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

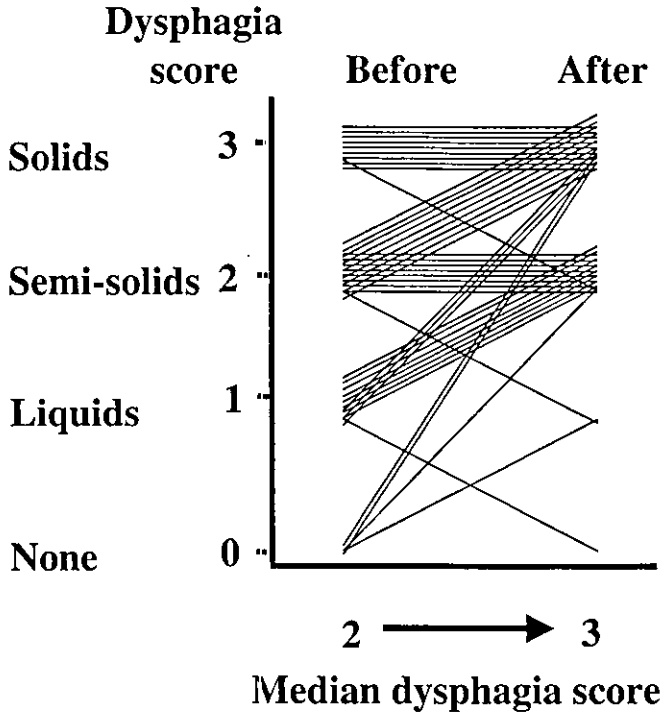

Fig. 1. Improvement of dysphasia score in the patients with esophageal stricture after completion of definitive chemoradiotherapy.

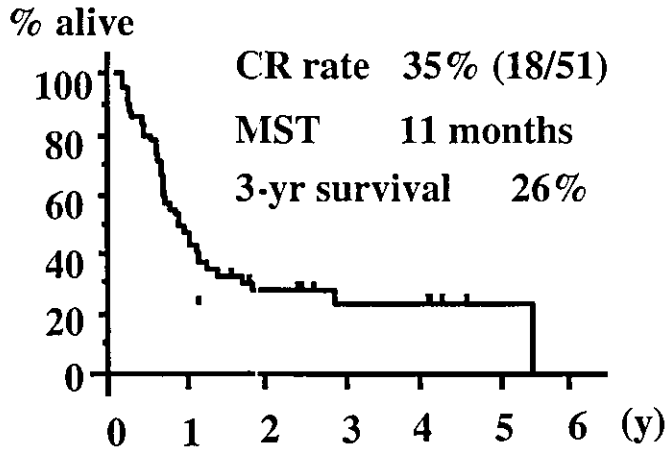

Fig. 2. Overall survival of the patients with T4 esophageal cancer treated with definitive chemoradiotherapy.

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-

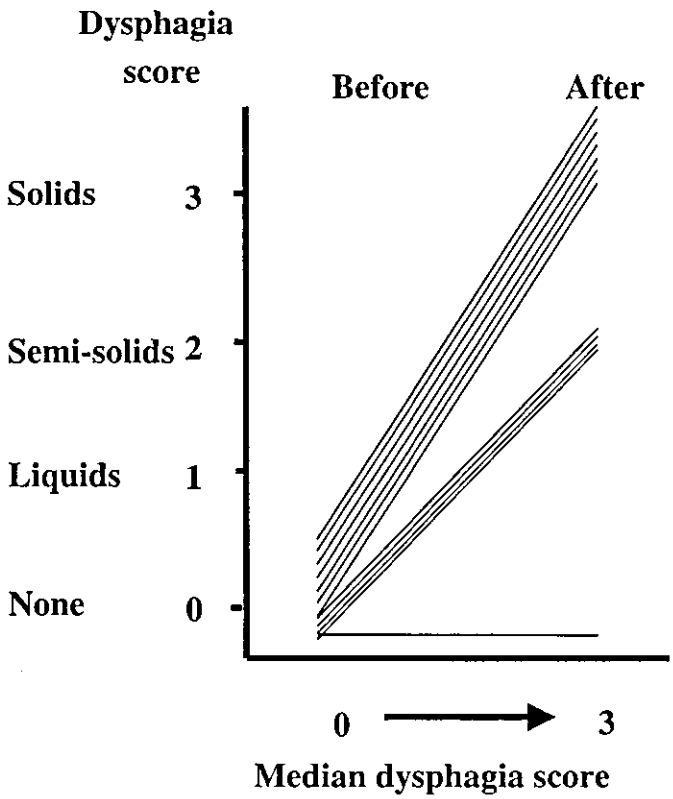

Fig. 3. Improvement of dysphasia scores in esophageal cancer patients with malignant fistula after completion of definitive chemoradiotherapy.

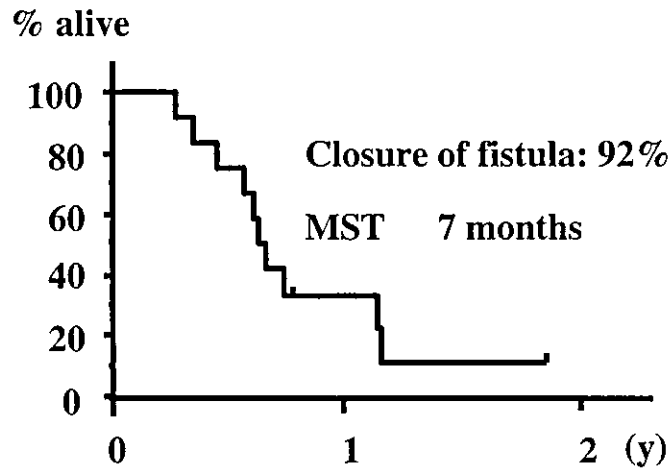

Fig. 4. Overall survival of esophageal cancer patients with malignant fistula treated with definitive chemoradiotherapy.

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

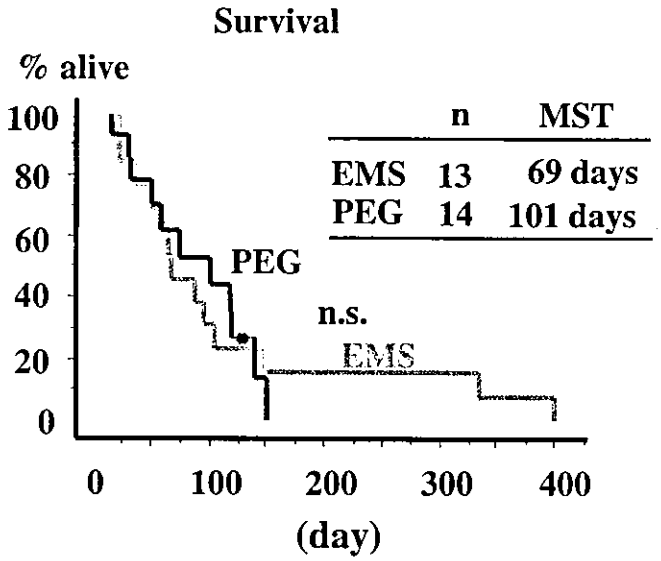

Fig. 5. Comparison of the overall survival between the patients inserted with a self-expandable metallic stent and those treated by percutaneous endoscopic gastrostomy.

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

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)

(%); * $p < 0.005$.

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]

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)

Kaoru Ishida[1], Nobutoshi Ando[2], Seiichiro Yamamoto[3], Hiroko Ide[4] and Masayuki Shinoda[5]

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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

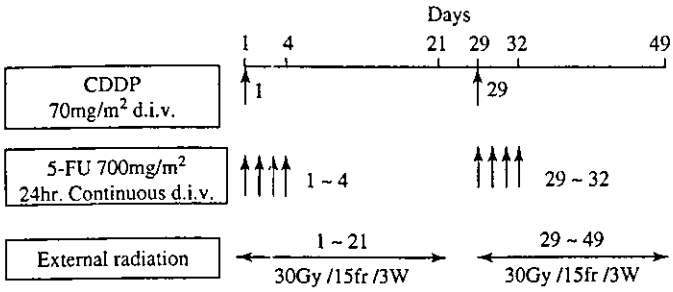

Figure 1. Treatment schedule. CDDP, cisplatin; 5-FU, 5-fluorouracil.

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

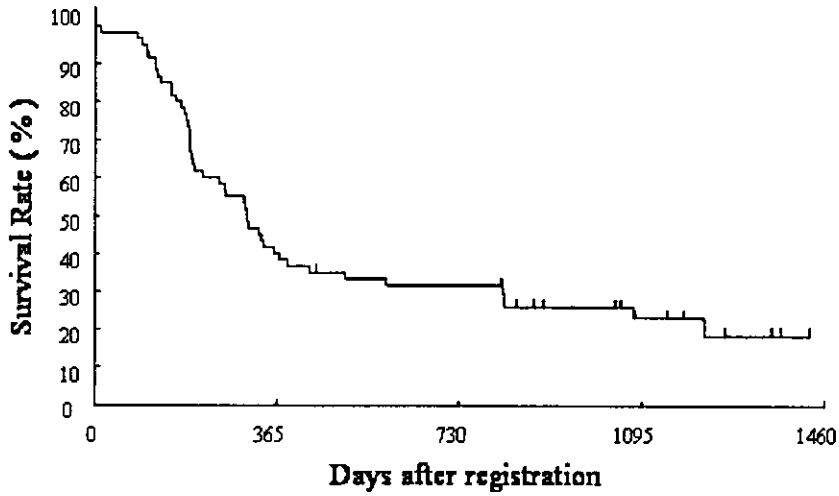

Figure 2. Overall survival among all patients (n = 60).

[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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Clinical Significance of Serum Carcinoembryonic Antigen, Carbohydrate Antigen 19-9, and Squamous Cell Carcinoma Antigen Levels in Esophageal Cancer Patients

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Abstract. Serum carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and squamous cell carcinoma (SCC) antigen levels were assessed to determine if their levels are useful for staging esophageal cancer preoperatively and for predicting patient survival after esophagectomy. Hence their seropositivity was investigated for a correlation with resectability, clinicopathologic parameters of tumor progression, and treatment outcomes in patients with unresectable esophageal cancer ($n = 63$) and those undergoing esophagectomy for resectable disease ($n = 267$). Abnormal elevation of serum SCC antigen levels showed a significant correlation with resectability ($p < 0.0001$), depth of tumor invasion ($p < 0.0001$), lymph node status ($p = 0.0015$), TNM stage ($p < 0.0001$), lymphatic invasion ($p = 0.0019$), blood vessel invasion ($p = 0.0079$), and poor survival after esophagectomy ($p = 0.0061$). A significant relation ($p = 0.0145$) was found between elevated serum CEA levels and distant metastasis, whereas the seropositivity of CA 19-9 showed no association with resectability, tumor progression, or patient survival. These results indicate that abnormal elevation of serum SCC antigen is a useful predictor of advanced esophageal cancer associated with poor survival after esophagectomy.

Treatment outcomes of patients with esophageal cancer have been poor even after radical esophagectomy [1] because the disease has already progressed to an advanced stage by the time it is diagnosed, rendering most cases incurable. Consequently, various tumor markers have been used in attempts to detect esophageal cancer at an early stage. Carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, and squamous cell carcinoma (SCC) antigen are some of the tumor markers commonly used in the management of patients with esophageal cancer [2–4]. Many studies have reported that tumor markers have limited utility in the early detection of esophageal cancer; the sensitivities of these tumor markers are unacceptably low, particularly in cases of early esophageal cancer [4, 5]. However, it is not yet known whether preoperative serum levels of CEA, CA 19-9, and SCC antigen are predictive of resectability, curability, or long-term survival after esophagectomy in patients with esophageal cancer. Furthermore, it is not known whether the preoperative serum levels of these tumor markers are significant predictors of postoperative outcomes independent of the clinicopathologic factors that serve as a major component of the TNM staging system [6].

Therefore the purposes of the present study were to (1) clarify which clinicopathologic factors associated with tumor progression correlate with preoperative serum levels of CEA, CA 19-9, or SCC (or any combination thereof); (2) evaluate the usefulness of these tumor markers for predicting resectability, curability, or postoperative survival and if these prognostic factors are independent of the clinicopathologic factors known to be authentic prognostic indicators; and (3) determine the role of the preoperative serum levels of these tumor markers in managing patients with esophageal cancer.

Patients and Methods

Patients

Between 1992 and 1999 a total of 359 patients were admitted to the Division of Digestive and General Surgery, Niigata University for treatment of esophageal cancer. The ages of these patients ranged from 40 to 91 years (average 65.2 years). There were 318 men and 41 women. At our institution since 1992, serum levels of CEA, CA 19-9, and SCC antigen have been routinely measured in patients with esophageal cancer prior to treatment.

Of the 359 patients, 83 did not undergo esophagectomy. In most of the 83 cases it was due to the advanced status of the disease, which was evidenced by direct involvement of adjacent vital organs via local tumor extension ($n = 54$) or the presence of distant organ metastasis ($n = 12$); in others, it was due to poor performance status ($n = 15$); and in several, it was due to the patients' refusal to undergo the operation ($n = 5$). These 83 patients underwent feeding gastrostomy or jejunostomy ($n = 21$); endoscopic stent implantation ($n = 9$); chemotherapy, radiotherapy, or both ($n = 73$); or no further treatment ($n = 10$). Altogether, 63 patients in whom esoph-

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agectomy could not be performed because of advanced disease were included in the present study as the NR group.

The remaining 276 patients underwent tumor removal by esophagectomy ($n = 267$) or endoscopic mucosal resection ($n = 9$). The 267 patients undergoing esophagectomy were included in the present study as the ER group. Of these 267 patients, 251 underwent transthoracic esophagectomy with bilateral cervical, mediastinal, and abdominal lymphadenectomy ($n = 73$) or with mediastinal and abdominal lymphadenectomy ($n = 57$); and 118 underwent transhiatal esophagectomy with lower mediastinal and abdominal lymphadenectomy for thoracic esophageal cancer. The remaining 16 patients underwent total esophagectomy through the transhiatal approach with cervical lymphadenectomy for carcinoma of the cervical esophagus.

Preoperative Staging

Chest radiography, esophagography, esophagoscopy, endoscopic ultrasonography, percutaneous ultrasonography, and computed tomography were routinely performed to stage the esophageal tumors. Cases showing distant organ metastasis or definite direct involvement of adjacent vital organs by local tumor extension by any of these diagnostic modalities were regarded as unresectable. Magnetic resonance imaging, bronchofiberoscopy, or bone scintigraphy was additionally performed if indicated for the determination of individual resectability.

Tumors

All 330 patients included in the present study had squamous cell carcinoma. In the 267 patients of the ER group, anatomic subsites, histopathologic grading, the depth of the primary tumor, and stage grouping were defined by the TNM classification of the International Union Against cancer (UICC) [6]. The quality of tumor clearance was determined using the residual tumor (R) classification of the UICC-TNM classification [6]: Cases with no residual tumor, microscopic residual tumor, or macroscopic residual tumor after tumor resection were classified as R0, R1, or R2, respectively. In addition, the presence or absence of lymph node metastasis, intramural metastasis [7], lymphatic invasion, and blood vessel invasion were histologically examined in the ER group. Based on the results of our earlier study [8], the number of positive nodes per patient (0, 1–4, ≥ 5) was also assessed as a prognostic factor after esophagectomy. These clinicopathologic variables were determined by pathologic examination of the resected specimens. These 267 cases were classified into 12 cases of stage 0, 60 cases of stage I, 32 cases of stage IIA, 28 cases of stage IIB, 90 cases of stage III, and 45 cases of stage IV disease.

For the 63 patients of the NR group, stages were determined using imaging techniques. These 63 cases included 46 cases of stage III disease and 17 cases of stage IV disease.

Tumor Markers

Serum concentrations of CEA, CA 19-9, and SCC antigen were measured in all patients before the initiation of treatment for esophageal cancer. They were assessed in 61, 59, and 53 patients of the NR group, respectively, and in 266, 262, and 245 patients of the ER group, respectively.

The SCC antigen was measured by the SCC antigen microparticle enzyme immunoassay (EIA) (Dainabot, Tokyo, Japan). The cutoff value for SCC antigen was determined to be 1.5 ng/ml, as previously reported [9]. CEA and CA 19-9 were measured by EIA using a Lumipulse 1200 (Fujirebio, Tokyo, Japan) with cutoff values of 5 ng/ml and 37 U/ml, respectively.

Table 1. Seropositivity of CEA, CA 19-9, and SCC in the ER and NR groups.

Tumor marker	ER group ($n = 267$)	NR group ($n = 63$)
CEA	87/266 (32.7%)	25/61 (41.0%)
CA 19-9	23/262 (8.8%)	4/59 (6.8%)
SCC	75/245 (30.6%)*	35/53 (66.0%)*

Results are the seropositivity rates.

CEA: carcinoembryonic antigen; CA: carbohydrate antigen; SCC: squamous cell carcinoma; ER: patients undergoing esophagectomy; NR: patients in whom esophagectomy could not be performed owing to advanced disease.

*$p < 0.0001$.

Statistical Analysis

Differences in frequency were detected by the χ^2 test. In the ER group, survival rates were calculated from the time of tumor resection until death or the latest follow-up for surviving patients using the Kaplan-Meier method. The equality of the survival curves was assessed using the generalized Wilcoxon test. Follow-up data were available for all patients of the ER group, with a median follow-up period of 33 months (range 1–98 months). Cox's proportional hazard model was used for multivariate survival analysis. A value of $p < 0.05$ was considered significant. All analyses were performed with StatView J4.11 (Abacus Concepts, Berkeley, CA, USA).

Results

Relation between Serum Tumor Marker Level and Resectability

The median values of serum CEA, CA 19-9, and SCC antigen concentrations were 4.0 ng/ml (0.7–74.7 ng/ml), 11.0 IU/ml (2.0–63.0 IU/ml), and 2.0 ng/ml (0.3–46.1 ng/ml), respectively, in the NR group. Abnormal elevations of serum CEA, CA 19-9, and SCC antigen levels beyond the respective cutoff values was observed in 41.0%, 6.8%, and 66.0% of the patients in this group (Table 1). The median serum CEA, CA 19-9, and SCC antigen concentrations were 3.5 ng/ml (0.9–464.5 ng/ml), 11.0 IU/ml (2.0–1696.0 IU/ml), and 1.0 ng/ml (0.3–60.7 ng/ml), respectively, in the ER group. Abnormal elevations of the respective tumor markers in the sera were found in 32.7%, 8.8%, and 30.6%, respectively, of the ER patients (Table 1). The positive rate of serum SCC antigen assessment was significantly higher in the NR group than in the ER group ($p < 0.0001$). However, no significant difference was detected in the positive rate of either serum CEA or CA 19-9 between these two groups.

Correlations between Serum Tumor Marker Levels and Clinicopathologic Variables

Positive rates for serum CEA, CA 19-9, and SCC antigen in the ER group are shown in Table 2, according to patient gender, primary site, histopathologic grading, depth of the primary tumor, lymph node status, disease stage, presence or absence of distant organ

Table 2. Positive rates of serum CEA, CA 19-9, and SCC levels according to clinicopathologic variables in the ER group.

Variable	CEA		CEA 19-9		SCC	
	Positive	*p*	Positive	*p*	Positive	*p*
Gender		NS		NS		NS
Male	79/232 (34.1%)		21/228 (9.2%)		65/213 (30.5%)	
Female	8/34 (23.5%)		2/34 (5.9%)		10/32 (31.3%)	
Tumor location		NS		NS		0.0103
Cervical	4/16 (25.0%)		1/14 (7.1%)		8/15 (53.3%)	
Upper thoracic	9/15 (60.0%)		1/15 (6.7%)		1/14 (7.1%)	
Middle thoracic	40/125 (32.0%)		11/123 (8.9%)		29/117 (24.8%)	
Lower thoracic	34/110 (30.9%)		10/110 (9.1%)		37/99 (37.4%)	
Histopathologic grading		NS		NS		0.0392
Well differentiated (G1)	27/78 (34.6%)		8/75 (10.7%)		30/69 (43.5%)	
Moderately differentiated (G2)	44/146 (30.1%)		13/145 (9.0%)		38/140 (27.1%)	
Poorly differentiated (G3)	12/30 (40.0%)		2/30 (6.7%)		6/29 (20.7%)	
Undifferentiated (G4)	1/4 (25.0%)		0/4		0/2	
Depth of invasion (pT)		NS		NS		<0.0001
Tis, T0, T1	33/101 (32.7%)		6/101 (5.9%)		9/91 (9.9%)	
T2	5/14 (35.7%)		2/14 (14.3%)		4/13 (30.8%)	
T3	39/120 (32.5%)		13/117 (11.1%)		46/111 (30.8)	
T4	10/31 (32.3%)		2/30 (6.7%)		16/30 (53.3%)	
Lymph node involvement (pN)		NS		NS		0.0015
N0	35/111 (31.5%)		10/110 (9.1%)		18/98 (18.4%)	
N1	52/153 (33.3%)		13/150 (8.7%)		57/145 (39.3%)	
Metastatic nodes (pN –no.)						
Negative	35/111 (31.5%)		10/110 (9.1%)		18/98 (18.4%)	
≤ 4	30/104 (28.8%)		7/101 (6.9%)		34/98 (35.7%)	
≥ 5	21/49 (42.9%)		6/49 (12.2%)		22/47 (46.8%)	
Distant metastasis (pM)		0.0145		NS		NS
M0	65/221 (29.4%)		21/218 (9.6%)		61/202 (30.2%)	
M1	22/45 (48.9%)		2/44 (4.5%)		14/43 (32.6%)	
Stage (TNM)		NS		NS		<0.0001
0,1	21/72 (29.2%)		5/72 (6.9%)		7/65 (10.8%)	
IIA, IIB	21/60 (35.0%)		7/59 (11.9%)		13/54 (24.0%)	
III	23/89 (25.8%)		9/87 (10.3%)		41/83 (49.4%)	
IV, IVA, IVB	22/4567 (48.9%)		2/44 (4.5%)		14/43 (32.6%)	
Lymphatic invasion		NS		NS		0.0019
Negative	28/107 (26.2%)		6/105 (5.7%)		19/98 (19.4%)	
Positive	59/158 (37.3%)		17/156 (10.9%)		56/147 (38.1%)	
Blood vessel invasion		NS		NS		0.0079
Negative	46/148 (31.1%)		11/146 (7.5%)		31/134 (23.1%)	
Positive	41/117 (35.0%)		12/115 (10.4%)		44/111 (39.6%)	
Intramural metastasis (IM)		NS		NS		NS
Absence	69/216 (31.9%)		19/213 (8.9%)		55/197 (27.9%)	
Presence	18/50 (36.0%)		4/49 (8.2%)		20/48 (41.7%)	
Residual tumor		NS		NS		NS
R0	73/230 (31.7%)		20/228 (8.8%)		62/209 (29.7%)	
R1, R2	14/36 (38.9%)		3/34 (8.8%)		13/36 (36.1%)	

metastasis, lymphatic invasion, blood vessel invasion, intramural metastasis, and postoperative residual tumor status. There were strong correlations between serum SCC antigen positivity and tumor location ($p = 0.0103$), depth of the primary tumor ($p < 0.0001$), nodal metastasis ($p = 0.0015$), number of metastatic nodes ($p = 0.0010$), disease stage ($p < 0.0001$), histopathologic grading ($p = 0.0392$), blood vessel invasion ($p = 0.0079$), and lymphatic invasion ($p = 0.0019$). Serum CEA positivity showed a significant correlation with distant organ metastasis ($p = 0.0145$). No significant association was observed between serum CA 19-9 positivity and any of the clinicopathologic variables.

Relations between Serum Tumor Marker Levels and Patient Outcome

The overall survival rate was 45.1% at five years after tumor resection in the ER group. Survival curves of the ER group patients according to the preoperative serum CEA, CA 19-9, and SCC antigen levels are shown in Figure 1. The survival curve of patients with a positive SCC antigen assay was significantly worse than that of patients with a negative SCC antigen assay ($p = 0.0061$). However, relative to the positive or negative results of preoperative CEA and CA 19-9 assessment, no significant differences in patient survival were observed.

Significant Prognostic Factors

Univariate analysis showed that the depth of the primary tumor invasion, lymph node metastasis, number of positive nodes, distant organ metastasis, disease stage, lymphatic invasion, blood vessel invasion, intramural metastasis, and postoperative residual tumor status, in addition to the positivity of the preoperative serum SCC assay, were significant prognostic factors in the ER group (Table 3). Of these prognostic factors revealed by univariate analysis, the depth of the primary tumor invasion, number of metastatic nodes,

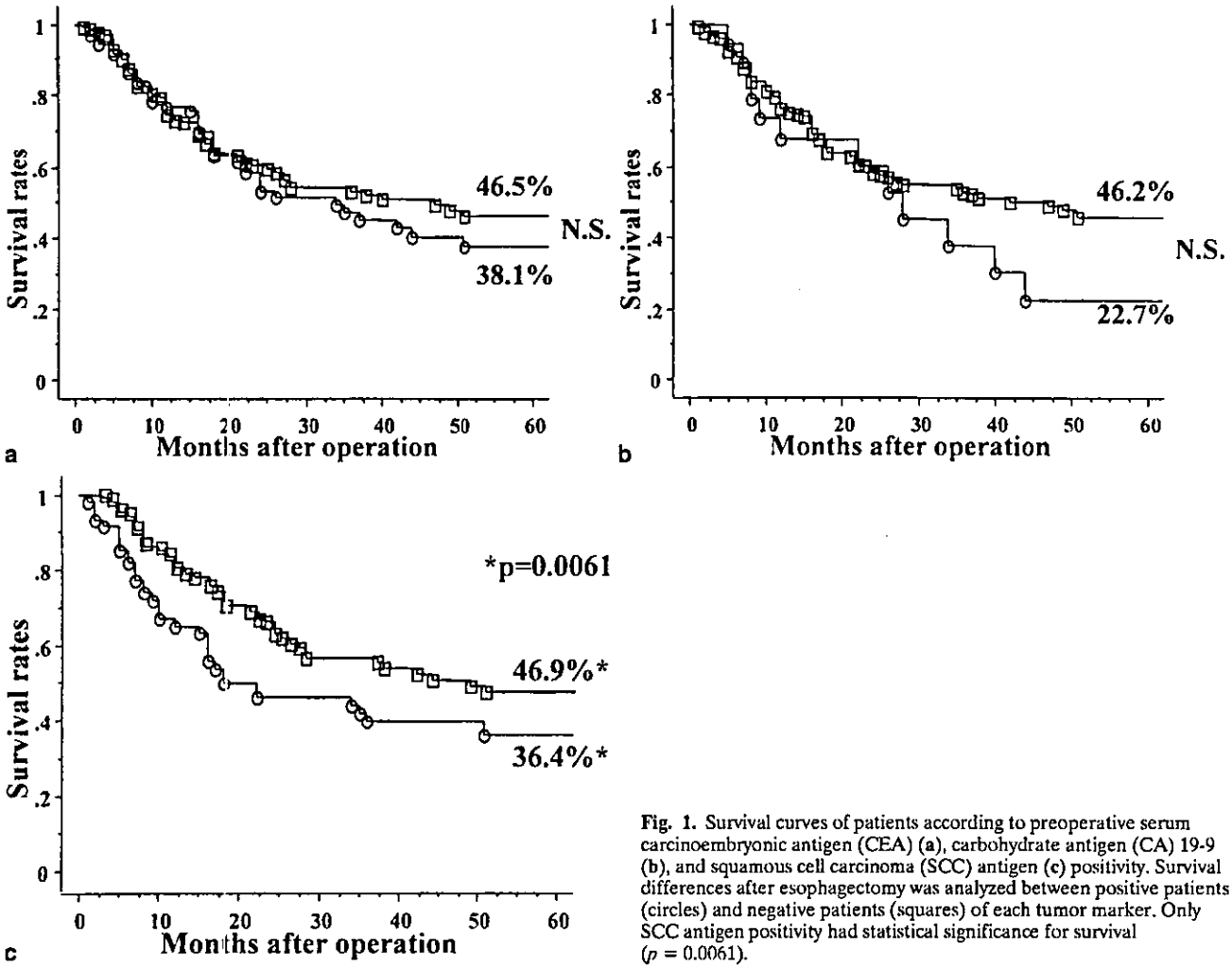

Fig. 1. Survival curves of patients according to preoperative serum carcinoembryonic antigen (CEA) (a), carbohydrate antigen (CA) 19-9 (b), and squamous cell carcinoma (SCC) antigen (c) positivity. Survival differences after esophagectomy was analyzed between positive patients (circles) and negative patients (squares) of each tumor marker. Only SCC antigen positivity had statistical significance for survival ($p = 0.0061$).

Table 3. Univariate analysis of prognostic factors in the ER group.

Variable	5-year survival (%)	p
pT (T1/T2/T3/T4)	79.8/34.9/27.1/18.0	< 0.0001
pN (N0/N1)	70.4/27.1	< 0.0001
pN no. (N0/1–4/≥ 5)	70.4/36.8/8.1	< 0.0001
pM (M0/M1)	48.5/17.9	< 0.0001
Stage (I/II/III/IV)	86.2/56.7/21.4/17.9	< 0.0001
Lymphatic invasion (−/+)	58.4/34.5	< 0.0001
Blood vessel invasion (−/+)	59.6/25.6	< 0.0001
IM (−/+)	50.6/13.9	< 0.0001
Residual tumor (R0/R1/R2)	50.1/25.0/3.5	< 0.0001
Serum SCC antigen positivity (−/+)	48.5/34.6	0.0061

IM: intramural metastasis.

Table 4. Multivariate analysis of prognostic factors in the ER group.

Variables	Exponent	p	95% CI
Depth of invasion			
T2	2.807	0.0733	0.907–8.689
T3	3.949	0.0006	1.805–8.639
T4	5.816	0.0002	2.270–14.898
No. of metastatic nodes			
≤ 4	1.943	0.0536	0.990–3.814
≥ 5	3.824	0.0009	1.728–8.462
Intramural metastasis present	2.079	0.0025	1.295–3.340
SCC antigen positivity	0.917	0.7122	0.578–1.454

CI: confidence interval.

and intramural metastasis were shown by multivariate analysis to be independent prognostic factors (Table 4). An elevated preoperative serum SCC antigen level, however, was not found to be a significant independent prognostic factor.

Discussion

Esophageal cancer is one of the most difficult malignancies to cure regardless of the treatment modality. To improve treatment outcome, several tumor markers assessed in patient sera have been tested for their utility in screening, diagnosis, establishing prognosis, monitoring treatment, and detecting relapse in patients with esophageal cancer [10]. CEA, CA 19-9, and SCC antigen are several of the tumor markers commonly used in the management of esophageal cancer patients [2–4]. Although some studies have reported that CYFRA 21-1 has higher sensitivity for detecting esophageal cancer than other tumor markers [11–13], the sensitivity of CEA, CA 19-9, SCC antigen, and even CYFRA 21-1 has been re-

ported to be less than 10% in patients with early esophageal cancer [4], suggesting that these tests have limited utility for detecting this disease at an early stage. However, whether the assessment of serum levels of these tumor markers prior to the initiation of treatment is useful for staging esophageal cancer or for predicting survival after esophagectomy remains unclear.

Previous studies have suggested the potential usefulness of CEA and CA 19-9 when screening or monitoring disease recurrence and response to treatment [2, 3]. Gion et al. reported that the CEA assay showed a positive rate of 27.1% and was directly related to the clinical stage in patients with esophageal cancer [14]. In contrast, Clark et al. found no relation between preoperative CEA elevation and tumor stage or patient survival [15]. In the present study, seropositivity of CEA and CA 19-9 before treatment had no correlation with resectability, most clinicopathologic parameters of tumor progression, or patient survival. In accord with the results of our study, Kim et al. found that the CEA level did not predict resectability or survival in patients with esophageal cancer [16]. However, the present study revealed a significant relation between preoperative elevation of serum CEA levels and the presence of clinically inapparent distant metastases. Our findings are similar to those of Munck-Wikland et al., who reported that the appearance of distant metastases was associated with increased CEA levels [2]. In addition, Sanders et al. reported that the abnormal elevation of serum CEA levels may reflect the metastatic potential of esophageal cancer cells [17].

In the present study, in contrast to the preoperative serum levels of CEA and CA 19-9, those of SCC antigen exhibited significant correlation with resectability, location of the primary tumor, histopathologic grading, and clinicopathologic parameters of tumor progression, including depth of tumor invasion, lymph node status, TNM stage, lymphatic invasion, and blood vessel invasion. Although judging resectability based on preoperative serum SCC antigen levels is not practical, it may serve as an ancillary tool to predict resectability. Distribution of the disease stage revealed that the NR patients had significantly more advanced disease than did the ER patients ($p < 0.0001$). This may explain the significantly higher rates of serum SCC antigen positivity in the former group than in the latter group. Both mucosal and submucosal carcinomas of the esophagus are defined as T1 tumors by the UICC's TNM classification system. However, recent studies have demonstrated that esophageal T1 tumors comprise an oncologically heterogeneous subgroup; that is, mucosal carcinomas are usually a local disease associated with excellent treatment results, whereas submucosal carcinomas frequently display extraesophageal spread associated with a significantly worse prognosis than that of the mucosal tumors [18]. On the other hand, the prognosis of patients with T4 esophageal carcinoma is extremely poor. When the data from patients with mucosal carcinomas and T4 tumors were eliminated and survival rates were recalculated in the remaining ER group, univariate analysis showed that the positivity of the preoperative serum SCC antigen assay was not a significant prognostic factor ($p = 0.1558$, data not shown). Because a strong correlation between serum SCC positivity and the depth of the primary tumor was observed, there may be no significant difference in patient survival relative to the positive or negative results of preoperative SCC antigen assessment in patients without T4 tumors. Our findings are similar to those of Nakamura et al., who found a significant correlation between preoperative serum SCC antigen levels and TNM stage in patients with esophageal cancer [4]. On the other hand, Kawaguchi et al. found no relation between the serum SCC antigen levels and the TNM stage [12]. Their study sample was smaller than that used in the study of Nakamura et al. [4]. The findings in the present study may partly explain the contradictory results.

The present study revealed that elevated preoperative levels of serum SCC antigen indicated an adverse outcome regarding patient survival after esophagectomy. To our knowledge, such a prognostic impact of serum SCC antigen levels has not been previously reported. The fact that our study sample was larger and the follow-up period after esophagectomy longer than in previous studies might account for the fact that the prognostic significance of preoperative serum SCC antigen levels in patients with esophageal cancer was detected. We did not find preoperative seropositivity of SCC antigen to be an independent prognostic factor by multivariate analysis, although our findings reconfirmed that the depth of tumor invasion, number of positive nodes, and intramural metastasis were independent prognostic factors. However, these results may not necessarily diminish the utility of preoperative serum SCC antigen assessment because the amount of elevation of these factors regarding the degree of tumor spread is often difficult even by the current imaging techniques prior to esophageal resection, particularly in patients with resectable esophageal cancer [19]. Nishimaki and associates reported that preoperative stage grouping was only 56% accurate for resectable, localized esophageal cancer [19]. Therefore preoperative serum SCC antigen levels may be a useful prognostic predictor in these cases although not independent of the clinicopathologic factors known to be authentic prognostic indicators. Furthermore, measurement of serum SCC antigen levels is convenient as well as less expensive.

Recently, CYFRA 21-1, which is recognized as a soluble cytokeratin-19 fragment, has been tested for its clinical utility in patients with esophageal cancer. Some investigators have reported that serum CYFRA 21-1 levels are superior to SCC antigen levels because the former are more sensitive and correlate more significantly with tumor progression [11–13]. Notably, other researchers have found that CYFRA 21-1 is not superior to CEA or SCC antigen, particularly in patients with superficial esophageal cancer [5]. Nakamura et al., for example, reported finding a significant correlation between serum CYFRA 21-1 and SCC antigen levels in patients with esophageal cancer [4]. Although further study, enrolling a large number of patients, is needed to determine the most useful tumor marker in the management of patients with esophageal cancer, the present study suggests that preoperative assessment of serum SCC antigen levels is useful for staging esophageal cancer as an ancillary tool to assess the extent of disease.

Conclusions

An abnormal elevation of the serum SCC antigen level is a useful predictor of advanced esophageal cancer associated with poor survival after esophagectomy. Serum CEA levels may be of use in predicting clinically inapparent distant metastasis. Preoperative assessment of serum CA 19-9 levels, in contrast, has no clinical significance in the management of patients with esophageal cancer.

Résumé. Afin de clarifier si l'évaluation préopératoire des taux de l'ACE, du CA 19-9 et du SCC étaient utiles pour le staging et pour prédire la survie des patients après oesophagectomie, on a analysé la séropositivité de ces marqueurs et on a corrélé les résultats avec la résecabilité, les paramètres cliniques et pathologiques de la progression tumorale ainsi qu'avec

l'évolution chez les patients, respectivement, porteurs d'un cancer non résecable de l'oesophage (n = 63) et ayant eu une oesophagectomie pour maladie réséquable (n = 267). Une élévation anormale de SCC était corrélée de façon statistiquement significative avec la résecabilité ($p < 0.0001$), la profondeur de l'invasion tumorale ($p < 0.0001$), l'état ganglionnaire lymphatique ($p = 0.0015$), le stade TNM ($p < 0.0001$), l'invasion lymphatique ($p = 0.0019$), l'invasion vasculaire ($p = 0.0079$), et la survie après oesophagectomie ($p = 0.0061$). On a retrouvé une corrélation significative ($p = 0.0145$) entre le taux élevé d'ACE dans le sérum et l'existence de métastases à distance. Cependant, aucune association entre la séropositivité de l'antigène CA 19-9 et la réséquabilité, la progression tumorale ou la survie n'a pu être mise en évidence. Ces résultats indiquent que l'élévation anormale de SCC dans le sérum est un facteur prédictif utile d'un cancer avancé de l'oesophage, et qu'elle est associée à une survie médiocre après oesophagectomie.

Resumen. El trabajo tiene como objetivo el averiguar si en el preoperatorio los niveles séricos de CEA, CA 19-9, y SCC son útiles para la estadificación del cáncer de esófago y para pronosticar la supervivencia de los pacientes tratados mediante esofaguectomía. Investigamos si la positividad sérica de estos marcadores tumorales se correlacionaba con la tasa de resecabilidad, parámetros clínicopatológicos de la extensión tumoral y resultados del tratamiento, tanto en pacientes con cáncer irresecable (n = 63) como resecable (n = 267). Una elevación anormal de los niveles séricos del SCC mostró una correlación significativa con la resecabilidad ($p < 0.0001$), profundidad de la invasión tumoral ($p < 0.0001$), afectación ganglionar ($p = 0.0015$), estadificación TNM ($p < 0.0001$) invasión linfática ($p = 0.0019$), de los vasos sanguíneos ($p = 0.0079$) y escasa supervivencia tras la esofaguectomía ($p = 0.0061$). Una correlación significativa se constató entre los niveles séricos elevados de CEA y las metástasis a distancia. Sin embargo, la positividad sérica del CA19-9 no mostró relación alguna con la resecabilidad, extensión tumoral y supervivencia de los pacientes. Nuestros resultados demuestran que la elevación anormal en suero del marcador tumoral SCC constituye un factor pronóstico útil en el cáncer avanzado de esófago, asociándose a una corta supervivencia tras esofaguectomía.

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DISEASES OF THE ESOPHAGUS

Original article

Flavopiridol as a radio-sensitizer for esophageal cancer cell lines

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SUMMARY. **Flavopiridol is a synthetic flavone that has shown an antitumor effect against several cancers. Here, we investigated the in vitro effect of flavopiridol alone and the combined effect of low-dose flavopiridol plus radiation on esophageal squamous cell carcinoma cell lines. Esophageal squamous cell carcinoma cell lines (TE8, TE9 and KE4) were exposed to flavopiridol (0.05–400 nmol/L) for 48 h. Growth inhibition was evaluated by MTT assay, cell cycle distribution was determined by flow cytometry, and cyclin D1, Bcl-2 and Rb protein expression was detected by Western blotting. The effect of 0.05 nmol/L flavopiridol as a radio-sensitizer was determined by clonogenic assay. The IC_{50} was approximately 110–250 nmol/L. Exposure to 0.05 nmol/L flavopiridol for 48 h increased the G_2/M population, while 300 nmol/L increased the G_1 population. At a concentration of 300 nmol/L, nuclear fragmentation and chromatin condensation were observed in all three cell lines. Exposure to 300 nmol/L flavopiridol decreased the levels of cyclin D1 and Rb protein in all three cell lines and Bcl-2 protein was also decreased in TE8 and KE4 cells. Moreover, exposure to 0.05 nmol/L flavopiridol slightly decreased the levels of cyclin D1, Rb and Bcl-2 protein in KE4 cells. Flavopiridol treatment (0.05 nmol/L) enhanced the radio-sensitivity in all three cell lines. Low-dose flavopiridol augmented the response of esophageal squamous cell carcinoma cell lines to radiation. Administration of a low dose of flavopiridol could be a potent new therapeutic approach for improving the efficacy of radiotherapy against esophageal cancer.**

KEY WORDS: **cell cycle, chemoradiation, cyclin-dependent kinase inhibitor, esophageal squamous cell carcinoma, radio-sensitivity.**

INTRODUCTION

Esophageal cancer has a poor prognosis among the gastrointestinal tract cancers, and its incidence continues to increase in the USA.[1] In the recent past, the incidence of esophageal adenocarcinoma has risen dramatically, whereas the incidence of squamous cell carcinoma has remained relatively steady.[2] In Japan, almost all patients with esophageal cancer have squamous cell carcinoma. Generally, radiotherapy and chemoradiotherapy using conventional chemotherapy agents are effective against esophageal squamous cell carcinoma.[3] Over the past two decades, there has been a dramatic improvement in the 5-year survival rate of patients with squamous cell carcinoma,[4] however, it remains an aggressive neoplasm with an extremely poor prognosis. Therefore, more effective anticancer agents with a radio-sensitizing potential need to be developed.

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Flavopiridol is a synthetic flavone and is the first cyclin-dependent kinase (CDK) inhibitor to enter clinical trials. It has been shown to induce cell cycle arrest at G_1 or G_2/M, in association with direct inhibition of cdk-1, -2, -4, -6 and -7, and it induces apoptosis independently of an effect on pRb, p53 and Bcl-2 expression.[5]

In addition to direct inhibition of cdks, it has been suggested that other targets may be involved. Flavopiridol decreases cyclin D1 and Bcl-2 expression and inhibits a variety of protein kinases,[6–9] including protein kinase A, ErbB-1 receptor tyrosine kinase, pp60 Src, PKC and Erk-1.[5,10,11] Moreover, it has been suggested that flavopiridol has an anti-angiogenic effect since it decreases the induction of vascular endothelial growth factor by hypoxia in human monocytes.[12] Although the mechanisms of flavopiridol-induced antiproliferative activity have not been fully elucidated, inhibition of cyclin-dependent kinases may contribute to the anticancer effect, along with additional actions such as promotion of apoptosis, interaction with DNA and a decrease of cyclin D1.

Anticancer activity of flavopiridol against various malignancies has been demonstrated and it has