

Is a modification of the radiotherapeutic target volume necessary after resection of glioblastomas with opening of the ventricles?

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Received: 10 October 2015 / Accepted: 22 January 2016 / Published online: 30 January 2016
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Abstract Extensive surgical resection of centrally localized, newly diagnosed glioblastoma can lead to opening ventricles and therefore carries a potential risk of spreading tumor cells into the cerebrospinal fluid. However, whether ventricle opening consequently implies a greater frequency of distant tumor recurrence after radiation therapy—and, therefore, reduced survival—remains unknown. Therefore, is an adaption of target volumes in radiation therapy necessary to account for a potential tumor cell spread into the ventricle system? The present study assessed the resection statuses of 311 primary-glioblastoma patients who underwent radiation therapy. Overall, in 78 cases (25.1 %) the ventricle system was opened during surgical resection. This study assessed the connection between ventricle opening and *progression-free survival*, *overall survival*, and distant and multifocal recurrence. OS rates of patients that

underwent *gross total resection* were superior to patients with *subtotal resection* ($p = 0.002$). PFS ($p = 0.53$) and OS ($p = 0.18$) did not differ due to ventricle opening during surgical resection. However, in a subsample of STR cases increased survival was observed when the ventricle system was opened (16.8 vs. 14.3 months; $p = 0.03$). The occurrence of distant ($p = 0.75$) and contralateral recurrence ($p = 0.87$) was not influenced by ventricle opening. Newly diagnosed glioblastoma patients whose ventricle systems were opened during microsurgical resection did not experience decreased survival or show increased likelihoods of distant and contralateral progressions following radiation therapy. In short, patients profit from surgical resections that are as extensive as reasonably possible, even if this entails ventricle opening. Thus, additional inclusion of the ventricles in the radiation therapy target volume after ventricle opening does not seem to be indicated.

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Keywords Glioblastoma · Ventricle system · Ventricle opening · Microsurgical resection · Radiotherapy · Target volume definition

Introduction

Glioblastoma (GBM) is the most common type of malignant primary brain tumor, has a very poor prognosis, and accounts for some 30 % of all central nervous-system tumors. It is true, of course, that, over the past decade, multimodal therapy based on genomic and metabolic characteristics and consisting of microsurgical resection, intensive adjuvant *radiation therapy* (RT), and *temozolomide* (TMZ) have improved outcome significantly. Yet, overall outcomes still remain poor, with a median survival time for GBM patients of 14.6 months [1]. *Gross total*

resection (GTR) or *subtotal resection* (STR) of macroscopic tumor masses is a prerequisite for receiving good responses to radiation therapy and chemotherapy and, therefore, for prolonged, *progression-free survival* (PFS) [2, 3].

Approximately half of all GBMs are located near the ventricular system. Infiltration of the lateral ventricle and subventricular zones, a neuronal stem-cell niche, are associated with decreased survival [4, 5]. Moreover, these tumors appear to present anatomically with higher rates of multifocal occurrence and distant recurrences than tumors without contact to the ventricle system [6, 7]; neural stem cells' adjacency to the lateral ventricles might account for SVZ tumors' invasiveness [8, 9].

GTR seems to be the primary cause of prolonged survival in glioblastoma cases. Consequently, the extent of surgical resection is mostly limited by anatomical boundaries and aim to preserve neurological function and patient health. In GBM, meanwhile, tumor mass tends to spread along cortical fibers, and therefore in some locations as the central region, toward the ventricle walls. In these cases neurosurgeons face the dilemma of having to remove the tumor mass as completely as possible without opening the walls of the ventricle system (Fig. 1), and might therefore result in tumor cell spread in the ventricles. Extensive GTR and STR periventricular-glioma resection might also lead to surgical entry into the ventricular system.

It is, as yet, unclear if extensive, ventricle-opening surgeries obviate the effects of extensive surgical resections by increasing the likelihood of ventricular associated complications and recurrence, and distant glioblastoma dissemination. To avoid trapping *cerebro spinal fluid* (CSF) in the resection cavity, ventriculostomies should

proceed with sufficient width so as to prevent a valve gear. Placing an external ventricular drainage into the cavity for possible rescue drainage can offer a sufficient solution. Most patients tolerate ventricle openings well and do not suffer significant side effects or other signs of deteriorated CSF circulation. Tumor-cell spread into the CSF bears the risk of more frequent distant-tumor recurrence, neoplastic meningitis [10, 11], spinal metastasis [12, 13], and hence, reduced survival.

Glioblastoma target volumes in radiation therapy generally cover *contrast-enhancing lesions* (CEL) on T1-weighted MRI as well as the T2-hyperintense regions. To account for microscopic tumor spread a safety margin of approximately 2 cm is added to the target volume. Ventricle structures are not considered accessorially.

Previous studies have reported that GBMs in close proximity to the ventricular system are related to reduced PFS [9, 14] and a higher risk of multifocal and distant progression [4, 6]. However, the impact of opening the ventricle system during microsurgical resection has not yet been systematically examined. Does an extensive surgical resection with potential ventricle opening allow for good therapeutic results, or does it negate the effects of gross-tumor resection and radiation therapy by potentially causing distant dissemination? Is the adaption of target volumes in radiation therapy necessary to account for potential cell spread in the CSF?

This study seeks to answer these questions by analyzing the impact of ventricle openings that have occurred during microsurgical resections for GBM on survival and recurrence patterns after radiation therapy.

Materials and methods

The study retrospectively analyzed 462 patients with histologically proven primary GBMs. All patients received RT or *chemoradiation* (CRT) according to the Stupp scheme [1] at University Hospital Heidelberg between 2006 and 2013.

A total of 151 patients (32.7 %) received diagnosis confirmation from stereotactic or open biopsy alone and were excluded from this analysis. After this, of the 311 patients (199 males and 112 females; median age: 59.1 years (range 17–87 years)) who initially underwent STR 190 cases (61.1 %) could be evaluated. GTR was achieved in the other 121 cases (38.9 %), and overall, in 78 cases (25.1 %) the lateral ventricle was opened during the first surgery (Table 1). O-6-methylguanine-DNA-methyltransferase (MGMT) promoter methylation statuses could be assessed in 189 cases (60.8 %). In 51 cases (41.8 %) a methylation of the MGMT promoter region could be identified.

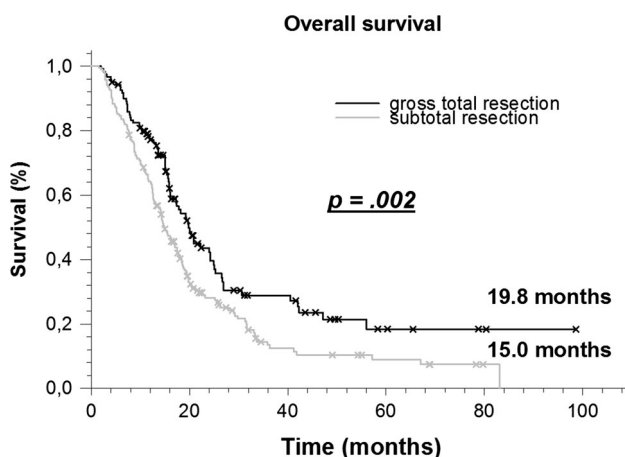


Fig. 1 Influence of surgical resection status on overall survival (OS) in glioblastoma patients. Gross total resection (GTR): n = 121, subtotal resection (STR): n = 190

Table 1 Patient characteristics of patients with glioblastoma with and without ventricle opening

	With ventricle opening (n = 78)	Without ventricle opening (n = 233)
Confactors		
Median age in years	60.3	60.7
Median Karnofsky performance scale	80 %	80 %
Gross total resection	32 (41.0)	89 (38.2)
Subtotal resection	46 (59.0)	144 (61.8)
TMZ–	19 (24.4)	66 (28.3)
TMZ+	59 (75.6)	176 (71.7)
Multifocality–	67 (87.0)	201 (87.0)
Multifocality+	10 (13.0)	30 (13.0)
n.e.	1 (1.3)	2 (1.0)
Subependymal spread–	50 (64.1)	199 (85.4)
Subependymal spread+	28 (35.9)	28 (12.0)
n.e.	0 (0)	6 (2.6)

Numbers in brackets represent percentages and refer to the absolute values in front

TMZ temozolomide

GTR (complete resection of the preoperative contrast-enhancing lesion) or STR (residual contrast-enhancing lesion) was defined based on MR-imaging generally performed within 48 h after surgery. *Ventricle opening* was defined as the creation of a discontinuity in the wall of the lateral ventricle and the ventricular system's communicating with the surgical cavity on MR-imaging or if noted in the surgical documentation.

Subsequently, all patients received RT with a median total dosage of 60.0 Gy (range 40.05–68.0 Gy), in fractions with a median of 2.0 Gy (1.8–3.0 Gy) once a day, five times per week. All studied patients completed the RT protocol. Influenced by patient heterogeneity several fractionation schemes were used during the period of investigation.

Median *Karnofsky performance status* (KPS) was 80 for both groups. Of the patients sampled, 226 (72.7 %) received concomitant RCHT with TMZ. 85 patients (27.3 %) did not receive TMZ due to various reasons (hypofractionated RT in elderly patients, poor performance status, comorbidities and refusal).

Preoperative MRIs, treatment-planning CTs and MRIs, and follow-up MRIs were available for all patients in the sample. Every patient also received a follow-up with contrast-enhancing MR imaging 1.5 months after undergoing the procedure and, successively, every 3 months until death. Target volume definition was performed

including the primary tumor, defined by all CEL on T1-weighted MRI as well as the T2-FLAIR-hyperintense regions. A safety margin of 2 cm was added to account for potential microscopic spread.

In accordance with RANO criteria (T1-weighted sequences with contrast medium on axial and coronal views), *progression-free survival* (PFS) was calculated as the period between the first radiotherapeutic treatment and the first appearance of local or distant progression based on MR imaging. If pseudo-progression was suspected, further MR imaging was necessary until progression was radiographically confirmed.

Overall survival (OS) was defined as the timespan between neuropathologic diagnosis and death. Tumor localization and relapse localization were determined with T1-weighted sequences with contrast medium on axial and coronal views. *Local progression* was defined as a recurrence occurring contiguous to the initial tumor, and *distant progression* was defined as a recurrence that was not non-contiguous to the initial lesion or in the contralateral hemisphere. KPS was determined at the time RT was initiated.

A Kaplan–Meier analysis was used to estimate PFS and OS in the period following surgical resection and RT. Univariate and multivariate regression models were used to calculate the hazards ratio and odds ratios, and corresponding 95 % confidence intervals for subgroup distribution. Statistical analyses were conducted using SigmaPlot12 (Systat Software Inc., San Jose, United States of America).

Ethics

All procedures were in accordance with the ethical standards of the responsible institutional and national committees on human experimentation and with the Helsinki Declaration of 1975 in its most recent version. The study was approved by the ethics committee, University of Heidelberg (No. S-056/2015).

Results

Median PFS for the sample was 9.2 months (range 7.7–10.7 months), and median OS was 17.0 months (range 15.3–18.7 months). Overall, in 78 cases (25.1 %) the lateral ventricle was opened during surgical resection. For these 78 cases the median PFS was 8.6 months (range 6.0–11.2 months), and their OS was 18.1 months (range 13.0–23.2 months) compared with an overall median PFS of 9.3 months (range 7.6–11.1 months; $p = 0.943$) and an overall median OS of 16.3 months (range 14.6–18.0 months; $p = 0.208$).

A subsample of 121 patients (38.9 %) underwent GTR. In this group, the ventricle was opened 32 times (26.5 %). In the group of 190 that underwent STR, the lateral ventricle was opened in 46 cases (24.2 %). No difference between PFS rates was observed for these subgroups. Notably, though, patients who experienced ventricle opening during STR enjoyed a significant increase in OS compared with patients who did not, with the former achieving a median OS of 16.8 months (range 10.9–22.7 months) versus the latter's achieving a median OS of only 14.3 months (range 12.6–16.1 months; $p = 0.029$) (Fig. 1). Univariate analysis for cofactors on PFS and OS are depicted in Table 2. PFS for patients who underwent GTR and STR did not differ significantly (8.7 vs. 6.9 months; $p = 0.262$), while OS rates for cases of GTR were superior to those for subtotal resection (19.8 vs. 15.0 months; $p = 0.002$). Finally, CRT with TMZ increased PFS rates (from 6.6 to 10.4 months; $p = 0.008$) and OS rates (from 12.5 to 19.3 months; $p < 0.001$) versus RT alone.

To validate the possible effects of ventricle opening on survival, a multivariate analysis was performed (Table 3). Interestingly, besides known prognostic cofactors [age ($p = 0.009$), TMZ therapy ($p = 0.048$), KPS ($p = 0.029$) and resection status ($p = 0.046$)] ventricle opening had a beneficial influence on survival rates (HR: 0.64; $p = 0.018$). Furthermore the present study grouped its subjects by favorable (age < 60 years; GTR) and unfavorable (age ≥ 60 years; STR) statuses. With regards to ventricle-opening status, though, no significant survival-rate difference between subgroups was observed (Fig. 2). Of note as well, there was an not significantly increased tendency toward improved survival for the favorable subgroup if the ventricle system was not opened (PFS: 10.3 vs. 6.0 months, $p = 0.53$; OS: 18.2 vs. 15.0 months, $p =$

0.811), while subtotally resected and young patients (< 60 years) seemed to enjoy not significantly increased OS if the ventricle system was opened (OS: 22.0 vs. 16.9 months, $p = 0.074$).

Distant progression was observed in 68 cases (27.8 %), whereas local disease progression was observed in 176 cases (72.1 %). After ventricle opening, progression was local in 42 cases (67.7 %) and distant in 20 cases (32.3 %), of which nine (14.5 %) were located contralateral non-contiguous to the initial lesion. Similar results were found for cases with surgeries during which ventricle opening did not occur: progression was local in 134 cases (73.6 %) and distant in 48 cases (26.4 %), of which 26 (7 %) were located in the contralateral hemisphere noncontiguous to the initial lesion. Patients without pretherapeutic ventricle involvement who underwent surgical resection with ventricle opening experienced ventricle involving relapses in 17.6 % (3/17) compared to only 4.1 % (4/104) in patients without ventricle opening ($p = 0.13$). However, opening the ventricle system in these patients did not negatively influence survival rates (PFS: $p = 0.38$; OS: $p = 0.62$).

It was observed that no statistical association existed between ventricle openings and distant recurrences (OR: 0.75, 95 % CI: 0.402–1.407, $p = 0.466$) and contralateral recurrences (OR: 1.02, 95 % CI: 0.449–2.31, $p = 0.869$).

Discussion

In its sample of over 300 primary glioblastoma patients, the present study found that ventricle openings neither negatively influenced progression-free intervals nor increased the occurrence of distant cerebral-glioblastoma dissemination following radiation therapy. On the contrary, cases

Table 2 Univariate proportional -hazards regression analysis of cofactors on progression-free and overall survival in glioblastoma patients

Cofactors	HR	95 % CI	P value
Univariate proportional-hazards regression analysis of cofactors associated with progression-free survival			
Age < 60 years	0.74	0.56–0.98	0.036
Karnofsky performance status > 70	0.86	0.66–1.17	0.527
Gross total resection	0.95	0.72–1.25	0.708
Ventricle opening	1.01	0.75–1.37	0.943
Temozolomide therapy	0.70	0.52–0.95	0.023
Univariate proportional-hazards regression analysis of cofactors associated with overall survival			
Age < 60 years	0.59	0.44–0.78	< 0.001
Karnofsky performance status > 70	0.75	0.54–0.96	0.007
Gross total resection	0.64	0.49–0.85	0.002
Ventricle opening	0.83	0.61–1.12	0.220
Temozolomide therapy	0.56	0.38–0.67	< 0.001

CI Confidence interval; HR hazard ratio

$>$ higher; $<$ lower

Table 3 Multivariate proportional-hazards regression analysis of cofactors on progression-free survival and overall survival in glioblastoma patients

Cofactors	HR	95 % CI	P value
Multivariate proportional-hazards regression analysis of cofactors associated with progression-free survival			
Age <60 years	0.74	0.50–1.08	0.120
Karnofsky performance status >70	0.84	0.62–1.47	0.327
Gross total resection	1.07	0.80–1.42	0.658
Ventricle opening	1.15	0.80–1.66	0.440
Temozolomide therapy	1.23	0.86–1.77	0.254
Multivariate proportional-hazards regression analysis of cofactors associated with overall survival			
Age <60 years	0.60	0.41–0.88	0.009
Karnofsky performance status >70	0.63	0.44–0.93	0.029
Gross total resection	0.74	0.58–1.00	0.046
Ventricle opening	0.64	0.45–0.93	0.018
Temozolomide therapy	0.71	0.50–1.00	0.048

CI Confidence interval; HR hazard ratio

> higher; < lower

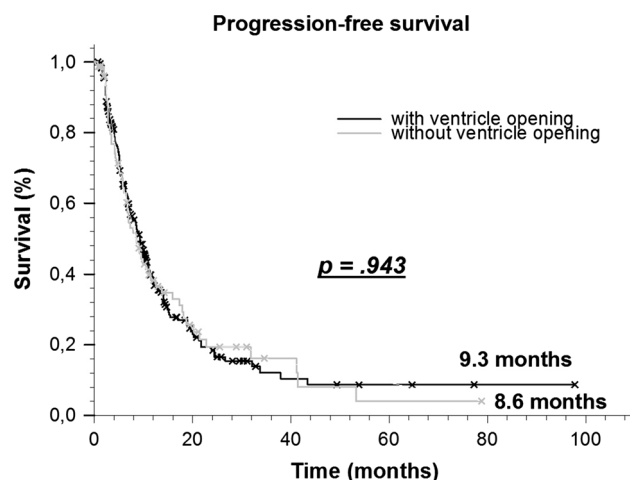


Fig. 2 Influence of ventricle opening during surgical tumor resection on progression-free survival (PFS) in glioblastoma patients. Ventricle opening: $n = 78$, reference group: $n = 233$

of younger patients with subtotal-resected tumors seem to profit for more aggressive surgical resections, as indicated by ventricle openings, by enjoying a tendency to prolonged progression-free intervals. Furthermore, the present data confirms that GTR results in superior outcomes when compared with STR [2, 15]. Aggressive surgical resection, as indicated by ventricle opening, showed a protective effect in STR cases.

Based on observational evidence, these results suggest that near-complete neurosurgical resection is beneficial, but randomized data are missing [6, 16, 17]. The optimal extent of surgical resection depends on multiple variables, amongst tumor localization, performance status and experience of the surgeon [2]. Moreover, selection bias is likely,

as patients with low performance statuses and unfavorable tumor localizations were more likely to receive tumor biopsies followed by primary CRT [16]. No statistically significant negative influence on survival rates with regards of a ventricle-system opening could be observed and validated in the univariate and multivariate analysis to account for potential bias. Interestingly, aggressive surgical resection, as indicated by ventricle openings, showed a protective effect in the multivariate analysis ($p = 0.018$). Here, removing as much macroscopic tumor tissue as reasonable achievable might be reason for the protective effect of ventricle openings during surgery. Furthermore, tumor localization in regard of neurological functions is crucial for the decision of the neurosurgical procedure. GBM located in eloquent cerebral regions may benefit of a subtotal resection with preservation of neurological functions [18]. However, reduction of tumor mass is an important predictor for improved survival [2, 19, 20]. Our survival results for patients that underwent GTR (19.8 months) and STR (15.0 months) are comparable to the cited literature [2, 18–22].

Our data indicate that removing macroscopic glioma tissue as completely as possible is a crucial part of the multimodal therapy and that GTR resulting in opening the ventricle system did not impair survival rates. Hence intraoperative MR-imaging [23] to evaluate the extend of tumor resection and fluorescence-guided surgery (FGS) with 5-aminolevulinic acid (5-ALA) [24] to visualize tumor tissue are widely used to optimize surgical management. Real-time evaluation of neurological function per awake craniotomy with electrophysiological mapping can help to achieve good tumor removal in critical areas while preserving neuronal function [25]. On the contrary,

aggressive subtotal-resected young patients who experience ventricle-system opening showed a tendency to increased survival when compared with those who did not. This finding might be explained as resulting from the reduced tumor mass that accompanies aggressive surgical interventions [2] in which the neurosurgeon decides to open the ventricle system. In general, tumor resection of periventricular gliomas bear the risk of opening the ventricle system. The majority of patients tolerate ventricle-wall discontinuation and do not experience deteriorating CSF circulation. Thus, possible tumor-cell spread into the CSF is likely associated with life-limiting disease patterns like distant and multifocal tumor recurrence [7], neoplastic meningitis, and spinal metastasis [26]. We could not observe a prognostic influence of ventricle opening during surgery in regard of distant of multifocal recurrence. Recurrence of GBM mainly occurs locally [6, 27, 28], but approximately 10 % are diagnosed in distant localizations [6, 29]. Another topic that merits further investigation is the occurrence of neoplastic meningitis following ventricle openings, and this will be addressed separately. MGMT promoter status, one of the strongest prognostic factors for survival, could not be determined in a great proportion of the collective and might therefore present a potential bias in the survival analysis.

From the perspective of a radiation oncologist it is still unclear if the target volume has to be adapted after ventricle opening. Including ventricles into the clinical target volume if the tumor involves the ventricle walls may be a potential approach to account for potential tumor cell spread into the CSF. However, this intervention increases the radiation dose on normal tissue that should be spared and therefore has to be assessed critically. Further investigations of target volumes, treatment plans and dose distributions are needed to elaborate if an adaption of treatment volumes is necessary, especially in patients with ventricle involvement and ventricle opening.

This work cannot answer the abovementioned question with absolute certainty; however our data could not show a negative association between ventricle opening, survival and recurrence patterns, and therefore modifications of treatment volumes do not appear to be reasonable. We planned to assess the RT treatment volumes and their association with the ventricles in a next step. However, on base of this study a wider radiation field in regard of ventricle involvement or surgical ventricle opening is not indicated for any subgroup.

In summary, the present data show there is no negative influence of opening the ventricle system during microsurgical glioblastoma resection and patient survival after radiation therapy. Furthermore, ventricle opening was not associated with higher rates of distant and multifocal progression. Therefore, our results highlight the importance of

a reasonable extensive resection, even if this entails ventricle opening. Based on these data additional inclusion of the ventricles in the radiation therapy target volume after ventricle opening does not seem justified for any subgroup.

Author's contribution CSJ, AU, SEC, SR and JD treated the patients. SA and CD collected the data. SA and JD evaluated the dataset and performed statistical analysis. SA, CSJ, CD, SR, SEC and JD wrote and edited the manuscript. All authors read and approved the final version of the manuscript.

Compliance with ethical standards

Conflict of interest The author(s) indicated no potential conflicts of interest.

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