Precision medicine and quantitative imaging in glioblastoma

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

Team #1

Contents

1 Research plan

1.1 A brief background to the field

1.1.1 Glioblastoma multiforme

Brain tumors consist of abnormally growing tissue that has no physiological function in the brain. Brain tumors lead to abnormal neurological symptoms. The number of people who get brain tumors in developed countries has increased with 300% according to "National Brain Tumor Foundation" (NBTF) in the United States [**1**][**2**]. Early diagnosis of brain tumors is very important in order to improve the outcome of treatment and hence the survival. There is a growing interest in machine learning and deep learning for better and more robust diagnostization of brain tumors [**1**].

Brain tumors can be classified as either metastatic or primary brain tumors. In primary brain tumors the cells are originally brain cells, while in metastatic brain tumors the cancer cells has spread to the brain from a primary tumor located in another area of the body. Glioma is one type of tumor in the brain which is much researched today. There are different types of Gliomas, from high grade tumors, which are called glioblastoma multiforme, also known as glioblastoma, to low grade tumors, like oligodendrogliomas and astrocytomas. Chemotherapy, radiotherapy and surgery can treat gliomas [**1**]. Glioblastomas are the most common primary brain tumors in adults. They account for 45.2% of malignant primary brain tumors and tumors in the central nervous system (CNS) [**3**]. Glioblastomas has a median survival of 15 months. Primary glioblastomas which occur in older patients with a mean age of 62 years account for 80% of all glioblastomas. Secondary glioblastomas progress from lower-grade gliomas in patients with a mean age of 45 years. Secondary glioblastomas has better prognosis than primary glioblastomas. The World Health Organization (WHO) classifies glioblastoma multiforme as a grade 4 cancer. Glioblastoma multiforme is characterized as malignant, mitotically active and predisposed to necrosis by WHO. This cancer type has a very poor prognosis [**3**]. The most common treatment of glioblastoma multiforme is surgery followed by radiotherapy and chemotherapy [**4**].

1.1.2 MRI imaging of glioblastoma multiforme

Magnetic resonance imaging (MRI) is widely applied for diagnosis of brain tumors. MRI is now replacing computed tomography (CT), mostly because of the advantage of influence from multiple tissue and machine parameters of the signal intensities in MRI [**5**]. In addition, MRI has better soft tissue contrast than CT and imaging can be done in various planes and multi-slices. One disadvantage of MRI compared to CT imaging is poor delineation of calcification and hemorrhage [**5**].

MRI is the standard for radiographic characterization of glioblastomas. Basic MRI sequences like T1 weighted (T1w), contrast enhanced (T1ce), T2-weighted (T2w), T2-fluid-attenuated inversion recovery (T2-FLAIR) and Gadolinium-enhanced T1 weighted imaging (T1wGd) provide critical clinical information about the tumor [**6**]. These basic sequences are shown in figure 1. More advanced multi-parametric MRI sequences can characterize glioblastomas more comprehensively. These include dynamic susceptibility contrast (DSC), dynamic contrast enhanced (DCE), higher order diffusion techniques and MR spectroscopy (MRS) [**6**]. Early mapping of tumor characteristics using imaging modalities like MRI is extremely important for diagnosis, treatment planning and treatment response. We will use MRI images to help decide which patients diagnosed with glioblastoma that will benefit the most from protontherapy instead of conventional radiotherapy with photons after surgery.

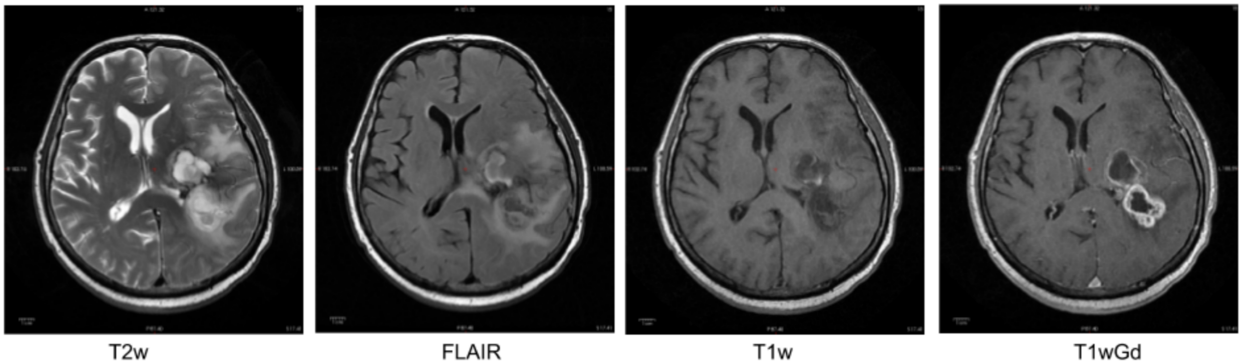

Figure 1: This figure shows some of the basic MRI modalities used for extracting important clinical inforamtion about brain tumors like glioblastomas.

1.1.3 Radiotherapy

Radiotherapy is a central modality in treatment of glioblastomas, and is typically given after surgery. The goal of this treatment is to damage the DNA in tumor cells, while protecting nearby healthy tissue [**7**].

The most common form of radiation treatment is conventional photon-based radiotherapy, where you deliver photons (x-rays) with a goal to reduce or stop the growth of the tumor. However, with the use of this treatment, some of the x-rays will pass through the rest of the body, thereby putting the patient in risk of damage to healthy tissue [**7-8**]. Reducing this risk is especially important in children and other young patients with glioblastomas, since many of those who are cured end up with long-term adverse effects, such as learning and memory problems, hearing loss or secondary cancers later in life [**7**][**9**].

In recent years, proton therapy has emerged as an alternative to this treatment. The protons are accelerated to therapeutic energies with a cyclotron or synchrotron. Afterwards, they are extracted and transmitted to a treatment room [**10**]. While travelling through the brain, the high-energy protons will deposit most of their energy within the tumor, therefore reducing the ”exit-dose” to healthy tissue. As a result of this, it is possible to achieve significant reductions in radiation doses to normal tissue around the tumor, compared to conventional photon-based radiotherapy. The risk of long-term effects and development of secondary cancers will also be decreased, which can be of great value to many patients [**7**][**8**][**10**].

As of today, proton therapy is not a standard treatment for most cancer patients. There are few proton centers around the world, and there are high costs associated with developing and operating these [**7-8**]. The evidence so far indicates that proton therapy can have many clinical benefits, especially in pediatric brain tumors and some head-and-neck cancers [**7**]. However, much of the evidence is based on small studies, which means that there is a demand for more high-quality research [**8**]. In the future, it is expected that proton therapy will gain more awareness, and be available as a treatment for a larger number of cancer patients [**7**].

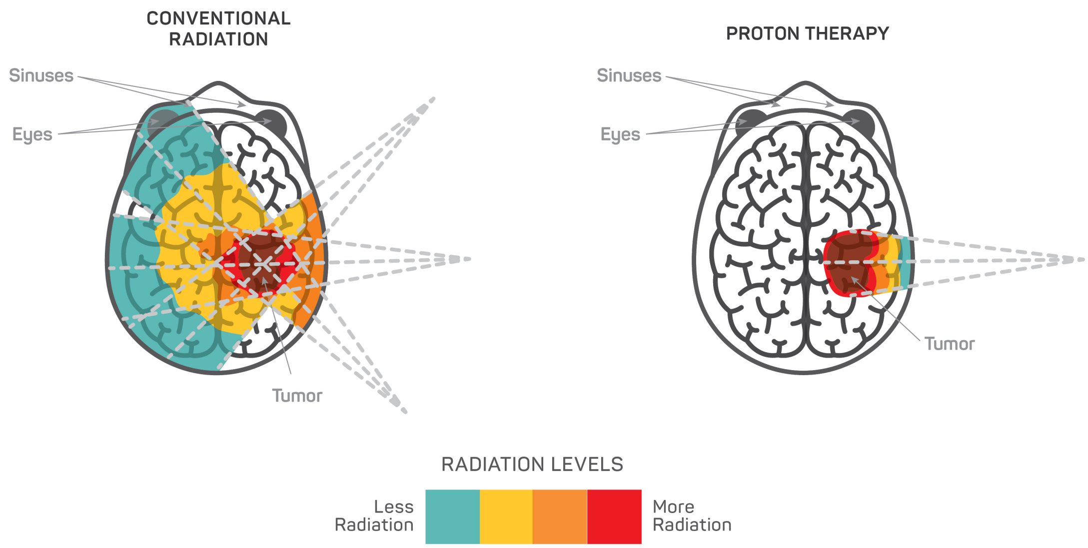

Figure 2: This figure shows how proton therapy can more precisely target the tumor than conventional photon therapy [**11**].

1.2 Objectives and expected impact

Our goal is to aid in the process of determining if a patient with glioblastoma is a good candidate for proton therapy, instead of conventional photon therapy. We wish to do this by using machine learning on both relevant clinical data and information from MRI scans.

Proton therapy in use for treatment of cancer is relatively new, but there has been an increase of interest and research in this field [**7-8**]. The costs associated with this treatment has been a drawback for many, which means there is a demand for easier and more available methods to identify the patients who are likely to benefit from proton therapy compared to other forms of radiotherapy. This will increase the cost effectiveness, reduce the risk of toxicity and treatment-related secondary cancer and potentially improve the life quality of many cancer patients [**7**][**8**][**10**].

Another way this machine learning approach is highly relevant is because of the two proton treatment centers that are being built in Norway. Workers in the field also say that not everyone will be able to get proton therapy and that they will have to prioritise [**12**]. In the beginning the model should be used as an asset by the doctors to help them prioritise which patients should get proton therapy treatment, something that will help to reduce the capacity problem as well.

Similar studies have been conducted showing the need, motivation and interest for it in the medical field. For example has machine learning and deep learning been used to try to help doctors choose better lung cancer treatments [**13**] [**14**]. Very few studies has yet to be done with respect to better treatment for glioblastoma patients, something that indicates what potential this project has.

1.3 Material and methods

This study uses classification models and supervised learning, which are subcategories of machine learning, on a dataset containing information from MRI images and clinical information about the patient.

Machine learning is a specialization within artificial intelligence, where statistical methods are used to let computers find patterns in big datasets [**15**]. Supervised learning, which is one of the main categories within machine learning, uses labeled datasets to train algorithms to classify data or predict outcomes accurately [**16**].

In supervised learning, the data is split into training-, validation- and test data [**17**]. The training-, validation- and test-sets include inputs (a matrix X), and the corresponding output (a vector y). The model will be evaluated by comparing the predicted output with the desired output. The output which is included in the dataset is decided by doctors and professionals. The training set is used to teach the model to give the desired output. The validation set is used to choose the best model, do feature engineering and tune the hyperparamaters [**17**]. The test dataset is the sample of data which is used to provide an unbiased evaluation of a final model fit on the training dataset [**17**]. The dataset will be split into 60 percent training data, 20 percent validation and 20 percent test data. The trained model will be able to predict if the patient should be prioritized for proton radiation on datasets that do not contain a known y-vector.

Supervised learning can be separated into two main types of problems; classification and regression [**16**]. While regression is used to understand the relationship between dependent and independent variables and often predicts a number, classification models uses an algorithm to accurately assign test data into specific categories [**16**]. Since the goal of this study is to create a program that will predict which type of radiation therapy that will have the best affect on the specific patient, the problem will be treated as a classification problem.

Classification models recognizes specific entities within the dataset and attempts to draw conclusions on how those entities should be labeled or defined. Some common classification algorithms are random forest, decision trees, k-nearest neighbor and support vector machines (SVM) [**16**].

1.4 Evaluation

When creating a classification model an important aspect of the process is to measure the performance after the model has been trained. Both precision and recall are viable for this. These are metrics that give insight in how well the model is at giving the correct predictions as well as false predictions. For better visualisation of this a confusion matrix should be used. When classifying the possible outcomes the goal is to predict either proton radiation treatment or conventional radiation treatment. The confusion matrix would therefore be a 2x2 matrix consisting of the number of true positives, true negatives, false positives and false negatives. The number of true positives refers to have many of the patients labeled as proton treatment where actually predicted to be proton treatment, while true negatives is the number of patients labeled as radiation treatment that were correctly predicted to be so as well. The true labels of the dataset is the opinions of doctors when looking at the same features that make up the data for the project. Figure 3 shows the layout of the confusion matrix.

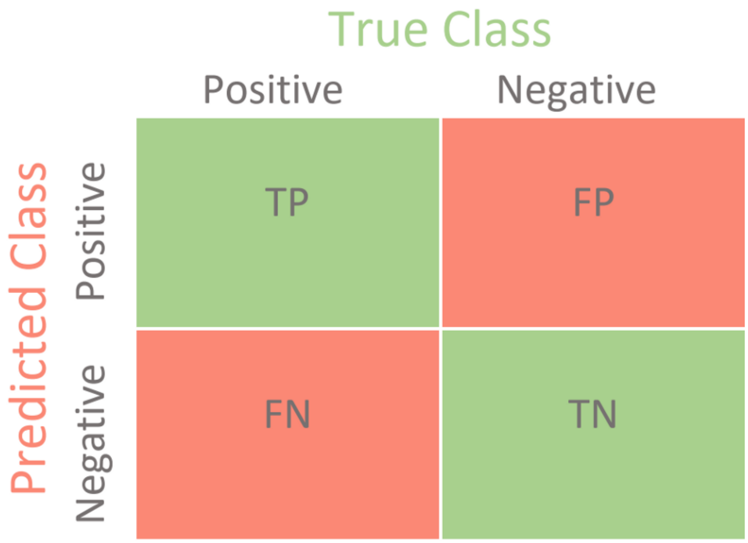

Figure 3: Layout of the confusion matrix.

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2 Data management plan and ethical considerations

2.1 Description of generated data and code

TCGA-GBM is an openly available collection of matched data on the tissue genotypes, radiological phenotypes and patient outcomes of different GBM tumors [**1**]. We will use data from the TCGA-GBM data collection to pre-train our model on recognising tumors that doctors would prioritize for proton therapy. We assume that the patients are already diagnosed with GBM and that the data includes both preoperative and postoperative MRI images.

The dataset that will be used in this study contains information from MRI images including location, the size of the tumor, how aggressive it is etc. It will also consist of clinical information about the patients, such as age, sex, underlying ailments and vital status. The clinical data is retrieved from patient records, blood tests and biopsies. During preprocessing, features with low correlation will be removed. In order to make our model able to generalize and make as precise judgements as possible, it should be trained on a large repository of data. We therefore plan to initiate collaboration with Haukeland university hospital to access more images and clinical data from patients.

The design of the software will relate to training and testing of the model, and to the user interface.

2.2 Sharing of data and code

Code for the machine learning model will be made publicly available on GitHub such that it may be to help for others with similar projects. Additionally, all data retrieved from the collaboration with Haukeland university hospital will be treated according our agreement with them. Patient data will be anonymized and published only if the patient gives their consent. All training data gathered from TCGA is publicly available.

2.3 Ethical considerations

Before conducting the study, it must be approved by the Regional Committees for Medical and Health Research Ethics (REK) [**2**]. This applies for all medical and health research involving humans, human biological material or health data.

There are many ethical considerations to take into consideration when creating a program using machine learning, especially when it is for medical and health purposes. Examples are privacy and avoiding leakage of data [**3**]. Since the amount of ethical considerations regarding AI is huge, only a few essential ones will be covered in this paper. These are the following.

1. The data which the model is trained on contains output given by doctors and other medical professionals. An issue when training models on outputs provided by humans is that humans make mistakes, and it is important not to train the model to make the same mistakes that humans do.
2. Another relevant ethical question to consider is about who will be held responsible for the program's predictions, especially if something wrong happens. Will it be the ones who created the program, the ones who approved it, the owners, or the doctors who created the output which the model was trained on.
3. It is important that the study follows the seven pillars of medical ethics. These are Beneficence, Nonmaleficence, Autonomy, Informed Consent, Truth-Telling, Confidentiality, Justice [**4**]. Beneficence, Nonmaleficence, Autonomy and justice are considered to be the most essential and are often referred to as the four pillars of ethics [**5**].

2.3.1 The four pillars of ethics

Beneficence is the obligation to act for the benefit of the patient and balancing the benefits and risks [**4**][**5**]. Since the data used in this study is preexisting, the patients are not harmed during the gathering of information concerning this specific study. The data which is used in this project is accessible by the public, the patients providing the data have given consent and the data is anonymous. The study is also designed to help doctors suggest which treatment the specific patient will benefit the most from. Supervised learning is used to train the model, with the goal of creating a model with little bias, as well as being able to control the building of the model, to avoid ”black-box” scenarios. Therefore, if the study is successful, it will benefit the patients, and if it is not successful, the participants in this stage of the study have not been caused any harm. These arguments also answer to the next pillar, nonmaleficence, which is the obligation not to harm the patient [**4**].

The term autonomy concerns the patients ability to make his or her own decision. The principle of autonomy says that each person has the right to make their own decision, as long as the person is capable of making his or her own decision. Providers have a moral obligation to respect this right, and in relationships like clinician-patient, the patient autonomy can be vulnerable [**6**].

The principle of justice is the obligation to equitably distribute benefits, risks, costs, and resources [**5**]. Distributive justice, which is the category of justice that is most relevant for clinical ethics, refers to the fair distribution of healthcare resources. The goal of this study is to create a program which will tell us which patients that should be prioritized for proton beam therapy. Since it can seem unethical to let a machine do health prioritization, a field with several guidelines and recommendations from i.e. ”Lønning-II-utvalget”, the program is to be used as an asset to help doctors do the correct prioritizations and not as a solution [**7**].

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