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.

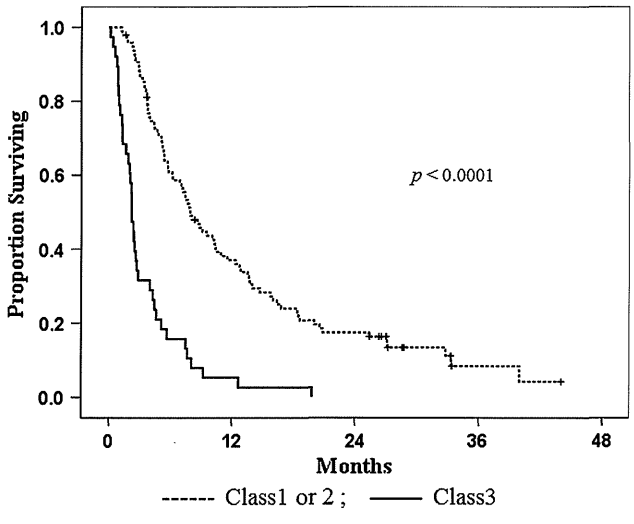

Fig. 1 Kaplan–Meier survival curve for overall survival by RPA criteria

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

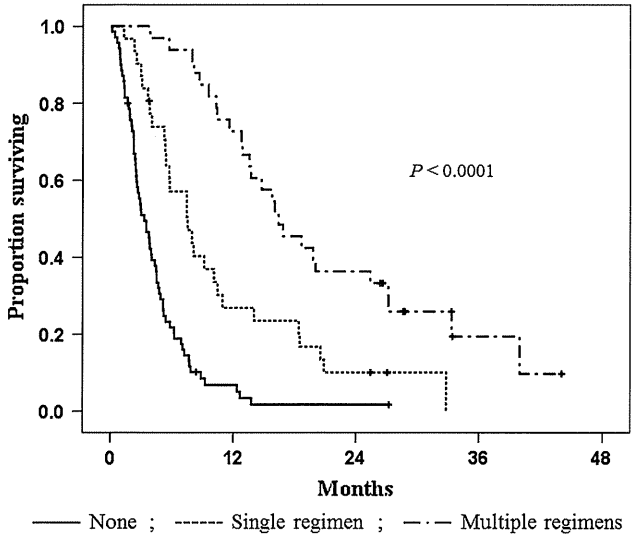

Fig. 2 Kaplan–Meier overall survival curve by the use of chemotherapeutic regimen after WBRT

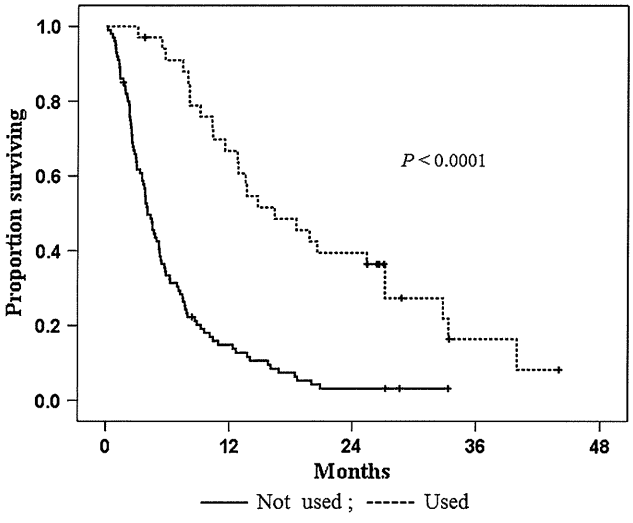

Fig. 3 Kaplan–Meier overall survival curve by the use of molecular-targeted therapy after WBRT

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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Risk Factors for Treatment-Related Death Associated with Chemotherapy and Thoracic Radiotherapy for Lung Cancer

Yuko Minami-Shimmyo, MD, Yuichiro Ohe, MD, PhD,* Seiichiro Yamamoto, PhD,† Minako Sumi, MD, PhD,‡ Hiroshi Nokihara, MD, PhD,* Hidehito Horinouchi, MD,* Noboru Yamamoto, MD, PhD,* Ikuo Sekine, MD, PhD,* Kaoru Kubota, MD, PhD,* and Tomohide Tamura, MD**

Introduction: The aim of the study is to evaluate the current status of treatment-related death (TRD) in lung cancer patients.

Methods: We retrospectively analyzed the incidence and risk factors of TRD in lung cancer patients who received chemotherapy and/or thoracic radiotherapy using logistic regression analyses.

Results: Between January 2001 and December 2005, 1225 (222 small cell and 1003 non-small cell lung cancers) patients received chemotherapy and/or thoracic radiotherapy as the initial treatment. Of these, 43 patients receiving chemotherapy followed by thoracic radiotherapy were included into both the chemotherapy-alone and radiotherapy-alone groups. There were a total of 23 (1.9%) TRDs. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 from drug-induced lung injury, 2 from pneumonia, and 1 from unknown cause. Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 from radiation pneumonitis and 1 from pneumonia. Thoracic radiotherapy-related deaths occurred in 4 of 96 (4.2%) patients. The incidence of chemotherapy-related death was correlated with poor performance status (odds ratio [OR]: 11.4, 95% confidence interval [CI]: 3.53–37.1), the presence of hypoxia (OR: 19.3, CI: 6.06–61.7), hyponatremia (OR: 45.5, CI: 13.4–154), and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (OR: 8.56, CI: 2.48–29.5), whereas the incidence of concurrent chemoradiotherapy-related death was correlated with pulmonary fibrosis (OR: 22.2, CI: 5.61–87.8). Radiotherapy results were not analyzed because there were too few patients.

Conclusions: TRD occurred in 1.9% of the patients as a result of treatment-related lung injury in the majority of the cases.

Key Words: Lung cancer, Treatment-related death, Risk factor, Chemotherapy, Thoracic radiotherapy.

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*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital; †Division of Cancer Information and Epidemiology, National Cancer Center Research Institute; and ‡Division of Radiation Oncology, National Cancer Center Hospital, Tsukiji, Chuo-ku, Tokyo, Japan.

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Address for correspondence: Ikuo Sekine, MD, PhD, Department of Medical Oncology, Graduate School of Medicine, Chiba University, Inohana 1-8-1, Chuo-ku, Chiba 260-8670, Japan. E-mail: isekine@chiba-u.jp

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Before any medical interventions are undertaken in patients with lung cancer, they must be clearly informed about the risks and benefits of the intervention(s) and about alternative treatment options. Careful delivery of this is particularly important if the planned treatment may not only result in cure but may also be harmful. Provision of accurate information to help patients make the most appropriate decision is therefore crucial. However, the risks of death from drug toxicity and the incidences of such events tend to be uncertain[1–4] and also constantly change with the wide use of newer agents, such as third-generation chemotherapy agents, and molecular-targeted agents. In addition, the incidence of treatment-related deaths (TRDs) has not been thoroughly examined in clinical settings outside of clinical trials. Prospective clinical trials for poor-risk patients are often difficult to perform because of poor accrual, reflecting the reluctance of physicians to subject patients with underlying comorbid illness to the toxic effects of chemotherapy and radiation.

Our ultimate goal is to prospectively identify individuals who are at a high risk of TRD so as to provide the most precise estimation of the possible risks to each patient. In this study, we retrospectively examined the data of patients with locally advanced or metastatic lung cancer who were treated at the National Cancer Center Hospital, Tokyo, Japan, focusing on the risks and incidences of TRD associated with chemotherapy and radiotherapy.

PATIENTS AND METHODS

Patients

Between January 2001 and December 2005, a total of 1623 lung cancer patients were admitted to the thoracic oncology ward at the National Cancer Center Hospital. All patients were admitted in this period to be treated as part of standard practice in Japan. Patients who received chemotherapy alone usually stayed in the hospital for 7 to 10 days for one cycle of chemotherapy, and those who received concurrent chemoradiotherapy stayed for 6 weeks. Among these, a total of 1225 patients who had received first-line chemotherapy and/or radiotherapy on an inpatient basis were extracted from the institutional database. Additional details about the patients, including the diagnostic imaging findings, were then reviewed from the patients' medical records. The data of patients receiving chemotherapy and/or thoracic radiotherapy

as the initial treatment were evaluated. They included patients with stage III to IV disease and postoperative recurrent disease who received chemotherapy; those with stage III disease who received chemoradiotherapy or radiotherapy alone; and those with stage III disease who received preoperative induction therapy or postoperative adjuvant therapy. All the patients had been followed for at least 4 weeks after the completion of treatment.

Treatment Selection

After a thorough evaluation of the operability and/or curability, the eligibility of each patient for enrollment in an open clinical trial was determined. Although patient recruitment for protocol treatments is a priority of ours, patients were free to refuse treatment. If no appropriate clinical trials were scheduled or under way, the known best standard treatments were administered.

Best Standard Treatments

For first-line treatment, patients with non-small cell lung cancer (NSCLC) who were deemed inoperable but curable with good local control with chemoradiotherapy received three to four cycles of cisplatin (CDDP) 80 mg/m^2 on day 1 + vinorelbine (VNR) 20 mg/m^2 on days 1 and 8, every 4 weeks, along with early concurrent thoracic radiotherapy, usually at a total dose of 60 Gy/30 fractions.[5] Sequential chemoradiotherapy, rather than concurrent chemoradiotherapy, was offered if the calculated percentage of the total lung volume receiving radiation in excess of 20 Gy (V_{20}) was more than 40%.[6] Thoracic radiotherapy alone was selected if chemotherapy could not be given due to comorbidity. If the radiation field involved the contralateral hilum or if the patients had malignant effusion and/or distant metastasis, platinum doublet therapy was administered; the most common combination was four cycles of carboplatin (CBDCA) area under the curve = 6 on day 1 + paclitaxel (PTX) 200 mg/m^2 on day 1, every 3 weeks.[7] For limited-disease SCLC, four cycles of a combination of CDDP 80 mg/m^2 on day 1 + etoposide 100 mg/m^2 on days 1 to 3, every 4 weeks, were administered concurrently with hyperfractionated thoracic radiotherapy at a total radiation dose of 45 Gy in fractional doses of 1.5 Gy, administered twice a day.[8] In patients with extensive-disease SCLC, four cycles of a combination of CDDP 60 mg/m^2 on day 1 and irinotecan (CPT) 60 mg/m^2 on days 1, 8, and 15, every 4 weeks, were usually administered.[9] Radiotherapy was given using megavoltage photons (6–15 MV). The routine radiation schedule without chemotherapy for locally advanced NSCLC was a total radiation dose of 60 to 66 Gy, or as high as 70 Gy, administered in fractional doses of 2.0 Gy once a day.

Definition of TRD

Chemotherapy-related death was defined as death occurring within 4 weeks of the completion of treatment, without clear evidence of any other cause of death, or death obviously caused by treatment toxicity. Radiotherapy-related death was defined as death secondary to hypoxia or to complications of corticosteroid administration after the diagnosis of radiation pneumonitis. Steroid therapy was administered based on the attending physician's discretion, without a standardized treatment dose or duration, for the management of radiation-induced lung injury.[10]

Definition of Treatment-Induced Lung Injury

The criteria of drug-induced lung injury in this study were as follows: (1) appearance of new symptoms and radiological abnormalities in the course of chemotherapy with the onset within a few months of the start of the therapy; (2) diffuse or multifocal ground-glass opacities and intralobular interstitial thickening without segmental distribution in computed tomography (CT) scans of the chest; and (3) no evidence of underlying heart disease, infection, or lymphangitic carcinomatosis. Lung biopsy was not routinely performed in our hospital because patients were frequently too frail to undergo biopsy. The criteria of radiation-induced lung injury were (1) appearance of new symptoms and radiological abnormalities with the onset within 6 months of the end of thoracic radiotherapy; (2) opacification, diffuse haziness, infiltrates, or consolidation conforming to the outline of the sharply demarcated irradiated area in CT scans; and (3) a reduction in lung volume within the irradiated area and linear, ground-glass opacities or reticular shadows beyond the irradiated area developing during clinical course. In contrast, the criteria of bacterial pneumonia were (1) clinical suspicion of pneumonia including rapidly developing fever and/or productive cough; and (2) consolidation spreading through anatomical structure of the lung in CT scans.

Statistical Analysis

We investigated the associations between chemotherapy-related or concurrent chemoradiotherapy-related death and the potential risk factors at the time of diagnosis. The following potential risk factors were investigated: sex, age (≥70 years versus <70 years), performance status (Eastern Cooperative Oncology Group criteria; 2–4 versus 0–1), smoking history (presence versus absence), partial pressure of oxygen (70 mmHg ≤ PO_2 versus >70 mmHg), hemoglobin (Hgb < 13.7 g/dl versus ≥ 13.7 g/dl), platelet (Plt > 367 × 10^9/L versus ≤367 × 10^9/L), albumin (Alb < 3.7 g/dl versus ≥3.7 g/dl), sodium (Na < 138 mEq/L versus ≥138 mEq/L), clinical trial (in versus out), and chemotherapy regimen (The cutoff values of hemoglobin, platelet, albumin, and sodium are the institutional normal limits [above or below]). For concurrent chemoradiotherapy-related factors, the presence of coincidental diseases such as emphysema (with versus without) or pulmonary fibrosis (with versus without) and the location of the primary tumor (lower lobe versus other lobes) were also included in the analyses. The diagnostic criteria of pulmonary fibrosis were a linear, ground-glass attenuation or reticular shadows on chest radiographs and CT scans before treatment that were predominant in the lower zone of the lung. Also, the influence of the chemotherapy regimens was evaluated.

In the univariate preliminary analysis, the relation between previously defined variables at the time of presentation and the occurrence of the outcome variable (toxic death) was assessed using the χ^2 test. To adjust for each factor, multivariate logistic regression analyses were planned. When the number of observed events was less than 10, multivariate

analysis was not performed. When the number of patients for each factor was small, the factor was excluded from the model, even when it appeared to be statistically significant. All the analyses were performed using the STATISTICA 4.1J program (StatSoft, Inc., Tulsa, OK).

RESULTS

Patient Characteristics

The patient characteristics before treatment are listed in Table 1. Of the 1225 patients (SCLC: 222; adenocarcinoma: 652; squamous cell carcinoma: 194; NSCLC not otherwise specified: 111; large cell carcinoma: 7; others: 39), chemotherapy alone was administered in 884 patients, concurrent chemoradiotherapy in 245, sequential chemoradiotherapy in 43, and thoracic radiotherapy alone in 53 patients. To evaluate the incidence of TRD among the patients who received chemotherapy, radiotherapy, or a combination of these modalities, we included the 43 patients who received sequential chemoradiotherapy into both the chemotherapy-alone group and the thoracic radiotherapy-alone group. Therefore, the patients who received sequential chemoradiotherapy were regarded as having been exposed to the risks of treatment twice. The groups were therefore analyzed as chemotherapy alone in 927 patients, concurrent chemotherapy in 245 patients, and thoracic radiotherapy alone in 96 patients. In these groupings, the percentages of patients enrolled in clinical trials were 62, 53, and 23%, respectively.

Cumulative Incidence and Causes of TRD

The cumulative incidence and causes of TRD are listed in Table 2. Of the 1225 patients, a total of 23 (1.9%) TRDs occurred. Chemotherapy-related deaths occurred in 7 of 927 (0.8%) patients, including 4 (0.4%) from drug-induced lung injury (gefitinib, $n = 3$ and CBDCA + gemcitabine, $n = 1$), 2 (0.2%) from pneumonia (CBDCA + PTX, $n = 2$), and 1 (0.1%) from unknown cause. The patient who died of unknown cause experienced hemodynamic instability (shock) of unknown etiology within 24 hours of ingestion of the first dose of gefitinib (250 mg). No TRDs from sepsis occurred in this series.

Concurrent chemoradiotherapy-related deaths occurred in 12 of 245 (4.9%) patients, including 11 (4.5%) from radiation pneumonitis and 1 (0.4%) from pneumonia during the last planned cycle of CDDP + VNR. Radiotherapy-

TABLE 1. Patient Characteristics

Characteristics	Chemotherapy Alone[a] ($n = 927$)	Concurrent Chemoradiotherapy ($n = 245$)	Radiotherapy Alone[a] ($n = 96$)
Sex			
Male	639	201	43
Female	288	44	53
Age			
Median (range)	64 (27–86)	59 (18–77)	67 (35–81)
Performance status			
0–1	871	245	88
2	140	0	8
3–4	16	0	0
Stage			
III	297	235	71
IV	454	2	17
Postoperative recurrence	176	8	8
Histology			
Non-small cell carcinoma	760	191	88
Small cell carcinoma	167	54	8
Coincidental lung disease			
Pulmonary fibrosis	34	1	4
Pulmonary emphysema	69	30	1
Chemotherapy regimen			
Platinum + taxane	368	21	—
Platinum + irinotecan	133	1	—
EGFR-TKI	125	0	—
Platinum + etoposide	95	54	—
Platinum + antimetabolite	85	0	—
Platinum + vinca alkaloid	37	168	—
Others	84	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

TABLE 2. Treatment-Related Death and Its Cumulative Incidence

Characteristics	Chemotherapy Alone[a] (n = 927)	Concurrent Chemoradiotherapy (n = 245)	Radiotherapy Alone[a] (n = 96)
No. of treatment-related deaths	7	12	4
Cumulative incidence (%)	0.8	4.9	4.2
Sex			
Male	5	11	4
Female	2	1	0
Age of patients who died of treatment (yr)			
Median (range)	69 (46–77)	68 (50–77)	75 (65–77)
Causes			
Treatment-induced lung injury	4	11	4
Infectious pneumonia	2	1	0
Unknown	1	0	0
Chemotherapy regimen			
Platinum + taxane	2	2	—
EGFR-TKI	4	—	—
Platinum + antimetabolite	1	—	—
Platinum + etoposide	0	1	—
Platinum + vinca alkaloid	0	8	—
Others	0	1	—

[a] Forty-three patients who received sequential chemotherapy followed by radiotherapy are included in the analysis of both the chemotherapy-alone group and radiotherapy-alone group, as described in the text.

EGFR-TKI, epidermal growth factor receptor-tyrosine kinase inhibitor.

related deaths occurred in 4 of 96 (4.2%) patients: all 4 (4.2%) patients died of radiation pneumonitis.

Risk Factors for TRD from Chemotherapy

Statistically significant factors identified by the univariate analysis were a performance status of 2 to 4, hypoxia, hypoalbuminemia, hyponatremia, out of clinical trials, and treatment with epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) (Table 3). Although statistically significant, the degrees of hyponatremia in the events were neither clinically significant nor symptomatic for the range of 133 to 137 mEq/L. Pulmonary fibrosis and emphysema were noted in 34 and 69 patients, respectively, among the 927 patients. None of these patients with lung disease died of treatment in this study. Multivariate analysis was not performed because the number of observed events was too small (n = 7).

Risk Factors for TRD from Concurrent Chemoradiotherapy

None of the factors, except for pulmonary fibrosis, were found to be statistically significant in the univariate analysis, although a trend toward increase in the risk of TRD was observed in patients of advanced age (>70 years) and with lower lobe as the primary tumor site (Table 4). Pulmonary fibrosis appeared to be a statistically significant risk factor for TRD; however, it was excluded from the multivariate analysis because of its limited incidence. Thus, we did not perform multivariate analysis for chemoradiotherapy group, and an analysis of the risk of TRD associated with thoracic radiotherapy alone was not conducted because of the limited number of cases.

DISCUSSION

We identified a total of 23 TRDs out of the 1225 patients (1.9%) enrolled in this study, which is lower than the rate (2.7%) indicated in a previous report, particularly in relation to the number of TRDs from infections, including pneumonia and sepsis.[1] The reason for the decrease in the incidence of infection-related deaths is likely explained by the infrequent use of triplet regimens when compared with previous studies. Especially, mitomycin-C-containing regimens are regarded as effective regimens in the treatment of lung cancer; however, prolonged neutropenia has been observed with these regimens. Ohe et al.[1] reported that combined mitomycin-C + vindesine + CDDP (MVP regimen) therapy is a risk factor for chemotherapy-related TRD (toxic deaths occurred in 9 of 301 patients; odds ratio [OR] = 9.36, 95% confidence interval [CI] = 1.29–68.0, p = 0.027). In this study, only 35 patients, the majority (89%) of whom were enrolled in a clinical trial, received the MVP regimen. In the past, however, the MVP regimen was widely used as part of practice-based regimens (only 28% recorded under clinical trials). In most cases, patients who were not eligible for clinical trials ended up receiving the MVP regimen. Another reason is the relatively frequent use of EGFR-TKI (in 13.5% of the patients in this study) at present, which does not induce myelosuppression. The reduction in the frequency of TRD might also be explained by a progress in supportive care in the treatments given for cancer treatment toxicities.

This study revealed that drug-induced lung injury was the most frequent cause of TRD in the era of molecular-targeted therapy. Three (75%) of four TRDs from drug-induced lung injury were associated with gefitinib. The re-

TABLE 3. Risk Factors for Treatment-Related Death from Chemotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	288	0.8	1	
Male	639	0.7	1.13 (0.22–5.76)	0.89
Age				
<70	689	0.6	1	
≥70	238	1.3	2.17 (0.51–9.30)	0.30
PS				
0–1	870	0.5	1	
2–4	57	5.2	11.4 (3.53–37.1)	<0.001
Smoking history				
No	271	0.4	1	
Yes	656	0.9	2.49 (0.30–20.8)	0.40
PaO_2 (Torr)				
≥70	812	0.2	1	
<70	105	4.8	19.3 (6.06–61.7)	<0.001
Hemoglobin (g/dl)				
≥13.7	371	0.5	1	
<13.7	556	0.9	1.67 (0.33–8.39)	0.54
Albumin (g/dl)				
≥3.7	663	0.3	1	
<3.7	264	1.9	6.28 (1.51–26.1)	0.012
AST (IU/L)				
≤33	831	0.6	1	
>33	96	2.1	3.46 (0.75–16.0)	0.11
Na (mEq/L)				
≥138	819	0.1	1	
<138	108	5.6	45.5 (13.4–154)	<0.001
Clinical trial				
No	355	1.7	1	
Yes	572	0.2	0.10 (0.58–0.019)	0.001
Platinum + taxane				
No	559	0.9	1	
Yes	368	0.5	0.61 (0.12–3.14)	0.55
EGFR-TKIs				
No	802	0.4	1	
Yes	125	3.2	8.56 (2.48–29.5)	0.001
Platinum + antimetabolite				
No	842	0.7	1	
Yes	85	1.1	1.66 (0.20–13.9)	0.64

Multivariate analysis was not performed because the number of observed events was too small ($n = 7$).

OR, odds ratio; CI, confidence interval; PS, performance status; AST, aspartate transaminase; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors.

TABLE 4. Risk Factors for Treatment-Related Death from Concurrent Chemoradiotherapy

Factors	No. of Patients	Cumulative Incidence (%)	Univariate Analysis OR (95% CI)	*p*
Sex				
Female	44	2.3	1	
Male	201	5.2	2.41 (0.35–16.6)	0.37
Age (yr)				
<70	221	4.1	1	
≥70	24	12.5	3.07 (0.92–10.3)	0.069
PS				
0	114	5.3	1	
1	131	4.6	0.87 (0.29–2.62)	0.81
Smoking history				
No	32	3.2	1	
Yes	213	5.2	1.65 (0.23–11.9)	0.24
Fibrosis				
No	244	4.5	1	
Yes	1	100	22.2 (5.61–87.8)	<0.001
Emphysema				
No	215	4.7	1	
Yes	30	6.7	1.43 (0.33–6.25)	0.63
Location of the tumor				
Other lobes	189	3.7	1	
Lower lobe	56	8.9	2.41 (0.82–7.13)	0.11
Histology				
SCLC	54	1.9	1	
NSCLC	191	5.8	3.11 (0.47–20.6)	0.24
Hemoglobin (g/dl)				
≥13.7	146	4.1	1	
<13.7	99	6.1	1.48 (0.49–4.42)	0.48
Albumin (g/dl)				
≥3.7	198	4.5	1	
<3.7	47	6.4	1.40 (0.40–4.99)	0.6
Na (mEq/L)				
≥138	219	5.0	1	
<138	26	3.8	0.77 (0.11–5.60)	0.79
Clinical trial				
No	114	5.3	1	
Yes	131	4.6	0.87 (0.29–2.62)	0.81
Platinum + taxane				
No	224	4.5	1	
Yes	21	9.5	2.25 (0.46–11.0)	0.32
Platinum + vinca alkaloid				
No	77	5.2	1	
Yes	168	4.8	0.91 (0.27–3.13)	0.88

Multivariate analysis was not performed because only fibrosis was significant in univariate analysis.

OR, odds ratio; CI, confidence interval; PS, performance status; NSCLC, non-small cell lung cancer.

ported risk factors for interstitial lung disease in NSCLC patients treated with gefitinib are male sex, history of smoking, and underlying interstitial pneumonitis.[11] In this study, however, none of these factors were associated with TRD from chemotherapy. Another TRD from drug-induced lung injury occurred in a patient who received gemcitabine, but this patient was also free from underlying pulmonary disease or concomitant use of taxanes, which are reported to be risk factors for gemcitabine-associated interstitial lung disease.[12]

For patients who receive concurrent chemoradiotherapy, we would like to emphasize the previous finding that the

presence of evidence of pulmonary fibrosis on a plain chest x-ray is an extremely strong risk factor for TRD (OR = 166, 95% CI = 8.79–3122, $p < 0.001$).[1] In this study, only one patient with pulmonary fibrosis was identified, and pulmonary fibrosis was not included in the multivariate analysis because of the small number of patients with this factor, because we generally exclude patients with evidence of pulmonary fibrosis on the chest x-ray from consideration of concurrent chemoradiotherapy. This study also suggested that advanced age may be a risk factor for TRD. This is consistent with the results of previous studies.[1,13–15] The association between advanced age and fatal radiation-induced lung injury may be explained by the increased likelihood of these patients developing comorbid lung disease, particularly among patients with a history of heavy tobacco exposure. A meta-analysis of chemoradiotherapy using individual data from 1764 patients with locally advanced NSCLC showed that the benefit of chemoradiotherapy was obtained in elderly patients (≥71 years) as well as in younger patients. However, it might be assumed that patients who are included in such trials are fit patients with minimal comorbidities. In addition, despite the increase in toxicity that accompanied chemoradiotherapy in elderly patients, it seemed that they had disease control and survival rates similar to those of younger patients.[16]

In conclusion, TRD occurred in a total of 1.9% of patients and was caused in the majority of the cases by treatment-related lung injury. This finding is in clear contrast with previous reports which suggested that the principal cause of TRD in lung cancer patients was septic shock.

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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*

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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

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

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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

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

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.

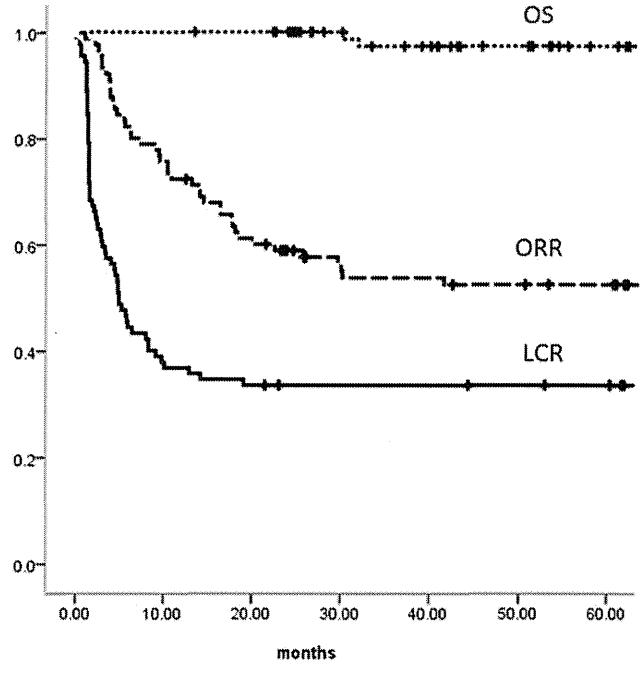

Fig. 1. Kaplan-Meyer curves of local control rate (LCR), ocular retention rate (ORR), and overall survival (OS).

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 ±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.

* $P<.05$.

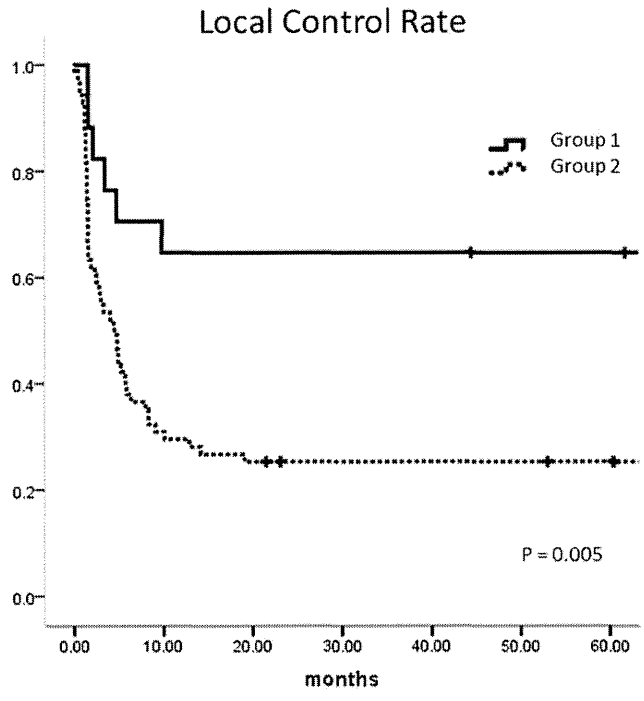

Fig. 2. Local control rate (LCR) according to the group classification by the International Classification of Retinoblastoma and biological effective dose (BED) with $\alpha/\beta = 10$ Gy of the reference depth (for details refer to the text).

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.

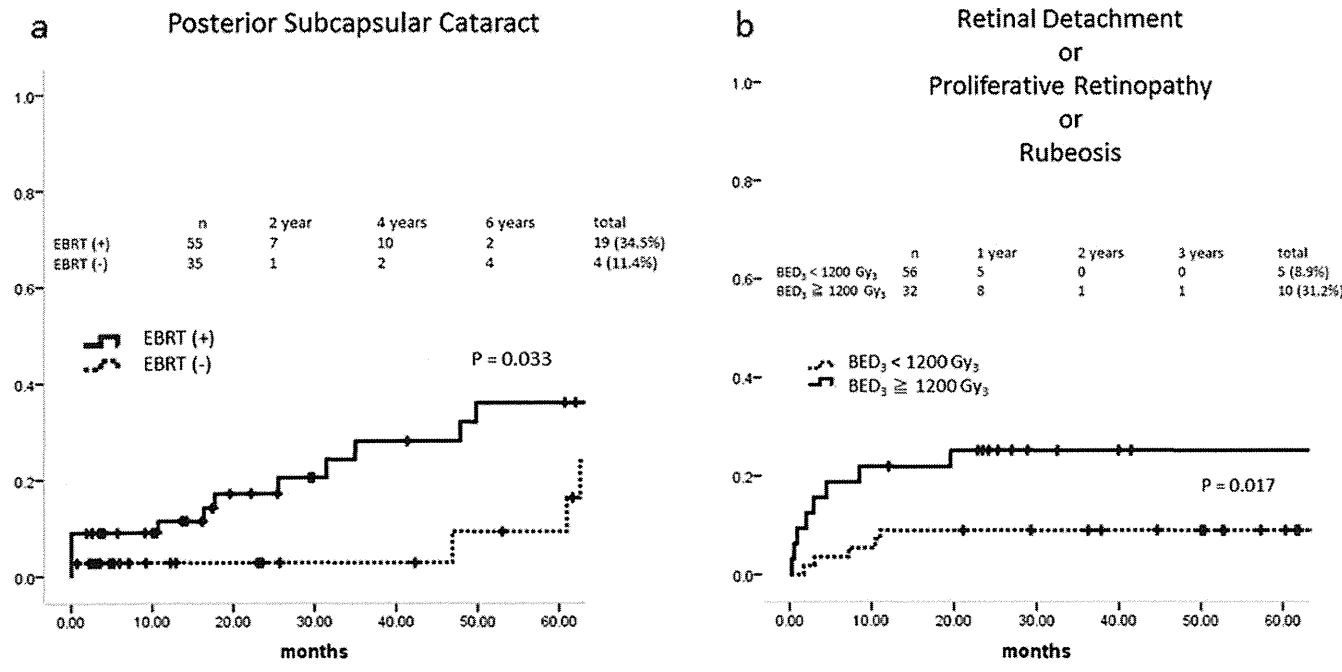

Fig. 3. (a) Cumulative incidence of posterior subcapsular cataract according to whether external beam radiation therapy (EBRT) was administered. (b) Cumulative incidence of retinal detachment, proliferative retinopathy and rubeosis stratified by biological effective dose (BED) with $\alpha/\beta = 3$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

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CLINICAL INVESTIGATION **Thoracic Cancer**

PHASE I STUDY OF CONCURRENT HIGH-DOSE THREE-DIMENSIONAL CONFORMAL RADIOTHERAPY WITH CHEMOTHERAPY USING CISPLATIN AND VINORELBINE FOR UNRESECTABLE STAGE III NON-SMALL-CELL LUNG CANCER

IKUO SEKINE, M.D., PH.D.,* MINAKO SUMI, M.D.,PH.D.,† YOSHINORI ITO, M.D.,† HIDEHITO HORINOUCHI, M.D.,* HIROSHI NOKIHARA, M.D., PH.D.,* NOBORU YAMAMOTO, M.D., PH.D.,* HIDEO KUNITOH, M.D., PH.D.,* YUICHIRO OHE, M.D., PH.D.,* KAORU KUBOTA, M.D., PH.D.,* AND TOMOHIDE TAMURA, M.D.*

*Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan; and †Division of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan

Purpose: To determine the maximum tolerated dose in concurrent three-dimensional conformal radiotherapy (3D-CRT) with chemotherapy for unresectable Stage III non–small-cell lung cancer (NSCLC).

Patients and Methods: Eligible patients with unresectable Stage III NSCLC, age ≥20 years, performance status 0–1, percent of volume of normal lung receiving 20 GY or more (V_{20}) ≤30% received three to four cycles of cisplatin (80 mg/m^2 Day 1) and vinorelbine (20 mg/m^2 Days 1 and 8) repeated every 4 weeks. The doses of 3D-CRT were 66 Gy, 72 Gy, and 78 Gy at dose levels 1 to 3, respectively.

Results: Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were enrolled at dose levels 1 to 3, respectively. The main reasons for exclusion were V_{20} >30% (n = 10) and overdose to the esophagus (n = 8) and brachial plexus (n = 2). There were 26 men and 5 women, with a median age of 60 years (range, 41–75). The full planned dose of radiotherapy could be administered to all the patients. Grade 3–4 neutropenia and febrile neutropenia were noted in 24 (77%) and 5 (16%) of the 31 patients, respectively. Grade 4 infection, Grade 3 esophagitis, and Grade 3 pulmonary toxicity were noted in 1 patient, 2 patients, and 1 patient, respectively. The dose-limiting toxicity was noted in 17% of the patients at each dose level. The median survival and 3-year and 4-year survival rates were 41.9 months, 72.3%, and 49.2%, respectively.

Conclusions: 72 Gy was the maximum dose that could be achieved in most patients, given the predetermined normal tissue constraints. © **2012 Elsevier Inc.**

Lung cancer, Chemotherapy, Radiotherapy, High dose, Conformal.

INTRODUCTION

Approximately one third of patients with non–small-cell lung cancer (NSCLC) present with locally advanced Stage III disease at the initial diagnosis (1). Of this category, Stage IIIA disease with bulky N2 and Stage IIIB disease without pleural effusion are characterized by a large primary lesion and/or involvement of the mediastinal or supraclavicular lymph nodes. In addition, the majority of these patients have occult systemic micrometastases. Concurrent thoracic radiotherapy and chemotherapy has been the standard care for these patients with unresectable disease (2, 3). A platinum doublet with a third-generation anticancer agent combined with thoracic radiotherapy was reported to yield a median overall survival time (OS) of more than 2 years and long-term survivors (4–6), but the effect of platinum-based chemotherapy has reached a plateau.

The failure pattern in patients with Stage III NSCLC treated by concurrent chemoradiotherapy was roughly local recurrence alone in one third of the patients, both local and distant recurrence in another third of patients, and distant metastasis without local failure in the remaining third of patients (2, 5).

Reprint requests to: Ikuo Sekine, M.D., Ph.D., Division of Internal Medicine and Thoracic Oncology, National Cancer Center Hospital, Tsukiji 5-1-1, Chuo-ku, Tokyo 104-0045, Japan. Tel : (+81) 3-3542-2511; Fax: (+81) 3-3542-3815; E-mail: isekine@ncc.go.jp

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