Precision medicine and quantitative imaging in glioblastoma

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

Team #2

1 Research plan

1.1 A brief background to the field

On gliablastoma:

Glioblastoma is a grade IV diffuse astrocytoma, the grading and description of which clearly illustrates the nature of this tumor: it is a highly infiltrative brain tumor, hence diffuse, with a high resistance towards treatment given, leaving the patient affected faced with a poor prognosis. Approximately 90% of cases are primary de novo glioblastomas, with a median overall survival of 9.9 and 15 months, depending on whether treatment includes surgery and radiotherapy or surgery, radiotherapy and chemotherapy, respectively [1, 2]. Of these, radiotherapy has proven to be the most effective [3].

On imaging:

MRI (Magnetic Resonance Imaging) is an imaging technique used to form images of a body using radio frequency, magnetic fields and a set of magnetic gradient coils. The magnetic field together with the radio frequency will make protons precess and release energy as a resonance frequency. This resonance frequency is proportional to the strength of the magnetic field. The magnetic field gradients created by the coils makes it possible to sort the frequencies of the protons dependent on their spatial location, then using the signal intensity to create an image [4].

MRI is advantageous when scanning the brain because it does not ionize, it can create images in every spatial plane and MRI can depict soft tissue in great detail, which the brain is made of. Some of the disadvantages are exclusion of patients with metal components in their body, the cost of the system compared to other image modalities and the time it takes to scan each patient (typically around 30-40 min)[4].

Mp-MRI (Multiparameter MRI) uses multiple parameters to scan the body. In this project, the parameters used is FLAIR, T2-weighted and T1-weighted MRI, with and without gadolinium contrast. T1- and T-2 weighted MRI shows relaxation times of the proton precess, where T1 shows the z-component and T2 the x- and y-components

[4]. FLAIR (Fluid-Attenuated Inversion Recovery) is a technique which makes it possible to see brain lesions in the MRI image [5].

Positron emission tomography, or PET, is a nuclear imaging modality which is used to exhibit activity in cells and tissue [6]. PET uses radioactive isotopes that emit radiation of positrons. Radioactive isotopes are defined as any nuclei that can change its quantum mechanical properties. Radiotracers are molecules that are labeled with radioactive isotopes, i.e. one of the atoms in the molecule is replaced with a radioactive isotope. Radiotracers are used to reveal and measure changes in metabolic and physiological processes. The radiotracer is introduced into the patient's body through injection or inhalation and transported within the body with its regular biochemical processes [7]. There are several different types of radiotracers that can be exploited, depending on the activity one wants to disclose.

The isotopes will be concentrated within areas where the rate of cell division is the highest, typically in tumors [6]. The emitted positron will interact with tissue and lose its energy. Afterwards the positron will annihilate with an electron and generate two photons in opposite directions [7]. The emitted gamma radiation will be picked up by a rotating set of gamma cameras that detect the gamma rays and provide projection data, from which tomographic images are reconstructed [6]. PET acquires data from all angles continuously and acquires therefore true 3D data [7]. The significance and relevance of positron emission tomography is increasing for the diagnosis, prognosis and monitoring of glioblastomas and offers further comprehension beyond MRI into the biology of gliomas. This is due to the extended availability of radioactively labeled amino acids allowing extensive applications in diagnosis and therapy [8].

On radiation therapy and hypoxia:

Treatment of newly diagnosed glioblastoma requires a multidisciplinary approach [9]. The current standard treatment for glioblastomas was developed in 2005 and is called the "Stupp protocol" [3]. This protocol includes resection surgery of the glioblastoma to remove cancerous tissue, followed by concurrent radiotherapy and chemotherapy. The radiotherapy alone considerably increases patient survival [3].

Radiotherapy relies on ionizing radiation to kill cancer cells by breaking strands in the DNA and thus preventing the cell from performing life sustaining processes and preventing cell division.The ionizing radiation can interact with the cells in different ways. Direct action of the radiation is interaction directly with the critical target in the cell, e.g. the atoms of the DNA double helix. Indirect action happens when free radicals produced by the ionizing radiation interact with the DNA molecules [3]. The majority of the radiation damage to DNA comes from this indirect action of the radiation. The radiation interactions can produce both single strand and double strand breaks in the DNA molecule. In a double strand break, both strands of the DNA molecule are broken in the same place, resulting in extensive damage that is difficult to repair and ultimately, cell death. Single strand breaks on the other hand trigger DNA-damage responses such as base excision repair in the cell that repair the damage, diminishing the effect of the single strand breaks [3].

Hypoxia in tumors plays a fundamental role in determining the radiotherapy outcome for several cancer types [10]. Hypoxia is a condition where the cells are deprived of oxygen, and the demand for oxygen exceeds the supply (O_2 partial pressure (pO_2) less than 10mmHg) [11]. Under hypoxic conditions, there is diminished production of free radicals due to the low levels of oxygen, and thus the cells become more radioresistant [3]. Cells that are hypoxic during irradiation are about three times more resistant to radiation than cells that are well oxygenated [12]. Tumor hypoxia has been looked at as one of the leading causes of failure in tumor response to radiotherapy in several cancer types [10].

Hypoxia in tumors occurs when the tumor loses blood supply, either by outgrowing the blood supply or having fragile blood vessels. This may result in significant oxygen diffusion restriction [11]. Tumor hypoxia is frequent in glioblastomas and occurs because the vessels that feed the tumor are highly permeable and easily collapse due to excessive proliferation of endothelial cells, which is caused by secretion from the tumor. The blood vessels that feed the tumor are also fragile as they lack structure support [3].

The current practice in radiotherapy is to irradiate the tumor volume with a homogenous dose of about 60 Gy over a number of fractions with 2 Gy per fraction [3]. This practice does not take the difference in radiosensitivity of tissue into account during a treatment fraction, which may result in poor tumor control. Being able to account for tumor hypoxia when deciding on radiation dose to the tumor would increase the tumor control and make radiotherapy an even better treatment option. To do this it is necessary to be able to quantify the hypoxia in the tumor.

On 18-FMISO usage in hypoxia:

One possible way of quantifying hypoxia is to use PET-imaging with radiotracers that detect hypoxic tissue. One such radiotracer is 18F-FMISO ([18F]-fluoromisonidazole). Unlike 18F-FDG, FMISO does not accumulate in normal brain tissue, making it possible to provide images of hypoxic brain tumors with high contrast [13]. In non-hypoxic cells, the FMISO molecule will be oxidized, and can diffuse out of the cell. In hypoxic cells this oxidation is absent and the molecule is accumulated. It has been shown that glioblastoma patients imaged with FMISO show high uptake of the radiotracer in the tumor [13], making FMISO imaging a tool for finding the hypoxic regions in the tumor. This then offers a way to visualize and quantify regions of increased radioresistance, which may benefit from dose escalation strategies [10].

1.2 Objectives and expected impact

The aim of this study is to make a tool that can aid physicians and physicists in making more effective and targeted radiation dose plans in radiotherapy as a treatment of glioblastomas. We want to achieve this by using deep learning on multimodal MRI and 18F-FMISO PET data as a segmentation tool. Using a nnU-NET architecture, inspired by Fabian Isensee et al [14], the winners of the 2020 BraTS challenge, we want to be able to create a model that effectively segment the tumor into regions that are the target for radiotherapy as well as regions of increased radioresistance due to hypoxia.

A tool that delineates the radioresistant areas opens up the possibility for physicists whose job it is to calculate tumor dose to use dose escalation strategies [10] where the hypoxic regions receive a larger dose than non-hypoxic tumor. Dose escalation strategies have the potential to increase the tumor control as more radiation can be given to the radioresistant regions to make up for the decreased effectiveness of the radiation.

1.3 Material and methods

Our aim is to train a nnU-Net model that can segment a tumor into different tumor regions. To do this, multiparametric MRI images, as well as 18F-FMISO PET images will be used to segment the tumor. With these different modalities, the tumor can be segmented into different tumor regions: whole tumor, enhancing tumor, tumor core and hypoxic tissue. These are regions that will be relevant for physicians and physicists when a radiation dose plan for radiotherapy will be drawn. Figure 1 shows an example of the different image modalities the model will be trained on. These are images from a study by Hirata et al. [13].

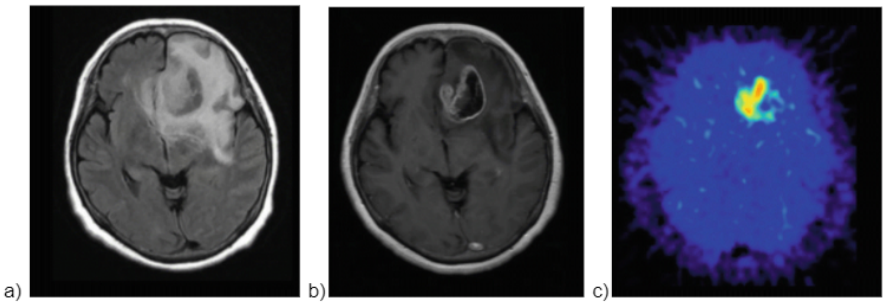

Figure 1: Glioblastoma imaged with different modalities. a) FLAIR MRI sequence. b) T1 weighted with gadolinium contrast. c) FMISO PET uptake in tumor.

nnU-Net is a deep learning-based segmentation method that configures itself automatically, including preprocessing, network architecture, training, and post-processing for any new task [14]. One of several advantages of nnU-Net is that it does not require manual intervention nor expert knowledge nor computing resources beyond standard network training. Another benefit of nnU-Net is that it handles a broad variety of datasets and target images properties and the results of the segmentations are state of the art quality [14]. We therefore consider nnU-Net to be the most prefarable method for our project compared to other supervised-based learning methods that we have considered.

Quantification of tumor oxygenation based on 18FMISO has been done by another study [10]. However, this study did not use deep learning-based segmentation to quantify tumor oxygenation based on 18FMISO. Thus, we thought it would be interesting to apply the same method as this study to quantify tumor oxygenation levels and further apply deep learning-based segmentation by using nnU-Net. The aim here is to train nnU-Net to predict unseen images by segmenting the tumor and tumor oxygenation levels. Thus, radiation therapy can be administered to patients based on the hypoxic levels in the tumor cells.

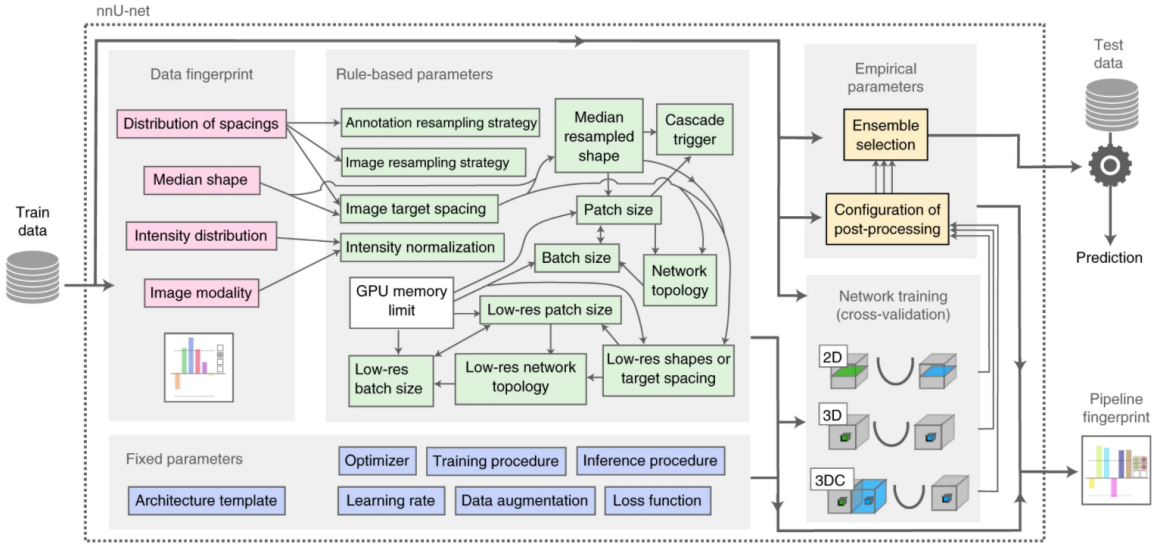

Figure 2: This figure is taken from the study by Fabian Isensee et al. [14]. The figure shows a proposed automated configuration for deep learning-based biomedical image segmentation.

The automated method configuration of nnU-Net is divided into three parameters: 1) fixed parameters, 2) rule -based parameters and 3) empirical parameters. First, the fixed parameters collect design decisions that do not require adaptation between datasets and identify a robust configuration [14]. Second, the rule-based parameters distill knowledge about segmentation method design into heuristic rules that connect dataset properties ("data fingerprint") and segmentation pipeline design choices [14]. Lastly, the empirical parameters learn only the remaining decisions empirically from the data. nnU-Net extracts dataset properties ("data fingerprint") from PET images. This information is then used to create three nnU-Net configurations: a 2D U-Net, a 3D U-Net that operates on full resolution as well as a 3D U-Net cascade.

In this study, we utilize a conversion function to determine hypoxic target volume (HTV) in tumor cells as applied in the study of Lazzeroni M. et al. [10]. Equation 1 describes the sigmoid function applied at voxel level to the FMISO PET image to derive oxygen partial pressure, pO_2 distributions:

$$pO_2(r) = \frac{c(a - Uptake(r))}{b + Uptake(r) - a} \tag{1}$$

With parameters a, b, and c equal to 10.9, 10.7, and 2.5 [10]. The parameter 'Uptake' in Eq.1 is calculated by dividing the voxel values in the FMISO PET images to the average value in the well-oxygenated reference volume (WOV) and the results were multiplied by the tracer uptake predicted by the conversion function (Eq. 1) for the assigned pO_2 in the WOV [10]. In other words, we can determine the hypoxic target volume (HVT) from the distributions of FMISO uptake with the help of the conversion function (Eq. 1). Figure 2 shows hypoxic target volume (HTV). The PET images of hypoxic target volume using conversion function can be used to train nnU-Net such that it can predict unseen images. Thus, when new PET images acquired from patients with 18F-FMISO are transferred into nnU-Net, hypoxia regions in the tumor can be segmented and these patients can be treated with a higher dose to regions of hypoxia.

1.4 Evaluation

As difference in injected activity will influence the strength of the signal from the PET-scanner, it is necessary to use a well oxygenated region to use for reference to be able to compare FMISO-images. A reference sphere in the shoulder with an assigned oxygen level of 60 mmHg will be used, which is one of the methods Lazzeroni et al suggest [10]. This allows us to give a defined hypoxia region using formula 1. For the MRI images, a manual segmentation of the tumor is necessary before training the model.

For evaluation of the performance we will use the Intersection-over-union metric. This is the metric most commonly used in semantic segmentation and is very effective. The IoU is calculated as the area of overlap between predicted segmentation and actual segmentation divided by the area of union between predicted and actual. Testing the model on unseen test data after training is important, as it shows if the trained model is able to generalize and predict new data. This is an indicator of how well it could work in the clinic [15].

2 Data management plan and ethical considerations

2.1 Description of generated data and code

For this project various imaging data of glioblastoma patients will be used. The collected data will therefore consist of MRI images and PET scans from patients that have been injected with the 18F-FMISO radiotracer. In addition to the imaging information, some biomedical facts about the patients would be necessary. Age, gender and treatment details are important features that will be taken into consideration.
To train the machine learning model, huge amounts of data is necessary in the training dataset. Since the information gathered from patient records may not be able to exceed the needed amount, Generative Adversarial Networks, or GANs, could be used to generate more data. GANs are an approach to generative modeling using deep learning in order to automatically discover and learn patterns in the training dataset [16]. The model can thereafter be used to generate new examples that the nnU-NET model needs for further training [16].

2.2 Sharing of data and code

In the course of this project, we aim to ensure a *Gold class reproducibility standard*, according to criteria proposed by Heilman et al. [17]:

1. Data published and downloadable
2. Models published and downloadable
3. Source code published and downloadable
4. Dependencies set up in a single command
5. Key analysis details recorded
6. Analysis components set to deterministic
7. Entire analysis reproducible with a single command

The largest obstacle we expect to be the data availability for external researchers. The data will, as when analysed within our own group, be anonymised when provided to external researchers. Without having a clear overview of the bureaucracy behind data management and security within the Helse Vest, we intend to establish an early contact to discuss the infrastructure as of today, and how we can help each other in contributing to the emerging effort for reproducibility within this domain of research.

2.3 Ethical considerations

As a first step, the study will apply for permission to be conducted from the Regional Ethical Committee. In developing the model according to the project aims we will ensure informed consent from participants of the study, as well as anonymisation and security of sensitive data. The following discussion explores the ethics related to the potential implementation of this model in effective treatment of patients.
The ethics regarding use of Deep Learning (DL) models in real clinical settings is as of today a hot topic under rapid discussion and transformation. That makes it impossible to point out every relevant aspect in this project description. Therefore, in execution of the study, the team will adhere to the *proposed four ethical principles in the context of AI systems* by the EU [18]. We will use this framework to limit our discussion, in which we will try our best to point to relevant literature.

Respect for human autonomy:

The study will ensure informed consent and data anonymity. The patients will know what they sign up for, including the potential risks inherent to this project. In obtaining this mutual understanding, the team will heavily rely on methods described within the domain of shared decision-making [19]. If implemented correctly, this way both the physician offering and patient undergoing the treatment will best be on the same page.

Prevention of harm:

Altering the radiation dosage, based on the hypoxia maps provided by the PET-MR, may have effects both for the better or worse. As mentioned, the patient will be informed about the potential risks of both over- and undertreatment, inherent to the trial of a new treatment pipeline. The team does acknowledge this unavoidable risk of effectively harming the patient and will from this concern consult the Norwegian Cancer Association (Kreftforeningen) for assistance in how best to develop a program as safe as possible for the patients, and their closest relatives, included in the study.

Fairness:

Another inherent risk of using learning models in real life clinic is the implementation of bias. The model of this project will, however, only assess medical brain images and nothing else. The MRI-images used will be defaced, using algorithms such as afni_refacer or pydeface, to avoid gender-biases or other noise not relevant for our evaluation of the brain [20]. Hence, we deem it appropriate to offer an inclusion in the study to all glioblastoma patients accessible.

Explicability:

As of now, AI models, such as DL, exhibit a low level of transparency, leading to the today "black-box" view of how these operate. One may wish to know exactly how the model delivered its results, i.e. to be explainable. These insights can indeed help identifying potential errors, biases and causes of assumed suboptimal performance. Performance measures are, however, calculated based on groups of objects, in this case voxels and radiation dosage, and can thereby not display ant true accuracy for the individual patient [21]. This is part of the risk described above, inherent in this kind of research. Of course, the team will do the utmost to communicate the project pipeline and progress to both patient and close relatives, a level of transparency we indeed can guarantee.

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