Table 3. Toxicity

	Grade										
	Level 1			(n = 13)	Level 2			(n = 12)	Level 3			(n = 6)
Toxicity	2	3	4	(3+4 %)	2	3	4	(3+4 %)	2	3	4	(3+4 %)
Leukopenia	4	6	2	(62)	1	3	8	(92)	1	3	2	(83)
Neutropenia	4	4	4	(62)	0	1	10	(92)	1	3	2	(83)
Anemia	8	2	2	(31)	7	3	1	(33)	2	2	0	(50)
Thrombocytopenia	0	0	0	(0)	1	1	0	(8)	0	0	0	(0)
Febrile neutropenia	–	1	0	(8)	–	3	0	(25)	–	1	0	(17)
Infection	0	0	1	(8)	0	1	0	(8)	2	0	0	(0)
Esophagitis	1	1	0	(8)	2	1	0	(8)	0	0	0	(0)
Lung toxicity	2	0	0	(0)	0	0	0	(0)	0	1	0	(17)
Anorexia	3	0	0	(0)	2	2	0	(17)	0	0	0	(0)
Nausea	3	0	0	(0)	3	0	0	(0)	0	0	0	(0)
ALT elevation	1	1	0	(8)	0	0	0	(0)	1	0	0	(0)
CRN elevation	7	0	0	(0)	4	0	0	(0)	0	0	0	(0)

Abbreviations: ALT = alanine aminotransferase; CRN = creatinine.

Of the 13 patients at dose level 1, one was excluded from the analysis of the DLT because he received only one cycle of chemotherapy as a result of the development of cisplatin-induced renal toxicity. Two (17%) of the remaining 12 patients at this dose level developed DLT: Grade 3 esophagitis in 1 patient and Grade 4 septic shock in the other. At dose level 2, two (17%) DLTs were noted: Grade 3 esophagitis in 1 patient and treatment delay by more than 15 days in the other. One (17%) of the 6 patients at dose level 3 developed Grade 3 bronchial stenosis without local recurrence of the disease. This was considered to be a Grade 3 lung toxicity and was counted as DLT. No other DLTs were noted. Thus, inasmuch as the incidence of DLT was below 33% at all dose levels, MTD was not reached.

Preliminary efficacy results

Objective responses and survival were evaluated in the 31 patients. Two patients showed complete responses and 27 showed partial responses, which represented a response rate (95% CI) of 94% (79–99). Disease progression was noted in 23 patients, and the median PFS was 11.6 months with a median duration of follow-up of 30.5 (range, 9.0–49.5) (Fig. 2). The first relapse sites aresummarized in Table 4. Brain metastasis alone as the first relapse site was noted in 7 (23%) patients. The median OS was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively (Fig. 3).

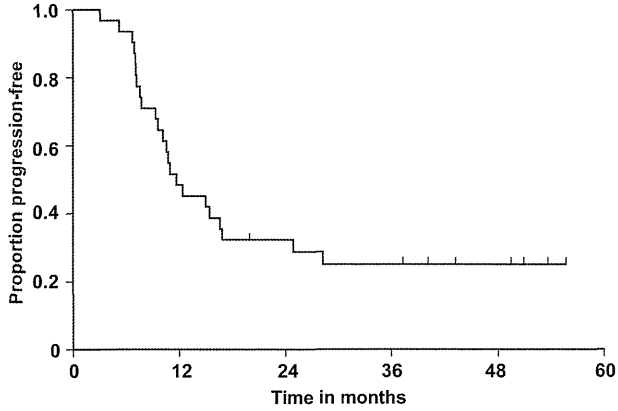

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

DISCUSSION

This study showed that concurrent 3D-CRT to the thorax with cisplatin plus vinorelbine chemotherapy was safe even up to 78 Gy in patients with unresectable Stage III NSCLC. This does not mean, however, that doses as high as 78 Gy can be given to all patients with this disease, because the safety in this study was shown only in highly selected patients by a PET/CT and DVH evaluation and by the standard staging procedure. Twenty-five of the 33 patients met the eligibility criteria for enrollment at dose levels 1 and 2, whereas only 6 of the 24 patients could be enrolled at dose level 3 in this study—that is, only one fourth of the patients could be treated with 78 Gy. Thus, this study showed that 72 Gy was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints, which forced three quarters of the enrolled patients at the 78-Gy level to not

Table 4. First relapse sites (n = 31)

Sites	n	(%)
Local recurrence alone	6	(19)
Local and distant metastasis	6	(19)
Distant metastasis alone	11	(35)
Brain alone	7	(23)
No relapse	8	(26)

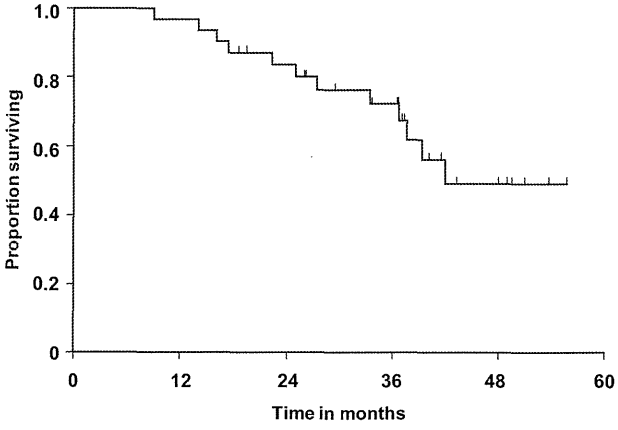

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

be eligible on the basis of those normal tissue constraints, and that the maximum tolerated dose was not determined because of this issue.

One obstacle to enrolling patients at dose level 3 was that the lung V_{20} often exceeded 30% when the total dose was increased to 78 Gy. This lung V_{20} dose constraint might have been too strict. According to a recent review, it is prudent to limit V_{20} to ≤30–35% with conventional fractionation, but there is no sharp dose threshold below which there is no risk for severe radiation pneumonitis (17). This is partly because DVH-based parameters will change at specific phases of the respiratory cycle when CT images for DVH evaluation have been obtained, there is uncertainty regarding how much of the bronchus should be defined as lung, and the lung edges may vary with the CT window level setting. In addition, patient-associated factors such as age, smoking status, lung function, and preexisting lung damage may influence the incidence and severity of radiation pneumonitis (18). If the threshold of V_{20} were set at higher than 30% (*e.g.*, 35%), then more patients would meet the eligibility criteria, but safety might not be guaranteed. Given that the definite threshold cannot be determined, a strict constraint should be introduced. This study showed that the lung toxicity was acceptable when the V_{20} was kept within 30%; therefore, we decided to use this eligibility criterion for concurrent chemotherapy and high-dose radiotherapy for a subsequent Phase II study.

Another obstacle was overdose to the esophagus and brachial plexus, which were close to the subcarinal (No. 7) and supraclavicular lymph nodes, respectively, that were frequently involved in patients with advanced NSCLC; therefore, the volume of these serial organs were included, in part, in the PTV in many patients with Stage III disease. The radiation tolerance doses of these organs have been defined as no higher than 72 Gy when one third of the organs are included in the irradiation volume (19). However, few data are available on the radiation tolerance doses of normal organs in humans; therefore, whether or not radiation doses above 72 Gy may be tolerated is unknown, especially when only small percentages of the organs are actually included in the irradiation volume. Notwithstanding, we do not agree that the radiation dose can be increased close to the intolerable level, because serious radiation toxicity to these serial organs could be irreversible, frequently leaves severe sequelae, and is fatal in some cases.

The toxicity observed in this trial was comparable to that in our previous study of concurrent chemoradiotherapy with vinorelbine and cisplatin chemotherapy plus thoracic radiation at a total dose of 60 Gy administered in 30 fractions: Grade 3–4 neutropenia in 77% and 67% of patients, Grade 3–4 esophagitis in 6% and 12% of patients, and Grade 3–5 lung toxicity in 3% and 7% in the current and previous studies, respectively (5). This suggests that patient selection using PET/CT and DVH evaluation may be useful to keep the toxicity associated with high-dose thoracic radiation within the range of toxicity induced by conventional-dose thoracic radiation.

In this study, a remarkably high proportion (74%) of subjects had adenocarcinoma, which may provide an explanation for the high rate of subsequent brain metastases. Patient selection also affects the treatment efficacy considerably; therefore, it is difficult to compare it between the current and previous studies. However, the median PFS of 11.6 months and median OS of 41.9 months sound promising. We are conducting a Phase II study of concurrent 3D-CRT at a total dose of 72 Gy and chemotherapy with cisplatin and vinorelbine.

In conclusion, concurrent 3D-CRT with cisplatin and vinorelbine chemotherapy was feasible up to 72 Gy, in patients with unresectable Stage III NSCLC. At the level of 78 Gy, however, only 25% of the patients assessed for eligibility were found to be actually eligible. Thus, 72 Gy in 36 fractions was the maximum dose that could be achieved in most patients given the predetermined normal tissue constraints when administered concurrently with cisplatin and vinorelbine.

REFERENCES

1. Yang P, Allen MS, Aubry MC, *et al.* Clinical features of 5,628 primary lung cancer patients: Experience at Mayo Clinic from 1997 to 2003. *Chest* 2005;128:452–462.
2. Furuse K, Fukuoka M, Kawahara M, *et al.* Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17: 2692–2699.
3. Curran WJ, Scott C, Langer C, *et al.* Phase III comparison of sequential vs concurrent chemoradiation for patients with unresectable stage III non-small-cell lung cancer (NSCLC): Initial report of the Radiation Therapy Oncology Group (RTOG) 9410. *Proc Am Soc Clin Oncol* 2000;19: 484a.
4. Sekine I, Noda K, Oshita F, *et al.* Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for

unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
5. Sekine I, Nokihara H, Sumi M, *et al.* Docetaxel consolidation therapy following cisplatin, vinorelbine, and concurrent thoracic radiotherapy in patients with unresectable stage III non-small cell lung cancer. *J Thorac Oncol* 2006;1:810–815.
6. Kiura K, Takigawa N, Segawa Y, *et al.* Randomized phase III trial of docetaxel and cisplatin combination chemotherapy versus mitomycin, vindesine and cisplatin combination chemotherapy with concurrent thoracic radiation therapy for locally advanced non-small cell lung cancer: OLCSG 0007. *J Clin Oncol* 2008;26(Suppl):400s (abstr. 7515).
7. Perez CA, Pajak TF, Rubin P, *et al.* Long-term observations of the patterns of failure in patients with unresectable non-oat cell carcinoma of the lung treated with definitive radiotherapy. Report by the Radiation Therapy Oncology Group. *Cancer* 1987; 59:1874–1881.
8. Birim O, Kappetein AP, Stijnen T, *et al.* Meta-analysis of positron emission tomographic and computed tomographic imaging in detecting mediastinal lymph node metastases in nonsmall cell lung cancer. *Ann Thorac Surg* 2005;79:375–382.
9. Nestle U, Walter K, Schmidt S, *et al.* 18F-deoxyglucose positron emission tomography (FDG-PET) for the planning of radiotherapy in lung cancer: High impact in patients with atelectasis. *Int J Radiat Oncol Biol Phys* 1999;44:593–597.
10. Purdy J. Three-dimensional conformal radiation therapy: Physics, treatment planning, and clinical aspects. In: Halperin E, Perez C, Brady L, editors. Principles and practice of radiation oncology. 5th ed. Philadelphia: Wolters Kluwer Lippincott Williams & Wilkins; 2008.
11. Rosenzweig KE, Sura S, Jackson A, *et al.* Involved-field radiation therapy for inoperable non small-cell lung cancer. *J Clin Oncol* 2007;25:5557–5561.
12. Sanuki-Fujimoto N, Sumi M, Ito Y, *et al.* Relation between elective nodal failure and irradiated volume in non-small-cell lung cancer (NSCLC) treated with radiotherapy using conventional fields and doses. *Radiother Oncol* 2009;91: 433–437.
13. Socinski MA, Morris DE, Halle JS, *et al.* Induction and concurrent chemotherapy with high-dose thoracic conformal radiation therapy in unresectable stage IIIA and IIIB non-small-cell lung cancer: A dose-escalation phase I trial. *J Clin Oncol* 2004;22: 4341–4350.
14. Rosenman JG, Halle JS, Socinski MA, *et al.* High-dose conformal radiotherapy for treatment of stage IIIA/IIIB non-small-cell lung cancer: Technical issues and results of a phase I/II trial. *Int J Radiat Oncol Biol Phys* 2002; 54:348–356.
15. Miller KL, Shafman TD, Marks LB. A practical approach to pulmonary risk assessment in the radiotherapy of lung cancer. *Semin Radiat Oncol* 2004;14:298–307.
16. Therasse P, Arbuck SG, Eisenhauer EA, *et al.* New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92: 205–216.
17. Marks LB, Bentzen SM, Deasy JO, *et al.* Radiation dose-volume effects in the lung. *Int J Radiat Oncol Biol Phys* 2010;76(3 Suppl):S70–S76.
18. Mehta V. Radiation pneumonitis and pulmonary fibrosis in non-small-cell lung cancer: Pulmonary function, prediction, and prevention. *Int J Radiat Oncol Biol Phys* 2005;63:5–24.
19. Emami B, Lyman J, Brown A, *et al.* Tolerance of normal tissue to therapeutic irradiation. *Int J Radiat Oncol Biol Phys* 1991; 21:109–122.

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Regular Paper

Impact of concurrent chemotherapy on definitive radiotherapy for women with FIGO IIIb cervical cancer

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The purpose of this retrospective study is to investigate the impact of concurrent chemotherapy on definitive radiotherapy for the International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer. Between 2000 and 2009, 131 women with FIGO IIIb cervical cancer were treated by definitive radiotherapy (i.e. whole pelvic external beam radiotherapy for 40–60 Gy in 20–30 fractions with or without center shielding and concomitant high-dose rate intracavitary brachytherapy with 192-iridium remote after loading system for 6 Gy to point A of the Manchester method). The concurrent chemotherapy regimen was cisplatin (40 mg/m^2/week). After a median follow-up period of 44.0 months (range 4.2–114.9 months) and 62.1 months for live patients, the five-year overall survival (OS), loco-regional control (LRC) and distant metastasis-free survival (DMFS) rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that lack of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; $P = 0.001$) and DMFS (HR = 2.53; 95% CI 1.39–4.61; $P = 0.002$), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; $P = 0.322$). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$). In conclusion, concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer.

Keywords: cervical cancer; IIIb; chemotherapy; radiotherapy; HDR

INTRODUCTION

External beam radiotherapy (EBRT) combined with intracavitary brachytherapy (ICBT) is the standard treatment for women with cervical cancer [1–3]. A combination of EBRT plus high-dose rate (HDR) ICBT for Japanese women with cervical cancer has provided acceptable outcomes and late complication rates despite the lower dose prescription in Japan than in the US [4–9]. In 2000s concurrent chemoradiotherapy (CCRT) became standard after the National Cancer Institute (NCI) announcement recommending concurrent chemotherapy in 1999 [10], however, the benefits of concurrent chemotherapy on definitive radiotherapy might not be applicable to concomitant EBRT plus HDR-ICBT and are not clear yet in Japan and other Asian countries [9]. We therefore performed a retrospective analysis in a mono-institutional group with newly diagnosed International Federation of Gynecology and Obstetrics (FIGO) IIIb cervical cancer treated by definitive radiotherapy, the purpose of this study being to investigate the impact of concurrent chemotherapy on definitive radiotherapy for Japanese women.

MATERIALS AND METHODS

Patients

We reviewed our database looking for women with newly diagnosed FIGO IIIb uterine cervical cancers with a

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maximum diameter over 4 cm treated with definitive radiotherapy at the National Cancer Center Hospital between 2000 and 2009. Patients who received palliative EBRT alone, postoperative radiotherapy, interstitial brachytherapy or an experimental regimen of concurrent chemotherapy were excluded. A total of 131 women treated with EBRT plus HDR-ICBT were admitted to this retrospective analysis. All patients underwent pelvic examination, cystoscope, urography, computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and blood tests. Maximum tumor diameters were measured based on the MRI findings and/or US. FIGO staging was allocated for tumor boards of gynecological, medical and radiation oncologists. The pathological diagnosis was carried out with a central pathology review at our pathological division.

Treatment

Treatment selection was determined by the gynecological cancer board, our treatment policy for FIGO IIIb cervical cancer is CCRT to aim for loco-regional control (LRC) even if distant metastasis is not ruled out. Neoadjuvant chemotherapy was prohibited. The concurrent chemotherapy regimen was cisplatin (40 mg/m^2/week). Supportive treatments such as blood transfusions were encouraged during radiotherapy.

Radiotherapy

The radiotherapy field selected was the whole pelvis but exceptions were as follows: para-aortic node (PAN) area irradiation was acceptable in cases with suspicions of PAN metastasis, bilateral inguinal node area irradiation was acceptable in cases with vaginal involvement of more than two-thirds of total vaginal length. Radiotherapy doses of 40–60 Gy in 20–30 fractions were carried out with a 4-field box or the anterior–posterior technique. Center shield radiotherapy (CS) was performed for a shorter overall treatment time (OTT) reducing organ at risk (OAR) exposure depending on tumor shrinkage. CS was carried out 3–4 days/week, and HDR-ICBT 1–2 days/week, but both therapies were not carried out on the same day. All patients underwent EBRT with 10-, 15- and 20-MV X-rays from linear accelerators (Clinac IX, Varian, Palo Alto, CA, USA). Two-dimensional conventional radiotherapy (2DCRT) was employed between 2000 and 2005, and three-dimensional conformal radiotherapy (3DCRT) was used between 2005 and 2010. All patients underwent HDR-ICBT with 192-iridium remote after loading system (RALS, Microselectron). The point A dose prescription for 6 Gy using the Manchester method was performed with the ICBT planning system (Plato®, Nucletron). Image-guided optimization was not applicable even in the case of CT-based ICBT planning. A tandem-cylinder was used only in cases with vaginal involvement of more than one-third of total vaginal length or of an extraordinarily narrow vagina.

Follow-up

All patients were evaluated weekly for toxicity during radiotherapy through physical examinations and blood tests. CT and/or MRI scans and cytology were performed 1–3 months after radiotherapy for initial response, physical examination and blood tests were performed regularly every 1–6 months. Disease progression was defined by the response evaluation criteria in solid tumours (RECIST) version 1.1, new clinical symptoms or observable pelvic deficits.

Statistical analysis

Patient and treatment characteristics were compared using the Mann-Whitney U test and Pearson's chi-square test. OS was estimated from the beginning of radiotherapy to the date of death considered as an event, and censored at the time of last follow-up. LRC rate was estimated from the beginning of radiotherapy to the date of LRC failure including both central and lateral pelvic relapse considered as an event, and censored at the time of death or last follow-up. DMFS rate was estimated from the beginning of radiotherapy to the date of distant metastasis considered as an event, and censored at the time of death or last follow-up. The cumulative incidence rate of late rectal complication was estimated from the beginning of radiotherapy to the date of any grade rectal hemorrhage according to common terminology criteria for adverse events (CTCAE) version 4.0. [11] OS, LRC and DMFS, and the cumulative incidence rates of late rectal complication were calculated using the Kaplan–Meier method [12].

As a measure of radiotherapeutic intensity to point A, we used the equivalent dose in 2-Gy fractions (EQD_2) calculated from total irradiated dose (D) and each dose (d) with α/β for 10 Gy and potential doubling time (Tpot) defined as five days' subtraction from EQD_2 with correction for tumor proliferation associated with OTT (EQD_2T) as shown in the following formula:

$$EQD_2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$$

$$\mathrm{EQD_2}T = \mathrm{EQD_2} - \frac{\log_{e^2}}{\alpha}\frac{\mathrm{T}-\mathrm{T}}{T_{pot}} \Big/ \left(1+\frac{2}{\alpha/\beta}\right)$$

T_K is the kick-off time of accelerated repopulation and was defined as 21 days, and 0.3 for α [13]. These parameters are not well estimated for cervical cancer so we used those for head and neck squamous cell carcinoma (SCC) and extrapolated them. The survival curves were compared using the log-rank test and Cox's proportional hazards model. In order to carry out univariate and/or multivariate

analysis comparing OS, LRC and DMFS rates, patients were categorized as follows: age (<60 vs ≥60), tumor bulk (<55 vs ≥55 mm), OTT (<6 vs ≥6 weeks), hemoglobin (Hb) before (<11.9 vs ≥11.9 mg/dl) and concurrent chemotherapy. We added univariate and multivariate analysis to assess the impact of concurrent chemotherapy on OS, LRC and DMFS after stratified analysis for age and tumor bulk. All statistical analyses were performed using PASW statistics (Version 18.0, SPSS Japan Inc., an IBM company, Chicago, IL, USA). A P value of <0.05 was considered significant.

RESULTS

Patient and treatment characteristics are shown in Table 1. There were differences in age and Hb level after treatment between the radiotherapy alone and CCRT groups. After a median follow-up period of 44.0 months (range 4.2–114.9 months) collectively and 62.1 months for live patients, five-year OS, LRC and DMFS rates were 52.4, 80.1 and 59.9%, respectively. Univariate and multivariate analyses revealed that default of concurrent chemotherapy was the most significant factor leading to poor prognosis for OS (HR = 2.53; 95% CI 1.44–4.47; $P = 0.001$) and DMFS (HR = 2.53; 95% CI 1.39–4.61; $P = 0.002$), but not for LRC (HR = 1.57; 95% CI 0.64–3.88; $P = 0.322$). (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without concurrent chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$) (Fig. 1). After stratifying 131 patients for age and tumor bulk, subgroup analysis with or without concurrent chemotherapy revealed that non-elderly women (HR = 2.78; 95% CI 1.25–6.18; $P = 0.012$) with even bulky length (HR = 2.53; 95% CI 1.26–5.07; $P = 0.009$) clearly benefit from concurrent chemotherapy (Table 3).

DISCUSSION

Various predictors such as treatment duration and anemia had been reported in the last decade before CCRT [14–18]. Concomitant EBRT with HDR-ICBT, which requires shorter treatment duration, was originally the mainstream treatment for women with cervical cancer in Japan [5]. Treatment durations of gross tumor irradiation had a median of 42 days, and were mostly 6 weeks, which is much shorter than the 8 weeks recommended by the American brachytherapy society (ABS) [14]. Concurrent chemotherapy has the potential hazard of treatment interruption associated with acute toxicities, however OTT was not significantly different between radiotherapy alone and CCRT (42 (30–69) vs 42 (36–62) days; $P = 0.217$). In this situation, OTT is no longer a prognostic factor [17]. Similarly, a low Hb value before radiotherapy has no impact on survival, and is no longer a prognostic factor if anemia has been actively corrected using blood transfusion during radiotherapy [18].

Randomized trials have shown survival benefits of CCRT for cervical cancer [19–23]. Incorporating concurrent chemotherapy contributed to improvement in both LRC and DMFS [19–23]. This impact is less in stages III–IV than in stages I–II [20–23]. Our study also supported this impact on OS and DMFS even in cases of FIGO IIIb, but not on LRC (Table 2). The cumulative incidence rates of late rectal complications after definitive radiotherapy were not significantly different with or without chemotherapy (any grade at five years 23.9 vs 21.7%; $P = 0.669$) and reached a plateau (Fig. 1), though limited by the short follow-up period for late radiation-induced complications of other organs such as bladder or small intestine [7].

There were important limitations on this retrospective analysis: the advantage of concurrent chemotherapy might merely indicate that the reasons for not undergoing concurrent chemotherapy were associated with poor prognosis. Forty-two women with FIGO IIIb cervical cancer did not undergo concurrent chemotherapy in our study because of advanced age (77 (72–85) years) for 17 patients (40.4%), and the other half (53 (36–70)) had the following reasons for not undergoing concurrent chemotherapy:PAN irradiation for eight patients (19.0%), renal failure for three patients (7.2%), lack of patient's consent for five patients (11.9%), chronic hepatitis for two patients (4.8%), active pyometra, uncontrolled anemia, synchronous double cancer, hypertrophic cardiomyopathy, low white blood cell counts and sequential chemotherapy for one patient each (2.4%). These reasons not to perform concurrent chemotherapy seem to be clinically ordinary and acceptable, but could indicate a potential selection bias that modified the impact of concurrent chemotherapy. Our study revealed that concurrent chemotherapy is the most significant predictor of definitive radiotherapy, thus we conclude that concurrent chemotherapy combined with definitive radiotherapy for FIGO IIIb cervical cancer is advantageous for survival improvement.

Development of the optimal chemotherapy regimen and schedule to increase chemotherapeutic intensity as a cytotoxic agent but not a radiosensitizer seems to be warranted because our results indicated concurrent chemotherapy has impacts on DMFS but not on LRC. It is not reasonable for Japanese women with cervical cancer to undergo increased intensity of dose-dense concurrent chemotherapy due to a lack of relevant feasibility [24]. There is no evidence that platinum-doublet is superior to platinum-alone as concurrent chemotherapy for cervical cancer [22–23]. Therefore, devising the best form of concurrent chemotherapy is considered to be a limitation. The efficacy of adjuvant chemotherapy after definitive CCRT is unclear but worth testing as it is a feasible method [25].

Table 1. Patient and treatment characteristics for RT alone and CCRT

		RT alone ($n = 42$)	CCRT ($n = 89$)	P
Age	Median (range)	66 (36–85)	55 (29–73)	0.000
Tumor bulk	mm	55 (45–87)	55 (40–95)	0.302
Pathology	SCC	37 (88.1%)	82 (92.1%)	0.454
	non-SCC	5 (11.9%)	7 (7.9%)	
Hb before RT	mg/dl	11.9 (6.4–14.2)	11.9 (7.1–14.5)	0.653
Hb after RT	mg/dl	11.3 (7.6–14.4)	10.3 (6.9–12.3)	0.002
OTT	days	42 (30–69)	42 (36–62)	0.217
EQD_2	Gy	56.4 (44.0–74.0)	54.0 (52.2–74.0)	0.128
EQD_2T	Gy	50.0 (40.9–66.2)	48.2 (39.2–61.2)	0.177
wCDDP courses	1	0	5 (5.6%)	0.000
	2	0	6 (6.8%)	
	3	0	12 (13.5%)	
	4	0	23 (25.8%)	
	5	0	30 (33.7%)	
	6	0	13 (14.6%)	
Reason for RT alone	Advanced age	17 (40.4%)	0	0.000
	PAN irradiation	8 (19.0%)	0	
	No consent	5 (11.9%)	0	
	Renal function	3 (7.2%)	0	
	Hepatitis	2 (4.8%)	0	
	Others	7 (16.7%)	0	
Follow-up	months	30.7 (4.2–100.3)	48.8 (7.3–114.9)	0.001

RT = radiotherapy, CCRT = concurrent chemoradiotherapy, FIGO = International Federation of Gynecology and Obstetrics, SCC = squamous cell carcinoma, Hb = hemoglobin, OTT = overall treatment time, EQD_2 = the equivalent dose in 2-Gy fractions, $EQD_2T = EQD_2$ with correction for tumor proliferation associated with OTT, wCDDP = weekly cisplatin, ns = not significant.

Table 2. Univariate and multivariate analyses on OS, LRC and DMFS

		OS				LRC			DMFS		
Variants		***n***	**Five years**	**uni**	**multi**	**Five years**	**uni**	**multi**	**Five years**	**uni**	**multi**
Age	<60	72	51.4	0.631	0.121	73.3	0.129	0.076	56.0	0.173	0.033
	≥60	59	53.7			89.2			64.8		
Tumor bulk	<55 mm	54	59.8	0.358	0.486	79.5	0.768	0.856	74.4	0.010	0.027
	≥55 mm	77	47.6			80.6			50.2		
OTT	<6 weeks	75	53.1	0.789	0.639	78.5	0.532	0.258	63.5	0.626	0.918
	≥6 weeks	56	50.8			82.6			56.0		
Hb before RT	<11.9 mg/dl	62	53.1	0.627	0.934	74.5	0.380	0.599	59.3	0.527	0.988
	≥11.9 mg/dl	69	52.2			84.8			60.6		
Concurrent chemotherapy	Yes	89	60.4	0.002	0.001	82.6	0.583	0.322	66.6	0.005	0.002
	No	42	33.5			68.3			44.7		

OS = overall survival, LRC = loco-regional control, DFMS = distant metastasis free survival, uni = univariate analysis, multi = multivariate analysis, OTT = overall treatment time, Hb = hemoglobin, ns = not significant.

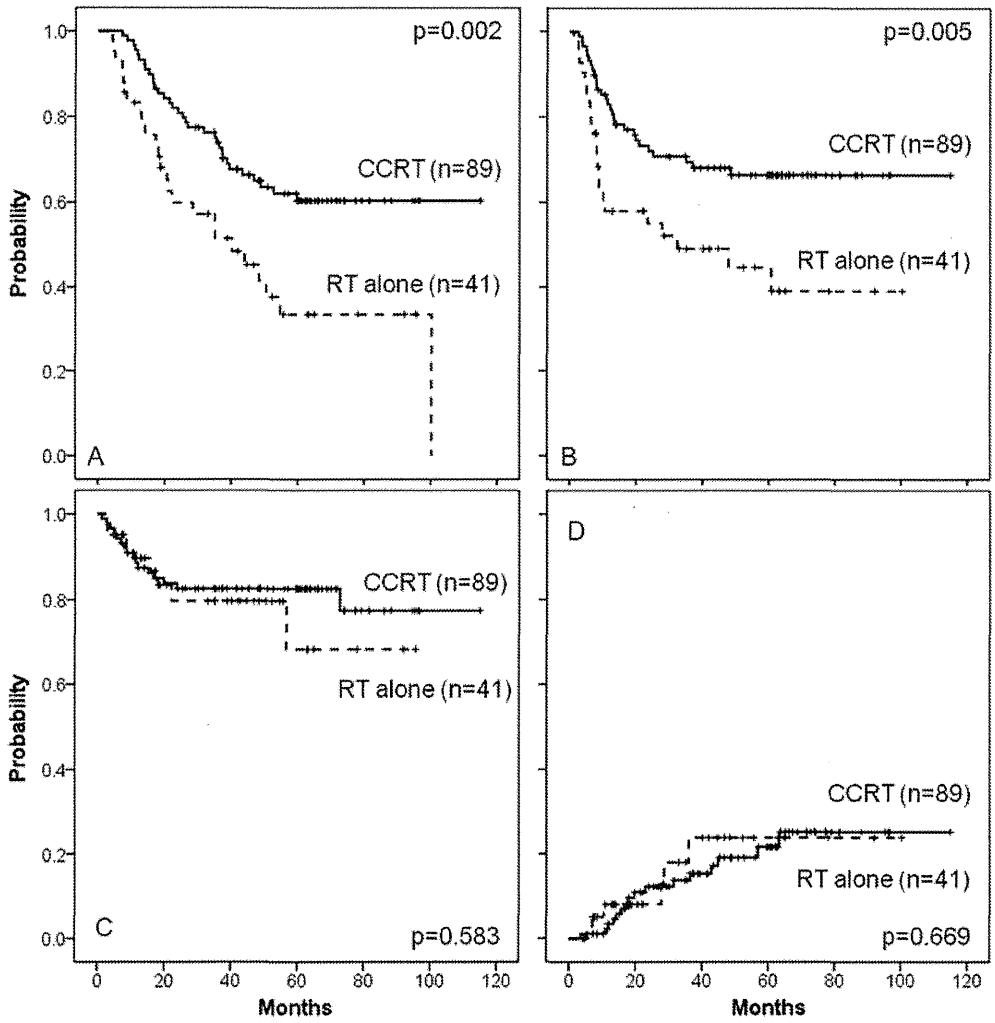

Fig. 1. OS (**A**), DMFS (**B**), LRC (**C**) and the cumulative incidence rates of late rectal complication (**D**) of women with FIGO IIIb cervical cancer after definitive radiotherapy with or without concurrent chemotherapy. Solid line for CCRT, dashed line for RT alone. OS = overall survival, DMFS = distant metastasis free survival, LRC = loco-regional control, CCRT = concurrent chemoradiotherapy, RT = radiotherapy.

Table 3. Impact of concurrent chemotherapy on OS, LRC and DMFS in the stratified analysis

		OS			LRC			DMFS		
		Log-rank	Cox's		Log-rank	Cox's		Log-rank	Cox's	
Variates		***P***	**HR (95%CI)**	***P***	***P***	**HR (95%CI)**	***P***	***P***	**HR (95%CI)**	***P***
Age	<60	0.005	2.78 (1.25–6.18)	0.012	0.145	2.31 (0.76–6.96)	0.136	0.001	2.83 (1.32–6.05)	0.007
	≥60	0.023	2.55 (1.10–5.89)	0.028	0.942	1.05 (0.23–4.85)	0.942	0.079	2.29 (0.88–5.94)	0.087
Tumor bulk	<55 mm	0.118	2.36 (0.85–6.52)	0.096	0.108	5.87 (1.27–27.0)	0.023	0.043	3.46 (1.01–11.9)	0.049
	≥55 mm	0.018	2.53 (1.26–5.07)	0.009	0.587	0.75 (0.22–2.49)	0.645	0.085	2.23 (1.12–4.44)	0.021

OS = overall survival, DMFS = distant metastasis free survival, ns = not significant.

In conclusion, though limited to a mono-institutional retrospective analysis, this study revealed that concurrent chemotherapy is valuable in definitive radiotherapy for Japanese women with FIGO IIIb cervical cancer. A randomized controlled trial is needed to establish the optimal chemotherapy combined with definitive radiotherapy for women with advanced cervical cancer.

ACKNOWLEDGEMENTS

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REFERENCES

1. Thoms WW, Jr, Eifel PJ, Smith TL *et al.* Bulky endocervical carcinoma: a 23-year experience. *Int J Radiat Oncol Biol Phys* 1992;**23**:491–9.
2. Perez CA, Grigsby PW, Nene SM *et al.* Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone. *Cancer* 1992;**69**:2796–806.
3. Landoni F, Maneo A, Colombo A *et al.* Randomised study of radical surgery versus radiotherapy for stage Ib-IIa cervical cancer *Lancet* 1997;**350**:535–40.
4. Eifel PJ, Moughan J, Erickson B *et al.* Patterns of radiotherapy practice for patients with carcinoma of the uterine cervix: a patterns of care study. *Int J Radiat Oncol Biol Phys* 2004;**60**:1144–53.
5. Toita T, Kodaira T, Shinoda A *et al.* Patterns of radiotherapy practice for patients with cervical cancer (1999–2001): patterns of care study in Japan. *Int J Radiat Oncol Biol Phys 2008*;**70**:788–94.
6. Toita T, Kato S, Niibe Y *et al.* Prospective multi-institutional study of definitive radiotherapy with high-dose-rate intracavitary brachytherapy in patients with nonbulky (<4-cm) stage i and ii uterine cervical cancer (JAROG0401/JROSG04-2). *Int J Radiat Oncol Biol Phys* 2012;**82**:49–56.
7. Nakano T, Kato S, Ohno T *et al.* Long-term results of high-dose rate intracavitary brachytherapy for squamous cell carcinoma of the uterine cervix. *Cancer* 2005;**103**:92–101.
8. Toita T, Moromizato H, Ogawa K *et al.* Concurrent chemoradiotherapy using high-dose-rate intracavitary brachytherapy for uterine cervical cancer. *Gynecol Oncol* 2005;**96**:665–70.
9. Nagase S, Inoue Y, Umesaki N *et al.* Evidence-based guidelines for treatment of cervical cancer in Japan: Japan Society of Gynecologic Oncology (JSGO) 2007 edition. *Int J Clin Oncol* 2010;**15**:117–24.
10. NCI Issues Clinical Announcement on Cervical Cancer: Chemotherapy Plus Radiation Improves Survival. http://www.nih.gov/news/pr/feb99/nci-22.htm (11 April 2012, date last accessed).
11. National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03, 2010. http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf (10 April 2012, date last accessed).
12. Kaplan EL, Meier P Nonparametric estimation from incomplete observations *J Am StatAssoc* 1958;**53**:457–81.
13. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist: Time, Dose, and Fractionation in Radiotherapy, 6th edn.* Philadelphia: Lippincott Williams & Wilkins, 2006, 378–97.
14. Nag S, Erickson B, Thomadsen B *et al.* The American Brachytherapy Society recommendations for high-dose-rate brachytherapy for carcinoma of the cervix. *Int J Radiat Oncol Biol Phys* 2000;**48**:201–11.
15. Lanciano RM, Martz K, Coia LR *et al.* Tumor and treatment factors improving outcome in stage III-B cervix cancer. *Int J Radiat Oncol Biol Phys* 1991;**20**:95–100.
16. Toita T, Kakinohana Y, Ogawa K *et al.* Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer: analysis of dose and fractionation schedule. *Int J Radiat Oncol Biol Phys* 2003;**56**:1344–53.
17. Chatani M, Matayoshi Y, Masaki N *et al.* High-dose rate intracavitary irradiation for carcinoma of the uterine cervix. The adverse effect of treatment prolongation. *Strahlenther Onkol* 1997;**173**:379–84.
18. Grogan M, Thomas GM, Melamed I *et al.* The importance of hemoglobin levels during radiotherapy for carcinoma of the cervix. *Cancer* 1999;**86**:1528–36.
19. Rose PG, Bundy BN, Watkins EB *et al.* Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med* 1999;**340**:1144–53.
20. Morris M, Eifel PJ, Lu J *et al.* Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med* 1999;**340**:1137–43.
21. Eifel PJ, Winter K, Morris M *et al.* Pelvic irradiation with concurrent chemotherapy versus pelvic and para-aortic irradiation for high-risk cervical cancer: an update of radiation therapy oncology group trial (RTOG) 90-01. *J Clin Oncol* 2004;**22**:872–80.
22. Green JA, Kirwan JM, Tierney JF *et al.* Survival and recurrence after concomitant chemotherapy and radiotherapy for cancer of the uterine cervix: a systematic review and meta-analysis. *Lancet* 2001;**358**:781–6.
23. Chemoradiotherapy for Cervical Cancer Meta-Analysis Collaboration. Reducing uncertainties about the effects of chemoradiotherapy for cervical cancer: a systematic review and meta-analysis of individual patient data from 18 randomized trials. *J Clin Oncol* 2008;**26**:5802–12.
24. Watanabe Y, Nakai H, Shimaoka M *et al.* Feasibility of concurrent cisplatin use during primary and adjuvant chemoradiation therapy: a phase I study in Japanese patients with cancer of the uterine cervix. *Int J Clin Oncol* 2006;**11**:309–13.
25. Dueñas-González A, Zarbá JJ, Patel F *et al.* Phase III, open-label, randomized study comparing concurrent gemcitabine plus cisplatin and radiation followed by adjuvant gemcitabine and cisplatin versus concurrent cisplatin and radiation in patients with stage IIB to IVA carcinoma of the cervix. *J Clin Oncol* 2011;**29**:1678–85.

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

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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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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

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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 ($\geq$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 $\leq$ PO_2 versus $>$70 mmHg), hemoglobin (Hgb $<$ 13.7 g/dl versus $\geq$ 13.7 g/dl), platelet (Plt $>$ 367 $\times$ 10^9/L versus $\leq$367 $\times$ 10^9/L), albumin (Alb $<$ 3.7 g/dl versus $\geq$3.7 g/dl), sodium (Na $<$ 138 mEq/L versus $\geq$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

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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.

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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-

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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

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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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REFERENCES

1. Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment-related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.
2. Morittu L, Earl HM, Souhami RL, et al. Patients at risk of chemotherapy-associated toxicity in small cell lung cancer. *Br J Cancer* 1989;59: 801–804.
3. Radford JA, Ryder WD, Dodwell D, et al. Predicting septic complications of chemotherapy:an analysis of 382 patients treated for small cell lung cancer without dose reduction after major sepsis. *Eur J Cancer* 1992;29A:81–86.
4. Stephens RJ, Girling DJ, Machin D. Treatment-related deaths in small cell lung cancer trials: can patients at risk be identified? Medical Research Council Lung Cancer Working Party. *Lung Cancer* 1994;11: 259–274.
5. Sekine I, Noda K, Oshita F, et al. Phase I study of cisplatin, vinorelbine, and concurrent thoracic radiotherapy for unresectable stage III non-small cell lung cancer. *Cancer Sci* 2004;95:691–695.
6. Graham MV, Purdy JA, Emami B, et al. Clinical dose-volume histogram analysis for pneumonitis after 3D treatment for non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 1999;45:323–329.
7. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18:317–323.
8. Takada M, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104. *J Clin Oncol* 2002;20: 3054–3060.
9. Noda K, Nishiwaki Y, Kawahara M, et al; Japan Clinical Oncology Group. Irinotecan plus cisplatin compared with etoposide plus cisplatin for extensive small-cell lung cancer. *N Engl J Med* 2002;346:85–91.
10. Sekine I, Sumi M, Ito Y, et al. Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients. *Radiother Oncol* 2006;80:93–97.
11. Ando M, Okamoto I, Yamamoto N, et al. Predictive factors for interstitial lung disease, antitumor response, and survival in non-small-cell lung cancer patients treated with gefitinib. *J Clin Oncol* 2006;24:2549–2556.
12. Barlési F, Villani P, Doddoli C, et al. Gemcitabine-induced severe pulmonary toxicity. *Fundam Clin Pharmacol* 2004;18:85–91.
13. Yuen AR, Zou G, Turrisi AT, et al. Similar outcome of elderly patients in intergroup trial 0096: cisplatin, etoposide, and thoracic radiotherapy administered once or twice daily in limited stage small cell lung carcinoma. *Cancer* 2000;89:1953–1960.
14. Schild SE, Stella PJ, Geyer SM, et al. North Central Cancer Treatment Group. The outcome of combined-modality therapy for stage III non-small-cell lung cancer in the elderly. *J Clin Oncol* 2003;21:3201–3206.
15. Schild SE, Stella PJ, Brooks BJ, et al. Results of combined-modality therapy for limited-stage small cell lung carcinoma in the elderly. *Cancer* 2005;103:2349–2354.
16. Aupérin A, Le Péchoux C, Pignon JP, et al; Meta-Analysis of Cisplatin/carboplatin based Concomitant Chemotherapy in non-small cell Lung Cancer (MAC3-LC) Group. Concomitant radio-chemotherapy based on platin compounds in patients with locally advanced non-small cell lung cancer (NSCLC): a meta-analysis of individual data from 1764 patients. *Ann Oncol* 2006;17:473–483.

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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. © 2012 Elsevier Inc.

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

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

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 $\alpha/\beta = 10$ Gy for tumor control and $\alpha/\beta = 3$ 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.

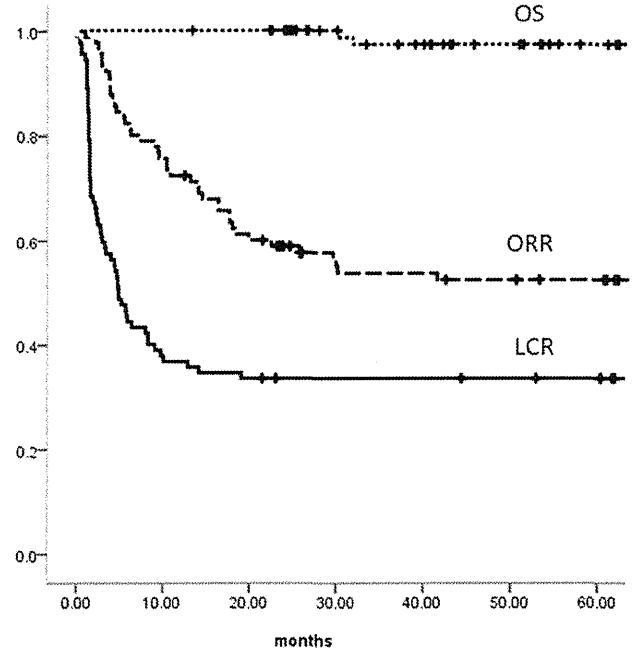

Fig. 1. Kaplan-Meyer curves of local control rate (LCR), ocular retention rate (ORR), and overall survival (OS).

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.

* $P<.05$.