Precision medicine and quantitative imaging in glioblastoma - a multiscale approach

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

Team #4

1 Research plan

1.1 A brief background to the field

There are over one hundred different types of brain tumors, and those who originate from the brain's glial cells are known as gliomas [1]. Gliomas are graded from I to IV after their aggressiveness, microscopic cell picture and malignancy. The most aggressive form is a subtype of diffuse astrocytoma called glioblastoma multiforme (GBM) or just glioblastoma [2, 3]. GBM is a grade IV glioma, and also the most common type of primary malignant brain tumor that occurs among adults [4]. It can be primary or secondary, with the primary being associated with a worse prognosis. The secondary type is arising from a lower grade of glioma [5].

GBM is the type of brain tumor with the worst prognosis. It depends on several factors such as age, degree of malignancy, tumor size, treatment, histological findings, molecular genetic factors, location of tumor etc. [6] Elderly people usually have a worse prognosis since they do not tolerate the tough treatment that younger people are given. 95% of the GBM tumors arise in the supratentorial region located in the cerebral hemispheres. A few percent arise from the spinal cord, cerebellum or brain stem [7]. Despite surgery, chemo- and radiation therapy, recurrence of GBM is often seen due to its infiltrating growth pattern and invasiveness [8]. In Norway, the number of GBM-incidents is around 200 per year, and only around 25% survives the first year. The survival rate is 5% in a 5 year's period [3].

When diagnosing GBM, radiological imaging modalities, such as MRI an PET-CT, are the best methods for examining the tumor. Since GBM rarely metastasize to other parts of the body, CT scans for parts other than the head are usually not performed. Unlike prostate or breast cancer, GBM have no known tumor marker that can detect the presence of a tumor [3].

Treatment of GBM is normally multimodal therapy, including neurosurgery, chemo- and radiation therapy, and medical management e.g., corticosteroids [9]. Other treatments, such as symptom palliation, are also given. Surgery, with the aim of maximum surgical resection, is without a doubt, the most important procedure. The operation itself is very individualized, and treatment depends on the patient's prognosis, and the patient's general condition. During an operation, the neurosurgeon removes as much of the tumor as possible, while also being careful to prevent neurological damage or disabilities for the patient [10]. After surgery most patients receive radiation therapy, often combined with chemotherapy. The patients outcome is closely related to the generic measure for disease burden, called QALY [11].

QALY or Quality-Adjusted Life Years (QALYs) is a score based on the quality of life after a medical or surgical intervention. QALY range from 1 (one year of perfect health) to 0 (death) per year and is influenced by the health-related quality of life of the patient. Mathematically, QALY is based on the amount of years gained, multiplied with the utility value of a given state of health. QALY = A years * B Utility, where Utility is a value associated with a certain degree of disability. Both a lower quality of life and fewer than 12 months lived in a given year will lead to a QALY below 1, while one year of perfect health will equal to 1 QALY [12]. Without treatment the patient will die very rapidly and also experience a lot of devastating symptoms. The treatment on the other hand is also a great risk for the patient, involving brain damage and other major health impacts from additional medication such as radiation and chemo. The balance is therefore to treat with minimal harm and at the same time prolonging the patients life expectancy.

We want to use deep learning to analyze, differentiate and classify the tissue of the tumor in MRI scans. Different types of brain tissue and different types of functional areas in the brain need to be classified so that the computer can predict the risk of a certain outcome of surgery in that area. The machine needs to be fed with input that consists of available knowledge about the anatomy of a normal, healthy brain. In some regions the plasticity of the brain enables it to move certain task to other areas. In others, this is not a possibility. The plasticity of the brain depends on a patients age and personal qualities such as ability and will to do the job that is necessary to rehabilitate. GBM located in the diencephalon or brain stem is associated with poorer outcome as well as crossing of the midsection and multifocal disease [13]. We want to use data that contains both pictures, and information on the patients outcomes. The data will preferably contain both MRI- and Pet-CT- scans from before and after operation. We can only include cases where the diagnosis is verified by sampling the tumor. We want to use data from Biobank Haukeland dating back 25 years who fit the criteria set for this study. Patients with a very high age and/or multiple comorbidity must be excluded. It is also vital that the data set contains multiple follow up pictures (preferably both MRI and pet-CT) from within the first year of surgery. We are hoping this will bring more insight to the study and treatment of GBM.

1.2 Objectives and expected impact of the study

The objective of this study is to create a program able to assist the surgical team in evaluating the level of invasiveness necessary to accomplish an optimal prognosis when treating for GBM. To optimize the treatment, the program needs to take into account the postoperative quality of life of the patient as well as the life-expectancy. The parameter QALY will be used to train the computer model to find the surgical treatment that will both improve the quality of life and increase the patient's life-expectancy.

By creating a program trained through machine learning and based on a vast dataset of pre-operative and post-operative diagnostic imaging scans, this study hopes to construct a tool that can show the optimal resection of neural tissue surrounding the tumor in operative treatment of GBM, i.e. the optimal delineation of the resection volume.

1.3 Material and methods

This study uses supervised Deep Learning (DL) to delineate regions of interest (ROIs) in Magnetic Resonance Imaging (MRI) images, namely GBMs. MRI provides valuable anatomical information because it distinguishes between different types of soft tissues. Owing to this and the fact that MRI scanners are available in most hospitals, MRI is considered to be a standard technique in tumor segmentation [14]. The most common type of deep learning in medical imaging is Convolutional Neural Networks (CNNs) [15]. A possible approach in brain tumor segmentation with DL is therefore a combination of the Stationary Wavelet Transform (SWT) and Growing Convolutional Neural Network (GCNN) [16]. The preoperative and postoperative MRI images (T1, T2, FLAIR and contrast enhanced T1) are preprocessed with normalization and noise removal before they are skull stripped, i.e. skull, fat, skin and the section of brain that are not ROI(i.e. the brain) are separated. SWT is then used to extract features for the purpose of segmentation. That is, the imaging-derived bio markers for GBM. The processed images will then be segmented into risk areas and the tumor using the Random Forrest classifier (RF). The DL algorithm GCNN will now be used to train a model based on our data, and predict the delineation of resection volume that will acquire the highest possible postoperative QALY.

Our input layer to the GCNN will consist of the RF-classified images from before and after surgery, as well as the relevant metadata, described in table **1**. All of these variables will act as our X-data in the dataset. The y-value in this case is the delineation of the resection volume, calculated from the dissimilarities in the preoperative and postoperative MRI-images. Then the model will be trained based on these data. The images will be split into voxels, and the information will be transferred through the layers in the GCNN. Every voxel has a value attached, which makes the weighted channels. This makes the algorithm able to extract significant features from the images and the neural network will be able to find patterns and connections in the data. When applying the model to new patients, the neural network will make predictions based on the input data, and predict which tissue that should be removed surgically in order to obtain the highest possible postoperative QALY. The whole procedure is illustrated in figure **1**.

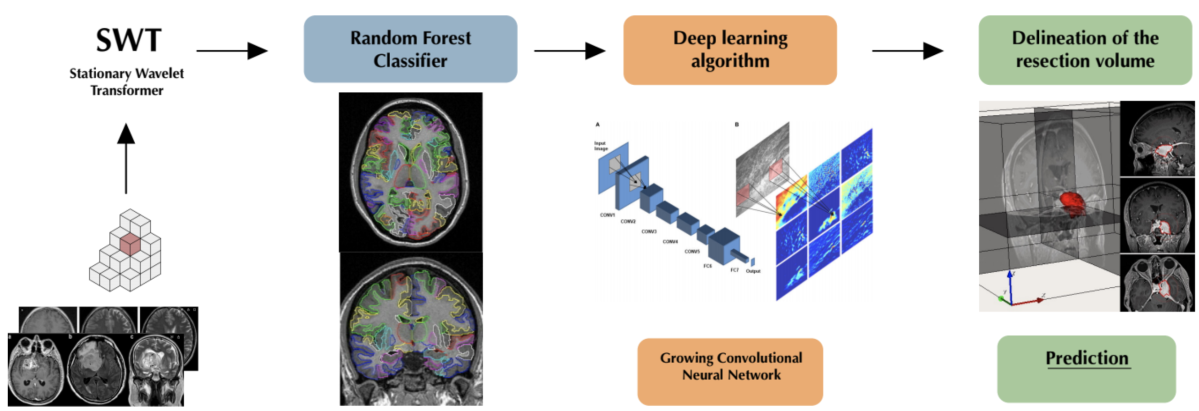

Figure 1: The DL-process. Modified from [17], [18], [19]

1.4 Evaluation

The output from the supervised learning can be evaluated using a score function on the ground truth delineation of the resection volume, y_{test}, and the model prediction, y_{pred}. The dice similarity coefficient (DSC), which is computed as the overlap between y_{test} and y_{pred}, will be used as a measure of accuracy [20]. Additionally, the positive predictive value (PPV) and sensitivity (true-positive rate) will be assessed.

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2 Data management plan and ethical considerations

2.1 Description of generated data and code

This study is a cohort study, where a group of patients will be observed over time. In this case, the relevant data will be MRI-images as well as the relevant parameters, described in table **1**, for patients with GBM before and after surgery. This is convenient because MRI is part of the standard clinical procedure for GBM management for planning and evaluation of treatment, i.e. a large amount of MRI-images are available [1].

It is crucial that the data is balanced regarding gender and age. Patients whose brain is not fully developed will not be included in this study, as well as elderly patients who are likely to die of other causes within a short time frame. Therefore, patients younger than 25 or older than 85 will be excluded to minimize the noise in the algorithm. The data is also limited to only include MRI-images taken with a 3 Tesla magnet field in the past 20 years, to maintain a sufficient quality. Patients with a lot of comorbide factors will also be excluded.

The data will be split into 80% training and 20% test data before applying the models described in section 1.3.

Table 1: Variables contained in X-data in addition to preoperative and postoperative MRI-images.

Variables	**Levels**
Gender	0 (male), 1 (female)
Age	25-40, 41-50, 51-60, 61-70, 71-75, 76-80, 81-85
Preoperative and postoperative QALY	
Preoperative and postoperative PET-images	
Months of survival	
Radiotherapy	0 (none), 1 (TMZ), 2 (other)
Chemotherapy	0 (none), 1 (WBRT), 2 (IFRT), 3 (other)
Corticosteroids	0 (no), 1 (yes)

2.2 Sharing of data and code

The project code will be made open access by publishing it on Github. The data used in the study will be available through an IEEE dataport, while other relevant data will be returned to Biobank Haukeland as per our agreement. Contact information to Haukeland Biobank is shared, so that future studies may receive such data in the future [2].

2.3 Ethical considerations

In order to make better AI-systems, both medical experts and patients must be taken into consideration. It must also include the broader context around them. There is no doubt that AI will have the potential to improve many facets of neurosurgery and radiology in an incredibly way. The fact that AI is a rapidly growing, prominent technology, raises several ethical questions related to security, autonomy, economy, responsibility, justice and the environment to name a few. Based on this, we have decided on the following plan.

The study is to be sent to “Regionale komiteer for medisinsk og helsefaglig forskningsetikk” (REK) at Haukeland Universitetssykehus (HUS) for ethical consideration before any data gathering is started. The study will follow the four principles of ethics which include beneficence, non-maleficence, justice and autonomy [3].

First and foremost, the study should do good, by developing a useful tool to assist neurosurgical teams in deciding the optimal resection-volume of GBM. Secondly, the study will ensure that no participant is harmed during the data collection or training of the model by only using previously retrieved data. Thirdly, participants are to be treated fairly. The study will guarantee that data used, is in agreement with contracts signed by participants when data is stored from Haukeland Biobank. All participants will be anonymized. Lastly, the autonomy of the participants is to be respected by only using data from patients who autonomously agreed to the sharing of their data from Haukeland Biobank.

In addition to this the AI model must continuously be trained on new datasets, to ensure that the model is giving results which are up to date technologically, medically and ethically. In the nearest future it is likely that we will be more and more assisted by or that we delegate decisions to AI systems. As a result, we must take responsibility for ensuring that these systems are fair in their impact on human life. The AI model must be made in accordance with fundamental ethical values, and the project must seek to achieve this. In this project there are no simple solutions, and it is highly desirable that a framework about liability should be created. This should also include the responsibility that neurosurgeons, radiologists, engineers and other experts have over patients using AI in Precision Medicine and quantitative imaging in GBM.

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