

conducted at the alpha level of 0.05 with a 95 % confidence interval. All the statistical analyses were performed by using SPSS Statistics version 17.0 (SAS Institute, Tokyo, Japan).

Results

Outcomes for the entire group

Median survival time (MST) for the entire patients from the start of WBRT was 5.7 months. The 6 months, 1- and 2-year survival rate were 43, 28 and 12 %, respectively. MST of the patients with RTOG's RPA Class 1 ($n = 5$), 2 ($n = 91$) and 3 ($n = 38$) were 10.3, 7.8 and 2.2 months, respectively (Fig. 1). Median intracranial progression-free survival (PFS) were 4.7 months, with 6 months, 1- and 2-year PFS of 35, 14 and 4 %, respectively. A total of 49 patients developed intracranial recurrence after WBRT. The sites of first recurrence after WBRT were as follows: local only (regrowth of preexisted tumors): 25 (51 %); new metastasis only: 10 (20 %); both of local and new metastasis: 12 (24 %); and leptomeningeal dissemination: 2 (4 %). Median local progression-free duration and median intracranial new metastasis-free duration for the entire patients were 9.7 and 18.0 months, respectively. At the time of analysis, 5 patients were alive with disease. The causes of death were identified in 118 patients. Of these, 38 patients (32 %) were due to intracranial tumor progression, whereas 76 patients (64 %) were due to systemic disease. Four patients (3 %) died from intercurrent disease. None had died directly from toxicity of WBRT.

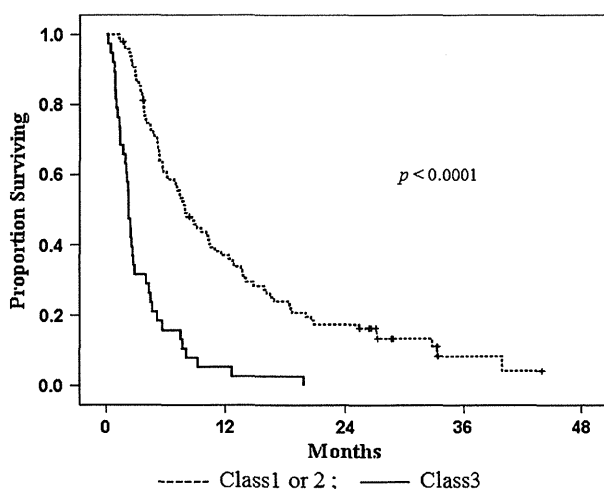


Fig. 1 Kaplan–Meier survival curve for overall survival by RPA criteria

Factors influencing survival after WBRT: univariate and multivariate analyses

Univariate analysis was performed on 12 different variables to evaluate their potential value on survival after WBRT. Univariate analyses identified 9 variables which significantly associated with good prognosis (Table 2).

Multivariate analysis was performed on 9 independent variables. Table 3 summarizes the result of the multivariate analysis for survival after WBRT. Multivariate analysis revealed that KPS (≥ 70 vs. 70, hazard rate (HR): 2.540, $p < 0.0001$), gender (female vs. male, HR: 2.293, $p < 0.0001$), activity of extracranial disease (absent/stable vs. progressive, HR: 2.134, $p = 0.015$), time to develop brain metastasis (< 3 vs. ≥ 3 months, HR: 1.926, $p = 0.042$), and use of chemotherapy after WBRT (multiple vs. none/single regimens, HR: 3.406, $p < 0.0001$) were independent prognostic factors for overall survival.

Survivals depending on chemotherapy after WBRT

After WBRT, only two patients had no evidence of extracranial tumor. The two patients didn't receive further chemotherapy until disease progression. Another 132 patient had known extracranial tumor including primary, nodal or distant sites. They were indicated to start or continue chemotherapy when it was clinically applicable. A total of 64 patients with extracranial systemic disease underwent chemotherapy after WBRT. Thirty-one patients (23 %) received only a single chemotherapeutic regime, and 33 patients (25 %) received multiple regimens. Figure 2 shows the survival curve by the use of chemotherapy after WBRT. The MST of the patients who received none, single and multiple regimens after WBRT were 3.3, 7.5 and 16.4 months, respectively ($p < 0.0001$). The use of multiple chemotherapeutic regimens after WBRT was found to be associated with better survival after WBRT in multivariate analysis ($p < 0.0001$). Among 95 patients with pre-irradiation KPS ≥ 70 , 59 patients (62 %) received chemotherapy, whereas 5 patients (13 %) with KPS < 70 received chemotherapy. Among patients with KPS ≥ 70 , the MST of the patients who received none, single and multiple regimens after WBRT were 4.5, 7.9 and 16.4 months, respectively ($p < 0.0001$). Overall, 95 % of the patients included in this study received chemotherapy either before or after WBRT.

The effect of molecular-targeted therapy after WBRT

A total of 34 patients (25 %) received molecular-targeted therapy after WBRT for 1 month or more. Of these patients, the sites of primary disease were lung in 28, breast

Table 2 Results of univariate analyses for survival after WBRT

Parameters	n	Median survival time (months)	6-months survival (%)	1-year survival (%)	2-year survival (%)	p value
Overall patients	134	5.7	43	28	12	–
Age						
<65	87	7.4	54	31	13	
≥65	47	4.9	38	22	11	0.31
Gender						
Male	69	4.5	32	17	6	
Female	65	9.1	66	40	20	0.0009
Karnofsky performance status						
≥70	95	7.9	62	39	17	
<70	39	2.2	15	3	0	<0.0001
Neurologic status						
0–1	72	7.9	58	44	22	
2–4	62	4.5	36	1	0	<0.0001
RPA criteria						
Class 1–2	96	7.9	61	37	18	
Class 3	38	2.2	16	5	0	<0.0001
Site of primary tumor						
Lung	75	7.4	55	39	21	
Others	59	4.5	39	14	2	0.001
Activity of extracranial tumor						
Absent/stable	20	9.1	60	40	25	
Progressive	114	5.2	46	26	10	0.015
Time to develop brain metastasis						
<3 months	21	16.9	75	65	40	
≥3 months	113	5.2	43	21	7	0.002
Number of brain metastasis						
1–4	40	5.1	39	21	10	
≥5	94	6.2	52	31	13	0.53
Size of the largest lesion						
<20 mm	69	7.4	53	36	16	
≥20 mm	65	5.1	42	20	8	0.11
Chemotherapeutic regimens before WBRT						
None/single	50	7.2	52	42	20	
Multiple	84	5.2	46	19	8	0.019
Chemotherapeutic regimens after WBRT						
None/single	101	4.0	33	13	4	
Multiple	33	16.4	94	73	36	<0.0001

RPA recursive partitioning analysis, WBRT whole brain radiotherapy

in 5 and kidney in 1. All of the histological diagnoses of lung primary patients were adenocarcinoma. Twenty-seven lung primary patients received epidermal growth factor

receptor-tyrosine kinase inhibitor (EGFR-TKI) for a median duration of 7 months. Figure 3 shows the survival curve by the use of molecular-targeted therapy after

Table 3 Results of multivariate analysis for survival after WBRT

Variables	Factors	Hazard rate (95 % CI)	<i>p</i> value
Karnofsky performance status	≥70 versus <70	2.540 (1.627–3.966)	<0.0001
Gender	Female versus male	2.293 (1.541–3.412)	<0.0001
Extracranial disease status	Absent/stable versus progressive	2.134 (1.160–3.928)	0.015
Time to develop brain metastasis	<3 versus ≥3 months	1.926 (1.025–3.620)	0.042
Number of chemotherapeutic regimens after WBRT	Multiple regimens versus none/single regimen	3.406 (2.013–5.761)	<0.0001

CI confidence interval, WBRT whole brain radiation therapy

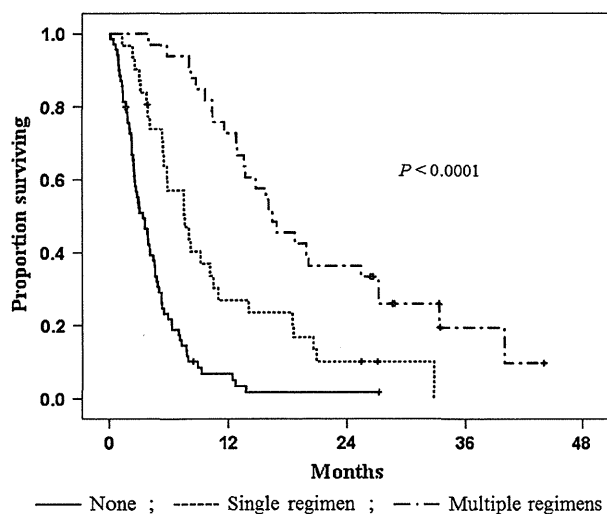


Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

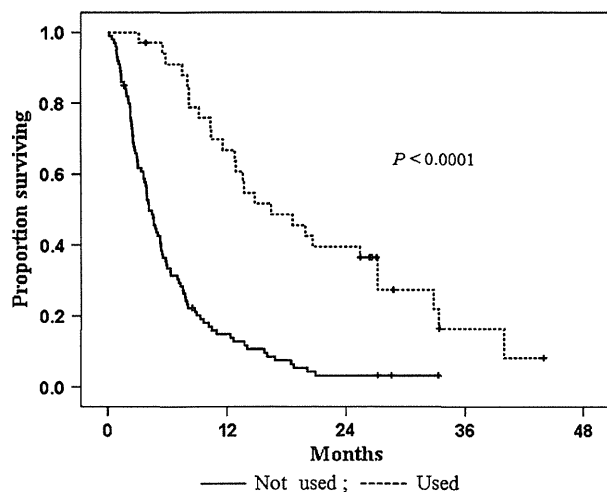


Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

WBRT. The MST of the patients who received molecular-targeted therapy after WBRT was significantly longer than that of those who did not (16.4 vs. 4.0 months, $p < 0.0001$).

Discussion

Significant progress has been made over the last decades for a subset of patients with single or few brain metastases and well controlled systemic disease. In prospective randomized clinical trials, surgical resection or SRS combined with WBRT significantly prolonged survival in selected patients with single or few brain metastases (Patchell et al. 1990; Vecht et al. 1993; Andrews et al. 2004). MST of these patients who received combined therapy ranges 7–10 months. SRS alone in patients with one or few brain metastases was comparable to SRS combined with WBRT at least in terms of overall survival, with a MST of 8 months (Aoyama et al. 2006). Unfortunately, the patients who entered into these clinical trials represent only a small minority of patients with brain metastases. In clinical practice, it remains unclear whether these aggressive therapies have sufficient benefit for the majority of patients with uncontrolled systemic disease or numerous brain metastases. Currently, only WBRT is the standard treatment of choice for these patients. The indication of SRS for patients with brain metastases in clinical practice continues to be a matter of debate.

Various prospective and retrospective studies have shown that the treatment modality is the first most important prognostic factor on long-term survival, although the effect of patient selection bias is inevitable (Andrews et al. 2004; Lagerwaard et al. 1999; Patchell et al. 1990). To minimize the selection bias, we investigated only patients primarily treated with WBRT alone in this study. Numerous studies on prognostic factors in patients with brain metastases have been published previously. The results of this study re-confirmed the value of established prognostic factors reported in the literature. Multivariate analysis showed that good KPS, stable extracranial disease and female gender were independent predictors of better survival after WBRT, in line with previous literatures (Lagerwaard et al. 1999; Patchell et al. 1990; Aoyama et al. 2006; Gaspar et al. 1997; Swinson and William 2008). Dose these pretreatment characteristics fully determine the prognosis of patients with brain metastases?

Performance status is regarded as the second most important prognostic factor in patient's characteristics (Lagerwaard et al. 1999; Aoyama et al. 2006; Gaspar et al. 1997; Fleckenstein et al. 2004; 20). Generally, patients with low KPS are not indicated for aggressive therapy other than WBRT alone. In this study, the MST of the patients with KPS < 70 was only 2.2 months. The Performance status of the patients with brain metastases frequently deteriorated by extended intracranial disease. Additionally, patients with very low performance status were not indicated for further chemotherapy despite the existence of systemic disease. In this study, only 5 patients (13 %) with pre-treatment KPS < 70 received chemotherapy after WBRT. We conclude that poor survival time of the patients with low KPS is due to the systematic disease progression, as well as intracranial disease progression.

In line with our study, activity of extracranial primary disease is the third most important prognostic factor reported in the literature (Lagerwaard et al. 1999; Aoyama et al. 2006; Fleckenstein et al. 2004; 20). These finding suggests that survival of patients with brain metastases is in a large part, regulated by the extracranial status. Seventy-six patients (64 %) included in this study died due to systemic disease. This percentage is comparable to the reports of prospective clinical trials with SRS alone or SRS + WBRT for single or fewer numbers of brain metastases with well controlled systemic disease (Sneed et al. 1999; Andrews et al. 2004; Aoyama et al. 2006). This result highlights the modest effectiveness of WBRT on brain metastases. WBRT alone have adequate efficacy to avoid neurologic death for about two-thirds of patients with brain metastases. If we consider the high morbidity rate from systemic disease after WBRT, chemotherapy is the primary therapeutic approach for the control of extracranial disease. Therefore, systemic chemotherapy for chemoresponsive cancer prolongs survival despite the presence of treated brain metastases. Irradiated brain metastases will lose their prognostic significance in a large number of patients.

The role of chemotherapy in brain metastasis itself has been limited. Although there is some breakdown of blood–brain barrier (BBB) around brain metastases, the concentrations of most of the chemotherapeutic agents are still very limited within the lesion (Gerstner and Fine 2007). However, some chemotherapeutic agents are known to have activity of crossing BBB. Temozolomide (TMZ) is a third generation alkylating agent, and it can cross the BBB because of its small size and lipophilic properties (Ostermann et al. 2004). Some clinical trials suggest that single agent TMZ has some activity in patients with recurrent brain metastases (Christodoulou et al. 2001; Siena et al. 2010). Several Phase II clinical trials of TMZ combined with WBRT were performed with promising results

(Antonadou et al. 2002; Addeo et al. 2008). These trials proved improved response rate and neurologic function with addition of TMZ to WBRT. A phase III clinical trial of WBRT plus SRS with or without TMZ or Erlotinib in patients with brain metastases is now ongoing (ClinicalTrials.gov identifier: NCT00096265). Patients with 1–3 brain metastases from histologically confirmed non-small cell lung cancer, well circumscribed, maximum diameter of 4 cm or less, no metastasis within 10 mm of the optic apparatus, no metastasis in the brain stem and stable extracranial metastases are enrolled. Patients are randomized to three groups: Arm 1: WBRT + SRS, Arm 2: WBRT + SRS + TMZ, Arm 3: WBRT + SRS + erlotinib. Patients in Arm 2 and 3 begin TMZ or erlotinib on the first day of WBRT and continue up to 6 months. The primary endpoint is overall survival, and secondary endpoint includes time to CNS progression, performance status at 6 months, steroid dependence at 6 months, cause of death and effect of non-protocol chemotherapy.

Topotecan is a semi-synthetic analogue of the alkaloid camptothecin, which selectively inhibits topoisomerase I. Topotecan crosses the BBB, because of its low protein binding property (Baker et al. 1996). Single agent topotecan has positive activity in patients with brain metastases from small cell lung cancer (Korfel et al. 2002). A phase III multicentric clinical trial of topotecan and WBRT for patients with brain metastases form lung cancer was planned, however, was terminated because of low patient accrual (Neuhauser et al. 2009). This trial failed to show clear benefit of adding topotecan to WBRT. Another multicentric phase III clinical trial is ongoing (ClinicalTrials.gov identifier: NCT00390806). Patients with at least one brain metastasis form non-small cell lung cancer, who have received previous chemotherapy are enrolled. Patients are randomized to two groups: experimental arm: topotecan + WBRT, control arm: WBRT alone. The primary endpoint is overall survival, secondary endpoint includes response rate, time to response, time to progression, brain tumor symptom, safety and tolerability. We think that these clinical trials for brain metastasis should evaluate the effect of non-protocol chemotherapy on survival. In the next 5 years, the results of these phase III, multicentric clinical trials will become available to further define the role of these chemotherapeutic agents when combined with WBRT and SRS, or both.

Some investigators suggest that the permeability of BBB in brain tumors can alter during or ever after fractionated radiotherapy (Yuan et al. 2006; Wilson et al. 2009; Cao et al. 2005). After irradiation, the BBB may be partially disrupted so that some chemotherapeutic agents can reach a therapeutic level in the metastatic tumors. This is another explanation of the value of systemic chemotherapy after WBRT. In fact, subset analysis of this study showed that

the use of chemotherapy after WBRT was also an independent prognostic factor predicting longer local tumor progression-free duration (data not shown). We believe that some brain metastases become sensitive to chemotherapy after irradiation. Chemo-sensitivity of brain metastases can affect the survival of a part of patients with treated brain metastases. Therefore, systemic chemotherapy will be a treatment of choice for those who have systemic disease with irradiated brain metastases. If a patient have a plan of definitive chemotherapy for primary disease after the treatment of brain metastases, such patient can be a good candidate for more aggressive therapy for brain metastases.

Another topic of debate is whether molecular-targeted therapy has a significant role on brain metastasis or not. Some investigators advocated that EGFR-TKI has promising activity on previously untreated brain metastases from lung adenocarcinoma (Wu et al. 2007; Kim et al. 2009; Katayama et al. 2009). Another investigator reported activity of trastuzumab on brain metastasis from HER2-overexpressing breast cancer (Park et al. 2009). In this study, the MST of the patients who received molecular-targeted therapy after WBRT was significantly longer than that of those who did not. In the subset analysis of this study, use of molecular-targeted therapy after WBRT was also a significant predictor of longer local progression-free duration (data not shown). We believe that molecular-targeted therapy could have some activity on the local control of some brain metastases.

Patients with “synchronous” brain metastasis survived significantly longer than “metachronous” brain metastasis patients in this study. Short time to develop brain metastasis was marginally independent prognostic factor in multivariate analysis. This is in line with a literature of surgical removal or SRS for brain metastasis (Flannery et al. 2008; Bonnette et al. 2001; Hu et al. 2006). It is easy to assume that systematic disease of patients with “synchronous” brain metastasis would more likely to respond to the following chemotherapy. The “synchronous” brain metastasis may be more sensitive to radiotherapy, when compared to brain metastasis emerged after repeated chemotherapies. Also in agreement with some literature (Lagerwaard et al. 1999; Swinson and William 2008), female patients survived significantly longer than male patients. In particular, the prognosis of female patients with brain metastasis from lung primary has reported to be significantly better than that of male patients (Lagerwaard et al. 1999; Sánchez de Cos et al. 2009). We should further continue to investigate these clinical characteristics of brain metastases.

We acknowledge that the present study had certain limitations because of its retrospective nature. First, the results of this study might be highly influenced by patient’s selection bias. Patients with brain metastases which well

responded to WBRT may have more opportunity for receiving multiple chemotherapy after WBRT. Second, our cohort should deviate to patients with numerous brain metastases with uncontrolled systemic disease. Because we included only patients with brain metastases primarily treated by WBRT alone, patients with poor prognosis should be negatively selected for this study. Currently, we are investigating the patients with one or few brain metastases primarily treated by SRS alone, and it will be described in another report. Actual prognostic value of chemotherapy on survival after WBRT for brain metastases should be validated in future prospective clinical trials.

Conclusions

In addition to the confirmed prognostic factors previously reported in the literature, the use of multiple chemotherapeutic regimens after WBRT was associated with better survival. Systemic chemotherapy for chemo-responsive cancer prolongs survival despite the presence of treated brain metastases. Irradiated brain metastases will lose their prognostic significance in a large number of patients. Systemic chemotherapy will be a treatment of choice for patients who have systemic disease after WBRT for brain metastases. These results should be validated in future prospective clinical trials.

Conflict of interest None.

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