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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 (≥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

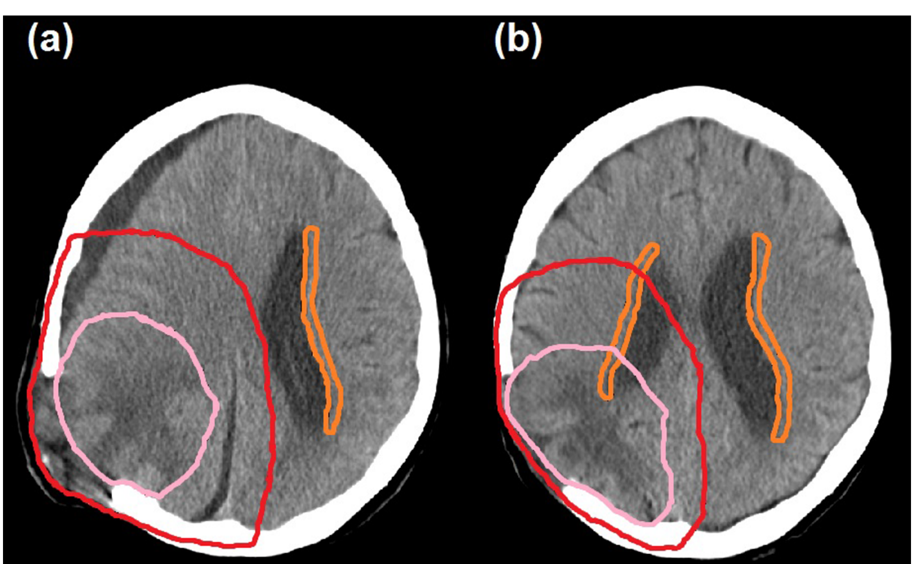

Fig. 1. Initial (primary) CT (CT1) (a) and follow-up (secondary) CT (CT2) (b) with the contours for planning target volume (PTV) in red, gross tumor volume (GTV) in pink and subventricular zone (SVZ) in orange. Although the two images were captured on the same plane, initially the ipsilateral structures 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 $p < 0.05$.

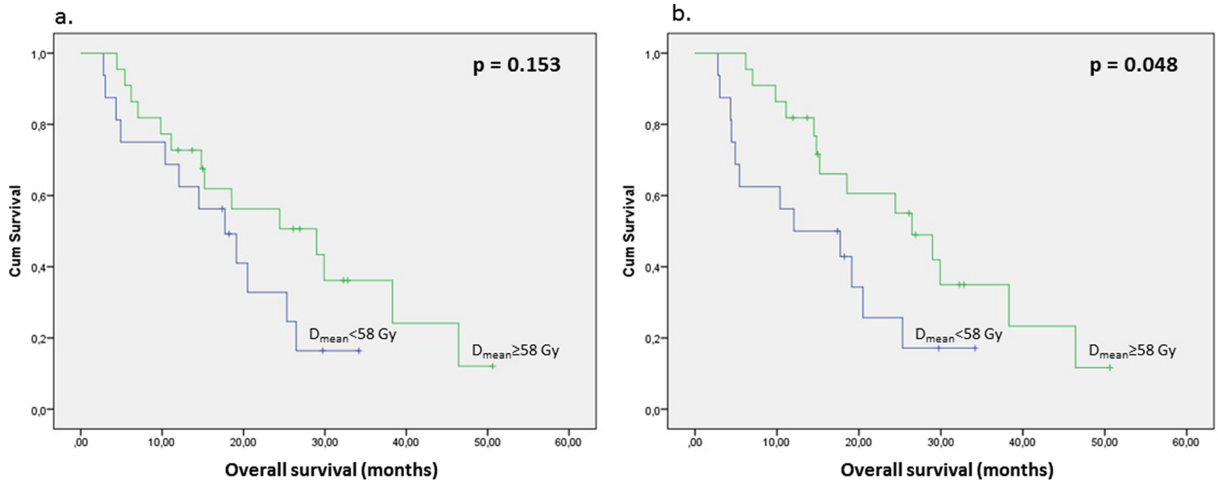

Fig. 2. Kaplan–Meier survival curves illustrating the overall survival difference between groups that received high and low mean doses (D_{mean} < 58 Gy and D_{mean} ≥ 58 Gy) to their ipsilateral subventricular zone on primary CT (a) and secondary CT (b) ($p < 0.05$ with the log-rank test).

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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