Preliminary Clinical Outcomes of Image-guided 3-Dimensional Conformal Radiotherapy for Limited Brain Metastases Instead of Stereotactic Irradiation Referral

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Abstract. *To determine the preliminary clinical outcomes of image-guided 3-dimensional conformal radiotherapy (IG-3DCRT) for limited but variably-sized brain metastases (BM). Sixty-two lesions in 24 patients were retrospectively evaluated; out of these patients 75% were ≥65 years of age, and 37.5% were categorized into recursive partitioning analysis (RPA) class 3. The median value for the maximum diameter of the lesions was 19 mm (range=4-72 mm). The median sole treatment dose was 36 Gy in 10 fractions. The median survival durations after IG-3DCRT were 12.0 months and 3.2 months for patients categorized into RPA classes ≤2 and 3, respectively. Local recurrences occurred in two lesions with a 6-month local control probability of 93.0%. Major toxicities included radiation necrosis in two patients. IG-3DCRT is feasible even for patients with limited BM who are categorized into RPA class 3, and confers clinical outcomes comparable to those of stereotactic radiosurgery, including excellent local control and minimal toxicity even for large tumors.*

The optimal management of patients harboring brain metastases (BM), particularly those with large tumors in eloquent locations, elderly patients, or those with an unfavorable performance status (PS), remains a controversial matter (1, 2). The radiotherapeutic options for BM include whole-brain radiotherapy (WBRT), stereotactic radiosurgery (SRS), or a combination thereof (2); in contrast, previous reports on 3-dimensional conformal radiotherapy (3DCRT) for BM have been extraordinarily limited (3–8). Given the limitations of single-session SRS for large tumors in terms of efficacy and safety (9, 10), hypofractionated stereotactic irradiation (STI) also referred to as stereotactic radiotherapy has been increasingly adopted despite the inevitably required longer treatment durations (11, 12). STI implementation, however, requires specific pre-requisites, including investment of capital in equipment, labor, and the collaboration of experts across multiple disciplines. Accordingly, the *status quo* is that the provision of STI is not yet centralized, and it is confined to a limited number of institutions worldwide (13). Furthermore, the on-site availability of STI strongly influences decisions regarding its application in patients with BM along with factors of clinical eligiblity (13, 14).

At diagnosis, a substantial number of patients with BM also exhibit extracranial active disease that requires simultaneous or even preferential focal and/or systemic treatment. Given that the Gamma knife or Cyberknife is the only radiotherapeutic equipment in the vast majority of Japanese centers, referral to another institution for STI might therefore lead to the discontinuation or deferred initiation of systemic treatment.

In clinical practice, radiotherapeutic BM management would be individually tailored to each patient, and the clinical challenge would be the best method for incorporating these modalities into the entire spectrum of cancer treatment in order to remedy symptoms, retain neurological function, and improve the overall outcome. Since 2009, we have adopted image-guided (IG)-3DCRT, either alone or in conjunction with WBRT for selected patients with limited but variably sized BM, all of whom were diagnosed and treated at a regional community hospital capable of standard image-guided radiotherapy (IGRT) but not STI, and deemed unsuitable for referral to another institution for STI. Herein, we describe the preliminary clinical results with respect to the feasibility, efficacy, and safety of IG-3DCRT for BM on the basis of our 4-year experience. To our knowledge, this is the first report on IG-3DCRT for BM; the adoption of the

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Key Words: Brain metastases, clinical outcome, image-guided radiotherapy, poor performance status, three-dimensional conformal radiotherapy.

Table I. *Demographic and clinical characteristics and treatment parameters of the study cohort.*

	Median	IQR	Range	Note
Age	71	(64, 79)	[54-87]	≥65: 18 (75%)
Gender	Male/female=12/12			
KPS	70	(60, 80)	[30-100]	
RPA	Class 1/2/3=1/14/9	Class 3: 37.5%		
GPA	1.0	(0.1, 1.5)	[0.0-3.5]	≤1.0: 66.7%
Primary site	Lung 15, breast 4, stomach 2, colon 1, rectum 1, unknown 1			
Histology	Adeno 18, small cell 3, non-small (NOS) 2, squamous cell 1			
Primary control	Controlled/active=12/12	Active: 12 (50%)		
Extracranial metastases	Absent/present=4/20	Active: 20/20 (83.3%)		
Related symptoms	16 (66.7%)			
Previous surgery	GTR 2, STR 3, biopsy 2, cyst drainage 1			
Previous radiotherapy	WBRT 3, SRS 2			
Eloquence[a]	Grade 1/2/3=26/18/18	Grade 3: 18 (29.0%)		
Location grade[b]	Grade 1/2/3=36/18/8	Grade 2+3: 26 (41.9%)		
Max. diameter (mm)	19	(12, 30)	[4-72]	
CTV (cm^3)	3.1	(0.9, 11.6)	[0.1-78.4]	
PTV (cm^3)	9.2	(3.6, 26.3)	[0.9-136.8]	
Total dose (Gy) [Sole][c]	36	(36.0, 38.0)	[30.0-69.0]	
Total dose (Gy) [Boost][d]	12.5	(12.5, 12.5)	[9.0-12.5]	
Dose/fr (Gy) [Sole][c]	3.8	(3.6, 3.8)	[2.4-4.5]	
Dose/fr (Gy) [Boost][d]	2.5	(2.5, 2.5)	[2.5-3.0]	
Fractions [Sole]c	10	(10, 10)	[7-29]	
Fractions [Boost]d	5	(5, 5)	[3-5]	
BED10 (Gy) [Sole][c]	49	(48.1, 52.4)	[39.0-91.8]	
BED10 (Gy) [Boost][d]	62.5	(62.5, 62.5)	[58.8-62.5]	
BED2 (Gy) [Sole][c]	110.2	(100.8, 140.0)	[78.8-195.0]	
BED2 (Gy) [Boost][d]	114.4	(114.4, 114.4)	[106.9-114.4]	
Chemotherapy[e]	Concurrent/sequential=12/14			
RT for other site(s)	Concurrent/sequential=3/3			

IQR, Interquartile range; GPA, graded prognostic assessment (37); NOS, not otherwise specified; GTR, gross total resection; STR, subtotal resection. [a]Sawaya's functional grading (38); [b]based on the depth from the brain surface (10); [c]initial and salvage settings included; [d]IG-3DCRT followed by WBRT; [e]including targeted agent or hormonal therapy.

planning method, as well as the dose fractionation schemes (DFS), differ from those in previous reports.

Patients and Methods

Study population. Between December 2009 and December 2013, a total of 62 brain metastases (BM) in 24 consecutive patients were treated with 30 sessions of IG-3DCRT at the Chuno Kosei Hospital, the only regional institution capable of radiotherapy; these patients constituted the study population. The demographic, clinical, and treatment characteristics of the study cohort are summarized in Table I, of whom 73%, 55%, 42%, and 25% were aged ≥65 years, ≥70 years, ≥75 years, and ≥80 years, respectively. IG-3DCRT was adopted as the sole irradiation method in 17 patients with 41 lesions and was used either for the initial BM treatment or as an adjuvant treatment following surgical interventions for either debulking or drainage (Tables I and II); 6 of these patients presented with synchronously-diagnosed BM along with primary cancer. IG-3DCRT was applied as a salvage treatment for recurrent or newly developed lesions in four patients with prior histories of WBRT or SRS; in these patients, a total of 14 lesions were irradiated in seven sessions. IG-3DCRT was also applied as a boost after WBRT to seven selected large and presumably symptom-causing tumors in three patients who had 3-18 (median=12) lesions at initial diagnosis. The reasons for adopting IG-3DCRT for each patient are summarized in Table II.

Among the entire cohort, the Karnofsky performance scale (KPS) scores were ≤60 in nine patients (37.5%). The primary tumors were uncontrolled in half of the patients, and most patients (83.3%) had additional active extracranial diseases. The median diameter and volume of the largest lesion per patient were 32 mm (range=8-72 mm) and 10.3 cm^3 (0.5-78.4 cm^3), respectively. Nine patients (37.5%) had a single BM at the time of IG-3DCRT, whereas two patients each in the salvage and boost groups had more than 10 tumors at the initial BM diagnoses. Two patients had contraindications to the use of contrast material and one had claustrophobia; for these patients, treatment planning was accordingly performed on the basis of pre-contrast computed tomography (CT)/magnetic resonance and post-contrast CT images, respectively. For the vast majority of patients, IG-3DCRT or preceding WBRT commenced the day after the initial consultation.

Notably, systemic chemotherapy was continued or initiated concurrently during IG-3DCRT in half of the patients, and palliative radiotherapy was also applied concurrently or sequentially to symptomatic primary or metastatic sites in 6 patients (Table I). Among the patients with non-small cell lung cancer, epidermal growth factor receptor (*EGFR*) mutation was verified in only one female patient. Chemotherapy regimens having some level of blood–brain barrier penetration such as pemetrexed was administered to four patients with lung adenocarcinoma (15); only one patient received the small-molecule EGFR inhibitor, erlotinib, sequentially after IG-3DCRT.

Written informed consent was obtained from all patients or their relatives according to the premise of providing information regarding the applicable radiotherapeutic options, including on-site WBRT, referral for STI, on-site IG-3DCRT, or a combination thereof.

Treatment procedures. IG-3DCRT was delivered by using a Clinac iX (Varian Medical Systems, Inc., Palo Alto, CA, USA) with a central leaf width of 5 mm and 6-MV X-rays, and was commissioned with the Eclipse ver 8.6 (Varian Medical Systems, Inc.), which was equipped with an On-board imager (OBI) (Varian Medical Systems, Inc.). Patients were immobilized with a general thermoplastic mask. Planning CT images with 3-mm slice thickness were acquired and fused with MR images with 5-mm thickness. The clinical target volume (CTV) was contoured around the visible tumor and further isotropically expanded by 3-mm to form the planning target volume (PTV). The CTV contours were generally overdrawn according to the image slice thicknesses. The actual PTV margin would therefore be 4-5 mm. Planning was based on the use of five (range=5-7) static coplanar multi-beams arranged at 70-72˚; in some patients, a non-coplanar beam was added to mitigate the dose to the organs-at-risk and a dynamic wedge was also used to optimize the dose distribution. The leaf margin to the PTV boundary was set anisotropically; this was usually 3 mm laterally and 6 mm cranio-caudally to ensure that ≥95% of the PTV encompassed by 90-95% isodose surface was normalized to 100% at the isocenter. The prescribed dose was specific to the isocenter. Although the initial basic dose prescription was 36 Gy administered in 10 fractions (36 Gy/10 fractions) for previously untreated lesions, the DFS for each patient was individually tempered and determined after considering the tumor volume, location, prior radiation dose, performance status, and expected survival. Additionally, a boost treatment was applied to selected patients in a response-adaptive manner. Dose calculations were based on a pencil beam convolution according to the Batho power law for heterogeneity correction. The simultaneous irradiation of two to three lesions located near each other was adopted in selected patients; this technique targeted a single isocenter *via* collimator angle optimization. IGRT was implemented *via* online 3D translational verification and correction, and 2-dimensional matching was performed on the basis of a pair of orthogonal kV images obtained by using OBI. To compare the different DFS, the biologically effective doses (BED) were calculated according to the following linear-quadratic (LQ) formula: BED_n (Gy)=total dose × [1+(dose per fraction)/n], where n represents the α/β ratio (α/β=10 for the antitumor effect and 2 for normal tissues).

Outcome evaluation. Neurological death was defined as death attributable to central nervous system metastases, including carcinomatous meningitis (CM) or radiation-induced injury. The initial response of each irradiated tumor was defined as shrinkage of the tumor by ≤70% in the maximum diameter within three months after IG-3DCRT. Local control (LC) was defined as a maximum retained diameter of ≤120% at any time after IG-3DCRT. However, this definition could include tumor recurrence or radiation necrosis (RN) in cases in which the tumor had initially shrunk to ≤50% in size with subsequent regrowth to approximately 100% of the original size. Therefore, sustained tumor regression was defined as the maximum retained diameter of ≤70% at the last follow-up without transient enlargement of either the tumor size or perilesional edema (a more rigorous measure). The actuarial probabilities of overall survival (OS), neurological death-free survival, LC, and the development of secondary brain lesion(s), and radiation injuries were estimated according to the Kaplan–Meier method beginning the commencement of IG-3DCRT unless otherwise indicated; the differences between the subgroups were compared with the log-rank test. The Spearman rank correlation coefficient was used to evaluate any correlations between continuous variables. Along with the attending physicians, K.O. was involved in the initial consultation, informed consent, treatment planning, prescription dose decision, and follow-up symptom and imaging findings evaluations for all patients.

Table II. *Reason(s) for choosing image-guided three-dimensional conformal radiotherapy (overlapping permitted).*

	n (%)
Patient factors	
Unfavorable performance status (difficulty in referral)	11 (45.8%)
Need for simultaneous treatment of extracranial active disease	17 (70.8%)
Synchronous brain metastases	6 (25.0%)
Refusal of referral to another institution for STI	2 (8.3%)
Tumor factors	
Large tumor (≥2.5 cm)	16 (66.7%)
Irregular and/or blurred margination	10 (41.7%)

STI, Stereotactic irradiation.

Results

The actuarial probabilities of OS, neurological death-free survival, LC, secondary BM (including carcinomatous meningitis), and RN development are shown in Figure 1. Both the BED_{10} (Spearman's ϱ=0.40 and p=0.013) and the number of fractions (Spearman's ϱ=0.49 and p=0.002) correlated positively with the CTV, thus reflecting the volume-dependent DFS with higher BED for larger tumors. The median follow-up durations were 7.5 months (range=0.1-27.8 months) for the entire cohort and 15.6 months (1.9-27.5 months) for the survivors. Six patients were alive in January 2014 with a median KPS score of 80 (30-100). All patients, except 1, completed the planned IG-3DCRT, with a completion rate of 96.7% (29/30 sessions). The single discontinuation in a patient requiring a boost case was consequent to deterioration of the patient's general condition.

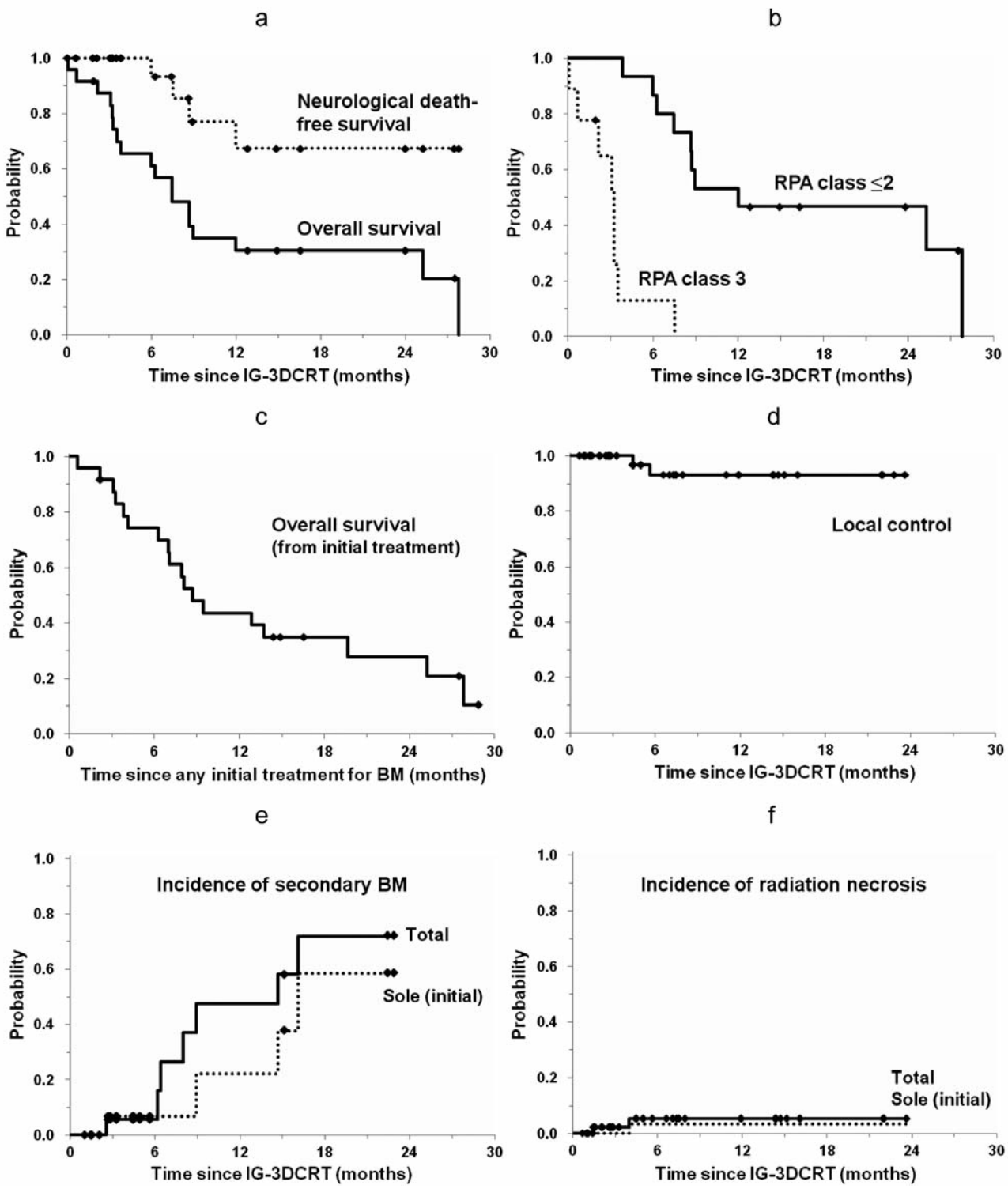

Figure 1. *The actuarial probabilities of overall survival (OS) (a, b), neurological death-free survival (a), local control (d) and the incidence of secondary brain metastases (BM), including carcinomatous meningitis (e), and radiation necrosis (RN) (f) from the commencement of image-guided three-dimensional conformal radiotherapy (IG-3DCRT). Comparison of OS for recursive partitioning analysis (RPA) class 3 vs. ≤2 (b). OS from the any initial treatment for BM (c). Comparative incidence of secondary BM (e) and RN (f) for the entire cohort and the sole setting as an initial treatment (dashed lines). Censored cases (= survivors) are indicated by tick marks on each line.*

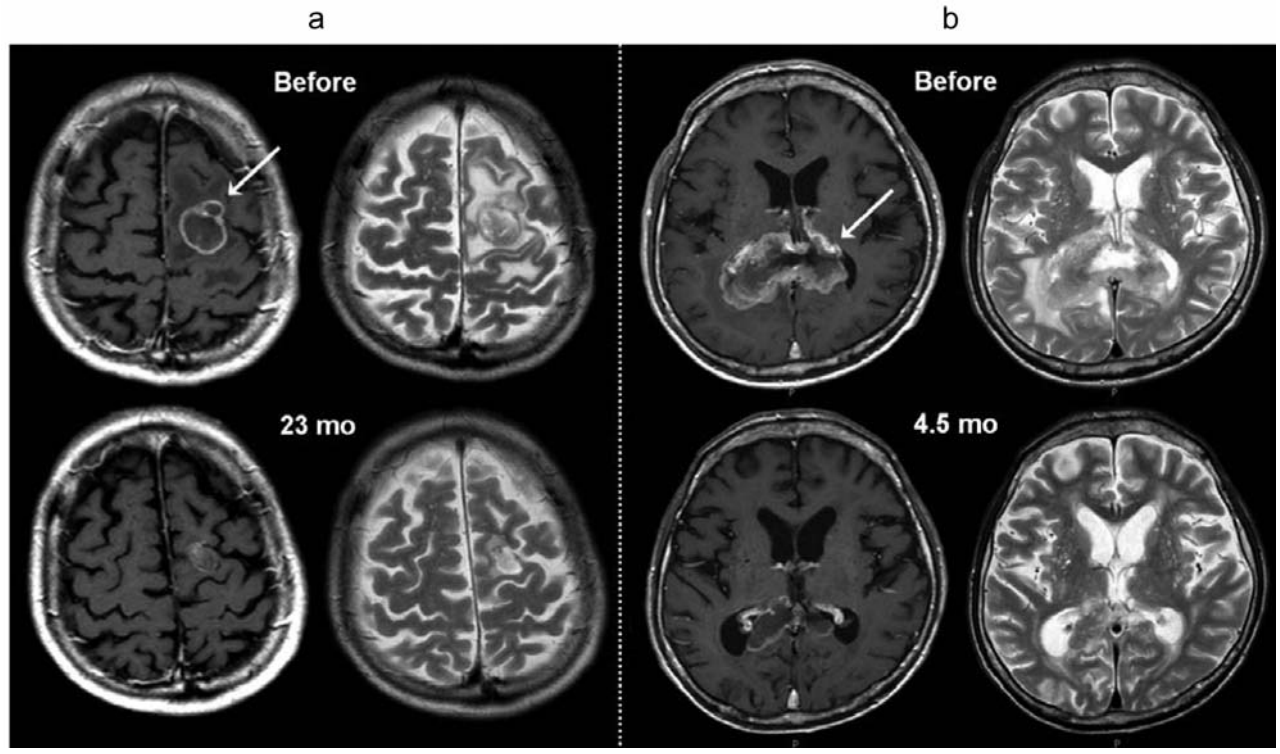

Figure 2. *Illustrated cases harboring brain metastases (BM) from lung adenocarcinoma treated with image-guided three-dimensional conformal radiotherapy (IG-3DCRT) alone. Contrast-enhanced T1-weighted (left) and T2-weighted (right) images before and after IG-3DCRT. The dose-fractionation schemes are 36 Gy/10 fractions for a 27-mm lesion (arrow) (a) and 57.6 Gy/24 fractions followed by a boost with 12 Gy/5 fractions for a 72-mm lesion (arrow) (b). mo, Months.*

The median survival time (MST) after IG-3DCRT was 7.5 months for the entire cohort, with the 6 and 12-month OS rates of 61.1% and 30.6%, respectively (Figure 1a). The MST of 3.2 months for patients categorized into RPA class 3 was significantly shorter than that of 12.0 months for patients categorized into RPA class ≤2 ($p<0.001$) (Figure 1b) (16).

The initial response and LC were evaluable in 56 lesions (90.3%) that were treated in 27 sessions. Initial responses were observed in 40 lesions (71.4%), whereas lesion enlargement at the initial evaluation was only observed in one lesion with RN. Local recurrences occurred in two lesions, and the 6- and 12-month LC rates were both 93.0% (Figure 1d). Notably, sustained tumor regression was observed in 41 lesions (73.2%). Representative cases considering the efficacy are shown in Figure 2. Two patients experienced recurrences, including a 23-mm BM from a lung squamous cell carcinoma and a 33-mm BM from a colon adenocarcinoma that had been treated with 39 Gy/10 fractions and 40 Gy/10 fractions, respectively; neither of these patients received chemotherapy during or after IG-3DCRT.

Intra-cranial progression outside the irradiated lesion occurred in 7 patients at a median interval of 6.4 months (2.6-14.7 months) after IG-3DCRT (Figure 1e); these included asymptomatic secondary BM in 5 patients with a total of 12 lesions and symptomatic fatal CM in 2 patients. The latter patients with breast and small cell lung cancers have previous histories of surgical debulking and preceding WBRT for 18 lesions, respectively, whereas eight lesions in the former patients had been successfully salvaged *via* IG-3DCRT alone.

Regarding adverse events, no significant acute toxicities were observed with IG-3DCRT alone except for focal alopecia in 85.7% of the patients. No neurological deterioration attributable to aggravation of edema, seizures, or intratumoral hemorrhaging was observed during or immediately after IG-3DCRT. Late toxicity was remarkable in terms of RN, which was observed in two patients; the 6- and 12-month incidence of RN were 5.3% and 3.5% for the entire cohort and those who underwent the sole initial treatment, respectively (Figure 1f). The first patient who showed late toxicity was an 81-year-old man with lung adenocarcinoma who was treated with IG-3DCRT (35.0 Gy/10 fractions) followed by a boost (24.0 Gy/10 fractions) for a 31-mm tumor located in the motor cortex. Symptomatic RN occurred four months later and gradually worsened. The other patient was a 57-year-old woman with lung adenocarcinoma who underwent salvage IG-

3DCRT (36.0 Gy/10 fractions) for a 33-mm recurrent occipital lobe tumor; she had a previous history of WBRT (37.5 Gy/15 fractions) and prior salvage IG-3DCRT (30.0 Gy/ 10 fractions to an adjacent site). Symptomatic RN occurred 1.5 months later with subsequent resolution after bevacizumab-containing chemotherapy.

Sixteen patients (66.7%) exhibited focal BM-related neurological symptoms (Table I); these symptoms abated at least temporarily in 10 patients (62.5%) and remained unchanged in 6. No neurological worsening was observed in the remaining eight patients without prior symptoms. The neurological statuses at the final evaluation indicated improvement in 7, no change in 10, and worsening in 7 patients relative to the statuses before IG-3DCRT. The worse statuses in the seven patients were attributable to secondary CM in two patients, the aforementioned local recurrences in two, radiation-induced brain damage in two (including prior WBRT in one), and undetermined reasons in one patient. Neurological death occurred in 4 patients because of CM in two patients, local failure in one, and sustained pre-existing symptoms with subsequent aggravation in one patient (Figure 1a).

Discussion

SRS has retained a viable role in the management of relatively small and limited BM. As patients' lives are extended because of improved systemic control (17), the need for durable, minimally-toxic control for BM has also significantly increased. In STI, sufficient dose prescription is compromised by the 'volume effect', with reduced doses to larger tumors and *vice versa* (10, 12, 18). Large tumor volumes therefore negatively affect the LC and OS following SRS (19, 20). Given the intrinsically-ablative nature of the dosage, various acute and late complications of STI have been documented (21, 22). Acute adverse events include seizures, aggravation of edema, and hemorrhage, which could potentially lead to disastrous outcomes (23, 24). The incidence of RN also increases at a rate that is higher than expected as patients' lives are extended, even in patients with relatively small tumors who were treated with the generally accepted dose (9, 10, 25). In addition to RN, transient enlargement of the enhancing lesions might occur in association with aggravated edema (26).

Because patients with unfavorable PS are generally deemed unsuitable for STI, the optimal management of these cases remains a matter of controversy (1, 2, 27). WBRT is usually considered as a radiotherapeutic option (2), although some practitioners remain skeptical about the significance of WBRT (27, 28). Patients with poor PS will likely be more susceptible to the intrinsic and acute adverse reactions related to WBRT, which would lead to acute declines in the quality of life (29, 30). WBRT would therefore not necessarily guarantee true palliation for these patients. In contrast, protracted and continuous steroid use becomes a problem in supportive care alone using comfort measures. Nevertheless, radiotherapy has retained a role in the treatment on a subset of patients who present with severe neurological symptoms and declining PS with a life expectancy of several months (31). Given the limited life expectancy of patients categorized into RPA class 3 (Figure 1b) and the latency period of secondary BM (Figure 1e), palliation of the existing neurological symptoms as well as control of the overt BM should be a higher priority than the control of other asymptomatic, miniscule/small tumors or prophylaxis for occult tumors.

The IG-3DCRT study population included patients at a comparatively high-risk who had been deemed ineligible for STI as described above; the patients' factors included a preponderance of elderly subjects, a poor PS, uncontrolled extracranial disease, and contraindication for contrast media, whereas the tumor factors included a large volume, eloquent location, and irregular margination. Notwithstanding these unfavorable factors, IG-3DCRT was generally considered feasible, yielded a high rate of symptom amelioration, and provided excellent LC with minimal toxicity. Although the OS for patients categorized into RPA class 3 was unfavorable, the MST of 12 months for patients categorized into RPA class ≤2 was comparable to that obtained with STI (32). Regarding durability, 28.6% of the patients experienced LC for >1-year (Figures 1d). Given the proportion of large tumors included in this study, the incidence of RN was rather low relative to that observed with SRS (9,25).

IG-3DCRT implementation is a simple extension of standard 3DCRT; therefore, it is used to provide expedited treatment commencement (the next day for most of the patients) and variable and flexible fractionation schedules that are tailored to individual patients. The use of a general mask would abate the discomfort associated with head immobilization, compared with the use of a rigid frame or dedicated tight mask (33).

On-site IG-3DCRT implementation possesses several additional advantages, including systemic therapy continuation or necessary changes as well as the administration of palliative care by the primary attending practitioners. Because IG-3DCRT only requires a 10 to 15-min period per isocenter treatment, the remaining time can be used to administer other treatments and/or care. In this study cohort, a substantial number of patients received other systemic or focal treatments for active extracranial diseases during or after IG-3DCRT. Although the administration of IG-3DCRT in 10 fractions requires a period of approximately two weeks, a longer treatment period would not be a significant disadvantage in comparison to STI. The lack of a required transfer to a referred Hospital could mitigate the burdens of patients and their families, especially of those patients with poor PS. The advantages of IG-3DCRT, compared to those of WBRT alone,

Table III. *Literature on three-dimensional conformal radiotherapy for brain metastases.*

Authors	Application	Patient (n)	Lesion (n)	WBRT (Gy)	3DCRT Total dose (Gy)	Fractions	BED10 (Gy)	Setup margin (mm)	Local control	Survival
Aoki *et al*. (3)	Sole	44	65	None	24.0 (18.0-30.0)	4, 5	38.4 (37.5-48)	10	78.4% (6 months), 71.9% (12 months)	72.4% (6 months), 50.8% (12 months)
Levy *et al*. (7)[a]	Sole	1	1	None	40.0	8	60.0	10	100% (4 months)	0% (6 months)
Casanova *et al*. (4)	Boost	53	NA	25.0 (25.0-45.0)	9.0 (7.5-18.0)	NA	NA	10 (10-25)	98.1% (6 months), 75.2% (12 months)	80.9% (6 months), 61.2% (12 months)
Assouline *et al*. (5)[a]	Boost	49	NA	30.0 (20.0-30.0)	20.0 (16.0-20.0)	8-10	47.2-63.0	10	NA	58% (6 months), 35% (12 months)
Levy *et al*. (6)[a]	Boost	30	NA	30.0 (20.0-30.0)	20.0 (16.0-20.0)	8-10	47.2-63.0	10	NA	60% (6 months), 30% (12 months)
Ge *et al*. (8)	Boost	32	NA	40.0 (40.0-40.0)	16.0-20.0	8-10	67.2-72.0	3	75.9% (41.6%)[b] (12 months)	50.8% (40.4%)[b] (12 months)
Present study	Sole (initial)	17	41	None	38.0 (32.0-69.0)	10 (8-29)	52.4 (43.8-91.8)	3	91.6% (6 months), 91.6% (12 months)	68.8% (6 months), 37.5% (12 months)
	Sole (salvage)	4	14	37.5 (25.0-40.0)	31.5 (30.0-36.0)	10 (7-10)	47.3 (39.0-49.0)	3	100% (2.1-22.0 months)	50.0% (6 months)
	Boost	3	7	34.0 (27.5-37.5)	12.5 (9.0-12.5)	5 (3-5)	58.8 (39.1-62.5)	3	100% (1.0-7.9 months)	33.3% (6 months)

n, Number; NA, not available; [a]reports from the same institution; [b]results for cases with radiotherapy alone in parentheses.

are largely similar to those of STI. Medical oncologists might hesitate to recommend standard-dose chemotherapy during or immediately after WBRT because of fear of potentially exacerbating adverse reactions. Furthermore, WBRT might interfere with chemotherapy schedules for up to several weeks after administration while patients continue to recover from the acute adverse effects. In contrast, none of the study cohort participants experienced severe acute toxicities related to either chemotherapy or IG-3DCRT. Therefore, 'focal irradiation' would be favored over WBRT when contemplating the use of a simultaneous systemic therapy.

As shown, IG-3DCRT was rather unique in terms of the associated DFS and setup margin when compared with other studies (Table III). We adopted an intermediary dose of 3.6-3.8 Gy/fraction for patients receiving IG-3DCRT as the sole treatment; this dose was an intermediate between the dose for WBRT such as 3 Gy/fraction and that for hypofractionated schemes of ≥5-6 Gy/fraction (Table III), and the median of 10 fractions was analogous to that of WBRT. The BED10 for the 36 Gy/10 fractions, calculated according to the LQ model, was lower than the SRS dose of 20 Gy (49.0 Gy *vs*. 60.0 Gy), whereas the BED10 based on the LQ-cubic model (34, 35) for 36 Gy/10 fractions was slightly higher than 20 Gy/fraction (48.1 Gy *vs*. 45.2 Gy). Meanwhile, the BED2 of IG-3DCRT was generally lower than that of STI, which notably led to the low incidence of delayed radiation injuries in this study population. Nonetheless, IG-3DCRT with the adoption of DFS offered a favorable LC rate with limited toxicity for variably sized BM. The efficacy of this technique might be attributable to the relatively large number of fractions and to the chemotherapeutic augmentation (36). For a substantial number of patients, the treatment paradigm for BM was the *de facto* concurrent and/or sequential 'chemoradiotherapy' regimen, with a certain amount of blood–brain barrier penetration (15). A large number of fractionation number might be beneficial, especially for large tumors that are not amenable to SRT (11, 12). In this series, dose prescription was predicated with a different volume-based dose selection from that used for STI, including a higher BED for large tumors treated with IG-3DCRT *vs*. a lower BED for large tumors treated with SRS. To ensure equivalent tumor control, a higher BED would be required for larger tumors because the fractions of hypoxic, clonogenic, and quiescent cells tend to increase as the tumor volume increases. Nonetheless, the enthusiasm for improving LC should be tempered against the possible impact of the treatment on the quality of life, therefore, a dose greater than 10 fractions might therefore be suitable for relatively small tumors in patients with poor PS. Therefore, the optimal DFS for IG-3DCRT according to the patient and tumor characteristics deserved further investigation.

We used a 3-mm setup margin to reduce the dose to the surrounding tissues while considering the contouring method and the use of IGRT. In contrast to previous perceptions, the current image-guidance system confers increased setup accuracy and stability for immobilization, even while using a general thermoplastic mask for conventional radiotherapy (33). Given

the LC rate in this series, this rather conservative setup margin might be sufficient for IG-3DCRT for intracranial lesions.

We must declare that this study featured several intrinsic limitations, including its retrospective nature, selection bias, rather limited observation period, small cohort size, and study population heterogeneity. Furthermore, the level of the affected brain tolerability is unknown for patients in whom salvage WBRT is indicated for progression after IG-3DCRT. The efficacy of IG-3DCRT for radioresistant tumors also remains unknown, as none of the present cases involved melanomas, renal cell carcinomas, or sarcomas; therefore, the relevant literature was also limited (7). Furthermore, the OBI-mediated verification of residual post-treatment setup errors was not performed for any patient. Therefore, we cannot exclude the possibility of unexpected intra-fractional motion that might have led to local failure.

In conclusion, IG-3DCRT was generally feasible and conferred excellent LC and minimal toxicity for limited but variably-sized BM, as well as survival comparable to that achieved with STI. The on-site implementation of IG-3DCRT also allows the concurrent/sequential administration of systemic/focal treatments for extracranial active disease. Given its convenience and feasibility, IG-3DCRT could be a valuable alternative both to WBRT-alone for patients with unfavorable PS and to STI for patients who require simultaneous treatment for symptomatic extra-cranial disease. Whether IG-3DCRT is a comparable alternative to WBRT or STI for such subsets of patients and the type of patients who would primarily benefit from IG-3DCRT appears to be worthwhile subject for further investigation.

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