STEREOTACTIC IRRADIATION FOR BRAIN METASTASES : ANALYSIS OF PROGNOSTIC FACTORS IN SURVIVAL

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Abstract
Stereotactic radiotherapy (SRT) has become an established therapeutic option for patients with brain metastases. The purpose of this study was to evaluate the effcacy of SRT for brain metastases and to identify prognostic factors affecting survival. We analyzed 74 patients with brain metastases encountered at Akita University from June 2000 to February 2003. The survival rate was assessed by the Kaplan-Meire method, and the significance of differences was determined with the log-rank test. The Cox regression analysis was used adjusting for factors including age, gender, Karnofsky performance status (KPS), tumor volume, tumor number, extracranial disease status. This study showed the median survival after SRT for the whole group was 7.9 months, and KPS and extracranial disease status are independent factors for survival. Patients with KPS <70 and extracranial progressive disease had a very poor outcome with a median survival of 3.3 months, and are unlikely to benefit from SRT.

Key words : stereotactic radiotherapy, brain metastases, prognostic factors

Introduction

Brain metastases occur in 25-50% of all cancer patients[1,2)]. In adults, lung cancer is the main cause of brain metastases (50-60%), followed by breast cancer (15-20%)[3)]. Over the past few decades, whole brain radiation therapy (WBRT) has been considered the standard therapeutic treatment for brain metastases[3)]. The prognosis of patients with brain metastases is generally poor. Selected patients, however, can survive relatively longer with aggressive treatment. For instance, patients with solitary brain metastasis treated with surgical resection plus WBRT can survive longer (median, 40 weeks) than patients treated with WBRT alone (median, 15 weeks)[4)]. More recently, stereotactic radiosurgery (SRS) has emerged as a promising therapeutic option for these patients, and appears equivalent to surgical resection in terms of local control and survival[5,6)].

The most commonly used prognostic system is the Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) derived from 1,200 patients from three consecutive RTOG brain metastatic studies[7)]. Patients in RPA class I are characterized by an age of <65 years, a Karnofsky performance status (KPS) score of ≥70, the absence of extra-cranial metastases, and good control of systemic disease. Patients in RPA class III are those with a KPS score of <70. All other patients belong to RPA class II.

Our institution has utilized linac-based stereotactic radiotherapy (SRT), including SRS and hypofractionated stereotactic radiotherapy (HSRT), for patients with brain metastases since June 2000. On the expectation of ad-

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vantages such as improved quality of life and survival time, the policy was to apply SRT to patients with brain metastases wherever possible. There appears to be a trend toward an increasing incidence of brain metastases, and patients with systemic malignancies can live longer because of earlier diagnosis and/or better treatment. SRT would be increasingly used in the management of brain metastases, and careful selection of patients for SRT may be required. Should we apply the RPA classification for patient selection ?

The purpose of this retrospective study was to identify factors predicting a poor outcome and to help identify who are unlikely to survive long enough.

Methods and Materials

Patient characteristics

From June 2000 to February 2003, 74 patients with brain metastases were treated using SRT. Of these, 25 patients displayed solitary brain metastasis, and 50 had multiple metastases (range, 2-6 metastases). A total of 278 lesions were treated. Patient characteristics are listed in Table 1.

The most frequent primary tumor was lung carcinoma ($n=35$). Other primary tumors comprised breast adenocarcinoma ($n=7$), renal cell carcinoma ($n=7$), colorectal adenocarcinoma ($n=6$), and other malignant neoplasms ($n=19$). Median patient age was 66 years (range, 30-89 years). Median KPS was 70 (range, 30-100). Extracranial disease status indicated progressive disease (PD) in 36 patients, partial response (PR) in 20 patients and complete clinical response (CCR) in 19 patients. Median volume of the largest treated lesion was 1.12 cm^3 (range, 0.03-43.9 cm^3).

Distribution of patients according to the RTOG RPA classification[7] is shown in Table 1. Only 8 patients (11%) were classified as RPA I (age <65, KPS ≥70, controlled primary tumor and absence of extracranial metastases). Thirty-four patients (45%) were RPA III (KPS <70), and 33 patients (44%) were RPA II (not RPA I or III).

No patients displayed clinical or radiological evidence of meningeal carcinomatosis.

Table 1. Demographic.

Total patients	74
Age-years	
Median (range)	66 (30-89)
< 65 years	31 (41.9)
≥ 65 years	43 (58.1)
Gender (%)	
Male	39 (52.7)
Female	35 (47.3)
Primary tumor (%)	
Lung	35 (47.3)
Breast	7 (9.5)
Kidney	7 (9.5)
Colorectal	6 (8.0)
Others	19 (25.7)
KPS (%)	
≥ 70	40 (54.1)
< 70	34 (45.9)
Number of lesions (%)	
Single	25 (33.8)
Multiple	49 (66.2)
Procedure(s) (%)	
1	56 (75.7)
2	13 (17.5)
3	4 (5.4)
4	1 (1.4)
RTOG-RPA† classes (%)	
I	8 (10.8)
II	32 (43.3)
III	34 (45.9)
Extracranial disease status (%)	
PD	36 (48.6)
Not PD	38 (51.4)
Combined WBRT	
Yes	6 (8.1)
No	68 (91.9)
Type of radiotherapy	
SRS	43 (58.1)
HSRT	31 (41.9)

†Radiation Therapy Oncology Group-Recursive Partition Analysis, as defined by Gaspar *et al.*[7]
Abbreviations : KPS=Karnofsky performance status ; PD=progressive disease ; WBRT=Whole brain radiation therapy ; SRS=Stereotactic radiosurgery ; HSRT=hypo fractionated stereotactic radiation therapy.

Treatment

Patients were treated with 6-MV photons using a linac-based stereotactic system. Treatment methods were performed according to lesion size. If lesions were <2.5 cm in diameter, they were treated at one time, using SRS. If the diameter of lesions was ≥2.5 cm, hypofractionated stereotactic radiation therapy (HSRT) was selected. In these cases, patients were immobilized using a thermo-shell and headrest made exclusively for each patient. Clinical target volume was defined as identical to gross tumor volume, represented by the contrast-enhanced area on magnetic resonance imaging (MRI). The planning target volume (PTV) provided an additional margin of 1 mm in all directions.

Basic fractionation schedules were determined to be 34 Gy in 4 fractions over a 4-6day period at the isocenter and 27.2 Gy at the periphery of the PTV for HSRT. For SRS, we basically prescribed 28 Gy at the isocenter and 22.4 Gy at periphery of the PTV. Total dose was modified according to size, shape and location. Median peripheral doses were 26.24 Gy for HSRT and 21.50 Gy for SRS.

All patients underwent follow-up with both clinical and imaging examinations. General physical and neurological examinations and contrast-enhanced MRI were performed 4-6 weeks after treatment. After the first re-evaluation, patients were evaluated at 3-month intervals.

Statistical analysis

The endpoint of the study was overall survival. The survival time was calculated from the starting date of SRT to the date of death or last patient contact using the method of Kaplan Meire. Survival curves were compared using the log-rank test. The objective response rate was reported with its 95% confidence interval (CI). The hazard ratio (HR) and CI were estimated for each variable using the Cox univariate model. A multivariate Cox proportional hazard model was also adopted using stepwize regression with predictive variables which were significant in the univariate analyses.

The covariates examined in all cases were : age (<65 vs. ≥65), gender (male vs. female), KPS (<70 vs. ≥70), number of tumors (single vs. multiple), volume of largest treated lesion (<5 vs. ≥5, <10 vs. ≥10, <15 vs. ≥15), extracranial disease status (PD vs. not PD), combination of WBRT and radiation method (SRS vs. HSRT). Patient groups categorized by the RPA classification were also analyzed. All analyses were conducted using the programming language R (Version 2.11.1).

Results

Median survival for all patients was 7.9 months (95% CI, 5.3-11.5). One-year survival rate was 30.0% (Fig. 1). Survival curves for gender, volume of largest treated lesion, number of lesions, combination of WBRT and radiation methods did not demonstrate any significant differences among subsets by log-rank test. However, KPS and extracranial disease status subset curves differed significantly, with values of $p<0.001$ and $p=0.001$, respectively. Actuarial median survival was 11.5 months (95%CI, 9-infinite) for patients with KPS ≥70, 5.2 months (95% CI, 2.5-7.9) for those with KPS <70, 11.2 months (95% CI, 9-infinite) for patients with not PD (CCR or PR), and 5.2 months (95% CI, 2.8-8.2) for patients with PD. Although a trend survival improvement was found for patients younger than 65 years, this trend did not reach statistical significance ($P=0.05$). Multivariate analyses also identified KPS and extracranial dis-

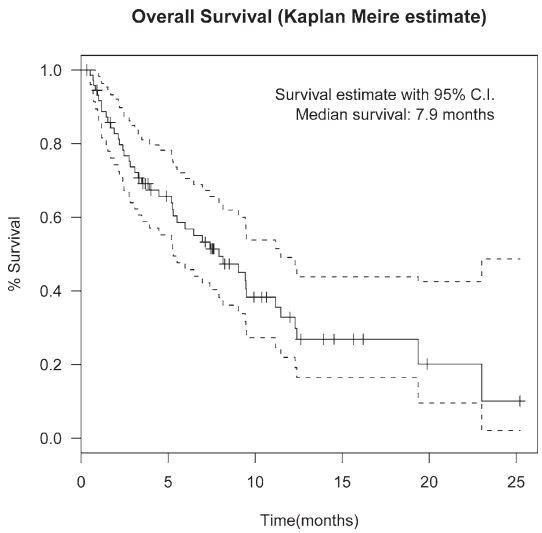

Fig. 1. Overall survival for the entire group.

Table 2. Univariate and multivariate analysis of prognositic factors for overall survival.

Overall survival	Univariate Analysis		Multilple Analysis	
	HR (95% CI)	*p* value	HR (95% CI)	*p* value
Gender (male vs. female)	1.33 (0.73-2.43)	0.351	-	-
Number of lesions (single vs. multiple)	0.71 (0.37-1.41)	0.329	-	-
Combined WBRT (yes vs. no)	0.95 (0.33-2.76)	0.930	-	-
Type of radiotherapy (SRS vs. HSRT)	1.02 (0.55-1.90)	0.940	-	-
Tumor volume				
<5 vs. ≥5	0.87 (0.44-1.74)	0.697	-	-
<10 vs. ≥10	0.98 (0.53-1.81)	0.938	-	-
<15 vs. ≥15	0.97 (0.50-1.91)	0.933	-	-
Age (<65 vs. ≥ 65)	0.53 (0.28-1.01)	0.050	1.00 (0.47-2.11)	0.995
KPS (<70 vs. ≥70)	3.42 (1.79-6.50)	<0.001	3.00 (1.41-6.38)	0.004
Extracranial status (PD vs. not PD)	2.87 (1.47-5.43	0.001	2.39 (1.24-4.62)	0.010
RTOG-RPA† classes				
(II vs. I)	5.64 (0.74-43.1)	0.061	-	-
(III vs. II)	2.56 (1.33-4.92)	0.004	-	-
(III vs. I)	4.03 (1.47-11.0)	<0.001	-	-
Our original classes				
(B vs. A)	4.65 (1.71-12.6)	0.001	-	-
(C vs. B)	1.97 (1.91-3.83)	0.043	-	-
(C vs. A)	7.77 (2.78-21.7)	<0.001	-	-

†Radiation Therapy Oncology Group-Recursive Partition Analysis, as defined by Gaspar *et al.*[7]
Abbreviations : KPS=Karnofsky performance status ; PD=progressive disease ; WBRT=whole brain radiation therapy ; SRS=stereotactic radiosurgery ; HSRT=hypofractionated stereotactic radiation therapy ; CI=confidence interval ; HR=hazard ratio

ease status as significant prognostic factors (Table 2).

Based on these results, we defined three prognostic subgroups. Class A : extracranial disease status of CCR or PR (not progressed), and KPS ≥70 ; Class C : progressive extracranial disease status, and KPS <70 ; Class B : all other patients (Table 3). Application of this classification revealed 24 patients fit the criteria for Class A, 30 for Class B, and 20 for Class C.

Table 3. Definition of classes A-C.

Class A (*n*=24)	Class B (*n*=30)	Class C (*n*=20)
Extracranial disease not progressive	All others	Extracranial disease progressive
KPS ≥70		KPS <70

Median survival of patients in Class A, Class B, and Class C were 23 months (95% CI, 11.2-infinite), 7.4 months (95% CI, 5.3-infinite), and 3.3 months (95% CI, 2.1-7.9), respectively. On univariate analysis, Comparison of the subgroups A-C showed that median survival differed significantly.

Applying the RTOG RPA classification, only 8 patients were classified as RPA class I, 32 were RPA class II, and

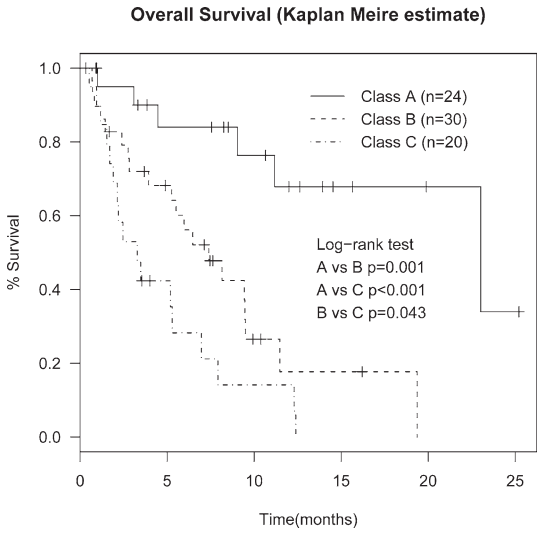

Fig. 2. Survival according to our original class.

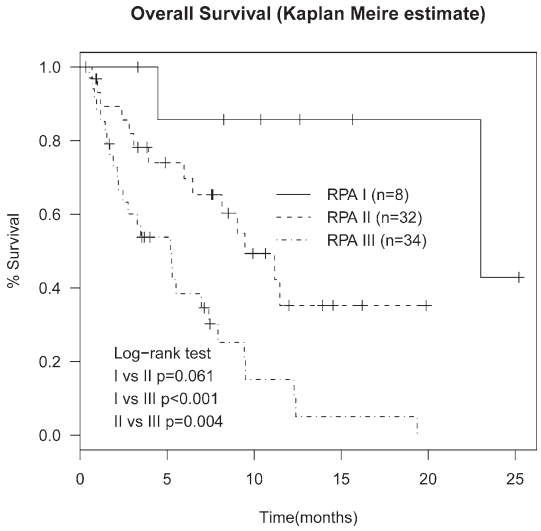

Fig. 3. Survival according to RPA class.

34 were RPA class III. Median survival was 23 months (95% CI, 23-infinite) for patients in RPA class I, 9.5 months (95% CI, 6.5-infinite) for patients in RPA class II, and 5.2 months (95% CI, 2.5-7.9) for patients in RPA III. Survival curves comparing RPA class III to class I, or class II differed significantly, comparison between RPA class II and class I was marginally significant (Table 2).

Patients in Class C are regarded as patients in RPA class III with PD. Therefor we divided RPA class III patients into two subgroups based on extracranial disease status, and analyzed the survival outcome between the two subgroups. RPA class III patients without PD had a median survival of 7.4 months (95%CI, 5.3-infinite) compared with 3.3 months (95%CI, 2.1 -7.9) in patients who classified as RPA class III with PD (our Class C). Although there was a trend toward worse survival in RPA class III patients with PD (Class C), these differences were not significant ($p=0.152$) (Fig. 4).

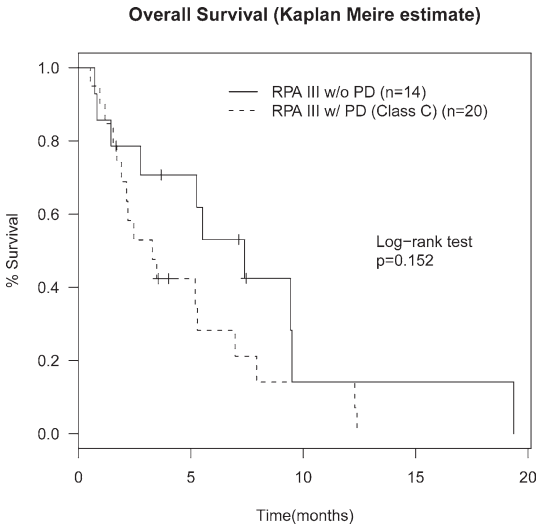

Fig. 4. Survival according to extracranial disease status in RPA class III.

Discussion

Our present study showed that the median survival was 7.9 months (95%CI, 5.3-11.5), and one-year survival rate was 30.0% for the entire group. Similar results have been reported[8-14]. In this study, KPS and extracranial disease status indicated independent prognostic factors, and patients with KPS <70 and PD (Class C) had poor survival (median, 3.3 months) regardless of the treatment.

WBRT, standard therapeutic method for patients with brain metastases, can prolong survival compared to steroid therapy only[3]. Moreover, SRS can provide better survival benefit compared to WBRT[15-17]. Surgery is an

important therapeutic modality for patient with single brain metastasis, and can improve patient's survival time [4]. O'Neil *et al.*[5] and Schöggl *et al.*[6] evaluated SRS plus WBRT vs. surgical resection plus WBRT for the initial management of patients with single brain metastasis, and revealed no significant differences in survival between the two groups. Aoyama *et al.*[13] reported equivalence of HSRT and SRS in local control and survival for patients with brain metastases.

The most commonly used prognostic system is the RTOG RPA classification, and our results also validated the system for patients with brain metastases. Median overall survival in RPA class I, class II and class III were 23 months (95% CI, 23-infinite), 9.5 months (95% CI, 6.5-infinite) and 5.2 months (95% CI, 2.5-7.9), respectively. There is little doubt that RPA class I patients seem to be most likely to profit from aggressive treatment strategies including SRT. Meanwhile, should RPA class III patients be excluded from active treatment? Morris *et al.*[18] reviewed 102 patients with metastatic malignant melanoma treated with WBRT and mentioned RPA class III patients should not receive palliative WBRT because of short survival (median, 3 weeks). On the other hand, Lutterbach *et al*.[19] studied 916 patients with brain metastases treated with WBRT or surgery plus WBRT, and identified the favorable subgroup (age <65 years, primary tumor controlled, single brain metastasis) within RPA class III patients (median, 3.2 months). Our study showed a trend toward better survival among patients who classified as RPA class III without PD compared to those of patients with PD. Although overall survival did not differ significantly between the two groups, this result suggests that RPA class III can include favorable subgroup in survival. Therefore, in our opinion, only RPA class III is not acceptable for exclusion criterion for SRT. Instead, we recommend our Class C (RPA class III patients associated with PD) as an index for patient exclusion.

Kondziolka *et al*.[20] studied long-term (4 years or longer) survived patients (n=44) with brain metastases after SRS. The authors compared those patients with a cohort of patients who had the shortest survival (shorter than 3 months, n=100) and identified higher KPS, fewer metastases, and less extracranial disease burden were significant prognostic factors. A randomized comparison between surgery plus WBRT and WBRT alone, which included more patients with active extracranial disease failed to show a benefit from surgery[21]. Those studies emphasize the importance of extracranial disease status for survival after SRT. In our current study, as previously mentioned, patients defined as Class C showed worse overall survival with a median survival time of 3.3 months (95% CI, 2.1-7.9). Although SRT may offer some improvement in quality of life, and perhaps in survival time, it would be difficult to justify the use of expensive and time consuming SRT for a very poor prognosis patients.

In conclusion, our study results showed performance status before SRT and extracranial disease status were independent prognostic factors for patients with brain metastases treated by SRT. Patients with KPS <70 and PD are unlikely to benefit from SRT.

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