Monitoring of anatomical changes during adaptive brain radiotherapy in glioma patients

Ph.D. Thesis

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1. Introduction

Primary diffuse brain tumors contribute greatly to cancer mortality despite the introduction of novel systemic treatment approaches (i.e., molecular targeted therapies and immunotherapies) into the management of malignant tumors.

Modern radiotherapy techniques, including intensity-modulated radiotherapy (IMRT), stereotactic radiotherpy (SRT), and radiosurgery (SRS), provide better dose coverage to the target volumes decreasing the treatment-related complications. Recently, the radiation oncology is changing following towards the ‘‘precision oncology” era.

Adaptive radiotherapy (ART) could be used to reduce dose to organs at risk (OARs) and ultimately to improve quality of life. In this regard, an accurate delineation of tumor volumes and organs at risk is critical to ensure maximum target dose and protect of the surrounding normal brain structures to maintain high tumor control, while minimizing treatment-related toxicity.

Glioblastoma multiforme (GBM) is one of the tumors most aggressively invading the surrounding tissues, growing infiltrative and spreading in different brain tissues. Therefore, the definition of the clinical target volume on the postoperative images is highly challenging task.

Recently, there has been an increased focus on dose to the subventricular zone (SVZ), the region around the lateral ventricles (LVs), postulated as a main niche of pluripotent neural stem cells in the brain. Recent studies support the hypothesis that in a subgroup of glioblastoma (the SVZ-associated GBM), the neural stem cells in the SVZ could transform into cancer stem cells and play an important role in both the origin and recurrence of glioblastoma.

Anatomical deformations may occur during radiation delivery due to tumor shrinkage or growth, changes of the resection cavity, and an increase or decrease in perifocal and brain edema. These changes in the target and organs at risk can significantly influence the dose distribution defined on the planning CT. This may be highly relevant with regard to the lateral ventricle and subventricular zone in patients with brain cancer, where these structures lie in close proximity to the target volume.

2. Aims

We investigated the extent of changes in the anatomical position, shape and volume of LVs and SVZs. We included other critical OARs to examine their contribution to the dose delivered to these regions. Additionally, the correlation between the SVZ radiation dose and clinical outcome was analyzed using the median SVZ dose as a cut-off value for both of the structures defined on the first planning CT and the data on the changed ipsi- and contralateral SVZs on the repeated CT during the course of irradiation.

3. Patients and methods

3.1.Study population

Group 1: 41 patients treated between 1/2013 and 11/2015 with GBM tumor were enrolled in the study. The average age of the patients was 57 years. All the patients underwent surgical management, and the tumor type was confirmed with histology. The average time to planning CT after surgery was 2.8 weeks (0.7–5.1 weeks). Patient data, including demographics, imaging data, treatment and clinical outcomes were retrospectively collected.

Group 2: Between 1/2013 and 11/2021, 53 patients with GBM tumor were administered and included to the retrospective study. Patients belonged to the elderly age group with an average age of 63 years. All the patients underwent surgical management, and the tumor type was confirmed with histology. Most of the patients started the radiotherapy 4.3 weeks after surgery.

3.2 Imaging

Patient positioning and fixation were performed using a 3-point individual thermoplastic mask followed by a topometric CT scan in the supine position with 5 mm slice thickness. Pre-operative imaging data (T1-weighted MRI pre- and post-contrast and FLAIR sequence) were assessed to define the tumor volume and the tumor localization with regard to the SVZ. The preoperative and postoperative (i.e., within 48 h) MR images were coregistered to the planning CT for more accurate GTV/CTV delineation. Each patient underwent adaptive replanning for boost definition on an additional (secondary) CT/MRI scan (3.9 (3.7–4.0) weeks after start of radiotherapy, 7.7 (5.3–14.3) weeks after surgery) in accordance with the institutional protocol.

3.3 Target and OARs delineation

3.3.1 Target volume delineation

The gross tumor volume (GTV) was the contrast enhancing lesion on T1-weighted MRI or the surgical cavity with residual contrast-enhancement. The clinical target volume (CTV) was built with a 15-25 mm margin around the GTV, and then was edited to include the FLAIR signal abnormality and adjust it to anatomic barriers. The planning target volume (PTV) was finally built with a 3-mm isotropic margin expansion, adjusted to the anatomical structures.

Gross tumor volume (GTV1), clinical target volume (CTV1) and planning target volume (PTV1) were defined on primary CT (CT1). After the first period of treatment, a second CT (CT2) was performed using the same technical parameters and patient positioning. This was registered to the initial planning CT (CT1). Gross tumor volume 2 (GTV2), clinical target volume 2 (CTV2) and planning target volume 2 (PTV2) were also defined on the secondary CT (CT2).

3.3.2 Organs at risk delineation

OAR segmentation was performed in axial reconstructions of the CT/MRI coregistred data set. Ipsilateral LV (iLV), contralateral LV (cLV), ipsilateral SVZ (iSVZ) and contralateral SVZ (cSVZ) contouring were retrospectively segmented by a radiologist.

Relevant OARs such as brain, brainstem, chiasm, ipsilateral and contralateral eye, ipsilateral and contralateral lens, ipsilateral and contralateral optic nerve were delineated by atlas-based and manual segmentation.

3.4 Treatment planning

Glioblastoma multiforme (GBM) was treated with a total dose of 60 Gy at a 2 Gy dose per fraction with concomitant temozolomid (75 mg/m2 daily) followed by temozolomid monotherapy. PTV1 was treated with 3-dimensional conformal radiotherapy (3D-CRT) or IMRT to 40 Gy in 20 fractions for GBM patients. PTV2 was treated with 3D-CRT or IMRT delivering an additional 20 Gy in 10 fractions for GBM. Both LVs and SVZs were also

contoured retrospectively on the planning and replanning images, along with the other OARs, which did not exhibit relevant changes on secondary CT. Registration and contouring were performed with Advantage SIM software (version 4.7, General Electric Healthcare, Chicago, Ill., USA). All plans were created and optimized in the Xio Planning System (version 4.7, Electa, Stockholm, Sweden). Radiotherapy (RT) plan optimization to the adapted target volume (GTV2 – CTV2 – PTV2) was performed in all cases and the homogeneity criteria was specified by the ICRU 83 ($D_{98\%} > 95\%$ and $D_{2\%} < 107\%$).

Volumetric data for the LVs and SVZs on the primary and secondary CT were collected. For the dosimetric study, dose-volume histograms of glioblastoma cases were calculated and the following doses were extracted for ipsilateral and contralateral LVs and SVZs for the complete course of radiotherapy with and without replanning: $D_{2\%}$, $D_{10\%}$, $D_{25\%}$, $D_{50\%}$, $D_{75\%}$, $D_{98\%}$, D_{mean} and D_{max}. Furthermore, the dose differences to these structures and the impact of the mean doses of SVZs on overall survival were analyzed.

For other OARs dosimetric evaluation $D_{50\%}$, $D_{90\%}$ and D_{mean} were extracted from dose-volume histogram (DVH) and performed a comparison between treatment plans with and without replanning.

3.5 Statistical analysis

Statistical analysis was performed using the SPSS statistical analysis software package (version 20; SPSS, Chicago, Ill., USA), and patientand tumor-related factors (age, performance state, type of surgery, time interval between surgery and start of radiotherapy, midline shift and tumor size) and any parameter that showed measurable anatomical changes during the volumetric and geometric analysis were included in the study. A value of $p < 0.05$ was considered statistically significant. All p-values are two-sided.

A paired samples t-test was carried out to examine anatomical changes on the re-scanned CT as compared to the first time point of the treatment course. Parametric data were expressed as mean ± standard deviation (SD). In addition, an independent samples t-test was administered to investigate the relationship between midline deformation and LV and SVZ volume changes, respectively. Subsequently, a paired samples t-test was used to compare dosimetric data summing up the dose from the initial and the adaptive dose distribution for structures defined for primary and complementary (boost) irradiation. Potential factors to impact overall survival

(OS), such as age, performance status, tumor location, tumor size and extent of surgical resection, were tested as covariates.

In addition, the dose received by ipsilateral and contralateral SVZs defined retrospectively on both planning CTs was assessed for prognostic significance. The survival probability was estimated using the Kaplan–Meier method. OS was calculated from the date of surgery to the date of death. The log-rank test was used to test the significance between different groups in the prognostic factors. Survival distributions were compared based on the log-rank test at the 58 Gy cut-off point and the contralateral SVZ dose at the 27 Gy cut-off point. The factors exhibiting a correlation to the survival in a univariate test, such as the midline shift, RT start date from surgery (Opus RT date), performance status (PS) and dose to the iSVZ, were further analyzed with the multivariate Cox regression.

4. Results

4.1. Dosimetric comparison of LVs and SVZs during adaptive brain radiotherapy

Radiotherapy planning took place 2.8 (0.7–5.1) weeks on average post-surgery. The extent of the tumor removal of the study group was biopsy (N = 7), partial resection (N = 29) and gross tumor resection (N = 5). RT generally started 1 week after the planning CT, and thus the interval between surgery and RT was 26.6 (12–42) days.

The largest average diameter of the tumor on the preoperative MRI was 51 mm (range 24–80 mm). We sorted the patients according to the presence or absence of midline deformation. This defect is related to the size of the edema and could influence the volume change of LV and SVZ. A significant correlation between the midline shift and the volume difference of the ipsilateral structures was detected in all cases when a primary midline deformation was present.

However in our GBM patient group, no significant correlation was detected between the presence of the midline shift and OS ($p = 0.830$). Significant differences were observed within each volumetric parameter, and a major discrepancy was revealed by analyzing ipsilateral LVs and SVZs in individual patients. Volumetric changes were above 2–3 cm^3, which resulted in a higher than 17% volumetric change of ipsilateral SVZ.

The change in volume is accompanied by significant alterations in the location of these structures. Location shift was observed in mm range on both sides (within 3 mm in the case of ipsilateral structures).

As a result, the first plan would have led to an incorrect dose distribution for the iSVZ and cSVZ. Dose distribution analysis on the SVZ structures contoured at the 4-week interval showed significant differences between the two time points on the dose volume histograms, with higher difference and higher standard deviation at higher-volume doses. The mean dose difference to the SVZ on CT1 and CT2 was significant for the iSVZ. Following the replanning, the total dose to these structures was higher at each volume dose level than on CT1. The dose difference was on average around 1 Gy on the ipsilateral side and about 0.5 Gy on the contralateral side, but this difference even reached a 5–10 Gy dose in some individual patients. Moreover, most of these dosimetric changes resulted in statistically significant differences in this study. The large PTV1 encompassing the primary tumor volume, the peritumoral edema and 2 cm margin due to potential microscopic tumor spread resulted in the incorporation of a high portion of the iSVZ, while the involvement of the iSVZ was reduced in the shrunken PTV2 defined for replanning. Consequently, the dose to the structures con cerned showed greater differences due to the anatomical changes re vealed on the repeated CT2 for the 20 Gy boost treatment. The dosimetric impact of these topometric and volumetric changes of LV and SVZ was calculated by taking into account the dose distribution for PTV1 up to 40 Gy and the dose distribution after replanning with the dose prescription of 20 Gy to PTV2, which add up representative re levant dose differences during the delivery of a 60 Gy total dose. A significant difference ($p = 0.048$) was proven between mean OS at 15.6 months versus 27.8 months and mean dose to the ipsilateral SVZ2 delineated on CT2 with a 58 Gy cut-off point. If the ipsilateral mean SVZ1 dose based on the CT1 contour was analyzed with the same cut-off value, there was no statistical difference ($p = 0.153$) between 17.6 and 26.6 months in this patient population.

This analysis revealed no statistically significant correlations between the contralateral SVZ dose and OS, assessed at the two time points ($p = 0.477$ and $p = 0.283$, respectively). A Kaplan–Meier analysis of the Opus RT date and OS showed that RT started within 26.6 days results in a higher mean OS with a significant p-value (27.9 vs. 15.8 months, $p = 0.036$). Furthermore, PS had a relevant effect on OS, and a Karnofsky performance status with a higher value (≥70%) resulted in better OS ($p = 0.007$). In a multivariate Cox regression analysis with an iSVZ2 mean dose, of the Opus RT date and PS, only PS was significant with regard to OS.

4.2. Dosimetric comparison of organs at risk during adaptive brain radiotherapy

The largest average diameter of the tumor on the preoperative MRI was 47 mm (range 26 - 60 mm). RT generally started 1 week after the planning CT, and thus the interval between surgery and RT was 30 days. The average volume difference of the GTV and PTV ($V_{PTV1} - V_{PTV2}$ (cc) and $V_{GTV1} - V_{GTV2}$ (cc)) during replanning was 151.81 ± 143.00 and 13.49 ± 32.78.
We observed that the average of all investigated dose parameters to these structures was lower at each volume dose level than on CT1 and replanning caused significant differences on most of them. The dose difference was on average around 0.5-1 Gy on every structures, but this difference even reached a 2-5 Gy dose in some individual patients. Repeated imaging and adaptive planning leads to improved follow of the anatomical changes and tumor response, resulting more accurate residual GTV definition and consequent healthy brain tissue sparing in the case of tumor schrinkage achieved.

5. Discussion

We have investigated the role of SVZ involvement into the high dose region of GBM postoperative irradiation to the outcome of the disease and the impact of the anatomical changes to the dose distribution during the course of radiation delivery.

Recently, a number of analyses of tumor recurrence patterns and dosimetry data related to patient survival have revealed the importance of elimination of brain cancer stem cells, which may play a key role in tumor relapse. The majority of the pluripotent neural stem cells reside in the SVZ; therefore, it represents the structure, which could be included in the clinical target volume for glial tumors located in close proximity to it. All of these studies examined survival by dividing the patients into groups based on certain cut-off values of the bilateral, ipsilateral and contralateral SVZ mean dose.

Our results highlight the importance of the anatomy deformation shortly after surgery and the relevant changes, which may occur during the course of radiotherapy, influencing the volume and location of such small volume structures as the cancer stem cell niches. The structural changes during radiation delivery could be caused by tumor shrinkage or growth, deformation of the resection cavity, and increase or decrease in perifocal and brain edema. The postoperative change decreases by the time, but in the case of GBM it would pose a high risk for relevant

residual tumor growth in the case of delayed chemoradiotherapy (CRT). Meanwhile, the optimal interval between surgery and start of CRT is a matter of debate in the literature, and a clear conclusion cannot be drawn. In our patient group, the shorter time to CRT proved to be a significant factor for longer OS. The start of CRT within 3 weeks after surgery may result in relevant changes of the target and organs at risk, which can significantly influence the dose distribution calculated on the planning CT. A significant correlation between OS and the high ipsilateral SVZ2 dose (above 58 Gy) was found in our patient population; meanwhile, no statistical difference was detected ($p = 0.153$) in OS if the SVZ1s were used, which were contoured on the CT1 acquired five weeks earlier, 2–3 weeks after surgery. We have to notice that the difference between the survival curves regarding the initial iSVZ mean dose (< 58 Gy versus ≥ 58 Gy) thought has not reached the significance level, the same tendency could be observed, and an analysis including larger number of patients may resulted in significant relationship. In any case, after surgery with primary brain tumor, patients may show significant anatomical changes throughout the entire treatment course. As a consequence of volume alteration and displacement of the SVZ, a significant difference between the actual delivered dose and the initial planned dose is anticipated, which may ultimately result in underdosage of this region if defined as part of the target. Previously, adaptive radiotherapy (ART) was mainly proposed for extracranial regions, where the daily variation of the location of the target and surrounding organs is thought to be high. However, no previous research has examined repeated CT images to determine patient-specific anatomical variations of LV and SVZ during the course of RT delivery, for which the treatment plan could be modified. This investigation aims to fill this gap in the research on anatomical variations of LV and SVZ taking place during irradiation.

This study however has some limitations. The analysis of tumor related factors was outside of the scope of this study, but several factors are known to influence the survival. Furthermore, its retrospective nature, and relatively small patient number may have biased some of the results. However, this study also has several strengths. Our results underline the importance of including iSVZ in the target volume for GBM, but it is equally important that the volume and localization of brain substructures may vary widely by time and individual. An additional margin of 3 mm to the iSVZ would encompass the potential morphologic changes, which occurs during the adjuvant chemo-irradiation. Furthermore, significant longer survival for patients with good performance status (Karnofsky > 70%) and shorter time interval between the surgery and start of the CRT was proven. Prospective clinical studies should be designed to draw a valid conclusion on a target definition for high-grade brain tumors as regards the inclusion of the

SVZ and other structures. Moreover, in addition to involvement in stratification, known and recently emerged molecular prognostic factors (MGMT metilation status, IDH1 and ATRX) and time- and treatment-dependent morphological changes should also be taken into account. However, considering all the limitations, our analysis documents survival advantage from full target dose to the iSVZ and could suggest including this brain region in the clinical target volume. The other finding of this study is the need for high-accuracy delineation of iSVZ with careful follow-up of changes.

6. Summary, conclusions

Following our retrospective evaluation of the postsurgical anatomy of the relevant brain structures and irradiation plans at two time points, clinically relevant changes in LV and SVZ volumes and location were revealed, resulting in significant dose alterations to these structures. This should be taken into consideration when cancer stem cell radiation is planned and a defined dose is prescribed to the SVZ. In addition dosimetric changes were found during the statistical analysis of other brain structures and confirm the necessity of replanning.

Stemming from the clinical relevance of the anatomical changes in the brain during radiation delivery, revision and replanning are recommended to facilitate adaptation to these changes. Future prospective studies are necessary to determine the optimal time point for repeating CT/MR imaging and replanning for brain tumor patients undergoing radiotherapy/radiochemotherapy.

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List of full papers that served as the basis of the Ph.D. thesis

I. **Darázs B.**; Ruskó L.; Végváry Z.; Ferenczi L.; Dobi Á.; Paczona V.; Varga Z.; Fodor E.; Hideghéty K.
Subventricular Zone Volumetric and Dosimetric Changes during Postoperative Brain Tumor Irradiation and its Impact on Overall Survival.
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II. Végváry Z.; **Darázs B**.; Paczona V.; Dobi Á.; Reisz Z.; Varga Z.; Fodor E.; Cserháti A.; Oláh J.; Kis D.; Barzó P.; Hideghéty K.
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