dilator), the wire-guided bougie type (Savary-Gilliard® dilator), and the through-the-scope (TTS) balloon type [12]. Endoscopic balloon dilatation (EBD) using a TTS balloon is a widely accepted procedure because of the low incidence of complications compared with other methods [13].

Several studies have reported on the safety and efficacy of EBD for the treatment of benign anastomotic strictures after esophagectomy. The rate of incidence of perforation was 0.0–0.4 %, with success rates of 83–100 % [12, 14, 15]. In contrast, the perforation rate and efficacy of EBD after nonsurgical treatment such as CRT or EMR has not been clarified. In this study we evaluated retrospectively the safety and efficacy of EBD for benign fibrotic strictures after nonsurgical treatment and compared them to those for strictures after esophagectomy.

Patients and methods

Patients

The subjects were recruited from our database of patients who had undergone treatments for esophageal carcinoma in our hospital, according to the following criteria: (1) histologically confirmed squamous cell carcinoma or adenocarcinoma of the thoracic esophagus; (2) age <85 years; (3) performance status (eastern cooperative oncology group) 0–2; (4) clinical stage I–IVA; (5) adequate organ function; confirmation of cure after treatments such as CRT, EMR, surgery, or their combination, in patients with newly diagnosed esophageal cancer; and (6) both complaint of dysphagia (dysphagia score 2–4) due to benign stricture and the inability to pass an endoscope 11 mm in diameter. We used the dysphasia score published by Knyrim et al. [16]. Dysphagia severity was graded according to a 5-point score: 0, able to consume a normal diet; 1, able to swallow some solid foods; 2, able to swallow only semisolid food; 3, able to swallow liquids only; 4, unable to swallow liquids. Patients with active synchronous carcinoma in other organs were excluded. Furthermore, patients with active ulcers immediately after EMR or patients who were not cured after CRT and patients who underwent preventive EBD were excluded.

The study population was classified into surgery group and nonsurgery group. Nonsurgery group included two subgroups: the CRT group and the EMR group. The CRT group and the surgery group consisted of patients treated with multiple modalities. The CRT group consisted of patients treated with CRT alone and CRT followed by EMR or PDT, and the surgery group consisted of patients treated with surgery alone and CRT followed by surgery.

Initial treatments

Concurrent CRT was performed with 5-fluorouracil (5-FU) plus cisplatin (CDDP) combined with radiotherapy at 10-MV intensity. EMR was performed by the strip biopsy method [17] and ESD was performed with an insulation-tipped (IT) knife (Olympus). Esophagectomy was performed with three-field lymph node dissection.

Endoscopic balloon dilatation

All patients provided informed written consent for the procedure. After intravenous pethidine hydrochloride (25–50 mg) was administered, EBD was performed with a TTS balloon (CRE, Boston Scientific, Natick, MA, USA) under fluorography (Fig. 1). Under endoscopic observation, the balloon size was chosen according to the degree of the stricture. A 15–18 mm diameter or a 12–15 mm diameter balloon was used for moderate strictures (5–10 mm diameter) and severe strictures (<5 mm diameter), respectively. To minimize the risk of perforation due to excess balloon dilation, we instructed the patients to ring a bell if they felt any discomfort during the procedure. After balloon inflation, we confirmed whether the endoscope had passed through the stricture and then looked for any mucosal tears or perforations. Computed tomography (CT) was performed if a deep tear or perforation was suspected after EBD. After the procedure, patients rested in a recovery room for 1 h under nurse observation; they were allowed to go home after they could drink a cup of water. The degree and length of their strictures, balloon size, maximal inflated pressure, ability to pass the endoscope after EBD, and complications were recorded in the endoscopic reports at the individual EBD sessions. The endoscopic reports were used as a reference for the next EBD session.

We routinely used fluoroscopy and contrast (Urografin® 60 %, Bayer Healthcare, Berlin, Germany) inside the balloon to help properly position the balloon and determine whether a complete dilation had been achieved by ablating the waist in the balloon where it crosses the stricture.

EBD was repeated every 2 weeks; however, the interval was adjusted according to the degree of dysphagia or stricture. If the patient was able to eat semisolid foods and little solid foods (dysphagia score 2) and the dysphagia was not worse within 2 weeks, the interval of EBD was prolonged to every 3 or 4 weeks The sessions were repeated until the patient's dysphagia and strictures were resolved.

Analysis and statistics

Complications were evaluated at every EBD procedure. Perforation was defined as a mucosal tear with findings of subcutaneous or mediastinum emphysema diagnosed with

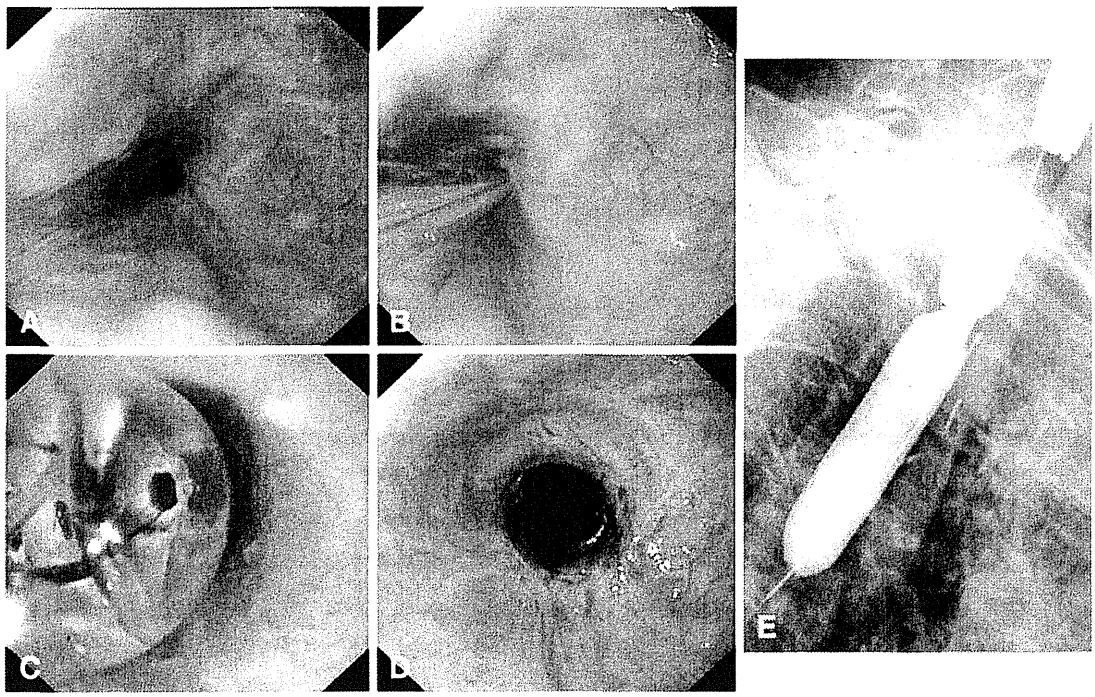

Fig. 1 EBD in patients with esophageal cancer and dysphagia caused by benign stricture. The balloon was inserted through the endoscope. The center of balloon was positioned at the middle of the stricture and carefully inflated with water-soluble contrast medium under fluoroscopic guidance until the stricture disappeared or the patient felt discomfort. **a** Severe stricture more than 20 mm in length after CRT. **b** Insertion of balloon to stricture through the endoscope. **c** Dilating with EBD. **d** The status just after EBD. **e** Confirmation of the position and shape of balloon under fluoroscopy during EBD

CT. Bleeding was defined as that requiring intervention or blood transfusion. The treatment efficacy of EBD was evaluated in patients who were followed up for more than 3 months after the last dilatation, and three indexes were used: treatment success rate, time to treatment success, and refractory stricture rate. Treatment success was defined as satisfying all of the following conditions: (1) the patient's dysphagia was resolved for normal food or some solid food intake (dysphagia score 0 or 1), (2) the endoscope could pass through the stricture, and (3) EBD was not required during the subsequent 3 month period. Time to treatment success was the period from the initial EBD to the last EBD session in those patients evaluated as having successful treatment. A refractory stricture was defined as a stricture for which six or more EBD sessions were required to achieve treatment success or for which successful treatment was not achieved [18].

Fisher's exact test was applied to compare complications, treatment success rates, and refractory rates among groups. Time to treatment success of the three groups was calculated according to the Kaplan–Meier method, and the differences were compared using the log-rank test (SPSS for Windows, SPSS Inc, Chicago, IL, USA). Any death, treatment failure, or introduction of other treatments was considered as the censor data. All information was collected from medical records and provided by the patients' physicians. This retrospective study was approved by institutional review board of the National Cancer Center and was performed in accordance with the Declaration of Helsinki.

Results

Patients' characteristics

Between October 2004 and November 2007, a total of 823 patients at our institution were given definitive treatments for esophageal cancer, consisting of 242 surgeries and 581 with nonsurgical treatment (Fig. 2). One hundred twenty-two patients, 60 who had surgery and 62 who did not have surgery (32 CRT, 30 EMR), were recruited for this study. The incidence rate of benign strictures was 25 % after surgery and 11 % after nonsurgery treatments (11 % for CRT and 12 % for EMR). Tumor length and circumference of the lesion were not different between the groups despite different clinical stages (Table 1). Of the 60 patients who had surgery, 8 (13 %) received salvage surgery after CRT. Fifty-nine percent of patients in the CRT group received complex treatments such as salvage EMR or PDT after

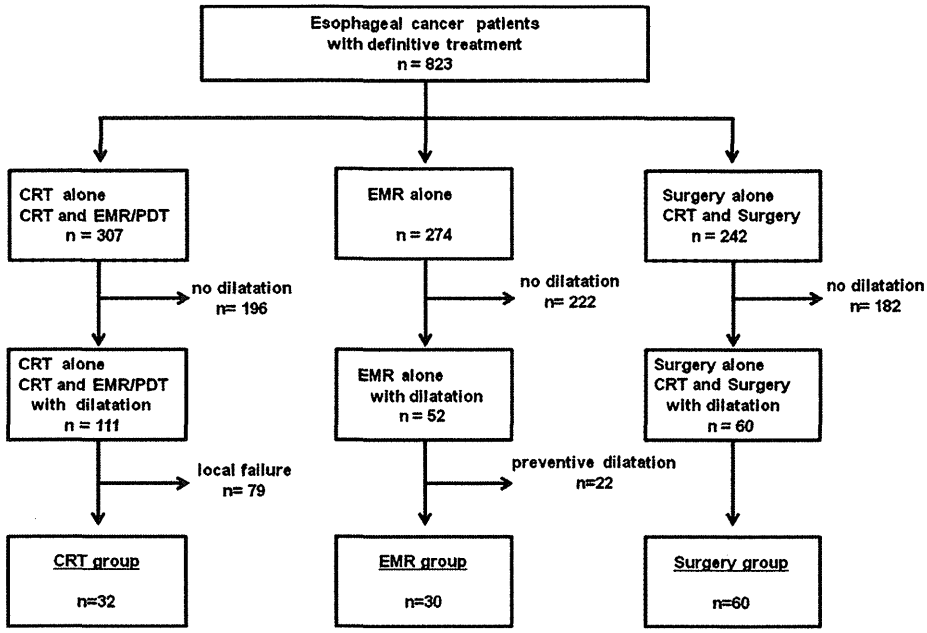

Fig. 2 Selection of patients for this study. Of 307 patients with esophageal cancer treated with CRT, 111 patients were treated with EBD for stricture. Of these 111 patients, 79 patients who had malignant stricture were excluded. In 274 patients treated with EMR, 52 patients were treated with EBD for stricture. Of these 52 patients, 22 who were treated with preventive EBD were excluded. In 242 patients treated with surgery, 60 were treated with EBD

CRT, and the remaining 41 % were treated with CRT alone.

Characteristics of stricture and endoscopic balloon dilatation

As shown in Table 2, the frequencies of severe stricture in the surgery and nonsurgery groups were 18 and 11 % (6 % for CRT and 13 % for EMR), respectively, and there were no significant differences between the groups. In contrast, the frequency of stricture length being more than 20 mm in the surgery and nonsurgery groups was 2 and 42 % (47 % for CRT and 37 % for EMR), respectively, and the difference between the surgery and nonsurgery groups was significant ($p < 0.01$). The nonsurgery group had a larger population with long strictures.

A total of 1,077 sessions of EBD for the 122 patients were evaluated. The median number of EBD sessions per patient was 7 (range 1–32), and the median number of sessions for the surgery group and the nonsurgery group were 5 and 10, respectively.

Treatment efficacy

Treatment efficacy for EBD was evaluated in those patients who were followed up for more than 3 months after the last dilatation, i.e., 110 (90.2 %) of 122 patients (Table 3). The remaining 12 patients were not evaluated because of five had cancer recurrence, one was lost to follow-up, and six died from other causes. Of the 110 patients, 102 (93 %) achieved success with EBD, with the success rate in the surgery and nonsurgery groups 94 and 91 %, respectively. Treatment success rate was over 90 % in both groups, and dysphagia in these patients was resolved such that they had a normal diet or take some solid food.

The nonsurgery group had a significantly larger population with refractory strictures compared with surgery group (75 vs. 45 %, $p < 0.01$). (Table 3). Furthermore, the median time to achieve treatment success in the surgery and nonsurgery groups was 2.3 and 5.6 months, respectively, and the difference between the groups was significant ($p = 0.02$, log rank test) (Table 3 and Fig. 3).

The analysis of the subsets of the nonsurgery group is presented in Table 4. The success rate in the CRT and EMR groups was 93 and 90 %, respectively. The refractory stricture rate in the CRT and EMR groups was 86 and 66 %, respectively ($p = 0.12$). Compared to surgery group, the refractory stricture rate was higher in both subgroups, with the difference significant only in the CRT group ($p < 0.01$). The median time to achieve treatment success in the CRT and EMR groups was 7.0 and 4.4 months, respectively ($p = 0.15$, log rank test). The time to achieve treatment success was significantly longer for the CRT group than for the surgery group ($p = 0.01$, log rank test). In contrast, no significant difference was seen between the EMR and surgery groups ($p = 0.85$, log rank test) with respect to time to treatment success.

To elucidate the difference between the two groups, a subanalysis was performed. The degree and length of stricture, success rate, time to treatment success, and

Table 1 Characteristics of patients with dysphagia caused by benign stricture

	Nonsurgery group		Surgery group ($n = 60$)	Total ($n = 122$)
	CRT group ($n = 32$)	EMR group ($n = 30$)		
Sex				
Men/women	28/4	24/6	51/9	103/19
Age				
Median (range)	64 (48–84)	68 (57–83)	67 (55–83)	65 (48–84)
Baseline clinical TNM stage				
I	9	30	12	51
II	9	0	28	37
III	9	0	19	28
IV-A	5	0	1	6
Length of tumor before treatment (cm)				
<2	0	0	2	2
2 to <4	3	8	14	25
4 to <6	18	15	33	66
6 ≤	11	7	11	29
Circumference of tumor before treatment				
<¼	0	0	4	4
¼ to <½	1	1	6	8
½ to <¾	9	4	16	29
¾ ≤	22	25	34	81
Complex treatment				
Yes	19[a]	–	8[b]	27
No	13	30	52	95

[a] 19 of 32 in the CRT group received salvage EMR and PDT after CRT

[b] 8 of 60 in the surgery group underwent surgery after CRT

refractory stricture rate in the CRT-alone group were compared to findings for the CRT–salvage treatment (CRT followed by EMR or PDT) group. The data showed that there were no significant differences in these parameters between the CRT alone and the CRT–salvage treatment groups.

The median follow-up period for the 110 patients was 12 months, ranging from 3 to over 24 months. Only 9 (8 %) patients had recurrent dysphasia after achieving treatment success and EBD sessions were reintroduced.

Complications

Perforation occurred in 3 of 1,077 sessions (0.3 %), with 2 in one patient in the surgery group (0.5 %) and 1 in one patient in the nonsurgery group (0.1 %). The patient who suffered a perforation during EMR had a severe stricture after circumferential mucosal resection. The patient who suffered perforation in the surgery group had received radical chemoradiation and salvage surgery. All patients with perforations recovered with intravenous administration of antibiotics and fasting for approximately a week, without surgical intervention. There was no case of bleeding that required intervention or blood transfusion.

Table 2 The degree and length of stricture

	Nonsurgery group		Surgery group ($n = 60$)	Total ($n = 122$)
	CRT group ($n = 32$)	EMR group ($n = 30$)		
Degree of stricture[a]				
Moderate	30	26	49	105
Severe	2 (6 %)*	4 (13 %)**	11 (18 %)	17 (14 %)
Length of stricture				
<5 mm	1	3	44	48
5–20 mm	16	16	15	47
20 mm ≤	15 (47 %)***	11 (37 %)****	1 (2 %)	27 (22 %)

[a] Moderate stricture is 5–10 mm and severe stricture is <5 mm in diameter

* $p = 0.13$ (vs. surgery group); ** $p = 0.77$ (vs. surgery group); *** $p < 0.01$(vs. surgery group); **** $p < 0.01$ (vs. surgery group)

Table 3 Efficacy of EBD in surgery and nonsurgery groups

	Nonsurgery group ($n = 57$)	Surgery group ($n = 53$)	Total ($n = 110$)
Success (%)	52 (91 %)	50 (94 %)	102 (93 %)
Median time to treatment success (month)	5.6*	2.3	3.3
Number of EBD sessions			
1	4	10	14
2	2	7	9
3	1	5	6
4	5	4	9
5	2	3	5
6≤	43 (75 %)**	24 (45 %)	67 (61 %)

* $p = 0.02$ (vs. surgery group); ** $p < 0.01$(vs. surgery group)

Discussion

In the present study we examined the safety and efficacy of EBD for benign fibrotic strictures after nonsurgical treatment. Because the efficacy of EBD for benign esophageal strictures after nonsurgical treatment such as CRT or EMR has not been clarified, we evaluated it using treatment

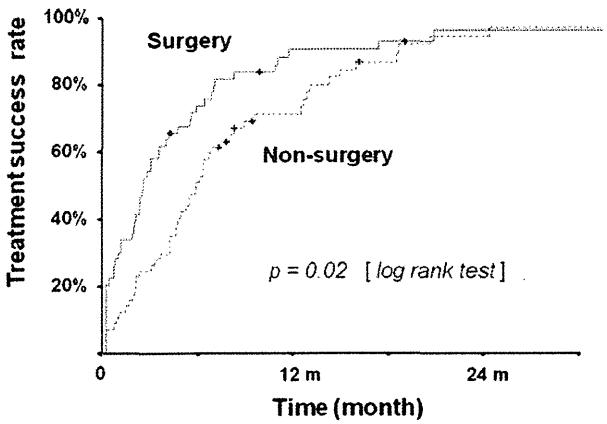

Fig. 3 Time to treatment success from the initiation of EBD in both groups of patients with esophageal cancer and dysphagia caused by benign stricture. *Red line* is surgery group and *blue line* is nonsurgery group

Table 4 Efficacy of EBD in subgroups of nonsurgery group

	CRT group ($n = 28$)	EMR group ($n = 29$)	p Value
Success (%)	26 (93 %)	26 (90 %)	1.0
Median time to treatment success (months)	7.0*	4.4***	0.15
Number of EBD sessions			
1	–	4	
2	1	1	
3	–	1	
4	2	3	
5	1	1	
6≤	24 (86 %)**	19 (66 %)****	0.12

* $p = 0.01$ (vs. surgery group); ** $p < 0.01$(vs. surgery group); *** $p = 0.85$ (vs. surgery group); **** $p = 0.10$ (vs. surgery group)

success rate, time to treatment success, and refractory stricture rate indexes. The strictures in nonsurgery patients were more often refractory and required many EBD sessions for resolution compared to those of the surgery group, while the success rate was equivalent between the surgery and nonsurgery groups. As like complications, the perforation rate was low and acceptable in both groups.

In regard to the efficacy of EBD, the success rate of dilatation in treating anastomotic strictures has been reported to be 77–97 %, with recurrence rates of 30–51 % [19–21]. In contrast, the success rate of dilatation for benign strictures caused by radiotherapy has been reported to be 58–100 %, with recurrence rates of 46–100 % [20–22]. This suggests that many patients will maintain patency only short term and will require additional dilatation. In the present study, the success rate was 93 %, with only subtle differences among the three groups, and the recurrence rate was 8 % in all patients. Treatment efficacy and recurrence rate were relatively better than those of previous reports. However, our study has some limitations that should be discussed. This is a retrospective study at a single institution, and the follow-up period (median = 12 months, range = 3–24 months) is not long enough. We defined success rate as when EBD was not required during the subsequent 3 month period and the dysphagia score was 0–1. However, it was not known whether 3 months was an adequate period to evaluate success. It cannot be denied that these limitations overestimate the success and recurrence rates of this study.

Nonsurgery groups required a longer period and a greater number of EBD sessions to achieve treatment success. In the surgery group, 42 % of patients could achieve treatment success with three or fewer sessions of EBD, whereas 21 % in the EMR group and only 4 % in the CRT group showed similar results. The refractory stricture rate was significantly higher in the CRT group and tended to be higher in the EMR group compared with the surgery group. A possible reason for the high refractory rate in the CRT group is that the CRT radiation field is usually wide to cover both the primary tumor and locoregional lymph nodes. This radiation can cause acute and chronic lumen toxicity that can lead to severe fibrosis of the esophagus [23]. Therefore, strictures after CRT can be longer and tighter. In fact, the frequency of long strictures (>20 mm) was greater in the CRT group than in the surgery group. Because our study was retrospective and conducted at a single center, inevitable biases cannot be ruled out. However, this is the first report giving a detailed examination of esophageal benign strictures after nonsurgical treatment for esophageal cancer.

The necessity of fluoroscopy guidance during EBD is still controversial. Fluoroscopy guidance is advocated when EBD is performed for strictures through which an endoscope cannot be passed. In contrast, several studies have reported that EBD without fluoroscopy is safe for benign strictures [19, 21]. However, according to American Society for Gastrointestinal Endoscopy (ASGE) guidelines, fluoroscopy is recommended when using non-wire-guided dilators during dilatation of complex esophageal strictures or in patients with a tortuous esophagus [24]. In the present study, all EBD sessions used a TTS balloon under fluoroscopy guidance according to ASGE guidelines. We believe that fluoroscopy had some advantage with respect to safety and efficacy, especially for complex strictures. It is difficult to keep the balloon properly positioned and to confirm the degree of the stricture during procedure without fluoroscopy. The operator can carefully adjust the balloon position and confirm the achievement of complete dilation when using fluoroscopy guidance.

If the stricture cannot be dilated with EBD to an adequate diameter and it recurs within a short time interval, alternative treatment modalities such as incision therapy, stent placement, or revisional surgery should be considered. Kim et al. [25] reported that the patency rate 3 months after temporary stenting was 42 % in 55 patients with refractory benign esophageal stricture. We believe that the results of the present study might help in making the decision to introduce other modalities for benign refractory stricture.

In conclusion, EBD sessions under fluoroscopy guidance were safe and effective for esophageal benign strictures regardless of previous treatments for esophageal cancer. Although strictures caused by CRT and EMR were more refractory than those caused by surgery, all resolved with a high success rate. However, patients with fibrotic strictures after nonsurgical treatment required significantly longer periods of repeated EBD treatments to achieve recovery from dysphagia compared with the patients with anastomotic strictures after surgery.

Disclosure Y. Yoda, T. Yano, K. Kaneko, S. Tsuruta, Y. Oono, T. Kojima, K. Minashi, H. Ikematsu, and A. Ohtsu have no conflicts of interest or financial ties to disclose.

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Photodynamic therapy as salvage treatment for local failure after chemoradiotherapy in patients with esophageal squamous cell carcinoma: A phase II study

Tomonori Yano[1], Manabu Muto[2], Keiko Minashi[1], Junko Iwasaki[1], Takashi Kojima[1], Nozomu Fuse[1], Toshihiko Doi[1], Kazuhiro Kaneko[1] and Atsushi Ohtsu[1]

[1] Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, Japan
[2] Department of Gastroenterology and Hepatology, Kyoto University Graduate School of Medicine, Kyoto, Japan

Local failure at the primary site is a major problem after chemoradiotherapy (CRT) in patients with esophageal squamous cell carcinoma (ESCC). Salvage surgery is the only treatment option with curative intent, but it is associated with high morbidity and mortality. The aim of this study was to evaluate the efficacy and safety of salvage photodynamic therapy (PDT) after CRT. Patients with histologically proven local failure limited to the submucosal layer, and without any metastasis after definitive CRT (≥50 Gy) for ESCC were enrolled in the study. PDT began with intravenous administration of 2 mg/kg of porfimer sodium followed 48–72 hr later by excimer dye laser irradiation with a fluence of 75 J/cm^2. The primary endpoint was a complete response (CR) to treatment with PDT, and the secondary endpoints were toxicity related to PDT, progression-free survival (PFS) and overall survival (OS). Twenty-five patients were enrolled in the study. A CR was attained in 19 of 25 patients treated with PDT (CR rate, 76%; 95% CI, 55–91%). One treatment-related death (4%) caused by gastrointestinal hemorrhage at the irradiated site occurred 33 days after PDT. No adverse events greater than grade 3 were related to PDT in the other patients. After a median follow-up of 48 months after PDT, the PFS and OS at 3 years were 40% (95% CI, 21–59%) and 38% (95% CI, 17–60%), respectively. PDT is a potentially curative and tolerable salvage treatment after CRT for carefully selected patients with local failure without any metastasis.

Chemoradiotherapy (CRT) is a curative treatment option for esophageal squamous cell carcinoma (ESCC). However, local failure without distant metastasis after completion of CRT remains a major problem that must be overcome to achieve a cure. Although salvage esophagectomy is now indicated for such patients, it has a higher morbidity and mortality compared with primary or planned esophagectomy.[1–4] The development of curative and safe salvage treatment options for local failure is needed to improve the survival of patients treated with CRT.

Key words: esophageal squamous cell carcinoma, chemoradiotherapy, photodynamic therapy, salvage treatment

Abbreviations: CR: complete response; CRT: chemoradiotherapy; EMR: endoscopic mucosal resection; ESCC: esophageal squamous cell carcinoma; NCI-CTCAE: National Cancer Institute Common Terminology Criteria for Adverse Events; NSAIDs: non-steroidal anti-inflammatory drugs; OS: overall survival; PDT: photodynamic therapy; PFS: progression-free survival; UMIN: University hospital Medical Information Network

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Correspondence to: Tomonori Yano, Department of Gastroenterology and Gastrointestinal Oncology, National Cancer Center Hospital East 6-5-1, Kashiwanoha, Kashiwa 277-8577 Japan, Tel.: +81-4-7133-1111, Fax: +81-4-7131-4724, E-mail: toyano@east.ncc.go.jp

After completion of CRT, a subset of ESCC patients develops local failure at the primary site without distant metastasis. In such patients, salvage surgery could be a curative treatment option, especially for those with T2 or earlier T-stage tumors or for those without lymph node metastasis.[1,2] Onozawa *et al.* reported that regional nodal failure within the field of elective lymph node irradiation is rare in patients achieving a complete response (CR) after CRT (1%; 95% CI, 0.0–5.3%).[5] These data have encouraged the use of local salvage treatment at only the primary site as a minimally invasive treatment in carefully selected patients.

We reported previously on the potentially acceptable results of endoscopic mucosal resection (EMR) or photodynamic therapy (PDT) as a salvage treatment for local failure after CRT.[6–8] PDT is a more deeply penetrating method than EMR for esophageal cancer even in the salvage setting, because, in our experience, PDT can cure patients with deep invasion of the submucosal layer or T2 local failure. In addition, PDT can be indicated both as a curative treatment for superficial esophageal cancer[9,10] and as a palliative treatment to relieve dysphagia caused by stenosis in more advanced esophageal cancer.[11] We believe that PDT might be a curative and effective treatment option for patients with local failure at the primary site after definitive CRT. We conducted a prospective study to evaluate the efficacy and safety of salvage PDT after CRT.

Material and Methods

This was a single-arm, open-label, single-center phase II study. The primary endpoint of this study was the CR rate at the primary site after PDT. The secondary endpoints were toxicity related to salvage PDT, progression-free survival (PFS) and overall survival (OS). All adverse events were evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 3.0.[12] The study protocol was approved by the institutional review board of the Japanese National Cancer Center in January 2005. The study was carried out according to the ethical principles of the Declaration of Helsinki. Before enrollment, all patients provided written informed consent. This study was registered with the University hospital Medical Information Network (UMIN) Clinical Trials Registry, and the identification number is C000000244.

Eligibility and exclusion criteria

The eligibility criteria of this study were as follows: (*i*) local failure after definitive CRT (≥50 Gy) for ESCC; (*ii*) the patient's refusal to undergo salvage surgery; (*iii*) histologically proven squamous cell carcinoma by biopsy specimen of the local failed lesions; (*iv*) local failed lesions limited to the submucosal layer; (*v*) EMR not indicated for reasons of concomitant deep ulceration, severe fibrosis caused by radiation or a lesion invading to the deep submucosal layer; (*vi*) Eastern Cooperative Oncology Group performance status ≤2; (*vii*) adequate bone marrow function (white blood cell count ≥2,000/mm,^{3} platelet count ≥75,000/mm^3), renal function (serum creatinine level ≤2.0 mg/dL) and liver function (serum bilirubin level <2.0 mg/dL, both alanine aminotransferase and aspartate aminotransferase <100 IU/L) and (*viii*) provision of written informed consent. The exclusion criteria were as follows: (*i*) active malignancy other than early gastrointestinal cancer that was curable with endoscopic treatment within 1 year; (*ii*) systemic infection requiring antibiotics; (*iii*) significant cardiovascular disease (uncontrolled hypertension, myocardial infarction, unstable angina, congestive heart failure), uncontrolled diabetes mellitus, or liver cirrhosis; (*vi*) baseline stage T4 before CRT; (*v*) presence of lymph node or distant metastasis confirmed by computed tomography (CT) after CRT and (*vi*) known porphyria.

Evaluation of baseline clinical stage and the effect of CRT

Baseline clinical stage was determined using the TNM classification of the International Union Against Cancer.[13] Clinical T stage was evaluated by endoscopy, endoscopic ultrasound (EUS) and CT of the chest. Clinical N and M stages were evaluated by EUS and CT of the neck, chest and abdomen. In this study, lymph node metastasis was diagnosed clinically if the lymph node was ≥10 mm in diameter on CT. After completion of CRT, all patients were followed-up with both endoscopy and CT at 1, 3, 6, 9 and 12 months, and then every 4 months after completing CRT.

Evaluation of the local failure at the primary site after CRT

Before PDT, the depth of all failure lesions was evaluated using EUS (EU-M2000, Olympus Co. Ltd., Tokyo, Japan). We carefully observed the lesions with a high-frequency (20 MHz) miniature probe. When we detected a hetero-echoic solid component in the submucosal layer, we diagnosed it as a local failure lesion.

PDT treatment and surveillance

All PDTs were performed as inpatient procedures. PDT began with intravenous administration of 2 mg/kg of porfimer sodium (Photofrin, Pfizer Japan Inc.) followed by excimer dye laser irradiation. Porfimer sodium was reconstituted as a 2.5 mg/mL solution in 5% glucose. It was injected within 5 min, and the injection rate was less than 12 mL/min. A 630 nm wavelength laser beam was emitted by an excimer dye laser (EDL-1, Hamamatsu Photonics, Hamamatsu, Japan), and the laser light was delivered *via* a microlens- tip fiber, without any balloon or light diffuser, through the operative channel of the scope. An attachment was fitted to the tip of the scope to keep it facing the lesion and to maintain the distance between the tip of microlens fiber and the surface of the lesion during the procedure. The laser treatment was performed 48 hr after the injection of porfimer sodium. The fluence was 75 J/cm^2, with a fluence rate of 160 mW/cm^2 (4 mJ/pulse, 40 Hz pulse frequency). If the lesions were larger than 1 cm^2, multiple treatment fields were overlapped to cover the entire lesion. If the effect (*e.g.*, ischemic change of mucosa) after the laser treatment change, as evaluated by endoscopic observation was insufficient, additional laser irradiation was performed at a second session, 72 hr after the injection.[8,14,15]

All patients were instructed to avoid direct exposure to sunlight for 1 month after the injection of porfimer sodium to protect them from the adverse effects of skin photosensitization. Patients were discharged 2 weeks after laser irradiation, if there were no complications related to PDT. Adverse events were identified through a physical examination and endoscopic evaluation performed every 2 weeks until 2 months after PDT. One month after PDT, patients were assessed through a physical examination, measurement of haematological and biochemical variables in blood and endoscopic examination. The endoscopic examination with biopsy was repeated at least every month thereafter to evaluate the response and luminal toxicity of PDT until the response was confirmed. CT was used to evaluate distant organ or lymph node metastasis every 3 months for the first 2 years and every 6 months thereafter.

Statistical analysis

The primary endpoint of this study was the CR rate with salvage PDT. The sample size was determined assuming a binomial distribution. A threshold CR rate was considered to be 30%, and a CR rate of 60% was considered to be of potential interest. The planned accrual was calculated as 25 patients

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 ≥ 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

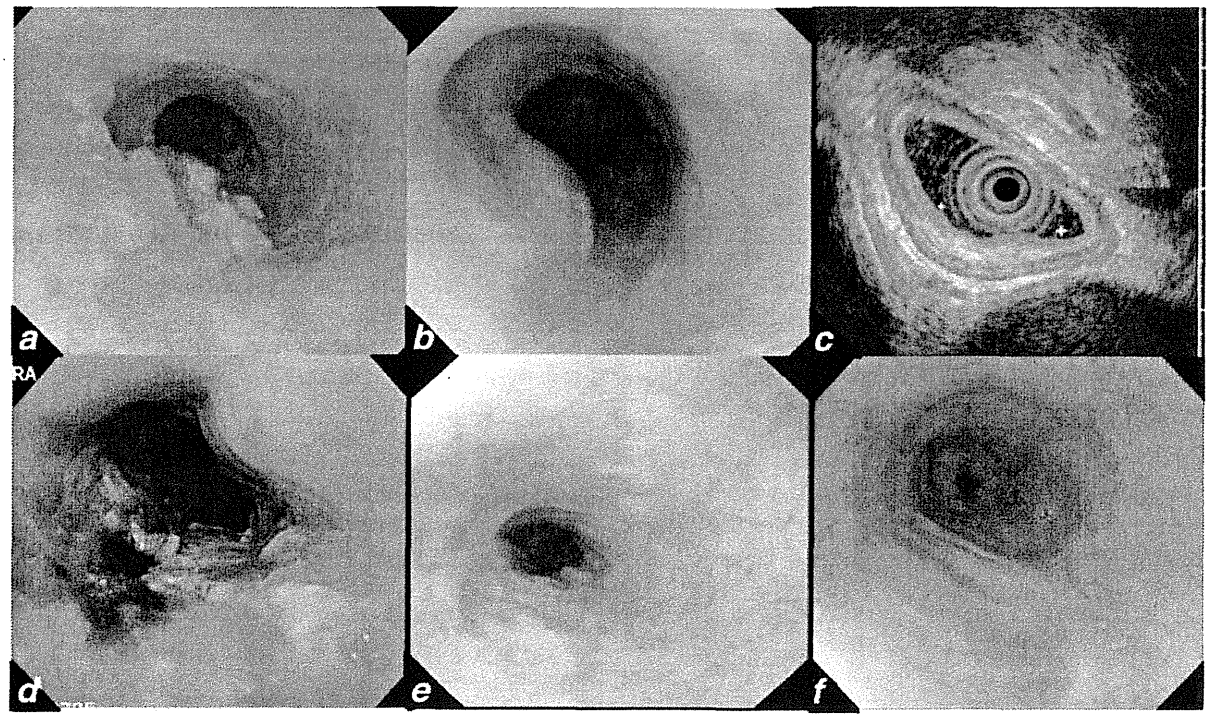

Figure 1. A patient who achieved a complete response (CR) with salvage photodynamic therapy (PDT) is presented. (*a*) Before chemoradiotherapy (CRT), the baseline stage was T2N0M0. (*b*) A local residual lesion was detected at the primary site after CRT. (*c*) The residual lesion was limited to the submucosal 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.

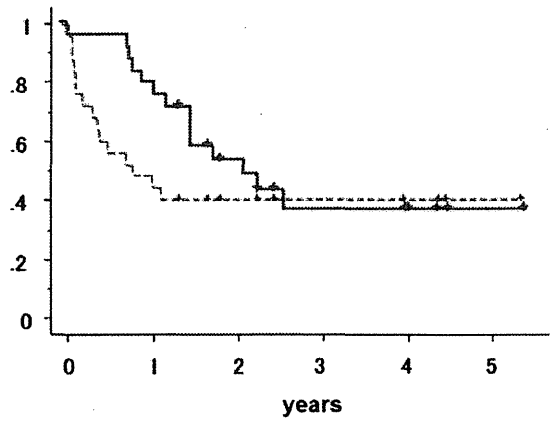

Figure 2. Progression-free survival (red dotted line) and overall survival (blue line) of 25 patients after the initiation of salvage photodynamic therapy (PDT).

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,

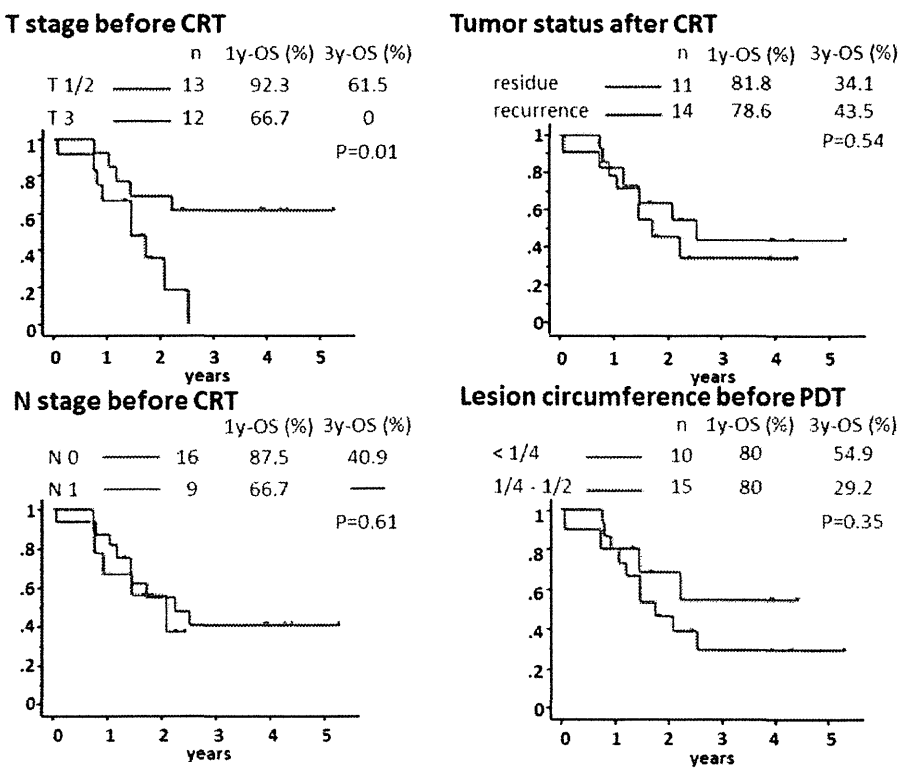

Figure 3. Comparisons of overall survival according to various clinical variables before chemoradiotherapy and before photodynamic therapy.

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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