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# Impact of subventricular zone irradiation on outcome of patients with glioblastoma

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> Abstract

**Purpose:** Glioblastoma (GBM) is characterized by early relapse and mortality. Treatment resistance could be a characteristic exhibited by pro-genitor neoplastic cells that reside in the subventricular zone (SVZ). This retrospective study was conducted to assess the correlation of SVZ doses and survival in patients with GBM.
**Materials and Methods:** Forty-seven patients with GBM treated with radiotherapy, concurrent and adjuvant temozolomide therapy, and whose dosimetry data were available were included. The ipsilateral and contralateral SVZs were delineated on co-registered magnetic resonance imaging-computed tomography images as a 5-mm margin along the lateral wall of the lateral ventricles. Median radiotherapy dose prescribed was 59.4 Gy. The mean ipsilateral, contralateral, and bilateral SVZ doses were 56.3 Gy (range 33–63 Gy), 50.4 Gy (range 23–79 Gy), and 52 Gy (28–69 Gy). The progression-free survival (PFS) and overall survival (OS) were calculated from the date of surgery to the date of radiologic and/or clinical progression and death/last follow–up, respectively. Survival probability was estimated using the Kaplan–Meier method. Log-rank test was used to test the significance between groups. Cox proportional hazards analyses were used to identify prognostic factors.
**Results:** At a median follow-up of 19 months, all patients had relapsed. Most recurrences were infield ($n$ = 39). The median PFS and OS were 17 and 19 months, respectively. The PFS and OS at 2 years were 36.2% and 21.3%, respectively. Patients who received ipsilateral SVZ dose of ≥56 Gy appeared to have better but nonsignificant median PFS and OS. Patients receiving contralateral SVZ doses ≥50 Gy showed a similar trend. Only the number of adjuvant temozolomide (≥6 cycles) showed prognostic impact.
**Conclusion:** This retrospective study indicated a trend toward improved–albeit nonsignificant–survival with higher dose to the ipsilateral and contralateral SVZs. A well-designed prospective randomized study is required to identify patients who would benefit from intentional SVZ targeting.

**Keywords:** Glioblastoma, radiotherapy, subventricular zone

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## > Introduction

Glioblastoma (GBM) is the most common primary brain tumor in adults. Surgery followed by radiotherapy with concurrent and adjuvant chemotherapy with temozolomide is the standard of care for newly diagnosed GBMs.[1] GBMs are highly aggressive tumors, with early relapse and mortality being the norm. Attempts to enhance survival including radiation dose escalation, direct interstitial implantation, particle beam therapy, alternate chemotherapy, biological targeting, and gene therapy have failed to improve outcome.

GBM resistance has been postulated to be due to the presence of pro-genitor neoplastic cells that exhibit an inherent resistance to radiotherapy and chemotherapy. These cells are considered to primarily reside in the subventricular zone (SVZ). The fact that certain tumors were found to be in contact with the SVZ at presentation and recurrence lends credence to this theory. With increasing data showing the SVZ as the site of self-renewal and tumor propagation, treatment directed at SVZ is expected to potentially reduce recurrences. This study was designed to assess the impact of SVZ irradiation on the progression-free survival (PFS) and overall survival (OS) of patients with GBM who underwent radical radiotherapy and chemotherapy. The study was approved by the Institutional Review Board.

## > Materials and Methods

Patients with histopathology proven GBM treated during January 1, 2010–December 31, 2012, were identified from the Hospital Cancer Registry database. Among a total of 220 patients, those who received radical radiotherapy by computed tomography (CT)-based planning (three-dimensional conformal radiotherapy/intensity-modulated radiotherapy/volumetric-modulated arc therapy) for whom complete dosimetry data were accessible and received concurrent temozolomide and adjuvant temozolomide for at least 6 months were considered eligible for this study. Patients who progressed while on treatment or had to discontinue treatment due to unacceptable toxicity were included. Patients who discontinued treatment with radiotherapy and/or temozolomide due to reasons other than progression or unacceptable toxicity were excluded from the study.

Forty-seven patients who met the stated criteria were included in this analysis. The median age was 52 years (19–58 years). There were 33 males and 14 females. Twenty-six patients (55%) had WHO performance status (PS) score of 1 at presentation and 15 and 6 patients were of PS scores 2 and 3, respectively. Multiple ipsilateral cerebral lobes were involved in 15 patients. Forty-one patients had tumors that were in contact with the lateral ventricle on preoperative imaging.

Forty-one (87%) patients had gross total resection of the tumor. Three patients each had subtotal resection and biopsy. The median radiotherapy dose prescribed was 59.40 Gy at 180 cGy/fraction (range: 55–59.4 Gy). All the 47 patients had completed the planned radiotherapy with concurrent temozolomide. One patient had treatment interruption of 12 days during radiotherapy due to seizures, but was able to resume and complete the treatment. After completion of radiation, patients received adjuvant temozolomide at dosage of 150 mg/m$^2$ for cycle 1 and at 200 mg/m$^2$ for subsequent cycles. Out of the 47 patients, 19 received 6 cycles of chemotherapy. Fifteen patients received >:6 cycles, out of which 13 patients completed 12 cycles. Thirteen patients received <:6 cycles. No patients had been tested for methylguanine-DNA methyltransferase status.

The magnetic resonance imaging-CT co-registered virtual simulation images and treatment plans of these 47 patients were retrieved from the treatment planning system. The ipsilateral and contralateral SVZs were retrospectively contoured on the CT images. The SVZ contour was defined as a 5-mm margin along the lateral wall of the lateral ventricles [Figure 1]. The average ipsilateral, contralateral, and bilateral SVZ volumes were 5.5 cm$^3$, 6.1 cm$^3$, and 11.6 cm$^3$, respectively. The mean ipsilateral, contralateral, and bilateral SVZ doses were 56.3 Gy (range: 33–63 Gy), 50.4 Gy (range: 23–79 Gy), and 52 Gy (range: 28–69 Gy), respectively.

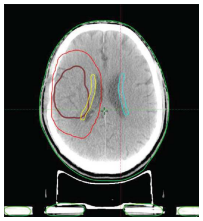

Figure 1: Delineation of the subventricular zone in the planning computed tomography (brown-clinical target volume, red-planning target volume, yellow-ipsilateral subventricular zone, cyan blue-contralateral subventricular zone)

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### Statistical analyses

Data analysis and statistical tests were completed with SPSS software (version 11.0, SPSS Inc., LEAD Technologies, Inc., US). The study end points of PFS and OS were calculated from the date of surgery to the date of radiologic and/or clinical progression and death/last follow–up, respectively.

Age, performance status, and extent of surgical resection were tested as covariates as they are known to impact survival. In addition, tumor contact with lateral ventricle, number of adjuvant chemotherapy cycles, and dose received by ipsilateral and contralateral SVZs were assessed for prognostic

significance. The survival probability was estimated using Kaplan–Meier method. To test the significance between different groups in the prognostic factors, log-rank test was used. Univariate Cox proportional hazards analysis was used to identify the relative risk among the prognostic factors for PFS and OS.

## > Results

The median follow-up was 19 months (range: 3–46 months). All patients relapsed. Thirty-two patients (68.1%) relapsed after completion of planned treatment and 15 patients (31.9%) relapsed during the adjuvant temozolomide phase. Most recurrences were infield ($n$ = 39). Four patients each had ipsilateral recurrence outside radiotherapy field and at distant brain site.

The median PFS for the entire cohort was 17 months (range: 14–19 months). The 1- and 2-year PFS were 63.8% and 21.3%, respectively. The median OS was 19 months (range: 14–23 months). The 1- and 2-year OS rates were 68.1% and 36.2%, respectively.

### Ipsilateral subventricular zone dose

The dose for stratification based on ipsilateral SVZ dose was considered as 56 Gy according to the mean dose distribution. Twenty-four patients received dose of ≥56 Gy. The median PFS of patients who received ≥56 Gy was 17 months (range: 14–19 months) as compared to 15 months (range: 6.5–23.4 months) for the 23 patients who received <:56 Gy. The corresponding PFS was 29.2% versus13% ($P$ = 0.178) at 2 years [Figure 2].

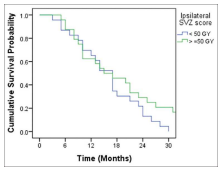


Figure 2: Progression-free survival correlation with ipsilateral subventricular zone dose

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The median OS was 19 months (range: 12–21 months) for SVZ dose of ≥56 Gy compared to 17 months (range: 5–32 months) for <:56 Gy. The respective OS were 45.8% and 26.1% at 2 years [Figure 3]. An ipsilateral SVZ dose of ≥56 Gy trended toward improved OS ($P$ = 0.116; hazard ratio [HR] =0.61; and 95% confidence interval [CI]: 0.33–1.13) and PFS ($P$ = 0.20; HR = 0.67; 95% CI: 0.36–1.23).

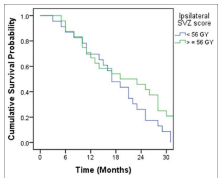


Figure 3: Overall survival according to ipsilateral subventricular zone dose

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### Contralateral subventricular zone dose

Patients were stratified as those who received contralateral SVZ dose of ≥50 Gy and <:50 Gy according to the mean distribution. The median PFS was 17 months (range: 14.1–19.8 months) versus 12 months (range: 8–15.9 months) for the ≥50 Gy and <:50 Gy groups, respectively. The median OS was 21 months (range: 16.1–25.8 months) versus 15 months (range: 7.1–22.8 months), respectively. The 2-year PFS and OS of patients who received contralateral SVZ dose <:50 Gy were 17.4% and 30.4%, respectively. For the patients who received ≥50 Gy, the PFS and OS at 2 years were 25% and 41.7%, respectively [Figure 4] and [Figure 5]. Patients who received contralateral SVZ dose of ≥50 Gy appeared to have better OS ($P$ = 0.16; HR = 0.65; 95% CI: 0.36–1.18) and PFS ($P$ = 0.14; HR = 0.64; 95% CI: 0.35–1.15).

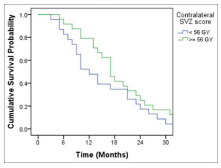


Figure 4: Progression-free survival correlation with contralateral subventricular zone dose

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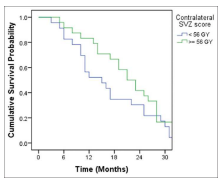


Figure 5: Overall survival according to contralateral subventricular zone dose

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Analyses of known prognostic factors such as age (≤50 years vs. >:50 years), performance status, and extent of surgery showed improved–albeit nonsignificant–outcomes for younger age, better performance status, and gross total resection [Table 1].

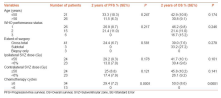

Table 1: Progression-free survival and overall survival according to prognostic factors

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Majority of the patients (87%) had tumor in contact with lateral ventricle. The PFS and OS for those patients were 19.5% and 36.6% at 2 years, respectively. The remaining six patients had no recurrence at 1 year and 33% were recurrence free at 2 years. Patients who received >:6 cycles of chemotherapy had statistically significant difference in survival. The PFS of patients who received >:6 cycles was 88.2% and 29.4% at 1 year and 2 years, respectively. The corresponding OS was 94.1% and 50%, respectively.

## > Discussion

Over the years, the radiotherapy treatment volumes for GBM have evolved from a historical whole-brain + boost approach to partial-brain irradiation. The optimal margin to be used is not yet clearly defined. The Radiation Therapy Oncology Group defines a much larger volume for treatment than the European counterparts. However, routine targeting of the SVZ is not practiced.

Recent interest in SVZ as a component of the clinical target volume emerged from the recognition that the cancer stem cells residing in SVZ dose may to some extent be responsible for tumor regrowth and recurrence. Studies published by Lim *et al*. and Adeberg *et al*. on large number of patients have reported that those with tumor in contact with the SVZ/lateral ventricle had a worse prognosis.[2],[3] In this study of 47 patients, 87% had tumor in contact with the lateral ventricle. The PFS and OS for those patients were 58.5% and 63.4% at 1 year but 19.5% and 36.6% at 2 years, respectively. The remaining six patients had no recurrence at 1 year and 33% were recurrence free at 2 years.

There are conflicting reports regarding the impact of SVZ dose on survival. A study published by Gupta *et al*. in 2012 reported that mean ipsilateral SVZ dose was an independent predictor of survival and that increasing mean dose to the ipsilateral SVZ could potentially improve OS.[4] They also observed worse PFS and OS for patients who received a higher than median of mean contralateral SVZ dose.

Two larger studies published in 2013 described benefit for higher ipsilateral SVZ doses. Chen *et al*. reported statistically longer PFS for 21 patients whose ipsilateral SVZ doses exceeded 59.4 Gy, but there was no effect on OS.[5] Lee *et al*. found that mean ipsilateral SVZ doses of >:40 Gy significantly improved both PFS and OS in patients who had undergone gross total resection.[6] In this study, there was an improved albeit nonsignificant PFS and OS when the ipsilateral SVZ received dose was ≥56 Gy. The same was noted for patients whose contralateral SVZ received 50 Gy or more. The small number of patients could account for the inability to demonstrate statistical significance.

However, another retrospective study published by Elicin *et al*. showed negative impact for higher contralateral SVZ dose (>59.2 Gy) on median PFS and OS for patients who underwent subtotal resection/biopsy.[7] High ipsilateral SVZ dose of >:62.25 Gy was associated with poor PFS in both subgroups of high performance status and SVZ without tumoral contact. They concluded that the available results on the subject are inconsistent and not compelling enough to warrant a change in the current clinical practice.

Another interesting fact is that in this study majority of the patients (87%) had tumor defined as the contrast enhancing edge-in contact with the lateral ventricle. In such cases, it is to be assumed that the target volume will by default include the SVZ and that this region will receive a higher dose and potentially result in improved outcomes. However, no such difference could be noted. Similar reports have been also published.[3],[8]

The only statistically significant factor noted in this study was the number of chemotherapy cycles. Patients who received 6 or more cycles had improved PFS and OS. It must be noted that among this cohort of 34 patients, 13 received 12 cycles of chemotherapy. Although all patients completed the planned concurrent chemotherapy, those who received <6 adjuvant cycles had a comparatively dismal outcome.

The main drawback of this study is its retrospective nature and small number of patients. The inclusion and exclusion criteria were intentionally designed to include only patients who were treated with a radical curative intent and for whom contemporary modern radiotherapy planning and delivery techniques were employed such that spurious results regarding possible benefits could be avoided. The cohort size was not adequate enough to demonstrate significant differences for even known prognostic factors such as age, performance status, or extent of surgical resection. This poses a question that given the positive trends noted could studies including larger number of patients determine advantage for higher SVZ doses.

All the available data put together appear to make a case for a well-designed prospective randomized controlled study addressing this issue and incorporating analyses of effect of known clinical and molecular prognostic factors in order to identify subsets of patients who would benefit most from intentional SVZ irradiation if at all. In the lack of published prospective results, adopting such an approach in clinical practice is likely to be more toxic and dangerous.

## > Conclusion

GBM poses a serious treatment challenge with bleak outcomes. The present study was aimed to assess the implications of higher dose irradiation of the stem cell niches in the SVZ and the potential benefits. This study showed that patients who received higher dose in the ipsilateral and contralateral SVZ showed a trend toward improved outcomes, although it did not reach statistical significance. The findings of this study are not practice changing. However, the implication that patients who receive higher SVZ doses may survive longer necessitates further evaluation in the form of a randomized prospective study.

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**Conflicts of interest**

There are no conflicts of interest.

> References


1. Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, *et al.* Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. Lancet Oncol 2009;10:459-66.
2. Lim DA, Cha S, Mayo MC, Chen MH, Keles E, VandenBerg S, *et al.* Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol 2007;9:424-9.
3. Adeberg S, König L, Bostel T, Harrabi S, Welzel T, Debus J, *et al.* Glioblastoma recurrence patterns after radiation therapy with regard to the subventricular zone. Int J Radiat Oncol Biol Phys 2014;90:886-93.
4. Gupta T, Nair V, Paul SN, Kannan S, Moiyadi A, Epari S, *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.
5. Chen L, Guerrero-Cazares H, Ye X, Ford E, McNutt T, Kleinberg L, *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.
6. Lee P, Eppinga W, Lagerwaard F, Cloughesy T, Slotman B, Nghiemphu PL, *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.
7. Elicin O, Inac E, Uzel EK, Karacam S, Uzel OE. Relationship between survival and increased radiation dose to subventricular zone in glioblastoma is controversial. J Neurooncol 2014;118:413-9.
8. Chaichana KL, McGirt MJ, Frazier J, Attenello F, Guerrero-Cazares H, Quinones-Hinojosa A, *et al.* Relationship of glioblastoma multiforme to the lateral ventricles predicts survival following tumor resection. J Neurooncol 2008;89:219-24.


Figures

[Figure 1], [Figure 2], [Figure 3], [Figure 4], [Figure 5]

Tables

[Table 1]



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