was achieved in 142 (group A), 90%–99% in 74 (group B), and less than 90% in 5 (group C). The cumulative rates of symptom control at 5 years were 93%, 71%, and 60% in groups A, B, and C, respectively. According to these results, a high rate of tumor infarction was achieved with gelatin sponge in conjunction with a favorable long-term clinical outcome (7,26).

In conclusion, UAE with gelatin sponge is safe, with efficacy equivalent to previous data for other widely used embolic materials. Gelatin sponge should be an option for UAE, but randomized controlled trials including cost analysis will be needed to determine the impact of gelatin sponge on UAE clinical practice.

Acknowledgments: The authors thank the patients, doctors, nurses, and staff members who participated in this multicenter trial for their dedicated cooperation. We also thank the JIVROSG head office staff for their generous assistance.

References

1. Goodwin SC, Spies JB, Worthington-Kirsch R, et al. Uterine artery embolization for treatment of leiomyomata: long-term outcomes from the FIBROID Registry. Obstet Gynecol 2008; 111: 22–33.
2. Pelage JP, Le Dref O, Soyer P, et al. Fibroid-related menorrhagia: treatment with superselective embolization of the uterine arteries and midterm follow-up. Radiology 2000; 215:428–431.
3. Spies JB, Roth AR, Jha RC, et al. Leiomyomata treated with uterine artery embolization: factors associated with successful symptom and imaging outcome. Radiology 2002; 222:45–52.
4. Walker WJ, Pelage JP. Uterine artery embolisation for symptomatic fibroids: clinical results in 400 women with imaging follow up. Br J Obstet Gynaecol 2002; 109:1262–1272.
5. Banovac F, Lin R, Shah D, White A, Pelage JP, Spies J. Angiographic and interventional options in obstetric and gynecologic emergencies. Obstet Gynecol Clin North Am 2007; 34:599–616.
6. Katsumori T, Nakajima K, Mihara T, Tokuhiro M. Uterine artery embolization using gelatin sponge particles alone for symptomatic uterine fibroids: midterm results. AJR Am J Roentgenol 2002; 178:135–139.
7. Katsumori T, Kasahara T, Akazawa K. Long-term outcomes of uterine artery embolization using gelatin sponge particles alone for symptomatic fibroids. AJR Am J Roentgenol 2006; 186:848–854.
8. Kobayashi T, Arai Y, Takeuchi Y, et al. Phase I/II clinical study of percutaneous vertebroplasty (PVP) as palliation for painful malignant vertebral compression fractures (PMVCF): JIVROSG-0202. Ann Oncol 2009; 20:1943–1947.
9. Goodwin SC, Bonilla SM, Sacks D, et al. Reporting standards for uterine artery embolization for the treatment of uterine leiomyomata. J Vasc Interv Radiol 2001; 12:1011–1020.
10. Hovsepian DM, Siskin GP, Bonn J, et al. Quality improvement guidelines for uterine artery embolization for symptomatic leiomyomata. J Vasc Interv Radiol 2004; 15:535–541.
11. Spies JB, Allison S, Flick P, et al. Polyvinyl alcohol particles and tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a randomized comparative study. J Vasc Interv Radiol 2004; 15: 793–800.
12. Spies JB, Allison S, Flick P, et al. Spherical polyvinyl alcohol versus tris-acryl gelatin microspheres for uterine artery embolization for leiomyomas: results of a limited randomized comparative study. J Vasc Interv Radiol 2005; 16:1431–1437.
13. Rasuli P, Hammond I, Al-Mutairi B, et al. Spherical versus conventional polyvinyl alcohol particles for uterine artery embolization. J Vasc Interv Radiol 2008; 19:42–46.
14. Siskin GP, Shlansky-Goldberg RD, Goodwin SC, et al. A prospective multicenter comparative study between myomectomy and uterine artery embolization with polyvinyl alcohol microspheres: long-term clinical outcomes in patients with symptomatic uterine fibroids. J Vasc Interv Radiol 2006; 17: 1287–1295.
15. Volkers NA, Hehenkamp WJ, Birnie E, et al. Uterine artery embolization in the treatment of symptomatic uterine fibroid tumors (EMMY trial): periprocedural results and complications. J Vasc Interv Radiol 2006; 17:471–480.
16. Spies JB, Ascher SA, Roth AR, Kim J, Levy EB, Gomez-Jorge J. Uterine artery embolization for leiomyomata. Obstet Gynecol 2001; 98:29–34.
17. Lohle PN, Boekkooi FP, Smeets AJ, et al. Limited uterine artery embolization for leiomyomas with tris-acryl gelatin microspheres: 1-year follow-up. J Vasc Interv Radiol 2006; 17:283–287.
18. Hovsepian DM, Ratts VS, Rodriguez M, Huang JS, Aubuchon MG, Pilgram TK. A prospective comparison of the impact of uterine artery embolization, myomectomy, and hysterectomy on ovarian function. J Vasc Interv Radiol 2006; 17:1111–1115.
19. Spies JB, Roth AR, Gonsalves SM, Murphy-Skrzyniarz KM. Ovarian function after uterine artery embolization for leiomyomata: assessment with use of serum follicle stimulating hormone assay. J Vasc Interv Radiol 2001; 12: 437–442.
20. Golzarian J, Lang E, Hovsepian D, et al. Higher rate of partial devascularization and clinical failure after uterine artery embolization for fibroids with spherical polyvinyl alcohol. Cardiovasc Intervent Radiol 2006; 29:1–3.
21. Ryu RK, Omary RA, Sichlau MJ, et al. Comparison of pain after uterine artery embolization using tris-acryl gelatin microspheres versus polyvinyl alcohol particles. Cardiovasc Intervent Radiol 2003; 26:375–378.
22. Dembek CJ, Pelletier EM, Isaacson KB, Spies JB. Payer costs in patients undergoing uterine artery embolization, hysterectomy, or myomectomy for treatment of uterine fibroids. J Vasc Interv Radiol 2007; 18:1207–1213.
23. Spies JB. What evidence should we demand before accepting a new embolic material for uterine artery embolization? J Vasc Interv Radiol 2009; 20: 567–570.
24. Pelage JP, Guaou NG, Jha RC, Ascher SM, Spies JB. Uterine fibroid tumors: long-term MR imaging outcome after embolization. Radiology. 2004; 230: 803–809.
25. Siskin GP, Beck A, Schuster M, Mandato K, Englander M, Herr A. Leiomyoma infarction after uterine artery embolization: a prospective randomized study comparing tris-acryl gelatin microspheres versus polyvinyl alcohol microspheres. J Vasc Interv Radiol 2008; 19:58–65.
26. Katsumori T, Kasahara T, Kin Y, Nozaki T. Infarction of uterine fibroids after embolization: relationship between postprocedural enhanced MRI findings and long-term clinical outcomes. Cardiovasc Intervent Radiol 2008; 31:66–72.

J Cancer Res Clin Oncol (2012) 138:1239–1247
DOI 10.1007/s00432-012-1198-y

ORIGINAL PAPER

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

Hiroshi Mayahara · Minako Sumi · Yoshinori Ito · Syuhei Sekii · Kana Takahashi · Kouji Inaba · Yuuki Kuroda · Naoya Murakami · Madoka Morota · Jun Itami

Received: 10 January 2012 / Accepted: 5 March 2012 / Published online: 23 March 2012

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

This study was presented in part at the 53rd Annual Meeting of the American Society for Radiation Oncology in Miami, October 2-6, 2011.

H. Mayahara (✉) · M. Sumi · Y. Ito · S. Sekii · K. Takahashi · K. Inaba · Y. Kuroda · N. Murakami · M. Morota · J. Itami
Division of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: hmayahar@ncc.go.jp

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.

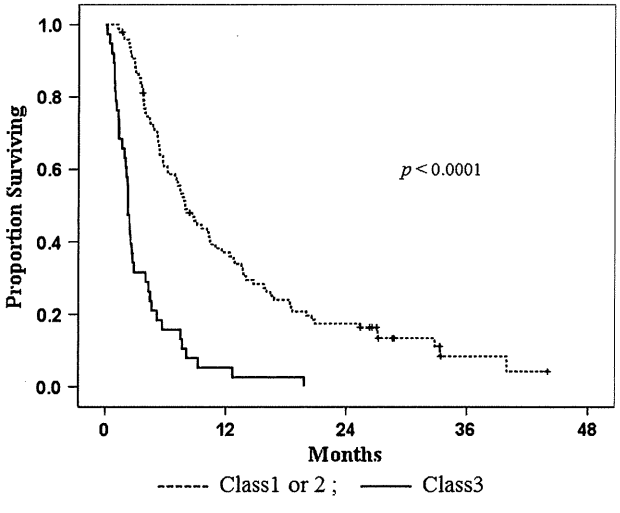

Fig. 1 Kaplan–Meier survival curve for overall survival by RPA criteria

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

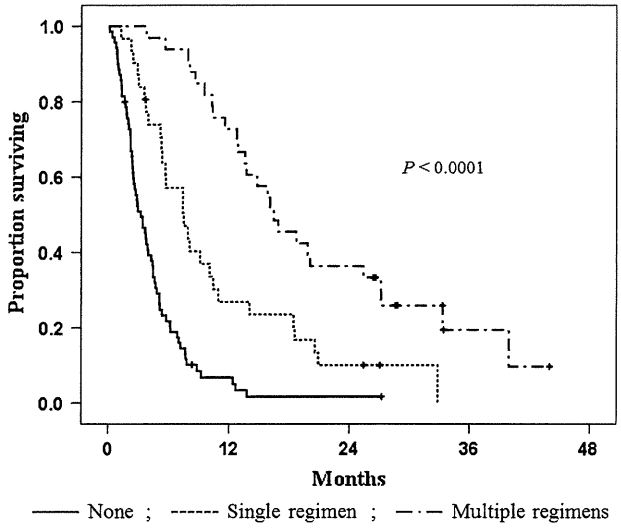

Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

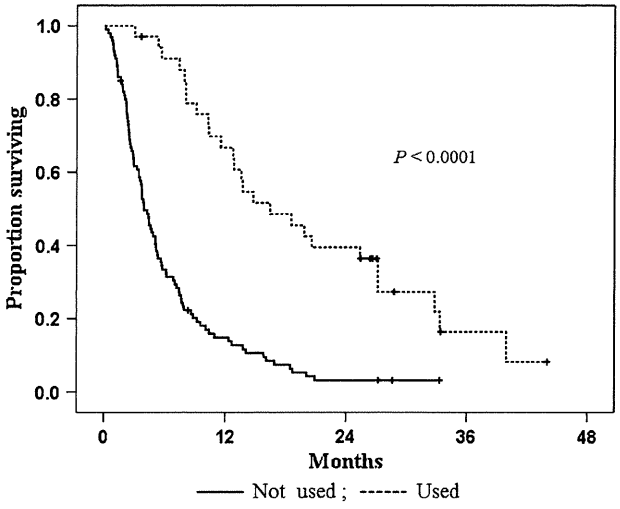

Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

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

International Journal of
Radiation Oncology
biology • physics

www.redjournal.org

Clinical Investigation: Central Nervous System Tumor

^{106}Ruthenium Plaque Therapy (RPT) for Retinoblastoma

Naoya Murakami, MD,* Shigenobu Suzuki, MD,† Yoshinori Ito, MD,* Ryoichi Yoshimura, MD, PhD,‡ Koji Inaba, MD,* Yuki Kuroda, MD,* Madoka Morota, MD, PhD,* Hiroshi Mayahara, MD, PhD,* Mototake Sakudo, MS,* Akihisa Wakita, MS,* Hiroyuki Okamoto, MS,* Minako Sumi, MD, PhD,* Yoshikazu Kagami, MD,* Keiichi Nakagawa, MD, PhD,§ Kuni Ohtomo, MD, PhD,§ and Jun Itami, MD, PhD*

*Departments of *Radiation Oncology and †Ophthalmic Oncology, National Cancer Center Hospital, Tokyo, Japan; ‡Department of Diagnostic Radiology and Oncology, Head and Neck Reconstruction Division, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan; and §Department of Radiology, University of Tokyo Hospital, Tokyo, Japan*

Received Mar 13, 2011, and in revised form Oct 30, 2011. Accepted for publication Nov 1, 2011

Summary

One hundred one ^{106}ruthenium plaque therapies were retrospectively analyzed that were performed in 90 eyes of 85 patients with retinoblastoma between 1998 and 2008.

Purpose: To evaluate the effectiveness of episcleral ^{106}ruthenium plaque therapy (RPT) in the management of retinoblastoma.

Methods and Materials: One hundred one RPTs were retrospectively analyzed that were performed in 90 eyes of 85 patients with retinoblastoma at National Cancer Center Hospital between 1998 and 2008. Each RPT had a corresponding tumor and 101 tumors were considered in the analysis of local control. Median follow-up length was 72.8 months. Median patient age at the RPT was 28 months. Median prescribed doses at reference depth and outer surface of the sclera were 47.4 Gy and 162.3 Gy, respectively.

Results: Local control rate (LCR) and ocular retention rate (ORR) at 2 years were 33.7% and 58.7%, respectively. Unilateral disease, International Classification of Retinoblastoma group C or more advanced at the first presentation or at the time of RPT, vitreous and/or subretinal seeding, tumor size greater than 5 disc diameter (DD), reference depth greater than 5 mm, dose rate at reference depth lower than 0.7 Gy/hour, dose at the reference depth lower than 35 Gy, and (biologically effective dose with an α/β ratio of 10 Gy) at the reference depth lower than 40 Gy_{10} were associated with unfavorable LCR. Two patients died of metastatic disease. Radiation complications included retinal detachment in 12 eyes (13.3%), proliferative retinopathy in 6 (6.7%), rubeosis iris in 2 (2.2%), and posterior subcapsular cataract in 23 (25.6%).

Conclusion: RPT is an effective eye-preserving treatment for retinoblastoma.

Introduction

Retinoblastoma is the most common intraocular malignancy of childhood that arises from neuroepithelial cells of the retina. The reported incidence of retinoblastoma is 1 in 16,653-22,166 live births in Japan (1).

For the management of children with retinoblastoma, mutilating enucleation and external beam radiation therapy (EBRT) are

Reprint requests to: Naoya Murakami, MD, Department of Radiation Oncology, National Cancer Center Hospital, 5-1-1, Tsukiji Chuo-ku, Tokyo 104-0045, Japan. Tel: +[81]-3-3542-2511; Fax: +[81]-3-3545-3567; E-mail: namuraka@ncc.go.jp

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 84, No. 1, pp. 59–65, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.11.002

employed with a decreasing frequency, because of the facial disfigurement and increased incidence of the secondary malignancies after EBRT (2). Chemotherapy has been replacing EBRT as the modality for organ preservation (3, 4). Although chemotherapy can shrink the retinoblastoma lesion, local therapy is indispensable to attain local control. Episcleral plaque brachytherapy has emerged as a treatment option as a focal therapy in the primary or secondary treatment of retinoblastoma (3-5). Low-energy gamma-ray emitting ^{125}I plaque is most used around the world, which is inexpensive and can be customized to fit each tumor shape by arranging seed locations in the episcleral applicator (5-7). In contrast, the pure beta ray-emitting ^{106}ruthenium (^{106}Ru) plaque is used mainly in Europe (8, 9). Although ^{106}Ru plaque is very expensive and cannot treat tumors with a height greater than 5-6 mm because it emits purely beta rays (energy 3.54 MeV) (8-11), the thickness of the applicators is only 1 mm in contrast to 3 mm thickness of the I-125 applicators, which is greatly advantageous when an infant's very small eyes are dealt with. In Japan, National Cancer Center Hospital is the only institution performing episcleral brachytherapy using ^{106}Ru plaque applicators. This retrospective study analyzes the results of ^{106}Ru plaque therapy (RPT) in the management of retinoblastoma.

Methods and Materials

We retrospectively reviewed the clinical records of all patients undergoing RPTs for retinoblastoma between December 1998 and November 2008 in the National Cancer Center Hospital, Japan. One hundred one tumors of 90 eyes in 85 patients were treated by RPT during this period. In 10 eyes, multiple tumors were treated by simultaneous application of the plaques. Local status of the 101 tumors could be evaluated. All tumors were followed at least for 1 year. Patient and tumor characteristics at the initial presentation are listed in Table 1. Tumor stage is based on International Classification of Retinoblastoma (ICRB) (4, 12, 13). Only 31 (30.7%) of the 101 tumors presented with confined diseases of group A or B. Vitreous and subretinal tumor seedings were seen in 41.6% and 35.6%, respectively.

When RPT was the initial treatment, it was considered as the first-line treatment. When RPT followed after local and/or systemic therapies that had successfully reduced the tumor, it was considered as the second-line treatment. RPT was considered as salvage therapy, provided that it was employed to treat a refractory or relapsed tumor after the preceding therapies. In the current series, RPT was employed in only 4 tumors as the first-line therapy. The other 62 tumors underwent RPT as the second-line therapy and 35 as salvage therapy (Table 2). Some too-large tumors, apparently not suitable to be treated by RPT, underwent RPTs, because there was a strong wish of the parents to conserve

Table 1 Characteristics of patients and 101 tumors at the initial presentation

Characteristics	Number
Patients	85
Gender	
Male	52
Female	33
Age at the first brachytherapy	28 mo (range 7-240)
Laterality	
Bilateral	60
Unilateral	25
Family history	
Positive	9
ICRB	
Group A	2 (2.0%)
Group B	29 (28.7%)
Group C	15 (14.9%)
Group D	43 (42.6%)
Group E	7 (6.9%)
Unknown	5 (5.0%)
Tumor with vitreous seeding	42 (41.6%)
Tumor with subretinal seeding	36 (35.6%)
Median tumor size	5 DD (range 0.8-20)

Abbreviations: DD = disc diameter; ICRB = International Classification of Retinoblastoma.

Table 2 Tumor and treatment characteristics at the 101 first RPTs

Tumor characteristics	Number (%)
First-line therapy	4 (4.0)
Second-line therapy	62 (61.4)
Salvage therapy	35 (34.6)
ICRB at brachytherapy	
Group A	9 (8.9)
Group B	29 (28.7)
Group C	20 (19.8)
Group D	37 (36.6)
Group E	6 (5.9)
Tumor with subretinal seeding	28 (27.7)
Tumor with vitreous seeding	42 (41.6)
Response to preceding therapy	
Good	34 (33.7)
Stable	41 (40.6)
Poor	17 (16.8)
Unknown	5 (5.0)
Tumor size (DD)	
Median	5 DD (range 0.5-22)
Brachytherapy dose at outer surface of sclera	
Median	162.3 Gy (range: 61.3-950.0)
Brachytherapy dose at outer surface of sclera (BED_3)	
Median	854.9 Gy_3 (range 101.2-4317.0)
Dose rate at outer surface of sclera	
Median	7.5 Gy/h (range 4.5-10.3)
Brachytherapy reference depth	
Median	5 mm (range 3-9)
Dose rate at reference depth	
Median	0.83 Gy/h (range 0.11-2.22)
Brachytherapy dose at reference depth	
Median	47.4 Gy (range 24.3-86.1)
Brachytherapy dose at reference depth (BED_{10})	
Median	65.6 Gy_{10} (range 27.0-131.3)
Brachytherapy treatment time	
Median	53.3 h (range: 20.5-332.3)

Abbreviations: BED = biological effective dose; DD = disc diameter; ICRB = the International Classification of Retinoblastoma; RPT = ruthenium plaque brachytherapy.

the eyes of their children. For far more advanced disease in which tumor spread toward anterior structures of the eye or infiltrates into the optic disc, and if a massive hemorrhage was developed in retina or vitreous space with a loss of vision, enucleation was employed with or without systemic chemotherapy according to the pathological risk features. Systemic chemotherapy regimen mostly used in this cohort was 3-drug chemotherapy with carboplatin, etoposide, and vincristine.

Tumor response to the preceding therapies was defined as follows. The tumor whose stage attained down-grouping was classified as a good response, up-grouping as a poor response, and no group change as stable.

All episcleral ^{106}Ru plaque applicators (BEBIG Isotopen und Medizintechnik GmbH, Berlin, Germany) were inserted under general anesthesia. Before the operation, tumor location and height were assessed by slit lamp examinations with or without ultrasound and an appropriate plaque was selected. The plaques are hemispherically shaped with radii of 12 and 14 mm. CIA and CIB are used to treat anteriorly located tumor because they are semicircularly shaped concave in order to avoid cornea. COC are used to treat the tumor located in the posterior pole with a notch to avoid optic disc. CCA and CCB are round shaped and used to treat tumors which are away from cornea or optic disc. The diameters of A and B are 15.5 mm and 20 mm, respectively. To insert the plaques, extraocular muscles were separated temporarily. The selected plaques were sutured through the plaque eyelets to the sclera surface. The plaques were removed also under general anesthesia after the planned duration of radiation. The duration of radiation was calculated to administer prescription dose of 40 Gy to the reference depth. The reference depth was the height of tumor plus sclera thickness (1 mm) with a safety margin of 1 mm. Lateral tumor margin was set to 2-3 mm (10). Before July 2005, reliable ultrasound was not available to determine tumor height; therefore, the slit lamp was used to estimate it using its focus. Therefore before July 2005, only tumor width expressed by disc diameter (DD) and reference depths diagnosed approximately by slit lamp were available in the medical records. And for tumors with vitreous seeding, reference depth was set to 5-6 mm, which was regarded as the limit of the range of RPT. Hence, tumors with vitreous seeding without description of reference depth in medical record could be recalculated as having a reference depth of 5-6 mm. Before September 2006, the reference depth was 5 mm and thereafter it was set to 6 mm because of the dose tables provided by the manufacturer. Since May 2002, BEBIG has delivered its ^{106}Ru eye plaques with new protocols of radioactivity measurements in accordance with the National Institute of Standards and Technology calibration system. Therefore recalculations were performed for this study to correct the prescribed dose before the introduction of the new calibration system by using the conversion factor table provided by BEBIG (14). Because most of the conversion factors, which differ by applicator type and reference depth, were greater than 1.0, median dose at the reference depth became greater than 40 Gy after the recalculation (Table 2).

Because the biological effect of RPT could differ by dose rate and combined effect with EBRT must be considered, biologically effective dose (BED) was calculated according to the method of Dale (15) and is given by

$$\mathrm{BED} = \text{Total dose} \times 1 + \frac{2R}{\mu}\left(\frac{\beta}{\alpha}\right)\{1 - 1/\mu T[1 - \exp(-\mu T)]\}$$

where R indicates dose rate, T the treatment time, and μ the repair rate constant of sublethal damage. The value of μ was assumed as 0.46 hour^{-1} (corresponding to repair half time of 1.5 hours) (15). The α/β values used in this analysis were α/β = 10 Gy for tumor control and α/β = 3 Gy for late normal tissue morbidities. In 85 of 101 RPTs, the reference depth and prescribed dose could be obtained and BED_{10} (BED with an α/β ratio of 10 Gy) could be calculated. Because the outer surface of the sclera directly touches the plaque applicator (depth 0 mm), dose and BED_3 (BED with an α/β ratio of 3 Gy) of the outer surface of sclera could be calculated for 97 procedures whose applicator type and treatment time were known. For deriving total BED_3 of outer surface of sclera, BED_3 of EBRT, if any, before and after the RPT was added. In 16 eyes in which part of retina had overlapping multiple RPTs, BED_3 of outer surface of sclera of each RPT was added.

Ophthalmologic follow-up was performed with examinations under anesthesia every 1-2 months after the therapy until tumor control was achieved. Thereafter, examinations were performed every 2-6 months as needed.

The probabilities of local control rate (LCR), ocular retention rate (ORR), and overall survival (OS) were calculated using the Kaplan-Meyer method (16). For LCR, 101 tumors treated by 101 RPTs were taken into account. Local control was assessed by retinal diagram before and after the RPTs. Tumor persistent or regrowing within margins of the retina covered by the plaque applicator was considered as local failure. For the estimate of ORR, enucleation from disease progression or treatment-related complications and death from any causes were scored as an event and 90 eyes were subjects of the analysis. ORR was calculated from date of the last RPT to date of the events or to the last follow-up. The relationships between clinical and treatment variables and LCR were analyzed by the univariate and multivariate analyses. A P value of $<.05$ was considered statistically significant. The continuous variables were dichotomized to give the lowest P values in the log-rank test. The variables with P values $<.05$ were further analyzed in multivariate analysis by Cox proportional hazards test.

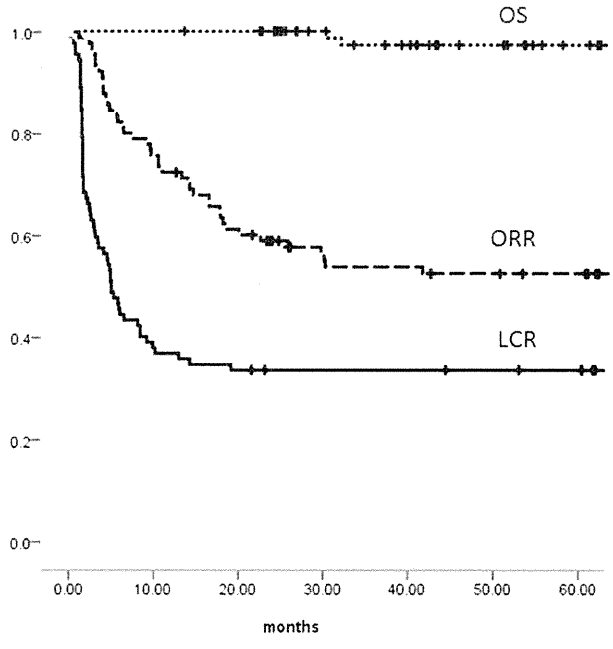

Fig. 1. Kaplan-Meyer curves of local control rate (LCR), ocular retention rate (ORR), and overall survival (OS).

Results

Tumor and treatment characteristics at the 101 RPTs were summarized in Table 2. Median patient follow-up length was 72.8 months (range 12.2-130). LCR of the 101 tumors treated by the 101 RPTs was 33.7% in 2 years with 31 tumors controlled (Fig. 1). All local failures were seen within 24 months after RPTs. The locally failed tumors were managed by various modalities including repeated RPT. Forty-two eyes (46.7%) were enucleated during the follow-up period and estimated 2 and 4 years ORR rates are 58.7% and 52.2%, respectively (Fig. 1).

Univariate analysis revealed clinical and treatment factors related with LCR (Table 3). Unilateral disease, ICRB group C or more at the presentation or at the time of RPT and vitreous seeding/subretinal seedings at the time of RPT, tumor size greater than 5 DD, dose at the reference depth lower than 35 Gy, BED_{10} for the reference depth lower than 40 Gy_{10}, reference depth greater than 5 mm, and dose rate at reference depth lower than 0.7 Gy/hour were associated with unfavorable LCR. Multivariate analysis revealed that ICRB group C or more at the initial presentation or at the time of RPT, and BED_{10} for the reference depth tumor lower than 40 Gy_{10} were statistically significant predictive factors for unfavorable LCR (Table 3). The tumors were classified into 2 groups according to the ICRB and BED_{10} for reference depth (BED_{10}). Group 1 was defined as ICRB A/B both at initial presentation and at RPT and BED_{10} for the reference depth $\geqq 40$ Gy_{10}. All other tumors were classified into group 2. There were 17 tumors in group 1 and 71 in group 2. Sixteen RPTs and 5 tumors lack the information of reference depth and initial ICRB, respectively. But if the tumor ICRB was not A/B at the time of RPT, it could be classified as group 2 even if neither reference depth nor initial ICRB were unknown. Therefore total number included in this grouping was above 85 but below 101. Two-year LCR were 64.7% and 25.4% in group 1 and group 2, respectively, with a statistical significant difference (Fig. 2). During the follow-up period, 2 patients died of brain metastasis with 3-year OS rate of 97.3% (Fig. 1).

As for morbidities, in 1 case, sclera ruptured during the operation, which required systemic chemotherapy but resulted in chemotherapy-refractory relapse and eventual enucleation. Twelve eyes (13.3%) developed retinal detachment, 6 eyes (6.7%) proliferative retinopathy, and 2 eyes (2.2%) rubeosis with abnormal neovascularization of iris. Both eyes with rubeosis eventually were enucleated because of glaucoma or disease progression. Twenty-three (25.6%) of 90 eyes developed posterior subcapsular cataract and 6 eyes required surgery for cataract. Median interval to cataract development after RPT was 35.0 months (range 0-87.33). Posterior subcapsular cataract development related only with whether or not EBRT was performed during the entire clinical course with cataract occurring in 28.1% of the patients undergoing EBRT at 3 years and 2.9% of those without EBRT ($P=.033$) (Fig. 3a). Thirty-four eyes (37.8%) had a retinal and vitreous hemorrhage after RPT. The incidence of retinal detachment, proliferative retinopathy, and rubeosis showed a correlation with radiation dose of the outer surface of sclera. $BED_3 \geqq 1200$ Gy_3 of the outer surface of sclera was significantly associated with a higher incidence either of retinal detachment, proliferative retinopathy or rubeosis ($P=.017$) (Fig. 3b).

There were 2 enucleations without tumor progression—1 of which developed after circulatory collapse of the retina after repeated selective ophthalmic arterial infusions (17) and transpupillary thermotherapy (18) for posterior pole of the retina. The other developed rubeosis iris caused by RPT as mentioned previously.

Two patients had a second malignancy after RPT. Both patients had hereditary retinoblastoma and 1 had family history of retinoblastoma. Both patients received EBRT and 1 had also received chemotherapy. One patient developed rhabdomyosarcoma in the nasal cavity within EBRT radiation field 27 months after the EBRT and 6 months after the RPT. The other had Ewing sarcoma in right mandible outside of EBRT fields 89 months after the EBRT and 76 months after RPT.

Discussion

In this study, we reported treatment results for RPTs for 101 retinoblastomas in 90 eyes of 85 patients in 10 years.

LCR of EBRT was reported to be 31%-64% (19, 20). Although small tumors could be controlled by 40-46 Gy of conventional fractionated EBRT, the control rate of greater tumors was unsatisfactory. Recently, 2 retrospective studies of RPT for retinoblastoma have been published (8, 9). Schueler et al (8) achieved excellent results of 92.9% LCR and eyes could be preserved in 88.6%. Abouzeid et al (9) also showed good results of 59%-73% eye preservation rate. Another radionuclide of ^{125}I also attained an excellent LCR ranging between 83% and 95% (6, 7). The prescribed dose of ^{125}I plaque brachytherapy was 40 Gy (6, 7) but those of RPT has not yet been standardized. In the study of Schueler et al (8) using the National Institute of Standards and Technology dosimetry standard, the dose at the apex ranged from 53-233 Gy and a mean dose extended up to 138 Gy with an estimated accuracy of no better than $\pm 35\%$. They concluded that the recommended dose should be 88 Gy at the tumor apex, although they mentioned the possibility of dose de-escalation (8). On the other hand, Abouzeid et al (9) prescribed 50 Gy at the tumor apex and found that the apical dose was not a predictive factor of local failure. They concluded that favorable tumor control could be achieved with a median dose at the tumor apex of 51.7 Gy. In this study, recalculated median dose at the tumor apex was 47.4 Gy (range 24.3-86.1 Gy) and comparable to that of Abouzeid et al (9). However, 2-year LCR of the current study was 33.7% and inferior to the other studies of RPT. The unfavorable LCR can be explained by the facts that 62.3% of the patients belonged to ICRB group C or more with unfavorable factors of vitreous seeding or subretinal seedings in the current study. In contrast, other studies included only the patients with tumors up to ICRB group C with a limited vitreous seedings. However, it has to be emphasized that as shown in Table 3, even with the presence of vitreous seedings about 20% of tumors could be controlled by RPT. Although tumor control rate of RPT with unfavorable factors were dismal, progressed tumors could be ultimately salvaged by enucleation without risking survival; therefore, it is meaningful to try to treat advanced tumors with a conservative approach including RPT especially for the patients whose contralateral eye had already been enucleated. As shown in Fig. 2, LCR for tumors without unfavorable factors were comparable to the other series (8, 9).

Factors that influenced LCR were disease laterality, ICRB, vitreous/subretinal seeding, tumor size, reference depth, dose, and dose rate at reference depth. It was in accordance with other reports that pointed out that vitreous seeding, subretinal seeding, and dose at the tumor apex were prognostic factors of local

Table 3 Univariate and multivariate analysis of potential predictive factors influencing LCR*

Factors	LCR					
	2-y	*P* value in uni	*P* value in multi	Hazard ratio	95% CI	
Gender						
Male	36.2	.462				
Female	29.4					
Laterality						
Bilateral	38.9	.017*	.133			
Unilateral	15.0					
ICRB at initial presentation						
Group A/B	53.3	.022*	.001*	10.323	2.737	38.932
Group C/D/E	24.1					
ICRB at brachytherapy						
Group A/B	55.9	<.001*	.027*	0.441	0.213	0.911
Group C/D/E	20.7					
Applicator type						
CIA/CCA	42.1	.141				
CIB/CCB	26.0					
Prior EBRT						
Yes	32.0	.707				
No	35.7					
Treatment type						
First-line/second-line	27.1	.152				
Salvage	45.5					
Vitreous seeding at brachytherapy						
Yes	18.9	.016*	.892			
No	43.6					
Subretinal seeding at brachytherapy						
Yes	19.2	.04*	.785			
No	39.4					
Response to preceding therapy						
Good	43.8	.116				
Stable/poor	28.6					
Tumor size at brachytherapy (DD)						
<5 DD	52.5	.001*	.252			
≧5 DD	19.6					
Dose rate at outer surface of sclera						
<3 Gy/h	29.5	.271				
≧3 Gy/h	36.4					
Reference depth						
<5 mm	47.1	.01*	.295			
≧5 mm	21.4					
Dose rate at reference depth						
<0.7 Gy/h	17.9	.011*	.105			
≧0.7 Gy/h	40.4					
Dose at reference depth (Gy)						
<35 Gy	11.8	.008*	.448			
≧35 Gy	37.9					
Dose at reference depth (BED_{10})						
<40 Gy_{10}	0.0	.001*	.034*	2.237	1.063	4.710
≧40 Gy_{10}	36.9					
Treatment time						
<53 h	37.8	.195				
≧53 h	29.8					

Abbreviations: BED = biological effective dose; CI = confidence interval; DD = disc diameter; EBRT = external beam radiation therapy; ICRB = the International Classification of Retinoblastoma; LCR = local control rate; multi = multivariate analysis; uni = univariate analysis.

* $P<.05$.

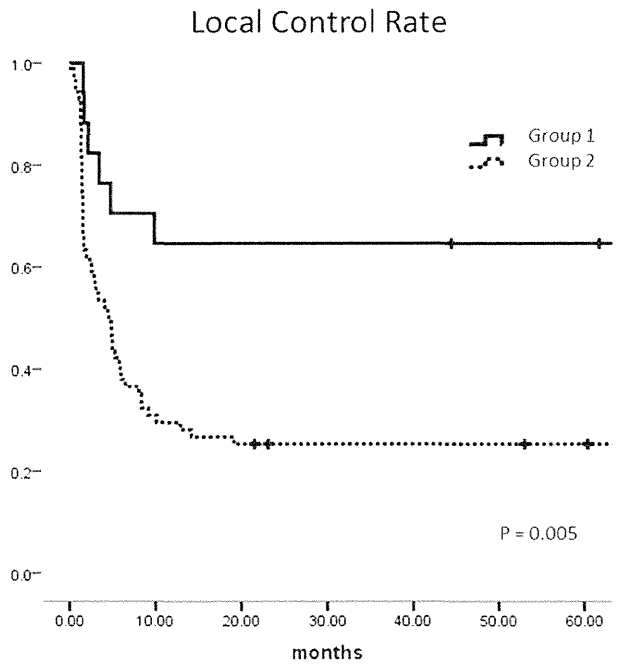

Fig. 2. Local control rate (LCR) according to the group classification by the International Classification of Retinoblastoma and biological effective dose (BED) with $\alpha/\beta = 10$ Gy of the reference depth (for details refer to the text).

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.

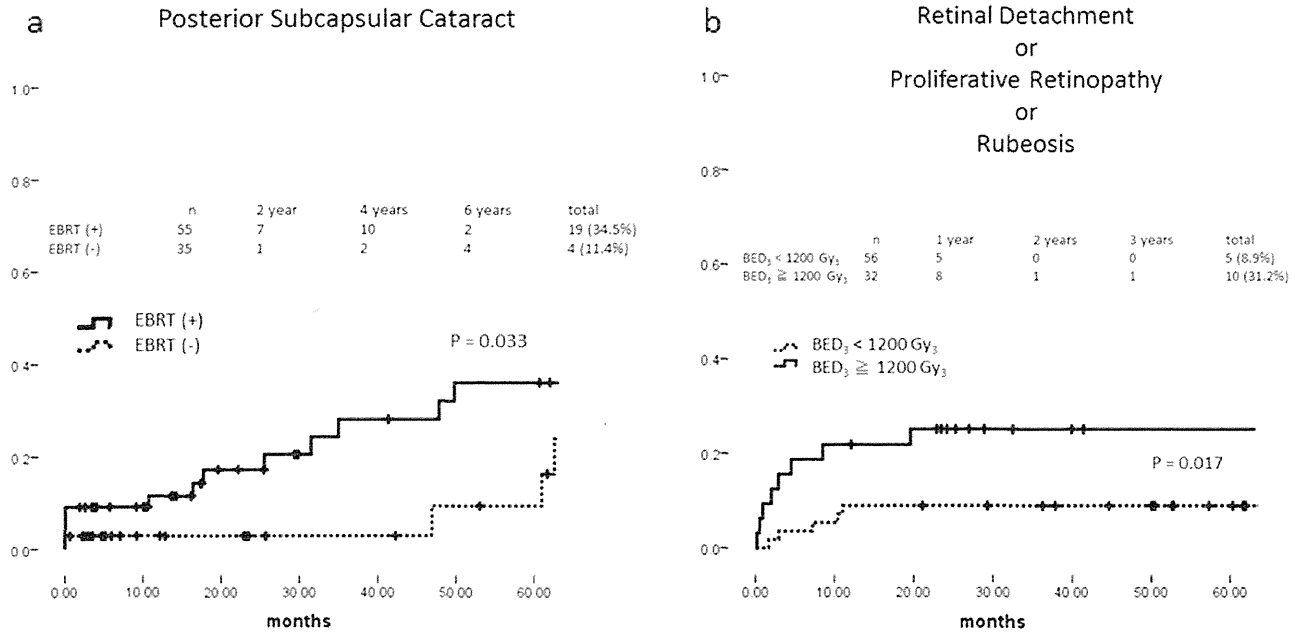

Fig. 3. (a) Cumulative incidence of posterior subcapsular cataract according to whether external beam radiation therapy (EBRT) was administered. (b) Cumulative incidence of retinal detachment, proliferative retinopathy and rubeosis stratified by biological effective dose (BED) with $\alpha/\beta = 3$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

Mayahara et al. BMC Cancer 2012, 12:609
http://www.biomedcentral.com/1471-2407/12/609

BMC Cancer

RESEARCH ARTICLE Open Access

Salvage chemoradiotherapy after primary chemotherapy for locally advanced pancreatic cancer: a single-institution retrospective analysis

Hiroshi Mayahara[1*], Yoshinori Ito[1], Chigusa Morizane[2], Hideki Ueno[2], Takuji Okusaka[2], Shunsuke Kondo[2], Naoya Murakami[1], Madoka Morota[1], Minako Sumi[1] and Jun Itami[1]

Abstract

Background: There is no consensus on the indication for salvage chemoradiotherapy (CRT) after failure of primary chemotherapy for locally advanced pancreatic cancer (LAPC). Here we report on the retrospective analysis of patients who received salvage CRT after primary chemotherapy for LAPC. The primary objective of this study was to evaluate the efficacy and safety of salvage CRT after primary chemotherapy for LAPC.

Methods: Thirty patients who underwent salvage CRT, after the failure of primary chemotherapy for LAPC, were retrospectively enrolled from 2004 to 2011 at the authors' institution. All the patients had histologically confirmed pancreatic adenocarcinoma.

Results: Primary chemotherapy was continued until progression or emergence of unacceptable toxicity. Eventually, 26 patients (87%) discontinued primary chemotherapy because of local tumor progression, whereas four patients (13%) discontinued chemotherapy because of interstitial pneumonitis caused by gemcitabine. After a median period of 7.9 months from starting chemotherapy, 30 patients underwent salvage CRT combined with either S-1 or 5-FU. Toxicities were generally mild and self-limiting. Median survival time (MST) from the start of salvage CRT was 8.8 months. The 6 month, 1-year and 2-year survival rates from the start of CRT were 77%, 33% and 26%, respectively. Multivariate analysis revealed that a lower pre-CRT serum CA 19–9 level (≤ 1000 U/ml; $p = 0.009$) and a single regimen of primary chemotherapy ($p = 0.004$) were independent prognostic factors for survival after salvage CRT. The MST for the entire patient population from the start of primary chemotherapy was 17.8 months, with 2- and 3-year overall survival rates of 39% and 22%, respectively.

Conclusions: CRT had moderate anti-tumor activity and an acceptable toxicity profile in patients with LAPC, even after failure of gemcitabine-based primary chemotherapy. If there are any signs of failure of primary chemotherapy without distant metastasis, salvage CRT could be a treatment of choice as a second-line therapy. Patients with relatively low serum CA19-9 levels after primary chemotherapy may achieve higher survival rates after salvage CRT. The strategy of using chemotherapy alone as a primary treatment for LAPC, followed-by CRT with salvage intent should be further investigated in prospective clinical trials.

Trial registration: 2011–136

Keywords: Pancreatic cancer, Locally advanced pancreatic cancer, Induction chemotherapy, Salvage therapy, Chemoradiotherapy, Prognostic factor

* Correspondence: hmayahar@ncc.go.jp
[1]Division of Radiation Oncology, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
Full list of author information is available at the end of the article

Background

The prognosis of pancreatic cancer remains dismal. The 5-year overall survival of patients with pancreatic cancer is < 5%. In Japan, about 27,000 patients are estimated to have pancreatic cancer, and almost the same numbers of deaths annually are attributable to this cancer. Although surgical resection offers the opportunity for cure, less than 20% of patients are diagnosed with pancreatic cancer at an early resectable stage. At initial diagnosis, ≥ 80% of patients with pancreatic cancer have locally advanced or metastatic disease.

Locally advanced pancreatic cancer (LAPC) is defined as surgically unresectable disease without detectable metastases. Historically, concurrent chemoradiotherapy (CRT) with 5-fluorouracil (5-FU) has been the standard treatment since it offers survival benefit when compared with best supportive care [1], radiotherapy alone [2] and chemotherapy with 5-FU alone [3]. Recently, 5-FU has been replaced by oral fluorouracil analogues such as S-1 in East Asia [4] and capecitabine in Western countries. When taken orally these drugs are much more convenient to administer than 5-FU, which usually requires protracted venous infusion. S-1 is an oral agent that contains tegafur, gimeracil and oteracil in a molar ratio of 1:0.4:1 [5]. S-1 is reported to be at least equivalent to or even more active than 5-FU when combined with radiotherapy for LAPC [6-8].

The standard method used for the detection of metastases from pancreatic cancer is computed tomography (CT). Several investigators have reported that intraoperative staging can reveal occult peritoneal dissemination in 6–37% of the patients with CT-diagnosed LAPC [9-11]. Analysis of patterns of failure after definitive CRT for LAPC has shown that more than half of the patient will have distant metastasis at the first time of failure [12]. Because radiotherapy involving the primary site offers little benefit to patients with occult distant metastasis, increasingly more oncologists believe that chemotherapy would be a preferable initial therapeutic approach for patients with LAPC [13]. During initial chemotherapy, rapidly progressive chemotherapy-resistant distant metastases will present within a few months. After 3–6 months of induction chemotherapy, LAPC that remained local would be an indication for consolidative or salvage CRT. However, there is no consensus on the indications for additional CRT following primary chemotherapy for LAPC, as well as the optimal time period for the administration of primary chemotherapy. Here we report on the results of a retrospective analysis of this strategy, including primary chemotherapy and salvage CRT, for patients with LAPC. The primary objective of our study was to evaluate the efficacy and safety associated with salvage CRT following primary chemotherapy for LAPC. The secondary objective was to elucidate the prognostic factors that affect survival after CRT.

Methods

Patients

Between October 2004 and August 2011, 98 patients who were diagnosed as having LAPC underwent CRT at the author's institution. Sixty-seven patients were excluded from the study because they had received definitive CRT as the first therapeutic modality. One patient was excluded because he had undergone consolidative CRT after primary chemotherapy. The remaining 30 patients underwent salvage CRT after the failure of primary management with chemotherapy alone. All of the patients had histologically confirmed pancreatic adenocarcinoma. They were subjected to intensive analysis. The clinical data from these patients were entered into the database in September 2012. Our institutional review board (Institutional Ethical Review Board of the National Cancer Center) approved this study.

Treatment strategy

At the first diagnosis, multidetector row CT involving the chest and abdomen were performed for the assessment of the local extension of the primary tumor, and for excluding distant metastases. CT based criteria regarding tumor unresectability included encasement or occlusion of the celiac trunk, common hepatic artery, superior mesenteric artery or aorta. All of the patients with obstructive jaundice underwent biliary drainage prior to treatment.

Until December 2007, primary management with CRT combined with 5-FU was the principal treatment of choice for patients with LAPC [14]. Since 2006, several prospective phase II clinical trials involving patients with LAPC were conducted at the authors' institution [4,8,15,16]. CRT combined with S-1 has been regarded as an optional treatment of choice in Japan [7,8]. A multi-institutional phase II trial with gemcitabine (GEM) alone for LAPC yielded promising results with a low toxicity profile [15]. Additionally, our retrospective study revealed that there was no difference in the survival rates of the patients who received CRT or GEM-based chemotherapy alone as a primary therapy for LAPC [17]. Although direct comparison between primary CRT and primary chemotherapy alone has not yet been made in a prospective clinical trial, GEM monotherapy has been regarded as the first treatment of choice in clinical practice since January 2008.

Currently, all of the patients with LAPC are informed of two first-line treatments of choice, namely GEM monotherapy and CRT combined with S-1. If a patient with LAPC has an indication suitable for participation in a clinical trial, the patient will be given additional information about that trial. The patients themselves selected

one of these treatments. The current study included patients who initially entered prospective clinical trials involving primary chemotherapy and who subsequently received CRT as a salvage treatment.

Eligibility criteria for salvage CRT

Indications for salvage CRT following chemotherapy included the following: no distant metastasis; no prior radiotherapy of the upper abdomen; Karnofsky performance status (KPS) ≥ 70; adequate hematologic function (leucocyte count ≥ 3,500/μL and platelet count ≥ 100,000/μL); and hepatic function (bilirubin ≤ 2.0 mg/dL, aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 150 U/L) and renal function (serum creatinine < 1.5 mg/ml). The exclusion criteria were the presence of: an active gastroduodenal ulcer; watery diarrhea; ascites; active infection; or mental disorder. Written informed consent was obtained from each patient before starting each treatment.

First-line chemotherapy

Primary chemotherapy was continued until disease progression, the emergence of unacceptable toxicity or a patient's refusal of treatment. First-line chemotherapy mostly consisted of GEM alone [Table 1]. GEM was administered intravenously at a dose of 1,000 mg/m^2 over 30 min on days 1, 8 and 15, and was repeated every 4 weeks as one course. Patients with grade 3–4 hematological toxicities underwent dose reduction to 800 mg/m^2 or skipped at least one administration of GEM. Prophylactic granulocyte-colony stimulating factor support was not used.

Chemoradiotherapy

A planning CT was required to determine target volumes on the three-dimensional treatment planning system. A total dose of 50.4 Gy was delivered in 28 fractions using a linear accelerator of energy ≥ 10 MV. The clinical target volume (CTV) included the gross primary tumor and metastatic lymph nodes only. Elective nodal irradiation was not applied in this cohort. The planning target volume (PTV) was defined as the CTV plus 1 cm in all directions and a 1.5-2.0 cm margin in the craniocaudal direction to account for respiratory organ motion. The dose was prescribed to the center of the PTV. Typically, a 4 or 5 field technique was used to minimize high-dose radiation exposure in the surrounding organs.

Radiotherapy was delivered concomitantly with either 5-FU or S-1. Protracted 5-FU infusion was mainly administered until July 2008, and oral S-1 was given thereafter. Concomitant 5-FU was administered as a protracted venous infusion at a dose of 200 mg/m^2/day from days 1–5 each week during the course of radiotherapy [14]. S-1 was administered orally twice daily after breakfast and dinner on weekdays (Monday through Friday) during irradiation. The standard dose of S-1 with concurrent radiotherapy for LAPC was 80 mg/m^2/day [4]. Maintenance chemotherapy with S-1 was indicated for patients without obvious clinical progression during CRT, with sufficient performance status and organ function.

Table 1 Patient characteristics (n = 30)

Characteristic	No. of patients	% patients
Age (years)		
Median (range)	65 (42–81)	
Gender		
Male	16	53
Female	14	47
Karnofsky performance status		
90-100	22	73
70-80	8	27
0-60	0	0
Tumor location		
Head	15	50
Body and Tail	15	50
Nodal status		
Negative	18	60
Positive	12	40
Baseline tumor diameter (cm)		
Median (range)	4.5 (2.1-7.8)	
Baseline serum CA19-9 level (U/ml)		
Median (range)	872 (0–35490)	
≥ 1,000	14	47
100-1,000	11	37
< 100	5	17
Pre-CRT tumor diameter (cm)		
Median (Range)	4.1 (1.9-8.4)	
Pre-CRT serum CA19-9 Level (U/ml)		
Median	631 (0–50440)	
≥ 1,000	11	37
100-1,000	12	40
< 100	7	23
Regimens of primary chemotherapy		
Gemcitabine alone	24	80
Gemcitabine + α	6	20

CRT chemoradiotherapy.

Response and toxicity assessment

All of the medical charts of the eligible patients were reviewed. Information on potential prognostic factors was collected and included: age; gender; performance status; tumor diameter; change in serum carbohydrate