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Clinical Article

Radiosurgery for Recurrent Brain Metastases after Whole-Brain Radiotherapy : Factors Affecting Radiation-Induced Neurological Dysfunction

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Objective : We retrospectively analyzed survival, local control rate, and incidence of radiation toxicities after radiosurgery for recurrent metastatic brain lesions whose initial metastases were treated with whole-brain radiotherapy. Various radiotherapeutical indices were examined to suggest predictors of radiation-related neurological dysfunction.

Methods : In 46 patients, total 100 of recurrent metastases (mean 2.2, ranged 1-10) were treated by CyberKnife radiosurgery at average dose of 23.1 Gy in 1 to 3 fractions. The median prior radiation dose was 32.7 Gy, the median time since radiation was 5.0 months, and the mean tumor volume was 12.4 cm^3. Side effects were expressed in terms of radiation therapy oncology group (RTOG) neurotoxicity criteria.

Results : Mass reduction was observed in 30 patients (65%) on MRI. After the salvage treatment, one-year progression-free survival rate was 57% and median survival was 10 months. Age (<60 years) and tumor volume affected survival rate (p=0.03, each). Acute (≤1 month) toxicity was observed in 22% of patients, subacute and chronic (>6 months) toxicity occurred in 21%, respectively. Less acute toxicity was observed with small tumors (<10 cm^3, p=0.03), and less chronic toxicity occurred at lower cumulative doses (<100 Gy, p=0.004). "Radiation toxicity factor" (cumulative dose times tumor volume of <1,000 Gy × cm^3) was a significant predictor of both acute and chronic CNS toxicities.

Conclusion : Salvage CyberKnife radiosurgery is effective for recurrent brain metastases in previously irradiated patients, but careful evaluation is advised in patients with large tumors and high cumulative radiation doses to avoid toxicity.

KEY WORDS : Brain · Metastasis · Radiotherapy · Toxicity · Radiosurgery · Recurrence.

INTRODUCTION

The incidence of brain metastasis is increasing as the survival of cancer patients is prolonged by advanced cancer therapy. Up to 15% of cancer patients can be expected to develop brain metastasis[22] and as many as 50% of patients dying from cancer have brain metastases on autopsy[23]. Whole-brain radiotherapy (WBRT) has been considered as a palliative treatment for these patients. Several reports confirm that WBRT increases survival by 3-6 months and improves quality of life with minimal toxicity[6,12,20]. However, conventional WBRT do not provide long-term local control as the recurrence rates reached to 80-100% at more than a year follow-up.

Recurrent brain metastases present special treatment challenges for patients already treated with radiation. Salvage conventional radiation therapy has been tried in selected patients, but whether survival is enhanced without intolerable toxicity is unclear[8,13,29]. Radiosurgery has shown to be as effective as surgery plus WBRT in patients with a single brain metastasis[5] and more effective when combined with WBRT than WBRT alone in patients with multiple brain metastases[15]. Local control rates were improved to 65-69% at 2 years[3,10]. Radiosurgery has been suggested as a treatment of choice for primary single-to-oligo brain metastasis[9,10]. A rapid treatment response, short treatment time, and reduced radiation to normal tissue make radiosurgery a reasonable option for recurrent brain metastasis.

Salvage treatment is not feasible in many patients, however, because of poor performance status, the presence of

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systemic disease, and short expected survival. This is especially true in patients whose initial brain metastases were treated with WBRT rather than radiosurgery[26]. It is thought that prior WBRT increases the risk of radiation-induced toxicity from salvage radiosurgery because the cumulative dose to the brain is absolutely higher than that of up-front treatment. Some reports have suggested a short-term benefit of salvage radiosurgery for recurrent brain metastasis, but the incidence of long-term radiation toxicity has not been investigated thoroughly and clear guidelines for assessing the risk of radiation toxicity from summated radiation do not exist. In this study we evaluated local control rate and survival after salvage radiosurgery and their relation to clinical factors. Also, as a preliminary step for establishing guidelines of radiosurgery in such cases, radiation-induced neurological dysfunction relative to the time since treatment (acute, subacute and chronic) was correlated with various radiotherapeutic indices.

MATERIALS AND METHODS

Patient characteristics

Pre-treatment clinical characteristics of patients were summarized in Table 1. There were 21 females and 25 males.

Table 1. Clinical and radiotherapeutical characteristics of treated patients

Characteristics	Number of patients (%)
Age	
<60	28 (61)
≥60	18 (39)
KPS	
<70	8 (17)
≤70	38 (83)
RPA class	
Class 1 and 2	38 (83)
Class 3	8 (17)
Histology	
GI tract and renal	9 (20)
Others	37 (80)
Time from WBRT to CK	
<1 year	30 (65)
≥1 year	16 (35)
Planned tumor volume	
<10 cm^3	25 (54)
≥10 cm^3	21 (46)
Radiosurgery dose	
≤20 Gy	32 (70)
>20 Gy	14 (30)
Hypofractionation	
Single	29 (63)
3 fractionation	17 (37)

Mean age was 52.8 years (range 13-68 years). Karnofsky Performance Status (KPS) ranged from 40 to 100 (median 80). According to recursive partitioning analysis (RPA) of radiation therapy oncology group (RTOG)[12], five patients were class 1, 33 patients were class 2 and eight patients were class 3. Twenty-six patients had primary lung tumors, including 7 with small cell lung cancer. Seven patients had primary breast and 2 each had stomach, liver, colon and cervix cancer. Five remaining patients had leiomyosarcoma, head and neck, kidney, testicular tumors, or metastasis of unknown origin each. Patients having gastrointestinal tract and renal cell cancers, which are thought to be radioresistant, were conveniently grouped together against the other cancers when analyzing local control and survival factors. The average number of metastatic lesions treated per patient was 2.2. Twenty-nine patients (63%) were treated for a single lesion, but 3 patients had 2 lesions, 7 had 3, 2 had 4, 2 had 5, 1 had 6, and 2 patients had 10 lesions. Twenty-three patients (50%) having lesions abutted to motor, language area or located in posterior fossa, were assigned to be in "eloquent" area. The median interval between the end of WBRT and CyberKnife treatment was 5 months (range 1-93, mean 13.3 months). Thirty patients (65%) received re-treatment within a year.

Eligibility criteria and pretreatment evaluation

From June 2002 to July 2005, 46 of the 117 patients treated by CyberKnife stereotactic radiosurgery (SRS) or hypo-fractionated stereotactic radiation therapy (SRT) for brain metastases met the following criteria and were enrolled in this study; 1) recurrent lesion; 2) patients previously underwent WBRT for metastatic brain tumors; 3) systemic status of primary cancer was evaluated within 3 months of re-treatment, and; 4) MRI follow-up occurred at least once within 3 months and possibly at 6 months post-treatment. SRT (3 fractionation) was applied by physician's choice to reduce possible radiation toxicity in case of critical location or tumor volume without a definite criteria. The treatment protocol was approved by the Institutional Review Board of Korea Cancer Center Hospital. All patients signed an informed consent and were aware of being part of investigational protocol.

CyberKnife hypo-fractionated SRS treatment

The CyberKnife is an image-guided frameless radiosurgery system capable of fractionated treatment with stereotactic accuracy comparable to frame-based systems. It consists of a lightweight 6 MV linear accelerator manipulated by a computer-controlled robotic arm[2,27]. Non-invasive immobilization using an Aquaplast mask (WFR/Aquaplast Corp., Wyckoff, NJ) was applied during the planning CT and throughout

treatment. Digitally reconstructed radiographs (DRR) were generated from the thin-slice (2.0 mm) CT data set. Dynamic Tracking System (version 3.0, Accuray Inc., Sunnyvale, CA) was used to deliver planned radiation. Rapid registration of intraoperative X-rays to DRRs enables the system to determine the exact location of the patients and communicate changes in position to the robot. Fractions were separated by approximately 24 hours and the fraction dose was determined by dividing total dose by number of fractions.

Evaluation of dosimetry

Dose volume histograms of the tumor and the critical structures were obtained in every case. The marginal dose to the planned tumor volume (PTV) from different fractionation schedules was converted to linear quadratic equivalent dose (LQED) and single equivalent dose (SED) for the purpose of comparison. We used the linear quadratic formula, in which N represents number of fractions and d equals dose per fraction (LQED = Nd $(\alpha/\beta+d)/(\alpha/\beta+2)$), assuming an α/β ratio of 10 and a 2-Gy fraction dose[11]. The previous WBRT dose was added to the apparent tumor marginal dose, both of the doses in terms of LQED, to derive a summated dose (SumD). This quantity did not take into account the time since WBRT. A "radiation toxicity factor" was obtained by multiplying SumD by the PTV (cm^3); this quantity expressed the combined contribution of dose and tumor volume to radiation-induced toxicity.

Measurement of response

Follow up evaluations, which included clinical evaluation and MRI, were performed at one month, 3 months, and 6 months post-treatment and then every 6 months, if possible. The mass response was evaluated on MRI in all patients and initial response was defined as the best response observed during the first 9 months post-treatment. Tumor volume was measured on axial T1-weighted gadolinium-enhanced images using Image Tool software (version 2.0, alpha 3, University of Texas Health Science Center, San Antonio). Complete response (CR) was defined as disappearance of enhancing tumor. A partial response (PR) was defined as a decrease in tumor volume of 50% or more. Progressive disease (PD) was defined as the appearance of any new lesions or an increase of more than 25% in the tumor volume. If tumor volumes decreased less than 50% or increased less than 25% and no new tumors appeared, this was classified as stable disease (SD).

Evaluation of radiation toxicity

Compliance with treatment and patient complaints were monitored and recorded by an assigned nurse throughout the treatment. Side effects which necessitated medical attention were carefully reviewed on medical records. We adopted RTOG central nervous system (CNS) toxicity criteria[24] and toxicity greater than grade 3 was considered evidence of radiation-induced toxicity for statistical analysis whether it was reversible or not. We classified radiation toxicity according to the time of occurrence as follows : 1) acute-clinical symptoms occurred within 1 month after the treatment; 2) subacute-symptoms appeared between 1 and 6 months, and; 3) chronic-toxicity occurred at least 6 months post-treatment. Cases of documented progression of treated tumors were excluded from the toxicity counts, but toxicity that seemed to be caused by previous WBRT (e.g., global dementia with brain atrophy) was included. Radiation necrosis was identified only when it could be differentiated from tumor recurrence based on one of following conditions; 1) histopathologically proven as radiation necrosis after surgical excision, 2) evident cystic change of treated area without hyperuptake on PET image. We defined dementia as the radiation toxicity in the patients showing prolonged disorientation disturbing independent daily activity with brain atrophy on MRI follow-up.

Statistical method

We used SPSS software (version 11.0, Chicago, IL) and established statistical significance at $p<0.05$. To evaluate clinical factors affecting mass response and radiation-induced toxicity, a simple Chi-square test was used. The local control rate and patient survival were obtained by the Kaplan-Meier method and other factors were compared by log-rank tests. Multivariate analysis was conducted using the Cox proportional hazard model.

RESULTS

Patients were followed from 2 to 35 months (median 8 months), and all were eligible for analysis of mass response and acute side effects. Analyses of subacute and chronic radiation toxicity were based on surviving patients.

Radiotherapeutic indices

The dose of previous WBRT ranged from 18.0 to 54.9 Gy (mean 32.9 Gy) delivered in various fractionation schedules at 1.8-3.0 Gy per fraction. Twenty-nine (59%) patients had received 30 Gy in 10 fractions. Thirty-nine (85%) patients had undergone WBRT only before the SRS. Seven patients received single-fraction SRS in addition to WBRT before this study. Four of them were treated for newly developed distant lesion and the other 3 patients showed the regrowth of the treated lesion after their first

time SRS, which was also applied 3 to 16 months after the initial WBRT. Mean tumor volume measured on planning software was 12.4 cm^3 (0.2-58.3 cm^3). Average dose of 23.1 Gy (range 10-36 Gy) was delivered to planned tumor margin at a mean 80.1% isodose line (range 65-84%) in a single fraction in 29 patients (63%) and in 3 fractions in the other 17 patients (37%). This marginal dose was equivalent to 49.0 Gy in LQED and 19.5 Gy in SED.

Mass response, local control and survival of patients

MRI after salvage radiosurgery showed shrinkage of the enhancing lesion in 30 (65%) patients (CR in 6 patients and PR in 24 patients). Four patients (8.7%) showed both clinical and radiological progression without a discernible remission period. The other 12 (26%) patients had SD whether they experienced clinical remission or not. No significant relationship was obtained between mass response and age (< or ≥60), sex, KPS (< or ≥70), marginal dose (> or ≤20 Gy), planned tumor volume (PTV) (< or ≥10 cm^3) or primary histology (radio-resistant or not) (p-values not shown).

The local control after the salvage treatment was obtained in 30 patients at the last follow-up. The median local control of re-treated lesion was 21 months and the 1-year control rate was 64% (Fig. 1). Fourteen patients developed new lesions remote from the treated lesions. The median control of the whole brain was 14 months and 1-year control rate was 57%. RPA class and the factors listed above were correlated with local control (Table 2); only PTV was nearly significantly predictive of local control (p=0.07 in univariate and p=0.10 in multivariate). Twenty-eight (61%) patients died by the end of the study. A median survival after re-treatment was 10 months (range 2-35) and the 1-year survival rate was 39% (Fig. 2). Overall survival of patients from the first diagnosis of brain metastasis was 24 months, separately.

The factors evaluated for the local control rate were again analyzed if they affected the survival significantly (Table 3). The median survival of RPA class 1 and 2 patients was 11 months and that of class 3 patients was 5 months, although the survival difference failed to reach statistical significance. In univariate analysis, PTV was the most significant factor affecting the survival (p=0.006) and followed by age factor (p=0.02). Both factors were also significant for survival in multivariate analysis (p=0.03). Time from WBRT to CyberKnife re-treatment (time to recurrence; <1 year vs. ≥1 year) did not affect the survival after the salvage treatment significantly.

Radiation toxicity according to time period

The number of followed patients and the percentage of radiation toxicity according to stage were depicted in Fig. 3 and we summarized patients' radiation-induced symptoms

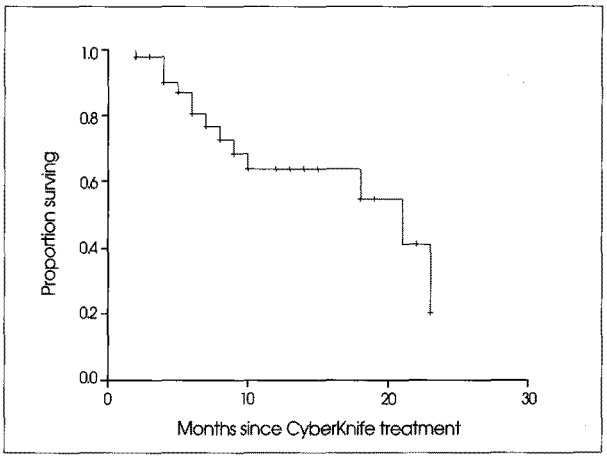

Fig. 1. Local control of treated lesions. The graph illustrates the median local control of treated lesions is 21 months and 1-year progression free survival is 64%.

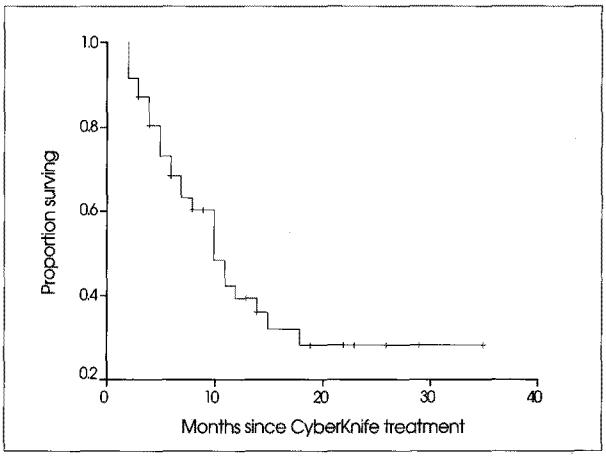

Fig. 2. Survival of patients. The median survival after CyberKnife treatment for recurrent brain metastases is 10 months and 1-year survival rate is 39%.

Table 2. Univariate and multivariate analysis of factors affecting local control rate

Factors	Univariate	Multivariate	
	p-value	p-value	95% CI
RPA class (1 and 2 vs. 3)	0.89	0.60	0.29-8.37
Age (<60 vs. ≥60)	0.68	0.56	0.48-3.85
KPS (<70 vs. ≥70)	0.25	0.37	0.54-5.47
Histology (GI tract and renal)	0.35	0.47	0.54-3.85
PTV (<10 cm^3 vs. ≥10 cm^3)	0.07	0.10	0.86-5.35
*Dose (≤20 Gy vs. >20 Gy)	0.70	0.52	0.54-3.38

*marginal dose converted to single fraction equivalent dose using linear quadratic formula. RPA : recursive partitioning analysis, KPS : Karnofsky Performance Status, PTV : planned tumor volume

Table 3. Univariate and multivariate analysis of factors affecting survival rate

Factors	Univariate	Multivariate	
	p-value	*p*-value	95% CI
RPA class (1 and 2 vs. 3)	0.25	0.93	0.2-3.37
Age (<60 vs. ≥60)	0.02	0.03	1.14-7.13
KPS (<70 vs. ≥70)	0.25	0.15	0.18-1.29
Histology (GI tract and renal)	0.89	0.87	0.35-2.43
PTV (<10 cm^3 vs. ≥10 cm^3)	0.006	0.03	1.10-7.07
*Dose (≤20 Gy vs. >20 Gy)	0.53	0.22	0.71-4.28
Time from WBRT to CK (<1 year vs. ≥1 year)	0.93	0.28	0.22-1.56

*marginal dose converted to single fraction equivalent dose using linear quadratic formula. RPA : recursive partitioning analysis, KPS : Karnofsky Performance Status, PTV : planned tumor volume

Table 4. Number of patients experiencing symptoms of severe radiation toxicity according to time after re-treatment (n=number of patients evaluated).

Symptoms	Acute (n=46)	Subacute (n=38)	Chronic (n=33)	*Total observation period (n=46)
Focal neurologic deficit	5	3 (1)	2 (1)	7
Global dysfunction	5 (3)	2	-	5
Radiation necrosis	-	1	2 (1)	2
Dementia with brain atrophy	-	2	3 (1)	3
Total	10 (22%)	8 (21%)	7 (21%)	17 (37%)

*Number of patients in "Total observation period" represent the number of patients who showed the toxicities throughout whole observation period, not representing the sum of each period. The number in parentheses represents the number of patients showing the symptoms only at that observation period

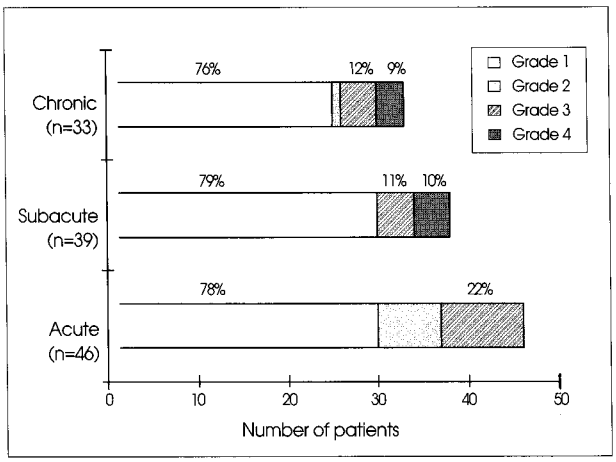

Fig. 3. Incidence of radiation-induced central nervous system toxicity according to the time after the treatment.

in Table 4. Seventeen (37%) out of 46 patients suffered from radiation toxicity at least once during observed period. Acute radiation toxicity was evaluated in all 46 patients (Fig. 3). No toxicity (grade 1) was observed in 29 patients and seven patients required short-term steroids treatment at outpatient clinic (grade 2). The other ten patients (22%) were evaluated as grade 3. Five patients showed confusion and/or mild somnolence, which were classified as global dysfunction, and the other five patients suffered from transient motor deficit including two of postictal paralysis (Table 4). All these grade 3 acute toxicity were transient and normalized by medication. Thirty-eight patients were followed to evaluate subacute toxicity; four patients (11%) had grade 3 and another four had grade 4 toxicity. All of grade 3 patients were responsive to steroids. Two patients revealed definite symptoms of dementia and were hospitalized for severe loss of performance status at 2 months and 5 months after the CyberKnife treatment, respectively. Follow-up MRI showed generalized brain atrophy while treated lesions remain stable status. Another patient with grade 4 toxicity had surgically confirmed radionecrosis at an eloquent site. Evaluation of chronic toxicity was possible in 33 patients. Four patients (12%) showed grade 3 toxicity and three (9%) patients suffered grade 4 toxicity. Two of grade 3 patients harbored suspicious radionecrosis based on MRI and PET findings, in which the enhancing lesion on MRI showed no uptake on PET. Their symptoms were treated conventionally. The third patient who had cystic enlargement of treated lesion at cerebellar hemisphere was evaluated as radiation necrosis on stereotactic aspiration and biopsy. The fourth grade 3 patient had a difficulty of behavioral control including urination and incoherent comprehension. MRI of the patient showed borderline finding of brain atrophy and normal pressure hydrocephalus and the patient was classified to dementia based on clinical observation. Among 3 of grade 4 patients, two patients with dementia with brain atrophy had been suffered their symptoms from the subacute period. The other grade 4 patient was who had already undergone surgical extirpation of radiation necrosis at subacute period. The patient revealed growing symptomatic cystic lesion at previous surgical site, which necessitated stereotactic aspiration. Thus, total occurrence of radiation necrosis based on patient number was 2 (4.3%) and that of dementia with brain atrophy was 3 (6.5%) during whole follow-up period. There was no fatal toxicity in our series.

Analysis of radiotherapeutical factors related to radiation toxicity

Previous dose, summated dose (SumD), PTV, eloquency (motor, language and posterior fossa), hypo-fractionation and time interval between WBRT and CyberKnife (less than 1 year or not) were the factors analyzed to evaluate the correlation with CNS toxicity of each time-period (Table 5).

Table 5. Analysis of radiotherapeutic factors for the occurrence of radiation-induced CNS toxicities

Factors	p-value		
	Acute (<1 month)	Subacute (1-6 months)	Chronic (>6 months)
Previous dose (<33 Gy)	0.28	0.01*	0.16
†Summated dose (<100 Gy)	0.67	0.04	0.004*
PTV (<10 cm^3)	0.03*	0.70	0.08
‡Radiation Toxicity Factor (<1000 Gy × cm^3)	0.01*	0.09	0.04*
Location (eloquent and PF)	0.72	0.11	0.40
Fractionation (single vs. 3 fraction)	1.00	0.65	0.65
Time from WBRT to CK (<1 year vs. ≥1 year)	0.28	0.69	0.66

*denote significant p value (<0.05), †summation of marginal dose, which was converted to linear quadratic equivalent dose, to previous dose (See details in Methods), ‡radiation toxicity factor is computed by multiplying summated dose to PTV (See details in Methods). PTV : planned tumor volume, PF : posterior fossa

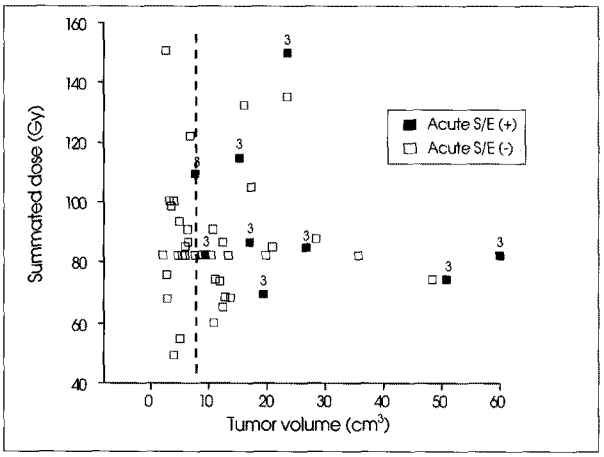

Fig. 4. Scatter diagram of acute side effects plotted as a function of summated dose versus tumor volume. Filled rectangle represents occurrence of radiation-induced side effect with its grade on the top of it. Dotted line indicates lower limit of tumor volume for the occurrence of acute side effect.

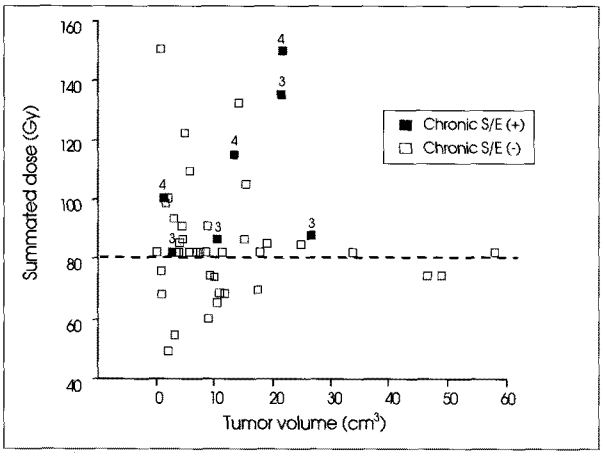

Fig. 5. Scatter diagram of chronic side effects plotted as a function of summated dose versus tumor volume. Filled rectangle represents occurrence of radiation-induced side effect with its grade on the top of it. Dotted line indicates lower limit of summated dose for the occurrence of chronic side effect.

PTV was the only significant predictor of acute toxicity among these factors (p=0.03). The tendency for tumor volume to predict acute toxicity can be seen clearly in the scatter plots in Fig. 4. The acute toxicity occurred at the volumes of 8.2 cm^3 or more; as the tumor volume increased, the toxicity developed in the greater proportion of patients at relatively low summated dose (around 80 Gy). Summated dose of less than 100 Gy was associated with a reduced incidence of both subacute (p=0.04) and chronic toxicity (p=0.01). The smallest dose producing chronic toxicity was 82.5 Gy; Fig. 5 illustrates that chronic toxicity occurred at larger doses and grade 4 toxicities developed at doses greater than 100 Gy. The combined influence of cumulative dose and PTV was captured by the radiation toxicity factor (RTF), obtained by multiplying SumD (Gy) by PTV (cm^3). The RTF (<1,000 Gy × cm^3) was the best predictor for both acute and chronic CNS toxicity (Table 5).

DISCUSSION

Role of hypo-fractionated SRS for Recurrent Brain Metastases

It seems clear that the longer patients are followed after WBRT, the higher the incidence of chronic radiation toxicity is. Nieder et al.[19] reported an actuarial 30-80% rate of radiation toxicity after WBRT of 30 Gy in 3-Gy fractions, and brain atrophy appears on MRI in 100% of cases if follow-up is long enough. Thus, salvage treatment for recurrent brain metastases after WBRT, whether it is conventional radiation or radiosurgery, inevitably poses a high risk of toxicity from cumulative radiation doses.

The few published studies of conventional radiation as a salvage treatment for recurrent brain metastases after WBRT reported dismal outcomes (Table 6). Hazuka and Kinzie[13] reported their experience with re-irradiation in 44 patients. Only 27% showed clinical improvement, with a marginal survival benefit of 8 weeks. They concluded that re-treatment of brain metastases was seldom worthwhile and the patients were at high risk of developing brain necrosis if they survived for extended periods following re-irradiation. Subsequent reports were more favorable, with a response rate of 42-70% and median survival of 4-5 months (Table 6). Improved outcomes were attributed to the selection of patients with a longer time between WBRT and recurrence[8] or the absence of extracranial disease[29]. Still, survival of less than 6 months in these studies was too short to observe chronic toxicity.

Table 6. Published results of salvage treatment for recurrent brain metastases

Treatment mode	Author (year)	Salvage dose (SED)	Tumor volume	Mass response/ Local control	Median survival	Complication
CRT after WBRT	Hazuka (1988)	25 Gy in 3 Gy fx (14 Gy)	Not available	27% clinical/ Not available	8 weeks	Brain necropsies in 8/42
	Cooper (1990)	25 Gy/10 fx (13 Gy)	Not available	42% clinical/ Not available	5 months	No acute toxicity
	Wong (1996)	20 Gy/10 fx (11 Gy)	Not available	70% clinical/ 2.75 months	4 months	No acute toxicity 5/86 showed radiographic changes
RS after WBRT	Loeffler (1990)	15.5 Gy	d=27 mm	Not available/ 90% controlled	Not available	No symptomatic radionecrosis Steroid requirement in 4/18
	Shaw (2000)	12-24 Gy	*8.2 cm^3	*42%/ *50% at 2-year	7.5 months	22% of severe toxicities and operation for necrosis in 8% at 1-yr
	Manning (2000)	27 Gy/3 fx (18 Gy)	2.2 cm^3	45% radiological/ Not available	12 months	2/32 showed necrosis on image
	Noel (2001)	16.2 Gy	1.2 cm^3	56% radiological/ 91% at 1-year	7.8 months	No severe toxicity
	Chao (2008)	9.6-24 Gy	d=2 cm	Not availabe/ 68% at 1-year	9.9 months	2/111 showed radiation necrosis Otherwise no major toxicities
	This study	23.1 Gy/1-3 fx (19.5 Gy)	9.0 cm^3	65% radiological/ 64% at 1-year	10 months	2/46 showed radiation necrosis

*figures mixed with the results of primary brain tumor. SED : single equivalent dose, CRT : conventional radiation therapy, RS : radiosurgery, WBRT : whole-brain radiation therapy, fx : fraction

Until the mid-1990's SRS was primarily offered as a salvage modality rather than as a substitute for conventional WBRT. It was also selectively applied as an alternative to surgical resection in cases of small-volume single or oligo tumors in patients of good performance status and/or controlled systemic disease[1,3,10,16,17]. The results were quite impressive; response rates up to 79% were obtained[1], local control was near 90% at one year, and minimal toxicity (controllable with steroids) was observed[10,17]. However, these were not controlled studies; tumor volumes and radiosurgical doses, important factors determining both the response rate and the risk of radionecrosis, varied widely.

Recent reports of salvage SRS/SRT revealed a median survival of 6-12 months and a much-improved local control rate (Table 6). RPA class was proven to be significant in these studies[7,18,21]. Also, the longer time of recurrence from WBRT was a favorable prognostic factor[7,21]. Recently, Chao et al. retrospectively analyzed the result of SRS salvage for 111 patients who underwent WBRT as their initial management for brain metastases. The median survival of 9.9 months after salvage SRS was effective and significantly affected by the time of recurrence after WBRT (12.3 months for >6 months, 6.8 months for ≤6 months). These results may reflect the initial radiosensitivity of metastatic lesion could be transmitted to the recurrent lesion while they didn't prove it in terms of tumor response.

Unfortunately, we don't have a controlled, randomized prospective study yet, comparing conventional radiation with radiosurgery as a salvage treatment. Such a study would be facilitated by a consensus regarding methods for calculating cumulative doses from repeated radiation spread across time intervals and different radiation volumes. In the absence of such a controlled study, SRS/SRT as salvage treatment for brain metastases may still be limited to selected patients.

Factors related to risk of radiation-induced toxicity

The ability of normal brain tissue to withstand radiation depends on factors such as the amount of previous radiation, its fractionation, and the size and proximity of the treated volume, as well as the time interval between courses of treatment, which can determine how well tissue recovers from radiation exposure[9,28]. The time from initial WBRT to recurrence varies within and across studies. It is difficult to detect differences in outcomes as a function of time since initial treatment (range of median 4-9 months) reported in the studies listed in Table 6, and there are few, if any, articles that focus on the influence of this variable on the occurrence of radiation toxicities. In animal experiments, it has been shown that a longer latency period was associated with increasing the time between irradiations[28] and that occult white matter injury recovered at 2 years in primates when a relatively small dose was delivered as the initial dose[4]. However, in clinical situations the time interval between radiations in brain metastases patients is determined

by the urgent necessity of salvage therapy, not by the time it takes to recover from the initial treatment; and a time interval of a year or less is obviously too short to allow sufficient recovery.

According to the results of WBRT as the salvage treatment, there was little, if any, severe acute toxicity after the treatment, but studies of SRS indicate a certain percentage of patients experience acute toxicity (Table 6). A possible explanation for this difference is that the absolute fraction dose is small in WBRT compared to SRS/SRT. Manning et al.[18] performed a prospective study to evaluate the efficacy and toxicity of hypofractionated SRT in selected patients with brain metastasis. They assumed fractionation would be more beneficial in these cases than in benign tumors. Their treatment parameters were similar to ours in terms of SRT dose and fractions (27 Gy in 3 fractions), and all patients also received WBRT to a dose of 30 Gy. They showed improved survival of 12 months after SRT and no acute toxicity except seizure (which we did not count as a severe complication as long as it was controlled). Two out of 32 of their patients experienced radiation necrosis, one of whom underwent surgical resection while the other was controlled with steroids. Their apparently excellent results should be compared to ours with caution because two-thirds of their patients underwent upfront WBRT, which meant those patients were treated for the first occurrence of brain metastases, not recurrence. Such patients would naturally survive longer. In addition, the median tumor volume was smaller (2.2 cm^3) than in our patients. In summary, delivering stereotactic radiation in fractions may or may not reduce the incidence of complications; the decision to fractionate treatment should be based on a consideration of the fraction number and the radiosensitivity of both the tissue at risk and the tumor to achieve the desired effect[25].

In our study, severe acute toxicity was significantly more likely in tumors larger than 8.2 cm^3, as shown in Fig. 4. However, Fig. 4 dose not reveal a clearly proportional correlation between volume and acute toxicity. Furthermore, the minimum volume of 8.2 cm^3 resulting in acute toxicity should not be interpreted as an absolute value. The combined effect of dose and volume in radiosurgery on the incidence of radiation toxicity was well-reflected in the final report of the RTOG 90-05 study[24]. Shaw et al.[24] studied salvage single-fraction SRS for recurrent primary brain tumors and recurrent brain metastases. Their protocol was designed to determine reasonable dose ranges based on an unacceptable toxicity rate (≥20%); they obtained maximum tolerated doses of 12-24 Gy, with higher doses tolerated in patients with smaller tumors (≤20 mm). Tumor diameter (i.e., tumor volume) was the most significant factor determining maximum tolerated dose. Their results also showed the effect of volume on acute toxicity and dose on chronic toxicity. Patients with tumor diameters less than 20 mm showed no acute toxicity despite receiving the highest doses, but chronic toxicity occurred in proportion to both dose and tumor diameter. In the present study, we observed that tumor volume significantly affected the incidence of acute but not chronic toxicity, while cumulative dose predicted chronic but not acute toxicity (Table 5). We should note the RTOG 90-05 study included patients with either primary brain tumors or brain metastases; prior radiation doses differed according to tumor type (median 60 Gy for primary and 30 Gy for metastatic tumor), so it is difficult to evaluate an effect of cumulative dose quantitatively on the incidence of radiation toxicity based on this study.

Noel et al.[21] reported the results of salvage radiosurgery in patients similar to ours. They obtained superior results, with local control rates of 91% and 84% at 1 and 2 years than ours and observed no major complications. However, these authors treated much smaller tumor volumes (median 1.2 cm^3) than ours (median 9.0 cm^3) or those of the RTOG 90-05 study (8.2 cm^3), at which 22% of patients experienced severe toxicity (Table 6). As such, this difference clearly exemplifies the effect of tumor volume on the incidence of radiation toxicity. Joseph et al.[14] studied the factors affecting the incidence of delayed radiation toxicity in patients underwent radiosurgery for their brain metastases. They found that prior or concurrent WBRT and larger tumor volumes significantly increased the likelihood of toxicity. These observations accord well with our concept of the radiation-toxicity factor, obtained by multiplying the treated tumor volume by cumulative dose, which was significant predictor for both acute and chronic toxicity. Although further investigation is necessary, the radiation-toxicity factor showed strong relation to radiation toxicity at each time period after salvage treatment and regardless of the clinical manifestation.

CONCLUSION

CyberKnife SRS for patients with recurrent brain metastases after WBRT resulted in a durable local control rate (64% at 1-year) and enhanced patient survival (median 10 months). However, there was a considerable incidence of clinically significant radiation toxicity (21-22%) including radiation necrosis. Treated tumor volume significantly affected the incidence of acute toxicity, which was more likely at volumes greater than 8.2 cm^3. Cumulative dose predicted the occurrence of chronic side effects; patients receiving cumulative doses less than 80 Gy showed no

chronic toxicity. The radiation-toxicity factor, obtained by multiplying the tumor volume by the cumulative dose, reflects the toxicity risk most clearly in our series. Although the meaning and validity of the absolute value of these factors should be evaluated further, it seems obvious that tumor volume and cumulative dose should both be considered when contemplating SRS/SRT for recurrent brain metastases.

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