Precision medicine and quantitative imaging in glioblastoma

ELMED219 (Artificial Intelligence and Computational Medicine), 4-29 January 2021

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

Team #1

1 Research plan

1.1 A brief background to the field

Glioblastoma multiforme (GBM) is a high-grade cancerous neoplasm of the brain. Accounting for 15% of all intracranial tumors and around 50% of all malignant primary brain tumors, it's etiological mechanisms still remain largely unknown. Prominent characteristics include an aggressive growth in a diffuse pattern, angiogenesis and necrosis [1]. With a median survival of 12 months [3] and hardly any long-term survivors, novel therapies and clinical tools is imperative to better combat GBM.

Due to the low curative potential of current treatments, the aim of therapeutical intervention is commonly to prolong the patients life and reducing or preventing further detriment to quality of life [4]. Despite these good intentions, contemporary interventions, usually a combination of radical surgery, radiotherapy and chemotherapy, always involve trade-offs in terms of possibility of complications, treatment-induced adverse effects and other burdens on the patient. Clinicians are therefore faced with the difficult task of predicting the "terrain" of patient well-being and survival, and then balance therapeutical action and inaction to lead the patient on the best possible path through this terrain from diagnosis to end of life. With the advent of modern artificial intelligence, machine-learning techniques and powerful computational hardware, we claim a certain optimism in the potentiality for aid with the aforementioned challenges in decision-making, by utilizing these with imaging data and other relevant patient information.

The human body consists primarily of fat and water, which makes hydrogen the most common atom in the body. The core of the hydrogen atom is a proton, whose properties the MRI system leverages. These properties includes mass, charge, and most importantly spin [7]. Magnetic resonance imaging is a noninvasive form of imaging. A strong magnetic field is created around the subject, typically at 1.5-3 Tesla, which forces the protons in the body to align with the field [7]. Additionally the system generates magnetic gradients. These magnetic gradients are used to get the protons out of order, yielding more information from the scan. For a short period of time a radio magnetic wave, an RF-pulse, is emitted towards the body, which manipulates the protons that are out of order. As the protons realign to the magnetic field, they emit a second signal. This allows us to detect the locations of the protons, and to calculate an image. The MRI system is sensitive to soft tissue contrast. Based on the fact that diseases leads to fluid changes in the body, the MRI is a fine modality when we want to detect tumors and infections [7].

Positron emission tomography is a nuclear image modality, which may yield unique information about various physiologic processes in the body [8]. The patient is injected with a radiotracer, a molecule where an atom has been replaced by a radioactive isotope [8]. When injected into the patient, the radiotracer will follow the biological process in which the unmodified molecule would normally occur in. The radioactive isotopes emits positrons, and as a positron interacts with an electron, they annihilate. The annihilation results

in two gamma rays, and because of the laws of conservation, the gamma rays travels in the exact opposite directions of each other. When the two gamma rays are detected by a detector, we get a line of response, LOR [8]. Sufficient detection results in a illuminated area.

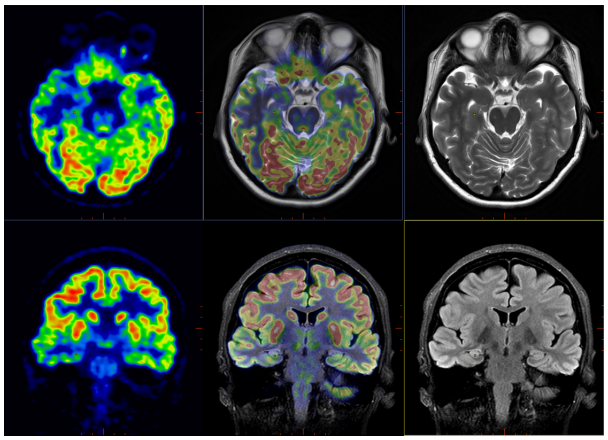

Figure 1: Illustration of PET, PET-MRI fused and MRI.
(image from https://www.cam.ac.uk/research/news/cambridge-extends-world-leading-role-for-medical-imaging-with-powerful-new-brain-and-body-scanners)

MRS is an imaging technique which analyses the chemical compound of tissue. Protons residing in different molecules has differing magnetic properties. The different magnetic properties results in different resonance frequencies. This difference makes it possible to collect information about the chemical substances of a chosen area in the body. The nuclear magnetic resonance signal is quantitative and presented in a spectrum curve. As the chemical compound of tumor tissue differs from the chemical compound of healthy tissue one can analyse the occurrence of certain markers which is characteristic in tumors such as GBM.

Isocitrate dehydrogenases (IDH) is an enzyme that plays a significant role in cellular metabolism and cancer [5]. It has been shown that IDH is promising as a prognostic marker for GBM. The different IDH mutations gives us an opportunity to differentiate between different stages of gliomas, as well as between subtypes of glioblastoma. The IDH1 mutation is detected in about 60-80% of secondary glioblastomas, whereas in primary GBM this mutation only appears in 5% or less [6]. 2-hydroxyglutarate (2-HG) is a metabolite which accumulates in the brain when the IDH1 mutation is present [9]. It is possible to detect 2-HG in vivo by using MRS [9], which makes this a MRS-related marker to indirectly detect IDH1 mutations.

Glutathione, GSH, is one of the most important antioxidants. It is part of the most important defense system we have against free radicals, radiotherapy, and chemotherapy attacks [10]. The radio sensitivity of the tumor influences the response a given tissue will have to radiation therapy. In order to achieve the greatest effect of the radiation fractions we want the tissue to have high radio sensitivity. Tumors with low GSH level has shown to be radio sensitive [10]. By checking the level of GSH it can be possible to predict the response a given tumor will have to radiation therapy. The MRS technique makes is possible to quantify the GSH concentration, and gives us an indication on the radio sensitivity of the GBM.

Another matter one have to take into consideration when planning a treatment is hypoxia. Radiation therapy using photons is indirectly ionizing. This means that the beam interacts with water molecules which further produces free radicals. These free radicals then damages the target, which is the DNA of the cancer cell. Hypoxic cells are cells deprived of oxygen. This is problematic due to the fact that it is the oxygen which makes the damage induces by the free radicals permanent. Without oxygen present, it is possible to repair the damages. This allows the hypoxic cells to survive irradiation fractions. Hypoxia in GBM triggers

the cancer cells to become more invasive [11]. Knowing whether or not the GBM is hypoxic is therefore crucial for the treatment planning.

Hypoxia is also an indication of necrosis. Necrosis is death of tissue. It is caused by lack of oxygen or blood supply to the tissue [12]. The development of a necrotic core in a tumor indicates a high-grade tumor which has increased in size [13]. Furthermore this indicates a poor prognosis. Possible markers one can use in MRS to detect hypoxia is hyperpolarized (13)C Pyruvate and (13)C Lactate [20] .

To make predictions of prognosis there are two additional phenomena which need to be accounted for. Tumor pseudoprogression is when a lesion has increased in size as a result from the treatment. Further this can stimulate the disease and make it more progressive [15]. Tumor pseudoresponse can easily be misinterpreted when only studying MRI. It may seem like the tumor is responding to the treatment, but in reality it is stable and it may even have progressed [16]. In a study of 22 glioblastoma patients tumor pseudoprogression was detected with 96% accuracy [17]. The modality used was PET with the 18F-FET tracer [17]. The enhancement of the 18F-FET tracer will therefore work as a feature for this phenomena. To identify tumor pseudoresponse MRS can be used to detect the cerebral blood volume [16].

1.2 Objectives and expected impact

The aim of this project is to explore the potential of utilizing machine-learning models as an aid in decision-making regarding treatment of GBM patients. Specifically, we will train these models to provide useful prognostic information on survival and neurophysiology-related Quality-of-Life (QOL) parameters, taking into account the specific therapeutical interventions that could be considered. Due to availability and the array of sub-modalitites, the model(s) will rely primarily on data from magnetic resonance imaging (MRI) and magnetic resonance spectroscopy (MRS). PET imaging can with certain hardware be combined with MRI (PET-MRI), such that our model(s) will also utilize information from this imaging modality using the 18F-FET tracer. Additionally, the model(s) will take as parameters known prognostically significant patient-factors and the specific details of treatment. In a clinical setting, the product that results from this project would provide clinicians with survival and QOL projections for input treatment parameters, giving them the opportunity to explore predicted outcomes and potentially select the one that best suits the patients wishes.

As previously stated, there are virtually no long-term survivors from GBM. This fact underlines the importance of every remaining month of life to be well spent and well lived. At the same time, every patient is different and has different standards for what they consider a good life. By providing the product described in this project, our hopes is that GBM patients will be empowered to get the most out of their remaining time.

1.3 Material and methods

As we use MRS to detect the chemical compound of the tumor, we want information about the location and size of the tumor from MRI. By defining region of interest and volume of interest, it is possible to extract geometric features such as size and volume of the given GBM [18]. We also want to extract information about the growth rate. To do this we need pictures taken over a period of time. When planning the treatment it is crucial to have knowledge about which parts of the brain is affected by the GBM. This determines the way one choose to irradiate or operate, and also which side effects one can expect. For example medulla, the most vital part of the brain. Any damage to the medulla can result in instant death [19]. For the model to be able to detect the location of the GBM we will exploit the different image contrasts MRI offers, which is T1, T2, and proton density [7]. With these different contrast we want the data to be able to segment the different parts of the brain.

The collected data consists mainly of patient- MRI and MRS scans at the time of inclusion of and throughout the study. We will use T1, T2, Flair and T1-Gd MRI-sequences, as well as 2-Hydroxyglutarate and GSH MRS-measurements. Journal data from time of admission, especially factors determined to be

Category	Features
Patient	Age Gender MGMT-methylation status
Treatment parameters	Radiation (total dosage) Chemotherapy Extent of surgical intervention
MRI	Size Location
PET	18F-FET
MRS	2-HG GSH

Table 1: Features.

prognostically significant in GBM patients, will be collected and used as features by the model(s). Such data include, but is not limited to, age, gender and MGMT status. Additionally, the specifics of the provided treatment will be highly relevant in terms of predicting survival and quality of life, such as total dosage of radiation, type of chemotherapy and the extent of surgical resection. The latter factor is a complex parameter that is not easily described in a machine-readable manner. To represent this information in our model(s), we will derive it by "subtraction" of post-surgical MR-image from pre-surgical MR-image to yield a segment of surgically removed tissue.

Quality of life will be assessed using the validated FACT-Br questionnaire. The quality of life will be evaluated monthly following inclusion due to the mean survival time of GBM patients, found to be 12 Months 95% [CI]:(9.9-14) [3]

The tasks are predicting the patients quality of life and predicting survival. The quality of life score is a number based on the total score from the questionnaire. Both tasks take the same feature parameters, but will with all probability end up using different models. Different machine learning algorithms will be tested and tweaked to find the best performing model. The hyperparameters related to the different models will be found by running a grid search and cross-validation.

Before the data is provided to the machine learning model to train, there is often a need to pre-process the data. An example of this is if the different parameters have a big variation in value ranges. The performance of the model can be improved by normalizing the values of the data.

The data will be trained on different models to see which ones gives the best result. When training, the data will be split into training and testing data with a 70-30 split.

For the conventional machine learning algorithms, one would need to process the images, segment and define several features. Deep neural networks however requires no feature extraction. They automatically learn and extracts features from the pictures. Deep learning algorithms have also been outperforming conventional machine learning methods in computer vision tasks. However a caveat of deep neural networks are that they require a lot more data than the conventional machine learning algorithms. There are different ways to work around this when the data set is smaller. One of them is image data augmentation. Image data augmentation increases the size of the data set by slightly augmenting the original images and also training the model on these augmented copies. Another method is transfer learning, where an already trained neural network is used as a starting point. This neural network is often trained for a similar task, providing a good basis.

1.4 Evaluation

Evaluation of a model is crucial to understanding its performance. There are different evaluation metrics for a regression model. An example is Mean Square Error (MSE) as well Root Mean Square Error (RMSE). MSE measures the average squared error difference between between the predicted values and the actual values.

$$MSE = \frac{1}{n}\sum_{i=1}^{n}(y_i - x_i)^2$$

RMSE is the sqaure root of MSE. The number produced does not say much alone, but it is useful when comparing the results of different models.

Before the machine learning model would be integrated in a clinic's workflow it would need additional user testing. This testing would be to let the fully trained model give predictions on new real data and compare it to the actual results later. It would in this case not be used as a tool while testing, but instead stay on the sidelines for evaluating the models practicality.

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2 Data management plan and ethical considerations

2.1 Description of generated data and code

The data collected in association with this project will consist of various imaging data (MRI, MRS, PET), Data from patient journal regarding prognostically relevant patient factors and details of treatment, and finally data on survival and patients' quality of life. The data will be stored in a secure, digital storage space, and will by default persist for the duration of this project only. If given a secondary, explicit consent by the patient, the data may be anonymized and made publibly available.

The generated code will primarily relate to the software structure surrounding the machine-learning models, as well as a user interface to provide clinicians a way to obtain the models' predictions in a user-friendly manner.

2.2 Sharing of data and code

If given explicit consent by patients, all data will be anonymized and uploaded for public use. All generated code and software will be open-source to facilitate improvement of software and the advancement of new tools with similar purposes.

2.3 Ethical considerations

The study plan must be approved by the Regional Committee for Medical and Health Research Ethics (REC) before any experiments can be done.

All clinical data will be anonymized, and personally identifiable information (PII) will be stored on a secure server and separate from clinical data. All PII will be stored according to the General Data Protection Regulation (GDPR) and will be deleted after the study is done. Anonymized MRI data will be published together with the results of the study.

Collection of PET and MRI data may be uncomfortable for the patients. PET scanning also involves ionizing radiation, which may be harmful to patients. We will collect informed consent before inclusion in the study, and the patients will be able to withdraw from the study at any time, in accordance with Norwegian law.

The use of machine learning in clinical decision making is controversial. The decision making processes of neural networks and other machine learning tools are highly complex and often opaque, referred to as the "black box" of AI [1]. The model takes an input and produces an output, but what happens in between is unclear to the user. Not being able to explain exactly how the models we create are operating can make it hard to justify their use in a clinical setting, and health care workers are often reluctant to using tools without clarity as to the workings of the model [2]. Therefore, we will focus on using machine learning tools that are able to provide us with an intelligible explanation of their models.

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