Table 1. Treatment results of definitive chemoradiotherapy in randomized trials

	Chemotherapy	RT (Gy)	*n*	2-Year survival	3-Year survival	*P* Value
RTOG 85-01	FP	50	61	38%	30%	<0.0001
	Control	64	62	10%	0%	
RTOG 94-05	FP	50	109	40%	NR	NS
	FP	64	109	31%	NR	

FP, 5-fluorouracil + cisplatin; NR, not reported; NS, not significant; RT, radiotherapy

Table 2. Randomized trials of preoperative chemoradiotherapy + surgery versus surgery alone

Author	*n*	Histology	Treatment	pCR	MST (months)	3-Year survival	*P* Value
Bosset et al.[19]	282	100% Squamous cell carcinoma	CRT + S	26%	19	36%	0.8
			S	0%	17	36%	
Walsh et al.[18]	113	100% Adenocarcinoma	CRT + S	25%	16	32%	0.01
			S	0%	11	6%	
Urba et al.[20]	100	75% Adenocarcinoma 25% Squamous cell carcinoma	CRT + S	28%	17	30%	0.15
			S	0%	17	15%	

pCR, pathological complete response; MST, median survival time; CRT, chemoradiotherapy; S, surgery

The findings of a comprehensive review of the recent literature on chemoradiotherapy for the treatment of esophageal cancer are presented here.

Overview of chemoradiotherapy based on the results of clinical trials

Definitive chemoradiotherapy

Although there have been several trials comparing radiation therapy alone with chemoradiotherapy, most of the studies used suboptimal doses of radiation therapy or inadequate systemic chemotherapy.[8–11] The only trial which was designed to administer adequate chemotherapy with an optimal dose of radiotherapy was the RTOG 85-01 trial (Table 1).[4,11] In this study, patients in the radiation-alone group received irradiation alone, at a total dose of 64 Gy, and those in the chemoradiotherapy group received continuous infusion of 5-fluorouracil (5-FU; 1000 mg/m^2 per day for 4 days), cisplatin (75 mg/m^2, day 1), and concurrent irradiation, at a total dose of 50 Gy (2 Gy/day; 25 fractions). Histologically, the majority (82%) of the patients registered had squamous cell carcinoma. This study revealed a significant improvement of survival in terms of both median survival times (14 months vs 9 months) and 5-year survival (27% vs 0%; $P < 0.001$) in favor of chemoradiotherapy. With a minimum follow-up period of 5 years, the 8-year survival rate of the chemoradiotherapy group was 22%.[12] This study established definitive chemoradiotherapy as the standard of care for the nonsurgical management of esophageal cancer. However, local failure remained a major issue: 45% of the patients in the chemoradiotherapy group developed local failure.

To improve the local control rate, the intergroup randomized trial (INT 0123/RTOG 94-05) was conducted.[13] In this study, a slightly modified RTOG 85-01 chemoradiotherapy regimen was used as the control arm and was compared with an intensified dose, of 64.8-Gy radiation therapy, with the same chemotherapy. The modifications to the original RTOG 85-01 regimen were: using 1.8-Gy fractions to a total of 50.4 Gy, treating patients with 5-cm proximal and distal margins with 50.4 Gy, and chemotherapy being delivered every 4 weeks. This trial also included a majority (85%) with squamous cell carcinoma. However, no significant differences in 2-year survival (40% in the control arm vs 31% in the higher-radiation-dose arm) or in local failure and/or local persistence rate of disease (52% vs 56%) were observed in this study. These results demonstrated that intensification of the radiation dose did not improve the results of chemoradiotherapy.

Despite the failure of improvement by intensification of the radiation dose, this survival outcome from definitive chemoradiotherapy appearred to be comparable to that of primary surgery in the West.[14,15] However, no randomized trials comparing surgery with definitive chemoradiotherapy have been published, and accordingly, little is known about their comparative outcomes, although there have been a few series of retrospective comparisons that suggested similar survivals in both groups.[16,17]

Preoperative chemoradiotherapy followed by surgery in comparison with surgery alone

To improve surgical outcomes, preoperative chemoradiotherapy has been extensively investigated, as compared with surgery alone, in randomized trials although these studies have produced conflicting results (Table 2).[18–20] Walsh et al.[18] reported a randomized trial comparing preoperative chemoradiotherapy followed by surgery with surgery alone in 113 patients with adenocarcinoma of the esophagus. Radiation, at a total dose of 40 Gy in 15 frac-

Table 3. Randomized trials of chemoradiotherapy with and without surgery

Study	Stage	Treatment	*n*	SM	MST (months)	3-Year survival	*P* Value
French	T3M0	CRT	130	1%	19.3	31%	0.56
Responders only		CRT + S	129	9%	17.7	29%	
German	T3-4M0	CRT	88	2%	15.2	24% (54%)	0.06
		CRT + S	89	9%	16.3	31% (54%)	

Figures in parentheses are results of patients who responded to chemoradiotherapy
SM, surgical mortality; MST, median survival time; CRT, chemoradiotherapy; S, surgery

tions, was delivered concurrently with chemotherapy consisting of 5-FU, at 15 mg/kg per day for 5 days and cisplatin at 75 mg/m^2 on day 1. Significantly better 3-year survival (32% vs 6%) was observed in favor of the trimodality arm. However, there was a major criticism, of the high surgical mortality rate of 9% and the low 3-year survival of 6% in the surgery-alone arm.

Urba et al.[20] have also reported the results of a randomized trial comparing trimodality therapy with surgery alone, in 100 (75% with adenocarcinoma) patients with esophageal cancer. Patients were randomly allocated to either preoperative 5-FU, cisplatin, vinblastine, and radiation therapy (45 Gy) followed by transhiatal esophagectomy or surgery alone. Although there was a trend for improved survival (30% vs 15% at 3 years) for patients treated with the trimodality therapy, the difference did not reach statistical significance. Two other similar randomized trials failed to demonstrate a survival advantage of preoperative chemoradiotherapy.

Based on these results, there still remain controversies in regard to the survival advantage of preoperative chemoradiotherapy over surgery alone. Limitations of sample sizes in these studies, and the high mortality rate after preoperative chemoradiotherapy may be the major causes of the negative results. However, it seems likely that preoperative chemoradiotherapy is a reasonable treatment approach, particularly in patients with adenocarcinoma, although a definitive answer has not been obtained yet.

Preoperative chemoradiotherapy followed by surgery in comparison with definitive chemoradiotherapy

Two large randomized trials examining whether or not surgery is necessary after chemoradiotherapy were reported at the annual meetings of the American Society of Clinical Oncology in 2002 and 2003 (Table 3). The first study was reported from France (FFCD 9102).[21] This study included patients with T3NanyM0, who received, firstly, chemoradiotherapy comprising two courses of 5-FU and cisplatin with concurrent radiation therapy ranging from 30 to 46 Gy, and then were randomly allocated to receive surgery or additional chemoradiotherapy (three courses of the same chemotherapy and 20 Gy of irradiation) if they had responded to the initial chemoradiotherapy. A total of 451 patients were enrolled, with 259 patients who responded to the initial chemoradiotherapy entered into the randomized stage of the study. No significant differences in overall survival were observed between the surgery and additional chemoradiotherapy arms. Median survival times and 2-year survival rates in the two arms were 17.7 months and 34%, respectively, in the surgery arm, and 19.3 months and 40%, respectively, in the additional-chemoradiotherapy group. Mortality rates within 3 months were higher in the surgery group than in the chemoradiotherapy group (9% vs 1%). However, there were no significant differences in quality of life between the two arms, although the scores were superior in the chemoradiotherapy group during the first 2 years of treatment. The second study was reported from Germany.[22] Patients with T3–4NanyM0 squamous cell carcinoma were randomized to receive chemoradiotherapy followed by surgery or definitive chemoradiotherapy alone. The chemoradiotherapy consisted of three cycles of chemotherapy (5-FU + leucovorin + etoposide + cisplatin) followed by chemoradiotherapy (etoposide + cisplatin + irradiation up to 40 Gy for the trimodality group, or up to 60 Gy for the chemoradiotherapy group). A total of 177 patients were registered for the study. Mortality rates during the treatment were higher in the trimodality arm than in the chemoradiotherapy group (9% vs 2%). Survival differences between the groups showed a tendency in favor of the trimodality arm ($P = 0.06$) and the trend appeared more remarkable after 3 years, though the difference did not reach statistical significance. However, in patients who responded to the initial chemoradiotherapy, there were no obvious differences in survival between the two arms, similar to the result seen in the FFCD 9102 trial (Table 3).

Toxicity of chemoradiotherapy

With the addition of synchronous chemotherapy to radiotherapy, acute treatment-related toxicity is significantly increased. The major toxicities are myelotoxicity and esophagitis. In the RTOG 85-01 trial, grade 3 or 4 esophagitis occurred in 33% of patients receiving chemoradiotherapy, compared with 18% in those receiving radiotherapy alone.[11] The risk of myelosuppression increases with an increasing number of chemotherapy agents or with increases of dose intensity. When the standard chemotherapy regimen, 5-FU and cisplatin, is incorporated into chemoradiotherapy, the treatment is usually safe. However, in patients who received mitomycin C, vinblastine, paclitaxel, or etoposide in addition to 5-FU and cisplatin, high rates of severe myelotoxicity have been reported.[23–26]

Table 4. Late toxicity of definitive chemoradiotherapy in 78 patients achieving a CR

	Grade (G)			
	2	3	4	≥G3 (%)
Pleural effusion	7	8	–	10.3
Pericarditis	8	7	1	10.3
Heart failure	–	–	2	2.6
Radiation pneumonitis	1	3	–	3.8

Regarding the late toxicity of chemoradiotherapy, our group has reported its incidence and outcomes in 78 patients who achieved a complete response with definitive chemoradiotherapy.[27] Major late toxicities included pleural effusion, pericarditis, and radiation pneumonitis: the incidences of grade 3 or 4 of these toxicities were 10.3%, 10.3%, and 3.8%, respectively (Table 4). The median times to the onset of grade 3 or 4 pleural effusion, pericarditis, and pneumonitis were 15, 18, and 5 months, respectively, from the initiation of chemoradiotherapy. In total, 8 patients died without cancer recurrence, and their causes of death may have been related to cardiopulmonary toxicity. One of the reasons for the significant late toxicity may have been the wide elective nodal irradiation, of up to 40 Gy with anteroposterior opposed portals, which means that more than 60% of the entire heart volume received at least 40 Gy. Additional investigation to minimize toxicities to normal tissues is warranted.

When chemoradiotherapy was combined with surgery, the reported postoperative mortality ranged from 0 to 29%, with a mean value of 9%.[28] Adult respiratory distress syndrome, anastomotic leakage and breakdown, pneumonia, and sepsis were the most common causes of death following esophagectomy.

Current status of chemoradiotherapy by stage

Stage I disease

In the Western studies described above, few patients with stage I disease were included, and the impact of chemoradiotherapy for this stage has not been clarified. From Japan, Ura et al.[29] reported a retrospective series of definitive chemoradiotherapy in 73 patients with stage I disease. There were 68 (93%) complete responses, and the remaining 5 patients with residual tumor were successfully treated with endoscopic resection (ER) or surgery. Salvage ER or surgery was also safely indicated for recurrent local tumors. Ura et al.[29] achieved 3- and 5-year survival rates of 80% and 77%, respectively, which are comparable to those for ordinary surgery. Similar results have been reported from a multiinstitutional prospective study from the Japan Clinical Oncology Group (JCOG 9708) in patients with stage I disease.[30] A total of 72 patients were registered, and a 96% complete response rate was achieved with definitive chemoradiotherapy. Patients who developed recurrence were successfully treated with ER and surgery. The 2-year survival and recurrence-free survival were 93%, and 75%, respectively. These results are comparable to those for primary surgical resections,[31] and chemoradiotherapy may be a standard treatment option, although salvage ER or surgery is necessary. A randomized trial comparing primary chemoradiotherapy with surgery for stage I disease is now being planned by the JCOG.

Stage II–III (non-T4)

Controversies still remain in regard to the primary treatment of resectable disease. Based on the results from randomized trials, definitive chemoradiotherapy is considered a standard treatment for the nonsurgical approach and the survival results are comparable with Western series of surgical resections. However, it is clear that both the nonsurgical and surgical approaches have limited success, with 3- to 5-year survivals of 20% to 30%. Trimodality therapy, i.e., preoperative chemoradiotherapy followed by surgical resection, is considered the preferred modality, particularly in patients with adenocarcinoma, although a definitive advantage over surgery alone has not been confirmed yet. Other major concerns are whether the prognosis improves after surgery in patients who have residual tumors after definitive chemoradiotherapy, and whether there is better local control with the trimodality therapy. To elucidate this issue, useful information was obtained from the two European (French and German) randomized trials that compared chemoradiotherapy with and without surgery.[21,22] Although the target populations were slightly different (only T3 in the French trial and T3-4 in the German trial), the two studies showed similar results: 9% surgical mortality in both studies and no significant differences in survival between the two arms in patients who responded to the initial chemoradiotherapy. These results suggest that additional surgery has little impact on survival if patients achieve an objective response to the initial chemoradiotherapy. However, the German study, which included nonresponsive patients, tended to show borderline differences in survival in favor of additional surgery, while the French study also demonstrated better local control in the surgery group. These results may support the clinical utility of additional surgery. The National Comprehensive Cancer Network (NCCN) practice guidelines in the United State indicate that both esophagectomy and chemoradiotherapy with doses of 50–50.4 Gy are considered to be the standard treatment.[7] The recommendations also include surgery after chemoradiotherapy and adjuvant chemoradiotherapy after primary surgery, particularly in patients with adenocarcinoma, as recommended approachs, although these modalities are still investigational.

In Japan, compared with the West, there are significant differences in tumor biology and surgical treatments: histologically, in Japan, most tumors are squamous cell carcinoma, and radical surgery with extensive nodal dissection is commonly indicated. A retrospective comparison of surgical resection and definitive chemoradiotherapy at our insti-

tution revealed comparable survivals,[17] and these results seem to be similar to surgical outcomes at other Japanese institutions.[32] However, the recent JCOG randomized trial comparing radical surgery alone with radical surgery plus adjuvant chemotherapy (JCOG 9204) has reported survivals superior to those in retrospective series: the 5-year survivals of the surgery-alone and surgery- plus-adjuvant chemotherapy arms were 52% and 61%, respectively.[33] This study was based on postoperative registration, in which surgical mortality and patients with poor condition after surgery were excluded, and, therefore, there may have been some selection biases toward superior survival. However, these results are better than those for definitive chemoradiotherapy in Japan and for Western surgical series. To date, radical surgical resection with adjuvant chemotherapy is considered the standard care for this stage; for patients who are not suitable candidates for surgery, or for those who do not wish to have surgery, primary chemoradiotherapy is considered the standard care.

Unresectable T4/M1 lymphnode (LYM) disease

For patients with T4 disease, although aggressive surgical resection has been attempted in Japan, the outcome was very poor, with 5-year survival rates of less than 10% and high mortality and morbidity rates.[34] Ando et al.[32] reported outcomes of surgery in a sample of 419 patients from a single Japanese institution. In their series, although more than half of the patients underwent radical dissection, no patients with T4 disease survived for longer than 5 years. Nevertheless, there have been some Japanese reports of primary surgery for M1 LYM disease that resulted in 5-year survival rates of 14%–25%.[35,36] These results may support the use of surgery for M1 LYM disease. However, these data were based on pathological stage and it is unclear whether all clinical M1 LYM disease was included. Therefore, controversy remains regarding the indication of primary surgery for clinically relevant M1 LYM disease.

Several clinical studies of chemoradiotherapy specific to this stage have been carried out in Japan. Our group conducted a multicenter phase II study of concurrent chemoradiotherapy, consisting of 5-FU and cisplatin with 60 Gy of irradiation, for unresectable T4 and/or M1 LYM squamous cell carcinoma of the thoracic esophagus.[37] Fifty-four patients participated in the study: there were 36 patients with T4 disease and 18 patients with non-T4 (only M1 LYM) disease. Of the 54 patients, 18 (33%) achieved a complete response: 9 (25%) with T4 disease and 9 (50%) with non-T4 disease. Major toxicities were leukocytopenia and esophagitis, and there were four (7%) treatment-related deaths. The median survival time was 9 months, and the 3-year survival rate was 23%. We concluded that, despite its significant toxicity, this combined modality seemed to have curative potential, even in patients with locally advanced carcinoma of the esophagus. To confirm long-term outcomes, survival and toxicity data were updated in February 2003, which was over 5 years after the last accrual. Nine patients had survived for more than 5 years, with an actuarial 5-year survival rate of 17% (9/54): the rates were 14% (5/36) in patients with T4 disease and 22% (4/18) in those with non-T4 disease (unpublished data). Similar survival outcomes were obtained in retrospective analyses of subsequent patients treated in daily practice.[38,39] Nishimura et al.[40] reported a prospective trial of definitive chemoradiotherapy, consisting of 5-FU, cisplatin, and concurrent external-beam radiation, at a total of 60 Gy, for 28 patients with T4 esophageal cancer with or without fistulae. This study provided a complete response rate of 32%, and 2-year survival of 27% in patients with stage III disease (T4NanyM0), which appeared to be comparable to the results in our study.

Based on these recent results, mentioned above, chemoradiotherapy should be the primary treatment for T4 disease, independently of whether it will be followed by surgery. Outcomes of these studies, showing 2- to 3-year survival rates of approximately 20%, are obviously better than outcomes for palliative therapies; these survival rates could be a landmark in the treatment of T4 disease. Another major concern is whether the patients' prognoses improve following surgery. To elucidate this issue, useful information was obtained from the two European randomized trials that compared chemoradiotherapy with and without surgery.[21,22] As mentioned previously, these results may support the clinical efficacy of additional surgery, although this approach is still investigational.

Future perspectives in chemoradiotherapy

Improving local control

The major issue in primary chemoradiotherapy at present is the insufficient local control rate. Regarding this issue, intensification of radiation dose has been attempted in the INT 0123 trial, but it failed to improve the local control rate.[13] Other trials with accelerated or hyperfractionation radiation methods also showed no benefit in local control or survival, whereas there were significantly higher incidences of severe esophagitis.[41–43] These results showed the limitations of intensifying the radiation dose. The addition of new agents, other than 5-FU plus cisplatin, may be more promising. Preliminary results of adding paclitaxel to the standard chemoradiotherapy regimen showed encouraging results, with a pathological complete response rate of around 70%,[44] which warrants further investigation. The use of molecular targeting agents in combination with chemoradiotherapy could be optimal, because their toxicity profiles are clearly different from those of cytotoxic agents. In the field of head and neck cancer, cetuximab, a monoclonal antibody to epidermal growth factor receptor (EGF-R), in combination with radiation therapy, significantly prolonged survival in patients with locally advanced disease as compared with radiation alone.[45] Gefitinib, a post-EGF-R tyrosine kinase inhibitor, as monotherapy, has also shown activity against esophageal cancer.[46] Investigation of these new agents in addition to the

current standard chemoradiotherapy will be a major focus in future studies.

Salvage treatment after failure of definitive chemoradiotherapy

The survivals of patients who do not achieve a complete response with definitive chemoradiotherapy are dismal, and salvage treatment for such patients is indicated to improve the overall treatment results. The current standard radiation dose in definitive chemoradiotherapy is 50 Gy, which seems not significantly different from the doses used preoperatively (40–45 Gy). Some small studies have shown the feasibility and efficacy of salvage surgery.[47,48] Reduction of the high mortality after chemoradiotherapy is another important issue that warrants investigation. A reliable means of identifying those who are unlikely to achieve a pathological complete response is required. Some biological markers can predict prognosis and response to chemoradiotherapy, though these should be confirmed in a prospective manner in studies with a large sample size.[49,50] The optimal timing and modes of salvage surgery should also be investigated in future studies. In our practical experience,[51] when residual or recurrent tumors were limited to within the submucosal layer, ER was a safe and effective salvage treatment, and these endoscopic treatments also warrant further investigations. Until high rates of local control can be consistently achieved with chemoradiotherapy alone, these salvage treatments appear to be an integral component of multimodality treatment for esophageal cancer, and they should be active areas for clinical investigations.

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UPPER DIGESTIVE TRACT STRICTURE

TREATMENT STRATEGIES FOR ESOPHAGEAL STRICTURE BEFORE OR AFTER CHEMORADIOTHERAPY FOR ADVANCED ESOPHAGEAL CANCER

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ABSTRACT

Esophageal stricture due to advanced cancer is one of the serious complications of esophageal cancer as it causes dysphagia. A self-expandable metallic stent is easily inserted in such patients and provides immediate symptomatic relief of dysphagia. Alternatively, definitive chemoradiotherapy has demonstrated a significant improvement in local control and overall survival, and is now commonly used for not only unresectable esophageal cancer patients but also in resectable cases. However, little is known about its role in relief of dysphagia. Therefore, we reviewed our experience of patients with esophageal stricture who were treated with chemoradiotherapy. We expect that the findings in this article might be useful in future clinical practice.

Key words: esophageal stricture, chemoradiotherapy, self-expandable metallic stent, percutaneous endoscopic gastrostomy.

INTRODUCTION

Patients with locally advanced esophageal cancer sometimes develop an esophageal stricture, which is one of the serious complications of esophageal cancer as it causes dysphagia. Self-expandable metallic stents (EMS) have been used for palliation and provide immediate symptomatic relief of dysphagia.[1,2] Alternatively, definitive chemoradiotherapy (CRT) has demonstrated a significant improvement in local control and overall survival[3–6] and is now accepted as one of the standard treatments for esophageal cancer;[7,8] however, little is known about its role in relief of dysphagia.

Selection of treatment for patients with stricture due to untreated esophageal cancer

First, we should consider patients with newly diagnosed esophageal cancer with severe stricture at presentation. If they have unresectable T4 (TNM classification) tumors, how are those patients best managed? We know that EMS is easily deployed for such patients and resolves dysphagia promptly. However, it is only palliative therapy and does not provide a survival benefit. To evaluate the role of relief of dysphagia by CRT, we reviewed our experience of 51 patients with unresectable T4 esophageal cancer who were treated with definitive CRT. The CRT consisted of 60 Gy of external beam irradiation in 30 fractions concurrent with chemotherapy (5-fluorouracil (5FU) + cisplatin or nedaplatin). The ability to swallow was evaluated before and after completion of CRT and expressed as a dysphagia score: a score of 0 denoted complete dysphagia; (1) the ability to swallow only liquid; (2) the ability to eat semi-solids only; and (3) the ability to eat solid food. The results are shown in Figures 1 and 2. The dysphagia score improved in most patients. The median dysphagia score was 2 before CRT, and 3 after completion of CRT (Fig. 1). In addition, the complete response rate was 35% (18/51), and definitive CRT achieved a three-year survival rate of 26% (Fig. 2). These results indicate that definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival.

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CRT for patients with malignant fistulae due to esophageal cancer

How are esophageal cancer patients with malignant fistulae best managed? Most physicians and surgeons believe that radiotherapy or CRT for the patients with malignant fistula is contraindicated, because it may worsen the fistula. We previously reported that malignant fistulae closed in 92% (11/12) of patients after the completion of CRT, and most of them had improved the dysphagia scores[6] (Fig. 3). While the median survival time (MST) of patients with fistulae has been reported to be one to six weeks, the MST of those treated by definitive CRT was 7 months in our previous study (Fig. 4). This indicates that definitive CRT provides a chance of closure of fistulae and improves the survival.

Risks of EMS combined with CRT

Data regarding the combination treatment of EMS placement with subsequent CRT for patients with esophageal stricture due to advanced cancer is quite limited. Recently, Nishimura *et al.* reported an important investigation on the placement of stents before or during radiotherapy to the patients with advanced esophageal cancer.[9] They gathered

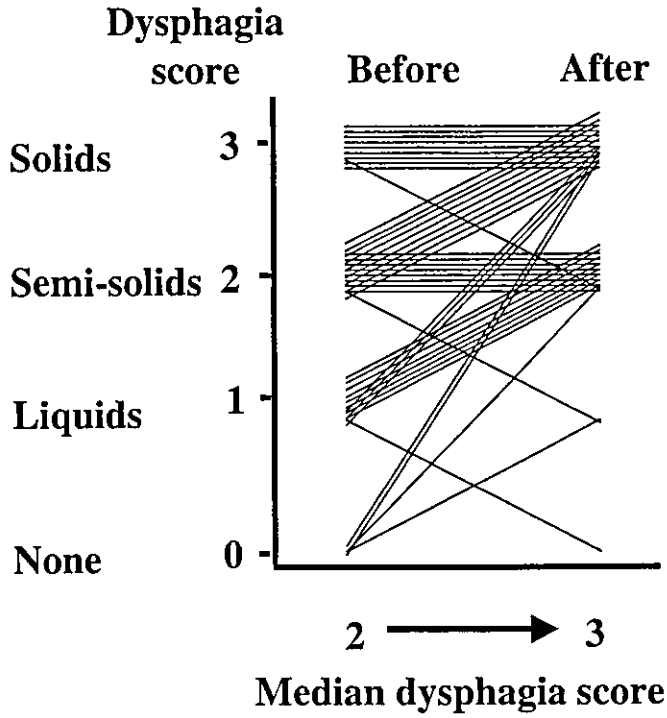

Fig. 1. Improvement of dysphasia score in the patients with esophageal stricture after completion of definitive chemoradiotherapy.

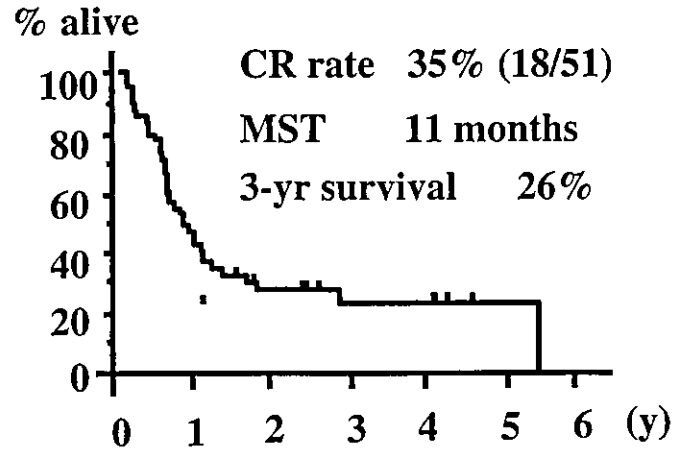

Fig. 2. Overall survival of the patients with T4 esophageal cancer treated with definitive chemoradiotherapy.

clinical data of 47 patients from 17 institutions in Japan. Covered metallic stents were used for 30 patients, uncovered metallic stents for 13 patients, plastic or silicon prosthesis for three patients, and an unknown type for one patient. Esophageal intubation was performed before the start of radiation for 23 patients and during the course of radiation for remaining 24 patients. The median total external beam radiotherapy dose was 60 Gy (6–70) and two-thirds of the patients received more then 50 Gy. Formation of or a worsening esophageal fistula occurred in 28% of such patients. Furthermore, possible treatment-related deaths were 21%. They concluded that patients with an esophageal stent introduced before or during radiotherapy have a high risk of life-threatening compli-

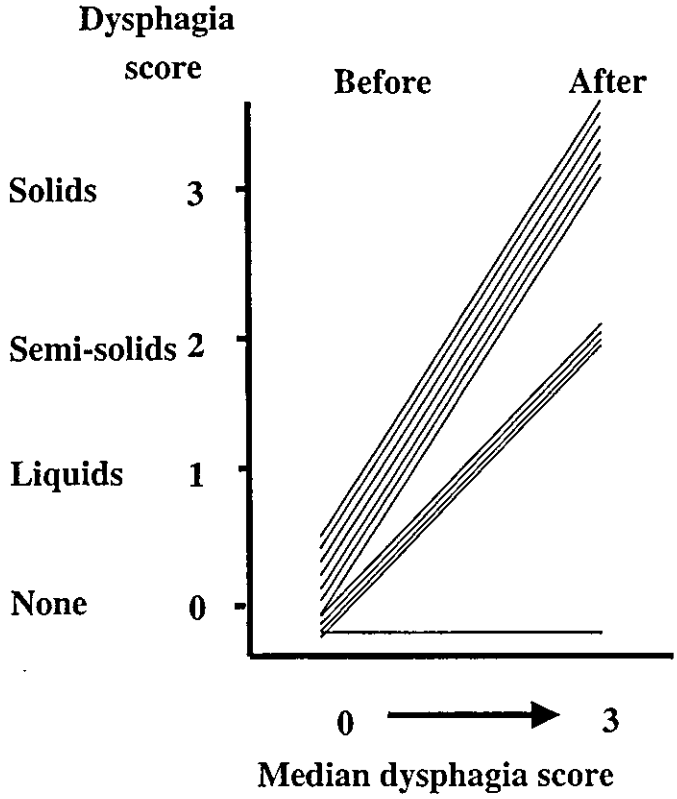

Fig. 3. Improvement of dysphasia scores in esophageal cancer patients with malignant fistula after completion of definitive chemoradiotherapy.

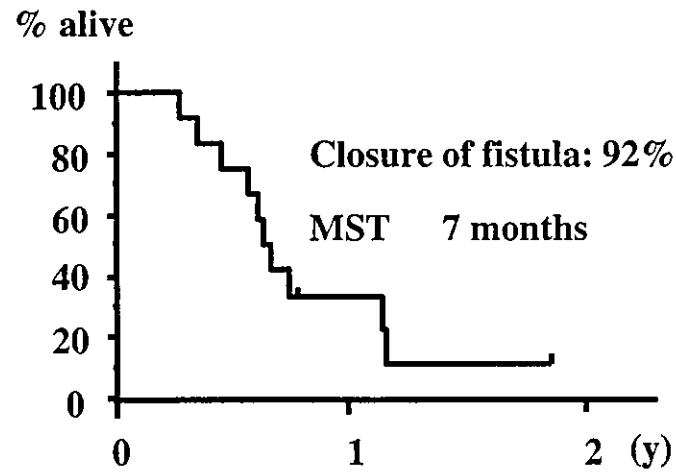

Fig. 4. Overall survival of esophageal cancer patients with malignant fistula treated with definitive chemoradiotherapy.

cations. Palliative stent placement should be delayed until radiotherapy or CRT appears to have failed, because a longer survival time is expected for patients with locally advanced esophageal cancer after CRT.

Risk of EMS placement for recurrent stricture after failure of CRT

Dysphagia due to recurrent stricture after failure of CRT means that the patient will suffer similarly to those with non-

Table 1. Self-expandable metallic stent placement for recurrent esophageal stricture after failure of radiotherapy and/or chemotherapy

Authors	Year	*n*	Rate of life-threatening complications	Does it increase the risk?
Kinsman K *et al.*[11]	1996	22	36%	Yes
Bethge N *et al.*[12]	1996	13	23%	Yes
Siersema PD *et al.*[13]	1998	20	43%	Yes
Raijman I *et al.*[14]	1997	39	8%	No
Muto M *et al.*[10]	2001	13	54%	Yes
Kaneko K *et al.*[15]	2002	12	17%	Yes
Sumiyoshi T *et al.*[16]	2003	22	High	Yes

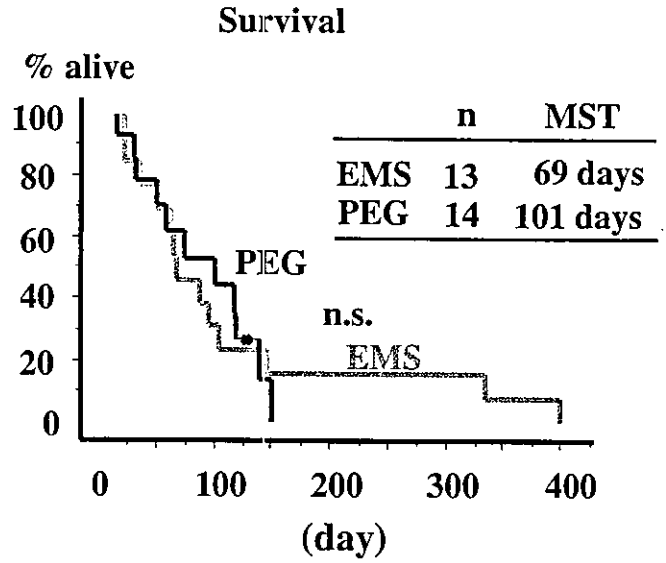

Fig. 5. Comparison of the overall survival between the patients inserted with a self-expandable metallic stent and those treated by percutaneous endoscopic gastrostomy.

treated esophageal cancer at presentation. Therefore, the main goal of palliative treatment is to relieve dysphagia even in such patients. However, it has been suggested that prior radiotherapy to the EMS placement may be associated with an increased rate of complications. We have also reported that although EMS after failure of definitive CRT improved the dysphagia score, it increased the risk of life-threatening pulmonary complications.[10] To date, many investigators have also reported the results of EMS placement for recurrent esophageal stricture after failure of radiotherapy or CRT.[11–16] We have summarized the rates of life-threatening complication in their reports (Table 1) and most concluded that EMS after failure of radiotherapy or CRT increased the rate of complications.

How should patients with recurrent dysphagia be managed after failure of CRT?

We compared the efficacy and safety between EMS and percutaneous endoscopic gastrostomy (PEG) after failure of CRT. The types of EMS deployed are summarized in Table 2. A covered stent was used for eight patients and a non-covered type was used for five. A 'one step button' was used for all PEG procedure. As for clinical events, the incidence of high fever, severe chest pain that required analgesics, and inflammation were significantly higher in the EMS group (Table 3). Survival was not different between the two groups (Fig. 5). Therefore, to improve the patients' quality of life (QOL), it seems that PEG is more feasible and safer than EMS placement.[17]

Table 2. Self-expandable metallic stent (EMS) devices and percutaneous endoscopic gastrostomy used for recurrent dysphagia after failure of definitive chemoradiotherapy

		n	Total
EMS			
Ultraflex (covered)		7	
Ultraflex (non-covered)		2	
Wall (covered)		1	
Wall (non-covered)		1	
Z-stent		2	13
PEG			
One step button	18Fr	4	
	24Fr	10	14

Table 3. Comparison between self-expandable metallic stent (EMS) and percutaneous endoscopic gastrostomy (PEG) after failure of definitive chemoradiotherapy

	EMS ($n = 13$)	PEG ($n = 14$)
High fever*	11 (85)	3 (21)
Severe pain*	8 (73)	2 (14)
CRP ↑	11 (85)	8 (57)
Pneumonia/Mediastinitis*	7 (54)	0 (0)
Peritonitis	0 (0)	1 (7)
Hospital stay (Median day, range)	28 (10–106)	13 (6–36)

(%); * $p < 0.005$.

CONCLUSION

Although SEM placement provides effective palliation for patients with esophageal stricture due to advanced cancer, long-term survival is not expected by this modality. In contrast, definitive CRT provides not only symptomatic relief of dysphagia but also a chance of survival. Therefore, we should

carefully select the treatment for such patients in consideration of the advantages for their QOL and survival.

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Clinical Trial Note

Phase II Study of Cisplatin and 5-Fluorouracil with Concurrent Radiotherapy in Advanced Squamous Cell Carcinoma of the Esophagus: a Japan Esophageal Oncology Group (JEOG)/ Japan Clinical Oncology Group Trial (JCOG9516)

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Background: In Japan, concurrent chemoradiotherapy is the standard treatment for unresectable esophageal cancer. The optimal combination of chemotherapeutic agents and radiotherapy dose remains controversial. The present study consists of a phase II trial of a cisplatin (CDDP)/5-fluorouracil (5-FU) infusion with concurrent radiotherapy in patients with unresectable, advanced esophageal cancer.

Methods: Between March 13, 1996, and April 28, 1998, 60 patients with advanced squamous cell carcinoma of the thoracic esophagus having either T4 tumor or distant lymph node metastasis (M1 Lym) were enrolled in this study. CDDP 70 mg/m^2 was administered on days 1 and 29, and 5-FU 700 mg/m^2/day was administered on days 1–4 and 29–32. Fractionated radiotherapy was performed on days 1–21 and 29–49; a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction.

Results: The overall response rate of all the 60 registered patients was 68.3% (41/60), and the complete response rate was 15% (9/60). The median survival time was 305.5 days, and the 2-year survival rate was 31.5%. One toxicity-related death occurred. The major form of toxicity exceeding grade 2 was found to be myelosuppression; grade 4 toxicity was observed in five patients.

Conclusion: Based on the overall response rate, the results obtained from the present trial do not appear to be promising. However, it is currently suitable for the treatment of patients with unresectable, advanced esophageal cancer because of certain clinical advantages, a higher CR rate and a lower incidence of fistula formation. A phase II/III trial will be started in order to compare low-dose continual CDDP/5-FU infusion and concurrent radiotherapy with the results obtained in this study.

Key words: esophageal cancer – cisplatin – 5-fluorouracil – chemoradiotherapy – phase II study

INTRODUCTION

In Japan, the standard treatment for advanced esophageal cancer has not been established. Although surgery was performed on patients with locally advanced esophageal cancer, the outcome was not satisfactory due to high invasiveness and morbidity. Several clinical trials have been conducted to evaluate the efficacy and safety of radiotherapy and chemoradiotherapy, which could be more beneficial for the patients. Herskovic et al. (1) compared concurrent chemoradiotherapy (using 5-fluorouracil [5-FU] and cisplatin [CDDP] along with radiation) with radiation therapy alone in patients with locally advanced cancer of the thoracic esophagus (T1–3, N0–1, M0). They reported that the 2-year survival rate was 38% in the group that received chemoradiotherapy, and it was significantly higher than that observed in the group that received radiotherapy alone. As a result of this trial, concurrent chemoradiotherapy using 5-FU and CDDP has become a standard treatment for T1–3 disease. However, data regarding

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treatment of patients with more advanced disease are not available. We had previously conducted a phase II trial consisting of chemotherapy, using a combination of 5-FU and CDDP, followed by radiation therapy (sequential radiotherapy) in patients having T4 disease or distant lymph node metastasis (M1 Lym) and demonstrated that the response rate (RR) was 64.4% (2). Although the RR was found to be high in the group having a far advanced disease, it was felt that the concurrent chemoradiotherapy regimen would be more beneficial as compared with the sequential regimen because the radiosensitizing effect could be therapeutically more beneficial for the patients. Therefore, the present phase II trial (JCOG9516) was performed to evaluate the efficacy and safety of concurrent chemoradiotherapy.

Objective

The objective of this study was to evaluate the efficacy and safety of chemoradiotherapy regimen using CDDP/5-FU along with concurrent radiation therapy in order to determine whether this regimen merited further investigation by a phase III trial. The clinical hypothesis was that the above regimen would achieve a higher tumor response with acceptable levels of toxicity as compared to the former phase II trial that utilized a sequential regimen of CDDP/5-FU infusion and radiation therapy. The primary endpoint of this study was the observation of an overall response to this therapy. The secondary endpoints were concerned with the overall survival and toxicity.

SUBJECTS AND METHODS

Patients

Patients with histological proof of advanced squamous cell carcinoma (SCC) of the thoracic esophagus having T4 tumor or distant lymph node metastasis (M1 Lym) were considered to be eligible. Patients with esophagomediastinal fistula were included in this study, whereas those with esophagotracheal or esophagobronchial fistula and distant organ metastases were excluded. The other eligibility criteria were as follows: (i) age $\leq$75 years, (ii) performance status (PS) of 0–2 based on the classification criteria of the Eastern Cooperative Oncology Group, (iii) adequate renal (serum creatinine $\leq$1.2 mg/dl; BUN $\leq$25 mg/dl; creatinine clearance $\geq$60 ml/min), hepatic (total bilirubin $\leq$1.2 mg/dl; GOT $\leq$2.0 $\times$ normal value; GPT $\leq$2.0 $\times$ normal value), pulmonary ($PaO_2 \geq$70 mmHg) and bone marrow (Hb $\geq$10.0 g/dl; WBC $\geq$4000 /μl; platelets $\geq$100 000/μl) functions. Patients having other active synchronous carcinoma, concurrent uncontrolled medical illness, prior chemotherapy or radiation therapy for any neoplasms and pregnant or lactating women were excluded from the study. All patients provided written informed consent before registration in accordance with the policies of the JCOG. After assessment of the inclusion/exclusion criteria, the patients were centrally registered at the JCOG Data Center (JCOG DC); the orders were transmitted by telephone or fax.

Evaluation

Responses were assessed by barium esophagogram, computed tomography (CT) or magnetic resonance imaging (MRI) and esophageal endoscopy in accordance with the 'Guide Lines for Clinical and Pathologic Studies on Carcinoma of the Esophagus' 8th edition (3), issued by the Japanese Society for Esophageal Disease. A complete response (CR) was defined as a complete disappearance of all evidence of tumor without the appearance of new lesions for at least 4 weeks. A partial response (PR) was defined as a $\geq$50% reduction in the sum of the products of the two perpendicular diameters (SPD) of lesions that could be measured in two directions or a $\geq$30% reduction in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. No change (NC) was defined as a <50% reduction and <25% increase in the SPD of lesions that could be measured in two directions or <30% reduction and <25% increase in the sum of the longest diameters of lesions that could be measured in one direction without the appearance of new lesions for at least 4 weeks. Progressive disease (PD) was defined as a $\geq$25% increase in the SPD of lesions that could be measured in two directions or in the sum of the longest diameters of lesions that could be measured in one direction or the appearance of new lesions. All responses (CR + PR) were reviewed and confirmed by X-rays, CT scan and endoscopic findings at regular JCOG meetings.

Statistical Analysis

Simon's two-stage minimax design (4) was used to investigate whether the overall response rate (CR + PR) was sufficient to proceed to phase III trials. The sample size was calculated based on an expected response rate of 80% and an acceptable lowest rate of 65%, with both alpha and beta error of 0.1; a total of 60 cases were required. In this design, when the number of responses exceeds 43 of 60 cases, this leads to the rejection of the hypothesis that true response rate is below 65%. Overall response rate was defined as the proportion of patients with CR or PR divided by the total number of registered patients. The confidence intervals for the response rate were based on the exact binomial distribution. Overall survival time was calculated from the date of registration to death due to any cause. Overall survival was estimated by the Kaplan–Meier method, and confidence intervals were based on Greenwoods' formula (5). The toxicity was graded based on the Japan Clinical Oncology Group Toxicity Criteria (6). All analyses were performed using SAS software version 6.12 (SAS Institute, Cary, NC) at 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 the accrual.

Treatment

The treatment schedule is summarized in Fig. 1. CDDP 70 mg/m^2 was administered by slow drip infusion on days 1 and 29, and 5-FU 700 mg/m^2/day was administered by continuous

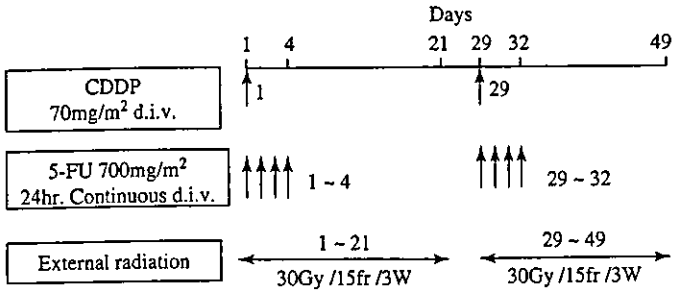

Figure 1. Treatment schedule. CDDP, cisplatin; 5-FU, 5-fluorouracil.

infusion for 24 h on days 1–4 and 29–32. Radiation was administered via a 6~20 MV X-ray. Fractionated radiotherapy was performed on days 1–21 and 29–49, and a total dose of 60 Gy was delivered at the rate of 2 Gy per fraction (one fraction per day and five fractions per week). When the tumor was located in the upper or middle third of the thoracic esophagus, the treatment volume included the bilateral supraclavicular nodes as well as the mediastinum in a T-shaped pattern. When the tumor was located in the lower esophagus, the mediastinum and celiac axis lymph nodes were irradiated. However, in the celiac region, the dose was reduced to 46 Gy to avoid any adverse effect on gastrointestinal function. Oblique fields were used to spare the spinal cord after 40 Gy of radiation was delivered by anterior-posterior opposed pair portals. In the subsequent courses, the dose of CDDP was halved if creatinine level increased to ≥1.3 mg/dl or creatinine clearance decreased to <60 ml/min, and terminated when the creatinine level increased to ≥2.5 mg/dl or creatinine clearance decreased to <40 ml/min. Radiotherapy was suspended when the WBC count decreased to ≤2000/μl or the platelet count decreased to ≤50 000/μl and resumed when the WBC count recovered to ≥3000/μl or the platelet count recovered to ≥75 000/μl within 3 weeks, respectively. The study protocol was approved by the Clinical Trial Review Committee of JCOG and the institutional review board of each participating institution prior to the initiation of the study. The JCOG Data Center was in charge of the data management.

RESULTS

Between March 13, 1996 and April 28, 1998, a total of 60 patients from 15 institutions were registered in this study. The names of the 15 institutions, the number of registered patients from each institution and the names of the attending physicians are listed in Table 1. Among the 60 registered patients, there were 58 males and two females with a median age of 62 (range 45–74) years; no patients were found to be ineligible. The treatment was terminated in 14 patients for following reasons: disease progression in three patients, toxicities in seven patients, iatrogenic death in one patient, pulmonary tuberculosis in one patient, protocol violation in one patient and refusal of treatment by one patient. The characteristics of the patients and the target lesions are listed in Table 2.

Table 1. Names of the 15 institutions, number of registered patients in each institution and names of the attending physicians

Institution	No. of patients	Attending physicians	
Iwate Medical University	7	K. Ishida	T. Ynagisawa
National Cancer Center East	1	A. Ohtu	T. Ogino
Chiba University	1	K. Isono	T. Ariga
National Cancer Center	8	H. Watanebe	Y. Kagami
Tokyo Women's Medical College	8	H. Ide	T. Okawa
Keio University	8	N. Ando	H. Ito
Tokyo Medical Dental University	2	M. Endo	H. Shibuya
Tokai University	2	T. Mitomi	T. Omosato
Kanagawa Cancer Center	3	H. Koizumi	H. Yamashita
Niigata Cancer Center	7	O. Tanaka	M. Saito
Nigata University	4	T. Nishimaki	K. Sakai
Aichi Cancer Center	5	M. Shinoda	Y. Ito
Kyoto University	1	M. Imamura	Y. Nishimura
Shikoku Cancer Center	2	W. Takiyama	M. Kataoka
Kurume University	1	H. Yamana	M. Jo

Table 2. Patients' characteristics

Characteristic	$n = 60$
Sex	
Male	58
Female	2
Age (years)	
Median	62
Range	45–74
Target lesion (overlapped)	
Esophagus	60
Cervical lymph node	23
Mediastinal lymph node	33
Abdominal lymph node	13
Others	1

Table 3. Response rate and prognosis

No. of eligible patients	60/60 registered patients
Response rate	68.3% (9 CR + 32 PR/60 patients; 95% CI = 55.0–79.7%)
Median survival time	303.5 days (95% CI = 200–387 days)
2-year survival rate	31.5% (95% CI = 19.7–43.3%)

Forty-six (77%) patients completed the treatment regimen. Objective tumor responses observed among the 60 registered patients were as follows: 9 CR, 32 PR, 10 NC and 7 PD. Two patients could not be evaluated. The overall response rate (Table 3) was 68.3% (41/60, 95% confidence interval

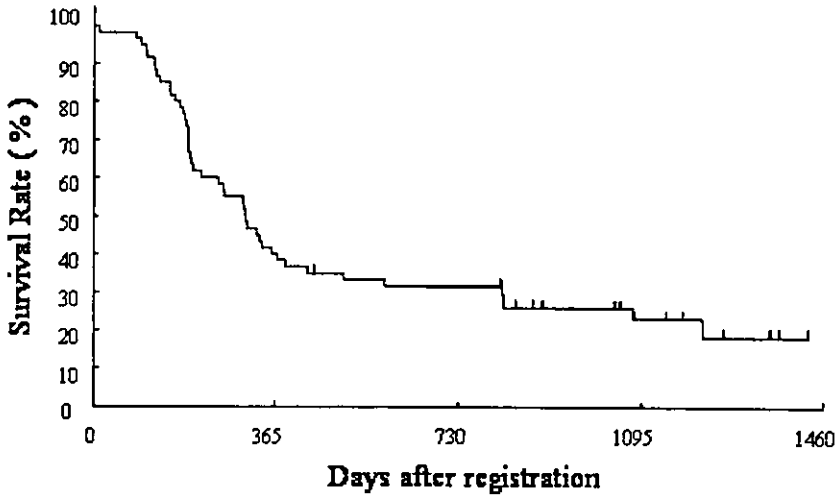

Figure 2. Overall survival among all patients (n = 60).

[CI] = 55.0–79.7). Forty-six patients out of a total of 60 died; 43 due to progressive disease, one due to iatrogenic cause and two due to other diseases. At the final follow up in May 2000, 13 patients remained alive, and one patient was lost to follow up. The overall survival curves for all patients are shown in Fig. 2. The median survival time (MST) was 305.5 days (95% CI = 200–387) and the 2-year survival rate was 31.5% (95% CI = 19.7–43.3). The toxicities observed in the patients are summarized in Table 4; hematologic toxicity was observed to be the dominant toxicity. Two iatrogenic deaths (3.3%) were observed either during or immediately following treatment. One patient died of hemorrhage from the tumor on day 6 following the first course, and this was considered to be an iatrogenic death. The other patient died due to sepsis from severe pulmonary infection, 26 days after the end of the treatment. Serious dyspnea was observed in one patient; this might be attributed to the radiation therapy. Grade 4 thrombocytopenia was observed in two patients.

Table 4. Toxicities: no. of cases (n = 60)

	Grade					% grade 4
	0	1	2	3	4	
Leukocyte	3	7	30	20	0	0
Neutrophil	14	12	27	5	0	0
Hemoglobin	16	12	28	4	–	0
Platelet	45	7	5	1	2	0
Total bilirubin	48	–	10	1	0	2.5
AST	33	17	7	3	0	0
ALT	32	17	5	6	0	0
PaO_2	23	32	2	0	0	0
Creatinine	52	8	0	0	0	0
Nausea/vomiting	1	27	18	3	–	0
Stomatitis	49	7	4	0	0	0
Diarrhea	50	6	3	1	0	0
Esophagitis	28	22	7	2	0	0
Dyspnea	57	1	0	1	1	1.7
Infection	46	10	3	0	1	1.7
Alopecia	58	2	0	0	0	0
Fever	29	23	8	0	0	0

DISCUSSION

There have been few reports on concurrent chemoradiotherapy for advanced esophageal cancer. Ohtsu et al. (7) reported a 3-year survival rate of 23% in 59 patients having T4 and/or M1 Lym esophageal cancer using definitive CT-RT consisting of 60 Gy irradiation along with CDDP and 5-FU. Furthermore, Nishimura et al. (8) initiated a prospective trial that aimed to evaluate the safety and efficacy of concurrent chemoradiotherapy using a protracted infusion of 5-FU and cisplatin in T4 esophageal cancer patients. They concluded that despite significant toxicity, which could result in the development or worsening of an esophageal fistula, their protocol appeared feasible and effective for the treatment of T4 esophageal cancer patient with or without fistula.

In the present study, the efficacy and safety of concurrent chemoradiotherapy was assessed using 5-FU and CDDP along with 60 Gy of radiotherapy in patients with advanced esophageal cancer in order to develop more effective treatment. The same concurrent chemoradiotherapy regimen used in the US study (1) was used in the present study. The overall tumor RR and CR rate were found to be 68.3 and 15%, respectively. From a statistical point of view, the overall tumor response rate was insufficient to reject the null hypothesis specified earlier in the protocol. One possible reason for this result was excessive expectation regarding the tumor response that could be achieved by this regimen; the expected RR appeared to be much higher than necessary. Although the efficacy of this regimen could not be demonstrated as planned, other efficacy endpoints, such as MST (305 days), 2-year survival rate (31.5%) and grade 4 toxicities (6.7%), were found to be better

than those in the previous study. Ishida et al. (2) investigated the efficacy and safety of sequential chemoradiotherapy in the same patients included in the present study and reported that the overall RR was 64.4%, CR rate was 8.9%, MST was 215 days, 2-year survival rate was 13.3% and life-threatening toxicities (grade 4) were observed in five patients (11%). Therefore, although not based on a direct comparison with sequential chemoradiotherapy, it is concluded that the concurrent regimen is more promising for the treatment of advanced esophageal cancer.

Other trials have used different combinations of chemotherapeutic agents and radiotherapy doses/methods with varying outcomes. John et al. (9) treated 21 patients with 5-FU, CDDP and Mitomycin C (MMC) along with local radiotherapy and reported that the 2-year survival rate was 29% and serious adverse events were observed in five patients (23.8%). Calais et al. (10) initiated a phase II trial that aimed to evaluate the feasibility of a combined treatment using 5-FU, CDDP and MMC chemotherapy and an external radiation dose of 60 Gy in patients with unresectable esophageal cancer and reported that the 3-year survival rate was 27% and WHO grade 4 toxicity rate was 7%. Gaspar et al. (11) conducted a trial of concurrent chemotherapy using 5-FU during both external beam radiation and brachytherapy in patients with potentially curable esophageal cancer and reported that the 1-year survival rate was 49%, MST was 11 months, life-threatening toxicities were observed in 24% patients and iatrogenic deaths occurred in 10% patients. These reports suggest that neither three-drug combination chemotherapy along with radiation nor concurrent chemoradiotherapy along with brachytherapy are more promising than our regimen. It is concluded that the two-drug combination of 5-FU and CDDP along with concurrent radiotherapy is effective and well tolerated. A phase II/III trial is being planned for comparing the regimen used in JCOG9516 and low-dose continuous CDDP/5-FU chemotherapy with radiotherapy (JCOG0303) in order to develop a more effective and less toxic concurrent chemoradiotherapy regimen.

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DISEASES OF THE ESOPHAGUS

Original article

Phase I study of the combination of nedaplatin, adriamycin and 5-fluorouracil for treatment of advanced esophageal cancer

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SUMMARY. **This trial was conducted to determine the maximum-tolerated dose, principal toxicity, and recommended dose (RD) for the phase II study of the combination of nedaplatin (NED), adriamycin (ADM), and 5-fluorouracil (5-FU) in patients with advanced esophageal cancer. Patients with previously untreated esophageal cancer were eligible if they had performance status 0–1, were 75 years or younger and had adequate organ function. The dose of NED, the key anticancer platinum complex drug, was increased from 60 to 70, and 80 mg/m^2 on day 1. ADM and 5-FU were administered at fixed doses (30 mg/m^2 on day 1, and 700 mg/m^2 on days 1–5). The dose-limiting toxicities of NED were neutropenia and severe diarrhea, and its maximum-tolerated dose and RD were 70 mg/m^2 and 60 mg/m^2, respectively. There were four responders among the six patients administered the RD. The present study thus revealed combination chemotherapy with NED, ADM, and 5-FU to be active and well-tolerated and to warrant phase II study.**

KEY WORDS: **cancer, chemotherapy, esophagus, nedaplatin, phase I.**

INTRODUCTION

Esophageal cancer has a poor prognosis. In recent years, several strategies including presurgical chemotherapy, either alone or with radiotherapy, and chemoradiotherapy without surgery have been used in attempts to improve the prognosis.

Cisplatin (CDDP)-based combinations have been reported to yield high response rates and,[1] among the various combinations tested, that with 5-fluorouracil (5-FU) has proved to be a most effective, safe and standard regimen.[2] However, because CDDP itself has substantial toxicity, including renal and gastrointestinal toxicity, newer platinum analogs have been developed. (Glyconate-O,O) diammineplatinum (II) (Nedaplatin, hereafter NED), a second-generation platinum complex developed in Japan, is designed to reduce the adverse effects of CDDP and to further improve its antitumor effect.[3] It was reported that the response rate for NED as a single agent was 42.9% in a phase II study, with little toxicity observed.[4] It has been shown in vitro that NED can exert synergic effects with 5-FU.[5] Moreover, it was reported that the combination of NED and 5-FU yielded a 54% response rate among patients who had previously been treated with CDDP.[6]

Combination chemotherapy with 5-FU, adriamycin (ADM), and CDDP (FAP) has been reported to be useful in the treatment of advanced gastric cancer, esophageal cancer and other tumors.[7,8]

Based on these findings, we planned a phase I and II study of the combination of NED, ADM, and 5-FU for treatment of previously untreated advanced esophageal cancer. The main purpose of the present study was to determine the maximum-tolerated dose (MTD), principal toxicity, and recommended dose (RD) for the phase II study.

PATIENTS AND METHODS

Eligibility criteria

Between January 2003 and June 2003, 12 patients with advanced esophageal cancer cared for in Osaka National Hospital were enrolled for the study. Disease staging was performed according to the guidelines for the clinical and pathologic studies on carcinoma of the esophagus of the Japan Society for Esophageal Diseases.[9] Patients with histologically proven stage III or IVa or b disease who had not

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previously received chemotherapy, radiotherapy or surgical treatment were eligible for this study. Other eligibility criteria were: age between 20 and 75 years; Eastern Cooperative Oncology Group (ECOG) performance status of 1 or 0; a measurable lesion; life expectancy of 3 months or longer; adequate bone marrow function (white blood cell [WBC] count from 3000 to 12 000/μL, neutrophil count of 1500/μL or more, hemoglobin level of 8.0 g/dL, and platelet count level of 100 000/μL or more), acceptable renal function (serum creatinine levels less than 1.5 mg/dL and creatinine clearance rate of 50 mL/min or more) and hepatic function (total serum bilirubin level less than 1.5 mg/dL, AST and ALT levels less than or equal to two and one-half times the upper limits of the normal ranges), and normal ECG. Patients were excluded if they had active infection, severe heart disease, pregnancy, active synchronous carcinoma, interstitial pneumonia or pulmonary fibrosis, peripheral neuropathy, pleural effusion or ascites, symptomatic brain metastasis, syndrome of inappropriate secretion of ADH (SIADH), or severe drug allergy. Written informed consent was obtained from all patients.

Treatment protocol

ADM (30 mg/m^2) was diluted with 100 mL of normal saline and administered as an intravenous drip infusion over 60 min on day 1. 5-FU (700 mg/m^2) was diluted with saline and administered as an intravenous drip continuously from day 1–5. NED was diluted with 500 mL of normal saline before injection and given as an intravenous drip infusion over 60 min on day 1. This chemotherapy regimen was repeated every 4 weeks and given for at least 1 cycle for phase I and for more than 2 cycles for phase II study.

MTD and dose-limiting toxicity

Three dose levels of NED were chosen for investigation: step 1, 60 mg/m^2; step 2, 70 mg/m^2; and step 3, 80 mg/m^2. The dose of NED was increased on the basis of toxicity during the first cycle of chemotherapy. No dose escalation was permitted for individual patients. Decision on MTD was made on the basis of dose-limiting toxicity (DLT) events that occurred during the first cycle of chemotherapy. DLT was defined as follows: (1) a WBC count less than 1000/μL or neutrophil count less than 500/μL; (2) grade 3 febrile neutropenia; (3) a platelet count less than 25 000/μL; (4) any grade 3 non-hematologic toxicity that met NCI-CTC, except for alopecia, fatigue and nausea/vomiting. At least three patients were enrolled at each dose step. If DLT was observed in one patient, three additional patients were accrued. If DLT was observed in two or more of the initial patients or three or more of the six patients, patient accrual was discontinued and the dose level was considered the MTD. Once the MTD was determined, the previous dose level was chosen as the recommend dose (RD).

Toxicity and evaluation of response

Toxicities were assessed and graded according to NCI-CTC (National Cancer Institute Common Toxicity Criteria Version 2.0, 1999). A total of 21 courses were given. The median number of courses given per patient was two (range, 1–3). The World Health Organization criteria were used to define the following: complete response (CR), the disappearance of all known disease for at least 4 weeks; partial response (PR), 50% or more decrease in total tumor load of the lesions estimated by two observations no less than 4 weeks apart; no change (NC), no significant change for at least 4 weeks, which includes stable disease, estimated decrease of less than 50%, and lesions with estimated increase of less than 25%; and progressive disease (PD), appearance of any new lesions not previously identified or estimated increase of existing lesions by 25% or more.

RESULTS

Patient characteristics

Twelve patients were enrolled from January 2003. All patients could be assessed for toxicity (Tables 1 and 2). The study population included 11 men and one woman, with a mean age of 65 years (range, 46–74). Seven patients had performance status '0', and five patients '1'. The histologic diagnosis of 12 patients was squamous cell carcinoma of the esophagus. Four patients had stage III disease, three patients stage IVa disease, and five patients stage IVb disease. Moreover, four patients underwent esophagectomy after the combination chemotherapy.

Table 1 Dose-escalation scheme and dose limiting toxicity (DLT) in the first cycle of chemotherapy

Dose level	Nedaplatin (mg/m^2)	No. of patients	Total no. of courses	Patients with DLT
1	60	6	11	1
2	70	6	9	2

Table 2 Patient characteristics

Total no. of patients (level 1/level 2)	12 (6/6)
Sex, M/F	11/1
Age, years (range)	65 (46–74)
Stage, III/IVa/IVb	4/3/5
Performance status, 0/1	7/5

Table 3 Hematologic and nonhematologic toxicities by dose level in the first cycle

	Dose level	No. of patients	Neutropenia	Thrombocytopenia	Anemia	Nausea/ vomiting	Diarrhea	Elev. of creatinine	Elevation of transaminase
Grades of toxicity			1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4	1 2 3 4
No. of patients	1	6	1 1 2 1	0 0 1 0	3 2 1 0	2 0 0 0	0 0 0 0	0 0 0 0	0 0 0 0
with each grade	2	6	2 1 1 1	0 0 0 0	4 1 0 0	3 0 0 0	1 0 1 0	1 0 0 0	0 0 0 0

DLT, MTD and RD as judged from toxicity

A total of 20 courses were given (Table 1). The median number of courses given per patient was two (range, 1–3). Administration of NED was started at 60 mg/m^2, and increased to 70 mg/m^2, which was determined to be the MTD. The RD of NED was 60 mg/m^2. DLTs were myelosuppression, especially neutropenia and grade 3 diarrhea during the first course (Table 1). Leukocytes and neutrophils reached a nadir in 9–22 days (median, 17 days) after the first administrations of NED, and 3 or 4 days (median, 3 days) were required for recovery from the nadir to 3000/mm^3 leukocytes. Grade 4 neutropenia occurred in two patients, and G-CSF was administered for 4 days to one of them. Platelet count reached a nadir in 7–20 days (median, 15 days) after the first administration, and 0–14 days (median, 7 days) were required for recovery from the nadir to 100 000/mm^3 (Table 3).

Nausea was the most frequent non-hematologic toxicity, and was grade 1 and transient. Moreover, only one patient, at the second step, had grade 3 non-hematologic toxicity diarrhea. Neither hepatic, cardiac or renal functions were impaired in any of the patients (Table 3).

Antitumor effects by dose of the first step of NED (60 mg/m^2) were follows: four patients achieved PR and two patients were NC, among six patients who were assessed for RD at the first step.

DISCUSSION

Patients with advanced esophageal cancer rarely benefit from chemotherapy. Several types of combination therapy have been employed, but the reported objective response rates have been only 15% with CDDP and bleomycin,[10] 42% with CDDP and mitomycin,[11] 29% with CDDP, bleomycin and vindesine,[12] and 35–60% with CDDP and 5-FU.[2,13,14] Cure is not possible and the prognosis of esophageal carcinoma remains unsatisfactory.

We designed the present study to determine the MTD, principal toxicity and RD of combination chemotherapy with NED, ADM and 5-FU (NAF) for advanced esophageal carcinomas.

The CDDP and 5-FU combination (FP) has been considered the standard regimen for patients with esophageal cancer, and investigators have reported response rates of 60% for resectable or localized tumors,[13] and 36% for recurrent, metastatic, or bulky unresectable carcinoma.[14] The most frequent toxicity of FP was gastrointestinal, and included nausea and vomiting.

Furthermore, combination chemotherapy with 5-FU, ADM and CDDP (FAP) has been reported to be useful in the treatment of advanced gastric cancer, esophageal cancer and other carcinomas.[7,8] Gisselbrecht *et al.* reported that the FAP regimen was administered to 21 patients with advanced esophageal cancer,[7] seven of them had an objective response (CR: 2, PR: 5), with no severe myelosuppression or nephrotoxicity observed.

NED, a novel second-generation platinum compound, has shown superior antitumor activity and less renal and gastrointestinal toxicity than CDDP in some preclinical and clinical studies.[3,4] With NED and 5-FU combination chemotherapy, a response rate of greater than 60% in assessable patients was achieved with a duration of 7 months (range 3–37) for advanced esophageal cancer.[15] Moreover, it was reported that a combination of NED and 5-FU yielded a 54% response rate among those who had previously been treated with CDDP.[6] In a phase II study of the combination of NED and 5-FU for metastatic squamous cell carcinoma of the esophagus, the overall response rate was 40% and the median survival time was 8.9 months. This phase II study showed that grade 4 neutropenia and thrombocytopenia occurred in 2–7%, and grade 3 diarrhea and nausea occurred in 2% and 12%, respectively. This combination therapy was previously found to be safe and active.[16] Our study showed that the combination of NED, ADM, and 5-FU was also generally well-tolerated and attractive.

A phase II study of combination chemotherapy with NED, ADM, and 5-FU for advanced esophageal cancer should be planned at the recommended dose.

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