a contrarian philosophy that in some patients, the intracranial disease is truly limited—the so-called oligometastases situation. For patients who truly have limited intracranial disease, the potential exists that WBRT could be replaced by focal therapeutic options such as resection or stereotactic radiosurgery (SRS), which delivers high-dose, focal radiation.[1-4]

The adverse effects of WBRT require a further examination of its role. Acute adverse effects are generally limited in severity and duration; however, the long-term risks of serious and permanent toxic effects, including cognitive deterioration and cerebellar dysfunction, are poorly understood.[5,6] In the attempt to minimize potential long-term morbidity following WBRT, treatments initially relying on focal therapeutic options are being used with increasing frequency. Although there have been several retrospective reports,[7-14] only 1 prospective randomized study compared the outcome of conventional surgery alone and surgery followed by WBRT.[6] Sneed et al[7] collected raw data on 983 patients from 10 institutions and suggested that there was no survival difference between patients treated with SRS alone and those treated with WBRT plus SRS. Flickinger et al[8] reviewed 116 patients with solitary brain metastases who underwent SRS with or without fractionated large-field radiotherapy and found improved local control, but not improved survival, with the addition of fractionated large-field radiotherapy. Regine et al[9] suggested that SRS alone is associated with an increasingly significant risk of brain tumor recurrence and neurologic deficit with increasing survival time. Pirzkall et al[10] showed a trend for superior local control and survival when SRS was combined with WBRT in 236 patients with 311 brain metastases. Aoyama et al,[11] Chidel et al,[12] and Shirato et al[13] have all shown that omission of WBRT from initial management was not detrimental in terms of overall survival, but brain tumors recurred in more than 50% of patients treated in this manner. Patchell et al[6] have shown that patients with cancer and single metastases to the brain who receive treatment with surgical resection and postoperative WBRT have fewer recurrences of cancer in the brain and are less likely to die of neurologic causes than are similar patients treated with surgical resection alone.

Herein, we report the results of a prospective, multi-institutional, randomized controlled trial comparing WBRT plus SRS vs SRS alone for patients with limited (defined as ≤4) brain metastases. Through a literature search and examination of clinical trial registries, we confirmed that this is the first multi-institutional, prospective, randomized comparison of WBRT plus SRS vs SRS alone.

METHODS

Eligibility Criteria

Patients were eligible who were aged 18 years or older with 1 to 4 brain metastases, each with a maximum diameter of no more than 3 cm on contrast-enhanced magnetic resonance imaging (MRI) scans, derived from a histologically confirmed systemic cancer. Patients with metastases from small cell carcinoma, lymphoma, germinoma, and multiple myeloma were excluded. Eligible patients had a Karnofsky Performance Status (KPS) score of 70 or higher. The protocol was approved by the institutional review boards of Hokkaido University, Sapporo, Japan, and of 10 other institutions that participated in the trial through the Japanese Radiation Oncology Study Group (JROSG 99-1). Written informed consent was obtained from each patient before entry into the study.

Randomization and Treatment

Randomization was performed at the Hokkaido University Hospital Data Center. A permuted-blocks randomization algorithm was used with a block size of 4. A randomization sheet was created for each institution. After written informed consent was obtained, eligible patients were randomly assigned to receive either up-front WBRT combined with SRS or SRS without up-front WBRT. Prior to randomization, the patients were stratified based on number of brain metastases (single vs 2-4), extent of extracranial disease (active vs stable), and primary tumor site (lung vs other sites). Extracranial disease was considered to be stable when the tumor had been clinically controlled for 6 months or longer prior to the detection of brain metastases.

The WBRT dosage schedule was 30 Gy in 10 fractions over 2 to 2.5 weeks. The WBRT treatment visit proceeded to SRS when patients were assigned to the WBRT + SRS group. The SRS dose was prescribed to the tumor margin. Metastases with a maximum diameter of up to 2 cm were treated with doses of 22 to 25 Gy and those larger than 2 cm were treated with doses of 18 to 20 Gy. The dose was reduced by 30% when the treatment was combined with WBRT because the optimal combination of WBRT and SRS had not been studied in well-conducted, prospective, phase 1 dose escalation trials. In the 1990s, the Radiation Therapy Oncology Group (RTOG) initiated a phase 1 dose escalation trial of SRS alone in patients who had previously undergone radiation treatment.[14] This trial was stopped early without reaching the maximum tolerance dose, and tumor size–dependent dose recommendations for SRS alone were described. No phase 1 trial has ever tested the combination of WBRT and SRS doses. Therefore, there is no well-known or scientifically recommended dose for the combination of WBRT and SRS. There are clearly concerns that the combination could be potentially deleterious. Therefore, various studies have adopted different approaches for selection of the dose combinations to be tested. Several retrospective data suggested that the RTOG dose guidelines might be associated with a higher frequency of late radiation toxic effects when used with WBRT.[10,15] Our preexisting experience of SRS with a 30% reduced SRS dose

combined with WBRT indicated that there is not a significant difference in local tumor control (data not shown) compared with SRS with the dose suggested in the RTOG protocol. Therefore, we decided to use a 30% reduced SRS dose in the WBRT + SRS group in this study.

Follow-up Protocol

We performed clinical evaluations and MRI scans 1 and 3 months after treatment and every 3 months thereafter. In cases in which a recurrence was detected, further treatment was administered at the discretion of the attending physician. The size of the treated lesions was measured in 3 dimensions, and this size, the development of new brain metastases, and the development of leukoencephalopathy associated with radiological findings (according to the National Cancer Institute's Common Toxicity Criteria version 2.0[16]) were scored based on serial MRI scans. Local tumor progression was defined as a radiographic increase of 25% or more in the size of a metastatic lesion (bidimensional product). If an MRI result showed central or heterogeneous low intensity and if the lesion size decreased on serial studies, brain necrosis was scored; positron emission tomography or surgical resection was encouraged as appropriate to confirm MRI findings.

At each visit, functional status and neurologic toxic effects were scored. Systemic functional status was evaluated by using the KPS score. Neurologic function was evaluated according to the criteria listed in TABLE 1.[17] Neurosurgeons or radiation oncologists specializing in neuro-oncology measured the neurologic status as well as the KPS score at the clinic. We did not attempt to blind the investigators with regard to patients' treatment assignments. Systematic functional status and neurologic function were scored by the physicians who treated the patients. An acute toxic effect was identified as an event that arose within 90 days of the initiation of radiotherapy and a late toxic effect was considered as an event that occurred thereafter, according to the central nervous system toxicity criteria listed among the RTOG Late Radiation Morbidity Scoring Criteria.[18] For all patients who died, the cause of death was determined. The cause of death was determined by autopsy in 1 patient and by clinical evaluation based on the definition proposed by Patchell et al[6] in all other patients. Patients were considered to have died of neurologic causes if they had stable systemic disease and

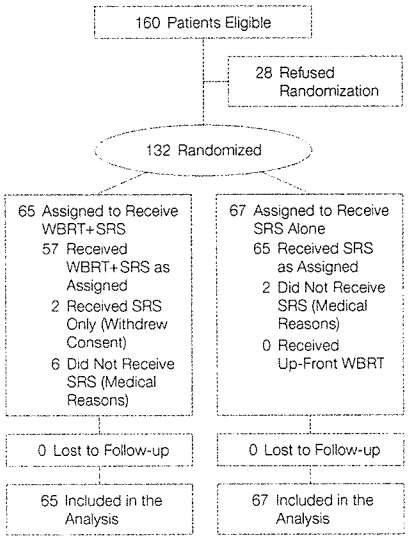
Table 1. Baseline Characteristics*

Characteristics	WBRT + SRS (n = 65)	SRS Alone (n = 67)
Age at diagnosis, mean (range), y	62.5 (36-78)	62.1 (33-86)
<65	32 (49)	34 (51)
≥65	33 (51)	33 (49)
Men	46 (71)	53 (79)
No. of brain metastases		
1	31 (48)	33 (49)
2-4	34 (52)	34 (51)
Primary tumor site		
Breast	6 (9)	3 (4)
Lung	43 (66)	45 (67)
Colorectal	5 (8)	6 (9)
Kidney	5 (8)	5 (7)
Other	6 (9)	8 (12)
Primary tumor status		
Stable	30 (46)	33 (49)
Active	35 (54)	34 (51)
Extracranial metastases		
Stable	41 (63)	38 (57)
Active	24 (37)	29 (43)
RPA		
Class 1 (aged <65 years; no active extracranial disease)	11 (17)	8 (12)
Class 2 (aged ≥65 years; active extracranial disease)	54 (83)	59 (88)
Histological status		
Squamous cell	11 (17)	11 (16)
Adenocarcinoma	43 (66)	43 (64)
Large cell	2 (3)	4 (6)
Other	9 (14)	9 (13)
KPS score†		
70-80	31 (48)	23 (34)
90-100	34 (52)	44 (66)
Neurologic function		
No symptoms (grade 0)	38 (59)	47 (70)
Minor symptoms, fully active without assistance (grade 1)	12 (18)	13 (19)
Moderate symptoms; fully active but requires assistance (grade 2)	8 (12)	4 (6)
Moderate symptoms; less than fully active, requires assistance (grade 3)	7 (11)	3 (5)
Severe symptoms; totally inactive (grade 4)	0	0
Chemotherapy after brain treatment	18 (38)	19 (40)
Maximum diameter of brain metastases, cm		
Mean (SD)	1.53 (0.78)	1.42 (0.79)
Median (range)	1.40 (0.2-3.0)	1.30 (0.2-3.0)
SRS dose at the tumor margin, mean (SD), Gy	16.6 (3.6)	21.9 (2.7)

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Data are expressed as No. (%) of participants unless otherwise noted.
†A higher score indicates better performance.

progressive neurologic dysfunction. Patients with severe neurologic disability who died of intercurrent illness were also included among neurologic deaths, as were patients with both rapidly progressive systemic disease and advancing neurologic dysfunction, because these patients also represent brain treatment failures.

Figure 1. Flow of Study Participants



SRS indicates stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

End Points and Statistical Analysis

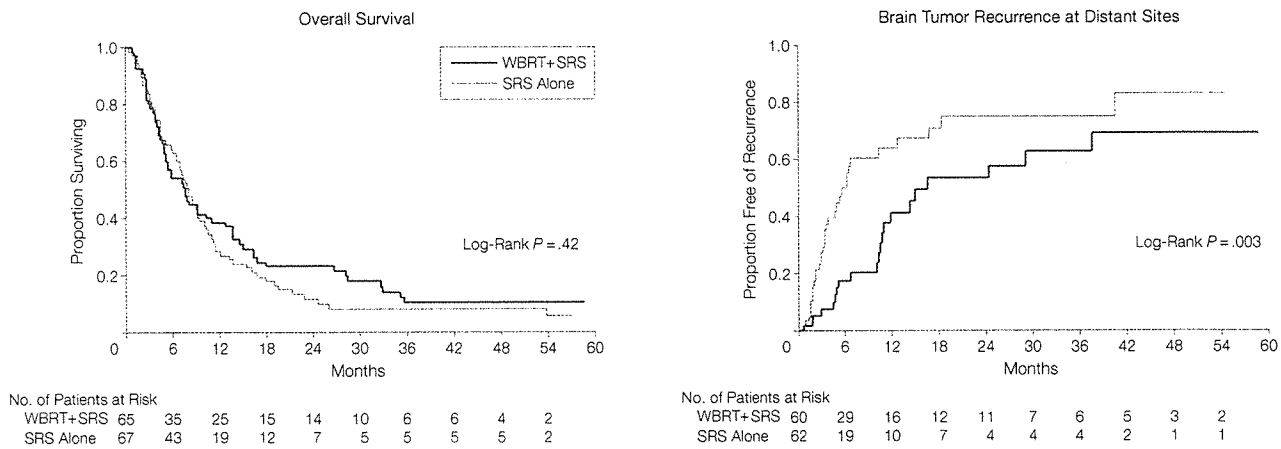
The primary end point of the study was overall survival. Secondary end points were cause of death, functional preservation, brain tumor recurrence, salvage treatment, and toxic effects of radiation. All analyses were conducted on an intention-to-treat basis. The study was designed to have 80% power to detect an absolute difference of 30% in the median survival time, with a 2-sided α level of .05. Using an estimated median survival time of 8.7 months for the group receiving SRS alone[11] and a follow-up time of 15 months, the sample size required to detect this difference was 89 patients per group. An interim analysis was planned wherein 50 patients would be assigned to each group to determine whether the sample size was large enough to show a significant difference with a 2-sided α level of .05. End points were measured beginning at the date of randomization. Univariate analyses were carried out by the Kaplan-Meier method.[19] We assumed that the survival rate was always higher in the WBRT + SRS group than in the SRS-alone group based on the suggestions in a retrospective study, and we used the log-rank test to compare differences between the groups. The χ^2 test was used to determine the relationship between 2 categorical variables, and the Fisher exact test was used when small cell sizes were encountered in 2×2 contingency tables. A 2-tailed t test was used to compare the means of continuous variables between the treatment groups. Multivariate analyses were performed to evaluate the factors selected via the univariate analyses ($P<.10$). Stratification in the randomization was taken into account in the statistical analysis. The Cox proportional hazards model was used to calculate hazard ratios and 95% confidence intervals (CIs).[20] A 2-sided P value of .05 or less was considered to reflect statistical significance. Additional covariates were examined as appropriate and are noted in the "Results" section. All statistical analyses were initially performed by a physician (H.A.) using a commercial statistical software package (StatView version 5.0J, SAS Institute Inc, Cary, NC), and all results were verified by a statistician (G.K.) using a different software package (SAS, version 9.1, SAS Institute Japan Ltd, Tokyo, Japan).

RESULTS

Patients and Treatment

The recruitment period was from October 1999 to December 2003. There were

Figure 2. Overall Survival and Brain Tumor Recurrence at Distant Sites



The mean survival time was 7.5 months for patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) and 8.0 months for patients receiving SRS alone. This difference was not significant ($P=.42$). There was a statistically significant decrease in brain tumor recurrence in the WBRT+SRS group ($P=.003$).

160 eligible patients, of whom 132 (83%) were randomized (65 to WBRT + SRS and 67 to SRS alone) (FIGURE 1). The date of last follow-up was April 2005. The interim analysis was performed with 122 patients (about 60 in each group), which takes into account the possible number of patients with protocol violations. Patient accrual was terminated before the planned final accrual number had been reached because the results of the interim analyses indicated that at least 805 patients were necessary to detect a significant difference in the primary end points. In addition, the numbers of patients appeared sufficient to detect a significant difference in brain tumor recurrence rates: 31 patients in each group were shown to be enough to detect a 30% difference in the median month of 50% brain tumor recurrence (16.2 months with WBRT + SRS vs 5.5 months with SRS alone).

There was no statistical difference between the groups in the baseline characteristics of the patients (Table 1). The median follow-up time was 7.8 months (range, 0.5-58.7 months) for the entire study and 49.2 months (range, 19.6-58.7 months) for survivors. Ninety-two percent of the patients included in the study completed the assigned treatment (Figure 1).

Survival and Cause of Death

By the time of the last follow-up visit in April 2005, 57 patients in the WBRT + SRS group and 62 patients in the SRS-alone group had died. Death was attributed to neurologic causes in 13 patients (22.8%) in the WBRT + SRS group and in 12 patients (19.3%) in the SRS-alone group ($\chi^2 = 0.21$; $P = .64$). The median survival time was 7.5 months with WBRT + SRS and 8.0 months with SRS alone. The higher median survival time with SRS alone was discordant with the 1-year actuarial survival rates of 38.5% (95% CI, 26.7%-50.3%) for the WBRT + SRS group and 28.4% (95% CI, 17.6%-39.2%) for the SRS-alone group ($P = .42$). FIGURE 2A shows that this discordance was due to the crossing of the 2 survival curves. The results of the univariate and multivariate analyses are shown in TABLE 2 and TABLE 3. The number of patients in each institution was too small to allow for a meaningful comparison among institutions. Recursive partition analysis was not included in the multivariate analysis because it is not independent of age and extracranial metastases. Treatment group was not found to be significant in either analysis.

Posttreatment Neurologic Toxicity

A summary of posttreatment neurologic toxicity is given in TABLE 4. Symptomatic acute neurologic toxicity was observed in 4 patients receiving WBRT + SRS and in 8 patients receiv-

Table 2. Univariate Survival Analysis

	No. of Participants	Survival Time, Median (Range), mo	*P* Value
Treatment group			
WBRT + SRS	65	7.5 (0.8-58.7)	.42
SRS alone	67	8.0 (0.5-57.0)	
Age, y			
<65	66	8.9 (0.9-58.7)	.07
≥65	66	6.5 (0.5-55.6)	
Sex			
Male	99	7.1 (0.5-58.7)	.20
Female	33	10.5 (0.8-57.0)	
No. of brain metastases			
1	68	8.6 (1.4-58.7)	.02
2-4	64	7.3 (0.5-55.6)	
Primary tumor site			
Lung	88	8.1 (0.5-58.7)	.33
Other	44	7.1 (0.9-57.0)	
Primary tumor status			
Stable	69	9.2 (0.9-58.7)	<.001
Active	63	6.5 (0.5-53.8)	
Extracranial metastases			
Stable	79	13.3 (1.1-58.7)	<.001
Active	53	6.1 (0.5-55.6)	
RPA			
Class 1	19	16.0 (0.9-58.7)	<.001
Class 2	113	7.5 (0.5-55.6)	
KPS score			
70-80	54	5.0 (0.5-58.7)	<.001
90-100	78	9.2 (0.8-57.0)	
Chemotherapy after brain treatment			
Yes	37	10.1 (1.3-53.8)	.34
No	95	6.8 (0.5-58.7)	

Abbreviations: KPS, Karnofsky Performance Status; RPA, recursive partition analysis; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Table 3. Multivariate Survival Analysis

Variables*	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	1.37 (0.93-1.98)	.11
Age (<65 y)	1.48 (1.01-2.16)	.04
No. of brain metastases (1)	1.36 (0.94-1.97)	.10
Primary tumor status (stable)	1.62 (1.11-2.36)	.01
Extracranial metastases (stable)	2.35 (1.55-3.55)	<.001
KPS score (90-100)	1.69 (1.16-2.47)	.007

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*Referents appear in parentheses.

Table 4. Treatment-Related Neurotoxic Effects*

	No. in WBRT + SRS Group (n = 65)				No. in SRS-Alone Group (n = 67)			
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 1	Grade 2	Grade 3	Grade 4
Acute toxic effects	2	1	1	0	3	3	2	0
Seizure	0	0	1	0	1	2	1	0
Other	2	1	0	0	2	1	1	0
Late toxic effects	3	0	2	2	1	0	0	2
Radiation necrosis	1	0	0	2	0	0	0	1
Leukoencephalopathy	1	0	2	0	0	0	0	0
Other†	1	0	0	0	1	0	0	1
Radiological leukoencephalopathy	2	3	2	0	1	1	0	0

Abbreviations: SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.
*From the National Cancer Institute's Common Toxicity Criteria version 2.0.[35]
†Other effects included 1 case of slight lethargy (grade 1) in the WBRT + SRS group and 1 case each of seizure (grade 4) and headache (grade 1) in the SRS-alone group.

Table 5. Univariate Analysis of Development of New Metastases at Distant Brain Sites

	Actuarial Rate, %		Log-Rank *P* Value
	6 mo	12 mo	
Treatment group			
WBRT + SRS	17.5	41.5	.003
SRS alone	49.9	63.7	
Age, y			
<65	34.5	55.9	.65
≥65	33.9	49.0	
Sex			
Male	32.7	51.5	.39
Female	36.3	55.9	
No. of brain metastases			
1	27.3	39.2	.03
2-4	42.4	69.9	
Primary tumor site			
Lung	29.5	52.0	.40
Other	43.1	55.9	
Primary tumor status			
Stable	32.8	44.8	.20
Active	37.1	69.6	
Extracranial metastases			
Stable	29.5	38.4	.02
Active	37.3	69.3	
KPS score			
70-80	43.2	57.4	.05
90-100	29.9	50.8	
Chemotherapy after brain treatment			
Yes	37.1	59.0	.33
No	32.9	50.0	

Abbreviations: KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

ing SRS alone ($P=.36$), including 1 and 2 patients with grade 3 toxicity, respectively, in each group. The symptoms developed a median of 6 days after initiation of treatment (range, 1-64 days) in the WBRT + SRS group and 10 days (range, 1-86 days) in the SRS-alone group. Symptomatic late neurologic radiation toxic effects were observed in 7 patients in the WBRT + SRS group and in 3 patients in the SRS-alone group ($P=.20$). Toxic effects were experienced for a median of 15.6 months (range, 6.7-59.4 months) in the WBRT + SRS group and 6.2 months (range, 5.8-8.1 months) in the SRS-alone group. There were 3 cases of radiation necrosis (grade 1, n = 1; grade 4, n = 2), 3 cases of leukoencephalopathy (grade 1, n = 1; grade 3, n = 2), and 1 case of slight lethargy (grade 1) in the WBRT + SRS group. In patients receiving SRS alone, the following effects were observed: 1 case of radiation necrosis (grade 4), 1 of seizure (grade 4), and 1 of headache (grade 1). Radiation necrosis was diagnosed using positron emission tomography or surgical resection in all cases. Radiological findings consistent with leukoencephalopathy were observed in 7 patients in the WBRT + SRS group and in 2 patients in the SRS-alone group ($P=.09$). Three of these 9 patients also experienced symptomatic leukoencephalopathy; the other 6 patients were asymptomatic.

Brain Tumor Recurrence

Brain tumor recurrence at either distant or local sites in the brain was observed in 63 patients (23 in the WBRT + SRS group and 40 in the SRS-alone group). The 12-month actuarial brain tumor recurrence rate was 46.8% (95% CI, 29.7%-63.9%) in the WBRT + SRS group and 76.4% (95% CI, 63.3%-89.5%) in the SRS-alone group ($P<.001$).

Fifty-five patients had new brain metastases at distant sites (21 in the WBRT + SRS group and 34 in the SRS-alone group). The 12-month actuarial rate of developing new brain metastases was 41.5% (95% CI, 24.4%-58.6%) in the WBRT + SRS group and 63.7% (95% CI, 49.0%-78.4%) in the SRS-alone group ($P=.003$) (Figure 2B).

The multivariate analysis revealed that WBRT + SRS was associated with a reduced risk of recurrence (hazard ratio, 0.32; 95% CI, 0.18-0.58; $P<.001$) (TABLE 5 and TABLE 6).

During the follow-up period, 122 patients (92% of the total patients enrolled) had at least 1 follow-up MRI scan performed. In total, 581 follow-up MRI scans were performed; of these, 87 scans (15%) demonstrated new brain metastases; these 87 "event scans" were obtained in 55 patients. Sixteen percent of these "event scans" (14/87) were associated with neurologic symptoms at the time of the MRI examination.

A total of 247 metastases received initial treatment with SRS (117 in the WBRT + SRS group and 130 in the SRS-alone group). Follow-up MRI was available for 210 metastases (85%). The actuarial local tumor control rate at 12 months was 88.7% (95% CI, 80.1%-97.3%) in the WBRT + SRS group and 72.5% (95% CI, 60.3%-84.7%) in the SRS-alone group ($P=.002$) (FIGURE 3). The histopathological type (adenocarcinoma vs others) was not shown to be a significant factor ($P=.90$). The multivariate analysis also showed significantly better tumor control by WBRT + SRS treatment (hazard ratio, 4.83; 95% CI, 2.00-11.65; $P<.001$).

Salvage treatment for progression of brain tumor was required significantly more frequently in patients receiving SRS alone (29 patients) than in the WBRT + SRS group (10 patients) ($\chi^2=12.33$; $P<.001$). Salvage WBRT was applied in 11 patients in the SRS-alone group but was not used in any patients in the WBRT + SRS group. Salvage SRS was used in 19 patients in the SRS-alone group and in 9 patients in the WBRT + SRS group.

Systemic and Neurologic Functional Preservation

Systemic functional preservation rates (KPS score ≥70) at 12 months were 33.9% (95% CI, 22.2%-45.4%) in the WBRT + SRS group and 26.9% (95% CI, 16.3%-37.5%) in the SRS-alone group ($P=.53$). The decrease in the KPS score to below 70 was attributed to neurologic causes in 17 patients (29%) in the WBRT + SRS group and 14 (22%) in the SRS-alone group.

The actuarial rates of neurologic preservation at 12 months were 72.1% (95% CI, 58.8%-85.4%) with WBRT + SRS and 70.3% (95% CI, 55.6%-85.0%) with SRS alone ($P=.99$) when neurologic preservation was defined as a lack of any worsening of the neurologic grade on follow-up examination, compared with the pretreatment grade. In total, 85 patients (38 in the WBRT + SRS group and 47 in the SRS-alone group) did not have neurologic symptoms when brain metastases were diagnosed (grade 0). Among the 47 patients who had a pretreatment grade of 1 to 3, an improvement in neurologic status was observed at least once in 9 patients and 10 patients in the respective groups ($\chi^2=1.32$; $P=.24$). Deterioration of neurologic function was observed in 43 patients, including 7 who initially experienced improvement after treatment (22 in the WBRT + SRS group and 21 in the SRS-alone group; $\chi^2=0.09$; $P=.75$). This deterioration was attributed to either original or distant brain metastases in 13 patients (59%) in the WBRT + SRS group and 18 patients (86%) in the SRS-alone group ($\chi^2=3.78$; $P=.05$). Late neurologic radiation toxic effects were the cause of deterioration in 4 and 2 patients in each group, respectively. Either meningeal dissemination or spinal cord metastases induced neurologic deterioration in 5 and 1 patient in each group, respectively.

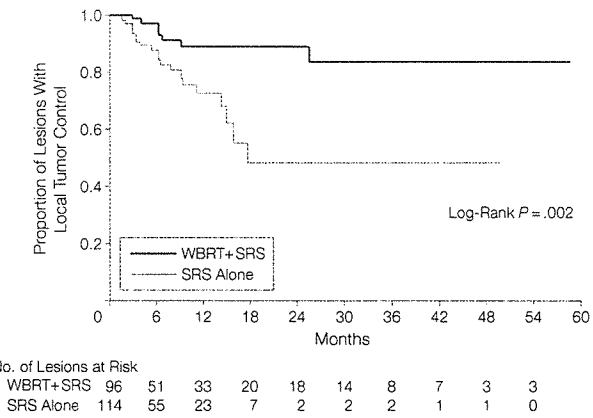
Neurocognitive function was optionally assessed using the Mini-Mental State Examination (MMSE). Among the 44 patients (25 in the WBRT + SRS group and 19 in the SRS-alone group) who lived 12 months or longer, MMSE data were available in 28 patients at least once (16 in the WBRT + SRS group and 12 in the SRS-alone group) at the median follow-up times of 30.5 months (range, 13.7-58.7 months) with WBRT + SRS and 20.7 months (range, 13.3-53.8 months) with SRS alone. The median MMSE pretreatment score was 28.0 (range, 23-30) in the WBRT + SRS

Table 6. Multivariate Analysis of Development of New Metastases at Distant Brain Sites

	Hazard Ratio (95% CI)	*P* Value
Treatment group (WBRT + SRS)	0.32 (0.18-0.58)	<.001
No. of brain metastases (2-4)	1.69 (0.97-2.93)	.06
Extracranial metastases (active)	2.06 (1.17-3.64)	.01
KPS score (70-80)	2.14 (1.17-3.93)	.01

Abbreviations: CI, confidence interval; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

Figure 3. Local Tumor Control



There was a statistically significant increase in local tumor control in patients receiving whole-brain radiation therapy (WBRT) plus stereotactic radiosurgery (SRS) ($P=.002$).

group and 27.0 (range, 23-30) in the SRS-alone group. The median score at the final follow-up was 27.0 (range, 21-30) in the WBRT + SRS group and 28.0 (range, 18-30) in the SRS-alone group.

COMMENT

Stereotactic radiosurgery is a method of delivering high doses of focal radiation to a tumor while minimizing irradiation of the adjacent normal tissue. This approach was originally developed by the Swedish neurosurgeon Lars Leksell as a substitute for direct surgical intervention.[21] Stereotactic radiosurgery is now available worldwide, and it is increasingly used to treat brain metastases because it is less invasive compared with direct surgical intervention, although a direct randomized comparison of the 2 modes has not been performed to date.

Whole-brain radiation therapy has been a standard treatment for brain metastases for several decades.[1-4,6,7,17] In more recent years, the importance of focal aggressive therapy combined with WBRT has been increasingly recognized.[3,4,22-24] Andrews et al[4] recently reported the results from RTOG 9508, a multi-institutional phase 3 trial of 333 patients with 1 to 3 brain metastases who received WBRT with or without SRS boost. A statistically significant improvement in median survival with the addition of SRS was seen in patients with a single brain metastasis.

To reduce the risk of late radiation effects,[1,2,5] WBRT is increasingly being omitted from the initial management strategy.[6-13] There is not yet a general consensus regarding the risks and benefits of omitting up-front WBRT. One study showed a trend toward improved survival among patients who received SRS alone,[12] whereas another study showed a trend toward worse survival among patients who received SRS alone.[10] A retrospective multi-institutional review of SRS alone vs SRS with WBRT in 569 patients failed to show any difference in survival between the 2 groups.[7] In a single-institution prospective randomized trial comparing WBRT with observation in patients who underwent conventional surgery,[6] a large increase in intracranial relapse and a concomitant increase in death due to neurologic causes were identified in the non-WBRT group; however, no survival difference was identified in that study. In the present study, no significant survival difference was observed between the groups receiving WBRT + SRS and SRS alone, although the number of patients was not large enough to allow detection of any differences that were smaller than we had assumed. In addition, no significant difference in the frequency of death due to neurologic causes was observed. Moreover, these results were obtained in spite of the rather large increase in intracranial failure when WBRT was omitted. A further observation of note from the present trial was the significant increase in local failure with SRS alone, even though the radiation dose in these patients was considerably higher than that administered to patients receiving WBRT + SRS. We have adapted the 30% reduced dose of SRS in the WBRT + SRS group, which could have lowered local control of the brain metastasis in the WBRT + SRS group. However, we have observed opposite results in this study; the local control rate was significantly higher in the WBRT + SRS group than in the SRS-alone group. This observation lends merit to the value of fractionation, which might help overcome some radiation resistance mechanisms, such as hypoxia.

Also of concern in this context is that higher brain recurrence rates are associated with neurologic deterioration.[9] In a previous randomized study of surgery with or without WBRT,[6] the time to neurologic deterioration was dramatically longer in the WBRT group, although no difference in functional independence was observed. In the current study, no significant difference in the preservation of neurologic function was observed. However, the present study might have less ability to detect small differences, and the present assessment of neurologic function was not conducted with sophisticated measures that might have detected differences between patient groups.

Although surgery and SRS are both focal treatments, SRS is less invasive and may be repeated more often than surgical intervention.[11] The optimal timing of these interventions is an issue that remains open for debate. Our results suggest that the early detection of a brain recurrence and early salvage brain treatment may prevent neurologic deterioration and neurologic death, even when WBRT is not included in the initial treatment. However, study participants more frequently undergo physical and radiological examinations than do patients in the community. Given that the majority of new brain metastases were initially detected in asymptomatic patients, studies assessing the benefits of scheduled imaging should be conducted in the future.

In conclusion, our findings demonstrated that SRS alone without up-front WBRT was associated with increased brain tumor recurrence; however, it did not result in either worsened neurologic function or increased risk of neurologic death. With respect to patient survival, the control of systemic cancer might outweigh the frequent recurrence of brain tumors. Therefore, SRS alone could be a treatment option, provided that frequent monitoring of brain tumor status is conducted.

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The only true hope for civilization—the conviction of the individual that his inner life can affect outward events and that, whether or not he does so, he is responsible for them.
—Stephen Spender (1909-1995)

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Treatment of lung damage

Retrospective analysis of steroid therapy for radiation-induced lung injury in lung cancer patients

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Abstract

Purpose: To disclose characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy.

Methods and materials: Radiographic changes, symptoms, history of corticosteroid prescription, and clinical course after 50–70 Gy of thoracic radiotherapy were retrospectively evaluated in 385 lung cancer patients.

Results: Radiation-induced lung injury was stable without corticosteroid in 307 patients (Group 1), stable with corticosteroid in 64 patients (Group 2), and progressive to death despite corticosteroid in 14 patients (Group 3). Fever and dyspnea were noted in 11%, 50% and 86% ($p < 0.001$), and in 13%, 44% and 57% ($p < 0.001$) patients in Groups 1–3, respectively. Median weeks between the end of radiotherapy and the first radiographic change were 9.9, 6.7 and 2.4 for Groups 1–3, respectively ($p < 0.001$). The initial prednisolone equivalent dose was 30–40 mg daily in 52 (67%) patients. A total of 16 (4.2%) patients died of radiation pneumonitis or steroid complication with a median survival of 45 (range, 8–107) days.

Conclusion: Development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily was selected for the treatment in many patients.

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Keywords: Radiation pneumonitis; Radiotherapy; Lung cancer; Corticosteroid

Thoracic radiotherapy is widely used for the curative and palliative treatment of lung cancer. Radiation-induced lung injury was first described as early as 1922 [1,2], and two types of lung injury, radiation pneumonitis and radiation fibrosis, were recognized in 1925 [3]. Radiation pneumonitis occurs in 5–15% of patients who have received radiation therapy for lung cancer. Its clinical symptoms are characterized by cough, dyspnea and fever developing between 1 and 3 months after the end of radiotherapy. Distinctive radiographic changes of radiation pneumonitis are a ground-glass opacification or diffuse haziness in early phase, and then alveolar infiltrates or dense consolidation in late phase in the region corresponding to the irradiated area [4–7]. Radiation pneumonitis may persist for a month or more and subside gradually. In severe cases, however, pneumonitis progresses to death due to respiratory failure within few weeks [4].

Use of adrenocorticotropic hormone (ACTH) and cortisone for radiation pneumonitis in a case was first reported in 1951 [8], and 9 cases of radiation pneumonitis treated with cortisone therapy in the literature were reviewed in 1968 [9]. Although no case series or clinical trials of corticosteroid therapy have been reported since that time, prednisolone has been given in patients with severe pneumonitis in clinical practice. The initial dose of prednisolone, approximately 30–100 mg daily, and very slow tapering schedule are in agreement among experts [4–6,10], because early withdrawal results in aggravation of pneumonitis [11–13]. There is no consensus, however, about criteria to define when steroids are required for radiation-induced lung injury. The objective of this study is to disclose general characteristics of lung cancer patients developing radiation-induced lung injury treated with or without corticosteroid therapy, to obtain data on the initiation criteria, dose, and taper schedule of corticosteroid therapy for further prospective trials.

Patients and methods

Consecutive lung cancer patients treated with thoracic radiotherapy at a total dose of 50–70 Gy in National Cancer

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Center Hospital between January 1998 and December 2003 were subjects of this study. We retrospectively reviewed all chest X-ray films taken during 6 month period from the end of thoracic radiation to identify the first radiographic change and its progress. History of corticosteroid prescription, symptoms at the time of and one-month period after the first radiographic change in a chest X-ray film, and clinical course of radiation-induced lung injury were obtained from medical charts. The diagnosis of radiation-induced lung injury was defined as radiographic changes including opacification, diffuse haziness, infiltrates or consolidation conforming to the outline of the sharply demarcated irradiated area in a chest X-ray film. During clinical course, scarring (fibrosis) was developed within the irradiated area leading to a reduction in lung volume. In contrast, pulmonary infection spreads through anatomical structure of the lung, and the boundary of infiltrates corresponds to anatomical boundary of the lung. For patients with fever, the radiographical response to antibiotics was also evaluated. Observed differences in the proportions of patients in various patient subgroups were evaluated using Chi-square test. Differences between continuous variables were compared using Mann–Whitney tests. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for all statistical analyses.

Results

Of 544 lung cancer patients receiving thoracic radiotherapy at a total dose of 50–70 Gy, 111 patients were excluded from this study because they were not evaluable: loss of follow-up in 88 patients, early lung cancer progression in 18 patients, chemotherapy-induced neutropenic fever and pneumonia in three patients, death of bleeding from the esophageal stent in one patient, and no chest X-ray films available in one patient. In addition, 48 patients (11% of 433 evaluable patients) were also excluded because no radiation-induced lung injury was noted. Thus, the subject of this study was 385 patients.

Of the 385 patients, 78 (20%) received corticosteroid therapy for radiation-induced lung injury, and 307 did not. Radiation-induced lung injury was stable without corticosteroid in the 307 (80%) patients (Group 1), stable or in remission with corticosteroid in 64 (17%) patients (Group 2), and progressive to death despite corticosteroid in 14 (4%) patients (Group 3). No difference in sex, total dose, intent of radiotherapy, and combination chemotherapy was noted among three Groups, but median age of patients was higher in Group 3 (Table 1). Fever was developed in 50% of patients in Group 3 at the initial radiographic change, and in 86% of them during subsequent clinical course, while it was developed in only 11–12% of patients in Group 1 through their clinical course (Table 2). Dyspnea was developed in 57% of patients in Group 3 and in 44% of patients in Group 2 during clinical course, while it was developed in only 14% of patients in Group 1 (Table 2). A total of 88 patients developed fever at the initial change in chest X-ray and/or during subsequent clinical course. Of these, 43 patients received antibiotics, but no radiographical response was obtained in these patients. Five (2%) and seven (2%) patients in Group 1 developed bloody sputum and chest pain, respectively, but none in Group 2 or 3 developed these symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was 1.7 weeks for group 1, 1.3 weeks for group 2, and 0.9 weeks for group 3 ($P < 0.001$, Table 3). Interval between the end of radiotherapy and the first change in a chest X-ray was shorter in Group 3 than in Group 2 or Group 1 (Table 3). Of 57 patients in whom the first radiographic change was noted within three weeks, 9 (16%) died of pneumonitis, while radiation-induced lung injury that occurred 10 weeks or later after the end of radiation was easily managed with or without steroid therapy (Table 3). Oxygen content in the blood at the start of steroid therapy was examined in 70 patients of Groups 2 and 3. Oxygen content

Table 1
Patient demographics and radiotherapy performance

Characteristics	Total *N* (%)	Group 1	Group 2	Group 3	*p*-value
		N (%)	*N* (%)	*N* (%)	
Total	385 (100)	307 (80)	64 (17)	14 (4)	
Sex					
Male	300 (78)	240 (78)	47 (73)	13 (93)	0.28
Female	85 (22)	67 (22)	17 (27)	1 (7)	
Age median (range)	65 (28–87)	63 (28–87)	65 (37–83)	71 (65–84)	0.008
Total dose (Gy)					
Median (range)	60 (50–70)	60 (50–70)	60 (50–61)	60 (50–60)	0.50
Intent of radiotherapy					
Curative	298 (77)	232 (76)	52 (81)	14 (100)	0.074
Palliative	87 (23)	75 (24)	12 (19)	0 (0)	
Chemotherapy					
None	121 (31)	101 (33)	15 (23)	5 (36)	0.48
Sequential	121 (31)	93 (30)	25 (39)	3 (21)	
Concurrent	143 (37)	113 (37)	24 (38)	6 (43)	

Table 2
Symptoms through clinical courses

Symptom	At the initial change in chest X-ray				During subsequent clinical course			
	Group 1	Group 2	Group 3	p	Group 1[a]	Group 2[b]	Group3[b]	p
Cough	96 (31)	35 (56)	5 (36)	0.001	85 (28)	38 (59)	5 (36)	<0.001
Sputum	32 (10)	11 (18)	4 (29)	0.049	30 (10)	11 (17)	3 (21)	0.12
Hemosputum	5 (2)	0 (0)	0 (0)	0.53	4 (1)	0 (0)	0 (0)	0.60
Chest pain	7 (2)	0 (0)	0 (0)	0.40	2 (0.6)	0 (0)	0 (0)	0.78
Fever								
None	269 (88)	35 (56)	7 (50)	<0.001	272 (89)	32 (50)	2 (14)	<0.001
37.0–37.9 °C	18 (6)	11 (18)	2 (14)	24 (8)	16 (25)	5 (35)		
38 °C⩽	13 (4)	14 (22)	5 (36)	8 (3)	13 (20)	7 (50)		
Not specified	7 (2)	3 (4)	0 (0)	3 (1)	3 (4)	0 (0)		
Dyspnea	43 (14)	14 (22)	6 (43)	0.007	40 (13)	28 (44)	8 (57)	<0.001
Fever or dyspnea	75 (24)	37 (58)	10 (71)	<0.001	65 (21)	49 (77)	14 (100)	<0.001
Any	150 (49)	51 (81)	13 (93)	<0.001	118 (38)	60 (94)	14 (100)	<0.001

[a] During one month period following the initial change in the chest X-ray.
[b] At the start of steroid therapy.

Table 3
The chest X-ray intervals and first radiographic change

Weeks	Group 1	Group 2	Group 3	p-value
The average interval of chest X-rays (weeks)[a]				
Median (range)	1.7 (0.7 to 6.0)	1.3 (0.5 to 4.4)	0.9 (0.5 to 3.8)	<0.001
Duration between the end of radiotherapy and the first radiographic change (weeks)				
Median (range)	9.9 (−2.9 to 45.1)	6.7 (0 to 24.9)	2.4 (0.4 to 10.1)	<0.001
<6	82 (27)	26 (41)	11 (79)	<0.001
6–11.9	116 (38)	29 (45)	3 (21)	
12–17.9	71 (23)	7 (11)	0 (0)	
18⩽	38 (12)	2 (3)	0 (0)	

[a] Calculated as follows: the average interval of chest X-rays = (the first radiographic change − the start of radiotherapy)/the number of chest X-rays taken during this period/7).

was slightly decreased (PaO2 = 70–74.9 Torr) in 12 (19%) patients of Group 2 and one (7%) patient of Group 3, and moderately to severely decreased (PaO2 ⩽ 69.9 Torr or SpO2 ⩽ 92%) in 21 (33%) patients of Group 2 and 7 (50%) patients of Group 3 ($p = 0.38$).

Prednisolone was administered as the initial therapy in 69 (88%) patients of Groups 2 and 3. The initial prednisolone equivalent dose of steroid was 30–40 mg daily in 52 (67%), and 60 mg of higher only in 8 (10%) patients (Table 4). The median duration of the initial dose was 10 (range, 2–64) days, and the dose was reduced within 14 days in 57 (77%) patients. The median duration of steroid therapy was 10 (range, 2–28) weeks (Table 4). Steroid pulse therapy (methylprednisolone 1000 mg daily for three days) was administered as the initial therapy in one patient, and as salvage therapy in six patients at the time of pneumonitis aggravation. Among the seven patients, six died of respiratory failure due to progressive radiation pneumonitis.

Outcome of steroid therapy was evaluated in 76 patients (Fig. 1). Symptomatic relief was obtained and the steroid dose was reduced in 71 (93%) of the 76 patients, while no effect was noted in the remaining five patients, who all died of radiation pneumonitis despite escalated steroid administration. Of the 71 patients, 15 (21%) developed recurrent symptoms at the median daily prednisolone dose of 20 mg (range, 10–40 mg) within median 33 days (range, 21–42 days) from the start of the steroid therapy, and required steroids to be escalated. Of the 15 patients, nine died of radiation pneumonitis and one died of complication of steroid therapy. A total of 54 (71%) patients were in remission from pneumonitis and steroid therapy was terminated. The remainder 22 patients died during steroid therapy, 14 of radiation pneumonitis, two of infectious complication (bacterial pneumonia in one, and lung aspergillosis in another patient), five of lung cancer progression, and one of hemoptysis. Thus, 16 patients, who accounted for 4.2% of 385 patients receiving 50–70 Gy of thoracic radiotherapy, and who accounted for 21% of 78 patients treated with steroid therapy, died of radiation pneumonitis or complication associated with steroid therapy. Median survival from the start of steroid therapy in these patients was 45 (range, 8–107) days.

Discussion

Patients with radiation-induced lung injury have been managed in compliance with the expert opinions, because there has been no case series or clinical trial report on clinical course and corticosteroid use for this lung injury. This

Table 4
Corticosteroid, dose and duration of steroid therapy

	N (%)
Corticosteroid	
Prednisolone	69 (88)
Dexamethasone	4 (5)
Betamethasone	4 (5)
Methylprednisolone	1 (1)
Initial dose, mg/body daily (prednisolone equivalent)	
Pulse therapy	1 (1)
60	7 (9)
50	1 (1)
40	10 (13)
30	42 (54)
10–25	17 (22)
Duration of the initial dose, days	
Median (range)	10 (2–64)
⩽14	57 (77)
15–28	9 (12)
29⩽	8 (11)
Not evaluable	4
Total duration of steroid therapy, weeks	
Median (range)	10 (2–28)
⩽6	16 (30)
6.1–12	19 (35)
12.1–18	14 (26)
18.1⩽	5 (9)
Not evaluable	24

study is the first systemic review of these patients both who received corticosteroid therapy and who did not. Comparison between the expert opinions and the results of this study is given below. First, radiation-induced lung injury is severer when a radiographic change appears earlier [5]. In this study, the initial change in a chest X-ray film was observed in 9.9 (range, −3 to 45) weeks in Group 1, in 6.7 (range, 0–25) weeks in Group 2, and 2.4 (range, 0–10) weeks in Group 3 after the end of thoracic radiotherapy. If patients present with symptoms, presumably they receive a chest X-ray. Thus, the patients with symptoms may have radiographic findings seen sooner, since they receive an X-ray when they complain of symptoms. The average interval of chest X-rays taken between the start of radiotherapy and the first appearance of radiographic change was longer in Group 1 than that in groups 2 and 3. The difference, however, was negligibly small when compared with the difference in duration between the end of radiotherapy and the first radiographic change. Second, steroid administration is determined generally based on the severity of symptoms [5]. In this study steroid was used when patients developed dyspnea or fever. Dyspnea has been thought to be the cardinal symptom of radiation pneumonitis but fever to be unusual [5,10]. In this study, however, fever was highly associated with fatal radiation pneumonitis; fever was noted in 12% patients of Group 1, in 58% patients of Group 2, and 86% patients of Group 3. This study failed to show utility of blood gas analysis. An oxygen content in the blood was decreased moderately to severely in only 28 (36%) patients in Groups 2 and 3, and did not differ between the two groups. The oxygen content in Group 1 was measured in only small number of patients, and therefore it was not evaluable in this study. Third, 30–100 mg/day of prednisolone has been recommended as the initial dose [4–6,10]. In our practice, a dose of 30–40 mg was the most frequently used. We selected this relatively low dose of steroid mostly because steroid therapy was started in out patient clinic. Forth, duration of the initial dose was within two weeks in 73% of patients, which is consistent to most expert opinions [6,10]. In contrast, tapering schedules varied between a pa-

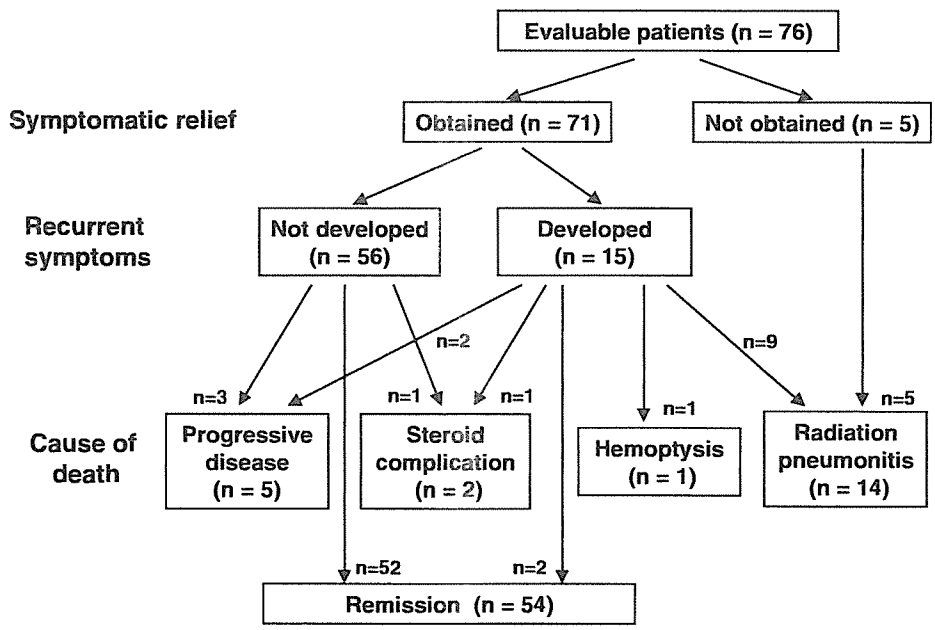

Fig. 1. Outcome of patients who received steroid therapy. Two patients were excluded because of loss of follow-up. Of 76 evaluable patients, 71 (93%) experienced symptomatic relief by steroid therapy.

tient and another in this study. This may be partly due to the diversity in clinical course of radiation pneumonitis, but mostly due to lacking in available recommendation for tapering schedules. In this study, median total duration of steroid therapy was 10 weeks, which may be a tentative guide. A guideline of taper schedule appeared in the latest textbook: the dose should be tapered by 10 mg every two weeks, and be terminated in 12 weeks [10].

Although our clinical practice mostly followed the expert opinions on the management of radiation-induced lung injury as mentioned above, there is little evidence that our steroid use, dose and duration for radiation-induced lung injury were correct. In this study, 21% of patients received steroid therapy and 4% of patients died of radiation pneumonitis among lung cancer patients treated with thoracic radiotherapy at a total dose of 50 Gy or higher. These figures are comparable to the incidence of grade 3 pneumonitis, 3–20%, and that of fatal pneumonitis, 1–4%, in other reports [10].

In conclusion, development of fever and dyspnea, and short interval between the end of radiotherapy and the first radiographic change were associated with fatal radiation-induced lung injury. Prednisolone 30–40 mg daily for two weeks followed by slow taper was selected for the treatment in many patients.

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Docetaxel Consolidation Therapy Following Cisplatin, Vinorelbine, and Concurrent Thoracic Radiotherapy in Patients with Unresectable Stage III Non-small Cell Lung Cancer

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Background: To evaluate the feasibility and efficacy of docetaxel consolidation therapy after concurrent chemoradiotherapy for unresectable stage III non–small cell lung cancer (NSCLC).

Patients and Methods: The eligibility criteria included unresectable stage III NSCLC, no previous treatment, age between 20 and 74 years, and performance status 0 or 1. Treatment consisted of cisplatin (80 mg/m^2 on days 1, 29, and 57), vinorelbine (20 mg/m^2 on days 1, 8, 29, 36, 57, and 64), and thoracic radiotherapy (TRT) (60 Gy/30 fractions over 6 weeks starting on day 2), followed by consolidation docetaxel (60 mg/m^2 every 3 to 4 weeks for three cycles).

Results: Of 97 patients who were enrolled in this study between 2001 and 2003, 93 (76 males and 17 females with a median age of 60) could be evaluated. Chemoradiotherapy was well tolerated; three cycles of chemotherapy and 60 Gy of TRT were administered in 80 (86%) and 87 (94%) patients, respectively. Grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 62, 11, and 3 patients, respectively. Docetaxel consolidation was administered in 59 (63%) patients, but three cycles were completed in only 34 (37%) patients. The most common reason for discontinuation was pneumonitis, which developed in 14 (24%) of the 59 patients. During consolidation therapy, grade 3 or 4 neutropenia, esophagitis, and pneumonitis developed in 51, 2, and 4 patients, respectively. A total of four patients died of pneumonitis. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or more severe radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas the median V_{20} for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test). The response rate was 81.7% (95% confidence interval [CI], 72.7–88.0%), with 5 complete and 71 partial responses. The median progression-free survival was 12.8 (CI, 10.2–15.4) months, and median survival was 30.4 (CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively.

Conclusion: This regimen produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

Key Words: Non-small cell lung cancer, Chemoradiotherapy, Consolidation, Docetaxel.

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Locally advanced unresectable non–small cell lung cancer (NSCLC), stage IIIA with bulky N2 and stage IIIB disease without pleural effusion, is characterized by large primary lesions and/or involvement of the mediastinal or supraclavicular lymph nodes and occult systemic micrometastases. A combination of thoracic radiotherapy and chemotherapy is the standard medical treatment for this disease, but the optimal combination has not been established.[1] Although the available data are insufficient to accurately define the size of a potential benefit,[2] concurrent chemoradiotherapy using a platinum doublet has been shown to be superior to the sequential approach in phase III trials of this disease.[3–5] However, third-generation cytotoxic agents, which have provided better patient survival with extrathoracic spread than the old-generation agents, must be reduced when administered concurrently with thoracic radiotherapy.[6] Thus, it has been hypothesized that the addition of systemic dose chemotherapy with a new cytotoxic agent to concurrent chemoradiotherapy, either as induction or as consolidation chemotherapy, might further improve patient survival.[1]

The consolidation chemotherapy with docetaxel was based on the observation that this drug was highly active in the primary treatment of metastatic NSCLC, producing a response rate (RR) as high as 20% after platinum-based chemotherapy failed.[7–9] Highly encouraging results of a me-

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dian survival time (MST) of more than 2 years and a 3-year survival rate of nearly 40% were obtained in a phase II trial of docetaxel consolidation after chemoradiotherapy with cisplatin and etoposide in patients with stage IIIB NSCLC (SWOG study S9504).[10]

We have developed a combination chemotherapy schedule with cisplatin and vinorelbine concurrently administered with thoracic radiotherapy at a total dose of 60 Gy in 30 fractions in patients with unresectable stage III NSCLC. The results of a phase I study in 18 patients were very promising, with a RR of 83%, a MST of 30 months, and a 3-year survival rate of 50%.[6] Thus, addition of docetaxel consolidation to this regimen is a particularly interesting therapeutic strategy. The objectives of the current study were to evaluate the feasibility of docetaxel consolidation therapy after concurrent chemoradiotherapy with cisplatin and vinorelbine and to evaluate the efficacy and safety of the whole treatment regimen including both the chemoradiotherapy and consolidation therapy in patients with unresectable stage IIIA and IIIB NSCLC.

PATIENTS AND METHODS

Patient Selection

The eligibility criteria were histologically or cytologically proven NSCLC; unresectable stage IIIA or IIIB disease; no previous treatment; measurable disease; tumor within an estimated irradiation field no larger than half the hemithorax; age between 20 and 74 years; Eastern Cooperative Oncology Group performance status (PS) of 0 or 1; adequate bone marrow function (12.0×10^9/liter $\geq$ white blood cell [WBC] count $\geq 4.0 \times 10^9$/liter, neutrophil count $\geq 2.0 \times 10^9$/liter, hemoglobin ≥ 10.0 g/dl, and platelet count $\geq 100 \times 10^9$/liter), liver function (total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value), and renal function (serum creatinine ≤ 1.5 mg/dl and creatinine clearance ≥ 60 ml per minute); and a PaO_2 of 70 torr or more under room air conditions. Patients were excluded if they had malignant pleural or pericardial effusion, active double cancer, a concomitant serious illness such as uncontrolled angina pectoris, myocardial infarction in the previous 3 months, heart failure, uncontrolled diabetes mellitus, uncontrolled hypertension, interstitial pneumonia or lung fibrosis identified by a chest x-ray, chronic obstructive lung disease, infection or other diseases contraindicating chemotherapy or radiotherapy, pregnancy, or if they were 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 computed tomographic (CT) scan, brain CT scan or magnetic resonance imaging, abdominal CT scan or ultrasonography, and radionuclide bone scan.

Treatment Schedule

Treatment consisted of a chemoradiotherapy phase with three cycles of cisplatin and vinorelbine followed by a consolidation phase with three cycles of docetaxel (Figure 1). Cisplatin 80 mg/m^2 was administered on days 1, 29, and 57 by intravenous infusion for 60 minutes with 2500 to 3000 ml of fluid for hydration. Vinorelbine diluted in 50 ml of normal saline was administered intravenously on days 1, 8, 29, 36, 57, and 64. All patients received prophylactic antiemetic therapy consisting of a $5HT_3$-antagonist and a steroid.

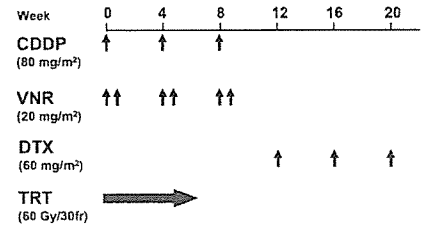

FIGURE 1. Treatment schema. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

Radiation therapy was delivered with megavoltage equipment ($\geq$6 MV) using anterior/posterior opposed fields up to 40 Gy in 20 fractions including the primary tumor, the metastatic lymph nodes, and the regional nodes. A booster dose of 20 Gy in 10 fractions was given to the primary tumor and the metastatic lymph nodes for a total dose of 60 Gy using bilateral oblique fields. A CT scan–based treatment planning was used in all patients. The clinical target volume (CTV) for the primary tumor was defined as the gross tumor volume (GTV) plus 1 cm taking account of subclinical extension. CTV and GTV for the metastatic nodes (>1 cm in shortest dimension) were the same. Regional nodes, excluding the contralateral hilar and supraclavicular nodes, were included in the CTV, but the lower mediastinal nodes were included only if the primary tumor was located in the lower lobe of the lung. The planning target volumes for the primary tumor, the metastatic lymph nodes, and regional nodes were determined as CTVs plus 0.5- to 1.0-cm margins laterally and 1.0- to 2.0-cm margins craniocaudally, taking account of setup variations and internal organ motion. Lung heterogeneity corrections were not used.

The criteria for starting consolidation chemotherapy were completion of three cycles of cisplatin and vinorelbine and a full dose of thoracic radiotherapy, the absence of progressive disease, adequate general condition within 6 weeks of the start of the third cycle of cisplatin and vinorelbine (PS 0 or 1, WBC count $\geq 3.0 \times 10^9$/liter, neutrophil count $\geq 1.5 \times 10^9$/liter, hemoglobin ≥ 9.0 g/dl and platelet count $\geq 100 \times 10^9$/liter, total bilirubin ≤ 1.5 mg/dl and transaminase no more than twice the upper limit of the normal value, and a PaO_2 of 70 torr or more at room air). Docetaxel (60 mg/m^2) was administered intravenously for 1 hour every 3 to 4 weeks for three cycles.

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. Acute toxicity was graded according to the NCI Common Toxicity Criteria, and late toxicity associated with thoracic radiother-

apy was graded according to the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme. Vinorelbine administration on day 8 was omitted if any of the following were noted: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. Subsequent cycles of cisplatin and vinorelbine chemotherapy were delayed if any of the following toxicities were noted on day 1: WBC count $<3.0 \times 10^9$/liter, neutrophil count $<1.5 \times 10^9$/liter, platelet count $<100 \times 10^9$/liter, serum creatinine level ≥1.6 mg/dl, elevated hepatic transaminase level or total serum bilirubin of at least grade 2, fever ≥38°C, or PS ≥2. 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 or docetaxel was reduced by 25% in all subsequent cycles if any of the following toxicities were noted: WBC count $<1.0 \times 10^9$/liter, platelet count $<10 \times 10^9$/liter, or grade 3 or 4 infection or liver dysfunction. Thoracic radiotherapy was suspended if any of the following were noted: fever ≥38°C, grade 3 esophagitis, PS of 3, or PaO_2 <70 torr. 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 60 days. The use of granulocyte colony-stimulating factor during radiotherapy was not permitted unless radiotherapy was on hold. The criteria for termination of docetaxel consolidation were not defined in the protocol.

Response Evaluation

Objective tumor response was evaluated according to the Response Evaluation Criteria in Solid Tumor.[11] Local recurrence was defined as tumor progression in the primary site and in the hilar, mediastinal, and supraclavicular lymph nodes after a partial or complete response; regional recurrence as the development of malignant pleural and pericardial effusions; and distant recurrence as the appearance of a distant metastasis.

Study Design, Data Management, and Statistical Considerations

This study was conducted at three institutions: the National Cancer Center Hospital, National Cancer Center Hospital East, and Tochigi Cancer Center. The protocol and consent form were approved by the institutional review board of each institution. Registration was conducted at the registration center. Data management, periodic monitoring, and the final analysis were performed by the study coordinator.

The primary objective of the current study was to evaluate the feasibility of docetaxel consolidation therapy. The secondary endpoints were toxicity observed during chemoradiotherapy and consolidation therapy, the best response, and overall survival in all patients eligible to participate in this study. Because no standard method to evaluate consolidation chemotherapy after chemoradiotherapy has been established, we arbitrarily defined the primary endpoint of this study as a ratio (R) of the number of patients receiving docetaxel without grade 4 nonhematological toxicity or treatment-related death to the total number of patients receiving docetaxel. The sample size was initially estimated to be 34 patients with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.95 would indicate potential usefulness, whereas a R of 0.8 would be the lower limit of interest, and that 85% of patients would move into the consolidation phase. An analysis of the first 13 patients, however, showed that only 8 (61%) patients advanced into the consolidation phase. The reasons for not receiving docetaxel were disease progression in one, delay in completion of chemoradiotherapy in two, grade 3 esophagitis in one, and death due to hemoptysis in one patient. Considering that the SWOG trial S9504 included 83 patients, we decided to revise the number of patients in the current study. According to Simon's two-stage minimax design, the required number of patients was calculated to be 59 with a power of 0.80 at a significance level of 0.05, under the assumption that a R of 0.85 would indicate potential usefulness, whereas a R of 0.7 would be the lower limit of interest.[12] Assuming that 61% of registered patients would move into the consolidation phase, the sample size was determined to be 97 patients.

Overall survival time and progression-free survival time were estimated by the Kaplan–Meier method, and confidence intervals (CI) were based on Greenwood's formula.[13] Overall survival time was measured from the date of registration to the date of death (from any cause) or to the last follow-up. Progression-free survival time was measured from the date of registration to the date of disease progression, death (from any cause), or the last follow-up. Patients who were lost to follow-up without event were censored at the date of their last known follow-up. A CI for RR was calculated using methods for exact binomial CIs. The Dr. SPSS II 11.0 for Windows software package (SPSS Japan Inc., Tokyo, Japan) was used for statistical analyses.

RESULTS

Registration and Characteristics of the Patients

A total of 97 patients were enrolled in this study between April 2001 and June 2003. Four patients were excluded from this study before the treatment was started because the radiation treatment planning disclosed that their tumors were too advanced for curative thoracic radiotherapy. Thus, 93 patients who received the protocol-defined treatment were the subjects of this analysis (Figure 2). There were 76 males and 17 females, with a median age of 60 (range 31–74). Body weight loss was less than 5% in 77 patients; adenocarcinoma histology was noted in 57 patients, and stage IIIA disease was noted in 41 patients (Table 1).

Treatment Delivery

Treatment delivery was generally well maintained in the chemoradiotherapy phase (Table 2). Full cycles of cisplatin and vinorelbine and the full dose of thoracic radiotherapy were administered in 80 (86%) and 87 (94%) patients, respectively. Delay in radiotherapy was less than 5 days in 61 (66%) patients. In contrast, the delivery of docetaxel was poor (Table 2). A total of 59 (63%) patients could enter the consolidation phase, and only 34 (37%) patients completed three cycles of docetaxel chemotherapy. The reasons for not

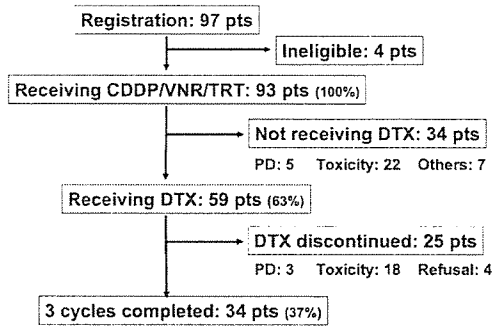

FIGURE 2. Patient registration. CDDP, cisplatin; DTX, docetaxel; TRT, thoracic radiotherapy; VNR, vinorelbine.

receiving consolidation were toxicity in 22 (65%) patients including pneumonitis in seven patients, myelosuppression in five patients, esophagitis in four patients, liver dysfunction in two patients, infection in two patients, other toxicity in two patients, progressive disease in five (15%) patients, patient refusal in three (9%) patients, early death due to hemoptysis in one (3%) patient, and other reasons in three (9%) patients. Of the 59 patients, 18 (31%) discontinued docetaxel consolidation because of toxicity, including pneumonitis (n = 14) and esophagitis, infection, gastric ulcer, and allergic reaction (n = 1 each), four (7%) because of patient refusal, and three (5%) because of progressive disease.

Toxicity

Acute severe toxicity in the chemoradiotherapy phase was mainly leukopenia and neutropenia, whereas grade 3 or 4 thrombocytopenia was not noted (Table 3). Severe nonhematological toxicity was sporadic, and grade 3 esophagitis and pneumonitis were observed in only 11 (12%) and 3 (3%) patients, respectively. Acute severe toxicity in the consolidation phase also consisted of neutropenia and associated infection (Table 4). In addition, grade 3 or 4 pneumonitis developed in 4 (7%) patients. The R observed in this study was 0.05 (3 out of 57 patients), which was much lower than the hypothetical value. Grade 3 or 4 late toxicities were included lung toxicity in four patients, esophageal toxicity in two patients, renal toxicity in one patient, and a second esophageal cancer that developed 35.4 months after the start of the chemoradiotherapy in one patient. Treatment-related

TABLE 1. Patient Characteristics

Characteristics	n	%
Gender		
Male	76	82
Female	17	18
Age median (range)	60	31–74
Weight loss		
<5%	76	81
5–9%	12	13
≥10%	3	3
Unknown	2	2
Histology		
Adenocarcinoma	57	61
Squamous cell carcinoma	23	25
Large cell carcinoma	12	13
Others	1	1
Stage		
IIIA	41	44
IIIB	52	56

TABLE 2. Treatment Delivery

Variables	n	%
Cisplatin and vinorelbine chemotherapy		
Total number of cycles		
3	80	86
2	10	11
1	3	3
Number of vinorelbine skips		
0	63	68
1	25	27
2–3	5	5
Thoracic radiotherapy		
Total dose (Gy)		
60	87	94
50–59	4	4
<50	2	2
Delay (days)		
<5	61	66
5–9	20	22
10–16	6	6
Not evaluable (<60 Gy)	6	6
Docetaxel consolidation		
Number of cycles		
3	34	37
2	12	13
1	13	14
0	34	34

TABLE 3. Acute Toxicity in Chemoradiotherapy (n = 93)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	54	18	72	77
Neutropenia	33	29	62	67
Anemia	21	0	21	23
Infection	15	1	16	17
Esophagitis	11	0	11	12
Hyponatremia	11	0	11	12
Anorexia	9	1	10	11
Nausea	5	—	5	5
Pneumonitis	3	0	3	3
Syncope	2	0	2	2
Hyperkalemia	2	0	2	2
Ileus	0	1	1	1
Cardiac ischemia	1	0	1	1

TABLE 4. Acute Toxicity in Consolidation Therapy (n = 57)

	Grade			
Toxicity	3	4	3 + 4	%
Leukopenia	33	11	44	77
Neutropenia	24	26	50	88
Anemia	5	0	5	9
Infection	5	1	6	11
Esophagitis	2	0	2	3
Anorexia	1	0	1	2
Pneumonitis	2	2	4	7

death was observed in four (4%) patients. Of these, three received docetaxel, and one did not. The reason for death was pneumonitis in all patients. We calculated a V_{20} (the percent volume of the normal lung receiving 20 Gy or more) on a dose–volume histogram in 25 patients. Of these, five patients developed grade 3 or severer radiation pneumonitis. A median V_{20} for these five patients was 35% (range, 26–40%), whereas that for the remaining 20 patients was 30% (range, 17–35%) (p = 0.035 by a Mann–Whitney test).

Objective Responses, Relapse Pattern, and Survival

All 93 patients were included in the analyses of tumor response and survival. Complete and partial responses were obtained in 5 (5%) and 71 patients (76%), respectively, for an overall RR of 81.7% (95% CI, 72.7–88.0%). Stable and progressive diseases occurred in 12 (13%) and 5 (5%) patients, respectively. With a median follow-up period of 29.7 months, 38 patients developed locoregional recurrence, 32 developed distant recurrence, 4 developed both locoregional and distant recurrences, and 19 did not. The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months (Figure 3). Two patients underwent salvage surgery for a recurrent primary tumors. Conventional chemotherapy and gefitinib monotherapy were administered after recurrence in 20 and 25 patients, respectively. The median overall survival time was 30.4 (95% CI, 24.5–36.3) months. The 1-, 2-, and 3-year survival rates were 80.7, 60.2, and 42.6%, respectively. (Figure 4).

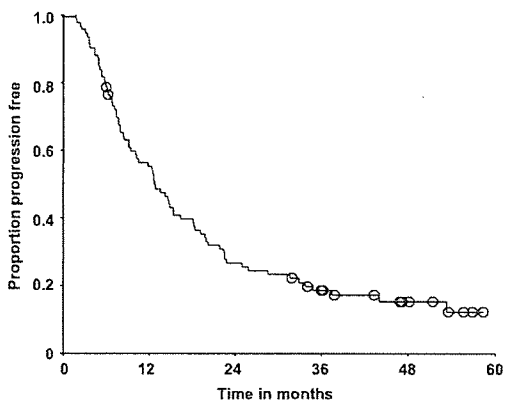

FIGURE 3. Progression-free survival (n = 93). The median progression-free survival time was 12.8 (95% CI, 10.2–15.4) months.

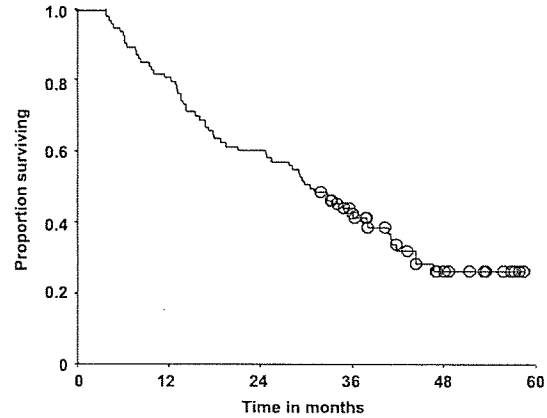

FIGURE 4. Overall survival (n = 93). The median overall survival time was 30.4 (95% CI, 25.4–35.4) months. The 1-, 2-, and 3-year survival rates were 80, 60, and 40%, respectively.

DISCUSSION

This study showed that concurrent chemoradiotherapy with cisplatin, vinorelbine, and standard thoracic radiotherapy was well tolerated, with a high completion rate exceeding 80%. The incidence of acute toxicity, including 67% (62/93) of grade 3 or 4 neutropenia, 12% (11/93) of grade 3 esophagitis, and 3% (3/93) of grade 3 pneumonitis, were comparable with other reports of concurrent chemoradiotherapy.[3,4,10] In contrast, consolidation docetaxel could be administered in only 59 of 93 (63%) patients eligible to participate in this study. Of the remaining 34 patients, 22 (65%) patients did not receive consolidation chemotherapy because of toxicities affecting various organs. Other studies also showed that not all patients proceeded to the consolidation phase after completion of concurrent chemoradiotherapy: 61 to 78% of patients after two cycles of cisplatin and etoposide with radiotherapy,[3,10] and 54 to 75% of patients after weekly carboplatin and paclitaxel with radiotherapy.[14,15] Thus, for 20 to 40% of the patients, concurrent chemoradiotherapy was as much as they could undergo, and the additional chemotherapy was not practical.

Furthermore, the number of patients who fulfilled the three cycles of consolidation docetaxel was only 34 (58%) of the 59 patients, which corresponded to only 37% of those eligible in this study. The reason for the termination of docetaxel in the 25 patients was toxicity in 18 (72%) patients, especially pneumonitis in 14 (56%) patients. The grade of pneumonitis during the consolidation phase was within grade 2 in most cases, and this was probably because docetaxel was discontinued early. Considering that pneumonitis associated with cancer treatment is more common in Japan, docetaxel consolidation is not thought to be feasible in the Japanese population. The MST and the 3-year survival rate in all eligible patients were 33 months and 44% in this study, but docetaxel consolidation was unlikely to contribute to these promising results because only 37% of patients received full cycles of docetaxel. This contrasts clearly with the result of

the SWOG study S9504, a phase II trial of two cycles of cisplatin and etoposide with thoracic radiation followed by three cycles of docetaxel. In this trial, 75% of patients starting consolidation and 59% of those entering the trial received full cycles. In addition, docetaxel consolidation seemed to prolong survival, although this was drawn from a retrospective comparison of the results between the two SWOG studies S9504 and S9019.[10]

There is no widely used definition of consolidation therapy following chemoradiotherapy. Given that consolidation therapy is arbitrarily defined as chemotherapy with three cycles or more after the completion of concurrent chemoradiotherapy, only one randomized trial is available in the literature. The randomized phase III trial of standard chemoradiotherapy with carboplatin and paclitaxel followed by either weekly paclitaxel or observation in patients with stage III NSCLC showed that only 54% of patients proceeded to randomization, and overall survival was worse in the consolidation arm (MST, 16 versus 27 months).[15] Thus, there have been no data supporting the use of consolidation therapy, especially when a third-generation cytotoxic agent such as paclitaxel and vinorelbine is incorporated into concurrent chemoradiation therapy.

The low complete-response rate of 5% in this study may be explained partly by an inability to distinguish between inactive scarring or necrotic tumor and active tumor after radiotherapy. Positron emission tomography (PET) using 18F-fluorodeoxyglucose showed a much higher rate of complete response than conventional CT scanning and provided a better correlation of the response assessment using PET with patterns of failure and patient survival.[16] In addition, the high locoregional relapse rate in this study clearly showed that the conventional total dose of 60 Gy was insufficient. Three-dimensional treatment planning, omission of elective nodal irradiation, and precise evaluation of the gross tumor volume by PET may facilitate the escalation of the total radiation dose without enhanced toxicity.

In conclusion, cisplatin and vinorelbine chemotherapy concurrently combined with standard thoracic radiotherapy and followed by docetaxel consolidation produced promising overall survival in patients with stage III NSCLC, but the vast majority of patients could not continue with the docetaxel consolidation because of toxicity.

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SURVEY REPORT

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JASTRO平成15・16年度研究課題報告 医療実態調査研究による放射線治療施設構造基準化（案）の改訂（日本版ブルーブック）

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REVISION OF GUIDELINE FOR STRUCTURE OF RADIATION ONCOLOGY BY THE PATTERNS OF CARE STUDY

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Abstract: "Guidelines for Structure of Radiation Oncology in Japan" was revised by referring to annual change of structure and process in Japan and to other international guidelines. These results were published as so called "Japanese Blue Book Guidelines". Number of cancer patients who require radiation is increasing by more than 7% annually. The standard guidelines for annual patient load per FTE radiation oncologist were set at 200 (warning level 300), those per FTE radiation technologist 120 (warning level 200), and those per one external beam equipment 250-350 (warning level 400). As the standards of process, establishment of verifiable information system like radiotherapy database and hospital cancer registration was proposed. Economic analysis showed that enough profit to meet with these guidelines became available recently in most radiotherapy institutions except for the smallest group.

Key words: Patterns of Care Study, Radiation Oncology, Structural Guideline, Japanese Blue Book Guideline

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