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Original Article

Efficacy of Concurrent Chemoradiotherapy as a Palliative Treatment in Stage IVB Esophageal Cancer Patients with Dysphagia

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Objective: To retrospectively assess the efficacy and safety of palliative chemoradiotherapy in Stage IVB esophageal cancer patients with dysphagia due to the primary lesion.
Methods: Forty patients with dysphagia caused by metastatic esophageal cancer, which had been treated between January 2004 and June 2009, were retrospectively investigated. The treatment consisted of two courses of chemotherapy (5-fluorouracil and cisplatin) and concurrent irradiation of 40 Gy in 20 fractions to the esophageal primary tumor. The grade of dysphagia was evaluated; nutrition-support-free survival was evaluated using the status of nutritional support of patients. Response to treatment, overall survival, progression-free survival and toxicities were also evaluated.
Results: Dysphagia score improved in 75% of the patients. Seventeen of the 20 patients (85%) who had required nutritional support at baseline improved their oral intake to no longer need the support, in a median time of 43 days. The median nutrition-support-free survival was 301 days in the 20 patients who had had adequate oral intake before the treatment. Disease control rate of the primary lesion was 95%, including 12 patients (30%) who achieved a complete response. The overall response rate was 55%. The median survival was 308 days, and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days. Toxicities were generally well tolerated. Major toxicities (Grade 3 or 4) involved hemoglobin (23%), leukocytes (15%), neutrophils (20%), anorexia (10%), nausea (3%), esophageal perforation (5%) and febrile neutropenia (3%). Two patients (5%) died within 30 days of terminating radiotherapy.
Conclusions: Palliative chemoradiotherapy using 5-fluorouracil plus cisplatin combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival.

Key words: esophageal cancer – squamous cell carcinoma – Stage IVB – dysphagia – palliative chemoradiotherapy

INTRODUCTION

Esophageal cancer is the sixth most common form of cancer in male and the sixth most common cause of all cancer death. In 2008, estimated 482 600 new cases are diagnosed, and the estimated deaths were 406 800 worldwide (1). In Japan, 11 669 patients died of esophageal cancer in 2007 (2). For 8.6% of the patients, the disease has already spread to other organs of the body at the time of diagnosis (3), and a cure is not expected. Most of these metastatic patients experience dysphagia due to the progression of the primary lesion.

Dysphagia is the most common and serious symptom of esophageal cancer. It severely affects the patient's quality of

life and necessitates nutritional support, such as intravenous infusion or feeding through percutaneous gastrostomy or nasogastric tube, when inadequate oral intake persists. For patients with unresectable, metastatic esophageal cancer, long-term relief of dysphagia is one of the most important issues in their daily life (4).

Of the multiple treatment options for dysphagia, radiotherapy and metallic stent placement have been considered to be the standard of care. When rapid relief of dysphagia is required, stent placement is the preferred treatment; however, its efficacy is short term due to the fact that the tumor masses are only pressed mechanically. Stent deployment in inoperable patients has been reportedly associated with a median survival time of only 13–20 weeks (5–7). For patients in better health, radiotherapy could offer a more prolonged effect (8).

According to the National Comprehensive Cancer Network (NCCN) clinical practice guidelines in oncology™ v.1.2010, palliative chemotherapy is proposed as the standard treatment in metastatic patients, with the aims of controlling tumor growth, improving quality of life and prolonging survival. Response rates to chemotherapy alone ranged from 16 to 43% for metastatic disease (9–14). However, there is little evidence to suggest that chemotherapy alone improves survival and/or quality of life including dysphagia in patients with metastatic disease (9,15,16).

With respect to palliative chemoradiotherapy in patients with further advanced esophageal cancer, including metastatic cases, previous studies have shown considerable effects in the improvement of dysphagia (17–23). However, there have been only a few studies covering exclusively Stage IVB esophageal cancer.

The aim of this retrospective study was to provide basic data on the efficacy and toxicity of palliative chemoradiotherapy in Stage IVB esophageal cancer. We especially focused on the improvement of dysphagia, and survival time without nutritional support, because these parameters reflect clinically relevant symptomatic indices in patients suffering from dysphagia due to incurable, metastatic esophageal cancer.

PATIENTS AND METHODS

Patients

The subjects were recruited from our database of patients who were treated at National Cancer Center Hospital East (Kashiwa, Chiba, Japan) between January 2004 and June 2009, according to the following criteria: (i) histologically confirmed squamous cell carcinoma of the esophagus; (ii) metastatic disease classified as Stage IVB, according to the TNM classification of malignant tumor of UICC, sixth edition; (iii) radiation therapy consisted of 2 Gy fractions (Fr) daily for 20 days (total 40 Gy); (iv) chemotherapy consisted of 5-fluorouracil (5-FU) and cisplatin (CDDP); (v) primary lesion present in thoracic esophagus; (vi) age 20–75 years; (vii) performance status (PS) $\leq$2 on the Eastern Cooperative Oncology Group scale; (viii) no previous history of chemotherapy or radiotherapy; (ix) white blood cell count between 4000 and 20 000/μl; (x) platelet count 100 000/μl or more; (xi) adequate liver function, as indicated by serum concentrations of total bilirubin $\leq$2.0 mg/dl, aspartate aminotransferase $\leq$200 IU/l and alanine aminotransferase (ALT) $\leq$200 IU/l; (xii) serum creatinine concentration $\leq$1.5 mg/dl. The metastatic lesions were confirmed with computed tomography scans. The presence of a measurable metastatic lesion was not mandatory. Patients with other active synchronous carcinomas or concurrent uncontrolled medical illness were excluded. The study was performed in accordance with the Declaration of Helsinki and Japanese ethical guidelines for epidemiological research. We obtained an institutional review board (IRB) waiver to conduct this study from the chairperson of the IRB.

Treatment Schedule

Chemotherapy comprised protracted infusion of 5-FU combined with a 2 h infusion of CDDP with adequate hydration and antiemetic coverage. In general, patients were treated with 5-FU 700 mg/m^2 on days 1–4 and 29–32, and CDDP 70 mg/m^2 on days 1 and 29 (Fig. 1). Doses were modified according to the judgment of the attending physician: the doses of 5-FU and CDDP were generally reduced to 50–80% when Grade 4 hematological or Grade 3 or 4 non-hematological toxicity occurred. Once serious toxicity was observed, treatment was suspended until recovery.

Radiation treatment (10 MV) was administered for 4 weeks (5 days/week) at 2 Gy/day with a total radiation dose of 40 Gy/20 Fr, concomitantly with chemotherapy (Fig. 1). The chemotherapy and radiotherapy were started within 7 days of each other. The targeted area for irradiation included only the primary tumor with a 3 cm superior and inferior margin and a 2 cm lateral margin. Metastatic lesions were not included in the targeted area. Irradiation was applied in anterior and posterior opposed fields.

When there was a need, nutritional support was provided by fluid administration including intravenous hyperalimentation or feeding through a percutaneous gastrostomy tube.

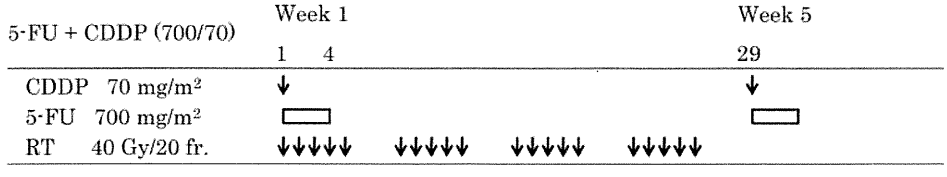

Figure 1. Treatment schedule. 5-FU, 5-fluorouracil; CDDP, cisplatin; RT, radiotherapy.

For patients who showed an objective response to treatment, additional courses of chemotherapy alone were administered, which consisted of the same regimen or protracted infusional 5-FU 800 mg/m^2/day on days 1–5 and a 2 h infusion of CDDP 80 mg/m^2/day on day 1. These treatments were repeated every 4 weeks until disease progression, development of unacceptable toxicity or the patient's refusal to continue. Further additional courses of chemotherapy were optional. When disease progression or unacceptable toxicities were observed, second-line chemotherapy was initiated.

Response and Toxicity Evaluation

The grade of dysphagia was determined by the dysphagia score as described previously and shown in Table 1 (24,25). Improvement of dysphagia was defined as a decrease of at least 1 point in dysphagia score.

Objective responses of measurable metastatic lesions were evaluated according to the response evaluation criteria in solid tumors (RECIST v 1.0) guideline. Tumor response was evaluated using computed tomography scan every 8 weeks after the initiation of treatment. Response of the primary tumor was evaluated by the criteria of the Japan Esophageal Society (26,27). Complete response (CR) of the primary lesion is judged, using endoscopy, with the fulfillment of all of the following conditions: (i) disappearance of all endoscopic findings that suggest the presence of tumor, such as irregular erosive lesions, ulcerative lesions or obvious elevated lesions; (ii) no histologic findings of malignant cells by endoscopic biopsy from the area where the primary tumor had been; (iii) the entire esophagus can be observed by endoscopy; and (iv) no findings of active esophagitis by endoscopy. Progressive disease (PD) of the primary lesion means distinct tumor growth or progression in esophageal stenosis during treatment. Incomplete response/stable disease (IR/SD) means that the response of the primary lesion does not meet the conditions for CR or PD.

Toxicity was evaluated according to the Common Terminology Criteria for Adverse Events v3.0 (CTCAE v3.0). Toxicity was assessed on a weekly basis during chemoradiotherapy and then biweekly during the subsequent chemotherapy.

Table 1. Dysphagia score

Score	Swallowing status
0	Asymptomatic
1	Eat solid diet with some dysphagia
2	Eat semi-solid diet
3	Drink liquid diet
4	Complete dysphagia

Statistical Analysis

Overall survival was calculated from the initiation of treatment to the date of death or the last follow-up day in survivors. Progression-free survival was calculated from the initiation of treatment to the detection of disease progression or death from any cause. In patients who had not required

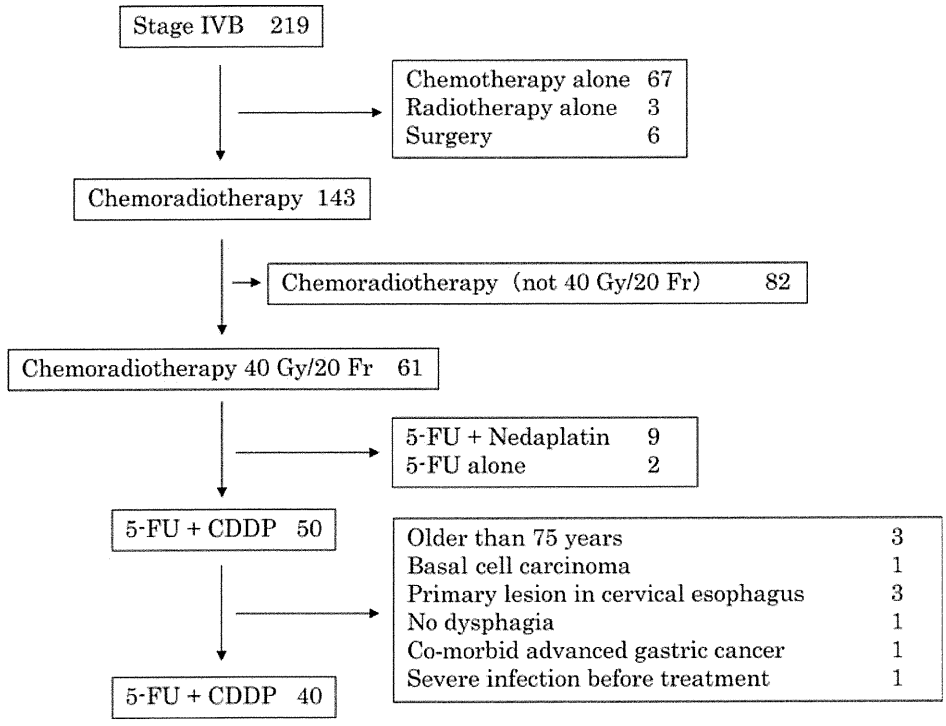

Figure 2. Between January 2004 and June 2009, 219 patients with Stage IVB esophageal cancer were treated at National Cancer Center Hospital East.

nutritional support before chemoradiotherapy, nutrition-support-free survival was calculated from the initiation of treatment to the date when nutritional support was first started. The oral intake of patients who had initially required nutritional support was considered to have improved when nutritional support could be stopped. Overall survival, progression-free survival and nutrition-support-free survival were calculated using the Kaplan–Meier method and the SPSS software program.

RESULTS

Patients' Characteristics and Treatment

From January 2004 to June 2009, 219 patients with Stage IVB esophageal cancer were treated in our hospital. Of these 219 patients, 143 patients were treated with chemoradiotherapy, 67 with chemotherapy alone, 3 with radiotherapy alone and 6 received palliative surgery as initial management (Fig. 2).

Of the 143 patients treated with chemoradiotherapy, 50 were treated with the palliative regimen of chemotherapy with 5-FU and CDDP and 40 Gy/20 Fr of irradiation to exclusively the primary lesion. Of these 50 patients, 10 were excluded from our study: 3 were older than 75 years; 1 had basal cell carcinoma; 3 had a primary lesion located in the cervical esophagus; 1 did not experience dysphagia; 1 had advanced gastric cancer; and 1 developed a severe infection immediately before treatment started. The remaining 93 patients had been treated with other regimens, such as 5-FU and CDDP combined with 50.4 or 60 Gy irradiation, or 5-FU plus nedaplatin with radiation.

The characteristics of the 40 eligible patients are shown in Table 2. Most of the patients (95%) had good PS of 0 or 1.

Table 2. Patients' characteristics ($n = 40$)

Characteristic	
Age (years), median (range)	64 (43–74)
Sex	
Male	36
Female	4
PS	
0	24
1	14
2	2
Primary tumor site[a]	
Ut	8
Mt	20
Lt	12
Macroscopic type	
1	3
2	18
3	18
4	1
T stage	
T1	0
T2	0
T3	24
T4	16
Tumor length (cm), median (range)	8 (3–17)
Tumor circumference	
$<1/3$ of circumference	1
$\geq 1/3$ and $<2/3$ of circumference	7
$\geq 2/3$ of circumference, but not entire circumferential	9
Entire circumferential	23
Metastatic organs	
Lymph nodes	24
Distant organs	16
Liver	10
Lung	8
Others	4

PS, performance status; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus.
[a]Anatomical subsites of esophagus are defined according to the TNM classification of malignant tumors, seventh edition.

Compliance and Efficacy

All patients completed the planned radiotherapy. Radiation schedule was interrupted for 1 day or more in seven cases (18%) because of infection or high fever (Grade 1 or 2), but all completed the program after an intermission.

The median number of courses in the initial regimen of chemotherapy was four, ranging from one to seven courses. Treatment discontinuation within two courses was observed in two patients. The regimen was changed to 5-FU and nedaplatin in one patient at the physician's discretion. Chemotherapy was terminated in the other patient because of disease progression after the first course of chemotherapy. In seven patients, the dose was reduced (to 50–80%) for the second course because of toxicities observed in the first course.

The responses of the primary lesions are shown in Table 3: 12 patients (30%) achieved a CR in their primary lesion and 26 (65%) were categorized as having IR/SD. Of these patients, 24 demonstrated apparent regression of the primary lesion, which means that 90% of the patients showed volume reduction in the primary lesion after chemoradiotherapy. As for the overall response including metastatic lesions, objective improvement was seen in 22 patients, a 55% response rate (Table 4).

Evaluation of Dysphagia and Survival

All patients were assessable for degree of dysphagia, history of oral intake, toxicity, overall survival and progression-free

Table 3. Response of the primary lesion ($n = 40$)

Response of primary lesion	No. of patients
CR	12 (30%)
IR/SD	26 (65%)
PD	0 (0%)
NE	2 (5%)
Disease control rate	95%

CR, complete response; IR/SD, incomplete response/stable disease; PD, progressive disease; NE, not evaluated.

Table 4. Overall response to treatment ($n = 40$)

Overall response	No. of patients
CR	2 (5%)
PR	20 (50%)
SD	10 (25%)
PD	6 (15%)
NE	2 (5%)
Response rate	55%

PR, partial response.

Table 5. Change in dysphagia score after treatment ($n = 40$)

Improved	Unchanged	Worsened	Improvement rate
30	7	3	75%

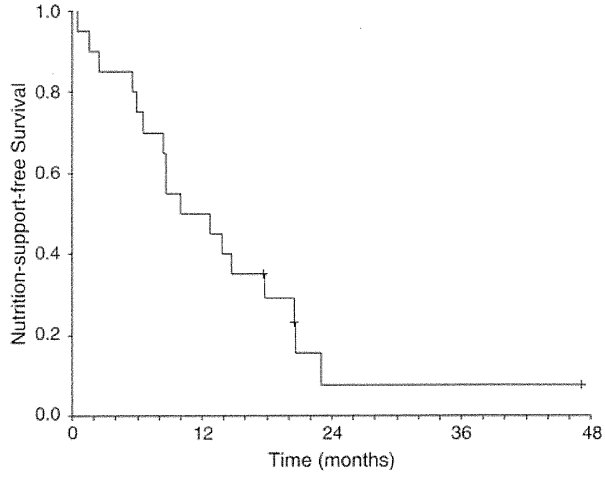

Figure 3. Nutrition-support-free survival ($n = 20$).

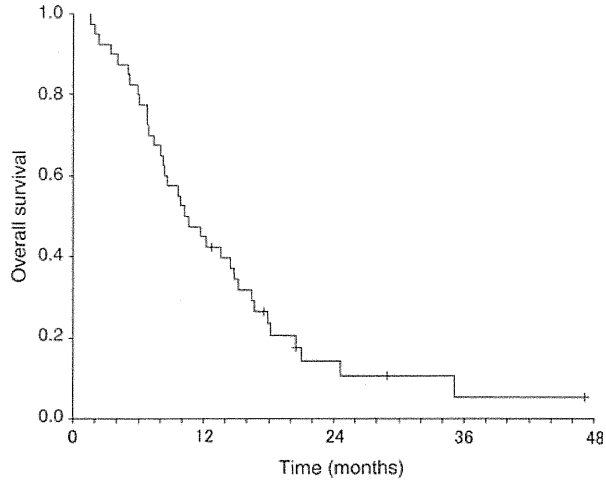

Figure 4. Overall survival ($n = 40$).

survival. Nutrition-support-free survival could also be assessed in all patients. Twenty patients who had received nutritional support of total parenteral nutrition or percutaneous gastrostomy at the onset of treatment were assessable for improvement in oral intake.

The overall improvement rate of dysphagia score was 75% (30/40) (Table 5). The nutrition-support-free survival of the 20 patients with initially adequate oral intake is shown in Fig. 3. The median nutrition-support-free survival was 301 days (10.0 months). The median overall survival in this group of patients was 410 days (13.7 months). Of the other 20 patients who had initially required nutritional support, 85% (17/20) were relieved from nutritional support: median overall survival was 249 days (8.3 months). Of the 17 patients who were relieved from nutritional support, the median time until relief of nutritional support was 43 days (1.4 months) and the median nutrition-support-free duration was 137 days (4.6 months).

The median follow-up period was 617 days in survivors at the time of analysis. The overall survival time is shown in Fig. 4. The median survival time was 308 days (10.3 months), and the 1-year-survival rate was 45.0%. The median progression-free survival was 139 days (4.6 months) (Fig. 5).

Toxicity

The grades of toxicity during the treatment course (radiotherapy and first and second course of chemotherapy) are summarized in Table 6. Toxicity profiles with Grade 3 and 4 are shown except for platelet. Hematological toxicities were generally mild. Anemia was the most common hematological toxicity, but only 23% of the patients experienced Grade 3 or 4 anemia. Grade 3 or 4 neutropenia and leukopenia occurred in 15 and 20% of the patients, respectively. Grade 3 or 4 non-hematological toxicities were hyponatremia (18%), anorexia (10%), nausea (3%), esophageal perforation (5%), ALT (5%), creatinine (3%), febrile neutropenia (3%), rash (3%) and constipation (3%).

No patient died during radiotherapy. However, early death, within 30 days of terminating radiotherapy, occurred

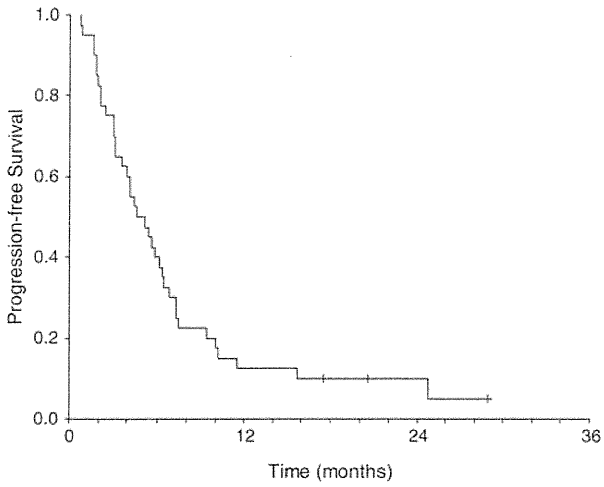

Figure 5. Progression-free survival ($n = 40$).

Table 6. Adverse events ($n = 40$)

CTCAE VER3.0	Gr. 1	Gr. 2	Gr. 3	Gr. 4	≥Gr. 3
Hemoglobin	10	17	8	1	9 (23%)
Leukocytes	13	10	5	1	6 (15%)
Neutrophils	19	13	8	0	8 (20%)
Platelet	9	5	0	0	0 (0%)
Rash	1	0	1	0	1 (3%)
Anorexia	11	8	4	0	4 (10%)
Constipation	3	2	1	0	1 (3%)
Mucositis/stomatitis	4	3	0	0	0 (0%)
Nausea	16	7	1	0	1 (3%)
Esophageal perforation	0	0	2	0	2 (5%)
Alanine aminotransferase	16	2	2	0	2 (5%)
Creatinine	8	2	1	0	1 (3%)
Hyperkalemia	21	3	1	0	1 (3%)
Hyponatremia	28	—	7	0	7 (18%)
Febrile neutropenia	0	0	1	0	1 (3%)

Two patients (5%) died within 30 days of completion of radiotherapy.
CTCAE, Common Terminology Criteria for Adverse Events.

in two patients: one was a 64-year-old man who had supraclavicular lymph node metastases. The primary tumor had not invaded adjacent organs (T3), but one metastatic lymph node had invaded the wall of the aorta. On the 13th day after terminating radiotherapy, the patient was admitted to the hospital as an emergency due to severe right pneumonia; he died the next day. Chest X-ray indicated pneumonia due to aspiration or perforation, so the probability of radiation pneumonitis was low. The other patient was a 71-year-old man who had deep cervical and supraclavicular lymph node metastases and pericardial dissemination. The primary tumor invaded the wall of the aorta, bronchus and pericardium (T4). On the 26th day after terminating radiotherapy, the patient complained of severe back pain. After a few hours, he was found in cardiac arrest. The causes of death in these two cases are not clear, but they could be related to treatment.

DISCUSSION

Palliative chemoradiotherapy using 5-FU plus CDDP combined with concurrent 40 Gy irradiation effectively improved the symptom of dysphagia in Stage IVB esophageal cancer with acceptable toxicity and favorable survival in our study.

To date, the best palliative method for dysphagia due to advanced esophageal cancer has not been established. Of the multiple treatment options, chemoradiotherapy had been reported to be effective for the palliation of dysphagia through tumor regression in advanced, incurable esophageal cancer (17–23). However, these previous studies included patients who were not uniform in terms of TNM clinical classification. In palliative chemoradiotherapy for patients with Stage IVB esophageal cancer accompanied by dysphagia, it is most important to balance management of primary and metastatic sites with tolerance of toxicity. Therefore, to prolong survival without nutritional support, it is important to establish the appropriate dose of individual agents and irradiation dose and field. Our study is one of only a few to investigate the palliative effects of chemoradiotherapy exclusively in patients with Stage IVB esophageal cancer.

In our study, the palliative chemoradiotherapy was satisfactory, with an overall improvement rate in dysphagia score as high as 75%. Of the patients who had required nutritional support at the onset of treatment, 85% no longer needed the support after the treatment. The toxicity was tolerable, and the median overall survival was 10.3 months in patients with Stage IVB esophageal cancer accompanied by dysphagia. We suggest that concurrent chemoradiotherapy of 5-FU plus CDDP combined with 40 Gy irradiation is effective in improving dysphagia.

Published reports of palliative chemoradiotherapy are summarized in Table 7 (17,18,20–23). The chemotherapy regimens in these studies are basically a combination of 5-FU and another agent, and the radiation dose ranges between 30 and 54 Gy, which is generally lower than the dose used in definitive chemoradiotherapy. Our regimen, chemotherapy with 5-FU and CDDP, and concurrent radiation of 40 Gy, can be properly categorized in the spectrum of palliative therapy. Hayter et al. (18) showed in detail the palliative efficacy of 30 Gy radiation in 10 Fr with concurrent chemotherapy consisting of 5-FU and mitomycin C in 22 patients with advanced incurable esophageal cancer. In that study, complete relief of dysphagia was observed in 68% of the patients. The median time to normalization of swallowing was 5 weeks, and the median dysphagia-free interval from the onset of improvement was 11 weeks. In the other reports, the improvement rate of dysphagia ranged

Table 7. Previous reports of palliative concurrent chemoradiotherapy for dysphagia in inoperable, advanced esophageal cancer

Literature	*n*	Pathology	Chemotherapy	Radiotherapy (Gy)	Treatment failure (%)	TRD rate (%)	Improvement rate of dysphagia (%)	Survival (months)
Coia (22)	49	SCC, Adeno	5-FU, MMC	50	NS	NS	91	8
Urba and Turrisi (23)	27	SCC, Adeno	5-FU, CBDCA	40	0	4	59	6
Hayter et al. (18)	22	SCC, Adeno	5-FU, MMC	30	NS	5	68	5
Harvey et al. (17)	106	SCC, Adeno, small cell, undifferentiated and others	5-FU, CDDP	35	5	6	78	7
Burmeister et al. (20)	24	SCC, Adeno	5-FU	30–35	17	NS	67	9
Cho (21)	27	SCC	S-1, CDDP	54	0	0	77.8	11.6
Present study	40	SCC	5-FU, CDDP	40	5	5	75	10.3

TRD, treatment-related death; SCC, squamous cell carcinoma; Adeno, adenocarcinoma; 5-FU, 5-fluorouracil; MMC, mitomycin C; NS, not stated; CBDCA, carboplatin; Small cell, small cell carcinoma; Undifferentiated, undifferentiated carcinoma; CDDP, cisplatin.

from 67 to 91% (Table 7). The effects of our palliative regimen are comparable to those reported in these studies.

Our treatment regimen was well tolerated. No patient failed to complete radiation, and only two patients (5%) received fewer than two complete courses of the planned chemotherapy. Death within 30 days of completion of radiation was observed in two patients (5%). The rates of treatment failure and treatment-related deaths in the previous studies are shown in Table 7. As for these two parameters, the toxicity profile of our regimen is equivalent to those of the previous studies.

There have been some studies evaluating chemotherapy for locally advanced or metastatic squamous cell esophageal cancer (10–14). Bleiberg et al. (12) reported that WHO Grade 3 and 4 toxicities were observed from combined chemotherapy of 5-FU and CDDP: leukocytes in 14% of the patients and platelets in 14%. Iizuka et al. (14) evaluated the combination of 5-FU and CDDP in advanced squamous cell carcinoma of the esophagus and reported WHO Grade 3 and 4 toxicities of hemoglobin, leukocytes and platelets in 13, 8 and 5% of the patients, respectively. In our study, CTCAE Grade 3 and 4 leukocytes, hemoglobin and platelets developed in 15, 23 and 0% of the patients, respectively. The higher rates of hematological toxicities in our study seem to arise because of the concurrent radiation. In the studies of definitive chemoradiotherapy with a radiation dose of 50–70 Gy (20,28–32), Grade 3 and 4 toxicities were observed at a rate of 9–33% hemoglobin, 24–78% leukocytes and 14–20% platelets. These figures are generally higher than in our study, probably due to the higher radiation dose. Non-hematological toxicities were not severe in our study. Although Grade 3 esophageal perforation and febrile neutropenia occurred in 5 and 3% of the patients, respectively, they were properly managed.

Regression of the primary lesion was observed in 90% of the patients and 12 (30%) achieved CR. This effect probably results in the effective improvement of dysphagia. In definitive chemoradiotherapy of esophageal cancer, the irradiation dose to the primary lesion is 50.4 or 60 Gy in Japan. The CR rates of the primary lesion following definitive chemoradiotherapy are 62% in T3 cases and 37% in T4 cases, respectively (33). The CR rate of the primary lesion in our study was lower than this, probably because of the lower radiation dose of 40 Gy. A higher dose could lead to better and longer dysphagia relief through tumor regression, but it is important to balance palliative outcome with the costs of treatment, namely toxicities of higher irradiance and the effort of hospital visits, especially in those patients who cannot expect a cure.

The prognosis of Stage IVB esophageal cancer is poor. The median survival time has been reported to be 5–11 months (7,11,17,18,22,23,29,34) in patients who receive any treatment (including chemotherapy, chemoradiotherapy or surgery). In our study, the median survival time was 10.3 months, which is relatively good compared with previous studies of palliative therapies including chemoradiotherapy (Table 7). The survival effect is an important therapeutic aim in incurable Stage IVB esophageal cancer. Our result suggests that the addition of 40 Gy of radiotherapy to palliative chemotherapy is not associated with a negative effect on survival. However, we have to accept that there could be a selection bias in our retrospective study. It should be noted that 24 out of 40 patients have only lymph node metastasis in our study, who are known to have better outcome than those with visceral metastasis.

As for the histological type of the tumor, both squamous cell carcinoma and adenocarcinoma were included in the western studies (17–20,23), whereas only squamous cell carcinoma was included in Asian studies, including ours (21). The incidence of adenocarcinoma of the esophagus has increased considerably in western countries over the past three decades (35), whereas squamous cell carcinoma remains the major histological type of esophageal cancer in Japan and most Asian countries. It has been reported that there has been no dramatic increase in adenocarcinoma in Japan (36). Our study included only patients with squamous

cell carcinoma, in order that we represent actual Japanese clinical practice.

In conclusion, our retrospective study suggests that our palliative regimen of chemoradiotherapy, 5-FU plus CDDP combined with concurrent 40 Gy irradiation, can provide effective palliation of dysphagia through tumor regression with a tolerable toxicity profile in incurable Stage IVB esophageal cancer. However, since there are inevitable biases that could not be ruled out in our retrospective study, further prospective studies are required to elucidate the most durable and swift palliation with lower toxicity and better survival.

Conflict of interest statement

None declared.

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Appendix

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Clinical Outcome of Small Cell Lung Cancer with Pericardial Effusion but without Distant Metastasis

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Background: Pericardial effusion is defined as M1a in the Union Internationale Contre le Cancer seventh tumor, node, metastasis edition for lung cancer. The clinical course of small cell lung cancer (SCLC) with pericardial effusion but without distant metastasis (M1a) has not been adequately investigated.

Methods: The medical records of patients with SCLC treated at the National Cancer Center Hospital East between July 1992 and December 2007 were reviewed. During this period, 766 patients were newly diagnosed as having SCLC. Thirty-three of the 416 patients with limited disease (LD) SCLC (8%) had pericardial effusion. Seventy-nine patients with LD-SCLC (19%) had ipsilateral pleural effusion or dissemination. Of these, 16 patients had both pericardial and ipsilateral pleural effusion. We divided the 96 M1a patients into two subgroups: group A ($n = 33$) included patients with pericardial effusion, and group B ($n = 63$) included patients with ipsilateral pleural effusion or disseminated pleural nodules but without pericardial effusion.

Results: The median survival time among the patients with LD-M1a was 13.4 months (95% confidence interval: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively. The survival of the patients with LD-M1a was intermediate between those of the patients with LD-M0 and patients with extensive disease M1b ($p < 0.0001$). The overall survival period was not statistically different between groups A and B ($p = 0.5182$). Nineteen patients in group A received chemoradiotherapy, but only two patients survived for more than 2 years (2- and 5-year survival rate: 11% both). Twenty-six patients in group B received chemoradiotherapy, and four patients survived for more than 5 years (5-year survival rate: 18%).

Conclusions: Long-term survival was achieved among patients with SCLC with pericardial effusion but without distant metastasis who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in patients with SCLC with ipsilateral pleural effusion but without pericardial effusion or distant metastasis.

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Disclosure: The authors declare no conflicts of interest.

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Lung cancer is the leading cause of cancer-related deaths worldwide. Small cell lung cancer (SCLC) accounts for approximately 15% of all forms of lung cancer. Compared with non-SCLC, SCLC grows rapidly, quickly disseminates to the regional lymph nodes and distant sites, and is sensitive to chemotherapy with a response rate of 70 to 80%. The Veterans Administration Lung Study Group proposed a clinical two-stage system for SCLC that distinguishes limited disease (LD) and extensive disease (ED). LD is defined as being limited to one hemithorax, including mediastinal, contralateral hilar, and ipsilateral supraclavicular lymph nodes, whereas ED represents tumor spread beyond these regions.[1] The current standard care for LD-SCLC is a combination of chemotherapy and thoracic radiotherapy (TRT). Conversely, ED-SCLC is treated with chemotherapy alone. The original definition of LD was a tumor volume that could be encompassed by a reasonable radiotherapy plan. According to the International Association for the Study of Lung Cancer (IASLC)'s consensus report, however, the classification of LD-SCLC includes bilateral hilar or supraclavicular nodal involvement and ipsilateral pleural effusion, regardless of whether the cytological findings are positive or negative.[2] Pericardial effusion has not been defined precisely.

In 2007, the IASLC proposed a new tumor, node, metastasis (TNM) classification for lung cancer,[3–6] and the Union Internationale Contre le Cancer (UICC) seventh TNM edition has been available since 2009. According to the UICC seventh TNM edition, malignant pleural or pericardial effusion and tumor with pleural nodules are defined as M1a, leading to stage IV. An analysis of 12,620 patients with SCLC in the IASLC database demonstrated that patients who have ipsilateral pleural effusion without extrathoracic metastases (M1a) have a survival that is intermediate between stages I and III without effusion and stage IV. Nevertheless, no information regarding the presence of pericardial effusion is available in the IASLC database.[7]

Our previous retrospective analysis also demonstrated that the survival of patients with LD-SCLC with ipsilateral pleural effusion was intermediate between those of patients with LD without ipsilateral pleural effusion and patients with

ED, and long-term survival was achieved by patients with LD-SCLC who successfully underwent definitive TRT after their ipsilateral pleural effusion had disappeared after induction chemotherapy.[8] In this retrospective study, we investigated the clinical course and overall survival among patients with LD-SCLC with pericardial effusion, compared with those among patients with ED-SCLC or LD-SCLC with or without ipsilateral pleural effusion.

PATIENTS AND METHODS

In this study, LD-SCLC was defined as disease limited to one hemithorax, including mediastinal, contralateral hilar, and supraclavicular lymph nodes, ipsilateral pleural effusion, and pericardial effusion; ED-SCLC was defined as tumor spread beyond these manifestations.

We retrospectively reviewed the medical records of patients with lung cancer treated at the National Cancer Center Hospital East between July 1992 and December 2007.

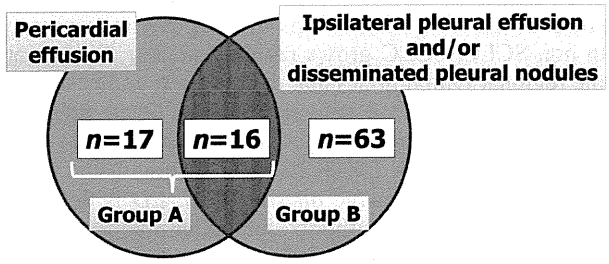

FIGURE 1. Patients with small cell lung cancer with M1a. Group A included patients with pericardial effusion, and group B included patients with ipsilateral pleural effusion or disseminated pleural nodules, but without pericardial effusion.

During this period, 766 patients were newly diagnosed as having SCLC. Four hundred sixteen patients were diagnosed as having LD-SCLC and 350 were diagnosed as having ED-SCLC using conventional staging procedures, including a medical history and physical examination, chest radiography, computed tomography (CT) scan of the chest, CT scan or ultrasound of the abdomen, bone scan, and CT scan or magnetic resonance imaging of the brain. Thirty-three of the 416 patients with LD-SCLC (8%, 95% confidence interval [CI]: 6–11%) had pericardial effusion and were included in this study. Seventy-nine of the 416 patients with LD-SCLC (19%, 95% CI: 15–23%) had ipsilateral pleural effusion or dissemination. Four patients had a disseminated mass without pleural effusion detected using CT scan. Sixteen patients with LD-SCLC had both pericardial and ipsilateral pleural effusion. Therefore, 63 patients with LD-SCLC had ipsilateral pleural effusion or dissemination without pericardial effusion. We divided the 96 M1a patients into two subgroups: group A included patients with pericardial effusion, and group B included patients without pericardial effusion. Group B patients had ipsilateral pleural effusion or disseminated pleural nodules (Figure 1).

The overall survival time was defined as the interval between the start of treatment and death or the final follow-up visit. The median overall survival time was estimated using the Kaplan-Meier analysis method.[9] Survival data were compared among the groups using a log-rank test. This study was approved by an institutional review board.

RESULTS

The patient characteristics are listed in Table 1. Eighty-three percent of the patients were male, and 81% had a performance status of 0 or 1. Fifty-four percent of the patients

TABLE 1. Patient Characteristics

	ED-SCLC (M1b)	LD-SCLC with Pericardial Effusion (M1a) (Group A)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B)	LD-SCLC (M0)
No. of patients	350	33	63	320
Sex				
Male	291	29	50	262
Female	59	4	13	58
Age (yr)				
Median	66	67	68	66
Range	28–85	37–82	46–83	22–87
Performance status				
0	22	0	4	108
1	224	25	47	190
2	63	6	9	15
3–4	41	2	3	7
Treatment delivered				
Chemotherapy	316	14	36	50
Chemoradiotherapy	25	19	26	224
Surgery + chemotherapy	0	0	0	33
Surgery alone	0	0	0	10
Best supportive care	9	0	1	3

LD, limited disease; SCLC, small cell lung cancer; ED, extensive disease.

TABLE 2. Timing of Thoracic Radiotherapy in Patients with M1a Small Cell Lung Cancer

Timing of Thoracic Radiotherapy	LD-SCLC with Pericardial Effusion (M1a) (Group A, n = 19)	LD-SCLC with Ipsilateral Pleural Effusion but without Pericardial Effusion (M1a) (Group B, n = 26)
Concurrently with the first course of chemotherapy	0	3
Concurrently with the second course of chemotherapy	0	4
Concurrently with the third course of chemotherapy	8	5
Concurrently with the fourth course of chemotherapy	4	0
Sequentially after chemotherapy	7	14

LD, limited disease; SCLC, small cell lung cancer.

received chemotherapy, and 38% received chemoradiotherapy. Six percent of the patients underwent surgical resection with or without adjuvant chemotherapy. Among the 96 patients with LD-M1a, all but one patient received chemotherapy (n = 50) or chemoradiotherapy (n = 45). Three patients underwent TRT (twice daily, 45 Gy in total) concurrently with the first course of chemotherapy. Four, 13, and four patients underwent TRT (once daily, 50 Gy in total) concurrently with the second, third, and fourth courses of chemotherapy, respectively. Twenty-one patients underwent TRT (once daily, 50 Gy in total) sequentially after chemotherapy. Among the group A patients, 12 patients underwent TRT concurrently with the third or fourth course of chemotherapy, and seven patients underwent TRT sequentially after chemotherapy. TRT was conducted if the pericardial effusion disappeared after induction chemotherapy. Among the group B patients, 12 patients underwent TRT concurrently with chemotherapy, and 14 patients underwent TRT sequentially (Table 2). Thirteen patients received prophylactic cranial irradiation of 25 Gy (seven patients in group A and six patients in group B).

Figure 2 shows the survival of all 766 patients with SCLC belonging to category M. The survival of patients with LD-M1a was intermediate between those of patients with LD-M0 and ED-M1b ($p < 0.0001$). Six hundred eighty-two patients have died. The median follow-up time was 65.8 months, ranging from 3.2 to 160.1 months. The median survival time among the patients with LD-M1a was 13.4 months (95% CI: 10.7–16.6 months), and the 1-, 2-, 3-, and 5-year survival rates were 56%, 18%, 9%, and 8%, respectively.

Survival analyses for the subgroup of patients with LD-M1a (n = 96) are shown in Figures 3, 4 and Table 3. Overall survival was not statistically different between groups A and B (p = 0.5182). All 14 patients who received chemotherapy in group A died within 3 years. One patient in

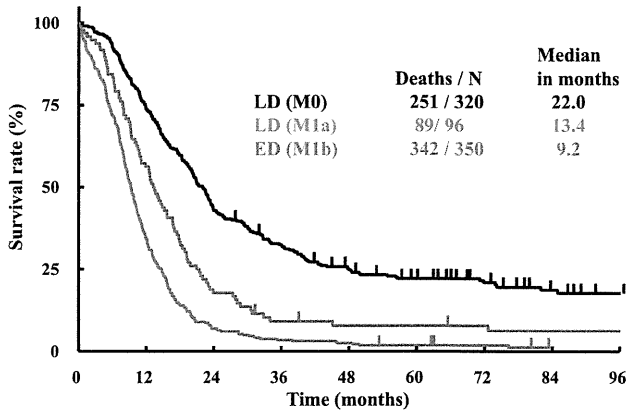

FIGURE 2. Overall survival among all 766 patients with M-category small cell lung cancer. LD, limited disease; ED, extensive disease.

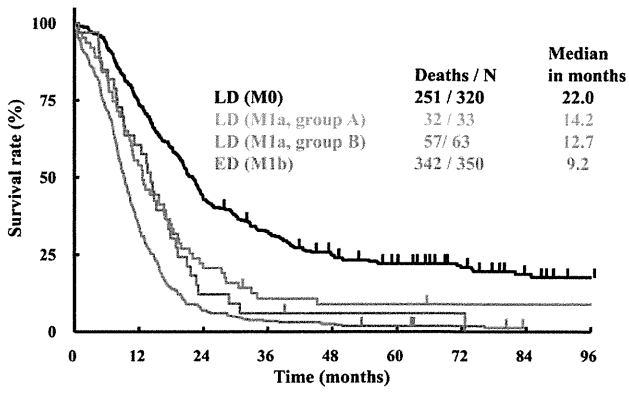

FIGURE 3. Overall survival among patients with M-category small cell lung cancer, subgroups A and B. LD, limited disease; ED, extensive disease.

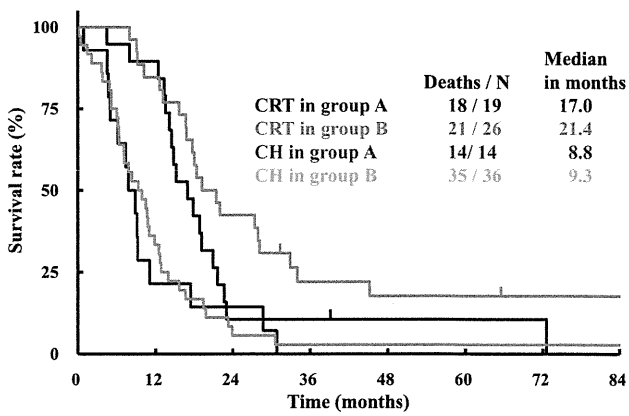

FIGURE 4. Overall survival among M1a patients with small cell lung cancer according to subgroups A, B, and initial treatment delivered. CRT, chemoradiotherapy; CH, chemotherapy.

group B who received chemotherapy as an initial treatment survived for more than 5 years, but this patient received chemoradiotherapy as a second-line treatment after a local

TABLE 3. Survival Data

Subgroup	No. of Patients	Median Survival Time (mo) (95% CI)	1-yr Survival Rate (%)	2-yr Survival Rate (%)	3-yr Survival Rate (%)	5-yr Survival Rate (%)
ED (M1b)	350	9.2 (8.5–10.0)	34	7	3	2
LD (M0)	320	22.0 (20.0–23.5)	74	43	33	22
LD with pericardial effusion (group A)	33	14.2 (9.1–17.5)	61	12	6	6
Receiving CRT	19	17.0 (13.6–21.0)	89	11	11	11
Receiving Chemotherapy	14	8.8 (4.7–11.1)	21	14	0	0
LD with ipsilateral pleural effusion but without pericardial effusion (group B)	63	12.7 (10.2–16.7)	54	21	11	9
Receiving CRT	26	21.4 (16.7–28.2)	85	42	22	18
Receiving chemotherapy	36	9.3 (6.3–11.8)	33	6	3	3

CI, confidence interval; ED, extensive disease; LD, limited disease; CRT, chemoradiotherapy.

TABLE 4. Six Patients with M1a Small Cell Lung Cancer who Survived for More Than 5 yr

Age (yr)	Sex	Group	Initial Treatment	Survival Time (mo)	State
64	M	A	Chemoradiotherapy	72.6	Dead
70	F	B	Chemoradiotherapy	146.5	Alive
53	M	B	Chemotherapy[a]	140.4	Alive
73	F	B	Chemoradiotherapy	138.0	Alive
72	M	B	Chemoradiotherapy	117.0	Alive
68	M	B	Chemoradiotherapy	65.5	Alive

[a] This patient received chemoradiotherapy as a second-line treatment after a local recurrence. Therefore, all six patients received chemoradiotherapy and achieved long-term survival for more than 5 yr.

M, male; F, female.

recurrence. Four of the 26 patients who received chemoradiotherapy in group B survived for more than 5 years (Table 4). Conversely, only 2 of the 19 patients who received chemoradiotherapy in group A survived for more than 2 years. One patient developed a local recurrence at 4 years and 10 months after the initiation of first-line chemoradiotherapy and died of lung cancer 14 months later. The remaining patient also developed a local recurrence at 2 years and 9 months after the initiation of first-line chemoradiotherapy and received second-line chemotherapy. This patient was still alive at the time of the data cutoff.

DISCUSSION

This retrospective analysis demonstrated that the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) was intermediate between those of M0 and M1b patients. It is suitable that patients with ipsilateral pleural effusion or pericardial effusion belong to M1a category in the UICC seventh TNM edition. No statistically significant difference in the overall survival between M1a patients with pericardial effusion (group A) and those with ipsilateral pleural effusion but without pericardial effusion (group B) was observed. Among the patients who successfully underwent chemoradiotherapy, the patients in group B had 2-, 3-, and 5-year survival rates of 42%, 22%, and 18%, respectively, whereas the patients in group A had a 2-year survival rate of only 11%. Our previous retrospective analyses demonstrated that the median survival time of patients with cytologically positive and cytologically negative pleural effusion were 9.3 and 12.7 months, respectively. Furthermore, all 11 patients with cytologically positive pleural effusion died within 3 years.[8] Long-term survival for more than 5 years was achieved only by patients with cytologically negative pleural effusion. We speculate that an inflammatory process, such as atelectasis, causes ipsilateral pleural effusion in some patients. Conversely, most pericardial effusion is believed to be malignant. Therefore, long-term survival was seldom achieved by patients with pericardial effusion, even if they received chemoradiotherapy.

Recently, the applicability of the UICC seventh TNM edition for SCLC was investigated using the California Cancer Registry database. This database included 108 and 1518 M1a patients with pericardial effusion and pleural dissemination, respectively. No significant difference in overall survival was observed among patients with pleural or pericardial effusion (median survival time: 7 versus 7 months, 2-year survival rate: 16.7% versus 9.7%, respectively).[10] These data were comparable with our results. Nevertheless, no information regarding the treatment performed for the M1a patients was included in the previous article.

Our retrospective analysis has several limitations. First, the number of M1a patients with pericardial effusion was only 33, because only 8% of the patients with LD-SCLC exhibited pericardial effusion. Second, we did not conduct a cytological examination of the pericardial effusion. Pericardial puncture or drainage is usually performed in patients with cardiac tamponade. None of the patients in group A had cardiac tamponade; therefore, a pericardial puncture was technically difficult. Third, examination period was more than 15 years, from 1992 to 2007. Irinotecan, active for SCLC, has been commonly used from 2000 in Japan. Patients in this study were treated with a potential range of different chemotherapeutic agents during the period, which was not controlled.

Only 2 of 19 patients (11%) who received chemoradiotherapy in group A survived for more than 3 years. Con-

versely, all 14 patients who did not receive chemoradiotherapy in group A died within 3 years. TRT probably improves local control and achieves long-term survival in some patients. Definitive TRT is recommended in M1a patients with SCLC, if ipsilateral pleural or pericardial effusion has disappeared after induction chemotherapy.

In conclusion, the survival of patients with SCLC and ipsilateral pleural or pericardial effusion (M1a) is intermediate between those of M0 and M1b patients. No statistically significant difference in the overall survival of M1a patients with pericardial effusion and those with ipsilateral pleural effusion but without pericardial effusion was observed. Long-term survival was achieved among M1a patients with pericardial effusion who successfully underwent chemoradiotherapy, although 5-year survival rate in these patients was relatively lower than in M1a patients with ipsilateral pleural effusion but without pericardial effusion.

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Long-term results of salvage photodynamic therapy for patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma

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Background and study aims: Local failure after chemoradiotherapy (CRT) remains a major problem for patients with esophageal squamous cell carcinoma (ESCC). The aim of this study was to clarify the long-term results of salvage photodynamic therapy (PDT) for local failure.

Patients and methods: Patients were treated with CRT, consisting of more than 50 Gy irradiation and concurrent chemotherapy. The indications for salvage PDT were as follows: 1) absence of lymph-node or distant metastasis after CRT; 2) failure lesion limited to T2; 3) refusal by patient to undergo salvage esophagectomy; 4) written informed consent. PDT was performed using an excimer dye laser at 48 and 72 hours after administration of Photofrin.

Results: A total of 37 consecutive patients underwent salvage PDT. The baseline stage before CRT was as follows: T1/T2/T3/T4 in 3/4/24/6 and N0/1 in 13/24 patients, respectively. Prior to PDT, 20 patients had a uT1 lesion, and 17 had a uT2 lesion; 24 patients had histologically proven local failure. A complete response was achieved in 22 patients (59.5%) following PDT. Esophageal fistulae, stenosis, and phototoxicity occurred in 4 (10.8%), 20 (54.1%), and 2 (5.4%) patients, respectively. Over a median follow-up period of 55 months, the 5-year progression-free (PFS) and overall survival rates of 37 patients following PDT were 20.7% and 36.1%, respectively. The 5-year PFS and overall survival of 24 patients with proven local failure were 17.6% and 34.6%, respectively.

Conclusion: Salvage PDT is a curative treatment option for patients with local failure after CRT for ESCC.

Introduction

Chemoradiotherapy (CRT) is a curative treatment option for esophageal squamous cell carcinoma (ESCC). However, local failure at the primary site after completion of CRT remains one of the major problems to be overcome for patients with ESCC. Salvage esophagectomy is now indicated for such patients, and it could be curative particularly for patients with T2 or earlier T-stage tumor or for patients without lymph node metastasis [1,2]. However, salvage esophagectomy is still associated with relatively higher morbidity and mortality compared with primary or planned esophagectomy [1–4]. Therefore, the development of curative and safety salvage treatment options for local failure is essential for improving the survival of patients treated with CRT.

We previously reported that patients who achieved complete response with CRT were very unlikely (< 1.0%) to experience a recurrence in locoregional lymph nodes [5]. This may lead to the hypothesis that, in patients who have only local failure after CRT, salvage local treatments such as endoscopic mucosal resection (EMR), and photodynamic therapy (PDT), could have curative potential. In fact, we first introduced EMR as a salvage treatment for local failure after CRT [6,7] and found that the long-term survival could be acceptable [7]. However, the indications for salvage EMR are limited to superficial lesions, and the procedure requires highly skilled endoscopists.

In contrast, PDT is indicated not only for superficial esophageal cancer as a curative treatment [8,9], but also as a palliative treatment for dysphagia due to stenosis of more advanced cancer [10]. Therefore, we consider that PDT could be a more powerful tool for salvage treatment after CRT. We previously reported acceptable short-term results of salvage PDT for local failure after definitive CRT for patients with ESCC [11]. Long-term results, however, have not been reported previously. The aim of the present study was to clarify the long-term survival of consecutive patients who have undergone salvage PDT for local failure after definitive CRT for ESCC.

Patients and methods

Patients

Between January 1998 and December 2004, 405 patients with ESCC were treated with CRT at the National Cancer Center Hospital East, Kashiwa, Japan. CRT consisted of more than 50 Gy external beam irradiation concurrent with two cycles of continuous infusion of 5-fluoruracil and cisplatin. In cases of renal insufficiency or cardiovascular disease, nedaplatin was used instead of cisplatin, because nedaplatin does not require hydration and has shown a low risk of renal toxicity [12].

The indications for salvage PDT were as follows: 1) absence of lymph node or distant metastases by computed tomography (CT) before PDT; 2) residual or recurrent tumor at primary site staging limited to within uT2 by endoscopic ultrasound (EUS); 3) EMR not indicated for reasons of concomitant deep ulceration or severe fibrosis due to radiation or lesion invading the deep submucosal layer; 4) refusal by patient to undergo surgery or physical complications that would have made surgery intolerable and; 5) provision of written informed consent. **Fig. 1** shows the flow of the patients through the study.

Of the 405 patients treated with definitive CRT, a complete response was achieved at the primary lesion in 234; the remaining 171 patients did not show a complete response. Of the 234 patients, 50 developed local recurrence at the primary site and eight patients were indicated for salvage PDT. Two patients with local recurrence were referred from another hospital to receive salvage PDT. Among the 171 patients with an incomplete response following CRT, 26 were indicated for salvage PDT, and one was referred from another hospital to receive salvage PDT. In total, therefore, 37 consecutive patients with local failure after definitive CRT were treated with salvage PDT and enrolled in the study. All information was collected from medical records and provided by the patients' physicians. This retrospective study was performed in accordance with the Declaration of Helsinki.

Staging

Clinical staging was determined by the TNM classification of the International Union Against Cancer [13]. Clinical T stage was evaluated by endoscopy, EUS, and CT, and clinical N and M stages were evaluated mainly by CT of the neck, chest, and abdomen. In this study, lymph node metastasis was clinically diagnosed if the lymph node was more than 10 mm in diameter on CT. All of the patients who were treated with definitive CRT at our institution are routinely evaluated by endoscopy and CT after completing CRT. Complete response at the primary site was defined as follows: i) disappearance of the tumor lesion and ulceration by endoscopic examination; ii) the absence of cancer cells in biopsy specimens [14]. The complete disappearance of metastatic lesions by CT was defined as complete response.

After confirmation of complete response, follow-up examination with endoscopy and CT was performed every 3 months for 2 years, and every 6 months thereafter. Biopsies of the primary site were routinely obtained at each follow-up endoscopic examination.

Local failures were classified into two groups: residual lesions and recurrent lesions. Residual lesions were defined as lesions that did not achieve complete response immediately after CRT. Recurrent lesions were defined as lesions that relapsed after achieving complete response. If the primary site showed obvious growth or if cancer cells were detected in a biopsy specimen, the lesion was diagnosed as a recurrence. Submucosal tumors or slightly protruding lesions at the primary site were suspected of representing a recurrence and were re-evaluated with EUS.

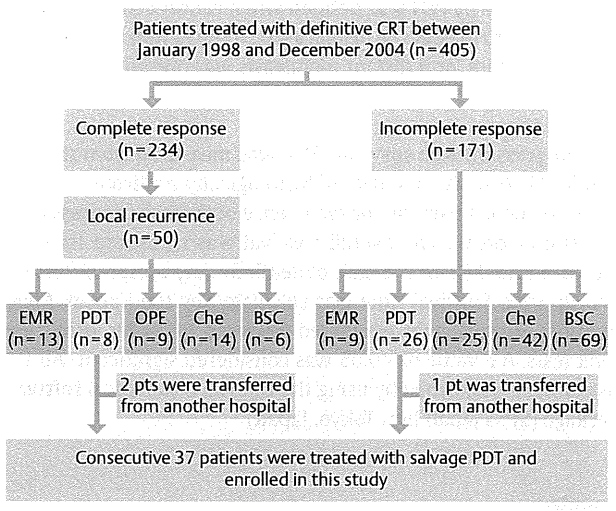

Fig. 1 Flow of patients through the study. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; PDT, photodynamic therapy; OPE, esophagectomy; Che, chemotherapy; BSC, best supportive care.

Before PDT, all patients were evaluated and staged using EUS (EU-M2000; Olympus Co. Ltd., Tokyo, Japan). Lesions were carefully examined with a high-frequency (20 Hz) ultrasound probe. When a hetero-echoic solid component in a submucosal or deeper layer was detected, a diagnosis of local failure lesion was made. The depth of the residual lesions by EUS was divided into either uT1 or uT2. Stage uT1 described lesions whose invasion was limited to the submucosal layer, and uT2 described those invading the muscularis propria layer.

Photodynamic therapy

PDT commenced with intravenous administration of 2 mg/kg of Photofrin (Pfizer Japan Inc.) followed by dye laser irradiation. A 630-nm wavelength laser beam was emitted by an excimer dye laser (EDL-1, Hamamatsu Photonics, Hamamatsu, Japan). The laser treatment was performed in two sessions at 48 and 72 hours after injection of Photofrin. The excimer dye laser was delivered via a microlens-type straight-tip fiber without any light diffuser introduced into the operative channel of the fiberscope (GIF-Q20; Olympus Co., Ltd.) and positioned in the esophagus. The total light density was 75 J/cm^2 with 4 mJ/pulse maximum pulse energy and 40 Hz pulse frequency, and no adaptation of delivered energy to radiotherapy time.

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of Photofrin in order to protect them from skin photosensitization. To confirm the ulceration and development of tissue necrosis after PDT, patients were examined endoscopically 1 week after laser irradiation. To evaluate the response and luminal toxicity of PDT, endoscopic examination with biopsy was repeated at least every month until the response was confirmed. CT was used to evaluate the distant organ or lymph node metastasis every 3 months for the first 2 years, and every 6 months thereafter. The response to PDT was classified into two groups: 1) complete response, if there was no macroscopic or microscopic evidence of cancer; 2) incomplete response, if a tumor was seen at endoscopy and confirmed histologically to contain cancer cells. Recurrence after achieving com-

plete response by PDT was defined when cancer cells were histologically confirmed at the primary site, if the lymph node was larger than 10 mm, or if distant metastasis was present.

Statistics

The progression-free survival (PFS) was measured from the date of initial PDT to the first date of histologically confirmed residual lesion at the primary site or recurrence or disease progression at any site or death. The overall survival was measured from the date of initial PDT to the date of death for any reason or last follow-up visit. Survival time was calculated by the Kaplan–Meier method. Survival was compared between variables using log-rank tests. A P value of < 0.05 was considered significant. All statistics were performed by using the Dr SPSS II statistical software package (SPSS Japan Inc., Tokyo, Japan)

Results

Patient characteristics

The baseline characteristics of patients before CRT are summarized in **Table 1**.

The patients consisted of 35 men and two women, with a median age of 64 years (range 50–75 years). No patients had distant organ metastasis, and all lesions were histologically proven to be ESCC before CRT. Lesion characteristics before PDT are summarized in **Table 2**.

Histological confirmation could not be obtained in 13 patients; however, we strongly suspected local failure because the apparent elevation or ulcer formation occurred at the primary site.

Response to salvage PDT

The interval between the last day of radiotherapy and initiation of PDT was 4 months (range 1–85 months) in the entire group of patients, 16 months (range 7–86 months) in 10 patients with local recurrence after achieving a complete response with CRT, and 2.5 months (range 1–17 month) in 27 patients with a residual lesion after CRT. The median total light dose for PDT was 675J (range 300–1000J), and the median hospital stay was 11 days (range 6–33 days). Complete response was attained in 22 of 37 patients with PDT, resulting in a complete response rate of 59.5% for salvage PDT (95% confidence interval [CI] 42.1–75.3). The complete response rate of the 20 patients with uT1 local failure was 75.0% (15/20; 95% CI 50.9–91.3), and that of the 17 patients with uT2 was 41.2% (7/17; 95%CI 18.4–67.1). The median time to confirm a complete response was 102.5 days (range 35–199 days).

Major complications of salvage PDT

Four patients (4/37, 10.8%) developed esophageal fistulae after salvage PDT. Their clinical T stages before CRT were T3 in three patients and T4 in one. All of them had local residual lesions just after CRT, and their T stages before PDT were uT2 in one patient and uT1 in three patients. All of them were treated with ≥ 600J PDT irradiation. In one patient, the fistula closed with conservative treatment, and complete response was achieved without any metastasis. Another patient developed mediastinitis due to esophago-mediastinal fistula. Despite this patient being treated conservatively, by total parenteral nutrition and intravenous administration of antibiotics, she died with bleeding from the primary site at 63 days after PDT. An esophageal-aortic fistula was confirmed at autopsy. The remaining two patients died with cancer progression. Thus, treatment-related death with PDT was 2.7% (1/37).

Other complications occurred in 20 patients (20/37, 54.1%) who developed esophageal stenosis requiring balloon dilation. Among them, a complete response could not be achieved in 12 patients following PDT; it is therefore possible that their stenoses might have been caused by progressive refractory tumor as well as by lumen toxicity caused by PDT. Cutaneous phototoxicity requiring medication was experienced in two patients (2/37, 5.4%).

Clinical course after salvage PDT

The median follow-up period of all patients following salvage PDT was 55 months (range 18–75 months). The clinical flow chart of the 22 patients who achieved complete response with salvage PDT is presented in **Fig. 2**.

Table 1 Baseline patient and lesion characteristics before chemoradiotherapy.

Characteristics	No. of patients (n = 37)
Sex	
Male	35
Female	2
Age, median (range), years	64 (50–75)
Tumor location	
Upper	6
Middle	24
Lower	7
T-stage	
T1	3
T2	4
T3	24
T4	6
N-stage	
N0	13
N1	24
TNM-stage	
I	2
II	11
III	22
IV	2

Table 2 Lesion characteristics before photodynamic therapy.

Characteristics	No. of patients (n = 37)
Tumor status after chemoradiotherapy	
Recurrent	10
Residual	27
Tumor stage evaluated with EUS	
uT1	20
uT2	17
Ulceration	
Present	17
Absent	20
Circumference of the lesion	
< ¼	4
¼ – < ½	20
½ – < ¾	12
> ¾	1
Histologically proven cancer cells	
Positive	24
Negative	13

EUS, endoscopic ultrasound.

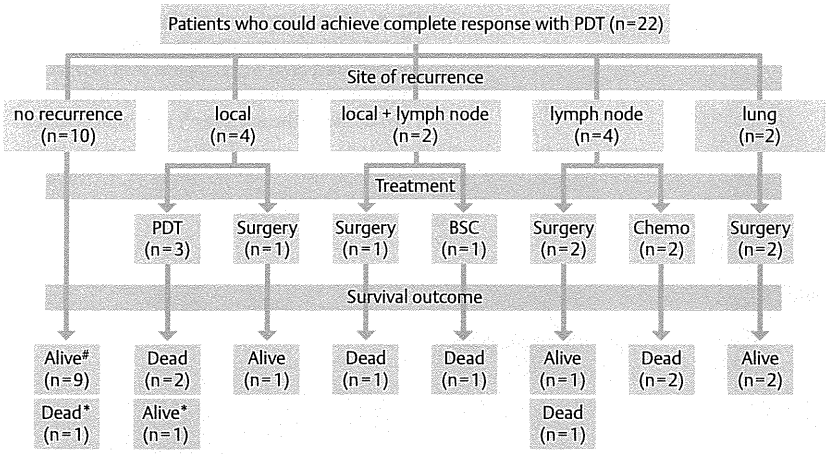

Fig. 2 The clinical flow chart of 22 patients in whom a complete response was achieved with salvage PDT. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Dead*, dead from another disease; Alive#, alive with disease.

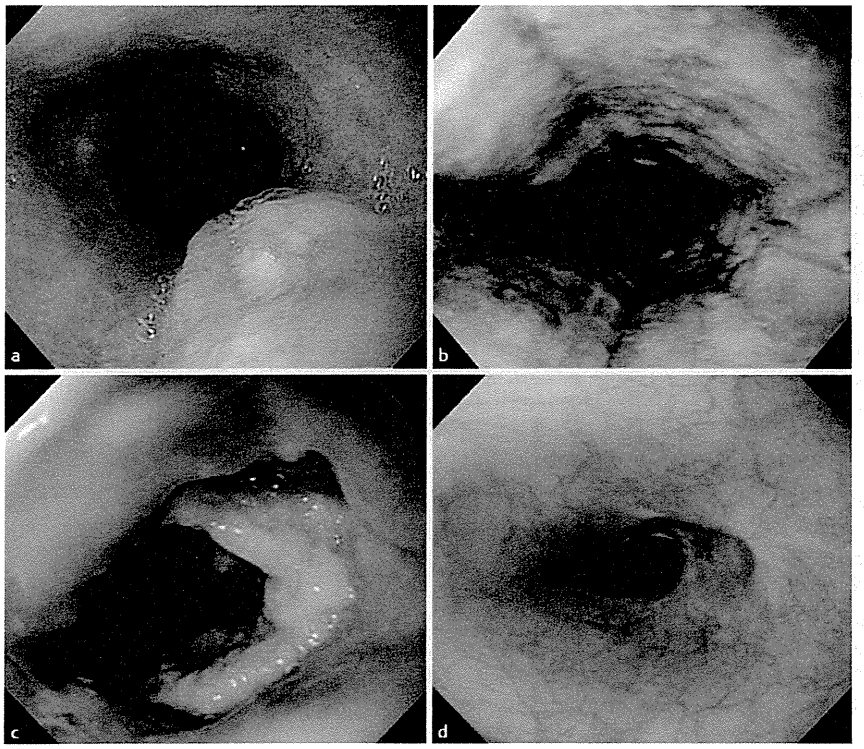

Fig. 3 A patient in whom complete response was achieved with salvage photodynamic therapy (PDT). **a** Local recurrence was detected after chemoradiotherapy and evaluated as uT1 with endoscopic ultrasound. **b** At 3 days after salvage PDT, circumferential ischemic change was observed. **c** At 1 month after salvage PDT, deep ulceration with dense necrotic tissue was observed at the primary site. **d** At 3 years after salvage PDT, treatment was evaluated as a complete response without any recurrence.

Ten patients did not develop any recurrence. Nine of them are still alive, and the tenth died of pneumonia without any esophageal cancer recurrence approximately 4 years after PDT. The details of these 10 patients are as follows: the baseline clinical stages before CRT were T1 (n = 1), T2 (n = 4), T3 (n = 3), and T4 (n = 2); N0 (n = 5) and N1 (n = 5); and stage I (n = 1), stage II (n = 4), stage III (n = 3), and stage IV (n = 2). Lesion characteristics before PDT were uT1 (n = 7) and uT2 (n = 3); six had histologically proven local failure before PDT and the other four had histologically unproven lesions before PDT. Moreover, the baseline tumor stage of five patients, except for the patient who died of pneumonia, with histologically proven local failure who survived without any recurrence before CRT was T1 (n = 1), T2 (n = 4), and all failure lesions were uT1 before PDT.

A representative case of a patient in whom complete response was achieved without any recurrence after salvage PDT is shown in **Fig. 3**.

Local recurrence at the primary site was detected in four patients, one of whom was cured with salvage esophagectomy and is still alive without recurrence. The remaining three patients were treated with a second PDT, but none of them achieved complete response. In two patients, local recurrence and simultaneous lymph node metastasis were detected. One of these was treated with esophagectomy and the other was followed with the best supportive care; however, both died of disease progression. Lymph node metastasis without local recurrence was detected in four patients, of whom two underwent surgery and the other two were treated with systemic chemotherapy. One of the patients who received curative resection for metastatic lymph node is still alive without recurrence; however, the remaining three patients died of cancer progression. Solitary lung metastasis was detected in two patients; both underwent surgery and are still alive without recurrence.

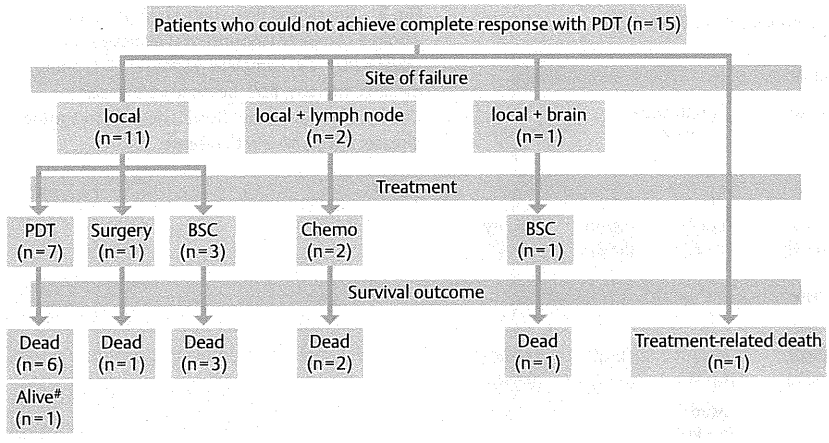

Fig. 4 Clinical flow chart of 15 patients in whom salvage photodynamic therapy did not achieve a complete response. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Alive#, alive with disease.

A flow chart for the 15 patients in whom PDT could not achieve a complete response is shown in **Fig. 4**.

One patient died of bleeding after PDT as described above, 13 died of cancer progression, and one remains alive with the disease. The clinical courses of 13 patients without histologically proven carcinoma before PDT are as follows: nine patients achieved complete response after PDT, in three patients histologically proven residual tumors were detected after PDT, and the remaining patient died with aortic rupture, as described above. Of the nine patients showing complete response for PDT, four of them are still alive without any recurrence, three patients have developed histologically proven local recurrence after achieving complete response, one patient developed lymph node metastases without local recurrence, and one patient developed a solitary lung metastasis without local recurrence.

Survival

The PFS rates at 3 and 5 years from the initiation of salvage PDT were 31.9% (95%CI 16.7–47.1) and 20.7% (95%CI 6.4–30.5), respectively. The overall survival rates at 3 and 5 years from the initiation of salvage PDT were 47.4% (95%CI 30.9–63.8) and 36.1% (95%CI 19.2–53.0), respectively (**Fig. 5**).

In addition, PFS and overall survival of 24 patients at 5 years with histologically proven local failure were 17.6% (95%CI 1.1–34.0) and 34.6% (95%CI 14.5–54.7), respectively. Furthermore, comparisons of PFS according to various clinical variables before CRT and before PDT are presented in **Fig. 6**.

Patients with clinical T1 or T2 had significantly higher 5-year PFS rates than those with T3 or T4 (T1/2 vs. T3/4 = 71.4% [95%CI 38.0–104.9] vs. 9.1% [95%CI −2.4 to 20.7]; $P = 0.005$), whereas there was no significant difference between patients with N0 and N1 (N0 vs. N1 = 27.7% [95%CI 2.1–53.3] vs. 16.2% [95%CI −1.2 to 33.6]; $P = 0.33$). On the other hand, the 5-year PFS of patients with uT1 before PDT was significantly higher than those with uT2 (uT1 vs. uT2 = 30.0% [95%CI 7.9–52.1] vs. 8.8% [95%CI −0.4 to 24.0]; $P = 0.02$). Patients with recurrence after complete response had a better 5-year PFS rate than patients with residual tumor (recurrent vs. residual = 40.0% [95%CI 9.6–70.4] vs. 13% [95%CI −2.2 to 28.1]; $P = 0.07$), although the difference was not statistically significant. There was no significant difference in progression-free survival between patients with and those without histologically proven cancer cells before PDT (negative vs. positive = 30.8% [95%CI 5.7–55.9] vs. 17.6% [95%CI 1.1–34.0]; $P = 0.61$).

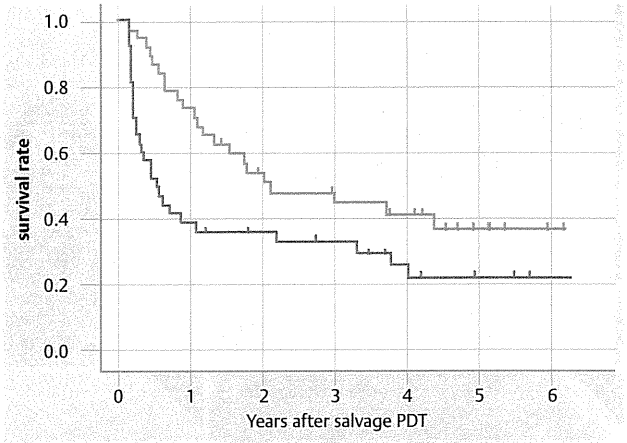

Fig. 5 Overall survival (blue line) and progression-free survival (red dotted line) of all 37 patients from the initiation of salvage photodynamic therapy (PDT).

Discussion

In the present study, salvage PDT for local failure after CRT for ESCC showed a high complete response rate. Moreover, the long-term survival was acceptable, because the prognosis of patients with local failure after CRT is usually quite dismal [14,15]. EMR is a salvage treatment option for local failure after CRT if the failure lesion is superficial. Indeed, we have reported the long-term results for salvage EMR, and the 5-year survival was 49.1% [7]. The difference in 5-year survival between salvage PDT and salvage EMR may depend on both their baseline clinical stage before CRT and clinical stage before salvage treatment. In salvage EMR, more than half of the patients had baseline clinical T1 lesions before CRT, and all of their local failure lesions were within the submucosal layer before EMR [7]. On the other hand, more than 80% (30/37) of patients had baseline clinical T3/4 lesions before CRT, and approximately half (17/37) of failure lesions were uT2 before PDT in the present study. Moreover, salvage EMR is technically quite difficult if the failure lesion has a severe fibrosis after CRT or if there is massive invasion of the submucosal layer. Therefore, PDT might be recommended as a salvage treatment for failure lesions evaluated as uT1 or when EMR is not indicated due to the abovementioned reasons.

The 5-year survival rate after salvage surgery is reported to be approximately 30% [1,2,4]. Most of the patients who achieved

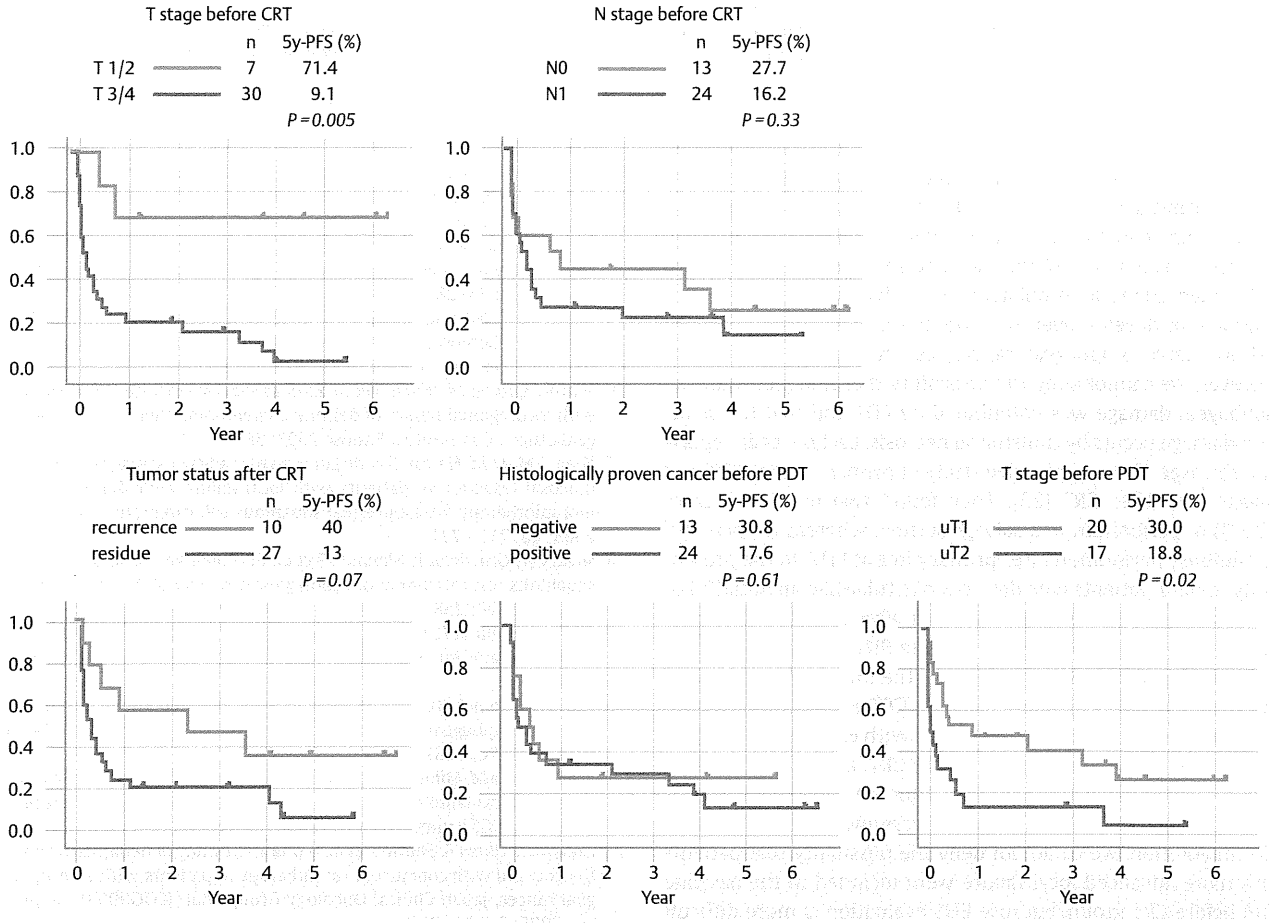

Fig. 6 Comparisons of progression-free survival curves according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

long-term survival after salvage surgery showed T1 or T2 local failures without lymph node metastasis [1,2,4]. Swisher et al. reported that 5-year survival of patients with pathological T1 or T2N0 was 60% in salvage surgery; however no patient with pathological T3, or T4, or N1 survived longer than 7 months [1]. These data suggest that it is difficult to salvage patients with local failure more advanced than T3 and/or lymph node metastasis, even when they are treated with salvage surgery. However, these data cannot be simply compared with the results of salvage PDT, because these reports included patients with deeper local failure or locoregional lymph node metastasis.

The problem with the salvage surgery was a high incidence of complications (15%–39%) and a high treatment-related mortality rate (8%–22%) [1–4,16]. While, we have experienced one case (2.7%) of treatment-related death with salvage PDT in this study, the incidence rate was lower than for salvage surgery and no severe adverse events were associated with PDT. Thus, salvage PDT was a less-invasive treatment option compared with salvage surgery for patients with local failure after CRT. PDT is a treatment option, if local failure after CRT is limited to the muscularis propria layer, especially the submucosal layer without lymph node metastasis, and in patients in whom surgery would be intolerable because of physical complications. Therefore, PDT has a niche role between EMR and surgery in the salvage setting after CRT.

In the present study, 13/37 (35.1%) patients did not have a histologically proven tumor before PDT. We could not deny the possibility that the remarkable 5-year overall survival rate might be influenced by the patients with salvage surgery and by the patients without histologically proven tumor. Actually, of nine patients who are still alive without any recurrence, four patients had histologically unproven local failure before PDT. However, the 13 patients without histologically proven tumor were carefully evaluated by endoscopic examination and EUS and were found to have progressive development of ulceration of the space occupied by the lesion after achieving complete response for CRT. For the purpose of clarifying this disputable situation, we are now evaluating, in a prospective study, the efficacy and safety of salvage PDT only for histologically confirmed local failure after CRT for ESCC.

In the current study, 6 of 37 (16.2%) patients developed lymph node metastasis after PDT. Only one patient without local failure after PDT was cured by lymph node dissection. PDT has no curative potential if there is a high risk of lymph node metastasis. In salvage surgery, more than 30% of the patients developed locoregional or distant metastasis [1,16,17]. This means that the risk of lymph node metastasis is also high even for salvage surgery. Therefore, we have to investigate a more curative strategy for patients with high risk of recurrence even after salvage treatment.

The effect of second-line chemotherapy for patients with refractory or recurrent esophageal cancer after CRT is extremely limited. From the literature, the overall response rate of second-line systemic chemotherapy for previously treated esophageal cancer patients including local failure are low (0–16%), and complete