Table 1. Baseline patients' characteristics before CRT ($n = 25$)

Characteristics	Number of patients
Sex	
Male	23
Female	2
Median age	67 years
(range)	55–82
Location	
Upper	4
Middle	19
Lower	2
Histology	
W/D,SCC	0
M/D,SCC	7
P/D,SCC	3
SCC	15
Baseline TNM stage	
Stage I	5
Stage II	11
Stage III	7
Stage IVA	2
T stage	
T1	6
T2	7
T3	12
N stage	
N0	16
N1	9

Abbreviations: W/D, well differentiated; SCC, squamous cell carcinoma; M/D, moderate differentiated; P/D, poorly differentiated.

Table 2. Patients' characteristics before PDT ($n = 25$)

Characteristics	Number of patients
Regimen of chemotherapy	
Cisplatin + 5FU	23
Others	2
Radiation dose (Gy)	
50.4	15
≥60	10
Local failure pattern after CRT	
Recurrent	14
Residual	11
Lesion circumference of the lumen	
<1/4	10
1/4–1/2	15
Concomitant ulceration on the lesion	
Present	6
Absent	19

Abbreviation: 5FU, 5-fluorouracil.

(allowing for 10% ineligibility) with $\alpha = 0.1$ and $\beta = 0.1$. If the calculated one-sided lower 95% confidence limit of the CR rate was $\geq$ 30%, the primary endpoint was considered to have been met. The PFS was measured from the date of enrollment to the first date of recurrence, disease progression at any site, or death. The OS was measured from the date of enrollment to the date of death for any reason or to the last follow-up visit. Survival time was calculated by the Kaplan-Meier method. Survival time was compared between variables by using the log-rank test. An alpha value of < 0.05 was considered significant. All statistical analyses were performed using Predictive Analysis Software Statistics 18 (SPSS Japan Inc., Tokyo, Japan).

Results

Between April 2005 and January 2009, a total of 34 patients were recruited for this study. Nine of these patients were deemed ineligible (one with an active other malignancy within 1 year, seven with baseline stage T4 before CRT and one with a distant metastasis); thus, 25 patients were enrolled in this study. All 25 patients were treated with salvage PDT. The patients' baseline characteristics before CRT are summarized in Table 1. The patients included 23 men and two women, and the median age was 67 years (range, 55–82 years). The tumor location was the upper esophagus in four patients, middle esophagus in 19 patients and lower esophagus in two patients. The baseline clinical stages before CRT were: stage I in five, stage II in 11, stage III in seven and stage IVA in two patients, and no patient had distant organ metastasis before CRT. The patients' characteristics before PDT are summarized in Table 2. Most of the chemotherapeutic regimens of CRT comprised cisplatin and 5-fluorouracil with ≥50 Gy concomitant radiotherapy. Their failure patterns were recurrence after achieving a CR with CRT in 14 patients and residual lesions after CRT in 11 patients. All local failure lesions in this study were histologically proven T1b lesions within the radiation field. The median duration between the last day of radiation and the initiation of PDT was 192 days (range, 21–1,234 days).

Efficacy

In this study, the range of esophageal surface areas that were treated was 3–9 cm^2.CR was attained in 19 of 25 patients with PDT, resulting in a CR rate of 76% (95% CI, 55–91%). A representative case of a patient who achieved CR is shown in Figure 1. There was no dose-response relationship in this study. The median esophageal surface area was 6 cm^2 in 19 patients who achieved CR and in six patients who did not achieve CR with PDT. The relationship between the degree of baseline lymph node metastasis and CR rate was as

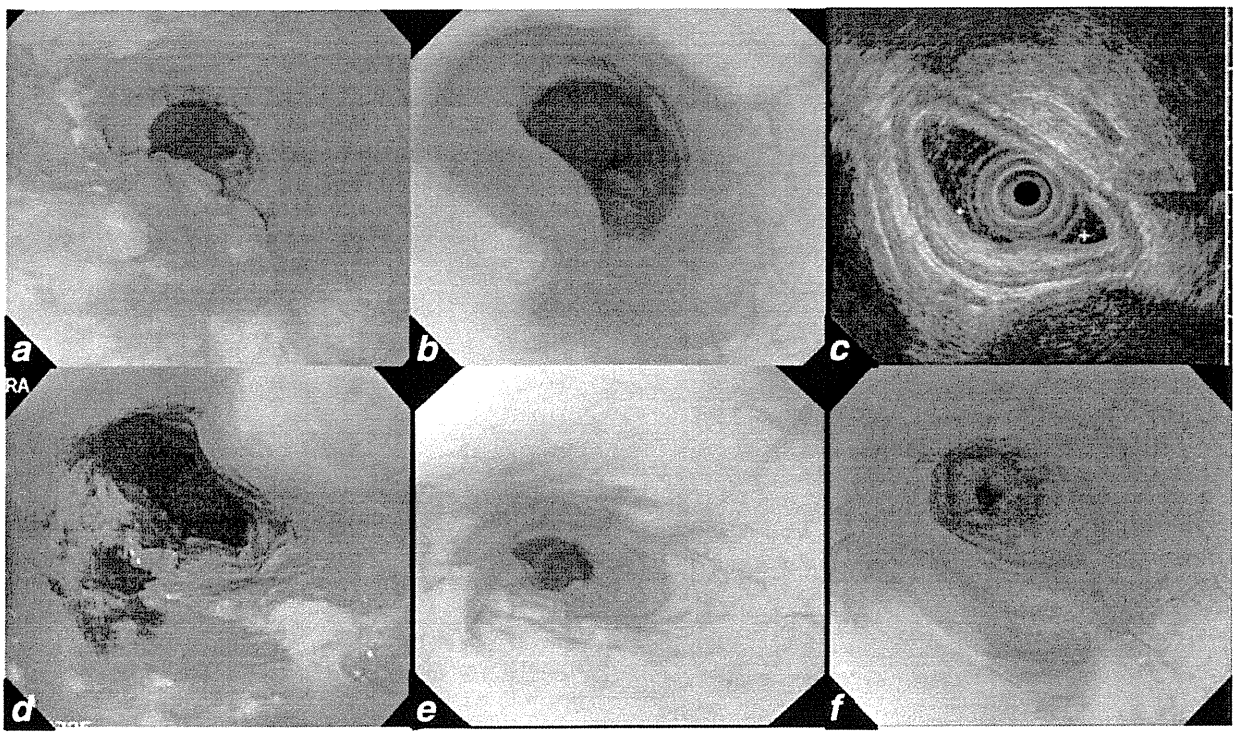

Figure 1. A patient who achieved a complete response (CR) with salvage photodynamic therapy (PDT) is presented. (*a*) Before chemoradiotherapy (CRT), the baseline stage was T2N0M0. (*b*) A local residual lesion was detected at the primary site after CRT. (*c*) The residual lesion was limited to the submucosal layer. (*d*) Two days after PDT, an ischemic change was observed at the laser-irradiated site. (*e*) One month after PDT, deep ulceration was observed at the laser-irradiated site. (*f*) A CR was achieved, and there was no recurrence at the primary site 3 years after PDT.

Table 3. Adverse events after PDT ($n = 25$)

	Grade (no. of patients)					
Adverse events	**1**	**2**	**3**	**4**	**5**	**% (any)**
Pain-Pharynx	3	1	0	0	0	17
Pain-Chest	11	3	0	0	0	61
Anorexia	1	0	0	0	0	4
Dysphagia	7	2	0	0	0	39
Nausea	1	0	0	0	0	4
Vomiting	1	0	0	0	0	4
Fever	11	0	0	0	0	48
Photosensitivity	7	1	0	0	0	32
Hemorrhage-GI	0	0	0	0	1	4

Abbreviation: GI, gastrointestinal.

follows: the CR rate of 16 N0 patients was 75% (12/16), whereas the CR rate of 9 N1 patients was 78% (7/9). The relationship between the baseline T stage before CRT and CR rate was as follows: the CR rate with baseline T1 or T2 was 85% (11/13, 95% CI, 55–98%), whereas that with baseline T3 before CRT was 67% (8/12, [95% CI, 35–90%]). Furthermore, the 1-year local control rate of patients with baseline T1 or T2 was significantly higher compared with that of patients with baseline T3 (T1 or 2 *vs.* T3 = 77% [95% CI, 54–100%] *vs.* 42% [95% CI, 14–70%], $p = 0.04$).

Safety

The safety of PDT in all 25 patients is shown in Table 3. Common adverse events after PDT were chest pain (61%), pharyngeal pain (17%), dysphagia (39%) and fever (48%). Photosensitivity was observed in eight (32%) patients. All patients' fevers were grade 1 with NCI-CTCAE, and most patients recovered within a day. Predose nonsteroidal anti-inflammatory drugs (NSAIDs) might not have been necessary based on the results of this study, because patients' fevers were not severe nor prolonged. Severe complications (≥grade 3) related to PDT limited to one patient death due to gastrointestinal hemorrhage 33 days after PDT. His baseline stage before CRT was T3N0M0, and a histologically confirmed local residual lesion was detected after CRT. After enrollment in this study, he was treated with a fluence of 75 J/cm^2 and a fluence rate of 160 mW/cm^2 for the treatment area of 9 cm^2. He received the maximum treatment field with the largest light dose in this study. He complained of continuous chest pain (grade 2) after PDT, but his pain was controlled with

oral administration of a NSAID. Although we could not confirm the origin of the hemorrhage with endoscopic observation or autopsy, deep ulceration was observed endoscopically at the PDT-irradiated site 1 week before his death. We thought that the hemorrhage was caused by an aortic-esophageal fistula at the laser-irradiated site. The death of this patient gave a 4% (1/25) rate of treatment-related death. No other patient developed an esophageal fistula. Six patients (24%) developed esophageal stenosis requiring balloon dilatation.

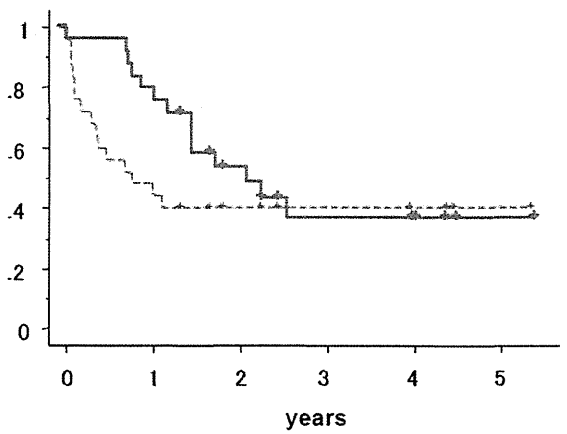

Figure 2. Progression-free survival (red dotted line) and overall survival (blue line) of 25 patients after the initiation of salvage photodynamic therapy (PDT).

Survival

The median follow-up was 48 months (range, 17–64 months). The clinical courses of the 19 patients who had achieved a CR with PDT were as follows. Of the 11 patients who did not develop recurrence, ten are still alive and one died of multiple liver metastases from a prior gastric adenocarcinoma without any esophageal cancer recurrence. Among the remaining eight patients, three developed local recurrence, and all three were treated with salvage esophagectomy, but none survived. Local recurrence was detected within a year (range, 5–10 months) after achieving CR in all three patients, and therefore, the local control rate at 1 year was 64% (16/25, [95% CI, 43–82%]). Lymph node metastasis without local recurrence was detected in three patients; one underwent surgery and the other two were treated with systemic chemotherapy, but all died of cancer progression. Two patients developed liver metastasis and were treated with systemic chemotherapy; one died because of disease progression,

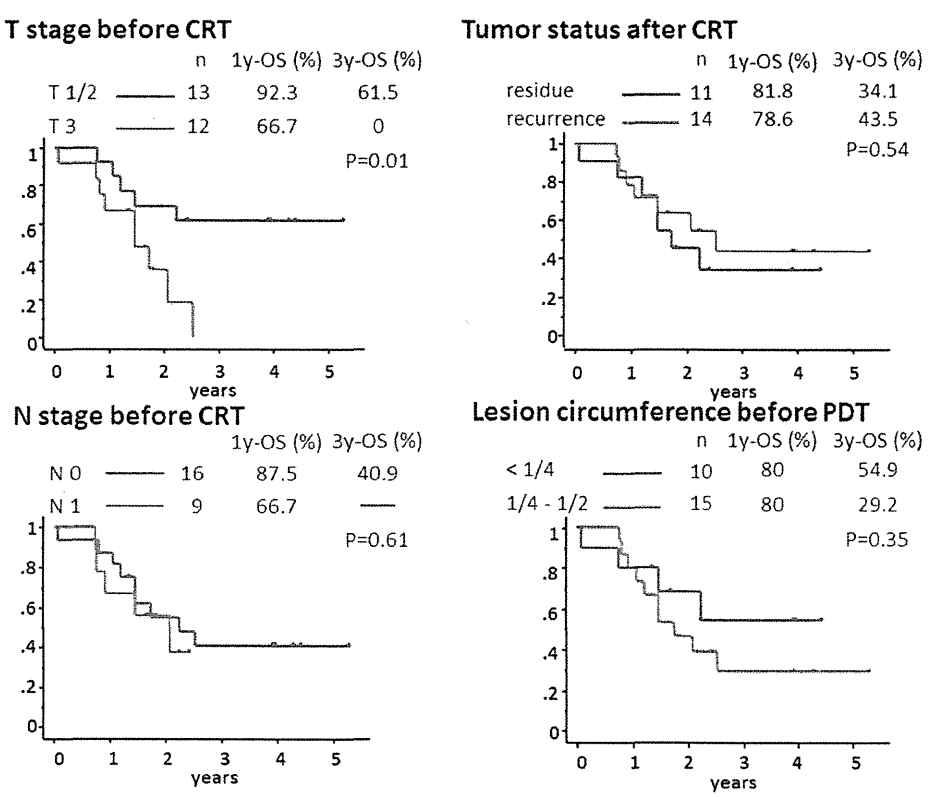

Figure 3. Comparisons of overall survival according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

and the other is still alive about 2 years after detection of liver metastasis. Six patients could not achieve a CR with PDT. Two were treated with systemic chemotherapy, two received salvage surgery and one was treated with a second PDT; all died because of disease progression. The remaining patient's death was classified as a treatment-related death, as described earlier. The PFS rates of all 25 patients at 1 and 3 years were 48% (95% CI, 28–68%) and 40% (95% CI, 21–59%), respectively, and the OS rates at 1 and 3 years were 80% (95% CI, 64–96%) and 38.4% (95% CI, 17–60%), respectively (Fig. 2). Comparisons of OS according to various clinical variables before CRT and before PDT are presented in Figure 3. Patients with clinical T1 or T2 before CRT had significantly higher OS than those with clinical T3 before CRT (T1 or T2 *vs.* T3: 1-year OS = 92.3% [95% CI, 77.8–106.8%] *vs.* 66.7% [95% CI, 40–93.3%], 3-year OS = 61.5% [35.1–88%] *vs.* 0%, $p = 0.01$), whereas there was no significant difference between patients with clinical N0 and N1 before CRT (N0 *vs.* N1: 1-year OS = 87.5% [95% CI, 71.3–103.7%] *vs.* 66.7% [95% CI, 35.9–97.5%], 3-year OS = 40.9% [95%CI, 16–65.8%] *vs.* not reached, $p = 0.61$). There was no difference in OS between patients with a residual lesion after CRT and a recurrent lesion after achieving CR (residual *vs.* recurrent: 1-year OS = 81.8% [95% CI, 59.0–104.6%] *vs.* 78.6% [95% CI, 57.1–100%], 3-year OS = 34.1% [95% CI, 4.8–63.4%] *vs.* 43.5% [95% CI, 14.4–72.6%], $p = 0.54$). Patients with a local failure lesion less than 1/4 the circumference of the lumen had a better OS than those with 1/4 to 1/2 circumference lesions; however, the difference was not statistically significant (<1/4 *vs.* 1/4-1/2: 1-year OS = 80% [95% CI, 55.2–104.8%] *vs.* 80% [95% CI, 59.8–100%], 3-year OS = 54.9% [95% CI, 21.1–88.7%] *vs.* 29.2 [95% CI, 4.1–54.3%], $p = 0.35$).

Discussion

To our knowledge, this is the first prospective study of salvage treatment for local failure after definitive CRT in patients with ESCC. In this study, the primary endpoint (CR rate) was met, and the results exceeded our expectations. The CR rate at the primary site was 76% (95% CI, 54.9–90.6%), suggesting that salvage PDT could be a curative treatment option for carefully selected patients with local failure at only a primary site after CRT. The 3-year survival rate of salvage PDT was 38.4%. This result indicates that salvage PDT can cure a subset of patients with local failure after CRT.

If the failure lesions are tiny and superficial, EMR could be a salvage treatment option for local failure after CRT. We have reported the long-term results for salvage EMR, and the 5-year survival rate was 49.1%.[7] In our report, more than half of the patients had baseline clinical T1 lesions before CRT, and all their local failure lesions were within the submucosal layer before EMR.[7] By contrast, in this study about half of the patients (12/25) had baseline clinical T3 lesions before CRT. Salvage EMR is technically difficult if the failure lesion is severely fibrotic after CRT or there is deep invasion of the submucosal layer. PDT could be a treatment option if local failure after CRT is limited to the submucosal layer without lymph node metastasis and in patients for whom surgery would be intolerable because of physical limitations. Therefore, PDT has a niche role between EMR and surgery in the salvage setting after CRT.

In general, salvage surgery is indicated for patients with local failure after CRT. However, the most serious problems with salvage surgery are the high rates of complications and treatment-related mortality. Compared with esophagectomy without CRT or esophagectomy after planned neoadjuvant CRT, salvage surgery is associated with several complications, such as a longer hospital stay and higher anastomotic leak rate. The treatment-related mortality rate ranges from 8 to 22%.[1–4,16] Therefore, the indications for salvage surgery should be carefully considered. Although treatment-related death occurred in one patient in this study, the incidence rate (4%) was lower than that for salvage surgery. This suggests that salvage PDT is a less morbid treatment option than salvage surgery for carefully selected patients with local failure at the primary site after CRT.

In this study, five patients received salvage surgery for local failure after PDT. Although their physical condition was evaluated as tolerable for salvage surgery, they refused surgery before enrollment in this study. When the failure after PDT was detected, we informed them that their failure lesions were unlikely to be cured with reapplication of PDT because their lesions were suspected to be progressive refractory tumors; they then accepted salvage surgery. None of these patients achieved cure with salvage esophagectomy after PDT, and their median survival time after esophagectomy was 13 months (range: 4–18 months).

At present, nine patients remain alive without disease and one patient is alive with liver metastasis and is being treated with systemic chemotherapy. All of these patients survived with esophagus preservation. Second-line chemotherapy is one treatment option for patients with residual ESCC after CRT, although it is not curative and has a limited effect; that is, the overall response rate of second-line chemotherapy is low (0–16%), and a CR is difficult to achieve (0–6%).[17–20] This suggests that second-line systemic chemotherapy is a palliative treatment.

From the results of a comparison of OS according to various clinical variables, patients with T1 or T2 stage before CRT had a significantly higher survival rate than those with T3 lesions before CRT. All failure lesions in this study were determined before PDT to be within the submucosal layer; however, more advanced failure lesions might be included in the T3 group because of the difficulty of EUS evaluation after CRT, especially in advanced cases. However, N stage before CRT did not affect the survival after PDT. Patients with earlier T stage before CRT tend to be cured with salvage PDT, and these data demonstrate the reproducibility of our retrospective analysis.[14]

Before this phase II study, we did not perform the laser dose escalation study for local failure after CRT for

esophageal cancer. The fluence of 75 J/cm^2 with a fluence rate of 160 mW/cm^2 in this phase II study was determined from the results of our preliminary experience.[8,14] The variable of total fluence depends on the lesion size. In this study, the range of esophageal surface areas that were treated was 3–9 cm^2, and multiple treatment fields were overlapped to cover large lesions. From the results of this study, the fluence of 75J/cm^2 is effective with tolerable toxicity for local failure after CRT. However, because of the risk of esophageal perforation, we should treat carefully if the lesion requires a large treatment field.

Salvage PDT provided an effective treatment for local failure at the primary site. To achieve CR by salvage PDT, early detection of local failure is critical. We reported previously that a submucosal tumor-like appearance is closely associated with local failure at the primary site.[21] Our previous report led us to believe that careful and close surveillance by endoscopy is needed to provide early detection of residual tumor at the primary site after completion of CRT. Although repeated endoscopic surveillance can be complicated, these efforts allow for early detection and provide a minimally invasive curative treatment with organ preservation.

In conclusion, salvage PDT is an effective and tolerable salvage treatment option for local failure after CRT for ESCC in patients whose failure lesion is limited to the submucosal layer without any metastasis.

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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.

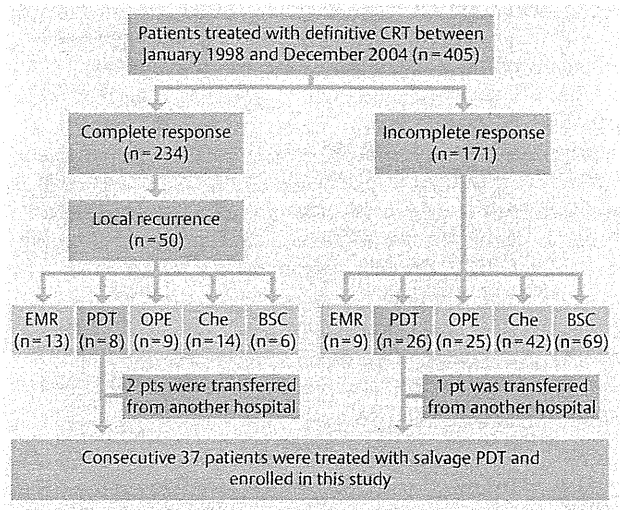

Fig. 1 Flow of patients through the study. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; PDT, photodynamic therapy; OPE, esophagectomy; Che, chemotherapy; BSC, best supportive care.

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.

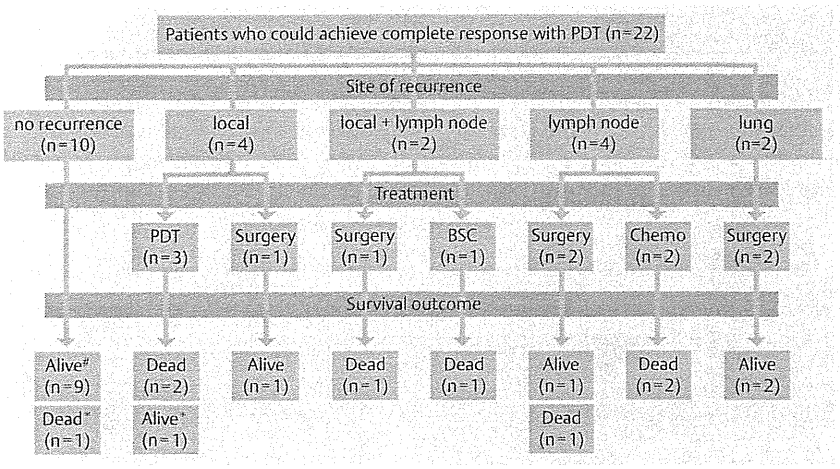

Fig. 2 The clinical flow chart of 22 patients in whom a complete response was achieved with salvage PDT. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Dead*, dead from another disease; Alive#, alive with disease.

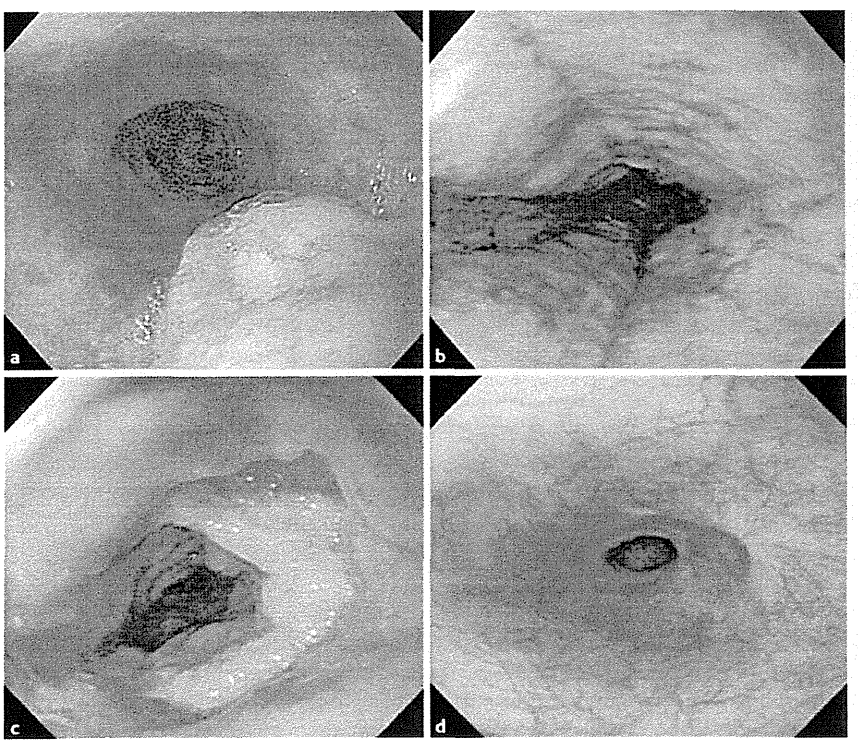

Fig. 3 A patient in whom complete response was achieved with salvage photodynamic therapy (PDT). **a** Local recurrence was detected after chemoradiotherapy and evaluated as uT1 with endoscopic ultrasound. **b** At 3 days after salvage PDT, circumferential ischemic change was observed. **c** At 1 month 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.

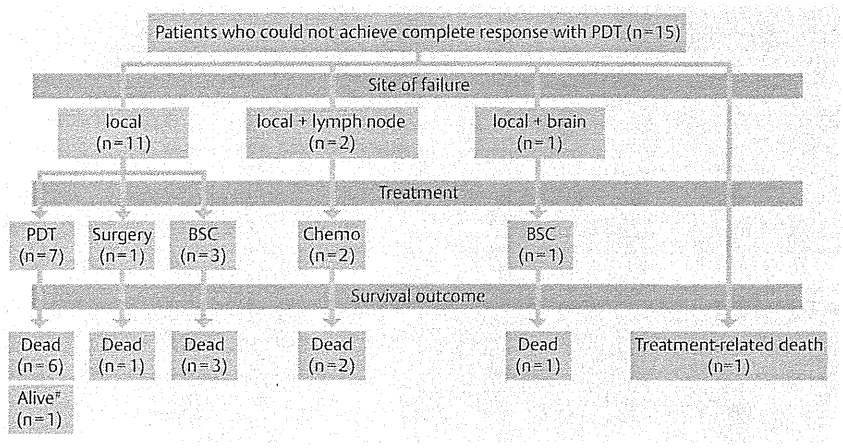

Fig. 4 Clinical flow chart of 15 patients in whom salvage photodynamic therapy did not achieve a complete response. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Alive#, alive with disease.

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]; $P = 0.61$).

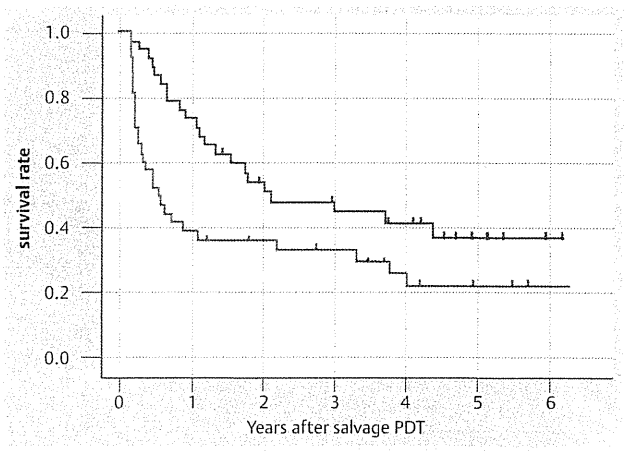

Fig. 5 Overall survival (blue line) and progression-free survival (red dotted line) of all 37 patients from the initiation of salvage photodynamic therapy (PDT).

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

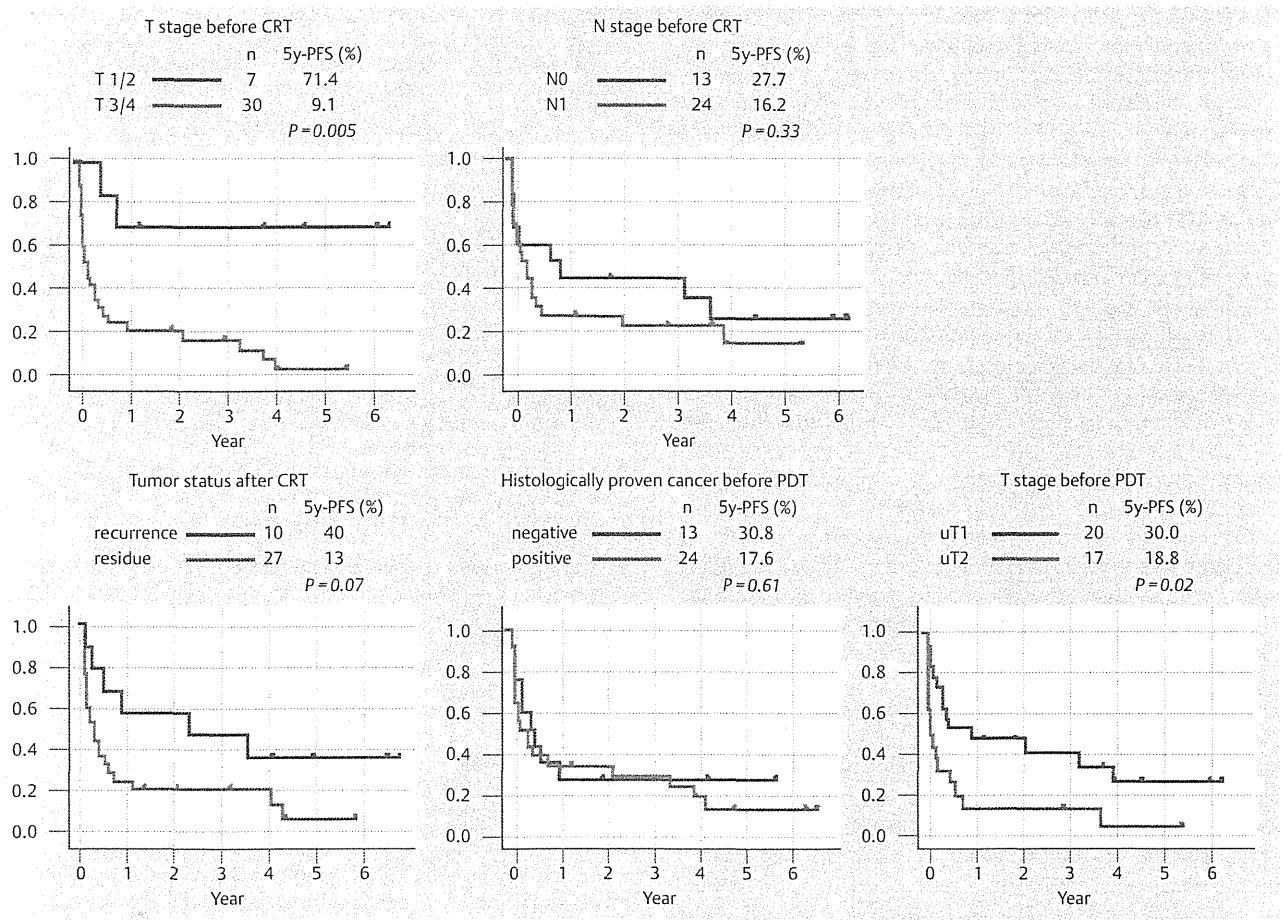

Fig. 6 Comparisons of progression-free survival curves according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

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

response is quite difficult to expect (0–6%) [18–21]. Therefore, second-line systemic chemotherapy for failure after CRT is only a palliative treatment. In fact, most of the patients with unresectable failure or distant metastasis were treated with second-line chemotherapy in the current study (**Fig. 1**). However, among the patients with local failure after CRT, some patients developed only local recurrence and these recurrent or residual lesions could be candidates for salvage PDT and expected to be cured.

As for major complications after salvage PDT, we experienced four cases (10.8%) of esophageal fistulae. Of these, one patient (2.7%) died due to an esophageal-aortic fistula. Esophageal perforation can develop even in patients receiving primary intent PDT for naïve esophageal cancer, as previously reported [8]. However, we cannot deny the possibility that radiation-induced esophageal damage was potentiated by PDT and that the structural damage occurs by transmural necrosis. Lecleire et al. reported a retrospective comparative study of primary intent PDT and salvage PDT after CRT [22]. They found two out of 15 cases (13.3%) of perforation in a salvage setting, whereas no cases (0/25) suffered perforation after primary intent PDT. In the present study, all four patients who developed fistulae had an initial T3 or T4 lesion and had a residual lesion just after CRT, and their total light dose was more than 600 J. Salvage PDT should be carefully performed, particularly in patients in the initial advanced stage and with residual local failure just after CRT. Furthermore, the total laser irradiation dose may correlate with esophageal fistulae.

Patients with baseline T1 or T2 before CRT, and uT1 before PDT tend to achieve long-term survival after PDT. In seven patients with baseline T1 or 2, six patients were evaluated uT1 before PDT. In addition, we could not deny the possibility that patients with more advanced local failure were included in the baseline T3/4 before CRT group, because EUS evaluation is more difficult just after CRT due to radiation esophagitis, especially in advanced cases. From the results of the present study, the treatment efficacy and long-term survival were quite different based on the T stage either before CRT or PDT, and earlier T-stage lesions tended to be cured with PDT, even in the salvage situation. In fact, the baseline tumor stage of five patients with histologically proven local failure who are still alive without any recurrence before CRT was T1 in 1, and T2 in 4, and all their failure lesions were uT1 before PDT. However, caution should be shown when interpreting these survival rates across different variables due to the small sample size.

In conclusion, salvage PDT could be a curative treatment option for patients with local failure after CRT for ESCC when their failure lesions are suspected at stage T2 or earlier without lymph node or distant metastasis.

Competing interests: None

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REPORT

PHASE II STUDY OF CHEMORADIOTHERAPY WITH 5-FLUOROURACIL AND CISPLATIN FOR STAGE II–III ESOPHAGEAL SQUAMOUS CELL CARCINOMA: JCOG TRIAL (JCOG 9906)

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Purpose: In this Phase II study, we evaluated the efficacy and toxicity of chemoradiotherapy (CRT) with cisplatin (CDDP) and 5-fluorouracil (5-FU) for Stage II–III esophageal squamous cell carcinoma (ESCC).
Patients and Methods: Patients with clinical Stage II–III (T1N1M0 or T2–3N0–1M0) thoracic ESCC were enrolled between April 2000 and March 2002. Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) on Days 1 and 8; this regimen was repeated every 5 weeks. Concurrent radiotherapy involved 60-Gy irradiation (30 fractions) for 8 weeks with a 2-week break. Responders received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1. Final analysis was conducted in March 2007. Survival and late toxicities were monitored for 5 years.
Results: The characteristics of the 76 patients enrolled were as follows: median age, 61 years; male/female, 68/8; performance status 0/1, 59/17 patients; Stage IIA/IIB/III, 26/12/38 patients. Of the 74 eligible patients, 46 (62.2%) achieved complete response. Median survival time was 29 months, with 3- and 5-year survival rates of 44.7% and 36.8%, respectively. Acute toxicities included Grade 3/4 esophagitis (17%), nausea (17%), hyponatremia (16%), and infection without neutropenia (12%). Late toxicities comprised Grade 3/4 esophagitis (13%), pericardial (16%) and pleural (9%) effusion, and radiation pneumonitis (4%), causing 4 deaths.
Conclusions: CRT is effective for Stage II–III ESCC with manageable acute toxicities and can provide a nonsurgical treatment option. However, further improvement is required for reduction in late toxicity. © **2010 Elsevier Inc.**

Esophageal squamous cell carcinoma, Chemoradiotherapy, Long-term toxicity, Salvage surgery.

INTRODUCTION

Esophageal cancer, a highly virulent malignancy, was responsible for 11,182 deaths in Japan in 2005, accounting for 3.4% of the country's total cancer deaths (1), with 35–40% of the patients diagnosed with Stage II–III disease. When this study was planned, the standard treatment for Stage II–III esophageal squamous cell carcinoma (ESCC) in Japan was esophagectomy with three-field lymph node dissection, followed by postoperative chemotherapy; the 5-year survival rate is reported to be 36.8–61% (2–4), with a high morbidity rate.

Chemoradiotherapy (CRT) has proved effective against resectable/unresectable ESCC. The Radiation Therapy Oncology Group (RTOG) trial 85-01 demonstrated the superiority of CRT with cisplatin (CDDP), 5-fluorouracil (5-FU), and concurrent irradiation (50.4 Gy) over radiotherapy alone (64 Gy) in patients with T1–3N0–1M0 esophageal cancer (5), in which the final outcome showed a 5-year survival rate of 26% in the CRT arm compared with 0% in the

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Conflict of interest: none.

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radiation-alone arm (6). Therefore, CRT is recognized as the standard noninvasive treatment for patients with localized esophageal cancer who opt for nonsurgical treatment.

CRT was introduced in Japan in the early 1990s as a treatment for potentially unresectable locally advanced ESCC. In a Phase II trial, 18 of 54 (33%) patients with clinical T4 and/or M1 lymph node ESCC, who received CDDP/5-FU with concurrent 60-Gy irradiation, achieved complete response (CR) with a 3-year survival rate of 23% (7). Since then, CRT has been clinically indicated for patients with resectable ESCC who refuse surgical resection. In a retrospective analysis, 55 patients with T1–3NanyM0 ESCC, who received CRT with CDDP, 5-FU, and concurrent 60-Gy irradiation, showed a CR of 70% and a 5-year survival rate of 46%, suggesting comparable outcomes with surgery (8). However, the results were retrospective. Thus, we conducted a Phase II study to evaluate the efficacy and toxicity, particularly the long-term outcome, of CRT for Stage II–III ESCC.

PATIENTS AND METHODS

Eligibility

The eligibility criteria were as follows: pathologically confirmed thoracic ESCC; clinical Stage II–III excluding T4 (T1N1M0 or T2–3N1–0M0: International Union Against Cancer [UICC] 1997); Eastern Cooperative Oncology Group (ECOG) performance status (PS), 0 or 1; and age, 20–70 years. Patients who had previously undergone therapy for esophageal cancer or chemotherapy/radiotherapy for other malignancies and who previously had had other active malignancies were excluded. All the patients had to meet the following laboratory criteria within 14 days before registration: leukocytes $\geq$3,000/mm^3; platelet count $\geq$100,000/mm^3; hemoglobin level $\geq$10 g/dL; aspartate aminotransferase (AST)/alanine aminotransferase (ALT) $\leq$2 $\times$ the upper normal limit at the institution; total bilirubin $\leq$1.5 mg/dL; serum creatinine $\leq$1.2 mg/dL; creatinine clearance $\geq$50 mL/min; PaO_2 $\geq$70 mm Hg; and no major electrocardiogram abnormalities. Written informed consent was obtained from all the patients. The study protocol was approved by the JCOG Clinical Trial Review Committee and institutional review boards of the participating institutions.

Chemotherapy

Chemotherapy comprised two courses of protracted infusion of 5-FU (400 mg/m^2/day) on Days 1–5 and 8–12, and 2-h infusion of CDDP (40 mg/m^2) with adequate hydration and antiemetic coverage on Days 1 and 8; this regimen was repeated every 5 weeks. Responders additionally received two courses of 5-FU (800 mg/m^2/day) on Days 1–5 and CDDP (80 mg/m^2) on Day 1 (Fig. 1), repeated every 4 weeks. No further treatment was administered to patients with CR until disease progression. Additional chemotherapy courses were optional for patients with visible disease.

Administration of both chemotherapy agents was discontinued until toxicity improved to $\leq$Grade 2. The doses were reduced by 25% in the subsequent course after at least one of the following toxicities was observed: leukocytes <1,000/mm^3; platelet count <30,000/mm^3; total bilirubin >2.0 mg/dL; serum creatinine $\geq$2.0 mg/dL; Grade 3/4 stomatitis; or Grade 3/4 esophagitis. Total parenteral nutrition was provided as necessary. Treatment was terminated when disease progression was observed, patients refused to continue, or recovery from toxicity delayed the initiation of the second course by >3 weeks from the planned schedule.

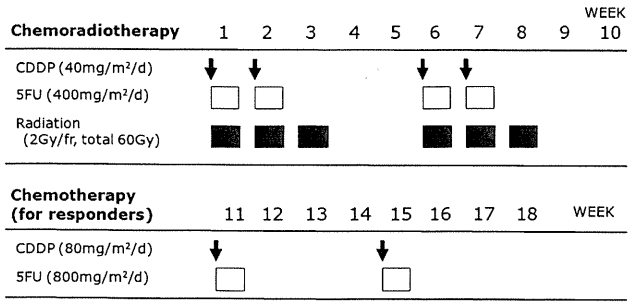

Fig. 1. Protocol scheme.

Radiotherapy

Radiotherapy was delivered using megavoltage ($\geq$6 MV) x-rays; a total dose of 60 Gy was administered in 30 fractions. A 2-week break was provided after 30-Gy irradiation, and radiotherapy was resumed on Day 36 with the second chemotherapy course. The clinical target volume (CTV) for 60-Gy irradiation included the primary tumor plus a 5-cm craniocaudal margin, and the metastatic lymph nodes plus a 1-cm margin. Planning target volume was defined as CTV plus 5- to 20-mm margins for uncertainty. Elective nodal irradiation (40 Gy) of mediastinal and perigastric lymph nodes for all cases, cervical lymph nodes for an upper thoracic primary tumor, and celiac lymph nodes for a lower thoracic primary tumor was also performed. Three-dimensional computed tomography (CT) or X-ray simulation was performed, allowing two-dimensional anterior–posterior opposed fields and bilateral oblique boost. Heterogeneity-uncorrected doses were used.

Assessments

Esophagoscopy and CT were carried out after each course to assess the response. Primary tumor response was evaluated by endoscopy using the modified criteria of the Japanese Society for Esophageal Diseases (9). Complete response of lymph node metastasis was defined as the disappearance of all visible lymph node metastases on the CT or size reduction to $\leq$1 cm for $\geq$3 months after the completion of treatment. Overall CR was declared by an attending physician when CR at both a primary tumor and a lymph node was obtained without the appearance of a new lesion. Complete response was confirmed by reassessment at $\geq$4 weeks after the first assessment. Complete response cases were centrally reviewed, and CR was confirmed by extramural review of the CT scan and images of endoscopy.

Acute toxicities were assessed weekly during CRT and every 2 weeks during additional chemotherapy for 90 days after the completion of CRT. Toxicities were evaluated based on the National Cancer Institute Common Toxicity Criteria (version 2.0). Late toxicity, which first occurred 90 days after CRT initiation, was assessed using the RTOG/European Organization for Research and Treatment of Cancer late radiation morbidity scoring scheme.

Statistical methods

The primary endpoint was overall survival (OS), which was defined as the time from the date of registration to that of death resulting from any cause, and it was censored at the date of the last follow-up for survivors. Progression-free survival (PFS) was defined as the time from the date of registration to that of disease progression or death resulting from any cause, and it was censored at the date of the last visit for patients without progression. Based on the JCOG 9204 trial results (2), in which the 3-year survival rate was 61% for esophagectomy with adjuvant chemotherapy, we initially calculated the sample size expecting a 3-year survival rate of 60%, with a threshold of 45%. With the alpha and beta error levels set at 0.05 and 0.2, respectively, the required number of eligible patients was 68. We finally decided on a sample size of 76, including ineligible patients. The planned accrual and follow-up periods after registration was closed were 1 and 2 years, respectively. For early termination of this study, an interim analysis was planned once 50% of the patients were accrued. A CR point estimate of <60% at the interim analysis would result in early termination of the study.

The JCOG 9204 had enrolled patients based on the pathologic stage after surgery, whereas we enrolled patients based on the clinical stage diagnosed from CT scans. Therefore, this study might include patients with more advanced stages than those in the JCOG 9204. Thus, the protocol was amended to recalculate the sample size from the expected 50% 3-year survival rate and a threshold of 35% in December 2000. The required sample size was 67. The target sample size remained unchanged. The second amendment in February 2007 prolonged the follow-up period to 5 years after the last enrollment to evaluate late toxicity. These amendments were approved by the Data and Safety Monitoring Committee of JCOG.

Secondary endpoints included CR rate, PFS, and acute and late adverse events. Time-to-event distribution was estimated using the Kaplan-Meier method, and confidence intervals (CIs) were calculated using Greenwood's formula. All analyses were performed using SAS Version 9.1.3 software (SAS Institute, Cary, NC, USA) at the JCOG Data Center, with the final analysis conducted in March 2007.

RESULTS

Patient characteristics

Seventy-six patients, whose characteristics are summarized in Table 1, were accrued between April 2000 and March 2002. The median age was 61 years (range, 39–70). Fifty-nine (78%) and 17 (22%) patients showed ECOG PS of 0 and 1, respectively. Fifty-two patients had T3 disease, and 50 had N1 disease. The clinical stages (UICC-TNM) were IIA for 26 patients, IIB for 12 patients, and III for 38.

Table 1. Patient characteristics

Characteristic	Patients ($n = 76$)	(%)
Male	68	89.4
Female	8	10.6
Age (y)		
Range	39–70	
Median	61	
Performance status		
0	59	77.6
1	17	22.4
Tumor location		
Upper	3	3.9
Middle	44	57.9
Lower	29	38.2
T factor		
T1	8	10.5
T2	16	21.1
T3	52	68.4
N factor		
N0	26	34.2
N1	50	65.8
Stage		
IIA	26	34.2
IIB	12	15.8
III	38	50.0

Response

Two patients were excluded from the efficacy analysis because of inadequate liver function and T4 disease diagnosed after registration (Fig. 2). Of the 74 eligible patients, 46 achieved CR, resulting in a CR rate of 62.2% (95% CI, 50.1–73.2). The confirmed CR rate in 23 patients with T1–2 disease was 78.3% (95% CI, 56.3–92.5), and that in 51 patients with T3 disease was 54.9% (95% CI, 40.3–68.9).

Survival

There were 49 deaths in the final analysis, and all except 5 patients were followed up for >5 years. The median survival time was 2.4 years (Fig. 3); the 3- and 5-year survival rates were 44.7% (90% CI, 35.2–53.8) and 36.8% (95% CI, 26.1-47.5), respectively. The lower limit of 90% CI for the 3-year survival rate exceeded the threshold of 35%, and the

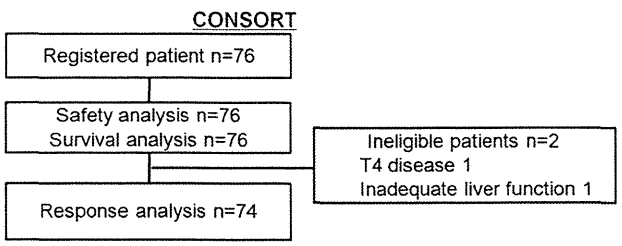

Fig. 2. Consolidated Standards of Reporting Trials diagram.

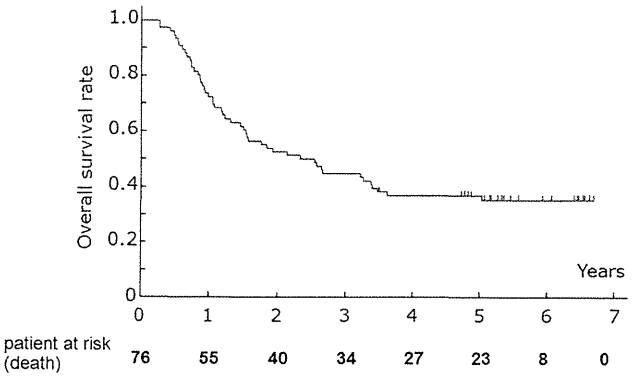

Fig. 3. Overall survival of the 76 patients enrolled in the study.

null hypothesis was rejected ($p = 0.019$). The median PFS was 1 year; the 3- and 5-year PFS rates were 32.9% and 25.6%, respectively (Fig. 4).

Acute toxicity

Data of adverse events for all 76 patients occurring within 90 days after CRT completion are shown in Table 2. Grade 4 leukopenia, neutropenia, anemia, and thrombocytopenia were observed in 1.3%, 1.3%, 2.6%, and 0% of the patients, respectively, whereas Grade 3/4 esophagitis, nausea, infection without neutropenia, and hyponatremia were observed in 17%, 17%, 12%, and 16% of the patients, respectively.

Fifty-three (69.7%) patients completed the 2-course CRT and 2-course additional chemotherapy. Seventy-two (95%) patients received the full dose (60 Gy) of radiation. The treatment protocol was terminated in 23 patients because of disease progression ($n = 10$), toxicity ($n = 11$), patient refusal ($n = 1$), and other reasons ($n = 1$). One early death occurred from esophageal perforation caused by disease progression 21 days after CRT completion. A relationship between early death and the treatment protocol was considered unlikely by the Data and Safety Monitoring Committee.

Late toxicity

Late toxicity data are shown in Table 3. Grade 3–4 late toxicities included pleural (9%) and pericardial (16%) effusion, stenosis, or esophageal fistula (13%), and radiation pneumonitis (4%). Four (5.3%) patients possibly died of treatment-related late toxicity at 3.1, 8.5, 21.3, and 27.8 months after registration. The cause of death were pneumonitis ($n = 2$), pericarditis ($n = 1$), and pleural effusion ($n = 1$). There was no evidence of residual or recurrent disease in these patients. The proportion of any Grade 3/4 late toxicity was 30.1% after 5 years from the initiation of chemoradiation.

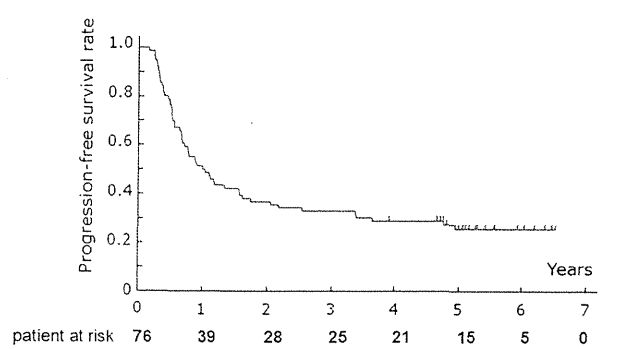

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

Salvage treatment

Twenty-six (34.2%) patients had residual disease or locoregional recurrence without distant metastasis after CRT. Because of inadequate conditions or patient refusal, 7 and 5 patients received chemotherapy and the best supportive care, respectively; the remaining 14 patients received unplanned curative-intent salvage therapy. Eleven patients underwent salvage esophagectomy for residual ($n = 4$) and recurrent ($n = 7$) disease, and the remaining 3 patients underwent endoscopic treatment such as endoscopic mucosal resection (EMR) or argon plasma coagulation. The characteristics of the patients who underwent salvage surgery are described in Table 4.

The median time to salvage surgery after CRT initiation was 13.9 months (range, 4.0–22.7). Six patients underwent esophagectomy with two- or three-field lymph node dissection, 3 patients underwent simple esophagectomy, and 1 underwent only lymphadenectomy; 1 patient could not undergo any resection because of extensive lymph nodes metastasis detected at thoracotomy. Reconstruction was performed using a gastric tube in 7 patients who had R0 resection. There was no operative mortality or hospital death. The median survival time and 3-year survival rate for these 10 patients who received salvage esophagectomy was 16.7 months and 40% (95%C.I: 12.3%–67.0%), respectively.

Of the 3 patients who underwent endoscopic treatment, 1 had mediastinal lymph node metastasis 3 months after argon plasma coagulation, 1 died of surgery-related complication of the pharynx detected 1 year after EMR, and 1 survived for >5 years with no evidence of disease.

DISCUSSION

From the results, CRT for Stage II–III ESCC showed a CR rate of 62.2% (95% CI, 50.1–73.2), a 3-year survival rate of 44.7% (90% CI, 35.2–53.8), and a 5-year survival rate of 36.8% (95% CI, 26.1–47.5). The 3-year survival rate, which is the primary endpoint of this study, met the decision criteria.

Clinically, it is very important to know whether definitive CRT can achieve survival comparable with surgery plus postoperative adjuvant chemotherapy. In this regard, there were several differences in the background between the present study and JCOG 9204 (2) described in Statistical Methods. The study conducted after JCOG 9204, which compared preoperative and postoperative adjuvant chemotherapy comprising the administration of 5-FU and CDDP to Stage II–III esophageal cancer patients (JCOG 9907) (10), could be a reference for this study, because the patients were registered before surgery based on the clinical stage. In the recently

Table 2. Toxicity (n = 76)

Toxicity	NCI-CTC Version 2.0				
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)
Leukocytes	5	34	32	1	43
Neutrophils	17	31	19	1	26
Hemoglobin	13	35	15	2	22
Platelets	15	13	4	0	5
Dysphagia, esophagitis	29	14	13	0	17
Nausea	25	20	13	–	17
Vomiting	16	6	0	0	0
Diarrhea	10	5	1	0	1.3
Stomatitis/pharyngitis	15	9	6	0	8
Radiation dermatitis	18	4	0	0	0
Febrile neutropenia	–	–	1	0	1.3
Infection without neutropenia	7	8	8	1	12
Hyponatremia	40	–	11	1	16
AST	35	4	3	0	3.9
ALT	43	7	2	1	3.9
Creatinine	15	13	1	0	1.3

Abbreviations: NCI-CTC Version 2.0 = National Cancer Institute Common Toxicity Criteria Version 2.0; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

published results of JCOG 9907, the preoperative chemotherapy arm was highly superior to the postoperative chemotherapy arm in terms of OS. The 5-year survival rate of the postoperative chemotherapy arm in JCOG 9907 did not differ significantly from that in the present study, that is, 38.4% and 36.8%, respectively (10). By contrast, the 5-year survival rate of the preoperative chemotherapy arm in JCOG 9907 was 60.1%, although further follow-up is needed to verify the data. CRT may produce comparable outcomes with surgery plus postoperative adjuvant chemotherapy; however, surgery after preoperative chemotherapy is considered to be superior to CRT. Nevertheless, CRT is one of the treatment options for patients with Stage II and III ESCC because of its apparent advantage of preserving the esophagus, which may provide better quality of life.

Chemoradiotherapy achieves prolonged survival with possibly more late toxicity. Late toxicity after thoracic radiotherapy has been reported in patients with esophageal cancer, lung cancer, and Hodgkin's lymphoma (11–13). Some reports have described that long-term toxicity after CRT results in serious, life-threatening complications. In a previous study, 2 of 78 patients with CR after CRT died of myocardial infarction, and 8 (10.2%) died of pericardial or pleural effusion (14) Late toxicity after CRT against ESCC has not yet been investigated in detail, and early reports of trial outcomes generally seem to underestimate the risk of late toxicity in long-term survivors (15). In the present study, the incidence of ≥Grade 3 late toxicity was similar to that reported in a previous study (14). Most of these events occurred several years after CRT. It is considered that reduction in radiation dose, careful observation, and control of late toxicity may improve post-CRT survival. RTOG 94-05 demonstrated that a higher irradiation dose (64.8 Gy) in CRT was not advantageous with regard to survival and local control, compared with the standard dose (50.4 Gy) (16). One of the reasons was the low tolerability of the high-dose arm because of toxicity. Whereas decreasing the irradiation dose in radiotherapy is essential for reducing late toxicity, the radiation volume is also

Table 3. Late toxicity (n = 76)

Late toxicity	RTOG/EORTC late radiation morbidity scoring scheme					
	Grade 1	Grade 2	Grade 3	Grade 4	≥Grade 3 (%)	≥Grade 4 (%)
Pleural effusion (nonmalignant)	24	5	7	0	9	0
Esophagus-related (dysphagia, stenosis, fistula)	11	4	4	6	13	8
Pericardial effusion	6	5	9	3	16	4
Radiation pneumonitis	33	6	2	1	4	1.3
Skin-related	3	0	0	0	0	0
Spinal cord—related	3	0	0	0	0	0

Abbreviation: RTOG/EORTC: radiation therapy oncology group/european organization for research and treatment of cancer.
four (5.3%) patients possibly died of treatment-related late toxicity: pericarditis (n = 1), pleural effusion (n = 1), and pneumonitis (n = 2).

Table 4. Characteristics and outcomes in patients who underwent salvage surgery

Characteristic	Patients (n = 11)	Characteristic	Patients (n = 11)
Male	11	Residual/Recurrent	4 /7
Female	0		
Age (y)		Surgical curability	
Range	46–70	R0	7
Median	59	R1 + R2	4
Tumor location			
Upper	0	Operative mortality or hospital death	0
Middle	6		
Lower	5	Relapse after surgery	8
Clinical stage*		No relapse	3
IIA	5		
IIB	0		
III	6		

* Clinical stage at the time of registration.

important. In this study, late toxicity might have been caused by the extended volume of irradiation, which corresponds to the dissected area in extended surgery. In the near future, three-dimensional conformal radiotherapy, which was not mandatory in this study, or other methods based on advanced technology such as intensity-modulated radiotherapy and proton therapy, may have potential advantages over conventional two-dimensional radiotherapy in terms of reduced doses for the heart. A clinical trial with these latest radiotherapy techniques is required (17).

Salvage treatment—*e.g.*, salvage surgery (18–20) or salvage EMR (21)—has recently been reported to have therapeutic potential for patients with local failure of CRT. In our study, one-third of the patients did not achieve CR, and 50% of the remaining patients had recurrence after achieving CR. For the latter, salvage treatment should be indicated, if applicable. Mucosal disease can be removed by EMR, and locoregional residual or recurrent disease can be curatively resected by surgery. It has been reported that 6–34% of patients undergo salvage esophagectomy after definitive CRT (22, 23). Although a high rate of hospital deaths (6–33%) is observed compared with that after surgery without preoperative therapy, some patients achieve long-term survival with a 5-year survival rate of 25–35% (24–26). In the present study, 11 (14.5%) patients underwent salvage esophagectomy and 7 had R0 resection. There was no operative mortality or hospital death. The limitations of salvage surgery include patient tolerance, capability of medical staff, and early detection of residual or recurrent disease; however, salvage esophagectomy can achieve long-term survival. Some patients benefit from salvage surgery after definitive CRT; therefore, this procedure is worth further investigation.

Neoadjuvant CRT has recently been recognized as a standard therapy for resectable esophageal cancer in Western countries. According to CALGB 9781, CRT followed by surgery prolonged survival (median survival time, 4.48 vs. 1.79 years) compared with surgery alone in the treatment of esophageal cancer (27). However, most participants in CALGB 9781 had esophageal adenocarcinoma. Meta-analysis has revealed the survival benefit of neoadjuvant CRT in patients with esophageal adenocarcinoma (28). According to FFCD 9102, which included 90% patients with squamous cell carcinoma, surgery after neoadjuvant CRT (40 Gy) and continuation of CRT to 60 Gy without surgery had the same impact on survival and quality of life for responders as induction CRT (29). The results of a randomized trial from Germany, in which 172 ESCC patients randomly received CRT with or without additional surgery, indicated equal efficacy of surgery and CRT. The median survival times were 16.4 months and 14.9 months, respectively, and the 2-year survival rates were 39.9% and 35.4% with and without surgery, respectively (30). This suggests that CRT, which can preserve organ function, is equally effective as surgery for responders. For nonresponders, salvage surgery can be a therapeutic option. Importantly, which types of patients are benefited by salvage surgery or how the surgical procedure is performed after CRT should be prospectively evaluated. We are planning a Phase II trial of CRT for resectable ESCC, followed by salvage surgery for residual or recurrent disease.

CONCLUSION

Chemoradiotherapy is effective for Stage II–III ESCC with manageable acute toxicities and can provide a noninvasive treatment option. However, further improvement is required for reduction in late toxicity.

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Phase I trial of combination chemotherapy with docetaxel, cisplatin and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer

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Background: We investigated the maximum tolerated dose (MTD) of combination therapy with docetaxel, cisplatin, and S-1 (TPS) in patients with locally advanced or recurrent/metastatic head and neck cancer (HNC).

Patients and methods: Treatment consisted of docetaxel (Taxotere) at doses of 50, 60, and 70 mg/m^2; cisplatin at 70 mg·m^2/day on day 1; and S-1 twice daily on days 1–14 at doses of 40, 60, and 80 mg·m^2/day, repeated every 3 or 4 weeks.

Results: Forty patients were enrolled. MTD was not reached until level 4. Subjects at expanded dose were limited to patients with locally advanced disease. Two dose-limiting toxic effects (DLTs) were observed at dose level 5 (TPS: 70/70/80 mg·m^2/day, every 3 weeks), namely one grade 3 infection and one grade 3 hyperbilirubinemia, establishing this as the MTD. Of 12 patients treated at dose level 6 (TPS: 70/70/60 mg·m^2/day, every 3 weeks), 2 DLTs were seen. Six achieved a complete response and 22 a partial response, giving a response rate of 70%.

Conclusions: TPS was well tolerated. The recommended phase II dose as induction chemotherapy for locally advanced HNC was determined as 70/70/60 mg·m^2/day every 3 weeks. Antitumor activity was highly promising and warrants further investigation.

Key words: cisplatin, docetaxel, head and neck cancer, S-1.

introduction

Head and neck cancers (HNCs) are the sixth most common cancer in the world, and ~500 000 new cases are projected annually [1]. An estimated 60% of these patients will present with locally advanced disease (stage III/IV).

Platinum-based chemotherapy is widely used for recurrent/metastatic HNC. The combination of docetaxel, cisplatin, and 5-fluorouracil (5-FU) (TPF) has been considered the standard regimen for induction chemotherapy for locally advanced squamous cell carcinoma of the head and neck (SCCHN) [2, 3]. Nevertheless, this combination is stressful to patients, and the continuous infusion of 5-FU in this combination reduces quality of life, owing not only to toxicity but also to inconvenience and catheter-related complications. Other options with improved safety profiles and greater convenience are thus highly desirable.

In response to this need, one growing trend has been the substitution of conventional 5-FU with the oral prodrug of 5-FU. S-1 is a novel oral fluoropyrimidine derivative, which consists of tegafur, gimeracil (5-chloro-2, 4-dihydrogenase; CDHP), and potassium oxonate (Oxo) at a molar ration of 1 : 0.4 : 1 [4]. Tegafur is a prodrug of 5-FU. CDHP augments the activity of 5-FU by inhibiting dihydropyrimidine dehydrogenase. Oxo reduces gastrointestinal (GI) toxicity by inhibiting orotate phosphoribosyl transferase and 5-FU phosphorylation in intestinal mucosa [5].

S-1 has shown activity against HNC, producing a response rate of 34% [6]. A combination of cisplatin and S-1 shows promising efficacy (response rate: 67.6%) with acceptable toxicity for locally advanced HNC [7]. Furthermore, a combination of docetaxel and S-1 has demonstrated promising efficacy with acceptable toxicity for many cancers [8–11].

Based on these promising results, we speculated that replacing 5-FU with S-1 in combination with docetaxel and cisplatin would be a reasonable alternative to continuous

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