

RESEARCH ARTICLE

Maximum Diameter of Intracranial Metastatic Lesions as a Prognostic Factor in Patients Following Whole Brain Radiotherapy

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Abstract

Purpose: To evaluate whether maximum diameter of intracranial metastatic lesions may be a prognostic factor in intracranial metastatic patients receiving whole brain radiotherapy. **Materials and Methods:** The records of 114 cases who between January 2005 and December 2007 were retrospectively reviewed. There were 85 who met the inclusion criteria. **Results:** In these 85, the one-year overall survival rate was 16.5% and the median survival time was 125 days. Median survival in relation to recursive partitioning analysis (RPA) classes I, II and III were 216, 133 and 85 days. Log-rank tests of initial prognostic factors were significant for RPA classifications, Karnofsky Performance Status (KPS), maximum diameters of intracranial metastatic lesions and presence of necrotic centers. The median survivals with a maximum diameter of the largest intracranial metastatic lesion <3cm and ≥3cm were 162 days and 104 days (p=0.027). Multivariate analysis also showed a statistical significance for maximum diameter of intracranial metastatic lesions and presence of necrotic centers. **Conclusions:** Maximum diameters of intracranial metastatic lesions could be used as a prognostic factor in patients receiving whole brain radiotherapy and may help radiation oncologists to make decisions on treatment plans.

Keywords: Brain metastasis - whole brain radiotherapy - intracranial lesion maximum diameter - prognostic factor

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Introduction

Brain metastasis is a common problem of intracranial malignancy and patients usually have less than 1-year survival. Whole brain radiotherapy (WBRT) is the standard of care in patients with brain metastasis and treatment should be given as soon as possible after the diagnosis (Nichols et al., 2013). Surgical resection or stereotactic radiosurgery is considered for single brain metastasis. Stereotactic radiosurgery alone for 4 or fewer lesions is an option for selected patients (Gibbs and Soltys, 2008). WBRT can improve survival over supportive care of about 3-6 months, and improved neurologic function is seen in approximately 50% of patients. Common complications of WBRT include hair loss, skin irritation, nausea and vomiting. Severe complications, such as severe brain edema or radiation brain necrosis, are rare (Borgelt et al., 1980).

Prognosis of symptomatic brain metastatic patients is generally very poor. Average survival is only one month in cases without steroid treatment and two months with steroid treatment (Ruderman and Hall, 1965; Markesbery et al., 1978). Gaspar et al. had reported

recursive partitioning analysis (RPA) classes for predicting prognosis using the RPA class I (Karnofsky performance score [KPS] ≥70, controlled primary, age <65 years, brain metastasis only), class II (not meeting requirements of classes I or III), and III (KPS <70) with demonstrated median survivals of 7.1, 4.2, and 2.3 months. Therefore, the major prognostic factors for patients with brain metastases are age, performance status, controlled primary and extracranial metastases (Gaspar et al., 1997). The number of metastatic brain lesions may also be one of prognostic factors. The outcome of patients with brain metastasis was significantly better for patients with a single brain metastasis (Lutterbach et al., 2002). The type of primary cancer was also shown to be related with survival in some studies (Sperduto et al., 2010; Phunggrassami and Sriplung, 2015).

At present computed tomography and magnetic resonance imaging is performed for diagnostic intracranial metastasis in most cases, but radiological findings are not useful to predict survival. We performed this retrospective study to determine whether, in brain radiotherapy, the maximum diameter of intracranial metastatic lesions could be related to prognosis.

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Materials and Methods

A retrospective analyses of patients with brain metastases who received whole brain radiotherapy in Srinagarind hospital, Faculty of Medicine, Khon Kaen university, Thailand was conducted between January 2005 and December 2007. This study had been approved by the Human Ethics Committee of Khon Kaen University (HE 581391). Patients with prior radiotherapy in the head region or insufficient information about imaging of metastatic lesions were excluded. The prognostic factors evaluated for overall survival were maximum diameter of brain metastasis, Karnofsky performance score (KPS), age, RPA class, whether the primary tumor was controlled, extracranial metastases, number of lesions, radiological findings, i.e. midline shifting, mass effect, necrotic center, radiotherapy technique, radiation dose, biologically effective dose (BED), complete treatment status and tumor response. Overall survival was calculated by Kaplan-Meier method. The log-rank test was used to compare the survival curves. A multivariate Cox's proportional-hazard analysis was used to evaluate prognostic variables with respect to overall survival.

Results

There were 114 intracranial metastatic patients who underwent whole brain radiotherapy. There were 85 patients included in this study; 48 were females and 37 were males. The median age at diagnosis of intracranial metastasis was 51 years (range 21-77 years). The Karnofsky performance score was less than 70% in 20 patients (23.52%) and 70% or more in 65 patients (76.47%). The primary tumors were lung cancer in 43 patients (50.5%), breast cancer in 13 patients (15.29%), colorectal cancer and cervical cancer in 3 patients (3.52%), other in 8 patients (9.41%) and unknown primary in 15 patients (17.64%). The histology showed adenocarcinoma in 24 patients (28.23%), ductal carcinoma in 12 patients (14.11%), squamous cell carcinoma in 10 patients (11.76%), other histology in 14 patients (16.47%) and unknown histology in 25 patients (29.41%). Thirty-four patients (40.00%) also had extracranial metastases and primary tumors were controlled in 29 patients (34.12%). There were 9 patients (10.58%) who had prior tumor removal of intracranial lesions before receiving brain radiotherapy. All of the patients were categorized into 3 groups, according to the RPA classification as class 1 in 15 patients (17.65%), class 2 in 50 patients (58.82%) and class 3 in 20 patients (23.53%). The median of maximum diameter of intracranial metastatic lesions was 3 cm. (range 0.5-6.4 cm.) and the mean of maximum diameter was 3.02cm (SD=1.42). The location of largest lesions were at frontal lobe in 23 patients (27.06%), parietal lobe in 15 patients (17.65%), cerebellum in 15 patients (17.65%), occipital lobe in 14 patients (16.47%) and other in 18 patients (21.18%). There were single brain metastatic lesions in 31 patients (36.47%) and more than 5 lesions in 25 patients (29.41%). Brain edema was found in 69 patients (81.17%) and twenty-eight (32.94%) patients had presented mass effects. The radiotherapy techniques

of whole brain radiotherapy used for treatment of these patients were two-dimensional in 84 of 85 patients (98.82%) and 3-dimension conformal radiotherapy (3DCRT) in only one patient. The dose fractionation schedules were titration doses in 51 patients (60.00%), 2

Table 1. Analysis of Survival by Treatment Factor

		Median survival (days)	Log-rank test (p-value)
Initial treatment factors			
Extracranial metastasis	Absent	109	0.27
	Present	159	
Primary controlled	Controlled	166	0.07
	Uncontrolled	68	
Surgery before radiotherapy	Yes	184	0.38
	No	121	
Solitary lesion	Yes	159	0.37
	No	112	
Midline shifting	Absent	121	0.57
	Present	104	
Mass effect	Absent	112	0.98
	Present	128	
Necrotic center	Absent	126	>0.01
	Present	52	
Dose per fraction (cGy)	180	206	0.33
	200	94	
	300	67	
	Titration dose	128	
Boost	No boost	121	0.63
	Boost	352	
Age	< 65 years	144	0.31
	≥ 65 years	116	
KPS	< 70	159	<0.01
	≥ 70	82	
RPA classification	1	216	0.01
	2	144	
	3	82	
Maximum lesion diameter	<3 cm	162	0.03
	≥3 cm	104	
Post radiotherapy factors			
Complete radiotherapy	Incomplete	35	<0.01
	Complete	172	
Dose	< 40 Gy	118	0.88
	≥ 40 Gy	154	
BED	<39 Gy10	79	0.01
	≥39 Gy10	172	
Clinical response	No response	52	<0.01
	Response	172	
Imaging response	Response	166	0.07
	Progress	121	
	Stable	118	

Table 2. Multivariate Cox's Proportional-Hazard Analysis

	Haz. Ratio	P-value	95% Conf. Interval
Initial treatment factors			
Necrotic center	3.25	0.02	1.19-8.87
KPS	1.07	0.9	0.37-3.10
RPA classification	1.56	0.23	0.76-3.22
Maximum lesion diameter	1.72	0.05	1.00-2.95
Post-treatment factors			
Complete radiotherapy	0.42	0.19	0.12-1.54
BED	0.95	0.88	0.46-1.94
Clinical response	0.42	0.12	0.14-1.27

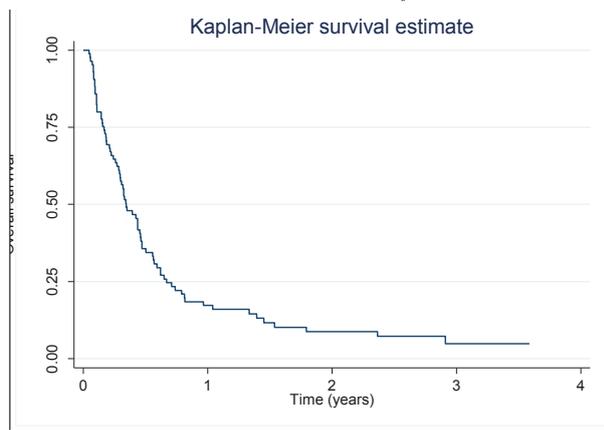


Figure 1. Overall Survival Curve

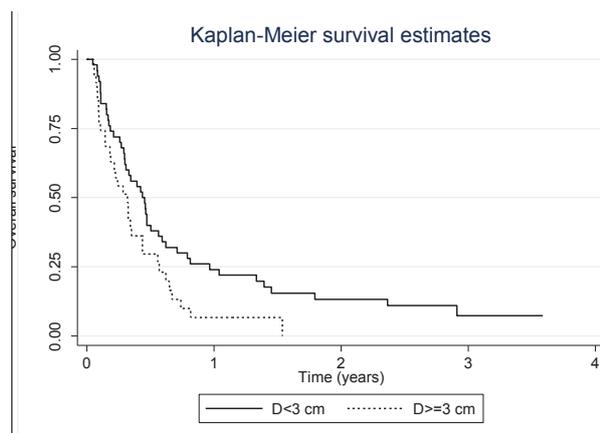


Figure 2. Overall Survival Curves Grouped by Maximum Lesion Diameter (D)

Gy per fraction in 24 patients (28.24%), 1.8 Gy/fraction in 8 patients (9.41%) and 3 Gy per fraction in 2 patients (2.35%). 3DCRT boost was given in 3 patients (3.53%) and 2D boost for one patient. The median whole brain radiotherapy dose was 39 Gy (range 0.05-41.4 Gy). The 3DCRT boost dose was 20 Gy in 2 patients and 18 Gy in one patient. The median treatment time was 30 days (range 1-77 days). The radiotherapy treatment was completed in 61 of 85 patients (71.76%). Clinical responses at the first follow up date were validated in 42 patients (49.41%). Only nineteen patients had been followed up with CT or MRI imaging. Radiological responses were classified as complete response in 3 patients (21.05%), partial response in 10 patients (52.63%), stable lesions in 3 patients (15.79%) and progressive disease in 2 patients (10.53%). The overall one and two-year survival rates were 16.47% and 7.06%. The median survival time was 125 days. The Kaplan-Meier estimation of overall survival is shown in Figure 1.

From initial treatment factors analysis, some factors were found to have statistical significance. The median survival, as related to RPA class 1, 2 and 3 were 216, 133 and 85 days ($p=0.012$). The maximum diameter of the largest intracranial metastatic lesion was shown to be another good predictor of survival. The median survival of patients with lesions smaller than 3 cm. was 162 days and 104 days in patients with lesions ≥ 3 cm. Accordingly, one-year overall survival of the patients with lesions < 3 cm. and ≥ 3 cm. were 24.00% and 5.71% and the two-year

overall survival rates were 12.00% and 0%. The Kaplan-Meier survival estimation of the patients with lesions < 3 cm. and ≥ 3 cm. are presented in Figure 2.

The log-rank test of overall survival as related to maximum diameter of the largest intracranial metastatic lesion was shown to have statistical significance ($p=0.027$). Median survivals of patients with and without necrotic centers were 30 days and 126 days ($p=0.01$). KPS ≥ 70 and < 70 also demonstrated better median survival ($p=0.005$). The analysis by log-rank test of post-treatment prognosis factors also showed differences in some predictors. The median survival of patients who received completed radiotherapy was 172 days and 35 days with incomplete radiotherapy ($p<0.01$). The median survival times of patients who had clinical responses at first time of follow-up was 172 days and 52 days in the group without clinical responses ($p<0.001$). The patients who received biological effective doses of radiation less than 39 Gy10 were 79 days in median survival and 172 days in not less than 39 Gy10 ($p<0.001$). Other analyses of log-rank test of initial treatment prognostic factors are summarized below and listed in Table 1.

The multivariate Cox's proportional-hazard analysis of initial treatment prognostic factors showed statistical significance in the maximum diameter of an intracranial metastatic lesion and presence of a necrotic center. The details of multivariate Cox's proportional-hazard analyses are shown in Table 2.

To summarize then, the current study showed log rank significant predictors of survival in the following criteria: 1) The maximum diameter of the largest intracranial metastatic lesion, 2) Presence of necrotic centers, 3) RPA class, 4) KPS ≥ 70 and < 70 classification, 5) Completion of radiotherapy, 6) Biological effective doses of radiation 7) Clinical responses at first time of follow-up.

Discussion

The most commonly used radiotherapy technique was whole brain radiotherapy with titrated doses for this study, in contrast to many studies using 3Gy per fraction. Amongst those series, some had shown benefit of boosting lesions after whole brain radiotherapy, but in the present study, boosting cannot be conclusive because of the small boost sample. As compared to other series, there were no different outcomes among different radiotherapy regimens (Tsao et al., 2005). In this study, the overall median survival of patients with metastatic brain tumors after receiving brain radiotherapy was 126 days, which was similar to the study of RTOG 79-16 (Komarnicky et al., 1991). Reviewing literature from many series, median survival was in the range of 4-6 months. Gaspar et al. reported median survival, according to the RPA classifications, of 7.1, 4.2 and 2.3 months comparable to this study of 8.6, 4.2 and 2.9 months in classes I, II and III. In conclusion, Gaspar et al. proved that the RPA classification was a good prognostic factor for the cases with brain metastasis (Gaspar et al., 1997; Gaspar et al., 2000). Hadara et al. also demonstrated that the RPA classification was useful as a prognostic factor comparable to this study (Harada et al., 2016). In this study, KPS was

also shown as good prognostic factors similar to the study by Kaul et al. (2015). Some studies demonstrated that many other factors such as age, extracranial metastasis, prior surgery, primary tumor control, neurological status, primary cancer and histology were also good survival predictors (Gaspar et al., 2000; Sperduto et al., 2010). Those factors were not statistically significant in this study. The number of imaged lesions, as reported in many series, was one of the major predictors of survival here, too (Sause et al., 1990; Oh et al., 2009; Tang et al., 2015). The present study noticed a relationship between numbers of lesions with survival, but, was not statistically significant, possibly due to the small sample.

This study demonstrated that maximum diameter of intracranial lesions treated with whole brain radiotherapy was a good predictor of survival. This had never been reported statistically significant in any other series before. Julio Sanchez et al. reported different survivals in asymptomatic brain metastasis in non-small cell lung cancer patients with the maximum diameter of the largest brain lesion, but without statistical significance (Sanchez de Cos et al., 2009). The relationship of lesion size and survival were reported in some series of radiosurgery. Two studies showed overall survival to be correlated inversely with the volume of the largest lesion (Oh et al., 2009; Baschnagel et al., 2013).

In this study it was also demonstrated that completion of the fore-planned radiotherapy and clinical response at first follow-up could be used as post- radiation prognostic factors. Some series showed imaging response as a good predictor but it was not demonstrated in this study (Swift et al., 1993). Moreover, the biological effective dose (BED) of radiation was another prognostic factor for survival, which seems to be similar to that reported of Gaspar et al. (2010).

In conclusion, The maximum diameter of an intracranial metastatic lesion could be used as a good prognostic factor in patients receiving whole brain radiotherapy and may help radiation oncologists to make decisions on treatment plans.

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