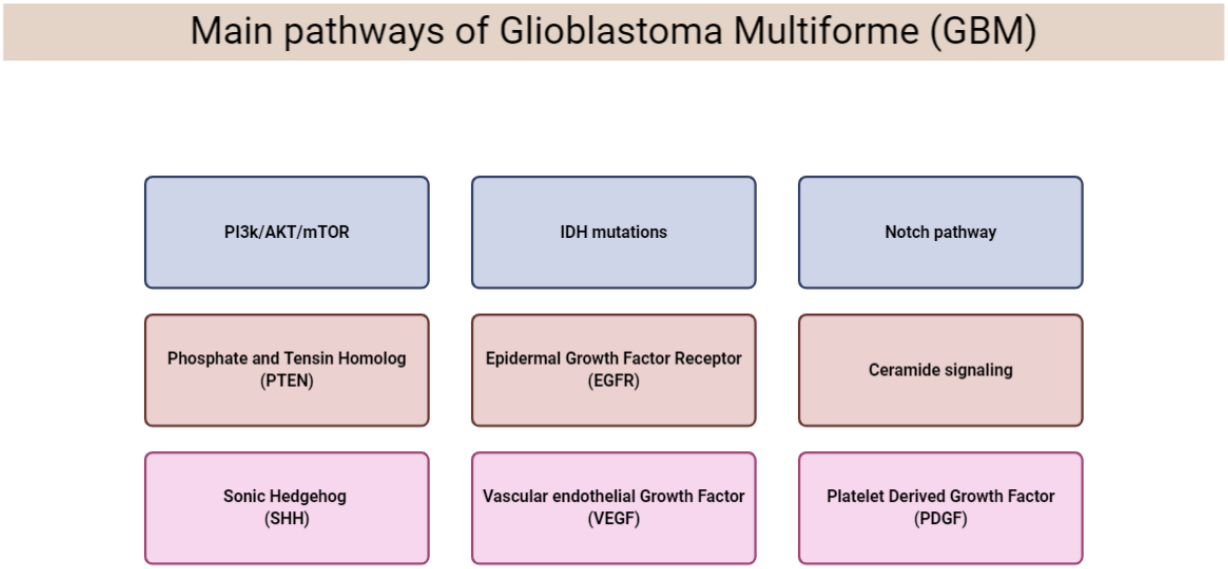

Figure 2: Common oncogenic pathways in GMB and simultaneously pathways that might be exploited in drug design

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2 Deep learning and Neural Network design

2.1 Brain tumor segmentation

In order for our machine learning pipeline as a whole to work, it is crucial to extract some important features of the MRI-images first. In this case this will be done through brain tumor segmentation. In order to achieve this sufficiently, one option could be to use the powerful deep learning library fastai [1] combined with the MONAI [2] library to develop a fast and accurate model on image data from the TCGA[3] and BraTS [4] data sets. Another option could be to use a model based on DeepMedic, which is an 11-layer deep multi-scale 3D CNN described in [5].

2.2 Histological analysis of dysplasia and GBM characteristics

With the solution above, the new data will act as input for another supervised machine learning model which will output a classified degree of dysplasia and some pointers to likelihood of prognosis. A CNN approach like ResNet50 described in [6] could be a viable option, where other features - like age can be integrated to the image-based classification using a logistic regression classifier for potential increase in accuracy[6].

2.3 Genomics analysis

We are hypothesising that applying a deep learning model like CNN or LSTM with genomic data as input [7] acquired from TCGA [3] could be a good way of identifying biomarkers and state of disease. This could help find mutations, expressions of genes and other patterns that help us predict prognosis and treatment. Another proposal is to apply unsupervised learning through an autoencoder similar to [8], to gain new knowledge about metadata in the gene sequence that could be further used and potentially have a big impact in terms of diagnostic accuracy. We are aware that this approach might not be well tested - but we see great potential in such an approach.

2.4 Prognosis and treatment prediction

Based on output obtained from previous segmentation results, a Vgg-16 based CNN model described in [9] can be used to predict survival rate with images after segmentation has taken place as input.

Coupled with both data obtained from the second model and genomics analysis as explained, this could be used to predict or give valuable information regarding prognosis and possible treatment options.

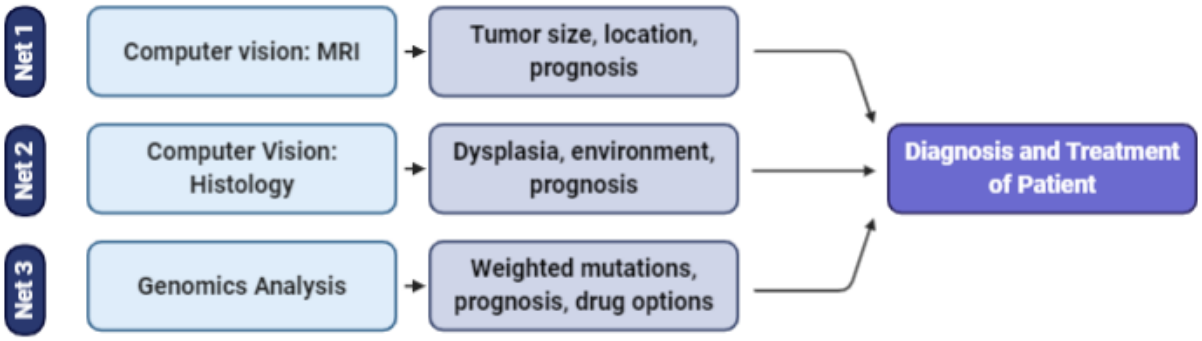

Figure 3: Proposed neural network pipeline. 3 separate network processing different data modalities, eventually all converging on a proposed prognosis

3 Novelty and expected impact

Although the modalities used in this project are well established and thoroughly researched, the congregation of the lot into a deep neural net to solve a common problem might be seen as a novelty. Through allowing several independent neural networks to solve similar tasks, and then together reaching a final conclusion of prognosis and potentially a treatment plan.

Through our approach we aim to facilitate the process of diagnosing individuals who are affected by this aggressive cancer. Through developing an in depth AI model, we seek not to replace the physician, but rather make his or her work as a doctor in the 21st century possible. With limitless amounts of data it is not reasonable for any given doctor to analyse all of the available data and extract from it all the clues that might hint towards a certain diagnosis. Our system proposes an aid to these physicians so that they can organize patient data and gain a bird's eye view of every patient. By eliminating the data crunching, each physician will have the opportunity to efficiently diagnose a patient, not only potentially extending a patient's lifetime, but allowing time for good communication and that human touch we believe is essential alongside an AI system like here proposed by the researchers. As a result, greater patient care as a whole, through both somatic treatment and good patient care.

4 Data management plan and ethical considerations

4.1 Sourcing of data for analysis

The Cancer Genome Atlas Glioblastoma Multiforme (TCGA-GBM) is a data bank of collected glioblastoma phenotypes and genotypes. [3] The purpose of this data collection is to form a research *community*, facilitating collaborations and progress by distributing open, anonymized data sets. Containing near half a million images and providing access to biopsies and genomics, we recognize this as a resource for pretraining our model. If the model is to be used at norwegian hospitals, we believe the model should receive further training on a population more similar to its integration. The goal would then be to establish a local data bank based on patients at Haukeland University Hospital. For this we propose a local data storage server, similar to the already established "translab" system used to store research data for all researchers working at UiBs faculty of biomedicine. This, of course, to properly secure the protection of patient data.

The use of, and storage of, patient data needs to be handled carefully and securely. As more and more patient data becomes available due to innovation and new diagnostic tools, the storage of data from these must be handled with great care, and minimizing the possibility of unwanted access must be a priority for any system handling patient data.

4.2 Sharing of data and code

We intend to publish our findings in a peer reviewed journal. All code used in the project will be available as the publishing format will be a jupyter notebook. The training data from TCGA is already publicly available. In the event that we are allowed access to patient data from haukeland university hospital, we expect only major highlights of the information, of course also anonymized, to be available for publication due to its confidential nature.

4.3 Ethical considerations

The ethical considerations of AI are too many to name in this article. The emerging field of AI leads to both predictable and unforeseen complex consequences. Threading carefully is therefore an important

approach. The commercial aspect of the many uses of AI leads to a skyrocketing value of patient data, due to the large amount of data needed to train and test algorithms. As seen in other technological ventures, diverting from strictly ethical uses of new technology may be a commercial force that seems nearly impossible to prevent. Short sighted financial gain may lead to enormous pitfalls that take years to come out of. [10]

Bias is unavoidable in any dataset, and radiologists and physicians have a responsibility to address and attempt to minimize the effect of this in AI models. At the centre of the code of conduct of AI use is protection of patients, transparency and control and regulation of data and algorithms. The speed of development of this new technology is vast, and requires rigorous discipline and work to keep up ethical standards. [10]

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