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A Phase II Trial of Chemoradiotherapy for Stage I Esophageal Squamous Cell Carcinoma: Japan Clinical Oncology Group Study (JCOG9708)

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Objective: The study objective was to evaluate the efficacy and toxicity of chemoradiotherapy with 5-fluorouracil (5-FU) plus cisplatin in patients with Stage I esophageal squamous cell carcinoma (ESCC). The primary endpoint was proportion of complete response (%CR).
Methods: Patients with Stage I (T1N0M0) ESCC, aged 20–75 years, without indication of endoscopic mucosal resection were eligible. Treatment consisted of cisplatin 70 mg/m^2 (day 1) and 5-FU 700 mg/m^2/day (days 1–4) combined with 30 Gy radiotherapy (2 Gy/day, 5 days/week, days 1–21). The cycle was repeated twice with 1-week split. Salvage surgery was recommended for residual tumor or local recurrence.
Results: From December 1997 to June 2000, 72 patients were enrolled. No ineligible patient or major protocol violation was observed. There were 63 CRs for %CR of 87.5% [95% confidence interval (CI): 77.6–94.1]. Six patients with residual tumor successfully underwent esophagectomy. There was no Grade 4 toxicity. Four-year survival proportion was 80.5% (95% CI: 71.3–89.7), and 4-year major relapse-free survival proportion was 68% (95% CI: 57.3–78.8) (mucosal recurrence removed by endoscopy was not counted as an event).
Conclusions: High CR proportion and survival proportion with mild toxicity suggest that this regimen could be considered as a candidate of new standard treatment to be compared with surgery in patients with Stage I ESCC.

Key words: esophageal neoplasms – combined modality therapy – clinical trial – Phase II – radiotherapy

INTRODUCTION

The more common endoscopy examinations have become, the more early stage (Stage I) esophageal squamous cell carcinomas (ESCC) have been detected. Stage I ESCC is categorized to mucosal (T1a) tumor or submucosal (T1b) tumor. Recently, most of the patients with mucosal tumor are potentially curable by endoscopic mucosal resection (EMR), which is considered a minimally invasive treatment. On the other hand, patients with submucosal tumors are generally treated by esophagectomy and prophylactic three-field lymphadenectomy (1,2). Although the survival proportion of patient with submucosal tumors treated surgically at 3 years is over 80%, surgery can cause high morbidity (2–4). To reduce the risk of post-operative morbidity, alternative, less toxic modalities have been tested in several clinical trials.

For patients with more advanced ESCC, the efficacy of concurrent chemoradiotherapy has already been demonstrated (5,6), and the concurrent chemoradiotherapy regimen consisted of 5-fluorouracil (5-FU) plus cisplatin and radiation was promising. As an effective method of treating patients with early-stage cancer, chemoradiotherapy seems promising (7–9).

In terms of toxicities, comparing with surgery, the concurrent chemoradiotherapy is considered to have an advantage because it does not cause loss of esophagus and there are no post-operative complications.

If the efficacy of concurrent chemoradiotherapy was equivalent to that of esophagectomy, it would become a standard therapy for the patients with Stage I ESCC. Therefore, we performed a Phase II trial (JCOG9708) to

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evaluate the efficacy and safety of concurrent chemoradiotherapy with 5-FU plus cisplatin as a candidate test-arm regimen in the subsequent Phase III trial for the patients with submucosal tumors.

PATIENTS AND METHODS

Patients

Patients were eligible if they had histologically proven Stage I [UICC-TNM classification (10): T1, N0, M0] thoracic ESCC which were diagnosed as a submucosal tumor and out of indications for EMR. Patients were also eligible if they had multiple lesions within the radiation field or multiple lesions which were indicated for EMR except the primary lesion. The other eligibility criteria were as follows: (i) age 20–75 years, (ii) performance status (PS) 0 according to the classification of the Eastern Cooperative Oncology Group (ECOG) and (iii) adequate renal function (i.e. serum creatinine $\leq$1.5 mg/dl, blood urea nitrogen $\leq$25 mg/dl and creatinine clearance $\geq$60 ml/min), hepatic function (i.e. total bilirubin $\leq$1.5 mg/dl, glutamate oxaloacetate transaminase (GOT) $\leq$1.5 times the upper limit of normal, glutamate pyruvate transaminase (GPT) $\leq$1.5 times the upper limit of normal), pulmonary function ($PaO_2 \geq 70$ mmHg) and bone marrow function (i.e. hemoglobin $\geq$10.0 g/dl, white blood cell (WBC) count $\geq$4000/μl and platelets $\geq$100 000/μl). Patients were excluded if they had an active synchronous cancer, had recurrence after prior EMR for ESCC, were HBs-Ag-positive or HCV-Ab-positive, had concurrent uncontrolled medical illness (severe cardiac disease, uncontrollable hypertension or diabetes, or active bacterial infection), had prior chemotherapy or radiation therapy for any neoplasm, or were pregnant or lactating women. All patients provided written informed consent before registration. After the assessment of inclusion and exclusion criteria, patients were registered centrally at the JCOG Data Center by telephone or fax. The Data Center was in charge of data management and central monitoring throughout the study.

Evaluation of Response and Relapse

Response was assessed by esophageal endoscope, chest computed tomography (CT), chest X-ray, and neck to abdominal CT or ultrasonography in accordance with study-specific response criteria. We used original study-specific criteria because there was no appropriate criterion for assessing the response of primary tumors of the esophagus accurately. A complete response (CR) required meeting all of the following criteria: (i) no evidence of tumor except flat erosion, flat fur or a scar, (ii) a negative biopsy, (iii) no new lesions and (iv) confirmation of (i)–(iii) with at least a 4-week interval. A progressive disease (PD) required meeting any of the following criteria: (i) tumor growth and (ii) appearance of any new lesions or metastasis. If neither the criteria of CR or PD were met, the response was categorized as non-CR/non-PD. Response was evaluated by physicians at 5 weeks after chemoradiotherapy. If (i)–(iii) CR criteria were met at the time of the first evaluation, re-evaluation to confirm CR was performed again at 4 weeks after the fist evaluation. All CRs were reviewed and confirmed by viewing endoscopy films at the regular meetings of Japan Esophageal Oncology Group (JEOG; subgroup of the JCOG).

We divided relapses into major relapses and minor relapses. Major relapse was defined as a relapse that could not be removed by endoscopic treatment. Minor relapse was defined as a relapse that could be removed by endoscopic treatment. The patients were assessed at least once every 6 months to find these possible relapses.

Statistical Analysis

Simon's (11) two-stage minimax design was used to investigate whether the %CR was high enough to evaluate in a future Phase III trial. Sample size was calculated on the basis of an expected %CR of 85% and a threshold %CR of 70% with α error 0.05 and β error 0.1, and 68 eligible patients were required. Considering some ineligible cases, we set the projected accrual number at 75 patients. In this design, the number of response exceeds 54 of 68 eligible's leads to the rejection of the null hypothesis that true %CR is $<$70%. %CR was defined as the proportion of the number of patients with CR divided by the total number of eligible patients. The confidence intervals (CIs) for the %CR were calculated on the basis of exact binomial distribution. Overall survival (OS) time was defined as the time from registration to death from any cause. Major relapse-free survival (major RFS) was calculated from the date of registration to the earliest occurrence of major relapse or death from any cause. RFS was calculated from the date of registration to the earliest occurrence of a major relapse, minor relapse or death from any cause. OS, major RFS and RFS were estimated by the Kaplan–Meier method and CIs were based on Greenwood's formula. Toxicity was graded according to Japan Clinical Oncology Group Toxicity Criteria (12). All analyses were performed by SAS software version 8 (SAS Institute, Cary, NC, USA) in the JCOG Data Center. The planned accrual period was 2 years, and the follow-up period was set as 2 years after the completion of accrual.

Treatment

The treatment schedule is summarized in Fig. 1. Cisplatin was administered at a dose of 70 mg/m^2 by slow drip infusion on days 1 and 29, and 5-FU was administered at a dose of 700 mg/m^2 per day by continuous infusion for 24 h on days 1–4 and 29–32.

Radiation therapy was delivered with megavoltage equipment ($\geq$6 MV) with anterior/posterior opposed and bilateral oblique (off-cord) portals. Patients were treated 5 days per week at 2 Gy/day for a total dose of 60 Gy. The superior and inferior borders of the radiation field were 3 cm beyond the

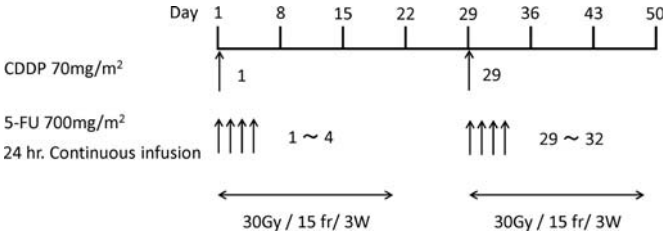

Figure 1. Treatment schedule. CDDP, cisplatin; 5-FU, 5-fluorouracil.

primary tumor. The lateral, anterior and posterior borders of the field were 1–2 cm beyond the borders of the primary tumor. Tumor size was defined by endoscopy (fiducial markers were used when needed). Elective nodes were not included. Two fields were treated each day, and port films were obtained at the beginning of treatment and the off-cord treatment, or more often if needed. Lung inhomogeneity corrections were not used.

All radiation simulator and port films and radiotherapy charts were reviewed by one radiation oncologist (S.I.). The JCOG criteria for assessing and scoring minor and major deviations, which are similar to the RTOG criteria, were used.

For patients with increased creatinine (i.e. 1.3 mg/dl or high), the cisplatin dose was reduced by 50%. If the creatinine level increased up to 2.0 mg/dl, protocol treatment was terminated. Radiotherapy was suspended when the WBC count decreased under 2000/μl, when the platelet count decreased under 50 000/μl, or when the hemoglobin decreased under 8.0 mg/μl. Radiotherapy was resumed if the WBC count was recovered 3000/μl or more, the platelet count was recovered 75 000/μl or more and the hemoglobin was recovered 8.0 mg or more within 3 weeks. The study protocol was approved by the Clinical Trial Review Committee of the JCOG and by the institutional review board of each participating institution before activation.

RESULTS

Between December 1997 and June 2000, 72 patients were registered in this study from 16 institutions. Among these 72 patients, 66 were men and 6 were women, with a median age of 62 (range 41–75) years, and no ineligible patient was enrolled. The characteristics of the patients and their tumors are shown in Table 1. Seventy (97%) patients completed the protocol treatment. In two patients, the treatment was terminated early for the following reasons: one due to patient refusal and the other due to the existence of advanced colon cancer was observed during the course of chemoradiotherapy. %CR was 87.5% (63/72, 95% CI: 77.6–94.1).

Fifty-three patients were still alive at the time of follow-up at December 2004. The OS curve for all patients is shown in Fig. 2. The 4-year survival proportion was 80.5% (95% CI: 71.3–89.7).

Thirty-six relapses (20 major relapses and 16 minor relapses alone) of 72 patients were observed at the time of final follow-up. Among these 20 major relapses, 6 relapses (5 local relapses and 1 lymph node relapse) were inside of the radiation field, 13 relapses were outside of the radiation field (1 local relapse, 7 lymph node relapses and 6 distant metastases) and 1 relapse was both inside and outside of the radiation field. Six of the patients with 20 major relapse (5 local and 1 lymph node) safely received radical esophagectomy. All 16 patients with a minor relapses underwent endoscopic treatment.

A second primary cancer in other organs were observed in 18 of 72 patients; 6, stomach; 2, pharynx; 2, tongue; 1, prostate; 1, urinary bladder; 1, pancreas; 2, lung; 1, colon and lung; 1, pharynx and stomach; and 1, pharynx and prostate.

The major RFS curve is shown in Fig. 3. The median major RFS was not estimable (95% CI: 4.7 to not estimable), and the 4-year proportion of major RFS was 68.1% (95% CI: 57.3–78.8). The RFS curve is shown in Fig. 4. The median RFS was 4.3 years (95% CI: 1.9 to not estimable) and the 4-year proportion of RFS was 52.8% (95% CI: 41.2–64.3).

Table 1. Patient characteristics

Characteristics	No. of patients
Sex	
Male	66
Female	6
Age	
Median	62
Range	41–75
History	
Hypertension	18
Diabetes	7
Cerebro-vascular disease	2
Ischemic heart disease	3
Tumor location	
Upper thoracic esophagus	10
Middle thoracic esophagus	45
Lower thoracic esophagus	17
Multiple lesions	
With	14
Without	58
Inactive multiple cancers in other organ	
No	60
Yes	12
Head and neck	6
Gastric	7
Lung	1

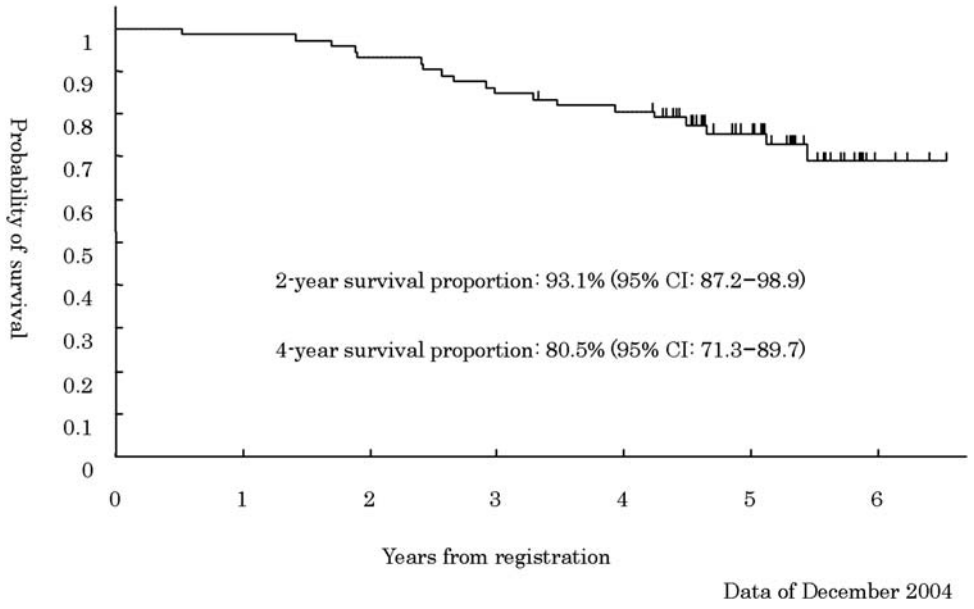

Figure 2. Overall survival. CI, confidence interval.

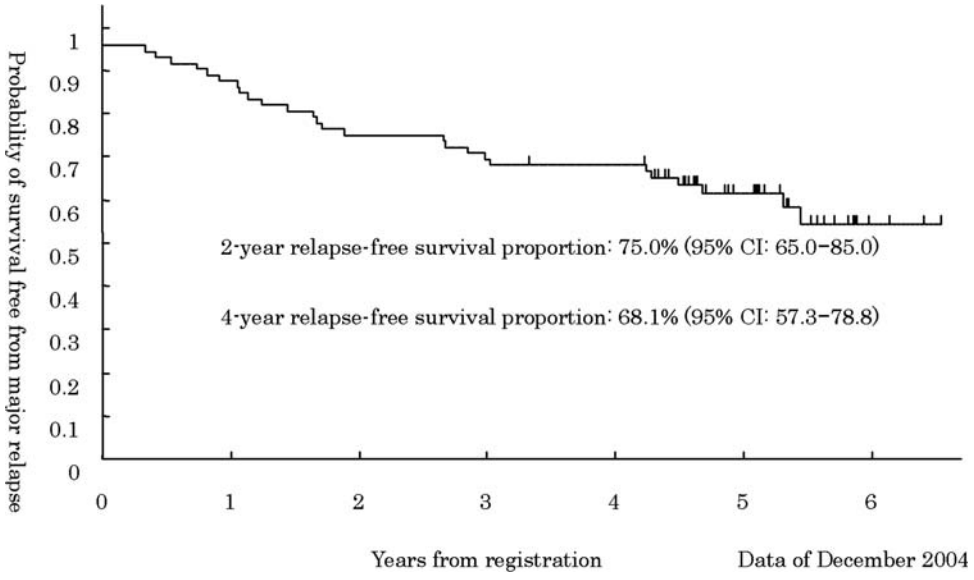

Figure 3. Major relapse-free survival.

The toxicities of the chemoradiotherapy are summarized in Table 2. Hematologic toxicity was dominant. No treatment-related deaths and serious (Grade 4) adverse events were observed.

The late toxicities are summarized in Table 3. One Grade 3 ischemic heart disease and two Grade 3 dyspnea were observed. No Grade 4 adverse event was observed.

As seen in Table 4, the percentage of patients with complete radiation therapy information was available for review at the time of the analysis was 87%. The incidence of acceptable and unacceptable deviations was 32% and 26%, respectively.

DISCUSSION

In this trial, %CR was high enough to reject the null hypothesis pre-specified in the study protocol. We concluded that concurrent chemoradiotherapy consisted of 5-FU plus cisplatin is promising for patients with Stage I ESCC who do not have indications for EMR.

The %CR was high (87.5%) comparing with that of the patients with advanced ESCC (21–47%) (6,13), the 4-year survival proportion was 80.5% (95% CI: 71.3–89.7), and equivalent to a result reported for esophagectomy in Stage I patients (~80%) (14).

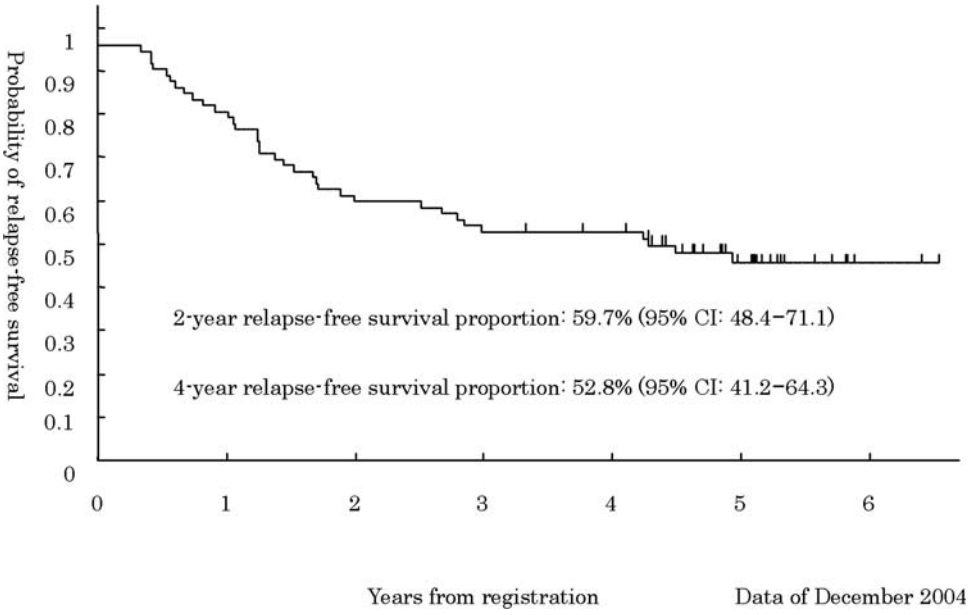

Figure 4. Relapse-free survival.

Table 2. Toxicities

	Grade					% Grade 3/4
	0	1	2	3	4	
Hematological						
Leukocyte	3	25	38	6	0	8
Neutrocyte*	18	19	32	2	0	2
Hemoglobin	47	16	9	0	—	0
Platelet	55	12	4	1	0	1
Non-hematological						
Total bilirubin	50	—	22	0	0	0
AST	47	23	1	1	0	1
ALT	42	27	2	1	0	1
PaO_2	31	39	2	0	0	0
Creatinine	55	16	1	0	0	0
Nausea/vomiting	31	26	15	0	—	0
Stomatitis	52	19	1	0	0	0
Diarrhea	58	11	3	0	0	0
Esophagitis	22	41	9	0	0	0
Dyspnea	71	0	1	0	0	0
Neuropathy: sensory	69	3	0	0	0	0
Alopecia	61	11	0	—	—	0
Fever	67	4	1	0	0	0
Constipation	66	5	1	0	0	0

No. of cases ($n = 72$). AST, aspartate aminotransferase; ALT, alanine aminotransferase; PaO_2, partial pressure of arterial oxygen.
*One missing data.

Table 3. Late toxicities

	Grade					% Grade 3/4
	0	1	2	3	4	
Esophagitis	49	21	2	0	0	0
Arrhythmia	68	3	1	0	0	0
Dyspnea	59	5	6	2	0	2.8
Neuropathy: sensory	71	1	0	0	—	0
Neuropathy: motor	72	0	0	0	0	0
Cardiac ischemia	70	0	1	1	0	1
Pericarditis	58	12	2	0	0	0

No. of cases ($n = 72$).

Table 4. Quality review results for radiotherapy

Evaluation	No. of cases	%
Per protocol	21	29
Deviation, acceptable	23	32
Deviation, unacceptable	19	26
Not evaluable	3	4
Not available	6	8
Total	72	

No. of cases ($n = 72$).

With respect to the safety, only two Grade 3 adverse events were observed during treatment, GOT elevation ($n = 1$) and GPT elevation ($n = 1$), and no Grade 4 toxicity was reported. These results seemed promising because these toxicities were less severe than observed in other trials in which chemoradiotherapy performed in more advanced disease (6,15). As to late toxicities due to chemoradiotherapy, Grade 3 toxicities such as ischemic heart disease ($n = 1$) and dyspnea ($n = 1$) were observed; however, all of them were treatable.

We found two possible reasons which might have contributed to the mildness of the toxicities in this trial: (i) the patient's PS was good (ECOG PS was 0) and (ii) the radiation field was intentionally limited to enable salvage surgery in case of relapse. The limited radiation field may also have contributed to the safe salvage surgery after recurrence of the disease. The proportion of patients who received salvage surgery after chemoradiotherapy seems to be appropriate in this population. However, there is no valid comparable data for it.

During or after the chemoradiotherapy, more recurrence in the esophagus is likely to occur because the esophagus itself remains in contrast to after surgery. In this trial, the 4-year RFS was 52.8% (95% CI: 41.2–64.3) when mucosal recurrences removable with EMR (minor relapse) were counted as event. When such recurrence was not counted, the 4-year major RFS was 68.1% (95% CI: 57.3–78.8). Although the recurrences were occurred in this way, the survival proportion was high because most of the minor relapses were salvaged by EMR.

The quality review results for radiotherapy were not optimal in this trial, because there were no dummy run study and no early review before or just after the start of treatment. These are important items to keep the high quality of clinical trials and proactive quality assurance programs have been introduced in JCOG trials since 2002.

In this trial, the survival proportion at 4 years was high and the toxicities were mild, so we are now conducting a Phase III trial (JCOG0502) to demonstrate non-inferiority of chemoradiotherapy comparing with surgery for the patients with clinical Stage I ESCC to confirm the results of this study.

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Conflict of interest statement

None declared.

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