Clinical Article

The Clinical Features of Spinal Leptomeningeal Dissemination from Malignant Gliomas

Jung-Sik Bae, M.D.,[1] Seung-Ho Yang, M.D.,[2] Woan-Soo Yoon, M.D.,[3] Seok-Gu Kang, M.D.,[1] Yong-Kil Hong, M.D.,[1] Sin-Soo Jeun, M.D.[1]

Department of Neurosurgery,[1] Seoul St. Mary's Hospital, The Catholic University of Korea, Seoul, Korea
Department of Neurosurgery,[2] St. Vincent Hospital, The Catholic University of Korea, Suwon, Korea
Department of Neurosurgery,[3] Incheon St. Mary's Hospital, The Catholic University of Korea, Incheon, Korea

Objective : The incidence of leptomeningeal dissemination from malignant glioma is rare, so the clinical features of this are not well documented yet. We attempted to determine the clinical features of leptomeningeal dissemination from malignant gliomas.
Methods : We retrospectively analyzed 11 cases of leptomeningeal dissemination of malignant glioma, who were treated at our institution between 2006 and 2009. We investigated the clinical features of these patients by considering the following factors : tumor locations, the events of ventricular opening during surgery and the cerebrospinal fluid (CSF) profiles, including the cytology.
Results : The group was composed of 9 males and 2 females. The histological diagnosis of their initial intracranial tumors were 4 primary glioblastoma, 3 anaplastic astrocytoma, 1 anaplastic oligoastrocytoma, 2 ganglioglioma and 1 pleomorphic xanthoastrocyotma with anaplastic features. The mean age of the patients at the time of the initial presentation was 42.8±10.3 years. The mean time between surgery and the diagnosis of spinal dissemination was 12.3±7.9 (3-28) months. The mean overall survival after dissemination was 2.7±1.3 months. All our patients revealed a history of surgical opening of the ventricles. Elevated protein in the CSF was reported for eight patients who had their CSF profiles checked.
Conclusion : We propose that in the malignant gliomas, the surgical opening of ventricles can cause the spinal leptomeningeal dissemination and the elevated protein content of CSF may be a candidate marker of leptomeningeal dissemination.

Key Words : Seeding · Malignant glioma · Spinal dissemination.

INTRODUCTION

The rate of leptomeningeal dissemination from malignant glioma may be underestimated. There were 2%[17] and 3.1%[13] clinically reported leptomeningeal dissemination rate from malignant glioma. But, autopsy studies have shown a high incidence of leptomeningeal seeding[5,16]. Some autopsy studies reported 6%[16], 20%[8], and 21%[18] incidence of spinal seeding from glioblastoma. One of the reasons for this is that rapid disease progression results in the loss of surveying for leptomeningeal dissemination. This fact is supported as dissemination appears to occur more frequently in young patients and in patients with prolonged survival times[9].

The new treatment modalities and recent advances in neurosurgical diagnosis allow achieving local control of malignant

gliomas to some extent, and so in proportion to long-term survivors, there is a growing population of patients who experience intracranial and/or spinal disseminations. However, reports on leptomeningeal dissemination of malignant gliomas are rare[15]. Furthermore, the natural history and risk factors associated with spinal leptomeningeal dissemination in patients with malignant gliomas are unclear[7]. The present report retrospectively followed up eleven consecutive patients who had spinal seeding of malignant glioma and we analyzed the clinical features of leptomeningeal dissemination.

MATERIALS AND METHODS

We retrospectively analyzed 124 consecutive patients with glioma. These patients had been treated at our institute between 2006 and 2009. Ninety-six of these cases of glioma were malignant gliomas. Pathological confirmation was obtained in all patients. The histological diagnosis was established by the World Health Organization classification. Eleven of the 96 patients were judged to have spinal leptomeningeal dissemination, if there was a symptom related to the leptomeningeal seeding, we checked the whole spinal MRI. Spinal leptomeningeal dissemination

was defined as contrast-enhancing leptomeninges with diffuse or enhancing mass lesions at the spinal canal. The spinal dissemination types were classified as the diffuse type (diffuse enhancement of the subarachnoid space on spinal MRI), nodular type (nodular tumor mass) and mixed type (both diffuse enhancement and nodular mass lesion).

The tumor location, the presence of a ventricular opening and the type of spinal dissemination were analyzed. The protein content of the cerebrospinal fluid (CSF) was checked to investigate the relation between leptomeningeal dissemination and the CSF protein level. The CSF cytology was also checked.

The statistical analyses were conducted using SPSS 12.0 for Windows (SPSS, Inc., Chicago, IL, USA). Numerical variables were expressed as the mean±standard error of the mean. Progression-free survival was measured from the start of the concurrent therapy to tumor progression. Overall survival was calculated from the date of the histological diagnosis to death or the last date of follow-up. At the time of diagnosis of spinal dissemination, the state of the primary lesion was evaluated as complete response (CR : complete disappearance of the targeted le-

sion), partial response (PR : 50% decrease in the sum of the products of the maximum perpendicular diameters of the targeted lesion), stable disease (SD : no clinical progression, with 50% reduction or 25% increase in the sum of the products of the maximum perpendicular diameters of the targeted lesion), and progressive disease (PD : increase in the volume of the targeted lesion)[12].

The Kasnofsky performance scale (KPS)[11] was checked when the patients were diagnosed with spinal leptomeningeal dissemination.

RESULTS

The group was composed of 9 males and 2 females (Table 1). The mean age of the patients at the time of the initial presentation was 42.8±10.3 years. All the patients were treated with radiotherapy and chemotherapy following the surgery for their intracranial lesions. One of them was given spinal radiotherapy (case 2). The tumors were located on the left periventricular area in Case 1 (Fig. 1A), the right parietal cortex in Case 2 (Fig.

Table 1. Clinical characteristics of the patients

Case	Age	Sex	Initial diagnosis	Disease state	KPS (%)	Initial operation	PFS (months)	OS (months)	FD (months)
1	37	M	AA	PD	60	Partial tumor resection	2	6	3
2	41	M	AA → GBM	SD	80	Gross total tumor resection	13	36	4
3	44	M	GG → GBM	SD	70	Sutotal tumor resection	54	96	5
4	46	M	GBM	PD	50	Subtotal tumor resection	13	18	3
5	62	M	GBM	PD	40	Gross total tumor resection	11	24	4
6	55	F	GBM	PD	40	Subtotal tumor resection	3	7	1
7	52	M	PXA c AF	PD	90	Subtotal tumor resection	10	11	2
8	37	F	GBM	PD	80	Partial tumor resection	2	3	1
9	28	M	AA	PD	80	Subtotal tumor resection	16	32	3
10	37	M	GG → GBM	PD	40	Growth total tumor resection	35	76	2
11	32	M	AOA	PD	80	Growth total tumor resection	7	20	2

M : male, F : female, AA : anaplastic astrocytoma, GBM : glioblastoma multiforme, GG : ganglioglioma, PXA c AF : pleomorphic xanthoastrocytoma with atypical feature, AOA : anaplastic oligoastrocytoma, SD : stable disease, PD : progressive disease, PFS : progression free survival of primary lesion, OS : overall survival, FD : follow up or survival after dissemination, KPS : Kasnofsky performance scale
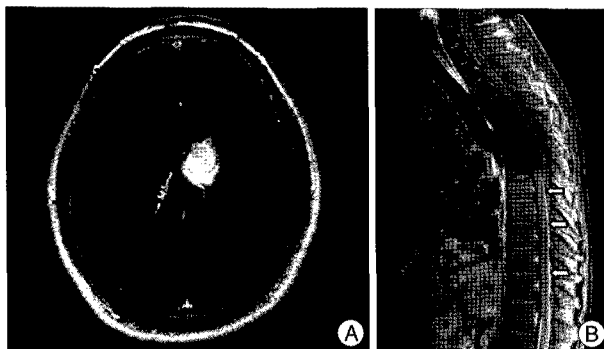

Fig. 1. Case 1 : A 37-year-old male patient. Pathologic diagnosis was anaplastic astrocytoma. A : Initial T1 enhanced axial brain MRI. Well enhanced tumor lesion locates in left lateral ventricle. B : At 4 months later, the patient presented decreased mentality. At this time T1 enhanced whole-spine sagittal MRI revealed leptomeningeal enhancement (arrows). Dissemination is diffuse type.
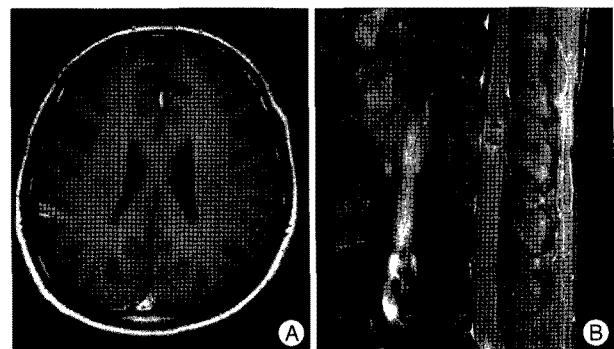

Fig. 2. Case 2 : Patient is 41-year-old male patient. Initial diagnosis was anaplastic astrocytoma. It progressed to glioblastoma 2 years later. A : Initial T1 enhanced axial MRI shows subtle enhanced lesion at right parietal sulci. B : At 14 months later after the surgery, the patient is presented both legs weakness. T1 enhanced L-spine sagittal MRI reveals mass on L2 level. It is nodular type dissemination.

335

2A), the left temporal lobe in Case 3, the right insular lobe in Case 4, the right frontal lobe in Case 5, the genu of the corpus callosum and the frontal horn of both lateral ventricles in Case 6, the left insular lobe and the trigone of the left lateral ventricle in Case 7 (Fig. 3A), the right temporal lobe in Case 8, the cerebellar vermis in Case 9, the right temporo-occipital lobe in Case 10 and the left frontal lobe in Case 11. And, all the tumors of 11 patients were in contact with CSF pathway (pial space or ventricle space).

The enrolled patients underwent surgery for the treatment of intracranial tumors. The histological diagnosis of their initial intracranial tumors were 4 primary glioblastoma, 3 anaplastic astrocytoma, 1 anaplastic oligoastrocytoma, 2 ganglioglioma and 1 pleomorphic xanthoastrocyotma with anaplastic features (Table 1). The one astrocytoma (case 2) and two gangliogliomas progressed to glioblastomas finally. The state of primary lesion was PD in nine patients and SD in two patients, at the time of diagnosis spinal dissemination. The two SD patients were all secondary glioblastomas (case 2, 3). The median KPS at the diagnosis of spinal dissemination was 70 (range 40-90). Gross to-
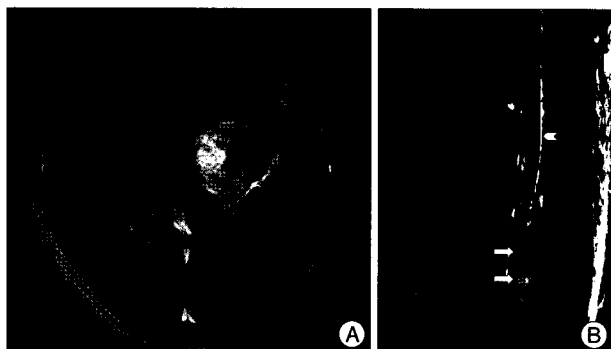

Fig. 3. Case 7 : A case with 52-year-old male. Initial diagnosis was pleomorphic xanthoastrocytoma with atypical feature. It progressed to glioblastoma. The patient had complaint of left arm weakness. A : Initial T1 enhanced axial MRI shows that a tumor locates on left insular lobe and trigone of left lateral ventricle. B : Whole spine T1 enhanced sagittal MRI reveals multinodular masses (white arrows) with leptomeningeal enhancement (arrow head). It shows mixed type dissemination.

tal resection, subtotal resection and partial resection of tumors were performed in 4 cases, 5 cases and 2 case, respectively.

All the cases showed clinical events of ventricular opening mechanically during the operation. Among the 96 malignant gliomas in our series, ventricular entry occurred in thirty-five cases. No such dissemination occurred in malignant glioma patients without ventricular opening during the surgery.

Six of our cases died (Cases 1, 5, 6, 8, 9 and 11) and the others (Cases 2, 3, 4, 7 and 10) are alive during the observation period. In the 6 expired cases, the mean survival time from the dissemination to death was 2.3±1.2 months. The mean time between the operation with opening the ventricle (s) and the diagnosis of dissemination was 10.7±6.6 (3-21) months in gliblastoma, 15.0±10.4 (4-28) months in WHO grade 3 glioma, and 12.3±7.9 (3-28) months totally. The mean overall survival after dissemination was 2.7±1.3 months.

All the patients revealed the symptoms of leptomeningeal dissemination (Table 2). Eight of them initially presented with mental change due to intracranial dissemination and three of them presented with spinal symptoms. The 8 patients initially presented with intracranial dissemination finally showed spinal symptoms such as weakness of extremities and they were diagnosed spinal dissemination. In six patients (Cases 1, 2, 3, 4, 7 and 10), intrathecal chemotherapy, composed of methotrexate were given. In particular, we tried new systemic chemotherapy for Cases 3, 7 and 10. It was the combination of bevacizumab and irinotecan[19].

There were eight patients in the diffuse type of spinal seeding (Fig. 1B), one patient in the nodular type (Fig. 2B), and two patients in the mixed type of spinal seeding (Fig. 3B). The patients in the nodular and mixed type of spinal seeding presented with paresthesia or weakness symptoms of extremities. Diffuse type patients presented with mental change, initially. We performed a surgical operation on Case 2 (nodular type spinal dissemination) and we could confirm the pathology as spinal dissemination.

CSF studies were done in Cases 1, 2, 3, 4, 7, 9, 10 and 11. In Cases 5, 6 and 8, we couldn't retrospectively find the CSF pro-

Table 2. Clinical features of spinal leptomeningeal dissemination

Case	Symptom	VO	CSF profile (protein : mg/dL)	TD (months)	Type of spinal dissemination	Treatment for spinal seeding
1	Mental change	+*	Protein : 3,660, Cytology : -	4	Diffuse	IT MTX
2	Leg paresthesia	+	Protein : 152, Cytology : -	13	Nodular	IT MTX Spinal radiation (4,000 cGy)
3	Leg paresth esiawea kness	+	Protein : 211, Cytology : -	6	Mixed	IT MTX Bev.+Irino.
4	Mental change	+	Protein : 386, Cytology : -	17	Diffuse	IT MTX
5	Mental change	+	Not checked	21	Diffuse	No treatment
6	Mental change	+	Not checked	6	Diffuse	No treatment
7	Arm weakness	+	Protein : 2,539, Cytology : -	10	Mixed	IT MTX Bev.+Irino.
8	Mental change	+	Not checked	3	Diffuse	No treatment
9	Mental change	+	Protein : 345, Cytology : -	28	Diffuse	No treatment
10	Mental change	+	Protein : 673, Cytology : -	9	Diffuse	IT MTX Bev.+Irino.
11	Mental change	+	Protein : 572, Cytology : -	18	Diffuse	No treatment

*It means occurring of ventricular opening during the operation or the tumor involvement to ventricles. VO : ventricular opening, TD : time to dissemination after surgery causing ventricular opening, IT MTX : Intrathecal Methotrexate, Bev.+Irino. : Bevacizumab+Irinotecan

files. All the eight cases showed an elevated protein level at least 3 times that of the normal range and 100 times at the most (152 -3,660 mg/dL). However, the cytological results were negative in all the eight patients. Otherwise, among the malignant glioma patients who didn't have a event of leptomeningeal dissemination, 6 patients were performed CSF studies and showed normal or slightly increased protein level of CSF (50-86 mg/dL). The difference of CSF protein level was significant between the patients with spinal dissemination and the patients without it (p<0.05 Student t-test).

DISCUSSION

The prior reports have shown various incidences of leptomeningeal dissemination from malignant gliomas. Choucair et al.[6] reported the incidence to be 5.0% and 8.5% for the patients with glioblastomas and anaplastic gliomas, respectively. Grabb et al.[9] found that 11 of 33 children with supratentorial malignant gliomas developed leptomeningeal dissemination. Other reports described that patients with hemispheric glioblastoma had spinal seeding in 6%[16], 21%[18] and 20%[8]. But these prior reported cases were from autopsy series, so the incidence is different from that of the ante-mortem studies. Another recent report showed that the incidence of intracranial and spinal dissemination was 25% and 8.8%, respectively, in an ante-mortem series[14]. In our study, the incidence of leptomeningeal dissemination was 8.8% in the patients with gliomas and 11.4% in the patients with malignant gliomas. Since most patients do not survive long enough for spinal metastasis to develop, symptomatic CSF dissemination occurs relatively late in the course of malignant gliomas[1]. But it is clear that with the help of advanced diagnostic tools and neurosurgical treatment modalities, the incidence of leptomeningeal dissemination in patients with malignant gliomas is increasing. Some reports have speculated that opening the ventricles during surgery may increase the risk of CSF dissemination[8,16], but few studies in the literature have specifically analyzed this factor[9,17]. Erlich and Davis[8] reported that surgery may be a predisposing factor for the development of subarachnoid metastases. Grabb et al.[9] reported that breaching the ependyma increases the risk of dissemination. However, there is no definite evidence that the surgical expansion of tumor to the ventricular system results in leptomeningeal dissemination. Elliott et al.[7] reported that surgical opening of ventricle was not associated with leptomeningeal dissemination. But most of the prior studies suggested that opening the ventricles may be a risk factor for leptomeningeal dissemination. The present study also suggest a relationship between ventricular opening and leptomeningeal dissemination for patients malignant gliomas. However, in order to confirm the statistical relationship, we need more cases with longer follow up periods.

The increased protein contents of the CSF may be a candidate marker of leptomeningeal dissemination. CSF studies were performed in our leptomeningeal dissemination cases and these revealed the meaningful elevation of the protein content. Saito et al.[16] reported the protein content of the CSF tended to decline after resection of the tumor, and it showed rapid increases preceding or simultaneous with the onset of symptoms due to spinal dissemination. They also regarded the presence of malignant cells in the CSF as one of the criteria for leptomeningeal dissemination[14]. However, false negative results are frequent on a CSF cytological examination[3,4]. Our present report did not show positive cytologic findings. Even though Case 2 was confirmed to have the same tumor tissue at the leptomeningeal disseminated site with intracranial glioma through the operation, there were no positive cytologic findings in the CSF profile. But, an elevated protein content in the CSF was reported in all of our cases. According to these aspects, we agree with the other opinions that the protein content of the CSF is more remarkable indicator than a cytologic examination for leptomeningeal dissemination of malignant gliomas[2,16]. Our cases revealed that the mean time between the operation with opening the ventricle(s) and the diagnosis of dissemination was 12.3±7.9 (3-28)months. Another study documented that the mean time was 12.7±10.2 months[16]. But these periods were longer than expected considering usual overall survival of malignant gliomas. Therefore, we should know that earlier detection of disseminated lesion could be resulted from the meticulous follow-up examination with especial attention to leptomeningeal dissemination and routine clinical use of MR imaging.

In Cases 2 and 3, the state of intracranial lesion was stable, but spinal leptomeningeal dissemination occurred. These facts showed that leptomeningeal dissemination can develop without progression of the intracranial primary lesion.

Most spinal dissemination of malignant glioma occurred in elderly patients from our cases. But Arita et al.[2] and Yung et al.[20] reported the frequent spinal dissemination occurred in young patients. Moreover, Arita et al.[2] reported larger proportion of leptomeningeal dissemination rate in children than in adult patient. The higher incidence of spinal leptomeningeal dissemination at the younger age can be explained in two ways. "First, the tumor cells in gliomas of younger patients may have a biological character prone to cause leptomeningeal dissemination. No cellular or molecular biological evidence exists to support this hypothesis. Second, meningeal spread has been reported to develop in patients with longer survivals. In general, younger patients with malignant gliomas live longer than the older patients and therefore, meningeal dissemination is more frequently seen in the younger patients"[2,15,20].

The diffuse and mixed type of spinal seeding are uncontrollable. But, there is operability in pure nodular type, such as our case 2. So this nodular type of spinal seeding may be more controllable. However, we had a few cases, hence additional studies are required to clarify any difference.

There is no satisfactory treatment for spinal metastasis. Surgical decompression allows for confirming the diagnosis and it may be helpful to control pain. However, leptomeningeal me-

tastases are often not amenable to surgical decompression because of the diffuse infiltrating nature of the disease[10]. In our cases, we tried intrathecal methotrexate chemotherapy in Cases 1, 2, 3, 4, 7 and 10. Especially in the Cases 3, 7 and 10, we applied a combination therapy of bevacizumab plus irinotecan[19]. These therapies have not yet produced satisfactory outcomes. But we expect these new trials with chemotherapy drugs and novel therapeutic agents will improve not only the patient's survival rate, but also their devastating symptoms that are related to leptomeningeal dissemination.

CONCLUSION

We observed 11 cases of spinal dissemination from malignant glioma, in which all of the cases had a history of surgical opening of the ventricle and the elevated protein content of CSF may be a candidate marker of leptomeningeal dissemination. Even though a tumor involves the ventricular system, physicians must be careful not to open the ventricular system during the operation. But, unfortunately, if ventricular entry had occurred during the operation, we should frequently check up spinal imaging in order to detect leptomeningeal dissemination early. And, if malignant glioma patients present with spinal symptoms, then physicians should consider the possibility of spinal dissemination from malignant gliomas.

References

1. Alatakis S, Malham GM, Thien C : Spinal leptomeningeal metastasis from cerebral glioblastoma multiforme presenting with radicular pain. Surg Neurol 56 : 33-37; discussion 37-38, 2001
2. Arita N, Taneda M, Hayakawa T : Leptomeningeal dissemination of malignant gliomas. Incidence, diagnosis, and outcome. Acta Neurochir (Wien) 126 : 84-92, 1994
3. Balhuizen JC, Bots GT, Schaberg A, Bosman FT : Value of cerebrospinal fluid cytology for the diagnosis of malignancies in the central nervous system. J Neurosurg 48 : 747-753, 1978
4. Bigner SH, Johnston WW : The cytopathology of cerebrospinal fluid. II. Metastatic cancer, meningeal carcinomatosis and primary central nervous system neoplasms. Acta Cytol 25 : 461-479, 1981
5. Bryan P : CSF seeding of intracranial tumors : a study of 96 cases. Clin Radiol 25 : 355-360, 1974
6. Choucair AK, Levin VA, Gutin PH, Davis RL, Silver BA, Edwards MS, et al. : Development of multiple lesions during radiation therapy and chemotherapy in patients with gliomas. J Neurosurg 65 : 654-658, 1986
7. Elliott JP, Keles GE, Waite M, Temkin N, Berger MS : Ventricular entry during resection of malignant gliomas : effect on intracranial cerebrospinal fluid tumor dissemination. J Neurosurg 80 : 834-839, 1994
8. Erlich SS, Davis RL : Spinal subarachnoid metastasis from primary intracranial glioblastoma multiforme. Cancer 42 : 2854-2864, 1978
9. Grabb PA, Albright AL, Pang D : Dissemination of supratentorial malignant gliomas via the cerebrospinal fluid in children. Neurosurgery 30 : 64-71, 1992
10. Han SR, Yee GT, Lee DJ, Whang CJ : Spinal metastases from supratentorial glioblastoma. J Korean Neurosurg Soc 38 : 475-477, 2005
11. Karnofsky DA, Burchenal JH : The clinical evaluation of chemotherapeutic agents in cancer in Macleod CM (ed) : Evaluation of Chemotherapeutic Agents. New York : Columbia University Press, 1949, pp 191-205
12. Lee YY, Glass JP, Geoffray A, Wallace S : Cranial computed tomographic abnormalities in leptomeningeal metastasis. AJR Am J Roentgenol 143 : 1035-1039, 1984
13. Mcdonald DR, Cascino TL, Schold SC Jr, Cairncross JG : Response criteria for phase II studies of supratentorial malignant glioma. J Clin Oncol 8 : 1277-1280, 1990
14. Onda K, Tanaka R, Takahashi H, Takeda N, Ikuta F : Symptomatic cerebrospinal fluid dissemination of cerebral glioblastoma. Computed tomography findings in 11 cases. Neuroradiology 32 : 146-150, 1990
15. Packer RJ, Siegel KR, Sutton LN, Litmann P, Bruce DA, Schut L : Leptomeningeal dissemination of primary central nervous system tumors of childhood. Ann Neurol 18 : 217-221, 1985
16. Saito R, Kumabe T, Jokura H, Shirane R, Yoshimoto T : Symptomatic spinal dissemination of malignant astrocytoma. J Neurooncol 61 : 227-235, 2003
17. Salazar OM, Rubin P : The spread of glioblastoma multiforme as a determining factor in the radiation treated volume. Int J Radiat Oncol Bio Phys 1 : 627-637, 1976
18. Vertosick FT Jr, Selker RG : Brainstem and spinal metastases of supratentorial glioblastoma multiforme : a clinical series. Neurosurgery 27 : 516-521; discussion 521-522, 1990
19. Vredenburgh JJ, Desjardins A, Herndon JE 2nd, Marcello J, Reardon DA, Quinn JA, et al. : Bevacizumab plus irinotecan in recurrent glioblastoma multiforme. J Clin Oncol 25 : 4722-4729, 2007
20. Yung WA, Horten BC, Shapiro WR : Meningeal gliomatosis : a review of 12 cases. Ann Neurol 8 : 605-608, 1980