Monitoring of anatomical changes during adaptive brain radiotherapy in glioma patients

Ph.D. Thesis

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

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Adaptive Radiotherapy for Glioblastoma Multiforme – The Impact on Disease Outcome.
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Related articles

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Deep-Learning-based Segmentation of Organs-at-Risk in the Head for MR-assisted Radiation Therapy Planning.
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List of abbreviations

3D-CRT	3-dimensional conformal radiotherapy
ART	adaptive radiotherapy
ATRX	alpha-thalassemia/mental retardation, X-linked
C	contralateral
CNS	central nervous system
CRT	chemoradiotherapy
CT	computer tomography
CTV	clinical target volume
D	dose
ESTRO	European Society Radiation Oncology
GBM	glioblastoma multiforme
GTR	gross total resection
GTV	gross tumor volume
I	ipsilateral
IDH1	isocitrate dehydrogenase 1
IGRT	image guided radiation therapy
IMRT	intensity modulated radiation therpy
LV	lateral ventricle
MGMT	O6-methylguanine methyltransferase
MRI	magnetic resonance imaging
OAR	organ at risk
OS	overall survival
PFS	progression-free survival
PS	performance status
PTV	planning target volume
RT	radiotherapy
SD	standard deviation
STR	subtotal resection
SVZ	subventricular zone
V	volume

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. A considerable amount of effort has been devoted to improving the outcome of local tumor treatment modalities, with the introduction of innovative techniques, such as navigation-based neurosurgery and highly selective radiation dose delivery methods: stereotactic intensity-modulated radiotherapy and proton and ion therapy [1,2]. Greater structural differentiation of the target has become available both for dose painting and to define intracerebral organs at risk (OARs) on the basis of the differing radiation susceptibility of the various regions and with advanced imaging [3,4,5].

Modern RT techniques, including intensity-modulated radiotherapy (IMRT), stereotactic RT (SRT), and radiosurgery (SRS), provide better dose coverage to the target volumes decreasing the treatment-related complications [6]. Recently, the radiation oncology is changing following towards the ‘‘precision oncology” era. Magnetic resonance imaging (MRI) is becoming increasingly important in precision radiotherapy due to its excellent soft-tissue contrast and versatile scan capabilities. Several recent advances in MRI have shown to be promising for improving MRI-guided radiotherapy and treatment outcomes (including clinical implementation of deep learning-based automatic OARs delineation on MRI) [7].

Adaptive radiotherapy (ART) could be used to reduce dose to OARs and ultimately to improve quality of life [8]. 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. Most radiation treatment centers are equipped with dedicated computed tomography (CT) scanners that provide accurate anatomic and geometric information of structures, as well as electron density information for precise dose calculation in treatment planning systems. Magnetic Resonance Imaging has gradually replaced CT imaging due to its excellent soft-tissue contrast, high spatial resolution, and widespread availability [9]. The direct, only MRI based planning is yet not mature, but the different MRI sequences are widely applied using image co-registration and fusion. Repeated imaging during the course of fractionated radiotherapy enable more accurate target definition, adaptation to the anatomic changes both due to normal tissue reaction (edema, resorption of postoperative bleeding, formation of surgical cavity) and to tumor response to the chemoradiotherapy.

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. The recommendations for contouring in the US and in Europe are differing substantially without final consensus [10].

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. These could differentiate into neurons or glial cells and migrate to places where regeneration is necessary in the central nervous system (CNS) [11,12]. 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 [13,14,15,16,17]. Thus, the concept of incorporating SVZ into the high-dose region to eliminate the population of cancer stem cells with irradiation emerged. However, the entire SVZ represents a huge volume addition to the 2–3 cm margin around the primary tumor bed in which the potential tumor spread may originate in the CNS. As a result, the potential consequences of brain irradiation must be carefully estimated, in particular when neural stem cell niche irradiation is considered. Numerous preclinical and clinical studies have demonstrated that radiation to the hippocampus may be associated with neurocognitive deficits [18,19,20]. The clinical evidence for SVZ irradiation resulting in cognitive deterioration is not as robust as in the case of hippocampus irradiation [21].

It has been demonstrated in several studies with retrospective dose distribution analysis that a high dose to the ipsilateral SVZ results in significant improvement of progression-free survival (PFS) and overall survival (OS) for glioblastoma patients [22–32]. A further prospective trial confirmed the correlation of SVZ dose to the outcome for highgrade brain tumors [33]. These results emphasize the importance of an accurate definition of the ipsi- and contralateral SVZ for treatment planning and follow-up during the course of radiotherapy (RT). Image guided radiation therapy (IGRT) and adaptive RT were introduced to many tumor sites to manage the daily and long term, i.e., a few weeks of structural uncertainties. However, there is insufficient data available on intracranial changes, and this is mainly limited to the volume dynamics of tumor bed alteration after surgical removal [36,37,38].

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 [37]. 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 glioblastoma multiforme 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 glioblastoma multiforme 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. The SVZ contour was

defined in accordance with protocols developed by Gupta et al. [24],whereby SVZ was defined as a 5mm margin along the wall of the LV on CT1 (Fig. 1(a)) and on CT2 (Fig. 1(b)).

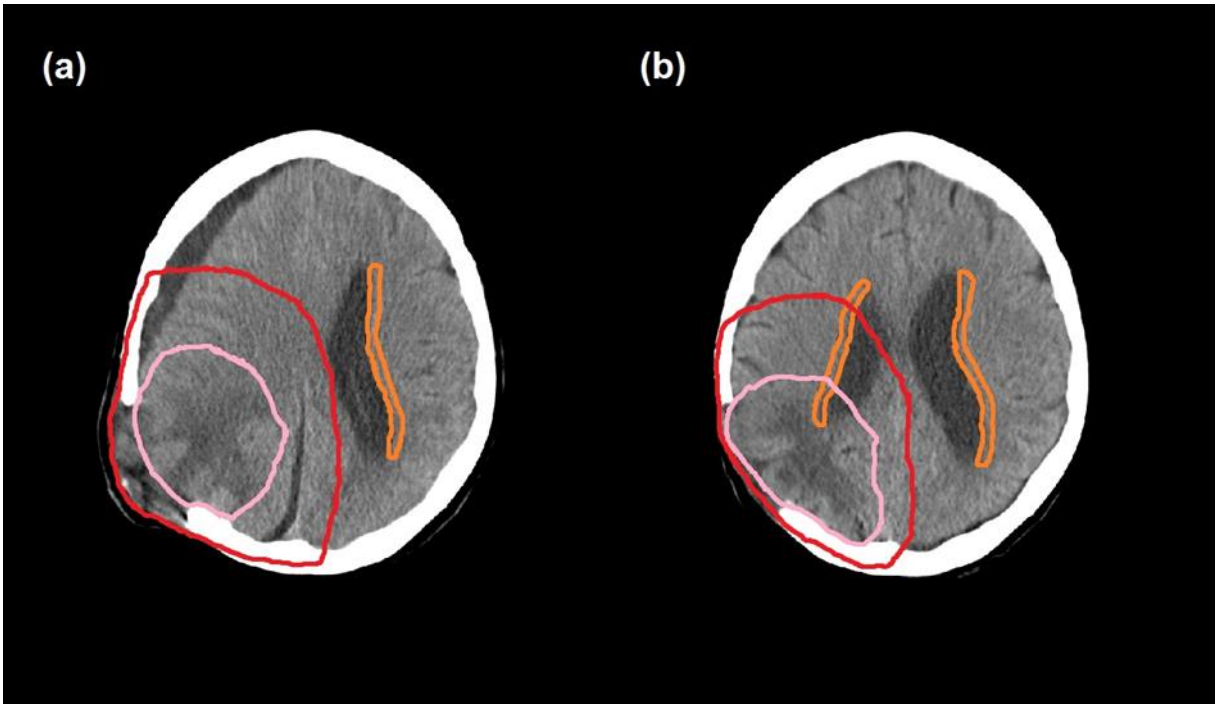

Fig 1. *Initial (primary) CT (CT1) (a) and follow-up (secondary) CT (CT2) (b) with the contours for planning target volume (PTV) in red, gross tumor volume (GTV) in pink and subventricular zone (SVZ) in orange. Although the two images were captured on the same plane, initially the ipsilateral structures are extremely deformed and thus undetectable. After 40 Gy irradiation, the ipsilateral lateral ventricle and SVZ appeared on CT2.*

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. All contours were reviewed and corrected by radiologist/physician according to online atlas published by Eekers et al. [39] for OAR delineation in neurooncology on behalf of the task group ‘‘European Particle Therapy Network” (EPTN) of ESTRO.

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

Intensity Modulated RT (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). 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 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 patient and tumor characteristics as well as the volumetric data for the defined targets are provided in Table 1.

Parameters		**Glioblastoma** Grade IV
N (male/female)		41 (20/21)
Age (years)	< 60	12
	≥ 60	29
Karnofsky performance status	<70%	16
	≥70%	25
Type of surgery		
Biopsy		7
STR (subtotal resection)		29
GTR (gross total resection)		5

Tumor size (Mean) (max. diameter in mm)	51.12
Tumor location	
Parietal	9
Frontal	10
Occipital	2
Temporal	16
Cerebellum	4
GTV1 (Mean ± SD) (cc)	111.49 ± 70.53
GTV2 (Mean ± SD) (cc)	103.91 ± 74.08
PTV1 (Mean ± SD) (cc)	540.58 ± 147.72
PTV2 (Mean ± SD) (cc)	356.25 ± 133.92
Midline deformation on CT1	
Yes	23
No	18
Relation of iSVZ1 to PTV1 on CT1	
Included completely	15
Included partly	25
Not intersected	1
Relation of iSVZ2 to PTV2 on CT2	
Included completely	6
Included partly	34
Not intersected	1

Abbreviations: iSVZ1/iSVZ2=ipsilateral subventricular zone on primary/secondary CT, CT1/CT2=primary/secondary CT, PTV1=planning target volume at CT1, PTV2=planning target volume at CT2

Table 1. *Patient characteristics (Group 1)*

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 (Table 2).

	Midline deformation		
	Yes	No	p^a
ΔV_{iLV} (cm^3)	5.82 ± 4.78	2.84 ± 2.97	0.011
ΔV_{cLV} (cm^3)	2.21 ± 1.81	1.55 ± 1.78	0.209
ΔV_{iSVZ} (cm^3)	2.79 ± 1.96	1.06 ± 0.79	0.003
ΔV_{cSVZ} (cm^3)	0.63 ± 0.83	0.60 ± 0.49	0.914

p^a = by independent samples t-test with statistical significance defined as $p < 0.05$

Table 2. *Comparison of the volume difference (ΔV: mean ± standard deviation) of the ipsilateral/contralateral lateral ventricle (ΔV_{iLV} / ΔV_{cLV}) and ipsilateral/contralateral subventricular zone (ΔV_{iSVZ} / ΔV_{cSVZ}) with or without midline deformation on primary CT*

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 (Table 3).

	Primary CT (CT1)				**Secondary CT (CT2)**			
	iLV1	cLV1	iSVZ1	cSVZ1	iLV2	cLV2	iSVZ2	cSVZ2
V (cm^3)	10.3 ± 8.9	15.0 ± 8.4	6.4 ± 3.6	8.6 ± 3.1	13.5 ± 8.6 (+30%)	16.5 ± 8.5 (+10%)	7.5 ± 3.3 (+17%)	9.0 ± 3.1 (+5%)
p^b					<0.001	<0.001	0.030	<0.001

p^b = by paired samples t-test with statistical significance defined as $p < 0.05$

Table 3. *Comparison of volume (V) (mean ± standard deviation) of the ipsilateral/contralateral lateral ventricle (iLV1/cLV1) and ipsilateral/contralateral subventricular zone (iSVZ2/cSVZ2) between CT1 and CT2*

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). All these changes resulted in relevant dosimetric impact, which is presented in Table 4.

	Primary CT (CT1)		**Secondary CT (CT2)**	
Dose parameter (p^b)	iSVZ1	cSVZ1	iSVZ2	cSVZ2
$D_{5\%}$ (Gy)	60.4 ± 0.5	53.7 ± 4.8	60.5 ± 0.4 (0.030)	53.8 ± 4.6 (0.006)
$D_{10\%}$ (Gy)	60.2 ± 0.4	50.7 ± 5.0	60.4 ± 0.5 (0.050)	50.8 ± 5.1 (0.028)
$D_{25\%}$ (Gy)	59.8 ± 1.3	39.7 ± 13.7	60.1 ± 1.2 (0.001)	40.1 ± 13.8 (0.005)

$D_{50\%}$ (Gy)	56.8 ± 7.7	33.8 ± 14.1	57.2 ± 7.3 (0.021)	34.0 ± 14.2 (0.007)
$D_{75\%}$ (Gy)	52.2 ± 12.1	26.1 ± 13.8	52.9 ± 12.0 (0.010)	26.3 ± 14.1 (0.053)
$D_{100\%}$ (Gy)	36.2 ± 18.7	13.9 ± 10.4	36.4 ± 18.3 (0.543)	14.0 ± 10.5 (0.230)
D_{mean} (Gy)	55.1 ± 6.9	33.1 ± 12.1	55.9 ± 7.1 (0.014)	33.3 ± 12.2 (0.076)
D_{max} (Gy)	61.3 ± 1.3	52.5 ± 10.1	61.4 ± 1.3 (0.283)	52.8 ± 9.9 (0.025)

Abbreviations: iSVZ/cSVZ=ipsilateral/contralateral subventricular zone,
$D_{x\%}$ (Gy) = dose covering x% volume of the structure under examination in Gy,
p^b = by paired samples t-test with statistical significance defined as $p < 0.05$

Table 4. *Dose parameters of the SVZ (comparing the same radiotherapy plan adapted to the primary CT and secondary CT) of the total 60 Gy irradiation*

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 (Fig. 2).

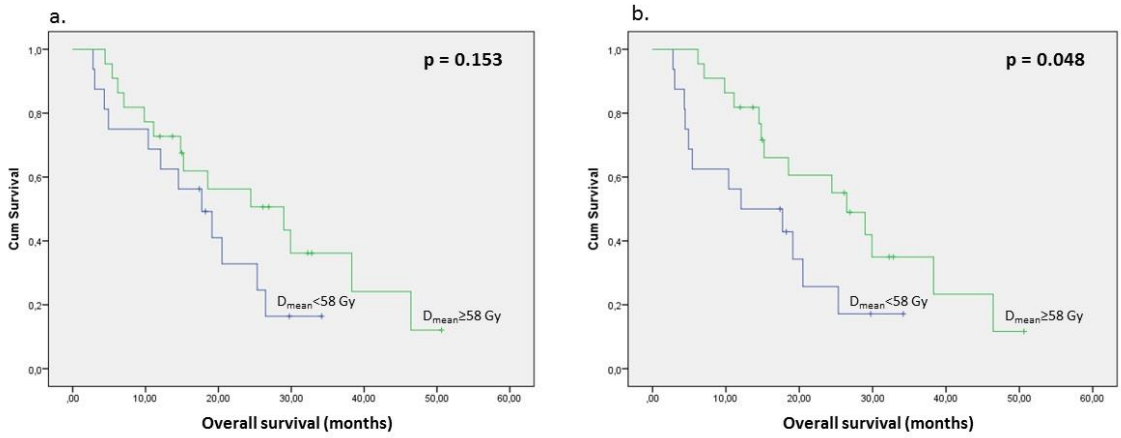

Fig. 2. *Kaplan–Meier survival curves illustrating the overall survival difference between groups that received high and low mean doses (D_{mean} < 58 Gy and D_{mean}≥58 Gy) to their ipsilateral subventricular zone on primary CT (a) and secondary CT (b) (p < 0.05 with the log-rank test).*

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 (Table 5).

Factor	OS (months)	p[c]
D_{mean} (iSVZ1) <58 Gy	17.6	
D_{mean} (iSVZ1) ≥58 Gy	26.6	0.153
D_{mean} (iSVZ2) <58 Gy	15.6	
D_{mean} (iSVZ2) ≥58 Gy	27.8	0.048
D_{mean} (cSVZ1) <27 Gy	22.2	
D_{mean} (cSVZ1) ≥27 Gy	26.8	0.477

D_{mean} (cSVZ2) <27 Gy	21.1	
D_{mean} (cSVZ2) ≥27 Gy	27.8	0.283
RT start <26.6 days	27.9	
RT start ≥26.6 days	15.8	0.036
KPS <70%	9.9	
KPS ≥70%	27.4	0.007

Abbreviations: iSVZ1/iSVZ2=ipsilateral subventricular zone on primary/secondary CT,
cSVZ1/cSVZ2=contralateral subventricular zone on primary/secondary CT,
D_{mean} = Mean Dose of the structure under examination in Gy,
RT start= Time interval between the opus and the radiotherapy start date in days
KPS=Karnofsky Performance Status in %
p^c =by log-rank test with statistical significance defined as $p < 0.05$

Table 5. *Analysis of factors possibly influencing the overall survival (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. The relevant patient and tumor characteristics are shown in Table 6.

Parameters		**Glioblastoma** Grade IV
N (male/female)		28/25
Age (years)	< 60	16
	≥ 60	37
Karnofsky performance status	<70%	15
	≥70%	38
Type of surgery		
Biopsy		10
STR (subtotal resection)		17
GTR (gross total resection)		26
Tumor size (Mean) (max. diameter in mm)		46.83
Tumor location		
Parietal		16

Frontal	15
Occipital	10
Temporal	7
Cerebellum	5
GTV1 (Mean ± SD) (cc)	106.67 ± 67.94
GTV2 (Mean ± SD) (cc)	92.12 ± 60.49
PTV1 (Mean ± SD) (cc)	497.12 ± 182.32
PTV2 (Mean ± SD) (cc)	339.14 ± 127.80

Abbreviations: GTV1=gross tumor volume at CT1, GTV2=gross tumor volume at CT2, PTV1=planning target volume at CT1, PTV2=planning target volume at CT2

Table 6. *Patient characteristics (Group 2)*

We observed that the average of all investigated dose parameters to these structures was lower at each volume dose level than on CT1 (Table 7.) 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.

	Dose parameter (CT1)			**Dose parameter (CT2)**		
Organ at Risk	**$D_{50\%}$** (Gy)	**$D_{90\%}$** (Gy)	**D_{mean}** (Gy)	**$D_{50\%}$** (Gy) (p^b)	**$D_{90\%}$** (Gy) (p^b)	**D_{mean}** (Gy) (p^b)
Brain	19.15 ± 12.64	3.50 ± 4.91	23.01 ±12.04	18.89 ± 10.52 (0.049)	3.19 ± 4.18 (0.031)	22.12 ± 11.32 (0.152)
Brainstem	8.72 ± 12.16	1.96 ± 2.12	9.89 ± 11.19	8.54 ± 11.26 (0.029)	1.80 ± 1.81 (0.072)	9.58 ± 10.59 (0.035)
Chiasm	8.00 ± 7.99	7.52 ± 7.54	7.99 ± 7.98	7.50 ± 7.22 (0.045)	6.86 ± 6.16 (0.083)	7.45 ± 7.09 (0.103)
Eye I	4.40 ± 4.66	2.93 ± 2.51	5.15 ± 4.75	4.20 ± 4.30 (0.213)	2.44 ± 2.12 (0.142)	4.99 ± 4.57 (0.107)
Eye C	3.39 ± 3.33	2.21 ± 2.15	3.99 ± 3.77	3.32 ± 3.28 (0.048)	2.12 ± 2.00 (0.150)	3.89 ± 3.72 (0.301)
Lens I	2.87 ± 2.26	2.54 ± 2.03	2.91 ± 2.26	2.76 ± 1.94 (0.118)	2.05 ± 1.71 (0.037)	2.35 ± 1.96 (0.118)
Lens C	2.41 ± 2.02	2.19 ± 1.78	2.45 ± 2.05	2.27 ± 1.94 (0.125)	2.05 ± 1.71 (0.047)	2.35 ± 1.96 (0.055)
Optic Nerve I	9.98 ± 13.79	8.19 ± 11.33	9.99 ± 14.04	9.69 ± 13.39 (0.039)	8.08 ± 11.19 (0.168)	9.86 ± 13.55 (0.129)

Optic Nerve C	7.10 ± 9.10	5.58 ± 6.43	7.10 ± 9.08		6.93 ± 9.18 (0.247)	5.60 ± 6.83 (0.154)	6.98 ± 9.11 (0.047)

Abbreviations: I/C=ipsilateral/contralateral,
$D_{x\%}$ (Gy) = dose covering x% volume of the structure under examination in Gy,
p^b = by paired samples t-test with statistical significance defined as $p < 0.05$

Table 7. *Dose parameters of the brain structures (comparing the same radiotherapy plan adapted to the primary CT (CT1) and secondary CT (CT2)) of the total 60 Gy irradiation*

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. Lim et al. [17] were the first to propose the prognostic significance of a connection of a tumor to the ipsilateral SVZ for GBM. Since then, further groups have confirmed this finding, and numerous retrospective clinical studies on high-grade glioma have suggested a significant relationship between radiation dose to the ipsilateral SVZ and disease outcome [22,24–28,30–32]. 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. In a pioneering study of 55 patients with high-grade brain tumors [22], the bilateral SVZ mean dose above 43 Gy significantly improved the median PFS and, as a result, was suggested as an independent factor in multivariate analysis. The authors of the following study included 40 patients, exclusively with GBM, and used the same cut-off value (43 Gy), yet no correlation was detected on PFS or OS either with the SVZ dose analyzed separately or as a bilateral structure [23]. Similarly, Chen et al. [29] examined a large number of patients with GBM (N = 116) and found no survival differences based on a higher ($D \geq 40$ Gy) or lower dose ($D < 40$ Gy) to the ipsilateral SVZ. However, they reported improved progression-free survival (PFS) and overall survival (OS) in the subgroup of patients who underwent gross total resection together with an ipsilateral SVZ dose of ≥40 Gy compared to those who received an

SVZ dose of < 40 Gy during postoperative chemoradiotherapy. The authors of more recent studies have included further relevant prognostic factors in their multivariate analysis, such as MGMT (O6-methylguanine methyltransferase) methylation status, and used higher cut-off mean doses for the ipsilateral SVZ (50–62.25 Gy). In these series of reports, Gupta et al. [24] found the mean dose of > 57.9 Gy of ipsilateral SVZ to be an independent factor on OS, whereas the same high dose to the contralateral SVZ had a reverse effect on survival. However, this finding could be explained with additional factors, such as the size of the tumor and its spread toward the contralateral hemisphere. Thereafter, Lee et al. [28] collected data on 173 patients from two centers and used different SVZ dose cut-off points. 59.4 Gy to the ipsilateral SVZ correlated significantly to PFS, but not to OS. This was confirmed to be an independent factor in multivariate analysis. Subsequently, another research team provided conflicting results, reporting either SVZ dose dependent improvement or, in contrast, a worsening of survival outcome confirmed by their retrospective analysis [29,30,31,32,34,35]. Nevertheless, these studies suggest that acute toxicity in connection with the delivery of a high radiation dose to the SVZ may be acceptable as there was no statistically significant difference in the Karnofsky Performance Status between the groups receiving a higher or lower SVZ dose. Finally, the single prospectively planned study [33] to involve the ipsilateral SVZ in the CTV provided encouraging results with a significantly improved median OS of 16 versus 14 months for patients with higher than 58 Gy doses to the iSVZ. This study revealed a novel factor, which could potentially account for such contradictory results. 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 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 [40,41,42,43]. 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 [37]. 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. So far, a small number of studies have been devoted to the assessment of postsurgical changes of the tumor bed for brain metastases [36,37,38]. 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. 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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8. References

[1] Zheng R, Fan R, Wen H, et al. Dosimetric comparison of intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for cerebral malignant gliomas. J Buon 2015;20(1):248‑52.

[2] Kong L, Gao J, Hu J,et al. Carbon ion radiotherapy boost in the treatment of glioblastoma: a randomized phase I/III clinical trial. Cancer Commun 2019;39(1). https://doi.org/10.1186/s40880-019-0351-2.

[3] Yang JC, Terezakis SA, Dunkel IJ, et al. Intensity-modulated radiation therapy with dose painting: a brain-sparing technique for intracranial germ cell tumors. Pediatr Blood Cancer 2016;63(4):646‑51.

[4] Barani IJ, Cuttino LW, Benedict SH, et al. Neural stem cell-preserving external-beam radiotherapy of central nervous system malignancies. Int J Radiat Oncol Biol Phys 2007;68:978‑85.

[5] Redmond KJ, Achanta P, Grossman SA, et al. A radiotherapy technique to limit dose to neural progenitor cell niches without compromising tumor coverage. J Neurooncol 2011;104:579‑87.

[6] Scaringi, C, Agolli L, Minniti G. Technical Advances in Radiation Therapy for Brain Tumors. Anticancer Res. 2018; 38; 6041–6045.

[7] Liu C, Li M, Xiao H, et al. Advances in MRI-guided precision radiotherapy. Prec Radiat Oncol. 2022; 6: 75– 84.

[8] Charlotte LB, Roel J.H.M. S, Johannes AL, Nanna MS. Identifying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in

head and neck organs at risk during radiotherapy provide information to help? Radiother Oncol 2015;115(3):285-294.

[9] Antonella C, Michele B, Francesco C, Luciano C, Natale Q, Pietro M, Andrea F, Giuseppe LC, Giuseppe M. Advanced Imaging Techniques for Radiotherapy Planning of Gliomas. Cancers 2021;13(5);1063.

[10] Moghaddasi L, Bezak E, Marcu LG. Current challenges in clinical target volume definition: tumour margins and microscopic extensions. Acta Oncol 2012;51:984.

[11] Kroonen J, Nassen J, Boulanger YG, et al. Human glioblastoma initiating cells invade specifically the subventricular zones and olfactory bulbs of mice after striatal injection. Int J Cancer 2011;129:574‑85.

[12] Farin A, Suzuki SO, Weiker M, et al. Transplanted glioma cells migrate and proliferate on host brain vasculature: a dynamic analysis. Glia 2006;53:799‑808.

[13] Shiras A, Chettiar ST, Shepal V, et al. Spontaneous transformation of human adult nontumorigenic stem cells to cancer stem stells is driven by genomic instability in a human model of glioblastoma. Stem Cells 2007;25:1478‑89.

[14] Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. J Neurosci 2002;22:629‑34.

[15] Liu C, Sage JC, Miller MR, et al. Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 2011;146:209‑21.

[16] Griffith B, Poisson L, Bangiyev L, et al. Relationship of subventricular zone with tumor blood volume, tumor genomics and patient survival in patients with glioblastoma: a TCGA glioma phenotype research group project. Paper presented at: 23rd Annual Meeting and Exhibition of ISMRM. 30 May-5 June 2015; Metro Toronto Convention Centre, Toronto, Ontario, Canada.

[17] Lim DA, Cha S, Mayo MC, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9(4):424‑9.

[18] Pokhrel D, Sood S, Lominska C, et al. Potential for reduced radiation-induced toxicity using intensity-modulated arc therapy for whole-brain radiotherapy with hippocampal sparing. J Appl Clin Med Phys 2015;16(5):5587.

[19] Sun B, Huang Z, Wu S, et al. Incidence and relapse risk of intracranial metastases within the perihippocampal region in 314 patients with breast cancer. Radiother Oncol 2016;118(1):181‑6.

[20] Tsai PF, Yang CC, Chuang CC, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol 2015;10(10):253.

[21] Goings GE, Sahni V, Szele FG. Migration patterns of subventricular zone cells in adult mice change after cerebral cortex injury. Brain Res 2004;996:213‑26.

[22] Evers P, Lee PP, DeMarco J, et al. Irradiation of the potential cancer stem cell niches in the adult brain improves progression-free survival of patients with malignant glioma. BMC Cancer 2010;10:384.

[23] Slotman BJ, Eppinga WSC, de Haan PF, et al. Is irradiation of potential cancer stem cell niches in the subventricular zones indicated in GBM? Int J Radiat Oncol Biol Phys 2001;81:S184.

[24] Gupta T, Nair V, Paul SN, et al. Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma? J Neurooncol 2012;109:195‑203.

[25] Adeberg S, Bostel T, Konig L, et al. A comparison of long-term survivors and shortterm survivors with glioblastoma, subventricular zone involvement: a predictive factor for survival? Radiat Oncol 2014;9:95.

[26] Kusumawidjaja G, Zhun Hong Gan P, et al. Dose-escalated intensity-modulated radiotherapy and irradiation of subventricular zones in relation to tumor control outcomes of patients with glioblastoma multiforme. OncoTargets and Therapy 2016;2016:9. 1115-1122.

[27] Jafri NF, Clarke JL, Weinberg V, et al. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neurooncology 2013;15:91‑6.

[28] Lee P, Eppinga W, Lagerwaard F, et al. Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: a pooled analysis. Int J Radiat Oncol Biol Phys 2013;86:609‑15.

[29] Chen L, Guerrero-Cazares H, Ye X, et al. Increased subventricular zone radiation dose correlates with survival in glioblastoma patients after gross total resection. Int J Radiat Oncol Biol Phys 2013;86:616‑22.

[30] Elicin O, Inac E, Uzel EK, et al. Relationship between survival and increased radiation dose to subventricular zone in glioblastoma is controversial. J Neuro-oncol 2014;118:413‑9.

[31] Anker CJ, Bagshaw HP, Sarkar V, et al. Impact of subventricular zone dose and relationship to glioblastoma tumor location on outcomes. Int J Radiat Oncol Biol Phys 2015;93:E110‑1.

[32] Khalifa J, Tensaouti F, Lusque A, et al. Subventricular zones: new key targets for glioblastoma treatment. Radiat Oncol 2017;12:67.

[33] Malik M, Akram KS, Joseph D, et al. Prospective study of irradiation of potential stem cell niches in glioblastoma. Int J Radiat Oncol Biol Phys 2015;3:S111.

[34] Mathew BS, Kaliyath SB, Krishnan J, et al. Impact of subventricular zone irradiation on outcome of patients with glioblastoma. J Cancer Res Ther 2018;14(6):1202‑6.

[35] Weinberg BD, Boreta L, Braunstein S, Cha S. Location of subventricular zone recurrence and its radiation dose predicts survival in patients with glioblastoma. J Neurooncol 2018;138(3):549‑56.

[36] Ahmed S, Hamilton J, Colen R, et al. Change in postsurgical cavity size within the first 30 days correlates with extent of surrounding edema: consequences for postoperative radiosurgery. J Comput Assist Tomogr 2014;38(3):457‑60.

[37] Atalar B, Choi CY, Harsh 4th GR, et al. Cavity volume dynamics after resection of brain metastases and timing of postresection cavity stereotactic radiosurgery. Neurosurgery 2013;72(2):180‑5. discussion 185.

[38] Jarvis LA, Simmons NE, Bellerive M, et al. Tumor bed dynamics after surgical resection of brain metastases: implications for postoperative radiosurgery. Int J Radiat Oncol Biol Phys 2012;84(4):943.

[39] Eekers D, In ’t Ven L, Roelofs E, Postma A, Troost EG. EPTN International Neurological Contouring Atlas. CancerData, 2017.

[40] Valduvieco I, Verger E, Bruna J, et al. Impact of radiotherapy delay on survival in glioblastoma. Clin Transl Oncol 2013;15:278.

[41] Han SJ, Rutledge WC, Molinaro AM, et al. The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. Neurosurgery 2015;77:248‑53.

[42] Randolph 2nd DM, McTyre ER, Paulsson AK, et al. Impact of timing of radiotherapy in patients with newly diagnosed glioblastoma. Clin Neurol Neurosurg 2016;151:73‑8.

[43] Osborn VW, Lee A, Garay E, et al. Impact of timing of adjuvant chemoradiation for glioblastoma in a large hospital database. Neurosurgery 2018;83(5):915‑21.

9. Appendix

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Original paper

Subventricular zone volumetric and dosimetric changes during postoperative brain tumor irradiation and its impact on overall survival

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ABSTRACT

Purpose: The aim of this retrospective study was to investigate the relationship between the dose to the subventricular zone (SVZ) and overall survival (OS) of 41 patients with glioblastoma multiforme (GBM), who were treated with an adaptive approach involving repeated topometric CT and replanning at two-thirds (40 Gy) of their course of postoperative radiotherapy for planning of a 20 Gy boost.

Methods: We examined changes in the ipsilateral lateral ventricle (LV) and SVZ (iLV and iSVZ), as well as in the contralateral LV and SVZ (cLV and cSVZ). We evaluated the volumetric changes on both planning CT scans (primary CT1 and secondary CT2). The survival of the GBM patients was analyzed using the Kaplan–Meier method; the multivariate Cox regression was also performed.

Results: Median follow-up and OS were 34.5 months and 17.6 months, respectively. LV and SVZ structures exhibited significant volumetric changes on CT2, resulting in an increase of dose coverage. At a cut-off point of 58 Gy, a significant correlation was detected between the iSVZ2 mean dose and OS (27.8 vs 15.6 months, $p = 0.048$). In a multivariate analysis, GBM patients with a shorter time to postoperative chemoradiotherapy (< 3.8 weeks), with good performance status ($\geq 70\%$) and higher mean dose (≥ 58 Gy) to the iSVZ2 had significantly better OS.

Conclusions: Significant anatomical and dose distribution changes to the brain structures were observed, which have a relevant impact on the dose-effect relationship for GBM; therefore, involving the iSVZ in the target volume should be considered and adapted to the changes.

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. A considerable amount of effort has been devoted to improving the outcome of local tumor treatment modalities, with the introduction of innovative techniques, such as navigation-based neurosurgery and highly selective radiation dose delivery methods: stereotactic intensity-modulated radiotherapy and proton and ion therapy [1,2]. Greater structural differentiation of the target has become available both for dose painting and to define intracerebral organs at risk (OARs) on the basis of the differing radiation susceptibility of the various regions and with advanced imaging [3,4,5]. 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. The recommendations for contouring in the US and in Europe are differing substantially without final consensus. [6]

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. These could differentiate into neurons or glial cells and migrate to places where regeneration is necessary in the central nervous system (CNS) [7,8]. Recent studies support the hypothesis that in a subgroup of

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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 [9,10,11,12,13]. Thus, the concept of incorporating SVZ into the high-dose region to eliminate the population of cancer stem cells with irradiation emerged. However, the entire SVZ represents a huge volume addition to the 2–3 cm margin around the primary tumor bed in which the potential tumor spread may originate in the CNS. As a result, the potential consequences of brain irradiation must be carefully estimated, in particular when neural stem cell niche irradiation is considered. Numerous preclinical and clinical studies have demonstrated that radiation to the hippocampus may be associated with neurocognitive deficits [14,15,16]. The clinical evidence for SVZ irradiation resulting in cognitive deterioration is not as robust as in the case of hippocampus irradiation [17].

It has been demonstrated in several studies with retrospective dose distribution analysis that a high dose to the ipsilateral SVZ results in significant improvement of progression-free survival (PFS) and overall survival (OS) for glioblastoma patients [18–28]. A further prospective trial confirmed the correlation of SVZ dose to the outcome for high-grade brain tumors [29]. These results emphasize the importance of an accurate definition of the ipsi- and contralateral SVZ for treatment planning and follow-up during the course of radiotherapy (RT). Image-guided radiation therapy (IGRT) and adaptive RT were introduced to many tumor sites to manage the daily and long term, i.e., a few weeks of structural uncertainties. However, there is insufficient data available on intracranial changes, and this is mainly limited to the volume dynamics of tumor bed alteration after surgical removal [32,33,34].

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 [33]. 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. We investigated the extent of changes in the anatomical position, shape and volume of LVs and SVZs and 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.

2. Materials and methods

2.1. Study population

41 patients treated between 1/2013 and 11/2015 with glioblastoma multiforme 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).

2.2. Contouring and treatment planning

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. The preoperative and postoperative (i.e., within 48 h) MR images were coregistered to the planning CT for more accurate GTV/CTV delineation. Glioblastoma multiforme (GBM) was treated with a total dose of 60 Gy at a 2 Gy dose per fraction with concomitant temozolomid (75 mg/m^2 daily) followed by temozolomid monotherapy. 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. Gross tumor volume (GTV1), clinical target volume (CTV1) and planning target volume (PTV1) were defined on primary CT (CT1). PTV1 was treated with 3-dimensional conformal radiotherapy (3D-CRT) or Intensity Modulated RT (IMRT) to 40 Gy in 20 fractions for GBM patients. 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). 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). The SVZ contour was defined in accordance with protocols developed by Gupta et al. [20], whereby SVZ was defined as a 5 mm margin along the wall of the LV on CT1 (Fig. 1(a)) and on CT2 (Fig. 1(b)).

Contouring was performed in axial reconstructions of the CT data set. All plans were created and optimized in the Xio Planning System

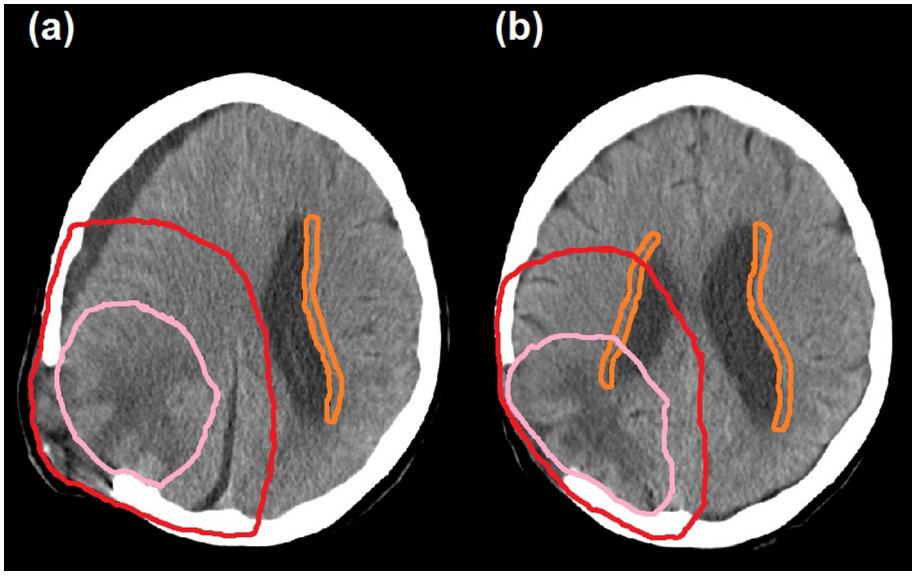

Fig. 1. Initial (primary) CT (CT1) (a) and follow-up (secondary) CT (CT2) (b) with the contours for planning target volume (PTV) in red, gross tumor volume (GTV) in pink and subventricular zone (SVZ) in orange. Although the two images were captured on the same plane, initially the ipsilateral structures are extremely deformed and thus undetectable. After 40 Gy irradiation, the ipsilateral lateral ventricle and SVZ appeared on CT2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

(version 4.7, Electa, Stockholm, Sweden). 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.

2.3. Statistical analysis

Statistical analysis was performed using the SPSS statistical analysis software package (version 20; SPSS, Chicago, Ill., USA), and patient- and 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 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.

3. Results

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 patient and tumor characteristics as well as the volumetric data for the defined targets are provided in Table 1.

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 (Table 2). 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 (Table 3). 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).

All these changes resulted in relevant dosimetric impact, which is presented in Table 4. 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

Table 1
Patient characteristics.

Parameters	Glioblastoma grade IV
N (male/female)	41 (20/21)
Age (years) < 60	12
Age (years) ≥ 60	29
Karnofsky performance status < 70%	16
Karnofsky performance status ≥70%	25
Type of surgery	
Biopsy	7
STR (subtotal resection)	29
GTR (gross total resection)	5
Tumor size (Mean) (max. diameter in mm)	51.12
Tumor location	
Parietal	9
Frontal	10
Occipital	2
Temporal	16
Cerebellum	4
GTV1 (Mean ± SD) (cc)	111.49 ± 70.53
GTV2 (Mean ± SD) (cc)	103.91 ± 74.08
PTV1 (Mean ± SD) (cc)	540.58 ± 147.72
PTV2 (Mean ± SD) (cc)	356.25 ± 133.92
Midline deformation on CT1	
Yes	23
No	18
Relation of iSVZ1 to PTV1 on CT1	
Included completely	15
Included partly	25
Not intersected	1
Relation of iSVZ2 to PTV2 on CT2	
Included completely	6
Included partly	34
Not intersected	1

Abbreviations: iSVZ1/iSVZ2 = ipsilateral subventricular zone on primary/secondary CT, CT1/CT2 = primary/secondary CT, PTV1 = planning target volume at CT1, PTV2 = planning target volume at CT2

Table 2
Comparison of the volume difference (ΔV: mean ± standard deviation) of the ipsilateral/contralateral lateral ventricle ($\Delta V_{iLV}/\Delta V_{cLV}$) and ipsilateral/contralateral subventricular zone ($\Delta V_{iSVZ}/\Delta V_{cSVZ}$) with or without midline deformation on primary CT.

	Midline deformation		
	Yes	No	p^a
ΔV_{iLV} (cm^3)	5.82 ± 4.78	2.84 ± 2.97	0.011
ΔV_{cLV} (cm^3)	2.21 ± 1.81	1.55 ± 1.78	0.209
ΔV_{iSVZ} (cm^3)	2.79 ± 1.96	1.06 ± 0.79	0.003
ΔV_{cSVZ} (cm^3)	0.63 ± 0.83	0.60 ± 0.49	0.914

p^a = by independent samples *t*-test with statistical significance defined as $p < 0.05$.

Table 3
Comparison of volume (V) (mean ± standard deviation) of the ipsilateral/contralateral lateral ventricle (iLV1/cLV1) and ipsilateral/contralateral subventricular zone (iSVZ2/cSVZ2) between CT1 and CT2.

	Primary CT (CT1)				Secondary CT (CT2)			
	iLV1	cLV1	iSVZ1	cSVZ1	iLV2	cLV2	iSVZ2	cSVZ2
V(cm^3)	10.3 ± 8.9	15.0 ± 8.4	6.4 ± 3.6	8.6 ± 3.1	13.5 ± 8.6 (+30%)	16.5 ± 8.5 (+10%)	7.5 ± 3.3 (+17%)	9.0 ± 3.1 (+5%)
p^b					< 0.001	< 0.001	0.030	< 0.001

p^b = by paired samples *t*-test with statistical significance defined as $p < 0.05$.

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 concerned showed greater differences due to the anatomical changes revealed 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 relevant 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 (Fig. 2). 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 (Table 5).

4. 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. Lim et al. [13] were the first to propose the prognostic significance of a connection of a tumor to the ipsilateral SVZ for GBM. Since then, further groups have confirmed this finding, and numerous retrospective clinical studies on high-grade glioma have suggested a significant relationship between radiation dose to the ipsilateral SVZ and disease outcome [18,20–24,26–28]. 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. In a pioneering study of 55 patients with high-grade brain tumors [18], the bilateral SVZ mean dose above 43 Gy significantly improved the median PFS and, as a result, was suggested as an independent factor in multivariate analysis. The authors of the following study included 40 patients, exclusively with GBM, and used the same cut-off value (43 Gy), yet no correlation was detected on PFS or OS either with the SVZ dose analyzed separately or as a bilateral structure [19]. Similarly, Chen et al. [25] examined a large number of patients with GBM (N = 116) and found no survival differences based on a higher (D ≥ 40 Gy) or lower dose (D < 40 Gy) to the ipsilateral SVZ. However, they reported improved progression-free survival (PFS) and overall survival (OS) in the subgroup of patients who underwent gross total resection together with an ipsilateral SVZ dose of ≥40 Gy compared to those who received an SVZ dose of < 40 Gy during postoperative chemoradiotherapy. The authors of more recent studies have included further relevant prognostic factors in their multivariate analysis, such as MGMT (O6-methylguanine methyltransferase) methylation status, and used higher cut-off mean doses for the ipsilateral SVZ (50–62.25 Gy). In these series of reports, Gupta et al. [20] found the mean dose of > 57.9 Gy of ipsilateral SVZ to be an independent factor on OS, whereas the same high dose to the contralateral SVZ had a reverse effect on survival. However, this finding could be explained with additional factors, such as the size of the tumor and its spread toward the contralateral hemisphere. Thereafter, Lee et al. [24] collected data on 173 patients from two centers and used different SVZ dose cut-off points. 59.4 Gy to the ipsilateral SVZ

Table 4
Dose parameters of the SVZ (comparing the same radiotherapy plan adapted to the primary CT and secondary CT) of the total 60 Gy irradiation.

	Primary CT (CT1)		Secondary CT (CT2)	
Dose parameter (p^b)	iSVZ1	cSVZ1	iSVZ2	cSVZ2
$D_{2\%}$ (Gy)	60.6 ± 0.6	53.8 ± 4.9	60.7 ± 0.5 (0.029)	53.9 ± 4.6 (0.007)
$D_{10\%}$ (Gy)	60.2 ± 0.4	50.7 ± 5.0	60.4 ± 0.5 (0.050)	50.8 ± 5.1 (0.028)
$D_{25\%}$ (Gy)	59.8 ± 1.3	39.7 ± 13.7	60.1 ± 1.2 (0.001)	40.1 ± 13.8 (0.005)
$D_{50\%}$ (Gy)	56.8 ± 7.7	33.8 ± 14.1	57.2 ± 7.3 (0.021)	34.0 ± 14.2 (0.007)
$D_{75\%}$ (Gy)	52.2 ± 12.1	26.1 ± 13.8	52.9 ± 12.0 (0.010)	26.3 ± 14.1 (0.053)
$D_{98\%}$ (Gy)	36.3 ± 18.5	14.1 ± 10.5	36.5 ± 18.1 (0.541)	14.3 ± 10.6 (0.232)
D_{mean} (Gy)	55.1 ± 6.9	33.1 ± 12.1	55.9 ± 7.1 (0.014)	33.3 ± 12.2 (0.076)
D_{max} (Gy)	61.3 ± 1.3	52.5 ± 10.1	61.4 ± 1.3 (0.283)	52.8 ± 9.9 (0.025)

Abbreviations: iSVZ/cSVZ = ipsilateral/contralateral subventricular zone, $D_{x\%}$ (Gy) = dose covering x% volume of the structure under examination in Gy, p^b = by paired samples *t*-test with statistical significance defined as $p < 0.05$.

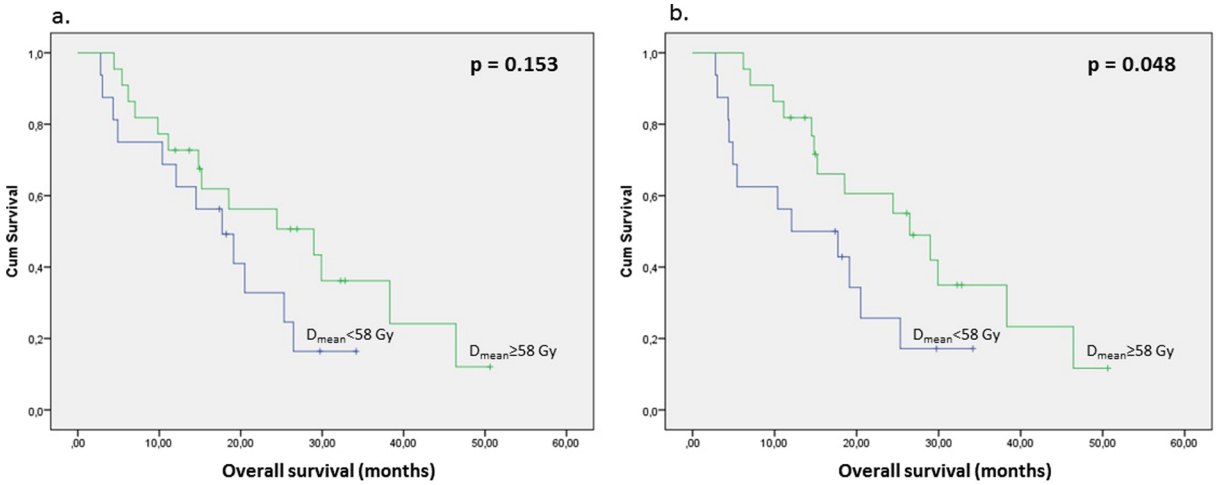

Fig. 2. Kaplan–Meier survival curves illustrating the overall survival difference between groups that received high and low mean doses (D_{mean} < 58 Gy and D_{mean} ≥ 58 Gy) to their ipsilateral subventricular zone on primary CT (a) and secondary CT (b) (p < 0.05 with the log-rank test).

Table 5
Analysis of factors possibly influencing the overall survival (OS).

Factor		OS (months)	p^c
D_{mean} (iSVZ1)	< 58 Gy	17.6	0.153
D_{mean} (iSVZ1)	≥ 58 Gy	26.6	
D_{mean} (iSVZ2)	< 58 Gy	15.6	0.048
D_{mean} (iSVZ2)	≥ 58 Gy	27.8	
D_{mean} (cSVZ1)	< 27 Gy	22.2	0.477
D_{mean} (cSVZ1)	≥ 27 Gy	26.8	
D_{mean} (cSVZ2)	< 27 Gy	21.1	0.283
D_{mean} (cSVZ2)	≥ 27 Gy	27.8	
RT start	< 26.6 days	27.9	0.036
RT start	≥ 26.6 days	15.8	
KPS	< 70%	9.9	0.007
KPS	≥ 70%	27.4	

Abbreviations: iSVZ1/iSVZ2 = ipsilateral subventricular zone on primary/secondary CT, cSVZ1/cSVZ2 = contralateral subventricular zone on primary/secondary CT, D_{mean} = Mean Dose of the structure under examination in Gy, RT start = Time interval between the opus and the radiotherapy start date in days. KPS = Karnofsky Performance Status in %.
p^c = by log-rank test with statistical significance defined as p < 0.05.

correlated significantly to PFS, but not to OS. This was confirmed to be an independent factor in multivariate analysis. Subsequently, another research team provided conflicting results, reporting either SVZ dose-dependent improvement or, in contrast, a worsening of survival outcome confirmed by their retrospective analysis [25,26,27,28,30,31]. Nevertheless, these studies suggest that acute toxicity in connection with the delivery of a high radiation dose to the SVZ may be acceptable as there was no statistically significant difference in the Karnofsky Performance Status between the groups receiving a higher or lower SVZ dose. Finally, the single prospectively planned study [29] to involve the ipsilateral SVZ in the CTV provided encouraging results with a significantly improved median OS of 16 *versus* 14 months for patients with higher than 58 Gy doses to the iSVZ.

This study revealed a novel factor, which could potentially account for such contradictory results. 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 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 [35,36,37,38]. 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 [33]. 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. So far, a small number of studies have been devoted to the assessment of postsurgical changes of the tumor bed for brain metastases [32,33,34]. 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.

5. 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. 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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References

[1] Zheng R, Fan R, Wen H, et al. Dosimetric comparison of intensity-modulated radiotherapy and three-dimensional conformal radiotherapy for cerebral malignant gliomas. J Buon 2015;20(1):248–52.
[2] Kong Lin, Gao Jing, Hu Jiyi, Lu Rong, Yang Jing, Qiu Xianxin, Hu Weixu, Lu Jiade J. Carbon ion radiotherapy boost in the treatment of glioblastoma: a randomized phase I/III clinical trial. Cancer Commun 2019;39(1). https://doi.org/10.1186/s40880-019-0351-2.
[3] Yang JC, Terezakis SA, Dunkel IJ, et al. Intensity-modulated radiation therapy with dose painting: a brain-sparing technique for intracranial germ cell tumors. Pediatr Blood Cancer 2016;63(4):646–51.
[4] Barani IJ, Cuttino LW, Benedict SH, et al. Neural stem cell-preserving external-beam radiotherapy of central nervous system malignancies. Int J Radiat Oncol Biol Phys 2007;68:978–85.
[5] Redmond KJ, Achanta P, Grossman SA, et al. A radiotherapy technique to limit dose to neural progenitor cell niches without compromising tumor coverage. J Neurooncol 2011;104:579–87.
[6] Moghaddasi L, Bezak E, Marcu LG. Current challenges in clinical target volume definition: tumour margins and microscopic extensions. Acta Oncol 2012;51:984.
[7] Kroonen J, Nassen J, Boulanger YG, et al. Human glioblastoma initiating cells invade specifically the subventricular zones and olfactory bulbs of mice after striatal injection. Int J Cancer 2011;129:574–85.
[8] Farin A, Suzuki SO, Weiker M, et al. Transplanted glioma cells migrate and proliferate on host brain vasculature: a dynamic analysis. Glia 2006;53:799–808.
[9] Shiras A, Chettiar ST, Shepal V, et al. Spontaneous transformation of human adult nontumorigenic stem cells to cancer stem stells is driven by genomic instability in a human model of glioblastoma. Stem Cells 2007;25:1478–89.
[10] Alvarez-Buylla A, Garcia-Verdugo JM. Neurogenesis in adult subventricular zone. J Neurosci 2002;22:629–34.
[11] Liu C, Sage JC, Miller MR, et al. Mosaic analysis with double markers reveals tumor cell of origin in glioma. Cell 2011;146:209–21.
[12] Griffith B, Poisson L, Bangiyev L, et al. Relationship of subventricular zone with tumor blood volume, tumor genomics and patient survival in patients with glioblastoma: a TCGA glioma phenotype research group project. Paper presented at: 23rd Annual Meeting and Exhibition of ISMRM. 30 May-5 June 2015; Metro Toronto Convention Centre, Toronto, Ontario, Canada.
[13] Lim DA, Cha S, Mayo MC, et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9(4):424–9.
[14] Pokhrel D, Sood S, Lominska C, et al. Potential for reduced radiation-induced toxicity using intensity-modulated arc therapy for whole-brain radiotherapy with hippocampal sparing. J Appl Clin Med Phys 2015;16(5):5587.
[15] Sun B, Huang Z, Wu S, et al. Incidence and relapse risk of intracranial metastases within the perihippocampal region in 314 patients with breast cancer. Radiother Oncol 2016;118(1):181–6.
[16] Tsai PF, Yang CC, Chuang CC, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. Radiat Oncol 2015;10(10):253.
[17] Goings GE, Sahni V, Szele FG. Migration patterns of subventricular zone cells in adult mice change after cerebral cortex injury. Brain Res 2004;996:213–26.
[18] Evers P, Lee PP, DeMarco J, et al. Irradiation of the potential cancer stem cell niches in the adult brain improves progression-free survival of patients with malignant glioma. BMC Cancer 2010;10:384.
[19] Slotman BJ, Eppinga WSC, de Haan PF, et al. Is irradiation of potential cancer stem cell niches in the subventricular zones indicated in GBM? Int J Radiat Oncol Biol Phys 2001;81:S184.
[20] Gupta T, Nair V, Paul SN, et al. Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma? J Neurooncol 2012;109:195–203.
[21] Adeberg S, Bostel T, Konig L, et al. A comparison of long-term survivors and short-term survivors with glioblastoma, subventricular zone involvement: a predictive factor for survival? Radiat Oncol 2014;9:95.
[22] Kusumawidjaja G, Zhun Hong Gan P, et al. Dose-escalated intensity-modulated radiotherapy and irradiation of subventricular zones in relation to tumor control outcomes of patients with glioblastoma multiforme. OncoTargets and Therapy 2016;2016:9. 1115-1122.
[23] Jafri NF, Clarke JL, Weinberg V, et al. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neurooncology 2013;15:91–6.
[24] Lee P, Eppinga W, Lagerwaard F, et al. Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: a pooled analysis. Int J Radiat Oncol Biol Phys 2013;86:609–15.
[25] Chen L, Guerrero-Cazares H, Ye X, et al. Increased subventricular zone radiation dose correlates with survival in glioblastoma patients after gross total resection. Int J Radiat Oncol Biol Phys 2013;86:616–22.
[26] Elicin O, Inac E, Uzel EK, et al. Relationship between survival and increased radiation dose to subventricular zone in glioblastoma is controversial. J Neuro-oncol 2014;118:413–9.
[27] Anker CJ, Bagshaw HP, Sarkar V, et al. Impact of subventricular zone dose and relationship to glioblastoma tumor location on outcomes. Int J Radiat Oncol Biol Phys 2015;93:E110–1.
[28] Khalifa J, Tensaouti F, Lusque A, et al. Subventricular zones: new key targets for glioblastoma treatment. Radiat Oncol 2017;12:67.
[29] Malik M, Akram KS, Joseph D, et al. Prospective study of irradiation of potential stem cell niches in glioblastoma. Int J Radiat Oncol Biol Phys 2015;3:S111.
[30] Mathew BS, Kaliyath SB, Krishnan J, et al. Impact of subventricular zone irradiation on outcome of patients with glioblastoma. J Cancer Res Ther 2018;14(6):1202–6.
[31] Weinberg BD, Boreta L, Braunstein S, Cha S. Location of subventricular zone recurrence and its radiation dose predicts survival in patients with glioblastoma. J Neurooncol 2018;138(3):549–56.
[32] Ahmed S, Hamilton J, Colen R, et al. Change in postsurgical cavity size within the first 30 days correlates with extent of surrounding edema: consequences for postoperative radiosurgery. J Comput Assist Tomogr 2014;38(3):457–60.
[33] Atalar B, Choi CY, Harsh 4th GR, et al. Cavity volume dynamics after resection of brain metastases and timing of postresection cavity stereotactic radiosurgery. Neurosurgery 2013;72(2):180–5. discussion 185.
[34] Jarvis LA, Simmons NE, Bellerive M, et al. Tumor bed dynamics after surgical resection of brain metastases: implications for postoperative radiosurgery. Int J Radiat Oncol Biol Phys 2012;84(4):943.
[35] Valduvieco I, Verger E, Bruna J, et al. Impact of radiotherapy delay on survival in glioblastoma. Clin Transl Oncol 2013;15:278.
[36] Han SJ, Rutledge WC, Molinaro AM, et al. The effect of timing of concurrent chemoradiation in patients with newly diagnosed glioblastoma. Neurosurgery 2015;77:248–53.
[37] Randolph 2nd DM, McTyre ER, Paulsson AK, et al. Impact of timing of radiotherapy in patients with newly diagnosed glioblastoma. Clin Neurol Neurosurg 2016;151:73–8.
[38] Osborn VW, Lee A, Garay E, et al. Impact of timing of adjuvant chemoradiation for glioblastoma in a large hospital database. Neurosurgery 2018;83(5):915–21.

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Adaptive Radiotherapy for Glioblastoma Multiforme – The Impact on Disease Outcome

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Abstract. *Background/Aim: To study the changes of glioblastoma multiforme during chemoradiotherapy (CRT) and to evaluate the impact of changes on dosimetry and clinical outcomes. Patients and Methods: Forty-three patients underwent volumetric imaging-based replanning. Prognostic factors and gross tumor volume changes in relation to overall survival and the effect of adaptive replanning were statistically analyzed. Results: Patients with total tumor removal, with shorter time to CRT (<27 days), with methylated O-6 methylguanine DNA methyltransferase and good performance status (>60%) had better survival. Tumor shrinkage in 24 patients resulted in improved survival compared to 19 in whom tumor was unchanged or progressed (25.3 vs. 11.1 months, p=0.04). Adapted planning target volume allowed a reduction in irradiated volume, while increasing survival (12.06 vs. 28.98 months, p=0.026). Conclusion: Tumor response during CRT has significant impact on the outcome. Adaptation of the planning target volume to the tumor changes proved to be beneficial and warrants further investigation.*

The advent of various forms of high-tech volumetric imaging has opened up the possibility of defining and following target and normal structures in the brain with high resolution prior to and during a course of radiation therapy (RT). Enhanced dose-delivery methods using new generation linear accelerators (LINAC) or increasingly available nuclear particle accelerators allow highly selective dose distribution for predefined structures (1-4). These developments can lead to a remarkably improved therapeutic ratio. Toward that goal, many newly defined structures have to be delineated. Furthermore, if the volume and location of the primarily contoured structures change, particularly small structures (such as chiasma, subventricular zone (SVZ) and hippocampus), those should also be followed and the RT plan subsequently modified (5). Several studies have investigated spatial and dosimetric changes in critical structures during treatment for different cancer types (6-8), but much less research has been performed on RT of the brain, which has great anatomical constancy due to the closed skull volume and lack of organ movement. However, tumor volume, the surgical cavity, the peritumoral region and several sensitive brain structures are assumed to undergo slow but evident changes (*e.g.* hemorrhage, edema and shift of anatomical structures) owing to the development of radiation-related reactions and residual tumor response (9-12). The importance of such anatomical changes during the course of RT increases if growing numbers of small substructures [target and organs at risk (OARs)] are defined for dose prescription. The standard OARs for brain tumor RT include the optic nerves, optic chiasm, eyes, lenses, brain and brainstem. Optionally, the cochleae, lacrimal glands, pituitary gland, hypothalamus and hippocampus could be taken into account for treatment planning when the tumor is in a location that will allow sparing without compromising the dose to the target (13-15).

Glioblastoma is a tumor that invades surrounding tissues aggressively, becomes infiltrative and spreads into different regions of the brain. Defining the clinical target volume (CTV) on postoperative images is therefore a highly challenging task (16-18). Preoperative contrast-enhancing volume cannot be directly used due to postoperative changes, and the resection cavity does not correspond accurately to the high number tumor cell region. Additionally, residual contrast-enhancing and non-enhancing tumor should be included in the CTV. Recently, advanced

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imaging techniques have been recommended to define the volume of the tumor mass, such as different sequences of magnetic resonance imaging (MRI) and amino acid-based positron-emission tomography images (^{11}C-methionine and O-(2- [^{18}F]fluoroethyl)-L-tyrosine) (17-19). Furthermore, different approaches to the definition of 'target volume' are practiced. The Radiation Therapy Oncology Group (RTOG) guidelines suggest two-phase irradiation, using larger CTV, including postoperative peritumoral edema, delineated on MRI T2-weighted fluid-attenuated inversion recovery (FLAIR) images, plus a 2 cm margin up to 46 Gy, followed by boost therapy encompassing the residual tumor with an additional margin of 2 cm (20). In Europe, the European Organisation for Research and Treatment of Cancer (EORTC) consensus guideline recommends single-phase irradiation with a 20 mm margin around the gross tumor volume (GTV), defined as the resection cavity plus residual contrast-enhancing tumor enlarged with a 3-5 mm margin for institutional set-up uncertainties (21). A recent retrospective analysis of the recurrence pattern exhibited no significant difference using such a limited (EORTC) approach or even further reduced margins (10 mm and 5 mm, respectively) around the GTV for glioblastoma to create the CTV (22). Whether to incorporate pre/postoperative edema is also a subject of debate. In recent years, growing attention has been paid to the dose in the SVZ, the region around the lateral ventricles, postulated as a main niche of pluripotent neural stem cells of the central nervous system. These cells, with their capacity to act as tumor stem cells, are able to differentiate into neurons or glial cells and serve as a source of tumor development and recurrence. Based on retrospective dose distribution analyses, a high dose to the ipsilateral SVZ resulted in significant improvement of progression-free (PFS) and overall (OS) survival for patients with glioblastoma (23-29). Therefore, the inclusion of the ipsilateral SVZ into the CTV may be considered.

The target volume definition of GBM varies remarkably at different institutions worldwide as a result of contradictory recommendations. The use of several MRI sequences at different time points, including preoperative MRI with a diffusion-weighted sequence for tractography and functional MRI, thereafter MRI within 48 hours post-surgery and a further pre-RT MRI, has recently become a standard requirement (30).

We investigated the potential of the use of repeated CT/MRI during two-phase RT delivery and adaptation of the structure definition for replanning and its impact on survival.

Patients and Methods

Study population. Forty-three consecutive patients with GBM treated at the Department of Oncotherapy University of Szeged, Hungary, between January 2013 and June 2016 were selected for a retrospective study. The patient and tumor characteristics as well as the volumetric data for the defined targets are provided in Tables I and II. The average age of the 43 patients (19 males and 24 females) was 58.6 (range=12-85) gears. Thirty-nine patients were treated with concurrent temozolomide chemotherapy during RT followed by temozolomide monotherapy, and four patients received only RT. All the patients underwent surgical tumor removal, with the tumor type confirmed by histology. The extent of the tumor removal of the entire study group was by subtotal resection in the majority of cases (N=27). The *O*-6 methylguanine DNA methyltransferase (*MGMT*) status was available for 33/43 tumor samples for the present analysis and 17 were defined as being promoter region methylated by immunohistochemistry. The average time to planning CT after surgery was 2.8 (range=0.7-5.1) weeks. RT generally started 1 week after the planning CT, thus the mean time interval between surgery and CRT was 29.1 days (range=5-59 weeks). GBM was treated with 75 mg/m^2 temozolomide each day during RT, with a 60 Gy total dose administered in two phases (40 Gy + repeated planning CT/MRI-based replanning of a 20 Gy boost) conventionally fractioned at 2 Gy per fraction. All the patients had an additional (secondary) replanning CT/MRI (mean=3.9, range=3.7-4.0 weeks) after the start of RT [mean=7.7 (range=5.3-14.3) weeks after surgery], which was registered to the initial (primary) planning CT. The University Ethics Committee and the local Institutional Review Board approved the study under registration no. 46/2015.

Table I. *Patient characteristics*.

Characteristic	Frequency, n
Gender	
Male	19
Female	24
Age	
≥60 Years	22
<60 Years	21
Histology	
Glioblastoma	43
Type of surgery	
Biopsy	7
Subtotal resection	27
Gross total resection	9
KPS	
>60%	16
≤60%	27
MGMT status	
>40%	17
≤40%	16
Unknown	10
RT start	
<27 Days	22
≥27 Days	21
Therapy	
Chemoradiotherapy	39
Radiotherapy alone	4

KPS: Karnofsky Performance Status; MGMT: O-6 methylguanine DNA methyltransferase promoter methylation; RT start: time interval between the surgery and the radiotherapy start date.

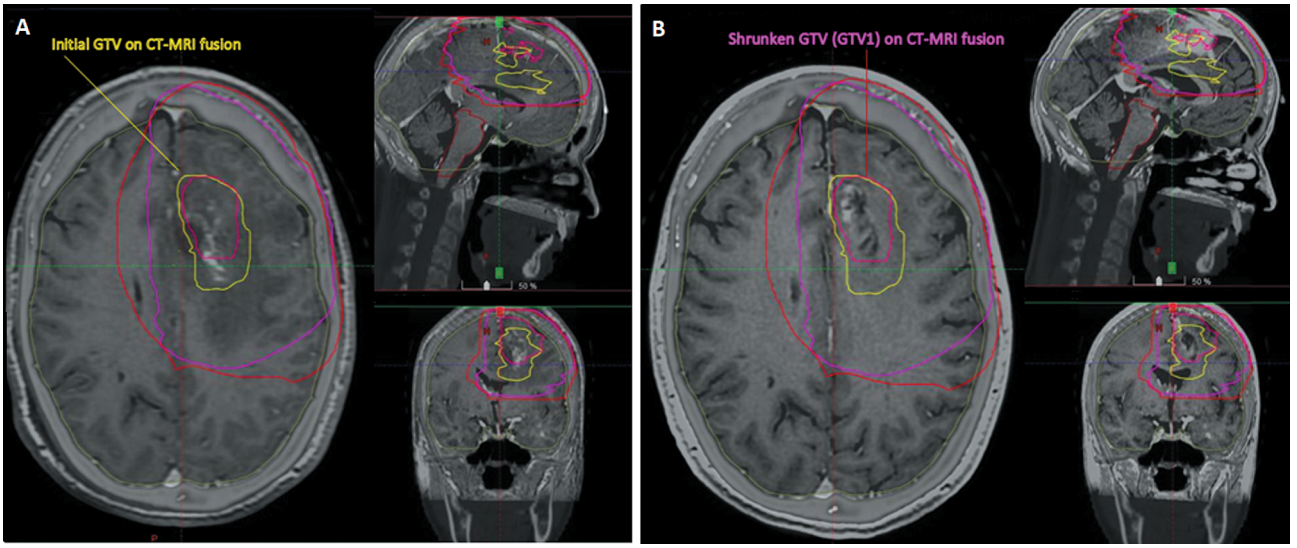

Figure 1. *A: Initial gross tumor volume (GTV - yellow) and planning target volume (PTV - red) after 40 Gy. B: Irradiation target volumes were recontoured (GTV1 - pink; PTV1 - purple).*

Table II. *Gross tumor volume (GTV) and planning target volume (PTV) on primary and on secondary (GTV1 and PTV1) computed tomography and their difference. Data are the mean±standard deviation.*

Volume	GTV (cm^3)	GTV1 (cm^3)	ΔGTV (cm^3)	PTV (cm^3)	PTV1 (cm^3)	ΔPTV (cm^3)
Overall	98.9±67.4 (n=43)	106.3±67.7	6.7±2.7	530.2±160.5 (n=43)	359.9±125.2	–183.2±130.5
Regression	113.1±69.4 (n=24)	85.5±56.9	–27.56±20.8	547.2±162.3 (n=41)	353.6±122.8	–193.6±124.4
No change/progression	94.6±66.2 (n=19)	113.5±75.5	19.2±1.8	460.0±114.5 (n=2)	489.6±140.6	29.6±26.0

ΔGTV=GTV1–GTV; ΔPTV=PTV1–PTV.

Contouring and treatment planning. Patients were positioned and fixed using a 3-point individual thermoplastic mask, with a CT scan taken with slice thickness of ≤5 mm with the patient in a supine position. The GTV and planning target volume (PTV) were defined on the primary CT using pre- and postoperative MRI images. Registration and contouring were performed with Advantage SIM software (version 4.7; General Electric Healthcare, Chicago, IL, USA). Contouring was performed in axial reconstructions of the CT data set after MRI-CT image fusion. The PTV margin around the GTV on the preoperative gadolinium-enhanced T1-weighted MRI sequence was defined according to our Institutional protocol based on the RTOG contouring guidelines. Around the GTV, a 20 mm margin was created encompassing the peritumoral edema defined on the basis of postoperative T2-FLAIR MRI. In the case of excessive edema, the margin was adapted manually in individual cases. All plans were made and optimized in the Xio Planning System (version 4.7; Elekta, Stockholm, Sweden). The PTV was treated with 3-dimensional conformal RT or intensity-modulated RT (IMRT) up to 40 Gy in 20 fractions with regular position control using portal imaging or cone-beam CT. After the first period of study, a second planning CT or, more recently, MRI, was performed. GTV1 and PTV1 were defined on the secondary planning CT. When an MRI was taken, image registration was applied for delineation of GTV1 and PTV1 on the planning CT (Figure 1). PTV1 was assigned by adding a 10 mm margin around GTV1. The PTV1 volume was treated with 3D-conformal RT/IMRT delivering an additional 20 Gy in 10 fractions.

Statistical analysis. The primary endpoint was OS and target-volume parameters. OS was measured from the date of histological diagnosis to the date of death from any cause. Patients who developed none of these time-to-event endpoints were censored on the date of their last follow-up. Survival distributions and median survival data were estimated using the Kaplan–Meier method, and comparisons were performed based on the log-rank test for categorical characteristics. Cox proportional hazards regression models were fitted to examine the association of RT parameters with OS. Variables with *p*-values of less than 0.05 in the univariate analysis were selected for the multivariate Cox proportional hazards model. Statistical analysis was performed using the SPSS statistical analysis software package (version 20; IBM, Armonk, NY, USA). Statistical significance was set at a threshold of $p<0.05$.

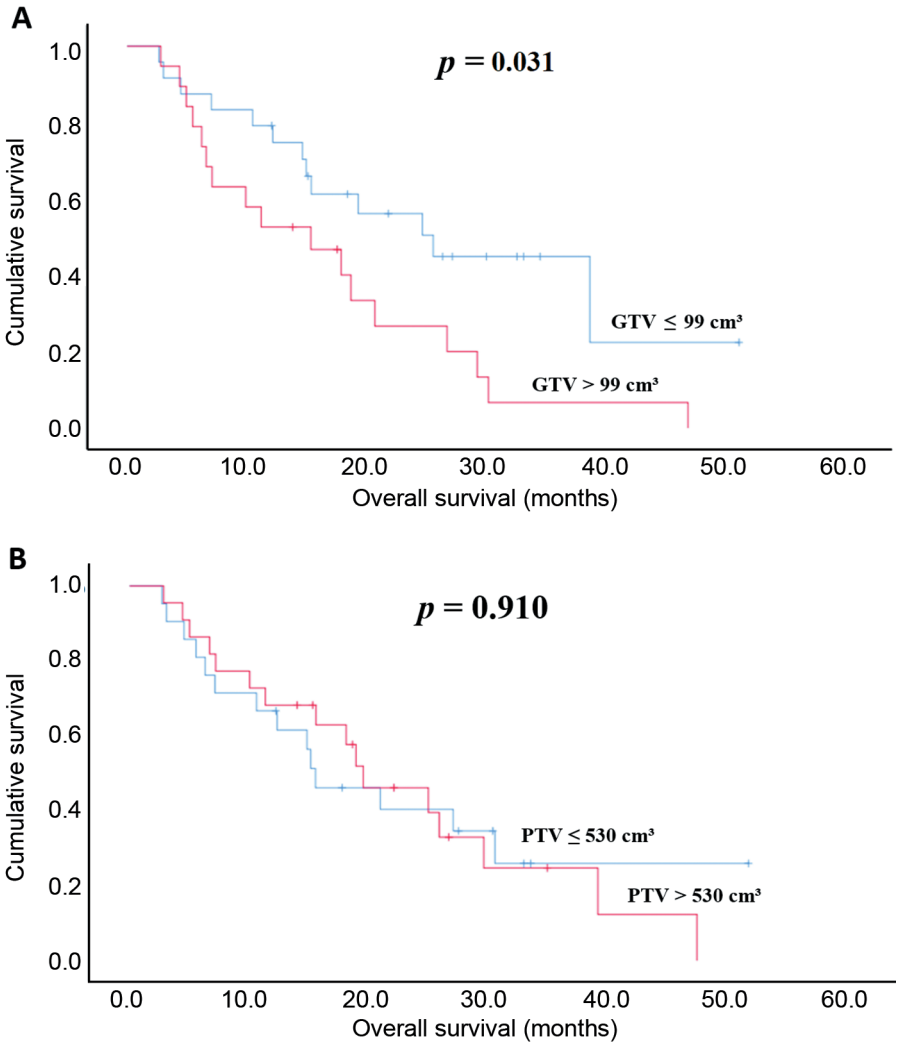

Figure 2. *Correlation of initial gross tumor volume (GTV) (A) and initial planning target volume on primary (PTV) (B) on primary computed tomography with overall survival.*

Results

The initial size of the GTV was strongly inversely correlated with OS. The patients were separated for the Kaplan–Meier analysise into two groups according to the mean GTV size: ≤99 cm^3 and >99 cm^3. The median OS was 25.33 months (95% CI=19.59-35.27 months) for the first group and 15.21 months (95% CI=10.82-22.27 months) for the second, corresponding to a hazard ratio (HR) of 1.006 (95% CI=1.00-1.01, p=0.031) (Figure 2A). Using the average value as cut-off point, the PTV did not exhibit a correlation with survival. Median OS was 15.21 months (95% CI=15.06-31.34 months) in the first group and 19.12 months (95% CI=15.64-28.67 months) in the second group corresponding to an HR of 1.001 (95% CI=0.99-1.01, p=0.910) (Figure 2B).

Anatomical changes in the brain and tumor growth or shrinkage occurred during RT. The GTV volume change (ΔGTV=GTV1−GTV) during RT was correlated with OS. The median OS was 25.33 months (95% CI=21.68-35.28 months) in the group with ΔGTV<0 cm^3, *i.e.* GTV regression, and 11.10 months (95% CI=10.63-22.69 months) in the group with ΔGTV≥0 cm^3, *i.e.* no change or progression of GTV, corresponding to an HR of 1.006 (95% CI=0.99-1.01, p=0.040) (Figure 3A). The recontouring and change of PTV was significantly different between the two groups: Patients with ΔPTV ≤183 cm^3 and those with ΔPTV >183 cm^3. The median OS was 12.06 months (95% CI=11.63-22.91 months) for the first group and 28.98 months (95% CI=22.36-38.82 months) for the second, corresponding to an HR of 1.001 (95% CI=0.99-1.01, p=0.026) (Figure 3B).

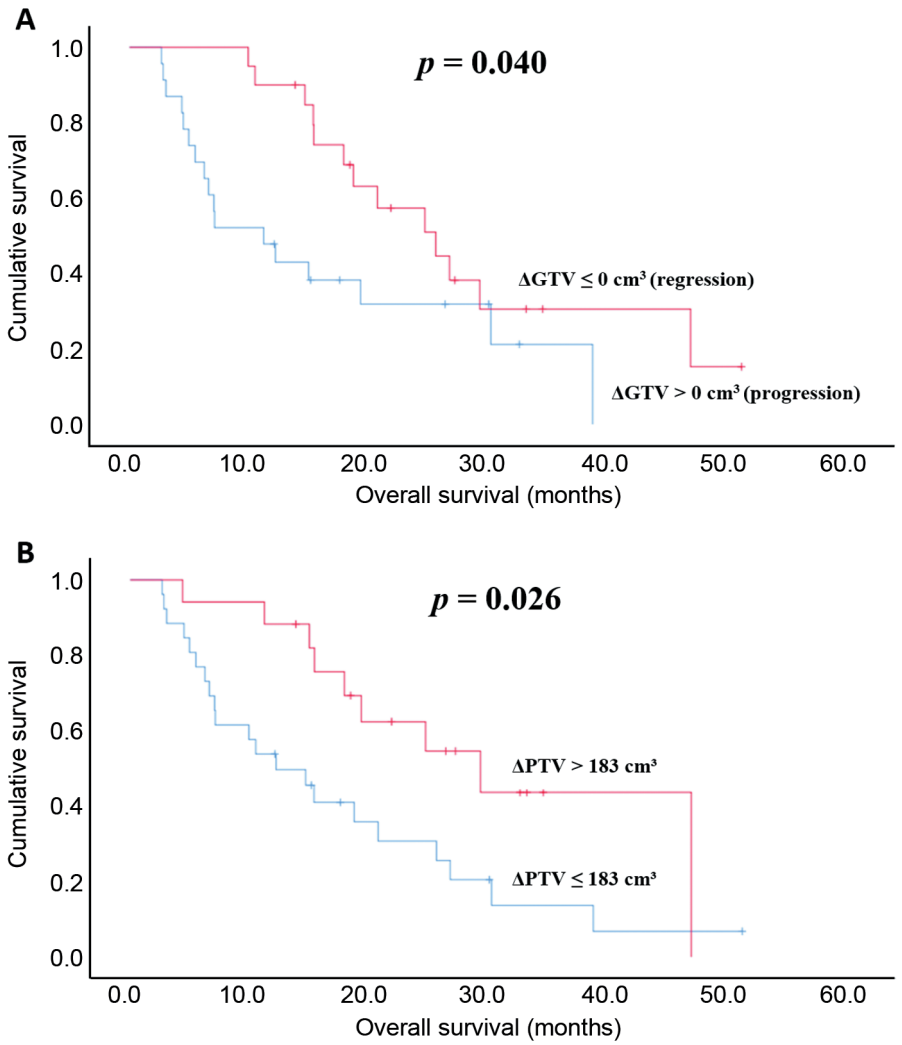

Figure 3. *Correlation of change in gross tumor volume (ΔGTV) (A) and in planning target volume (ΔPTV) (B) with overall survival.*

The type of surgery had a significant impact on survival, patients who underwent biopsy had a mean survival of 6.97 months, those with subtotal tumor resection 20.5 months and with gross tumor resection of 25.33 months (p=0.009) respectively. A Kaplan–Meier analysis of the time from surgery to the start of CRT and OS revealed that CRT started within 27 days resulted in a significantly higher mean OS (26.48 *vs*. 15.21 months, p=0.046). Our results demonstrated that *MGMT* promoter methylation was associated with significantly longer OS. The median OS was 7.03 (95% CI=7.58-18.44) months in those with non-methylated *MGMT* promoter (≤40%) and 26.48 (95% CI=19.54-35.86) months in those with >40% MGMT promoter methylation, corresponding to an HR of 1.017 (95% CI=0.99-1.03, p=0.065), retrospectively. Patients with higher postoperative Karnofsky Performance Status (KPS) status (KPS>60%) also demonstrated increased OS, with 38.31 (95% CI=27.46-42.01) months *versus* 11.10 (95% CI=10.11-17.75) months for the other group, corresponding to an HR of 0.949 (95% CI=0.92-0.97, p<0.001).

Discussion

In accordance with the literature, our data confirm the impact of general prognostic factors on disease outcome, *i.e*. better KPS, larger extent of tumor removal and methylated *MGMT* promoter status resulted in longer survival. The optimal time interval between the surgery and start of CRT is a matter of debate in the literature (29) and a clear conclusion cannot be drawn in our patient group, although the shorter time to CRT

proved to be significant factor for better OS. Adaptive RT has mainly been applied in patients with extra-cranial localization taking into account anatomical changes associated with weight loss, internal organ movement, organ filling, tissue edema and potential tumor regression. These changes may significantly influence the dose distribution, resulting in target volume missing or overdosing in the OAR region. The studies published on adaptive RT have varied between daily onboard imaging-based plan adaptation and CT/MRI-based replanning prior to boost definition. The final definition of the optimal time point and methodology for these resource-consuming procedures is yet to be determined. The advantageous effect of replanning for brain irradiation is not yet supported by strong clinical evidence despite the increased attention to adaptive techniques and a growing amount of clinical data for tumors in other locations. There are limited data available on adaptive RT including brain structures in publications on head and neck region RT. A study by Ho's team found no relevant effect of a daily assessment of dose-distribution changes for the brainstem and spinal cord in oropharyngeal cancer and hence did not recommend frequent replanning from this aspect (31). In contrast, numerous other studies have confirmed the benefit of adaptive RT for the treatment of head and neck tumors to outcomes (32-36). A recent study on adaptive RT of advanced head and neck cancer (36) demonstrated an improved therapeutic index by increasing the tumor coverage and dose reduction to the OARs. It confirmed that without replanning, the dose to some OARs would have exceeded their respective tolerance threshold, including central nerve system structures, *i.e.* the brainstem and spinal cord.

Unlike extra-cranial localizations, data on adaptive RT for brain tumors is sparse in spite of the fact that GBM is known as a rapidly growing tumor type, and CRT is applied postoperatively when relevant changes in post-surgical and tumor volume are supposed to occur (5, 9-12, 37). Both internationally applied guidelines (RTOG and EORTC) define target volume based on surgical cavity, edema and residual tumor. However, neither of them contains a recommendation for CT/MRI-based replanning during the course of RT. According to the institutional strategy at our Oncotherapy Department, two-phase irradiation is planned with the shrinking-volume technique. A pre-therapeutic boost definition is applied in conjunction with a recontouring of the residual tumor mass (GTV2) for repeated planning CT/MRI in an adapted CTV2-PTV2 approach. Recently, an evaluation on inter-fractional variation for completely resected GBM has been reported. Surgical cavities of 19 patients with glioblastoma with gross total resection were measured at three time points, 1 day following surgery, 4 weeks thereafter at the planning of RT and 5 weeks later (after 50 Gy was delivered) prior to boost planning. The differences between the surgical defect volumes were statistically significant ($p<0.001$), and based on the planning comparison, the authors concluded that the volume-adapted replanning during RT might reduce the irradiated volume of normal brain tissue and prevent a radiation target miss for boost RT (10). In line with this research, we detected relevant morphological changes on CT/MRI-based replanning performed prior to the boost irradiation. Moreover, patients were included with macroscopic tumors after partial resection and biopsy in which tumor response had contributed greatly to target volume changes in addition to post-surgical and RT-triggered reactions. In a preliminary study on three patients with GBM using integrated high-field MRI-LINAC, relevant volumetric changes in GBM tumor volume had been observed over the course of RT (37). Muruganandham *et al.* compared the status of tumor metabolic activity with MRI spectroscopy prior to and during the third week of RT, revealing a significant correlation with PFS (38). In our study, both the initial residual tumor volume and the extent of tumor shrinkage exhibited a significant impact on OS. The outcome of survival analysis showed no significant difference in terms of the initial size of the PTV. However, the GTV volume difference *i.e.* the difference between the GTV defined on the first plan and the tumorous mass seen on the replanning image, did show a significant correlation with OS in univariate analysis. Similarly, a relevant decrease in the size of the PTV (the PTV volume difference, analogous to the GTV volume difference) predicted better OS.

Our research has certain limitations due to its retrospective nature and relatively small number of patients. Thus, the correlation between the adapted boost volume and OS disappeared in the multivariate analysis, taking into account stronger prognostic factors, such as KPS and *MGMT* promoter methylation status. Furthermore, the first series of replanning took place using repeated CT images but in the later part of the study, all patients underwent repeated MRI. In order to compensate for the lack of MRI and increase the accuracy of the boost volume delineation, in all cases, two experts (one of them a neuro-radiologist) defined GTV1.

Our findings support the great importance of monitoring anatomical changes in the course of fractionated postoperative brain tumor irradiation. A follow-up of the residual tumor during CRT and adaptation of the PTV to tumor volume changes result in increased accuracy of dose delivery to the tumor and relevant normal brain tissue sparing. According to our data, reduction of the PTV did not compromise survival; in contrast, it seemed to be beneficial. Our preliminary data on improved survival on the basis of a higher degree of PTV reduction warrant further clinical studies to confirm these encouraging results.

The implementation of an adaptive RT approach is suggested for postoperative irradiation of GBM to optimize coverage of the target and minimize the dose to OARs. The reported data confirm that significant changes occur in different brain structures and in the residual tumor during

fractionated CRT. The tumor response and adapted boost volume definition exhibited a strong correlation to treatment outcome. Optimization of the imaging (MRI and amino acid-based PET/CT) for replanning could further improve the quality of the adaptive approach.

Conflicts of Interest

None of the Authors has a financial or personal relationship with other people or organizations that could inappropriately influence or bias the content of the article.

Authors' Contributions

KH, ÁD, DK, and PB contributed to the design and implementation of the research; ZV, ZV, EF, VP and ZR participated in data acquisition and analysis; AC performed the image analysis, BD performed the statistical analysis; JO helped in data evaluation, KH, BD and ZV wrote the article. All Authors were subsequently involved in data interpretation. All Authors revised and approved the article.

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References

1 Thibouw D, Truc G, Bertaut A, Chevalier C, Aubignac L and Mirjolet C: Clinical and dosimetric study of radiotherapy for glioblastoma: three-dimensional conformal radiotherapy *versus* intensity-modulated radiotherapy. J Neurooncol *137(2)*: 429-438, 2018. PMID: 29374810. DOI: 10.1007/s11060-017-2735-y

2 Briere TM, McAleer MF, Levy LB and Yang JN: Sparing of normal tissues with volumetric arc radiation therapy for glioblastoma: Single-institution clinical experience. Radiat Oncol *12(1):* 79, 2017. PMID: 28464840. DOI: 10.1186/s13014-017-0810-3

3 Exeli AK, Kellner D, Exeli L, Steininger P, Wolf F, Seldmayer F and Deutschmann H: Cerebral cortex dose sparing for glioblastoma patients: IMRT *versus* robust treatment planning. Radiat Oncol *13(1):* 20, 2018. PMID: 29409516. DOI: 10.1186/s13014-018-0953-x

4 Petr J, Platzek I, Hofheinz F, Mutsaerts HJMM, Asllani I, van Osch MJP, Seidlitz A, Krukowski P, Gommlich A, Beuthien-Baumann B, Jentsch C, Maus J, Troost EGC, Baumann M, Krause M and van den Hoff J: Photon *vs*. proton radiochemotherapy: Effects on brain tissue volume and perfusion. Radiother Oncol *128(1):* 121-127, 2018. PMID: 29370984. DOI: 10.1016/j.radonc.2017.11.033

5 Mehta S, Gajjar SR, Padgett KR, Asher D, Stoyanova R, Ford JC and Mellon EA: Daily tracking of glioblastoma resection cavity, cerebral edema, and tumor volume with MRI-guided radiation therapy. Cureus *10(3):* e2346, 2018. PMID: 29796358. DOI: 10.7759/cureus.2346

6 Zhang L, Wang Z, Shi C, Long T and Xu XG: The impact of robustness of deformable image registration on contour propagation and dose accumulation for head and neck adaptive radiotherapy. J Appl Clin Med Phys *19(4):* 185-194, 2018. PMID: 29851267. DOI: 10.1002/acm2.12361

7 Saito N, Schmitt D and Bangert M: Correlation between intrafractional motion and dosimetric changes for prostate IMRT: Comparison of different adaptive strategies. J Appl Clin Med Phys *19(4):* 87-97, 2018. PMID: 29862644. DOI: 10.1002/acm2.12359

8 Matsuo Y: A promising result of locoregional tumor control with biologically adaptive RT in patients with locally advanced non-small cell lung cancer. Transl Lung Cancer Res *7(2):* 111-113, 2018. PMID: 29780704. DOI: 10.21037/tlcr.2018.03.01

9 Tsien C, Gomez-Hassan D, Ten Haken RK, Tatro D, Junck L, Chenevert TL and Lawrence T: Evaluating changes in tumor volume using magnetic resonance imaging during the course of radiotherapy treatment of high-grade gliomas: implications for conformal dose-escalation studies. Int J Radiat Oncol Biol Phys *62(2):* 328-332, 2005. PMID: 15890571. DOI: 10.1016/j.ijrobp.2004.10.010

10 Kim TG and Lim DH: Interfractional variation of radiation target and adaptive radiotherapy for totally resected glioblastoma. J Korean Med Sci *28(8):* 1233-1237, 2013. PMID: 23960453. DOI: 10.3346/jkms.2013.28.8.1233

11 Grossman R, Shimony N, Shir D, Gonen T, Sitt R, Kimchi TJ, Harosh CB and Ram Z: Dynamics of FLAIR volume changes in glioblastoma and prediction of survival. Ann Surg Oncol *24(3):* 794-800, 2017. PMID: 27766560. DOI: 10.1245/s10434-016-5635-z

12 Champ CE, Siglin J, Mishra MV, Shen X, Werner-Wasik M, Andrews DW, Mayekar SU, Liu H and Shi W: Evaluating changes in radiation treatment volumes from post-operative to same-day planning MRI in high-grade gliomas. Radiat Oncol *7:* 220, 2012. PMID: 23259933. DOI: 10.1186/1748-717X-7-220

13 Liang HT, Chen WY, Lai SF, Su MY, You SL, Chen LH, Tseng HM, Chen CM, Kuo SH and Tseng WI: The extent of edema and tumor synchronous invasion into the subventricular zone and corpus callosum classify outcomes and radiotherapy strategies of glioblastomas. Radiother Oncol *125(2):* 248-257, 2017. PMID: 29056290. DOI: 10.1016/j.radonc.2017.09.024

14 Chatterjee A, Serban M, Abdulkarim B, Panet-Raymond V, Souhami L, Shenouda G, Sabri S, Jean-Claude B and Seuntjens J: Performance of knowledge-based radiation therapy planning for the glioblastoma disease site. Int J Radiat Oncol Biol Phys *99(4):* 1021-1028, 2017. PMID: 28870791. DOI: 10.1016/j.ijrobp.2017.07.012

15 Hofmaier J, Kantz S, Söhn M, Dohm OS, Bächle S, Alber M, Parodi M, Belka C and Niyazi M: Hippocampal sparing radiotherapy for glioblastoma patients: A planning study using volumetric modulated arc therapy. Radiat Oncol *11(1):* 118, 2016. PMID: 27609371. DOI: 10.1186/s13014-016-0695-6

16 Mann J, Ramakrishna R, Magge R and Wernicke AG: Advances in Radiotherapy for Glioblastoma. Front Neurol *8:* 748, 2018. PMID: 29379468. DOI: 10.3389/fneur.2017.00748

17 Niyazi M, Geisler J, Siefert A, Schwarz SB, Ganswindt U, Garny S, Schnell O, Suchorska B, Kreth FW, Tonn JC, Bartenstein P, la Fougère C and Belka C: FET-PET for malignant glioma treatment planning. Radiother Oncol *99(1):* 44-8, 2011. PMID: 21458093. DOI: 10.1016/j.radonc.2011.03.001

18 Ghose A, Lim G and Husain S: Treatment for GBM: Current guidelines and Canadian practice. Curr Oncol *17(6):* 52-58, 2010. PMID: 21151410. DOI: 10.3747/co.v17i6.574

19 Tsien C, Moughan J, Michalski JM, Gilbert MR, Purdy J, Simpson J, Kresel JJ, Curran WJ, Diaz A and Mehta MP: Phase I three-dimensional conformal radiation dose escalation study in newly diagnosed glioblastoma: Radiation Therapy Oncology Group Trial 98-03. Int J Radiat Oncol Biol Phys *73(3):* 699-708, 2009. PMID: 18723297. DOI: 10.1016/j.ijrobp.2008.05.034

20 Cabrera AR, Kirkpatrick JP, Fiveash JB, Shih HA, Koay EJ, Lutz S, Petit J, Chao ST, Brown PD, Vogelbaum M, Reardon DA, Chakravarti A, Wen PY and Chang E: Radiation therapy for glioblastoma: executive summary of an American Society for Radiation Oncology evidence-based clinical practice guideline. Pract Radiat Oncol *6(4):* 217-225, 2016. PMID: 27211230. DOI: 10.1016/j.prro.2016.03.007

21 Niyazi M, Brada M, Chalmers AJ, Combs SE, Erridge SC, Fiorentino A, Grosu AL, Lagerwaard FJ, Minniti G, Mirimanoff RO, Ricardi U, Short SC, Weber DC and Belka C: ESTRO-ACROP guideline "target delineation of glioblastomas". Radiother Oncol *118(1):* 35-42, 2016. PMID: 26777122. DOI: 10.1016/j.radonc.2015.12.003

22 Paulsson AK, McMullen KP, Peiffer AM, Hinson WH, Kearns WT, Johnson AJ, Lesser GJ, Ellis TL, Tatter SB, Debinski W, Shaw EG and Chan MD: Limited margins using modern radiotherapy techniques does not increase marginal failure rate of glioblastoma. Am J Clin Oncol *37(2):* 177-181, 2014. PMID: 23211224. DOI: 10.1097/COC.0b013e318271ae03

23 Gupta T, Nair V, Paul SN, Kannan S, Moiyadi A, Epari S and Jalali R: Can irradiation of potential cancer stem-cell niche in the subventricular zone influence survival in patients with newly diagnosed glioblastoma? J Neurooncol *109(1):* 195-203, 2012. PMID: 22555992. DOI: 10.1007/s11060-012-0887-3

24 Lee P, Eppinga W, Lagerwaard F, Cloughesy T, Slotman B, Nghiemphu PL, Wang PC, Kupelian P, Agazaryan N, Demarco J, Selch MT, Steinberg M and Kang JJ: Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: A pooled analysis. Int J Radiat Oncol Biol Phys *86(4):* 609-615, 2013. PMID: 23462418. DOI: 10.1016/j.ijrobp.2013.01.009

25 Chen L, Guerrero-Cazares H, Ye X, Ford E, McNutt T, Kleinberg L, Lim M, Chaichana K, Quinones-Hinojosa A and Redmond K: Increased subventricular zone radiation dose correlates with survival in glioblastoma patients after gross total resection. Int J Radiat Oncol Biol Phys *86(4):* 616-622, 2013. PMID: 23540348. DOI: 10.1016/j.ijrobp.2013.02.014

26 Elicin O, Inac E, Uzel EK, Karacam S and Uzel OE: Relationship between survival and increased radiation dose to subventricular zone in glioblastoma is controversial. J Neurooncol *118(2):* 413-419, 2014. PMID: 24668610. DOI:10.1007/s11060-014-1424-3

27 Anker CJ, Bagshaw HP, Sarkar V, Dritto M, Boucher K, Jensen RL and Shrieve DC: Impact of subventricular zone dose and relationship to glioblastoma tumor location on outcomes. Int J Radiat Oncol Biol Phys *93(3):* 110-111, 2015. DOI: 10.1016/j.ijrobp.2015.07.829

28 Khalifa J, Tensaouti F, Lusque A, Plas B, Lotterie JA, Benouaich-Amiel A, Uro-Coste E, Lubrano V and Cohen-Jonathan Moyal E: Subventricular zones: New key targets for glioblastoma treatment. Radiat Oncol *12(1):* 67, 2017. PMID: 28424082. DOI: 10.1186/s13014-017-0791-2

29 Darázs B, Ruskó L, Végváry Z, Ferenczi L, Dobi Á, Paczona V, Varga Z, Fodor E and Hideghéty K: Subventricular zone volumetric and dosimetric changes during postoperative brain tumor irradiation and its impact on overall survival. Phys Med *68:* 35-40. PMID: 31733404. DOI: 10.1016/j.ejmp.2019.10.039

30 Kruser TJ, Bosch WR, Badiyan SN, Bovi JA, Ghia AJ, Kim MM, Solanki AA, Sachdev S, Tsien C, Wang TJC, Mehta MP and McMullen KP: NRG Brain Tumor Specialists Consensus Guidelines for Glioblastoma Contouring. J Neurooncol *143(1):* 157-166, 2019. PMID: 30888558. DOI: 10.1007/s11060-019-03152-9.

31 Ho KF, Marchant T, Moore C, Webster G, Rowbottom C, Penington H, Lee L, Yap B, Sykes A and Slevin N: Monitoring dosimetric impact of weight loss with kilovoltage (kV) cone beam CT (CBCT) during parotid-sparing IMRT and concurrent chemotherapy. Int J Radiat Oncol Biol Phys *82(3):* 375-382, 2012. PMID: 22197229. DOI: 10.1016/j.ijrobp.2011.07.004

32 Brouwer C, Steenbakkers R, Langendijk J and Sijtsema N: Idenitfying patients who may benefit from adaptive radiotherapy: Does the literature on anatomic and dosimetric changes in head and neck organs at risk during radiotherapy provide information to help? Radiother Oncol *115(3):* 285-294, 2015. PMID: 26094076. DOI: 10.1016/j.radonc.2015.05.018.

33 Lim-Reinders S, Keller BM, Al-Ward S, Sahgal A and Kim A: Online adaptive radiation therapy. Int J Radiat Oncol Biol Phys *99(4):* 994-1003, 2017. PMID: 28916139. DOI: 10.1016/j.ijrobp.2017.04.023.

34 Robar JL, Day A, Clancey J, Kelly R, Yewondwossen M, Hollenhorst H, Rajaraman M and Wilke D: Spatial and dosimetric variability of organs at risk in head-and-neck intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys *68(4):* 1121-1130, 2007. PMID: 17398025. DOI: 10.1016/j.ijrobp.2007.01.030.

35 Marzi S, Pinnaro P, D'Alessio D, Strigari L, Bruzzaniti V, Giordano C, Giovinazzo G and Marucci L: Anatomical and dose changes of gross tumour volume and parotid glands for head and neck cancer patients during Intenisty-modulated radiotherapy: effect on the probability of xerostomia incidence. Clin Oncol *24(3):* e54-62, 2012. PMID: 22138192. DOI: 10.1016/j.clon.2011.11.006.

36 Surucu M, Shah KK, Roeske JC, Choi M, Small Jr W and Emami B: Adaptive radiotherapy for head and neck cancer: Implications for clinical and dosimetry outcomes. Technol Cancer Res Treat *16(2):* 218-223, 2017. PMID: 27502958. DOI: 10.1177/1533034616662165

37 Ruschin ME, Sahgal A, Chugh B, Lau A, Tseng CL, Myrehaug S and Lee Y: Preliminary investigation of adaptive glioblastoma radiation therapy using the integrated high-field MRI-LINAC. Int J Radiat Oncol Biol Phys *99(2):* 717, 2017. DOI: 10.1016/j.ijrobp.2017.06.2328

38 Muruganandham M, Clerkin PP, Smith BJ, Anderson CM, Morris A, Capizzano AA, Magnotta V, McGuire SM, Smith MC, Bayouth JE and Buatti JM: 3-dimensional magnetic resonance spectroscopic imaging at 3-Tesla for early response assessment of glioblastoma patients during external beam radiation therapy. Int J Radiat Oncol Biol Phys *90(1):* 181-189, 2014. PMID: 24986746. DOI: 10.1016/j.ijrobp.2014.05.014

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