not received any previous anticancer treatment were enrolled in this study. Their medical records, as well as their CT and MRI data, were reviewed retrospectively. The ethics committee of our institute approved this retrospective study and did not require patient informed consent. The initial diagnosis and the possibility of local tumour resection were assessed using contrast-enhanced dynamic CT, multiplanar reformation images, CT angiography and MR images. CT scanning was performed with either an 8- or a 16-detector CT scanner (Aquilion 8 or Aquilion 16; Toshiba Medical Systems, Tokyo, Japan). All images were assessed to determine the local extent of the tumour and the presence of metastases. The criteria used to consider a tumour non-resectable included the presence of a distant metastasis, multiple liver metastases, peritoneal dissemination with ascites, and involvement of a major vascular system (*i.e.* obstruction or bilateral invasion of the portal vein and/or tumour encasement of the coeliac axis or superior mesenteric arteries). Involvement of the superior mesenteric vein or the main portal vein was not a contraindication to resection, as the tumour could be resected and the portal venous system could be reconstructed. Chest CT was performed when necessary. Histopathological proof was obtained when possible; if histopathological confirmation was absent, the diagnosis was made on the basis of clinical and imaging findings. Tumour staging was performed using the Union International Contre le Cancer (UICC) classification [18].

MRI

All patients were examined using a 1.5 T superconducting MR system (Excelart XGS; Toshiba Medical Systems) with a 25 mT m^{-1} maximum gradient capability, a maximum slew rate of 130 mT m^{-1} ms^{-1} and gradient acoustic noise reduction system. An eight-element quadrature phased-array surface coil was used to optimize the signal-to-noise ratio. All patients underwent diffusion-weighted MRI in addition to the routine pancreatic MR protocol; pancreatic lesions suitable for ADC measurement were identified and selected. All MR examinations were performed with breath holding. The routine MR protocol included a transverse T_1 weighted fast gradient echo (fast field echo; repetition time/echo time (TR/TE), 187 ms/4 ms; flip angle, 77°; matrix, 160 × 320; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 19 slices; asymmetric *k*-space acquisition in the read-out), a transverse T_2 weighted fast spin-echo (TR/TE, 3000 ms/100 ms; echo train length, 19; matrix, 192 × 288; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 13 slices), and a transverse T_2 weighted single-shot fast spin-echo (TR/TE, 15 000 ms/80 ms; echo train length, 64; matrix, 192 × 192; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 300 mm; 15 slices; asymmetric k-space acquisition in the phase-encoding). MR cholangiopancreatography used a single-shot fast spin-echo sequence (effective TE, 250 ms; matrix size, 320 × 320; field of view, 350 mm) with thick (20–45 mm) or thin (4 mm) slices in the coronal or oblique coronal plane. Diffusion-weighted imaging was performed with different *b*-values to assess their ability for characterization of the tumour. Diffusion-weighted imaging was performed in a transverse plane using a spin-echo single-shot echo-planar imaging sequence with two sets of diffusion gradients, a middle *b*-value (b=400 s mm^{-2}) and a high *b*-value (b=1000 s mm^{-2}), along with three orthogonal directions: phase-encoding, frequency-encoding and section-select directions. In addition, images without motion-probing gradients (MPGs) (b=0 sec mm^{-2}) were obtained simultaneously. The following parameters were used to obtain the diffusion-weighted images: TR/TE, 4000 ms/110 ms; echo train length, 19; matrix, 128 × 208; section thickness, 8 mm; intersection gap, 1 mm; one signal acquired; field of view, 350 mm; 11 slices; asymmetric k-space acquisition in the phase-encoding; and acquisition time, 24 s. To reduce chemical shift artefacts, the selective water excitation technique was used for fat suppression. Diffusion-weighted imaging was performed using the parallel imaging technique, with a reduction factor of 2 to improve the signal-to-noise ratio.

Data analysis

All diffusion-weighted imaging data were transferred to a commercially available workstation (MKDN-008A, Toshiba Medical Systems). Isotropic images were created by averaging the data from all three orthogonal diffusion-weighted images. The ADC maps were generated by the workstation using the following equation:

$$\mathrm{ADC} = \ln(S_1/S_2)/(b_2 - b_1) \quad (1)$$

where S_1 and S_2 are the signal intensities of diffusion-weighted images obtained with one of the two *b* values (b_1 and b_2, respectively) on a voxel-by-voxel basis.

Each ADC of the primary tumour was determined by measurements of the region of interest (ROI) created on each ADC map. To analyse tumour characterization, cystic or necrotic areas were avoided when measuring the ADC. Several ROIs were placed within the largest area of the tumour on each ADC map, avoiding (if possible) cystic, necrotic or haemorrhagic components of the tumour seen on conventional MR images. The size of the ROI was chosen to be appropriate for each lesion, so that the maximum ROI was used without volume averaging. To ensure the same areas were measured, the ROI was copied and pasted onto each middle and high *b*-value ADC map. Tumour ADCs were determined by averaging each measured ADC. The tumour size was estimated by measuring the greatest diameter of the lesion on T_1 weighted MR images.

Patient follow-up

Patients were treated with gemcitabine at a dose of 1000 mg mm^{-2} given intravenously every week for 3 weeks, followed by 1 week's rest until disease progression or unacceptable toxicity was observed. When the patient agreed, both gemcitabine and TS-1 (a combination preparation consisting of tegafur, gimeracil and oteracil potassium [19]) were given simultaneously as part of a Phase I clinical trial. When severe toxicity

was observed, the next chemotherapy session was omitted and postponed to the next scheduled treatment day. Follow-up CT was performed every month to evaluate tumour response. Local tumour progression was determined according to RECIST (Response Evaluation Criteria in Solid Tumours) [20].

Statistical analysis

The patients were classified into two groups (progressive and stable) depending on their status 3 months and 6 months after the initial treatment. The groups were compared with respect to their ADC and clinical characteristics, including age, gender, tumour stage (UICC III/IV), anticancer agents used (gemcitabine only or gemcitabine and TS-1) and initial tumour size. The Wilcoxon signed rank test and the χ^2 test were used to compare the two groups.

To assess the relationship between progression and the ADC of the pancreatic cancer, patients were grouped based on the median value of each ADC. The two groups were compared with respect to tumour progression using the Kaplan–Meier method and the log-rank test. Statistical analyses were performed using SPSS software (Version 11.0; SPSS Inc., Chicago, IL). A difference with a p-value <0.05 was considered statistically significant.

Results

A diagnosis of pancreatic cancer was histologically confirmed in 54 (85.7%) patients; the biopsy was performed at the primary site in 42 (66.7%) patients and at a metastatic liver site in 12 (19.0%) patients. In the other nine (14.3%) patients, the final diagnosis was made on the basis of the clinical evaluation, including a complete history, physical examination, laboratory data and radiological findings. The UICC classification tumour stage was III in 27 (42.9%) patients and IV in 36 (57.1%) patients. Metastases included the liver in 25 patients, liver and para-aortic lymph nodes in 1 patient, liver and lungs in 2 patients, para-aortic lymph nodes in 5 patients, peritoneal dissemination in 2 patients, and vertebra in 1 patient. Pancreatic tumour size ranged from 1.8–12.0 cm (mean, 4.4 cm). The middle b-value ADC in the ROI ranged from 0.80–2.57 $\times 10^{-3}$ mm^2 s^{-1}, whereas the high b-value ADC ranged from 0.70–2.02 $\times 10^{-3}$ mm^2 s^{-1}. The size of the ROIs ranged from 0.63–2.87 cm^2. The average middle b-value ADC of the pancreatic cancer ranged from 0.93–2.42 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.50 $\times 10^{-3}$ mm^2 s^{-1}; median, 1.46 $\times 10^{-3}$ mm^2 s^{-1}), whereas the average high b-value ADC ranged from 0.72–1.88 $\times 10^{-3}$ mm^2 s^{-1} (mean, 1.21 $\times 10^{-3}$ mm^2 s^{-1}; median 1.23 $\times 10^{-3}$ mm^2 s^{-1}). The median duration between the initial MR examination and the first day of chemotherapy was 9 days (range, 2–36 days).

34 (54.0%) patients were treated with gemcitabine, whereas 29 (46.0%) patients were treated with concomitant gemcitabine and TS-1. On follow-up, progression was local in 39 (61.9%) patients and metastatic in 12 (19.0%) patients, including 10 patients with hepatic metastases and 2 patients with para-aortic lymph node metastases; newly recognized lesions were found in 10 (15.9%) patients, of whom 2 had hepatic metastases, 7 had peritoneal dissemination and 1 had a lung metastasis. Two (3.2%) patients did not show progression at the time of this analysis. 25 (40.0%) patients showed progression at 3 months, whereas 46 (73.0%) patients showed progression at 6 months after initial treatment. Progression time from the initial treatment ranged from 31–533 days (median, 123 days).

A comparison of the progressive and stable patients (Table 1) showed that the high b-value ADC of the progressive patients was significantly lower than that of the stable patients at 3 months (mean ADC, 1.11 ± 0.04 *vs* $1.25 \pm 0.03 \times 10^{-3}$ mm^2 s^{-1}; $p=0.03$) and 6 months (mean ADC, 1.17 ± 0.03 *vs* $1.28 \pm 0.05 \times 10^{-3}$ mm^2 s^{-1}; $p=0.04$) (Figures 1 and 2). The middle b-value ADC was not significantly different between progressive and stable patients. Clinical factors, including age, gender, UICC stage and tumour size, and the chemotherapy agents used, were not significantly different between the progressive and the stable patients at 3 months and 6 months.

Based on the Kaplan–Meier method and the log-rank test, the tumour progression rates were significantly higher in patients with a lower high b-value ADC than in those with a higher high b-value ADC (median progression time, 140 days *vs* 182 days; $p=0.01$) (Figure 3). Although patients with a lower middle b-value ADC showed a tendency towards higher rates of progression than those with a higher middle b-value ADC, there was

Table 1. Comparison of clinical factors and the apparent diffusion coefficent (ADC) with respect to tumour progression

	Clinical outcome					
	3 month			6 month		
Variable	Progressive	Stable	p-value	Progressive	Stable	p-value
Number of cases	25	38		46	17	
Age (years)	64.3±1.2	64.8±1.5	0.13	63.9±6.2	64.9±9.1	0.33
Gender (Male/female)	12/13	20/18	0.79	21/25	11/6	0.26
UICC stage (III/IV)	8/17	19/19	0.20	17/29	10/7	0.16
Tumour size (cm)	4.74±0.38	4.18±0.31	0.20	4.63±0.31	3.78±0.27	0.16
Chometherapy agent (gemcitabine/ gemcitabine and TS1)	16/9	18/20	0.21	27/19	7/10	0.26
ADC ($\times 10^{-3}$ mm^2 s^{-1})						
ADC (b=400 s mm^{-2})	1.48±0.05	1.50±0.05	0.89	1.48±0.05	1.51±0.06	0.68
ADC (b=1000 s mm^{-2})	1.11±0.04	1.25±0.03	0.03	1.17±0.03	1.28±0.05	0.04

Data comprise the number of patients, unless otherwise indicated.

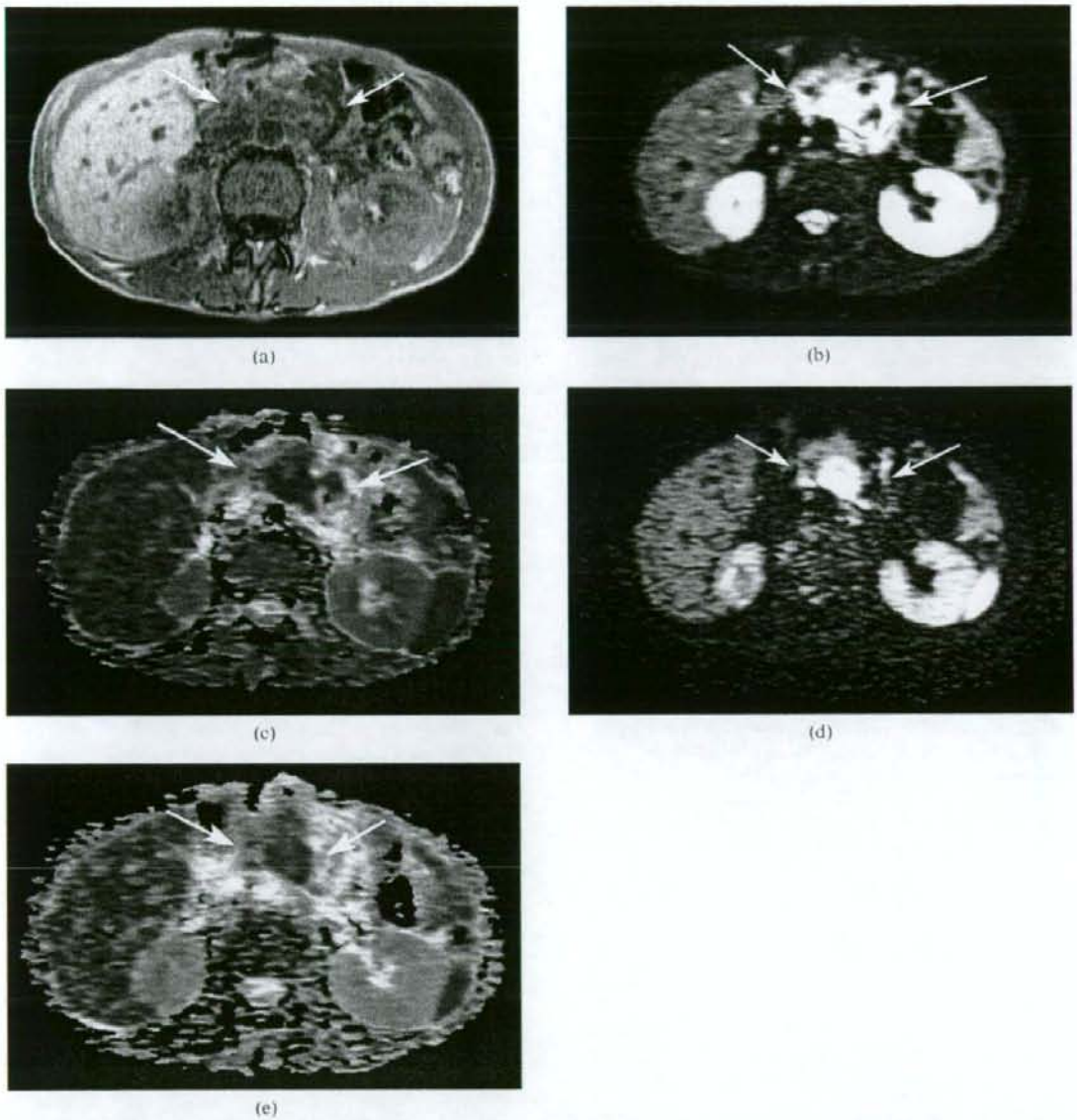

Figure 1. Images from a 65-year-old man with advanced pancreatic cancer who showed early progression. Progression was noted on the 2-month follow-up CT. (a) Transverse T_1 weighted fast-field echo image shows an irregularly shaped tumour at the pancreatic head (arrows). (b,c) Isotropic diffusion-weighted image (b) and the apparent diffusion coefficient (ADC) map (c) using the middle *b*-value (400 s mm^{-2}) show an inhomogeneous high-signal mass (arrows). The ADC was 0.98×10^{-3} mm^2 s^{-1}. (d) Isotropic diffusion-weighted image and (e) ADC map with a high *b*-value (1000 s mm^{-2}) show an inhomogeneous high-signal mass (arrows). The ADC was 0.84×10^{-3} mm^2 s^{-1}.

no significant difference using the log-rank test (median progression time, 101 days *vs* 140 days; p=0.10).

Discussion

Despite major recent advances in the management of cancer, pancreatic cancer remains a challenge to clinicians because of the difficulties encountered in early diagnosis and its relative chemoresistance. Some patients show improvements in survival and tumour response, whereas others only suffer from inconvenience and increased toxicity. It has been suggested that the burden of treatment should not add to the suffering of those with advanced pancreatic carcinoma. Therefore, the identification of prognostic factors before treatment would be helpful in

selecting the subgroups of patients for which chemotherapy improves survival and in determining efficient treatment strategies with reference to expected survival [21].

Among patients with advanced pancreatic cancer treated with chemotherapy, it was found that a lower pre-treatment high *b*-value ADC was correlated with early progression. Several reports relating to brain tumours and animal models have indicated a relationship between ADC and histological features [11–14, 16, 22]. ADC is a quantitative expression of the tissue

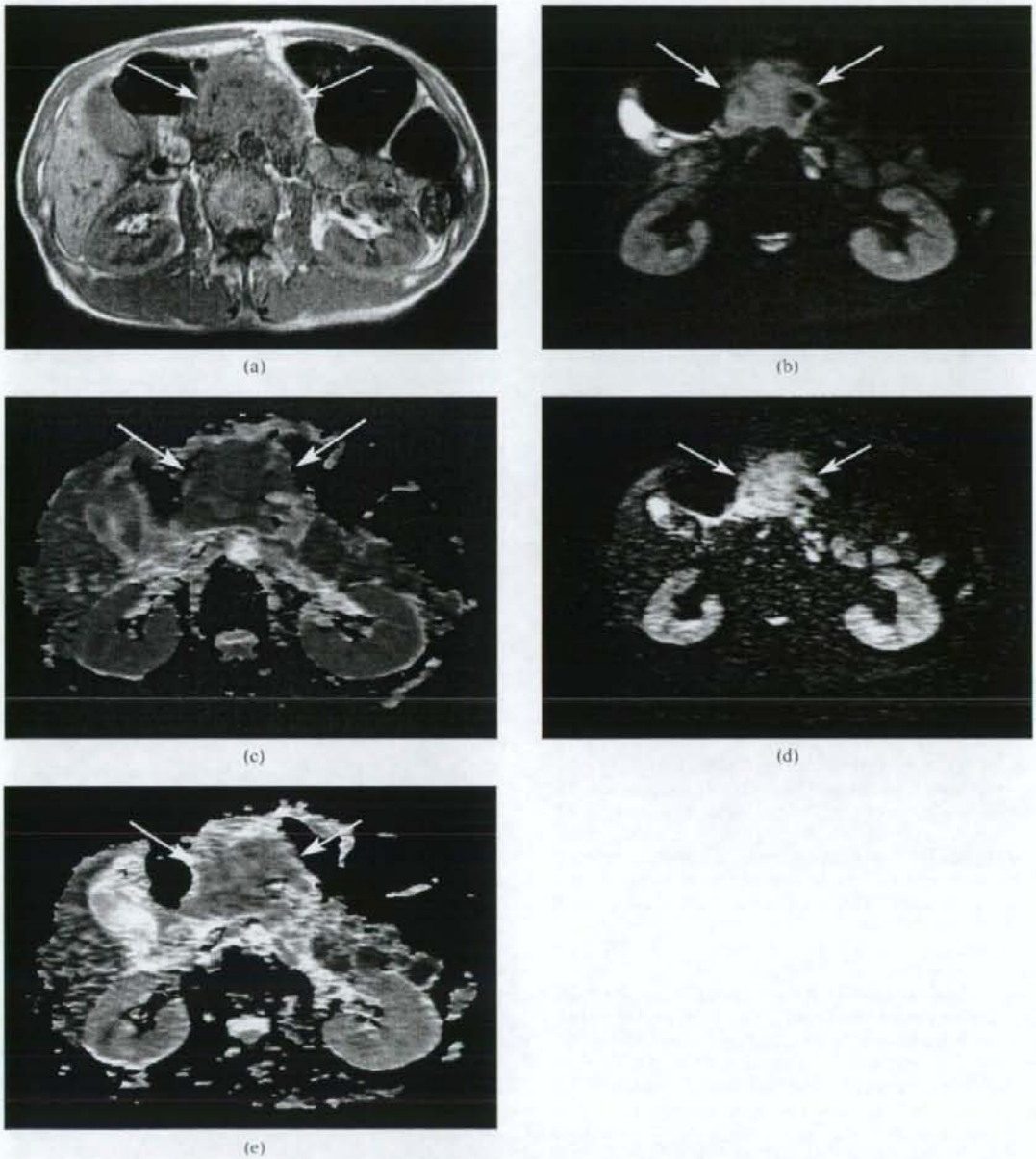

Figure 2. Images from a 66-year-old man with relatively stable advanced pancreatic cancer. Progression was noted on the 8-month follow-up CT. (a) Transverse T_1 weighted fast-field echo image shows an irregularly shaped tumour at the pancreatic head (arrows). (b) Isotropic diffusion-weighted image and (c) the apparent diffusion coefficient (ADC) map using the middle *b*-value (400 s mm $^{-2}$) show an inhomogeneous high-signal mass (arrows). The ADC was 1.42×10^{-3} mm^2 s^{-1}. (d) Isotropic diffusion-weighted image and (e) the ADC map with a high *b*-value (1000 s mm $^{-2}$) show an inhomogeneous high-signal mass (arrows). The ADC was 1.40×10^{-3} mm^2 s^{-1}.

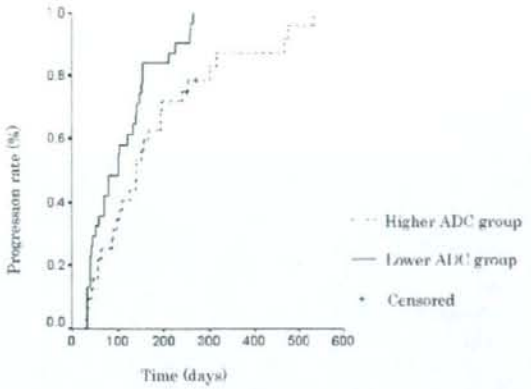

Figure 3. The graph shows the rates of local tumour progression in patients with advanced pancreatic cancer treated with chemotherapy. Patients with a lower apparent diffusion coefficient (ADC) using the high *b*-value (1000 s mm^{-2}) had a significantly higher rate of progression than those with a higher ADC ($p<0.01$, log-rank test).

diffusion characteristics; it is related to the proportion of extracellular and intracellular components. A high ADC is thought to reflect the presence of a necrotic fraction, which leads to increased extracellular water, whereas a low ADC is thought to reflect higher tumour cellularity or cell density, which results in more restricted water diffusion. Cell density may be indicative of tumour aggressiveness. The results of several clinical studies suggest that tumours with a high cellularity have an increased metastatic capacity [23]. Although the reason for the correlation between a lower pancreatic cancer ADC and early progression is unclear, it is possible that a lower ADC reflects a higher cellularity and a more aggressive tumour. Conversely, pancreatic cancers generally include desmoplastic tissue in the baseline tumour volume, which may also affect ADC independent of the cellularity. To the best of our knowledge, there have been no previously published reports dealing with the correlation between diffusion-weighted imaging and histological examination findings in pancreatic cancer. In this study, we did not look for any correlation between histology grade and ADC because it was inappropriate to analyse specimens of a part, small amount or metastatic site of the tumour. Further studies are needed to correlate the pancreatic cancer ADC with the tumours' histological features.

Several investigators have attempted to use the ADC as a pre-treatment predictor of response to chemotherapy or chemoradiation. Investigators have used various methods to analyse the data and their results have varied. Higano et al [24] reported that a lower minimum pre-treatment ADC correlated with brain tumour progression. The ADC of the tumour that was analysed avoided cystic or necrotic areas, and they hypothesized that the relationship between a lower tumour ADC and early progression was related to high cellularity or a highly proliferative portion of the tumour; our results are similar to these. Conversely, several investigators reported that a higher pre-treatment ADC was related to a poor response to chemotherapy in rectal cancer patients, patients with colorectal hepatic metastasis and animal models [12, 13, 15, 17]. In these studies, the ROI for ADC measurement involved the whole tumour; the investigators hypothesized that the reason for the poor response with a higher pre-treatment ADC may be due to the presence of necrosis in the tumour. In this situation, the tumour may experience hypoxia and thus have a slower metabolism, which would result in a lower sensitivity to chemotherapy [12]. Although measuring ADC values of a whole tumour might be less subjective and more reproducible, we attempted to measure the ADC while avoiding cystic or necrotic components of the tumour in this study, which might reflect tumour cell characterization. In the future, a proper method for analysis of pancreatic cancer needs to be developed.

In the present study, early progression did not correlate with the middle *b*-value ADC but did with the high *b*-value ADC. Middle *b*-value diffusion-weighted imaging produces relatively good imaging quality, but the middle *b*-value ADC is affected by so-called "T_2-shine through" and a local vessel perfusion effect. These factors may affect the middle *b*-value ADC in pancreatic cancer; as a result, the middle *b*-value ADC may not truly reflect tumour characteristics. Other scanning factors, such as MPG pulse direction, *b*-factor, matrix size and the reduction factor on parallel imaging, may also affect imaging quality.

The present study had several potential limitations. Firstly, single-shot echo planar imaging has a relatively low spatial resolution, a low signal-to-noise ratio and shows imaging distortion. We used all of the currently available techniques to improve imaging quality. However, the ADCs of small lesions may still be unreliable. The use of high field-strength imagers or pulse-triggered scanning can potentially improve the signal in diffusion-weighted MRI [25, 26]. Secondly, although a high *b*-value of 1000 s mm^{-2} on diffusion-weighted imaging was used to reduce confounding relaxation phenomena, the so-called T_2-shine through effects and the perfusion effect, these factors may still have affected the ADC [27–29]. Diffusion-weighted images with a higher *b*-value (*i.e.* 4000 s mm^{-2}) should provide more information about the slow diffusion of water molecules, which may be more sensitive at distinguishing cellular or tissue characteristics [12]. However, on abdominal scanning, current MR units cannot provide enough higher *b*-value signals. Thirdly, the patient population was relatively small, and substantial overlap was noted between progressive and stable patients. Tumour stage and size varied in this study; however, these factors were not significantly different between progressive and stable patients. In addition, some patients had not been histologically proven to have pancreatic cancer. Although primary pancreatic lymphoma might mimic pancreatic cancer, we carefully reviewed clinical data, and patients with a doubtful clinical diagnosis were not included in this study [30, 31]. Further larger clinical studies are needed to fully characterize pancreatic cancer for an appropriate analysis of ADC with tumour stage and size. Finally, the measurement reproducibility of ADC was not assessed in this study. Instead, we measured several ROIs in the tumour and then averaged these.

In conclusion, in patients with advanced pancreatic cancer treated with chemotherapy, a lower high *b*-value ADC may be predictive of early progression.

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ORIGINAL ARTICLE

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Safety of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) in Japan: a retrospective review of 48 patients with metastatic colorectal cancer

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Abstract
Background. A combination of irinotecan and infusional fluorouracil/leucovorin (FOLFIRI) has become one of the global standard chemotherapy regimens for metastatic colorectal cancer. The aim of this study was to evaluate the feasibility of FOLFIRI in a Japanese population with metastatic colorectal cancer.
Methods. This retrospective analysis included 48 patients with unresectable metastatic colorectal cancer who received FOLFIRI between May 2004 and June 2005. Evaluation points included adverse events, dose intensity, response rate, progression-free survival, and overall survival.
Results. Thirty-eight (79%) patients received FOLFIRI as first-line chemotherapy. Eighteen patients received original full-dose FOLFIRI and 30 patients received reduced FOLFIRI with irinotecan at 150 mg/m^2. Eighteen (38%) of the 48 patients experienced grade 3 or 4 neutropenia, 5 (10%) had grade 3 vomiting and 5 (10%) had grade 3 diarrhea. Toxicity was tolerable, with appropriate dose reduction if necessary. There were no treatment-related deaths or early deaths within the first 60 days of treatment. Median dose intensities (with relative dose intensities in parentheses) in all patients and in patients who received full-dose FOLFIRI were 129 mg/m^2 per 2 weeks (71%) and 144 mg/m^2 per 2 weeks (80%) for irinotecan and 2349 mg/m^2 per 2 weeks (84%) and 2376 mg/m^2 per 2 weeks (85%) for fluorouracil, respectively. The response rate in patients with measurable lesions was 37% (13/35; 95% confidence interval [CI], 21.1%–53.2%), and median progression-free survival was 8.4 months (95% CI, 6.4–10.3).
Conclusion. The dose intensity of irinotecan was relatively low, and toxicity was tolerable with appropriate dose reduction; efficacy was comparable to that previously reported. FOLFIRI is feasible and can be one of the standard treatment options for Japanese patients with metastatic colorectal cancer.

Key words FOLFIRI · Colorectal cancer · Irinotecan · Safety · Feasibility

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Introduction

Irinotecan combined with fluorouracil (5-FU)/leucovorin (LV) has proved superior to 5-FU/LV alone in terms of survival, progression-free survival (PFS), time to progression (TTP), and response rate (RR) for patients with metastatic colorectal cancer in two randomized controlled trials.[1,2] Bolus 5-FU/LV with irinotecan (IFL) was preferred in North America and infusional 5-FU/LV with irinotecan was preferred in Europe.[3] In Japan, IFL or its modified forms were popular because the prescribing information for levofolinate (Isovorin; *l*-LV; Wyeth, Tokyo, Japan) had recommended its use only with bolus injection of 5-FU until February 2005, when infusional 5-FU with levofolinate regimens were approved.[4] Therefore, irinotecan with infusional 5-FU/LV (FOLFIRI) was not common in Japan before that time.

In 2004, Goldberg et al.[5] reported that oxaliplatin with infusional 5-FU/LV (FOLFOX) was superior to IFL in terms of survival, TTP, and RR, and Tournigand et al.[6] reported that FOLFIRI followed by FOLFOX, and the reverse sequence, had almost equivalent efficacy. Based on these results, either FOLFIRI or FOLFOX is regarded as a standard first-line or second-line chemotherapy regimen for metastatic colorectal cancer, and IFL is regarded as an inferior regimen.

In May 2004, according to these results, the practical regimen for metastatic colorectal cancer at the National Cancer Center Hospital East was changed from IFL to

FOLFIRI. The purpose of this retrospective study was to evaluate the safety profile and efficacy of the FOLFIRI regimen in a Japanese population.

Patients and methods

Patients

A total of 63 patients with metastatic colorectal cancer who had received FOLFIRI between May 2004 and June 2005 were identified from the database at the National Cancer Center Hospital East. Data for 48 of these 63 patients who met the following criteria were analyzed retrospectively: unresectable histologically confirmed colorectal adenocarcinoma, age between 20 and 75 years, Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, no prior irinotecan therapy, neutrophil count 1500/mm^3 or more, platelet count 100000/mm^3 or more, serum creatinine 1.2 mg/ml or less and bilirubin 1.5× the upper limit of the normal range or less, and initial irinotecan dose 150 mg/m^2 or more. The reasons for the exclusion of 15 patients were: reduced dose of irinotecan (less than 150 mg/m^2) owing to poor condition in 7 patients, prior irinotecan therapy in 5 patients, age more than 75 years in 1 patient, poor PS in 1 patient, and low neutrophil count in 1 patient.

Treatment

FOLFIRI consisted of irinotecan at a dose of 180 mg/m^2 or a reduced dose of 150 mg/m^2 given as a 90-min infusion, and *l*-LV at 200 mg/m^2, given as a 2-h infusion, followed by bolus 5-FU at 400 mg/m^2 and a 46-h infusion of 5-FU at 2400 mg/m^2 (Fig. 1), repeated every 2 weeks. Infusional 5-FU could be increased to 3000 mg/m^2 if there was no toxicity exceeding grade 1 during the two first cycles. Chemotherapy was basically suspended until recovery in the case of neutrophil count less than 1500/mm^3, platelet count less than 100000 mm^3, or for significant persisting nonhematologic toxicity.[6] 5-FU and irinotecan doses were reduced because of toxicity according to each physician's decision. A 5-hydroxytryptamine-3 antagonist and dexamethasone were routinely administered as antiemetic prophylaxis. FOLFIRI was continued until disease progression, intolerable toxicity, or the patient's refusal. A central venous port was implanted before treatment.

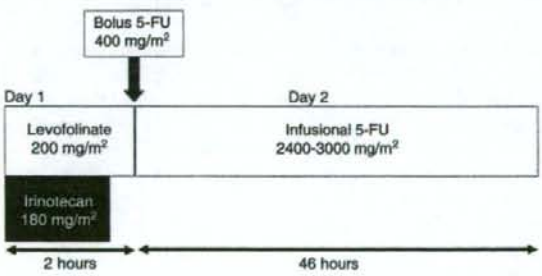

Fig. 1. Original schedule and doses of irinotecan and infusional fluorouracil (*5-FU*) /leucovorin (FOLFIRI)

Evaluation

All patients were submitted to routine physical examinations and laboratory analyses at each cycle and computed tomography basically every 2 to 3 months. Toxicity was graded using the National Cancer Institute Common Toxicity Criteria version 2.0 (in Japanese). Antitumor response was evaluated in the patients who had measurable lesions, using the Response Evaluation Criteria in Solid Tumors (RECIST).[7] PFS was defined as the time between the initial date of FOLFIRI and the first disease progression or death from any cause when no progression was recorded. Overall survival was defined as the time between the initial date of FOLFIRI and death from any cause. PFS and overall survival were determined by the Kaplan-Meier method, using Dr SPSS II for Windows, release 11.0.1J. (SPSS Japan, Tokyo, Japan).

Dose intensity (DI, in milligrams per square meter per 2 weeks) was calculated as the total cumulative dose divided by the duration of dosing ([{initial date of last cycle} – {initial date of first cycle} + 14]/14). Relative dose intensity (RDI) was calculated as the dose intensity divided by the planned DI, multiplied by 100. Planned DIs were 180 mg/m^2 per 2 weeks for irinotecan and 2800 mg/m^2 per 2 weeks for 5-FU.

Results

Patient characteristics

Baseline patient characteristics are listed in Table 1. Median age was 56.5 years (range, 37–73 years). The number of patients who received FOLFIRI as first-line chemotherapy was 38 (79%), including 9 patients who had received prior adjuvant chemotherapy that had been completed at least 6 months before. Ten patients had had prior chemotherapy, which was 5-FU plus *l*-LV or oral fluoropyrimidine. No patients had received prior oxaliplatin or other antineoplastic agents except for fluoropyrimidines. Eighteen patients (38%) received the original full-dose FOLFIRI. In 30 patients (62%), irinotecan was reduced to 150 mg/m^2 from the beginning of FOLFIRI according to each physician's decision.

Safety

The median number of cycles administered was 13 (range, 1–38 cycles). Toxicity in all patients is shown in Table 2, and toxicity in the patients whose initial irinotecan doses were 180 mg/m^2 and 150 mg/m^2 is shown separately in Table 3. There were no treatment-related deaths or early deaths within the first 60 days of treatment.

Although almost all treatments were conducted in an outpatient setting, two patients required admission because of toxicity. One patient stayed in hospital for 6 days owing to grade 3 diarrhea, and another patient stayed in hospital for 6 days owing to grade 3 febrile neutropenia and anorexia.

Table 1. Baseline patient characteristics

Parameter	No. of patients	
Demographic characteristics		
No. of patients	48	
Male	31	65%
Female	17	35%
Age (years)		
Median	56.5	
Range	37–73	
Performance status		
0	40	83%
1	8	17%
Primary site		
Colon	23	48%
Rectum	24	50%
Multiple	1	2%
Evaluable lesion		
Yes	35	73%
No	13	27%
Irinotecan dose		
180mg/m2	18	38%
150mg/m2	30	62%
First-line chemotherapy		
Yes	38	79%
No	10	21%
Metastatic sites		
Liver	25	52%
Lung	22	46%
Lymph node	14	29%
Peritoneum	8	17%
Local recurrence	8	17%
Bone	2	4%
Other	3	6%
No. of metastatic sites		
1	23	48%
2	17	35%
≥3	8	17%

Treatment failure

Thirty-five patients discontinued FOLFIRI owing to disease progression. Of these 35 patients, 3 patients received palliative radiotherapy and 27 received chemotherapy. Subsequent chemotherapy regimens included FOLFOX in 22 patients, oral fluoropyrimidines in 4 patients and anti-epidermal growth factor receptor monoclonal antibody in 1 patient.

Five patients discontinued FOLFIRI because of their refusal, the reasons for which were toxicity in two patients and other reasons in three patients. One of these five patients received FOLFOX and one received oral fluoropyrimidine after FOLFIRI.

Two other patients discontinued FOLFIRI because the central venous port had to be removed due to infection. They received modified IFL thereafter.

Dose intensity (DI)

Nineteen (40%) of the 48 patients required dose reduction of irinotecan and/or 5-FU owing to toxicity, mainly neutropenia, vomiting, and diarrhea. Of the 18 patients who received full-dose FOLFIRI, 10 patients (56%) required dose reduction. The median number of cycles at the time when dose reduction was first required was 5.5 (range, 2–11 cycles).

In 5 (10%) of the 48 patients, infusional 5-FU was increased to 3000 mg/m^2 from 2400 mg/m^2, but 4 patients required dose reduction to 2400 mg/m^2 after the dose increase. In 3 (10%) of the 30 patients who received a reduced dose of irinotecan, irinotecan was increased to 180 mg/m^2 from 150 mg/m^2 according to each physician's decision. The increased dose was continued until disease progression.

Values for median DI and RDI in all patients were 129 mg/m^2 per 2 weeks and 71% for irinotecan; and 2349 mg/m^2 per 2 weeks and 84% for 5-FU, respectively. Values for median DI and RDI in the patients who received full-dose FOLFIRI were 144 mg/m^2 per 2 weeks and 80%

Table 2. Toxicity in all patients (n = 48)

Toxicity	Grade 1 (no.)	Grade 2 (no.)	Grade 3 (no.)	Grade 4 (no.)	All grades (%)	Grade 3,4 (%)
Leukocytes	18	17	7	1	90	17
Neutrophils	12	7	16	2	77	38
Hemoglobin	27	8	2	0	77	4
Platelets	6	0	0	0	13	0
Fever	9	0	0	0	19	0
Febrile neutropenia			1	0		2
Anorexia	16	17	2	0	73	4
Nausea	20	15	1	0	75	2
Vomiting	6	6	5	0	35	10
Diarrhea	10	6	5	0	44	10
Stomatitis	17	8	1	0	54	2
Alopecia	20	6			54	
Fatigue	17	2	2	0	44	4
Hand-foot skin reaction	7	2	0		19	0

Table 3. Toxicity in the patients whose initial irinotecan doses were 180 mg/m² and 150 mg/m²

	180 mg/m² $n = 18$		150 mg/m² $n = 30$	
	All grades (%)	Grade 3/4 (%)	All grades (%)	Grade 3/4 (%)
Leukocytes	100	22	83	13
Neutrophils	78	33	77	40
Hemoglobin	89	0	70	7
Platelets	0	0	20	0
Fever	11	0	23	0
Febrile neutropenia		0		3
Anorexia	89	0	63	7
Nausea	83	6	70	0
Vomiting	50	22	27	3
Diarrhea	56	11	37	10
Stomatitis	50	0	57	3
Alopecia	67		47	
Fatigue	50	6	40	3
Hand-foot skin reaction	39	0	7	0

for irinotecan; and 2376 mg/m² per 2 weeks and 85% for 5-FU, respectively.

Efficacy

The RR in patients who had measurable lesions was 37% (13/35; 95% confidence interval [CI], 21.1%–53.2%), including 3% (1/35) complete response (CR). The disease-control rate, which included CR, partial response, and stable disease, was 83% (29/35; 95% CI, 66.4% –93.4%). In the patients treated with first-line chemotherapy, the RR was 39% (11/28; 95%, CI 21.5%–59.4%) and the disease-control rate was 82% (23/28; 95% CI, 63.1%–93.9%). In one patient who had sigmoid colon cancer with unresectable liver metastasis, 15 cycles of FOLFIRI allowed curative resection of the liver metastasis. With a median follow-up period of 17.9 months (range, 6.6–27.3 months), the median PFS was 8.4 months (95% CI, 6.4–10.3; Fig. 2). Overall survival is shown in Fig. 3. Median survival time (MST) has not been reached.

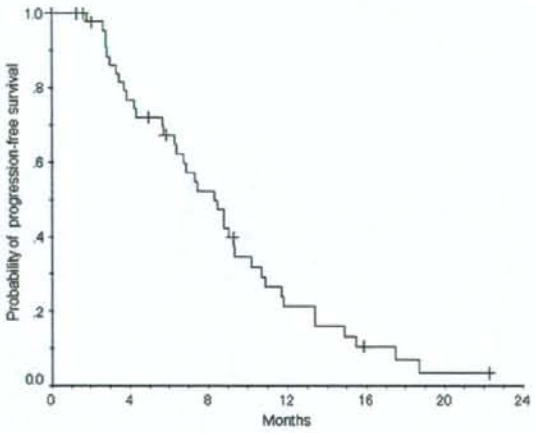

Fig. 2. Progression-free survival

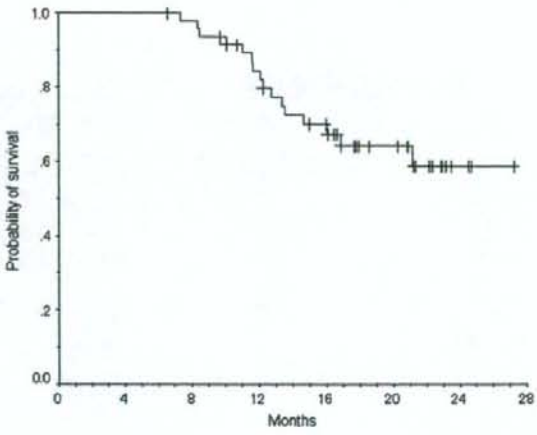

Fig. 3. Overall survival

Discussion

This retrospective study showed that FOLFIRI was manageable in an outpatient setting in a Japanese population, with adequate dose reduction and suspension. The median RDI of 71% for irinotecan in this study was lower than that in three previous randomized controlled trials, in which RDI ranged from 86% to 93%.[2,6,8] One of the reasons for the low DI was the reduced initial dose of irinotecan, but even in the full-dose FOLFIRI group, the median RDI for irinotecan was only 80%. Other reasons might be the difference between study-base and practice-base settings, or the influence of prior chemotherapy. Although 40% of the patients required dose reduction, toxicity was manageable with an appropriate dose reduction. As a result, RR (37%, including 3% CR) and PFS (median PFS, 8.4 months) were comparable to those in previous studies of FOLFIRI as

first-line treatment.[2,6] Thus, FOLFIRI is considered to be feasible in Japanese patients in our hospital if it is managed carefully.

Recent randomized trials have revealed that FOLFOX is better than IFL in terms of efficacy and toxicity[3,5] and that FOLFIRI has efficacy similar to that of FOLFOX, but with different toxicity profiles.[6,9] More recently, a direct comparison of FOLFIRI and modified IFL (mIFL; a shortened 2 weeks-on, 1 week-off schedule) was performed.[10] In that trial, patients were randomly allocated to FOLFIRI, or mIFL in combination with celecoxib or placebo in period 1. FOLFIRI demonstrated superiority to mIFL in terms of TTP (median TTP, 8.2 vs 6.0 months; $P = 0.01$) and overall survival (MST, 23.1 vs 17.6 months; $P = 0.10$). Consequently, FOLFIRI as well as FOLFOX is accepted as one of the standard treatments for metastatic colorectal cancer.

FOLFIRI usually means the regimen that was first reported by Andre et al.,[11] but in a broad sense it also means irinotecan with LV5FU2, which consists of 2 consecutive days of LV, bolus 5-FU, and a 22-h infusion of 5-FU. Although it was not a randomized trial, a retrospective study in which the original FOLFIRI was compared with irinotecan with LV5FU2 suggested the superior efficacy of the original FOLFIRI and different toxicity profiles: RR, 56.0% vs 33.1% ($P < 0.01$); median PFS, 8.5 vs 5.7 months (not significant); less frequent neutropenia and fatigue of grade 3 or more; and more frequent mucositis, nausea, and vomiting of grade 3 or more in the original FOLFIRI.[12] We adopted the original FOLFIRI regimen because of its convenient schedule.

The recommended-dose (RD) of irinotecan in FOLFIRI was established on the basis of the results of a dose-finding study.[13] In that study, irinotecan was administered once biweekly, at doses ranging from 100 to 300 mg/m^2, with LV5FU2. The maximum tolerated dose (MTD) as defined in the protocol was not reached. Taking into account the toxicity and compliance, the recommended irinotecan dose was established at 180 to 200 mg/m^2.

In Japan, two phase I trials have been conducted to determine the RD of FOLFIRI. The conclusions from these two trials coincided for the RD, which was same as that of the original FOLFIRI. In one trial, six patients received irinotecan at a dose of 180 mg/m^2, bolus 5-FU at 400 mg/m^2, and infusional 5-FU at 2400 mg/m^2, and no dose-limiting toxicity was observed. There was no higher dose and MTD was not reached.[14] In the other trial, MTD was reached at doses of 180 mg/m^2 for irinotecan, 400 mg/m^2 for bolus 5-FU and 3000 mg/m^2 for infusional 5-FU, and RDs were determined to be 180 mg/m^2 for irinotecan, 400 mg/m^2 for bolus 5-FU, and 2400 mg/m^2 for infusional 5-FU. After the additional enrollment of up to 27 patients for RDs, 52% patients experienced grade 3 or 4 neutropenia, 8% experienced grade 3 febrile neutropenia, and 4% experienced grade 3 diarrhea.[15] In our study, 38% of the patients had grade 3 or 4 neutropenia, 2% had grade 3 febrile neutropenia, and 10% had grade 3 diarrhea. The incidence of grade 3 or 4 neutropenia was higher in Japan than in previous studies (38%–52% vs 15%–24%) and the incidence of grade 3 or 4 diarrhea was equivalent or less (4%–10% vs 8%–14%).[6,11]

Uridine glucuronosyltransferase 1A1 (UGT1A1) is a key enzyme in irinotecan metabolism, which converts SN-38 to inactive SN-38 glucuronide. Some studies have revealed that UGT1A1 polymorphism is associated with severe neutropenia and diarrhea.[16,17] However, when the present study was conducted, the use of a UGT1A1 polymorphism assay kit was not common in clinical practice. Although UGT1A1 polymorphism may have been associated with severe neutropenia or diarrhea in our study, we could manage the toxicity and continued FOLFIRI after appropriate dose reduction. In the future, genotyping of UGT1A1 may enable us to administer an individualized irinotecan dose with less toxicity.

In Japan, the approved doses and schedules of irinotecan are 100 mg/m^2 once weekly or 150 mg/m^2 once biweekly. Because of this regulation, most physicians administered irinotecan at a dose of 150 mg/m^2 in FOLFIRI instead of standard full-dose FOLFIRI. Which dose of irinotecan – 150 mg/m^2 or 180 mg/m^2 – should be prescribed in daily practice is controversial in Japan. In the present analysis, there were no obvious differences in the incidence of grade 3 or 4 neutropenia or of grade 3 diarrhea between the two groups, while the incidence of grade 3 vomiting in the 180 mg/m^2 irinotecan group was higher than that in the 150 mg/m^2 irinotecan group. Although some patients required dose reduction, 8 of the 18 patients who received 180 mg/m^2 irinotecan could continue full-dose FOLFIRI and 3 patients in the 150 mg/m^2 irinotecan group could continue full-dose FOLFIRI after successful dose increases to 180 mg/m^2 until treatment failure. Because this study was not a prospective randomized trial, we could not determine which dose of irinotecan is more feasible for Japanese. However, it seems that not only reduced FOLFIRI but also full-dose FOLFIRI is feasible for some patients, and that FOLFIRI treatment can be continued safely in other patients after an appropriate interruption or modification of the dose if necessary. We conclude that full-dose FOLFIRI can be one of the standard treatments for Japanese patients with metastatic colorectal cancer with good performance status and adequate organ functions.

Recently, molecular targeting agents such as bevacizumab and cetuximab have been incorporated into the treatment of metastatic colorectal cancer,[18–20] for which FOLFOX and FOLFIRI are considered to be standard baseline cytotoxic regimens. Although neither bevacizumab nor cetuximab has been approved yet in Japan, registration studies of both agents are now underway, and they are expected to become commercially available soon. For the future appropriate use of these new agents in Japan, it is essential to manage FOLFOX and FOLFIRI adequately for Japanese patients. Based on the results of the present analysis, the FOLFIRI regimen is manageable and the regimen can be incorporated in combination with molecular targeting agents for Japanese patients, as such combinations have been carried out overseas.

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Long-term results of salvage endoscopic mucosal resection in patients with local failure after definitive chemoradiotherapy for esophageal squamous cell carcinoma

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Background and study aims: Local failure after definitive chemoradiotherapy (CRT) in patients with esophageal cancer remains one of the major problems in finding a cure. Endoscopic mucosal resection (EMR) is one treatment option when failure lesions are superficial. However, there are no relevant long-term survival data. The aim of this study was to clarify the long-term survival of salvage EMR.

Patients and methods: Between January 1998 and March 2004, 289 patients with esophageal squamous cell carcinoma were treated with definitive CRT at the National Cancer Center Hospital East, Japan. Of these 289 patients, 21 patients with local failure without lymph-node or distant metastases were treated with salvage EMR. The technique of salvage EMR involved a strip biopsy method. We retrospectively analyzed the long-term survival data for the patients who underwent salvage EMR.

Results: At a median follow-up period of 54 months (range, 16–108 months), eight of 21 patients (38%) were alive with no recurrence and two patients had died from another disease but with no recurrence of esophageal cancer. Local recurrence after EMR was detected in four patients, with local and lymph-node recurrence in two patients, and lymph-node and/or distant metastases in five patients. The 5-year survival rate from the initiation of salvage EMR was 49.1%. There were no severe complications associated with EMR.

Conclusion: EMR is one of the curative salvage treatment options for local failure after definitive CRT, if the failure lesion is superficial and there are no lymph-node or distant metastases.

Introduction

Local failure after definitive chemoradiotherapy (CRT) for esophageal cancer remains one of the major problems in achieving a cure. The optimal treatment strategy for local failure has not yet been established. Esophagectomy is generally indicated as a salvage treatment for such patients. However, we cannot afford to ignore the technical difficulties and the associated high mortality [1]. Furthermore, there is no curative chemotherapeutic agent.

Swisher et al. reported that if the residual or recurrent local tumor was pathologically proven to be T1 or T2, with no lymph-node or distant metastasis, the 5-year survival rate of patients who had undergone salvage esophagectomy was over 50% [1]. We have previously reported the short-term results of salvage endoscopic mucosal resection (EMR) in patients with local failure after definitive CRT [2]. Although the number of patients was small, their 3-year survival was similar to that of patients after salvage esophagectomy. These results indicate that if the residual or recurrent tumor is localized and superficial, local treatments such as EMR could have curative potential and could be minimally invasive treatment options. The aim of the current study was to clarify the long-term survival for salvage EMR. We therefore retrospectively analyzed the survival data for patients who had undergone salvage EMR with long-term follow-up periods.

Patients and methods

Between January 1998 and March 2004, 289 patients with esophageal squamous cell carcinoma were treated with definitive CRT at the National Cancer Center Hospital East, Kashiwa, Japan. CRT involved 60 Gy irradiation, together with two cycles of continuous infusion with 5-fluorouracil (5FU) and cisplatin (CDDP). The patients received a 24-hour continuous infusion of 5FU (400 mg/

m^2) on days 1–5 and 8–12 and intravenously administered CDDP (40 mg/m^2) with hydration on day 1 and day 8. These schedules were repeated twice every 5 weeks. Radiotherapy was initiated concurrently on the first day of the first and second courses of chemotherapy, and was delivered in 30 fractions of 2 Gy to a total of 60 Gy. Two courses of chemotherapy were also included for those patients who showed a good initial response to treatment.

Baseline staging of esophageal cancer was determined with the TNM classification of the International Union Against Cancer [3]. The clinical T stage was evaluated by endoscopy and endoscopic ultrasound (EUS), and the clinical N and M stages were evaluated mainly by computed tomography (CT) of the neck, chest, and abdomen. Clinical lymph-node metastasis was diagnosed in this study if the lymph node was more than 10 mm in diameter on CT. The definition of a complete response after CRT was as follows: 1) the disappearance of the tumor lesion; 2) the disappearance of ulceration at the primary site; 3) an absence of cancer cells in biopsy specimens [4].

Local failure lesions were characterized as one of two patterns; residual lesions or recurrent lesions. All the residual and recurrent lesions were diagnosed by endoscopic observations and confirmed histologically by cancer cells in the biopsy specimens. EUS was carried out with a 20 MHz ultrasound probe (UM-3R; Olympus Optical Co, Ltd, Tokyo, Japan) before the salvage treatment to confirm the depth of the tumor and to evaluate regional lymph nodes. The indication criteria for salvage EMR were: 1) no lymph-node or distant metastasis detected with EUS and CT of the lower neck, chest, or abdomen; 2) the absence of deep ulceration on the lesion; 3) tumor staging with EUS limited to within the submucosal layer; and 4) written informed consent obtained from patient.

The technique for salvage EMR involved the strip biopsy method, as modified by Momma et al. [5,6]. We initially identified the area of the lesion with chromoendoscopy and Lugol's iodine solution. Saline solution was then injected into the submucosal layer to detach the lesion from the muscularis propria. EMR was carried out with a dual endoscope (2T240; Olympus). First, we grasped the lesion with forceps from within one channel, then we removed it with a snare from another channel. If the lesion could not be removed en bloc for technical reasons, a piecemeal resection was done. Chromoendoscopy with Lugol's iodine solution confirmed the efficacy of the EMR. If an unstained area was detected at the margin of the mucosal defect by chromoendoscopy, we continued the EMR with piecemeal resection until no further unstained areas were found. If the lesion could not be removed completely because of severe fibrosis after CRT, the cancerous tissue was destroyed in the unresectable persistent area with argon plasma coagulation (APC: APC300 and ICC-200: Erbe, Movi, Italy). At the vertical margin of the lesion, it was very difficult to judge whether complete resection had been achieved during the EMR. After visual confirmation that the lesion was completely removed, additional APC was performed at the base of the mucosal defect, especially in those lesions that were assessed by EUS as having massive submucosal invasion. After the EMR, the removed specimens were histopathologically evaluated by experienced pathologists. When the deep margins were definitely cancer free, regardless of whether an en bloc resection had been achieved, the EMR was deemed to be completed, whereas if cancer cells were still present at the deep margin, the EMR was deemed to be incomplete.

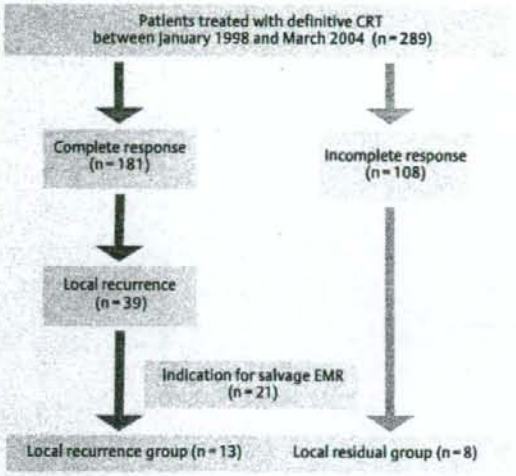

Fig. 1 Representative flowchart of the patient sample assessed in this study. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection.

The major complications associated with salvage EMR are major bleeding and perforation. In this retrospective study, major bleeding was defined as bleeding that required transfusion. Perforation was diagnosed endoscopically just after the EMR and/or by the presence of pneumomediastinum on chest CT or subcutaneous emphysema on physical examination.

Endoscopic examinations and CT were carried out at 3, 6, and 12 months after the salvage EMR, and every 6 months thereafter. Local recurrence after EMR was defined as histologically proven cancer cells in biopsy specimens from the scar. The recurrence of lymph-node and other organ metastases was diagnosed from CT. Overall survival was measured from the date of the initial salvage EMR to death or to the confirmed date of the last follow-up visit. Survival time was calculated by the Kaplan-Meier method. All information was collected from medical records or was provided by the patients' physicians. This retrospective study was performed in accordance with the Declaration of Helsinki.

Results

Of the 289 patients who were treated with definitive CRT, 181 patients achieved complete response, whereas 108 patients were evaluated as not having achieved a complete response at the primary lesion after the completion of CRT. Of the 181 patients who achieved complete response, local recurrence occurred in 39 patients. Of the 147 patients with local failure after definitive CRT, salvage EMR was contraindicated for 126 patients for the following reasons: lymph-node or distant metastases were detected with CT (n = 35); deep ulceration was present on the lesion or the local failure tumor staging was deeper than the submucosal layer (n = 91). Finally, 21 patients (13 in the local recurrence group, eight in the local residual group) with local failure without metastases were treated with salvage EMR (**Fig. 1**).

Table 1 Baseline patient and lesion characteristics before chemoradiotherapy

Characteristics	No. of patients (n = 21)
Sex	
Male	19
Female	2
Median age, years (range)	61 (47–73)
Tumor location	
Upper	5
Middle	11
Lower	5
T-stage	
T1	11
T2	0
T3	9
T4	1
N-stage	
N0	12
N1	9
TNM stage	
I	10
IIA	2
IIB	1
III	8

Table 2 Lesion characteristics before salvage endoscopic mucosal resection

	No. of patients (n = 21)
Tumor status after chemoradiotherapy	
Recurrent	13
Residual	8
Depth of the lesion with endoscopic ultrasound	
Mucosal	11
Submucosal	10
Macroscopic type of the lesion	
Depressed	15
Submucosal tumor	6
Median tumor size, mm (range)	8 (3–30)

Table 3 Clinical results of salvage endoscopic mucosal resection

	No. of patients (%) (n = 21)
Treatment method	
En bloc resection	7 (33)
Piecemeal resection	14 (67)
Histopathological evaluation	
Complete resection	12 (57)
Incomplete resection	7 (33)
No cancer cells	2 (10)
Complications	
Major bleeding	0
Perforation	0

The baseline characteristics of the 21 patients and their lesions before CRT are summarized in ○ **Table 1**. They included 19 men and two women, with a median age of 61 years (range, 47–73 years). The tumor was located in the upper esophagus in five patients, in the middle esophagus in 11 patients, and in the lower esophagus in five patients. The baseline clinical stages before CRT were as follows: T1 in 11 patients, T3 in nine patients, and T4 in one patient; N0 in 12 patients and N1 in nine patients; and stage I in 10 patients, stage IIA in two patients, stage IIB in one patient, and stage III in eight patients. All of the lesions were histologically proven to be squamous cell carcinomas by biopsy specimen analysis before CRT. The lesion characteristics before salvage EMR are presented in ○ **Table 2**. Thirteen patients developed local recurrence after initially achieving a complete response with definitive CRT, and the remaining eight patients had local residual tumors even after the completion of CRT. The median period between complete response and local recurrence in the 13 patients was 203 days (range 27–655 days). EUS examinations revealed that 11 tumors were located within the intramucosal layer and the remaining 10 tumors were located in the submucosal layer. The macroscopic appearance of the lesions before salvage EMR was depressed in 15 patients, and submucosal tumor-like in six patients. The median length of the tumors before salvage EMR was 8 mm (range, 3–30 mm). All of the lesions were diagnosed as local failures, with histological confirmation of cancer cells.

The clinical results of salvage EMR are summarized in ○ **Table 3**. En bloc resection was performed in seven patients (33%), and the remaining 14 patients (67%) underwent piecemeal resections. Histopathological evaluation of the removed specimens after EMR revealed that 12 lesions (57%) were completely resected. However, seven lesions (33%) were evaluated as incomplete resections. In the remaining two patients, no cancer cells were detected in their EMR specimens after removal, although cancerous tissue had been confirmed in the biopsy materials before EMR. No complications, such as major bleeding or perforation were experienced by any patient. Therefore, there were no treatment-related deaths with salvage EMR.

The clinical courses of patients after salvage EMR are summarized in ○ **Table 4**. At a median follow-up period of 54 months (range, 16–108 months) after salvage EMR, no recurrence of esophageal cancer was detected in ten patients and eight of

Table 4 Clinical course of patients after salvage endoscopic mucosal resection (EMR)

Recurrence after salvage EMR	Treatment for recurrence after salvage EMR	Survival outcomes
No recurrence (n = 10)		Alive (n = 8) Dead from another disease (n = 2)
Local (n = 4)	EMR (n = 1) Photodynamic therapy (n = 1) Esophagectomy (n = 2)	Alive (n = 1) Alive (n = 1) Dead from disease (n = 1) Dead from another disease (n = 1)
Local and lymph node (n = 2)	Chemotherapy (n = 2)	Dead from disease (n = 2)
Lymph node and/or distant (n = 5)	Chemotherapy (n = 5)	Dead from disease (n = 5)

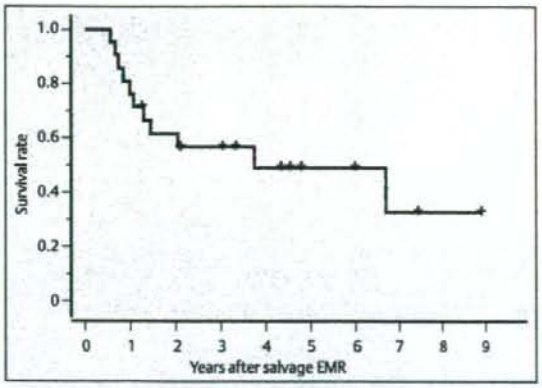

Fig. 2 Overall survival of all 21 patients from the initiation of salvage endoscopic mucosal resection (EMR).

them were still alive. However, one patient died of heart failure more than 5 years after salvage EMR, and another patient died of hypopharyngeal cancer progression without any evidence of esophageal cancer progression. Local recurrence at the primary site after salvage EMR was detected in six patients. Two of these were simultaneously diagnosed with lymph-node metastasis. Because they refused salvage surgery, they were treated with systemic chemotherapy. Two of the remaining four patients with local recurrence were cured with a second endoscopic salvage treatment (one with photodynamic therapy [PDT] and the other with EMR). The other two patients were treated with esophagectomy, but one patient died from heart failure 6 months after the procedure. Lymph-node metastasis was detected in three patients, and distant organ metastasis was detected in two patients. All five patients with lymph-node and/or distant metastasis without local recurrence were treated with systemic chemotherapy. However, they died of disease progression.

Therefore, the median overall survival time was 46 months, and the 3- and 5-year survival rates from the initiation of salvage EMR in all 21 patients were 56.1% and 49.1%, respectively (**O Fig. 2**).

Discussion

Definitive CRT is now considered to be one of the treatment options with curative intent for resectable esophageal cancer. Although CRT has shown a high response rate, local failure has been quite an important problem, which requires resolution. Herskovic et al. reported that local failure occurred in more than 40% of patients after definitive CRT [7]. We have also reported that local failure occurred in 34% of patients treated with definitive CRT [8]. The survival rates among these patients were quite dismal. In our experience, the overall survival at 3 years after CRT in patients who did not achieve complete response was 6%, and most of the patients died within 2 years [9]. Considering the improvement in survival after definitive CRT, curative local control is crucial. A higher dose of irradiation did not improve survival in a phase III study [10].

In this study, we have presented long-term survival data after salvage EMR in patients with early-stage local failure after definitive CRT. From the initiation of salvage EMR, the overall survival of all 21 patients after 5 years was 49.1%. This result is similar to those of salvage surgery for pathologically proven T1 and pT2 tumors. This indicates that if the local failure is identified in a superficial lesion, endoscopic treatment has curative potential.

However, endoscopic treatment has some limitations, such as the impracticability of treating lymph-node metastases or tumors at deeper layers. In this study, 24% (5/21) of patients developed lymph-node metastasis after salvage EMR. In such cases, surgical resection might be considered as the initial salvage treatment. However, the prediction of lymph-node recurrence is quite difficult and the selection of a salvage treatment should be made with care, considering the considerable differences in physical invasiveness between surgical and nonsurgical treatments.

In this study, 14% (2/14) of the patients who achieved complete resection developed local recurrence, whereas 57% (4/7) of the patients with incomplete resection developed local recurrence. Therefore, if salvage EMR fails to achieve complete resection, additional salvage surgery might be indicated to achieve a cure.

In addition, we should discuss the difficulty of exact tumor evaluation with EUS after CRT. If the initial T stage before CRT is T1, it could be easy to evaluate the local failure lesion using miniature-probe EUS (20MHz), which could clearly reveal a small lesion in the T1 layer. However, it is not easy to evaluate throughout the wall, especially in patients with residual lesions after CRT and in whom initial T stage was T3/4. We cannot deny the possible existence of residual cancer cells located in the deeper layers, and which cannot be evaluated using EUS. Actually, there is quite a difference in clinical course between patients with initial T1 staging and those with T3/4 staging: the 5-year survival rates following salvage EMR are 67.3% (T1, n = 11) and 30.0% (T3/4, n = 10). Therefore, we should make an effort to develop new diagnostic procedures that are capable of evaluation throughout the wall, even after CRT.

There are also limitations associated with salvage surgery, in terms of curability. To date, there have been few reports of salvage surgery in patients with failure after definitive CRT [1,11]. Swisher et al. reported their experience of salvage esophagectomy in 13 patients after definitive CRT [1]. In their report, long-term survival following salvage esophagectomy differed significantly between the subgroups with pathologically early (T1N0 or T2N0) and advanced (T3, T4, or N1) stages. No patient with pathological T3, T4, or N1 disease survived longer than 7 months. This suggests that it is quite difficult to salvage patients with advanced local failure and/or lymph-node metastasis after definitive CRT, even when they are treated with surgery. It also indicates that detecting local failure at an early stage is crucial in curative salvage treatments. Therefore, patients treated with CRT should be followed carefully and an effort should be made to establish an adequate follow-up schedule in order to detect local failure at an early stage.

The major complications following EMR are bleeding and perforation. In our study, there were no cases of severe bleeding requiring blood transfusion or perforation after salvage EMR. Shimizu et al. reported an occurrence rate for esophageal perforation after EMR of 1.6% (3/185) [12]. It is technically difficult to perform salvage EMR compared with an initial EMR because of the severe fibrosis that forms beneath the mucosal layer after CRT. Therefore, salvage EMR should be performed carefully to avoid incomplete resection or perforation.

We have previously reported the preliminary short-term results of salvage PDT after definitive CRT [13]. In the study, all six pa-

tients with T1 local failure and two of seven patients with T2 achieved a complete response with PDT. Therefore, PDT can even achieve complete response in patients after a failed salvage EMR, because PDT can theoretically obliterate the tumors in the submucosal and deeper layers. We are currently evaluating the efficacy and safety of salvage PDT with a prospective study at our institution. In the near future, we will be able to define an adequate salvage treatment option based on curability and the patient's condition and preferences.

We have shown that excellent long-term survival is achievable with salvage EMR without severe complications. The present data suggest that EMR is one of the curative salvage treatment options for local failure after definitive CRT, if the local failure lesion is superficial and there is no lymph-node or distant metastasis.

Competing interests: None

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Original article

Elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for squamous cell carcinoma of the thoracic esophagus

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ABSTRACT

Background and purpose: There are some reports indicating that prophylactic three-field lymph node dissection for esophageal cancer can lead to improved survival. But the benefit of ENI in CRT for thoracic esophageal cancer remains controversial. The purpose of the present study is to retrospectively evaluate the efficacy of elective nodal irradiation (ENI) in definitive chemoradiotherapy (CRT) for thoracic esophageal cancer.

Materials and methods: Patients with squamous cell carcinoma (SCC) of the thoracic esophagus newly diagnosed between February 1999 and April 2001 in our institution was recruited from our database. Definitive chemoradiotherapy consisted of two cycles of cisplatin/5FU repeated every 5 weeks, with concurrent radiation therapy of 60 Gy in 30 fractions. Up to 40 Gy radiation therapy was delivered to the cervical, periesophageal, mediastinal and perigastric lymph nodes as ENI.

Results: One hundred two patients were included in this analysis, and their characteristics were as follows: median age, 65 years; male/female, 85/17; T1/T2/T3/T4, 16/11/61/14; N0/N1, 48/54; M0/M1, 84/18. The median follow-up period for the surviving patients was 41 months. Sixty patients achieved complete response (CR). After achieving CR, only one (1.0%; 95% CI, 0–5.3%) patient experienced elective nodal failure without any other site of recurrence.

Conclusion: In CRT for esophageal SCC, ENI is effective for preventing regional nodal failure. Further evaluation of whether ENI leads to an improved overall survival is needed.

Surgery is the standard treatment for patients with resectable esophageal cancer. Radiation therapy alone has been indicated for unresectable or medically inoperable patients as a definitive or palliative treatment [1–3].

In the 1980s, some prospective studies showed encouraging results for chemoradiotherapy (CRT) of esophageal cancer [4,5]. The results of a phase III randomized trial comparing CRT with radiation alone (Radiation Therapy Oncology Group (RTOG) 85-01) have made CRT a standard treatment for patients who chose non-surgical definitive treatment for esophageal cancer [6–8]. During the last decade, most patients with newly diagnosed squamous cell carcinoma (SCC) of the esophagus were treated with definitive CRT in our institution.

Since the early 1980s, Japanese surgeons have practiced three-field regional lymph nodes dissection for esophageal cancer [9,10]. There are some reports indicating that prophylactic three-field lymph node dissection for esophageal cancer can lead to an improved survival [11,12]. In accordance with the concept of three-field lymph node dissection in curative surgery, ENI has been adopted for definitive CRT at our institution, but the benefit of ENI in CRT for thoracic esophageal cancer remains controversial [13–17]. The purpose of this study is to retrospectively evaluate the efficacy of ENI in CRT for thoracic esophageal cancer.

Methods and materials

Patient population

Patients newly diagnosed with SCC in the thoracic esophagus and treated with definitive CRT between February 1999 and April 2001 at our institution was recruited from our database on the basis of the following criteria: age ⩽75 years, adequate organ function, no other site of carcinoma except for early stage, and ENI treatment. Patients who could not complete the planned radiation therapy were excluded from this analysis. Informed consent was obtained from all patients.

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Pretreatment evaluation

Pretreatment evaluation included barium swallowing, endoscopy of the esophagus, and computed tomography (CT) of the neck, chest and abdomen. Lymph nodes were defined as metastatic if they were $\geqslant$1 cm in their greatest diameter on CT imaging.

Clinical staging was diagnosed according to the UICC TNM Classification of Malignant Tumors 6th edition.

Treatment details

Treatment consisted of two cycles of CDDP 40 mg/m^2 on days 1 and 8 and continuous infusion of 5FU 400 mg/m^2/d on days 1–5 and 8–12, repeated every 5 weeks, with concurrent radiation therapy of 60 Gy in 30 fractions over 8 weeks, including a 2-week break. An additional two cycles of CDDP 80 mg/m^2 on day 1 and continuous infusion of 5FU 800 mg/m^2/d on days 1 to 5 every 4 weeks were administered for responders.

All patients underwent CT-based planning. Up to 40 Gy, radiation therapy was delivered to the primary tumor, metastatic lymph nodes, and regional nodes as ENI using anterior–posterior opposed fields. Regardless of the subsite of primary tumor, the lower cervical, periesophageal, mediastinal and perigastric, except celiac, nodes were included as regional lymph nodes. For the tumor of the upper thoracic esophagus, supraclavicular nodes were also included and for lower esophagus, celiac nodes were included. A booster dose of 20 Gy was given to the primary tumor and the metastatic lymph nodes using bilateral oblique or multiple fields. The clinical target volume for the primary tumor was defined as the gross tumor volume plus 3 cm craniocaudally. The planning target volumes for primary tumors, metastatic lymph nodes and regional nodes were determined with a 1–1.5 cm margin to compensate for set-up variations and internal organ motion. The treatment portal covered the planning target volume plus 0.5 cm margin to account for penumbra. Fig. 1 shows an example of a radiation field. Lung heterogeneity corrections were not used.

Follow-up evaluation

The following evaluations were performed until disease progression every 3 months for the first year and every 6 months thereafter: physical examination, endoscopy of the esophagus, CT scan of the neck, chest, and abdomen. Biopsy of the primary tumor site was routinely performed at each follow-up examination. After disease progression was defined, clinical evaluations were performed as required.

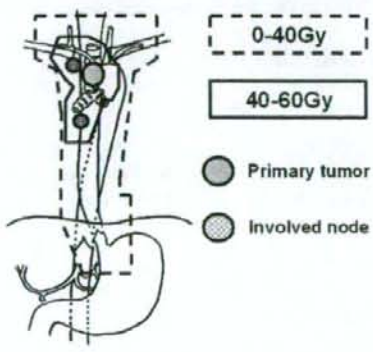

Fig. 1. An example of radiation field.

Response assessment

Complete response (CR) for the primary tumor was defined by endoscopy when all visible tumors, including ulcerations, disappeared with a negative biopsy.

Local control was defined as no detection of recurrent tumors in the same site from the time of CR until the last follow-up.

CR for metastatic lymph nodes was defined as the complete disappearance of all measurable and assessable disease for $\geqslant$4 weeks. Uncertain CR was defined as the persistence of small nodes (<1 cm) with no evidence of progression at $\geqslant$3 months after the completion of treatment, and patients with uncertain CR were grouped with those with CR for analysis.

Patterns of failure

Patterns of treatment failure were defined as the first site of failure. Local failure included the primary tumor. Involved node failure included the metastatic lymph nodes. Distant failure included any site beyond the primary tumor and regional lymph nodes. Elective nodal failure was defined as the recurrence of initially uninvolved lymph nodes within the ENI field.

Results

Patient characteristic

One hundred five patients received definitive CRT for esophageal cancer during the period examined. One hundred two patients matched the recruitment criteria, and three patients who could not complete the 60 Gy radiation therapy were excluded from the analysis. The reasons for stopping radiation therapy were (1) sever esophagitis at 56 Gy, (2) sepsis at 52 Gy, (3) disease progression at 48 Gy. The toxicities of remaining 102 patients were mild esophagitis and dermatitis. One hundred two patients characteristics are listed in Table 1. The median age was 64 years old, ranging from

Table 1
Patient characteristics.

Characteristic		Number of patients (n = 102)
Male/female		85/17
Age, years	Range	39–75
	Median	64
Histology	Squamous cell carcinoma	102
	others	0
Primary Site	Upper thoracic portion	14
	Mid-thoracic portion	50
	Lower thoracic portion	38
Tumor length, cm	Range	1–20
	Median	5
T	1	16
	2	11
	3	61
	4	14
N	0	48
	1	54
M	0	84
	1a	5
	1b	13
Stage	I	14
	IIA	28
	IIB	1
	III	41
	IVA	5
	IVB	13

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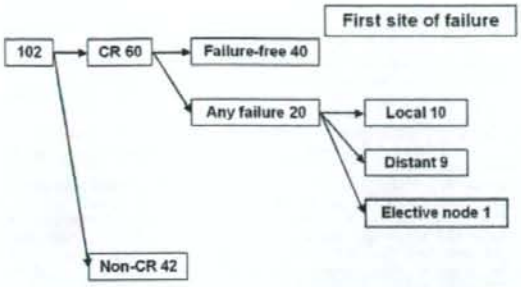

Fig. 2. The initial response after CRT and the patterns of failure.

39 to 75 years. The tumor histology was SCC in all patients. The subsites of the primary tumors were upper/middle/lower thoracic portions, 14/50/38; T1/T2/T3/T4, 16/11/61/14; N0/N1, 48/54; M0/M1a/M1b, 84/5/13; Stage I/II/III/IV, 14/29/41/18. The metastases sites of 11 M1b patients were lower cervical, supraclavicular or celiac lymph nodes.

The remaining two patients with tiny lung metastases were treated with definitive CRT at the physicians' discretion. After concurrent CRT, 69 patients who achieved CR or partial response received one or more additional cycles of chemotherapy.

Response, survival and patterns of failure

The initial response after CRT and the patterns of failure are shown in Fig. 2. The median follow-up durations for all patients and for surviving patients were 17 months (range 3–62 months) and 41 months (range 9–62 months), respectively. Fig. 3 shows overall survival data for all patients. Three-year overall survival rates were 43%. Sixty of 102 patients achieved CR (59%; 95% confidence interval [CI], 49% to 69%). After achieving CR, 40 patients never experienced any failure with a median follow-up period of 40 months (range 3 to 60 months).

In the remaining 20 patients, the first sites of failure were local (10 patients), distant (9 patients), and elective nodal failure (1 patient). The patient with elective nodal failure did not develop any other site of recurrence and died of pneumonia due to nodal failure.

Discussion

After an intergroup randomized controlled trial (RTOG 85-01) that compared definitive CRT with radiotherapy alone, the combined modality treatment became a standard therapy for patients who received non-surgical treatment for esophageal cancer. However, it was also reported that the persistence of loco-regional disease was the greatest cause of treatment failure, even in the CRT group in this trial [6–8]. In an attempt to improve local control, a dose escalation trial (Inter group study 0123) that compared the standard CRT dose (50.4 Gy/28 Fx) with a high dose (64.8 Gy/36 Fx) was conducted, but significant benefits of higher dose radiation therapy were not demonstrated [18–21]. As a result, the standard radiation dose is still 50.4 Gy/28 Fx for patients who receive 5FU/cisplatin-based combined modality therapy.

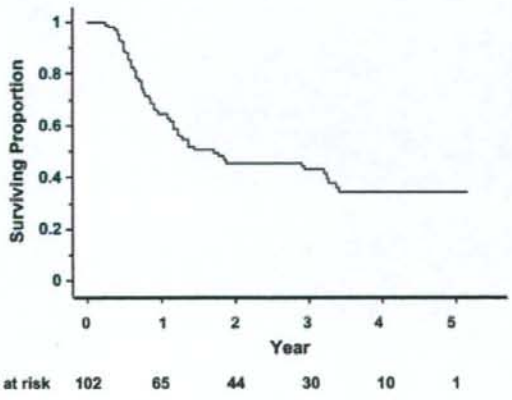

Fig. 3. The overall survival data for all patients.

Regarding the radiation field (target volume) of CRT for esophageal cancer, there is no global consensus for whether ENI should be performed or not. In the RTOG 85-01 trial, radiation was delivered at 30 Gy from the supraclavicular fossae to the esophagogastric junction as ENI, followed by cone down of 20 Gy to the primary tumor with 5 cm proximal and distal margins. On the other hand, in the INT0123 trial, ENI was omitted to improve the tolerance to treatment.

In our institution, ENI has been used because the results of most surgical series in Japan indicate a survival benefit of prophylactic three-field lymph node dissection for SCC in the thoracic esophagus [11,12]. Prophylactic three-field lymph node dissection has revealed occult regional lymph node metastasis, also known as micrometastases, found only through histopathology. It is thought that prophylactic three-field lymph node dissection improves the survival rate by eliminating micrometastases and reducing the regional lymph node recurrence rate.

In the current study, only one patient (1.0%; 95% CI, 0–5.3%) with elective nodal failure was identified without any failures of the other sites. This result suggests that if the gross tumor is controlled with CRT, ENI may prevent elective nodal failure. This preventive activity may occur through control of micromeastases.

However, it is not clear whether ENI improves overall survival. The incidence of local/regional failure and the persistence of disease in the CRT arm of RTOG 85-01, which used ENI, was lower than that in the standard dose arm of INT0123, which omitted ENI (46% vs. 55%), but the median survival times and the 2-year overall survival rates were similar in both groups (14.1 months, 36% vs. 18.1 months, 40%). On the other hand, there are concerns about the adverse effects of ENI. We previously reported long-term toxicity after definitive CRT for thoracic esophageal SCC [13]. Of 78 patients who achieved CR after CRT with the same regimen used in this study, 16 suffered from late cardiopulmonary toxicities and 8 were considered to die from toxicities related to CRT. Therefore, although ENI can reduce local/regional failures, substantial late toxicities may mitigate its survival benefits.

To minimize long-term toxicity without compromising the efficacy of CRT, we modified our radiation therapy technique for thoracic esophageal cancer in 2004. We adopted the same treatment regimen as the INT0123 trial by reducing the total dose from 60 to 50.4 Gy. The irradiation technique was also changed from conventional opposed fields to the multiple-field technique to avoid excessive dosing to the surrounding normal tissues. To maintain efficacy, we continued using ENI of 41.4 Gy in 23 fractions followed by 9 Gy in 5 fractions to the primary tumor and metastatic lymph nodes because our preliminary results suggested that ENI could control regional lymph node failure. We expect that the overall survival rate could be improved by reducing long-term toxicity.

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