effects and efficacy of the combination of post-operative radiotherapy and concurrent chemotherapy with low-dose cisplatin in selected patients who had squamous cell carcinoma of the cervical esophagus with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis.

PATIENTS AND METHODS

PATIENTS POPULATION AND ELIGIBILITY

From January 2005 through December 2008, 34 patients with previously untreated carcinoma of the cervical esophagus underwent surgical resection at the National Cancer Center Hospital East. The clinical and pathologic characteristics of the 34 patients are shown in Table 1. Pre-operative and post-operative staging was based on the 1997 International Union Against Cancer TNM classification. Cases with metastasis to the mediastinal lymph nodes were classified as M1-lymph disease.

All patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV) defined as complete removal of all macroscopic tumor masses were eligible for the study if they met all of the following criteria: histologically confirmed diagnosis of squamous cell carcinoma; age of 18 years or older and 75 years or younger; performance status of 0 or 1 according to the Eastern Cooperative Oncology Group scale; adequate bone marrow, hepatic and renal function; no previous chemotherapy or radiotherapy; and written informed consent provided before recruitment.

PRE-TREATMENT EVALUATION

Pre-treatment evaluations in all patients included physical examination, barium-swallow examination, endoscopy with biopsy, ultrasonography of the neck and computed tomography of the neck and chest.

STUDY TREATMENT

The protocol required that radiotherapy be performed as soon as satisfactory healing had occurred after surgery. The protocol also called for radiotherapy to start within 8 weeks after surgery.

The treatment consisted of two or three cycles of cisplatin at a dose of 20 mg/m^2 of body surface area on days 1–4, 22–25 and 43–46, repeated every 3 weeks, with concurrent radiotherapy to a total dose of 66 Gy in 33 fractions over 6 weeks.

Because gross tumors were already resected, gross tumor volume was not defined in the case of adjuvant radiotherapy. Clinical target volume (CTV) was defined as the total volume of the surgical bed of the primary tumor plus volumes and metastatic lymph nodes considered at risk of containing microscopic disease. The CTV was further categorized into two volumes: the CTV boost (CTVb), which included the surgical bed of the primary tumor and

Table 1. Clinical and pathologic characteristics of 34 patients undergoing surgery for squamous cell carcinoma of the cervical esophagus

Variable	No. of patients
Sex	
Female/male	8/26
Tumor location	
Ce/-Ph/-Ut	18/5/10
Ce-Ph-Ut	1
Clinical T status	
T1/2	5/2
T3/4	15/12
Clinical N status	
N0/1	16/18
Clinical M stage	
M0	25
M1 lymph	9
Clinical stage	
I/II/III/IV	4/8/12/10
Larynx	
Preserved	10
Laryngectomy	24
Pathologic T status	
T1/2	6/2
T3/4	17/9
Pathologic N status	
N0	13
N1	21
Pathologic M status	
M0	20
M1lymph/1 organ	13/1
Pathologic stage	
I/II/III/IV	2/10/8/14
Completeness of resection	
R0/1	30/3
R2	1

Ce, cervical esophagus; Ph, hypopharynx; Ut, upper third of thoracic esophagus.

metastatic lymph nodes, and the CTV subclinical (CTVs), which included the CTVb plus regional lymph nodes (cervical, supraclavicular and superior mediastinum lymph node areas) (Fig. 1). The upper cervical lymph node area (level II) was excluded from the irradiation field if no lymph node metastasis was found in this area. From four to eight beams were applied from various angles to the CTVs to a total dose of up to 46 Gy. A booster dose of 20 Gy was given to the CTVb using multiple fields to shield the spinal cord for a total dose of 66 Gy.
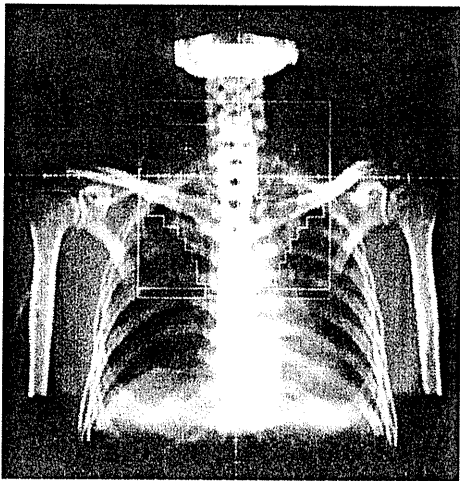
Figure 1. Planning film demonstrating a representative treatment field for post-operative radiation in a patient with metastases to the upper mediastinal lymph nodes.

TOXICITY ASSESSMENT AND DOSE MODIFICATION

Toxicity assessments, including complete blood cell counts and serum chemistry profiles, were performed weekly during chemoradiotherapy and every 3 weeks during the protocol study. Toxicity assessments for all patients were performed with the National Cancer Institute Common Toxicity Criteria (version 3.0). The dose was reduced by 20% if any toxicity reached Grade 3.

FOLLOW-UP

All patients were regularly followed up with routine physical and laboratory examinations at our hospital. Computed tomography of the neck and chest was performed annually to detect possible recurrent disease. The median follow-up period for all patients was 39.5 months (range, 12–64 months).

STATISTICAL ANALYSIS

Survival time was measured from the date of surgery until death or the most recent follow-up examination. Length of survival was determined with the Kaplan–Meier method, and the log-rank test was used for comparisons. All analyses were performed with the SPSS statistical software package (version 17.0.2; SPSS, Inc., Chicago, IL, USA).

RESULTS

PATIENT CHARACTERISTICS

Pathologic examination showed lymph node involvement in the upper mediastinum in 13 patients (Table 1). Eleven of 13 patients were enrolled to receive post-operative radiotherapy with concurrent chemotherapy, but 2 of the 13 patients refused post-operative adjuvant treatment. The baseline

characteristics of patients enrolled in this protocol are shown in Table 2. The median age was 58 years (age range, 40–70 years), and eight patients were men and three were women. More than 70% of tumors were clinically T3 or T4. Seventy-three percent of tumors had metastasized to lymph nodes before operation. Pathologic characteristics of selected patients with metastases to the upper mediastinal lymph node are listed in Table 3. Seventy-two percent of tumors were T3 or T4, and all patients had regional lymph node involvement. Complete resection (R0) was achieved in 82% of the patients.

COMPLIANCE WITH TREATMENT

Nine patients (82%) completed post-operative radiotherapy with two or more of concurrent chemotherapy with cisplatin. One patient who had received 66 Gy of radiotherapy stopped chemotherapy after receiving one cycle. Another patient stopped radiotherapy after receiving a radiation dose of 54 Gy. Toxicity was assessed in all 11 patients.

Table 2. Clinical characteristics of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)
Sex	
Female	3 (27)
Male	8 (73)
Age in years	
Median (range)	58 (40–70)
Tumor location	
Ce	7 (64)
Ce-Ut	3 (27)
Ce-Ph-Ut	1 (9)
Tumor status	
T1	1 (9)
T2	2 (18)
T3	2 (18)
T4	6 (55)
Node status	
N0	3 (27)
N1	8 (73)
Metastatic status	
M0	5 (45)
M1 lymph	6 (55)
Stage	
I	1 (9)
II	0
III	4 (36)
IV	6 (55)

Table 3. Pathologic characteristics and overall survival of selected patients with metastasis to the upper mediastinal lymph nodes

Characteristic	No. of patients (%)	1-year survival (%)	3-year survival (%)	*P* value
Tumor status				
T1/2	3 (27)	100	100	0.517
T3	4 (36)	75	75	
T4	4 (36)	75	50	
Node status				
N0	0			
N1	11 (100)	91	71	
Metastatic status				
M0	0			
M1 lymph	11 (100)	91	71	
Differentiation				
Well	5 (45)	80	60	0.486
Moderate	6 (55)	80	80	
Lymphatic invasion				
Negative	7 (64)	86	69	0.828
Positive	4 (36)	75	75	
Vascular invasion				
Negative	1 (9)	100	100	0.544
Positive	10 (91)	90	68	
Larynx				
Preserved	4 (36)	100	100	0.196
Laryngectomy	7 (64)	86	57	
Residual tumor				
R0	9 (82)	89	64	0.359
R1	2 (18)	100	100	

SURVIVAL AND PATTERN OF FIRST FAILURE

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%).

TOXICITY

All toxicities are listed in Table 4. The majority of treatment-related toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. No patients died during treatment. During and after treatment, no ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy was found in the reconstructed organs.
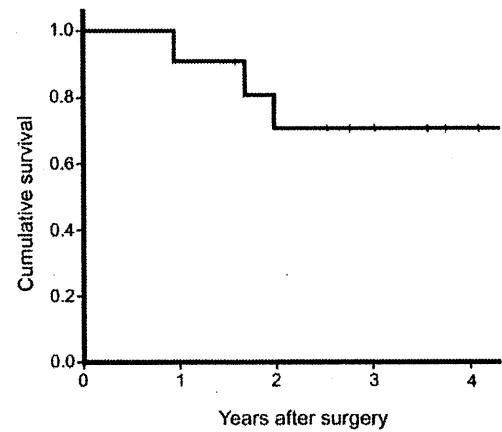

Figure 2. Overall survival curve.

Table 4. Hematologic and non-hematologic adverse events during post-operative radiation and concurrent chemotherapy

Events	G1, no. (%)	G2, no. (%)	G3, no. (%)	G4, no. (%)
Hematologic				
Leukopenia	0	6 (55)	4 (36)	0
Neutropenia	0	5 (45)	2 (18)	0
Anemia	0	2 (18)	0	0
Non-hematologic				
Nausea	7 (64)	0	0	0
Anorexia	7 (64)	1 (9)	0	0
Fatigue	6 (55)	0	0	0
Diarrhea	0	1 (9)	0	0
Esophagitis	1 (9)	0	0	0
Mucositis	2 (18)	0	1 (9)	0
Dysphagia	4 (36)	1 (9)	0	0
Radiation dermatitis	2 (18)	3 (27)	0	0
Renal (creatinine)	3 (27)	7 (64)	0	0

DISCUSSION

Carcinoma of the cervical esophagus extends easily and frequently upward to the hypopharynx or downward to the thoracic esophagus, and most tumors are located at the border of the hypopharynx or the thoracic esophagus. However, carcinoma of the cervical esophagus is a disease distinct from carcinoma of the hypopharynx or thoracic esophagus. Larynx-preserving esophagectomy for carcinoma of the cervical esophagus can be performed safely and can lead to the long-term survival of selected patients (2,3). In the present study, even if patients had metastasis to the upper mediastinal lymph nodes, larynx-preserving cervical esophagectomy could be performed (Table 3). The selection of reconstructive procedure depends on the resected length of the esophagus necessary to ensure adequate distal esophageal margins,

whether gastric pull-up adapts to total esophagectomy and whether free jejunal transfer accommodates the cervical esophagectomy with or without pharyngolaryngectomy.

Kakegawa et al. (4) have reported that the incidence of metastasis to the upper mediastinal lymph nodes (11.4%) is similar to that to the cervical paratracheal lymph nodes (14.3%) and deep cervical lymph nodes (14.3%). In the present study, the incidence of metastasis to the upper mediastinal lymph nodes was 38% (Table 1). The lymphatic drainage of the cervical esophagus is primarily to the paratracheal lymph nodes; therefore, carcinoma of the cervical esophagus spreads easily and frequently upward to the cervical lymph nodes or downward to the upper mediastinal lymph nodes or both. For this reason, we routinely perform dissection of the upper mediastinal lymph nodes as well as that of the bilateral cervical paratracheal and the deep cervical lymph nodes.

The reported 3- and 5-year survival rates for cervical esophageal carcinoma treated with surgical resection range from 18 to 35.4% and from 12 to 42%, respectively (2,5–8). The prognosis of patients with cervical esophageal cancer is worse than that of patients with hypopharyngeal cancer (7,8). Factors previously reported to influence the long-term survival of patients include both carcinoma of the cervical esophagus and carcinoma of the hypopharynx. Therefore, we reported prognostic factors affecting survival in our previous study, including carcinoma of the cervical esophagus (excluding hypopharyngeal cancer). In our previous study, prognostic factors affecting survival after surgical resection were sex, high T factor, lymph node involvement, palpable cervical lymph nodes, vocal cord paralysis, lymphatic invasion and extracapsular invasion (2). In particular, the 3-year survival rate in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV) was 0% (2). Therefore, we believe that carcinoma of the cervical esophagus requires multimodal treatment, such as post-operative radiotherapy with concurrent chemotherapy.

Cooper et al. (9) (Radiation Therapy Oncology Group 9501) and Bernier et al. (1) (European Organization for Research and Treatment of Cancer Trial 22931) have both reported that concurrent post-operative radiotherapy and chemotherapy with cisplatin for locally advanced cancers of the head and neck significantly improves the rates of local and regional control and of disease-free survival compared with post-operative radiotherapy alone. Bernier et al. have also demonstrated an improvement in the overall survival rate. Single-modality treatment after surgical resection cannot guarantee long-term survival; therefore, multimodal therapy, such as post-operative chemotherapy and radiotherapy, is essential for the treatment of cervical esophageal carcinoma. However, we are concerned about the adverse effects of post-operative chemoradiotherapy upon the reconstructed organs, especially free jejunal grafts, and the patient's general condition after the operation. Single- and multi-institutional randomized studies and retrospective studies have shown that the concurrent chemotherapy regimen

modified by reducing the platinum dose, increasing its frequency and adding a complementary chemotherapeutic agent remains well tolerated and is more effective than radiotherapy alone (10–12).

On the basis of the results of our previous study and these studies of post-operative adjuvant or definitive radiotherapy with concurrent chemotherapy for locally advanced carcinoma of the head and neck, we performed a pilot study and retrospectively assessed the toxic effects and efficacy of post-operative radiotherapy with concurrent low-dose cisplatin chemotherapy in selected patients with metastasis to the upper mediastinal lymph nodes (M1 lymph/Stage IV), a factor indicating an extremely poor prognosis. Nine patients (82%) completed post-operative radiotherapy and two or more cycles of concurrent chemotherapy with cisplatin. The majority of treatment toxicities included myelosuppression. Leukopenia, neutropenia and mucositis of Grade 3 or greater occurred in 36, 18 and 9% of the patients, respectively. However, during the protocol treatment, no Grade 4 treatment-related toxicity occurred and no patients died. A low dose of cisplatin decreases the likelihood of adverse effects and death related to post-operative treatment with the combination of radiotherapy and concurrent chemotherapy with cisplatin (1). During and after treatment, no reconstructed organs underwent ischemic change or necrosis due to the effects of radiation and concurrent chemotherapy. The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is a well-tolerated treatment with mild-to-moderate adverse effects which causes no damage to reconstructed organs.

With a median follow-up period of 39.5 months (range, 16–64 months), the median survival time was 33 months. The 1- and 3-year overall survival rates were 90 and 67%, respectively (Fig. 2). Tumors recurred in four patients (36%). The pattern of recurrence was more often distant metastasis (75%) than locoregional spread (0%). In our previous study, the 3-year survival rate was 0% in patients with metastasis to mediastinal lymph nodes (M1 lymph/Stage IV), and the pattern of recurrence after operation was more often locoregional spread (82%) than distant metastasis. Triboulet et al. (7) have reported that post-operative radiotherapy for carcinoma of the hypopharynx and cervical esophagus improves survival and achieves a 3-year survival rate of 35%. However, large randomized, controlled studies have demonstrated that the combination of post-operative radiotherapy with concurrent chemotherapy is superior to post-operative radiation alone (1). The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin improves the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the cervical esophagus. We advocate that the indications for the combination of post-operative radiation with concurrent chemotherapy be expanded to include patients with a high T factor and lymphatic invasion, as this treatment is well tolerated, is associated with mild-to-moderate adverse effects and improves survival rates.

CONCLUSION

The combination of post-operative radiation and concurrent chemotherapy with low-dose cisplatin is well tolerated, is associated with mild-to-moderate adverse effects and has the potential to improve the rates of locoregional control and overall survival in patients with locally advanced squamous cell carcinoma of the esophagus. Therefore, we advocate that the indications for this treatment be expanded to include patients with a high T factor and lymphatic invasion.

Conflict of interest statement

None declared.

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

Authors T. Yano[1], M. Muto[2], K. Minashi[1], M. Onozawa[3], K. Nihei[3], S. Ishikura[4], K. Kaneko[1], A. Ohtsu[1]

Institutions [1] Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan
[3] Division of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[4] Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo, Japan

Corresponding author
T. Yano, MD
Division of Digestive Endoscopy
and Gastrointestinal Oncology
National Cancer Center Hospital
East
6-5-1, Kashiwanoha
Kashiwa
277-8577 Japan
Fax: +81-4-71314724
toyano@east.ncc.go.jp

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

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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
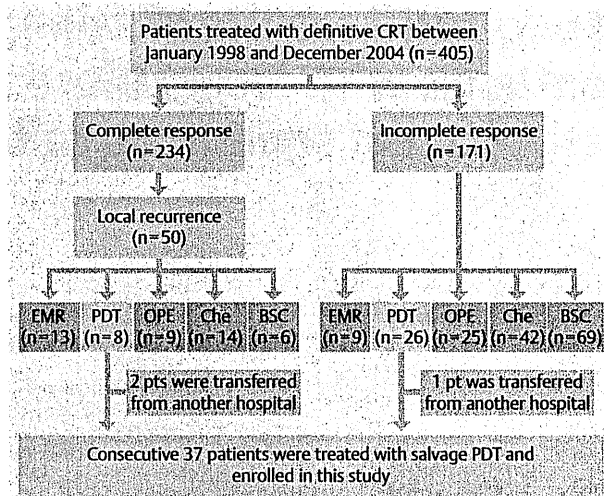

Fig. 1 Flow of patients through the study. CRT, chemoradiotherapy; EMR, endoscopic mucosal resection; PDT, photodynamic therapy; OPE, esophagectomy; Che, chemotherapy; BSC, best supportive care.

slightly protruding lesions at the primary site were suspected of representing a recurrence and were re-evaluated with EUS.

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 logrank 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

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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

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.

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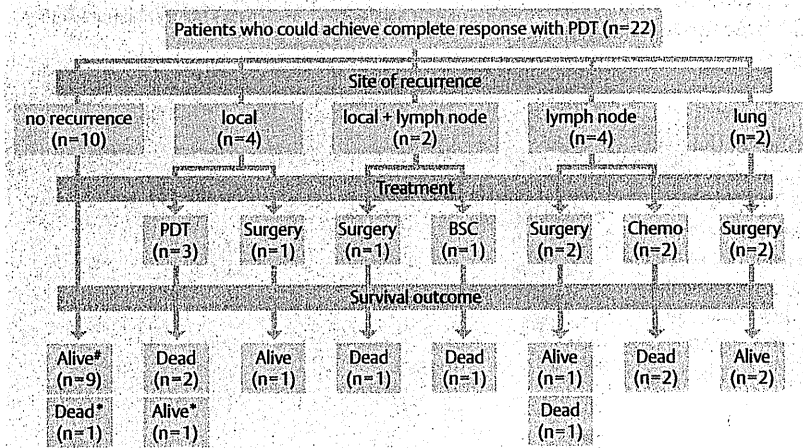
Fig. 2 The clinical flow chart of 22 patients in whom a complete response was achieved with salvage PDT. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Dead*, dead from another disease; Alive#, alive with disease.
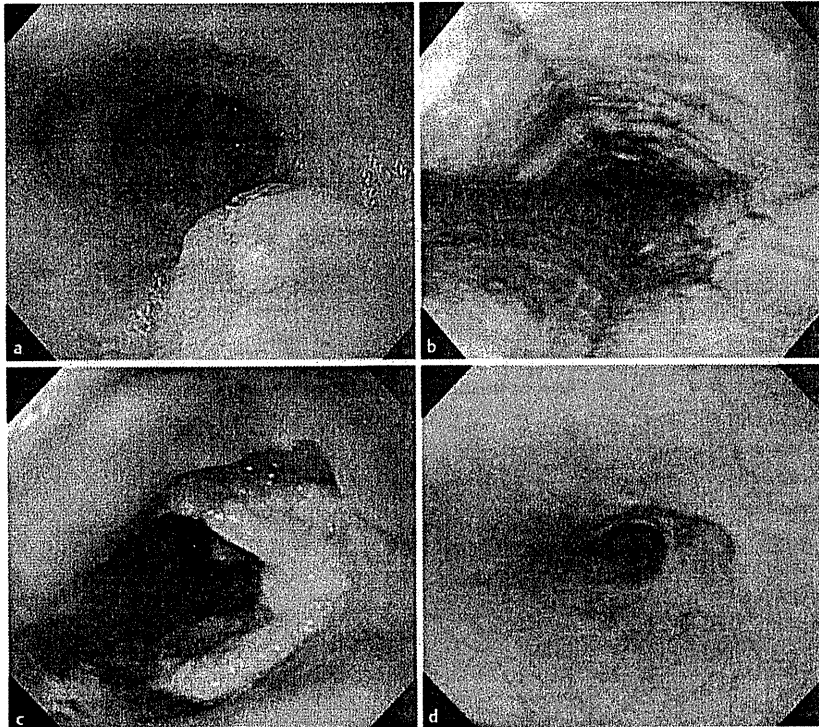

Fig. 3 A patient in whom complete response was achieved with salvage photodynamic therapy (PDT). a Local recurrence was detected after chemoradiotherapy and evaluated as uT1 with endoscopic ultrasound. b At 3 days after salvage PDT, circumferential ischemic change was observed. c At 1 month after salvage 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.
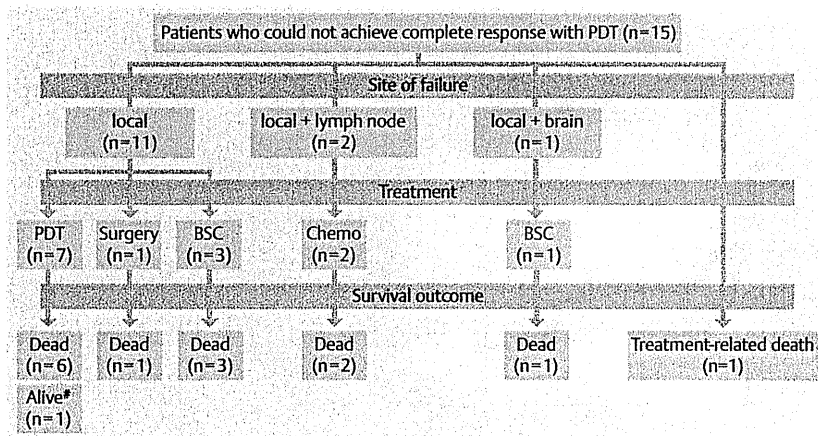
Fig. 4 Clinical flow chart of 15 patients in whom salvage photodynamic therapy did not achieve a complete response. CR, complete response; PDT, photodynamic therapy; BSC, best supportive care; Chemo, chemotherapy; Alive*, alive with disease.

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]; $P = 0.61$).
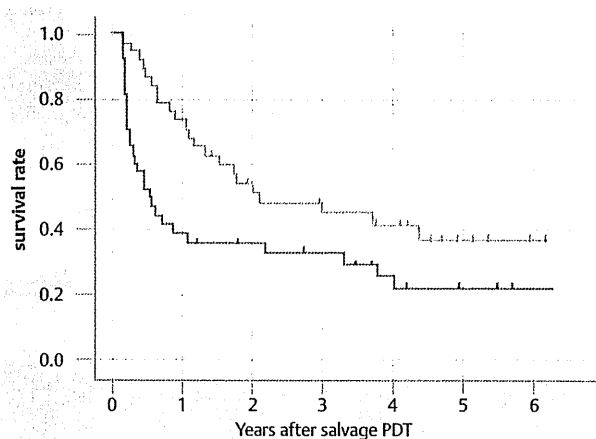

Fig. 5 Overall survival (blue line) and progression-free survival (red dotted line) of all 37 patients from the initiation of salvage photodynamic therapy (PDT).

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
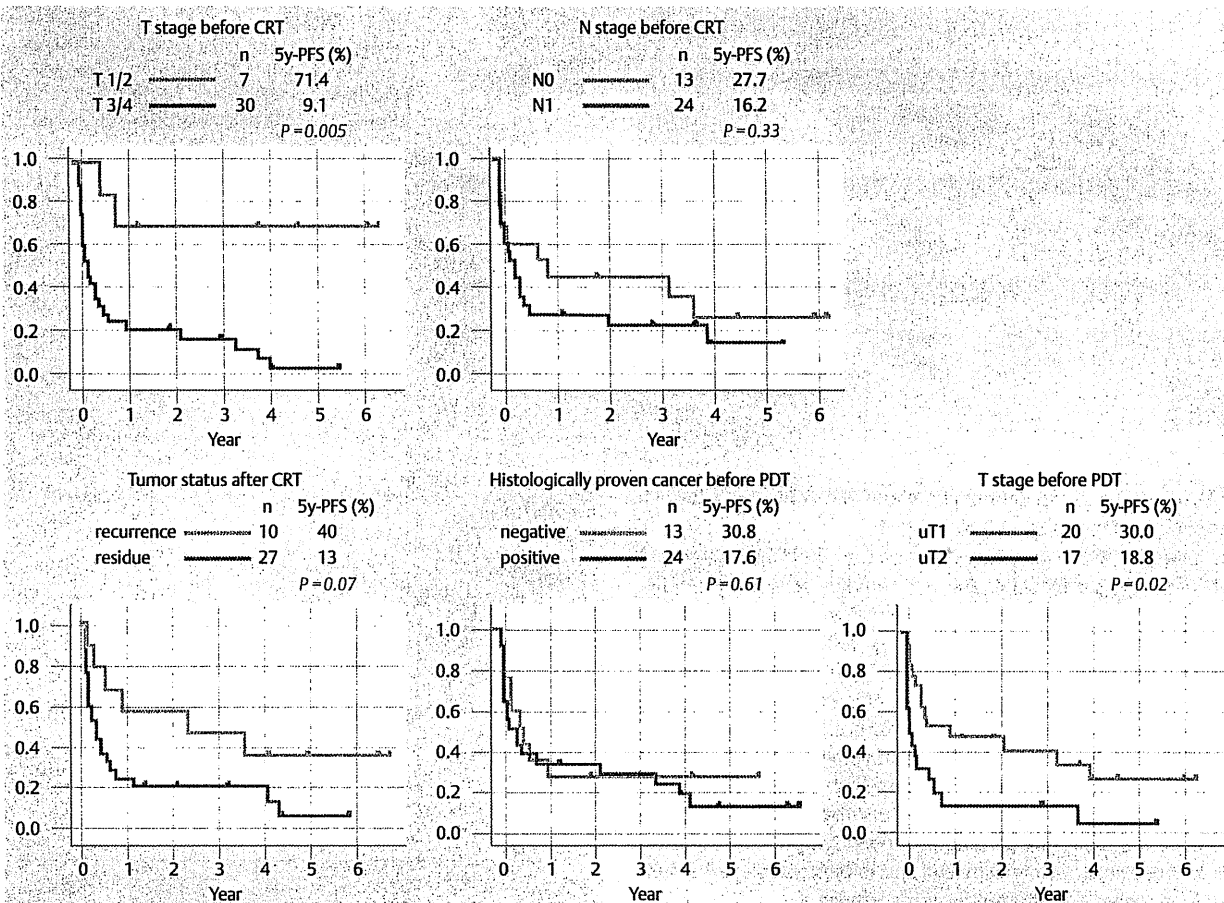
T stage before CRT

	n	5y-PFS (%)
T 1/2	7	71.4
T 3/4	30	9.1

P = 0.005

N stage before CRT

	n	5y-PFS (%)
N0	13	27.7
N1	24	16.2

P = 0.33

Tumor status after CRT

	n	5y-PFS (%)
recurrence	10	40
residue	27	13

P = 0.07

Histologically proven cancer before PDT

	n	5y-PFS (%)
negative	13	30.8
positive	24	17.6

P = 0.61

T stage before PDT

	n	5y-PFS (%)
uT1	20	30.0
uT2	17	18.8

P = 0.02

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 possi-

bility 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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CLINICAL INVESTIGATION   **Esophagus**

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

Ken Kato, M.D.,* Kei Muro, M.D.,*[†] Keiko Minashi, M.D.,[‡] Atsushi Ohtsu, M.D.,[‡]
Satoshi Ishikura, M.D.,[§] Narikazu Boku, M.D.,[¶] Hiroya Takiuchi, M.D.,[‖]
Yoshito Komatsu, M.D.,** Yoshinori Miyata, M.D.,[††] and Haruhiko Fukuda, M.D.[§]

Gastrointestinal Oncology Study Group of the Japan Clinical Oncology Group (JCOG)

*Gastrointestinal Oncology Division, National Cancer Center Hospital, Tokyo; [†]Department of Clinical Oncology, Aichi Cancer Center Hospital, Nagoya, Aichi; [‡]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Chiba; [§]Clinical Trials and Practice Support Division, Center for Cancer Control and Information Services, National Cancer Center, Tokyo; [¶]Division of Gastrointestinal Oncology, Shizuoka Cancer Center, Sunto-gun, Shizuoka; [‖]Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Osaka; **Department of Cancer Chemotherapy, Hokkaido University Hospital Cancer Center, Sapporo, Hokkaido; [††]Department of Internal Medicine, Saku Central Hospital, Nagano, Japan

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. © 2011 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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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 × 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
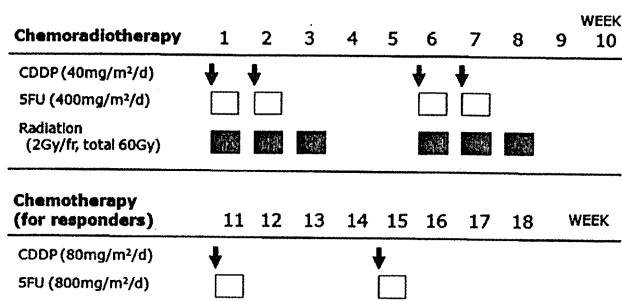

Fig. 1. Protocol scheme.

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.

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-

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

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.

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
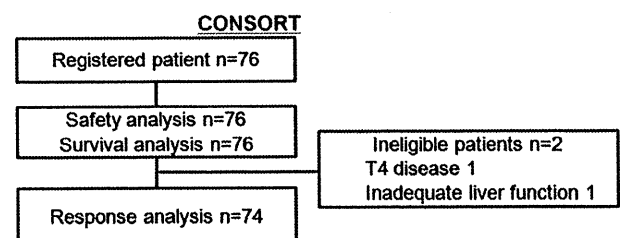

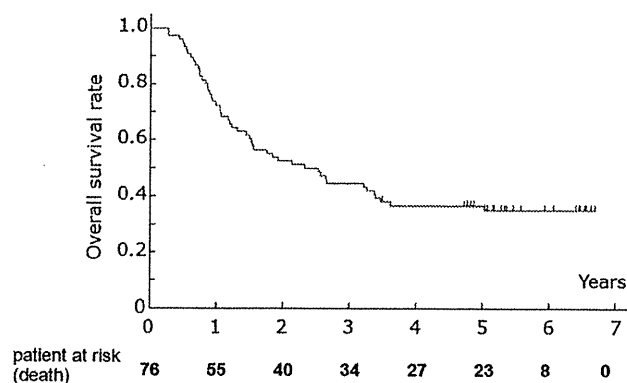Fig. 2. Consolidated Standards of Reporting Trials diagram.

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-
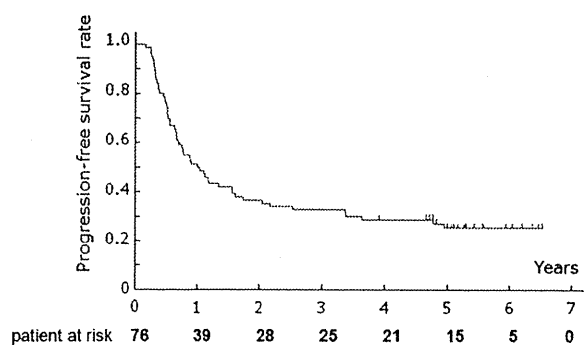

Fig. 4. Progression-free survival rate of the 76 patients enrolled in the study.

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.

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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ORIGINAL ARTICLE: Clinical Endoscopy

Long-term outcome of transoral organ-preserving pharyngeal endoscopic resection for superficial pharyngeal cancer

Manabu Muto, MD, PhD, Hironaga Satake, MD, Tomonori Yano, MD, Keiko Minashi, MD,
Ryuichi Hayashi, MD, Satoshi Fujii, MD, PhD, Atsushi Ochiai, MD, PhD, Atsushi Ohtsu, MD, PhD,
Shuko Morita, MD, Takahiro Horimatsu, MD, Yasumasa Ezoe, MD, Shinichi Miyamoto, MD, PhD,
Ryo Asato, MD, PhD, Ichiro Tateya, MD, PhD, Akihiko Yoshizawa, MD, PhD, Tsutomu Chiba, MD, PhD

Kyoto, Japan

Background: Early detection of pharyngeal cancer has been difficult. We reported that narrow-band imaging (NBI) endoscopy can detect superficial pharyngeal cancer, and these lesions can be treated endoscopically.

Objective: To assess the safety and long-term efficacy of transoral organ-preserving pharyngeal endoscopic resection (TOPER) for superficial pharyngeal cancer.

Design and Setting: Retrospective 2-center cohort study.

Patients: The study included 104 consecutive patients with superficial pharyngeal cancer.

Intervention: TOPER with the patients under general anesthesia.

Main Outcome Measurements: Safety of the procedure, long-term survival, clinical outcome.

Results: A total of 148 consecutive lesions were resected in 104 patients. There was no severe adverse event. Temporary tracheostomy was required in 17 patients (16%) to prevent airway obstruction. The median fasting period and hospital stay after TOPER were 2 days (range 1-20 days) and 8 days (range 3-58 days), respectively. Ninety-six patients (92%) had no local recurrence or distant metastases. Local recurrence at the primary site developed in 6 patients, but all were resolved by repeat TOPER. With a median follow-up period of 43 months (range 3-96 months), the overall survival rate at 5 years was 71% (95% CI, 59-82). Cause-specific survival rate at 5 years was 97% (95% CI, 93-100). The cumulative development rate of multiple cancers in pharyngeal mucosal sites at 5 years was 22% (95% CI, 12-33). The pharynx was preserved in all patients, and they experienced no loss of function.

Limitation: Retrospective design.

Conclusions: Peroral endoscopic resection of superficial pharyngeal cancer is a feasible and effective treatment with curative intent. (Gastrointest Endosc 2011;74:477-84.)

Pharyngeal cancer other than nasopharyngeal cancer (130,000 new cases and 83,000 deaths worldwide in 2002) is predominantly a cancer of men.[1] Smoking and alcoholic beverages are the class I carcinogens for these cancers.[2] Furthermore, acetaldehyde-associated alcoholic beverages were reclassified as a class I carcinogen in 2009 by the International Agency for Research on Cancer.[2]

Current affiliations: Department of Gastroenterology and Hepatology (M.M., S. Morita, T.H., Y.E., S. Miyamoto, A.Y., T.C.), Department of Head and Neck Surgery (I.T., R.A.), Department of Pathology (A.Y.), Kyoto University Graduate School of Medicine, Kyoto, Japan, Division of Gastrointestinal Oncology and Endoscopy (H.S., T.Y., K.M., A. Ohtsu), Division of Head and Neck Surgery (R.H.), Division of Pathology (S.F., A. Ochiai), National Cancer Center Hospital East, Kashiwa, Japan.

Reprint requests: Manabu Muto, MD, PhD, Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, 54 Kawaharacho, Shogoin, Sakyo-ku, Kyoto 606-8507, Japan.