compression and fixation (10) to reduce breathing-induced organ motion.

In this study, we evaluated the effectiveness of a body frame and its combination with a diaphragm press in restricting the range of lung tumor motion by tracking the three-dimensional real-time position of fiducial gold markers embedded near the tumor. We also investigated the effect on respiratory-induced organ motion of using the stereotactic body frame (SBF) together with a breathing cycle monitoring device (Abches), which was used to self-regulate the patient's breathing cycle.

MATERIALS AND METHODS

The real-time tumor-tracking radiotherapy system

The three-dimensional trajectories of fiducial markers near or at tumor sites were tracked via the real-time tumor-tracking radiotherapy (RTRT) system at the Radiotherapy Department of Hokkaido University Hospital ~~(5, 6)~~. This fluoroscopy-based system is composed of two pairs of an X-ray source and image intensifier and an image acquisition and recognition unit that is interfaced with a linear accelerator to perform gated-irradiation. The positions of the gold markers were acquired every 0.033 s.

Body frame, diaphragm press, and breathing cycle monitor

For patient immobilization, we used Elekta's SBF (Elekta Oncology Systems) (13, 14). The same body frame was used in an earlier investigation on respiratory tumor movement and setup error verification using X-ray simulator images (7, 9, 15). The SBF is made from a rigid material formed into a half-hexagonal shell that wraps around the patient's torso. Because of the restricted space inside the shell, the patient's arms had to be positioned outside the shell by raising them above the head. Patient fixation inside the body frame was accomplished by means of a vacuum pillow, the size of which was chosen to ensure that it could provide an exact fit to the patient's body contour.

An additional accessory to the SBF was a frame that supports a pentagonal plastic plate that can be placed against the patient's abdomen to restrict the diaphragm motion. The pressure applied by the plate was regulated depending on the tolerance of each patient and was used only in the part of our measurements where its effectiveness to control motion from respiration was evaluated.

A breathing cycle monitor (commercially available as Abches [APEX Medical Inc., Tokyo, Japan]) was also used in combination with the body frame to investigate whether self-regulated breathing can reduce the amplitude of respiratory-induced tumor and organ motion. As shown in Fig.1, the Abches consists of two extended arms, one for detecting abdominal movement and the other for detecting chest movement, and a respiration range indicator visible to the patient through a mirror attached to the head during the measurement.

Patient demographics

The patient population for this study was composed of 16 males and 3 females who were scheduled to undergo radiation therapy using the RTRT system in our hospital between 2006 and 2008. Table 1 shows the characteristics of the cohort for this study. The patients' ages ranged between 59 and 85 years (mean, 76 years). Fourteen patients had T1 lung cancer, whereas 5 had T2 and 1 had T3. No patient had lymph nodes irradiation and none of the patients had metastasis. Four patients had partial lung resection before the irradiation.

Table 1. Characteristics of the cohort for this study

Parameters	Number of patients
Sex	
Male	16
Female	3
Age range	59–85 (mean, 76)
Gold marker locations	
Upper right lobe	5
Middle lobe	1
Lower right lobe	4
Upper left lobe	6
Lower left lobe	3
Cancer classification	
T1N0M0	13
T2N0M0	5
T3N0M0	1

The locations of the gold markers were judged based on where they appeared in the computed tomography images of the patient. We classified the sample population into "upper lobe" or "middle or lower lobe" patients according to the location of gold markers in the lungs, because it has been reported that the relative locations in

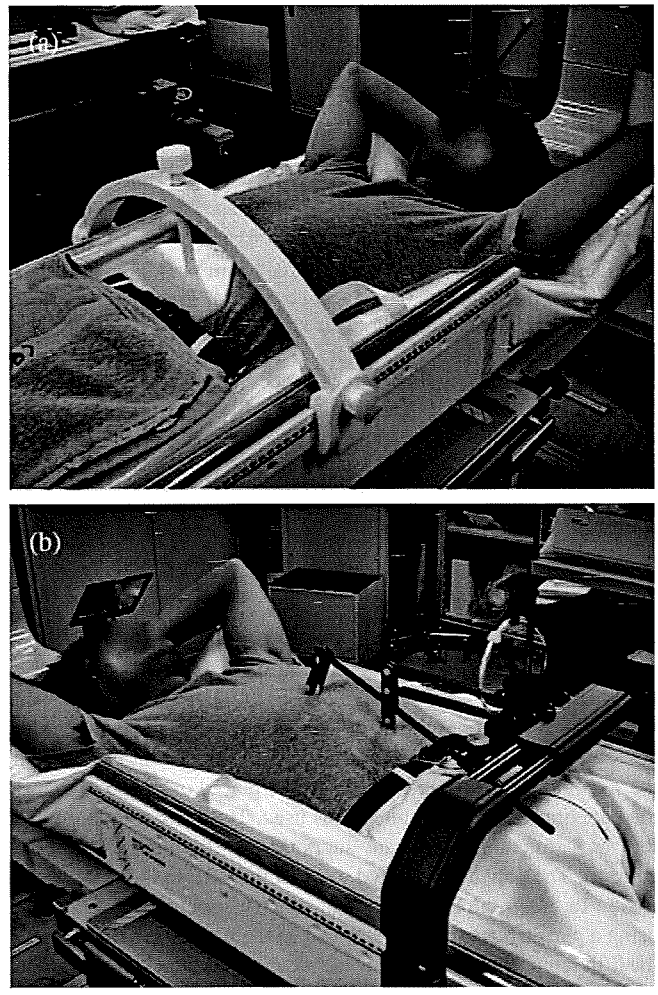

Fig. 1. Patient set-ups using the (a) stereotactic body frame (SBF)+diaphragm press (left) and the (b) SBF + Abches (right).

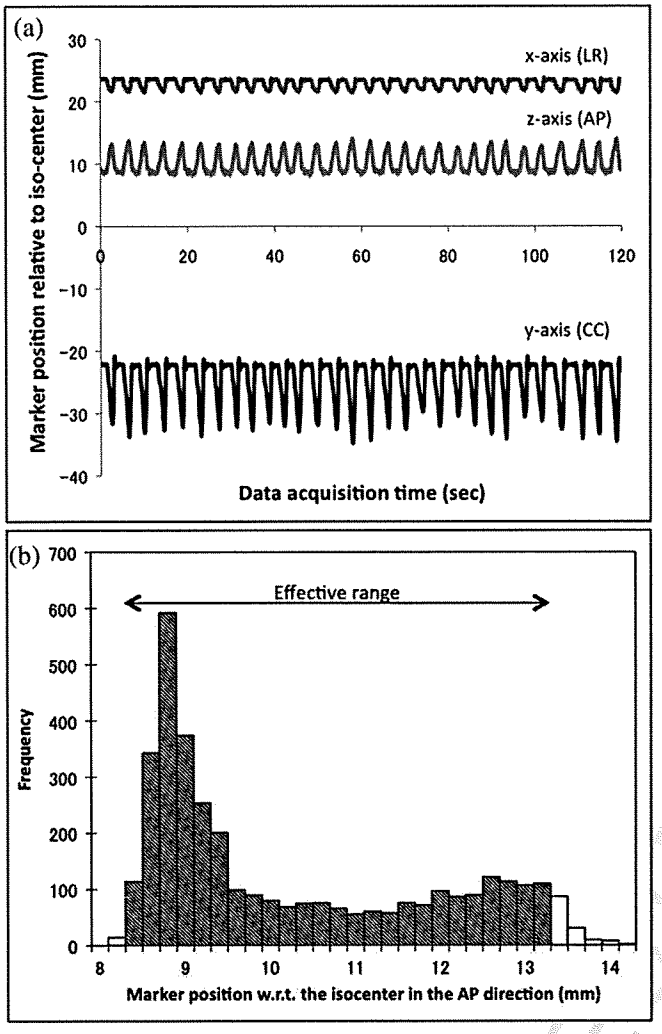

Fig. 2. Shown in (a) is an example of a 2-min tracking of the data from which the effective range was computed. The effective range along the z axis of the data in (a) is shown in (b).

the lung of the gold marker (16) and the tumor itself (17) influence the amplitude of their respective motions. Eleven of the 19 patients who participated in this study had gold markers embedded in the upper lobes of their lungs: 6 of the 11 had markers in the upper left and the other 5 had markers in the upper right. There was 1 patient with markers in the middle lobe and 7 patients with markers in either the lower left or lower right lobes of the lung.

Patient setup

Fluoroscopic tracking of the fiducial markers was performed in five different setups for each patient. In the first setup, the patient was made to lie on the treatment couch in the supine position with arms on the side. This was set as the reference patient position. In the second setup, the patient's arms were placed overhead to mimic the patient position when an SBF is used. The arms were not fixed into any structures, but were supported by cushions for patient comfort. The patient was asked to lie in the SBF in the third setup. Figure 1a shows the fourth setup, in which respiration was restricted using a plastic plate that pressed against the patient's diaphragm. In the fifth setup, shown in Fig. 1b, the Abches was attached to the SBF in the same manner as the abdominal press. The patients were able to monitor the relative amplitude of their breathing cycle from a respiration range indicator which was visible to the patient through a mirror.

Marker tracking

Tumor motion was monitored in real time by using 2-mm diameter gold markers, which were surgically placed near the tumor site and served as surrogate indicators of lung tumor motion (4). Three tracking measurements lasting for 5 min (2 min of tracking plus 3 min of rest) each were performed for every patient setup. The range of patient dose for the entire duration of marker tracking was between 14 and 591 mGy based on the estimates of Shirato *et al.* (18). Because the absorbed dose in the patient is strongly dependent on the tube voltage and pulse width, the X-ray tube settings were kept as low as possible during all the measurements.

Evaluation index and statistical analysis

The three-dimensional position of the gold marker relative to the iso-center is estimated by the RTRT system as it tracks the marker's motion. Sample tracking data are shown in Fig. 2a. The *effective range* of marker motion along each coordinate axis was computed about the mean marker position from the respective 2-min set of tracking data. Histograms similar to Fig. 2b with 0.2-mm position bins were constructed for each coordinate axis. The frequencies of the adjacent bins to the left and to the right of the median were accumulated until 95% of the total marker position frequency was achieved. The range of the included position bins was then defined as the *effective range* of the marker motion. The effective range along the z axis of the data in Fig. 2a is given as an example in Fig. 2b. A smaller effective range of the gold marker indicates less respiratory-induced organ motion.

The Mann-Whitney test was applied to assess the statistical significance of the differences in the effective ranges obtained between the reference setup and the other four setups.

This study was thoroughly discussed with the institutional review board of our hospital and its approval was received before the commencement of the measurements. Written patient consent was also received from all the participants in this research.

RESULTS

The effective ranges were observed to vary from patient to patient. In the reference setup (no SBF-arms down setup), the range was 0.60–5.27 mm, 0.93–19.93 mm, and 1.00–10.20 mm along the left-right (LR), craniocaudal (CC), and anteroposterior (AP) directions, respectively, among the 19 patients. The tumor motion, as indicated by the effective range of the tracked gold marker, was reduced in some patients by changing the patient setup, such as by placing the patient's arms overhead or by using the SBF and diaphragm press or Abches. However, this was not true for all the patients, because there were those whose range of tumor motion became worse in the setups other than the reference setup. Because of the small number of patients, we grouped the tumors into two categories: upper lobe and middle or lower lobe. In the reference setup, the CC direction yielded a significant difference in the mean effective range of the upper and middle or lower lobe markers, with a p value of 0.02. On the other hand, the differences in the mean effective range of markers in the upper lobe and the middle or lower lobes were not statistically significant for either the LR or AP direction in the reference setup.

We compared the effectiveness of each setup in reducing respiratory-induced intrafractional organ motion. Table 2

Table 2. Comparison between the mean effective ranges of motion (±1 SD) of the markers in the upper and middle or lower lobes for the 5 patient setups evaluated

		LR	CC	AP
No SBF, arms down (nSBF_AD)	Upper	2.15 ± 0.89 (0.60–3.20)	4.59 ± 3.01 (0.93–9.53)	3.39 ± 1.42 (1.00–5.87)
	Middle or lower	2.18 ± 1.60 (0.60–5.27)	10.93 ± 6.36 (1.07–19.93)	4.33 ± 3.05 (1.13–10.20)
	p value	0.66	0.02	0.72
No SBF, arms up (nSBF_AU)	Upper	2.21 ± 0.96 (0.67–3.73)	4.51 ± 3.06 (0.87–10.13)	3.23 ± 1.63 (1.00–6.27)
	Middle or lower	2.55 ± 1.56 (0.67–5.60)	10.6 ± 6.09 (1.07–19.00)	3.91 ± 2.45 (1.33–8.27)
	p value	0.72	0.03	0.72
With SBF (wSBF)	Upper	1.97 ± 0.89 (0.67–3.33)	4.23 ± 2.76 (0.67–9.53)	3.04 ± 1.54 (1.07–5.67)
	Middle or lower	2.98 ± 2.41 (0.87–6.93)	9.91 ± 5.67 (1.07–16.87)	4.43 ± 3.63 (0.93–10.60)
	p value	0.78	0.03	0.84
With SBF + diaphragm press (wSBF + DP)	Upper	1.95 ± 0.86 (0.60–3.33)	3.77 ± 2.57 (0.80–8.60)	3.09 ± 1.33 (1.20–5.27)
	Middle or lower	2.53 ± 2.23 (0.73–7.60)	9.43 ± 5.56 (0.80–16.33)	3.61 ± 2.64 (0.67–8.93)
	p value	0.90	0.03	0.97
With SBF + Abches (wSBF + Ac)	Upper	1.91 ± 0.81 (0.60–2.93)	3.98 ± 2.68 (0.73–8.33)	2.88 ± 1.23 (1.20–4.60)
	Middle or lower	3.27 ± 2.70 (0.67–7.73)	12.84 ± 6.37 (1.00–18.87)	5.04 ± 4.81 (0.93–13.40)
	p value	0.89	0.01	0.60

Abbreviations: LR = left-right; AP = anteroposterior; CC = craniocaudal; SBF = stereotactic body frame.
Given in brackets are the minimum and maximum effective ranges. The *p* values listed here are derived from the Mann-Whitney test.

shows the mean effective ranges of marker motion for all the patients in the five setups evaluated in this study. Also listed in Table 2 are the *p* values obtained from the nonparametric comparison of the mean effective marker range between the upper and the middle or lower groups of patients for each setup using the Mann-Whitney test. Measurements using these setups were carried out for all the patients except for 2 patients who decided not to continue with the measurements after the fourth setup. The sequences of setups for the tracking sessions were randomly changed between patients to minimize the possible bias from the setup sequence. Results of the RTRT measurement of the effective range of motion of fiducial markers showed that the use of the SBF, diaphragm press, or breathing cycle monitor to control the patient's breathing did not generally yield smaller effective marker ranges either for tumors in the upper lobe or those in the middle or lower lobes.

Motion of markers in the upper lobe

The mean effective ranges in the LR direction of the markers in the upper lobe showed little variation among the different patient setups. In the LR direction, they were around 2 mm for all setups (Fig. 3). The differences between the reference setup and the four other setups were no more than 1 mm, and none of these differences were statistically significant at the 5% level. Along the CC direction, the average effective ranges of the markers in the 5 setups were between 3.77 mm and 4.59 mm (Fig. 4). The mean and median of the effective range were around 2.88 mm to

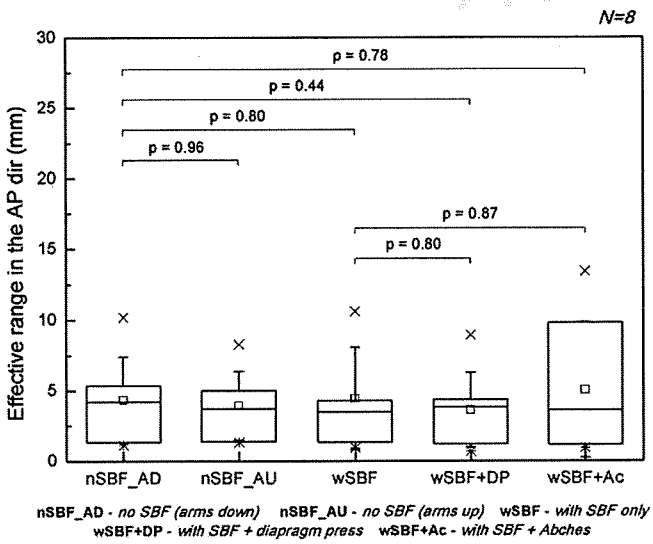

Fig. 3. The effective range along the lateral direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

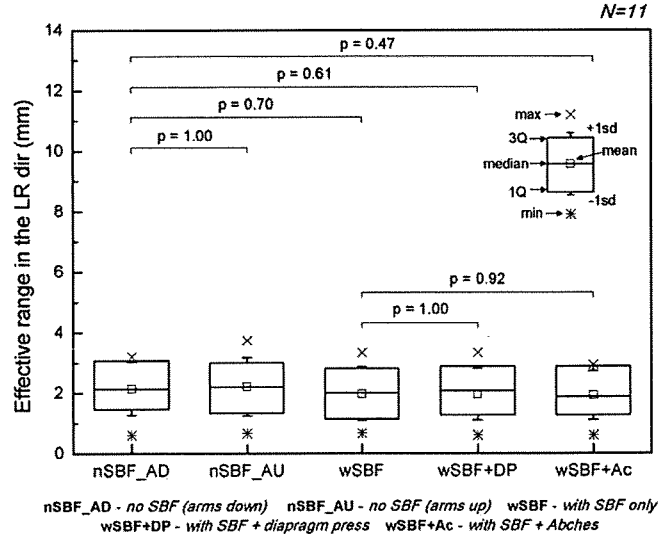

Fig. 4. The effective range along the craniocaudal direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

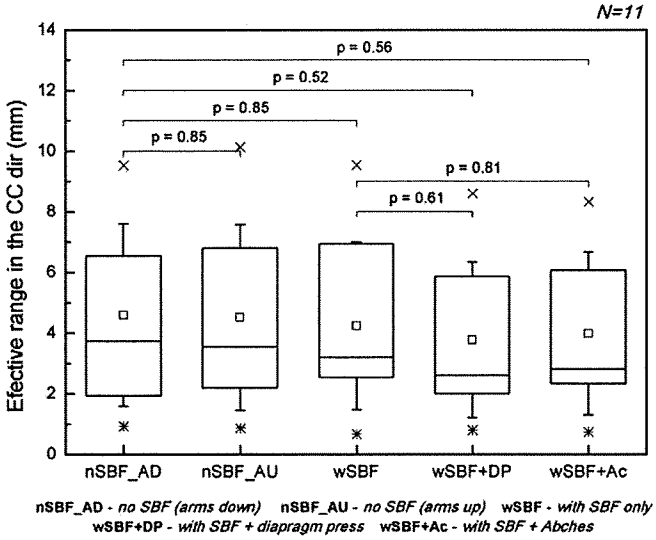

Fig. 5. The effective range along the anteroposterior direction of the gold markers in the upper lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

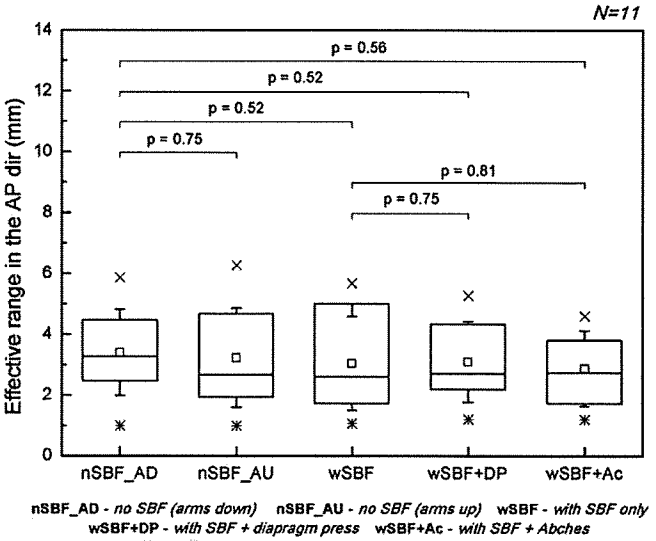

Fig. 6. The effective range along the lateral direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

3.39 mm in the AP direction (Fig. 5). The spread of the effective range values was largest along the CC direction, with a standard deviation of about 2.57–3.06 mm, and smallest along the LR direction, with a standard deviation of less than 1 mm. The maximum effective ranges of the markers obtained from the LR, CC, and AP directions were 3.73 mm, 10.13 mm, and 6.27 mm, respectively.

Motion of markers in the middle or lower lobes

As shown in Fig. 6, a slight variation in the mean effective range along the LR direction for the five setups was observed in the middle or lower lobe markers, with values between 2.18 mm and 2.98 mm; however, these differences were also not statistically significant (see The *p* values in Fig. 6).

The spread of the effective ranges for this group was greater than that for the upper lobe markers, which had standard deviations of 1.56–2.70 mm.

Shown in Fig. 7 are the effective ranges in the CC direction for the middle or lower lobe markers. Although the two setups without SBF had mean effective ranges greater than 10 mm and the mean effective ranges for the SBF setup and the SBF + diaphragm setup were less than 10 mm, the differences in the mean effective range between the setups were not statistically significant. The use of the Abches for this group of patients resulted in a mean effective range of about 13 mm. The standard deviations of the effective ranges in the CC direction were between 5.56 mm and 6.37 mm.

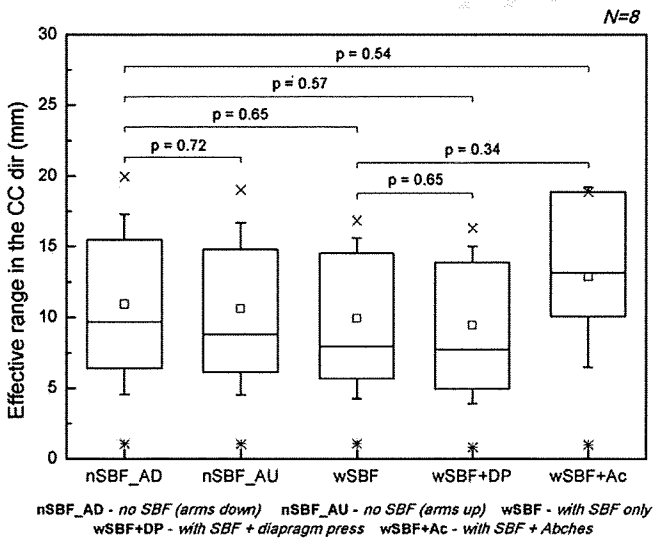

Fig. 7. The effective range along the craniocaudal direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

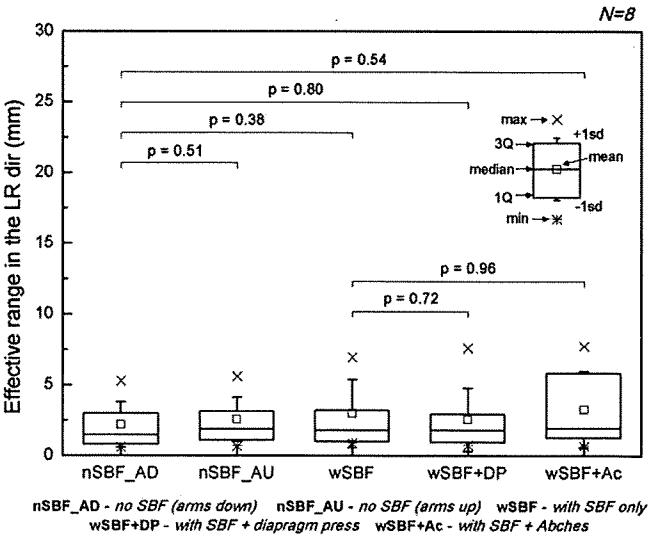

Fig. 8. The effective range along the anterior-posterior direction of the gold markers in the middle or lower lobes of the lung. Also indicated are the *p* values obtained from comparison of the effective ranges obtained in each patient setup.

The effective ranges in the AP direction for the middle or lower lobe markers were also greater than their upper lobe counterparts. The mean effective ranges shown in Fig. 8 for the five patient setups are between 3.61 mm and 5.04 mm with standard deviations between 2.45 mm and 4.81 mm. Again, no significant differences were noted among the five setups. The setup including the Abches had the largest mean effective range of 5.04 ± 4.81 mm.

DISCUSSION

In the present study, the real-time tracking capability of our RTRT system was used to determine the three-dimensional motion of fiducial gold markers embedded near or at the tumor to determine whether the respiration-induced motion of these markers can be controlled in free and restricted breathing setups. With the RTRT system, we were able to determine the instantaneous displacement of fiducial markers near the tumor, as has been done in previous studies ~~(7, 15, 20)~~, as well as the full range of motion of these markers. This allowed a more comprehensive evaluation of the feasibility of controlling respiratory-induced motion by using an SBF, diaphragm press and breathing cycle monitor.

The motions of fiducial markers were found to be highly patient-dependent and were influenced by the location where the markers were embedded in the lung. In general, markers in the upper lobes exhibited a smaller range of motions along the LR, CC, and AP directions compared with the motions of the markers in the lower lobes, which are consistent with the previous results reported by Seppenwoolde *et al.* (3) and Onimaru *et al.* (16). The average effective ranges of marker motion in the present study were comparable with the amplitudes obtained in the three-dimensional analysis by Seppenwoolde *et al.* (3) of tumor motion in the lung in a setup without SBF and with the patient's arms down.

The markers in the upper lobe of the lung exhibited ranges of motions, which did not vary significantly irrespective of the patient setup used. Additionally, their maximum effective ranges, which were all observed in the CC direction, were <10 mm. Engelsmann *et al.* (21) have previously reported that respiration-induced tumor motion of up to 10 mm does not drastically change the dose distribution. Thus, the patient breathing control may no longer be necessary for the majority of tumors in the upper lobes of the lung.

The markers in the middle or lower lobes of the lung exhibited larger motion in the CC direction and larger spread in the individual effective ranges in the LR, CC, and AP directions. Thus, respiration-induced tumor motion management for tumors in the lower lobes is worth considering, if possible (21).

We evaluated five patient setups in this study with the goal of reducing respiration-induced tumor motion; however, we found that the effective range of marker motions in the lower lobes of the lung was not significantly different among these setups. This result is different from the pioneering studies of Lax *et al.* (7) and Negoro *et al.* (9), which attempted to limit the abdominal motion of patients using the SBF and a diaphragm press. However, the comparisons between setups with or without a diaphragm press in the two aforementioned studies were done with a smaller number of patients compared with the present study (7, 8). Lax *et al.* noted that the diaphragmatic motion was reduced from a range of 1.5–2.5 cm to a range of 0.5–1.0 cm in 17 patients evaluated using fluoroscopy (7). Negoro *et al.* found that tumor motion in the CC direction was reduced from 8–20 mm for the setup with SBF down to only 2–10 mm for the setup using SBF and diaphragm press in 10 patients (9). However, they also had 1 patient whose tumor movement of 7 mm increased to 10 mm upon the use of diaphragm control. Compared with the previous visual measurement using AP fluoroscopy, the present study measured the three-dimensional motion of the internal fiducial markers with more objective and reproducible methods. Thus the discrepancy in the results between these pioneering works and the present study may have been related to the methods used or the precision of the measurements, together with other factors such as the patient background (*e.g.*, tumor stage, location of tumors).

Additionally, although the tracking sessions were performed using a random sequence of patient setups, this may not have completely eliminated some bias due to patient setup, since by the time the patient goes through the last setup, he or she would have been on the couch for at least 20 min longer compared with the first setup. We also cannot neglect the possibility that some patients might have benefited from any of the setups evaluated in this study because of the relatively small patient population. However, it is not possible from our study to recommend the use of the SBF alone or in combination with the diaphragm press or the Abches as a universally effective method to control respiratory intrafractional organ motion.

In conclusion, our RTRT measurement of the effective range of motion of fiducial markers showed that using the SBF, the diaphragm press, or a breathing cycle monitor for the purpose of controlling the patient breathing does not generally result in smaller effective marker ranges. Whether these patient setups will be effective in reducing respiratory-induced organ motion should be examined for individual patients before using them in the radiotherapy.

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CLINICAL INVESTIGATION

OUTCOMES IN PATIENTS WITH EARLY-STAGE HYPOPHARYNGEAL CANCER TREATED WITH RADIOTHERAPY

RYO-ICHI YOSHIMURA, M.D.,*† YOSHIKAZU KAGAMI, M.D.,* YOSHINORI ITO, M.D.,* MASAO ASAI, M.D.,‡ HIROSHI MAYAHARA, M.D.,* MINAKO SUMI, M.D.,* AND JUN ITAMI, M.D.*

Division of *Radiation Oncology and ‡Head and Neck Surgery, National Cancer Center Hospital, and †Department of Diagnostic Radiology and Oncology, Head and Neck Reconstruction Division, Graduate School, Tokyo Medical and Dental University, Tokyo, Japan

Purpose: To analyze the outcome in patients with early-stage hypopharyngeal cancer (HPC) who were treated with radiotherapy (RT).

Methods and Materials: Between February 1988 and February 2007, 77 patients with Stage I or Stage II HPC underwent definitive RT in the Division of Radiation Oncology at the National Cancer Center Hospital. Eleven of the patients received local irradiation, and the other 66 patients received elective bilateral neck irradiation and booster irradiation to the primary lesion. The median follow-up period for all the patients was 33 months from the start of RT, ranging from 3 to 229 months.

Results: The rates of overall survival, HPC-specific survival, HPC recurrence-free survival, and local control with laryngeal voice preservation for the 77 patients at 5 years were 47%, 74%, 57%, and 70%, respectively. The survival rates were not affected by the patient characteristics or treatment factors, but the RT field was significantly correlated with local control in a multivariate analysis. Seven of the patients had Grade 3 or greater complications, but these complications occurred after salvage surgery in 6 of the patients. Of the 77 patients, 83% had synchronous or metachronous malignancies, but these malignancies did not influence the survival of the patients if the malignancies were detected at an early stage.

Conclusion: RT is an appropriate treatment method for early-stage HPC. However, because synchronous or metachronous malignancies occur at a relatively high frequency, careful follow-up and the early detection of such malignancies are critical. © **2009 Elsevier Inc.**

Hypopharyngeal cancer, Radiotherapy, Synchronous malignancy, Metachronous malignancy.

INTRODUCTION

Patients with hypopharyngeal cancer (HPC) are often first diagnosed at an advanced stage. Because the diagnosis of early-stage HPC is relatively rare, few reports have analyzed the treatment results of early-stage HPC; thus, the optimal treatment for this condition remains uncertain (1).

Foote (2) reported that treatment options for early-stage HPC included endoscopic removal, open function-sparing partial laryngopharyngectomy, total laryngectomy with partial pharyngectomy, and radiotherapy (RT); factors in treatment selection were reported to be the extent and volume of the tumor (including anterior commissure involvement), patient preference (including occupational considerations), patient age, comorbid illnesses, patient compliance, voice quality, physician experience and skill, previous head-and-neck malignancy, risk of a second head-and-neck primary cancer, treatment cost, and physician and institutional biases.

At the National Cancer Center Hospital, patients with Stage I or II HPC are often treated with RT alone. In this study, we reviewed the data on patients who were treated with RT for early-stage HPC and analyzed the outcomes in these patients.

METHODS AND MATERIALS

Patient characteristics

Between February 1988 and February 2007, 77 patients with Stage I (T1N0M0) or Stage II (T2N0M0) HPC underwent RT in the Division of Radiation Oncology at the National Cancer Center Hospital. These patients consisted of 6 women and 71 men, ranging in age from 42 to 80 years (median, 63 years) (Table 1). All the tumors were diagnosed as squamous cell carcinoma by histopathologic examination of the biopsy specimens, and each tumor was staged retrospectively according to the 2002 UICC TNM classification system based on a complete patient history and physical

Reprint requests to: Ryo-ichi Yoshimura, M.D., Department of Diagnostic Radiology and Oncology, Head and Neck Reconstruction Division, Graduate School, Tokyo Medical and Dental University, 1-5-45, Yushima Bunkyo-ku, Tokyo 113-8519, Japan. Tel: +81) 3-5803-5311; Fax: (+81) 3-5803-0147; E-mail: ysmrmrad@tmd.ac.jp

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Table 1. Patient characteristics

Characteristic	Stage I (n = 42)	Stage II (n = 35)
Sex		
F	2	4
M	40	31
Age (y)		
Range (median)	42–80 (63)	48–79 (63)
HPC site		
Postcricoid region	6	6
Pyriform fossa	30	20
Posterior wall	6	9
Radiotherapy field and dose		
Local	6	5
Dose range (median) (Gy)	60–66 (60)	60–70 (61)
Locoregional	36	30
Primary dose range (median) (Gy)	58–70 (66)	60–70 (66)
Subclinical dose range (median) (Gy)	32–46 (40)	20–50 (40)
Concurrent chemotherapy		
CDDP + 5-FU	10	5
TS-1	1	0

Abbreviations: HPC = hypopharyngeal cancer; CDDP = cisplatin; 5-FU = 5-fluorouracil; TS-1 = tegafur-gimeracil-oteracil potassium.

examination record. The primary sites were the pyriform fossa (PS) in 50 patients (65%), the posterior wall (PW) in 15 (19%), and the postcricoid region (PC) in 12 (16%). At the time when the HPC was found, 21 patients (27%) had symptoms: 12 patients experienced pain in their pharynx, 9 experienced discomfort in their pharynx, and 1 patient experienced a change in his voice (hemilarynx fixation was not observed). Fifty-two patients (68%) were asymptomatic; their HPCs were found by gastrointestinal endoscopy performed as part of a follow-up examination for metachronous malignancies treated before to the diagnosis of HPC in 38 patients (49%: esophageal cancer in 31, gastric cancer in 2, oropharyngeal cancer in 2, oral cancer in 2, and esophageal and gastric cancer in 1), an examination performed before the treatment of some other disease in 10 patients (13%: esophageal cancer in 7, oral cancer in 1, gastric ulcer in 1, and pneumonia in 1), and as part of a general health examination in 4 patients. The symptoms of the remaining 3 patients were not documented.

Treatment

All the patients underwent definitive RT. Either a 4-MV or a 6-MV linac X-ray was used to administer a daily dose of 2 Gy 5 days a week, with a total dosage of 58–70 Gy (median, 66 Gy). A shell was used to immobilize the patient's head, and simulation X-ray radiographs or computed tomography simulation were used to determine the radiation portals and techniques. Local irradiation of the primary site was performed using parallel-opposed lateral fields in 11 patients with a total radiation dose of 60–70 Gy (median, 60 Gy). Elective bilateral neck irradiation was performed in 66 patients using parallel-opposed lateral fields with or without a matched anterior lower neck field or anterior and lateral wedge fields, with a total radiation dose of 20–50 Gy (median, 40 Gy). After the neck irradiation, the radiation to the primary lesion was boosted using a reduced parallel-opposed lateral field, with a total radiation dose of 10–40 Gy (median, 22 Gy).

Chemotherapy was administered concurrently with the RT in 16 patients for the treatment of synchronous cancers (esophageal cancer in 15, and oropharyngeal and laryngeal cancer in 1). Continuous infusions of 5-fluorouracil (5-FU; 600–1,250 mg/day; median, 1,100 mg/day) were given on the first 4 days of weeks 1 and 5 in combination with cisplatin (60–125 mg; median, 110 mg) on the first day of weeks 1 and 5 in the 15 patients with esophageal cancer, and TS-1 (100 mg/day) was successively used for 3 weeks in the 1 patient with oropharyngeal and laryngeal cancers.

Analysis

The median follow-up period was 33 months from the start of RT, ranging between 3 and 229 months. Fifteen patients were observed for less than 12 months: 3 patients died of HPC, 9 died of other cancers, 2 died of unknown reasons, and 1 was alive with another cancer. The median follow-up period for the 35 surviving patients who did not experience a recurrence was 48 months (range,10–229 months.

The overall, HPC-specific, and HPC recurrence-free survival rates and local control rate were calculated using the Kaplan-Meier method. Univariate and multivariate analyses were performed using the log-rank test and the Cox proportional hazards test. A p value of <0.05 and <0.007 was considered statistically significant in the univariate analyses and the multivariate analysis, respectively, resulting in an overall significance level of 5% (3).

Complications were assessed according to the Common Terminology Criteria for Adverse Events v3.0

RESULTS

Survival

The 5-year overall and HPC-specific survival rates for all 77 patients were 47% and 74%, respectively (Fig. 1). Thirty-nine patients died between 3.1 and 191 months (median, 15 months) after the start of RT; the causes of death were HPC in 13 patients who died 11–50 months (median, 15 months) after the start of RT, other malignancies in 16 patients (esophageal cancer in 9, lung cancer in 2, laryngeal

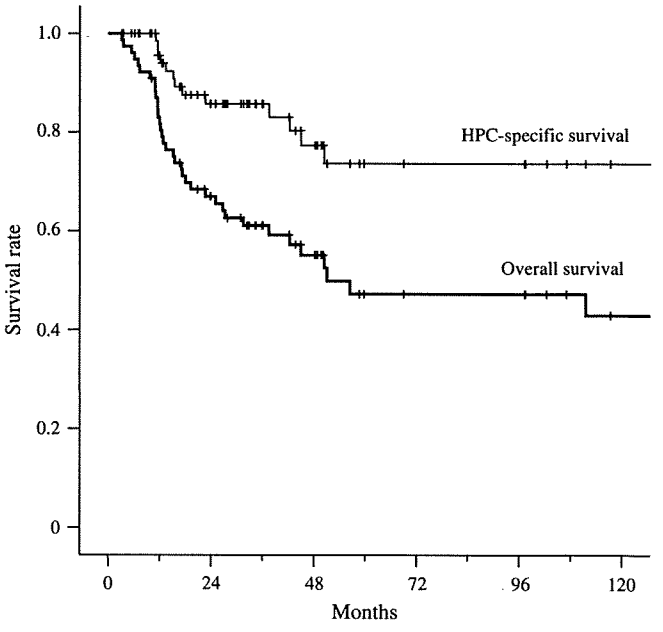

Fig. 1. Overall and hypopharyngeal cancer (HPC)–specific survival for all 77 patients.

Table 2. Overall and HPC-specific survival rates according to patient and clinical factors

Factors		*n*	Overall survival			HPC-specific survival		
			5-year (%)	Univariate *p*	Multivariate *p*	5-year (%)	Univariate *p*	Multivariate *p*
Total		77	47			74		
Sex	F	6	33			40		
	M	71	48	0.27	0.90	76	0.009	0.39
Age (y)	≤65	44	57			72		
	>65	33	34	0.12	0.042	77	0.96	0.60
HPC stage	I	42	52			85		
	II	35	43	0.43	0.18	62	0.024	0.032
HPC site	PC	12	52			59		
	PS	50	53			87		
	PW	15	27	0.052	0.058	43	0.005	0.064
RT field	Local	11	46			56		
	Locoregional	66	48	0.47	0.09	80	0.24	0.18
RT dose:	≤65	35	38			67		
primary (Gy)	>65	42	58	0.12	0.56	83	0.57	0.62
Concurrent CRT	Yes	16	23			69		
	No	61	53	0.085	0.029	74	0.92	0.22

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

cancer in 1, oropharyngeal cancer in 1, oral cancer in 1, renal cancer in 1, and malignant lymphoma in 1) who died 3.1–191 months (median, 12 months) after the start of RT, and other reasons in 10 patients (infectious pneumonia in 2, heart failure in 1, rupture of an abdominal aortic aneurysm in 1, suicide in 1, and unknown in 5) who died 3.5–57 months (median, 15 months) after the start of RT.

The relations between clinical factors and the overall and HPC-specific survival rates are shown in Table 2. Overall survival was not affected by any patient characteristics or treatment factors. Disease stage and primary site were significant factors for HPC-specific survival in the univariate analysis (disease stage, $p = 0.024$; primary site, $p = 0.005$), and the HPC-specific survival rate in patients with Stage II HPC or a primary site of PC or PW was much lower than that in patients with Stage I or a primary site of PS, but no factors were significant in the multivariate analysis.

Course of HPC

The 5-year HPC recurrence-free survival rate and local control rate with laryngeal voice preservation for all 77 patients were 57% and 70%, respectively (Fig. 2). One patient's tumor remained after RT, 1 patient was diagnosed with lymph node recurrence during RT, and 22 patients experienced disease recurrence 4–51 months (median, 10 months) after the start of RT. Thirteen (54%) of the 24 patients had local recurrences, 8 (33%) had lymph node recurrences, and 3 (13%) had local and lymph node recurrences. Distant metastases were observed in 6 patients (lung in 3, mediastinum in 2, and bone in 1) 11–49 months (median, 19 months) after the start of RT for HPC, but none of these metastases were found before local or lymph node recurrence. The relations between the clinical factors and the HPC recurrence-free survival rate and local control rate with laryngeal voice preservation are shown in Table 3. The HPC recurrence-free survival rate in patients with Stage I HPC or a locoregional RT field was significantly higher than that in patients with Stage II HPC ($p = 0.026$) or a local RT field ($p = 0.036$) in the univariate analysis, but no factors were significantly associated with HPC recurrence-free survival in the multivariate analysis. The primary site and RT field significantly affected the rate of local control with laryngeal voice preservation in the univariate analysis (primary site, $p = 0.036$; RT field, $p = 0.018$), and the local control rate in patients with irradiation of a locoregional field was significantly higher than that in patients with irradiation of a local field in the multivariate analysis ($p = 0.006$).

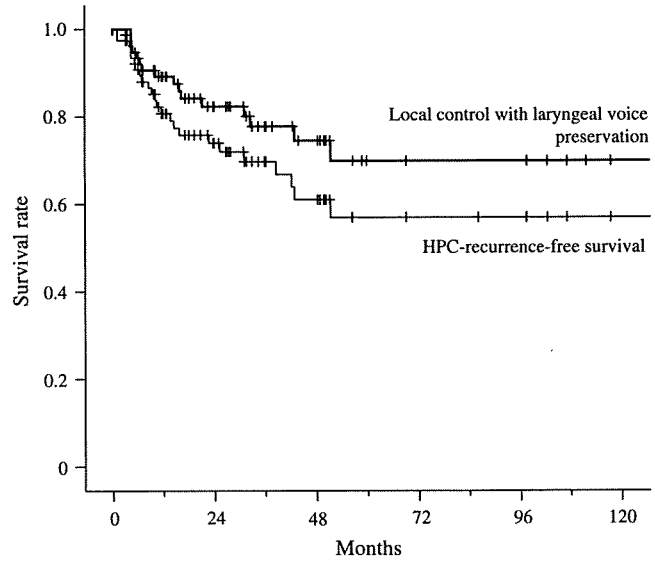

Fig. 2. Hypopharngeal cancer (HPC) recurrence-free survival and local control with laryngeal voice preservation for all 77 patients.

Table 3. HPC recurrence-free survival rate and local control rate with laryngeal voice preservation according to patient and clinical factors

Factors		n	HPC recurrence-free survival			Local control with voice preservation		
			5-year (%)	Univariate p	Multivariate p	5-year (%)	Univariate p	Multivariate p
Total		77	57			74		
Sex	F	6	50			67		
	M	71	57	0.28	0.90	70	0.35	0.98
Age (y)	≤65	44	49			65		
	>65	33	69	0.36	0.42	79	0.41	0.52
HPC stage	I	42	75			84		
	II	35	41	0.026	0.044	56	0.055	0.048
HPC site	PC	12	47			63		
	PS	50	62			76		
	PW	15	52	0.06	0.18	60	0.039	0.056
RT field	Local	11	38			42		
	Locoregional	66	59	0.036	0.10	73	0.018	0.006
RT dose: primary (Gy)	≤65	35	53			68		
	≥66	42	60	0.78	0.81	72	0.99	0.91
Concurrent CRT	Yes	16	56			83		
	No	61	56	0.4	0.96	68	0.5	0.52

Abbreviations: HPC = hypopharyngeal cancer; RT = radiotherapy; PC = postcricoid region; PS = pyriform fossa; PW = posterior wall; CRT = chemoradiotherapy.

Of 16 patients with local recurrence or local and lymph node recurrence, 12 underwent salvage surgery (total laryngopharyngectomy with or without neck resection in 11 and partial pharyngectomy in 1). One patient underwent chemotherapy, 2 received no treatment, and 1 patient was lost to follow-up after a local recurrence was detected. Of the 8 patients with lymph node recurrence, 6 underwent neck dissection, 1 patient underwent RT, and 1 patient received no treatment. All 3 patients who did not undergo salvage surgery died within 15 months. Only 5 patients with local recurrence and 3 patients with lymph node recurrence responded after surgery, and the 5-year overall survival rate for the 12 patients who were treated with salvage surgery was 39 % (Fig. 3). The difference in overall survival according to salvage therapy was significant ($p = 0.003$).

Of the total of 77 patients, 7 (9%) had Grade 3 or greater complications related to the treatment for HPC, and 6 of these patients experienced their complications after salvage surgery: 2 patients died as a result of arterial injury (Grade 5), 1 had a life-threatening arterial injury (Grade 4), 1 had an arterial injury requiring repair or revision (Grade 3), and 2 developed pharyngeal fistulas requiring operative intervention (Grade 3). One patient who did not have a recurrence developed otitis media with discharge (Grade 3).

Synchronous and metachronous malignancy

Of the 77 patients, 64 (83%) had synchronous or metachronous malignancies; the distribution of these malignancies is shown in Fig. 4. Forty-two had metachronous malignancies diagnosed before they underwent treatment for HPC, and 33 (79%) had esophageal cancer. These malignancies were under control at the start of treatment for HPC, but 19 of these patients had synchronous malignancies and/or metachronous malignancies after RT for HPC.

Overall, 23 patients had synchronous malignancies, 26 had metachronous malignancies after RT for HPC, and 8 had both synchronous and metachronous malignancies. The overall survival rate in the patients whose synchronous and/or metachronous malignancies were detected at an early stage (59% at 5 years) was not different from that in patients without synchronous or metachronous malignancies (48% at 5 years), but the survival rate in the patients whose synchronous or metachronous malignancies were detected at an advanced stage (17% at 5 years) was much lower than that in the patients without synchronous or metachronous malignancies

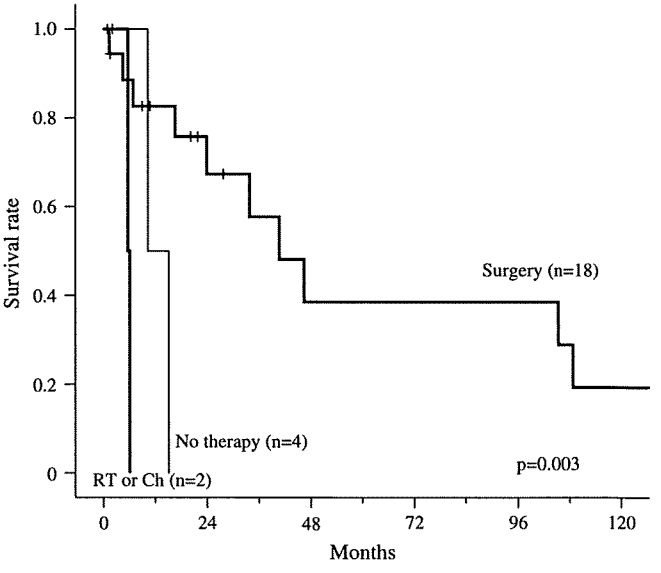

Fig. 3. Overall survival after hypopharyngeal cancer (HPC) recurrence according to salvage therapies (RT = radiotherapy; Ch = chemotherapy).

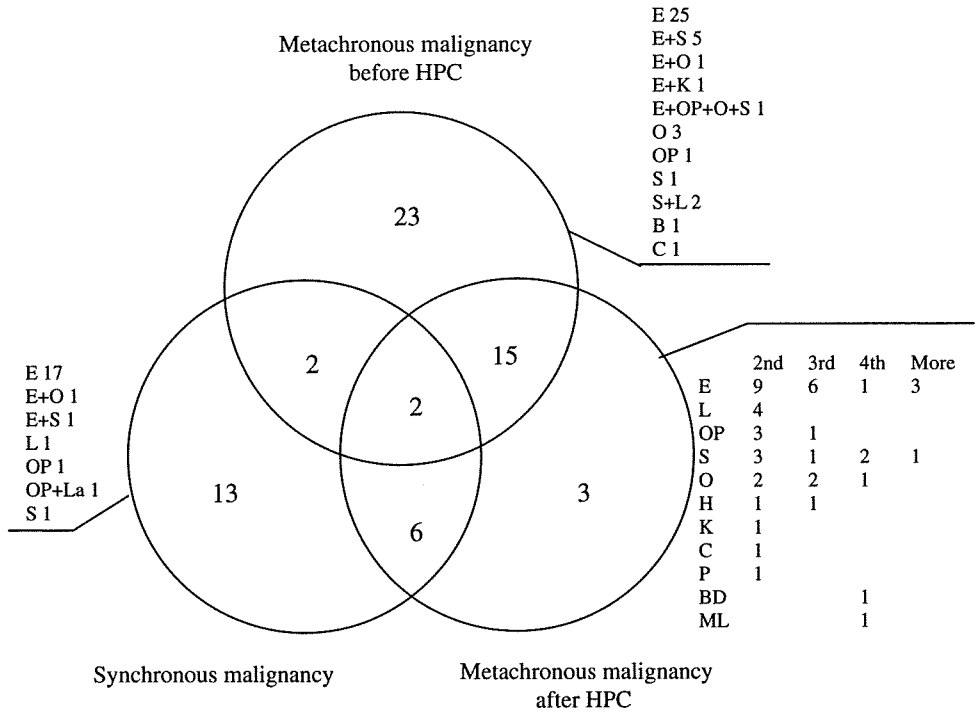

Fig. 4. Number of hypopharyngeal cancer (HPC) patients with synchronous and metachronous malignancy (E = esophagus; S = stomach; O = oral cavity; K = kidney; OP = oropharynx; B = bladder; C = colon; La = larynx; H = liver; P = prostate; BD = bile duct; ML = malignant lymphoma).

or the patients with early-stage synchronous or metachronous malignancies (Fig. 5). Advanced-stage synchronous malignancies were seen in 5 patients with esophageal cancer. All 5 patients received concurrent chemoradiotherapy, but died of their synchronous malignancies 5–13 months (median, 11 months) after the start of RT. Advanced-stage metachronous malignancies were seen in 7 of the 26 patients (lung cancer in 2, oropharyngeal cancer in 2, esophageal cancer in 1, renal cancer in 1, and prostate cancer in 1) 7.5–153 months (median, 12 months) after the start of RT for HPC. Five of these patients died of their advanced-stage metachronous malignancies (lung cancer in 2, oropharyngeal cancer in 1, esophageal cancer in 1, and renal cancer in 1).

The rates of metachronous malignancy after RT for HPC and HPC recurrence after RT, as calculated using the Kaplan-Meier method, are shown in Fig. 6. The rate of HPC recurrence increased rapidly for 2 years after RT and reached a plateau at 4 years. The rate of metachronous malignancy increased year by year after RT. The rate of second primary malignancy was 32% at 5 years and 56% at 10 years, that of third

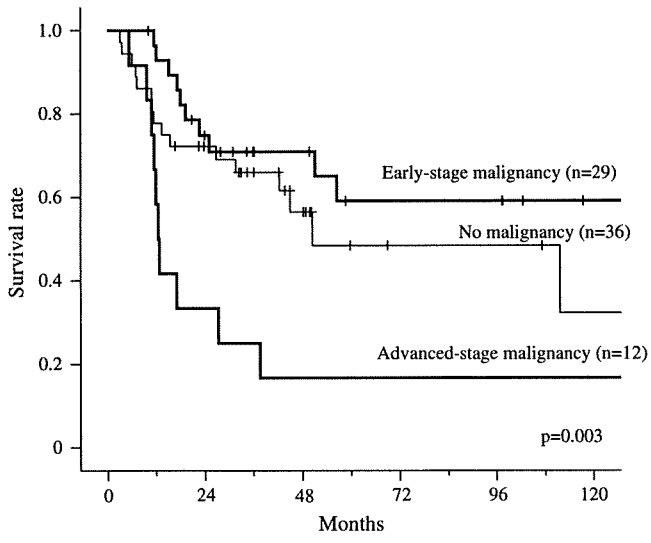

Fig. 5. Overall survival for patients with or without synchronous or metachronous malignancy after radiotherapy for hypopharyngeal cancer (HPC).

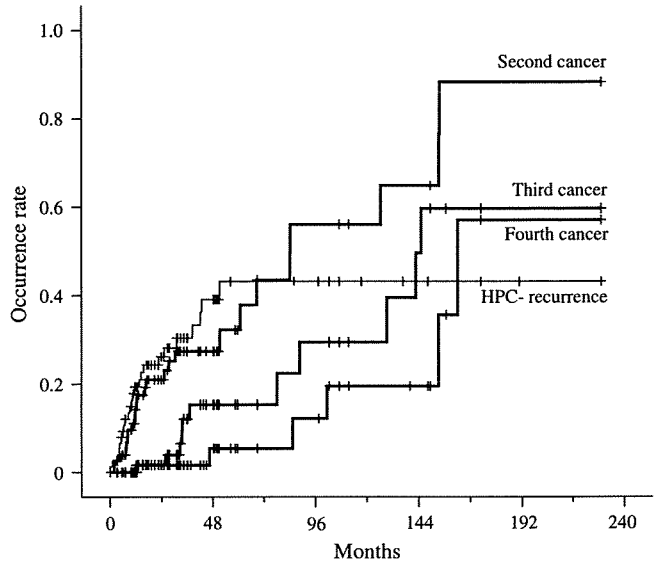

Fig. 6. Rates of hypopharyngeal recurrence and metachronous malignancy after radiotherapy.

malignancy was 15% at 5 years and 29% at 10 years, and that of fourth malignancy was 5% at 5 years and 19% at 10 years.

DISCUSSION

Radiotherapy has long been recognized as effective for early-stage squamous cell carcinoma of the hypopharynx (1, 2). However, few reports have analyzed large numbers of patients undergoing RT for early-stage HPC without lymph node metastasis, and to our knowledge, no reports have statistically analyzed predictors of survival. Concurrent chemoradiotherapy and the computed tomography–based tumor volume have been reported to be strong predictors of local control in HPC patients, including patients with advanced-stage HPC, but whether these factors affect local control or overall survival in patients with early-stage HPC remains unclear (1, 4). In our study, only the RT field significantly affected the local control rate with laryngeal voice preservation in the multivariate analysis, and a locoregional radiation field was appropriate for patients with early-stage HPC. Although disease stage affected the HPC-specific survival rate and the HPC recurrence-free survival rate and the primary site affected the HPC-specific survival rate and the local control rate in univariate analyses, these factors were not significant in a multivariate analysis. The patient and tumor characteristics had no effect on the treatment outcome of RT for early-stage HPC.

Nakamura *et al.* (1) reported the results of an analysis of 115 patients who underwent definitive RT for Stage I and Stage II HPC in a multi-institution study. Their overall and disease-specific survival rates at 5 years were 66% and 77.4%, respectively, and the progression-free survival and local control rates were 67.6% and 76.5% for patients with Stage I, and 51.5% and 62.6% for patients with Stage II at 5 years. Nakamura *et al.* (5) also reported an analysis of 43 other patients who underwent RT with or without salvage surgery for Stage I and II HPC in a single-institution study; the 5-year overall and disease-specific survival rates were 70.4% and 89.5%, respectively. Rabbani et al. (6) analyzed 123 patients with Stage T1–T2N0–N3M0 of the pyriform sinus; the 5-year overall survival, cause-specific survival, and local regional control rate for the 26 patients with T1N0M0 or T2N0M0 HPC were 58%, 85%, and 86%, respectively. In our study, the 5-year HPC-specific survival rate (74%), the HPC recurrence-free survival rate (57%), and the local control rate with laryngeal voice preservation (70%) were similar to these previously reported values, but the 5-year overall survival rate (47%) in our study was lower than the previously reported values (1, 5, 6). We suspect that the larger number of patients with synchronous and metachronous malignancies in the present study may be related to the lower rate of overall survival, compared with the results of previous reports.

The incidence of synchronous and metachronous malignancy in HPC patients has been reported to be approximately 20%, and the most common sites were the lung, the esophagus, and the urinary tract (7, 8). However, patients with early-stage primary tumors have a higher risk of developing a second primary tumor than do patients with advanced tumors because of their longer survival period (7); Nakamura et al. (1, 5) reported that the incidence of synchronous or metachronous malignancy in patients with early-stage HPC was 46.5–56.5%. In our study, 83% (64/77) of the patients had synchronous and/or metachronous malignancy and 53% (41/77) had synchronous malignancy and/or metachronous malignancy after RT for HPC; most of these malignancies were esophageal cancer. Because 54% (42/77) of these patients had a history of treatment for malignancy before the diagnosis of HPC, individual and/or environmental factors might have contributed to the formation of the multiple primary tumors in many of these patients (7). However, the overall survival rate for patients with early-stage synchronous malignancy and/or metachronous malignancy after RT for HPC was similar to that for patients without these malignancies, but the overall survival rate for patients with advanced-stage synchronous malignancy or metachronous malignancy after RT for HPC was significantly poorer. A more careful follow-up for detection of early-stage metachronous malignancy might have improved the overall survival rate in the present study.

The detection of early-stage HPC is as difficult as the detection of early-stage esophageal cancer, but the development of endoscopy has made both of these conditions detectable (9). In our study, HPC was diagnosed during gastrointestinal endoscopy examinations performed as pretreatment or follow-up examinations for other malignancies in 62% (48/77) of the patients. Recently, narrow band imaging has been reported to improve the diagnostic accuracy and sensitivity at which early-stage HPC can be detected (10). However, endoscopy techniques (*i.e.*, endoscopic laser resection) have been used only in a few institutions, and the indication for these treatments is unclear (9, 11). Although Shimizu *et al.* (9) performed endoscopic submucosal dissection in 4 patients with early-stage HPC and reported no local recurrences, no distant metastasis, and no early or late complications, Bernal-Sprekelsen *et al.* (11) performed endoscopic resection using a CO_2 laser and reported the need for a nasogastric feeding tube in 23.2% of the patients with small tumors, postoperative pneumonia in 5.7%, temporary postoperative coughing during oral intake in 28.1%, and severe swallowing difficulties in 3.8%. Thus, the factors associated with the occurrence and severity of various complications after endoscopic resection remain to be clarified (9).

In the present study, because we retrospectively analyzed the data of patients who underwent RT for early-stage HPC, we could not exclude some potential biases and study limitations from our results. However, we believe that RT is an appropriate treatment method for early-stage HPC, compared with surgical resection, because the outcome of RT was not affected by the patient or tumor characteristics in the present study, and cosmetic defects, swallowing disorders, aspiration pneumonia, and speech defects were avoided. Patients with early-stage HPC have a high risk of synchronous and metachronous malignancy, and their prognosis heavily depends on the development of such malignancies. However, if such malignancies are detected at an early

stage, patients whose HPC was treated using RT are often able to receive sufficient treatment for those malignancies, and their overall survival rate is as high as that in patients without these malignancies (1, 5, 6, 9). Patients with early-stage HPC should be carefully examined before and after the start of treatment and should be closely followed up at frequent intervals to ensure the early detection of synchronous and metachronous malignancies (7).

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ORIGINAL ARTICLE

Comparison of cisplatin and 5-fluorouracil chemotherapy protocols combined with concurrent radiotherapy for esophageal cancer

Toru Sakayauchi · Kenji Nemoto · Chikashi Ishioka
Hiroshi Onishi · Michinori Yamamoto
Tomoko Kazumoto · Masaoki Makino · Ryuji Yonekura
Jun Itami · Shigeru Sasaki · Gen Suzuki
Naofumi Hayabuchi · Hiroyasu Tamamura
Rikiya Onimaru · Shogo Yamada

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Abstract
Purpose. The optimal chemotherapeutic protocol for the treatment of esophageal cancer has not yet been established. This study was performed to identify the differences in toxicity and completion rates of various chemotherapy protocols with that goal in mind.
Materials and methods. A total of 61 patients with esophageal cancer were enrolled in this study between June 2002 and January 2004. The total radiotherapy dose was 64 Gy. Three chemotherapy protocols were used. Arm A comprised daily low-dose cisplatin (CDDP) and 5-fluorouracil (5FU) (CF protocol) (3 mg/m^2 and 180 mg/m^2, respectively). Arm B was intermediate between arm A and C (CDDP 7 mg/m^2 and 5FU 250 mg/m^2 on days 1–5, 8–12, 29–33, and 36–40). Arm C comprised two courses of standard CF (CDDP 70 mg/m^2 on day 1 and 5FU 600 mg/m^2/24 h on days 1–4).
Results. Although there were no significant differences in hematological toxicity between the protocols, leukocytopenia was slightly milder in arm A. Nausea was significantly more severe in arm C. The completion rate was higher in arm A. The 3-year survival rates were 40%, 31%, and 62%, respectively.
Conclusion. The daily low-dose CF protocol showed a trend of mild toxicity regarding leukocytopenia. However, we could not find statistical difference between arms. It also showed a better completion rate than the other two arms.

T. Sakayauchi (✉) · S. Yamada
Department of Radiation Oncology, Tohoku University School of Medicine, 1-1 Seiryomachi, Aoba-ku, Sendai 980-8574, Japan
Tel. +81-22-717-7312; Fax +81-22-717-7316
e-mail: sakayauchi-rad@umin.ac.jp

K. Nemoto
Department of Radiation Oncology, Yamagata University Faculty of Medicine, Yamagata, Japan

C. Ishioka
Department of Clinical Oncology, Tohoku University School of Medicine, Sendai, Japan

H. Onishi
Department of Radiology, Faculty of Medicine, University of Yamanashi, Yamanashi, Japan

M. Yamamoto
Department of Radiation Oncology, Kure Medical Center and Chugoku Cancer Center, Hiroshima, Japan

T. Kazumoto
Department of Radiology, Saitama Cancer Center, Saitama, Japan

M. Makino · R. Yonekura
Department of Radiology, Kagoshima Medical Center, Kagoshima, Japan

J. Itami
Department of Radiation Therapy and Oncology, International Medical Center of Japan, Tokyo, Japan

S. Sasaki
Department of Radiology, Shinshu University School of Medicine, Matsumoto, Japan

G. Suzuki · N. Hayabuchi
Department of Radiology, Kurume University School of Medicine, Kurume, Japan

H. Tamamura
Department of Nuclear Medicine, Fukui Prefectural Hospital, Fukui, Japan

R. Onimaru
Department of Radiology, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Key words Esophageal cancer · Chemoradiation therapy · Cisplatin · 5-Fluorouracil

Introduction

Concurrent chemoradiation therapy has been widely used for esophageal cancer. Cooper et al.[1] reported a 5-year survival rate of 26% in the group undergoing 50 Gy radiotherapy with chemotherapy consisting of cisplatin (CDDP) 75 mg/m^2 and 5-fluorouracil (5FU) 1000 mg/m^2. Today, this type of regimen, involving intermittent administration of CDDP and 5FU (standard CF protocol), is widely given; and it has been confirmed that it is better than radiotherapy alone.[2-4] Standard CF with radiotherapy is an effective form of treatment, although it is associated with relatively frequent, severe, acute toxicity.

On the other hand, daily administration of low-dose CDDP and 5FU (daily low-dose CF) with radiotherapy has been reported to result in less toxicity than standard CF.[5-11] Sasamoto et al.,[8] in a prospective study, showed less hematological toxicity in the daily low-dose group than in the standard CF group.

Furthermore, a new type of regimen, which would be classified as "intermediate CF" (between standard CF and daily low-dose CF) has emerged. Ohtsu et al.[12] reported 3-year survival of 23% with two courses of CDDP (40 mg/m^2 on days 1 and 8) and 5FU (400 mg/m^2/24 h on days 1–5 and 8–12).

However, to the best of our knowledge, there have been no prospective studies comparing the clinical outcomes of low-dose CF with standard CF. Thus, we tried to compare these three representative chemotherapy regimens (standard CF, daily low-dose CF, intermediate CF).

The purpose of this study was to evaluate the acute toxicities and completion rates of these three regimens using data obtained from our routine clinical work. Each participating institution used one of these three regimens as standard chemoradiation therapy for esophageal cancer. This study was supported by the Japanese Radiation Oncology Study Group (JROSG).

Materials and methods

Study design

This study was reviewed and approved by the review board of each participating institution, and all patients gave their written informed consent prior to enrolment in the study. The study was designed to evaluate differences in the acute toxicities and completion rates among the three chemotherapy protocols that were used as standard chemoradiation therapy in the daily clinical practice of each institution.

Chemotherapy arms

Three representative chemotherapy protocols were selected (standard CF, daily low-dose CF, intermediate CF). Each institution performed one of the chemotherapy regimens, which was then given concurrently with thoracic radiotherapy (64 Gy in 32 fractions).

These chemotherapy protocols, daily low-dose CF, intermediate CF, and standard CF, were named arm A, arm B, and arm C, respectively. The study schema is shown in Fig. 1.

Arm A involved daily low-dose CF (CDDP 3 mg/m^2/30 min and 5FU 180 mg/m^2/24 h) given on each day of radiotherapy. This regimen was based mainly on the report from Hsu et al.[5] in which study there was a 56% incidence of grade 3 leukocytopenia. Based on that study and other reports, we reduced the doses of the chemotherapeutic agents to less than those used in these previous studies to increase the completion rate.

Arm B consisted of CDDP 7 mg/m^2 and 5FU 250 mg/m^2/24 h on days 1–5, 8–12, and 29–33. This regimen was based on data from the study by Ohtsu et al.[12] As our total irradiation dose was higher than theirs and we did

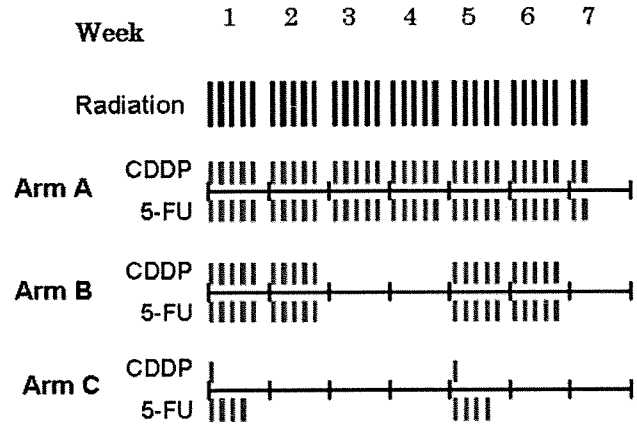

Fig. 1. Schema of the chemoradiation protocols. Radiation comprised 2.0 Gy/day, 5 days a week. Arm A [daily low-dose CDDP/5FU (CF) protocol]: CDDP (cisplatin) 3 mg/m^2/30 min + 5-fluorouracil (5FU) 180 mg/m^2/24 h on each day of radiotherapy. The total doses of CDDP and 5-FU were 96 and 5760 mg/m^2, respectively. Arm B (intermediate CF protocol): CDDP 7 mg/m^2 + 5FU 250 mg/m^2/24 h on days 1–5, 8–12, 29–33, and 36–40. Total doses of CDDP and 5FU were 140 and 5000 mg/m^2, respectively. Arm C (standard CF protocol): CDDP 70 mg/m^2 on days 1 and 29 + 5FU 600 mg/m^2/24 h on days 1–4 and 29–32. Total doses of CDDP and 5-FU were 140 and 4800 mg/m^2, respectively

not interpose radiotherapy, the dose of the chemotherapy was modified from their original regimen.

Arm C involved two courses of chemotherapy (CDDP 70 mg/m^2 on day 1 with 5FU 600 mg/m^2/24 h on days 1–4). This arm represents the standard CF protocol. The doses of CDDP and 5FU were slightly decreased for two reasons: Severe adverse effects occurred in 48% of patients in the Radiation Therapy Oncology Group (RTOG) 85–01 trial[1]; and the radiation dose in the present study was higher than that in the RTOG 85–01 trial.[1]

Thirteen JROSG member institutions were entered into the present study. Five were entered in arm A, five in arm B, and three in arm C.

Eligibility

Eligibility criteria included the following: (1) International Union against Cancer (UICC) TNM clinical stage I–IVA; (2) age between 20 and 80 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2; (3) adequate organ function—white blood cell (WBC) count >3000/mm^3, hemoglobin >8 g/dl, platelets >100 000/mm^3, total bilirubin <1.5 mg/dl, creatinine <1.0 g/dl, creatinine clearance >60 ml/min, no severe electrocardiogram changes (e.g., acute ischemic changes, poorly controlled arrhythmias); and (4) written informed consent to participate in the study. Exclusion criteria included esophageal perforation before treatment; history of another active cancer; or severe complications, such as poorly controlled heart disease, liver cirrhosis, diabetes, or infectious disease.

Overall, 61 patients (56 men, 5 women) with previously untreated esophageal squamous cell carcinoma were enrolled between June 2002 and January 2004. The details of the patients' characteristics are shown in Table 1. Two patients were excluded from the study before treatment began at their or their family's request. Two other cases that deviated from the eligibility criteria and another that deviated from the treatment protocol (excess radiation dose) were also excluded from the analysis.

Radiotherapy

We adopted 64 Gy of total irradiation dose based on the study by Minsky et al. (INT0122[13] and INT0123[14]). They compared 64.8 Gy and 50.0 Gy with chemotherapy and found no survival benefit with 64.8 Gy; however, they concluded that the dose escalation did not increase acute toxicities.

Two opposing anteroposterior fields with 6- to 20-MV photons, including the primary esophageal tumor, metastatic lymph nodes, and prophylactic lymph nodes, were irradiated with an initial dose of 40 Gy. The patients were treated 5 days per week with daily fractions of 2 Gy. The fields were extended approximately 4 cm longitudinally beyond the primary tumor margins with reference to radiotherapy planning computed tomography (CT) and endoscopic findings. The prophylactic area included bilateral supraclavicular fossa for patients with cervical and upper thoracic esophageal cancer and the root of the celiac artery for those with abdominal esophageal cancer.

After the initial radiotherapy dose of 40 Gy, a boost irradiation dose of 24 Gy to the macroscopic lesion was performed using the two opposing oblique fields to avoid the spinal cord.

Dose modifications

The chemotherapy dose was reduced by 50% if the WBC count was <2000/mm^3, the platelet count was <50 000/mm^3, the blood urea nitrogen (BUN) was >25 mg/dl, or the serum creatinine was >1.3 mg/dl. Fever >38°C was not considered tumor fever.

Table 1. Patients' characteristics

Characteristic	Arm A	Arm B	Arm C
Total no. of patients	20	27	14
Male/female	19/1	24/3	13/1
Age (years), median and range	69 (55–78)	68 (57–79)	58 (51–71)
Stage			
I	4 (20%)	2 (7%)	5 (36%)
IIA	4 (20%)	2 (7%)	0 (0%)
IIB	3 (15%)	4 (15%)	3 (21%)
III	7 (35%)	13 (48%)	5 (36%)
IV	2 (10%)	6 (23%)	1 (7%)

Statistics: age, $P = 0.079$; clinical stage, $P = 0.058$ (Kruskal-Wallis test)

Chemotherapy was canceled if the WBC count was <1000/mm^3, the platelet count was <30 000/mm^3, the BUN was >30 mg/dl, or the creatinine was >1.5 mg/dl.

Statistical analysis

The RTOG acute radiation morbidity criteria were used for evaluation of acute toxicities. Differences in toxicities and completion rates between arms were analyzed using the Kruskal-Wallis test.

Results

The incidence of acute toxicity in each arm is shown in Table 2. The differences in the incidence rates of grade 3/4 esophagitis between arms were not significant. Grade 4 esophagitis (esophageal perforation) was observed in one patient in arm A.

The incidence of Grade 3/4 leukocytopenia was slightly less in arm A than in the other arms, although the differences were not statistically significant (P = 0.051). The rate of grade 3/4 thrombocytopenia was lowest in arm A, although the differences between arms were not significant. Platelet transfusion was required in only one patient (arm B). There were no significant differences in the rate of anemia between arms.

Table 2. Adverse events

Adverse event	Arm A	Arm B	Arm C
Esophagitis	3 (18%)	3 (12%)	2 (14%)
Leukocytopenia	3 (18%)	7 (29%)	4 (29%)
Thrombocytopenia	0 (0%)	2 (8%)	1 (7%)
Erythrocytopenia	1 (6%)	2 (8%)	1 (7%)
Nausea	4 (24%)	4 (17%)	11 (79%)

All adverse events were grade 3/4 except for nausea, which was grade 2/3 [Radiation Therapy Oncology Group (RTOG) acute radiation morbidity criteria]

Nausea was significantly more severe in arm C (P < 0.01). There were no significant differences with regard to liver or renal function between arms, and there were no patients with grade 3/4 dysfunction among those included in the analysis.

One patient in arm C died of pneumonia during treatment. In this case, autopsy demonstrated that the cancer had disappeared. None of the other cases showed clinically significant respiratory symptoms (grade 2 or above).

Compliance

The completion rates of the patients in each arm were 100%, 74%, and 86%, respectively (P = 0.027). Of the 27 patients in arm B, 5 (19%) did not complete chemotherapy; two of these cases were due to myelosuppression, and the remaining three were due to renal dysfunction. Of the 14 patients in arm C, 2 (14%) did not complete therapy: one due to renal dysfunction and the other due to severe pneumonia. Overall, tolerability appeared to be better in arm A than in the other arms.

Survival

Although the observation period was relatively short and the number in each arm was small, a survival analysis was performed. The median observation period for all survivors was 45 months (range 7–70 months). The median survival time (MST) of all patients was 23 months, and the 3-year overall survival rate was 42%. The 3-year survival rates of arms A, B, and C were 40%, 31%, and 62%, respectively (Fig. 2). The 3-year disease-free survival rate of all patients was 29%, and those for each arm were 40%, 22%, and 27%, respectively. However, it was not possible to compare the survival rates among the arms because the patients' backgrounds differed.

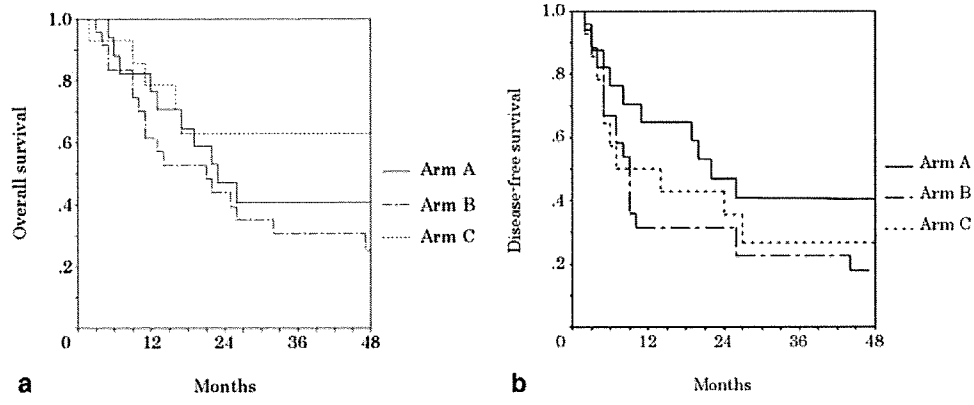

Fig. 2. **a** Overall patient survival (Kaplan-Meier). The 3-year survival rates for arms A, B, and C were 40%, 31%, and 62%, respectively. **b** The 3-year disease-free survival rates for arms A, B, and C were 40%, 22%, and 27%, respectively

There was one patient (arm B) with sudden cardiac arrest within 3 months after treatment. This patient had a past history of old myocardial infarction. The cause of death was unclear because no autopsy was performed; however, no obvious causal link between this episode and the protocol treatment was evident.

Discussion

Randomized controlled studies comparing chemoradiation therapy with radiotherapy alone for esophageal cancer have been reported since the 1990s.[1–4] Cooper et al.[1] reported in the RTOG 85–01 trial that the 5-year survival rate was 26% in the chemoradiation group undergoing 50-Gy radiotherapy with concurrent CDDP 75 mg/m^2 and 5FU 1000 mg/m^2/24 h chemotherapy. It has been confirmed that this regimen (standard CF) is better than radiotherapy alone, and it has been widely used. However, the regimen is associated with relatively high acute toxicity, which limits its use in elderly patients and in patients whose general condition is poor.

On the other hand, daily low-dose CF has been used for esophageal cancer with the expectation that it would have less acute toxicity. Hsu et al.[5] reported a 3-year survival rate of 24% in patients given chemoradiation therapy with daily CDDP and 5FU doses of 6 mg and 225 mg, respectively. They noted that 72% of patients could complete their planned chemoradiation therapy without interruption.

Recently, a daily low-dose CF protocol has been widely adopted in a number of institutions in Japan, and there have been many reports of its use [6–11] (Table 3). Furthermore, outcomes following daily low-dose CF may equal those following standard CF. Ito et al.[7] reported a 2-year survival of 24%, and they also noted that 85% of patients were able to complete their planned therapy. Sai et al.[9] reported that the median survival time was 15 months in the daily low-dose CF group and 14 months in the standard CF group. They also found that 79% of the daily low-dose CF group could complete

Table 3. Previous reports for chemoradiation therapy for esophageal cancer

Study	Year	Regimen (radiotherapy/CDDP/5FU)	MST (months)	Survival
Daily low-dose CF group				
Hsu[5]	1999	50–60 Gy CDDP 6 mg/m^2 5FU 225 mg/m^2	8	3-year: 24%
Itoh[7]	1999	60 (40.0–80.2) Gy + CDDP 3–6 mg/m^2 + 5FU 200 mg/m^2	10–11(?)	2-year: 24%
Sasamoto[8]	2007	60–70 Gy+ + CDDP 3–6 mg/m^2 + 5FU 250–300 mg/m^2	19	2-year: 40% 3-year: 32% 5-year: 20%
Sai[9]	2004	60 Gy + CDDP 5 mg/m^2 + 5FU 200 mg/m^2	15	2-year: 50%
Intermediate CF group				
Ohtsu[12]	1999	60 Gy + CDDP 40 mg/m^2 + 5FU 400 mg/m^2	9	3-year: 23%
Standard CF group				
Cooper[1] (RTOG 85-01)	1992	50 Gy + CDDP 75 mg/m^2 + 5FU 1000 mg/m^2*4	14.1	5-year: 26%
Hironaka[15]	2003	60 Gy + CDDP 80 mg/m^2 + 5FU 800 mg/m^2	33	3-year: 49% 5-year: 46%
Minsky[14] (INT0123)	2002	64.8 Gy + CDDP 75 mg/m^2 + 5FU 1000 mg/m^2	13	2-year: 31%
Sai[9]	2004	60 Gy + CDDP 70 mg/m^2 + 5FU 200 mg/m^2	14	2-year: 39%
Minsky[13] (INT0122)	1999	64.8 Gy CDDP 75 mg/m^2 5FU 1000 mg/m^2	20	3-year: 30% 5-year: 20%

MST, median survival time; CF, CDDP + 5FU protocol; CDDP, cisplatin; 5FU, 5-fluorouracil

their regimen, whereas 67% completed their regimen in the standard CF group.

However, the advantages of daily low-dose CF compared with standard CF have not been confirmed because there has been a paucity of prospective comparative studies. Furthermore, a new regimen that is between standard CF and daily low-dose CF, called intermediate CF, has emerged. Ohtsu et al.[12] administered two courses of chemotherapy consisting of CDDP 40 mg/m^2 on days 1 and 8 and 5FU 400 mg/m^2 on days 1–5 and 8–12, with total irradiation of 60 Gy.

Therefore, in the present study, because the ideal chemotherapy regimen with radiotherapy for esophageal cancer has not been established, we compared the acute toxicities and completion rates of these regimens.

The rate of grade 3/4 esophagitis ranged from 12% to 18% in each arm, with no significant differences between treatment groups. Grade 4 esophagitis (esophageal perforation) was observed in one case. However, it was not considered to be treatment-related as it was a T4 case, and perforation occurred soon after treatment started. Thus, there do not appear to be any differences with respect to esophagitis.

Nausea was significantly more severe in arm C than in the other regimens, which suggests that it depends on the CDDP dose. Based on this result, daily low-dose CF is better than standard CF.

Although the differences were not significant, the rate of hematological toxicity was lower in arm A than in the other regimens. Two reasons may explain why arm A was associated with less hematological toxicity. First, daily low-dose administration may have caused less toxicity. The dosages of the chemotherapeutic agents used in arm A were slightly lower than in the other arms. Furthermore, there was no difference in hematological toxicity between arms B and C, which had almost the same total doses of CDDP and 5FU. Therefore, arm A appears to have milder toxicity than the other arms, which is supported by the higher completion rate for arm A than for the other regimens.

Because this trial was not randomized and the number of patients was small, the conclusions that can be reached are limited. However, each arm did show comparatively good survival. Despite the high rate of patients with clinical stage III or above (45%, 71%, and 43% in arms A, B, and C, respectively), 3-year survival rates of 40%, 31%, and 62% were seen in each arm, respectively (Fig. 2). A larger, randomized, controlled trial is needed; and it has already begun as a Japan Clinical Oncology Group (JCOG) trial. On the basis of our results, differences in toxicity and survival between arms of the study may be small.

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