

Brain Metastasis of Undifferentiated Sarcoma and Response to Temozolomide Treatment

—Case Report—

Hiroto TANOAKA, Takashi SASAYAMA, Masamitsu NISHIHARA, Atsushi ARAI, Atsufumi KAWAMURA*, Naoki KANOMATA**, Tomoo ITOH**, and Eiji KOHMURA

Departments of Neurosurgery and **Pathology,
Kobe University Graduate School of Medicine, Kobe, Hyogo;
*Department of Neurosurgery, Hyogo Prefectural Kobe Children's Hospital, Kobe, Hyogo

Abstract

A 33-year-old woman presented with rare brain metastases from undifferentiated high-grade sarcoma manifesting as headache and vomiting. Magnetic resonance (MR) imaging demonstrated multiple tumors in the brain, subcutaneous soft tissue, and mediastinum. The patient underwent surgery, followed by chemotherapy and radiotherapy. The histological diagnosis was undifferentiated high-grade sarcoma. Radiotherapy was effective, but the brain tumors recurred 6 months later. The patient underwent high-dose methotrexate therapy, but showed no response. Promoter hypermethylation in the O⁶-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) genes was detected and MGMT protein expression was negative in the recurrent tumor, so temozolomide (TMZ) salvage chemotherapy was given, and follow-up MR imaging showed tumor reduction. This case suggests that TMZ may be effective for brain metastasis of undifferentiated sarcoma without MGMT protein expression.

Key words: undifferentiated sarcoma, brain metastasis, temozolomide, O⁶-methylguanine-deoxyribonucleic acid methyltransferase

Introduction

Brain metastasis from undifferentiated sarcoma is extremely rare.^{6,7)} The main therapeutic strategy for brain metastasis from soft tissue sarcoma (STS) is surgical resection, whereas radio- or chemotherapy is indicated for inoperable or recurrent cases. Some organs with metastatic lesions occasionally exhibit good response to chemotherapy, whereas brain metastasis is generally resistant to chemotherapy due to poor penetration of the blood-brain barrier (BBB).^{1,11)} Therefore, chemotherapeutic methods for brain metastasis from STS have not been established.

Temozolomide (TMZ) is a novel chemotherapeutic agent that crosses the BBB and has activity against many human solid tumors. TMZ may also enhance radiation treatment efficacy in primary central nervous system tumors, such as malignant gliomas.⁵⁾ TMZ therapy is reported to be effective against advanced STSs.^{7,21-23)} Recently, TMZ with an extended schedule showed activity in patients with advanced gynecologic leiomyosarcomas.⁷⁾

O⁶-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) is a deoxyribonucleic acid (DNA) repair enzyme that transfers alkyl adducts from the O⁶-position

of guanine in DNA to a cysteine residue in its own sequence. MGMT is ubiquitously expressed in normal human tissues.¹⁰⁾ Remarkably, MGMT activity is usually higher in malignant tissues than in their normal counterparts,^{12,13)} but MGMT expression is silenced in a subset of tumor cells mostly due to abnormal promoter methylation. Gliomas present with a high frequency of MGMT inactivation by promoter hypermethylation among human neoplasms.^{3,9)} However, the frequency of promoter hypermethylation in the MGMT gene in STS is unclear. Some clinical studies have suggested that loss of MGMT expression by aberrant promoter methylation correlates with sensitivity to TMZ in gliomas.^{3,9)} MGMT promoter methylation is associated with a favorable outcome after TMZ chemotherapy in patients with newly diagnosed glioblastoma.^{9,19)}

We treated a 33-year-old woman with multiple brain metastases from undifferentiated high-grade sarcoma of the soft tissue which were resistant to several treatments, but TMZ salvage therapy showed partial response. The tumor showed loss of MGMT expression by epigenetic silencing of the MGMT gene by promoter hypermethylation, suggesting that TMZ might be effective against brain metastasis of soft tissue undifferentiated high-grade sarcoma with low MGMT activity.

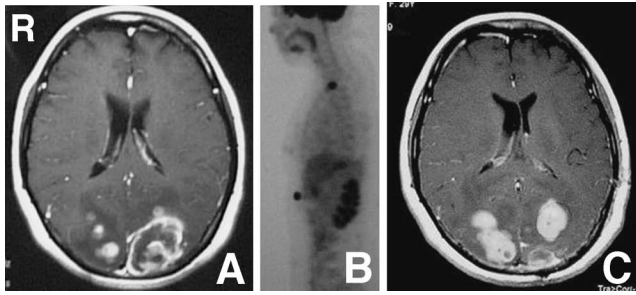


Fig. 1 A: Preoperative axial T₁-weighted magnetic resonance (MR) image with gadolinium showing multiple heterogeneously enhanced tumors with edema in the bilateral occipital lobes. B: Fluorodeoxyglucose positron emission tomography scan showing hyper-uptake in the abdominal subcutaneous region and mediastinum. C: Postoperative axial T₁-weighted MR image with gadolinium after first-line chemotherapy showing multiple occipital tumors and the remarkably enlarged residual tumors.

Case Report

A 33-year-old woman presented with headache and vomiting to another hospital. Computed tomography revealed intratumoral hemorrhage in the left occipital lobe, and magnetic resonance (MR) imaging demonstrated multiple mass lesions in the bilateral occipital lobes, right frontal lobe, and cerebellum, appearing as hypointense on T₁-weighted and hyperintense on T₂-weighted images, with heterogeneous enhancement by gadolinium (Fig. 1A). She underwent open surgery for the left occipital lesion for pathological diagnosis. Histological examination found large pleomorphic plump spindled to epithelioid cells (Fig. 2A, B). However, no diagnosis could be established and she was referred to our hospital.

Fluorodeoxyglucose positron emission tomography showed hyper-uptake in the subcutaneous soft tissue of the right chest and abdomen, and mediastinum (Fig. 1B). Biopsy of the subcutaneous tumor in the right chest was performed by a dermatologist. Histological examination showed mainly multiform large cells, with small lymphocyte and plasma cells in the background, very similar to the specimen of the brain tumor. Immunohistologically, the tumor cells were positive for vimentin and S-100 protein (Fig. 2C, D), but did not show any characteristic findings. Finally, the tumor was diagnosed as undifferentiated high-grade sarcoma. Because of the systemic disease, she was initially given combination chemotherapy regimens with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP), and etoposide, methylprednisolone, high-dose cytarabine, and platinum (ESHAP). Although the extracranial tumors responded slightly to the chemotherapy, the intracranial brain tumors enlarged (Fig. 1C). She was subsequently treated with radiation therapy directed at the whole brain (30 Gy), and to the occipital (30 Gy), chest and abdominal, and mediastinum (45 Gy) tumors. Subsequently, all extracranial tumors vanished and the intracranial tumor decreased. Gamma knife radiosurgery was performed for the residual in-

tracranial tumors.

About 6 months later, the bilateral occipital tumors regrew, resulting in blindness, and she underwent tumor resection for the occipital tumors three times. Subsequently, the tumors recurred in the right temporal lobe, right cerebellar hemisphere, and tentorium cerebelli, although none of the extracranial tumor recurred. She was treated with 3 courses of high-dose methotrexate (MTX) therapy, but showed no response. She complained of truncal ataxia, dysphagia, and dysarthria, and MR imaging showed that the brain stem was extremely compressed by the enlarged cerebellar tumor (Fig. 3A–D). Methylation-specific polymerase chain reaction (PCR) was performed to determine *MGMT* gene silencing, and *MGMT* promoter methylation was detected in the recurrent metastatic brain tumor (Fig. 4A). Furthermore, immunohistochemistry investigation of the *MGMT* protein expression of the brain tumor showed the tumor cells were negative for *MGMT* (Fig. 4B). *MGMT* expression in the brain tumors was quite low by epigenetic silencing of the *MGMT* gene, so TMZ treatment was expected to be effective against the chemoresistant brain tumors. After giving informed consent, the patient underwent TMZ treatment as a salvage therapy at an initial dose of 150 mg/m²/day for 5 days of a 28-day cycle, and a subsequent dose of 200 mg/m²/day for 5 days of every 28-day cycle, as well as the protocol for recurrent malignant glioma. Follow-up MR imaging showed reduced tumor size and disappearance of brain stem compression after 3 courses of TMZ therapy (Fig. 3E–H). Truncal ataxia, dysphagia, and dysarthria improved, but 4 months after the start of TMZ therapy, the right cerebellar tumors enlarged again. She received a total of 5 courses of TMZ therapy. She died 52 months after initial surgery, and 7 months after beginning the salvage TMZ therapy.

Discussion

Brain metastasis is thought to be a relatively uncommon event in the natural history of sarcoma,^{2,6,8,18,24} with the rate of brain metastasis from STSs of 1–4%. A review of 411 patients with various types of sarcomas identified 18 patients with brain metastasis, an overall incidence of 4.3%.¹⁵ Brain metastasis from STSs is less frequent than from bone sarcomas. In particular, brain metastasis from undifferentiated sarcoma is rare with few reported cases.^{16,17,20} The therapeutic regimens for STSs are surgical resection, chemotherapy, and radiation. Ifosfamide, doxorubicin, and dacarbazine are known to be effective for advanced STSs, but not for brain metastasis cases.^{4,11} Twenty-one cases of brain metastasis from sarcoma included seven osteosarcomas, four leiomyosarcomas, three malignant fibrous histiocytomas (MFHs), two alveolar soft-part sarcomas, three Ewing's sarcomas, and two unclassified sarcomas.² The median survival of these patients was 11.8 months, and complete removal of all brain metastases and Karnofsky performance status score >70 were associated with a favorable prognosis.²

In the present case, the multifocal tumors were located in the chest and abdominal subcutaneous soft tissue,

mediastinum, and brain. The patient was treated with CHOP and ESHAP chemotherapy after surgery. However, the chemotherapy was not effective for the brain metastasis, so the patient underwent radiotherapy and radiosurgery, which was remarkably effective for the brain metastasis. At the time of brain tumor recurrence, the

patient had undergone three courses of high-dose MTX therapy, which was ineffective.

TMZ is a well-known alkylating anticancer drug, widely used for malignant glioma. TMZ demonstrates broad-spectrum antitumor activity, good oral bioavailability, and favorable toxicity profiles in preclinical and clinical studies, so warranted evaluation in the treatment of patients with advanced STS. However, the first Phase II study performed in 1999 yielded disappointing results, because only one response was observed among 31 evaluated

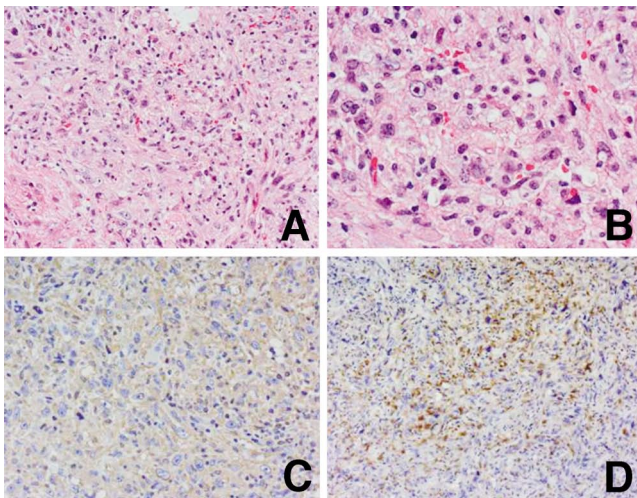


Fig. 2 A, B: Photomicrographs showing multiform large cells and small lymphocyte and plasma cells. Hematoxylin and eosin stain, original magnification A: $\times 100$, B: $\times 200$. C, D: Immunohistochemical staining showing tumor cells positive for vimentin (C) and S-100 protein (D). Original magnification C: $\times 200$, D: $\times 100$.

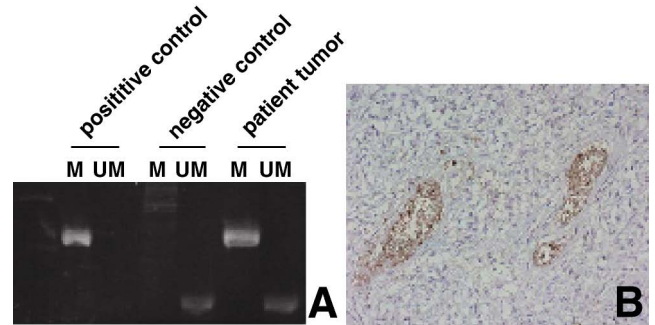


Fig. 4 A: Methylation-specific polymerase chain reaction revealing O⁶-methylguanine-deoxyribonucleic acid methyltransferase (MGMT) promoter hypermethylation in recurrent tumor cells. M: methylated, UM: unmethylated. B: Immunohistochemical staining with MGMT Ab-1 (Clone MT 3.1; Thermo Fisher Scientific Inc., Waltham, Mass., U.S.A.) at 1:20 for 60 minutes at room temperature showing loss of MGMT expression. Original magnification $\times 200$.

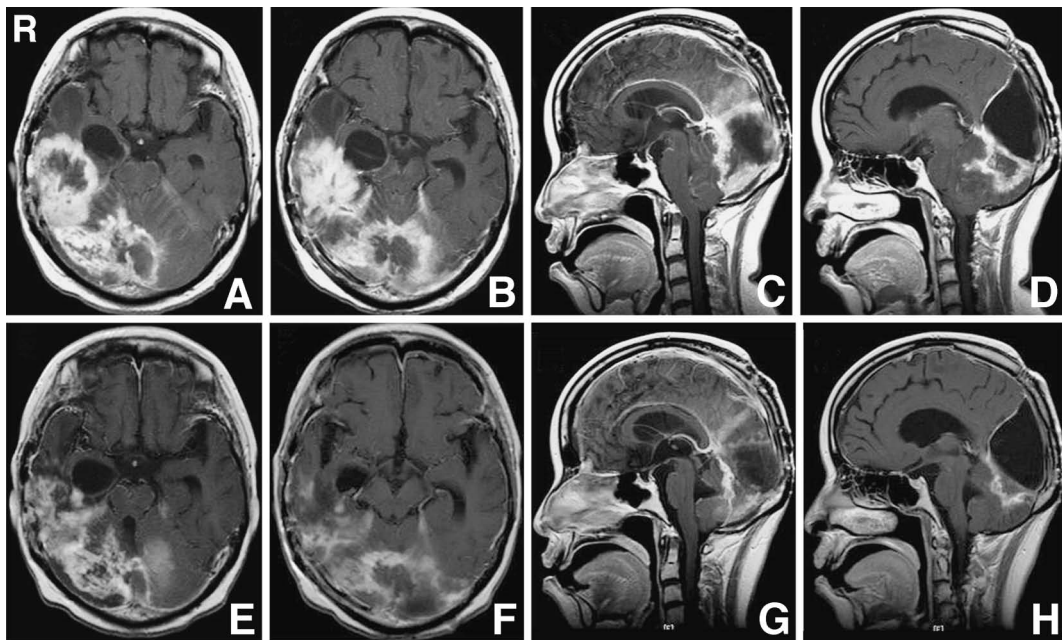


Fig. 3 A-D: Axial (A, B) and sagittal (C, D) T₁-weighted magnetic resonance (MR) images with gadolinium before temozolomide (TMZ) therapy showing large tumors in the right temporal lobe and cerebellum, markedly compressing the brain stem. E-H: Axial (E, F) and sagittal (G, H) T₁-weighted MR images with gadolinium after 3 courses of TMZ therapy showing reduced tumor size and improved brain stem compression.

patients (response rate 3.3%).²³⁾ A Phase II trial on a series of 39 STS patients treated with TMZ in 2003 found the median overall survival time was 11 months and the response rate was 5%.²²⁾ Treatment of 25 patients with metastatic STS showed the median overall survival was 13.2 months, and the response rate was 8%.²¹⁾ Recently, a Phase II trial of TMZ as a 6-week, continuous oral schedule (75 mg/m²/day) for 45 eligible patients with advanced STS resulted in median overall survival of 8.1 months and response rate of 16%.⁷⁾ Overall, the response rate was around 10%. Therefore, TMZ cannot be definitely considered effective for STSs, and more case experience is necessary. Most of the responding patients in these four available clinical studies had leiomyosarcoma, suggesting that leiomyosarcomas may be more responsive to treatment with TMZ than other STS histological subtypes, but the reason is not clear.

In the course of tumor development, gene silencing by DNA methylation is an early and important mechanism by which tumor suppressor genes are inactivated. Epigenetic silencing of the *MGMT* gene by promoter methylation is associated with loss of *MGMT* expression and diminished DNA-repair activity, but high levels of *MGMT* activity in cancer cells create a resistant phenotype by blunting the therapeutic effect of alkylating agents and may be an important determinant of treatment failure.⁹⁾ *MGMT* promoter methylation is known in some cases of STSs. The *MGMT* promoter methylation frequency was 15% (10/65 cases) in STSs, and *MGMT* promoter methylation was associated with tumor aggressiveness.¹³⁾ In these cases, the pathological subtype was MFH in 5 cases, malignant peripheral nerve sheath tumor in 3, and leiomyosarcoma in 2. *MGMT* promoter hypermethylation rate was reported as 33.9%, and the loss of *MGMT* protein expression as 32.3% in STSs.¹⁴⁾ The loss of *MGMT* expression was correlated with worse survival, but in the group receiving chemotherapy, loss of *MGMT* expression was independently associated with longer overall survival and was an independent prognostic factor in multivariate analysis ($p = 0.024$).¹⁴⁾

In the present case, *MGMT* expression was examined by methylation-specific PCR and immunohistochemistry, and revealed loss of *MGMT* expression in tumor cells. We obtained written informed consent and administered TMZ as salvage therapy when MR imaging showed her brain stem was markedly compressed by the extended temporal and cerebellar tumor. The result was favorable, as MR imaging after 3 courses of TMZ therapy demonstrated tumor reduction and disappearance of brain stem compression. The neurological symptoms, such as dysphagia and ataxia, were improved after TMZ therapy. Therefore, the present case suggests that TMZ therapy might be effective against brain metastasis from undifferentiated STS which has *MGMT* promoter methylation or loss of *MGMT* protein expression.

References

- 1) Aksoy S, Abali H, Kiliçkap S, Güler N: Successful treatment of a chemoresistant tumor with temozolomide in an adult patient: report of a recurrent intracranial mesenchymal chondrosarcoma. *J Neurooncol* 71: 333-334, 2005
- 2) Bindal RK, Sawaya RE, Leavens ME, Taylor SH, Guinee VF: Sarcoma metastatic to the Brain: Results of surgical treatment. *Neurosurgery* 35: 185-191, 1994
- 3) Brandes AA, Franceschi E, Tosoni A, Blatt V, Pession A, Tallini G, Bertorelle R, Bartolini S, Calbucci F, Andreoli A, Giampiero F, Leonardi M, Spagnoli F, Ermani M: *MGMT* promoter methylation status can predict the incidence and outcome of pseudoprogression after concomitant radiochemotherapy in newly diagnosed glioblastoma patients. *J Clin Oncol* 26: 2192-2197, 2008
- 4) Casali PG, Jost L, Sleijfer S, Verweij J, Blay JY: Soft tissue sarcomas: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Ann Oncol* 19 Suppl 2: ii89-ii93, 2008
- 5) Chakravarti A, Erkinen MG, Nestler U, Stupp R, Mehta M, Aldape K, Gilbert MR, Black PM, Loeffler JS: Temozolomide-mediated radiation enhancement in glioblastoma: A report on underlying mechanism. *Clin Cancer Res* 12: 4738-4746, 2006
- 6) Espat JN, Bilsky M, Lewis JJ, Leung D, Brennan MF: Soft tissue sarcoma brain metastases: Prevalence in a cohort of 3829 patients. *Cancer* 94: 2706-2711, 2002
- 7) Garcia del Muro X, Lopez-Pousa A, Martin J, Buesa JM, Martinez-Trufero J, Casado A, Poveda A, Cruz J, Bover I, Maurel J; Spanish Group for Research on Sarcomas: A phase II trial of temozolomide as a 6-week, continuous, oral schedule in patients with advanced soft tissue sarcoma: a study by the Spanish Group for Research on Sarcomas. *Cancer* 104: 1706-1712, 2005
- 8) Gupta T, Laskar S, Gujral S, Muckaden MA: Brain metastases in soft tissue sarcoma: Case report and literature review. *Sarcoma* 9: 147-150, 2005
- 9) Hegi ME, Diserens AC, Gorlia T, Hamou MF, de Tribolet N, Weller M, Kros JM, Hainfellner JA, Mason W, Mariani L, Bromberg JE, Hau P, Mirimanoff RO, Cairncross JG, Janzer RC, Stupp R: *MGMT* gene silencing and benefit from temozolomide in glioblastoma. *N Engl J Med* 352: 997-1003, 2005
- 10) Hegi ME, Liu L, Herman JG, Stupp R, Wick W, Weller M, Mehta MP, Gilbert MR: Correlation of O⁶-methylguanine methyltransferase (*MGMT*) promoter methylation with clinical outcomes in glioblastoma and clinical strategies to modulate *MGMT* activity. *J Clin Oncol* 26: 4189-4199, 2008
- 11) Hoshi M, Takami M, Ieguchi M: Pleomorphic malignant fibrous histiocytoma: response of bone, lung, and brain metastases to chemotherapy. *Radiat Med* 26: 499-503, 2008
- 12) Hou P, Ji M, Yang B, Chen Z, Qiu J, Shi X, Lu Z: Quantitative analysis of promoter hypermethylation in multiple genes in osteosarcoma. *Cancer* 106: 1602-1609, 2006
- 13) Kawaguchi K, Oda Y, Saito T, Yamamoto H, Takahira T, Kobayashi C, Tamiya S, Tateishi N, Iwamoto Y, Tsuneyoshi M: DNA hypermethylation status of multiple genes in soft tissue sarcomas. *Mod Pathol* 19: 106-114, 2006
- 14) Kim JI, Suh JT, Choi KU, Kang HJ, Shin DH, Lee IS, Moon TY, Kim WT: Inactivation of O⁶-methylguanine-DNA methyltransferase in soft tissue sarcomas: associated with K-ras mutations. *Hum Pathol* 40: 934-941, 2009
- 15) Postovsky S, Ash S, Ramu IN, Yaniv Y, Zaizov R, Futerman B, Elhasid R, Ben Barak A, Halil A, Ben Arush AW: Central nervous system involvement in children with sarcoma. *Oncology* 65: 118-124, 2003
- 16) Regel JP, Pospiech J, Baume B, van de Nes JA: Cerebral metastasis from an undifferentiated sarcoma of the left atrium. *Acta Neurochir (Wien)* 148: 595-596, 2006

- 17) Reichel C, Fehske W, Fischer HP, Hartlapp JH: Undifferentiated (embryonal) sarcoma of the liver in an adult patient with metastasis of the heart and brain. *Clin Investig* 72: 209–212, 1994
- 18) Salvati M, Cervoni L, Caruso R, Gagliardi FM, Delfini R: Sarcoma metastatic to the brain: a series of 15 cases. *Surg Neurol* 49: 441–444, 1998
- 19) Stupp R, Hegi ME, Mason WP, van den Bent MJ, Taphoorn MJ, Janzer RC, Ludwin SK, Allgeier A, Fisher B, Belanger K, Hau P, Brandes AA, Gijtenbeek J, Marosi C, Vecht CJ, Mokhtari K, Wesseling P, Villa S, Eisenhauer E, Gorlia T, Weller M, Lacombe D, Cairncross JG, Mirimanoff RO: Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial. *Lancet Oncol* 10: 459–466, 2009
- 20) Sudarshan G, Vamsy M, Murthy SS, Kumar VS: Undifferentiated sarcoma of the mitral valve with secondaries in brain in a girl of 22 years. *J Cancer Res Ther* 3: 47–49, 2007
- 21) Talbot SM, Keohan ML, Hesdorffer M, Orrico R, Bagiella E, Troxel AB, Taub RN: A Phase II trial of temozolomide in patients with unresectable or metastatic soft tissue sarcoma. *Cancer* 98: 1942–1946, 2003
- 22) Trent JC, Beach J, Burgess MA, Papadopolous N, Chen LL, Benjamin RS, Patel SR: A two-arm phase II study of temozolomide in patients with advanced gastrointestinal stromal tumors and other soft tissue sarcomas. *Cancer* 98: 2693–2699, 2003
- 23) Woll PJ, Judson I, Lee SM, Rodenhuis S, Nielsen OS, Buesa JM, Lorigan PC, Leyvraz S, Hermans C, van Glabbeke M, Verweij J: Temozolomide in adult patients with advanced soft tissue sarcoma: a phase II study of the EORTC Soft Tissue and Bone Sarcoma Group. *Eur J Cancer* 35: 410–412, 1999
- 24) Wronski M, Arbit E, Burt M, Perino G, Galicich JH, Brennan MF: Resection of brain metastases from sarcoma. *Ann Surg Oncol* 2: 392–395, 1995

Address reprint requests to: Takashi Sasayama, M.D., Department of Neurosurgery, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan. e-mail: takasasa@med.kobe-u.ac.jp