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Project description

Academic title and name: Kim Hochreuter, MSc

Project title: Combined Deep learning and Advanced Imaging for Improved Individualized Radiotherapy Target Definition in Glioblastoma Patients. A National DNOG study.

Background

Global problem

Glioblastoma patients (GBM) have a dismal prognosis due to its aggressive and infiltrative nature. The standard treatment of GBMs is maximal safe surgery and followed by chemo-radiation and adjuvant chemotherapy leading to a median survival of only 14 months(1). A potential for improvement in the outcome of this patient group lies in simultaneously handling two key radiation treatment challenges 1) More personalized irradiation of the entire tumor and 2) more accurate inclusion of microscopic spread into the treatment area. In this project we aim to focus on the latter problem. Currently, the radiation target is not precise enough, we are including a lot of healthy brain to account for any invisible microscopic tumor cells that might be there. Having a more precise target, will open up opportunities to further improve the outcome of patients after radiotherapy(RT).

Specific problem

Radiotherapy has been employed to treat GBM for a long time, but defining the exact target for irradiation remains challenging as the infiltrative part of the tumor cannot be visualized by current medical imaging(2,3). Addressing this problem with surgery is limited by functional deficits. Thus we need to use imaging along with all relevant clinical factor and knowledge of tumor migration patterns as surrogates for the microscopic spread. We know that GBM predominantly spread along white matter (WM) fibers with only marginal invasion into grey matter (GM) while respecting anatomical boundaries within the brain (e.g. bone, falx cerebri, tentorium cerebelli, ventricles) (4–6). However, current guidelines define the radiotherapy target as the surgical cavity including any visible tumor on standard MRI (7). To account for any potential invisible microscopic tumor cells, a 2 cm safety margin is added. The rationale behind the current strategies has largely been defined by postmortem histological findings and tumor recurrence analyses in a trade-off with neurotoxicity. For instance, most tumor recurrences are located around the surgical resection cavity (8,9), and within a distance of 2 cm or 3 cm from the cavity approximately, 80% or 95% of recurrences are located, respectively (10–12). However, the preferred directional migration pattern of glioblastomas is incompatible with an isotropic margin expansion. It leads to unnecessary irradiation of healthy brain tissue with negative radiation side effects. The volume used to irradiate unnecessary healthy brain tissue could be relocated to areas with higher risk of microscopic tumor spread and thereby cover a greater percentage of the recurrences into this new target concept. To further complicate the issue, there is a fair degree of heterogeneity of migrational patterns

within GBM patients. For example, central recurrence rates (i.e. in the high dose region) of only 60% are reported in patients with an MGMT- methylated tumor, while this is 90% for unmethylated tumors (13,14). In patients with an MGMT-methylated tumor, gross total surgical resection, and age <60 years, the central recurrence rate was only 40% (15). By combining knowledge of clinical parameters (MGMT, resection grade) and imaging we can help tailor the proposed target concept to the patient even further.

Hypothesis

A target volume concept that includes the migrational properties of GBM, MGMT status and resection grade is superior for recurrence coverage and sparing of healthy brain compared to a standard target volume.

Materials and methods

In order to test the hypothesis a number of steps are needed to be completed. The steps are divided into the following three work packages:

WP1: Deep Learning for segmentation of boundaries and recurrences
Deep Learning is a subdomain of Artificial Intelligence, i.e. self-learning computers, that uses an intricate constellation of computational nodes, much like our own brains, to solve relatively complex tasks such as segmentation of brain structures. The field has matured and seen a surge in use over the last decade with improved algorithms and computational processing power. Deep Learning has been applied widely to the field of medical imaging and one of its advantages is the versatility in problems which may be solved. In WP1 the applicant will employ Deep Learning as an integral part of setting up the boundary conditions for the tumor migration estimation. Setting up boundary conditions for the tumor migration calculation requires knowledge of the initial distribution of tumor cells (GTV) and where tumor cells tend to migrate fast (White Matter (WM)), slow (Grey Matter (GM)) and not at all (bone, ventricles, falx cerebri and tentorium cerebelli). Finally, Deep Learning will also be used to segment recurrences to evaluate the performance of the tumor migration model. Brain MRIs (T1w + contrast, T2FLAIR) and planning CT with associated delineations of recurrences and all necessary boundary condition structures are available for 50 patients. A Convolutional Neural Network (CNN) of a 3D U-net structure (19,20) will be trained on these patients. We will perform a 6-fold cross-validation where we for each fold will train on 42 patients out of 50, leaving eight patients for validation. The six folds will be non-overlapping and selected at random. When subsequently using this network on the different datasets already available in

WP2 and the one that will be available in WP3, there will likely be a need for retraining or fine-tuning.

WP2: Fine-tuning the migrational parameters
The proposed target concept is based on mathematical modelling of tumor growth (21–23). For GBM the following three aspects are unique: 1) Tumor cells do not migrate across anatomical barriers 2) tumor cells have increased migration in WM and along WM tracts 3) tumor cells have reduced migration in GM. By combining the segmentation of these different tissue types inside the brain with diffusion tensor imaging(DTI) an improved target definition will be derived. The above traits can be combined into a Reaction-Diffusion equation known as the Fisher-Kolmogorov growth model where a number of parameters needs to be predefined. Among these are the initial normalized distribution of tumors cells (U(x,t)), the proliferation constant (*rho*), the migration (or diffusion) coefficient in white (Dw) and gray matter (Dg) and the diffusion anisotropy weighting factor(*lambda*)(22,23). Of initial interest is the migration coefficients in white and grey matter where the literature consistently suggests that tumor cells infiltrate gray matter much less than white matter (24). This suggests a large value for Dw/Dg>>1, however whether the ratio is 10, 100 or much larger is not known. Moreover, there may be a dependence on clinical parameters, such as MGMT gene promotor methylation status. Within the WP2 we aim to investigate the ratio Dw/Dg) through the longitudinal analysis of the 810 patients received from the EORTC. The unique dataset includes MRI scans and clinical data from participants of two phase 2 and 3 trials CENTRIC (17) and CORE (18). We will employ the CNN from WP1 to estimate the boundary conditions and tumor extent at all available timepoints. We will vary the Dw/Dg ratio within the tumor growth model to minimize the difference between the spatial tumor extent in the model and the data at all subsequent timepoints. We will optimize the tumor growth model for patient groups with different prognostic factors (MGMT status, resection grade etc.). The data will be divided into a training, validation and test set to ensure that the extracted parameter values are robust. Tumor cells within the WM are known to migrate along the compact fibers. Through DTI it is possible to estimate the dominant fiber directions throughout the brain and via the diffusion anisotropy weighting factor *lambda* this can be integrated into the tumor growth model. Again little is known about *lambda* and its clinical dependencies. The estimation of migration coefficients Dw and Dg from the EORTC data will be used in the tumor growth modelling of the retrospective study from Aarhus University hospital. The retrospective Aarhus data has additional DTI imaging compared to the EORTC data and allows for further fine-tuning of *lambda*.

WP3: Prospective trial
This will be a national non-interventional study including 300 patients with newly diagnosed GBM referred to long course RT. Inclusion period of 3 years is estimated. Planning RT MRI will be prolonged by 15 minutes to allow DTI acquisition. The standard target volume (GTV) will be defined using T1 weighted MRI with contrast and expanded by 2 cm and adjusted for anatomical barriers according to national guidelines (dnog.dk). Imaging (planning MRI with

DTI sequence, recurrence MRI) and RT treatment plans will be collected in DcmCollab. An automated pipeline to facilitate data handling and pre-processing will be set up. All patients will be followed for progression using RANO criteria and for overall survival. Clinical data, radiation treatment plans and first progression MRIs will be collected. Based on the results and methods developed in WP1 and WP2 the tumor growth modelling will be performed. There will likely be a need for further fine-tuning of the model parameters for this data set and. Volumetric comparisons between standard, mathematical model derived targets and recurrence volumes will be performed using Hausdorff distance, surface Dice and Dice similarity coefficient. Wilcoxon signed rank test will be used to compare standard and DTI derived targets for recurrence volume coverage. Multivariate analysis will be used to assess the effect of clinical parameters (tumor location, MGMT status, resection) on DTI derived target.

Personnel

The applicant will carry out the tasks described in the three work packages with the contribution from local experienced researchers to ensure that the level of quality is high enough for clinical use, together with overall supervision by Associate Professor of Medical Physics at Aarhus University Jesper Folsted Kallehauge.

Research plan

Data is currently available for both WP1 and WP2 and the applicant should be able to start to focus on this right away while the data from WP3 matures. According to the Danish Neuro Oncology Registry (DNOR) the total number of treated patients from 2011 until 2018 (8 years) with Primary diagnosis within this time period was n=2444 (305/year). Of these n=2043 (255/year) underwent postoperative RT. Of this radiation population a total n=1574 (196/year) was planned to 60 Gy. Based on a pilot study within the group, we included 40 GBM patient in roughly 70 eligible patients over little less that a two-year period, thus we expect a participation rate of roughly 50 %. This means that we will have included all 300 patients within the 3 years. Median time to recurrence is 6.9 months (29) for GBMs and thus most of the recurrences locations will be available after 3.5 years. The applicant will, based on these considerations, not be able to see the prospective protocol to a finish. We will perform an interim analysis half way through of which the student will be lead on. The final analysis will be performed by the collaboration consortium and will lead into prospective interventional study. A timeline for the work packages can be seen in the following figure.

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Timeline

Patient impact & Clinical perspectives

The direct impact for the patients will be to treat them with a more accurate treatment margin. This will lead to an improved balance between tumor control and treatment toxicity. Our studied population concerns actual clinical patients and with the current national support this makes the method more easily available to all patients in Denmark in the future. The successful validation of the new CTV definition will result in a landslide improvement in GBM radiotherapy for the first time in decades. This will be the first step to move GBM radiotherapy into the era of individualized medicine.

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