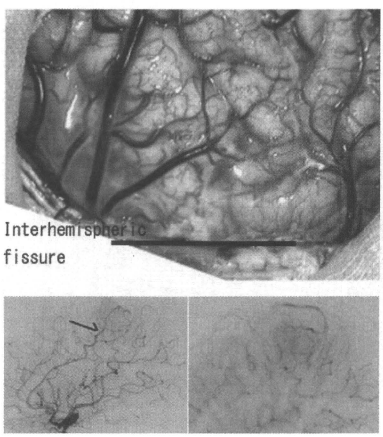

図9　30歳，男性，右 paracentral glioblastoma
血管撮影の所見どおり，内側から ACA よりの feeder が存在し，腫瘍後方へ A-V シャントを形成している．術中写真での右側に red vein が存在し，腫瘍摘出最後に処理する．

い，集学的治療法のなかでの手術術式や適応について常に見直す必要もある．

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REVIEW ARTICLE

Yoshitaka Narita · Soichiro Shibui

Strategy of surgery and radiation therapy for brain metastases

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Abstract Cancer patients with brain metastases have poor prognoses and their median survival time is about 1 year. Surgery with whole-brain radiation therapy (WBRT) has been used in the treatment of single brain metastasis measuring 3 cm or more. Stereotactic radiosurgery (SRS) including the use of the Gamma knife and Cyberknife is widely used for the treatment of small and multiple brain metastases; however, recent clinical studies have revealed that SRS + WBRT is superior to WBRT or SRS alone in terms of survival time and local tumor control rates. Here, surgical indications and the strategy of surgery and radiation therapy are discussed, based on many clinical trials of treatments for brain metastases. To improve the survival rate and quality of life for these cancer patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy with the close cooperation of physicians, surgeons, radiologists, and neurosurgeons, based on accumulated evidence.

Key words Brain metastases · Surgery · WBRT · SRS

Introduction

As cancer treatment has advanced, the survival of cancer patients has been prolonged, and the number of patients who have concomitant brain metastases has been increasing. According to the 11th edition of the Brain Tumor Registry of Japan,[1] the 1-year and 5-year survival rates of 4839 patients with brain metastases registered between 1991 and 1996 were 43.8% and 13.6%, respectively, whereas the corresponding rates for glioblastoma patients were 55.9% and 7.2%. The prognoses of patients with brain metastases and glioblastomas remain poor, showing similar treatment outcomes. Although various combinations of treatments, including surgery, whole-brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS) have been attempted, the median survival time (MST) of patients with brain metastases is about 1 year, because brain metastases is stage IV cancer and because their prognoses depend largely on the status of the primary focus. In Japan, there are currently about 50 gamma knife and 20 Cyberknife facilities that can easily provide SRS. Patients with multiple metastases or concomitant leptomeningeal metastases, for which WBRT is desirable, are also occasionally treated by SRS only. To improve the survival rate and quality of life (QOL) for these patients with brain metastases, it is necessary to choose the most suitable mode of surgery and radiotherapy, tailored to the individual needs of patients, based on accumulated evidence in different fields of medical practice (evidence-based medicine; EBM).

Y. Narita (✉) · S. Shibui
Neurosurgery Division, National Cancer Center Hospital (NCCH), 5-1-1, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3542-3815
e-mail: ynarita@ncc.go.jp or ynarita-tky@umin.ac.jp

Frequency of patients with brain metastases

According to the Metropolitan Detroit Cancer Surveillance System, brain metastases occurred in 9.6% of approximately 170000 patients diagnosed with cancer from 1973 to 2001.[2] In regard to the primary lesion, the incidence of brain metastases is reportedly 19.9% for lung cancer, 6.9% for melanoma, 6.5% for renal cancer, 5.1% for breast cancer, and 1.8% for colon cancer. A Dutch cohort study (2700 patients) found the incidence of brain metastases over 5 years to be 8.5%, and the incidences by primary lesion site were 16.3% for lung cancer, 7.4% for melanoma, 9.8% for renal cancer, 5.0% for breast cancer, and 1.2% for colon cancer.[3] Thus, approximately 10% of patients who had cancer developed brain metastases. According to Health and Welfare Statistics in Japan, there were 569000 patients with malignant neoplasms in 2001, and it is estimated that more than 50000 develop brain metastases annually. An analysis of autopsy cases revealed a higher frequency of brain metastases; brain metastases were found in 20%–40% of autopsied cancer patients.[4] The number of deaths from malignant neoplasms was approximately 336000 in 2007,

suggesting that there were 60000–120000 patients with brain metastases.[5] The cause of death in cancer patients with brain metastases was reported to be exacerbation of the primary lesion in 50%, and neural death due to brain metastases or leptomeningeal metastases in 30%,[6] suggesting that more than 20000 cases of neural death due to metastatic tumors occur in Japan annually. Considering that the number of annual deaths from primary malignant brain tumors, including glioma, in Japan is approximately 2000, controlling brain metastases is an important goal for neurosurgeons.

According to the 11th edition of the Brain Tumor Registry of Japan[1] based on collected data from mainly neurosurgical facilities, the frequencies of the primary foci in 10071 cancer patients with brain metastases registered between 1984 and 1996 were 52.3% for lung cancer, the highest, followed by breast (8.9%), renal (5.4%), rectal (5.2%), gastric (5.2%), colon (4.1%), head and neck (3.5%), hepatic (2.1%), uterine (1.7%), and thyroid (1.4%) cancers. Pathologically, adenocarcinoma was most frequent, accounting for 58.5%, whereas the frequency of squamous cell carcinoma was 13.5%.

The chief complaints of patients with brain metastases are focal signs including hemiparesis and aphasia (58%), signs of increased intracranial pressure (19%), and complaints without neurological symptoms (10%). Three percent of patients were asymptomatic and those patients were diagnosed by radiological findings.[1]

Prognostic factors

A Radiation Therapy Oncology Group (RTOG) study reviewed about 1200 patients enrolled in clinical trials that used WBRT, and analyzed prognostic factors by recursive-partitioning analysis (RPA) to classify them into RPA classes I-III.[7] Favorable prognostic factors for patients with metastatic brain tumor were Karnofsky performance status (KPS) of 70 or more, no distant metastasis other than brain metastases, controlled primary focus, and age less than 65 years; patients with these factors were considered to represent RPA class I (accounting for 20% of all subjects). KPS less than 70 was a poor prognostic factor, and such patients were categorized as RPA class III (accounting for 15%), whereas other factors were considered to represent RPA class II (accounting for 65%). MSTs were 7.1, 4.2, and 2.3 months for patients in RPA classes I, II, and III, respectively (Table 1). These RPA classes are commonly used when assessing treatment results for brain metastases.

Indications for surgery

Patients with brain metastases often have rapidly progressing neurologic symptoms, necessitating rapid determination of optimal therapeutic strategies. Figure 1 shows the therapeutic strategies used at the National Cancer Center in Japan.

Patients with a single metastasis measuring 3 cm or more, those with smaller tumors such as cerebellar neoplasms associated with severe neurologic symptoms due to cerebral edema, or those with multiple tumors with advanced neurologic symptoms in whom prompt improvement of neurologic symptoms is expected from surgery, undergo

Table 1. RPA classification and prognoses (MST) of cancer patients with brain metastases

Class I	KPS ≧70, age <64 years Controlled primary tumor No extracranial metastases
Class II	KPS ≧70 but other than class I
Class III	KPS <70

	n	Class I MST (months)	Class II MST (months)	Class III MST (months)
WBRT[7]	1176	7.1	4.2	2.3
SRS[16]	265	14.0	8.2	5.3
WBRT + SRS[16]	295	15.2	7.0	5.5
OPE + WBRT[10]	125	14.8	9.9	6.0

RPA, Recursive partitioning analysis; KPS, Karnofsky performance status; MST, median survival time; WBRT, whole-brain radiation therapy; SRS, stereotactic radiosurgery; OPE, operation

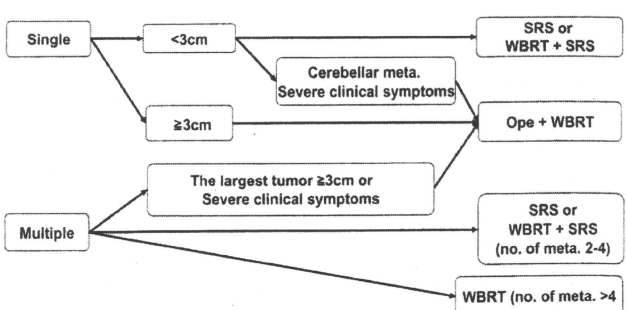

Fig. 1. Surgical and radiotherapy treatment of brain metastases (*meta*). *SRS*, Stereotactic radiosurgery; *WBRT*, whole-brain radiation therapy; *ope*, operation

craniotomy for tumor resection within 1 week of diagnosis and WBRT beginning 8 days after surgery, if possible. MST after WBRT without surgery is approximately 6 months, and therefore surgical candidates have a vital prognosis of at least 6 months. Considering that the MST of patients with brain metastases is approximately 1 year, it is critical to prevent worsening of neurologic symptoms and performance status (PS) in patients undergoing surgery.

Patients who have large cystic lesions in the eloquent area and those with poor PS or poor prognoses who are not good candidates for craniotomy for tumor resection under general anesthesia may undergo palliative insertion of an Ommaya reservoir for cystic tumor management. Removing the fluid content via the Ommaya reservoir to reduce the cyst prior to radiotherapy may effectively alleviate neurologic symptoms. Patients with a metastasis to the mesencephalic aqueduct, brainstem, or cerebellum, and those with obstructed cerebrospinal fluid (CSF) absorption resulting from carcinomatous meningitis may develop acute hydrocephalus. In these patients, endoscopic third ventriculostomy or ventriculoperitoneal shunt may ameliorate impaired consciousness.

Radiotherapy following surgery

According to the Brain Tumor Registry of Japan,[1] among 3793 patients with lung cancer who underwent surgery between 1981 and 1996, radiotherapy was added to the treatment protocol in 41.5%, whereas surgery alone was employed in 58.5%. Although surgery alone is a common therapeutic option in Japan, the 1-year survival rate was 50.9% for surgery combined with radiotherapy and 38.7% for surgery alone, showing better outcomes with the former treatment modality. Because approximately half of the patients undergoing surgery alone subsequently suffer recurrence,[8] the addition of radiotherapy is necessary. In patients with brain metastases, surgery combined with WBRT is the standard treatment worldwide. This strategy is based on the following findings. Patchell et al.[8] carried out a randomized controlled trial (RCT) of surgery + WBRT (36 Gy/12 fractions) vs surgery alone in patients with a single metastasis, and found that the MST was 10 months in the surgery + WBRT group and 3.75 months in the surgery-alone group. The local recurrence rates were 20% and 52%, respectively, and postoperative KPS was also more favorable in the surgery + WBRT arm. Similarly, Vecht et al.[9] reported that surgery combined with WBRT prolonged survival. On the other hand, a randomized study comparing surgery + WBRT (50.4 Gy) to surgery alone showed both local recurrence (10% vs 46%, respectively) and recurrence at other sites (14% vs 37%, respectively) to be significantly less frequent in patients given surgery + WBRT, although there was no significant intergroup difference in MST.[8] Based on the results of these RCTs, surgery combined with WBRT has become the standard treatment for a single brain metastasis. Agboola et al.[10] reported that MSTs with surgery + WBRT were 14.8, 9.9, and 6.0 months for patients in RPA classes I, II, and III (Table 1).

In Japan, postoperative local irradiation has commonly been applied to the site of tumor resection at various facilities. Indeed, until 2002, the National Cancer Center also employed focal radiation therapy (FRT) at 50 Gy in patients with a single tumor. However, there have been no RCTs comparing FRT and WBRT as modes of postoperative radiotherapy. At present, in consultation with radiologists and medical oncologists regarding the optimal postoperative radiotherapy, WBRT at 37.5 Gy (15 fractions/3 weeks) is generally used for patients in RTOG RPA class I postoperatively. In patients in RTOG RPA class II or III who have a poor prognosis due to their general condition, WBRT at 30 Gy (10 fractions/2 weeks) is applied, with the goal of an early return home if possible. An analysis of the mode of recurrence in 109 patients who underwent FRT at 50 Gy ($n = 58$) or WBRT at 30 Gy ($n = 51$) postoperatively at the National Cancer Center demonstrated the absence of recurrence in 43% and 59% of patients given FRT and WBRT, respectively. Thus, recurrence was less frequent in patients given WBRT than in those given FRT. The rates of recurrence at the site of surgery were 12% and 14%, respectively, showing no marked difference. However, recurrence in areas other than the surgical site was slightly more frequent after FRT (33%) than after WBRT (12%). Metastases to the spinal cord occurred in 3% and 4% of patients given FRT or WBRT, respectively, and the incidences of carcinomatous meningitis were 9% and 12%, respectively, showing no marked differences in dissemination of tumors between the two groups.

In 180 patients who underwent craniotomy for tumor resection combined with radiotherapy between 1990 and 2005 in the Neurosurgery Division at the National Cancer Center, MST was 12.3 months. In 47 patients with pulmonary adenocarcinoma, MST was 15.1 months, and the 5-year survival rate was 15.0%. MST and the 5-year survival rate in 18 patients with squamous cell carcinoma of the lung were 14.9 months and 23.2%, respectively, while the corresponding figures were 13.8 months and 32.5%, respectively, in 29 patients with breast cancer.

Surgical complications

The most important issue in the surgical treatment of brain metastases is to avoid deterioration of PS. Even if there is only a possibility that paralysis may be ameliorated by long-term rehabilitation training, partial resection should be employed rather than risking the exacerbation of paralysis due to total resection, and radiotherapy should be used to address possible residual tumor, given its anticipated efficacy.

Paek et al.,[11] who reviewed 208 patients treated surgically, reported that 1.9% died within 30 days, and that postoperative neurologic deterioration occurred in 6%. Systemic complications, including pneumonia, urinary infection, and venous thrombosis occurred in 13.9% of the patients.

In a series of 152 patients who underwent craniotomy for tumor resection between 2000 and 2006 at the National Cancer Center, complications occurred in 6 (3.9%). Exacerbation of paralysis occurred in 2 patients (1.3%) due to postoperative hematoma and in 1 (0.7%) due to tumor resection. One patient (0.7%) developed a surgical wound infection and another, spinal fluid leakage. Sudden cardiopulmonary arrest following suboccipital craniotomy occurred in 1 patient with a cerebellar metastasis from lung cancer. It was speculated that the cardiopulmonary arrest in this patient was attributable to circulatory volume loss due to the use of mannitol at the time of craniotomy, as the patient had had severe intracranial hypertension preoperatively and dehydration had been exacerbated by mannitol or glycerol before surgery. This patient was successfully resuscitated and craniotomy was performed again 1 week later, with successful tumor resection; the patient was discharged without neurologic abnormalities. This case provided a warning regarding the risk of mannitol use in dehydrated patients. There was one death (0.7%) within 30 postoperative days. This patient was elderly (80 years) and was found to have concomitant carcinomatous meningitis at autopsy.

Radiotherapy for patients not suitable for surgery

WBRT is the standard radiotherapy for patients who are not good candidates for surgery, usually with a radiation dose of 30 Gy (3 Gy × 10 fractions/2 weeks). This procedure is reported to exert a therapeutic effect equal to WBRT at 40 Gy (2 Gy × 20 fractions).[12] WBRT at 30 Gy has been widely employed because it requires only a short treatment period. However, irradiation at 37.5 Gy using a lower dose for each fraction (2.5 Gy × 15 fractions/3 weeks) has also been used in many clinical studies, conducted after the RTOG 9508 study, to reduce adverse reactions to irradiation. On the other hand, reported adverse reactions to WBRT include leukoencephalopathy and progressive dementia, ataxia, and incontinence due to radiation-induced necrosis, occurring in approximately 10% of patients.[13,14] SRS using Lekshell Gamma knife (Elekta; Stockholm, Sweden), Cyberknife (Accuray; Sunnyvale, CA, USA), X-knife (Radionics; Burlington, VT, USA), or Linear accelerator (Linac) (Elekta; Stockholm, Sweden) radiosurgery is also useful for treating tumors with diameters of 3 cm or less. In Japan, SRS alone is widely used for single lesions. Serizawa et al.[15] reported that an MST of 9.0 months was achieved in 521 patients who underwent gamma knife radiosurgery. Sneed et al.,[16] reported that MSTs with SRS alone were 14.0, 8.2, and 5.3 months for patients in RPA classes I, II, and III (Table 1).

Although there has been no RCT comparing SRS and WBRT, the Japanese Radiation Oncology Study Group (JROSG) carried out an RCT in patients who had four or fewer brain metastases measuring 3 cm or less to compare WBRT + SRS (65 patients) and SRS alone (67 patients).[17] The 1-year survival rate and MST were 38.5% and 7.5 months, respectively, in the WBRT + SRS group, and 28.4% and 8.0 months, respectively, in the SRS-alone group, respectively, showing no marked differences between the two groups. The frequencies of neural death due to brain metastases were 19.3% and 22.8%, respectively. The respective incidences of new lesions at 1 year and the rates of recurrence of brain metastases, including local recurrence, were 41.5% and 46.8% in the WBRT + SRS group, and 63.7% and 76.4% in the SRS-alone group, demonstrating significantly lower rates with the combination of WBRT and SRS. Additional stereotactic irradiation was required in 10 patients in the combined treatment group and 29 in the SRS-alone group. However, additional stereotactic irradiation was actually performed in 9 and 19 patients, respectively; salvage therapy could not be conducted in all patients with tumor recurrence. The mean memory test score (maximum score, 30 points) on the mini-mental state examination (MMSE) in patients who survived for more than 1 year was 27.0 (range, 23–30) in the combined group and 28.0 (range, 18–30) in the SRS-alone group, showing no significant difference between the two groups. Thus, SRS combined with WBRT did not increase the incidence of dementia as compared with SRS alone. In the randomized RTOG 9508 study, patients who had three or fewer metastatic foci measuring 4 cm or less in greatest dimension underwent WBRT (37.5 Gy/15 fractions) combined with SRS (164 patients, including 92 patients with a single tumor) or WBRT alone (167 patients, including 94 patients with a single tumor).[6] Among those with a single metastasis, MST was 6.5 months in the WBRT + SRS group and 4.9 months in the WBRT-alone group, showing a significant intergroup difference ($P = 0.039$). KPS at 6 months was well maintained or improved in 43% and 27% of the patients in the WBRT + SRS and WBRT-alone groups, respectively, showing significantly better results for the combined irradiation group. The response rate at 3 months and the local control rate at 1 year were also superior in the combined irradiation group, indicating the usefulness of additional SRS in patients with a single tumor. In patients with two to three metastatic foci, MST was 5.8 months after combined irradiation and 6.7 months after WBRT alone, showing no significant difference.

Based on the results of various prior clinical studies, WBRT combined with SRS might be considered to be a feasible standard treatment for a single metastasis.[16,18] However, in Japan, gamma knife radiosurgery alone is often used to treat patients with three to four lesions measuring 3 cm or less in diameter. On the other hand, when medical oncologists describe the above evidence to patients, an increasing number of patients choose gamma knife treatment after WBRT.

In patients with many (five or more) lesions and those who have concomitant leptomeningeal metastases, there is no evidence supporting the propriety of SRS treatment alone, and WBRT is therefore necessary.

When considering the mode of radiotherapy for brain metastases, it is necessary to look at clinical trials that use neurocognitive function as an endpoint, in addition to the survival period and the recurrence rate. There may be

future alterations in the standard treatment, as further evidence is accumulated.

Clinical studies of brain metastases in Japan

Although SRS is associated with more frequent recurrence in untreated areas than WBRT, it is advantageous in that the treatment time is shorter and anorexia and general malaise are mild, in contrast to symptoms seen during or immediately after WBRT. The efficacy of SRS, however, lacks corroborative evidence, in contrast to WBRT, as discussed above. Many patients, however, express concern about irradiation applied to normal brain tissue, believing that it induces progressive dementia. In this regard, the Japan Clinical Oncology Group (JCOG)-Brain Tumor Group started an RCT in 2006 to compare the efficacies of surgery combined with WBRT and surgery combined with additional salvage radiation therapy with SRS for residual tumors in patients with four or fewer brain metastases, using the overall survival period, incidence of dementia (proportion of patients showing worsening of MMSE results), and maintained QOL (proportion of patients with no deterioration of PS) as endpoints. This is a noninferiority study. If it is demonstrated that the test treatment (surgery + additional SRS) is not inferior to the standard treatment (surgery + WBRT) in terms of overall survival, the test treatment is regarded as being more useful. As noted above, WBRT combined with SRS is considered to be the standard treatment for patients suitable for SRS. The actual situation is that SRS alone, performed with a gamma knife or other systems, is employed without careful consideration, for fear of adverse reactions to WBRT. The above JCOG trial and various other clinical investigations, seeking to reduce adverse events and to enhance the efficacy of irradiation, are ongoing.

Recurrence after surgery and radiotherapy

There is no standard treatment for recurrence after surgery combined with WBRT or after radiotherapy. Patients undergo magnetic resonance imaging (MRI) studies every 2–3 months after treatment, and if recurrence is detected, surgery or SRS with a gamma knife will be performed. The therapeutic outcomes of operable patients are not necessarily poor. In patients with recurrence, MST after the second surgery is reportedly 11.5 months,[19] whereas MST after surgery in patients with recurrence after gamma knife radiosurgery is 11.1 months.[20] In a study reported before 1990, when additional gamma knife treatment was not available, patients with recurrences after WBRT at 30 Gy received another WBRT at 25 Gy. Therapeutic efficacy was achieved in 42% of these patients, and MST was 5 months, although there was no detailed discussion of safety.[21]

It is unclear whether these post-treatments achieve better survival or better QOL. The most suitable treatment should be chosen for recurrent cases, based on the patient's general condition, neurologic symptoms, and prognosis.

Leptomeningeal metastases or carcinomatous meningitis

In patients diagnosed with leptomeningeal metastases, MST is 3–6 months.[22] Intrathecal administration of methotrexate (MTX) or cytarabine (Ara-C) is a common treatment strategy. Ommaya reservoir insertion is often employed under local anesthesia to reduce the burden on the patient during lumbar puncture and to achieve intraventricular drug administration. Among the complications of this procedure, rates of extraventricular insertion, postoperative infection, and postoperative bleeding[23] are reportedly 3%–12%, 2%–9% and 1%–3%, respectively. Because postoperative deaths have also been reported, caution is required in selecting this procedure. In our hospital, patients with suspected leptomeningeal metastases undergo lumbar puncture and CSF cytology. Once a definitive diagnosis has been obtained, MTX is given intrathecally by lumbar puncture. When the CSF cell count decreases in response to intrathecal MTX, Ommaya reservoir insertion is carried out to allow intraventricular MTX administration. In patients with neurologic symptoms but no prior radiotherapy, WBRT is added. However, the MST of patients (n = 22) treated with MTX via an inserted Ommaya reservoir at our hospital was only 4 months, a poor outcome.

Use of steroids and anticonvulsants

When using steroids for cerebral edema due to brain metastases, attention should be paid to possible adverse reactions such as gastrointestinal bleeding, hyperglycemia, peripheral edema, mental symptoms including a depressive state and insomnia, osteoporosis, and infectious diseases including oral candidiasis.[24] In patients with paralysis, attention to pulmonary embolism due to deep venous thrombosis (DVT) is necessary. If DVT is suspected, the patient should undergo pelvic computed tomography (CT) and ultrasonography, and prophylactic treatment such as warfarinization or inferior vena cava filter placement should be administered.

Pneumonia resulting from decreased immunocompetence due to steroid therapy is common. It should be kept in mind that *Pneumocystis carinii* pneumonia (PCP) may occur in patients on prolonged steroid therapy or in those of advanced age. Patients treated at our hospital who developed PCP, presumably because of prolonged steroid therapy for malignant glioma, had received the equivalent of 15 mg or more prednisolone. From this experience, we have found that trimethoprim-sulfamethoxazole is effective prophylaxis for PCP.

Convulsive seizures occur in 20%–40% of patients with brain tumors, and it may be surprising that there is as yet no evidence showing a prophylactic effect of antiepileptic drugs on these seizures. In a study of valproic acid and placebo administration in patients with brain tumors (90% had brain metastases) with no history of convulsive seizures,[25] 35% and 24%, respectively, developed convulsions during the mean observation period of 7 months, indicating

that valproic acid exerted no prophylactic effect. The American Academy of Neurology (AAN) reviewed 12 previous studies and concluded that there was no distinct prophylactic effect of antiepileptic drugs on convulsive seizures. Thus, the AAN does not recommend regular administration of antiepileptic drugs to patients who have no history of convulsive seizures.[26]

Phenytoin, phenobarbital, and carbamazepine activate the hepatic enzyme cytochrome P450, thereby enhancing the metabolism of various concomitantly used molecular-targeting drugs and anticancer drugs such as nitrosourea (ACNU), MTX, irinotecan (CPT), and adriamycin (ADM), consequently lowering their blood concentrations. Thus, caution is necessary in continuing systemic chemotherapy.[27] In patients who have convulsive seizures and those at high risk for such seizures because of multiple lesions and other factors, medication should begin with a drug that does not activate P450 (e.g., valproic acid or zonisamide), but caution is necessary, as the anticonvulsant drug itself can cause bone marrow suppression.

Conclusions

MST in patients with brain metastases is only about 1 year. In the treatment of brain metastases, it is necessary to maintain the patient's QOL and activities of daily living. For this purpose, the therapeutic strategy should be decided with the close cooperation of internists, surgeons, radiologists, and neurosurgeons, taking into account the patient's clinical history, PS, neurologic findings, tumor size, number of lesions, control of the primary focus, and prognosis.

Conflict of interest

No author has any conflict of interest.

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INTRODUCTION TO REVIEW ARTICLES

Soichiro Shibui

Treatment of metastatic brain tumors

Received: June 15, 2009

The number of patients with metastatic brain tumors has been increasing because of advances in less invasive imaging modalities such as computed tomography (CT) scanning and magnetic resonance imaging (MRI), improvements in the treatment of extracranial cancers, and the increase of the elderly population. According to the Central Brain Tumor Registry of the United States, the incidence of primary brain tumors is 16.5 cases per 100000 person-years.[1] On the other hand, cancers are detected in 400 persons per 100000 population and of these individuals, 30% or 40% have metastatic brain tumors. This means that the incidence of metastatic brain tumors is estimated to be seven to nine times as high as that of primary brain tumors.

The diagnosis of metastatic brain tumors is usually made by MRI. Most of these tumors show isointensity on T1-weighted images (T1WI) and are highly enhanced by gadolinium-diethylenetriaminepentaacetic acid (DTPA). They are usually round-shaped and the central area shows low intensity on T1WI due to necrosis or fluid collection. Multiplicity is another characteristic of metastatic brain tumors; however, some glioblastomas and malignant lymphomas form multiple intracranial enhancing lesions. The final diagnosis should be made by biopsy if possible.

The prognosis of patients with metastatic brain tumors is poor and most of them have been treated only by irradiation of the whole brain. According to a recursive partitioning analysis of 1200 patients enrolled in three Radiation Therapy Oncology Group (RTOG) clinical trials (RTOG 79-16; 85-28; 89-05), patients with metastatic brain tumors could be classified into three groups. Class 1 includes patients with a Karnofsky performance status (KPS) of 70 or less, age less than 65 years,, controlled primary tumor, and no metastases except in the brain. Class 3 includes patients with a KPS below 70, while all other patients are classified as class 2. The median survivals in classes 1, 2, and 3 were 7.1, 4.2, and 2.3 months, respectively.[2]

On the other hand Patchell et al.[3] reported the significance of surgery for brain metastases. They randomized patients with a solitary brain metastasis into two groups, those receiving whole-brain radiotherapy (WBRT) and those receiving WBRT after craniotomy. The median survival of the WBRT group was only 8 weeks, while that of the surgery + WBRT group was 40 weeks; local recurrence appeared in 52% of the WBRT group and in 20% of the surgery + WBRT group.[3]

Stereotactic radiosurgery (SRS) was introduced for the treatment of brain metastases and has now been used for 20 years. A combination of SRS and WBRT showed better local control than WBRT alone, but longer survival compared with that in the WBRT group was obtained in only a limited subset of patients.[4] It is well known that WBRT influences the cognitive function of patients, and the non-inferiority testing of SRS compared with upfront WBRT is ongoing.

The effect of chemotherapy on brain metastases is controversial. It is difficult to conduct clinical trials because most of the patients receive radiotherapy, and the chemotherapeutic agents that would be chosen are commonly used for the primary cancers. Although most brain metastases are considered to be chemoresistant because of the presence of the blood-brain barrier, they sometimes shrink with only the chemotherapy used for the treatment of the primary cancer. Chemotherapy could be an important treatment modality, particularly for recurrent brain metastases after radiotherapy.

No standard therapy for brain metastases has been established yet. Surgical removal is necessary for large tumors, but only a few patients have a chance of undergoing surgery, because of tumor multiplicity and poor performance status. WBRT, SRS, and chemotherapy should be used appropriately to obtain long survival and maintain a good quality of life for the patients. The cooperation of neurosurgeons, oncologists, nursing staff, social workers, and the patient's family is essential for the optimal treatment of metastatic brain tumors.

S. Shibui (✉)
Neurosurgery Division, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Tel. +81-3-3542-2511; Fax +81-3-3542-3815
e-mail: sshibui@ncc.go.jp

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Image of the Month

A Case of Metastatic Intracranial Malignant Melanoma Mimicking Simple Subcortical Hemorrhage in an Elderly Woman

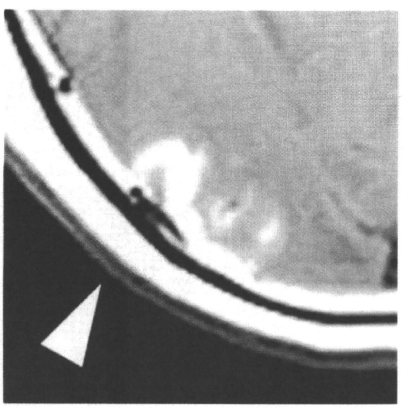

Figure 1.

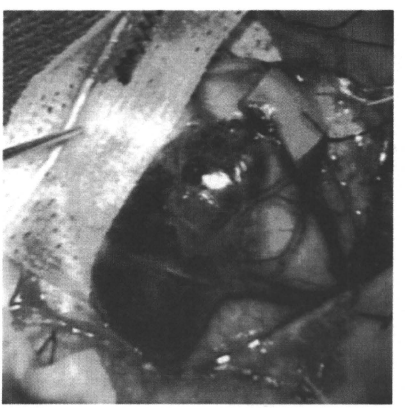

Figure 2.

A 78-year-old female was referred to our institution with a high-density area in an occipital lobe on computed tomographic scan without any signs and symptoms. She had a history of surgical interventions for a breast cancer 17 years ago and an inguinal synovial sarcoma 12 years ago. Systemic evaluation including positron emission tomographic scan demonstrated no active malignancies except for a slow growing thyroid papillary carcinoma. These three kinds of malignancies did not seem to be capable of metastatic spread and the diagnosis at that time was cerebral hemorrhage. Because she was elderly and had no symptom, she was followed as an outpatient. On follow-up magnetic resonance imaging (MRI) without contrast medium 6 months later (Fig. 1), a lesion, which showed high-intensity on MRI gradually increased in size. A high-intensity lesion on MRI would always turn into iso- or low-intensity field as time course if the lesion simply consisted of blood component. In view of the radiological findings and the clinical course, a craniotomy for her occipital lesion was carried out under the diagnosis of hemorrhagic brain tumor or vascular abnormality such as cavernoma. After opening the dura mater, a unique darkish well-circumscribed tumor (Fig. 2; note that a color version of this figure is available as supplementary data at http://www.jjco.oxfordjournals.org) was observed and it was totally removed. The diagnosis was a malignant melanoma. She subsequently received adjuvant radiation therapy. During irradiation for the brain her skin lesion on the forehead, which had been thought as a basal cell carcinoma, was excised and turned out to be a malignant melanoma.

Yasuji Miyakita and Soichiro Shibui
Neurosurgery Division
National Cancer Center Hospital
Tokyo, Japan
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CLINICAL STUDY – PATIENT STUDY

Prediction of malignancy grading using computed tomography perfusion imaging in nonenhancing supratentorial gliomas

Takaaki Beppu · Makoto Sasaki · Kohsuke Kudo · Akira Kurose · Masaru Takeda · Hiroshi Kashimura · Akira Ogawa · Kuniaki Ogasawara

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Abstract Tumor grade differentiation is often difficult using routine neuroimaging alone. Computed tomography perfusion imaging (CTP) provides quantitative information on tumor vasculature that closely parallels the degree of tumor malignancy. This study examined whether CTP is useful for preoperatively predicting the grade of malignancy in glioma showing no enhancement on contrast-enhanced magnetic resonance imaging (MRI). Subjects comprised 17 patients with supratentorial glioma without enhancement on MRI. CTP was performed preoperatively, and absolute values and normalized ratios of parameters were calculated. Postoperatively, subjects were classified into two groups according to histological diagnosis of grade 3 (G3) glioma or grade 2 (G2) glioma. Absolute values and normalized ratios for each parameter were compared between G3 and G2. Accuracies of normalized ratios for cerebral blood flow (*n*CBF) and cerebral blood volume (*n*CBV) in predicting a diagnosis of G3 were assessed. In addition, *n*CBV was compared between diffuse astrocytoma, G2 oligodendroglial tumor (OT), and G3 OT. Values for *n*CBF and *n*CBV differed significantly between G3 and G2. Using *n*CBV of 1.6 as a cutoff, specificity and sensitivity for distinguishing G3 were 83.3% and 90.9%, respectively. No significant difference in *n*CBV was seen between diffuse astrocytoma and G2 OT, whereas differences were noted between G2 and G3 OTs, and between diffuse astrocytoma and G3 OT. CTP offers a useful method for differentiating between G3 and G2 in nonenhancing gliomas.

Keywords Computed tomography perfusion imaging · Diffuse astrocytoma · Glioma · Nonenhancement · Oligodendroglioma · Preoperative diagnosis

T. Beppu (✉) · M. Takeda · H. Kashimura · A. Ogawa · K. Ogasawara
Department of Neurosurgery, Iwate Medical University, Uchimaru 19-1, Morioka 020-8505, Japan
e-mail: tbeppu@iwate-med.ac.jp

M. Sasaki · K. Kudo
Advanced Medical Research Center, Iwate Medical University, Morioka, Japan

A. Kurose
Department of Pathology, Iwate Medical University, Morioka, Japan

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Introduction

Glioma is graded according to World Health Organization (WHO) classification, with grade 1 or 2 graded as low-grade glioma (LGG) and grade 3 or 4 commonly defined as high-grade glioma (HGG) [1]. As treatment and prognosis differ substantially between LGG and HGG, the ability to differentiate between grade 2 (G2) glioma and grade 3 (G3) glioma, as the border between LGG and HGG, is very important. On contrast-enhanced computed tomography (CT) and magnetic resonance imaging (MRI), G2 gliomas are nonenhanced due to preservation of blood–brain barrier (BBB), whereas G3 gliomas are commonly enhanced due to increased vascular permeability caused by disruption of the BBB within the tumor [2–4]. However, the relationship between histological grading and contrast enhancement on CT and MRI is not always clear. Preoperatively differentiating between G3 and G2 gliomas that are nonenhanced on conventional neuroimaging is often difficult. When patients with nonenhancing glioma are encountered, neurooncologists may perform various examinations to differentiate between G3 and G2 gliomas, such as positron emission tomography (PET) for direct assessment of tumor

metabolism, magnetic resonance spectroscopy to detect magnetic resonance signals of metabolites, and diffusion-weighted MRI to clarify structures within and surrounding the tumor. Assessment of intratumoral vasculature is one approach that may help to clarify the intratumoral biological characteristics and malignancy of a tumor, as intratumoral angiogenesis and high vascularity, which are regulated by hypoxia and various vascular endothelial growth factors, are essential for tumor growth and progression [5–7].

Angiography enables direct observation of intratumoral vessels, but is hazardous and remains limited for depiction of intratumoral microvasculature. Magnetic resonance perfusion imaging (MRP) and CT perfusion imaging (CTP) provide reliable information on the intratumoral microvasculature [8–12]. Numerous studies of perfusion imaging have shown that increasing malignancy of the glioma is associated with increased intratumoral blood volume and vascular permeability [10, 13–15]. Quantitative evaluation from perfusion imaging thus depends on both the microvasculature (vascular density and diameter), and vascular permeability due to disruption or absence of the BBB within the tumor. Previous reports have shown good correlations between findings on perfusion imaging and malignancy grading in enhancing glioma. In contrast, the BBB of vessels is preserved in nonenhancing glioma, since extravasation of contrast medium through the BBB in tumor vessels is considered to represent the main cause of tumor contrast enhancement [4]. As MRI remains the preferred technique for assessing brain tumors, studies using MRP to thoroughly evaluate gliomas greatly outnumber those using CTP, and MRP has also been applied to neurooncological applications for nonenhancing gliomas, such as determining biopsy targets and predicting malignant progression [16–18]. In recent years, CTP has gained acceptance as a valuable imaging technique for assessing hemodynamics in brain tumors [13, 14, 19–22]. However, whether CTP is useful for grading malignancy of nonenhancing gliomas remains unclear. CTP retains the advantage of a linear relationship between attenuation changes on CT and tissue concentration of contrast medium, unlike MRP [8, 20]. We therefore hypothesized that CTP should accurately provide quantitative information on only the microvasculature within the tumor, excluding extravasation due to permeability, when limited to patients with nonenhancing glioma. In the present study, we performed CTP on patients with nonenhancing glioma, and compared cerebral blood volume (CBV), cerebral blood flow (CBF), and mean transit time (MTT), as quantitative values provided from CTP, with postoperative histological diagnosis. The present study aims to determine whether CTP is useful for prediction of preoperative malignancy grading (WHO G2 or G3) in nonenhancing glioma on contrast-enhanced MRI.

Patients and methods

Patients

The study protocol was approved by the Ethics Committee of Iwate Medical University, Morioka, Japan. Consecutive patients admitted to the Department of Neurosurgery at Iwate Medical University between September 2006 and January 2010 and meeting the entry criteria were recruited to this study. Entry criteria for this study comprised: diagnosis of supratentorial glioma; tumor bulk not clearly enhanced on gadolinium-enhanced T1-weighted MRI (Gd-T1WI); tumor bulk sited in the supratentorial cerebrum; no past history relating to the brain, including surgical operation, irradiation, administration of anticancer agents or steroids, stroke, infection, or other disorders such as demyelinating disease; and provision of written informed consent to participate. Subjects comprised 17 patients (7 men, 10 women) with mean age of 47.8 years. Patient data including age, tumor site, operation method, postoperative histological diagnosis, and malignancy grade are summarized in Table 1.

Table 1 Patient summary

No.	Age (years)	Tumor site	Surgery	Histology	WHO grade
1	76	Temporal lobe	Biopsy	AA	3
2	58	Frontal lobe	Resection	AO	3
3	45	Frontal lobe	Resection	AO	3
4	34	Frontal lobe	Resection	AO	3
5	29	Frontal lobe	Resection	AO	3
6	21	Frontal lobe	Resection	AOA	3
7	78	Frontal lobe	Biopsy	DA	2
8	68	Frontal lobe	Biopsy	DA	2
9	68	Parietal lobe	Biopsy	DA	2
10	65	Frontal lobe	Resection	DA	2
11	58	Frontal lobe	Resection	DA	2
12	52	Frontal lobe	Resection	Oli	2
13	46	Temporal lobe	Resection	Oli	2
14	42	Frontal lobe	Resection	OA	2
15	30	Frontal lobe	Resection	OA	2
16	27	Frontal lobe	Resection	DA	2
17	16	Temporal lobe	Resection	OA	2

AA anaplastic astrocytoma, *AO* anaplastic oligodendroglioma, *AOA* anaplastic oligoastrocytoma, *DA* diffuse astrocytoma, *Oli* oligodendroglioma, *OA* oligoastrocytoma

Conventional MRI and CTP

Conventional MRI was performed for all subjects within 7 days before surgery. Spin-echo Gd-T1WI was performed approximately 2 min after intravenous injection of gadolinium (0.2 ml/kg, Magnevist; Bayer Schering Pharma, Berlin, Germany), using a 3.0-T whole-body scanner (GE Yokogawa Medical Systems, Tokyo, Japan) with a standard head coil. We confirmed that the tumor in each patient did not show clear enhancement with gadolinium on Gd-T1WI.

CTP was also performed within 7 days before surgery using a 16-row multidetector CT system (Aquillion 16; Toshiba Medical Systems, Tokyo, Japan), in accordance with the methods described by Sasaki et al. [23]. After performing noncontrast CT to determine the location of the tumor balk, a multislice scan targeting the tumor bulk was performed (80 kV_p; 40 mA; 1.5 s/rotation, 30 rotations field of view, 240 × 240 mm^2; four contiguous 8-mm-thick sections; total scan time, 45 s). Five seconds after intravenously injecting 40 ml (4 ml/s) nonionic iodine contrast medium (Iopamiron 300; Bayer Schering Pharma) using a power injector, dynamic scanning was started and tissue attenuation of contrast medium was monitored on a slice. Radiation doses for the scanning protocol were as follows: volume CT dose index, 150 mGy; dose–length product, 480 mGy cm; and effective dose, 1.34 mSv. Data were transferred to a commercial workstation (M900 Quadra; Ziosoft, Tokyo, Japan), and scaled color maps for CBF, CBV, and MTT were automatically created. All mathematical analyses were performed by the deconvolution method [19, 24], using CTP analysis software supplied with the workstation described above. Among the three types of deconvolution algorithms implemented in this software, we used the block-circulant singular value decomposition method. Regions of interest (ROI) for venous output and arterial input functions were manually placed at the superior sagittal sinus and a single branch of the insular segment of the middle cerebral artery on either the pathological or nonpathological side, or A2 segment of the anterior cerebral artery, respectively. ROI were also placed over the entire tumor bulk and apparently normal white matter (ANWM) on the nonpathological side, on color maps for each parameter. Size of the ROI for ANWM was established as 1.0 cm^2. In the measurement of absolute values, the vascular-pixel elimination (VPE) method was used to exclude pixels from large vessels at the cerebral surface, sulci, and cisterns [23, 25]. In the present study, we established the VPE threshold as 6.0 ml/100 g for CBV, since high-CBV areas suggesting large cortical vessels on color map disappeared satisfactorily at 6.0 ml/100 g when the threshold was varied between 5.0 and 8.0 ml/100 g using our analysis software. Large vascular pixels were thus defined as pixels with CBV values >6.0 ml/100 g and were automatically eliminated. Regional absolute values (*r*CBF, *r*CBV, and *r*MTT) were then calculated automatically for all ROI. The measurements described above were performed twice for each patient by two investigators (M.S. and K.K.) who were blinded to all clinical data, including individual patient information and histological diagnosis. Absolute values of all parameters for each patient were determined as the mean of four measured values, as determined twice by each investigator. The second test was performed 1 week after the first test, with a different randomized order of measurements from the first test. We also calculated normalized ratios (*n*CBF, *n*CBV, and *n*MTT) as the absolute value for the tumor divided by the absolute value for the ANWM for each parameter in all patients. All patients underwent surgery, with tumor resection for 13 patients and CT-guided stereotactic needle biopsy for 4 patients (Table 1). The region targeted in stereotactic biopsy was based on findings from the CBV color map. If the color map showed heterogeneous perfusion within the tumor, the targeted region corresponded to the region with the highest perfusion area for CBV. In cases with tumor resection, histological diagnosis was determined by observation at the lesion showing the most malignant histological features in all preparations. Postoperatively, histological diagnosis using specimens obtained from surgery was made by one of the investigators (A.K.) with no prior knowledge of CTP data.

Statistical analyses

All data were analyzed using PASW Statistics version 18 software (SPSS Japan, Tokyo, Japan). Inter- and intrarater reliabilities for all absolute values were evaluated according to classification of the intraclass correlation coefficient (ICC) [26]. For $ICC_{(1,1)}$ and $ICC_{(1,k)}$ as interrater reliability, agreement of all absolute values (CBF, CBV, and MTT) between first and second tests was analyzed for tumor and ANWM for each investigator, using one-factor analysis of variance (ANOVA). For $ICC_{(2,1)}$ and $ICC_{(2,k)}$ as intrarater reliability, agreement of all absolute values between the two investigators was analyzed for tumor and ANWM for each test, using two-factor ANOVA. Patients were assigned to one of two histological grading groups according to histological classification: WHO G2 or WHO G3. Frequency of biopsy was compared between G2 and G3 groups using Fisher's exact probability test. We compared absolute values from the tumor lesion for each parameter between G2 and G3 using the Mann–Whitney *U* test. Furthermore, the normalized ratio for each parameter was compared between these groups again using the Mann–Whitney *U* test. The accuracy of *r*CBF and *n*CBV in predicting a diagnosis of G3 was assessed using receiver

operating characteristic (ROC) curves. ROC curves were calculated in increments of 0.1. Absolute values and normalized ratios for CBV were compared between diffuse astrocytoma, G2 oligodendroglial tumor (OT), and G3 OT, using the Mann–Whitney U test. G2 OTs comprised oligodendroglioma or oligoastrocytoma, whereas G3 OTs comprised anaplastic oligodendroglioma or anaplastic oligoastrocytoma. Statistical significance was established at the $P < 0.05$ level in all analyses.

Results

Based on histological diagnosis after surgery, 6 patients were assigned to the G3 group and 11 patients were assigned to the G2 group (Table 1). Of these 17 patients, 4 patients underwent stereotactic biopsy. Frequency of biopsy did not differ significantly between G3 and G2 groups ($P = 0.25$).

Interrater reliability was classified as "almost perfect" for both tumor and ANWM for each investigator: $ICC_{(1,1)}$ and $ICC_{(1,k)}$ for M.S. were 0.943 and 0.971 for tumor, and 0.961 and 0.980 for ANWM, respectively, and those for K.K. were 0.966 and 0.983 for tumor, and 0.942 and 0.970 for ANWM, respectively. Intrarater reliability was also classified as "almost perfect" for both tumor and ANWM in each test: $ICC_{(2,1)}$ and $ICC_{(2,k)}$ in the first test were 0.987 and 0.993 for tumor, and 0.973 and 0.987 for ANWM, respectively, and those in the second test were 0.971 and 0.985 for tumor, and 0.973 and 0.986 for ANWM, respectively. Absolute values of tumor lesions for each parameter in G3 and G2 groups are summarized in Table 2. Absolute values for all parameters varied widely, with no significant differences in any parameters identified between G3 and G2 groups. Normalized ratios for each parameter are summarized in Table 3. Significant differences between G3 and G2 groups were identified for nCBF and nCBV, with no significant differences in nMTT.

The cutoff for accuracy was defined as the point lying closest to the upper-left corner of the ROC curve.

Table 2 Absolute values for each parameter

	rCBF (ml/100 g/min)	rCBV (ml/100 g)	rMTT (s)
G3 ($n = 6$)			
Range	10.8–27.0	1.9–3.2	6.8–10.8
Mean ± SD	18.3 ± 5.3	2.5 ± 0.5	8.5 ± 1.5
G2 ($n = 11$)			
Range	8.8–23.3	1.3–2.6	7.0–12.2
Mean ± SD	15.5 ± 4.2	2.1 ± 0.4	8.8 ± 1.5
P	0.27	0.25	0.76

SD standard deviation

Table 3 Normalized ratios for each parameter

	nCBF	nCBV	nMTT
G3 ($n = 6$)			
Range	1.34–3.00	1.54–2.39	0.76–1.06
Mean ± SD	2.10 ± 0.57	1.92 ± 0.37	0.90 ± 0.12
G2 ($n = 11$)			
Range	0.92–2.00	0.91–1.75	0.79–1.07
Mean ± SD	1.41 ± 0.38	1.26 ± 0.28	0.91 ± 0.09
P	0.01	0.004	0.76

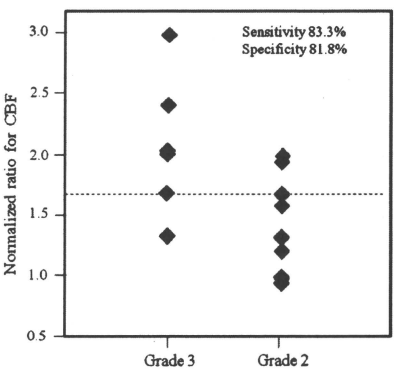

Fig. 1 Relationship between nCBF value and WHO grading. Using a cutoff of 1.7 (*dashed line*), nCBV was ≥1.7 for 5 (83.3%) of 6 patients with G3, compared with <1.7 for 9 (63.6%) of 11 patients with G2

Sensitivity and specificity in predicting a diagnosis of G3 were 83.3% and 81.8% for nCBF (cutoff 1.7), and 83.3% and 90.9% for nCBV (cutoff 1.6) (Figs. 1, 2). Accuracy for predicting a diagnosis of G3 was higher with nCBV than with nCBF.

A comparison of nCBV was made between G3 OT, G2 OT, and diffuse astrocytoma (Table 4). Significant differences in nCBV were identified between G3 and G2 OTs ($P = 0.009$), and between G3 OT and diffuse astrocytoma ($P = 0.02$), whereas no significant difference was seen between G2 OT and diffuse astrocytoma ($P = 0.36$).

Illustrative cases

We now describe the cases of two patients for whom CTP provided useful information for predicting tumor grading. Gd-T1WI for case 6 showed glioma with no clear enhancement in the right frontal lobe (Fig. 3a). Using the

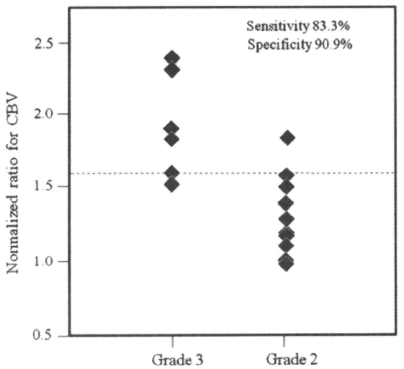

Fig. 2 Relationship between *n*CBV value and WHO grading. Using a cutoff point of 1.6 (*dashed line*), *n*CBV was ≥1.6 for 5 (83.3%) of 6 patients with G3 and <1.6 for 10 (90.9%) of 11 patients with G2

Table 4 Normalized ratio (mean ± SD) for CBV in G3 OT, G2 OT, and diffuse astrocytoma

	*n*CBV
G3 OT ($n = 5$)	1.99 ± 0.36
G2 OT ($n = 5$)	1.16 ± 0.24
Diffuse astrocytoma ($n = 6$)	1.35 ± 0.31

OT oligodendroglial tumors

VPE method, color mapping of CBV demonstrated large vessels of the cerebral surface to be successfully excluded (Fig. 3b). Color mapping of CBV depicted areas of hyperperfusion within the tumor. The *n*CBV for this case (*n*CBV = 2.3) was higher than the cutoff point. Tissue specimens obtained from gross total resection showed typical histological features of G3 anaplastic oligoastrocytoma.

Gd-T1WI for case 14 showed nonenhancing glioma of the right frontal lobe (Fig. 4a). The VPE method satisfactorily eliminated large vessels of the cerebral surface (Fig. 4b). On color mapping, areas of hyperperfusion seemed to be minor compared with those in case 6. The *n*CBV in this case (*n*CBV = 1.2) was lower than the cutoff point. After tumor resection, histological diagnosis was G2 oligoastrocytoma.

Discussion

Previous reports have documented that G3 gliomas make up 40–46% of nonenhancing gliomas on conventional MRI [3, 4]. Our finding of G3 tumors in 6 (35.2%) of 17 patients

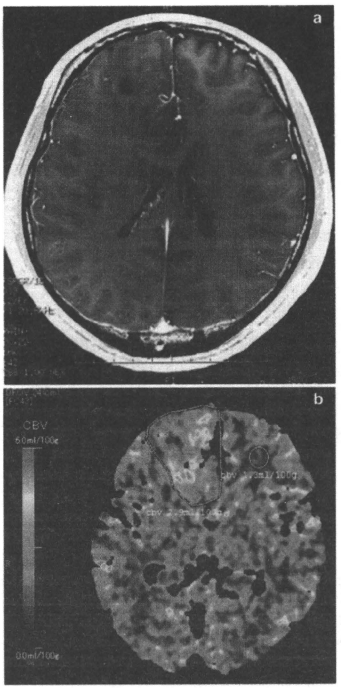

Fig. 3 Gd-T1WI (**a**) and color map of CBV (**b**) for case 6. *Circle* ROI covering the entire tumor bulk and ANWM localized on the nonpathological side

was close to this level. Thus, preoperative differentiation between G3 and G2 using MRI is often difficult. Biopsy or resection allowing histological diagnosis currently remain the basis for differentiation between G3 and G2 gliomas. However, neuroimaging can provide useful information on pathological diagnosis, particularly for patients who do not undergo biopsy or resection allowing histological diagnosis. Novel neuroimaging procedures other than routine MRI are thus desired. CTP and MRP provide reliable information on tumor vasculature, which can help to determine the extent of malignancy in glioma [8, 10, 22]. Although limitations of CTP include radiation dose and limited area of coverage compared with MRP, the linear relationship between attenuation changes on CT and tissue concentration of contrast medium and the lack of confounding sensitivity to flow artifacts allow CTP to

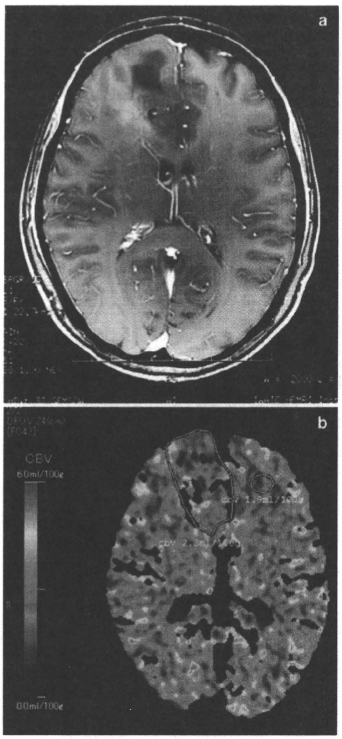

Fig. 4 Gd-T1WI (**a**) and color map of CBV (**b**) for case 14. *Circle* ROI covering the entire tumor bulk and ANWM localized on the nonpathological side

potentially offer a more accurate representation of tissue microvasculature than similar MRP studies [8, 20]. Furthermore, CTP offers advantages such as measurement of quantitative absolute values, greater availability, fast scanning time, high spatial resolution, low cost, and the ability to use this technique for patients who cannot undergo MRI due to the presence of metallic materials in the body [14, 22, 27].

CBF derived from CTP has been suggested to show a tendency toward overestimation, compared with that derived from PET [28]. Since overestimation of CBF in CTP was attributable to the presence of large vessels on the cerebral surface, as contrast materials act as a nondiffusible intravascular tracer in CTP unlike in PET, the VPE method has been proposed to eliminate flow in large vessels [25]. Accurate measurement of CBV contributes to accurate CBF and MTT, as these parameters are closely associated in the central volume principle as CBF = CBV/MTT [29]. We therefore used the VPE method in the present study. We think that optimal threshold differs according to the specific analysis software used for CTP. While VPE threshold was 8.0 ml/100 g in the report by Kudo et al. [25], we established a threshold of 6.0 ml/100 g, since high-CBV areas from cortical large vessels disappeared satisfactorily at this threshold for the analysis software used in our study. Another reason for using the VPE method is that OTs are commonly seen as superficially located tumors in the brain [30, 31]. Elimination of superficial large vessels at the cerebral surface, sulci, and cisterns thus seems warranted when CTP is performed for OTs.

In previous reports of CTP, *r*CBV values ranged from 2.3 to 8.87 ml/100 g for HGG and from 0.95 to 3.28 ml/100 g for LGG, differing significantly between HGG and LGG [13, 14, 20]. The present mean rCBV values in G3 and G2 (Table 2) agreed with previous findings. In addition, mean rCBV values in both G3 and G2 were less than half of 6.0 ml/100 g as VPE threshold. These findings suggest that the VPE method used in this study did not exclude tumor vessels along with other large vessels from CBV maps. While *r*CBV for G3 tended to be on the low side compared with previous reports, this could have resulted from the exclusion of patients with enhancing glioma as subjects in this study. Extravasation of contrast medium through the BBB in enhanced glioma may directly lead to increased CBV, due to the linear relationship between attenuation changes on CT and tissue concentration of contrast medium. Jain et al. [20] documented that *r*CBF and *r*CBV in nonenhancing G3 glioma do not differ significantly from those in nonenhancing G2 glioma, although sample size in that report was small. The present study with more subjects suggested that even nonenhancing G3 glioma retains more vascular density than G2, although the difference in *r*CBV between the two groups was minor (Table 2). However, this result might have been influenced by the disproportionate number of OTs in the G2 (42%) and G3 (83%) groups. If vascular density is significantly higher in G3 OT than in anaplastic astrocytoma, the large number of G3 OTs may have result in a high mean CBV for the G3 group in this study. This issue represents a definite limitation to the present study.

Concentration of contrast medium within the tumor might be subtly influenced by individual parameters such as body size and cardiac output volume, and differences in analytical software among institutes. We must emphasize the importance of estimation using normalized ratios, as

this allows us to ignore these differences. Ellika et al. [22] reported findings for *n*CBV using CTP in 19 patients with glioma, composed of a mixture of enhancing and nonenhancing WHO G1–G4 gliomas, and the utility of *n*CBF and *n*CBV for distinguishing HGG from LGG. They also documented *n*CBF and *n*CBV ranges of 0.78–3.75 and 1.5–3.7 in two patients with nonenhancing G3 glioma, and ranges of 1.26–1.48 and 0.94–1.72 in three patients with nonenhancing G2 glioma, respectively. Mean values of *n*CBF and *n*CBV in G3 and G2 in this study (Table 3) seemed close to the values reported by Ellika et al.

Radiographic grading of gliomas with conventional MRI is not always accurate, with 85.7% sensitivity for predicting HGG, even when including subjects with enhancing glioma [22]. When subjects are limited to those with nonenhancing gliomas, radiographic grading using conventional MRI should be more difficult. A previous report documented 85.7% sensitivity and 100% specificity for identifying HGG using *n*CBV [22]. In the present study, CTP could distinguish nonenhancing G3 glioma from nonenhancing G2 glioma with 83.3% sensitivity and 90.9% specificity using *n*CBV (Fig. 2). This was superior to the results for *n*CBF. Accuracy for distinguishing G3 using *n*CBV in the present study was by no means inferior to that reported by Ellika et al. [22], but subjects in this study were limited to those with nonenhancing glioma. These results suggest that *n*CBV in CTP is useful as an auxiliary examination in addition to routine neuroimaging for predicting the grade of malignancy in nonenhancing gliomas.

Previous studies using MRP have documented higher relative CBV in OT than in other gliomas [32–34]. Lev et al. [33] suggested that OTs tend to appear as high blood volume lesion on MRP, without respect to tumor grade. Two reports using MRP documented that G2 OTs show higher relative CBV than diffuse astrocytoma [32, 34]. Also in a report using CTP by Narang et al. [15], G2 OTs showed a trend towards higher CBV than G2 astrocytic tumors, although no significant difference was found, and no significant difference in CBV between G3 OTs and G2 OTs was identified. Those reports explained the high relative CBV of OT by a hypothesis based on the specific histological features of fine capillary networks [33]. Furthermore, those reports suggested that grading malignancy may be difficult when patients with OT are included, due to a high relative CBV. In the present study, no significant difference in *n*CBV was seen between diffuse astrocytoma and G2 OT, whereas significant differences were found between G3 OT and G2 OT. The difference between the reports described above and the present investigation might be explained by differences between MRP and CTP, and by the use of the VPE method in this study. Signal changes in dynamic susceptibility contrast (DSC) MRI for MRP do not depend on only the concentration of contrast material, but also on T2* or T2 relaxation rates, which are affected by calcified foci and hemorrhage within tumor tissue. These histological features are commonly seen in OTs. DSC signals might thus be higher in OTs than in diffuse astrocytoma, even when the microvascular densities are comparable. The VPE method may have eliminated pixels of high-CBV vessels in OTs, if vascular density in OTs is significantly higher than that in diffuse astrocytoma. However, exclusion of large vessels at the cerebral surface and sulci from CTP maps is important, as OTs grow superficially in the brain. Cha et al. [32] explained for reason of high relative CBV for OTs in MRP by the predominant cortical location in addition to distinct vascular pattern in OTs. We think that CTP with the VPE method is useful for simple malignancy grading in subjects with OTs. Conversely, MRP offers potential advantages for the diagnosis of OTs. However, CTP should not be performed additionally to MRP if the purpose in examination is achieved by MRP, as CTP retains drawbacks such as radiation dose and iodine contrast medium.

The present study possesses some limitations regarding the interpretation of study results. First, the number of patients in this study was small, with remarkably fewer cases of anaplastic astrocytoma compared with OT in G3, as mentioned above. Further investigation including a larger number of cases of anaplastic astrocytoma is needed. A second limitation is the possible discrepancy between histological diagnosis and the region of highest CBV within the tumor. The region targeted for stereotactic biopsy was not rigorously transferred from the region of highest *r*CBV ("hot spots"). However, risk of histological misdiagnosis caused by sampling error during biopsy might be negligible, since the number of patients who underwent biopsy was small in both G3 and G2, and no significant difference in frequency of biopsy was seen between groups. In patients who underwent tumor resection, histological diagnosis was not made using tissue specimens rigorously corresponding to "hot spots." However, histological diagnosis based on the most malignant histological features should be closely associated with high CBV, as increased malignancy is associated with higher vascular density. CTP with a 16-row multidetector CT scanner, covering only four contiguous 8-mm-thick sections, did not cover the entire tumor bulk in some patients. For those patients, histological diagnosis was made using tumor tissues corresponding to the area depicted in CTP. A third limitation was that data calculated from CTP in this study were not the highest CBV values for a small ROI placed in "hot spots" on a color map, but rather were mean values for a large ROI covering the entire tumor bulk. This issue also influences the second limitation. We thought that the simple protocol in this study, combining absolute values as a mean in a large ROI with histological diagnosis from the

area of the most malignant features, is suitable for application in clinical practice, as tissue sampling error of regions corresponding to a small ROI can be avoided. High ICC in inter- and intrarater reliabilities showed that the protocol used in this study offers high reproducibility.

Conclusions

We performed CTP combined with the VPE method for 17 patients, to clarify whether CTP can accurately differentiate between G3 and G2 nonenhancing glioma. Our results showed that *n*CBV from CTP was highly accurate in differentiating G3 from G2 nonenhancing gliomas. The most important result was that CTP enabled differentiation between G3 and G2 nonenhancing OTs. CTP combined with the VPE method offers a useful technique for differentiating between G3 and G2 in nonenhancing gliomas.

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Selection of chemotherapy for glioblastoma expressing O^6-methylguanine-DNA methyltransferase

YASUO IWADATE[1], TOMOO MATSUTANI[1], YUZO HASEGAWA[1], NATSUKI SHINOZAKI[1], TAKASHI OIDE[2], TORU TANIZAWA[2], YUKIO NAKATANI[2], NAOKATSU SAEKI[1] and SHUICHI FUJIMOTO[3]

Departments of [1]Neurological Surgery and [2]Diagnostic Pathology, Graduate School of Medicine, Chiba University, Chiba 260-8670; [3]Division of Chemotherapy, Chiba Cancer Center, Chiba 260-8717, Japan

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Abstract. The therapeutic benefit of nitrosoureas or temozolomide for glioblastoma is limited mainly by O^6-methylguanine-DNA methyltransferase (MGMT) expression. The aim of this study was to evaluate the effectiveness of various anticancer drugs for MGMT-positive glioblastoma. Seventy-four glioblastoma patients were administered various anticancer drugs according to drug sensitivity testing. For the individualization, drug-induced apoptosis was quantified by flow cytometry in the primary culture of surgically resected tumor cells. The MGMT protein expression was analyzed by immunohistochemistry. The median survival of the patients receiving the individualized chemotherapy was 19.4 months (95% CI, 15.9-22.1). The patients with negative MGMT immunostaining had significantly longer survival than those with positive MGMT immunostaining [median survival, 22.3 months (95% CI, 17.6-27.0) vs. 15.1 months (95% CI, 13.4-16.8); p=0.0188]. For MGMT-positive tumors, the platinum agents and the taxanes were more frequently selected for administration than the other categories of anticancer agents. The patient survival period of MGMT-positive glioblastomas treated with the platinum agents or the taxanes [median survival, 20.1 months (95% CI, 18.0-22.7)] was significantly longer than that of MGMT-positive tumors treated with nitrosoureas (p=0.0026), and was equivalent to that of MGMT-negative glioblastomas (p=0.3047). These results suggest that the platinum agents and the taxanes offer the best probability to be effective against immunohistochemically MGMT-positive glioblastomas.

Introduction

The currently available optimum treatment for glioblastoma consists of cytoreductive surgery followed by radiotherapy and chemotherapy (1). This conventional therapeutic strategy results in a median survival of 12-15 months in consecutive, non-selected glioblastoma patients (2-4). Most large-scale clinical studies on chemotherapy for malignant gliomas have utilized nitrosoureas (2,3), and have usually produced negative results regarding the survival gain for glioblastoma patients. Although temozolomide chemotherapy contributes to a significant improvement in patient survival, its benefit is usually restricted to tumors without O^6-methylguanine-DNA methyltransferase (MGMT) expression (4,5). Since the level of MGMT expression strongly influences the efficacy of nitrosoureas or temozolomide (5-9), the establishment of novel therapeutic strategies for MGMT-positive glioblastoma is one of the main issues in contemporary neurooncology.

Current cancer treatments for categories of patients generally require the selection of therapy made on the basis of clinical trials conducted on large populations. However, the heterogeneity in drug sensitivity partly reduces the clinical success gained with these empiric chemotherapeutic regimens used for the general patient population (1). A therapeutic strategy with a protocol modified case by case according to drug sensitivity is termed 'individualized' or 'tailor-made' chemotherapy (10). Published clinical studies using *in vitro* drug sensitivity tests (DST) have shown improved patient response rates as compared with empiric regimens (11-15). The lessons learned from individualized chemotherapy may be valuable in planning chemotherapy regimens for glioblastoma as various anticancer drugs are actually administered in clinics.

We treated glioblastoma patients with various anticancer agents according to individualized protocols selected by DST. However, individualization of chemotherapy cannot easily be adopted in every institution, since it is both time-consuming and non-economical. In this report, the efficacy of each anticancer agent for glioblastoma was retrospectively examined in relation to the MGMT expression status by immunohistochemistry. This information provides a clue for the selection of anticancer drugs against glioblastoma expressing a high level of MGMT or those harboring unmethylated promoter of the MGMT gene.

Materials and methods

Patients. Seventy-four consecutive patients newly diagnosed with glioblastoma according to WHO classification were

Correspondence to: Dr Yasuo Iwadate, Department of Neurological Surgery, Chiba University Graduate School of Medicine, 1-8-1 Inohana, Chuo-ku, Chiba 260-8670, Japan
E-mail: iwadatey@faculty.chiba-u.jp

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