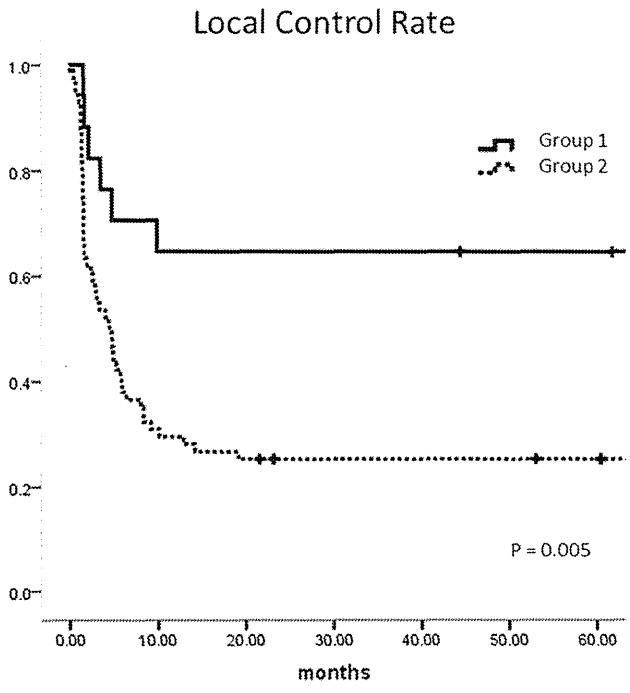

Fig. 2. Local control rate (LCR) according to the group classification by the International Classification of Retinoblastoma and biological effective dose (BED) with $\alpha/\beta = 10$ Gy of the reference depth (for details refer to the text).

control. Both reference depth and dose rate at reference depth were prognostic factors of local control suggesting that physical limitation of RPT, which is not suitable for treating tall tumors as previously reported (8-11).

The administration of previous EBRT did not influence LCR (Table 3), suggesting that response to RPT did not differ between relapsed or refractory tumors after EBRT and radiation-naive tumors as previously reported (9).

Concerning the morbidities, the incidence of posterior subcapsular cataract was influenced by EBRT but not by RPT whose dose to the lens is negligible. In the current study, the incidence of proliferative retinopathy was as low as 6.7%, which is similar to the low reported incidence of 2.4% in Abouzeid's study. In contrast, the incidence was reported to be as high as 17.1% in the series by Schueler et al in which a higher dose was employed. Proliferative retinopathy has been reported to occur in 13%-19% after ^{125}I plaque brachytherapy in which dose reached further than ^{106}Ru.

$BED_3 \geqq 1200$ Gy_3 of the outer surface of sclera was significantly correlated with the incidence of either retinal detachment or proliferative retinopathy or rubeosis (Fig. 3b). A higher dose for sclera was demonstrated to cause late complications associated with RPT; therefore, it is important to exclude tall tumors whose dose of the outer surface of sclera will be high in order to avoid complications. However, there were only 2 enucleations caused by the late complications of RPT, and RPTs were generally well tolerated.

There were 2 secondary malignancies in the current series. Both of them occurred in the patients with a hereditary retinoblastoma, 1 of them developed within the EBRT fields. In accordance with the literature (6, 7), plaque brachytherapy itself did not seem to increase the incidence of secondary malignancy.

Conclusion

RPT is an effective and safe focal therapy for retinoblastoma. However, optimal dose of RPT remains to be studied further.

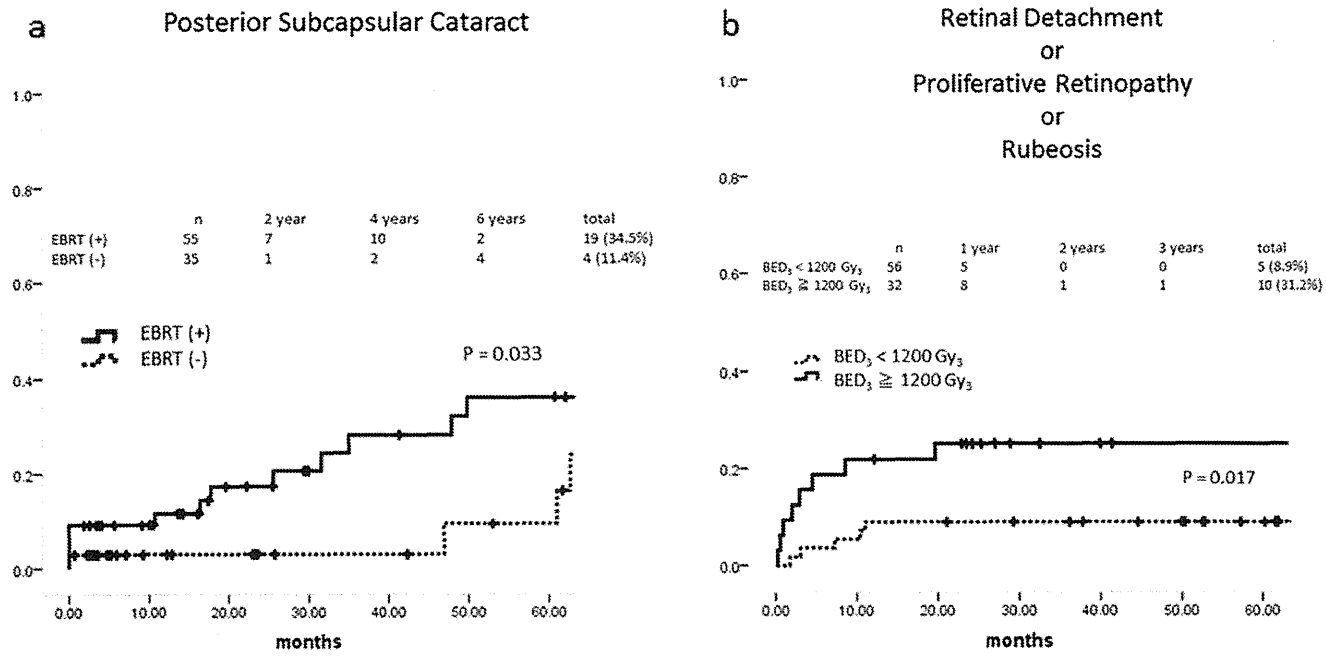

Fig. 3. (a) Cumulative incidence of posterior subcapsular cataract according to whether external beam radiation therapy (EBRT) was administered. (b) Cumulative incidence of retinal detachment, proliferative retinopathy and rubeosis stratified by biological effective dose (BED) with $\alpha/\beta = 3$ Gy at the outer surface of sclera.

References

1. National registry of retinoblastoma in Japan (1975–1982). The Committee for the National Registry of Retinoblastoma. *Nippon Ganka Gakkai Zasshi* 1992;96:1433-1442.
2. Kleinerman RA, Tucker MA, Tarone RE, et al. Risk of new cancers after radiotherapy in long-term survivors of retinoblastoma: an extended follow-up. *J Clin Oncol* 2005;23:2272-2279.
3. Abramson DH, Schefler AC. Update on retinoblastoma. *Retina* 2004; 24:828-848.
4. Lin P, O'Brien JM. Frontiers in the management of retinoblastoma. *Am J Ophthalmol* 2009;148:192-198.
5. Freire JE, De Potter P, Brady LW, et al. Brachytherapy in primary ocular tumors. *Semin Surg Oncol* 1997;13:167-176.
6. Shields CL, Shields JA, Cater J, et al. Plaque radiotherapy for retinoblastoma: long-term tumor control and treatment complications in 208 tumors. *Ophthalmology* 2001;108:2116-2121.
7. Shields CL, Mashayekhi A, Sun H, et al. Iodine 125 plaque radiotherapy as salvage treatment for retinoblastoma recurrence after chemoreduction in 84 tumors. *Ophthalmology* 2006;113:2087-2092.
8. Schueler AO, Fluhs D, Anastassiou G, et al. Beta-ray brachytherapy with 106Ru plaques for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2006;65:1212-1221.
9. Abouzeid H, Moeckli R, Gaillard MC, et al. (106)Ruthenium brachytherapy for retinoblastoma. *Int J Radiat Oncol Biol Phys* 2008;71: 821-828.
10. Nag S, Quivey JM, Earle JD, et al. The American Brachytherapy Society recommendations for brachytherapy of uveal melanomas. *Int J Radiat Oncol Biol Phys* 2003;56:544-555.
11. Jarvien H, Cross WG, Soares C, et al. Dosimetry of beta rays and low-energy photons for brachytherapy with sealed sources. *J ICRU* 2004;4: 2-175.
12. Linn Murphree A. Intraocular retinoblastoma: the case for a new group classification. *Ophthalmol Clin North Am* 2005;18:41-53. viii.
13. Shields CL, Mashayekhi A, Au AK, et al. The International Classification of Retinoblastoma predicts chemoreduction success. *Ophthalmology* 2006;113:2276-2280.
14. BEBIG. BEBIG Ruthenium Augenapplikatoren Kundeninformation: Einführung der neuen NIST-kalibrierten Dosimetrie Einführung der neuen PTB-kalibrierten Aktivitätsmessungen. 2002:version 1.03 v. 12.11.02.
15. Dale RG. The application of the linear-quadratic dose-effect equation to fractionated and protracted radiotherapy. *Br J Radiol* 1985;58:515-528.
16. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958;53:457-481.
17. Yamane T, Kaneko A, Mohri M. The technique of ophthalmic arterial infusion therapy for patients with intraocular retinoblastoma. *Int J Clin Oncol* 2004;9:69-73.
18. Oosterhuis JA, Journee-de Korver HG, Kakebeeke-Kemme HM, et al. Transpupillary thermotherapy in choroidal melanomas. *Arch Ophthalmol* 1995;113:315-321.
19. Foote RL, Garretson BR, Schomberg PJ, et al. External beam irradiation for retinoblastoma: patterns of failure and dose-response analysis. *Int J Radiat Oncol Biol Phys* 1989;16:823-830.
20. Hernandez JC, Brady LW, Shields JA, et al. External beam radiation for retinoblastoma: results, patterns of failure, and a proposal for treatment guidelines. *Int J Radiat Oncol Biol Phys* 1996;35: 125-132.

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ORIGINAL PAPER

Effect of chemotherapy on survival after whole brain radiation therapy for brain metastases: a single-center retrospective analysis

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Abstract
Background and purpose Whether chemotherapy for systemic disease affects survival of patients with brain metastases or not has not been elucidated before. We performed comprehensive analysis of patients with newly-diagnosed brain metastases primarily treated with whole brain radiation therapy (WBRT) alone.
Materials and methods Data from 134 patients with newly-diagnosed brain metastases primarily treated with WBRT from 2007 to 2008 was retrospectively reviewed. Univariate and multivariate analyses were performed to identify significant prognostic factors.
Results Median survival time (MST) of this cohort from the start of WBRT was 5.7 months. MST of patients with RPA Class 1, 2 and 3 were 10.3, 7.8 and 2.2 months, respectively. Multivariate analysis revealed that karnofsky performance status ($\geq$70, $p < 0.0001$), gender (female, $p < 0.0001$), activity of extracranial disease (stable, $p = 0.015$), time to develop brain metastasis (<3 months, $p = 0.042$) and use of chemotherapy after WBRT (multiple regimens, $p < 0.0001$) were independent prognostic factors for better survival.
Conclusions 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 the future prospective clinical trials.

Keywords Brain metastasis · Brain metastases · Radiation therapy · Whole brain radiation therapy · Chemotherapy · Prognostic factors

Introduction

Brain metastasis affects 20–40 % of cancer patients (Soffietti et al. 2002). Brain metastasis is one of the major causes of morbidity in cancer patients. The prognosis of patients with brain metastasis is generally poor with a median survival time (MST) of 1–2 months with corticosteroids only (Weissman 1988; Lagerwaard et al. 1999).

The route of metastatic dissemination to the brain is often hematogeneous, therefore, the entire brain can be seeded with micrometastatic focus. Traditionally, whole brain radiation therapy (WBRT) has been regarded as the standard treatment for patients with brain metastasis. Overall survival of the patients after WBRT ranges 3–6 months (Lagerwaard et al. 1999; Gaspar et al. 2010; Tsao et al. 2005). Various dose/fractionation schedules of WBRT were tested in clinical studies, which resulted in no significant difference in median survival time after WBRT (Tsao et al. 2005; Gaspar et al. 2010).

Recently, significant progress has been made for a subset of patients with single or few brain metastases and well controlled systemic disease. Surgical resection or stereotactic radiosurgery (SRS) combined with WBRT significantly prolonged survival (Patchell et al. 1990; Vecht et al. 1993; Andrews et al. 2004). Median survival of

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patients who received these aggressive therapies ranges 7–10 months. Unfortunately, patients who entered into these clinical trials represent only a small minority of the patients with brain metastases. For the majority of patients with multiple brain metastases and uncontrolled systemic disease, only WBRT is the standard treatment of choice.

The role of chemotherapy in brain metastasis has been limited because of the concern about the activity of chemotherapeutic agent to cross the blood–brain barrier (BBB). Recently, the activity of chemotherapy in brain metastasis is highlighted (Robinet et al. 2001; Walbert and Gilbert 2009; Mehta et al. 2010). Concurrent chemoradiation therapies with BBB permeable agents, such as Temozolamide or topotecan are currently under investigation in prospective clinical trials. Some investigators suggested that the permeability of BBB can alter after fractionated radiotherapy for brain metastasis (Yuan et al. 2006; Wilson et al. 2009). However, whether the use of chemotherapy affects survival of the patients with brain metastasis or not has not been elucidated before.

The primary aim of this study was to perform comprehensive analysis of 134 consecutive patients with newly-diagnosed brain metastases primarily treated by WBRT alone in a single institution. The secondary aim was to define independent prognostic factors associated with longer survival after WBRT. The final aim was to investigate the prognostic value of chemotherapy on survival after WBRT in patients with brain metastases.

Materials and methods

Patient characteristics

The database of patients who underwent radiotherapy for brain metastases at our institution was reviewed. A total of 264 patients were treated with WBRT between 2007 and 2008. Of these, 23 patients received WBRT as a salvage therapy after SRS. Another 39 patients received WBRT as an adjuvant therapy after resection of metastatic brain tumor. Forty-seven patients were metastases from radiosensitive primary tumor such as leukemia, lymphoma or small cell carcinoma. Excluding these patients, we reviewed the medical records of 155 patients with newly diagnosed brain metastases treated with WBRT as a primary therapy. Of these, 19 patients presented with symptoms or radiographic findings of leptomeningeal metastasis. We excluded these patients with leptomeningeal metastasis because they are known to have extremely limited survival. Two patients were ineligible for evaluation because of allergy to contrast media. Finally, a group of 134 patients were subjected to extensive analysis. The clinical and image interpretation data from these patients were entered into database in December 2010. Distribution of baseline patient and tumor characteristics is shown in Table 1.

Table 1 Distribution of baseline patient and tumor characteristics

Parameters	*n*	%	Parameters	*n*	%
Median age (years)	60		Extracranial distant metastases		
Gender			Absent	11	8
Male	69	51	Stable	16	12
Female	65	49	Progressive	107	80
Karnofsky performance status (KPS)			Activity of extracranical tumor		
100–90	46	34	Absent/stable	20	15
80–70	49	37	Progressive	114	85
60–50	29	22	Time to diagnosis of brain metastasis		
40–0	10	7	<3 months	21	16
Neurologic status			3–12 months	33	25
0	45	34	1–2 years	22	16
1	27	20	≥2 years	58	43
2	34	25	Type of the diagnostic brain image		
3	21	16	MRI	106	79
4	7	5	CT	28	21
RPA criteria			Number of brain metastases		
Class 1	5	4	1–4	40	30
Class 2	91	68	5–10	39	29
Class 3	38	28	11–24	29	22
Site of primary tumor			≥25	26	19
Lung	75	56	Size of the largest lesion		
Breast	27	20	≤10	31	23
Upper gastrointestinal tract	11	8	11–20	46	34
Colorectum	10	8	21–30	34	25
Genitourinary tract	5	4	>30	23	17
Others	6	5	Chemotherapeutic regimens before WBRT		
Histological type			None	22	16
Adenocarcinoma	114	85	Single	28	21
Squamous cell carcinoma	9	7	Multiple	84	63
Others	11	8	Chemotherapeutic regimens after WBRT		
Primary tumor status			None	70	52
Absent	57	42	Single	31	23
Stable	25	19	Multiple	33	25
Progressive	52	39	Molecular targeted therapy after WBRT (>1 month)		
			No	100	74
			Yes	34	26

RPA recursive partitioning analysis, *MRI* magnetic resonance imaging, *CT* computed tomography, *WBRT* whole brain radiation therapy

Imaging studies

Diagnosis of brain metastases was performed mainly with magnetic resonance images (MRI). In our institute, all patients with lung cancer routinely undergo brain imaging for initial staging or scheduled follow-up. Patients with other solid tumors underwent brain imaging when brain metastasis is clinically suspected. In this study, initial diagnostic brain images included MRI in 106 patients (79 %) and CT in 28 patients (21 %). Radiological features assessed included number, maximum tumor diameter and location. For follow-up brain images, change in size of the tumors and presence of new metastases were recorded. At least 20 % increase in diameter of the each preexisted tumor before WBRT, taking as reference on the smallest diameter after WBRT, was defined as local progression.

Treatment strategy

Treatment strategy for brain metastasis at our institution was previously described elsewhere (Narita and Shibui 2009; Hashimoto et al. 2011). Patients who received WBRT alone as a primary treatment for brain metastases were subjected for this study. Patients with brain metastases generally have extracranial systemic disease. After WBRT, patients with known systemic disease were indicated to start or continue chemotherapy if they still had active chemotherapeutic regimen with sufficient organ function and with Karnofsky performance status (KPS) of 70 or more. Salvage SRS was considered for recurrent brain metastases after WBRT. Some patients with known chemo-sensitive tumor continued palliative chemotherapy for recurrent brain metastases.

Consent for the treatment was obtained from each patient after the sufficient explanation of potential risks of treatment. All the patients provided written informed consent. Our institutional review board has approved this study.

Whole brain radiation therapy

One hundred and thirty-four patients were intended to receive WBRT. Of these, 128 patients were delivered to a dose of 30 Gy in 10 fractions. Another 3 patients were delivered to 37.5 Gy in 15 fractions, whereas one patient was delivered to 20 Gy in 5 fractions. Two patients discontinued irradiation course because of the deterioration of general condition at a dose of 12 and 24 Gy, respectively.

Retrospective analysis

All the medical charts of the eligible patients were reviewed. Information on potential prognostic factors (age, gender, KPS, neurologic status, site of primary tumor, primary tumor status, activity of extracranial distant metastases, time to develop brain metastasis, number of brain metastases, size of the largest lesion, use of chemotherapy before or after WBRT) was collected.

Initial neurological function was classified into 4 categories (No symptoms: grade 0, Minor symptoms; fully active without assistance: grade 1, Moderate symptoms; fully active but requires assistance: grade 2, Moderate symptoms; less than fully active: grade 3, Severe symptoms; totally inactive: grade 4). Radiation Therapy Oncology Group's (RTOG) recursive partitioning analysis (RPA) classes were coded into 3 categories as follows: Class 1: Patients with KPS $\geq$ 70, <65 years of age with controlled primary and no extracranial metastases; Class 3: KPS $<$ 70; Class 2: all the others (Gaspar et al. 1997).

For the evaluation of extracranial disease status, if there were no evidence of residual tumor after therapy, the activity was coded as "absent". If any tumor existed and there is no increase in size of the tumor for more than 6 months, the activity was coded as "stable". A continuous use of same chemotherapeutic regimen didn't impair the coding of "stable". If any tumor existed with any situation other than "stable", the activity was coded as "progressive".

Patients whose brain metastases were detected at the same time or soon after the diagnosis of primary tumor (so-called "synchronous" brain metastasis) may have different prognosis. We defined "synchronous" brain metastasis as those detected at the same time or detected within 3 months of the initial diagnosis of primary tumor.

For the analysis of prognostic effect of chemotherapy before or after WBRT, three different cohorts were defined: none, single regimen and multiple regimens. If a patient received two or more different types of chemotherapeutic regimens, the status was coded as multiple regimens. Any type of hormonal therapy was regarded as a single regimen. The status of the use of molecular targeted therapy was defined as "yes", if a patient continued to receive a specific regimen for more than 1 month.

Statistical analysis

Overall survival from the start of WBRT was calculated with the Kaplan–Meier method. For univariate and multivariate analysis, all the variables were dichotomized according to the clinical relevance from previous literature. Univariate analyses were performed by using log-rank test. Possible confounded variables were excluded from multivariate analysis. A Cox's proportional hazards model was developed to identify significant factors influencing survival after WBRT. All the tests of hypotheses were

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.

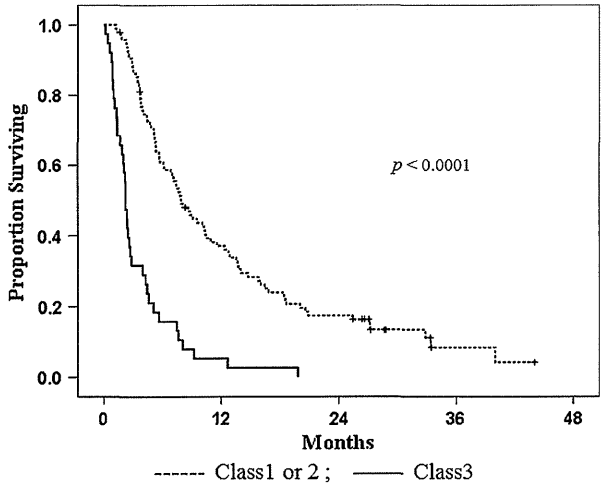

Fig. 1 Kaplan–Meier survival curve for overall survival by RPA criteria

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 extracranical 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)	*p* 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

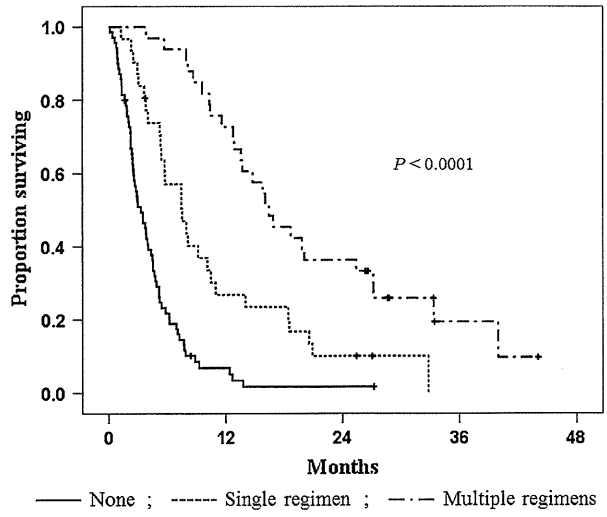

Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

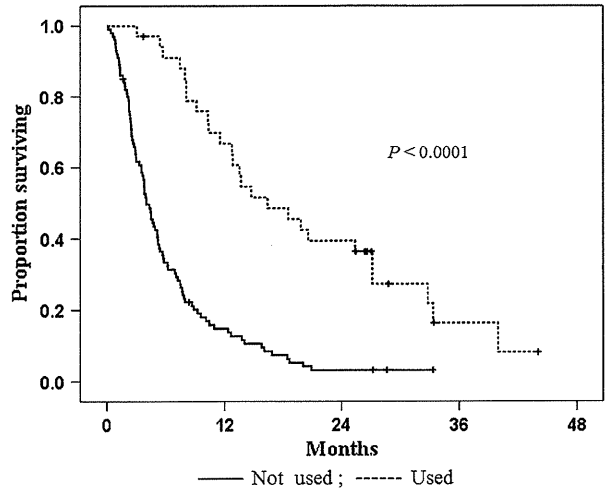

Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

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 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.

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 (Neuhaus 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 form 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.

References

Addeo R, De Rosa C, Faiola V et al (2008) Phase 2 trial of temozolomide using protracted low-dose and whole-brain radiotherapy for nonsmall cell lung cancer and breast cancer patients with brain metastases. Cancer 113:2524–2531

Andrews DW, Scott CB, Sperduto PW et al (2004) Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. Lancet 363:1665–1672

Antonadou D, Paraskevaidis M, Sarris G et al (2002) Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. J Clin Oncol 20:3644–3650

Aoyama H, Shirato H, Tago M et al (2006) Stereotactic radiosurgery plus whole-brain radiation therapy vs. stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. JAMA 295:2483–2491

Baker SD, Heideman RL, Crom WR et al (1996) Cerebrospinal fluid pharmacokinetics and penetration of continuous infusion topotecan in children with central nervous system tumors. Cancer Chemother Pharmacol 37:195–202

Bonnette P, Puyo P, Gabriel C et al (2001) Surgical management of non-small cell lung cancer with synchronous brain metastases. Chest 119:1469–1475

Cao Y, Tsien CI, Shen Z et al (2005) Use of magnetic resonance imaging to assess blood-brain/blood-glioma barrier opening during conformal radiotherapy. J Clin Oncol 23:4127–4136

Christodoulou C, Bafaloukos D, Kosmidis P et al (2001) Phase II study of temozolomide in heavily pretreated cancer patients with brain metastases. Ann Oncol 12:249–254

Flannery TW, Suntharalingam M, Regine WF et al (2008) Long-term survival in patients with synchronous, solitary brain metastasis from non-small-cell lung cancer treated with radiosurgery. Int J Radiat Oncol Biol Phys 72:19–23

Fleckenstein K, Hof H, Lohr F et al (2004) Prognostic factors for brain metastases after whole brain radiotherapy. Strahlenther Onkol 180:268–273

Gaspar L, Scott C, Rotman M et al (1997) Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys 37:745–751

Gaspar LE, Mehta MP, Patchell RA et al (2010) The role of whole brain radiation therapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96:17–32

Gerstner ER, Fine RL (2007) Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. J Clin Oncol 25:2306–2312

Hashimoto K, Narita Y, Miyakita Y et al (2011) Comparison of clinical outcomes of surgery followed by local brain radiotherapy and surgery followed by whole brain radiotherapy in patients with single brain metastasis: single-center retrospective analysis. Int J Radiat Oncol Biol Phys 81:e475–e480

Hu C, Chang EL, Hassenbusch SJ III et al (2006) Nonsmall cell lung cancer presenting with synchronous solitary brain metastasis. Cancer 106:1998–2004

Katayama T, Shimizu J, Suda K et al (2009) Efficacy of erlotinib for brain and leptomeningeal metastases in patients with lung adenocarcinoma who showed initial good response to gefitinib. J Thorac Oncol 4:1415–1419

Kim JE, Lee DH, Choi Y et al (2009) Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. Lung Cancer 65:351–354

Korfel A, Oehm C, von Pawel J et al (2002) Response to topotecan of symptomatic brain metastases of small-cell lung cancer also after whole-brain irradiation. A multicentre phase II study. Eur J Cancer 38:1724–1729

Lagerwaard FJ, Levendag PC, Nowak P et al (1999) Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. Int J Radiat Oncol Biol Phys 43:795–803

Mehta MP, Paleologos NA, Mikkelsen T et al (2010) The role of chemotherapy in the management of newly diagnosed brain metastases: a systematic review and evidence-based clinical practice guideline. J Neurooncol 96:71–83

Narita Y, Shibui S (2009) Strategy of surgery and radiation therapy for brain metastases. Int J Clin Oncol 14:275–280

Neuhaus T, Ko Y, Muller RP, Grabenbauer GG et al (2009) A phase III trial of topotecan and whole brain radiation therapy for patients with CNS-metastases due to lung cancer. Br J Cancer 100:291–297

Ostermann S, Csajka C, Buclin T et al (2004) Plasma and cerebrospinal fluid pharmacokinetics of temozolomide in malignant glioma patients. Clin Cancer Res 10:3728–3736

Park YH, Park MJ, Ji SH et al (2009) Trastuzumab treatment improves brain metastasis outcomes through control and durable prolongation of systemic extracranial disease in HER2-over-expressing breast cancer patients. Br J Cancer 100:894–900

Patchell RA, Tibbs PA, Walsh JW et al (1990) A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 322:494–500

Robinet G, Thomas P, Breton JL et al (2001) Results of a phase III study of early versus delayed whole brain radiotherapy with concurrent cisplatin and vinorelbine combination in inoperable brain metastasis of non-small-cell lung cancer: Groupe Francais de Pneumo-Cancerologie (GFPC) Protocol 95–1. Ann Oncol 12:59–67

Sánchez Cos J, Sojo González MA et al (2009) Non-small cell lung cancer and silent brain metastasis. Survival and prognostic factors. Lung Cancer 63:140–145

Siena S, Crinò L, Danova M et al (2010) Dose-dense temozolomide regimen for the treatment of brain metastases from melanoma, breast cancer, or lung cancer not amenable to surgery or radiosurgery: a multicenter phase II study. Ann Oncol 21:655–661

Sneed PK, Lamborn KR, Forstner JM et al (1999) Radiosurgery for brain metastases: is whole brain radiotherapy necessary? Int J Radiat Oncol Biol Phys 43:949–958

Soffietti R, Ruda R, Mutani R (2002) Management of brain metastasis. J Neurol 249:1357–1369

Swinson BM, William FA (2008) Linear accelerator stereotactic radiosurgery for metastatic brain tumors: 17 years of experience at the University of Florida. Neurosurgery 62:1018–1032

Tsao MN, Lloyd NS, Wong RKS et al (2005) Radiotherapeutic management of brain metastases: a systematic review and meta-analysis. Cancer Treat Rev 31:256–273

Vecht CJ, Haaxma-Reiche H, Noordijk EM et al (1993) Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery. Ann Neurol 33:583–590

Walbert T, Gilbert MR (2009) The role of chemotherapy in the treatment of patients with brain metastases from solid tumors. Int J Clin Oncol 14:299–306

Weissman DE (1988) Glucocorticoid treatment for brain metastases and epidural spinal cord compression: a review. J Clin Oncol 6:543–551

Wilson CM, Gaber MW, Sabek OM et al (2009) Radiation-induced astrogliosis and blood-brain barrier damage can be abrogated using anti-TNF treatment. Int J Radiat Oncol Biol Phys 74:934–941

Wu C, Li YL, Wang ZM et al (2007) Gefitinib as palliative therapy for lung adenocarcinoma metastatic to the brain. Lung Cancer 57:359–364

Yuan H, Gaber MW, Boyd K et al (2006) Effects of fractionated radiation on the brain vasculature in a murine model: blood–brain barrier permeability, astrocyte proliferation, and ultrastructural changes. Int J Radiat Oncol Biol Phys 66:860–866

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Brain metastases after definitive concurrent chemoradiotherapy in patients with stage III lung adenocarcinoma: Carcinoembryonic antigen as a potential predictive factor

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The predictive factors for the development of brain metastases in patients with stage III non-small-cell lung cancer receiving concurrent chemoradiotherapy remain unclear. Several studies have suggested adenocarcinoma as a predictive factor of brain relapses. In the current analysis, we tried to identify the factors associated with brain metastases in stage III lung adenocarcinoma. The demographic and clinical characteristics, site and date of recurrence, and date of death were reviewed in patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemoradiotherapy. In total, 116 patients were identified with a median (range) age of 57 (35–74) years. Of these, 86 (74%) were men, all patients had platinum-based chemotherapy, and 100 (86%) received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy. Of the 95 patients with disease progression or recurrence, 19 (16%) developed brain metastases as the sole site of initial recurrence. A total of 43 (37%) patients developed brain metastases at some time during follow-up. Time to brain metastases was significantly associated with the pretreatment carcinoembryonic antigen (CEA) value, with a hazard ratio (95% confidence interval) of 2.64 (1.39–5.02, $P = 0.003$). Patients who developed brain metastases as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) than those with metastases other than brain. In conclusion, stage III lung adenocarcinoma patients with an elevated CEA value before treatment had a higher risk of developing brain metastases after chemoradiotherapy. Further effort is mandatory to control brain metastases in this patient population by a therapeutic strategy based on the tumor histology and pretreatment CEA value. (*Cancer Sci* 2012; 103: 756–759)

Recent advances in chemotherapy added to radiotherapy have dramatically improved the prognosis of patients with inoperable stage III non-small-cell lung cancer (NSCLC). The current standard treatment for these patients, concurrent thoracic radiotherapy and platinum-based chemotherapy, yields a 5-year survival rate of 16–23%, with acceptable acute and late toxicity.[1,2] However, many patients still die of recurrent disease. Brain metastases, as well as loco-regional recurrences, are the most frequent types of initial failure. Observational studies in patients with stage III NSCLC who underwent chemoradiotherapy with or without surgery showed that the first recurrent site was the brain in only 8–35% of patients, and brain and other sites in 4–10% of patients, resulting in brain metastases as the first recurrent site in 17–43% of patients.[1,3,4] Prophylactic cranial irradiation (PCI) has been tried to eradicate undetectable micrometastases before they become clinically apparent. Prospective randomized trials comparing PCI and observation in patients with locally advanced NSCLC treated by thoracic radiotherapy with or without chemotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, PCI is not indicated for all patients with stage III NSCLC treated with chemoradiotherapy, but it would improve prognosis if used to treat selected patients who are more likely to develop brain metastases. Several clinical factors have been identified to predict brain metastases in locally advanced NSCLC patients, but they are inconsistent among studies.[9–11] Of these clinical factors, adenocarcinoma histology was suggested to have a higher risk of brain relapses.[11–16] The objectives of this study were to identify factors associated with development of brain metastases in stage III adenocarcinoma patients who received concurrent chemoradiotherapy and to identify potential candidates for intervention to reduce brain relapses.

Materials and Methods

Patient selection. Patients with unresectable stage III lung adenocarcinoma who underwent concurrent platinum-based chemotherapy and thoracic radiotherapy at the National Cancer Center Hospital (Tokyo, Japan) between 1994 and 2005 were eligible for this study. Patients treated with sequential chemotherapy and thoracic radiotherapy were excluded because we have considered the standard care for the stage III NSCLC patients to be concurrent chemoradiotherapy, and therefore, the sequential treatment was given only to patients with poor general condition or to patients who had a tumor too large for radiotherapy initially but decreasing enough for radiotherapy after chemotherapy. All patients underwent a systematic pretreatment evaluation and standardized staging procedures, which included physical examination, chest X-rays, CT scans of the chest and abdomen, a CT scan or MRI of the brain, a bone scintigram, and blood examinations including tumor markers.

Data collection and statistical analyses. Sex, age, performance status, body weight loss, carcinoembryonic antigen (CEA), clinical stage, nodal status, chemotherapy regimens, total dose of radiotherapy, tumor responses to treatment, sites and date of recurrence, and date of death were obtained from a retrospective medical chart review. As a routine clinical practice, tumor markers including CEA were examined in every patient eligible for chemotherapy and chemoradiotherapy before, during,

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and just after the initiation of treatment. Receiver operator characteristic (ROC) curves and the corresponding area under the curve (AUC) were used to evaluate the cut points of CEA values to predict brain metastasis as the sole, or one of the first, relapse sites. Tumor histological classification was based on the criteria of the World Health Organization.[17] Patients were staged using the 6th edition of Union for International Cancer Control TNM classification for lung cancer.

Time to brain metastases was measured from the start of initial chemoradiotherapy to when the brain metastases were confirmed by a brain CT scan or MRI. Although we monitor brain metastases regularly as a routine follow-up imaging study after chemoradiotherapy, there might be diversity in the frequency and methods of monitoring. Patients who did not develop brain metastases at the last follow-up were censored at that time. Time to brain metastases was evaluated using the Kaplan–Meier method, the log–rank test, and Cox's proportional hazard model.

Sex, age, performance status, body weight loss, smoking status, CEA value, stage, T-factor, and nodal status were included as covariates in the multivariate analyses (Cox's proportional hazard model analyses). All of these analyses were carried out using STATA 11.1 software for Windows (StataCorp, College Station, TX, USA).

This study was approved by the president of the National Cancer Center Hospital. The institutional review board and ethics review committee decided to exempt this study from the usual review process because of its retrospective nature.

Results

In total, 116 patients were identified. Females accounted for 26% of the study group. The median age was 57 years. Almost all patients were in good general condition with a performance status of 0–1. Of the 116 patients, 63% had tumor factor (T-factor) 1–2 disease and 93% had nodal factor (N-factor) 2–3 disease. All patients received platinum-based chemotherapy, and 86% received a total dose of 60 Gy in 30 fractions as definitive thoracic radiotherapy (Table 1). The response rate was 82%, median survival time was 24.5 months, and the 5-year survival rate was 24% in this study group.

Disease progression or recurrence was noted in 95 (82%) patients. Brain metastases as the sole site of initial recurrence were noted in 19 (16%) patients, and both brain and other sites were involved in 17 (15%) patients (Table 2). Of the 19 patients who had isolated brain failure, 10 developed recurrences subsequently at additional sites other than the brain, three died of progressive brain metastases without progression in other sites, and two developed meningitis carcinomatosa. Another two patients also died, but the cause of death was not identified because they were lost to follow-up. Brain metastases were controlled by radiotherapy in the other two patients.

A total of 43 patients (37%) developed brain metastases at some time during the course of follow-up. We examined various cut points of CEA value and found 20 ng/mL gave a relatively better AUC (56.2%) by the ROC analysis. Time to brain metastasis was significantly associated with pretreatment CEA value. The responses of CEA during chemoradiotherapy and the CEA level just after chemoradiotherapy did not have significant correlation with brain relapses. The multivariate analysis using Cox's proportional hazard model showed that the hazard ratio (95% confidence interval [CI], *P*-value) of a CEA value $\geq$20 ng/mL was 2.64 (1.39–5.02, $P = 0.003$, Table 3) compared to a CEA value of < 20 ng/mL. Sex, age, performance status, body weight loss, smoking history, T-factor, nodal status, and stage were not associated with the time to brain metastasis (Table 3). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively (Fig. 1).

Overall survival according to the first relapse site is shown in Figure 2. Patients who developed brain metastases only as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

Table 1. Characteristics of patients with stage III lung adenocarcinoma who participated in this study ($n = 116$)

Characteristic	*n*	%
Sex		
Female	30	26
Male	86	74
Age (years)		
Median (range)	57 (35–74)	NA
Performance status		
0	36	31
1	79	68
2	1	1
Body weight loss		
$\leq$4.9%	95	82
$\geq$5.0%	21	18
Smoking (pack-years)		
$\leq$10	29	25
$\geq$11	87	75
CEA (ng/mL)		
< 20	89	77
$\geq$20	27	23
Stage		
IIIA	57	49
IIIB	59	51
T-factor		
1–2	73	63
3–4	43	37
N-factor		
0–1	8	7
2–3	108	93
Chemotherapy type		
Cisplatin + vinorelbine	75	65
Cisplatin + vindesine + mitomycin	26	22
Nedaplatin + paclitaxel	8	7
Other combinations	7	6
Total radiation dose (Gy)		
60	100	86
<60	16	14

CEA, carcinoembryonic antigen; NA, not applicable; N-factor, nodal factor; T-factor, tumor factor.

Table 2. Sites of first recurrence in patients with stage III lung adenocarcinoma ($n = 95$)

Site of recurrence	*n*	%
Relapses including brain	36	38
Brain only	19	20
Brain and other sites	17	18
Sites other than brain	56	59
Unknown	3	3

Discussion

This study showed that CEA values before treatment were associated with time to brain metastasis in patients with stage III

Table 3. Time to brain metastases according to clinical factors in patients with stage III adenocarcinoma: Cox proportional hazard model analysis

Characteristic	Cox proportional hazard model (HR [95% CI])			
	Univariate	*P*-value	Multivariate	*P*-value
Sex				
Male	1	0.03	1	0.660
Female	2.00 (1.08–3.69)		1.24 (0.48–322)	
Age (years)				
≤ 57	1	0.17	1	0.110
≥ 58	0.65 (0.34–1.21)		0.58 (0.30–1.13)	
Performance status				
0	1	0.96	1	0.830
1–2	0.98 (0.53–1.83)		0.92 (0.44–1.92)	
Body weight loss (%)				
≤ 4.9	1	0.91	1	0.630
≥ 5.0	1.05 (0.47–2.36)		1.25 (0.51–3.05)	
Smoking (pack-years)				
≤ 10	1	0.01	1	0.290
≥ 11	0.43 (0.23–0.79)		0.58 (0.21–1.59)	
CEA				
< 20	1	0.01	1	0.003
≥ 20	2.17 (1.17–3.99)		2.64 (1.39–5.02)	
T-factor				
1–2	1	0.39	1	0.880
3–4	0.75 (0.39–1.44)		0.84 (0.37–1.90)	
N-factor				
0–1	1	0.33	1	0.520
2–3	2.02 (0.49–8.38)		1.40 (0.50–3.88)	
Stage				
IIIA	1	0.93	1	0.770
IIIB	1.03 (0.57–1.87)		0.85 (0.30–2.46)	

CEA, carcinoembryonic antigen; CI, confidence interval; HR, hazard ratio; N-factor, nodal factor; T-factor, tumor factor.

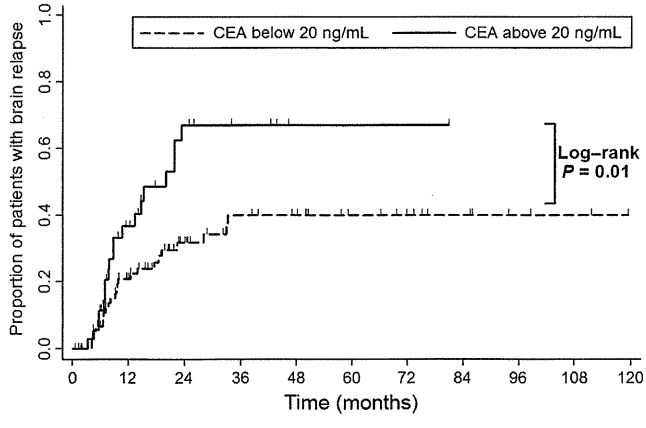

Fig. 1. Cumulative incidence of brain relapse in patients with stage III lung adenocarcinoma by carcinoembryonic antigen (CEA) value (ng/mL). Percentages of patients who developed brain metastases at 12 and 24 months were 37% and 67% in patients with elevated CEA value, and 21% and 32% in the others (log–rank test, $P = 0.01$), respectively.

lung adenocarcinoma who received concurrent platinum-based chemotherapy and thoracic radiotherapy. This is the first report showing that the CEA value might be associated with a higher risk of brain metastases in locally advanced lung adenocarcinoma.

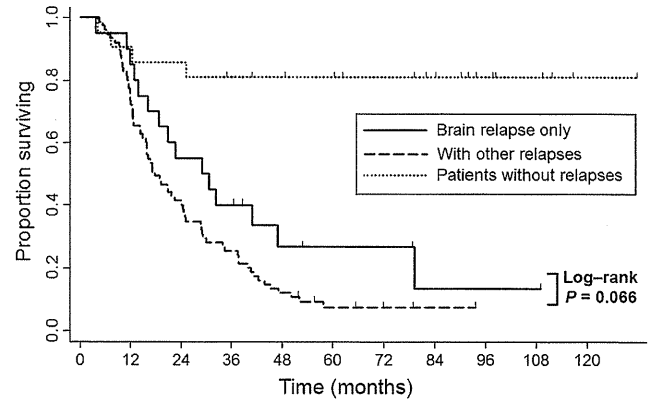

Fig. 2. Overall survival in patients with stage III lung adenocarcinoma according to the first relapse site. Dashed line, patients who developed extracranial recurrence with or without brain metastases; thick line, patients who developed brain relapse only; dotted line, patients who had no relapse. Patients who developed brain metastases as the first recurrent site had marginally better survival (log–rank test, $P = 0.066$) compared to those with metastases other than brain.

The median survival time (24.5 months) in the present study seemed better than the results observed in the study of Cox *et al.* (median survival time, 12.2–18.9 months) that included four clinical trials involving chemoradiotherapy.[12,18–21] The proportion of the participants whose first recurrent sites included brain metastases (38%, Table 2) in this study was substantially higher than the results observed in the analysis of Cox *et al.*[12] (16% with adenocarcinoma). Because the concurrent chemoradiotherapy with better survival failed to improve the proportion of brain relapses, the importance of the prevention of brain metastases has increased in this patient group. Furthermore, overall survival in patients who developed brain metastases as the sole site of the initial recurrence was marginally better than in those with metastases to other sites (log–rank, $P = 0.066$, Fig. 2) in our observation of patients with locally advanced lung adenocarcinoma. In fact, some patients with only brain relapses as the first recurrent site survived without further metastases after local treatment for the brain lesions.

Prospective randomized trials evaluating the effect of PCI in patients with locally advanced NSCLC after chemoradiotherapy showed a significant reduction in the development of brain metastases, but no survival benefit in the PCI arms.[5–8] Thus, it is necessary to identify the clinical factors of patients who are more likely to develop brain metastases and would be good candidates for PCI. In retrospective analyses of patients with locally advanced NSCLC, adenocarcinoma histology was suggested to have a higher risk of brain relapses and be worthy of more attention concerning brain metastases.[11–16] Therefore, locally advanced lung adenocarcinoma was specifically analyzed to identify clinical factors predicting brain metastases.

Among patients with disseminated adenocarcinoma without indications for definitive thoracic radiotherapy, a high CEA value (over 40 ng/mL) before treatment might be associated with a higher risk of brain relapses.[22] The present study involving patients with locally advanced lung adenocarcinoma after chemoradiotherapy showed that the CEA value was significantly associated with the time to brain metastasis on multivariate analysis (Table 3). This result suggested that patients with stage III lung adenocarcinoma and elevated CEA values might be good candidates for interventions to prevent brain metastases.

This study had several limitations. First, the number of patients included in the analysis was relatively small because we selected patients with stage III lung adenocarcinoma who

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underwent concurrent chemoradiotherapy. Second, there might be diversity in the frequency and methods of monitoring brain metastases because of the retrospective nature of the analysis. Third, we could not determine significant factors to predict solitary brain relapses which might be cured by prophylactic brain intervention, mainly because the number of patients with solitary brain relapse was too small for efficient statistical analysis.

In conclusion, the present analysis implies that patients with elevated CEA values before treatment have a higher risk of developing brain metastases after chemoradiotherapy for locally advanced lung adenocarcinoma. Further effort is mandatory to evaluate the clinical relevance of CEA value to predict brain relapses and select candidates for prophylactic interventions in future prospective trials.

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Disclosure Statement

The authors have no conflicts of interest.

References

1 Furuse K, Fukuoka M, Kawahara M *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999; **17**: 2692–9.

2 Kiura K, Takigawa N, Segawa Y *et al.* Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer:OLCSG 0007. *J Clin Oncol* 2008; **26**(Suppl): 400s (abstr7515).

3 Albain KS, Rusch VW, Crowley JJ *et al.* Concurrent cisplatin/etoposide plus chest radiotherapy followed by surgery for stages IIIA (N2) and IIIB non-small-cell lung cancer: mature results of Southwest Oncology Group phase II study 8805. *J Clin Oncol* 1995; **13**: 1880–92.

4 Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. *Cancer* 2007; **109**: 1668–75.

5 Cox JD, Stanley K, Petrovich Z, Paig C, Yesner R. Cranial irradiation in cancer of the lung of all cell types. *JAMA* 1981; **245**: 469–72.

6 Umsawasdi T, Valdivieso M, Chen TT *et al.* Role of elective brain irradiation during combined chemoradiotherapy for limited disease non-small cell lung cancer. *J Neurooncol* 1984; **2**: 253–9.

7 Russell AH, Pajak TE, Selim HM *et al.* Prophylactic cranial irradiation for lung cancer patients at high risk for development of cerebral metastasis: results of a prospective randomized trial conducted by the Radiation Therapy Oncology Group. *Int J Radiat Oncol Biol Phys* 1991; **21**: 637–43.

8 Gore EM, Bae K, Wong SJ *et al.* Phase III comparison of prophylactic cranial irradiation versus observation in patients with locally advanced non-small-cell lung cancer: primary analysis of radiation therapy oncology group study RTOG 0214. *J Clin Oncol* 2011; **29**: 272–8.

9 Robnett TJ, Machtay M, Stevenson JP, Algazy KM, Hahn SM. Factors affecting the risk of brain metastases after definitive chemoradiation for locally advanced non-small-cell lung carcinoma. *J Clin Oncol* 2001; **19**: 1344–9.

10 Carolan H, Sun AY, Bezjak A *et al.* Does the incidence and outcome of brain metastases in locally advanced non-small cell lung cancer justify prophylactic cranial irradiation or early detection? *Lung Cancer* 2005; **49**: 109–15.

11 Gaspar LE, Chansky K, Albain KS *et al.* Time from treatment to subsequent diagnosis of brain metastases in stage III non-small-cell lung cancer: a retrospective review by the Southwest Oncology Group. *J Clin Oncol* 2005; **23**: 2955–61.

12 Cox JD, Scott CB, Byhardt RW *et al.* Addition of chemotherapy to radiation therapy alters failure patterns by cell type within non-small cell carcinoma of lung (NSCCL): analysis of radiation therapy oncology group (RTOG) trials. *Int J Radiat Oncol Biol Phys* 1999; **43**: 505–9.

13 Andre F, Grunenwald D, Pujol JL *et al.* Patterns of relapse of N2 nonsmall-cell lung carcinoma patients treated with preoperative chemotherapy: should prophylactic cranial irradiation be reconsidered? *Cancer* 2001; **91**: 2394–400.

14 Keith B, Vincent M, Stitt L *et al.* Subsets more likely to benefit from surgery or prophylactic cranial irradiation after chemoradiation for localized non-small-cell lung cancer. *Am J Clin Oncol* 2002; **25**: 583–7.

15 Bajard A, Westeel V, Dubiez A *et al.* Multivariate analysis of factors predictive of brain metastases in localised non-small cell lung carcinoma. *Lung Cancer* 2004; **45**: 317–23.

16 Mamon HJ, Yeap BY, Janne PA *et al.* High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. *J Clin Oncol* 2005; **23**: 1530–7.

17 Travis WD. *Pathology & Genetics of Tumours of the Lung, Thymus And Heart, World Health Organization Classification of Tumours*, 1st edn. Switzerland: WHO Press, 2004.

18 Sause WT, Scott C, Taylor S *et al.* Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small-cell lung cancer. *J Natl Cancer Inst* 1995; **87**: 198–205.

19 Byhardt RW, Scott CB, Ettinger DS *et al.* Concurrent hyperfractionated irradiation and chemotherapy for unresectable nonsmall cell lung cancer. Results of Radiation Therapy Oncology Group 90-15. *Cancer* 1995; **75**: 2337–44.

20 Lee JS, Scott C, Komaki R *et al.* Concurrent chemoradiation therapy with oral etoposide and cisplatin for locally advanced inoperable non-small-cell lung cancer: radiation therapy oncology group protocol 91-06. *J Clin Oncol* 1996; **14**: 1055–64.

21 Komaki R, Scott C, Ettinger D *et al.* Randomized study of chemotherapy/radiation therapy combinations for favorable patients with locally advanced inoperable nonsmall cell lung cancer: Radiation Therapy Oncology Group (RTOG) 92-04. *Int J Radiat Oncol Biol Phys* 1997; **38**: 149–55.

22 Arrieta O, Saavedra-Perez D, Kuri R *et al.* Brain metastasis development and poor survival associated with carcinoembryonic antigen (CEA) level in advanced non-small cell lung cancer: a prospective analysis. *BMC Cancer* 2009; **9**: 119.

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Phase II study of concurrent chemoradiotherapy with high-dose-rate intracavitary brachytherapy in patients with locally advanced uterine cervical cancer: Efficacy and toxicity of a low cumulative radiation dose schedule ☆

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ABSTRACT

Objective. A multicenter phase II trial was conducted to assess the efficacy and toxicity of concurrent chemoradiotherapy (CCRT) with high-dose-rate intracavitary brachytherapy (HDR-ICBT) using a low cumulative prescribed dose schedule in patients with locally advanced uterine cervical cancer.

Methods. The Japanese Gynecologic Oncology Group (JGOG) study JGOG1066 enrolled patients with FIGO stages III–IVA uterine cervical cancer who had no para-aortic lymphadenopathy (>10 mm) assessed by CT. Patients received definitive radiotherapy (RT) consisting of external beam whole pelvic RT and HDR-ICBT. The cumulative linear quadratic equivalent dose (EQD2) was 62–65 Gy prescribed at point A. Cisplatin 40 mg/m^2 weekly was administered concurrently with RT for 5 courses.

Results. Of the 72 patients registered, 71 were eligible. With a median follow-up of 28 months, the 2-year progression-free survival rate and pelvic disease progression-free rate were 66% (95% CI, 54% to 76%) and 73% (95% CI, 61% to 82%), respectively. Progression-free survival decreased significantly with increased central tumor size (P=0.036). The 2-year cumulative late complication rates were 24% for all grades, 9% for grade 1, 12% for grade 2, 3% for grade 3, and 0 for grades 4/5.

Conclusions. The JGOG1066 demonstrated that CCRT using HDR-ICBT with a low cumulative RT dose schedule achieved comparable outcome as those achieved with global dose schedules (EQD2=85 Gy) with a lower incidence of late toxicity for locally advanced uterine cervical cancer in a Japanese population.

Introduction

Concurrent chemoradiotherapy (CCRT) has been shown to be superior to definitive radiotherapy (RT) alone in several randomized controlled trials (RCTs), and is now the standard of care for locoregionally advanced uterine cervical cancer [1]. Standard definitive RT consists of whole pelvic external beam RT (EBRT) and either high or low dose rate intracavitary brachytherapy (ICBT). The previously mentioned RCTs utilized only low dose-rate ICBT (LDR-ICBT) [1]. High dose-rate ICBT (HDR-ICBT) has become widely used in Japan [2], and many centers worldwide are also shifting to HDR-ICBT [3].

Several RCTs have demonstrated clinical equivalence in terms of both local control and toxicity between HDR-ICBT and LDR-ICBT in the setting of definitive RT (without chemotherapy) [4]. In CCRT, many investigators also reported favorable treatment results using HDR-ICBT in single institutional retrospective series [5–13]. The Gynecologic Oncology Group (GOG) and the Radiation Therapy Oncology Group (RTOG) now allow the use of HDR-ICBT as well as LDR-ICBT in recent clinical trials of CCRT for cervical cancer [14–18]. In these

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trials, however, the patients treated with HDR-ICBT were not evaluated separately. It is unclear whether concurrent chemotherapy delivery with RT increases late complications [19]. In view of potential narrow therapeutic window of HDR-ICBT, the optimum RT dose should be carefully determined especially in the CCRT setting. Late RT complications, even when mild to moderate (i.e., Grades 1–2), significantly reduce quality of life [20]. Recently, image-guided brachytherapy (IGBT) using CT/MRI has been investigated in order to decrease late toxicity as well as improve local control [21].

Japanese centers use lower cumulative dose schedules than those of the US and Europe [2,3]. Favorable local control results have been obtained with these lower dose schedules in retrospective series of RT alone [22,23]. However, these lower dose schedules have not been accepted in the US and Europe given the lack of prospective data. In this situation, prospective clinical trials on the efficacy and safety of the CCRT using HDR-ICBT with the low cumulative dose schedules are encouraged.

Based on this background, we conducted a phase II multi-institutional clinical trial on CCRT for locally advanced cervical cancer patients. Herein, we report the data of outcomes and late toxicity observed in the trial.

Materials and methods

Study design

The JGOG1066 trial was a multicenter phase II prospective study aimed at evaluating the efficacy and late toxicity of CCRT using HDR-ICBT for locally advanced uterine cervical cancer patients. This study was designed by the JGOG Cervical Cancer Committee in collaboration with the Japanese radiation oncologists with expertise in the cervical cancer treatment. The study was approved by the JGOG Clinical Trial Review Committee, and the local institutional review boards (IRB) of the participating institutions. This trial is registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR; number 000001042).

Patients

Patients with histologically proven squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of the uterine cervix with International Federation of Gynecology and Obstetrics (FIGO) stages IIIA, IIIB, or IVA disease with no para-aortic lymphadenopathy (<10 mm) assessed by computed tomography (CT), performed within 4 weeks prior to entry were eligible. Histopathological evaluation of the para-aortic nodes (e.g., retroperitoneal surgical exploration) was not required. Eligibility criteria also included patient age between 20 and 70 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS)<2. Patients with prior therapy (radiotherapy, surgery or chemotherapy) for cervical cancer were ineligible. Patients were also required to have abdomen-pelvic CT, pelvic MRI (T2 weighted image), chest X-ray/CT, within 28 days before entry. All patients were required to give written informed consent prior to enrollment in this study.

Radiotherapy

Protocol radiotherapy (RT) consisted of a combination of whole pelvic (WP) EBRT and HDR-ICBT. Interstitial brachytherapy was not allowed.

WP-EBRT was delivered with a photon beam of 6 MV or greater. Both anteroposterior (AP)–posteroanterior (PA) and a four-field technique were permitted. Intensity modulated radiation therapy (IMRT) was not allowed. When the four-field technique was utilized, the portal arrangement was changed to the AP–PA technique after the midline block (MB) was inserted. A tissue heterogeneity correction was not applied in the dose calculation. WP-EBRT was delivered for 5 days during a week to achieve a total dose of 50 Gy/25 fractions or 50.4 Gy/28 fractions. The WP-EBRT was initially delivered without a MB. Subsequently, the next phase of WP-EBRT was administered through the same WP field with a MB width of 3 or 4 cm. The MB was formed with multileaf collimators (MLC) or a custom cerrobend block. Four radiotherapy schedules were provided for the protocol (Table 1). Because these schedules are biologically nearly equivalent, the choice of schedule was left to the treating radiation oncologist. The upper boarder of the pelvic field was L4–5, and the lower border was a transverse line below the obturator foramen or pubic symphysis or 2 cm inferior from caudal end of the tumor. The lateral borders of the AP/PA portals were 1.5 to 2 cm beyond the lateral margin of the bony pelvis. For the lateral field, the anterior border was placed at a horizontal line drawn 0.5 cm anterior to the symphysis pubis anteriorly and the posterior border was placed at least 1.5 cm posterior from the surface of the sacrum. Boost EBRT of 6–10 Gy/3–5 fractions was indicated for patients with nodular parametrial involvement to the pelvic walls and/or nodal metastases (≥10 mm in shortest diameter).

The first HDR-ICBT was performed within 7 days after the MB insertion. HDR-ICBT was performed once a week with a fraction dose of 6 Gy prescribed at point A using Ir-192 afterloading machines. HDR-ICBT was not allowed on the same day as the EBRT. The total HDR-ICBT dose was determined by the timing of the MB insertion (Table 1). The cumulative linear quadratic equivalent doses (EQD2) [24] at point A, which were the summation of the EBRT doses without the MB and HDR-ICBT doses, ranged from 62 to 65 Gy. For patients who had an inadequate response to EBRT or failed tandem insertion, additional WP EBRT without the MB was allowed to a total dose of 50 or 50.4 Gy. The total HDR-ICBT dose was 11 Gy per 2 fractions (i.e., 6 Gy + 5 Gy or 5.5 Gy × 2) at point A for this situation. A tandem and ovoid combination was recommended except as restricted by the vaginal anatomy (e.g., narrow vagina) or significant (>1/2) vaginal disease. For these patients, a vaginal cylinder could be utilized. Source dwell patterns (i.e., times and positions) were determined according to the Manchester system [25]. A dose calculation was performed for each application, using two orthogonal radiographs. The isodose curves were plotted, and doses at the rectum and bladder were calculated according to the International Commission on Radiation Units and Measurements (ICRU) 38 criteria [26]. Three dimensional planning using CT and/or MRI was not applied.

For patients who could not receive HDR-ICBT appropriately even after the additional EBRT without MB to 50/50.4 Gy, a boost EBRT with reduced portals was given to a total dose ranging from 64.8 to 72 Gy. Treatment was to be completed within 56 days.

To maintain RT quality, the protocol included an integrated QA process. Credentialing of participating institutions and individual case reviews for all patients were performed. The details of the QA process and its results have been published elsewhere [27].

Table 1
Radiotherapy schedules.

External beam radiotherapy		HDR-ICBT	Total EQD2 at point A
WP	WP + MB		WP + HDR-ICBT
30 Gy/15 fs	20 Gy/10 fs	24 Gy/4 fs	62 Gy
30.6 Gy/17 fs	19.8 Gy/11 fs	24 Gy/4 fs	62 Gy
40 Gy/20 fs	10 Gy/5 fs	18 Gy/3 fs	64 Gy
41.4 Gy/23 fs	9 Gy/5 fs	18 Gy/3 fs	65 Gy

WP: whole pelvic radiotherapy, MB: midline block.
HDR-ICBT: high-dose-rate intracavitary brachytherapy.
EQD2: equivalent dose in 2 Gy per fraction.

Chemotherapy

Weekly cisplatin at a dose of 40 mg/m^2 (maximum dose of 70 mg/body) was administered for 5 courses during the radiotherapy period. The first course of cisplatin was administered on day 1 of radiotherapy. Cisplatin could be given on the same day of HDR-ICBT as well as EBRT.

Follow-up

Response was assessed by MRI T2 weighted images 3 months after the completion of treatment according to the RECIST criteria. Patients were followed every 3 months for the first 2 years. Follow-up included a pelvic examination with PAP smear and monitoring of tumor markers if initially elevated. CT scans of the abdomen and pelvis, and chest X-ray (or CT scan) were performed annually. Pelvic disease progression was defined as follows: pelvic recurrence after assessment of CR, pelvic disease progression with a >20% increase in the size of target lesions assessed by MRI T2WI, or initiation of salvage treatment (regardless of pathological findings) for pelvic disease.

Statistical design

This was a phase II trial with the primary endpoint of estimating 2-year cumulative progression-free survival rate (PFS). The secondary endpoints included the treatment completion rate (all, chemotherapy, and radiotherapy), adverse events (acute and late), compete response rate, 2-year cumulative overall survival rate (OS), 2-year cumulative pelvic disease progression-free rate (PDPF), and 2-year cumulative distant metastasis rate (DM). Details of feasibility and acute adverse events will be reported elsewhere (manuscript submitted for publication).

The sample size was initially calculated based on the following assumptions: an expected 2-year PFS rate of 60% versus the threshold value of 40% from the previous published data of RT alone series [28,29] and data of the US RCT's control arms [1]. CCRT would be considered superior to RT alone if the lower limit of the 95% confidence interval of the 2-year PFS rate exceeded the threshold value of 40%. To attain 90% power with a two-sided α error of 0.05, the minimum required sample size was estimated to be 68 patients. After the sample size was adjusted to allow for patient ineligibility or loss, the total sample size was 70 patients. We also performed a Monte-Carlo simulation to examine the effect of censoring on the power. We generated the exponential and Weibull random numbers to simulate censoring times, assumed the recruiting time and follow-up time of 2 years, and set the expected 2-year PFS rate to 60%. In various scenarios, we confirmed the lower limits of the 95% confidence intervals for 2-year PFS rates that exceeded the threshold value of 40% with the probability of more than 80%.

The cumulative outcomes and late complication curves were estimated by the Kaplan-Meier method. Differences in outcomes were compared using a log-rank test. PFS was measured from the time of registration until disease progression or death resulting from any cause. OS was measured from the time of registration until death resulting from any cause. Late adverse events were graded according to the National Cancer Institute Common Toxicity Criteria version 3.0. Complete response was assessed following the Response Evaluation Criteria in Solid Tumors. All analyses were performed with SAS software, version 9.2.

Results

Patient characteristics

Seventy-two patients were enrolled from 25 institutions between March 2008 and January 2009. One patient was ineligible because she had para-aortic lymphadenopathy of 10 mm in the shortest diameter assessed on pretreatment abdominal CT. She never received treatment on protocol and was not included into the following analyses. Therefore, 71 patients formed the patient cohort for this report. The clinical characteristics of the 71 patients are listed in Table 2.

Feasibility

Sixty-three of the 71 patients (89%) completed the protocol treatment as planned. Chemotherapy was administered for the planned 5 courses in 65 patients (92%). Planned radiotherapy was completed in 68 patients (96%). One patient could not receive HDR-ICBT due to uterine perforation that occurred after 4 Gy of EBRT was delivered and the first administration of cisplatin. Subsequently, she was discontinued from the protocol treatment and received EBRT irradiation as a salvage treatment. Individual case reviews on RT QA revealed favorable compliance with the RT protocol [27]. The median total EQD2 (WP-EBRT + HDR-ICBT) at point A was 62 Gy (range, 49–65 Gy). Prescribed point A doses per protocol were delivered in 63 patients (89%): WP-EBRT 30 Gy + HDR-ICBT 24 Gy in 10 patients, WP-EBRT 30.6 Gy + HDR-ICBT 24 Gy in 30 patients, WP-EBRT 40 Gy + HDR-ICBT 18 Gy in 15 patients, WP-EBRT 41.4 Gy + HDR-ICBT 18 Gy in 6 patients, and WP-EBRT 50 Gy + HDR-ICBT 11 Gy in 2 patients. Boost EBRT was delivered to the parametrium in 28 patients, enlarged nodes in 22 patients, and both in 11 patients.

The rectal and bladder dose calculation according to the ICRU 38 definition was performed for every fraction in 66 patients (93%). Median doses were 4.4 Gy (range, 2.6–9.4 Gy) for the bladder, and 4.3 Gy (range, 2.8–11.1 Gy) for the rectum. Median cumulative biologically effective doses (BEDs) (EBRT + HDR-ICBT) were 95 Gy_3 (range, 68–184 Gy_3) for the bladder, and 96 Gy_3 (range, 71–199 Gy_3) for the rectum. Nine out of 66 patients (14%) received over 120 Gy_3 for the rectum. The median overall treatment time was 50 days (range, 37 to 66 days) for 68 patients who completed the planned radiotherapy.

Table 2
Patient characteristics.

Clinical variable	n	%
Median age (range)	57 years (32–70 years)	
PS		
0	63	89
1	8	11
FIGO stage		
IIIA	3	4
IIIB	64	90
IVA	4	6
Histological diagnosis		
Squamous cell carcinoma	66	93
Adenosquamous carcinoma	2	3
Adenocarcinoma	3	4
Parametrial involvement (fixed to pelvic wall)		
No	4	6
Yes	67	94
Unilateral	47	66
Bilateral	20	28
Maximum tumor diameter (mm)[a]		
<40	16	22.5
40≤, <50	10	14
50≤, <60	16	22.5
60≤, <70	16	22.5
70≤, <80	6	8.5
80≤	7	10
Pelvic node enlargement[b]		
Yes	41	58
No	30	42

[a] Assessed by MRI T2WI.
[b] ≥10 mm in shortest diameter assessed by CT/MRI.

Efficacy and late toxicity

The median follow-up for the 71 patients was 28 months (range, 12 to 35 months). Fifty-six patients (79%) achieved a complete response and 25 patients had disease progression. Twenty-one patients had a pelvic recurrence: primary lesion in 14; pelvic node in 6; and pelvic peritoneum in 1. Seventeen patients developed distant metastases: para-aortic node in 11; lung in 4; bone in 2; liver in 1; and supraclavicular node in 1. The 2-year PFS rate was 66% (95% CI, 54% to 76%; Fig. 1). The 2-year OS, PDPF, and DM were 90% (95% CI, 80% to 95%), 73% (95% CI, 61% to 82%), and 25% (95% CI, 16% to 37%), respectively.

There were decreases in both PFS ($P=0.036$) and PDPF ($P=0.24$) with increased tumor diameter as assessed by MRI. The 2-year PFS and PDPF were, respectively, 77% and 85% for tumors <50 mm, 69% and 72% for tumors 50–70 mm, and 39% and 54% for tumors ≥70 mm. The 2-year DM was higher for patients with large diameter tumors (47% for ≥70 mm) compared with those with smaller diameter tumors (19% for <50 mm, 20% for 50–70 mm) ($P=0.067$). Patients with enlarged pelvic nodes (≥10 mm in the shortest diameter assessed by CT/MRI) had poorer PFS and PDPF, and higher DM than those with no enlarged nodes. The 2-year PFS, PDPF and DM were, respectively, 60%, 67% and 31% for the node positive patients and 71%, 78% and 20% for the node negative patients. There were no significant differences between these two groups for these endpoints.

Table 3 lists late adverse events. Only 3 patients (4%) suffered severe (≥grade 3) late toxicity. The 2-year cumulative late complication rates by grades were 24% for all grades, 9% for grade 1, 12% for grade 2, 3% for grade 3, and 0 for grades 4/5.

Table 3
Reported late adverse events (n=71).

Events	Grade (n)				3≤(%, 95% CI)
	1	2	3	4	
Gastrointestinal					
Colitis	2	5	0	0	0
Enteritis	1	1	0	0	0
Proctitis	3	2	0	0	0
Nausea	1	0	0	0	0
Vomiting	1	0	0	0	0
Other (hemorrhage, upper GI)	1	0	0	0	0
Renal/genitourinary					
Cystitis	2	5	1	0	1 (0–8)
Incontinence	0	1	0	0	0
Obstruction (ureter)	0	0	1	0	1 (0–8)
Urinary retention	0	1	0	0	0
Other					
Edema: limb	3	0	0	0	0
Creatinine	0	0	1	0	1 (0–8)
Pain (pelvis)	0	1	0	0	0

Discussion

This prospective multi-institutional phase II study (JGOG1066) demonstrated that CCRT using HDR-ICBT with a low cumulative dose schedule (EQD2 = 62–65 Gy prescribed at point A) achieved a 2-year PFS rate of 66% with a low incidence (4%) of severe late toxicity in stage III and IVA uterine cervical cancer patients. The lower limit of the 95% CI for PFS was 54%, which was higher than the threshold of 40%, confirming the superiority of CCRT over historical outcomes of RT alone, although the eligibility criteria regarding para-aortic node evaluation were different from the prior RCTs [1].

Although the cumulative doses prescribed at point A adopted in this study were remarkably lower than those used in global schedules, the pelvic control rate appeared to be comparable to previously reported data (Table 4). However, there remains room for improvement in local control, particularly for patients with large tumors (≥70 mm in the largest diameter) who frequently developed pelvic recurrences in this study. The data from previously published papers suggested that higher prescribed doses had no apparent impact for improving local control, but probably did increase the risk of severe late complications (Table 4).

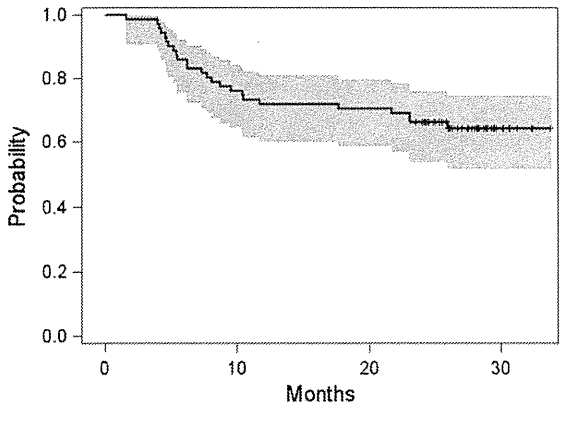

Fig. 1. Progression-free survival (PFS) of 71 eligible patients enrolled in JGOG1066.

In this study, 14% of the patients received over 120 Gy_3 at the ICRU38 rectal point, which is considered to be the threshold for developing severe proctitis [1]. We must bear in mind that these data, including those from our study, were for patients who were treated with ICBT that was planned only by a classical 2-dimensional (2-D) method, which prescribes doses at a single point A. Recently, 3-dimensional (3-D) image-guided brachytherapy (IGBT) using CT/MRI has become popular in clinical practice [30]. With IGBT, the actual tumor volume can be sufficiently covered with adequate prescribed doses while limiting the doses to surrounding organs at risk (OAR).

Dimopoulos et al. analyzed the dose–effect relationship between tumor diameter (at diagnosis and at time of HDR-ICBT) and local control for cases that were treated with IGBT [31]. They found a significant dose–effect relationship for local control within a dose range of 68 to 91 Gy using D90 HR-CTV for patients with large pretreatment tumor diameters and those with poor responses to EBRT [31]. A simple dose escalation for a single point A is an inappropriate approach to provide additional improvements in the therapeutic ratio. It is essential to investigate the therapeutic value of dose escalation using IGBT with careful monitoring of the doses to OAR, particularly for patients with large central tumors or, perhaps, those who responded poorly to prior EBRT.

In contrast, in this study, local control for patients with non-bulky tumors (<50 mm) was favorable (85%). Dimopoulos et al. showed excellent local control (97%) with no dose–effect relationship in patients with small tumors (2–5 cm) and those who had good responses to EBRT. Based on these results, they suggested that dose de-escalation with IGBT for these patient subsets might be appropriate [31]. Narayan et al. reported their experience with IGBT for cervical cancer [32]. Their goal with IGBT was to treat residual disease in the cervix and uterus after EBRT to a total dose of 80 Gy_{10}. They showed excellent local control with an average target dose of 79.2 Gy_{10} (resulting in 72 Gy_{10} at point A) for patients who had good responses to EBRT before ICBT and proper application of tandem applicator (i.e., inserted through the center of a cervical tumor) [32]. Unfortunately, for our study, we could not analyze local control based on both the response to EBRT and applicator laterality within a tumor, as we did not have a planned response evaluation or 3-D planning. A prospective study with IGBT to investigate local control with the prescribed doses used in this study is encouraged to determine whether dose de-escalation from global schedules is feasible for patients with

Table 4
Treatment results of cisplatin-based CCRT using HDR-ICBT for locally advanced cervical cancer.

Authors	n	Stage	III, IVA/all	EBRT (Gy) at point A	HDR-ICBT (Gy/fr) at point A	Total EQD2 (Gy) at point A	Median OTT	Median F/U	PC[a]	PFS[a]	Late toxicity[a] G3 <=	Subject for PC, and comments
Retrospective study												
Toita et al. [5]	40	IIB–IIIB	65%	40	18/3	64	48d	37 m	91% (3y)	67% (3y)	3%[b]	All stages
Novetsky et al. [6]	77	IB2–IV	40%	45	18/2	73	–	3.5y	68% (5y)	61% (5y)	6%[b]	Stages III and IVA
Ozsaran et al. [7]	81	IB–IVA	19%	50.4	18/3	73	–	42 m	78% (5y)	77% (5y)	0	>4 cm tumors
Parker et al. [8]	92	IB1–IVA	30%	45	24/4	77	61d	26 m	67% (5y)	–	4%[b]	All stages
Chen et al. [9]	70	IIB–IIIB	31%	45	24/4	77	–	43 m	87% (4y)	–	14%	All stages
Lim et al. [10]	69	IB1–IVA	26%	45	27.5/5, 30/5[c]	80, 84	8.4w	27 m	70% (2y)	59% (2y)	6%[b]	All stages
Anker et al. [11]	65	IB1–IVA	20%	45	30/5	84	–	25 m	97% (3y)	76% (3y)	17% (3y)	All stages, including RT alone cases (8%)
Forrest et al. [12]	122	IB–IV	25%	45	30/5	84	51d	18 m	86%[b]	70% (2y)	14% (2y)	All stages, including RT alone cases (16%)
Souhami et al. [13]	50	IIA–IVA	60%	46	30/3	96	–	27 m	68%[b]	–	26%[b]	Stage IIIB
Prospective study												
RTOG0128 [14]	77	IB1–IVA	21%	45	30/5	85	45d	24 m	74% (2y)	69% (4y)	16%[b]	All stages, HDR-ICBT was used in 35% of cases
Present study	71	III–IVA	100%	30–40	18/3, 24/4	62–65	50d	28 m	73% (2y)	66% (2y)	3% (2y)	Stages III and IVA

Abbreviations: CCRT = concurrent chemoradiotherapy; EBRT = external beam radiotherapy; HDR-ICBT = high dose-rate intracavitary brachytherapy; EQD2 = linear quadratic equivalent dose; PC = pelvic control rate; PFS = progression-free survival; d = days; w = weeks; m = months; y = year; NS = not stated; RT = radiotherapy.
[a] Actuarial rate.
[b] Crude rate.
[c] Point H.

non-bulky tumors or those with tumors that show good response. We believe that dose de-escalation has the potential to decrease the incidence of lower grade complications as well as high grade complications, which would contribute to improving patients' quality of life [20].

Distant failures, including para-aortic node metastases were frequently observed in this study. The incidence of distant failure increased with increased tumor size as well. In this study, histopathological examinations and PET/CT were not done to rule out para-aortic node metastases. This might have been one of the causes for frequent distant failures, including PAN recurrences. Reducing distant failures is another challenge that must be faced in order to improve the outcomes of patients with locoregionally advanced cervical cancer. A meta-analysis suggested that there might be therapeutic value with additional systemic chemotherapy after CCRT [19]. A phase I study to determine the optimum dose for adjuvant chemotherapy after definitive CCRT is now underway (JGOG1068).

One limitation of this study was that all of the patients were Japanese. Japanese women are generally smaller than Western women. This might have affected the toxicity incidences and grades. In addition, possible genetic differences between Japanese and Westerners cannot be completely ruled out. As mentioned previously, another limitation was that we did not use IGBT. For future multi-institutional prospective studies with IGBT, another quality assurance program on RT will be necessary [27].

In conclusion, despite the limited follow-up periods, the results of this study demonstrated that CCRT using HDR-ICBT with low cumulative RT dose schedules achieved comparable outcomes to those attained with global dose schedules with a lower incidence of late toxicity for locally advanced uterine cervical cancer patients in a Japanese population. If the presented RT dose schedules presented here are integrated into the current global standards, it would encourage the participation of Japanese patients in ongoing global studies. To further improve these outcomes, investigations on appropriate RT dose with IGBT and additional systemic treatment are warranted.

Conflict of interest statement
No conflict of interest.

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References

[1] Monk BJ, Tewari KS, Koh WJ. Multimodality therapy for locally advanced cervical carcinoma: state of the art and future directions. J Clin Oncol 2007;25:2952–65.
[2] Toita T, Kodaira T, Shinoda A, et al. Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. Int J Radiat Oncol Biol Phys 2008;70:788–94.
[3] Viswanathan AN, Creutzberg CL, Craighead P, et al. International brachytherapy practice patterns: a survey of the Gynecologic Cancer Intergroup (GCIG). Int J Radiat Oncol Biol Phys 2012;82:250–5.
[4] Stewart AJ, Viswanathan AN. Current controversies in high-dose-rate versus low-dose-rate brachytherapy for cervical cancer. Cancer 2006;107:908–15.
[5] Toita T, Moromizato H, Ogawa K, et al. Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. Gynecol Oncol 2005;96:665–70.
[6] Novetsky AP, Einstein MH, Goldberg GL, et al. Efficacy and toxicity of concomitant cisplatin with external beam pelvic radiotherapy and two high-dose-rate brachytherapy insertions for the treatment of locally advanced cervical cancer. Gynecol Oncol 2007;105:635–40.
[7] Ozsaran Z, Kamer S, Yalman D, et al. Treatment results and prognostic factors for cervical cancer patients treated by radiochemotherapy with weekly cisplatin. Eur J Gynaecol Oncol 2007;28:196–200.