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Clinical Evaluation of Low-dose Cisplatin and 5-Fluorouracil as Adjuvant Chemoradiotherapy for Advanced Squamous Cell Carcinoma of the Esophagus

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ABSTRACT

The aim of this retrospective study was to evaluate the effectiveness of low-dose cisplatin and 5-fluorouracil (low-dose FP) as an adjuvant chemoradiotherapy for resected advanced squamous cell carcinoma of the esophagus. From 1994 to 1999, 57 patients who showed an invasion of the tumor over the muscularis propria (T2-T4), regional lymph node metastasis (N1), and no distant metastasis (M0) were enrolled in this analysis. Postoperative chemoradiotherapy (CRT group) was performed on 14 of the patients, and they were compared to the patients who underwent surgery alone (S group) using the matched pair algorithm. In the CRT group, chemotherapy of low-dose FP was combined with concurrent radiotherapy after the esophagectomy. A side-effect of severe dysphagia (NCI-CTC Grade 3) was observed in 4 patients (28.6%) and leukocytopenia in 1 patient (7.1%) among the CRT group. The overall survival rate of the CRT group and matched S group were 35.7% and 28.5% at 5 years, respectively, with no significant difference. In the CRT group, 7 of 14 patients (50%) had a recurrence. The recurrence rate was slightly lower than in the S group (57%), with no significant difference. This combined chemoradiotherapy using low-dose FP did not improve the prognosis of patients with resected advanced esophageal carcinoma.

Key words: *Adjuvant therapy, Adjuvant chemoradiotherapy, Low-dose cisplatin and 5-fluorouracil, Advanced esophageal cancer*

The prognosis for esophageal cancer is pessimistic. The 5-year survival rate of patients who underwent esophagectomy has been low at 36%, especially with positive lymph node metastasis at 22%[16]. To improve the survival rate of patients with esophageal cancer, surgeons, especially in Japan, have tried to perform three-field lymphadenectomy (neck, mediastinum and abdomen). A number of reports have shown a significant improvement in survival rate[1,10]. This surgical strategy, however, seems to have increased the incidence of complications, e.g. recurrent nerve palsy and pneumonia. Thus, some limitations must be placed on the indications for extended lymphadenectomy. Another way to improve the prognosis is through the use of adjuvant therapy.

Various regimens of chemotherapy with or without radiation have been reported in the treatment of patients with esophageal cancer. However, the optimal preoperative or postoperative adjuvant therapy is still controversial. Between September 1990 and December 1993, we performed a postoperative adjuvant chemoradiotherapy (CRT) with cisplatin (CDDP), 5-fluorouracil (5-FU) and etoposide (VP-16) for patients with advanced esophageal cancer, but this regimen did not improve the prognosis[12]. Therefore, we set up a new regimen of postoperative adjuvant CRT with low-dose FP, which was expected to result in minimum side effects and a high rate of effectiveness. This paper revealed the outcome of this regimen in comparison with that of surgery alone using a matched control-case study.

PATIENTS AND METHODS

Patients

Between October 1994 and September 1999, 88 patients with esophageal squamous cell carcinoma underwent a curative surgical resection. Among them, 57 patients showed an invasion of the tumor over the muscularis propria (T2-T4), regional lymph node metastasis (N1), and no distant metastasis (M0) as determined by histological

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examination. Patient eligibility requirements for CRT were as follows: a leukocyte count greater than 3000/μl; a platelet count greater than 100000/μl; a creatinine level less than 1.4 mg/dl; creatinine clearance greater than 50 ml/min; a total bilirubin level less than 3 mg/dl, and AST and ALT levels less than 100 U/ml. Assessment of the suitability for CRT was made at 2 weeks after surgery. CRT was performed in 14 of the patients (CRT group). Informed consent was obtained from all of the patients. To evaluate the effect of CRT, matched pair analysis was carried out. The patients who underwent surgery alone (S group) were selected on the basis of an algorithm of the pathological TNM classification. The matching criteria in descending order of importance were pathological stage and pathological TNM classification (Table 1). Fourteen patients were selected from the group of 57 patients. The characteristics of the patients in the two groups are shown in Table 1. In all of them, the pathologic feature was squamous cell carcinoma.

Therapeutic Regimen

The regimen of postoperative CRT is shown in Fig. 1. The regimen comprised 4 weeks of chemotherapy with low-dose FP plus 5 weeks of concurrent radiation. The chemotherapy consisted of 5 mg/body CDDP on days 1 to 5 administered as a 1-hour (h) drip infusion, and 250 mg/m^2 5-FU on days 1 to 7 administered as a 24-h continuous drip infusion beginning at 2 weeks after surgery. The concurrent radiotherapy was started at 3 weeks after the surgery. The target volume included the superior or full mediastinum and the supraclavicular area, and the total dosage was 50 Gy.

Table 1. Factors used for selection of matched case-control study

Matching factor	Description
Factor 1	Histological stage (IIA, IIB, III)
Factor 2	T (T1, T2, T3, T4)
	N (N0, N1)

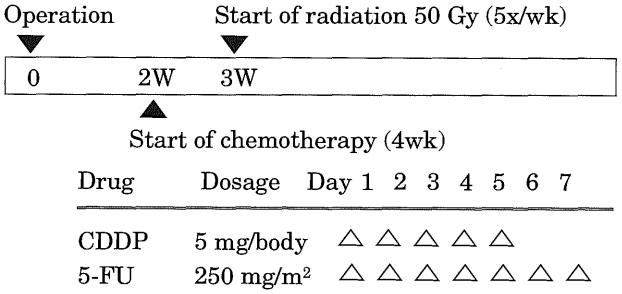

Fig. 1. Schedule of adjuvant chemoradiotherapy

Statistical Analysis

The survival curve was calculated by the Kaplan-Meier method and compared using the log-rank test. Comparisons between the two groups were made using Student's t-test for unpaired variables and Fisher's exact test. Statistical significance was defined at a probability level of less than 0.05.

RESULTS

There was no statistically significant difference in pathological TNM staging, sex ratio, age distribution, tumor localization, operative procedure, and pathological type between the CRT and S groups (Table 2).

The mean dosage of radiation received was 86%, and chemotherapy was 98% of the regimen. A total of 11 patients (78.6%) completed the planned treatment. Three patients (21.4%) did not complete the adjuvant therapy protocol because of severe leukocytopenia (1 patient) and dysphagia (2 patients). There was no adjuvant treatment-related toxic death. The side effects are shown in Table 3. Severe dysphagia (Grade 3) was observed in 4 patients (28.6%) and leukocytopenia (Grade 3) in 1 patient (7.1%).

The overall 5-year survival rate of the CRT group was 35.7%, and that of the S group was 28.5%, without a significant difference (Fig. 2). The disease-free survival rate was 35.7% in the

Table 2. Patients' characteristics according to treatment group

	Surgery alone	Chemoradiation
Number	14	14
Sex (Male/Female)	12/2	12/2
Age	65.7 ± 11.0	62.5 ± 7.1
Location Upper	1	2
Middle	9	9
Lower	4	3
Operation TTE	12	13
THE	2	1
Histology Well	1	2
Moderately	7	7
Poorly	6	5
pT T1	4	2
T2	2	4
T3	6	6
T4	2	2
pN N0	4	4
N1	10	10
pStage IIA	4	4
IIB	4	4
III	6	6

TTH: transthoracic esophagectomy, THE: transhiatal esophagectomy

Table 3. Incidence of side-effects in CRT group

	Grade					Grade 3/4 (%)
	0	1	2	3	4	
Dysphagia	1	4	5	4	0	28.6%
Nausea/vomiting	11	3	0	0	–	
Leucocyte	3	3	7	1	0	7.1%
Hemoglobin	7	7	0	0	0	
Platelet	13	1	0	0	0	
Creatinine	13	1	0	0	0	
T. Bilirubin	13	1	0	0	0	
AST/ALT	13	1	0	0	0	

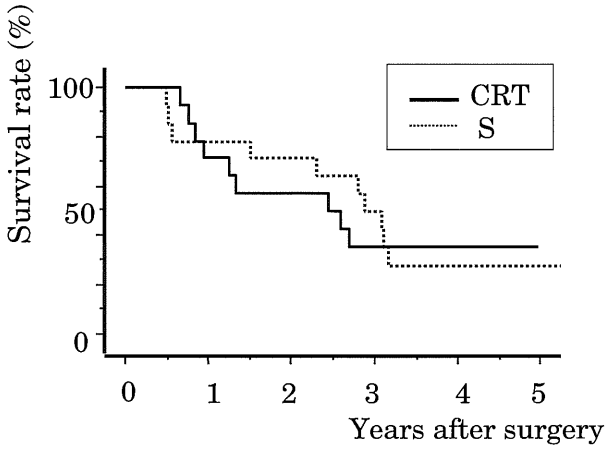

Fig. 2. The overall survival rate in the CRT group was 35.7% at 5 years, and it was demonstrated that CRT did not improve that survival rate when compared with the results from the matched S group. (28.5%, respectively)

Table 4. Recurrence site according to the treatment group

	Surgery alone	Chemoradiation
Number of recurrence cases (%)	8 (57)	7 (50)
Recurrence		
Local (%)	1 (7.1)	1 (7.1)
Dissemination (%)	0	2 (14.3)
Lymph node (%)	3 (21.4)	3 (21.4)
Cervical / Supraclavicular	1	2
Mediastinal	2	1
Abdominal	0	0
Organ (%)	4 (28.6)	1 (7.1)
Lung	1	0
Liver	3	1

CRT group and 28.5% in the S group at 5 years, without a significant difference.

In the CRT group, recurrence occurred in 7 (50%) of 14 patients. The recurrence rate of the CRT group was slightly lower than that of the S group (57%) with no significant difference (Table 4). The site of recurrence in the CRT group was local (n=1), cervical or supraclavicular lymph nodes (n=2), mediastinal lymph nodes (n=1), the liver (n=1), and pleural dissemination (n=2). Organ metastasis developed in 1 (7.1%) patient in the CRT group and in 4 (28.6%) in the S group.

DISCUSSION

With recent advances in perioperative management, operative morbidity and mortality after esophagectomy have decreased remarkably. However, extended lymphadenectomy seems to increase the incidence of complications. Recently, we suggested that post-operative complications might contribute to a poor prognosis[7]. Thus, effective perioperative adjuvant therapy should be developed instead of extended surgery with excessive surgical stress.

In a study by the Japan Clinical Oncology Group, postoperative adjuvant chemotherapy with CDDP and vindesine had no additive effect on survival in patients with esophageal cancer compared with surgery alone[2]. Several trials involving chemotherapy combined with CDDP and 5-FU in patients with squamous cell carcinoma of the esophagus have resulted in an improved tumor response. Iizuka et al previously reported the response rate to be 35.9% with 70 mg/m^2 of CDDP and 700 mg/m^2 of 5-FU[8]. Therefore, in a study by the Japan Clinical Oncology Group, postoperative adjuvant chemotherapy combined with chemotherapy consisting of CDDP and 5-FU was administered. However, the results suggested that adjuvant chemotherapy did not improve overall survival, although it resulted in improvement of the disease-free survival rate[3].

Recently, some investigators have attempted to establish an optimal therapeutic schedule for this combination. Shirasaka et al suggested that CDDP increases the antitumor activity of 5-FU as a biochemical modulator[15]. Ikeda et al reported that CDDP is administered by daily continuous infusions[9]. The optimal dose of low-dose daily CDDP infusion has not yet been established, but several investigators reported a range from 5 to 20 mg/body/day[11, 13]. Low-dose CDDP has the advantages of lower toxicity and the omission of hydration. In a phase II study reported by the Japan Esophageal Oncology Group, the response rate was 33.3% with daily 20 mg/m^2 of CDDP and 800 mg/m^2 of 5-FU[6].

The effect of postoperative radiotherapy on patients with esophagectomy has been controversial. In 1993 Fok et al carried out a prospective randomized controlled study on postoperative radiotherapy. They concluded that postoperative radiotherapy was associated with increased morbidity and death, and that it reduced the overall survival in comparison with control patients[5].

Recently, Xiao et al reported that postoperative radiotherapy improved the 5-year survival rate in esophageal cancer patients with positive lymph node metastasis and with stage III disease compared with similar patients who did not receive radiotherapy[17].

Multimodality treatment for esophageal cancer is still under investigation with the hope that the overall survival rate can be improved. In Japan, Saito et al reported that postoperative CRT with CDDP, vindesine and peplomycin improved the 5-year survival rate in esophageal cancer patients with TNM stage II-IV[14]. Recently, Bedard et al reported that postoperative CRT with CDDP, 5-FU and epirubicin improved the 5-year survival rate with positive lymph node metastasis[4]. However, the effect of postoperative CRT has been controversial because the 5-year survival rate of the surgery alone was low (5.1%) in the protocol of Saito et al, and adenocarcinoma was present in 70% of all the patients who underwent the protocol of Bedard et al. Thus, no prospective, randomized controlled study has been performed.

In our regimen, the radiotherapy and chemotherapy were performed concurrently, as the efficacy of the radiotherapy was expected to be enhanced when administered simultaneously with the anticancer drugs. However, the dosage of anticancer drugs was decreased in comparison with the dosage used when chemotherapy was administered alone so as to avoid severe toxicity. In this study, the overall survival rate in the CRT group was 35.7% at 5 years. In our previous study, chemotherapy consisted of 50 mg/m^2 CDDP on days 1 and 7 and 500 mg/m^2 5-FU and 60 mg/m^2 VP-16 on days 3 to 5 at 4 weeks after surgery, and this regimen was repeated twice with an interval of 4 weeks. In the current study, the survival rate was 10% higher than that of our previous study. This regimen is associated with a lower toxicity, and the rate of recurrence was 50%, which was lower than in our previous study (66%) (Table 5). In CRT, many problems have not been resolved concerning the timing of the therapy, the optimal radiation dosage, and the most effective chemotherapeutic agent. In this study, we chose a matched-pair study design for the elevation of the clinical results because the study input criteria (histological stage, TNM) were strict, making a randomized study impractical due to the small number of patients involved. Our next step is to await the results of the prospective randomized trials (phase III) still in progress. On the one hand, our next step toward improving in the prognosis is a new regimen including new chemotherapeutic agents (e.g. Taxan) and optimal radiation dosage.

In conclusion, in order to evaluate the efficiency of adjuvant CRT following surgery in patients with advanced esophageal carcinoma, combined chemotherapy consisting of low-dose cisplatin and 5-fluorouracil plus concurrent radiotherapy was administered. However, our results suggest that adjuvant CRT did not improve the prognosis for patients with advanced esophageal carcinoma.

Table 5. Comparison between low-dose CDDP + 5-FU and our previous study

	low-dose FP	EFP
5-year survival rate (%)	35.7	25.2
Number of recurrence cases (%)	50.0	66.7
Recurrence		
Local (%)	7.1	0
Dissemination (%)	14.3	16.7
Lymph node (%)	21.4	25.0
Organ (%)	7.1	25.0
Side-effect: Grade 3/4 (%)	28.6	47.0

EFP : CDDP, 5-FU and VP-16

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REFERENCES

1. **Akiyama, H., Tsurumaru, M., Udagawa, H. and Kajiyama, Y.** 1994. Radical lymph node dissection for cancer of thoracic esophagus. Ann. Surg. **220:** 364–372.
2. **Ando, N., Iizuka, T., Kakegawa, T., Isono, K., Watanabe, H., Ide, H., Tanaka, O., Shinoda, M., Takiyama, W., Arimori, M., Ishida, K. and Tsugane, S.** 1997. A randomized trial of surgery with and without chemotherapy for localized squamous cell carcinoma of the thoracic esophagus: the Japan Clinical Oncology Group Study. J. Thorac. Cardiovasc. Surg. **114:** 205–220.
3. **Ando, N., Iizuka, T., Ide, H., Ishida, K., Shinoda, M., Nishimaki, T., Takiyama, W., Watanabe, H., Isono, K., Aoyama, N., Makuuchi, H., Tanaka, O., Yamada, H., Ikeuchi, S., Kabuto, T., Nagai, K., Shimada, Y., Kinjo, Y. and Fukuda, H.** 2003. Surgery Plus Chemotherapy Compared with Surgery Alone for Localized Squamous Cell Carcinoma of the Thoracic Esophagus: A Japan Clinical Oncology Group Study- JCOG9204. J. Clin. Oncol. **21:** 4592–4596.
4. **Bedard, E.L., Inculet, R.I., Malthaner, R.A., Brecevic, E., Vincent, M. and Dar, R.** 2001. The role of surgery and postoperative chemoradiation therapy in patients with lymph node positive esophageal carcinoma. Cancer **91:** 2423–2430.
5. **Fok, M., Sham, J.S., Choy, D., Cheng, S.W. and Wong, J.** 1993. Postoperative radiotherapy for carcinoma of the esophagus. Surgery **113:** 138–147.
6. **Hayashi, K., Ando, N., Watanabe, H., Ide, H., Nagai, K., Aoyama, N., Takiyama, W., Ishida, K., Isono, K., Makuuti, H., Imamura, M., Shinoda, M., Ikeuchi, S., Kabuto, T., Yamana, H. and Fukuda, H.** 2001. Phase II Evaluation of Protracted Infusion of Cisplatin and 5-Fluorouracil in Advanced Squamous Cell Carcinoma of the

Esophagus: Jpn. J. Clin. Oncol. **31:** 419–423.
7. **Hihara, J., Hirai, T., Yamashita, Y., Yoshida, K., Kuwahara, M., Kagawa, Y. and Toge, T.** 1999. Poor prognosis in esophageal cancer patients with post-operative complications: surgical oncotaxis. Dis. Esophagus. **12:** 152–154.
8. **Iizuka, T., Kakegawa, T., Ide, H., Ando, N., Watanabe, H. and Takagi, I.** 1992. Phase II evaluation of cisplatin and 5-fluorouracil in advanced squamous cell carcinoma of the esophagus. Jpn. J. Clin. Oncol. **22:** 172–176.
9. **Ikeda, K., Terashima, M., Kawamura, H., Takiyama, I., Koeda, K., Takagane, A., Sato, N., Ishida, K., Iwaya, T., Maesawa, C., Yoshinari, H. and Saito, K.** 1998. Pharmacokinetics of cisplatin in combination cisplatin and 5-fluorouracil therapy: a comparative study of three different schedules of cisplatin administration. Jpn. J. Clin. Oncol. **28:** 168–175.
10. **Kato, H., Watanabe, H., Tachimori, Y. and Iizuka, T.** 1991. Evaluation of neck lymph node dissection for thoracic esophageal carcinoma. Ann. Thorac. Surg. **51:** 931–935.
11. **Kondo, K., Murase, M., Kodera, Y., Akiyama, S., Ito, K., Yokoyama, Y., Takagi, H. and Shirasaka, T.** 1996. Feasibility study on protracted infusional 5-fluorouracil and consecutive low-dose cisplatin for advanced gastric cancer. Oncology **53:** 64–67.
12. **Mukaida, H., Hirai, T., Yamashita, Y., Yoshida, K., Hihara, J., Kuwahara, M. and Toge, T.** 1998. Clinical Evaluation of Adjuvant Chemoradiotherapy with CDDP, 5-FU and VP-16 for Advanced Esophageal Cancer. Jpn. J. Thorac. Cardiovasc. Surg. **46:** 11–17.
13. **Ohtsu, A., Shimada, Y., Yoshida, S., Saito, H., Seki, S., Morise, K. and Kurihara, M.** 1994. Phase II study of protracted infusional 5-fluorouracil combined cisplatin for advanced gastric cancer. Eur. J. Cancer **14:** 2091–2093.
14. **Saito, T., Shigematsu, Y., Kinoshita, T., Shimoda, K., Abe, T., Nakamura, A., Chikuba, K. and Kobayashi, M.** 1993. Cisplatin, vindesine, pepleomycin and concurrent radiation therapy following esophagectomy with lymph adenectomy for patients with an esophageal carcinoma. Oncology **50:** 293–297.
15. **Shirasaka, T., Shimamoto, Y., Ohshimo, H., Saito, H. and Fukushima, M.** 1993. Metabolic basis of synergistic antitumor activities of 5-fluorouracil and cisplatin in rodent tumor models in vivo. Cancer Chemother. Pharmacol. **32:** 167–172.
16. **The Japanese Society for Esophageal Disease.** Long-term Results of Esophagectomy in Japan (1988–1997). 2002
17. **Xiao, Z.F., Yang, Z.Y., Liang, J., Miao, Y.J., Wang, M., Yin, W.B., Gu, X.Z., Zhang, D.C., Zhang, R.G. and Wang, L.J.** 2003. Value of radiotherapy after radical surgery for esophageal carcinoma. Ann. Thorac. Surg. **75:** 331–336.