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Cortactin, Fascin and Survivin Expression Associated with Clinicopathological Parameters in Brain Gliosarcoma

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Abstract

Gliosarcoma is a very rare primary neoplasm of the central nervous system classified as a variant of glioblastoma. Cortactin, fascin and survivin have been found in several human cancers to play important roles in tumor progression, but the expression pattern of these biomarkers in gliosarcoma is unclear. Immunostaining for cortactin, fascin and survivin was assessed in 6 surgical specimens of brain gliosarcoma, and the relationship between the expression of these biomarkers and tumor size or clinical parameters were examined. Five of our six patients with gliosarcoma survived 3-17 months. One patient is still alive for more than 24 months. The mean immunostaining scores for cortactin were significantly higher in the gliomatous (score 236.6 $\pm$ 45.4) and sarcomatous (score 233.3 $\pm$ 51.4) components than in normal brain tissues (score 21.6 $\pm$ 6.6). The mean cytoplasmic immunostaining scores for fascin and survivin were also significantly higher in the gliomatous and sarcomatous components than in normal brain tissues. In addition, survivin was also stained in the nucleus of tumor cells. Linear regression analysis showed that fascin score in the gliomatous component was significantly associated with tumor size (R = 0.69) and the fascin score in the sarcomatous component was significantly associated with patient's age (R = 0.87). In addition, the survivin cytoplasmic scores in the gliomatous and sarcomatous components were inversely associated with tumor size. Our results demonstrated that over-expression of cortactin, fascin and survivin is associated with malignant transformation of brain gliosarcoma. Development of drugs that target cortactin, fascin and survivin expression may be therapeutic to patients with gliosarcoma.

Key Words: gliosarcoma, cortactin, fascin, and survivin

Introduction

Gliosarcoma is a very rare primary neoplasm of the central nervous system classified by the World Health Organization (WHO) as a variant of glioblastoma and is, therefore, a grade IV tumor (3, 16). It has been estimated that gliosarcomas constitute 2% of all glioblastomas with the peak incidence occurring from the fourth to the sixth decades of life (mean age, 53 years). The male-to-female ratio is 1.8:1 (13). It is a biphasic tumor displaying both malignant glial and sarcomatous components.

Cortactin, a protein binding to cortical actin, has been identified as a src kinase substrate (4, 23).

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Table 1. Clinicopathological characteristics of six patients with brain gliosarcoma

Case	Age (years)	Sex	Tumor size (cm)	Anatomic site	Symptom	Treatment	Survival time (months)
1	54	F	3.2	Right parietal	Right face numbness	Craniotomy	Alive (>24)
2	40	M	3.4	Left parietal	Headache, weakness of four extremities	Craniotomy +CCRT	9
3	67	F	4.3	Right frontal	Conscious but drowsy	Craniotomy +CCRT	15
4	50	F	4.0	Bilateral frontal	Headache	Craniotomy	17
5	46	F	3.0	Right occipital	Headache	Craniotomy	3
6	37	M	5.0	Midline temporal	Headache, right side weakness	Craniotomy +CCRT	3

M: Male; F: Female; CCRT: concurrent chemoradiation

By activating the actin-related protein 2/3 (Arp2/3) complex, cortactin participates in the regulation of actin cytoskeleton formation and thereby participates in mechanisms for controlling tumor cell migration, invasion and metastasis (26). The cortactin gene in the amplified chromosome 11q13 region plays a critical role in carcinoma motility and invasion (20, 21).

Fascin is an actin-binding protein found in membrane ruffles, microspikes and stress fibers (25). The expression of fascin is markedly increased in many transformed cells as well as in specialized normal cells such as neuronal cells and antigen-presenting dendritic cells (1, 25). Fascin expression is associated with enhanced cell adhesion and motility (1) and also with poor prognosis of esophageal carcinoma (24) and gastric adenocarcinoma (19).

Survivin was originally identified as an inhibitor of apoptosis protein (10). It is expressed in the G2/M phase of the cell cycle and inhibits cell death (10). Survivin is almost undetectable in normal adult tissues, but over-expression of survivin has been reported in almost all malignancies of humans including cancers of the lung, breast, stomach, esophagus, liver and ovary (2). A recent study has shown that expression of survivin is associated with poor prognosis of glioblastoma (8).

The expression patterns of cortactin, fascin and survivin in gliosarcoma are unclear. In this study, we investigated possible correlation between the immunostaining scores of these three biomarkers of brain gliosarcoma and clinicopathological factors.

Materials and Methods

Specimens of resected tumors from 6 patients with gliosarcoma (2 men and 4 women; age range, 37-67 years; mean age, 49 years) were collected between 1990 and 2008. Cases that received biopsy were excluded from this study due to limited specimen. The specimens of the 6 patients were at least 2 cm × 1 cm in size. The paraffin-embedded tumor tissues were obtained from the Department of Pathology, Tri-Service General Hospital. Brain gliosarcoma was graded according to the WHO classification of tumors, tumor of the nervous system (16). Other clinicopathological factors such as age, sex, tumor size and treatment modality are shown in Table 1. No patient received radiation or chemotherapy before surgery. All cases were positively stained for GFAP and vimentin, and were reviewed by at least two experienced pathologists to verify the pathological diagnosis.

Immunohistochemistry Stains

Tissue section slides were dewaxed in xylene, rehydrated in alcohol, and immersed in 3% hydrogen peroxide for 5 min to suppress endogenous peroxidase activity. Sections were heated for 30 min in 0.01 M sodium citrate buffer (pH 6.0) for antigen retrieval, rinsed 3 times, each for 5 min, in phosphate buffered saline [PBS]), incubated for 1 h at room temperature with a polyclonal rabbit anti-human cortactin antibody (1:100; Santa Cruz Biotechnology, Santa Cruz, CA, USA), monoclonal mouse anti-human fascin antibody (1:100; NeoMarkers, Fremont, CA, USA), and rabbit anti-human survivin antibody (1:100, R&D Systems, Wiesbaden, Germany), all diluted in PBS, washed (3 times, each for 5 min) in PBS, incubated with biotin-labeled secondary immunoglobulin (1:100; DAKO, Glostrup, Denmark) for 1 h at room temperature,

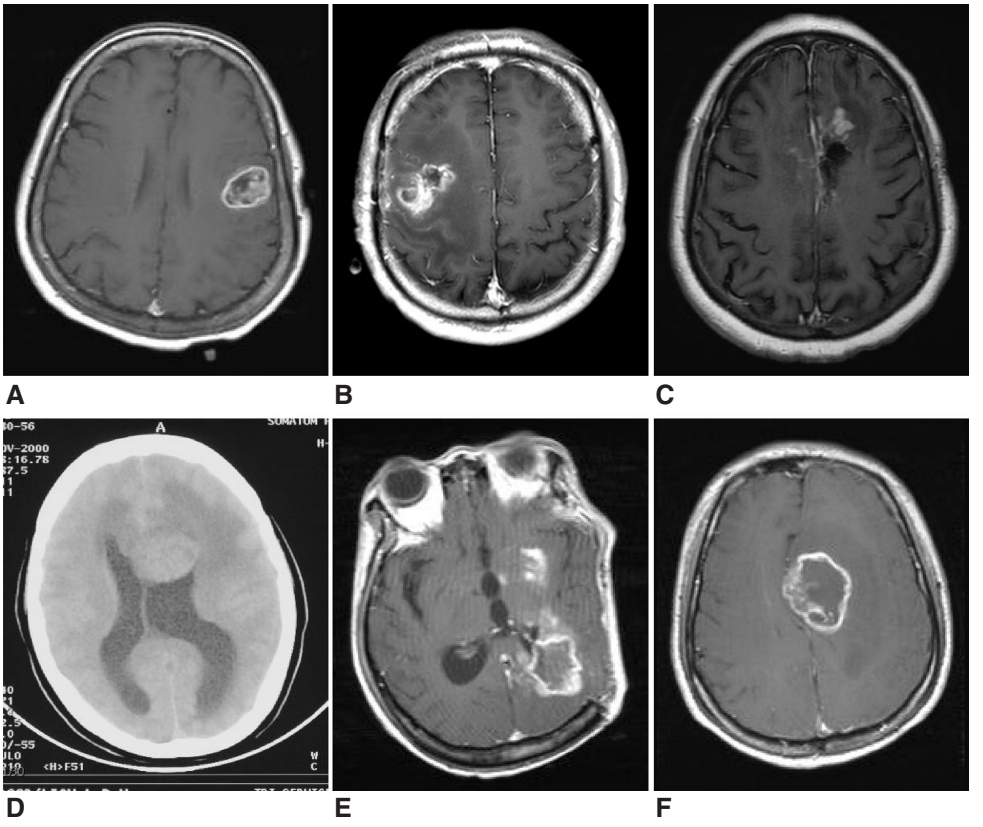

Fig. 1. Computer tomography (CT) or magnetic resonance image (MRI) of the six patients (A-F) with gliosarcoma. The tumor was located in the right parietal area (case 1, A), left parietal area (case 2, B), right frontal area (case 3, C), bilateral frontal area (case 4, D), right occipital area (case 5, E), and the midline temporal area (case 6, F).

washed 3 times, and treated with AEC+ substrate chromogen (DAKO) at room temperature to visualize peroxidase activity.

Cytoplasmic immunostaining intensity was assessed for cortactin, fascin and survivin on a scale of 0 (no staining) to 4 (strongest) based on the average intensity scale of at least two authors. Also, the percentage of cells at each immunostaining intensity was calculated on a scale of 0%, 25%, 50%, 75% and 100%. The immunostaining score, obtained by multiplying the percentage of cells by its corresponding immunostaining intensity, ranged from 0 to 400. In addition, for evaluation of nuclear stain for survivin, only the percentage nuclear stain for survivin was expressed.

Statistical Analysis

All results are presented as means ± standard error of the mean (SEM). The cortactin, fascin and survivin immunostaining scores for brain gliosarcoma were compared to the immunostaining score of normal brain tissue adjacent to the tumor, and their relationship to tumor size and patient's age were examined. Student's *t*-test was applied to establish possible statistical differences among the groups. A $P < 0.05$ value was considered to be statistically significant. Survival time was defined as the period from the date of surgery to the date of death. Statistical evaluations were performed by linear regression analyses. A $P < 0.05$ value was considered to be statistically significant.

Conflict of Interest

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Results

Clinicopathological Characteristics of Patients with Gliosarcoma

The clinicopathological characteristics of six patients with gliosarcoma are presented in Table 1. All patients received craniotomy, and patients 2, 3 and 6 also received concurrent chemoradiation. In the six patients, the tumor had a tendency to occur in the frontal-temporal-parietal lobe (Fig. 1). Five of

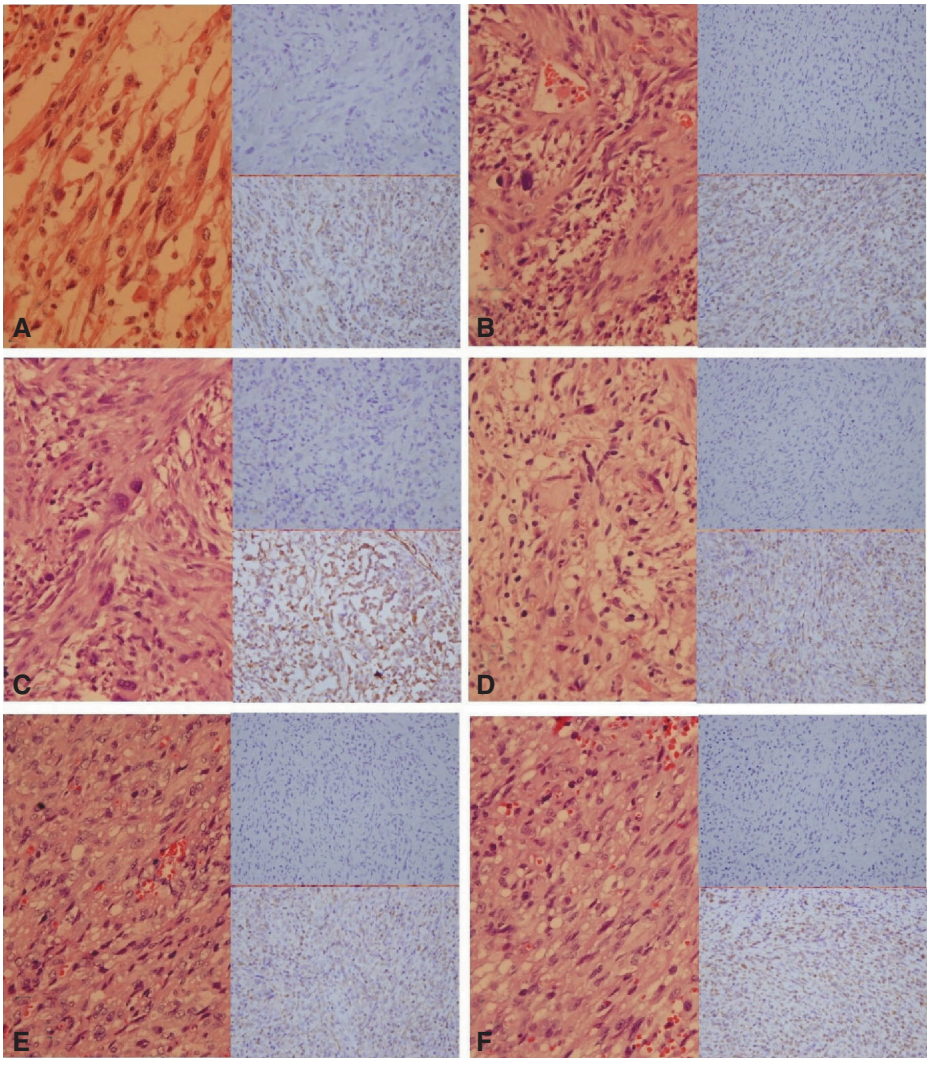

Fig. 2. Hematoxylin and eosin staining (A-F) and immunohistochemical staining of the sarcomatous component of six cases with brain gliosarcoma. Case 1 [A, upper panel (GFAP stain) and lower panel (vimentin stain)]; case 4 [D, upper panel (GFAP stain) and lower panel (vimentin stain)]; case 5 [E, upper panel (GFAP stain) and lower panel (vimentin stain)]; and case 6, [F, upper panel (GFAP stain) and l lower panel (vimentin stain)]. Case 2, [B, upper panel (GFAP stain) and lower panel (smooth muscle actin stain)]); and case 3, [C, upper panel (GFAP stain) and lower panel (smooth muscle actin stain)]. Original magnification × 400.

the six patients survived 3-17 months measured from the date of diagnosis. One patient is still alive with a survival period of more than 24 months.

The diagnosis of gliosarcoma was based on positive staining to glial fibrillary acidic protein (GFAP) in gliomatous component, and loss of GFAP stain in sarcomatous component with a concomitant positive staining for vimentin or smooth muscle actin. All the cases diagnosed as gliosarcoma were confirmed by at least two qualified pathologists.

Differentiation of Sarcomatous Component of Tumor

The differentiation of sarcomatous component of each case is presented in Fig. 2. Case 1 (panel A), case 4 (panel D), case 5 (panel E) and case 6 (panel F) show differentiation to fibrosarcoma with negative staining for GFAP (upper panel) and positive staining to vimentin (lower panel). In addition, case 2 (panel B) and case 3 (pane C) show differentiation to leiomyosarcoma with negative staining for GFAP (upper panel) and positive staining to smooth muscle actin (lower panel).

Expression of Cortactin in Gliosarcoma

Representative case (case 1) of the gliomatous component stained for cortactin are shown in Fig. 3B, while those of the sarcomatous component are shown in Fig. 4B. The cortactin staining intensity,

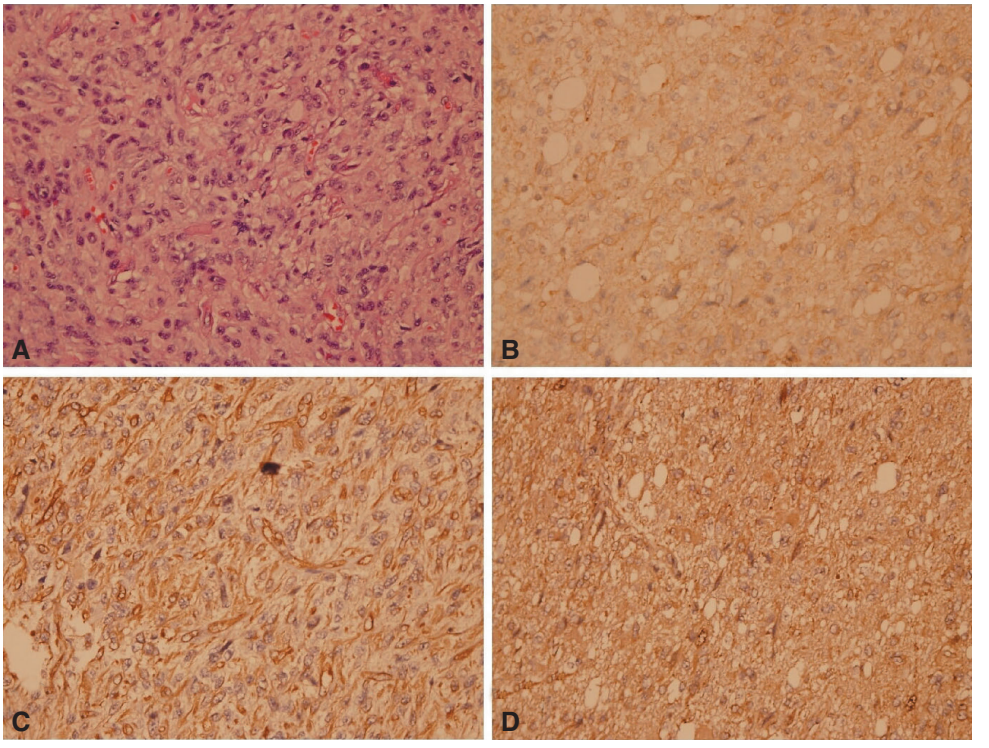

Fig. 3. Hematoxylin and eosin staining (A) and immunostaining for cortactin (B), fascin (C) and survivin (D) of the gliomatous component of a representative (case 1) brain gliosarcoma. Original magnification × 400.

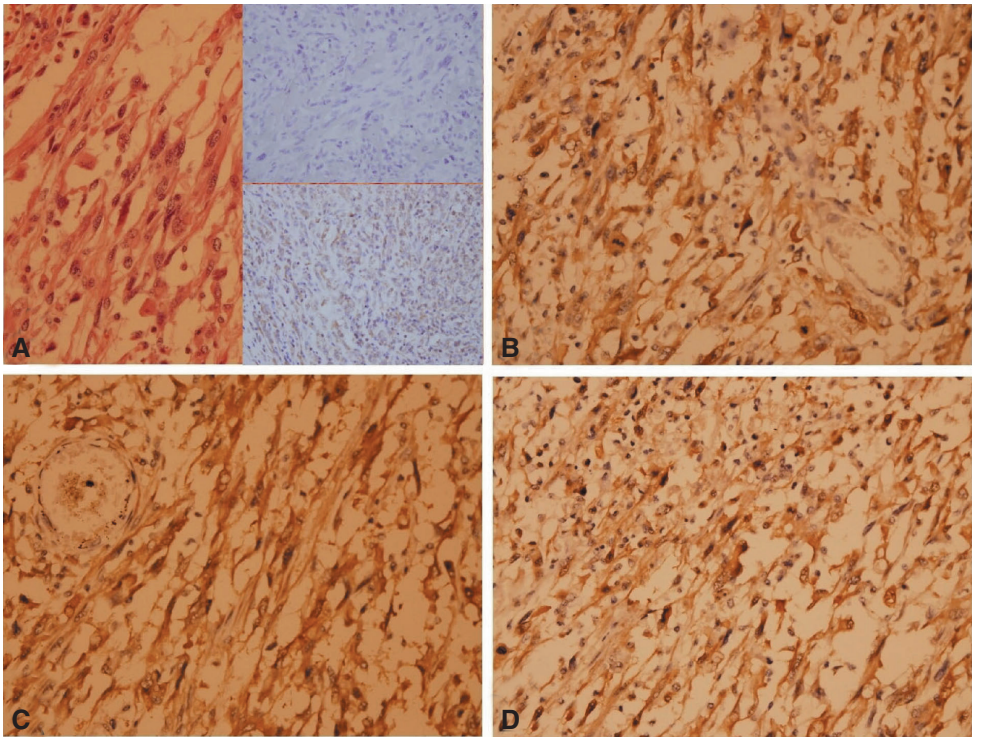

Fig. 4. Hematoxylin and eosin staining (A) and immunostaining for cortactin (B), fascin (C) and survivin (D) of the sarcomatous component of a representative (case 1) brain gliosarcoma. Upper panel of A (GFAP stain) and lower panel of A (vimentin stain). Original magnification × 400.

Table 2. Mean immunostaining scores of cortactin and fascin in the gliomatous component of brain gliosarcomas

Different staining	Staining pattern		
	Intensity	% staining	Total score
Cortactin staining			
Tumor (n = 6)	2.8 ± 0.4*	81.6 ± 3.4*	236.6 ± 45.4*
Normal brain (n = 6)	1.3 ± 0.2	15.0 ± 2.4	21.6 ± 6.6
Fascin staining			
Tumor (n = 6)	3.3 ± 0.5*	85.0 ± 8.4*	301.6 ± 61.1*
Normal brain (n = 6)	0.8 ± 0.2	16.6 ± 3.7	13.3 ± 4.6

Data are means ± standard error of the mean (SEM) of the immunostaining scores for cortactin and fascin in tumors and normal brain tissues. * indicates significant difference in cortactin and fascin expression between tumor and normal brain ($P < 0.05$).

Table 3. Mean immunostaining scores of cortactin, and fascin in the sarcomatous component of brain gliosarcomas

Different staining	Staining pattern		
	Intensity	% staining	Total score
Cortactin staining			
Tumor (n = 6)	2.7 ± 0.5*	85.0 ± 4.7*	233.3 ± 51.4*
Normal brain (n = 6)	1.5 ± 0.5	20.0 ± 4.0	33.0 ± 10.5
Fascin staining			
Tumor (n = 6)	2.7 ± 0.5*	86.6 ± 4.6*	235.0 ± 48.8*
Normal brain (n = 6)	0.8 ± 0.2	15.0 ± 2.4	12.3 ± 3.7

Data are presented as described in the footnote to Table 2.

percentage of cortactin positive cells and total scores are presented in Table 2 (for the gliomatous component) and Table 3 (for the sarcomatous component). The mean immunostaining score for cortactin was significantly higher in the gliomatous (score 236.6 ± 45.4) and sarcomatous (score 233.3 ± 51.4) components than in normal brain tissue (score 21.6 ± 6.6 and 33.0 ± 10.5, respectively).

Expression of Fascin in Gliosarcoma

Representative sections of the gliomatous component and sarcomatous component immunostained for fascin are shown in Figs. 3C and 4C, respectively. The fascin staining intensity, percentage of fascin positive cells, and total scores for the gliomatous and sarcomatous sections are presented in Tables 2 and 3, respectively. The mean immunostaining score for fascin was significantly higher in the gliomatous (score 301.6 ± 61.1) and sarcomatous (score 235.0 ± 48.8) components than in the normal brain tissue (score 13.3 ± 4.6 and 12.3 ± 3.7, respectively).

Expression of Survivin in Gliosarcoma

Representative sections of gliomatous component and sarcomatous component immunostained for survivin are shown in Figures 3D and 4D, respectively. The survivin cytoplasmic staining intensity, percentage of survivin positive cells, and total scores for the gliomatous and sarcomatous sections are presented in Table 4. The mean immunostaining score for survivin cytoplasmic stain was significantly higher in the gliomatous (score 198.3 ± 30.3) and sarcomatous (score 235.0 ± 15.4) components than in the normal brain tissue (score 26.6 ± 4.7 and 21.7 ± 1.7, respectively). The percentage nuclear stain for survivin was 7.6% for gliomatous component and 14% for sarcomatous component of gliosarcoma.

Correlation of Immunostaining Scores with Tumor Size and Patient's Age

Linear regression analysis of cortactin score for two groups (corresponding to the gliomatous component (Fig. 5a) and sarcomatous component (Fig. 5b) *versus* tumor size or patient's age found no significant between-group difference.

Linear regression analysis revealed strong correlation of fascin score (gliomatous component; Fig. 6a) with tumor size ($R = 0.69$, $P = 0.04$) and significant correlation of fascin score (sarcomatous

Table 4. Immunostaining scores of survivin in the gliomatous and sarcomatous components of 6 brain gliosarcomas

Different staining	Staining pattern		
	Intensity	% staining	Total score
Gliomatous component			
Cytoplasmic stain	2.3 ± 0.3	78.3 ± 4.0	198.3 ± 30.3*
Nuclear stain		7.6 ± 3.0	
Sarcomatous component			
Cytoplasmic stain	2.7 ± 0.1	86.7 ± 3.4	235.0 ± 15.4*
Nuclear stain		14.0 ± 3.8*	
Normal brain			
Cytoplasmic stain	1.0 ± 0.0	21.7 ± 1.7	21.7 ± 1.7
Nuclear stain		6.3 ± 2.8	

See footnote to Table 2.

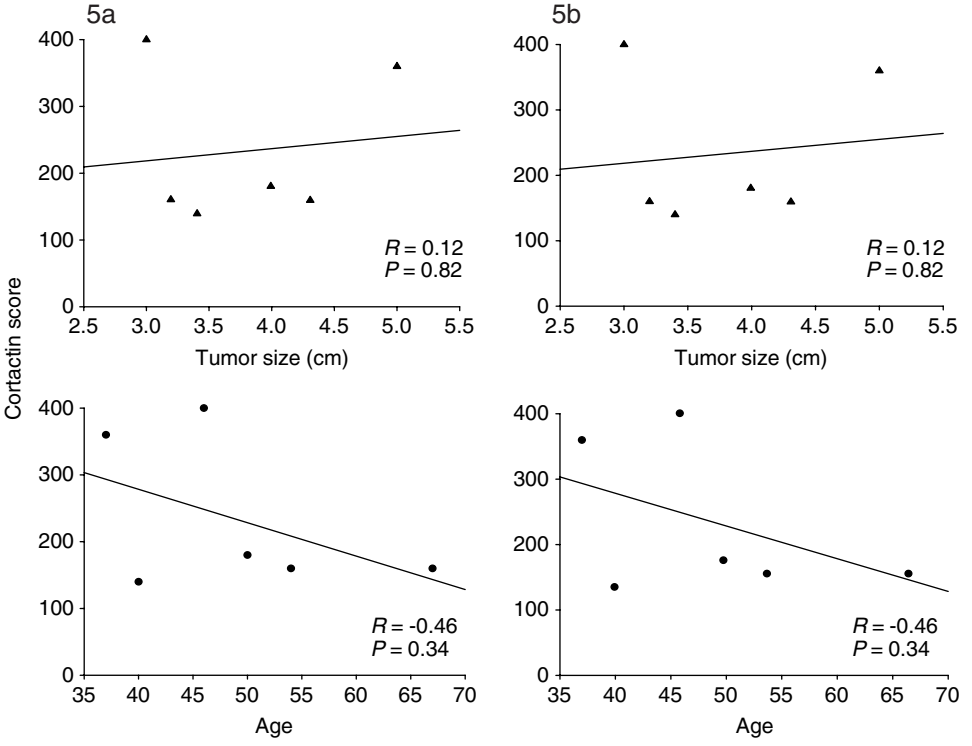

Fig. 5. Correlation between immunostaining score of cortactin in gliomatous (5a) and sarcomatous (5b) components with tumor size or age. Data were analyzed by linear regression analysis and no significance was reached ($P > 0.05$). R is the regression coefficient.

component; Fig. 6b) with patient's age ($P = 0.02$, $R = 0.873$).

The correlation of cytoplasmic survivin scores for both gliomatous (Fig. 7a) and sarcomatous (Fig. 7b) components revealed strong inverse correlation with tumor size ($P = 0.03$ for gliomatous component and $P = 0.04$ for sarcomatous component). No correlation was noted between the nuclear survivin stain and clinical parameters (data not shown).

Correlation of Immunostaining Scores with Survival Time

Linear regression analysis of cortactin score with survival time showed an inverse relation between cortactin score and survival time (Fig. 8). Although no significance was reached due to the limited case number, higher cortactin score has a tendency to be associated with lower survival time in both gliomatous

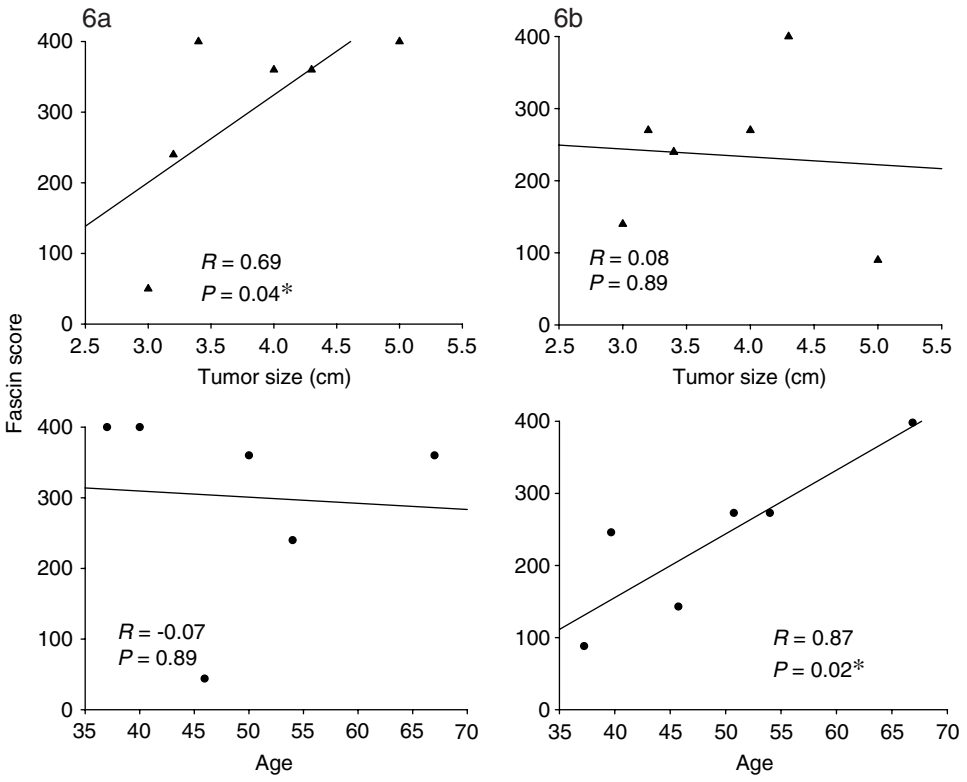

Fig. 6. Correlation between immunostaining score of fascin in gliomatous (6a) and sarcomatous (6b) components with tumor size or age. Data were analyzed by linear regression analysis. *R* is the regression coefficient and * indicates statistical significance ($P < 0.05$).

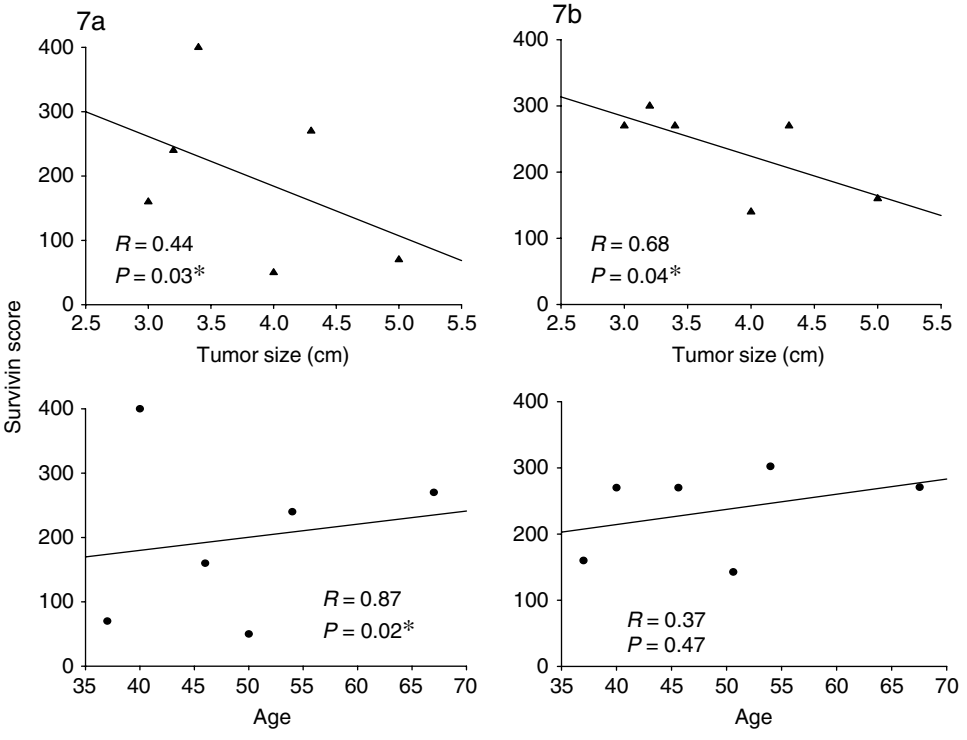

Fig. 7. Correlation between immunostaining score of survivin in gliomatous (7a) and sarcomatous (7b) components with tumor size or age. Data were analyzed by linear regression analysis. *R* is the regression coefficient and * indicates statistical significance ($P < 0.05$).

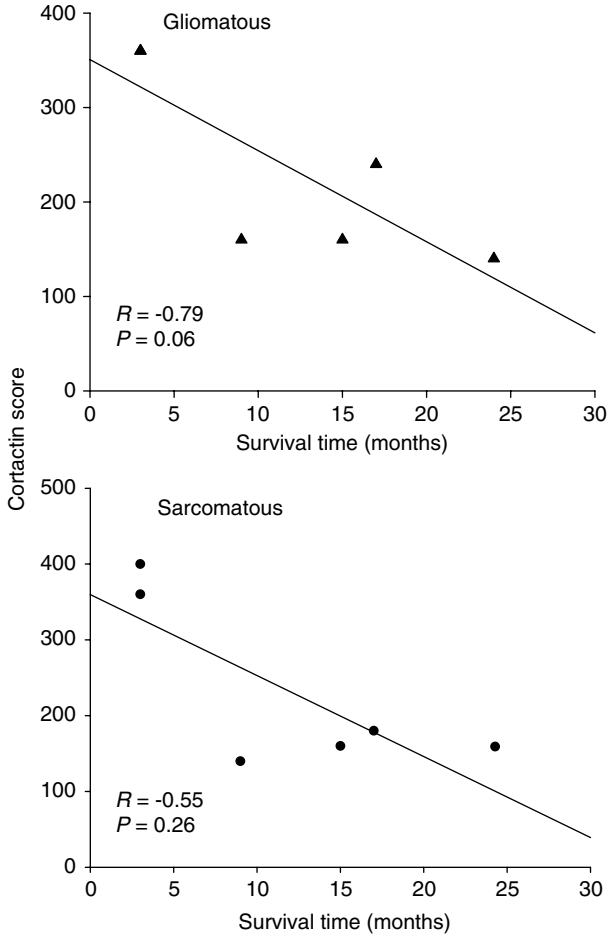

Fig. 8. Correlation between immunostaining score of cortactin in gliomatous (upper panel) and sarcomatous (lower panel) components with survival time. Data were analyzed by linear regression analysis. *R* is the regression coefficient and no statistical significance ($P < 0.05$) was reached.

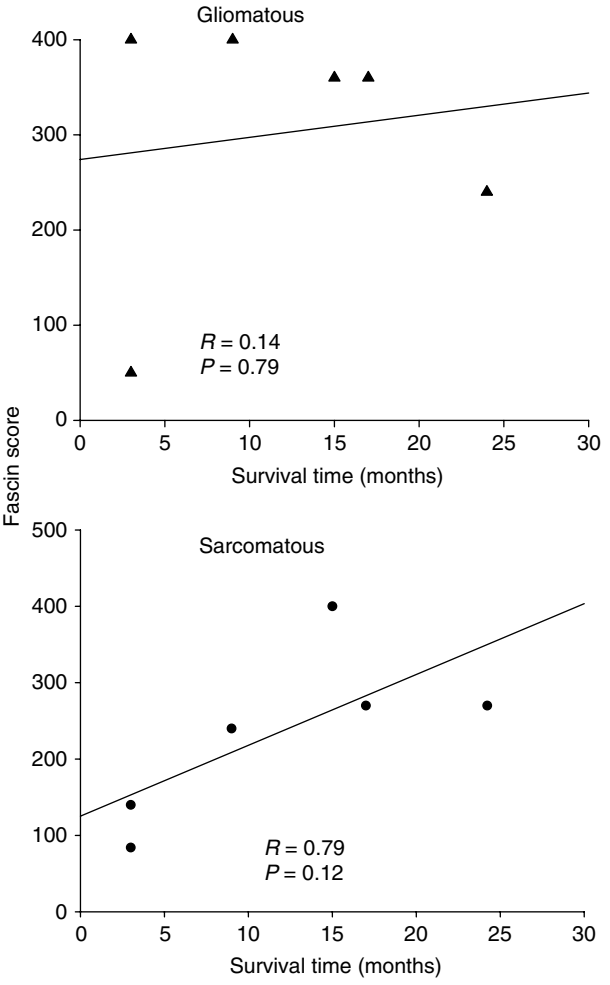

Fig. 9. Correlation between immunostaining score of fascin in gliomatous (upper panel) and sarcomatous (lower panel) components with survival time. Data were analyzed by linear regression analysis. *R* is the regression coefficient and no statistical significance ($P < 0.05$) was reached.

and sarcomatous components.

The correlation of survival time with fascin scores (Fig. 9) or survivin scores (Fig. 10) did not show a close relationship.

Discussion

Gliosarcoma is a rare morphological variant of glioblastoma. It occurs predominantly in males in the fourth to sixth decades of life and has a slight predilection for the temporal lobes (6, 14-17). In our current study, the mean age of patients with gliosarcoma was 49. We observe a predilection of gliosarcoma occurs over frontal-temporal-parietal lobe. Unlike some previous reports, no metastatic spread was found in any of our patients (22).

Primary gliosarcoma is clinically indistiguishable from glioblastoma, and both are associated with short clinical course, low median survival and a similar peak age of incidence (3, 7, 12, 14, 16-18). The treatment for both consists of surgical resection and, depending on clinical status, radiotherapy and/or chemotherapy (16, 17). Radiotherapy extends overall median survival (mean 10.6 months) compared to surgery only (mean 6.2 months) (17). In our series, the three patients who received adjuvant therapy had a mean overall survival of 9.0 months.

Although cortactin, fascin and survivin have an important role in tumor migration, invasion and metastasis, no relationship between expression of these biomarkers and gliosarcoma progression has been clearly established. In this study, immunostaining scores for cortactin, fascin and survivin were significantly higher in both the gliomatous and sarcomatous components of brain gliosarcomas suggesting that over-expression of these biomarkers is associated

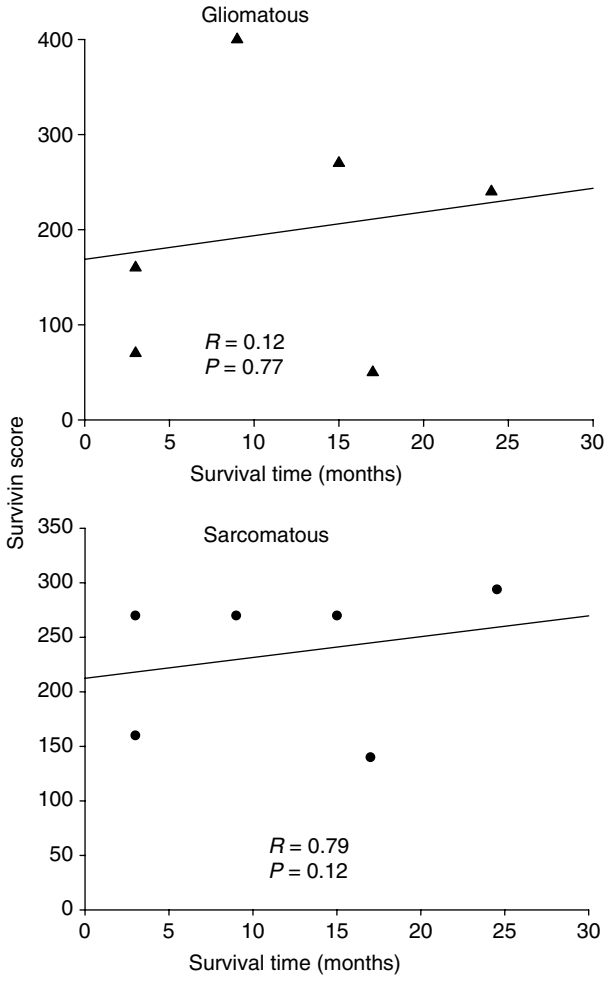

Fig. 10. Correlation between immunostaining score of survivin in gliomatous (upper panel) and sarcomatous (lower panel) components with survival time. Data were analyzed by linear regression analysis. *R* is the regression coefficient and no statistical significance ($P < 0.05$) was reached.

with malignant transformation of brain gliosarcoma.

The cortactin gene (an oncogene in the 11q13 region) has been associated in one study with cell migration and metastasis in esophageal squamous cell carcinoma (11). In other studies, expression of cortactin was associated with histologic grade, stage, and prognosis of gastric adenocarcinoma and head/neck squamous cell carcinoma (5, 19). Our study using an immunostaining scoring method found that cortactin is over-expression in both gliomatous and sarcomatous components of gliosarcoma, but it is not significantly correlated with tumor size or age.

Fascin overexpression has been previously correlated with poor prognosis in *in vitro* and *in vivo* studies (19, 25). In our study, fascin over-expression in the gliomatous component was significantly correlated with tumor size, and in sarcomatous component was significantly correlated with patient's age.

Survivin over-expression occurs in almost all malignancies in humans (2, 9, 10). Our results showed that cytoplasmic survivin over-expression in both the gliomatous and sarcomatous components is significantly inversely correlated with tumor size. Our results suggest cytoplasmic over-expression of survivin in gliosarcoma is negatively correlated with tumor size.

Although a previous study demonstrated expression of survivin in the nucleus of glioblastoma and correlation with poor prognosis of glioblastoma (8), we found only focal scatter nuclear stains for survivin in gliosarcoma in the six cases reported here.

In conclusion, our findings suggest that over-expression of cortactin, fascin and survivin is associated with malignant transformation of brain gliosarcoma. Development of drugs that target cortactin, fascin and survivin may have therapeutic benefit for patients with gliosarcoma.

Acknowledgments

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