JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Radiation Oncology

Clinical Research Article

Patterns of Recurrence in Malignant Glioma Patients: Association with Subventricular Zone and Radiotherapy Dose

Hiroshi Igaki, M.D., Ph.D.,[1,2,*] Taiki Magome, Ph.D.,[2] Madoka Sakuramachi, M.D.,[2] Akihiro Nomoto, M.D.,[2] Akira Sakumi, Ph.D.,[2] Mayuka Kitaguchi, M.D.,[1,2] Akihiro Haga, Ph.D.,[2] Jun Itami, M.D., Ph.D.,[1] Keiichi Nakagawa, M.D., Ph.D.[2]

[1]*Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan*

[2]*Department of Radiology, The University of Tokyo Hospital, Tokyo, Japan*

**Corresponding author: Dr. Hiroshi Igaki, M.D., Ph.D. Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan, Tel: +81-3- 3542-2511; Email: hirigaki@ncc.go.jp*

Received: 06-22-2015

Accepted: 08-25-2015

Published: 09-01-2015

Abstract

Background: Recent studies suggest that a higher radiation dose to the subventricular zone (SVZ) is associated with a longer survival period in malignant gliomas. The purpose of this study was to analyze the patterns of tumor recurrence with respect to the SVZ and prescription dose of adjuvant radiotherapy.

Materials and methods: Seventy four patients with histopathologically-proven glioblastoma or anaplastic astrocytoma underwent gross-total or subtotal resection or biopsy, followed by adjuvant chemoradiotherapy with prescription doses of 60 Gy or 80 Gy. Tumors at initial presentation and at recurrence were determined as SVZ-contiguous or SVZ-non-contiguous according to magnetic resonance images.

Results: Patients' median age was 61 years (range, 5-83). Radiotherapy doses were 60 Gy and 80 Gy for 55 and 19 patients, respectively. There were 34 SVZ-contiguous and 40 SVZ-non-contiguous tumors at initial presentation, while at recurrence the counterparts were 36 and 20, respectively. At the time of this analysis, 18 patients have no evidence of recurrence. When treated with 60 Gy, SVZ-contiguous recurrence was more frequently observed for SVZ-contiguous initial tumors than SVZ-non-contiguous tumors (p = 0.016). Among 80 Gy patients, however, the corresponding difference as 60 Gy group was not observed, because SVZ-contiguous and –non-contiguous recurrences were comparable for SVZ-contiguous and -non-contiguous initial tumor groups (p = 0.95). Times to progression and survival were not significantly different between 60 Gy and 80 Gy groups and between SVZ-contiguous and –non-contiguous initial tumor groups.

Conclusions: SVZ-contiguous initial tumors are more prone to SVZ-contiguous recurrences than the SVZ-non-contiguous tumors when treated by 60 Gy, but such disproportion between SVZ-contiguous and –non-contiguous recurrences were not observed after 80 Gy of radiotherapy.

Keywords: Malignant Glioma; Subventricular Zone; Recurrence; Radiotherapy

Abbreviations

AA: Anaplastic Astrocytoma;
CTV: Clinical Target Volume;
GBM: Glioblastoma Multiforme;
GTV: Gross Tumor Volume;
KPS: Karnofsky Performance Status;
PTV: Planning Target Volume;
RPA: Recursive Partitioning Analysis;
SVZ: Subventricular Zone

Introduction

Malignant gliomas (glioblastoma multiforme and anaplastic astrocytoma) are the most common types of malignant brain tumors in adults, and are generally treated by maximal resection followed by concurrent chemoradiotherapy with temozolomide and 60 Gy of radiotherapy [1]. The treatment results of malignant gliomas are poor because the tumors recur from the initial tumor sites in a majority of the patients. Thus researchers have tried to deliver higher doses to the primary tumor, but in spite of such efforts at dose escalation, most of the trials have resulted in no apparent benefit. [2-4].

We also have tried dose escalation up to 90 Gy of radiotherapy for patients with malignant gliomas. Our previous study revealed that the patients who received 80-90 Gy of radiotherapy had significantly longer overall survival than those who received conventional radiotherapy of 60 Gy [5]. In addition, cerebrospinal fluid dissemination without local recurrence was significantly more frequent in patients with glioblastoma who received 90-Gy radiotherapy than in those who received 80 Gy or 60 Gy. This suggested that better local control of the primary tumor can result in longer survival in malignant glioma patients.

Cancer stem cells are supposedly radioresistant and derived from the neurogenic region such as the subventricular zone (SVZ) or subgranular zone [6-8]. Recent studies showed potential associations between higher radiation dose to the SVZ and a longer survival period [9-12]. It is conceivable that a higher radiation dose to the SVZ effectively decimates cancer stem cells in the SVZ. On this presumption local control would be improved by higher radiation doses to those primary tumors located adjacent to the SVZ over those tumors separated from the SVZ, because the SVZ would also receive higher radiation doses by virtue of its location adjacent to the primary tumor. To test this hypothesis, the patterns of recurrence were analyzed for the patients with malignant gliomas who received 60 Gy or 80 Gy of adjuvant radiotherapy, with respect to contiguity to the SVZ and prescription dose of radiotherapy.

Materials and Methods

Patient selection

Seventy four patients with histopathologically confirmed glioblastoma multiforme or anaplastic astrocytoma who had been treated at the University of Tokyo Hospital between 2002 and 2012 were included in this analysis. All patients underwent gross-total or subtotal resection or biopsy, followed by adjuvant chemoradiotherapy or radiotherapy alone with prescription doses of 60 Gy in 30 fractions or 80 Gy in 40 fractions at isocenter by 3-dimensional conformal radiotherapy. Patients' characteristics are shown in Table 1.

Table 1. Patients' characteristics.

Characteristics		60 Gy	80 Gy
Age (years)		5-83	25-71
	Median (years)	62	52
Male : Female		30 : 25	15 : 4
Pathology	Anaplastic astrocytoma	12	4
	Glioblastoma multiforme	43	15
RPA class	I	4	1
	II	5	3
	III	4	1
	IV	22	7
	V	15	6
	VI	5	1
Chemotherapy	Temozolomide	39	16
	Others	8	3
	None	8	0
SVZ-contiguity at initial presentation	Contiguous	24	10
	Non-contiguous	31	9

Abbreviations: RPA: Recursive partitioning analysis; SVZ: subventricular zone.

Treatment planning and contiguity to the SVZ

Gross tumor volume (GTV), clinical target volume (CTV) 1, and CTV2 were defined as a gadolinium-enhanced volume on T1-weighted magnetic resonance images (MRI) or resection cavity, high intensity volume on T2-weighted or fluid-attenu-

ated inversion recovery (FLAIR) images with a 1.5-cm margin, and GTV with a 1.5-cm margin, respectively. Planning target volume (PTV) 1 and PTV2 were made by expanding CTV1 and CTV2 with a 5-mm margin, respectively. PTV1 was treated initially to 50 Gy by 2-Gy fractions. Cone-down plans covering PTV2 followed thereafter to 60 Gy or 80 Gy. Each portal was modified to shield organs at risk at the discretion of the attending physician. Each plan was composed of 3 to 6 portals including non-coplanar beams in general.

When a gadolinium-enhanced tumor was involved in a part of the lateral wall of the lateral ventricles by gadolinium-enhanced T1-weighted images, the tumor was considered as contiguous to the SVZ. If the tumor was separated from the lateral wall of the lateral ventricles, the tumor was considered as non-contiguous to the SVZ (Figure 1). Contiguity to the SVZ was determined at the time of initial presentation of the disease as well as at the time of recurrence.

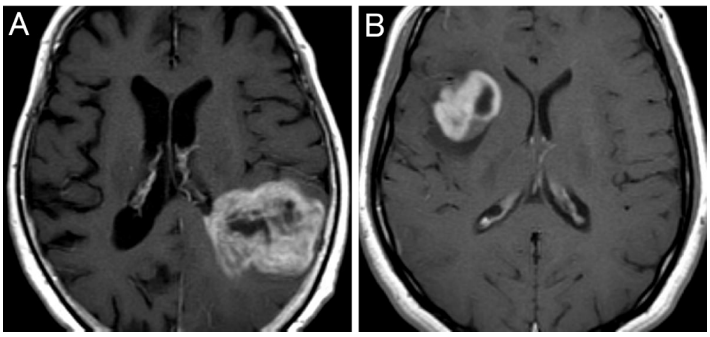


Figure 1. Definition of contiguity to the subventricular zone (SVZ). (A) Gadolinium-enhanced lesion of the tumor was involved in a part of the lateral wall of the lateral ventricle. Therefore, the tumor was classified as SVZ-contiguous. (B) The tumor was classified as SVZ-non-contiguous because the tumor was separated from the lateral wall of the lateral ventricles.

Outcome evaluation and statistical analysis

Times to progression and survival periods were calculated from the first day of radiotherapy. Tumor progression was determined as the first detection of an enlargement of a tumor by gadolinium-enhanced T1-weighted images. Survival rate and progression free rate were estimated by Kaplan-Meier method. The sites of recurrence were divided into 3 categories: within PTV2, outside PTV2 within PTV1, and outside PTV1.

Univariate and multivariate analyses were performed by log-rank and Cox proportional hazards analyses, respectively. *P* values of 0.05 or smaller were assumed as significant.

Results

Tumor's contiguity to the SVZ

There were 34 SVZ-contiguous and 40 SVZ-non-contiguous tumors at initial presentation. Hereafter, for the sake of brevity, SVZ-contiguous and SVZ-non-contiguous will be referred to as contiguous and non-contiguous, respectively. At the time of recurrence, 36 contiguous and 20 non-contiguous tumors were seen, and 18 patients currently have no evidence of recurrence at the time of this analysis.

Median time to progression and median survival time of all 74 patients was 13.3 months and 29.9 months, respectively. Progression free rates at 6 months, 12 months, and 24 months were 70.3%, 57.2%, and 34.1%, respectively. Overall survival rates at 6 months, 12 months, and 24 months were 95.9%, 84.5%, and 55.7%, respectively. For the patients with contiguous tumors at first presentation, progression free rates at 6 months, 12 months, and 24 months were 61.8%, 44.1%, and 31.5%, respectively, and overall survival rates at 6 months, 12 months, and 24 months were 91.2%, 75.5%, and 39.7%, respectively. For the patients with non-contiguous tumors at first presentation, progression free rates at 6 months, 12 months, and 24 months were 77.5%, 60.0%, and 36.4%, respectively, and overall survival rates at 6 months, 12 months, and 24 months were 100%, 92.2%, and 69.7%, respectively. There was a tendency for longer times to progression and survivals in patients with non-contiguous initial tumors than those with contiguous tumors, but the differences were not statistically significant (Figure 2).

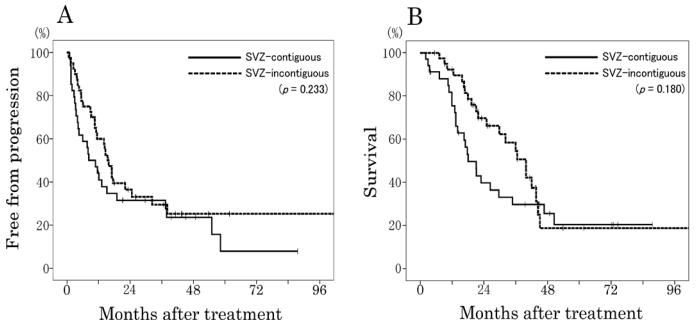


Figure 2. Kaplan-Meier curves of times to progression (A) and survivals (B) by SVZ-contiguity at initial presentation. There was a longer trend in patients with SVZ-non-contiguous tumors, but was not statistically significant.

The sites of recurrence were divided into three groups: inside PTV2, outside PTV2 within PTV1, and outside PTV1. The majority of the patients experienced recurrences within PTV2. Radiotherapy dose and contiguity to the SVZ at initial presentation were not predictive of the site of recurrence (Table 3).

Standard dose radiotherapy

When treated with 60 Gy, for the patients whose initial tumors were contiguous to the SVZ, 89% (16/18 patients) experienced contiguous recurrences. However, for patients with non-contiguous initial tumors, only 50% (11/22 patients) had

contiguous recurrences. Chi-square test revealed the significant difference in recurrence pattern between contiguous and non-contiguous initial tumors (p = 0.016) (Table 2).

Table 2. Sites of recurrence and the contiguity to the subventricular zone in recurrent tumor.

Dose	Contiguity to the SVZ at first presentation	# of patients	Median time to progression (months)	No recurrence	Recurrent tumor's contiguity to the SVZ		
					Contiguous	Non-contiguous	p value
60 Gy	Contiguous	24	4.5	6	16	2	0.016
	Non-contiguous	31	14.3	9	11	11	
80 Gy	Contiguous	10	10.8	1	5	4	0.95
	Non-contiguous	9	17.5	2	4	3	

Abbreviations: RPA: Recursive partitioning analysis.

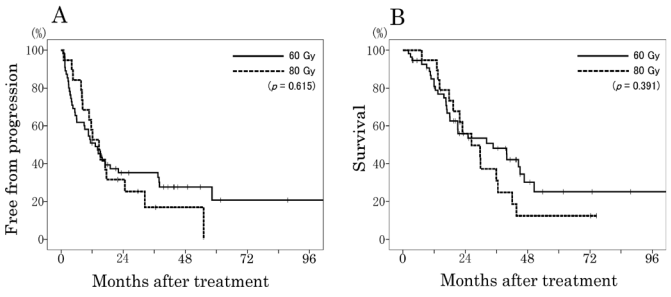
Table 3. Sites of recurrences with respect to the planning target volume.

Dose	Contiguity to the SVZ	Witin PTV2	Within PTV1, outside PTV2	Outside PTV1	No recurrence
60 Gy	Contiguous	17	0	1	6
	Non-contiguous	16	0	6	9
80 Gy	Contiguous	7	1	1	1
	Non-contiguous	5	1	1	2

Abbreviations: PTV: Planning target volume; SVZ: subventricular zone.

The progression free rates at 6 months, 12 months and 24 months were 65.5%, 50.9%, and 35.2%, respectively. The overall survival rates at 6 months, 12 months, and 24 months were 94.5%, 80.8%, and 55.9%, respectively (Figure 3).

Figure 3. Kaplan-Meier curves of times to progression (A) and survivals (B) by adjuvant radiotherapy dose. The differences were not statistically significant.



High dose radiotherapy

When treated with 80 Gy, contiguous and non-contiguous recurrences were comparable, irrespective of contiguity to the SVZ at initial presentation (p = 0.95 by chi-square test) (Table 2).

The progression free rates at 6 months, 12 months and 24 months were 84.2%, 57.9%, and 31.6%, respectively. The overall survival rates at 6 months, 12 months, and 24 months were 100%, 94.7%, and 55.8%, respectively (Figure 3).

Prognostic factors

With respect to time to progression, Karnofsky performance status (KPS) of 80 or greater was the only significant prognostic factor for all 74 patients in univariate (p = 0.004) and multivariate (p = 0.04) analyses. (Table 4). Tumor histopathology, higher radiation dose, extent of surgery, age, and tumor contiguity at initial presentation were not significant prognostic factors for time to progression. Although progression free rate at 6 months seemed better in 80 Gy than 60 Gy, the difference was not significant (p = 0.73) (Figure 3A).

Table 4. Summary of univariate and multivariate analyses.

	Factors		Univariate	Multivariate		
			p value	hazard ratio	range	p value
Time to progression	Histology	AA vs. GBM	0.266	0.718	(0.345-1.494)	0.376
	Radiotherapy dose	60 Gy vs 80 Gy	0.615	0.834	(0.452-1.539)	0.560
	Extent of surgery	Subtotal vs. others	0.079	1.431	(0.768-2.668)	0.259
	Age	<50 vs ≥50	0.401	0.937	(1.507-1.732)	0.837
	KPS	<80 vs. ≥80	0.004	1.949	(1.025-3.707)	0.042
	Contiguity to the SVZ at initial presentation	Contiguous vs. non-contiguous	0.233	1.255	(0.724-2.175)	0.419
Overall survival	Histology	AA vs. GBM	0.027	0.330	(0.134-0.813)	0.016
	Radiotherapy dose	60 Gy vs 80 Gy	0.391	0.807	(0.429-1.519)	0.507
	Extent of surgery	Subtotal vs. others	0.091	1.949	(1.000-3.801)	0.050
	Age	<50 vs ≥50	0.803	0.937	(0.468-1.873)	0.853
	KPS	<80 vs. ≥80	0.224	1.062	(0.498-2.263)	0.876
	Contiguity to the SVZ at initial presentation	Contiguous vs. non-contiguous	0.180	1.313	(0.703-2.453)	0.392

Abbreviations: AA: Anaplastic astrocytoma; GBM: Glioblastoma multiforme; KPS: Karnofsky performance status; SVZ: Ssubventricular zone.

Concerning survival, tumor histopathology of glioblastoma was a poorer prognostic factor than anaplastic astrocytoma for survival on univariate analysis (p = 0.027). On multivariate analysis, tumor histopathology (HR 0.33; 95% CI 0.13-0.81, p = 0.02) and extent of surgery (HR 1.95; 95% CI 1.00-3.80, p = 0.05) were significant prognostic factors for survival. Higher dose radiotherapy, age, KPS, and tumor contiguity at initial presentation were not significant prognostic factors for survival. (Table 4)

Discussion

We have demonstrated that contiguous initial tumors are more prone to contiguous recurrences than the non-contiguous tumors when treated by 60 Gy, but such disproportion between contiguous and non-contiguous recurrences were not ob-

served after 80 Gy of radiotherapy (Table 2).

The sites of recurrence in relation to the PTV were not influenced by radiation dose or contiguity to the SVZ (Table 3). Our results suggested that cancer stem cells located in the SVZ are likely to be decimated by 80 Gy of radiotherapy. However, this is not applicable to the glioma cells in the primary tumor site, because contiguous tumors in the 80 Gy group showed no tendency of contiguous recurrence, and exhibited similar progression free survival as patients with non-contiguous tumors (Table 2).

The progression free rates estimated by Kaplan-Meier method were not statistically different between 60 Gy and 80 Gy groups. But 80Gy group appeared to have a higher percentage of recurrence in general (Figure 3 and Table2). 15 out of 55 patients (27%) in 60 Gy group did not have recurrence, compared with 3 out of 19 patients (16%) in 80 Gy group. The possible reasons for this includes a small sample size bias and the difficulty in differentiation of local recurrences from radiation necrosis. Radiation necrosis was observed more often in the higher dose group [5]. In addition, it is difficult to differentiate radiation necrosis from local tumor progression only by diagnostic images. Accordingly, radiation necrosis without tumor progression might be diagnosed as recurrence in our series.

Malignant glioma was reported to have a tendency of recurring near the SVZ [13], which was also shown in our patients who had initial contiguous tumors and treated with 60 Gy. This can be explained by the presumption that the glioma cells from the SVZ where cancer stem cells are derived from migrate to the areas of recurrence [14, 15]. However, our patients with contiguous tumors who were treated with 80 Gy did not have an obvious tendency of contiguous recurrences (Table 2). In patients with contiguous tumors at initial presentation, greater portion of ipsilateral SVZ received higher radiation doses. In addition, higher dose of radiotherapy might kill radioresistant cancer stem cells located in the SVZ.

Several previous papers have reported that a higher radiation dose to the SVZ was associated with longer survivals or progression free survivals for the patients with glioblastomas [9-12]. Among these, Lee et al. reported the largest cohort study of 173 patients from two centers [12]. They demonstrated that 21 patients who received an ipsilateral SVZ dose > 59.4 Gy had significantly longer median progression-free and overall survivals. Gupta et al. and Chen et al. also described similar results of the analyses, although their threshold SVZ doses were different from that reported by Lee et al. [10, 11].

It is tempting to embrace the notion that cancer stem cells are derived from the SVZ in malignant glioma [14, 15], and that a higher radiation dose eradicated such cells in the SVZ. Nevertheless, we could not demonstrate a longer survival or time to progression of the patients with contiguous tumors treated by 80 Gy than 60 Gy of radiotherapy with a statistical significance. One of the reasons of failure to demonstrate benefit in these patients might be our method of analysis in dividing tumors into two groups of contiguous and non-contiguous tumors. SVZ involvement is reported to be associated with decreased survival or time to progression [16-18]. For this reason, the benefit of high dose radiotherapy might be negated in the patients with contiguous tumors. Other reasons of failure in this study to demonstrate benefit with 80 Gy of radiotherapy included a small number of the patients, patients' biases arising from the nature of retrospective analysis, and higher rate of morbidities caused by 80 Gy than with 60 Gy of radiotherapy [5]. In fact, 80 Gy of radiotherapy did not demonstrate better survival than with 60 Gy of radiotherapy in this series irrespective of tumor contiguity to the SVZ, inasmuch as the disciplines in radiotherapy planning were not different from a previous study [5].

Conclusions

Malignant gliomas with SVZ-contiguous initial tumors are more prone to SVZ-contiguous recurrences than the SVZ-non-contiguous tumors when treated by 60 Gy, but such disproportion between SVZ-contiguous and -non-contiguous recurrences were not observed after 80 Gy of radiotherapy despite the small number of patients analyzed in this series. There was also a difference in results for survival in high dose radiotherapy in this report and with our previous study [5]. Malignant gliomas probably have different characteristics clinically and biologically between SVZ-contiguous tumors and SVZ-incontiguous tumors [16-19]. In the next step, we are planning to analyze the recurrence patterns and survivals by SVZ dose using dose-volume histogram with further accrual of patients.

Conflict of Interest

The authors declare that they have no conflict of interests.

Acknowledgements

A part of this study was presented at American Society for Radiation Oncology 56th annual meeting.

This work was supported in part by Cancer Research and Development Fund of National Cancer Center 26-A-18.

References

1. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005, 352(10): 987-996.

2. Chang CH, Horton J, Schoenfeld D, Salazer O, Perez-Tamayo R et al. Comparison of postoperative radiotherapy and combined postoperative radiotherapy and chemotherapy in the multidisciplinary management of malignant gliomas. A joint radiation

therapy oncology group and eastern cooperative oncology group study. Cancer. 1983, 52(6): 997-1007.

3. Werner-Wasik M, Scott CB, Nelson DF, Gaspar LE, Murray KJ et al. Final report of a phase i/ii trial of hyperfractionated and accelerated hyperfractionated radiation therapy with carmustine for adults with supratentorial malignant gliomas. Radiation therapy oncology group study 83-02. Cancer. 1996, 77(8):1535-1543.

4. Souhami L, Seiferheld W, Brachman D, Podgorsak EB, Werner-Wasik M et al. Randomized comparison of stereotactic radiosurgery followed by conventional radiotherapy with carmustine to conventional radiotherapy with carmustine for patients with glioblastoma multiforme: Report of radiation therapy oncology group 93-05 protocol. Int J Radiat Oncol Biol Phys. 2004, 60(3):853-860.

5. Tanaka M, Ino Y, Nakagawa K, Tago M Todo T. High-dose conformal radiotherapy for supratentorial malignant glioma: A historical comparison. Lancet Oncol. 2005, 6(12): 953-960.

6. Galli R, Binda E, Orfanelli U, Cipelletti B, Gritti A et al. Isolation and characterization of tumorigenic, stem-like neural precursors from human glioblastoma. Cancer Res. 2004, 64(19):7011-7021.

7. Bao S, Wu Q, McLendon RE, Hao Y, Shi Q et al. Glioma stem cells promote radioresistance by preferential activation of the DNA damage response. Nature. 2006, 444(7120):756-760.

8. Facchino S, Abdouh M, Chatoo W Bernier G. Bmi1 confers radioresistance to normal and cancerous neural stem cells through recruitment of the DNA damage response machinery. J Neurosci. 2010, 30(30):10096-10111.

9. Evers P, Lee PP, DeMarco J, Agazaryan N, Sayre JW 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.

10. Gupta T, Nair V, Paul SN, Kannan S, Moiyadi A 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(1): 195-203.

11. Chen L, Guerrero-Cazares H, Ye X, Ford E, McNutt T 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(4): 616-622.

12. Lee P, Eppinga W, Lagerwaard F, Cloughesy T, Slotman B et al. Evaluation of high ipsilateral subventricular zone radiation therapy dose in glioblastoma: A pooled analysis. Int J Radiat Oncol Biol Phys. 2013, 86(4): 609-615.

13. Chen L, Quinones-Hinojosa A, Chaichana K, Ye X, Kleinberg L et al. Characterization of glioblastoma subventricular recurrence patterns. ASTRO abstract. 2013, 87(2):S17-S18.

14. Lim DA, Cha S, Mayo MC, Chen MH, Keles E et al. Relationship of glioblastoma multiforme to neural stem cell regions predicts invasive and multifocal tumor phenotype. Neuro Oncol. 2007, 9(4): 424-429.

15. Calabrese C, Poppleton H, Kocak M, Hogg TL, Fuller C et al. A perivascular niche for brain tumor stem cells. Cancer Cell. 2007, 11()1:69-82.

16. Chaichana K, Parker S, Olivi A Quinones-Hinojosa A. A proposed classification system that projects outcomes based on preoperative variables for adult patients with glioblastoma multiforme. J Neurosurg. 2010, 112(5): 997-1004.

17. Jafri NF, Clarke JL, Weinberg V, Barani IJ, Cha S. Relationship of glioblastoma multiforme to the subventricular zone is associated with survival. Neuro Oncol. 2013, 15(1):91-96.

18. Adeberg S, Bostel T, Konig L, Welzel T, Debus J 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.

19. Tchoghandjian A, Baeza-Kallee N, Beclin C, Metellus P, Colin C et al. Cortical and subventricular zone glioblastoma-derived stem-like cells display different molecular profiles and differential in vitro and in vivo properties. Ann Surg Oncol. 2012, 19 (Suppl 3): S608-S619.