of administration. If recovery from such toxicities was confirmed at a reduced dose, administration at the reduced dose was continued. If a patient with a BSA less than 1.25 m^2 experienced the above toxicities, then no further treatment with S-1 was performed. If a rest period of more than 4 weeks between two chemotherapy cycles of concurrent and consolidation phases was required or if the consolidation chemotherapy could not start within 6 weeks after SP-RT, then the SP treatment was discontinued.

Radiotherapy

All patients were treated with a linear accelerator photon beam of 6 MV or more from day 1. The primary tumor and involved nodal disease received 60 Gy in 2-Gy fractions over a period of 6 weeks. In this protocol, both 2- and 3-dimensional (D) treatment planning systems were allowed. The radiation doses were specified at the center of the target volume. The doses were calculated assuming tissue homogeneity without correcting for lung tissues for both 2- and 3-D treatment planning. Among the 54 patients assessable for toxicity, 2- and 3-D treatment planning were performed for 7 and 47 patients, respectively. The initial 40 Gy/20 fractions were delivered to clinical target volume 1 (CTV1), and the final 20 Gy/10 fractions were delivered to a reduced volume defined as clinical target volume 2 (CTV2). CTV1 included the primary tumor, ipsilateral hilum, and mediastinal nodal areas from the paratracheal (no. 2) to subcarinal lymph nodes (no. 7). For the primary tumors and the involved lymph nodes of 1 cm or more larger in the shortest diameter, a margin of at least 0.5 cm was added. The contralateral hilum was not included in CTV1. The supraclavicular areas were not treated routinely but were treated when the supraclavicular nodes were involved. CTV2 included only the primary tumor and the involved lymph nodes, with a margin of 0.5 to 1 cm. The spinal cord was excluded from the fields for CTV2 by appropriate methods, such as the oblique opposing method. The appropriate planning target volume margin and leaf margin were added for CTV1 and CTV2. When grade 4 hematologic toxicity, grade 3 to 4 esophagitis or dermatitis, pyrexia of ≥38°C, or a decrease in the partial pressure of arterial oxygen of 10 torr or more were compared with that before RT occurred, RT was interrupted. If a rest period of more than 2 weeks was required, then the patient was withdrawn from the study.

Evaluation of the Response and Toxicity

All registered patients, excluding those withdrawn from the study, received the following evaluations. Chest x-rays, complete blood cells, and blood chemistry studies were repeated once a week during the treatment period. Thoracic CT was performed every 1 or 2 months during the treatment period. After the treatment, a thoracic CT was obtained every 6 months, and other imaging examinations were obtained when recurrence was suspected. The response was evaluated in accordance with the RECIST version 1.0 guidelines.[21] In this study, the results of the response which an investigator determined were not used, and all responses were confirmed by the board members of the independent response review.

During the evaluation of both the initial staging and the antitumor effects, an extramural review was conducted. Only patients whose initial clinical stage was judged to be stage IIIA and IIIB and who were eligible for the study were analyzed for the response to treatment. The toxicity for all patients who received any treatment was assessed and graded by using the National Cancer Institute Common Terminology Criteria for Adverse Event version 3.

Statistical Analysis

The primary end point of this study was the objective tumor response rate. On the basis of the assumption that a response rate of higher than 80% would be expected from the combined modality treatment, while a rate below 60% would make a further investigation unnecessary, a sample size of 49 patients was required by the exact binomial test with a one-sided alpha error of 0.05 and a beta error of 0.1. Therefore, a total of 55 patients was the planned accrual size in view of possibly including ineligible patients. For determining the response rate, the exact binomial confidence interval (CI) was calculated. OS was defined as the time from registration until death from any cause. Progression-free survival (PFS) was defined as the time between registration and disease progression or death. The Kaplan-Meier method was used to estimate OS and PFS curves. All statistical analyses were done with SAS version 9.1.

RESULTS

Characteristics of Patients

Between November 2006 and December 2007, a total of 55 patients were enrolled from 18 institutes. One patient withdrew his consent and four patients were found to be ineligible by the extramural review (one malignant effusion, one carcinomatous lymphangitis, and 2 stage IV diseases). Therefore, the efficacy analyses were performed for the 50 remaining eligible patients. Safety analyses were performed for 54 patients who underwent SP-RT. Table 1 shows that 80% of the 50 eligible patients were male, with a mean age of 63 years (range, 40–74 years). Squamous cell carcinoma was the most common histological diagnosis, including 48% of the patients, and most patients had clinical stage IIIB disease (IIIA versus IIIB; 36% versus 64%). The most frequently classified TNM categories were T1-3N2 (36%), T1-3N3M0 (28%), and T4N0-1M0 (18%).

Adverse Events

The major adverse events (grade 3 and 4 toxicities) of SP-RT are listed in Table 2. Among the hematologic toxicities of the concurrent phase, grade 3 or higher leukopenia and neutropenia was observed in 17 patients (32%) and 14 patients (26%), respectively. Five patients (9%) developed grade 3 or higher thrombocytopenia. Among the nonhematologic toxicities, grade 3 and 4 febrile neutropenia was observed in four (7%) and one (2%) patient, respectively, whereas grade 3 esophagitis occurred in 4 patients (7%). Although no cases of severe pneumonitis occurred in the concurrent phase, two patients had a treatment-related death: one patient died of sepsis soon after the completion of the

TABLE 1. Patient Characteristics

No. of eligible patients	50
Age, yrs	
Mean (range)	63 (40–74)
Gender	
Male	40 (80%)
Female	10 (20%)
ECOG PS	
0	21 (42%)
1	29 (48%)
Smoking history	
Absent	2 (4%)
Present	48 (96%)
Histology	
Squamous cell carcinoma	24 (48%)
Adenocarcinoma	20 (40%)
Others	6 (12%)
cTNM	
Stage IIIA	18 (36%)
T1-3N2	18 (36%)
Stage IIIB	32 (64%)
T1-3N3M0	14 (28%)
T4N0-1M0	9 (18%)
T4N2M0	7 (14%)
T4N3M0	2 (4%)
Location of primary site	
Upper lobe	36 (72%)
Middle lobe	4 (8%)
Lower lobe	8 (16%)
Others	2 (4%)

ECOG, Eastern Cooperative Oncology Group; PS, performance status; TNM, tumor, node, metastasis.

TABLE 2. Hematological and Nonhematological Major Adverse Events

	Concurrent Chemoradiotherapy (n = 54)			Consolidation Chemotherapy (n = 39)		
	Grade			Grade		
Toxicities	3	4	Frequency of 3 or 4 (%)	3	4	Frequency of 3 or 4 (%)
Hematological						
Leukopenia	12	5	31.5	6	0	15.4
Neutropenia	10	4	25.9	4	0	10.3
Thrombocytopenia	1	4	9.3	4	0	10.3
Anemia	4	2	11.1	7	1	20.5
Nonhematological						
Febrile neutropenia	4	1	9.3	0	0	
Nausea	1	1	3.7	0	0	
Vomiting	2	0	3.7	0	0	
Anorexia	6	1	13.0	0	0	
Creatinine	0	0		0	0	
AST/ALT	1	1	3.7	0	0	
Diarrhea	2	0	3.7	0	0	
Stomatitis	1	0	1.9	0	0	
Pneumonitis	0	0		1	0	2.6
Esophagitis	4	0	7.4	1	0	2.6

AST, aspartate transaminase; ALT, alanine aminotransferase.

TABLE 3. Radiation Delivered (N = 50)

Radiation dose (Gy)	
Median (range)	60.0 (28–60)
Average	58.4
Reasons for interruption, N (%)	
Adverse events	7 (14.0)
Other	2 (4.0)
Rate of completion of treatment with 60 Gy, N (%)	47 (94.0)

TABLE 4. Chemotherapy Delivered (N = 50)

	N (%)
Concurrent chemotherapy	
Chemotherapy cycles	
1	50 (100)
2	46 (92.0)
Reasons for discontinuation	
Adverse event	2 (4.0)
Patient decision	2 (4.0)
Reasons for not proceeding to consolidation chemotherapy	
Adverse event	8 (16.0)[a]
Other	1 (2.0)
Consolidation chemotherapy	
Chemotherapy cycles	
1	37 (74.0)
2	31 (62.0)
Reasons for discontinuation	
Adverse event	5 (10.0)
Disease progression	1 (4.0)
Rate of completion of 4 cycles of treatment (95% CI)	62% (47.2–75.3)

[a] Two treatment-related deaths were included after completion of concurrent chemotherapy.
CI, confidence interval.

concurrent phase and the other patient died of pneumonia after the recovery from the bone marrow suppression because of that phase.

Thirty-nine (72%) of the 54 patients proceeded to consolidation chemotherapy. As shown in Table 2, the frequency of grade 3 or 4 in any major toxicity caused by consolidation chemotherapy was lower than that in concurrent chemoradiotherapy, except for anemia and pneumonitis. It was of note that no febrile neutropenia was observed.

Treatments Delivered to Eligible Patients

Tables 3 and 4 show RT and chemotherapy delivered to 50 eligible patients, respectively. Forty-six patients (92%) completed two cycles of SP concurrent with thoracic RT of 60 Gy. Two patients refused further protocol treatment after one cycle of chemotherapy because of adverse events. The other two patients did not meet the criteria to start the second cycle of SP because of prolonged neutropenia. Although 46 patients completed the concurrent phase of the SP-RT, seven patients could not proceed to the consolidation phase because of mainly prolonged hematological toxicity, and two patients

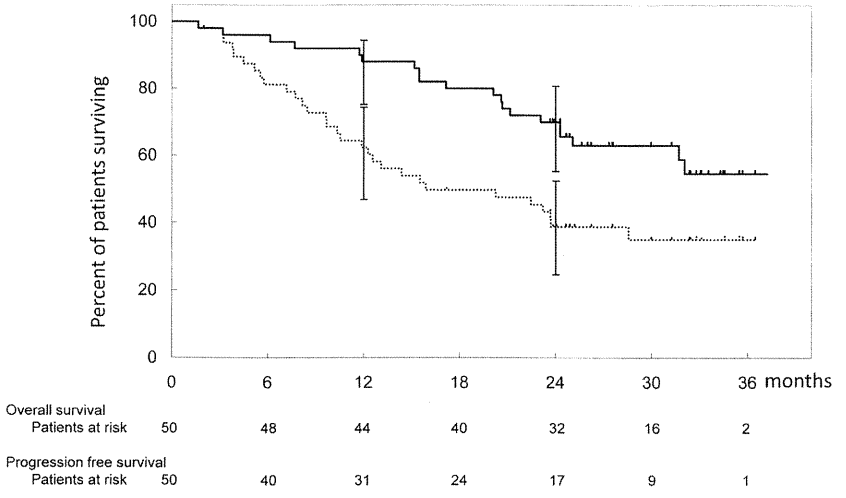

FIGURE 2. Overall survival (——) and progression-free survival (••••••). Each *tick* represents one patient who is alive with/without recurrence. The *bars* represent the 95% confidence intervals of the survival rate at 1 and 2 years after treatment.

were lost to treatment-related death. Of 37 patients, one and five patients received only one cycle of the consolidation chemotherapy because of disease progression and adverse events, respectively. Thus, a total of 31 (62%) of the 50 eligible patients received all four cycles of SP chemotherapy.

Response

Of the 50 patients eligible for efficacy analysis, 42 patients had responses (84%; 95% CI, 71–93%; $p < 0.0001$), including 1 patient with a complete response, and 2 patients with stable disease. Only one patient showed progressive disease. Five patients were unevaluable for a response. There were no differences in the response rate by histology (88% in squamous cell carcinoma versus 81% in others, $p = 0.704$ by the exact binomial test).

Survival

The overall median follow-up time for the 29 patients who were still alive as of January 2010 was 28 months (range, 24–37 months). As shown in Figure 2, the median PFS and OS was 20 months and not reached, respectively, and the OS rates at 1 and 2 years were 88% (95% CI, 75–94%) and 70% (95% CI, 55–81%), respectively.

Sites of First Failures

With respect to the sites of first failure among the 28 (56%) patients with disease progression of the 50 eligible patients, 19 (38%), 6 (21%), and 3 (6%) patients had distant metastases, intrathoracic local diseases, and both, respectively. Those nine occurred in the irradiated field. The frequently observed initial distant metastases were observed in bone in eight patients and in brain and lung in four each. Only four patients (8%) developed a brain metastasis alone as the initial failure site.

DISCUSSION

The purpose of concurrent chemoradiotherapy for NSCLC patients with stage III disease is to achieve local control, for which RT plays the main role, and also to eradicate occult distant metastases by chemotherapy. For the latter purpose, the development of regimens that can allow administration of the systemic (full) doses of chemotherapy during RT is necessary. Although the so-called "third generation" agents such as paclitaxel, vinorelbine, docetaxel, and gemcitabine have been evaluated in several concurrent studies in combination with platinum compounds, a lower dose of that agent plus the platinum compound has generally been used due to toxicities. Therefore, induction chemotherapy with sufficient systemic doses of the agents was considered a potentially effective addition to the concurrent chemoradiotherapy.[22] Nevertheless, a recent randomized trial (CALGB 39801) showed that two cycles of induction chemotherapy with full doses of CP did not provide a survival benefit over concurrent chemoradiotherapy alone, using weekly CP at lower doses.[23] Furthermore, the randomized phase III trial conducted by the Hoosier Oncology Group and U.S. Oncology Group demonstrated that the addition of consolidation chemotherapy using docetaxel after full-dose chemotherapy using cisplatin plus etoposide with concurrent RT (PE-RT) failed to achieve the primary end point of improved survival compared with PE-RT alone.[24] On the basis of these randomized trials, concurrent chemotherapy alone is recommended for the treatment of locally advanced-NSCLC. However, the optimal chemotherapy regimen remains to be determined.

In this study, SP-RT using systemic doses had the advantage of eradicating occult distant metastases. In addition, 5-FU has been reported to have a radiosensitizing effect in preclinical and clinical studies of various cancers, including NSCLC,[15,16] and S-1 is orally administered for 14 consecutive days in each course of chemotherapy, providing long-term potential radiosensitization. The antitumor effects of SP-RT might explain the high response rate of 82% and the prolonged median PFS of 20 months, as well as the median OS, which was not reached when follow-up time ranged from 24 to 37 months. Another SP-RT phase II trial with a similar schedule and dose, which was conducted during almost the same period as the present trial, also demonstrated a good overall response rate of 88%, median PFS of 12 months, and a median OS of 33 months, whereas the median follow-up

time was 25 months, ranging from 12 to 38 months.[25] Nevertheless, these data cannot be directly compared with our data. In this trial, the extraordinarily good results may not be only because of the chemotherapy regimen but also to the high frequency of the primary site being within the upper lobe. In completely resected NSCLC with N2 disease, the 5-year survival rate in patients with their primary site in the upper lobe is well known to be significantly better than that of patients with the primary tumor in the lower lobe.[26] In addition, the tumors in the upper lobe with upper mediastinal nodal metastases are easier to treat with RT than the tumors in the lower lobe in terms of the irradiation field.

Two additional cycles of the same chemotherapy after concurrent chemoradiotherapy were called consolidation chemotherapy in this trial. Although the original PE-RT regimen used two additional cycles of the same PE after PE (two cycles)-RT, the above-mentioned randomized trial did not use consolidation PE in both control and experimental groups.[24] Similarly, the original mitomycin, vindesine plus cisplatin (MVP)-RT regimen had the two additional cycles of the same MVP[5] after MVP (two cycles)-RT, whereas a recent randomized trial used MVP (two cycles)-RT alone as a control arm.[27] The median OS of PE (2 cycles)-RT and MVP (2 cycles)-RT was 23.2 and 23.7 months, respectively.[24,27] In addition, only 41% of the patients could complete four cycles of MVP in the MVP-RT group of a recent WJTOG phase III trial (WJTOG0105), which had a median OS of 20.5 months.[28] In this trial, 62% of the patients completed four cycles of SP despite a low frequency of severe toxicities, whereas the WJOG phase III trial showed that the safest regimen with concurrent RT was CP among MVP, CP, and carboplatin plus CPT-11, although the completion rate of two cycles in the consolidation chemotherapy of CP arm was only 50%.[28] These observations suggest that a phase III trial is necessary to clarify whether or not a total of four cycles of chemotherapy in this setting provides a better result than two cycles of chemoradiotherapy.

The irradiated dose of 60 Gy in 30 fractions with concurrent chemotherapy is currently used in the majority of institutes in Japan, whereas that of 66 Gy in 33 fractions in combination with chemotherapy in the United States seems to be the most common treatment regimen. Because PET/CT scan and 3-D planning were not used in all patients, it would therefore be interesting to elucidate whether or not the present survival of such patients can be prolonged by these techniques, including a total irradiated doses of 66 Gy.

Although the present treatment with SP-RT should be acceptably safe in terms of the frequency of grade 3 and 4 adverse events, the treatment-related death of two patients was observed. Therefore, it is necessary to keep in mind that there is no totally safe regimen for concurrent chemoradiotherapy. At present, the WJOG is conducting a randomized phase II trial comparing SP-RT to combination chemotherapy using cisplatin plus vinorelbine with concurrent RT.

REFERENCES

1. Pfister DG, Johnson DH, Azzoli CG, et al; American Society of Clinical Oncology. American Society of Clinical Oncology treatment of unresectable non-small-cell lung cancer guideline: update 2003. *J Clin Oncol* 2004;22:330–353.
2. Auperin A, Le Pechoux C, Rolland E, et al. Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer. *J Clin Oncol* 2010;28:2181–2190.
3. Ichinose Y, Nakai Y, Kudoh S, et al. Uracil/tegafur plus cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004;10:4369–4373.
4. Curran W, Scott C, Langer C. Phase III comparison of sequential vs concurrent chemoradiation for pts with unresected stage III non-small cell lung cancer (NSCLC): Initial report of Radiation Therapy Oncology Group (RTOG) 9410. *Lung Cancer* 2000;29(93s, suppl):abstr 303.
5. Furuse K, Fukuoka M, Kawahara M, et al. Phase III study of concurrent versus sequential thoracic radiotherapy in combination with mitomycin, vindesine, and cisplatin in unresectable stage III non-small-cell lung cancer. *J Clin Oncol* 1999;17:2692–2699.
6. Kawahara M, Furuse K, Segawa Y, et al; S-1 Cooperative Study Group (Lung Cancer Working Group). Phase II study of S-1, a novel oral fluorouracil, in advanced non-small-cell lung cancer. *Br J Cancer* 2001;85:939–943.
7. Ichinose Y, Yoshimori K, Sakai H, et al. S-1 plus cisplatin combination chemotherapy in patients with advanced non-small cell lung cancer: a multi-institutional phase II trial. *Clin Cancer Res* 2004;10:7860–7864.
8. Kubota K, Sakai H, Yamamoto N, et al. A multi-institution phase I/II trial of triweekly regimen with S-1 plus cisplatin in patients with advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:702–706.
9. Ichinose Y, Takanashi N, Yano T, et al. A phase II trial of oral tegafur and uracil plus cisplatin in patients with inoperable nonsmall cell lung cancer. *Cancer* 1995;75:2677–2680.
10. Ichinose Y, Yosimori K, Yoneda S, et al. UFT plus cisplatin combination chemotherapy in the treatment of patients with advanced nonsmall cell lung carcinoma: a multiinstitutional phase II trial. *Cancer* 2000;88:318–323.
11. Kubota K, Watanabe K, Kunitoh H, et al; Japanese Taxotere Lung Cancer Study Group. Phase III randomized trial of docetaxel plus cisplatin versus vindesine plus cisplatin in patients with stage IV non-small-cell lung cancer: the Japanese Taxotere Lung Cancer Study Group. *J Clin Oncol* 2004;22:254–261.
12. Ohe Y, Ohashi Y, Kubota K, et al. Randomized phase III study of cisplatin plus irinotecan versus carboplatin plus paclitaxel, cisplatin plus gemcitabine, and cisplatin plus vinorelbine for advanced non-small-cell lung cancer: Four-Arm Cooperative Study in Japan. *Ann Oncol* 2007; 18:317–323.
13. Schiller JH, Harrington D, Belani CP, et al; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med* 2002;346:92–98.
14. Okamoto I, Yoshioka H, Morita S, et al. Phase III trial comparing oral S-1 plus carboplatin with paclitaxel plus carboplatin in chemotherapy-naive patients with advanced non-small-cell lung cancer: results of a west Japan oncology group study. *J Clin Oncol* 2010;28:5240–5246.
15. Byfield JE, Calabro-Jones P, Klisak I, et al. Pharmacologic requirements for obtaining sensitization of human tumor cells in vitro to combined 5-Fluorouracil or ftorafur and x rays. *Int J Radiat Oncol Biol Phys* 1982;8:1923–1933.
16. Douple EB, Richmond RC. Enhancement of the potentiation of radiotherapy by platinum drugs in a mouse tumor. *Int J Radiat Oncol Biol Phys* 1982;8:501–503.
17. Gemma A, Kudoh S, Yoshimura A, et al. Pilot trial of a combination comprising of consecutive oral administration of UFT, and two-divided administration of CDDP in non-small cell lung cancer. *Anticancer Res* 1995;15:2691–2695.
18. Koizumi W, Tanabe S, Saigenji K, et al. Phase I/II study of S-1 combined with cisplatin in patients with advanced gastric cancer. *Br J Cancer* 2003;89:2207–2212.
19. Fukushima M, Sakamoto K, Sakata M, et al. Gimeracil, a component of S-1, may enhance the antitumor activity of X-ray irradiation in human cancer xenograft models in vivo. *Oncol Rep* 2010;24:1307–1313.
20. Takagi M, Sakata K, Someya M, et al. Gimeracil sensitizes cells to radiation via inhibition of homologous recombination. *Radiother Oncol* 2010;96:259–266.
21. Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of

the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 2000;92:205–216.
22. Vokes EE, Herndon JE II, Crawford J, et al. Randomized phase II study of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB non-small-cell lung cancer: cancer and leukemia group B study 9431. *J Clin Oncol* 2002;20:4191–4198.
23. Vokes EE, Herndon JE II, Kelley MJ, et al; Cancer and Leukemia Group B. Induction chemotherapy followed by chemoradiotherapy compared with chemoradiotherapy alone for regionally advanced unresectable stage III Non-small-cell lung cancer: Cancer and Leukemia Group B. *J Clin Oncol* 2007;25:1698–1704.
24. Hanna N, Neubauer M, Yiannoutsos C, et al; Hoosier Oncology Group; US Oncology. Phase III study of cisplatin, etoposide, and concurrent chest radiation with or without consolidation docetaxel in patients with inoperable stage III non-small-cell lung cancer: the Hoosier Oncology Group and U.S. Oncology. *J Clin Oncol* 2008;26:5755–5760.
25. Ohyanagi F, Yamamoto N, Horiike A, et al. Phase II trial of S-1 and cisplatin with concurrent radiotherapy for locally advanced non-small-cell lung cancer. *Br J Cancer* 2009;101:225–231.
26. Ichinose Y, Kato H, Koike T, et al; Japanese Clinical Oncology Group. Completely resected stage IIIA non-small cell lung cancer: the significance of primary tumor location and N2 station. *J Thorac Cardiovasc Surg* 2001;122:803–808.
27. Segawa Y, Kiura K, Takigawa N, et al. Phase III trial comparing docetaxel and cisplatin combination chemotherapy with mitomycin, vindesine, and cisplatin combination chemotherapy with concurrent thoracic radiotherapy in locally advanced non-small-cell lung cancer: OLCSG 0007. *J Clin Oncol* 2010;28:3299–3306.
28. Yamamoto N, Nakagawa K, Nishimura Y, et al. Phase III study comparing second- and third-generation regimens with concurrent thoracic radiotherapy in patients with unresectable stage III non-small-cell lung cancer: West Japan Thoracic Oncology Group WJTOG0105. *J Clin Oncol* 2010;28:3739–3745.

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Comparison of Intensity Modulated Radiotherapy and Dynamic Three-Dimensional Conformal Radiotherapy With Regard to Dose Distribution and Sparing of Organs at Risk

Yuzo HASEGAWA,[1] Toshihiko IUCHI,[1] Katsunobu OSATO,[1]
Takashi KODAMA,[2] Naoki TOYAMA,[2] and Kazuo HATANO[2]

Divisions of [1]Neurological Surgery and [2]Radiation Oncology, Chiba Cancer Center, Chiba

Abstract

Dose escalation to the target while sparing the organs at risk near the lesion has been difficult over the last decade. However, recent radiotherapy techniques can deliver more sophisticated doses to the target. This study evaluated whether intensity modulated radiotherapy can deliver more homogeneous and conformal doses to the target than dynamic three-dimensional conformal radiotherapy while sparing organs at risk near the lesion in 13 patients with central nervous system tumors and other tumors around the central nervous system. Dynamic three-dimensional conformal radiotherapy and intensity modulated radiotherapy plans were calculated and dose distributions were compared for all patients with regard to the planning target volume and organs at risk. The plan of intensity modulated radiotherapy was significantly superior to that of dynamic three-dimensional conformal radiotherapy in target dose conformity ($p = 0.0006$) and organs at risk sparing ($p = 0.0257$). Intensity modulated radiotherapy could deliver more homogeneous and conformal doses to the target than dynamic three-dimensional conformal radiotherapy with sparing organs at risk near the lesion and may improve local control of radioresistant tumors via dose escalation.

Key words: intensity modulated radiotherapy, conformity, dose distribution, organ at risk, dose escalation

Introduction

The goal of radiotherapy is to treat patients with the best therapeutic ratio that provides the highest local control and the lowest toxicity rates. Dose escalation to the lesion improves local control of the tumors,[8,12] but also increases the risk of normal tissue complication. Therefore, radiation dose distributions should be designed conforming to the entire lesion while sparing the surrounding normal tissues, especially organs at risk (OARs) which are radiosensitive and related to late complications, such as cataract of the eye lens.

Recent advancements in radiotherapy technologies have allowed sophisticated radiation dose delivery, including the use of dynamic three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT).[1,17] Both dynamic 3D-CRT and IMRT are linear accelerator therapies using the multileaf collimator (MLC), a computer-controlled device that uses movable "leaves" to conform the radiation beam to the shape of the tumor while protecting normal adjacent tissue. Dynamic 3D-CRT stereotactically delivers doses which conform to the shape of the each projected target using the MLC. IMRT can also use MLC but the shapes are not restricted to the projected images. In IMRT, the fixed radiation beam from each angle can be turned off and on, or set to deliver dose at different intensities freely. Therefore, the plans of IMRT are highly complicated so inverse-planning is usually selected. The planner defines targets and OARs, and gives target doses. Then, the most suitable treatment plan is calculated automatically (Fig. 1).

The present study tried to evaluate whether IMRT can deliver more homogeneous and conformal dose distributions to irregular shaped tumors than dynamic 3D-CRT with sparing of OARs near lesions in

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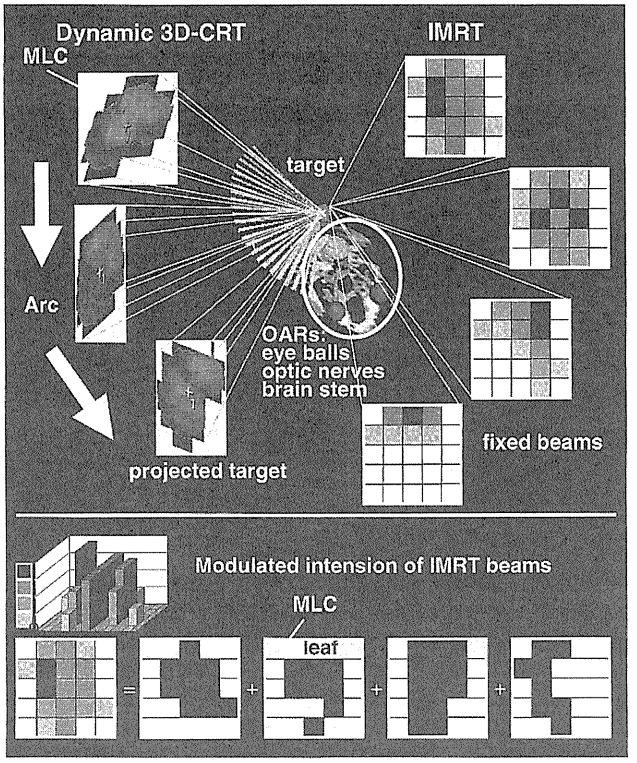

Fig. 1 Features of dynamic three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated radiotherapy (IMRT). Dynamic 3D-CRT stereotactically delivers doses which conform to the shape of the each projected target using multileaf collimator (MLC). IMRT also uses MLC but not stereotactic technologies. The most suitable treatment plan using intensity modulated fixed beams is inversely calculated automatically. Arc: gantry arc, OARs: organs at risk.

the central nervous system (CNS) and other tumors around the CNS. Various tumors have been already treated with these techniques[5,6,8,10,13,18,20] and recent studies compared the dose conformity of dynamic 3D-CRT with IMRT[7,9,14,19] but little attention has focused on the OARs, especially in the CNS.[3] Patients with CNS tumors and other tumors around the CNS were enrolled in this study because these tumors were very close to the OARs. We compared dynamic 3D-CRT with IMRT focusing on target dose homogeneity, target dose conformity, and mean dose to the OARs.

Patients and Methods

Thirteen patients, 8 males and 5 females aged 8–69 years (median 48 years), with 9 skull base tumors, 1 brain stem tumor, and 3 vertebral body tumors were randomly enrolled (Table 1). Both computed tomography (CT) and magnetic resonance (MR) imaging were used for planning, and three-dimensional geometrical registration of the CT and MR imaging data was performed. All patients were treated with IMRT.

Table 1 Thirteen patients with central nervous system tumors

Case No.	Age (yrs)	Sex	Lesion	Histology
1	45	M	skull base	squamous cell carcinoma
2	62	M	skull base	squamous cell carcinoma
3	62	M	skull base	squamous cell carcinoma
4	48	F	skull base	squamous cell carcinoma
5	69	M	skull base	adenoid cystic carcinoma
6	68	F	skull base	adenoid cystic carcinoma
7	62	M	skull base	multiple myeloma
8	37	M	skull base	olfactory neuroblastoma
9	50	F	skull base	plasmacytoma
10	8	F	brain stem	anaplastic ependymoma
11	32	F	vertebral body	myxoid liposarcoma
12	10	M	vertebral body	PNET
13	67	M	vertebral body	adenocarcinoma

F: female, M: male, PNET: primitive neuroectodermal tumor.

The planning target volume (PTV), which was defined as the area of the enhanced lesion with 3 mm margin, and OARs, such as the brain stem, eye balls, optic nerves, chiasma, and spinal cord, were delineated in the corresponding MR imaging and CT slices. Three OARs were chosen and numbered from 1 to 3 in order of distance from the lesion in each patient. OAR1 was closer to the PTV than the other OARs.

Both dynamic 3D-CRT and IMRT treatment plans were calculated for each patient by the same treatment planning system, Brain SCAN (BrainLAB GmbH, Heimstetten, Germany). To eliminate interoperator variations, the same operator established all treatment plans. The same prescribed dose was determined in the dynamic 3D-CRT and IMRT plans to compare the two treatment plans for the same patient. The IMRT plan covered the entire PTV with higher than 95% of the prescribed dose (V95 was 100%). The dynamic 3D-CRT plan covered the entire PTV with higher than 80% of the prescribed dose (V80 was 100%). The percentage of the corresponding prescribed dose was calculated for the OARs to facilitate dosimetric comparison because each patient was treated with different prescribed doses.

To compare the dynamic 3D-CRT plan and the IMRT plan, we used dosimetric distribution and dose volume histogram (DVH) techniques. Dosimetric distribution is a two-dimensional contour map of

delivered dose on some representative CT or MR imaging plane. The area inside the 80% contour line receives more than 80% of the prescribed dose. DVH is a three-dimensional dosimetric distribution in a graphical two-dimensional format, so DVH visualizes the volume not area. The vertical axis represents the percentage of total tissue volume that receives a dose more than a specified dose. The horizontal axis represents cumulative dose. Ideally, DVH displays 100% of the PTV receiving 100% of the prescribed dose and very low volumes of OARs receiving very low doses.

The homogeneity index (HI) was calculated using the following formula without using the prescribed dose: maximum dose within the PTV/minimum dose within the PTV. This formula is the simplest of several similar HIs. The HI is a useful tool to evaluate dose uniformity within the PTV and a value of HI close to 1 indicates better dose homogeneity in the treatment plan.[6]

The conformity index (CI) was calculated using the following formula: $1 + V_{normal}/V_{PTV}$. V_{normal} is the volume of the normal tissue and V_{PTV} is the volume of the PTV receiving the indicated dose; 95% of the prescribed dose in the IMRT plan and 80% in the dynamic 3D-CRT in this study. Therefore, V_{PTV} represented the entire PTV in both plans because we intended V95 as 100% in the IMRT plan and V80 as 100% in the dynamic 3D-CRT plan. A value of CI

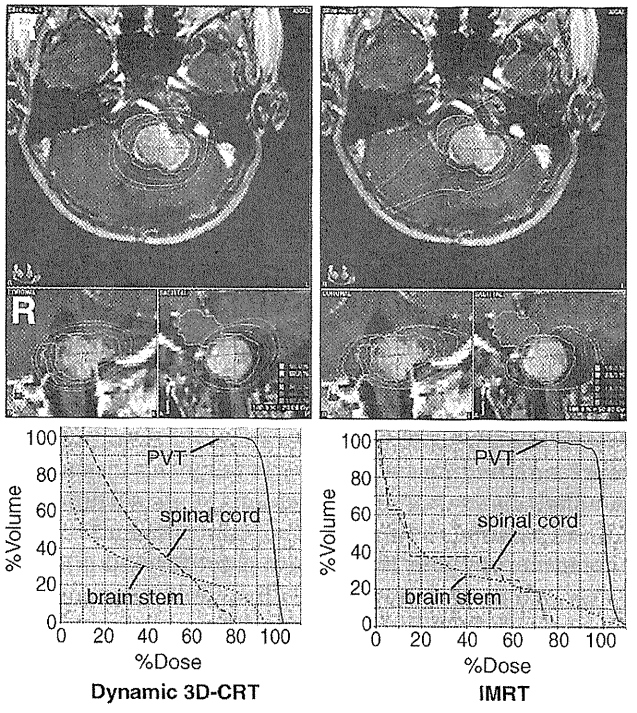

Fig. 2 Dosimetric distributions (*upper row*) and dose volume histograms (*lower row*) of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan (*left column*) and the intensity modulated radiotherapy (IMRT) plan (*right column*) in representative Case 10. An 8-year-old girl presented with recurrent brain stem anaplastic ependymoma. Magnetic resonance images showed an oval-shaped tumor which compressed the brain stem into a concave form. In the dynamic 3D-CRT plan, the conformal dose was delivered to the planning target volume (PTV) but the brain stem and the spinal cord were not spared. In the IMRT plan, flat dosimetric distribution spared the brain stem and the spinal cord. Dose volume histogram of the IMRT plan showed dose reduction to the spinal cord without dose reduction to the PTV.

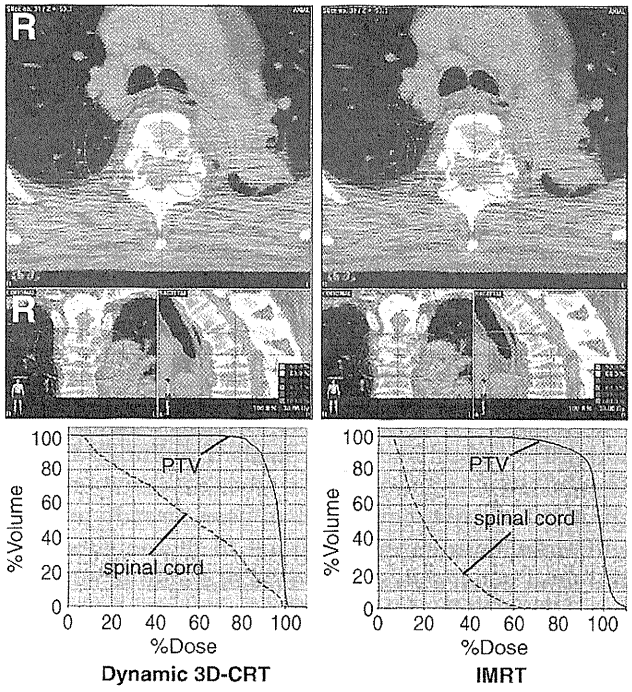

Fig. 3 Dosimetric distributions (*upper row*) and dose volume histograms (*lower row*) of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan (*left column*) and the intensity modulated radiotherapy (IMRT) plan (*right column*) in representative Case 13. A 67-year-old man presented with vertebral body metastasis from lung cancer. Computed tomography scans showed that the concave-shaped tumor surrounded the spinal cord. The dosimetric distribution of dynamic 3D-CRT was round and the spinal cord was not spared at all. The dosimetric distribution of IMRT was a conformal concave form corresponding with the planning target volume (PTV) and the spinal cord was spared. Dose volume histogram of the IMRT plan showed dose reduction to the spinal cord.

close to 1 indicates better reduction of normal tissue irradiation (V_{normal} is lower) in the treatment plan.[4]

The data were analyzed by the Mann-Whitney U test. A probability value of $p < 0.05$ was considered statistically significant. Statistical analyses were determined using StatView software (SAS Institute, Cary, North Carolina, USA).

Results

First, we show two representative cases in which IMRT was very effective.

Representative Case 10: An 8-year-old girl presented with recurrent brain stem anaplastic ependymoma. MR imaging showed an oval-shaped tumor which compressed the brain stem into a concave form. The brain stem, spinal cord, and optic nerve were defined as OARs, with the brain stem as OAR1. Dosimetric distributions are shown in Fig. 2. In the dynamic 3D-CRT plan, the conformal dose was delivered to the PTV but the brain stem and the spinal cord were not spared. In the IMRT plan, the flat dose distribution spared the brain stem and the spinal cord. DVH showed dose reduction to the spinal cord without dose reduction to the PTV. This patient was treated with IMRT using a prescribed dose of 50 Gy. MR imaging showed obvious tumor shrinkage. However, local recurrence was observed 9 months after IMRT treatment and the patient died 6 months after the recurrence. There was no complication due to IMRT.

Representative Case 13: A 67-year-old man presented with vertebral body metastasis from lung cancer. This lesion was impossible to treat with conventional radiotherapy because he had been already treated with conventional radiotherapy to the neighboring vertebral body with a total dose of 30 Gy in 10 fractions. The OAR of this patient was the spinal cord. CT showed that the concave-shaped tumor surrounded the spinal cord (Fig. 3). The dosimetric distribution of dynamic 3D-CRT was round and the spinal cord was not spared at all. We expected that this lesion would be difficult to treat with dynamic 3D-CRT practically because of the high dose to the spinal cord. The dosimetric distribution of IMRT was a conformal concave form corresponding with the PTV and the spinal cord was spared. DVH showed dose reduction to the spinal cord. This patient was treated with IMRT using a prescribed dose of 30 Gy. The patient had no local recurrence or radiological complication, such as paraparesis of the lower limbs, for 3.5 years.

Nine patients with skull base tumors were enrolled, 6 cases located at the maxillary sinus and the others

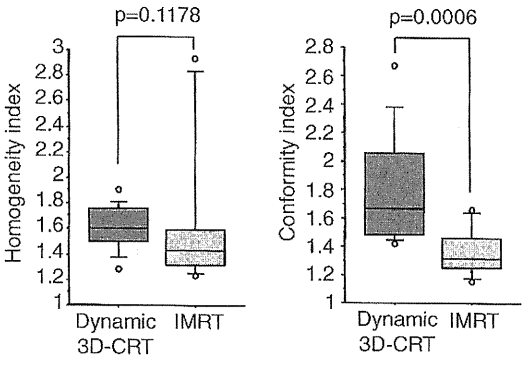

Fig. 4 Homogeneity index and conformity index of the dynamic three-dimensional conformal radiotherapy (3D-CRT) plan and the intensity modulated radiotherapy (IMRT) plan. In 11 of the 13 cases, the homogeneity index of the IMRT plan was lower than that of the dynamic 3D-CRT plan but the IMRT plan was not significantly superior to the dynamic 3D-CRT plan ($p = 0.1178$). The conformity index of the IMRT plan (mean 1.358) was significantly better ($p = 0.0006$) than that of the dynamic 3D-CRT plan (mean 1.802). Statistical analyses were determined using StatView software.

at the orbit, the upper pharynx, and the cribriform plate. The OARs were usually the eye balls, optic nerves, optic chiasm, and brain stem. The optic nerve was most frequently designated as the OAR1. Almost all PTVs of skull base cases were not concave and sparing the OARs was easier than in the 2 representative cases. The most frequent disease of the skull base was maxillary squamous carcinoma. All 4 patients had new lesions and underwent chemotherapy and IMRT with a prescribed dose of 54 Gy. All patients remained alive with mean overall survival of 1770 ± 253 days, although one patient experienced local recurrence. No radiological complication was observed.

The IMRT and dynamic 3D-CRT plans were compared for target dose homogeneity, target dose conformity, and mean dose to OARs. In 11 of the 13 patients, the HIs of the IMRT plans were lower than those of the dynamic 3D-CRT plans but the IMRT plan was not significantly superior to the dynamic 3D-CRT plan ($p = 0.1178$) because the HIs of IMRT plans of only two cases were extremely close to 3 (Fig. 4). In those cases, the PTV attached and surrounded the OAR1 (one of the two cases was representative Case 13) and the minimum dose within the PTV was very low to decrease the dose to the OAR1. The CI of the IMRT plan (mean 1.358) was significantly better ($p = 0.0006$) than that of the dynamic 3D-CRT plan (mean 1.802) (Fig. 4). The percentage of the corresponding prescribed dose of the

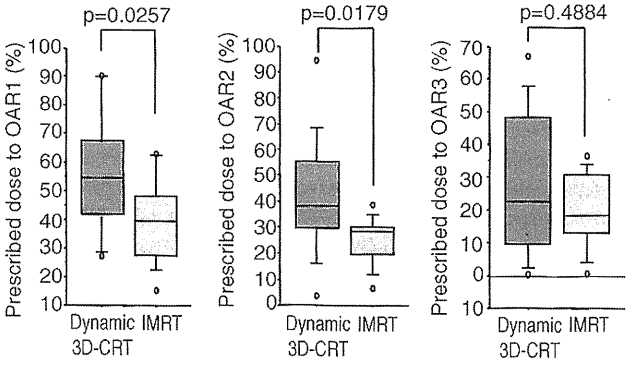

Fig. 5 Prescribed doses to the organs at risk (OARs) of the three-dimensional conformal radiotherapy (3D-CRT) plan and the intensity modulated radiotherapy (IMRT) plan. The percentage of the corresponding prescribed doses of the IMRT plan in the OAR1 (mean 41.0%) and OAR2 (mean 25.5%) were significantly lower than those of the dynamic 3D-CRT plan (mean 58.2% and 41.9%, respectively). Statistical analyses were determined using StatView software.

IMRT plan in mean dose to the PTV (mean 98.8%) was obviously higher ($p = 0.0052$) compared to that of the dynamic 3D-CRT plan (mean 96.3%) (figure not shown). The percentage of the corresponding prescribed dose of the IMRT plan in the OAR1 (mean 41.0%) was significantly lower ($p = 0.0257$) than that of the dynamic 3D-CRT plan (mean 58.2%) (Fig. 5). The percentage of the corresponding prescribed dose of the IMRT plan in the OAR2 (mean 25.5%) was also lower ($p = 0.0179$) than that of the dynamic 3D-CRT plan (mean 41.9%). However, there was no significant difference in the OAR3 between the plans ($p = 0.4884$).

Discussion

The aim of radical radiotherapy is to deliver a high dose to the tumor target while minimizing the dose to surrounding normal tissues. Recent innovations of irradiation technique may meet these contradictory requirements. Stereotactic radiosurgery/radiotherapy (SRS/SRT) is one of these novel irradiation techniques. SRS/SRT was chiefly developed in recent years for dose escalation sparing the OARs, and can deliver much conformal doses to spherical tumors. For spheroidal tumors, the two-isocenter plan is more effective than the one-isocenter plan.[11] However, SRS/SRT is not suitable for irregularly shaped tumors. The multiple-isocenter plan can deliver a more conformal dose, but is more complex and the technique has limits.[9] Dynamic 3D-CRT is one of the most excellent stereotactic radiotherapies.[2,16] Dynamic 3D-CRT with the MLC can deliver more conformal doses to the irregularly shaped tumors than SRS/SRT (Fig. 1), but sophisticated doses are still difficult to deliver to the concave form. In addition, SRS/SRT usually delivers a higher dose to the center of the PTV and the high dose spot over the prescribed dose is accrued within the PTV when the peripheral region receives a sufficient treatment dose.

IMRT is another advanced irradiation method without using stereotactic technologies, can modulate radiation intensity with MLC and deliver more homogeneous and conformal radiation doses using fixed beams based on inversely calculated planning (Fig. 1). The most important feature of IMRT is the excellent dose delivery conforming to irregularly shaped tumors, especially concave shaped tumors (representative Case 13). Our study showed that IMRT could deliver more homogeneous and conformal doses to irregularly shaped tumors than dynamic 3D-CRT, but the superior homogeneity was not statistically important because of sparing of the OAR surrounded by the PTV. In the treatment phase, the surgeon must determine whether the PTV has priority over the OAR or not. The decision is probably case-by-case.

Sparing of the OARs is very important as well as to treat the PTV with homogeneous and conformal dose. In our study, we intended that the entire PTV received higher than 95% of the prescribed dose in IMRT and 80% in dynamic 3D-CRT. Therefore, the percentage of the corresponding prescribed dose of the IMRT plan in the mean dose to the PTV was higher than that of the dynamic 3D-CRT plan. However, the receiving doses of the OARs were significantly lower in IMRT using the same planning. In OAR1 and OAR2, the differences in the dynamic 3D-CRT plan and the IMRT plan were significant but the difference in the OAR2 was greater than that in the OAR1. Therefore, the OAR adjoining the PTV is difficult to spare. In our case of brain stem tumor (representative Case 10), the lesion had compressed the brain stem into a concave form, but IMRT delivered a conformal dose to the PTV, sparing the spinal cord but not sparing the brain stem adequately. On the other hand, the difference in the OAR3 was not significant. Both dynamic 3D-CRT and IMRT plans could deliver treatment doses to the PTV sparing the OARs distant from the target.

Heavy charged particle radiotherapy is another promising treatment. Heavy charged particles, such as carbon ions, have excellent dose localizing properties compared with fast neutrons. The Bragg peak of the energy loss occurs immediately before the particles come to rest and the maximum depth of

penetration of a charged particle beam can be adjusted by varying the energy. These features of the particles result in excellent dose conformity. Comparisons of heavy charged particle radiotherapy and IMRT showed that heavy charged particle radiotherapy delivered a more sophisticated conformal dose to the target than IMRT.[15] However, few establishments worldwide have heavy ion medical accelerator equipment and the cost performance is usually poor. Presumably heavy charged particle radiotherapy will not become common as standard radiotherapy at the present time.

All of our 13 patients were treated with IMRT, and radiosensitive tumors were successfully controlled for several years with sufficient sparing of OARs. However, in radioresistant tumor such as anaplastic ependymoma, we could not inhibit tumor proliferation using IMRT with the usual irradiation dose. Dose escalation to the PTV improves local control of the tumors,[7,11] but also increases the risk of normal tissue complication. Safe irradiation requires delivery of homogeneous and conformal dose to the PTV and minimum doses to the OARs. Although IMRT is one of the best radiotherapies for dose escalation, the complex treatment plan and long treatment time are problems. In the choice of irradiation modality, we have to consider the cost/benefit ratio, and IMRT is suitable for irregularly shaped tumors close to OARs.

In this study, dynamic 3D-CRT and IMRT were compared with regard to dose distribution and sparing of OARs. IMRT was superior to dynamic 3D-CRT for irradiation of irregularly shaped tumors near the OARs. Therefore, dose escalation using IMRT will improve local control of radioresistant tumors in the future.

References

1) Bahri S, Flickinger JC, Kalend AM, Deutsch M, Belani CP, Sciurba FC, Luketich JD, Greenberger JS: Results of multifield conformal radiation therapy of nonsmall-cell lung carcinoma using multileaf collimation beams. *Radiat Oncol Investig* 7: 297–308, 1999
2) Dearnaley DP, Khoo VS, Norman AR, Meyer L, Nahum A, Tait D, Yarnold J, Horwich A: Comparison of radiation side-effects of conformal and conventional radiotherapy in prostate cancer: a randomized trial. *Lancet* 353: 267–272, 1999
3) Ding M, Newman F, Chen C, Stuhr K, Gaspar LE: Dosimetric comparison between 3DCRT and IMRT using different multileaf collimators in the treatment of brain tumors. *Med Dosim* 34: 1–8, 2009
4) Feuvret L, Noël G, Mazeron JJ, Bey P: Conformity index: a review. *Int J Radiat Oncol Biol Phys* 64: 333–342, 2006
5) Hanks GE, Hanlon AL, Pinover WH, Horwitz EM, Schultheiss TE: Surgical advantage for prostate cancer patients treated with high-dose three-dimensional conformal radiotherapy. *Cancer J Sci Am* 5: 152–158, 1999
6) Kam MK, Chau RM, Suen J, Choi PH, Teo PM: Intensity-modulated radiotherapy in nasopharyngeal carcinoma: dosimetric advantage over conventional plans and feasibility of dose escalation. *Int J Radiat Oncol Biol Phys* 56: 145–157, 2003
7) Khoo VS, Oldham M, Adams EJ, Bedford JL, Webb S, Brada M: Comparison of intensity-modulated tomotherapy with stereotactically guided conformal radiotherapy for brain tumors. *Int J Radiat Oncol Biol Phys* 45: 415–425, 1999
8) Kong FM, Ten Haken RK, Schipper MJ, Sullivan MA, Chen M, Lopez C, Kalemkerian GP, Hayman JA: High-dose radiation improved local tumor control and overall survival in patients with inoperable/unresectable non-small-cell lung cancer: long-term results of a radiation dose escalation study. *Int J Radiat Oncol Biol Phys* 63: 324–333, 2005
9) Kramer BA, Wazer DE, Engler MJ, Tsai JS, Ling MN: Dosimetric comparison of stereotactic radiosurgery to intensity modulated radiotherapy. *Radiat Oncol Investig* 6: 18–25, 1998
10) Kwong DL, Pow EH, Sham JS, McMillan AS, Leung LH, Leung WK, Chua DT, Cheng AC, Wu PM, Au GK: Intensity-modulated radiotherapy for early-stage nasopharyngeal carcinoma: a prospective study on disease control and preservation of salivary function. *Cancer* 101: 1584–1593, 2004
11) Mignano JE, Engler MJ, Tsai JS, Wazer DE: Comparison of radiobiologic modeling for one- and two-isocenter dose distributions applied to ellipsoidal radiosurgery targets. *Int J Radiat Oncol Biol Phys* 49: 833–837, 2001
12) Nieder C, Berberish W, Nestle U, Niewald M, Walter K, Schnabel K: Relation between local result and total dose of radiotherapy for brain metastases. *Int J Radiat Oncol Biol Phys* 33: 349–355, 1995
13) Sandler HM, Perez-Tamayo C, Ten Haken RK, Lichter AS: Dose escalation for stage C (T3) prostate cancer: minimal rectal toxicity observed using conformal therapy. *Radiother Oncol* 23: 53–54, 1992
14) Sankaranarayanan V, Ganesan S, Oommen S, Padmanaban TK, Stumpf J, Ayyangar KM: Study on dosimetric parameters for stereotactic radiosurgery and intensity-modulated radiotherapy. *Med Dosim* 28: 85–90, 2003
15) Schulz-Ertner D, Nikoghosyan A, Didinger B, Karger CP, Jäkel O, Wannenmacher M, Debus J: Treatment planning intercomparison for spinal chordomas using intensity-modulated photon radiation therapy (IMRT) and carbon ions. *Phys Med Biol* 48: 2617–2631, 2003
16) Singh IR, Brindha S, Ravindran BP, John S, Rajshekhar V, Rangad FV, Roul RK: Development of collimator insert for linac based stereotactic irradiation.

Phys Med Biol 44: 223–231, 1999
17) Teh BS, Mai WY, Grant WH 3rd, Chiu JK, Lu HH, Carpenter LS, Woo SY, Butler EB: Intensity modulated radiotherapy (IMRT) decreases treatment-related morbidity and potentially enhances tumor control. *Cancer Invest* 20: 437–451, 2002
18) Tsien C, Gomez-Hassan D, Ten Haken RK, Tatro D, Junck L, Chenevert TL, Lawrence T: Evaluating changes in tumor volume using magnetic resonance imaging during the course of radiotherapy treatment of high-grade gliomas: Implications for conformal dose-escalation studies. *Int Radiat Oncol Biol Phys* 62: 328–332, 2005
19) Wu VW, Kwong DL, Sham JS: Target dose conformity in 3-dimensional conformal radiotherapy and intensity modulated radiotherapy. *Radiother Oncol* 78: 78–79, 2005
20) Zelefsky MJ, Leibel SA, Kutcher GJ, Fuks Z: Three-dimensional conformal radiotherapy and dose escalation: where do we stand? *Semin Radiat Oncol* 8: 107–114, 1998

Address reprint requests to: Yuzo Hasegawa, MD, Division of Neurological Surgery, Chiba Cancer Center, 666–2 Nitona-cho, Chuo-ku, Chiba, Chiba 260–8717, Japan.

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ORIGINAL ARTICLE

Clinical practice and outcome of radiotherapy for esophageal cancer between 1999 and 2003: the Japanese Radiation Oncology Study Group (JROSG) Survey

Yasumasa Nishimura · Ryuta Koike · Kazuhiko Ogawa · Ryuta Sasamoto · Yuji Murakami · Yoshiyuki Itoh · Yoshiharu Negoro · Satoshi Itasaka · Toru Sakayauchi · Tetsuro Tamamoto

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Abstract
Background To determine the clinical results of radiotherapy (RT) for esophageal cancer in Japan.
Materials and methods A questionnaire-based survey was conducted for esophageal cancer treated by definitive RT between 1999 and 2003. Clinical results of definitive RT for patients were collected from 9 major institutions. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients were classified into three groups: (A) stage I, (B) resectable stages II–III, (C) unresectable stages III–IVA. For group A, all patients treated by RT alone or chemo-radiotherapy (CRT) were included. For groups B and C, only those treated by CRT were included.
Results In total, 167 patients were included in group A, 239 in group B, and 244 in group C. Approximately half of the patients in group A were treated by CRT. The median total RT dose ranged from 60 to 66 Gy. The median and range of the 5-year overall survival rates were 56% (48–83%) for group A, 29% (12–52%) for group B, and 19% (0–31%) for group C, respectively. A wide disparity in overall survival rates was noted among the institutions. A significant correlation between the number of patients treated per year and the 5-year overall survival rate was noted for groups B and C (both $p < 0.05$).
Conclusion Although the overall survival rates for stage I esophageal cancer were excellent, a significant disparity in survival rates was noted among the institutions for stage II–IVA tumors treated by CRT.

Keywords Esophageal cancer · Chemo-radiation therapy · Brachytherapy · National survey

Y. Nishimura (✉) · R. Koike
Department of Radiation Oncology,
Kinki University Faculty of Medicine, Ohno-Higashi,
Osaka-Sayama, Osaka 589-8511, Japan
e-mail: ynishi@med.kindai.ac.jp

K. Ogawa
Department of Radiology,
University of the Ryukyus, Okinawa, Japan

R. Sasamoto
Department of Radiology, Niigata University Medical and Dental Hospital, Niigata, Japan

Y. Murakami
Department of Radiation Oncology,
Hiroshima University, Hiroshima, Japan

Y. Itoh
Department of Radiology,
Nagoya University, Nagoya, Aichi, Japan

Y. Negoro
Department of Radiology, Tenri Hospital,
Tenri, Nara, Japan

S. Itasaka
Department of Radiation Oncology and Image-Applied Therapy,
Kyoto University, Kyoto, Japan

T. Sakayauchi
Department of Radiation Oncology,
Tohoku University, Sendai, Miyagi, Japan

T. Tamamoto
Department of Radiation Oncology,
Nara Medical University School of Medicine,
Kashihara, Nara, Japan

Introduction

In the treatment of esophageal cancer, significant improvements in local control and overall survival have been achieved with concurrent chemo-radiotherapy (CRT) compared with radiotherapy (RT) alone [1–3]. In a phase III randomized trial (RTOG-8501), four cycles of full-dose 5-FU/cisplatin (FP) combined with 50 Gy of RT was compared with RT alone (64 Gy), and the CRT arm showed a significant improvement in the overall survival rate [1, 2]. To improve these results, a phase III trial (INT-0123) comparing standard dose RT (50.4 Gy) and high-dose RT (64.8 Gy) concurrently combined with FP was conducted [4]. In the INT-0123 trial, however, the high-dose RT arm did not show a survival benefit compared with the standard-dose RT arm [4]. Therefore, four cycles of full-dose FP combined with 50.4 Gy of RT is the standard CRT regimen for esophageal cancer in the USA.

In Japan, surgical resection has been preferred for resectable esophageal cancer for T1–3N0,1M0 disease (International Union Against Cancer TNM classification; UICC 2002). Until the mid-1990s, many patients treated by CRT had unresectable T4 disease or metastatic cervical lymph nodes (M1-lymph). Even for these locally advanced T4 or M1-lymph esophageal cancers, 2-year overall survival rates of 20–30% have been reported by Japanese investigators using concurrent CRT of 60 Gy [5–7]. Because of the success of concurrent CRT for unresectable esophageal cancer, definitive CRT has been applied for resectable esophageal cancer (T1-3N0,1M0) since the late 1990s in Japan. Although no randomized clinical trials comparing definitive CRT and surgery for resectable esophageal cancer have been reported, clinical results of concurrent CRT for resectable esophageal cancer are very promising [8–10].

For superficial esophageal cancer (T1N0M0), RT alone with or without intraluminal brachytherapy (IBT) is also as effective as concurrent CRT [11–14]. Recently, a phase II clinical trial of concurrent CRT for superficial esophageal cancer with submucosal invasion has been reported by the Japan Clinical Oncology Group (JCOG) [15]. In the trial, 60 Gy of RT was combined with two courses of FP for 72 patients with stage I (T1N0M0) esophageal cancer, and the 4-year overall survival and major relapse-free survival rates were 81 and 68%, respectively. This survival rate is very similar to that of surgery.

In the early 2000s, concurrent CRT became one of the standard treatments for both resectable and unresectable esophageal cancers in Japan [10, 16, 17]. A questionnaire-based national survey on CRT or RT for esophageal cancer was conducted to evaluate the clinical results for esophageal cancer in major Japanese institutions.

Patients and methods

A questionnaire-based survey of RT for esophageal cancer treated definitively between January 1999 and December 2003 was conducted by the Japanese Radiation Oncology Study Group (JROSG). In May 2008, questionnaires on the results of definitive RT for patients with esophageal cancer were collected from 9 major institutions of the JROSG. Only patients with good performance status (PS 0–2) who received a total dose of 50 Gy or more were included. Patients treated by preoperative or postoperative RT (or CRT) were excluded.

Patients were classified into three groups: group A, those with superficial tumors (T1N0M0; stage I); group B, those with resectable tumors (T1N1M0, T2,3N0,1M0; stages II–III); group C, those with unresectable tumors (T4 or M1-lymph; stages III–IVA). For group A, all patients treated definitely by RT or CRT with or without IBT were included. For groups B and C, only those treated by concurrent CRT were included.

Results

Table 1 shows the numbers of patients in the institutions and groups. In total, 650 patients with esophageal cancer treated by definitive RT were included from nine institutions. All but 10 tumors (98.5%) were squamous cell carcinomas. The age of the patients ranged from 35 to 87 years, and the median ages at each institution ranged from 63 to 71 years. The clinical practice of each institution between 1999 and 2003 is also shown in Table 1. Periodic cancer board meetings consisting of radiation oncologists and surgical oncologists were performed at six institutions, and salvage surgery for locally recurrent or persistent esophageal tumors were performed at seven institutions. The median follow-up periods of surviving and censored patients ranged from 42 to 70 months with a median of 56 months.

Table 2 shows the treatment methods in the institutions between 1999 and 2003. For stage I disease (group A), 60 patients (36%) were treated by IBT following external RT. In terms of chemotherapy for stage I disease, 74 patients (44%) were treated by CRT with or without IBT, and 93 patients (56%) were treated by RT with or without IBT. For all institutions, the median total RT dose for CRT ranged from 60 to 66 Gy.

The type of chemotherapy given concurrently with RT differed significantly among the institutions. Full-dose FP was used most frequently, followed by low-dose FP. Various chemotherapy regimens of full-dose FP were included: (1) two cycles of cisplatin 70–80 mg/m^2 (day 1) and 5-FU 700–800 mg/m^2/day administered as continuous

Table 1 Numbers of patients and clinical practice in each institution

Institution	No. of patients				Cancer board	Salvage surgery	Median follow-up period of surviving patients (months)
	Group A	Group B	Group C	Total			
Nagoya Univ.	10	10	17	37 (1)	No	No	57
Niigata Univ.	16	12	17	45 (0)	No	No	56
Univ. Ryukyus	16	11	20	47 (1)	Yes	Yes	43
Kyoto Univ.	9	29	19	57 (2)	No	Yes	52
Kinki Univ.	7	17	42	66 (0)	Yes	Yes	69
Nara Med. Univ.	10	36	28	74 (1)	Yes	Yes	46
Hiroshima Univ.	38	15	26	79 (0)	Yes	Yes	70
Tenri Hospital	27	49	26	102 (2)	Yes	Yes	42
Tohoku Univ.	34	60	49	143 (3)	Yes	Yes	56
Total	167	239	244	650 (10)			

Values in parentheses indicate number of patients with non-squamous cell carcinoma histology

Group A, T1N0M0; Group B, T1N1M0,T2–3N0,1M0; Group C, T4,M1-lymph

Table 2 Treatment methods according to each institution between 1999 and 2003

Institution	Total no. of patients	Treatment for stage I			RT dose	Type of chemotherapy			
		CRT	RT	+IBT	Range (median)	Full FP	Low FP	Others	Consolidation
Nagoya Univ.	37	2	3	5	50–70 Gy (60 Gy)	1	19	11	No
Niigata Univ.	45	5	11	0	50–70.2 Gy (66 Gy)	1	22	11	No
Univ. Ryukyus	47	2	2	5	50–66.6 Gy (60 Gy)	28	4	0	No
Kyoto Univ.	57	2	2	5	60 Gy (60 Gy)	19	13	19	Some
Kinki Univ.	66	3	4	0	60 Gy (60 Gy)	11	51	0	Yes
Nara Med. Univ.	74	3	1	6	60–70 Gy (60.8 Gy)	10	58	0	No
Hiroshima Univ.	79	7	6	25	52–71 Gy (62 Gy)	16	15	19	No
Tenri Hospital	102	9	0	18	66 Gy (66 Gy)[a]	94	0	6	No
Tohoku Univ.	143	20	14	0	56–76 Gy (64 Gy)	57	23	49	Yes
Total	650	53	54	60 (21[b])		237	205	115	

[a] Hyperfractionation of 66/1.1 Gy b.i.d. was used

[b] Number of patients treated with CRT and IBT

intravenous infusion (IV) (days 1–4 or 1–5) [18–20], (2) two cycles of cisplatin 40 mg/m^2 (days 1 and 8) and 5-FU 400 mg/m^2/day as continuous IV (days 1–5 and 8–12) [6, 10], and (3) two or three cycles of cisplatin 60 mg/m^2 (day 1) and 5-FU 400 mg/m^2/day as continuous IV (days 1–4) [9, 21]. Low-dose FP included the following regimens: (1) two cycles of cisplatin 7 mg/m^2 (days 1–5 and 8–12) and 5-FU 250 mg/m^2/day as continuous IV (days 1–14) [5, 18, 19], and (2) six weekly cycles of cisplatin 3–5 mg/m^2 (days 1–5) and 5-FU 180–250 mg/m^2 as continuous IV (days 1–5 or 1–7) [19, 20, 22]. The other regimens included: (1) two cycles of *cis*-diammine-glycolatoplatinum (Nedaplatin) 55–80 mg/m^2 and 5-FU 300–700 mg/m^2 as continuous IV (days 1–5) [23], and (2) daily administration of 5-FU 300 mg/m^2/day as continuous IV for 6 weeks [7].

Two cycles of consolidation chemotherapy with cisplatin 70–80 mg/m^2 (day 1) and 5-FU 700–800 mg/m^2/day (days 1–4 or 1–5) were given after CRT at three institutions [10, 18]. No consolidation chemotherapy was given at the remaining six institutions.

Figure 1 shows the 3- and 5-year overall survival rates in the institutions for groups A, B, and C. The median and range of the 5-year overall survival rates of the nine institutions were 56% (48–83%) for group A, 29% (12–52%) for group B, and 19% (0–31%) for group C, respectively (Table 3). The 5-year overall survival rates for group A were good for all 9 institutions, although 56% of patients were treated by RT alone with or without IBT. A wide disparity in the 5-year overall survival rate was noted especially for group B.

The relationship between the number of patients treated per year and the 5-year overall survival rates of each

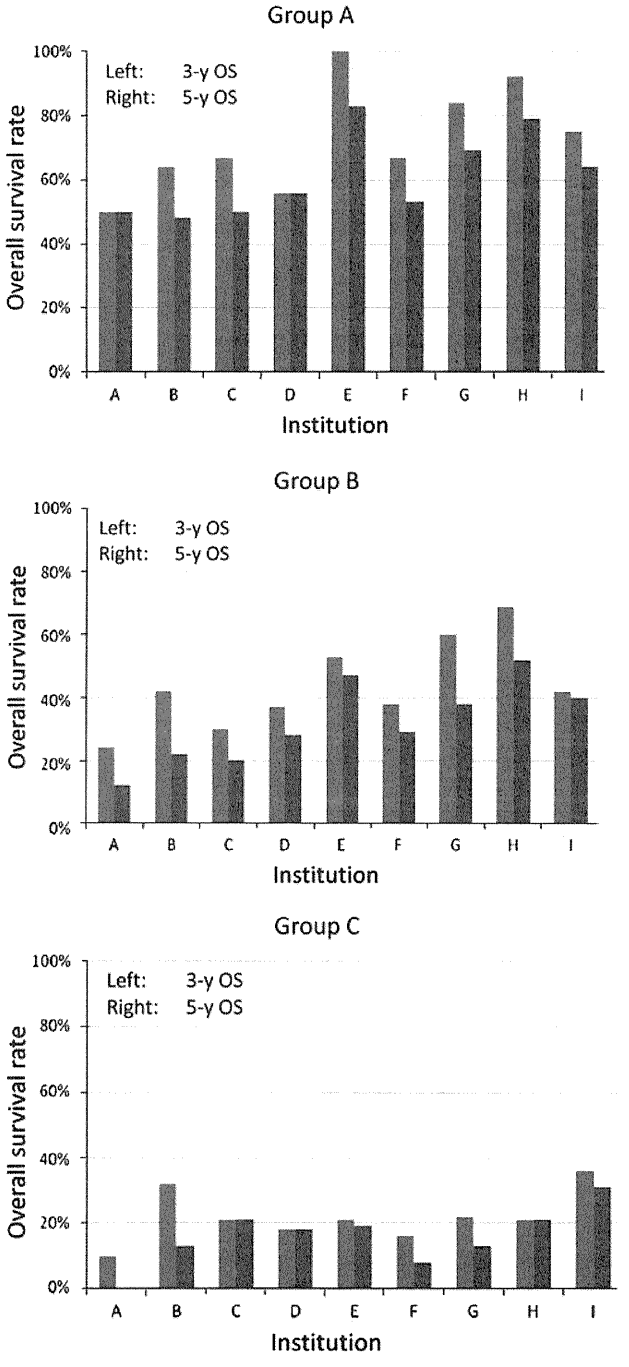

Fig. 1 The 3- and 5-year overall survival rates at each institution are shown for (**a**) group A, (**b**) group B, and (**c**) group C. The *left* and *right* columns are the 3- and 5-year overall survival rates of each institution, respectively

institution was analyzed for groups A, B, and C (Fig. 2). The correlation coefficient (r) and its 95% confidence interval for groups A, B, and C were 0.50 (−0.2455 to 0.8740), 0.70 (0.0602 to 0.9303), and 0.70 (0.0670 to 0.9312), respectively. A significant correlation between the number of patients treated per year and the 5-year overall

Table 3 The median and range of overall survival (OS) rates for patients with esophageal cancer treated between 1999 and 2003 at the 9 institutions

	3 years OS	5 years OS
Group A	67% (50–100%)	56% (48–83%)
Group B	42% (24–69%)	29% (12–52%)
Group C	21% (10–36%)	18% (0–31%)

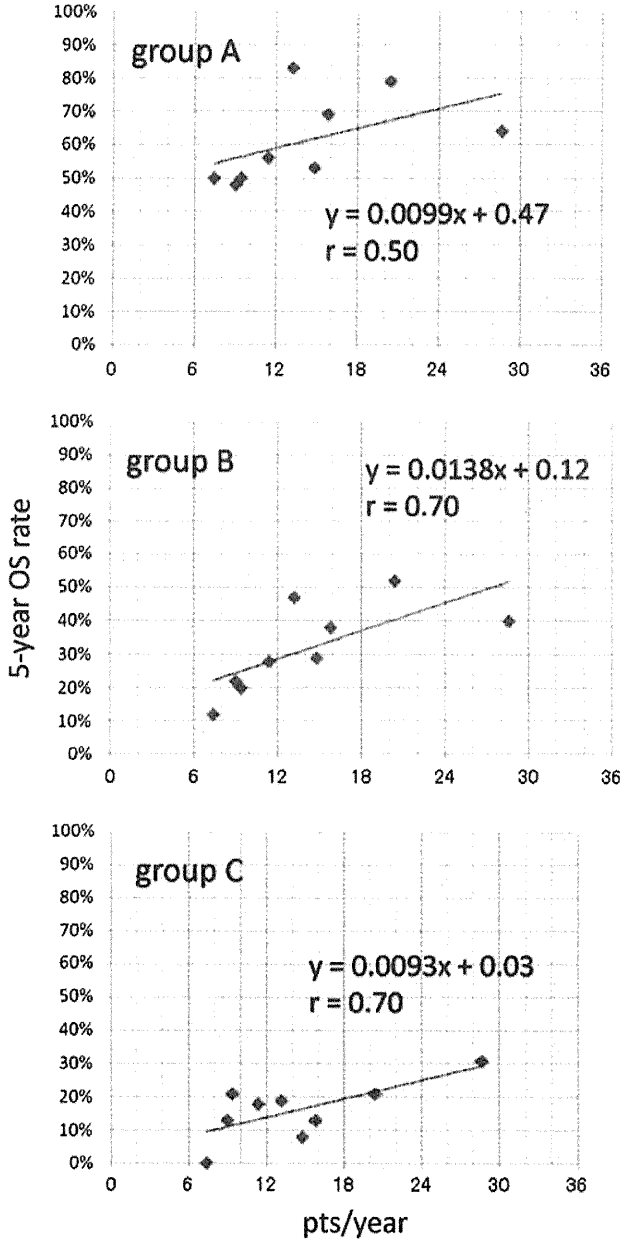

Fig. 2 Correlations between the number of patients treated per year (x-axis) and the 5-year overall survival rates of each institution (y-axis) for groups A, B, and C are plotted. The linear regression lines and correlation coefficients (r) for each group are shown

Table 4 Number of patients with serious late toxicities associated with CRT or RT

CTCAE version 3.0	Grade 3–4	Grade 5
Cardiac ischemia	1	3
Pericardial effusion	14	1
Pleural effusion	7	1
Radiation pneumonitis	4	2
Dysphagia	9	0
Hemorrhage, esophageal varices	1	0

survival rates was noted for groups B and C (both $p < 0.05$).

Based on the clinical charts of all patients, late toxicities of grade 3 or more (CTCAE version 3.0) were collected. The median and range of grade 3 or higher late toxicity rate for each institution were 11% (0–18%). Table 4 shows the number of patients with late toxicities of grade 3 or higher. Pericardial effusion and pleural effusion are most common late toxicities associated with CRT, followed by dysphagia and radiation pneumonitis. Although seven (1%) treatment-related deaths (grade 5) were reported, the deaths from cardiac ischemia may be coincidental.

Discussion

The present questionnaire-based survey revealed both clinical practice of care and outcomes for esophageal cancer treated by definitive RT or CRT in nine academic and major institutions between 1999 and 2003. The changes in clinical practice of RT for esophageal cancer in Japan have been well reported by the Japanese Patterns of Care Study (JPCS) [16, 17]. Based on the Comprehensive Registry of Esophageal Cancer in Japan for 2002, a total of 4,281 cases were registered from 222 institutions in Japan [24]. For cStage I–IIA (T1-3N0M0), the 5-year overall survival rates with concurrent CRT or RT alone were 52.0 and 32.5%, respectively. For cStage IIB–IVB, the 5-year overall survival rate with concurrent CRT was 14.9% [24]. However, no comparison of clinical outcomes of definitive RT or CRT at various institutions for esophageal cancer has been reported in Japan.

The JPCS between 1999 and 2001 revealed that CRT had become a common treatment for T2–4 esophageal tumors, although 72% of T1 tumors were treated by RT alone [16]. Therefore, clinical data for both RT alone and CRT were collected for stage I esophageal cancer (group A), although only data on CRT were collected for groups B and C. In the present analysis, 56% of the patients in group A were treated by RT alone and 44% were treated by CRT. Although the CRT rate for T1 tumors was higher than that in the JPCS between 1999 and 2001, more than half of T1 tumors were still treated by RT alone in Japanese academic and major institutions between 1999 and 2003. Following RT alone or CRT, 60 patients (36%) in group A were treated with IBT. The preference for IBT was heavily dependent on the institutional policy [9–12, 25].

For all institutions, medians of total RT dose for CRT ranged from 60 to 66 Gy. Although a total dose of 50.4 Gy combined with FP is the standard regimen for esophageal cancer in the USA, no institutions in this survey used a total dose of 50.4 Gy for definitive CRT. The type of chemotherapy differed significantly among the institutions. In Japan, low-dose protracted infusion chemotherapy combined with full-dose RT of 60–66 Gy used to be a popular regimen for locally advanced esophageal squamous cell carcinomas [5, 7, 16, 20, 22]. In the present analysis, full-dose FP was used most frequently (42.5%), followed by low-dose FP (36.8%) (Table 2). During this period, two clinical trials comparing full-dose FP and low-dose FP were performed at several institutions [18, 19]. In both trials, protracted low-dose FP with RT provided no advantage over standard short-term full-dose FP with RT for esophageal cancer. Low-dose FP will therefore decline in clinical practice in Japan.

The 5-year survival rates for stage I esophageal cancer exceeded 50% at most institutions, with a median 5-year survival rate of 56%. This survival rate seems excellent, as more than half of the patients were treated with RT alone. Thus, RT alone seems a definitive and effective treatment for elderly and complicated patients with superficial esophageal cancer.

One of the most notable findings in the present study was a significant disparity in overall survival rates among the institutions for patients with stage II–IVA disease treated definitively by CRT. The biggest difference in the 5-year overall survival rate was noted for group B. The highest 5-year overall survival rate of 52% was achieved at Tenri Hospital. At the hospital, definitive CRT was performed for responders to neoadjuvant CRT of 44 Gy/40 fractions, and surgery was performed for non-responders [9, 21]. This patient selection approach may be linked to the excellent survival rate. On the other hand, neither salvage surgery nor cancer board meetings were done for esophageal cancer at two hospitals showing poor 5-year survival rates of 12 and 22% for resectable esophageal cancer (Table 1). Thus, the disparity in overall survival rates may be related to the clinical practice at each institution.

A significant correlation between the number of patients treated per year and the 5-year overall survival rates was noted for groups B and C (both $p < 0.05$) (Fig. 2). A similar volume–outcome relation was demonstrated between the number of esophagectomy operations

performed per year and the operative mortality [26]. In terms of esophagectomy for cancer, a hospital with less than five esophagectomy operations per year was classified as a low-volume hospital with high operative mortality [26]. As the present series included only medium- and high-volume hospitals for CRT, survival rates by CRT at low-volume hospitals may be much lower than this series.

High rates of serious late toxicities, especially of the heart and pleura, associated with CRT have been reported [4, 27]. In this analysis, the median grade 3 or higher late toxicity rate of each institution was 11%. This late toxicity rate was considered acceptable, although it may have been underestimated due to the retrospective nature of the analysis.

In conclusion, the 5-year survival rates for stage I esophageal cancer were excellent, even with RT alone, at most institutions. However, for patients with stage II–IVA tumors treated definitively by CRT, a significant disparity in overall survival was noted among the institutions.

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Conflict of interest None declared.

References

1. Al-Sarraf M, Herskovic A, Martz K et al (1997) Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol 15:277–284
2. Cooper JS, Guo MD, Herskovic A et al (1999) Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. JAMA 281:1623–1627
3. Smith TJ, Ryan LM, Douglass HO Jr et al (1998) Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys 42:269–276
4. Minsky BD, Pajak TF, Ginsberg RJ et al (2002) INT 0123 (Radiation Therapy Oncology Group 94-05) phase III trial of combined-modality therapy for esophageal cancer: high-dose versus standard-dose radiation therapy. J Clin Oncol 20:1167–1174
5. Nishimura Y, Suzuki M, Nakamatsu K et al (2002) Prospective trial of concurrent chemoradiotherapy with protracted infusion of 5-fluorouracil and cisplatin for T4 esophageal cancer with or without fistula. Int J Radiat Oncol Biol Phys 53:134–139
6. Ohtsu A, Boku N, Muro K et al (1999) Definitive chemoradiotherapy for T4 and/or M1 lymph node squamous cell carcinoma of the esophagus. J Clin Oncol 17:2915–2921
7. Sakai K, Inakoshi H, Sueyama H et al (1995) Concurrent radiotherapy and chemotherapy with protracted continuous infusion of 5-fluorouracil in inoperable esophageal squamous cell carcinoma. Int J Radiat Oncol Biol Phys 31:921–927
8. Hironaka S, Ohtsu A, Boku N et al (2003) Nonrandomized comparison between definitive chemoradiotherapy and radical surgery in patients with T(2–3)N(any) M(0) squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 57:425–433
9. Murakami M, Kuroda Y, Nakajima T et al (1999) Comparison between chemoradiation protocol intended for organ preservation and conventional surgery for clinical T1–T2 esophageal carcinoma. Int J Radiat Oncol Biol Phys 45:277–284
10. Ariga H, Nemoto K, Miyazaki S et al (2009) Prospective comparison of surgery alone and chemoradiotherapy with selective surgery in resectable squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys 75:348–356
11. Nishimura Y, Okuno Y, Ono K et al (1999) External-beam radiation therapy with or without high-dose-rate intraluminal brachytherapy for superficial esophageal cancer. Cancer 86:220–228
12. Sai H, Mitsumori M, Araki N et al (2005) Long-term results of definitive radiotherapy for stage I esophageal cancer. Int J Radiat Oncol Biol Phys 62:1339–1344
13. Nemoto K, Matsumoto Y, Yamakawa M et al (2000) Treatment of superficial esophageal cancer by external radiation therapy alone: results of a multi-institutional experience. Int J Radiat Oncol Biol Phys 46:921–925
14. Nemoto K, Yamada S, Hareyama M et al (2001) Radiation therapy for superficial esophageal cancer: a comparison of radiotherapy methods. Int J Radiat Oncol Biol Phys 50:639–644
15. Kato H, Sato A, Fukuda H et al (2009) A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol 39:638–643
16. Murakami Y, Kenjo M, Uno T et al (2007) Results of the 1999–2001 Japanese patterns of care study for patients receiving definitive radiation therapy without surgery for esophageal cancer. Jpn J Clin Oncol 37:493–500
17. Kenjo M, Uno T, Murakami Y et al (2009) Radiation therapy for esophageal cancer in Japan: results of the Patterns of Care Study 1999–2001. Int J Radiat Oncol Biol Phys 75:357–363
18. Nishimura Y, Mitsumori M, Hiraoka M et al (2009) A randomized phase II study of cisplatin/5-FU concurrent chemoradiotherapy for esophageal cancer: short-term infusion versus protracted infusion chemotherapy (KROSG0101/JROSG021). Radiother Oncol 92:260–265
19. Sakayauchi T, Nemoto K, Ishioka C et al (2009) Comparison of cisplatin and 5-fluorouracil chemotherapy protocols combined with concurrent radiotherapy for esophageal cancer. Jpn J Radiol 27:131–137
20. Sai H, Mitsumori M, Yamauchi C et al (2004) Concurrent chemoradiotherapy for esophageal cancer: comparison between intermittent standard-dose cisplatin with 5-fluorouracil and daily low-dose cisplatin with continuous infusion of 5-fluorouracil. Int J Clin Oncol 9:149–153
21. Yamada K, Murakami M, Okamoto Y et al (2006) Treatment results of chemoradiotherapy for clinical stage I (T1N0M0) esophageal cancer. Int J Radiat Oncol Biol Phys 64:1106–1111
22. Sasamoto R, Sakai K, Inakoshi H et al (2007) Long-term results of chemoradiotherapy for locally advanced esophageal cancer, using daily low-dose 5-fluorouracil and *cis*-diammine-dichloroplatinum (CDDP). Int J Clin Oncol 12:25–30
23. Nemoto K, Matsushita H, Ogawa Y et al (2003) Radiation therapy combined with *cis*-diammine-glycolatoplatinum (Nedaplatin) and 5-fluorouracil for untreated and recurrent esophageal cancer. Am J Clin Oncol 26:46–49
24. Ozawa S, Tachimori Y, Baba H et al (2010) Comprehensive registry of esophageal cancer in Japan, 2002. Esophagus 7:7–22

25. Akagi Y, Hirokawa Y, Kagemoto M et al (1999) Optimum fractionation for high-dose-rate endoesophageal brachytherapy following external irradiation of early stage esophageal cancer. Int J Radiat Oncol Biol Phys 43:525–530
26. Fujita H, Ozawa S, Kuwano H et al (2010) Esophagectomy for cancer: clinical concerns support centralization operations within the larger hospitals. Dis Esophagus 23:145–152
27. Ishikura S, Nihei K, Ohtsu A et al (2003) Long-term toxicity after definitive chemoradiotherapy for squamous cell carcinoma of the thoracic esophagus. J Clin Oncol 21:2697–2702