registered clinical trials of RFA for liver tumors are listed in Table 1 [4, 5]. Twenty-four out of 32 are randomized controlled trials (RCTs); 14 RCTs evaluated RFA by comparing it with other treatment modalities such as surgery, and 10 RCTs evaluated additional treatments such as trans-catheter arterial chemo-embolization (TACE) combined with RFA. Most of the RCTs set challenging endpoints such as overall survival (OS) and/or progression-free survival (PFS). Clearly, most clinical trials in this field try to expand the indications of RFA or to replace other treatment modalities such as surgical resection. Since large numbers of patient enrollments are critical for such RCTs, most of clinical trials in this field have been carried out in China.

The registered clinical trials of RFA for lung and renal tumors are listed in Table 2 [4, 5]. The number of trials is much smaller than for liver tumors, because RFA has not yet been established as a standard treatment in these fields. Fortunately, phase I trials for both lung and renal tumors have been carried out in Japan. If phase II trials can provide promising results, it may be possible to move to phase III trials to evaluate RFA as the standard treatment modality. It is well known that surgical resection of renal tumors in patients with poor renal function is risky, and therefore RFA may replace surgical resection as the standard treatment for such selected patients. On the other hand, percutaneous cryoablation for renal tumors is available in practice at present. The indications of RFA should also be considered with that of cryoablation in the treatment for renal tumors. On the other hand, surgical treatments including thoracoscopic resection are firmly established as the standard treatment modality for small lung tumors. These surgical procedures can be performed with minimal invasion, and patients with poor pulmonary function not indicated for general anesthesia are also not good candidates for RFA. Therefore, establishing RFA as the standard treatment for lung tumors seems much more difficult than for renal tumor.

The main registered clinical trials of interventional oncology for palliative care are listed in Table 3 [4, 5]. In spite of advantages such as minimal invasiveness and short procedure time, there are few clinical trials of interventional oncology. One of the reasons may be the difficulty of performing clinical trials in this field. Despite the difficulty of measuring quality of life (QOL) of patients in the palliative stage, most trials use it as a primary endpoint. Japan is the most active country in this field, performing 12 out of 15 clinical trials. The main activity in this field is medical treatment such as administration of opioids, hence it is very challenging to establish RCTs of interventional oncology as a standard treatment.

There are many clinical trials of trans-catheter arterial treatments such as trans-catheter arterial chemo-emboli-

Table 1 Registered clinical trials of radiofrequency ablation (RFA) for liver tumors (from clinicaltrials.gov and UMIN-CTR) ($N = 32$)

Country		Disease		No. of patients		Study design		Details of RCTs		Primary endpoint of RCTs	
China	16	HCC	28	≤50	6	RCT	24	RFA vs. others	14	OS	14
USA	6	Metastasis	1	>50, ≤100	7	Phase II	3	RFA ± others	10	PFS	2
EU	4	HCC/Metastasis	1	<100, ≤200	13	Phase I, I/II	3			Others	8
Asia	3	Any neoplasm	1	<200	6	Observational	2				
Japan	2	Others	1								
Other	1										

Table 2 Registered clinical trials of RFA for lung and renal tumors (from clinicaltrials.gov and UMIN-CTR)

Country		Disease		No. of patients		Study design		Details		Primary endpoint	
USA	3	Lung tumor	7	≤50	5	Phase I, I/II	1	RFA alone	4	AE	2
Japan	2			>50, ≤100	2	Phase II	3	RFA c/w others	3	CR rate	2
China	1					Observational	3			PFS	2
Other	1									Other	1
USA	1	Renal tumor	3	≤50	2	Phase I/II	1	RFA alone	2	AE	1
Japan	1			>100	1	Phase II	1	RFA c/w others	1	CR rate	1
China	1					Observational	1			PFS	1

c/w comparing with, *AE* adverse events, *CR* complete response

Table 3 Registered clinical trials of interventional oncology for palliative care (from clinicaltrials.gov and UMIN-CTR)

Disease		Country		No. of patients		Study design		Intervention	Primary endpoint
Vena cava syndrome	3	Japan	2	≤50	3	Phase I/II	1	Stent	Safety
		Canada	1			RCT	1		QOL
						Observational	1		QOL
Persistent ascites	2	Japan	2	≤50	2	Phase I/II	1	Perito-neovenous shunt	Safety
						RCT	1		QOL
Colon stenosis		Japan	2	≤50	2	Phase II	1	Stent	QOL
		Company	1	>50, ≤100	1	RCT	1		QOL
						Observational	1		QOL
Broncheal stenosis		Canada	1	>50, ≤100	1	RCT	1	Stent	Patency
Painful bone tumor		Japan	2	≤50	2	Phase I/II	1	Cement injection	Safety
						RCT	1		QOL
Painful bone tumor		Japan	1	≤50	1	Phase I/II	1	RFA	Safety
Painful pelvic tumor		Japan	1	≤50	1	Phase I/II	1	RFA	Safety
Upper gastrointestinal obstruction		Japan	2	≤50	2	Phase II	1	PTEG	QOL
						RCT	1		QOL

PTEG percutaneous trans-esophageal gastric tubing

zation (TACE) and hepatic arterial infusion chemotherapy (HAIC) for liver tumors. TACE is established as the standard treatment modality for intermediate stage HCC, and the most important clinical question is the efficacy of the combination of TACE with molecular target agents such as solafenib. Trials to evaluate the superiority of such combinations require approximately 1000 cases, and therefore are carried out as pharmaceutical company oriented international RCTs with TACE ± molecular target agent design. However, details of TACE including selection of anti-cancer agents, selection of embolization materials, catheterization technique, TACE interval and imaging modalities employed vary in each trial. TACE is the standard treatment, but the details of TACE have not yet been standardized. Additionally, in most of these RCTs, overall survival (OS) is used for the primary endpoint. However, intermediate-stage HCC patients in whom TACE fails have the chance to receive other molecular target agents when the protocol is off, and such post-protocol treatments may influence their OS. Therefore, it is not easy to determine the true impact of TACE with molecular target agents on the prolongation of OS in this group of patients.

Issues of clinical trials in interventional oncology

There are several common problems when performing clinical trials in interventional oncology. It is important to understand these problems prior to making the appropriate evidence-based clinical decision in practice based on the results of clinical trials.

Level of skills

The essence of the treatment modality of interventional oncology is technical skill, although it may also sometimes depend upon various kinds of devices and drugs. Therefore, the technical skill directly influences the treatment outcome, which means that outcomes can vary in accordance with the technical skill of each study group even in the same procedure. Level of techniques can be seen in various fields of interventional oncology. For example, in clinical trials of HAIC for unresectable liver metastases from colorectal cancer, Kerr et al. [6] reported they could not start HAIC after port-catheter placement in 39 % of patients, while Tanaka et al. [7] reported that the success rate was 97 %. Additionally, there is a "learning curve" in technical procedures through experience. Even though the same physician performs the same procedure, the outcomes may well vary depending upon the number of cases experienced.

Variety of equipments and devices

The efficiency of equipment for image guidance such as ultrasonography, angiography and computed tomography greatly influences the outcomes of procedures in interventional oncology. However, this is quite varied in different countries and regions due to their economic situation. For example, CT-angio systems, which were developed in Japan and greatly influence the outcome of TACE for hepatocellular carcinoma [8], are routinely used in Japan, but are available in only a few institutions in Western countries. A micro-catheter, which is an indispensable

device for accurate super-selective TACE, is commonly used in some countries including Japan, but not used in other countries. On the other hand, microspheres for vascular embolization are commercially available in many countries, but have not yet been approved in Japan. In summary, the equipment and devices for interventional oncology are quite varied in different countries and regions.

Lack of methodology in clinical trial

The methodology of clinical trials in oncology has been developed to focus mainly on the development of anti-cancer agents. While the key concepts of clinical trials are the same in the field of interventional oncology, the design of clinical trials to evaluate safety in medical oncology cannot be adapted to interventional oncology. Commonly, in a phase I study to evaluate the safety of a newly developed agent, step-by-step dose escalation is used. However, the concept of dose escalation cannot be use in interventional oncology, because the procedure itself is being evaluated. Many new procedures have been developed in interventional oncology, but a clinical trial methodology to evaluate safety, the most important first step in introducing a newly developed procedure, is lacking and has not been established.

Difficulty of setting appropriate endpoints

Because all anti-tumor procedures in interventional oncology are loco-regional treatments, it is not easy to show a significant survival benefit such as OS. Of course, OS is one of the hardest endpoints, and loco-regional treatment should also show an advantage using such a hard endpoint. However, OS is sometimes influenced by additional treatments, and the advantages of loco-regional treatments on OS are minimized with additional factors. On the other hand, the result frequently observed when loco-regional treatment is effective is the improvement of symptoms, which is very important especially in palliative care. However, the evaluation of symptom improvement and quality of life is still difficult to use as a reliable hard endpoint. Therefore, most clinical trials of interventional oncology in palliative care must be performed with such unreliable endpoints.

Difficulty of employing blinded design

As with surgical treatments, interventional procedures cannot be performed without the physician's awareness. Therefore, it is usually impossible to use a blinded design for RCTs such as with or without procedures. Only when a part of the procedure is randomized, such as active drug injection versus placebo drug injection, can a double-blind design be applied for RCTs.

Table 4 Clinical trials of Japan Interventional Radiology in Oncology Study Group (JIVROSG)

JIVROSG-0201	Phase I/II of TTPVS for persistent ascites
JIVROSG-0202	Phase I/II of PVP for painful bone mets
JIVROSG-0203	Phase I/II of RFA for lung cancer
JIVROSG-0204	Phase I/II of RFA for painful intrapelvic tumor
JIVROSG-0205	Phase I/II of PTEG for upper GI obstruction
JIVROSG-0206	Phase I/II of stent therapy for colonic stenosis
JIVROSG-0208	Phase I/II of RFA for painful bone mets
JIVROSG-0301	Phase I/II of hepatic arterial GEM for cholangio carcinoma
JIVROSG-0302	Phase I/II of uterine artery embolization for uterine fibroid
JIVROSG-0401	Phase I/II of CDDP-TACE for HCC
JIVROSG-0402	Phase II of stent therapy for SVC/IVC syndrome
JIVROSG-0604	Phase II of EPI-Dox/Dox-Lipiodol-GS TACE for HCC (Korea–Japan)
JIVROSG-0606	Phase III of HAIC with FOLFOX for liver mets from CRC
JIVROSG-0701	Phase I/II of RFA for renal cancer
JIVROSG-0702	Phase II of RFA for lung cancer
JIVROSG-0703	Phase II of PVP for painful bone mets
JIVROSG-0704	Phase I/II of RFA for osteoid osteoma
JIVROSG-0803	Phase III of shunt for persistent ascites
JIVROSG-0804	Phase III of PVP for painful bone mets
JIVROSG-0805	Phase III of PTEG for upper GI obstruction
JIVROSG-0806	Phase III of stent therapy for colorectal stenosis
JIVROSG-0807	Phase III of stent therapy for SVC/IVC syndrome

TTPVS trans-jugular trans-hepatic peritoneovenous shunt, *PVP* percutaneous vertevroplasty, *GI* gastrointestinal, *GEM* gemcitabine, *CDDP* cisplatin, *SVC* superior venacava, *IVC* inferior venacava, *EPI* epirubicin, *Dox* doxorubicin, *GS* gelatin sponge, *HAIC* hepatic arterial infusion chemotherapy, *FOLFOX* combination chemotherapy with folinic acid, fluorouracil and oxaliplatin, *CRC* colorectal cancer

Clinical trials of interventional oncology in Japan

To establish evidence in interventional oncology, the Japan Interventional Radiology in Oncology Study Group (JIVROSG) was organized in 2002 with a grant from the Ministry of Health, Welfare and Labor. At present, JIVROSG is composed of certificated interventional radiologists from 90 institutions, and more than 20 clinical trials listed in Table 4 have been carried out. Through carrying out these trials, JIVROSG developed the "JIVROSG 3 × 3 method" as a new phase I study design for evaluating the safety of technical procedures, and has performed some phase I/II trials for newly developed procedures using this method [9, 10]. Additionally, phase III RCTs to evaluate procedures of interventional oncology in palliative care have been carried out since 2010. RCTs in palliative care are not easy, but if interventional oncology showed a significant advantage in these trials, it could become the

standard treatment in these fields. This is the primary challenge of interventional oncology for palliative care worldwide.

Conclusion

Interventional oncology has potential advantages as a better treatment in various fields of oncology because of its features. However, most procedures in interventional oncology have not been recognized as the standard treatment because of lack of firm evidence. Although there are issues in performing clinical trials of interventional oncology, establishment of evidence is critical to making interventional oncology the standard treatment in oncology. Interventional radiologists should know the importance of clinical trials, and should move ahead in this direction in a step-by-step manner.

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Conflict of interest The author declares that he has no conflict of interest.

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Clinical Investigation: Central Nervous System Tumor

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

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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

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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

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

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.

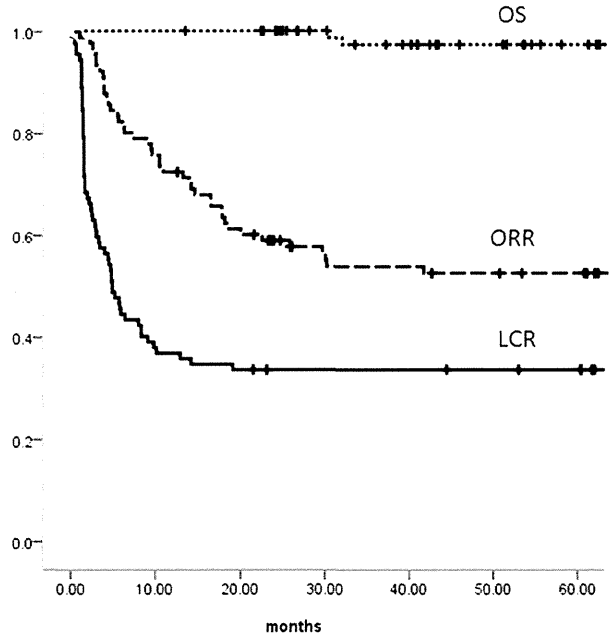

Fig. 1. Kaplan-Meyer curves of local control rate (LCR), ocular retention rate (ORR), and overall survival (OS).

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*

	LCR					
Factors	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.

* $P<.05$.

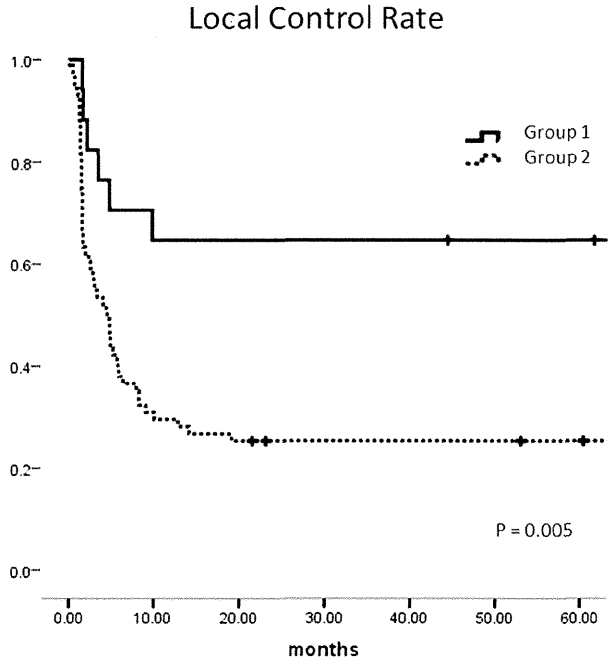

Fig. 2. Local control rate (LCR) according to the group classification by the International Classification of Retinoblastoma and biological effective dose (BED) with $\alpha/\beta = 10$ Gy of the reference depth (for details refer to the text).

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.

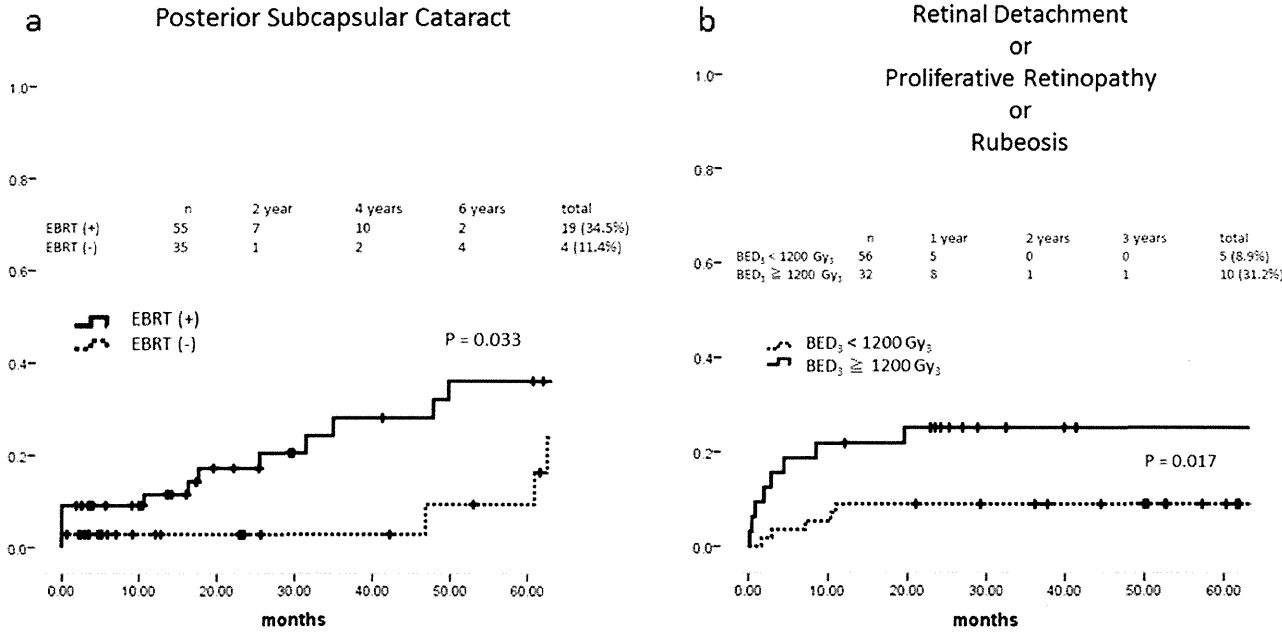

Fig. 3. (a) Cumulative incidence of posterior subcapsular cataract according to whether external beam radiation therapy (EBRT) was administered. (b) Cumulative incidence of retinal detachment, proliferative retinopathy and rubeosis stratified by biological effective dose (BED) with $\alpha/\beta = 3$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

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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.

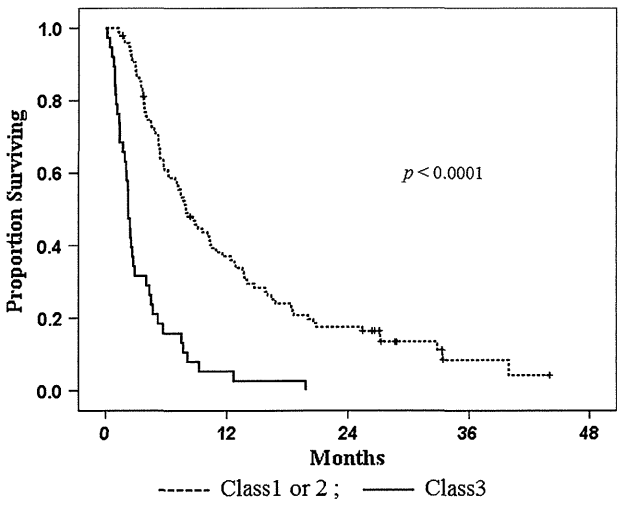

Fig. 1 Kaplan–Meier survival curve for overall survival by RPA criteria

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

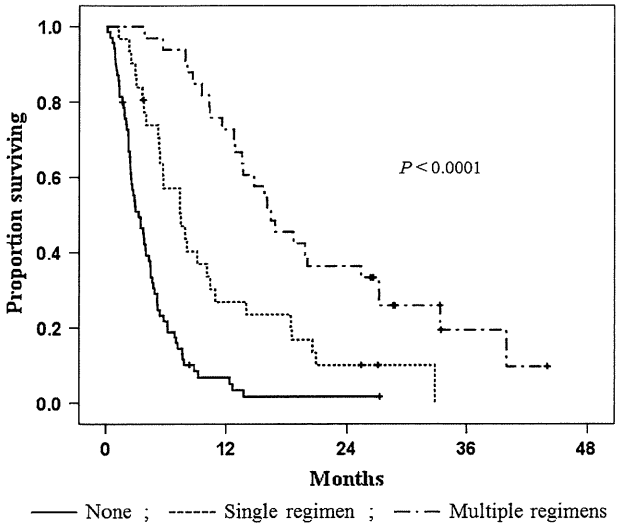

Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

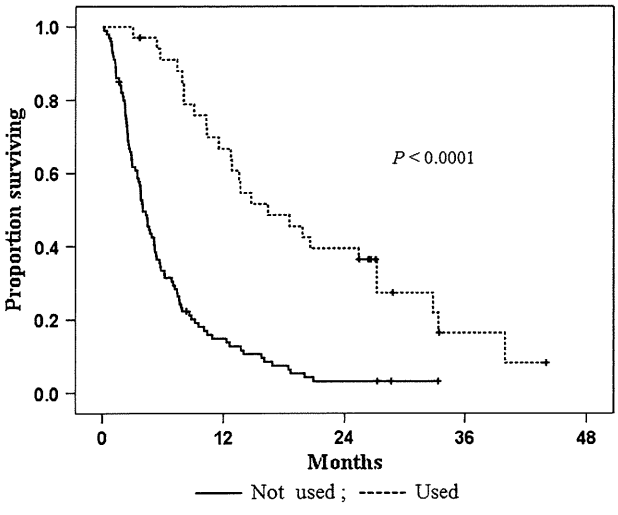

Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

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.

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