

# Dose-Volume Prediction of Radiation-Related Complications after Hypofractionated Conformal Radiotherapy for Brain Metastases in Critical Areas

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## Abstract

The use of hypofractionated radiotherapy to treat brain metastases and other lesions in critical areas demands an accurate understanding of the risks of complication.

We therefore analyzed risk factors for predicting complications after hypofractionation treatment (two to 10 fractions) for brain metastases based on data for 470 lesions in 367 patients treated with conformal radiotherapy using the CyberKnife.

Twenty-seven lesions in 24 patients exhibited complications over a median follow-up period of seven months (2-50 months). The tumor and brain volumes circumscribed with a single dose equivalent (SDE) of 14 Gy (V14) were found to be significant factors of complications in a univariate analysis. However, the V14 was the only significant factor in the multivariate analysis.

Other risk factors were analyzed based on differences between the groups in the characteristics of the 27 lesions. Consequently, the tumor location (cerebrum,  $p=0.003$ ), tumor volume ( $\geq 10\text{cm}^3$ ,  $p=0.01$ ), SDE of the maximum dose ( $\geq 40$  Gy,  $p=0.01$ ), and V14 ( $\geq 3\text{cm}^3$ ,  $p=0.001$ ) were identified to be significant predictive factors according to the t-test, while the marginal dose ( $\geq 31$  Gy) and fraction number ( $\leq$  five) were found to be borderline significant.

The actual risk of complications after hypofractionated conformal radiotherapy can be best predicted using a model that accounted for the SDE of the maximum dose and V14.

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**Categories:** Radiation Oncology, Neurosurgery

**Keywords:** brain edema, radiation necrosis, dose-volume prediction, complication risks, predictive factors, large brain metastases, hypofractionated conformal radiotherapy, multi-session radiosurgery, brain volumes, v14

## Introduction

Radiosurgery is an important therapeutic tool for the treatment of brain metastases in multiple clinical settings. The addition of radiosurgery to whole brain radiotherapy (WBRT) may improve intracranial tumor control compared to WBRT alone in selected patients [1-2], and radiosurgery is commonly used as salvage therapy for intracranial tumor progression after WBRT. Moreover, radiosurgery is increasingly used as a primary treatment modality in an attempt to prevent disturbances of neurocognitive function after WBRT [3]. However, single-session radiosurgery has dose limitations for treating large metastases with respect to preventing adverse effects on surrounding structures, such as the optic pathway and brainstem. Surgery is essential in patients with large brain metastases that cause progressive symptoms, such as hemiparesis or a disturbance of consciousness, although surgical removal carries a risk of inducing neurological deficits following the dissection of functional areas. Surgery also requires hospitalization for at least one week, with higher medical expenses than radiosurgery in this country.

Hypofractionated radiotherapy appears to be beneficial for metastases not causing clinical signs of impending cerebral herniation, and its use is supported by the findings of previously published series employing varying radiation doses and fractionation schedules [4-8]. However, the optimal dose and fraction have not yet been established, and the exact incidence of complications on the surrounding brain is unclear, especially in cases involving large tumors [8]. Morbidity, and even mortality, has been reported after fractionated radiosurgery for large brain metastases [9-10]. We previously reported the efficacy and toxicity of three-fraction and five-fraction radiotherapy for brain metastases in critical areas and recommended that larger fraction numbers should be selected for large brain metastases based on the dose-volume effects on the surrounding brain circumscribed with a single dose equivalent (SDE) of 14 Gy (V14: defined based on experiences of radiosurgery) to avoid radiation necrosis [11-12]. Although the dose-volume prediction of

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radiation-related complications is widely known to be effective in preventing radiation necrosis in patients undergoing single-session radiosurgery [13], there are currently no data for predicting complications after hypofractionation. The V14 seems to be a useful indicator for comparing the incidence of complications among various fractions after hypofractionated radiotherapy [14].

This report first presents predictive factors and the probability of complications of hypofractionation treatment performed at this institution as a useful treatment for brain metastases in critical areas in comparison with that observed in cases of single-session radiosurgery.

## Materials And Methods

All patients with brain metastases provided their written informed consent prior to undergoing the procedures and were treated with single-fraction radiosurgery or hypofractionated conformal radiotherapy at Kanto Neurosurgical Hospital between March 2005 and October 2013. Hypofractionated treatment (two to 10 fractions) was performed in 392 patients. The incidence of radiation-related complications was evaluated in relation to patients' age, sex, tumor location, tumor volume, prescribed isodose, marginal dose, fraction number, the surrounding brain volume (V14), and others.

### Definition of variables and end points

The treatment dose is expressed as the marginal dose used in hypofractionated radiotherapy. The maximum dose was obtained from the marginal dose and prescribed isodose for the lesion margin. A complication was defined as a neurological impairment (either the development of a new deficit or the significant deterioration of a pre-existing or recurrent deficit) and change in imaging studies after treatment. For all symptomatic complications, either computerized tomography scans or magnetic resonance imaging studies were examined. Clinical follow-up was considered to have stopped at the time of the most recent report from the patient or a representative or at the time of death.

### Inclusion and exclusion criteria

Three hundred and ninety-two patients were treated and found eligible for inclusion in this study. Twenty-five patients (6.4%) were excluded from the analysis because imaging studies were not available after treatment. All other patients (367) were included in the analysis.

### Patient characteristics

The median age of the patients was 68 years; 173 patients (47.1%) were 65 years of age or older. The primary cancers were located in the lungs, breast, gastrointestinal tract, kidney, uterus, larynx, ovary, or other regions (thyroid, liver, bladder, etc.). The tumors ( $n = 470$ ) treated with the hypofractionation protocol were located in and around critical areas previously reported [12]. Those were in the cerebral hemisphere, thalamus/basal ganglia, brainstem, and cerebellum. The median tumor volume of the 470 lesions was  $8.8 \text{ cm}^3$ . One hundred and fifteen tumors (24.5%) were larger than  $15 \text{ cm}^3$  (more than 3 cm in diameter). Thirty-one tumors measured  $30 \text{ cm}^3$  or more in size, up to  $78 \text{ cm}^3$ . Table 1 (left line) shows the patient characteristics.

Characteristics of patients		Treatment-related variables	
Number of patients	367	Prescribed isodose (%)	
Median age (range)	68 (28-93)	Median	58
Age ≥ 65	173	Range	49-77
Age < 65	194	Marginal dose (Gy)	
Sex		Median	30
Male	189	Range	18-48
Female	178	Fraction number	
Location of tumor	470 lesions	Median	3
Cerebral hemisphere	322	Range	2 - 10
Frontal	132	Lesions treated with 2-fraction	20
Parietal	60	3-fraction	226
Temporal	54	4-fraction	20
Occipital	76	5-fraction	156
Thalamus, basal ganglia	29	6-fraction	16
Brainstem	32	8-fraction	22
Cerebellum	87	10-fraction	10
Tumor volume, median (cm <sup>3</sup> )	8.8	Maximum dose (SDE, Gy)	
≥ 30.0	31	Median	46.4
20.0-29.9	37	Range	24.9-65.8
10.0-19.9	126	V14 (cm <sup>3</sup> )	
< 10.0	276	Median	4.9
Follow-up period (months)		Range	0-36.9
Median	7	Complications	27
Range	2-50	(radiation edema, necrosis)	(21, 6)

**TABLE 1: Characteristics of the patients treated for brain metastases in critical areas with hypofractionated conformal radiotherapy**

### Hypofractionated conformal radiotherapy

All patients evaluated in this study were treated consecutively with two to 10 fractions over sequential days using the CyberKnife (Accuray, Sunnyvale, CA). Patients with perifocal brain edema and symptoms were treated with the concomitant intravenous administration of glycerol and beta-methasone (osmo-steroid therapy). All treatment procedures were performed under computed tomography (CT) and MRI guidance, as previously reported [12]. Tumors located in and around critical areas, such as the motor cortex, thalamus, and brainstem, were intended to treat with a marginal dose of 26-35 Gy in two to five fractions depending on the size of the tumor. A marginal dose of 31-42 Gy in five to 10 fractions was intended to use to treat large tumors in order to decrease the incidence of adverse effects on the surrounding brain. The dose to the optic pathway (optic nerve, chiasm, and tract) was intended to be less than 10.8 to 20 Gy in two to 10 fractions rather than 12.3 to 30.2 Gy (the normal tissue dose constraint for the optic pathway in two- to ten-fraction treatment, an equivalent dose of 8 Gy in single-fraction treatment) [15] in order to reduce the risk of adverse effects (Table 2).

SDE		2-fraction	3-fraction	4-fraction	5-fraction	6-fraction	8-fraction	10-fraction
8 Gy	This study	10.8 Gy	12.8 Gy	14.3 Gy	15.6 Gy	16.7 Gy	18.5 Gy	20.0 Gy
	Timmerman	12.3 Gy*	15.3 Gy	19.2 Gy	23.0 Gy	24.2 Gy*	27.2 Gy	30.2 Gy*
	Timmerman2	11.6 Gy				24.4 Gy		30.6 Gy
14 Gy	This study	19.3 Gy	23.1 Gy	26.2 Gy	28.8 Gy	31.2 Gy	35.1 Gy	38.4 Gy
	Timmerman	18.5 Gy*	22.5 Gy	25.6 Gy	28.0 Gy	31.8 Gy*	33.6 Gy	39.8 Gy*
	Timmerman2	18.3 Gy				29.9 Gy		36.0 Gy

**TABLE 2: The single dose equivalent (SDE) of 8 Gy and 14 Gy in two- to ten-fraction treatment was selected and obtained based on the normal tissue dose constraint according to Timmerman's values [15]**

\*Doses at the 2-, 6- and 10-fraction levels were estimated according to a fitted cubic equation curve. Original data for the fitted curve was acquired from Timmerman and calculated using the least squares method [15]. Doses at the 2-, 6- and 10-fraction levels of the Timmerman2 (personal communication) were calculated with linear interpolations between the table values.

### Prescribed marginal doses and SDE of the maximum dose

The maximum dose was calculated from the marginal dose and prescribed isodose (ex. the maximum dose of a plan with marginal dose of 30 Gy at an isodose of 50% calculated was as 60 Gy). For the purpose of dose-response analyses, the maximum dose in two- to ten-fraction treatment was converted to SDE using the equation reported by Eaton, et al. and Park, et al. [8, 16] where D equals the total dose and a Dq of 1.8.

$$\text{SDE} = D - (n - 1) \times Dq$$

(Ex. The SDE of the maximum dose of 60 Gy in three-fraction treatment calculated as  $60 - (3 - 1) \times 1.8 = 56.4$  Gy)

### Evaluation of the brain volume around the lesions

The V14 (brain volume circumscribed with an SDE of 14 Gy) was measured and recorded in each patient in order to compare the risk of complications on the surrounding brain among the different two- to 10-fraction treatments. An SDE of 14 Gy (19.3 Gy in two-fraction to 38.4 Gy in 10-fraction) instead of 18.5 to 39.8 Gy (the normal tissue dose constraint for the spinal cord in two- to ten-fraction treatment, an equivalent dose of 14 Gy in single-fraction treatment) [15] was used (Table 2) for the dose-response analyses. The V14, as well as the tumor volumes, was calculated as previously reported [12].

### Follow-up evaluations and complications

Changes in neurological symptoms, such as paresis, sensory disturbances, aphasia, and visual disturbances, were examined after treatment. Serial imaging studies (MRI or CT) were requested six weeks after treatment and every two to three months thereafter. Complications were identified in association with neurological deterioration and imaging changes in the concomitant perifocal regions after treatment.

### Statistical analysis

The univariate and multivariate analyses were performed using logistic regression and Cox hazard models. Differences between the groups were evaluated using Student's t-test. All analyses used the conventional  $p < 0.05$  level of significance.

## Results

Four hundred and seventy lesions treated with hypofractionation were analyzed for the incidence of complications in relation to the predictive factors. The prescribed isodoses ranged from 49-77% (median, 58%). The marginal dose ranged from 18-48 Gy (median, 30 Gy). The treatment-related and post-treatment variables of 470 brain metastases are shown in Table 1 (right line). No new neurological deficits were observed in patients with lesions in or around critical areas, such as the optic pathway and brainstem.

### Complications and predictive factors

Twenty-seven lesions in 24 patients resulted in symptomatic complications (Table 3).

Characteristics of patients		Treatment-related variables	
Number of patients	24	Prescribed isodose (%)	
Median age (range)	59 (38-84)	Median	58
Age ≥ 65	9	Range	51-65
Age < 65	15	Marginal dose (Gy)	
Sex		Median	31
Male	11	Range	27-36
Female	13	Fraction number	
Location of tumor	27 lesions	Median	5
Cerebral hemisphere	25	Range	3-8
Frontal	9	Lesions treated with 3-fraction	9
Parietal	3	4-fraction	1
Temporal	5	5-fraction	12
Occipital	8	6-fraction	2
Basal ganglia	1	8-fraction	3
Cerebellum	1	Maximum dose (SDE, Gy)	
Tumor volume, median (cm <sup>3</sup> )	16.8	Median	47.3
≥ 30.0	4	Range	39.3-58.8
20.0-29.9	8	V14 (cm <sup>3</sup> )	
10.0-19.9	5	Median	5.4
< 10.0	10	Range	3.0-31.5

**TABLE 3: Characteristics of the 27 lesions with complications after hypofractionated conformal radiotherapy**

The median age of the patients was 59 years, with 15 subjects under 65 years of age. There were 13 females and 11 males. The tumor was located in the basal ganglia in one patient, the cerebellum in one patient and the cerebrum in 24 patients (frontal - 9, occipital - 8, temporal - 5, and parietal - 3). The median tumor volume was 16.8 cm<sup>3</sup>, and 17 tumors measured 10 cm<sup>3</sup> or more in size. The median prescribed isodose was 58%, and 18 lesions were treated with an isodose of 60% or less. The median marginal dose was 31 Gy, and 15 lesions received a dose of 31 Gy or more. The median fraction number was five, and 22 lesions were treated with five fractions or less. The median SDE of the maximum dose was 47.3 Gy, and 26 lesions received an SDE of 40 Gy or more. The median V14 was 5.4 cm<sup>3</sup>, and all 27 lesions were treated with a V14 of 3.0 cm<sup>3</sup> or more.

In the univariate analyses using logistic regression and Cox hazard models, the tumor volume and V14 were found to be significant factors for complications. However, only the V14 was identified to be significant in the multivariate analyses (Table 4).

Factor	OR	Univariate 95% CI	p value	Cox hazard p value	Multivariate p value
Age (per decade)	0.86	0.64-1.15	0.32	0.84	0.82
Sex	0.62	0.28-1.37	0.24	0.61	0.19
Location	1.06	0.87-1.31	0.56	0.81	0.25
Tumor volume	1.04	1.01-1.06	0.005*	0.007*	0.38
Isodose	0.96	0.89-1.03	0.29	0.32	0.19
Marginal dose	1.08	0.98-1.19	0.12	0.19	0.27
Fraction	1.21	0.99-1.48	0.06	0.17	0.43
SDE of max. Dose	1.04	0.98-1.11	0.19	0.19	0.26
V14	1.14	1.05-1.23	0.002*	0.006*	0.01*

**TABLE 4: Results of the univariate and multivariate analyses of risk factors for complications in the 470 lesions**

OR: odds ratio, CI: confidence interval, \*significant

Differences in each risk factor between the groups were analyzed using the t-test (Table 5).

Factor	Group 1 (n)	Group 2 (n)	p value
Age	≥ 65 y (9)	< 65 y (15)	0.16
Sex	F (13)	M (11)	0.28
Location	cerebrum (25)	other (2)	0.003*
	frontal (9)	parietal (3)	0.32
	basal ganglia (1)	others (26)	0.29
Tumor volume	≥10 cm <sup>3</sup> (17)	< 10 cm <sup>3</sup> (10)	0.01*
Isodose	> 60% (9)	≤ 60% (18)	0.38
Marginal dose	≥ 31 Gy (15)	< 31 Gy (12)	0.05
Fraction number	> 5 (5)	≤ 5 (22)	0.06
SDE of max. dose	≥ 40 Gy (26)	< 40 Gy (1)	0.01*
V14	≥ 3 cm <sup>3</sup> (27)	< 3 cm <sup>3</sup> (0)	0.001*

**TABLE 5: Risk factors for complications in the 470 lesions between the two groups analyzed using the t-test**

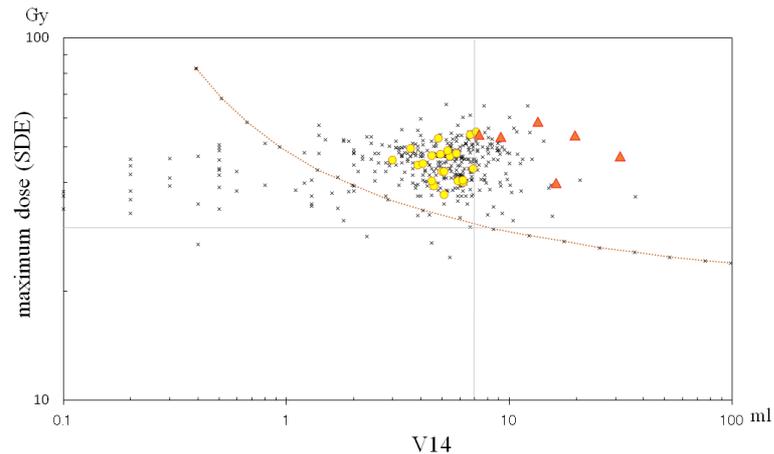
\*significant

Consequently, the tumor location (cerebrum), tumor volume ( $\geq 10 \text{ cm}^3$ ), SDE of the maximum dose ( $\geq 40 \text{ Gy}$ ), and V14 ( $\geq 3 \text{ cm}^3$ ) were shown to be significant factors for complications, whereas the marginal dose ( $\geq 31 \text{ Gy}$ ) and fraction number ( $\leq 5$ ) were borderline significant. Meanwhile, the SDE of the maximum dose and the V14 were more significant than the marginal dose and tumor volume, respectively.

### V14 values of the surrounding nrain and complications

The V14 was plotted in relation to the SDE of the maximum dose (Figure 1).

Fig. 1



### FIGURE 1: Scatterplot showing dose-volume interaction.

V14 values of 470 brain metastases plotted in relation to the SDE values of the maximum doses administered in hypofraction treatment. Symptomatic complications developed in 27 lesions, brain edema in 21 lesions (round) and radiation necrosis requiring surgical resection in six lesions (triangle). Kjellberg's 5% necrosis risk line [13] was converted and then drawn for five-fraction radiotherapy (dotted line).

The actual risk of complications was best predicted using a model accounting for the maximum dose (SDE) and V14. Lesions treated with a higher SDE of the maximum dose of 40 Gy or more and a V14 of 3 cm<sup>3</sup> or more exhibited a higher risk of complications than those treated with lower doses and lower V14 values. Notably, lesions treated with a V14 more than 7 cm<sup>3</sup> carried a risk of irreversible complications.

## Discussion

The role of radiosurgery has been described in 10 institutional studies of patients treated with radiosurgery and WBRT [17]. Radiosurgery also plays a role in the treatment of small multiple brain metastases in advanced cancer patients due to the short treatment time and absence of the need for general anesthesia. However, the treatment of large metastases in critical areas has dose limitations for single-fraction radiosurgery. The dose-volume prediction of complications after single-session radiosurgery has been reported [13] and widely used as the Kjellberg risk line. Blonigen, et al. and Minniti, et al. proposed that patients with a V10 Gy of > 10.5 cm<sup>3</sup> or V12 Gy of > 7.9 cm<sup>3</sup> and V12 Gy of > 8.5 cm<sup>3</sup> should be considered for hypofractionated radiotherapy, respectively [18-19]. The dose-volume prediction of complications after hypofractionated radiotherapy is required, as in single-session radiosurgery, to avoid complications.

In order to predict complications after hypofractionation treatment, the SDE in two- to ten-fraction treatment must be calculated. However, the exact calculation method for obtaining the proper single dose equivalent of 14 Gy in hypofractionated radiotherapy has not yet been established. A generalized linear-quadratic model appears to be suitable for this calculation [20-21]. We used an SDE of 8 Gy and 14 Gy, referring to Timmerman's report. The accumulation of clinical data regarding the use of the SDE, which can be converted for proper SDE in the future, may support the creation of an ideal calculation method for converting to SDE from hypofractionation.

We previously reported the efficacy and toxicity of three- and five-fraction treatment for brain metastases and suggested that the V14 is a useful indicator of radiation necrosis. [11-12]. In the present study based on data for 470 lesions, the statistical analyses of risk factors for complications showed the V14 to be a significant factor according to the univariate and multivariate analyses. The V14 values can be decreased, even in patients with large lesions undergoing hypofractionation treatment. In contrast, the tumor volume is not always a significant factor, as shown in the present multivariate analyses. The V14 is thus not only an indicator of necrosis, but also a best predictive factor of complications.

We analyzed the differences between the groups based on the characteristics of the 27 lesions. Consequently, the SDE of the maximum dose ( $\geq 40$  Gy) and V14 ( $\geq 3$  cm<sup>3</sup>) were found to be significant factors according to the t-test. The maximum dose, treatment volume, location (thalamus/brainstem) and patient' age have been shown to be predictive factors of radiation necrosis in patients undergoing single-session radiosurgery [13, 19, 22]. However, in the current series, the location of thalamic/brainstem lesions and the patient' age were not identified to be significant factors, and no complications were detected in the patients with brainstem lesions. It is possible to decrease the dose to surrounding critical structures while maintaining a proper treatment dose for the lesion when applying hypofractionated conformal radiotherapy.

Hypofractionation treatment is thus safe and less invasive for patients with high risk factors, such as large lesions or those located in critical areas, as well as elderly patients and/or individuals with general risks for surgery.

As to the results of the univariate and multivariate analyses, the t-test for differences between the groups, showed the V14 and SDE of the maximum dose to be important predictive factors for complications after hypofractionated radiotherapy. The actual risk of complications was best predicted using a model accounting for the maximum dose (SDE) and V14, as shown in Figure 1. In addition, Kjellberg's 5% necrosis risk line converted and drawn for five-fraction radiotherapy appeared to fit the current dose-volume prediction model; no lesions appeared on the 5% risk line in this series. Therefore, the percent risk of necrosis can be decreased in patients undergoing hypofractionation treatment more easily than in those undergoing single-session radiosurgery. In the present series, large lesions measuring 30 cm<sup>3</sup> or more were treated in 31 patients, four of whom developed symptomatic complications. One patient received surgery for radiation necrosis, while three patients treated with a V14 less than 7 cm<sup>3</sup> recovered from their complications and survived up to 18 months after treatment. Hence, the 5% necrosis risk line after hypofractionation treatment was drawn on a level higher than the maximum dose, versus Kjellberg's 5% necrosis risk line shown in Figure 1.

The Kjellberg risk line indicates the safe treatment dose for larger lesions in order to avoid radiation necrosis in single-session radiosurgery. Large lesions should be treated with doses below the risk line in patients undergoing single-session treatment. The current dose-volume prediction analysis suggests the proper dose and fraction number for hypofractionation treatment of large lesions in the brain. Therefore, the treatment dose and V14 can be decreased in reference to the results of this prediction analysis using an optimal dose and fraction for the treatment of large lesions in patients receiving hypofractionated radiotherapy.

## Conclusions

We herein reported predictive factors of complications after hypofractionated conformal radiotherapy for brain metastases. The actual risk of complications is best predicted using a model that accounted for the SDE of the maximum dose and V14. Assessing the brain volume (V14) is useful for preventing complications and appears to be helpful for determining the optimal dose and fraction number for hypofractionation treatment of large brain lesions in critical areas.

## Additional Information

### Disclosures

**Human subjects:** Consent was obtained by all participants in this study. **Animal subjects:** All authors have confirmed that this study did not involve animal subjects or tissue. **Conflicts of interest:** In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** All authors have declared that they have no financial relationships at present or within the previous three years with any organizations that might have an interest in the submitted work. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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