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Glioblastoma recurrence patterns

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Glioblastoma (GBM) is a very aggressive and fatal form of brain tumor with an extremely high recurrence rate. GBM is usually treated with surgery to remove the parts of the tumor that can be removed without damaging the healthy brain tissue. The surgery is followed by radiation therapy, and both surgery and radiation therapy is planned based on radiology scans. In most cases, the tumor will recur. This is often an effect of microscopic extensions, which are invisible in the scans. Currently, it is not possible to predict the location of the recurrence. This is accounted for in therapy planning by treating an area larger than the actual tumor, and as a result, a substantial amount of healthy brain tissue is treated, while the future area of recurrence may go untreated.

At the moment, medical personnel segment the gross tumor volumes (GTVs), i.e. the extent and location of the tumor is marked. This segmentation, as well as the type of recurrence (the location of the new, recurring tumor in relation to the original tumor), is manually determined from the scans, which is a time-demanding process.

The objective of this project is to construct a pipeline that can automatically segment the GTVs across the different scans and calculate relevant metrics about the tumors, including the above-mentioned type of recurrence. Hopefully, this can assist in analyzing the recurrence patterns of GBM.

At the moment, radiation therapy planning is done by finding the clinical target volume, which is determined by expanding the GTV by a standard margin in all directions. This is done in order to account for the microscopic extensions of the tumor that are not detected in the planning of treatment. By using the data generated by the pipeline to analyze the recurrence patterns, it will potentially be possible in the future to improve the clinical target volume to include as much of the potential recurrence as possible, while minimizing the amount of healthy tissue that receives radiation.

The data in the project consists of 3D images from MR and CT scans of 175 patients suffering from GBM and their journal information. The data includes a single CT scan and multiple MR scans for each patient. The scans include:

Diagnosis MR: MR scan used to diagnose the patient with GBM.
Post surgery MR: MR scan done right after surgery to check the result.
Planning MR and CT: MR and CT scan used to plan the radiation therapy area.
Recurrence MR: MR scan where the tumor has recurred.

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Description of pipeline

The overall structure of the pipeline is described in the figure 1 below. Each step of the process is described in further detail in this section.
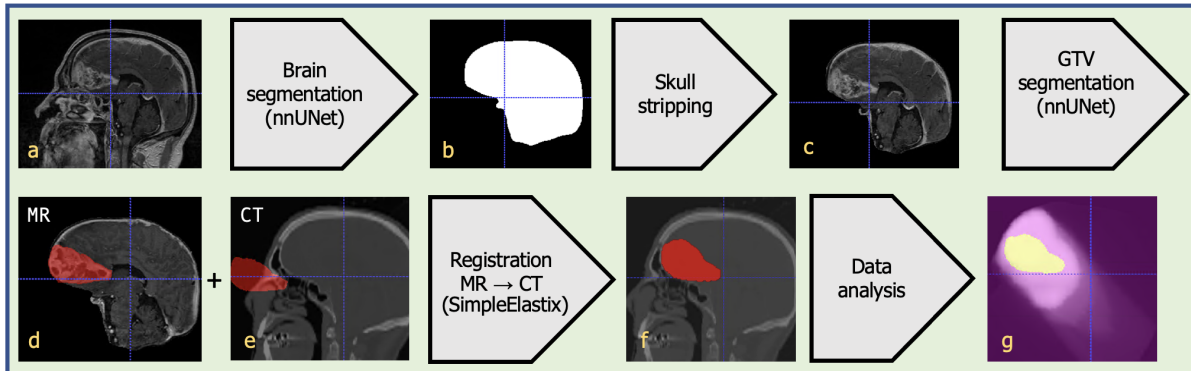

Figure 1: Overview of the steps in the pipeline.

Brain segmentation

Brain segmentation is the process of creating a mask of the location and extent of the brain in a scan. A mask is a binary 3D image with the same dimensions as the scan where 0 indicates background and 1 indicates brain (as an example see figure 1.b). This is done by using predictions from the deep-learning based software *nnUNet*: A model has been trained on scans with corresponding brain masks. When given a scan as seen in figure 1.a, the model can predict a brain mask (as seen in figure 1.b) that locates the brain in the given scan.

Skull-stripping

Skull-stripping consists of removing any parts of the scans which are not part of the brain. Both MR and CT scans are done on the entire head and part of the neck of the patient. Because other facial features and not just the brain is included, it becomes harder to segment the GTVs from the scans, since parts of the face (e.g. the eyes) and a tumor might be mistaken for each other in the segmentation process. In order to avoid such mistakes, we wish to remove everything from the scans that is not part of the actual brain. To do this, the brain masks generated in the previous step are used. For each scan, the parts of the scan which do not overlap with the corresponding mask are removed. A skull-stripped scan is seen in figure 1.c. As mentioned, skull-stripping is done to improve the quality of the GTV segmentations.

Gross tumor volume (GTV) segmentation

Another *nnUNet*-model has been trained to segment GTVs on skull-stripped brains. In this step, the network model is used to predict the GTVs, i.e. the location and extent of the tumors, in the now skull-stripped scans. An example of a GTV is marked as the red area in figure 1.d.

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Registration

The purpose of registration is to bring the different MR and CT scans onto the same 3-dimensional grid. The patient's brain in different MR scans may not always be lined up because the setup of the scanner and the positioning of the patient can vary across different time points. Furthermore, MR and CT scans are in different resolutions and spacings. This is illustrated in figure 1.d and 1.e. Here we also see that the GTV which has been segmented on an MR scan does not line up with the correct position in the CT scan. The aim of registration is to move the scans to a common coordinate space by lining up similar features in both scans. We use the software *SimpleElastix* to perform the registration.

In this step, all the available MR scans for a patient are moved to the coordinate space of the patient's CT scan. This allows us to compare the GTVs, which are visible on the MR scans, to the planned radiation therapy area, which is in the coordinate space of the CT. By moving all the MR scans to a common grid, we can also compare them across different time points to e.g. calculate the growth rate of the tumors.

Data analysis

To make it possible to analyze recurrence patterns different metrics are calculated:

- The 95% isodose area is calculated. This is the area of the brain that is treated with 95% or more of the target radiation dose and is generally considered the treatment area. This area is used in defining the type of recurrence and other metrics.
- The overlap between the 95% isodose area and the GTV at the recurrence time point is calculated. This is illustrated in figure 1.g, where it can be seen as the overlap between the yellow GTV and the brightly purple 95% isodose area. This is done to determine how successful the radiation therapy was in including the microscopic extent of the tumor.
- The type (location) of recurrence is classified using two different classification systems. One comparing the recurrence GTV to the baseline GTV and the other comparing the recurrence GTV to the 95% isodose area.
- The distance between the original tumor and the recurrence tumor is calculated.
- For all scans, the number of lesions, the volume of each lesion and the total volume of the tumor is determined. The growth rate of the tumor is calculated.

Results and product

The final product of the project is a GitLab repository with Python code handling each of the steps in the pipeline as explained above. Furthermore, a detailed description of the pipeline, explaining each individual step and how they are interconnected, is accessible in the README.md file in the repository, where the performance of the pipeline is also discussed. In the description, an example is included, which shows how the scans of a single patient are processed through the pipeline, that is, what do the scans look like before and after each step.