Table 3 Patient distribution according to RPA class

Author	Publication year	Origin	*N*	Patient distribution according to RPA				Overall survival			Predominant treatment
				RPA 1 (%)	RPA 2 (%)	RPA 3 (%)		RPA 1	RPA 2	RPA 3	
Gaspar	1997	Any (breast 12%)	1200	20	64	15	MST (months)	7.1	4.2	2.3	WBRT
Agboola	1998	Any (breast 10%)	125	21	50	36	MST (months)	14.8	9.9	6.0	Surgery + WBRT
Chidel	2000	Any	135	22	71	7	MST (months)	11.2		6.9	SRS
Sanghavi	2001	Any (breast 13%)	502	22	71	7	MST (months)	16.1	10.3	8.7	SRS + WBRT
Lorenzoni	2004	Any (breast 18%)	110	35	55	10	MST (months)	27.6	10.7	2.8	SRS
Samuel	2006	Any (breast 12%)	1288	11	67	21	MST (months)	12.2	6.4	2.2	WBRT
Frazier	2009	Any (breast 14%)	237	15	80	5	MST (months)	15.2	13.0	6.0	SRS
Golden	2008	NSCLC	169	16	75	9	MST (months)	14.6	16.1	7.2	SRS
Gregory	2009	NSCLC	835	11	66	19	MST (months)	13.0	6.2	2.5	WBRT
Liu	2006	Breast	48	23	35	42	MST (months)	23.0	10.2	2.3	WBRT
Viani	2007	Breast	174	22	26	51	MST (months)	11.7	6.2	3.0	WBRT
Akyurek	2007	Breast	49	8	90	2	–	–	–	–	SRS
Rades	2007	Breast	207	14	43	43	1-year (%)	72%	37%	7%	WBRT
Golden	2008	Breast	87	16	79	5	MST (months)	19.5	15.5	12.5	SRS
Le Scodan	2007	Breast	114	2	51	47	MST (months)	8		3	WBRT
Niwinska	2009	Breast	222	9	59	32	MST (months)	15	11	3	WBRT
Subtypes											
Triple negative				14	35	51					
HER2 positive				5	72	23					
Luminal subtype				10	62	28					

RPA recursive partition analysis, *MST* median survival time

This review included 7 publications dealing with BM of any origin [3, 5, 37–41], 2 publications dealing exclusively with NSCLC [4, 42], and 7 publications dealing exclusively with breast cancer [4, 31–33, 43–45]. Some interesting trends were observed as follows:

1. The percentage of patients with RPA III was higher in studies enrolling breast cancer patients (median 42%; range 2–51%) than in those including BM of any origin or BM from NSCLC (median 10%; range 7–36%).
2. The percentage of patients with RPA III was low in studies in which the predominant treatment method was SRS (median 7%; range 2–10%) compared with those in which the main method was WBRT (median 36%; range 15–51%), indicating that SRS was used only for highly selected patients.
3. Among the publications in which the predominant treatment method was WBRT, the percentage of patients with RPA III was higher in studies investigating breast cancer (median 43%; range 32–51%) than in other studies (median 20%; range 15–36%).
4. The median survival time (MST) by RPA classes was similar between breast cancer and the others. The MST for breast cancer and other cancers was, respectively, 17.6 and 14.6 months for RPA I, 10.6 and 10.1 months for RPA II, and 3.0 and 4.4 months for RPA III.

Based on these findings, I think that the prognosis for patients with BM of breast cancer can be accurately predicted by means of RPA, and that any different survival depends on the systemic conditions at the time of BM diagnosis; that is, the systemic status is worse in patients with breast cancer than in those with NSCLC. In relation to systemic status and prognostic factors specific to breast cancer, Niwinska et al. [31] reported that triple-negative breast cancer patients were more often found in RPA class III than patients in the HER2-positive and luminal subgroups (51, 23, and 28%, respectively). As a result, the median survival from BM for the triple-negative subtype was shorter than that for patients in the HER2-positive and luminal subgroups (3.7, 9, and 15 months, respectively). Of interest, positive HER2 status, which has been proved to confer an increased risk of developing BM [22], does not affect prognosis; further, one study has reported that the prognosis of patients with positive HER2 status might be better that of those with negative HER2 status [28]. Other risk factors for the development of BM, such as age, menopausal status, tumor stage, grade, and hormone receptor status, did not affect survival once BMs were diagnosed [23, 46].

Treatment

Trends in the treatment choice for BM in patients with breast cancer

The route of dissemination to the brain is hematogenous; therefore, it is logical to consider that the entire brain may be seeded with micro-metastases. As a result, WBRT has been a mainstay of treatment strategy for BM for a long while. However, the deterioration of neurocognitive function as a result of late radiation toxicity after WBRT among long-term survivors has been a matter of concern. In the early 1990s, a number of gamma knife units were installed in Japan. Since then, treatment relying only on SRS has been widespread. Matsumoto et al. [26] conducted a national questionnaire survey on the treatment choice for breast cancer patients with BM in Japan. They reported that only 8% of physicians considered WBRT as a first-choice treatment for BM. Interestingly, the choice of treatment seems quite different in other countries, including Korea. In their retrospective study of 198 patients with BM from breast cancer in Korea, Lee and colleagues [23] reported that a total of 157 (79.2%) patients received WBRT and only 22 (11%) patients underwent SRS.

Level 1 evidence regarding the treatment of brain metastases

There have been 4 RCTs assessing the value of focal aggressive treatment including conventional surgery [6–8] or SRS [11] combined with WBRT. As summarized in Table 1, 3 out of 4 RCTs exhibited a significant advantage of addition of focal aggressive treatment to WBRT in patients with only one BM [6, 7, 11].

In 2 RCTs, in which focal aggressive treatment (surgery or SRS) alone was compared with focal aggressive treatment in addition to WBRT [9, 10], no significant difference in overall survival was observed; however, a higher frequency of brain tumor recurrence (BTR) at the original or distant sites in the brain was reported. On the basis of these findings, Patchell et al. [9] concluded that WBRT should be given to all patients after surgical resection even when only one BM is present. On the other hand, Aoyama et al. [10] concluded that SRS alone could be a treatment option in cases in which scheduled monitoring of the brain tumor is possible. In order to salvage BTR successfully, we need to know which factors increase the risk of BTR. In a recent study (JROSG 99-1), the number of BM (2 or more), the existence of extracranial metastases, and omission of WBRT were identified as risk factors for BTR at distant sites in the brain. On the basis of these findings, I would like to propose a risk-grouping system based on the risk of

Table 4 Risk of developing distant BM after initial treatment according to the risk factors identified in JROSG99-1

Risk group	Early WBRT		Time after treatment		
			6 months (%)	12 months (%)	24 months (%)
High-risk					
Number of BM; 2 or more	No	BTR at distant site	57	78	78
		OS	61	20	5
Extracranial metastases; exist	Yes	BTR at distant site	21	56	67
		OS	50	32	16
Low-risk					
Number of BM; single	No	BTR at distant site	31	31	65
		OS	75	56	31
Extracranial metastases; none	Yes	BTR at distant site	9	9	22
		OS	67	60	47

BTR brain tumor recurrence

BTR at distant sites in the brain. I propose stratification into two groups, a low-risk group (no extracranial metastases and a single BM) and a high-risk group (existence of extracranial metastases and/or 2 or more BM). Table 4 shows the actuarial 6-month, 12-month, and 24-month BTR rates when patients are classified into low-risk and high-risk groups according to the use of WBRT. As can be seen, the risk of BTR for patients in the high-risk group was twofold higher than that for those in the low-risk group when looking at the BTR at around the MST (57% at 6 months in the high-risk group vs. 31% at 1 year in the low-risk group when WBRT was not used). The use of WBRT reduced the risk of BTR by approximately one-third in both the low-risk and high-risk groups (57% → 21% at 6 months in the high-risk group, and 31% → 9% at 12 months in the low-risk group). Therefore, I believe patients in the low-risk group might benefit from postponing or even omitting early WBRT, because in this way they might avoid its late adverse effects.

Inclusion in the low-risk group

In order to meet the criteria for the low-risk group, i.e., BTR at a distant site in the brain after treatment with SRS alone, patients should have a single BM, brain-only metastasis, and KPS $\geq$ 70. As reviewed in the previous section, the probabilities of single BM in patients with breast cancer and NSCLC were both in the range of 20–45%. However, the rate of brain-only metastases in patients with breast cancer was in the range of 13–32% [14, 47], which was lower than the rate in patients with NSCLC (61.4 and 76% in the reports by Mehta et al. [14]. and Gaspar et al. [16], respectively). In this regard, it is worth noting that HER2 status does not change the rate of brain-only metastases, as reported by Wolstenholme et al. [28] (the rate was 17% in HER2-positive and 22% in HER2-negative patients). Finally, the chance of having a KPS $\geq$ 70 among patients with breast cancer was approximately 60%, which is smaller than the chance in patients with NSCLC (approx. 80%), as shown in Table 3. Taken together, these results suggest that patients with BM from breast cancer are less likely to be included in the low-risk group than those with BM of NSCLC.

Conclusions

Epidemiologic data suggest that patients with BM from breast cancer are twice as likely to be classified into a poor prognostic group (RPA III) than patients with BM from NSCLC; in addition, the probability of brain-only metastases in patients with breast cancer is less than half that in patients with NSCLC. Considering these findings, we should be aware that most patients with BM from breast cancer are not good candidates for treatment with SRS alone, and, therefore, the important role of WBRT should be recognized.

Conflict of interest statement None.

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Clinical Outcomes of Stereotactic Brain and/or Body Radiotherapy for Patients with Oligometastatic Lesions

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Objective: Several recent studies have shown that oligometastatic disease has curative potential, although it was previously considered to signal a patient's last stage of life. Stereotactic body radiotherapy has been available for extra-cranial metastases in addition to stereotactic cranial radiotherapy for brain metastases. The aim of the present study was to retrospectively evaluate the clinical outcomes of stereotactic radiotherapy for patients with oligometastatic lesions.

Methods: Between 1999 and 2008, 41 patients with five or fewer detectable metastases were treated with stereotactic radiotherapy at our institution. The treated oligometastatic lesions were in the brain, lung and adrenal glands.

Results: With a median follow-up period of 20 months, the 3-year overall survival, progression-free survival, local control and distant control rates were 39%, 20%, 80% and 35%, respectively, and the respective 5-year rates were 28%, 20%, 80% and 35%. The median survival time was 24 months. According to interval to recurrence, the 3- and 5-year overall survival rates were 19% and 10%, respectively, for patients with <12 months ($n=18$), compared with 53% and 40% for those with ≥ 12 months ($n=23$) ($P=0.006$).

Conclusions: Precise stereotactic radiotherapy was effective in controlling oligometastatic lesions for patients with a median survival time of 24 months. Interval to recurrence may impact the overall survival rate and should be included in the stratification criteria in a prospective randomized trial to investigate the benefits of stereotactic radiotherapy for patients with oligometastases.

Key words: oligometastases – stereotactic body radiotherapy – stereotactic radiotherapy – radiosurgery

INTRODUCTION

Most patients who have had any recurrent or metastatic sites of cancer are considered to be in their last stage of life. However, stereotactic cranial radiosurgery (SCRS) and stereotactic cranial radiotherapy (SCRT) have been shown to be useful for prolonging useful life in patients with solitary or oligo brain metastases with or without whole brain radiotherapy (WBRT) (1,2). The treatment outcomes are related to the number of metastases and the presence or absence of extra-cranial disease (3). A Phase III study has suggested that SCRS with WBRT results in better survival than WBRT alone for patients with a single brain metastasis or patients with tumors > 2.0 cm in diameter (4). These studies have shed light on the possibility of improving treatment outcomes by using high-dose local radiotherapy with or without whole-body cancer treatment in patients with extra-cranial metastasis.

Stereotactic body radiotherapy (SBRT) with high local dose has been applied to extra-cranial diseases such as peripheral Stage I non-small cell lung cancer (NSCLC) and has been reported to provide excellent local control (LC) and survival compatible with surgery (5,6). Recently, indications for SBRT have been extended to include lung metastases (7–9), liver metastases (10,11), adrenal gland metastases (12,13), spinal metastases (14–16), and others (17). Excellent LC has been reported in these reports, but the clinical benefits of SBRT for extra-cranial metastasis are yet to be determined. In most of these studies, SBRT was used for patients with fewer than five metastatic sites or for those in the clinical state of so-called oligometastasis (18).

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum (18), who hypothesized that LC of oligometastases may yield improved systemic control and prolonged survival. Niibe et al. (19–21) have also reported the state of oligometastasis/oligo-recurrence. They suggested that some oligometastasis/oligo-recurrence patients could survive for as long as the patients with primary cancer only, and thus these patients must be treated curatively. Improvements in diagnostic modalities have facilitated early detection of small metastatic lesions, both intra-cranial and extra-cranial, and have provided a sound rationale for Hellman and Weichselbaum's hypothesis. Recent clinical research has shown that some patients with recurrence or distant metastases can expect long-term survival after SBRT and SCRT (7–11,19–23). It remains uncertain whether these results are due to selection bias or some positive effect of SBRT and SCRT. A prospective randomized trial should be undertaken to answer this question, but prognostic factors to stratify the patients are not yet well understood.

In this study, we retrospectively analyzed our experience with SBRT and/or SCRT/SCRS for patients with oligometastases.

PATIENTS AND METHODS

Patient Characteristics

A database of patients who received SBRT and SCRT/SCRS at our institution was used to select the patients whose primary sites were treated by surgery or definitive radiation therapy between 1995 and 2007. There were 41 patients who had five or fewer detectable oligometastatic lesions at the time of SBRT and/or SCRT and had been treated with SBRT and/or SCRT/SCRS between 1999 and 2008. Diagnosis of the oligometastatic lesions was based on whole-body computed tomography (CT) and brain magnetic resonance imaging (MRI) findings. Fluorodeoxyglucose-positron emission tomography was performed as needed. The oligometastatic lesions were diagnosed by diagnostic radiologists during the diagnostic evaluation.

The treatment methods for the primary sites were surgery in 23 patients and definitive radiotherapy in 18. Definitive radiotherapy consisted of conventional radiotherapy in 8 patients and SBRT in 10.

There were seven patients who had previously been treated by SBRT and/or SCRT/SCRS to oligometastatic sites prior to receiving surgery or radiotherapy at their primary sites. The treatment time interval between the surgery/definitive radiation therapy to the primary sites and the initial SBRT and/or SCRT/SCRS to oligometastatic sites ranged from 1 to 4 months (median 2 months) in these seven patients. In the other 34 patients, the median treatment interval time from primary sites to oligometastatic sites was 21 months (range 0–121 months). We defined the treatment interval time from primary sites to oligometastatic sites as interval to recurrence. In this study, all analyses started from the day of SBRT and/or SCRT/SCRS to oligometastatic sites.

The patient characteristics are given in Table 1. There were 22 men and 19 women, and the median age was 66 years (range 30–82 years). The primary cancers consisted of lung cancer, head and neck cancer, breast cancer, colorectal cancer, renal cell carcinoma, renal pelvic cancer, hepatocellular carcinoma, thymic cancer and apocrine gland cancer. The study patients were separated into a favorable group (breast, colorectal, renal, thymic and apocrine gland cancer) and others, according to Rusthoven et al. (10). The primary histology was mainly adenocarcinoma. The number of oligometastatic tumors was mainly one or two tumors; there were only two patients who had three oligometastatic tumors and only one patient who had five. The sites involved with the oligometastatic lesions were the brain, lung and adrenal gland. Lung and adrenal gland metastases were treated by SBRT. There were no patients with oligometastatic liver metastases treated by SBRT at our institution. Fourteen patients were treated by chemotherapy as an adjuvant therapy or as a treatment for recurrence or metastases. No chemotherapy was administered during the treatment for oligometastases. No patients underwent surgical removal of the metastatic lesions.

There were 24 patients who had single or multiple brain metastases. Brain metastases were treated by SCRT or SCRS. According to the recursive partitioning analysis, 5, 18 and 1 patients were classified as Class I, Class II and Class III, respectively.

SCRT/SCRS Technique

Fifteen of 24 patients were treated by SCRT alone, five by SCRS alone and four by SCRS with WBRT for their brain metastases. The patients who received WBRT were randomly assigned to the group of SCRS with WBRT by the clinical trial of the Japanese Radiation Oncology Study Group (JROSG 99-1) (2). These patients were treated with 6- or 10-MV photons using a linac-based stereotactic system and were immobilized by a thermoshell in SCRT and a stereotactic frame in SCRS. The gross tumor volume (GTV) was defined based on MRI and CT images. A 1–3-mm

Table 1. Patient characteristics (41 patients)

Characteristics	Value
Age (years)	
Median	66
Range	30–82
Gender (*n*)	
Male	22
Female	19
Primary cancer (*n*)	
Lung	25
Head and neck	6
Breast	3
Colorectal	2
Liver	1
Renal	1
Renal pelvic	1
Thymic	1
Apocrine gland	1
Primary histology (*n*)	
Adenocarcinoma	23
Squamous cell carcinoma	6
Thyroid cancer	2
Large cell carcinoma	2
Others	8
Treatment for primary cancer (*n*)	
Resection	23
SBRT	10
Conventional radiation therapy	8
Sites involved with oligometastatic disease (no. of tumors)	
Brain	33
Lung	22
Adrenal gland	5
Number of oligometastatic tumors (*n*)	
1	27
2	11
3	2
4	0
5	1
Number of oligometastatic involved organs (*n*)	
1	37
2	4

SBRT, stereotactic body radiotherapy.

margin was added to the GTV to create the planning target volume (PTV). Treatment was prescribed to the 100% isodose line, with the 80–90% isodose line covering the PTV. A total dose of 15–25 Gy was administered in one fraction for SCRS, and a total dose of 20–40 Gy was administered in four fractions for SCRT. A total dose of 30 Gy was administered in 10 fractions for WBRT.

SBRT Technique

All patients with lung metastases and 10 patients with primary lung cancer received SBRT as the definitive radiotherapy. They received real-time tumor-tracking radiotherapy (RTRT). The RTRT system has been described in detail elsewhere (24,25). In brief, 1.5–2.0-mm gold markers were implanted near the tumor by means of image-guided procedures. CT scans were taken with the patients holding their breath at the end of normal expiration. The GTV was contoured in axial CT images. The clinical target volume (CTV) was defined three dimensionally as the GTV on CT with a 6–8-mm margin for primary lung cancers and was considered to be equal to the internal target volume. We treated adrenal gland metastases using the RTRT system. The CTV was defined as the GTV on CT with a 3-mm margin for adrenal gland metastases and with a 5-mm margin for lung metastases. The PTV was three dimensionally defined as the CTV plus a 5-mm margin with optimal reduction near the organ at risk.

Treatment was prescribed to the 100% isodose line covering the PTV within the 80% isodose line. Patients were treated with 4-, 6- or 10-MV photons. SBRT was delivered by using multiple non-coplanar static ports. A total dose of 48 Gy was administered in eight fractions in patients with adrenal gland metastases. A total dose of 35–60 Gy was administered in four or eight fractions in patients with lung metastases or primary lung cancer, respectively.

Statistical Analysis

LC was defined as no progression of the tumor in the CTV, and marginal recurrence was counted as local failure in this study. Follow-up of the patients was based on clinical examination in the outpatient clinic and/or periodic radiological examination. In principle, radiological examinations such as chest X-ray, whole-body CT and brain MRI were performed once every 3–4 months, but the frequency strongly depended on the clinical situation. The overall survival (OS) and progression-free survival (PFS) rates were calculated from the day of SBRT and/or SCRT/SCRS to oligometastatic sites using the Kaplan–Meier method.

Possible prognostic factors were as follows: age, gender, primary cancer, primary histology, treatment for primary cancer, sites involved with oligometastatic disease, number of oligometastatic tumors and the treatment interval time from primary sites to oligometastatic sites (defined as interval to recurrence). The log-rank test was used to calculate the statistically significant differences. A value of $P < 0.05$ was considered to be statistically significant. Significant variables on univariate analysis (UVA) were tested with

multivariate analyses (MVA). MVA was performed using a Cox proportional hazards regression model.

RESULTS

Local Tumor Response and Distant Metastases

The median follow-up period was 20 months (range 1–111 months). The 3- and 5-year LC rates were each 80%, and the 3- and 5-year distant control (DC) rates were each 35% (Fig. 1).

Survival

The 3-year OS and PFS rates were 39% and 20%, respectively; and the respective 5-year rates were 28% and 20% (Fig. 2). The median survival time (MST) was 24 months. Patients with adrenal gland metastasis had an MST of 15 months.

Age, primary histology and the number of oligometastatic tumors were not found to be statistically significant prognostic factors for the OS rate; however, gender, primary cancer, treatment for primary cancer, oligometastatic lung disease and interval to recurrence were statistically significant prognostic factors for the OS rate in the UVA shown in Table 2.

The OS of female patients was significantly longer than that of male patients ($P = 0.01$), and the OS of patients who had undergone resection for primary cancer was significantly longer than those of others ($P = 0.0006$). For patients with primary cancer from favorable primary sites ($n = 8$), the 3- and 5-year OS rates were both 86%, compared with 27% and 17%, respectively, for patients with primary cancer from other primary sites ($n = 33$, $P = 0.02$). We separated the patients into two groups according to interval to recurrence of <12 or ≥ 12 months ($n = 18$, 23, respectively). The 3- and 5-year OS rates were 19% and 10%, respectively, for those with an interval to recurrence of <12 months, compared with 53% and 40%, respectively, for those with an interval to recurrence of ≥ 12 months (Fig. 3; $P = 0.006$). For patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$), the 3- and 5-year OS rates were both 63%, compared with 22% and 14%, respectively, for patients with only brain/adrenal metastases ($n = 25$) (Fig. 4; $P = 0.009$). MVA showed no statistically significant prognostic factors for the OS rate.

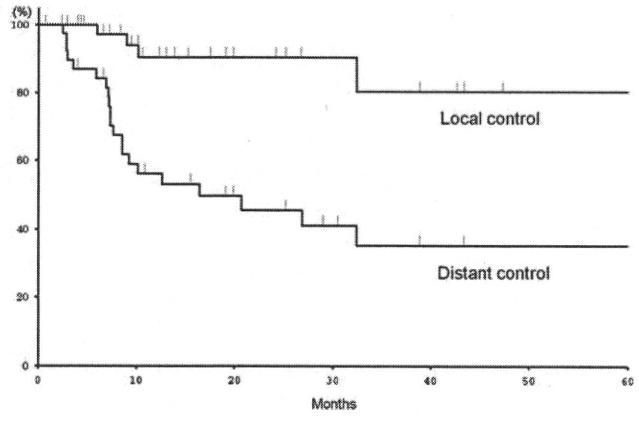

Figure 1. Kaplan–Meier actuarial local control and distant control rate.

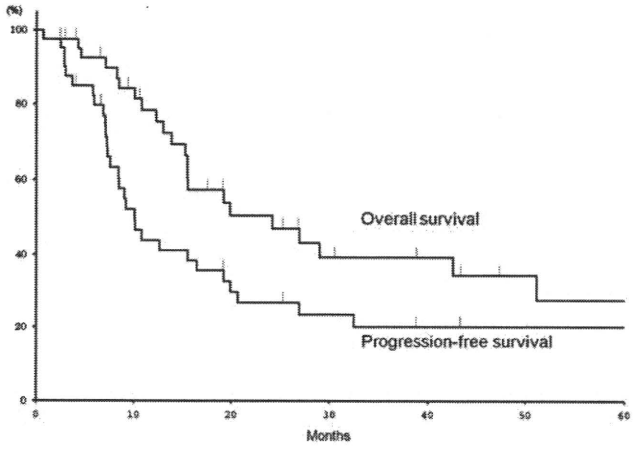

Figure 2. Kaplan–Meier actuarial overall survival (OS) and progression-free survival rate.

Table 2. UVA and MVA for OS rate

Variables	*P* value	
	UVA	MVA
Age		
<65 years	0.72	
Gender		
Female[a]	0.01*	0.72
Primary cancer		
Favorable[a]	0.02*	0.37
Primary histology		
Adenocarcinoma	0.84	
Treatment for primary cancer		
Resection[a]	0.0006*	0.26
Sites involved with oligometastatic disease		
Brain	0.09	
Lung	0.009*	0.47
Adrenal gland	0.09	
Number of oligometastatic tumors		
Single metastasis	0.47	
Interval to recurrence		
≥12 months[a]	0.006*	0.52

UVA, univariate analysis; MVA, multivariate analysis; OS, overall survival.
*Significant ($P < 0.05$).
[a]These variables were favorable predictors for overall survival rate on UVA.

Long Survivors

Four 5-year survivors consisted of two with lung adenocarcinoma, one with renal pelvic cancer and one with thymic cancer. One patient with lung adenocarcinoma had one brain metastasis treated by SCRT, whereas the other patient with lung adenocarcinoma had one brain metastasis treated by SCRS with WBRT and one lung metastasis treated by SBRT. The patient with renal pelvic cancer had two lung metastases treated by SBRT, and the patient with thymic cancer had one lung metastasis treated by SBRT.

Toxicities

Adverse effects were graded according to the Common Toxicity Criteria for Adverse Events, version 3.0. Grade 2 complications occurred in four patients (9.8%), radiation necrosis of the brain occurred in three patients and intercostal neuralgia occurred in one patient. No other adverse effects of Grade 2 or more were observed.

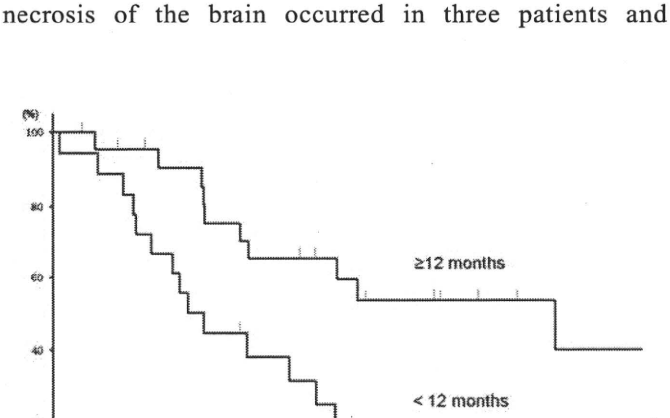

Figure 3. Kaplan–Meier curve of OS rates for patients with interval to recurrence of <12 months ($n = 18$) and ≥ 12 months ($n = 23$). Significant statistical difference was found ($P = 0.006$) between the two groups.

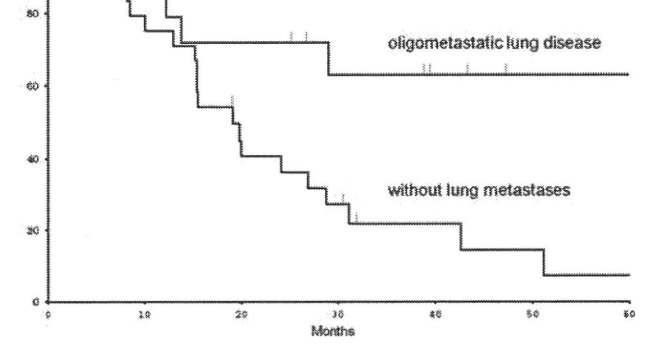

Figure 4. Kaplan–Meier curve of OS rates for patients with oligometastatic lung disease with or without brain/adrenal metastases ($n = 16$) and only brain/adrenal metastases ($n = 25$). Significant statistical difference was found ($P = 0.009$) between the two groups.

DISCUSSION

In this study, the OS rates at 3 and 5 years were 39% and 28%, respectively, and the MST was 24 months, which is equivalent to that in the study of oligometastases previously published, as follows. Milano et al. (22) reported the results of a Phase II trial using SBRT to a dose of 50 Gy in 10 fractions in the treatment of oligometastatic disease with 4-year OS, PFS, LC and DC rates of 28%, 20%, 60% and 25%, respectively. Patients with breast cancer fared significantly better with respect to OS, PFS, LC and DC rates (26), and those with adrenal metastases had significantly worse OS, LC and DC rates (13).

Rusthoven et al. (9,10) have recently reported the results of multi-institutional Phase I/II trials of SBRT for lung and liver metastases. The actual LC rate at 1 and 2 years after SBRT for oligometastatic lung tumors were 100% and 96%, respectively, and the MST was 19 months. The actual in-field LC rates at 1 and 2 years after SBRT for oligometastatic liver tumors were 95% and 92%, respectively, and the MST was 20.5 months. The primary tumor site was significantly predictive of survival. Primary tumors of the lung and ovary as well as non-colorectal gastrointestinal malignancies were found to be associated with poorer survival compared with breast, colorectal, renal, carcinoid and gastrointestinal stromal tumors as well as sarcoma.

Flannery et al. (23) have reported long-term survival in patients with synchronous solitary brain metastasis from NSCLC treated with radiosurgery. The MST was 18 months, and the 1-, 2- and 5-year actuarial OS rates were 71.3%, 34.1% and 21%, respectively. For patients who underwent definitive thoracic therapy, the 5-year actuarial OS rate was 34.6% compared with 0% for those who had non-definitive therapy. The Karnofsky performance status (KPS) also significantly impacted the OS rate.

SBRT and SCRT have been applied for the treatment of metastatic lesions recently; however, conventional radiotherapy remains a standard option for the treatment of metastatic lesions. Andrews et al. (4) reported the result of a Phase III study that compared WBRT with or without SCRS for brain metastases. This study showed WBRT with SCRS improved survival for patients with single brain metastasis or patients with tumors > 2.0 cm in diameter. To our knowledge, there has been no study that compared SBRT with conventional radiotherapy for extra-cranial metastases.

It is important to find prognostic factors related to long-term survival after definitive therapy such as SBRT and SCRT for oligometastatic lesions. According to the studies described above, KPS, the primary tumor site and the oligometastatic site can be predictive of survival. Low KPS, a primary tumor site such as the lung and adrenal metastasis were found to be associated with lower survival in the

previous study (9,10,13,22,23,26). However, our results have shown that some patients with lung cancer can survive >5 years after treatment for oligometastases and that some with adrenal metastatic tumors can expect an MST of 15 months. These findings are consistent with those of Khan et al. (27). It would therefore be useful to find prognostic factors that are independent of the primary and metastatic sites.

In this study, we identified another factor that can be used to predict long-term survival. The treatment interval time from primary sites to oligometastatic sites, defined as interval to recurrence, was found to be significantly associated with the OS rate in the UVA. A long interval to recurrence implies that the patient has a slowly growing tumor or is under good control with regard to primary and other sites except for the apparent metastatic lesions. In contrast, a short interval to recurrence indicates rapid tumor growth or poor control of the primary and other metastatic sites. Although it was difficult to distinguish between the natural course of the disease and the effects of treatment in this retrospective study, interval to recurrence was shown to be an independent parameter to predict prognosis for patients with oligometastases.

The clinical state of oligometastatic disease was proposed in 1995 by Hellman and Weichselbaum (18), but a clear definition for oligometastasis has not yet been established. Table 3 shows various definitions of oligometastasis reported previously in the literature. The number of oligometastases ranges from 1 to 6 tumors. Oligometastatic lesions are mainly in the lung, liver and brain, although oligometastases in the bone, adrenal gland, lymphatic nodes and soft tissue have also been reported. In the present study, we defined the number of oligometastases as ranging from 1 to 5 tumors, and oligometastatic lesions were found in the lung, brain and adrenal gland, which is consistent with several previous reports. A definitive definition of oligometastasis may not be possible, due to its diverse nature, but a clear definition is required for further investigation.

Table 3. Definition of oligometastasis

	Number of patients	Oligometastases	Oligometastatic lesions
Norihisa et al. (8)	34	1–2	Lung
Rusthoven et al. (9)	38	1–3	Lung
Rusthoven et al. (10)	47	1–3	Liver
Katz et al. (11)	69	1–6	Liver
Rades et al. (14)	521	1–3	Vertebrae
Salama et al. (17)	29	1–5	Lung, node, liver, bone, soft tissue, adrenal gland
Milano et al. (22)	121	1–5	Lung, node, liver, brain, adrenal gland, bone
Flannery et al. (23)	42	1	Brain
Khan et al. (27)	23	1–2	Lung, brain, soft tissue, adrenal gland, bone
Current study	41	1–5	Lung, brain, adrenal gland

One shortcoming of this paper is the retrospective nature of the analysis. Patients with sufficient medical conditions were probably selected beforehand to receive SBRT and SCRT. The large number of patients who died within a short period may have masked the possible progression of the disease and local failure. However, it is notable that there is a definite group of patients treated with SBRT and SCRT who experienced long survival even with distant metastasis. A large prospective trial is required to investigate the actual benefits of SBRT and SCRT for patients with oligometastases. Our findings suggest that interval to recurrence should be included in the stratification criteria in a prospective randomized trial comparing treatment with or without SBRT and SCRT.

In conclusion, precise SBRT and SCRT were effective in controlling oligometastatic lesions for patients with an MST of 24 months. Interval to recurrence may impact the OS rate and should be included in the stratification criteria of a prospective randomized trial to investigate the benefits of SBRT and SCRT for patients with oligometastases.

Conflict of interest statement

None declared.

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CLINICAL INVESTIGATION

IMPACT OF [^{11}C]METHIONINE POSITRON EMISSION TOMOGRAPHY FOR TARGET DEFINITION OF GLIOBLASTOMA MULTIFORME IN RADIATION THERAPY PLANNING

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Purpose: The purpose of this work was to define the optimal margins for gadolinium-enhanced T_1-weighted magnetic resonance imaging (Gd-MRI) and T_2-weighted MRI (T_2-MRI) for delineating target volumes in planning radiation therapy for postoperative patients with newly diagnosed glioblastoma multiforme (GBM) by comparison to carbon-11-labeled methionine positron emission tomography ([^{11}C]MET-PET) findings.

Methods and Materials: Computed tomography (CT), MRI, and [^{11}C]MET-PET were separately performed for radiation therapy planning for 32 patients newly diagnosed with GBM within 2 weeks after undergoing surgery. The extent of Gd-MRI (Gd-enhanced clinical target volume [CTV-Gd]) uptake and that of T_2-MRI of the CTV (CTV-T_2) were compared with the extent of [^{11}C]MET-PET (CTV–[^{11}C]MET-PET) uptake by using CT–MRI or CT–[^{11}C]MET-PET fusion imaging. We defined CTV-Gd (x mm) and CTV-T_2 (x mm) as the x-mm margins (where x = 0, 2, 5, 10, and 20 mm) outside the CTV-Gd and the CTV-T_2, respectively. We evaluated the relationship between CTV-Gd (x mm) and CTV– [^{11}C]MET-PET and the relationship between CTV-T_2 (x mm) and CTV– [^{11}C] MET-PET.

Results: The sensitivity of CTV-Gd (20 mm) (86.4%) was significantly higher than that of the other CTV-Gd. The sensitivity of CTV-T_2 (20 mm) (96.4%) was significantly higher than that of the other CTV-T_2 (x = 0, 2, 5, 10 mm). The highest sensitivity and lowest specificity was found with CTV-T_2 (x = 20 mm).

Conclusions: It is necessary to use a margin of at least 2 cm for CTV-T_2 for the initial target planning of radiation therapy. However, there is a limit to this setting in defining the optimal margin for Gd-MRI and T_2-MRI for the precise delineation of target volumes in radiation therapy planning for postoperative patients with GBM. © 2010 Elsevier Inc.

[^{11}C]Methionine-PET, Glioblastoma, Radiotherapy, Target definition, MRI.

INTRODUCTION

Glioblastoma multiforme (GBM) is the most common type of primary brain tumor in adults, and the treatment of GBM remains one of the most challenging endeavors in oncologic treatment. The current standard of care for newly diagnosed GBM is surgical resection, to the extent that it is feasible, followed by adjuvant radiotherapy and chemotherapy (1). Several studies over the past few decades have attempted to define the optimal radiation dose for GBM, yet the results have not been satisfying (2–4).

Highly accurate radiation therapy techniques such as stereotactic radiotherapy, radiosurgery, intensity-modulated radiotherapy, and proton therapy have recently developed. Improved survival by using such highly accurate radiation therapy is possible because high-dose irradiation to a limited target volume eradicates tumor cells while minimizing radiation exposure to normal, functional brain tissue. For this therapy to succeed, the first premise is that the extent of tumor must be correctly defined. Accurate definitions of the gross target volume (GTV) and the clinical target volume (CTV) are crucial.

To determine the radiation therapy treatment volume for GBM, many studies have used the enhanced area or peritumoral edema area on magnetic resonance imaging (MRI)

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or computed tomography (CT), respectively, to determine initial radiation treatment volume as well as boost volume (5–7). For instance, the method for target delineation of GBM at the University of Texas M. D. Anderson Cancer Center has been to define the CTV as the enhanced area (GTV) plus 2 cm and the planning target volume (PTV) as the CTV plus 0.5 cm (5). An alternate method, used by the Radiation Therapy Oncology Group (RTOG), is to define the initial field as the peritumoral edema plus 2 cm and the dose prescribed to this area is 46 Gy. The boost field is defined as the GTV plus 2.5 cm, and the dose prescribe to this area is 60 Gy (5–7). However, evidence for the margin of the enhanced area or the peritumoral edema of the GBM tumor is not sufficient (5).

Positron emission tomography (PET) has been used for 2 decades to assess the cerebral metabolism of patients with gliomas (8, 9). Carbon-11-labeled methionine PET ([^{11}C]MET-PET) plays an especially important role in improving diagnostic procedures for treating brain tumors (10). [^{11}C]Methionine is not taken up by normal brain tissue to a marked degree, and the sensitivity of [^{11}C]MET-PET for detecting glioma tumors appears to be high (11–16). [^{11}C]MET-PET uptake by normal brain parenchyma is relatively low, and so [^{11}C]MET-PET shows promise for assessing cerebral tumor dimensions (17). It has been suggested that [^{11}C]MET-PET may more precisely outline the true extent of viable tumor tissue than MRI, whereas MRI has the capability to better delineate the total extent of associated pathologic changes, such as edema, in adjacent brain areas (18).

We undertook the present study of quantified results of [^{11}C]MET-PET and those of MRI to compare their abilities to delineate the extent of GBM and to show the implications of [^{11}C]MET-PET for treatment planning. Therefore, the extent of gadolinium (Gd) enhancement on T_1-weighted MRI and the high-intensity area on T_2-weighted MRI were compared with the extent of uptake of [^{11}C]MET-PET by using CT–MRI or CT–[^{11}C]MET-PET fusion imaging. We conducted this study to investigate the extent to which tumor growth was present and to quantify this growth in GBM by comparing MRI and [^{11}C]MET-PET. We assumed [^{11}C]MET-PET was the gold standard in this study for delineating the CTV, and we determined the optimal margins of Gd enhancement and high-intensity areas on T_2-weighted imaging. We evaluated the validity of the margins by comparison with those reported in a study by Jansen et al. (19), which correlated results of histopathologic observations with CT/MR images.

METHODS AND MATERIALS

During the 2-year period between April 2006 and December 2008, 32 postoperative patients, newly diagnosed and histologically confirmed with GBM (Table 1), underwent stereotactic radiotherapy treatment planning at our department.

CT, Gd-enhanced T_1-weighted and T_2-weighted MRI, and [^{11}C]MET-PET were performed separately within 2 weeks after the 32 patients (18 men and 14 women; age range, 21-85 years; mean age, 64 years) underwent surgery. Steroid doses were not changed during the week in which MRI and [^{11}C]MET-PET were performed.

Table 1. Patient characteristics

Characteristics	Values
Age (y)	
Median	64
Range	21–85
Gender (*n*)	
Male (*n*)	18
Female (*n*)	14
RPA class	
III	3
IV	19
V	2
VI	8
Resection	
Gross total resection	16
Subtotal resection	10
Partial resection	6
Tumor location	
Frontal	9
Parietal	4
Temporal	12
Thalamus	1
Cerebellum	2
Basal ganglia	2
Two lobes	
Parieto-occipital	1
Temporo-occipital	1

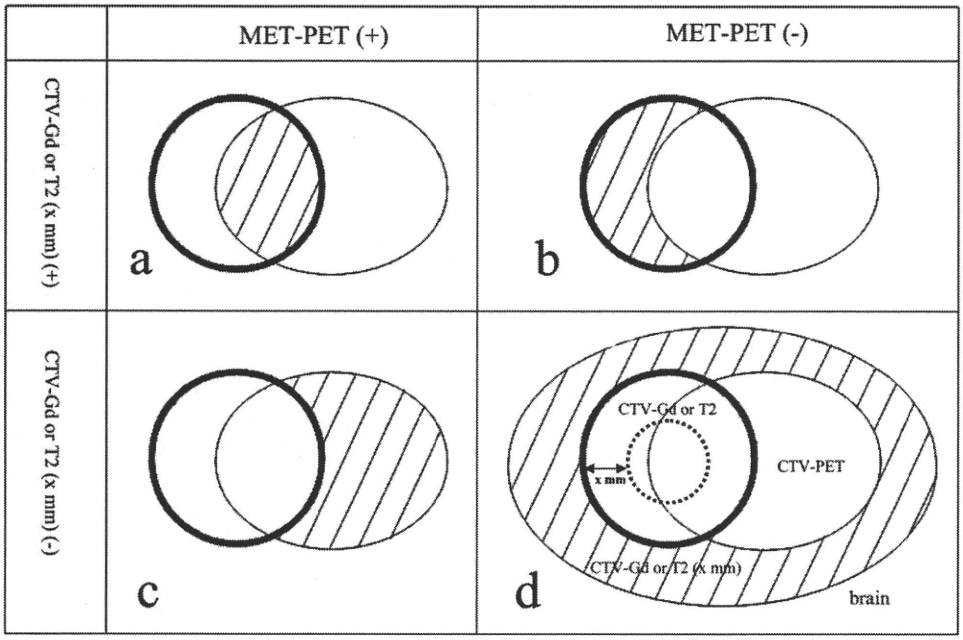
Abbreviation: RPA = RTOG recursive partitioning analysis.

Imaging

Computed tomography was performed using helical CT equipment (Light Speed; General Electric, Waukesha, WI). Patients' heads were immobilized in a commercially available stereotactic mask, and scans were performed in 2.5-mm-thick slices without a gap.

Magnetic resonance imaging for radiation treatment planning was performed using 1.5-T equipment (Light Speed; General Electric, Waukesha, WI). Images were acquired using a standard head coil without rigid immobilization. Axial, three-dimensional gradient echo T_1-weighted sequences (matrix size, 256 × 256; field of view, 25 cm × 25 cm) with contrast medium (gadolinium-diethylenetriamine-pentacetic acid [Gd-DTPA; Magnevist, Schering, Berlin, Germany], 0.1 mmol/kg of body weight) at 2.0-mm slice thicknesses were acquired from the foramen magnum to the vertex, perpendicular to the main magnetic field. The T_2-weighted (2600/102 [effective]) images were acquired with a 512 × 224 matrix and a 24-cm field of view with a 6-mm-slice thickness.

The [^{11}C]MET-PET study was carried out using a standardized procedure. All patients fasted for at least 5 h before undergoing [^{11}C]MET-PET, and they were advised to have only a light breakfast on the morning of the examination day to ensure standardized metabolic conditions. The PET scanner used was an Advance NXi imaging system (General Electric Yokokawa Medical System, Hino-shi, Tokyo, Japan), which provides 35 transaxial images at 4.25-mm intervals. The crystal width is 4.0 mm (transaxial). The in-plane spatial resolution (full width at half-maximum) was 4.8 mm, and scans were performed in standard two-dimensional mode. Before the emission scans were performed, a 3-min transmission scan was performed to correct the photon attenuation, using a ring source containing 68 Ge. A dose of 7.0 MBq/kg [^{11}C]



dotted line = CTV-Gd or T2, bold line= CTV-Gd or T2 (x cm), standard Line = CTV-PET

$$\text{Sensitivity} = \frac{a}{a+c} \qquad \text{Positive predictive value} = \frac{a}{a+b}$$

$$\text{Specificity} = \frac{d}{b+d} \qquad \text{Negative predictive value} = \frac{d}{c+d}$$

Fig. 1. We defined sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) by making comparison with the [^{11}C]MET-PET findings, which served as the gold standard in this study.

MET was injected intravenously, depending on the examination. Emission scans were acquired for 30 min, beginning 5 min after injection of [^{11}C]MET. During [^{11}C]MET-PET data acquisition, the patient's head position was continuously monitored using laser beams projected onto ink marks drawn over the forehead skin, and the head position was corrected as necessary.

Image registration was performed using Syntegra software (Philips Medical System, Fitchburg, WI) and a combination of automatic and manual methods. The quantitative accuracy of the mutual information registration was evaluated and approved by three observers, *i.e.*, a neurosurgeon, a radiation oncologist, and a nuclear medicine specialist.

Target volume delineation

The three observers delineated CTV using Gd-enhanced T_1-weighted MRI alone, T_2-weighted MRI alone, and [^{11}C]MET-PET alone, respectively. CTV volumes defined by [^{11}C]MET-PET, Gd-enhanced T_1-weighted MRI, and T_2-weighted MRI were delineated manually. Gd-enhanced T_1-weighted MRI CTV (CTV-Gd) was defined as the contrast-enhanced area on the Gd-enhanced T_1-weighted MRI, and the CTV-Gd (x mm) was defined as the x-mm (where x = 0-, 2-, 5-, 10-, and 20-mm) margin outside the CTV-Gd. The T_2-weighted MRI CTV (CTV-T_2) was defined as the high-intensity area on the T_2-weighted MRI, and we defined CTV-T_2 (x mm) as the x-mm (x = 0-, 2-, 5-, 10-, and 20-mm) margin outside the CTV-T_2 area (Fig. 1). The CTV-Gd (x-mm) and CTV-T_2 (x-mm) surfaces were then edited to limit expansion into adjacent skull. The [^{11}C]MET-PET CTV (CTV–[^{11}C]MET-PET) was defined as the area of accumulation of [^{11}C]MET, which was apparently higher than that in normal tissue on [^{11}C]MET-PET. The CTV– [^{11}C]MET-PET tumor/normal tissue index of 1.3 was considered the threshold for malignant activity. It is not clear which threshold value for the tumor/normal tissue index should become the reference value for determining GBM. For primary brain tumor, some reports have used 1.3 or 1.7 to determine the threshold value (12, 20). Although we used 1.3 as the threshold for tumor delineation in this study, the final determination of tumor delineation was obtained by consensus among three observers, and they did not necessarily adhere to a uniform threshold value of 1.3 for the tumor/normal tissue index. The same window parameters were used for all patients included in the trial.

Analysis

We defined sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) by making comparisons with the [^{11}C]MET-PET findings, which served as the gold standard in this study (Fig. 1). For statistical analyses, the statistical significance of the differences in the relationship between CTV-Gd (x mm) and CTV- [^{11}C]MET-PET and those of the relationship between CTV-T_2 (x mm) and CTV- [^{11}C]MET-PET were examined by using Tukey's test for multiple comparisons. A p value of <0.05 was considered statistically significant. We evaluated the validity of the margins by comparison with those reported in a study by Jansen et al. (19), which correlated results of histopathologic observations with CT/MR images.

RESULTS

The clinical characteristics and tumor locations of the 32 patients included in this study are given in Table 1. Patients

Table 2. Sensitivity, specificity, PPV, and NPV of CTV-Gd and CTV-T_2

Protocol	Sensitivity*	Specificity	PPV	NPV
CTV-Gd Mean (SD) (%)	**28.6 (5.2)**	99.4 (1.0)	73.6 (29.7)	95.1 (4.2)
CTV-Gd (2 mm) Mean (SD) (%)	**44.3 (30.1)**	98.8 (1.6)	68.0 (27.2)	95.9 (4.0)
CTV-Gd (5 mm) Mean (SD) (%)	**55.6 (30.2)**	**97.8 (2.3)**	**59.8 (24.5)**	**96.5 (3.7)**
CTV-Gd (10 mm) Mean (SD) (%)	**72.0 (27.9)**	**94.8 (4.2)**	**44.3 (19.6)**	**97.4 (3.3)**
CTV-Gd (20 mm) Mean (SD) (%)	**86.4 (21.5)**	**84.2 (8.7)**	**24.7 (13.5)**	**98.4 (2.5)**
CTV-T2 Mean (SD) (%)	61.1 (25.5)	97.2 (2.8)	**58.0 (26.8)**	**97.1 (2.8)**
CTV-T2 (2 mm) Mean (SD) (%)	72.4 (24.2)	95.1 (4.2)	**48.9 (24.7)**	**98.0 (2.5)**
CTV-T2 (5 mm) Mean (SD) (%)	81.9 (21.5)	**92.2 (5.7)**	**40.4 (21.8)**	98.4 (2.2)
CTV-T2 (10 mm) Mean (SD) (%)	89.4 (15.1)	**85.5 (8.8)**	**28.5 (16.6)**	**98.9 (1.7)**
CTV-T2 (20 mm) Mean (SD) (%)	96.4 (7.0)	**68.3 (13.4)**	**15.9 (9.6)**	**99.6 (1.3)**

Abbreviations: NPV = negative predictive value; PPV = positive predictive value; SD = standard deviation.

* Values in boldface type indicate $p < 0.05$ using Tukey-type multiple comparisons.

were grouped according to the RTOG recursive partitioning analysis (RPA) class (21). Most patients were put into RPA class IV ($n = 19$), and smaller numbers were in classes VI ($n = 8$), III ($n = 3$), and V ($n = 8$).

Table 2 shows sensitivity, specificity, PPV, and NPV for CTV-Gd (x mm) and CTV-T_2 (x mm). The sensitivity of CTV-Gd (20 mm) (86.4%) was significantly higher than that of the other CTV-Gd ($x = 0, 2, 5, 10$ mm). The specificity of CTV-Gd (x = 0, 2, 5 mm) was significantly higher than that of the other CTV-Gd (x = 10, 20 mm). The PPV of CTV-Gd (x = 0, 2 mm) was significantly higher than that of the other CTV-Gd (x = 5, 10, 20 mm). The NPV of CTV-Gd (x = 20 mm) was significantly higher than that of the other CTV-Gd (x = 0, 2, 5, 10 mm). The sensitivity of CTV-T_2 (20 mm) (96.4%) was significantly higher than that of the other CTV-T_2 (x = 0, 2, 5 mm). The specificity of CTV-T_2 (x = 0 mm) was significantly higher than that of the other CTV-T_2 (x = 5, 10, 20 mm). The PPV of CTV-T_2 ($x = 0$ mm) was significantly higher than that of the other CTV-T_2 ($x = 0, 2, 5, 10, 20$ mm). The NPV of CTV-T_2 ($x = 20$ mm) was significantly higher than that of the other CTV-T_2 (x = 0, 2, 5, 10 mm).

Figure 2 shows the sensitivity and specificity values of CTV-Gd (x = 0, 2, 5, 10, 20 mm) and that of CTV-T_2 (x = 0, 2, 5, 10, 20 mm). The highest sensitivity and lowest specificity values were shown by CTV-T_2 ($x = 20$ mm). The lowest sensitivity and highest specificity values were shown by CTV-Gd ($x = 0$ mm). Table 3 compares our results with those reported by Jansen *et al.* (19), correlating histopathologic observations and use of CT or MR images. Hochberg *et al.* (22) reported 29/35 (82.9%) tumor cells were within 2 cm

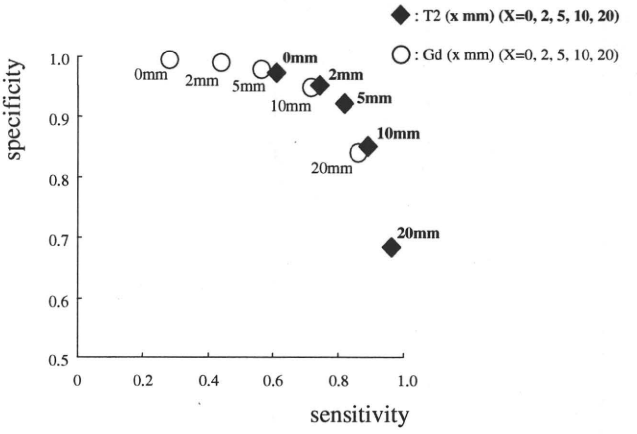


Fig. 2. Scatter plot of T_2-weighted MRI (x mm) (where $x = 0, 2, 5, 10, 20$ mm) and Gd (x mm) ($x = 0, 2, 5, 10, 20$ mm) with respect to sensitivity and specificity, respectively.

of the tumor mass on CT, and in our study, 86.4% of tumor cells were within 2 cm of the tumor mass on MRI. Burger *et al.* (23) reported 5/5 (100%) tumor cells were within the necrotic area plus 3 cm. Although we do not discuss CTV-Gd plus 3 cm in our study, we expect results were nearer to 100% (more than CTV-Gd [20 mm]). Halperin *et al.* (24) reported 9/11 (81.8%) tumor cells were beyond the enhancement area on CT, and 11/11 (100%) tumor cells were within the edema area; in our study, 71.4% of tumor cells were beyond the Gd enhancement area, and although we do not discuss CTV-T_2 plus 3 cm, we expect results were almost 100% (more than CTV-T_2 [20mm]). Because other studies (25–27) included patients with not only GBM but also anaplastic astrocytoma, results differ slightly from our data.

DISCUSSION

Brain tumor tissue can be visualized with MRI and CT because of the increased water content (edema) compared with normal brain tissue and because of disruption of the blood–brain barrier, and the tumor tissue is visualized as contrast enhancement. However, neither contrast enhancement nor edema is always a real measure of the extent of tumor for gliomas. Tumor cells have been detected beyond the margins of contrast enhancement, in the surrounding edema and even in adjacent brain tissue that appears normal. After neurosurgery or radiotherapy, blood–brain barrier disturbances and edema can also be treatment-related, and they cannot be differentiated from persistent tumor on CT or MRI (25, 28–31). Therefore, after the introduction of CT and MRI as planning methods for irradiation of postoperative GBM, many investigators have tried to define the optimal treatment volume. However, there are many studies that report where tumor exists outside of the edema and the enhanced area of CT and MRI, and this topic is still a matter of heated debate.

Comparative analyses among CT, MRI, and [^{11}C]MET-PET and stereotactic biopsies suggest that [^{11}C]MET-PET

Table 3. Comparison of correlations of histopathologic observations and use of CT or MR images

Institution (ref)	No. of patients	No. of GBM tumor cells/total no. of AA	CT or MRI	Pathologic findings	Results	This results
MGH (22)	35	Not specified	CT	Tumor cells within 2 cm of tumor mass on CT	29/35 (82.9%)	86.4%
Duke (23)	5	5/0	CT	Tumor cells within Necrotic area plus 3 cm	5/5 (100%)	86.4% <
Duke (24)	11	15/0	CT	Tumor cells go beyond enhancement	9/11 (81.8%)	71.4%
				Tumor cells within Edema plus 3 cm	11/11 (100%)	96.4% <
Mayo (25)	40	8/7	CT/MRI	Tumor cells within hypodense (CT), T_2 high (MRI)	15/16 (93.8%)	61.1%
				Tumor cells within isodense (CT), T_2 high (MRI)	14/14 (100%)	
Brain R.I. Niigata (26)	18	6/12	CT/MRI	Tumor cells go beyond T2 high (MRI)	4/18 (22.2%)	38.9%
Barrow (27)	5	3/2	MRI	Tumor cells within T2 high (MRI)	5/5 (100%)	61.1%

Abbreviations: MGH = Massachusetts General Hospital, MA; Duke = Duke University, NC; Mayo = Mayo Clinic, MN; Brain R.I. Niigata = Brain Research Institute, Niigata, Japan; Barrow = Barrow Neurological Institute; AZ GBM = glioblastoma multiforme; AA = anaplastic astrocytoma.

has greater accuracy for defining the extent of glioma than CT and MRI (10, 13, 18). The integration of [^{11}C]MET-PET into radio-oncologic treatment planning has provided encouraging results because [^{11}C]MET-PET is highly sensitive in the context of brain tumor tissue. In the present study, the biological target volume using [^{11}C]MET-PET helped to describe tumor morphology (GTV) with greater accuracy than traditional radiologic modalities (such as MRI) alone (10, 18, 32). The results of this study demonstrate that [^{11}C]MET-PET improves visualization of the extent of GBM (Fig. 3).

Table 3 compares the present results with those reported by Jansen et al. (19), correlating histopathologic observations and CT/MR images. Although some studies report different results (22–27), for example, tumor cells exist within the tumor plus α and edema plus β, those results almost corresponded to our results, for which [^{11}C]MET-PET findings served as the gold standard in this study. In a word, it is thought that our results are valid by near correspondence to histopathologic observations.

Methionine is a natural amino acid that is briskly taken up by glioma cells, with only a low uptake in normal cerebral tissue. The uptake is mediated mainly by the L-type amino acid transport system. Methionine may be used for protein synthesis or is converted to *S*-adenosylmethionine, which is the primary methyl donor for transmethylation reactions and a precursor of polyamide synthesis. A smaller part of MET is metabolized by decarboxylation. However, several experiments have suggested that during [^{11}C]MET-PET studies, the tumor uptake of [^{11}C]MET mainly reflects increased amino acid transport (12, 13, 20). Therefore, [^{11}C]MET-PET does not directly receive the influence of the operation easily, because of the high possibility of showing the tumor localization. It is thought that an

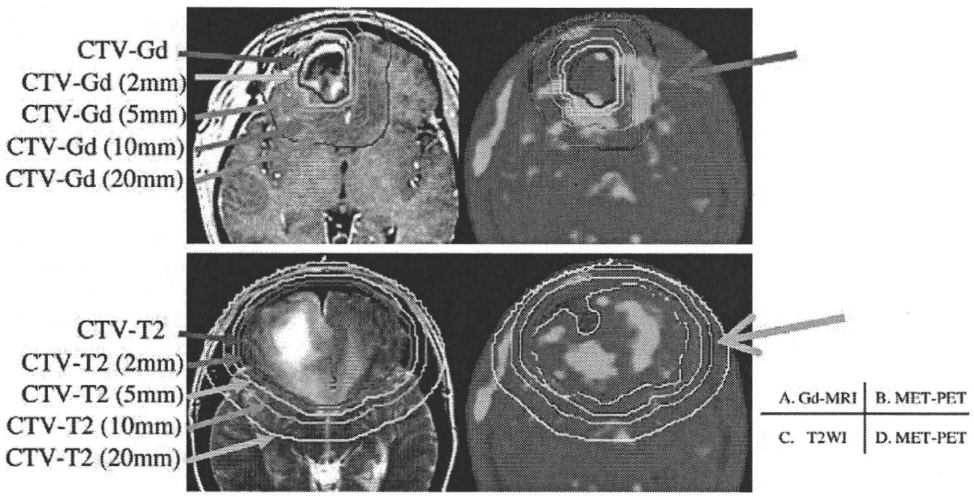


Fig. 3. Example of Gd-enhanced MRI scans illustrating (A, upper left) CTV-Gd (x mm) as x mm (x = 0-, 2-, 5-, 10-, and 20-mm) margin outside the CTV-Gd, respectively. And these lines were superimposed onto [^{11}C]MET-PET images (B, upper right) in the same patient. (C, lower left) Example of T_2-weighted MRI scans illustrating CTV-T2 (x mm) as x mm (x = 0-, 2-, 5-, 10-, 20-mm) margin outside the CTV-T2, respectively. These lines were superimposed onto [^{11}C]MET-PET images (D, lower right) in the same patient. The area is too small (red arrow) to contain CTV-PET by CTV-Gd (20mm) line (B). The area is too large (green arrow) to minimize the radiation exposure to the normal brain tissue (D).

excellent agreement was seen this time. We believe the results of this study demonstrate that [^{11}C]MET-PET has a substantial impact on visualizing the extent of GBM.

To optimize tumor control and prevent local failure, it is necessary to raise the sensitivity of the defined target as much as possible. In our study, when we used a 2-cm margin to the CTV-Gd, the sensitivity was 86%, so this was not adequate. When a 2-cm margin to the CTV-T_2 was used, the sensitivity was 96%, so a 2-cm margin to the CTV-T_2 is best to optimize tumor control and to prevent local failure. Therefore, it is necessary to use at least a 2-cm margin to the CTV-T_2 for the initial target planning of radiation therapy. However, if dose escalation to the 2-cm margin is performed in the CTV-T_2, because the specificity is 68%—and this is low—then the dose of radiation to the normal tissue increases and the possibility of radiation damage to normal tissue is expected to rise. [^{11}C]MET-PET cannot be used to target the dose escalation, and it is necessary to set an appropriate margin to the CTV-Gd or CTV-T_2 in each case. Therefore, there is a limit to the optimal margin when using Gd-MRI and T_2-MRI.

CONCLUSION

It is necessary to use a margin of at least 2 cm in T_2-MRI for the initial target planning of radiation therapy. However, in radiation planning for postoperative patients with GBM, the CTV-Gd and CTV-T_2 margins differed considerably from that of CTV- [^{11}C]MET-PET. There is a limit to the optimal margin in this setting of the Gd-MRI and T_2-MRI. Thus, rather than using Gd-MRI and T_2-MRI, [^{11}C]MET-PET has promising potential for precisely delineating target volumes in planning radiation therapy for postoperative patients with GBM.

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Original Article

Long-term Outcomes of Fractionated Stereotactic Radiotherapy for Intracranial Skull Base Benign Meningiomas in Single Institution

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Objective: To investigate the outcome of linac-based fractionated stereotactic radiotherapy over the last 10 years for intracranial skull base benign meningiomas in patients who were inoperable, who had residual tumors with some components of high mitotic index after surgery and who experienced relapse of the tumor.

Methods: Twenty-seven patients with intracranial skull base benign meningiomas treated with fractionated stereotactic radiotherapy were retrospectively reviewed. Twenty-seven cases were diagnosed as benign meningiomas on pathological (17 cases) or radiological (10 cases) examination. The median follow-up time was 90 months after initial treatment and 63 months after fractionated stereotactic radiotherapy. The median biological equivalent dose calculated using an α/β ratio of 2.0 Gy was 82.0 Gy (range, 60–106 Gy).

Results: The 5-year overall survival was 95.7 (95% confidence interval: 87.3–100)% after initial treatment and 96.2 (88.8–100)% after fractionated stereotactic radiotherapy. The 5-year overall survival and local control rate of patients who received fractionated stereotactic radiotherapy alone were both 100%. The 5-year progression-free survival and local control rate after fractionated stereotactic radiotherapy were all 100% with a tumor volume of <9.1 cc and 68.2 (37.2–99.2) and 75.8 (45.2–100)% for the tumors 9.1 cc, respectively. The difference was significant in progression-free survival ($P = 0.022$) and local control rate ($P = 0.044$). The local control rate was significantly worse in patients who received fractionated stereotactic radiotherapy for relapsed tumors ($P = 0.01$). No late radiation damage was observed in the follow-up period.

Conclusions: The long-term outcome suggests that fractionated stereotactic radiotherapy is a safe and effective treatment for intracranial skull base benign meningioma, especially for those who have tumors <9.1 cc or would receive fractionated stereotactic radiotherapy with or without surgery as the initial treatment.

Key words: radiation therapy – meningioma – stereotactic – skull base – fractionation

INTRODUCTION

Radiotherapy is increasingly being used for the treatment of meningiomas after incomplete resection, after recurrence and when tumor histology is atypical or malignant (1,2). When meningiomas are located in the intracranial skull base region, tumor excision is frequently incomplete and even