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).

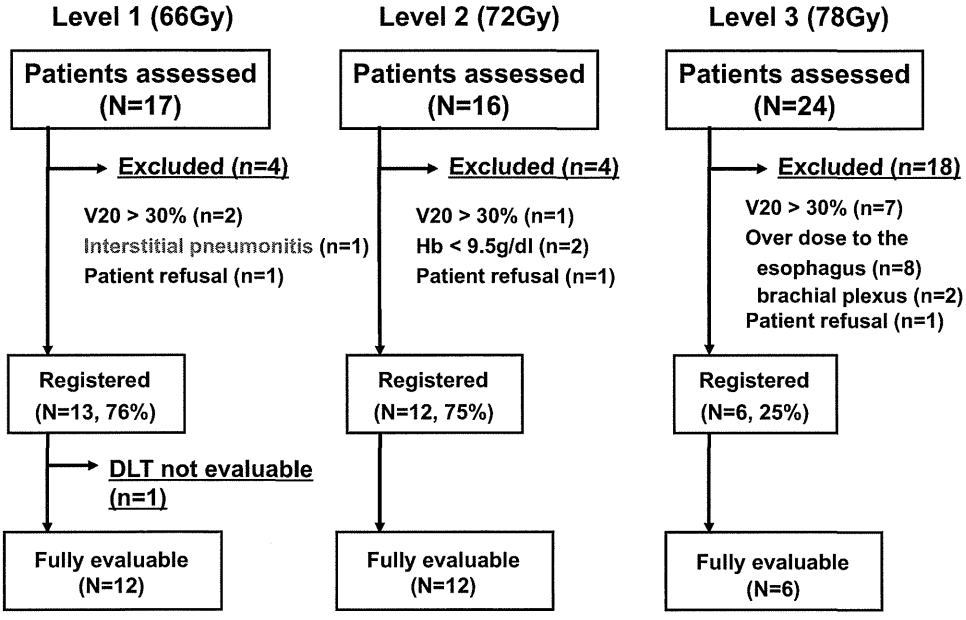

Fig. 1. Algorithm illustrating the flow of the patients. Of the 17, 16, and 24 patients assessed for eligibility, 13 (76%), 12 (75%), and 6 (25%) were actually enrolled at dose levels 1, 2, and 3, respectively.

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).

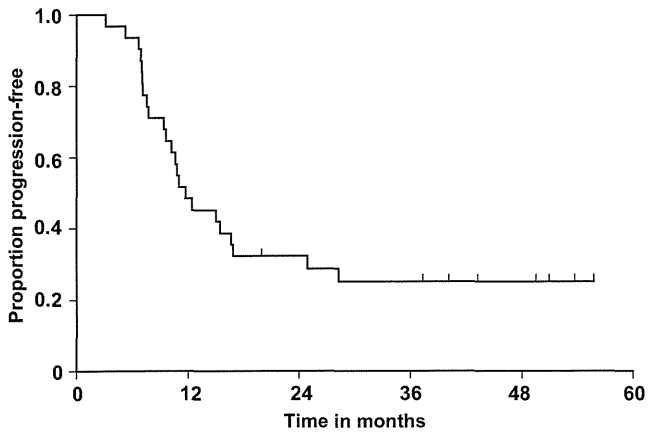

Fig. 2. Progression-free survival (n = 31). The median progression-free survival was 11.6 months, with a median duration of follow-up of 30.5 months (range, 9.0–49.5 months).

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)

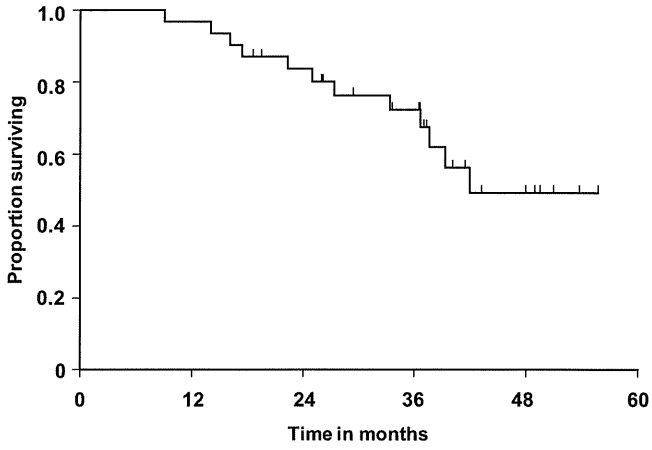

Fig. 3. The median overall survival was 41.9 months, and the 2-, 3-, and 4-year survival rates (95% CI) were 83.6% (65.0–92.8), 72.3% (51.9–85.2), and 49.2% (26.2–68.7), respectively.

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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International Journal of
Radiation Oncology
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Clinical Investigation: Gynecologic Cancer

Patterns of Radiotherapy Practice for Patients With Cervical Cancer in Japan, 2003–2005: Changing Trends in the Pattern of Care Process

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Received Mar 28, 2011, and in revised form Sep 27, 2011. Accepted for publication Oct 4, 2011

Summary

This study reports changes in the patterns of practice of definitive radiotherapy for cervical cancer in Japan since 1995 by comparing 3 patterns of care surveys. There has been a significant trend toward use of concurrent chemotherapy consistent with randomized trial data. External beam radiation has became progressively more standardized. Intracavitary brachytherapy, however, still has not reached consistent levels of quality.

Purpose: The patterns of care study (PCS) of radiotherapy for cervical cancer in Japan over the last 10 years was reviewed.

Methods and Materials: The Japanese PCS working group analyzed data from 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with definitive radiotherapy in Japan.

Results: Patients in the 2001–2003 survey were significantly younger than those in the 1999–2001 study ($p < 0.0001$). Histology, performance status, and International Federation of Gynecology and Obstetrics stage were not significantly different among the three survey periods. Use of combinations of chemotherapy has increased significantly during those periods (1995–1997, 24%; 1999–2001, 33%; 2003–2005, 54%; $p < 0.0001$). The ratio of patients receiving concurrent chemotherapy has also dramatically increased (1995–1997, 20%; 1999–2001, 54%; 2003–2005, 83%; $p < 0.0001$). As for external beam radiotherapy (EBRT), the application rate of four-field portals has greatly increased over the three survey periods (1995–1997, 2%; 1999–2001, 7%; 2003–2005, 21%; $p < 0.0001$). In addition, the use of an appropriate beam energy for EBRT has shown an increase (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). As for intracavitary brachytherapy (ICBT), an iridium source has become increasingly popular (1995–1997, 27%; 1999–2001, 42%; 2003–2005, 84%; $p < 0.0001$). Among the three surveys, the ratio of patients receiving ICBT (1995–1997, 77%; 1999–2001, 82%; 2003–2005, 78%) has not changed. Although

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This study was presented at the 51st Annual Meeting of the American Society of Therapeutic Radiology and Oncology, Chicago, IL, Nov 1–5, 2009.

This study was supported by a Grant-in-Aid for Cancer Research (no. 18-4) from the Ministry of Health, Labor and Welfare.

Conflict of interest: none.

Int J Radiation Oncol Biol Phys, Vol. 83, No. 5, pp. 1506–1513, 2012
0360-3016/$ - see front matter
doi:10.1016/j.ijrobp.2011.10.013

follow-up was inadequate in each survey, no significant survival differences were observed ($p = 0.36$), and rates of late Grade 3 or higher toxicity were significantly different ($p = 0.016$). **Conclusions:** The Japanese PCS has monitored consistent improvements over the past 10 years in the application of chemotherapy, timing of chemotherapy, and EBRT methods. However, there is still room for improvement, especially in the clinical practice of ICBT. © 2012 Elsevier Inc.

Keywords: Cervix, Chemotherapy, Japan, Patterns of care study, Radiotherapy

Introduction

In Japan, the number of uterine cervical cancers decreased from the 1980s to 2000 but has been steadily increasing since then (1). The age-adjusted mortality rate due to cervical cancer has also shown an increase, especially in the younger generation in Japan (3). Radiation therapy is established as an integral component for cervical cancer. Over the past 10 years, some changes have occurred in the cervical cancer radiotherapy policy in Japan. Given the increases in cervical cancer and age-adjusted mortality rates, to optimally treat Japanese cervical cancer patients, it is important to accurately delineate intrinsic changes taking place in the national practice process of radiotherapy for cervical cancer in Japan. The patterns of care study (PCS) (2) initially surveyed radiotherapy practice in the United States. In the United States, PCS has been conducted for more than 30 years, and the structure, process, and outcomes of radiotherapy, as well as various problems in clinical practice, have been identified for cervical cancer (4, 5). The Japanese PCS began in 1996 and used the same methods (6). We previously reported Japanese PCS results for radiotherapy practice in cervical cancer patients treated in 1995–1997 and 1999–2001 (7, 8). We report here the corresponding results for 2003–2005, and the changes in radiotherapy practice that occurred over the years from the 1995–1997, 1999–2001, and 2003–2005 survey periods are also examined.

Methods and Materials

Between 2006 and 2008, the Japanese PCS working group conducted a third national survey of patients with uterine cervical cancer treated with radiotherapy. Patients who were eligible for the survey (*1*) had carcinoma, (*2*) were treated between January 2003 and December 2005, and (*3*) had no distant metastasis, (*4*) no prior or concurrent malignancy, (*5*) no gross para-aortic lymph node metastasis, and (*6*) no previous pelvic radiotherapy. Sixty-one of 640 institutions were selected for this survey by using a stratified two-staged cluster sampling method. Before the random sampling, all institutions were divided into four groups. Institutions were classified by type and number of patients treated with radiotherapy. The Japanese PCS working group stratified Japanese institutions as A1, academic institutions treating ≥430 patients annually; A2, academic institutions treating <430 patients; B1, nonacademic institutions treating ≥130 patients annually; and B2, nonacademic institutions treating <130 patients. Detailed criteria for stratification have been shown elsewhere (6). The Japanese PCS surveyors performed on-site chart reviews at each participating facility, using an originally developed database format for cervical cancer. Data collection included patient characteristics, details of the pretreatment workup, therapeutic information, and treatment outcome. The Japanese PCS collected clinical data for 487 patients with cervical cancer, who were treated with radiotherapy from 61 institutions. In this study, 285 patients treated with radiotherapy without planned surgery were analyzed. These included 114 patients from A1 institutions, 87 patients from A2 institutions, 50 patients from B1 institutions, and 34 patients from B2 institutions. There were unknown and missing data in the tables because no valid data were found in the given resources.

In addition, the current study compared data for three Japanese PCS surveys of 1,200 patients (1995–1997, 591 patients; 1999–2001, 324 patients; 2003–2005, 285 patients) with cervical cancer treated with radiotherapy with curative intent. Methods for the 1995–1997 and 1999–2001 PCS were the same as those for the 2003–2005 study. Ratios were calculated without unknown or missing data. Statistical significance was tested using the chi-square test.

Results

Patient characteristics in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

Table 1 shows characteristics of the 285 patients in the 2003–2005 survey and changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods. The ages of the analyzed cohorts were significantly different among the three survey periods ($p < 0.0001$). The ages of the analyzed cohort were not different between the 1995–1997 and 1999–2001 surveys ($p = 0.34$) but were significantly different between the 1999–2001 and 2003–2005 surveys ($p < 0.0001$). Karnofsky performance status (KPS), histology, and International Federation of Gynecology and Obstetrics (FIGO) stages were not significantly different among the three survey periods, as shown in Table 1.

EBRT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, EBRT was performed in 283 patients (99%). Major treatment parameters for pelvic EBRT in the 2003–2005 survey are shown in Table 2. Treatment parameters in the 2003–2005 survey other than those shown in Table 2 are as follows. In 220 cases (78%), multileaf collimators were used to shape the portals. For 265 patients (94%), the planning target volume included the whole pelvic region. The upper border of the pelvic field was at level of the L4–L5 interspace in 245 of the 265 patients (92%). Only 6 patients (2%) received extended field radiotherapy that included the para-aortic region. The median radiation treatment time was 6.0 weeks (range, 1.1–13.0 weeks). The median radiation treatment time exceeded 8 weeks in 7 patients (3%).

Table 1 Patient and tumor characteristics of patients with uterine cervical cancer treated with radiotherapy in each surveillance period

Characteristic	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Age (years)				<0.0001
Range	28–94	26–100	25–95	
Median	70	71	67	
KPS				0.21
≤70	133 (23)	64 (21)	52 (18)	
80–90	421 (72)	217 (72)	193 (68)	
100	28 (5)	21 (7)	40 (14)	
Unknown/missing	9 (–)	22 (–)	0 (–)	
Histology				0.99
Squamous cell	554 (95)	300 (94)	257 (92)	
Adenocarcinoma	23 (4)	14 (4)	14 (5)	
Adenosquamous cell	4 (1)	4 (1)	5 (2)	
Other	4 (1)	2 (1)	3 (1)	
Unknown/missing	6 (–)	4 (–)	6 (–)	
FIGO stage				0.89
I	57 (10)	43 (14)	27 (10)	
II	171 (29)	102 (34)	85 (30)	
III	280 (48)	122 (40)	132 (46)	
IVA	75 (13)	35 (12)	41 (14)	
Other	5 (1)	0 (0)	0 (0)	
Unknown/missing	3 (–)	22 (–)	1 (–)	

Abbreviations: FIGO = International Federation of Gynecology and Obstetrics; KPS = Karnofsky performance status.

Changes in radiotherapy practice over the 1995–1997, 1999–2001, and 2003–2005 survey periods are also shown in Table 2. The ratio of appropriate EBRT beam energy levels of more than or equal to 10 MV showed a tendency to increase over the three surveys (1995–1997, 67%; 1999–2001, 74%; 2003–2005, 81%; $p = 0.064$). In addition, application of four-field portals greatly increased over the three surveys ($p < 0.0001$). Use of a midline block, single-daily fraction doses, and total point A doses were not significantly different among the three survey periods.

ICBT in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

No patient surveyed received interstitial brachytherapy in the 2003–2005 survey. Fifty-nine patients (27%) received ICBT at another facility. Details of ICBT in the 2003–2005 survey are shown in Table 3. In most patients, all high-dose-rate ICBT (HDR-ICBT) procedures (applicator insertion, radiograph generation, and treatment) were performed in the same room, but these data for dose calculations for the rectum and bladder and the ICBT method showed a considerable rate of unknown or missing data.

Changes in ICBT practice over the years are also shown in Table 3. A ratio of Ir-192 source showed a significant increase among the three surveys ($p < 0.0001$). The number of patients who received no supportive medication before or during the applicator insertion significantly decreased over the three survey periods ($p < 0.0001$), but conscious sedation was still used for a few patients. The use of ICBT, dose rate, method of ICBT, and single-daily fraction dose were not different among the three survey periods. The use of *in vivo* dosimetry and International Commission on Radiation Units and Measurements (ICRU) report 38 calculations for bladder and rectum were not different among the three survey periods, although these data also showed an appreciable rate of unknown or missing data.

Chemotherapy in the 2003–2005 survey and trends in the 1995–1997, 1999–2001, and 2003–2005 surveys

In the 2003–2005 survey, chemotherapy was given to 149 patients (54%), as shown in Table 4. Neoadjuvant chemotherapy was given to 16 patients before they received radiation therapy (11%), and 124 patients (83%) were treated with concurrent chemoradiation (CCRT). Weekly cisplatin was the agent most frequently used with CCRT (45%), and cisplatin was the most common agent in CCRT (55%) regimens.

Changes in chemotherapy practice over the years are also shown in Table 4. Application of chemotherapy significantly increased over the three survey periods ($p < 0.0001$). In addition, concurrent use of chemotherapy with radiotherapy has dramatically increased ($p < 0.0001$). On the other hand, the ratio of neoadjuvant chemotherapy in the most recent survey (2003–2005, 11%) decreased compared to those of 1995–1997 (58%) and 1999–2001 (50%).

Comparison of outcomes and toxicity between the 1995–1997, 1999–2001, and 2003–2005 surveys

Overall survival rates of patients in each survey are shown in Figure 1. Two-year survival rates in the 1995–1997, 1999–2001,

Table 2 Treatment parameters of pelvic external beam radiotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

	No. of patients (%)			
Parameters	1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Beam energy				0.064
Co-60 and 3–5 MV	96 (17)	32 (11)	20 (7)	
6–9 MV	82 (14)	45 (15)	30 (11)	
10–14 MV	338 (59)	220 (71)	191 (70)	
≥15 MV	45 (8)	9 (3)	31 (11)	
Other	10 (2)	0 (0)	1 (0)	
Unknown/ missing	20 (–)	2 (–)	12 (–)	
Technique				<0.0001
AP-PA	560 (98)	269 (87)	205 (75)	
Four-field box	11 (2)	21 (7)	57 (21)	
Other	1 (0)	17 (6)	11 (4)	
Unknown/ missing	19 (–)	1 (–)	12 (–)	
Midline block				0.56
Yes	386 (69)	215 (75)	186 (69)	
No	171 (31)	72 (25)	82 (31)	
Unknown/ missing	34 (–)	1 (–)	17 (–)	
Daily fraction size (Gy)				0.10
<1.8	13 (2)	25 (8)	3 (1)	
1.8	259 (45)	135 (44)	142 (51)	
>1.8 to <2	0 (0)	2 (1)	8 (3)	
2	299 (52)	137 (45)	120 (43)	
>2	3 (1)	6 (2)	4 (2)	
Unknown/ missing	17 (–)	3 (–)	8 (–)	
Total point A dose (Gy)				0.39
0–20	23 (8)	13 (5)	23 (9)	
20–30	42 (14)	40 (14)	58 (21)	
30–40	119 (38)	121 (42)	128 (47)	
40–50	57 (18)	62 (22)	46 (11)	
>50	69 (22)	49 (17)	17 (17)	
Unknown/ missing	17 (–)	39 (–)	12 (–)	
Median	32.2	32.4	32.4	

Abbreviations: AP-PA = opposing anteroposterior-posteroanterior; EBRT = external beam radiotherapy.

and 2003–2005 surveys were 83.4%, 78.4%, and 80.5%, respectively, with a median follow-up of only 2.4, 1.4, and 1.7 years, respectively, in the three studies. These differences did not reach a statistically significant level (p = 0.36).

Rates of developing late Grade 3 or higher toxicity of cervical cancer patients surveyed in each survey are shown in Figure 2. Two-year rates of developing late Grade 3 or higher toxicity in the 1995–1997, 1999–2001, and 2003–2005 surveys were 4.4%, 2.3%, and 8.5%, with a median follow-up of only 2.3, 1.4, and 1.7 years, respectively, in the three studies. Rates of late toxicity were significantly different (p = 0.016).

Discussion

The current study showed that, in Japan, a significant increase was observed in the rate of patients who received chemotherapy over the three periods of 1995–1997, 1999–2001, and 2003–2005. Several RCTs conducted in the 1990s demonstrated that CCRT reduced mortality risk in cervical cancer patients compared with radiotherapy alone (9). The current study showed that a combination of chemotherapy with radiotherapy has become widely used in Japan, similar to the change in the United States in the late 1990s. Concurrent use of chemotherapy also significantly increased over the three survey periods. Our study suggests that more appropriate management of uterine cervical cancer has been adopted in Japan. On the other hand, more than half of the patients (125 patients did not receive chemotherapy; and 25 of the patients who did receive chemotherapy did not receive CCRT) were not treated with CCRT in the 2003–2005 survey, although not all of these patients needed CCRT. Some Japanese physicians remain cautious about employing CCRT as a standard treatment for two reasons. The first reason concerns the feasibility of using the standard chemotherapy of weekly cisplatin concurrently with radiotherapy. Several reports have found Japanese cervical cancer patients frequently experienced severe toxicities, and investigators concluded that CCRT using weekly 40 mg/m^2 dosages of cisplatin might not be feasible for Japanese patients (10). The second reason is that there are limited data for CCRT using HDR-ICBT. A large amount of data concerning excellent outcomes and acceptable toxicity have been reported for patients treated with the Japanese standard schedules, but most of this information was derived from retrospective analyses, and CCRT data are limited (11). Therefore, a prospective study (Japanese Gynecologic Oncology Group study 1066) was undertaken to evaluate toxicities and outcomes in patients treated with CCRT by using the standard dosage/schedule of cisplatin and the standard Japanese radiotherapy dosage schedules for HDR-ICBT (12). On the other hand, whereas several RCTs revealed the negative therapeutic value of neoadjuvant chemotherapy in the mid-1990s, more than 10% of patients were still treated with this strategy during the most recent survey period. However, the current study showed that the ratio of neoadjuvant chemotherapy decreased in the recent survey (2003–2005, 11%) compared to those in the 1995–1997 (58%) and 1999–2001 (50%) surveys. Cisplatin was the agent most commonly used in CCRT (55%) in the 2003–2005 survey. Previous recommendations have been limited to platinum-based chemoradiotherapy, but a recently released individual patient data meta-analysis (13) has shown a significant benefit also associated with non-platinum regimens, specifically those containing 5-fluorouracil and/or mitomycin-C, although those results are not based on a direct comparison. Therefore, detailed information about chemotherapy regimens other than cisplatin will need to be evaluated in future PCS surveys of radiotherapy for cervical cancer.

The current study showed that the four-field technique was gradually applied more frequently over the three survey periods and that the ratio of the four-field technique during the 2003–2005 period was 21%. However, most patients were still treated with the opposing anteroposterior (AP-PA) technique in

Table 3 Details of intracavitary brachytherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameter	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
ICBT given				0.66
Yes	454 (77)	265 (82)	222 (78)	
No	132 (23)	58 (18)	63 (22)	
Unknown/missing	5 (–)	1 (–)	0 (–)	
Dose rate				0.47
HDR	386 (89)	215 (89)	205 (93)	
LDR	37 (9)	27 (11)	13 (6)	
Other	10 (2)	0 (0)	2 (1)	
Unknown/missing	21 (–)	23 (–)	65 (–)	
Source				<0.0001
Ir-192	113 (27)	102 (42)	183 (84)	
Co-60	269 (64)	112 (46)	23 (11)	
Cs-137	33 (8)	21 (9)	12 (5)	
Ra-226	9 (2)	7 (3)	0 (0)	
Unknown/missing	33 (–)	23 (–)	67 (–)	
Method of ICBT				0.65
Tandem plus vaginal applicator	352 (87)	202 (83)	190 (89)	
Tandem only	30 (8)	26 (11)	14 (7)	
Vaginal applicator	22 (5)	16 (6)	6 (3)	
Others	0 (0)	0 (0)	3 (1)	
Unknown/missing	50 (–)	21 (–)	9 (–)	
Applicator				0.025
Rigid	NA	166 (72)	158 (85)	
Nonrigid	NA	66 (28)	27 (15)	
Unknown/missing	NA	33 (–)	100 (–)	
In vivo dosimetry: bladder				0.73
Yes	NA	8 (4)	9 (5)	
No	NA	207 (96)	171 (95)	
Unknown/missing	NA	50 (–)	105 (–)	
In vivo dosimetry: rectum				0.24
Yes	NA	71 (33)	75 (41)	
No	NA	145 (67)	108 (59)	
Unknown/missing	NA	49 (–)	102 (–)	
ICRU 38: bladder				0.12
Yes	NA	48 (25)	57 (35)	
No	NA	146 (75)	106 (65)	
Unknown/missing	NA	71 (–)	122 (–)	
ICRU 38: rectum				0.38
Yes	NA	65 (34)	68 (40)	
No	NA	128 (66)	104 (60)	
Unknown/missing	NA	72 (–)	113 (–)	
Preparation				<0.0001
None	199 (53)	90 (54)	33 (19)	
NSAIDs administered orally/rectally	107 (28)	68 (41)	86 (49)	
IV conscious sedation	29 (8)	5 (3)	7 (4)	
Others	2 (1)	3 (2)	49 (28)	
Unknown/missing	117 (–)	99 (–)	110 (–)	
All procedures performed in the same room*				0.58
Yes	NA	167 (94)	157 (92)	
No	NA	11 (6)	13 (8)	
Unknown/missing	NA	37 (–)	115 (–)	
Each fraction was planned*				0.16
Yes	NA	159 (76)	157 (84)	
No	NA	49 (24)	30 (16)	
Unknown/missing	NA	7 (–)	98 (–)	

(*continued on next page*)

Table 3 (*continued*)

Parameter	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Single-point A dose of HDR-ICBT (cGy)				<0.0001
0–499	16 (5)	43 (20)	14 (7)	
500–599	100 (33)	79 (37)	59 (29)	
600–699	145 (47)	48 (22)	123 (59)	
700–799	43 (14)	15 (7)	10 (5)	
>800	2 (1)	2 (1)	1 (1)	
Unknown/missing	21 (–)	28 (–)	65 (–)	
Median	600	524	600	
Total point A dose of HDR-ICBT (Gy)				<0.0001
0–10	4 (1)	5 (3)	6 (3)	
10–20	80 (26)	58 (31)	71 (34)	
20–30	145 (48)	113 (61)	127 (61)	
30–40	77 (25)	8 (4)	4 (2)	
>40	0 (0)	1 (0)	0 (0)	
Unknown/missing	21 (–)	24 (–)	64 (–)	
Median	24.0	20.3	24.0	

Abbreviations: HDR = high-dose rate; ICBT = intracavitary brachytherapy; ICRU = International Commission on Radiation Units and Measurements; LDR = low-dose rate; NA = not applicable; NSAIDs = nonsteroidal anti-inflammatory inflammatory drugs.
* A total of 222 patients were treated with HDR-ICBT.

Japan, and rates of the use of the four-field technique remained low during the latest period. According to a report of the status of Japanese radiation oncology, one of the problems for the national practice process of radiotherapy in Japan was structural immaturity, especially in terms of personnel (14). Results of our study indicated that radiotherapy characteristics are still developing in Japan. The current study also revealed a change in the beam energy used for radiotherapy in Japan over the three survey periods. Only 7% of the patients were treated with Co-60 and 3 to 5 MV in 2003–2005, whereas these energies were used in 17% of patients in 1995–1997 and 11% of patients in 1999–2001. In addition, the use of appropriate beam energies of 10 to 14 MV and ≥15 MV increased over the three survey periods. In conjunction with the increased numbers of full-time equivalent radiation oncologists in both academic and nonacademic institutions (15),

Table 4 Details of chemotherapy in the 1995–1997, 1999–2001, and 2003–2005 survey periods

Parameters	No. of patients (%) 1995–1997 (n = 591)	1999–2001 (n = 324)	2003–2005 (n = 285)	p
Chemotherapy given				<0.0001
Yes	140 (24)	104 (33)	149 (54)	
No	434 (76)	213 (67)	125 (46)	
Unknown/missing	17 (–)	7 (–)	11 (–)	
Timing*				<0.0001
Neoadjuvant	81 (58)	52 (50)	16 (11)	
Concurrent	28 (20)	56 (54)	124 (83)	
Adjuvant	31 (22)	15 (14)	34 (23)	
Agent†				NA
CDDP weekly	NA	NA	49 (45)	
CDDP daily	NA	NA	5 (5)	
CDDP plus 5-FU	NA	NA	6 (5)	
Others	NA	NA	49 (45)	
Unknown/missing	NA	NA	15 (–)	

Abbreviations: 5-FU = 5-fluorouracil; CDDP = cisplatin; NA = not applicable.
* Some patients overlap in the timing column.
† The indicated agent was used for patients who received concurrent chemotherapy.

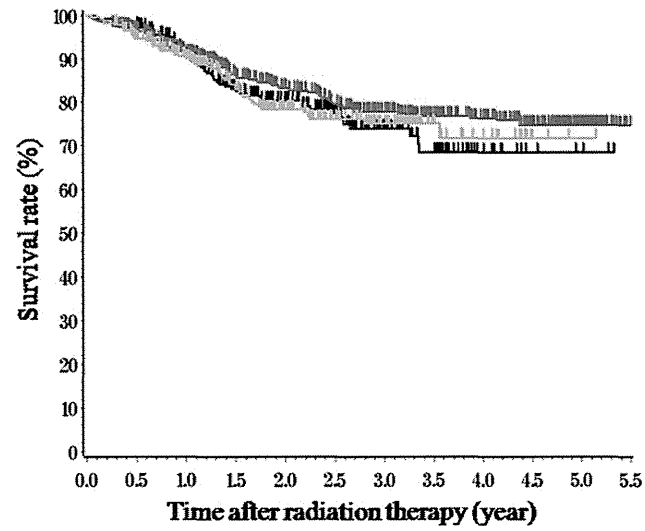

Fig. 1. Kaplan-Meier estimates of overall survival are shown for cervical cancer patients surveyed in the 1995–1997 (blue line, n = 573 patients), 1999–2001 (yellow line, n = 310 patients), and 2003–2005 (black line, n = 279 patients) patterns of care studies in Japan.

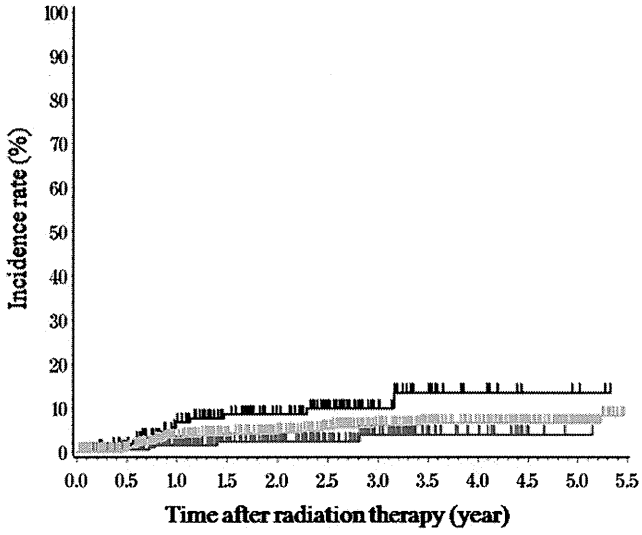

Fig. 2. The rate of developing late Grade 3 or higher toxicity are shown for cervical cancer patients surveyed in the 1995–1997 (blue, $n = 445$), 1999–2001 (yellow, $n = 224$), and 2003–2005 (black, $n = 166$) patterns of care studies in Japan.

Japanese cervical cancer patients are increasingly undergoing more appropriate methods.

The ratio of patients receiving ICBT did not increase over the three surveys. A considerable number of patients, 22%, were still not given ICBT during 2003–2005, and the application rate was lower in Japan than in the United States (4, 5). Therefore, ICBT should be applied more routinely for cervical cancer patients treated with definitive radiotherapy in Japan. One reason for the fact that some patients were not given ICBT might have been insufficient equipment, because 27% of patients received ICBT at another institution compared with 8.5% in the United States (16). The use of Ir-192 in 2003–2005 increased significantly compared with that in 1995–1997 and 1999–2001. The rapid increase in the use of Ir-192 might have been due to the result of the Japanese Society for Therapeutic Radiology and Oncology recommendation in the early 2000s that stated Co-60 should be avoided as a remote afterloading brachytherapy source in Japan because of source attenuation consistent with age. The American Brachytherapy Society (ABS) made a number of recommendations regarding HDR-ICBT techniques (17). Doses to the rectum were more often determined by using a dosimeter than by ICRU 38 reference point calculations. In fact, many studies showed that late rectal complications can be predicted by calculated doses at the ICRU 38 reference points (18). According to the ABS survey, rectal/bladder doses were evaluated in 80% or more patients at U.S. institutions, where HDR radiation was performed (19). However, our study showed that doses to the rectum and bladder in ICBT were evaluated, at most, in 40% of patients in Japan, and this status has significant scope for further improvement. Because accurate insertion can hardly be achieved if patients experience discomfort in ICBT, the ABS also recommends conscious sedation for HDR-ICBT applicator insertions (17). The current study showed that the number of patients who received no supportive medication before or during the applicator insertion significantly decreased, but conscious sedation was still used for a few patients. Although there are some limitations to the interpretation of these data due to an appreciable rate of unknown or missing data, we believe that additional improvements in the management of ICBT are still needed.

The current study also showed that patients' ages in the 1999–2001 survey were significantly different than those in the 2003–2005 survey, and the median age of 71 years old in the 2003–2005 survey was younger than that of the median age of 67 years old in the 1999–2001 survey. We think this may be due to the recent change in the age-specific incidence rate of cervical cancer in Japan. The age-specific incidence rate of cervical cancer in women over 40 years old has fallen gradually since the 1980s, while that in patients under 40 has gradually increased (21). Thus, the percentage of younger patients treated with radiotherapy may have increased. Konno *et al.* (22) organized the critical public health issues about cervical cancer in Japan in their cervical cancer working group report. In Japan, a national program for screening of cervical cancer was enacted in 1982. However, Organization for Economic Cooperation and Development data showed high rates of cervical cancer screening coverage in the United States and Europe but low coverage in Japan (23.4%) (20). With regard to cervical cancer prevention in Japan, in 1983, the government passed a Health and Medical Service Law for the Aged, leaving screening up to regional governments. A human papilloma virus vaccine was licensed in 2009 in Japan.

No significant survival improvement in patient outcome was observed among the three surveys. On the other hand, rates of late toxicity were significantly different in each study. One possible cause for these differences was the dramatic increase in the use of CCRT over the three survey periods. However, the current study has limitations in terms of outcome and toxicity analysis because of an inadequate follow-up time and significant variations in follow-up information according to institutional stratification (6). Therefore, we cannot draw any conclusions about Japanese radiotherapy practice in cervical cancer from these outcome and toxicity data.

Conclusions

In conclusion, we reported the status of definitive radiotherapy for uterine cervical cancer in Japan between 2003 and 2005 and examined the changes over the years in radiotherapy practice in the 1995–1997, 1999–2001, and 2003–2005 survey periods. By comparing the results of previous surveys with those of the 2003–2005 PCS survey, we delineated the changes in the process of care for cervical cancer patients treated with radiotherapy in Japan. Study data indicate a significant trend toward a combination of chemotherapy and concurrent use of chemotherapy and radiation therapy due to the adoption of recommendations found in RCTs. EBRT conditions such as beam energy and technique were gradually standardized to more appropriate methods over the three periods. Regarding ICBT, the patterns of both clinical procedure and quality assessment have still not reached sufficient quality. We believe that the three surveys of Japanese patterns of care for cervical cancer clearly show distinct improvements, while several problems remain to be resolved.

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Int. J. Radiation Oncology Biol. Phys., Vol. 82, No. 2, pp. 946–952, 2012

0360-3016/$ - see front matter

doi:10.1016/j.ijrobp.2010.12.045

CLINICAL INVESTIGATION **Thoracic Cancer**

PROGNOSTIC IMPACT OF THE 6TH AND 7TH AMERICAN JOINT COMMITTEE ON CANCER TNM STAGING SYSTEMS ON ESOPHAGEAL CANCER PATIENTS TREATED WITH CHEMORADIOTHERAPY

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Purpose: The new 7th edition of the American Joint Committee on Cancer TNM staging system is based on pathologic data from esophageal cancers treated by surgery alone. There is no information available on evaluation of the new staging system with regard to prognosis of patients treated with chemoradiotherapy (CRT). The objective of this study was to evaluate the prognostic impact of the new staging system on esophageal cancer patients treated with CRT.

Methods and Materials: A retrospective review was performed on 301 consecutive esophageal squamous cell carcinoma patients treated with CRT. Comparisons were made of the prognostic impacts of the 6th and 7th staging systems and the prognostic impacts of stage and prognostic groups, which were newly defined in the 7th edition.

Results: There were significant differences between Stages I and III ($p < 0.01$) according to both editions. However, the 7th edition poorly distinguishes the prognoses of Stages III and IV ($p = 0.36$ by multivariate analysis) in comparison to the 6th edition ($p = 0.08$ by multivariate analysis), although these differences were not significant. For all patients, T, M, and gender were independent prognostic factors by multivariate analysis ($p < 0.05$). For the Stage I and II prognostic groups, survival curves showed a stepwise decrease with increase in stage, except for Stage IIA. However, there were no significant differences seen between each prognostic stage.

Conclusions: Our study indicates there are several problems with the 7th TNM staging system regarding prognostic factors in patients undergoing CRT. © 2012 Elsevier Inc.

Esophageal cancer, Chemoradiotherapy, American Joint Committee on Cancer, TNM, Prognostic factor.

INTRODUCTION

Staging systems for cancer have evolved over time and continue to change as knowledge of cancer increases. The TNM staging system is one of the most widely used staging systems, and was based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of distant metastasis (M). Tumor stage is the most important prognostic factor for any type of cancer, and planning for optimal treatment is mainly decided according to tumor stage (1).

The TNM staging system was recently revised in the 7th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) cancer staging manual, which was published in 2009 (2). The main differences between the 6th and 7th editions include: 1) T is was redefined and T4 was subclassified as T4A and T4B and 2) regional lymph nodes were redefined. N was subclassified according to the number of positive regional lymph nodes, and 3) M was redefined. In addition, prognostic staging, including histological grade and cancer site, was defined for T1-3N0M0 patients.

The 7th edition staging system for esophageal cancer was also revised and was based on retrospective analysis of pathologic data from patients treated only by primary surgical resection (3). However, because of poor outcomes with surgery alone, the current treatment for esophageal cancer incorporates neoadjuvant chemotherapy or chemoradiotherapy (CRT) (4–6). Definitive CRT has been established as a curative treatment for esophageal cancer, and its clinical utility has been recently expanded (7–9). To our best knowledge, the prognostic impact of the 7th edition staging system has been not evaluated in detail for esophageal cancer patients undergoing CRT.

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Presented at 2011 Gastrointestinal Cancers Symposium, San Francisco, CA, January 20, 2011.

Conflicts of interest: none.

Acknowledgment—We appreciate the statistical advice and expertise of Keitaro Matsuo.

Received Oct 20, 2010, and in revised form Dec 21, 2010. Accepted for publication Dec 29, 2010.

Therefore, the objective of the present study was to evaluate the prognostic impact of clinical staging in the 7th edition on esophageal squamous cell cancer patients treated with CRT. We performed two analyses: 1) the prognostic impacts of the TNM staging systems of the 6th and 7th editions were compared and 2) the prognostic impacts of stage and prognostic groups, which incorporate TNM, cancer site, and histological grade, on patients with Stage I and II cancers were also compared.

METHODS AND MATERIAL

Patients

This was a retrospective cohort study of esophageal cancer patients treated with CRT at the Aichi Cancer Center Hospital between January 2003 and January 2009.There were a total of 301 patients who met the following inclusion criteria: 1) carcinoma of thoracic esophagus; 2) histological diagnosis of primary esophageal squamous cell carcinoma; 3) total radiation dose ≥50 Gy; 4) concomitant chemotherapy consisting of 5-fluorouracil and platinum agents; 5) no previous thoracic radiotherapy (RT); 6) no previous thoracic surgery; and 7) no salvage surgery. Patients who received chemotherapy followed by CRT were also included in this analysis.

Pretreatment staging and treatment planning

Pretreatment staging evaluations included physical examination, laboratory tests, esophagogastroduodenoscopy, barium esophagography, and contrast-enhanced computed tomography scans (CT) from the neck to upper abdomen. Positron emission tomography (PET) scans were performed especially after 2005 if the clinician thought it necessary to reveal distant metastasis such as bone metastasis. PET scans were rarely performed until 2005 since it had not been approved in Japan. Pretreatment staging was performed according to the 6th edition of the AJCC Cancer Staging Manual during a team conference, which included thoracic surgeons, radiologists, gastroenterologists, and medical oncologists. The treatment strategy was also decided at this conference. In general, patients with Stage I disease were treated by surgery alone, or endoscopic mucosal resection, or CRT. Patients with Stage II-IV disease were treated by surgery plus chemotherapy or CRT.

Three-dimensional RT planning and treatment

During this study period, RT was delivered using a linear accelerator (Clinac 21EX, Clinac 2100C; Varian Medical Systems, Palo Alto, CA) with a 6- or 10-MV photon beam. In general, patients received 2 Gy/day for 5 days per week, to a total radiation dose of 60 Gy. The primary gross tumor volume (GTV-P) and volume for involved lymph nodes (GTV-N) were determined. The primary clinical target volume (CTV-P) included the GTV-P with a 20-mm margin (craniocaudal direction); the lymph node clinical target volume for (CTV-N) included the GTV-N without an additional margin (9). The regional nodal site was not added to the CTV for prophylaxis. The planning target volume (PTV) included both CTVs with lateral and anteroposterior 5- to 10-mm margins and 10- to 20-mm craniocaudal margins. In addition, 5- to 8-mm leaf margins were added to the PTV. All fields were treated each day. There were patients initially treated with 36–40 Gy using an anteroposterior field technique that included the PTV. A boost dose was given to the PTV for a total dose, using bilateral oblique or multiple fields to exclude the spinal cord from the field. Spinal cords never received more than 45 Gy. If the patients had distant organ metastases or had nonregional lymph node metastasis (with the exception of supraclavicular lymph node metastasis), the radiation fields were minimized to include only the primary lesion.

The chemotherapy regimens used with RT consisted of 5-fluorouracil and cisplatin or nedaplatin. The doses and schedules were determined and administered as previously reported (9–12).

Follow-up

A history and physical examination, complete blood cell count, gastrointestinal endoscopy, chest X-ray, and CT scanning of the neck, chest, and abdomen were performed approximately every 3–6 months for 3 years after initiation of treatment. Patient vital status and disease status were confirmed by checking medical records at the last follow-up visit. For a patient lost to follow-up, his or her vital status was confirmed from the annual census registration. In that case, if a patient was determined to have died, the cause of death was treated as unknown.

Data collection and restaging

The following information was recorded from the medical record and radiological images of each patient: treatment initiation date, age, sex, cancer site, tumor length, histological grade, clinical stage, total radiation dose, final date assessing survival, and date of death. TNM staging, including number of lymph nodes, was independently redetermined by two radiologists (M.N., T.K.) according to the 6th and 7th AJCC editions. A lymph node was considered positive for metastasis if the short axis was greater than 5 mm (13). If restaging was different from pretreatment staging, the redetermined stage was adopted for this analysis.

Statistical analysis

Overall survival was calculated from the time of treatment to the time of death from any cause, or to time of last follow-up. Survival curves were constructed using the Kaplan-Meier method. To evaluate the impact of each factor on overall survival, univariate and multivariate Cox proportional hazards modeling was applied. Therefore, the measure of association in this study was the hazard ratio along with the 95% confidence interval (95% CI). Statistical analyses were performed using the SPSS statistical software package version 11 (SPSS Inc., Chicago, IL), and a p value of less than 0.05 was considered statistically significant.

RESULTS

Patient characteristics

Between January 2003 and January 2009, 513 consecutive patients with esophageal cancer received RT. There were 212 patients excluded from this analysis for the following reasons: adenocarcinoma (n = 15), small-cell carcinoma (n = 1), carcinoma of cervical esophagus (n = 40), total radiation dose <50 Gy (n = 45), underwent RT alone (n = 37), underwent primary endoscopic mucosal resection (n = 23), chemotherapy other than 5-fluorouracil and platinum (n = 18), and missing analysis data (n = 33). Thus, a total of 301 patients were analyzed in this study. Study patient characteristics are summarized in Table 1. The chemotherapy regimens with RT were 5-fluorouracil and cisplatin (n = 281, 93.4%) or 5-fluorouracil and nedaplatin (n = 20, 6.6%). Chemotherapy before CRT was performed in 31 (10.3%) patients. In the 6th edition, the 3-year survival rates

Table 1. Patient and tumor characteristics

Characteristic	Patients (n = 301)	%
Age (y)		
Median	65	
Range	39–82	
Gender		
Male	265	88
Female	36	12
PS		
0	88	29
1	210	70
2	3	1
Total dose		
Median	60 Gy	
Range	50–66.5 Gy	
Tumor length		
Median	5 cm	
Range	1–17 cm	
Cancer site		
Ut	61	20
Mt	168	56
Lt	72	24
T stage (7th)		
1	81	27
2	18	6
3	132	44
4	70	23
N stage (7th)		
0	92	31
1	116	39
2	76	25
3	17	6
M stage (7th)		
0	231	77
1	70	23
Histological grade		
Grade 1	49	16
Grade 2	128	43
Grade 3	28	9
Grade X	96	32

Abbreviations: PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion; Mt = mid-thoracic portion; Lt = lower thoracic portion.

of Stage I, II, III, and IV were 88.6%, 64.5%, 37.1%, and 29.1%, respectively. In 7th edition, the 3-year survival rates of Stage I, II, III, and IV were 87.6%, 62.0%, 32.3%, and 24.6%, respectively. The median follow-up period was 52 months, with 148 patients dead at the time of analysis.

Comparison of 6th and 7th edition staging systems

Table 2 shows the distribution of patient classifications according to the TNM staging systems of the 6th and 7th AJCC editions. Two patients were shifted to a higher stage in the 7th edition compared with the 6th. One patient shifted from Stage IIB to IIIA, and the other patient went from Stage III to IV. Eighty-four patients were shifted to a lower stage, and most of these went from Stage IV to III (n = 74).

Table 3 shows the univariate and multivariate analyses for each prognostic factor. By multivariate analysis, T stages, which remained the same in both the 6th and 7th editions,

Table 2. Patient distribution according to 6th and 7th editions of TNM classifications

	6th edition					
	I	IIA	IIB	III	IVA	IVB
7th edition						
IA	52					
IB		5				
IIA		19				
IIB			17		4	6
IIIA			1	22	6	20
IIIB				3	2	18
IIIC				28	7	21
IV				1	7	62

had significant impact on prognosis. The difference for each N stage was not prominent compared with T stages. M1 had no significant impact on survival compared with M0 in multivariate analysis (p = 0.13). When the 7th-edition M was categorized according to nonregional lymph node metastasis (M1-lym: n = 34 with supraclavicular nodes, n = 4 with supraclavicular nodes and abdominal nodes, n = 2 with abdominal nodes, and n = 2 with cervical nodes) and distant organ metastasis (M1-organ), only distant metastasis was significantly associated with prognosis.

According to the 4 major stage classifications (Stage I, II, III, IV; Table 4), there were significant differences between Stages I and III (p = 0.05) for each edition (Fig. 1a, b). However, the 7th edition poorly distinguished between Stages III and IV (p = 0.36 by multivariate analysis, Table 4) in comparison to the 6th edition (p = 0.08, Table 4). In the 6th edition, the 3-year survival rates of Stage III, IV-lym, and IV-organ were 37.1%, 34.2%, and 9.1%, respectively. In 7th edition, the 3-year survival rates of Stages III, IV-lym, and IV-organ were 32.3%, 36.2%, and 9.1%, respectively. When Stage IV was subclassified into Stage IV-lym or Stage IV-organ in accordance with the M1 subclassifications, the survival impact of Stage IV-lym almost completely overlapped with Stage III (p = 0.59), although there were significant differences between Stage IV-lym and Stage IV-organ (hazard ratio 1.90, 95%CI 1.02–3.56, p = 0.044) (Table 4, Fig. 2a, b).

Comparison between stage group and prognostic group for patients Stages I and II by the 7th edition

By multivariate analysis (Table 3), no cancer site had significant impact on survival. For histological grade, there was a significant difference between grade 1 and grade 2 (p = 0.008) by univariate analysis; however, the difference was not significant by multivariate analysis (p = 0.1). Table 5 shows the distribution of patients according to stage and prognostic classifications. In stage group, the 3-year survival rates of Stage IA, IB, IIA, and IIB were 88.6%, 66.7%, 48.0%, and 71.6%, respectively. In prognostic group, the 3-year survival rates of Stage IA, IB, IIA, and IIB were 92.0%, 79.7%, 54.4%, and 66.5%, respectively. The survival curves of the prognostic groups show a stepwise decrease

Table 3. Univariate and multivariate analyses of factors

		Univariate analysis			Multivariate analysis		
	Patients $n = 301$	HR	95% CI	p	HR	95% CI	p
Age (y)							
<65	142	1.00	–	–	1.00	–	–
>65	159	0.92	0.67–1.27	0.62	0.96	0.69–1.35	0.83
Gender							
Male	265	1.00	–	–	1.00	–	–
Female	36	0.61	0.35–1.08	0.09	0.50	0.28–0.91	0.023
PS							
0	88	1.00	–	–	1.00	–	–
1 or 2	213	2.99	1.8–4.97	<0.001	0.76	0.36–1.56	0.45
Tumor length							
<Median	143	1.00	–	–	1.00	–	–
>Median	128	1.78	1.26–2.52	0.001	1.24	0.82–1.86	0.32
Cancer site							
Ut	61	1.00	–	–	1.00	–	–
Mt	168	0.88	0.59–1.30	0.51	1.27	0.82–1.96	0.28
Lt	72	0.73	0.45–1.18	0.20	1.30	0.75–2.28	0.35
Grade (7th)							
1	49	1.00	–	–	1.00	–	–
2	128	2.13	1.22–3.73	0.008	1.64	0.91–2.97	0.10
3	28	2.10	1.04–4.26	0.039	1.38	0.66–2.88	0.39
X	96	2.33	1.31–4.15	0.004	1.91	1.05–3.47	0.033
T stage (6th, 7th)							
1	81	1.00	–	–	1.00	–	–
2	18	2.60	1.11–6.09	0.027	2.67	1.02–7.00	0.046
3	132	4.71	2.74–8.09	<0.001	3.96	1.79–8.77	0.001
4	70	6.53	3.70–11.53	<0.001	6.09	2.52–14.69	<0.001
N stage (6th)							
0	112	1.00	–	–	1.00	–	–
1	189	2.43	1.68–3.51	<0.001	1.05	0.67–1.66	0.80
N stage (7th)							
0	92	1.00	–	–	1.00	–	–
1	116	2.78	1.76–4.40	<0.001	1.56	0.93–2.60	0.09
2	76	4.06	2.51–6.57	<0.001	1.71	0.97–3.02	0.063
3	17	4.76	2.33–9.69	<0.001	1.89	0.85–4.23	0.12
M stage (6th)							
0	148	1.00	–	–	1.00	–	–
1	153	2.88	2.04–4.05	<0.001	2.01	1.34–3.01	0.001
M stage (7th)							
0	231	1.00	–	–	1.00	–	–
1	70	2.06	1.45–2.92	<0.001	1.34	0.91–1.93	0.13
1 lym	42	1.63	1.04–2.54	0.032	1.01	0.64–1.61	0.96
1 organ	28	2.90	1.82–4.62	<0.001	2.17	1.30–3.60	0.003
Neoadjuvant chemotherapy							
No	270	1.00	–	–	1.00	–	–
Yes	31	1.21	0.73–2.00	0.47	1.09	0.65–1.82	0.75

Abbreviations: PS = Eastern Cooperative Oncology Group performance status; Ut = upper thoracic portion; Mt = mid-thoracic portion; Lt = lower thoracic portion; HR = hazards ratio; CI = confidence interval; lym = metastasis to nonregional lymph nodes.

with increase in stage, except for Stage IIA (Fig. 3b). However, there were no significant differences between each stage in either group (Fig. 3a, b).

DISCUSSION

Although neoadjuvant chemotherapy, CRT followed by esophagectomy, or CRT as definitive treatment have been standard therapies for resectable esophageal squamous cell cancer (4–9), the 7th edition of the AJCC/UICC cancer staging system for esophageal cancer was based on pathologic data from esophageal cancer treated by primary surgical resection alone (3). However, pathologic staging criteria have been thought to be inadequate for patients receiving neoadjuvant therapy, including CRT (14, 15). Thus, this study was conducted to evaluate the prognostic impact of the new TNM staging system on esophageal cancer treated with CRT.

In the 7th edition, the N factor, which is based on the number of positive regional lymph nodes, is one of the major changes from the 6th edition. With clinical N staging, the accurate number of positive lymph nodes is difficult to determine

Table 4. Comparison between the 6th and 7th editions of TNM classifications

	7th edition						6th edition					
	Univariate			Multivariate*			Univariate			Multivariate*		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
Stage I	1.00	–	–	1.00	–	–	1.00	–	–	1.00	–	–
Stage II	3.04	1.31	7.04	0.01	3.15	1.30	7.65	0.01	3.81	1.48	9.82	0.01	3.78	1.41	10.69	0.01
Stage III	7.93	3.82	16.46	<0.001	8.15	3.45	19.30	<0.001	7.60	3.16	18.28	<0.001	7.24	2.62	20.00	<0.001
Stage IV	9.15	4.31	19.45	<0.001	9.61	4.02	22.97	<0.001	10.70	4.66	24.40	<0.001	10.87	4.20	28.12	<0.001
Stage III	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–	1.00	–	–	–
Stage IV	1.15	0.80	1.67	0.44	1.19	0.82	1.72	0.36	1.39	0.92	2.10	0.11	1.48	0.96	2.27	0.08
Stage IV lym	0.92	0.58	1.45	0.69	0.88	0.55	1.41	0.59	1.26	0.82	1.92	0.29	1.24	0.79	1.96	0.35
Stage IV organ	1.67	1.03	2.70	0.04	2.23	1.22	4.10	0.01	2.27	4.00	1.30	0.004	2.94	1.61	5.56	<0.001

Abbreviations: HR = hazards ratio; CI = confidence interval; lym = metastasis to nonregional lymph nodes.
* According to performance status, age, gender, tumor length, location, and grade.

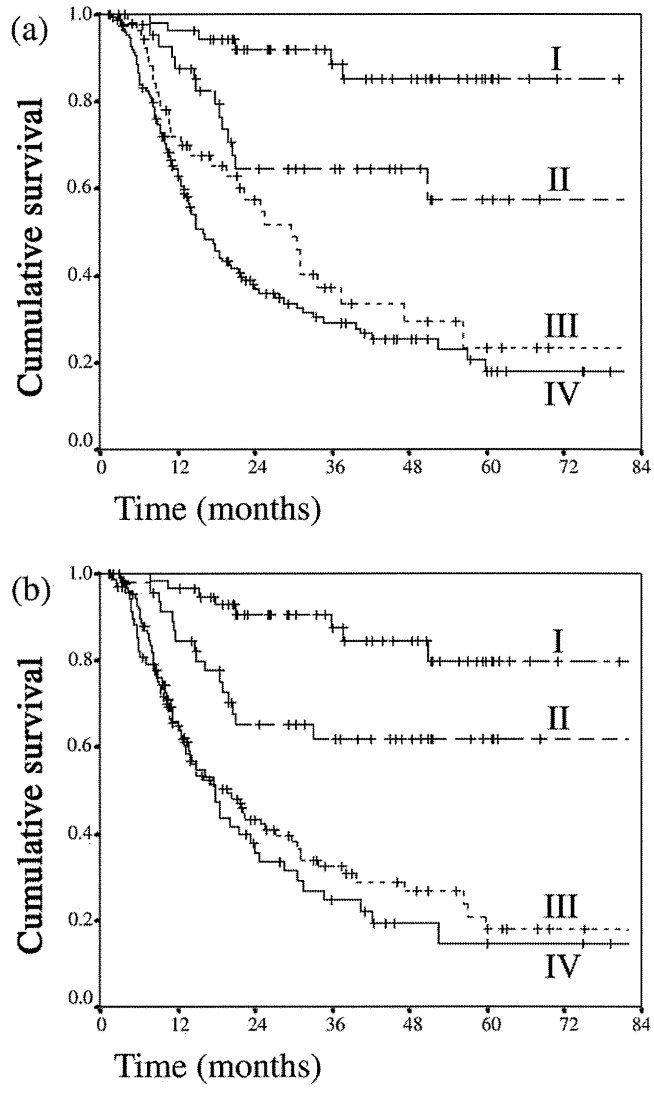

Fig. 1. Survival curves of patients stratified according to the 6th (a) and 7th (b) edition staging systems classified into four major stages. In 6th edition, the 3-year survival rates of Stage I, II, III, and IV were 88.6%, 64.5%, 37.1%, and 29.1%, respectively. In 7th edition, the 3-year survival rates of Stage I, II, III, and IV were 87.6%, 62.0%, 32.3%, and 24.6%, respectively. Statistical differences in survival between groups were analyzed by Cox proportional hazards model. By multivariate analysis, there were significant differences between Stages I and II ($p = 0.01$ in 6th and $p = 0.01$ in 7th), Stages II and III ($p = 0.014$ in 6th and $p = 0.006$ in 7th) for each edition.

before treatment. In our study, the number of lymph nodes was determined according to enhanced CT. Our results indicated that the difference between each N stage was not great compared with the difference between each T stage. In addition, the prognostic impact of N is generally lower than the prognostic impact of T. Our analysis of M factors shows that the survival curve of Stage IV-lym was significantly different from the curve for Stage IV-organ. There were 34 (81.0%) M1 lymph patients with metastatic supraclavicular nodes that were relatively small, and their radiation fields covered the entire PTV. However, in patients with metastasis to a distant organ, their limited radiation fields could not cover all tumor

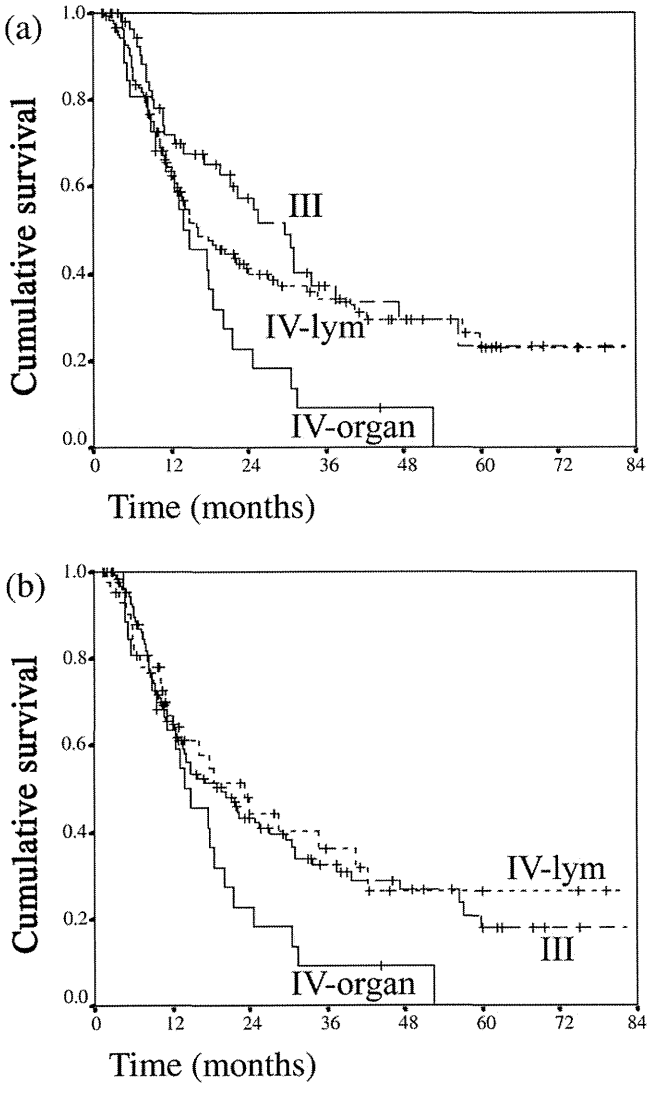

Fig. 2. Survival curves of patients stratified according to the 6th (a) and 7th (b) edition staging systems when Stage IV was subclassified as Stage IV-lym or Stage IV-organ. In the 6th edition, the 3-year survival rates of Stages III, IV-lym, and IV-organ were 37.1%, 34.2%, and 9.1%, respectively. In the 7th edition, the 3-year survival rates of Stage III, IV-lym, and IV-organ were 32.3%, 36.2%, and 9.1%, respectively.

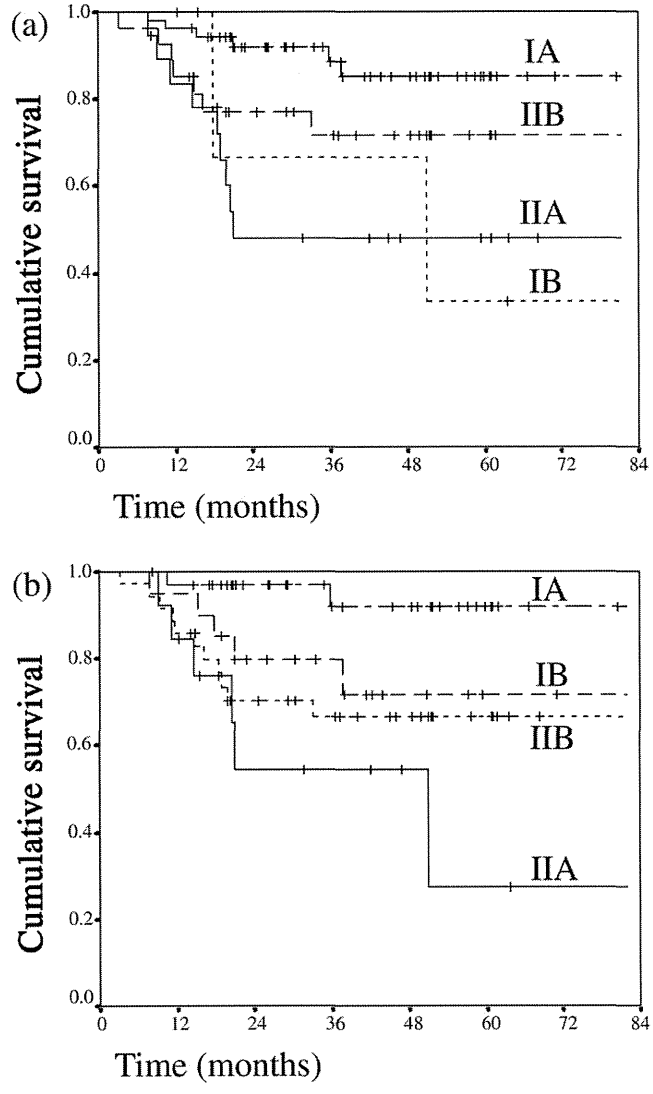

Fig. 3. Survival curves of patients stratified according to stage group (a) and prognostic group (b). In stage group, the 3-year survival rates of Stages IA, IB, IIA, and IIB were 88.6%, 66.7%, 48.0%, and 71.6%, respectively. In prognostic group, the 3-year survival rates of Stages IA, IB, IIA, and IIB were 92.0%, 79.7%, 54.4%, and 66.5%, respectively.

lesions. This may be the major reason why patients with M1-lym had significantly better survival compared with patients with M1-organ. Moreover, recent reports have indicated that early tumor response to CRT predicts improved survival of esophageal cancer (16). Therefore, prediction of esophageal cancer sensitivity to CRT may be more important for predicting prognosis after CRT.

Table 5. Distribution of the stage and prognostic groups

	Stage group			
	IA	IB	IIA	IIB
Prognostic group				
IA	34			
IB	18	1	2	
IIA		3	11	
IIB		1	7	27

For N0M0 cancer patients, incorporation of new prognostic factors, including histological grade and cancer site, are other major changes in the 7th edition. Studies have shown that histological grade and cancer site are prognostic factors for survival in esophageal carcinoma (17, 18). However, Hsu *et al.* reported results of comparisons between the prognostic impacts of the 6th and 7th TNM staging systems in esophageal squamous cell carcinoma treated with primary surgical resection alone, and did not find a significant prognostic role for these two factors (19). Our results also showed that these two factors were not significant for esophageal squamous cell carcinoma treated with CRT. Moreover, by multivariate analysis, the T factor was the most significant