uncorrected depth-output curve measured with the MOSFET detector. The "Simulation with Correction" curve depicts results corrected without the necessity of applying the experimentally determined MOSFET response corrections to the "Simulation" curve. Thus, given $cf_{mono}(d_{PE})$ of Eq. (6) for the mono-energetic proton beam, we can obtain $cf_{SOBP}(d_{PE})$ for various SOBP-width proton beams by simulating the SOBP beam using the Bragg curve of a mono-energetic proton beam.

D. Bolus experiments

Figure 6 compares the lateral dose distributions obtained for a 190 MeV proton beam using IC and MOSFET detectors at PE thicknesses of 0 (a), 100 (b), 105 (c), 110 (d) and 115 (e) mm. The error bar in Fig. 6 includes the reproducibility of the MOSFET measurements and calculation errors of 3% to account for uncertainties in the PBA (as described in Materials and Methods Section C.2). In Fig. 6(a), a bump and dip structure is evident near x = 0. This is the result of edge scattering effects due to the abrupt change in thickness. The uncorrected MOSFET results agreed well with the IC measurements, and the MOSFET response due to LET did not change at this depth. Thus, in shallow regions, depth-dose distribution corrections are unnecessary.

On the other hand, the MOSFET detector response began to change at x < 0 and the uncorrected MOSFET output deviated significantly from the IC response (Fig. 6(b)). Because the depth at x < 0 is close to the Bragg peak position, the MOSFET response was reduced. Since edge scattering causes the lateral dose distribution near x = 0 to be determined by protons with a distribution of energies, we expected that changes in the MOSFET response would be complex. However, the corrected output of the MOSFET detector agreed well with the IC results within an average difference of 4.4%, demonstrating that MOSFET detectors are suitable for proton dosimetry when the response is corrected. Despite the drastic change in MOSFET detector response near x < 0 for PE thicknesses of 105, 110 and 115 mm, the corrected output agreed with the IC results (Figs. 6(c), 6(d), and 6(e)) within 3.2% (1 sigma).

Figure 7 is a comparison of the lateral-dose distribution obtained using the IC and MOSFET detectors at PE thicknesses of 0 (a), 50 (b) and 100 (c) mm for an SOBP proton beam. The corrected MOSFET output agreed well with the IC results. For the SOBP beam, the accuracy of the dose measurement was approximately 2.3% (1 sigma).

By employing correction methods for LET and angular dependence, it is possible to perform *in vivo* proton dosimetry using a MOSFET detector. However, the correction method for LET effects is highly dependent on the precision of the PBA calculation, and further improvements to the dose calculation algorithm (for instance the application of Monte Carlo methods) would be desirable in situations involving tissues with significant heterogeneity.[19-23]

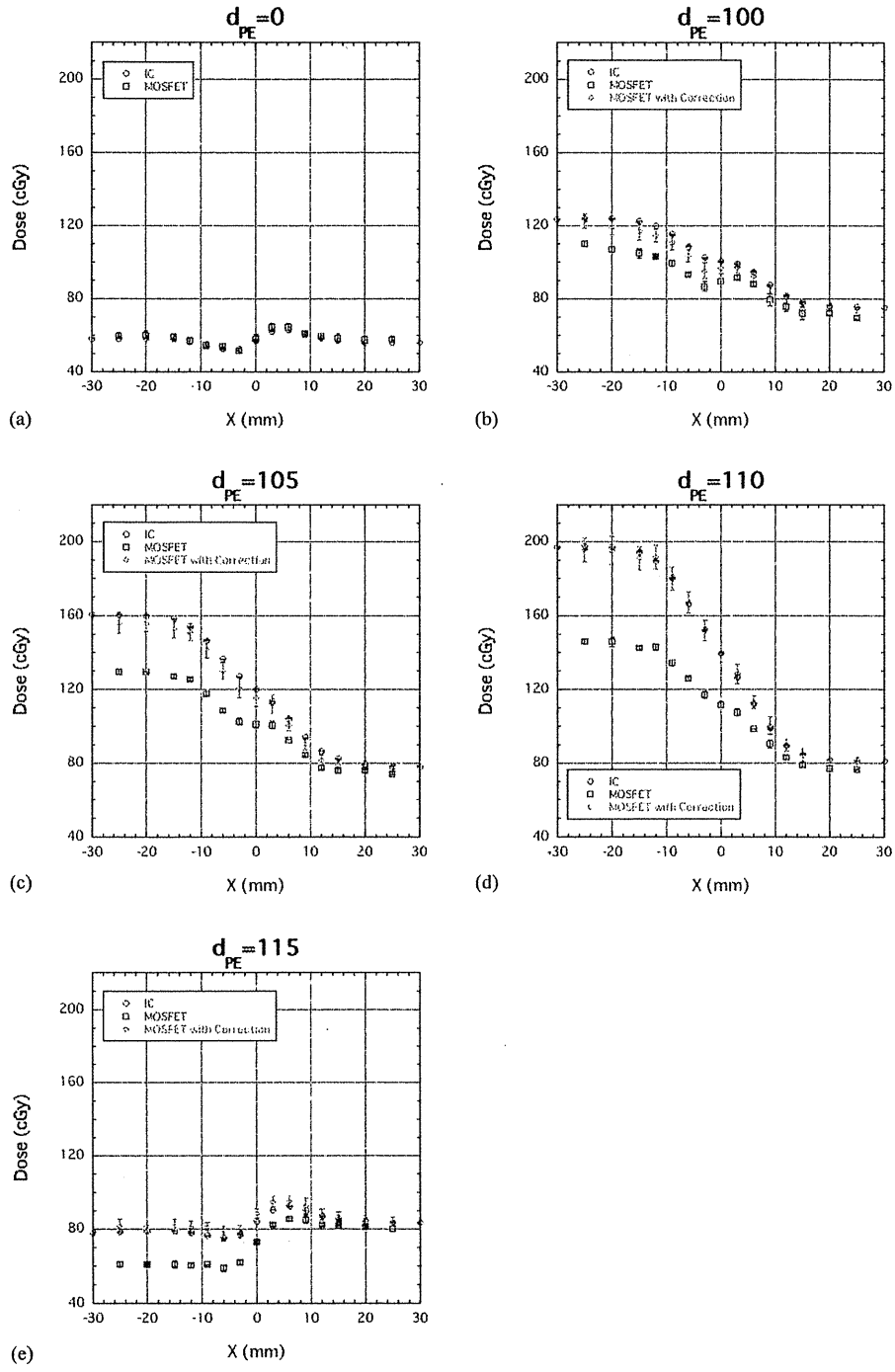

FIG. 6. Comparison of lateral-dose distribution obtained using IC, uncorrected MOSFET (MOSFET) and corrected MOSFET detectors (MOSFET with Correction) at PE thicknesses of 0 (a), 100 (b), 105 (c), 110 (d) and 115 (e) mm for a 190 MeV mono-energetic proton beam.

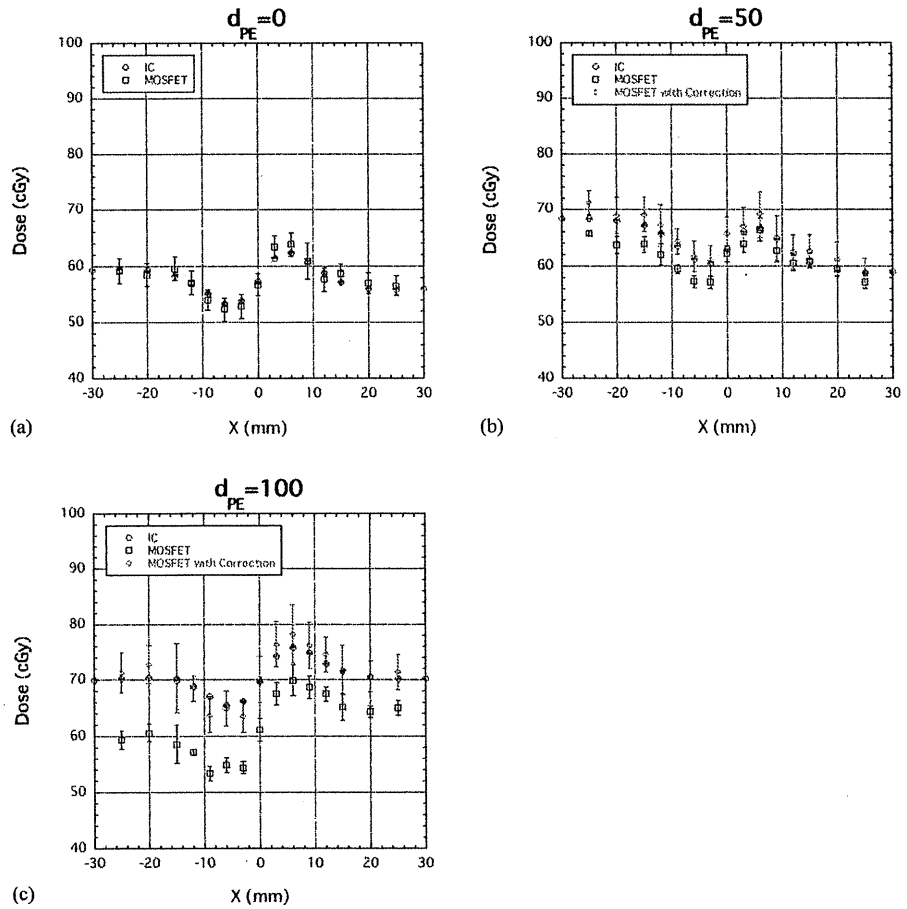

FIG. 7. Comparison of lateral-dose distribution measurements obtained using IC, uncorrected MOSFET (MOSFET) and corrected MOSFET detectors (MOSFET with Correction) at PE thicknesses of 0 (a), 50 (b) and 100 (c) mm for a SOBP proton beam.

IV. CONCLUSIONS

We experimentally evaluated the proton beam dose reproducibility, angular dependence and depth-dose relationships for a new TN-252RD MOSFET detector at high-bias voltages. The reproducibility of the MOSFET detector was within 2%, and the angular dependence was less than 9%. For depth-dose distribution measurements, the relative response of the MOSFET detector at the Bragg peak region was 26% lower than measurements obtained using an ionization chamber. A thinner oxide layer thickness improved the LET dependence in proton dosimetry, although LET dependence was still the limiting factor in accurate depth-dose estimation.

In order to measure dose distributions using a MOSFET detector, we developed a practical method for correcting the MOSFET response to proton beams. For dose distributions resulting from protons passing through an L-shaped bolus, the corrected MOSFET dose agreed well with the IC results. Absolute proton dosimetry was performed using MOSFET detectors with a precision of approximately 3% (1 sigma), and from this we conclude that it is possible to measure proton doses using MOSFET detectors.

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CLINICAL INVESTIGATION **Brain**

COMPARISON OF CLINICAL OUTCOMES OF SURGERY FOLLOWED BY LOCAL BRAIN RADIOTHERAPY AND SURGERY FOLLOWED BY WHOLE BRAIN RADIOTHERAPY IN PATIENTS WITH SINGLE BRAIN METASTASIS: SINGLE-CENTER RETROSPECTIVE ANALYSIS

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Purpose: Data comparing the clinical outcomes of local brain radiotherapy (LBRT) and whole brain RT (WBRT) in patients with a single brain metastasis after tumor removal are limited.

Patients and Methods: A retrospective analysis was performed to compare the patterns of treatment failure, cause of death, progression-free survival, median survival time, and Karnofsky performance status for long-term survivors among patients who underwent surgery followed by either LBRT or WBRT between 1990 and 2008 at the National Cancer Center Hospital.

Results: A total of 130 consecutive patients were identified. The median progression-free survival period among the patients who received postoperative LBRT ($n = 64$) and WBRT ($n = 66$) was 9.7 and 11.5 months, respectively ($p = .75$). The local recurrence rates (LBRT, 9.4% vs. WBRT, 12.1%) and intracranial new metastasis rate (LBRT, 42.2% vs. WBRT, 33.3%) were similar in each arm. The incidence of leptomeningeal metastasis was also equivalent (LBRT, 9.4% vs. WBRT, 10.6%). The median survival time for the LBRT and WBRT patients was 13.9 and 16.7 months, respectively ($p = .88$). A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the WBRT group ($p = .99$). The Karnofsky performance status at 2 years was comparable between the two groups.

Conclusions: The clinical outcomes of LBRT and WBRT were similar. A prospective evaluation is warranted.

Local brain radiotherapy, Whole brain radiotherapy, Single brain metastasis, Clinical outcomes, Long-term result.

INTRODUCTION

Whole brain radiotherapy (WBRT) has served as the standard of care for patients with brain metastases worldwide (1, 2). In patients with a single brain metastasis, postoperative WBRT has demonstrated better intracranial tumor control for both surgical lesions and nonsurgical new lesions and a lower rate of a neurologic cause of death compared with surgery alone (3). However, the addition of WBRT did not result in a survival benefit or extend the duration of the interval that the patients remained functionally independent. Some prospective trials, with the exception of one, and pooled analyses have clarified that a survival benefit for surgery followed by WBRT does exist compared with WBRT alone (1, 4–7). Other studies have also revealed that surgery followed by WBRT increased the duration of neurocognitive functional independence, as well as intracranial tumor control (4–6, 8, 9). Accordingly, surgery followed by WBRT has been the standard of care for patients with a single brain metastasis.

The median survival time of patients with brain metastases is considered to be approximately 2–7 months; favorable and unfavorable subgroups can be classified using recursive partitioning analysis (RPA) (10). However, about 2–8% of patients with brain metastasis can achieve longer survival periods (11, 12). Delayed WBRT toxicity, hypopituitarism, dementia, and memory disturbances influencing cognitive function have also been discussed, although the primary brain lesion is mainly responsible for the deterioration of functional independence (11, 13, 14).

Because WBRT is widely believed to induce dementia in patients with brain metastases, local brain RT (LBRT) as a substitute for WBRT has been widely accepted in some

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Table 1. Patient characteristics (n = 130)

Characteristic	All patients	Range	LBRT (n = 64)	WBRT (n = 66)	p
Age (y)	58	24–87	58 (38–87)	58 (24–79)	.35
Karnofsky performance status	70	40–100	70 (40–100)	70 (40–100)	.35
RPA class	II	I–III	II (I–III)	II (I–III)	.78*
I	40	30.8	19	21	
II	55	42.3	26	29	
III	35	26.9	19	16	
Cancer type (%)					.96*
Lung cancer	55	42.3	29	26	
Non–small-cell lung cancer	54		29	25	
Small-cell lung cancer	1		0	1	
Breast cancer	18	13.8	9	9	
Colorectal cancer	14	10.8	6	8	
Skin cancer	6	4.6	3	3	
Other	37	28.5	17	20	
Diameter of brain tumor (mm)	38	10–65	38 (10–65)	38 (15–60)	.57
Removal status					.11
Gross total removal	124	95.4	59	65	
Partial removal	6	4.6	5	1	

Abbreviations: RPA = recursive partitioning analysis; WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy,
Data presented as median, with range in parentheses.
* Chi-square test.

institutions in Japan (15). LBRT delivered by linear accelerator to the tumor bed with a margin determined using the two-field technique (opposing portal irradiation) according to a dose-fractionated schedule had been applied for the treatment of single brain metastasis after surgical removal at the National Cancer Center Hospital before September 2004. This was based on the ethics that we presumed we could treat intracranial relapse using stereotactic RT after LBRT. After discussion with neurosurgeons, radio-oncologists, and medical oncologists, however, the treatment policy was changed. WBRT has been used for the treatment of all patients with single brain metastasis after tumor removal since October 2004. A Phase I-II clinical trial of postoperative LBRT was reported, and the investigators concluded that LBRT was not a suitable substitute for WBRT (16). However, that previous study included only 12 patients, and 7 of these patients died of intracranial tumor progression. The median survival time was 7.2 months, similar to that after WBRT. Another retrospective study implied that LBRT might have a similar benefit to that of WBRT in patients with a single brain metastasis (17). Bahl *et al.* (18) reported 7 cases of postoperative LBRT, of which 4 cases recurred at the same site. These studies included only a small number of patients, and any conclusions regarding the clinical outcome of postoperative LBRT, especially compared with that of postoperative WBRT, are thus difficult to make. In the present analysis, we retrospectively compared the clinical outcomes of patients with a single brain metastasis who received surgery followed by either WBRT or LBRT.

PATIENTS AND METHODS

Patient population

From the database of the neurosurgery division at the National Cancer Center Hospital, we identified patients who had undergone brain tumor removal followed by RT between 1990 and 2008. The patients were included in the present analysis if they met the following criteria: age ≥18 years, a single brain metastasis identified by magnetic resonance imaging, and tumor removal followed by either WBRT or LBRT. The exclusion criteria were as follows: extracranial malignant lymphoma or hematological tumor; brain biopsy only; previous brain RT; surgery followed by observation, with brain RT once progression was recognized; and postoperative gamma knife or linear accelerator-based radiosurgery. All the patients who received LBRT (n = 64) were treated before October 2004, and all the patients who received WBRT (n = 66) were treated after October 2004.

Data collection and definitions of terms

All the medical charts for the eligible patients were reviewed. To compare the clinical outcomes of postoperative WBRT and LBRT, we collected the following data:; preoperative magnetic resonance imaging; date of surgery and RT; RPA classification before surgery; Karnofsky performance status (KPS) at presentation; primary tumor site; date of recognition of local recurrence or intracranial new metastases; patterns of progression; leptomeningeal metastasis development; date of death; and neurologic cause of death. For the additional evaluation of long-term survivors (≥2 years after surgery), we also reviewed the KPS at 2 years after surgery.

Local recurrence was defined as recurrence at the surgical site. Intracranial new metastases included the detection of new brain metastases other than those occurring at the surgical site or the development of leptomeningeal metastases. Leptomeningeal metastases were diagnosed using a cytologic examination of cerebrospinal fluid.

Surgery and RT

The surgical indications for single brain metastasis were generally as follows: tumor diameter ≥30 mm or a tumor diameter of <30 mm with neurologic dysfunction.

Whole brain RT was administered through two lateral ports covering the brain and meninges to the foramen magnum. Normally, WBRT was delivered using a 4-MV or 6-MV linear accelerator at

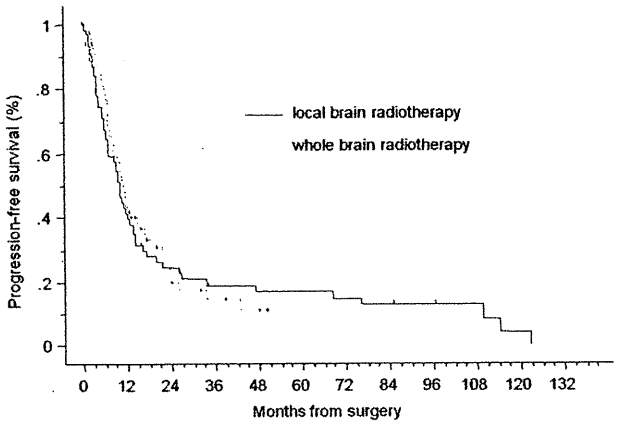

Fig. 1. Progression-free survival for patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

a total dose of 30 Gy in 10 fractions or 37.5 Gy in 15 fractions. Patients who received LBRT underwent computed tomography simulation in the supine position. The clinical target volume consisted of the tumor cavity plus a 1.5-cm margin, and the planning target volume was created by expanding the clinical target volume by 0.5 cm. LBRT was administered using a 6-MV linear accelerator to the tumor bed using a two-field technique according to a dose-fractionated schedule. Normally, LBRT was delivered at a total dose of 50 Gy in 25 fractions.

Statistical analysis

Postoperative differences in local recurrence, intracranial new metastases, the development of leptomeningeal metastases, and neurologic cause of death were compared between the WBRT and LBRT groups using the Fisher exact test. Numeric data, including RPA, KPS, and age, were compared using the Mann-Whitney *U* test. Progression-free survival was defined as the interval between the date of surgery to the date of the recognition of local recurrence or intracranial new metastases. Death was treated as an event, and the absence of disease progression was treated as a censored observation on the last day of follow-up. Overall survival was defined as the interval from the date of surgery to the date of death. Patients who were lost to follow-up were treated as a censored observation on the last day of follow-up. Univariate and multivariate analyses using the Cox proportional hazard model were performed to identify relevant factors affecting survival. The numeric factors analyzed in the Cox analyses were dichotomized according to the median number. All statistical analyses were performed using StatView, version 5.0 (SAS Institute, Tokyo, Japan).

RESULTS

Of the 421 surgical cases, we identified 130 patients who met the eligibility criteria. The characteristics of these patients are listed in Table 1. Of the 130 patients, 66 had received postoperative WBRT and 64 had received postoperative LBRT. Of the 66 patients who had received WBRT, 34 (51.5%) were treated to a dose of 30 Gy delivered in 10 fractions, and 31 (47.0%) were treated to a dose of 37.5 Gy delivered in 15 fractions. Of the 64 patients who received LBRT, 57 (89.1%) were treated to a dose of 50 Gy in 25 fractions, and 7 were treated with a variety of dose-fractionation schedules (24 Gy in 12 fractions to 60 Gy in 30 fractions).

The median progression-free survival period for the patients who received postoperative LBRT and WBRT was 9.7 and 11.5 months, respectively ($p = .75$; Fig. 1). The patients who underwent LBRT and WBRT developed 33 and 30 recurrences, respectively. The local recurrence rates (9.4% vs. 12.1%) and intracranial new metastases rates (42.2% vs. 33.3%) were not significantly different between the LBRT and WBRT groups (Table 2). The incidence of leptomeningeal metastases in patients receiving LBRT and WBRT was 9.4% and 10.6%, respectively ($p = .99$).

The median survival time for patients who received postoperative LBRT and WBRT was 13.9 and 16.7 months, respectively ($p = .88$; Fig. 2). Of the 64 patients who received LBRT and the 66 patients who received and WBRT, 59 and 49 died, respectively. A neurologic cause of death was noted in 35.6% of the patients in the LBRT group and 36.7% of the patients in the WBRT group ($p = .99$; Table 2). Univariate analyses revealed that only the RPA classification correlated significantly with survival (hazard ratio [HR], 0.436; $p = .002$). In particular, RT (LBRT vs. WBRT) did not correlate with survival (HR, 1.031; $p = .88$; Table 3). Multivariate analyses revealed that RPA was the only significant factor associated with survival (HR, 0.399; $p = .001$). Neither LBRT nor WBRT was related to survival (HR, 0.933; $p = .74$; Table 4).

Table 2. Patterns of treatment failure in patients who received WBRT and LBRT

Variable	LBRT ($n = 64$)	WBRT ($n = 66$)	
Total recurrences identified *(n)*	33	30	*p*
Local recurrence	6 (18.2)	8 (26.7)	.61
Distant metastasis	27 (81.8)	22 (73.3)	.61
Development of leptomeningeal metastases *(n)*	6	7	.99
Total deaths identified *(n)*	59	49	
Neurologic cause of death	21 (35.6)	18 (36.7)	.98*
Other	21 (35.6)	17 (34.7)	
Unknown	17 (28.8)	15 (30.6)	

Abbreviations: WBRT = whole brain radiotherapy; LBRT = local brain radiotherapy.
Data in parentheses are percentages.
* Chi-square test.

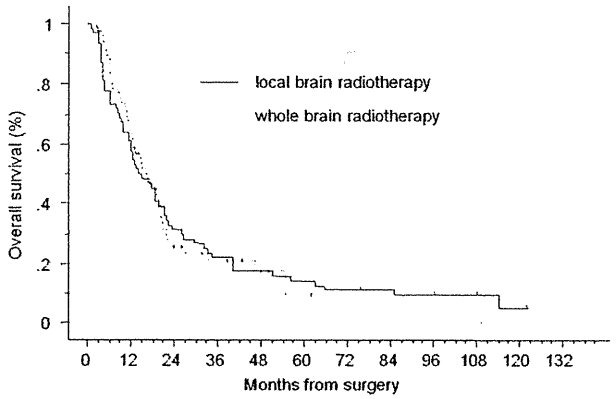

Fig. 2. Overall survival in patients with local brain radiotherapy (black line) and whole brain radiotherapy (dashed line).

We further analyzed the patterns of RT after recurrence in patients who received either postoperative LBRT or WBRT. Of the 33 patients who developed recurrences after postoperative LBRT, additional RT was performed in 15 (45.5%). Of the 15 patients, 6 underwent gamma knife or linear accelerator-based radiosurgery. LBRT was performed in 5 patients, and 4 received WBRT. Of the 30 patients who developed recurrences after postoperative WBRT, 16 (53.3%) received additional RT. Of the 16 patients, 13 received gamma knife or linear accelerator-based radiosurgery, and 3 received LBRT.

Among the patients who survived for >2 years, we compared the KPS at 2 years after surgery. A total of 20 patients who had received postoperative LBRT and 13 who had received postoperative WBRT were identified. The median KPS score at 2 years for these patients in the LBRT and WBRT groups was 80 (range, 60–100) and 80 (range, 60–100; $p = .99$), respectively. Of the 20 patients who had received LBRT, 9 experienced relapse in a local lesion, 2 had focal signs without relapse, which might have indicated radiation necrosis, and 7 had been well without relapse. For 2 other patients, this information was not available.

DISCUSSION

We have revealed the clinical outcomes of postoperative LBRT among patients with single metastasis and compared them with those of patients who underwent postoperative WBRT. The clinical outcomes, including progression-free survival, overall survival, local recurrence, intracranial new metastases, development of leptomeningeal metastases, and neurologic cause of death, were not significantly different between the two groups. In an analysis of relapse patterns, the patients treated with LBRT tended to have a lower probability of developing local recurrence (9.4% vs. 12.1%) and a greater probability of developing intracranial new metastases (42.2% vs. 33.3%), although these values were not significantly different. The probability of developing leptomeningeal metastases was also similar in each group (9.4% vs. 10.6%).

Previous reports have indicated that the addition of WBRT after tumor removal significantly reduces the local recurrence rate (3, 9). However, approximately 6–50% of patients develop relapses at new intracranial sites in the brain (5, 9, 19). Furthermore, about 20–30% of patients with brain metastasis die of neurologic causes even if a radiation boost has been added using stereotactic radiosurgery to increase local control, although the presence of extracranial lesions is the strongest factor for predicting survival (7, 20, 21). In our study, intracranial new metastases were predominant in both groups. The frequency of intracranial recurrence (new local and intracranial metastases) was somewhat greater than in previous series, although the rate of a neurologic cause of death was equivalent. Importantly, the patterns of treatment failure were similar in the LBRT and WBRT groups. Muacevic *et al.* (22) insisted that postoperative WBRT should be applied in patients with a single brain metastasis to destroy so-called micrometastases, based on the results of their randomized trial. They compared patients with a small single metastasis who received either surgery plus WBRT or gamma knife surgery alone. Their sample size was underpowered, although the risk of intracranial new metastases seemed to be lower in the WBRT cohort. To date, no randomized trials comparing the clinical outcomes of postoperative WBRT and postoperative gamma knife or linear accelerator-based radiosurgery, or LBRT have been reported.

We have demonstrated a similar efficacy for LBRT and WBRT. WBRT has problems in terms of delayed toxicity developing leukoencephalopathy, although the number of long-term survivors with brain metastasis seems to be somewhat low (11, 12). LBRT might be beneficial with regard to the protection of normal brain tissue. We compared the KPS

Table 3. Univariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	1.031	0.698–1.523	.88
RPA classification			
I vs. III	0.436	0.259–0.733	.002
II vs. III	0.808	0.514–0.127	.35
Removal status (gross total removal vs. partial removal)	0.948	0.385–2.334	.91
Tumor diameter (≥38 vs. <38 mm)	1.053	0.718–1.543	.79
Cancer type (lung cancer vs. other)	0.694	0.470–1.025	.062

Abbreviations: RT = radiotherapy; HR = hazard ratio; CI = confidence interval; other abbreviations as in Table 1.

Table 4. Multivariate analyses regarding survival

Variable	HR	95% CI	*p*
RT (LBRT vs. WBRT)	0.933	0.614–1.416	.743
RPA classification			
I vs. III	0.399	0.232–0.688	.001
II vs. III	0.736	0.455–1.191	.22
Removal status (gross total removal vs. partial removal)	0.622	0.239–1.615	.33
Tumor diameter (≥38 vs. <38 mm)	0.852	0.559–1.297	.45
Cancer type (lung cancer vs. other)	0.662	0.438–1.001	.05

Abbreviations as in Tables 1 and 3.

at 2 years to examine any delayed toxicity. Because of the nature of the present retrospective study, the detailed neurocognitive function or quality of life of the patients could not be identified. Among the long-term survivors, however, the KPS was preserved in both treatment groups. Thus, LBRT might be indicated for elderly patients at risk of developing dementia if LBRT has the same ability to control primary brain tumors, which is considered to be the main factor affecting neurocognitive function (14).

The present study had some limitations because of its retrospective nature. First, the radiation dose varied. About 90% of the LBRT patients received a dose of 50 Gy delivered in 25 fractions, and approximately 50% of the WBRT patients received a dose of 30 Gy delivered in 10 fractions; the others received a dose of 37.5 Gy delivered in 15 fractions. According to the summary by Tsao *et al.* (1), no differences in terms of survival or neurocognitive function were observed among the various dose-fraction schedules of WBRT. Second, the present study was a historical case-control study comparing LBRT and WBRT. Patients at risk of developing multiple metastases might have undergone WBRT during the period before 2004, when we started performing WBRT as the standard of care. Thus, the patients who were treated with LBRT might have had better general condition compared with the patients who were treated with WBRT. We compared the baseline characteristics of each treatment arm and used multivariate analyses to reduce any potential biases.

CONCLUSIONS

We have demonstrated the clinical efficacy of LBRT compared with WBRT on a large scale. The clinical outcomes, including progression-free survival, overall survival, patterns of treatment failure, development of leptomeningeal metastases, and a neurologic cause of death, were similar in both treatment groups. The KPS at 2 years was also similar when the two groups were compared. This result should be evaluated in a prospective manner.

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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

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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).

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Thus, improvement of local control and suppression of distant metastasis are essential for prolongation of patient survival.

The conventional total dose of thoracic radiotherapy in patients with inoperable NSCLC has been 60 Gy administered in 30 fractions. This dose was established in 1987 by randomized Radiation Therapy Oncology Group trials that demonstrated better 3-year survival with a radiation dose of 60 Gy than with lower doses (7). In these trials, two-dimensional treatment planning was used, wherein the tumor volume was defined on kilovoltage radiographs (7). Thereafter, the standard initial target volume included the primary tumor, metastatic lymph nodes, and adjacent uninvolved ipsilateral hilar and mediastinal regions (elective nodal irradiation: ENI). Except for selected patients, excessive toxicity hampered an increase of the total dose to over 60 Gy in patients with locally advanced NSCLC.

It is, however, time now to reconsider the optimal dose of thoracic radiotherapy using new techniques in patients with locally advanced NSCLC, for the following reasons. First, positron emission tomography (PET) provides more accurate diagnosis of mediastinal lymph node metastases (8) and more accurate quantification of the tumor volumes, especially when atelectasis is present (9). Second, three-dimensional conformal radiation therapy (3D-CRT) enables radiation oncologists to delineate the tumor and adjacent normal tissue more sharply and to choose beam angles to maximize tumor coverage with minimum irradiation of normal tissues (10). Third, omission of the ENI resulted in improvement of radiation-associated toxicity without worsening the local control rate of the tumor (11, 12). Thus, by use of these new techniques, the optimal dose of thoracic radiation could exceed the conventional 60 Gy.

Two dose escalation studies in patients with locally advanced NSCLC showed that the total dose of thoracic radiotherapy could be increased up to 90 Gy in concurrent chemoradiotherapy using the 3D-CRT technique combined with weekly carboplatin and paclitaxel chemotherapy (13, 14). In these trials, chemoradiotherapy was administered after induction chemotherapy. However, it remained unclear whether these doses could be delivered safely to the majority of patients with locally advanced NSCLC, because it is not known how many patients were screened for the trials and how many of them were actually registered, and because some of the registered patients were excluded from the chemoradiotherapy phase after induction chemotherapy. The total number of patients evaluated in the two trials was also limited. Furthermore, chemotherapy other than weekly carboplatin and paclitaxel has not been evaluated in the setting of combined chemotherapy with high-dose thoracic radiotherapy, to our knowledge. The objectives of the current study were (1) to evaluate the toxicity of concurrent high-dose 3D-CRT without ENI with cisplatin and vinorelbine for unresectable Stage III NSCLC, (2) to determine the maximum tolerated dose (MTD) of thoracic radiotherapy, and (3) to observe the antitumor effects of this regimen.

PATIENTS AND METHODS

Study design

This study was designed as a Phase I study at the National Cancer Center Hospital. The protocol and consent form were approved by the Institutional Review Board of the National Cancer Center on July 28, 2005. We planned to treat 12 patients at a dose level and follow them up at least 6 months, and then escalate to the next level if 67% of the patients did not experience dose-limiting toxicity (DLT). We followed widely accepted normal tissue dose constraints. Patients with percent volume of the normal lung receiving 20 Gy or more (V_{20}) of greater than 30% were excluded and treated outside the study. Other dosimetric constraints were applied at the discretion of the treating radiation oncologist. Maximum doses exceeding 50 Gy to the spinal cord, 66 Gy to the esophagus, or 66 Gy to the brachial plexus were generally excluded.

Patient selection

Previously untreated patients with locally advanced NSCLC without effusion were screened for entry into this study. The eligibility criteria were (1) histologically or cytologically proven NSCLC, (2) unresectable Stage IIIA or IIIB disease confirmed by both computed tomography (CT) and PET, (3) no previous treatment, (4) measurable disease, (5) $V_{20} \leq 30\%$, (6) age ≥ 20 years, (7) Eastern Cooperative Oncology Group performance status (PS) of 0 or 1, and (8) adequate bone marrow function (white blood cell [WBC] count $\geq 4.0 \times 10^9$/L, hemoglobin ≥ 9.5 g/dL, and platelet count $\geq 100 \times 10^9$/L), liver function (total bilirubin ≤ 1.5 mg/dL and transaminase ≤ 80 IU/L), renal function (serum creatinine ≤ 1.5 mg/dL), and pulmonary function ($PaO_2 \geq 70$ Torr under room air). Patients were excluded if (1) they had malignant pleural or pericardial effusion or (2) they had a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonitis or lung fibrosis identified by a chest x-ray, infection, or other diseases contraindicating chemotherapy or radiotherapy, or (3) they were pregnant or breast feeding. All patients gave their written informed consent.

Pretreatment evaluation

The pretreatment assessment included a complete blood cell count and differential count, routine chemistry determinations, creatinine clearance, blood gas analysis, electrocardiogram, lung function testing, chest x-rays, chest CT scan, brain CT scan or magnetic resonance imaging, abdominal CT, and PET.

Treatment schedule

Chemotherapy consisted of cisplatin 80 mg/m^2 on Day 1 and vinorelbine 20 mg/m^2 on Days 1 and 8, repeated every 4 weeks for three to four cycles. Cisplatin was administered by intravenous infusion for 60 minutes with 2,500 to 3,000 mL of intravenous fluid for hydration and prophylactic antiemetic therapy consisting of a 5-hydroxytriptamine-3 antagonist on Day 1 and a corticosteroid on Days 1 to 5. Vinorelbine, diluted in 50 mL of normal saline, was administered intravenously.

Radiation therapy started on Day 1 of the first cycle of chemotherapy and was delivered with megavoltage equipment (6–10 MV) once daily for 5 days a week. The total dose was 66 Gy in 33 fractions at level 1, 72 Gy in 36 fractions at level 2, and 78 Gy in 39 fractions at level 3. All patients underwent a 3D treatment planning CT 3 to 7 days before the start of the treatment, and the eligibility was finally confirmed based on evaluation using the

dose–volume histogram (DVH). The gross tumor volume (GTV) was defined as the primary tumor delineated on pulmonary windows of the chest CT or on the diagnostic PET scans. Atelectasis or secondary changes in the peripheral lung region of the primary tumor were not included. Metastatic lymph nodes defined as nodes of 1 cm or larger visualized on mediastinal windows of the CT images or PET-positive lymph nodes were also included in the GTV. The clinical target volume (CTV) was equivalent to the GTV. Uninvolved mediastinum or supraclavicular fossae were not included in the CTV. The planning target volume (PTV) was determined as the CTV plus 1.0 cm for the anterior, posterior, medial, and lateral margins and a 1.0 to 2.0 cm for the superior and inferior margins, taking account of setup variations and internal organ motion. The spinal cord dose was typically limited to 44 Gy, but a maximum of 50 Gy was allowed. The lung V_{20} was limited to 30% in all patients. The maximum dose to the brachial plexus and esophagus did not exceed 66 Gy. The 100% dose was prescribed to the reference point located in the central part of the PTV, and the entire PTV was covered with 95–107% of the prescribed dose principally, but variation of ±10% was allowed. Lung heterogeneity corrections using the equivalent path length algorithm were applied in all patients.

Toxicity assessment and treatment modification

Complete blood cell counts and differential counts, routine chemistry determinations, and a chest x-ray were performed once a week during the course of treatment. Toxicity was graded according to the Common Terminology Criteria for Adverse Events (CTCAE v3.0). The lung toxicity grade was defined as the highest grade among cough, dyspnea, obstruction/stenosis of airways, pneumonitis/pulmonary infiltrates, and pulmonary fibrosis in the pulmonary/upper respiratory section (15).

Vinorelbine administration on Day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on Day 1: WBC count $<3.0 \times 10^9$/L, neutrophil count $<1.5 \times 10^9$/L, platelet count $<100 \times 10^9$/L, serum creatinine level ≥1.6 mg/dL, Grade 2–3 elevation of the serum hepatic transaminase level or total serum bilirubin levels, Grade 2–3 infection, Grade 2–3 pneumonitis, other ≥Grade 3 nonhematologic toxicity, body temperature ≥38°C, or PS of 2–3. If these toxicities did not recover within 6 weeks from Day 1 of the previous cycle of chemotherapy, subsequent cycles of chemotherapy were stopped. The dose of cisplatin was reduced by 25% in all subsequent cycles if the serum creatinine level rose to 2.0 mg/dL or higher. The dose of vinorelbine was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/L, platelet count $<25 \times 10^9$/L, or Grade 3 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: body temperature ≥38°C, Grade 3 esophagitis, PS of 3, or suspected radiation pneumonitis. Thoracic radiotherapy was terminated if any of the following were noted: Grade 4 esophagitis, Grade 3 or 4 pneumonitis, PS of 4, or duration of radiotherapy of over 62 days (level 1), 67 days (level 2), or 70 days (level 3). Any protocol-defined treatments were terminated if Grade 4 nonhematologic toxicities other than transient electrolyte disturbances or a PS of 4 was noted.

Dose-limiting toxicity and maximum tolerated dose

The DLT was defined as the following toxicities observed during a 6-month period from the start of treatment: (1) Grade 3 esophagitis, lung toxicity, myelitis, dermatitis associated with radiation, and cardiac toxicity associated with radiation, (2) Grade 4 nonhematologic toxicity, or (3) treatment termination due to prolonged toxicity. Twelve patients were enrolled at each dose level. All patients were followed up for at least 6 months to evaluate DLT. During the period, if none to 4 of the 12 patients experienced DLT, the next cohort of patients was treated at the next higher dose level. If 5 or more of the 12 patients experienced DLT, that level was considered to be the MTD. The recommended dose for Phase II trials was defined as the dose preceding the MTD.

Response evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) ver. 1.0 (16).

Follow-up

Patients who completed the protocol therapy were followed up to monitor toxicity, response, and recurrence. CT of the chest was performed every 2 to 4 months for 1 year, every 6 months for 2 years, and then yearly for 2 years. The relapse pattern was categorized into (1) local alone, including relapse from the primary site or the hilar, mediastinal, or supraclavicular lymph nodes, (2) distant metastasis alone, including pleural dissemination, pleural and pericardial effusions, and distant metastases, and (3) local and distant.

Statistical analyses

Progression-free survival time (PFS) and OS were estimated by the Kaplan-Meier method. The PFS was measured from the date of registration to the date of disease progression or death resulting from any cause or date of last follow-up. The OS was measured from the date of registration to the date of death resulting from any cause or date of last follow-up. Patients who were lost to follow-up without events were censored at the date of their last known follow-up. A confidence interval (CI) for the response rate was calculated by the method used for exact binomial CIs. The Dr. SPSS II 11.0 software package for Windows (SPSS Japan Inc., Tokyo, Japan) was used for the statistical analyses.

RESULTS

Registration and characteristics of the patients

From August 2005 to September 2008, 57 patients were deemed to initially be eligible. Of these, 3 patients were excluded because idiopathic interstitial pneumonitis ($n = 1$) and anemia ($n = 2$) developed. Explanation of the study using the consent form was given to 54 patients, and informed consent was obtained in 51 patients. The 51 patients underwent 3D treatment planning, and eligibility was finally confirmed in 31 patients. Those 31 were enrolled into this study. A total of 20 patients were excluded as a result of the DVH evaluation: because of V_{20} higher than 30% in 10 patients, overdose to the esophagus in 8 patients, and overdose to the brachial plexus in 2 patients. Eventually, of 17 patients assessed as to their eligibility for dose level 1, 16 patients for dose level 2, and 24 patients to dose level 3, 13 (76%), 12 (75%), and 6 (25%) patients were actually enrolled into levels 1 to 3, respectively (Fig. 1).

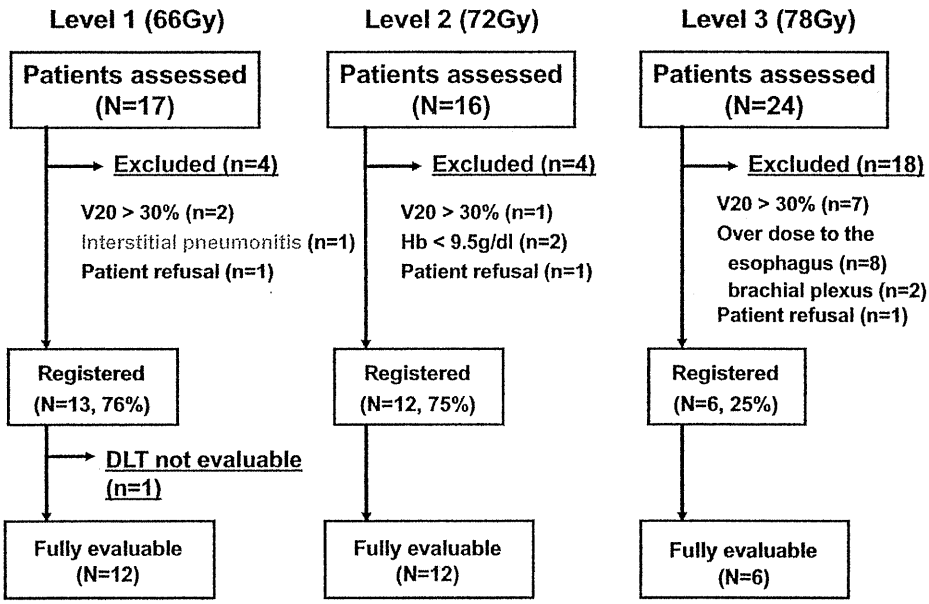

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

The pretreatment characteristics of the patients enrolled in this trial are shown in Table 1. The majority of the patients were in good general condition, with a PS of 0 in 25 (81%) and no weight loss in 26 (84%) patients. Adenocarcinoma was the predominantly encountered histological characteristic, seen in 23 (74%) patients.

Treatment delivery

The treatment delivery to the patients was fairly good (Table 2). The planned dose of radiotherapy was administered to all patients of all the three dose levels. More than 80% of the patients received three to four cycles of chemotherapy without or with only one omission of vinorelbine on Day 8, regardless of the dose levels.

Toxicity and DLTs

The hematologic toxicity was comparable to that of other concurrent chemoradiotherapy (Table 3). Grade 4 septic shock was encountered during the fourth cycle of chemotherapy in 1 patient enrolled at dose level 1, but it was manageable by standard care with antibiotics. Other nonhematologic toxicities were mild and acceptable.

Table 1. Patient characteristics

Characteristic	*n*	(%)
Sex		
M	26	(84)
F	5	(16)
Age (y)		
Median (range)	60	(41–75)
Performance status		
0	25	(81)
1	6	(19)
Body weight loss (%)		
0	26	(84)
0.1–5.0	2	(6)
≤5.0	3	(10)
Histology		
Adenocarcinoma	23	(74)
Squamous cell carcinoma	4	(13)
NSCLC, not otherwise specified	4	(13)
Stage		
IIIA	20	(65)
IIIB	11	(35)

Abbreviation: NSCLC = non–small-cell lung cancer.

Table 2. Treatment delivery

	Level 1 (n = 13)	Level 2 (n = 12)	Level 3 (n = 6)
Radiotherapy			
Total dose (Gy)			
66	13 (100)	–	–
72	–	12 (100)	–
78	–	–	6 (100)
Delay (days)			
≤5	11 (85)	5 (42)	5 (83)
6–10	2 (15)	6 (50)	0
11–15	0	1 (8)	1 (17)
Chemotherapy			
No. of cycles			
4	6 (46)	6 (50)	4 (67)
3	6 (46)	4 (33)	2 (33)
2	0	1 (8)	0
1	1 (8)	1 (8)	0
No. of VNR omissions			
0	10 (77)	7 (58)	2 (33)
1	2 (15)	4 (33)	3 (50)
2	0	0	1 (17)
3	1 (8)	1 (8)	0

Abbreviation: VNR = vinorelbine administered on Day 8.

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).

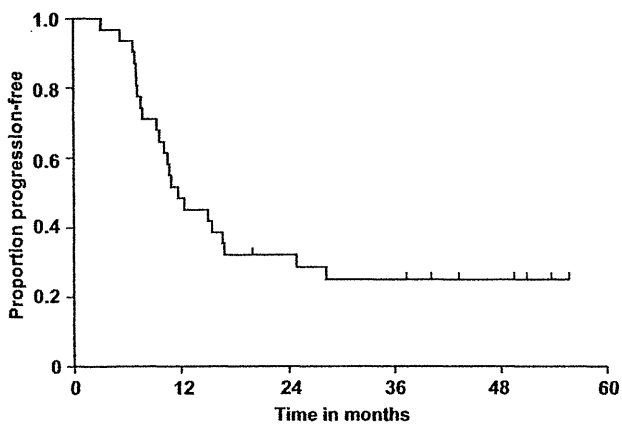

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

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)

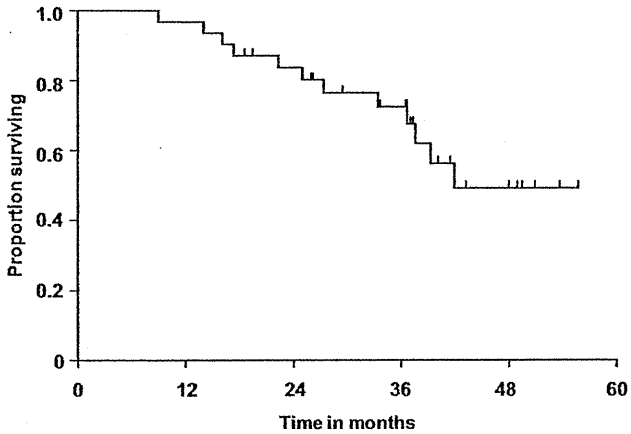

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

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.

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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

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.