JBUON 2013; 18(2): 430-436
ISSN: 1107-0625 • www.jbuon.com
E-mail: info@jbuon.com

ORIGINAL ARTICLE

Prognostic value of peritumoral edema and angiogenesis in intracranial meningioma surgery

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Summary

Purpose: *In a series of 78 consecutive patients we analyzed the influence of peritumoral edema (PTE) and angiogenesis (vascular endothelial growth factor/ VEGF expression) on the prognosis of morbidity and postoperative complications after intracranial meningioma surgery.*

Methods: *A retrospective analysis was performed of clinical, neuroradiological and histological data of 78 microsurgically treated patients with intracranial supratentorial meningioma, with follow-up period of at least one year.*

Results: *The severity of PTE showed significant correlation with VEGF expression, and all patients with large PTE (>40 mm) had strong VEGF expression (>50%). Treatment outcome was significantly better in patients with low VEGF expression ($p<0.05$). All of the monitored postoperative complications were more frequent in the group with PTE.The duration of intensive care treatment in the group with PTE (mean 6.85 days) was significantly longer than in the group without PTE (mean 3.68 days) ($p=0.003$). In the group without PTE, the outcome was significantly better than in patients with PTE ($p<0.01$).*

Conclusion: *PTE in intracranial meningiomas has significant influence on the prognosis in surgically treated patients in terms of increased risk of morbidity and postoperative complications. VEGF expression is strongly correlated with PTE formation, which also affects the outcome in the management of patients with intracranial meningioma.*

Key words: *intracranial meningioma, outcome of treatment, peritumoral edema, VEGF expression*

Introduction

PTE in intracranial neoplasms is a serious complication [1], thus the severity and extent of PTE may limit the operative exposure and increase the difficulty of resection. Severe PTE usually develops in malignant brain tumors, including glioblastoma multiforme and metastatic brain tumors [2] because malignant tumor vessels often lack the tight junctions that are normally present in cerebral microvessels, resulting in vasogenic edema.

Meningiomas represent about 15% of all intracranial neoplasms, and are generally extra-axial and benign, but in more than 50% are accompanied by PTE with no obvious relation to the size or their histological features [3]. PTE is often of vasogenic type due to disruption of the blood-brain barrier with leakage of fluid and proteins out of the vessels and into the brain tissue [4]. Several factors such as tumor size, tumor location, histologic type, blood supply to tumor, degree of VEGF expression and sex hormone receptors in the tumor, have been reported to correlate with PTE, but still mechanisms by which meningiomas produce PTE is not fully elucidated [5-7].

Vascularisation type of meningiomas and the amount of blood supply have significant influence on PTE production, and in that sense are related to higher morbidity and postoperative complications in surgically treated patients [8,9]. Hypervascular meningiomas particularly fed by the pial-cortical arteries exhibit significantly more severe edema compared with those supplied only from the meningeal arteries [9]. Large tumor volume and high grade histology (atypical or malignant type) may

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Received: 22/10/2012; Accepted: 30/11/2012

also be associated with the development of PTE that influences the perioperative morbidity and mortality [9].

Several studies have suggested that increased expression of VEGF plays significant role in meningioma hypervascularity, PTE genesis and cell proliferation, factors that influence the recurrence rate and prognosis after surgical treatment [10,11].

The aim of the present study was to investigate the influence of PTE and angiogenesis (VEGF expression) on the prognosis of morbidity and postoperative complications after intracranial meningioma surgery.

Methods

This study enrolled 78 patients with intracranial meningioma of supratentorial localization, surgically treated at the Department of Neurosurgery of the Clinical Hospital Center Zemun- Belgrade from January 2009 to April 2011. Their postoperative status was monitored until the end of April 2012, so the patient follow up period was at least one year.

The studied patients were divided into two groups: I) the first group- with presence of PTE; and II) the second group (control group)- without PTE.

Presence or absence of PTE was examined on preoperative CT scan or MRI, and the width of PTE was measured in mm (in the direction of maximal tumor diameter; Figure 1). The severity of PTE was divided as follows: small edema (1-20 mm); moderate edema (21-40 mm); and large edema (> 40 mm).

In all of the cases radical surgical tumor resection was performed (complete tumor excision with resection and ablation of dural attachment- Simpson [12] grade I, or coagulation of dural attachment in falx meningioma and cranial base meningioma cases- Simpson grade II.

Histological analysis included the samples of 78 resected meningiomas and took place at the Department of Clinical Pathology, Clinical Hospital Center Zemun- Belgrade. The histological report contained WHO grade and histologic type of meningioma. Each sample was processed in multiple sections and stained with standard hematoxylin & eosin and other routine methods.

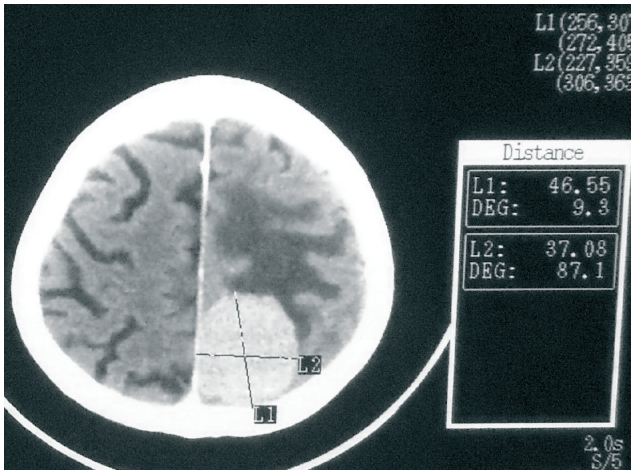

Figure 1. Cranial CT scan. Parietal parasagital meningioma (maximal tumor diameter 46 mm) with large peritumoral edema (>40 mm).

Immunohistochemistry

Immunohistochemistry was carried out on formalin-fixed, paraffin-embedded 4-micron sections of each tumor specimen using the streptavidin-biotin-peroxidase method (LSAB-2/HRP system, Dako Corporation, Glostrup, Denmark) with 3,3-diaminobenzidine-tetrahydrochloride (DakoCytomation, code no.K3468) as chromogen. The antibodies used were specific for Ki-67 antigen (MIB-1 DakoCytomation, code no.N1633), VEGF (DakoCytomation, code no.M7273 and DakoCytomation code no.N1633) and CD34 (DakoCytomation, code no.LS039). Negative controls for each tissue section were made by leaving out the primary antibody for Ki-67, VEGF and CD34. Mantle cell lymphoma tissue was used as positive control. All samples were processed under the same conditions. The percentages of cells expressing Ki-67 were determined by counting 1000 cells per slide in areas of highest density of staining ("hot spot") over a minimum of 10 high-power fields. To evaluate the microvascular density (MVD) of the meningiomas, we immunostained the tissue sections for CD34, which identifies vascular endothelial cells. A microscopic field of the most intense vascularization in each specimen under ×200 magnification was photographed as a JPEG file with a microscope digital color camera. Slides were analyzed using a Leica DM1000® light microscope.

Immunoexpression of VEGF was measured according to presence of cytoplasm immunopositivity in meningioma cells (Table 1).

The following variables were analyzed in relation to the presence or absence of PTE: age, gender, clinical/neurological presentation, tumor volume, histological type, WHO grade, VEGF, MVD and Ki-67 expressions, postoperative neurological deterioration, signs of intracranial hypertension after surgery, intracranial hematoma on postoperative CT scan, edema with mass effect on postoperative CT scan, ischemic lesion(s) on

Table 1. Immunohistochemical analysis of VEGF expression

Imnunoexpression of VEGF %	*Grade*
0- 25	1
26-50	2
51-75	3
>75	4

postoperative CT scan, hospital stay after surgery, and duration of treatment in intensive care unit after surgery. The patients' outcome at discharge and during the follow-up period was assessed by the Glasgow Outcome Score (GOS) scale.

Statistics

All data were processed and analyzed using the Statistical Package for Social Sciences (SPSS) software (version 14).

For nominal dichotomous variables chi square or Fisher's exact test were used according to the frequency of cases in each category (for N<5, Fisher's exact test was used), and for continuous variables with normal distribution Student's t-test was used (in case of non-normal distribution based on Kolmogorov-Smirnoff testing, Mann-Whitney U test was preferred).

P-values < 0.05 were considered as statistically significant.

Results

The study included 61 (78.2%) women and 17 (21.8%) men. Age ranged from 37 to 80 years (mean 60.76) and symptom duration ranged from 1 to 60 months (mean 7.49). PTE was present in 53 (67.9%) patients and absent in 25 (32.1%).

Patient gender and PTE

In both groups (with and without PTE) there was a marked female predominance. In the group of 53 patients with PTE, there were 13 (24.5%) men and 40 (75.5%) women (x^2, p=0.000). In the group without PTE, there were 4 (16.0%) men and 21 (84.0%) women (x^2, p=0.001). However, no statistically significant difference in sex distribution was noted between these two groups.

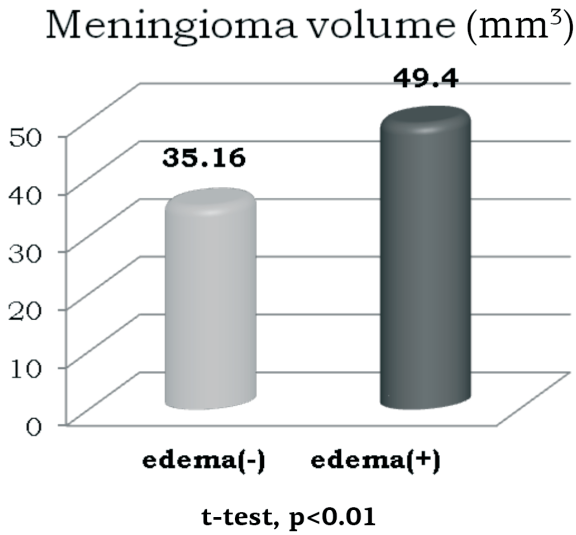

Figure 2. Tumor volume and peritumoral edema. Tumor volume significantly correlated with peritumoral edema. However, tumor volume was not correlated with severity of peritumoral edema.

Clinical presentation and PTE

Twenty one (39.6%) patients in the group with PTE had pyramidal deficit on admission and 10 (18.9%) patients had psychoorganic syndrome, while in the group without PTE 14 (56%) patients had focal or generalized seizures (Table 2). There was a significant difference in the neurological presentation between patients with and without presence of PTE (x^2, p<0.01).

Tumor volume and PTE

Tumor volume in the group with PTE (mean volume 49.4 cm^3) was significantly larger than in those without edema (mean volume 35.16 cm^3; Student's t-test, p<0.01; Figure 2). However, tumor volume was not correlated with the severity of PTE.

VEGF expression and PTE

In the group without PTE, 24 (96%) patients had low level (up to 25%) of VEGF expression, while in the group with PTE 17 (32.1%) patients had high level (50-100%) of VEGF expression and that difference was statistically significant (x^2, p<0.01; Figure 3).

MVD was also significantly higher in the group with PTE (mean 41.34) than in the group without PTE (mean 29.68; Student's t-test, p<0.01). Proliferative cell potential (with Ki 67 antigen) was significantly higher in meningiomas with PTE (mean 5.55) compared to meningiomas without PTE (mean 3.56; Student's t-test, p<0.05).

The severity of PTE showed significant correlation with VEGF expression. All patients with large PTE (> 40 mm) had high level of VEGF expression (> 50%) (x^2, p<0.05).

Table 2. Analysis of clinical presentation in patients with meningiomas with and without PTE (x^2, p< 0.01)

Clinical presentation on admission	*Meningioma with PTE N (%)*	*Meningioma without PTE N (%)*
Without deficit	6 (11.3)	3 (12)
Focal or generalized seizures	8 (15.1)	14 (56)
Pyramidal deficit	21 (39.6)	5 (20)
Dysphasia	4 (7.5)	0 (0)
Visual disturbance	0 (0)	2 (8)
Psychoorganic syndrome	10 (18.9)	0 (0)

PTE: peritumoral edema

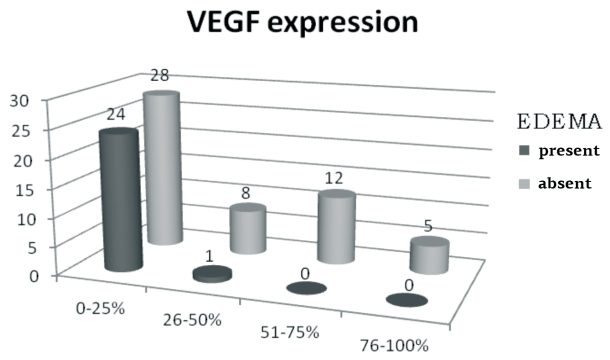

Figure 3. VEGF expression showed significant correlation with the presence of peritumoral edema.

VEGF expression and outcome

VEGF expression showed significant correlation with treatment outcome as assessed by the GOS scale. At discharge and after one year follow-up period, the outcome was significantly better in patients with low VEGF expression compared to patients with high expression of VEGF (x^2, $p<0.05$; Table 3).

Postoperative neurological complications and PTE

Appearance or worsening of neurological deficits in the early postoperative period had 19 (35.8%) patients with PTE and 6 (24%) without PTE (x^2, $p>0.05$). Signs of intracranial hypertension with altered level of conciousness appeared in 10 (18.9%) patients with PTE and in one (4%) without PTE postoperatively (x^2, $p>0.05$). Furthermore, significant intracranial hematoma on control CT scan had 13 (24.5%) patients with PTE and 2 (8%) without PTE (x^2, $p>0.05$). Ischemic lesion(s) on postoperative CT scan appeared in 6 (11.3%) patients with PTE and in 2 (8%) without PTE (x^2, $p>0.05$). All of these complications were more frequent in the group of meningiomas with PTE, but these differences were not statistically significant. However, postoperative edema with mass effect on control CT scan appeared in 16 (30.2%) patients with PTE as opposed to only one (4%) patient without PTE (x^2 , $p<0.01$).

Duration of hospitalization and intensive care treatment

The duration of postoperative hospitalization in the group with PTE (mean 14.45 days) did not differ significantly compared to patients without PTE (mean 12.96 days), but the duration of treatment in intensive care unit in the group with PTE (mean 6.85 days) was significantly longer than in the group without PTE (mean 3.68 days; Student's t-test, $p<0.03$; Table 4).

Table 3. VEGF expression and outcome assessed by the Glasgow Outcome Score (GOS) scale (x^2, $p<0.05$)

GOS scale	*VEGF expression*			
	<25% N (%)	*25-50% N (%)*	*51-75% N (%)*	*76-100% N (%)*
Good recovery	18 (34.6)	1 (11.1)	1 (8.3)	0 (0)
Moderate disabilities	25 (48.1)	4 (44.4)	3 (25)	2 (40)
Severe disabilities	6 (11.5)	3 (33.3)	7 (58.3)	3 (60)
Lethal outcome	3 (5.8)	1 (11.1)	1 (8.3)	0 (0)
Total	52	9	12	5
p-value	0.000	0.392	0.046	0.655

Table 4. Patient outcome assessed by the Glasgow Outcome Score (GOS) scale (after one year follow up period) in the groups with and without peritumoral edema

GOS scale	*Peritumoral edema*	
	With N (%)	*Without N (%)*
Good recovery	17 (32.1)	17 (68)
Moderate disabilities	28 (52.1)	4 (16)
Severe disabilities	5 (9.4)	2 (8)
Lethal outcome	3 (5.7)	2 (8)
x^2, p-value	0.000	0.009

Table 5. Duration of hospitalization and intensive care unit treatment in patients with meningiomas with and without peritumoral edema

Peritumoral edema	*Duration of hospitalization, days Median (range)*	*Duration of intensive care unit treatment, days Median (range)*
Without	12 (6-27)	3 (1-27)
With	13 (2-33)	4 (2-28)
T- test	-1.095	-6.018
p- value	>0.05	<0.03

PTE and outcome

The outcome of patients at the end of treatment and after one year follow-up was significantly different between groups with and without peritumoral edema (x^2,$p<0.05$; after one year follow-up x^2,$p<0.01$). In the group without PTE, the outcome was significantly better than in patients with PTE (Table 5).

Discussion

Several studies showed that intracranial meningiomas occurred more frequently in females. In adults, there is a marked female predominance with female to male ratio 3:2 to 2:1 [13]. The annual occurrence of meningiomas is 2-7/100000 per year for women, and 1-5/100000 per year for men [14,15]. However, in the Manitoba study female predominance was noticeable in patients only after the 5th decade of life [16].

In our study, significant female predominance in the whole patient population (78.2%), and in both groups (with PTE- 75.5%, without PTE- 84%) was present. These results are in agreement with previous findings, and might suggest a certain role of progesterone and estrogens in the genesis and growth of meningiomas. The average age of patients in our series was about 60 years, which is in accordance with other reports that meningiomas show rising incidence with age and are most common in the 6th and 7th decade of life [13].

PTE was present in 67.9% of patients in our study, corresponding to reports from the literature that from 50% up to two-thirds of intracranial meningiomas are accompanied by PTE [17-19] .The clinical presentation of meningiomas with PTE differed significantly from meningiomas without PTE, with most common manifestation pyramidal deficits (39.6%), then psychoorganic syndrome (18.9%), while meningiomas without PTE presented most often with focal or generalized seizures (56%). These results showed that in meningiomas with PTE functional damage of the cerebral cortex is dominating (with different clinical manifestations depending on tumor localization), while in meningiomas without PTE excitating cortical dysfunction due to direct contact with tumor tissue is of strong importance.

In a large prospective study Lee et al. [9] analyzed the clinical, neuroradiological, and pathological characteristics related to the formation of PTE in 79 patients with intracranial meningiomas and showed that large tumor volume, atypical or malignant histological subtype, and pial-cortical arterial supply were correlated with PTE in univariate analysis, whilst in multivariate analysis only pial-cortical arterial supply was associated with PTE. According to their results, large tumor volume is closely related to pial-cortical blood supply considered to be the most important critical factor for the development of PTE that influences the perioperative morbidity and mortality in the management of patients with meningioma.

Ide et al. [20] analyzed 39 cases of intracranial meningiomas to identify factors causing peritumoral brain edema. Edema was significantly correlated with tumor size and the destruction of the leptomeninges and cortex. There was no correlation between the presence of edema and location of the tumor or histological features. Larger tumors destroy the leptomeninges and cerebral cortex, allowing direct transmission of humoral edema - promoting factor or edema fluid into the white matter, resulting in vasogenic edema.

A group of Turkish authors [21] analyzed the relationship between patient age and gender, meningiomas location, histological subtype, size, and PTE. The authors reported that none of the factors analyzed influenced PTE, except patient age 61-70 years, which correlated with PTE.

In our study, there was no significant difference in patient age between groups with and without PTE. However, tumor volume correlated significantly with presence of PT, which is in agreement with previous findings [9,20]. In the group of patients with PTE, meningioma volume was significantly larger than in patients without PTE.

In several studies, the cerebral-pial blood supply and VEGF have been implicated as causative factors of PTE. Yoshioka et al. [11] investigated 73 supratentorial meningiomas to identify factors, including type of arterial blood supply and VEGF expression, that may influence the development of meningiomas-associated PTE. In meningiomas with cerebral-pial supply, the extent of PTE increased significantly in conjuction with strong VEGF expression. In contrast, meningiomas without cerebral-pial supply developed little or no PTE and showed less VEGF expression. These results suggest that VEGF expression contributes to PTE formation in meningiomas only when a cerebral-pial blood supply exists. Similarly, Bitzer et al. [22] found that development of tumor supply from cerebral arteries may be important for formation of meningioma-related edema. Therefore, VEGF may represent a potent mediator in the evolution of this type of vascularisation in meningiomas. Otsuka et al.[23] examined the influence of VEGF expression and its two major receptors, Flt-1 and Flk-1, on the development of PTE in intracranial meningiomas. After immunohistochemical study, their data suggested that the expressions of VEGF and VEGF receptors positively related to each other and to the formation of PTE in patients with meningiomas.

Our study of 78 patients with intracranial meningiomas showed significant difference in VEGF expression in relation to presence of PTE. High levels of VEGF expression were found in about one third of patients with meningiomas

with PTE. Also, MVD and proliferative cell potential were significantly higher in meningiomas with PTE, confirming the findings of Smith et al. [24] that tumors with increased cellularity, vascularity, and mitotic activity show edema more frequently.

Yamasaki et al. [25] in their study of supratentorial intracranial meningiomas with convexity localization, and follow up period of at least 3 years after complete surgical resection, found that high levels of VEGF expression constituted the most useful predictor of recurrence and prognosis, compared to other analyzed factors. In our study, the level of VEGF expression had significant influence on treatment outcome, so patients with low expression of VEGF had better recovery. These results suggest that angiogenesis might have strong correlation with prognosis in surgically treated patients with intracranial meningiomas.

In a prospective study with follow up period of one year, Vignes et al. [8] evaluated the clinical and surgical significance of PTE in intracranial meningiomas. Edema was associated with a shorter course of clinical disease, which suggests that neurological symptoms are exacerbated by PTE. There was no significant increase in mortality in their group of patients with PTE, but edema was related to higher morbidity in the surgical management of meningiomas. PTE was also associated with a longer hospitalization, increased difficulty of surgical resection, and increased risk of postoperative intracranial hematoma and intracranial hypertension compared to meningiomas without PTE. Their study showed that PTE in meningiomas affects the surgical prognosis and confers a higher risk of morbidity and postoperative complications.

The results of our prospective study showed that all of the monitored postoperative complications (appearance or worsening of neurological deficits, intracranial hypertension, intracranial hematoma, and ischemic lesions) were more frequent in the group of patients with PTE. Edema with mass effect on postoperative CT scan was significantly more common in patients with meningiomas and presence of PTE. Likewise, the duration of intensive care treatment was significantly longer in patients with PTE. Finally, the outcome of patients at the end of treatment, and after one year of follow up, was significantly better in the group of patients with meningiomas without presence of PTE.

Conclusion

Our study showed that PTE in intracranial meningiomas has significant influence on prognosis in surgically treated patients, in terms of increased risk of morbidity and postoperative complications. VEGF expression is strongly correlated with PTE formation, and also affects the outcome in the management of patients with intracranial meningioma.

References

1. Abe T, Black PM, Ojemann RG et al. Cerebral edema in intracranial meningiomas: evidence for local and diffuse patterns and factors associated with its occurrence. Surg Neurol 1994;42:471-475.
2. Hasso AN, Bell SA, Tadmor R. Intracranial vascular tumors. Neuroimaging Clin N Am 1994;4:849-870.
3. Tamiya T, Ono Y, Matsumoto K, Ohmoto T. Peritumoral brain edema in intracranial meningiomas: effects of radiological and histological factors. Neurosurgery 2001;49:1046-1051.
4. Nakano T, Asano K, Miura H et al. Meningiomas with brain edema: radiological characteristics on MRI and review of the literature. Clin Imaging 2002; 26: 243-249.
5. Kalkanis SN, Carroll RS, Zhang J et al. Correlation of vascvular endothelial growth factor messenger RNA expression with peritumoral vasogenic cerebral edema in meningiomas. J Neurosurg 1996;85:1095-1011.
6. Lobato RD, Alday R, Gomes PA et al. Brain oedema in patients with intracranial meningioma. Correlation between clinical, radiological, and histological factors and the presence and intensity of oedema. Acta Neurochir (Wien) 1996; 138:485-493.
7. Vries J, Wakloo AK. Cerebral oedema associated with WHO-I, WHO-II, WHO-III meningiomas: correlation of clinical, computed tomography, operative and histological findings. Acta Neurochir (Wien) 1993; 125:34-40.
8. Vignes JR, Sesay M, Rezajooi K, Gimbert E, Liguoro D. Peritumoral edema and prognosis in intracranial meningioma surgery. J Clin Neurosci 2008; 15: 764-768.
9. Lee KJ, Joo WI, Rha HK et al. Peritumoral brain edema in meningiomas: correlations between magnetic resonance imaging, angiography, and pathology.Surg Neurol 2008;69:350-355.
10. Provias J, Claffey K, delAguila L et al. Meningiomas: role of vascular endothelial growth factor/vascular permeability factor in angiogenesis and peritumoral edema. Neurosurgery 1997;40:1016-1026.
11. Yoshioka H, Hama S, Taniguchi E, Sugiyama K, Arita K, Kurisu K. Peritumoral brain edema associated with meningioma: influence of vascular endothelial growth factor expression and vascular blood supply. Cancer 1999;85:936-944.

12. Simpson D. The recurrence of intracranial meningiomas after surgical treatment. J Neurol Neurosurg Psychiatry 1957; 20:22-39.
13. Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ. Meningiomas. In: Kleihues P, Cavenee WK, (Eds): Pathology and genetics. Tumours of the nervous system. WHO classification of tumors. Lyon: IARS Press, 2000, pp 176-184.
14. Lantos P, van den Berg SR, Kleihues P. Tumours of the nervous system. In: Graham DI, Lantos PL (Eds): Greenfield's Neuropathology (6th Edn). London: Arnold; 1996, pp 583-879.
15. Longstreth WT, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TD. Epidemiology of intracranial meningioma. Cancer 1993;72:639-648.
16. Sutherland GR, Florell R, Louw D et al. Epidemiology of primary intracranial neoplasms in Manitoba, Canada. Can J Neurol Sci 1987;14:586-592.
17. Salpietro FM, Alafaci C, Lucerna S et al. Peritumoral edema in meningiomas: microsurgical observations of different brain tumor interfaces related to computed tomography. Neurosurgery 1994; 35:638-641.
18. Maiuri F, Gangemi M, Cirillo S et al. Cerebral edema associated with meningiomas. Surg Neurol 1987; 27:64-68.
19. Alaywan M, Sindou M. Prognostic factors in the surgery for intracranial meningioma. Role of the tumoral size and arterial vascularisation originating from the pia matter. Study of 150 cases. Neurochirurgie 1993; 39:337-347.
20. Ide M, Jimbo M, Kubo O, Yamamoto M, Imanaga H. Peritumoral brain edema associated with meningioma- histological study of the tumor margin and surrounding brain. Neurol Med Chir (Tokyo) 1992; 32: 65-71.
21. Gurkaniar D, Uygur ER, Sanli M, Ozkan M, Sekerci Z. Peritumoral brain edema in intracranial meningiomas. J Clin Neurosci 2005; 12: 750-753.
22. Bitzer M, Opitz H, Popp J et al. Angiogenesis and brain oedema in intracranial meningiomas: influence of vascular endothelial growth factor. Acta Neurochir (Wien) 1998; 140: 333-340.
23. Otsuka S, Tamiya T, Ono Y et al. The relationship between peritumoral brain edema and the expression of vascular endothelial growth factor and its receptors in intracranial meningiomas. J Neuro-Oncol 2004; 70: 349-357.
24. Smith HP, Challa VR, Moody DM et al. Biological features of meningiomas that determine the production of cerebral edema. Neurosurgery 1981; 8: 428-433.
25. Yamasaki F, Yoshioka H, Hama S et al. Recurrence of meningiomas. Cancer 2000; 89: 1102-1110.