

SPATIAL PROXIMITY BETWEEN SUBVENTRICULAR ZONE AND GLIOMA IN HUMAN PATIENTS

Rong Wang¹, Jiaqi Ma¹, Bolang Yu¹, Ed X. Wu², and Jian Yang¹

¹Department of Radiology, the First Affiliated Hospital of Medical College, Xi'an Jiaotong University, Xi'an, Shaanxi, China, People's Republic of; ²Laboratory of Biomedical Imaging and Signal Processing, The University of Hong Kong, Hong Kong SAR, China, People's Republic of

Introduction: Subventricular zone (SVZ) is the largest depot of neural stem cells (NSCs) in adult human brain [1]. Mounting evidence has indicated that brain tumor stem cells (BTSCs) exist in gliomas, which may be responsible for tumor growth, chemoresistance [2] and recurrence. Moreover, similar features among NSCs and BTSCs can be observed, such as self-renewing, multiplication, high motility and migration etc [3-4]. Furthermore, they share the same specific markers such as Nestin, CD133, musashi-1 and bmi-1 etc [5]. Therefore, it has been suggested that BTSCs arise from anomalous NSCs that reside in the SVZ [6-7]. An earlier study has demonstrated that malignant gliomas contain more BTSCs than low-grade gliomas [8]. This study aimed to examine the spatial relationship between SVZ and brain tumors (both gliomas of different grades and metastatic tumors) by MRI, and to examine the stem cells in different brain tumors by immunohistochemistry methods.

Method: In this retrospective study, 128 patients with 128 gliomas and 67 patients with 109 metastatic brain tumors were examined in our institution. Among them, all glioma patients and 6 patients with solitary metastatic brain tumors were verified by pathology. Other metastatic brain tumors were confirmed by history of external primary tumor. All imaging examinations were performed on a 1.5 T MRI (Philips Gyroscan) before neurosurgery. Each patient was analyzed based on the gadolinium-enhanced T1-weighted images to define brain tumor boundary. Non-enhanced lesions were excluded from this study. As a result, 118 patients (with 118 gliomas) and 67 patients (with 109 metastatic lesions) were retained for this study. To define SVZ, the wall of the lateral ventricle was divided into four regions: frontal horn, body, atrium/occipital horn, and temporal horn. The spatial relationship between tumor and SVZ was semi-quantitatively classified as contact or segregation based on whether tumor bordered with any one region of lateral ventricle. Results were statistically analyzed using SPSS. Comparisons were performed by Chi-square test, P value < 0.05 was considered to be statistically significant. Tumor tissues from 10 patients (9 gliomas and 1 brain metastasis) were processed for hematoxylin and eosin (HE) staining and immunohistochemical staining for nestin.

Results: The glioma group (48 women and 70 men, 11 to 73 years old with median age of 42 years) consisted of 20 cases of astrocytoma I, 51 cases of astrocytoma II, 39 cases of astrocytoma III and 8 cases of glioblastoma IV according to WHO classification. The metastatic tumor group included 37 men and 30 women (33 to 78 years old with median age of 59 years). Fig. 1 shows the typical gliomas of different grades that exhibited spatial proximity to SVZ with varying degrees. The ratios of such SVZ-contacting gliomas are shown in Table 1. In 26 patients, multiple regions of SVZ were in contact with gliomas, including 13 astrocytomas II and 13 gliomas III-IV. In four regions of SVZ, the frontal horn was the most commonly contacted region ($P < 0.05$) (Table 2). In 5 patients, the lateral ventricular lining in contact with mass showed enhancement. Among the 67 metastatic tumor patients, the ratio of tumor contacting lateral ventricular wall was 8.6%, significantly lower than that in glioma group ($P < 0.05$). Histological analysis indicated that the nestin expressions were relatively strong in III-IV grade of gliomas, weak in grade I-II astrocytomas and negative in metastatic brain tumor (Fig. 2).

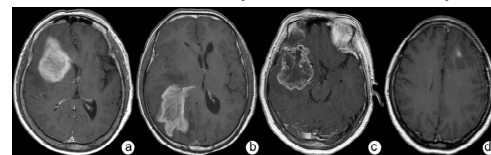


Fig 1. Typical gadolinium enhanced T1WI of gliomas with different grades.

a. astrocytoma III; b. astrocytoma II; c. glioblastoma; d. astrocytoma I.

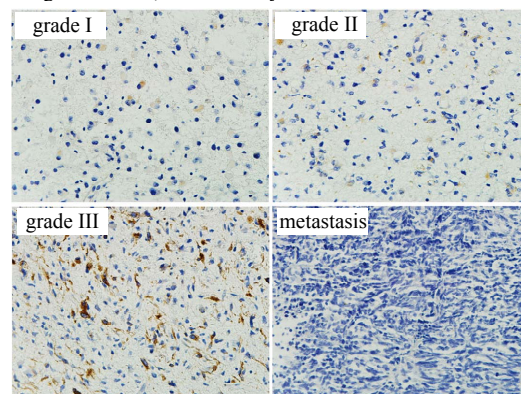


Fig 2. Immunohistochemical staining of nestin. (X400)

Table 1. SVZ-contacting ration based on gadolinium enhanced T1WI.

WHO classification	Contacting instances (%)	P-value
Astrocytoma I	10/20 (50%)	
Astrocytoma II	44/51 (86.3%)	
Glioma III-IV	42/47 (89.4%)	
Total	96/118 (81.4)	<0.001

Table 2. Proportion of gliomas contacting various regions of lateral ventricle.

Regions of lateral ventricular	Contacting instances (%)	P-value
Frontal horn	42 (35.7%)	
Temporal horn	19 (16.1%)	
Atrium/Occipital horn	41 (34.7%)	
Body	17 (14.4%)	
Total	119	<0.001

Discussion and Conclusion: In contrast to brain metastatic tumors, gliomas showed spatial proximity to SVZ. There was a positive correlation between glioma grades and the SVZ-contacting ratios. In this study, the most common SVZ region bordered glioma was the frontal horn. This was inconsistent with an earlier report [9]. The discrepancy may be attributed to the exclusion of gliomas with grade I in that study. In this study, immunohistochemistry analysis demonstrated that nestin-positive stem cells were present in glioma tissues, particularly in III-IV glioma tissue, but absent in the metastatic brain tumor tissue. In conclusion, this retrospective study indicated that gliomas exhibited spatial proximity to SVZ when compared to metastatic tumors, implicating and supporting the possibility that the genesis of gliomas and brain tumor stem cells may originate from the mutational NSCs in SVZ.

Reference: [1] Alvarez-Buylla A, et al., J Neurosci 2002; 22: 629-34. [2] Liu G, et al. Mol Cancer 2006; 5:67. [3] Singh SK, et al., Cancer Res, 2003, 63 : 5821-5828. [4] Singh SK, et al., Nature, 2004, 432: 396-401. [5] Wechsler-Reya R J., Recent Prog Horm Res, 2003; 58:227-248. [6] Sanai N, et al., N Engl J Med 2005; 353: 811-22. [7] Uchida K, et al., Neurosurgery 2004; 55:977-87. [8] Zhang M, et al., J Exp Clin Cancer Res 2008; 27:85. [9] Barami K, et al., J Clin Neurosci 2009; 16:195-201.