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

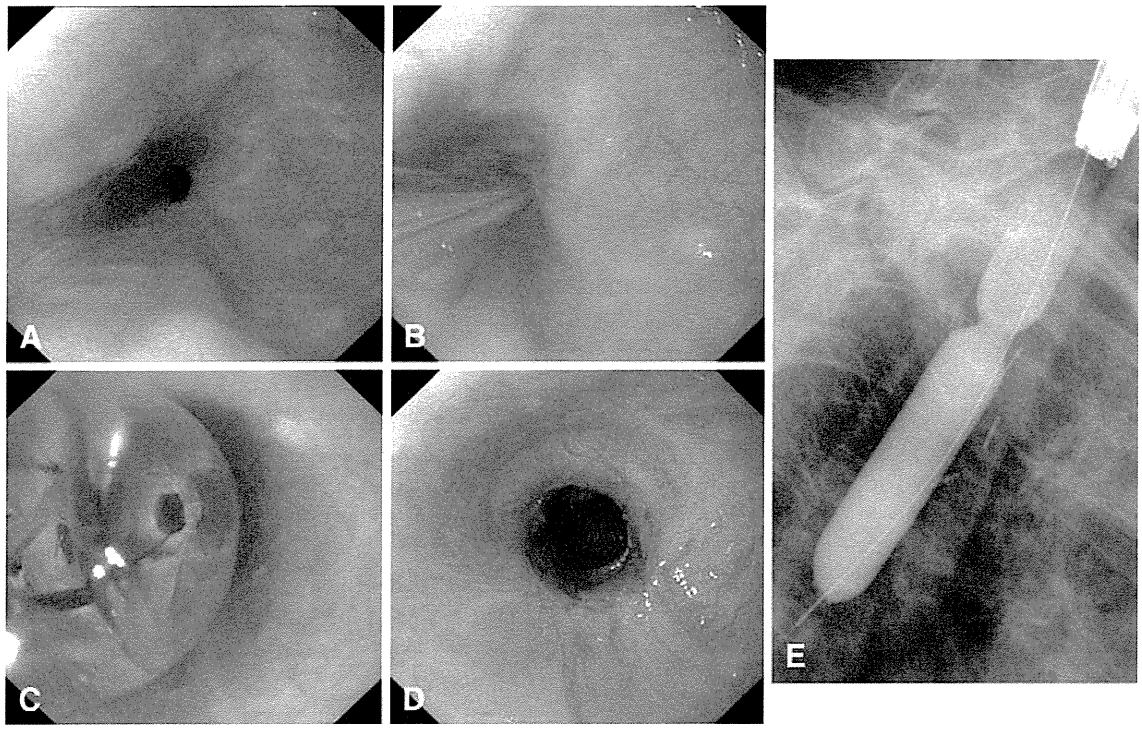

Fig. 1 EBD in patients with esophageal cancer and dysphagia caused by benign stricture. The balloon was inserted through the endoscope. The center of balloon was positioned at the middle of the stricture and carefully inflated with water-soluble contrast medium under fluoroscopic guidance until the stricture 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

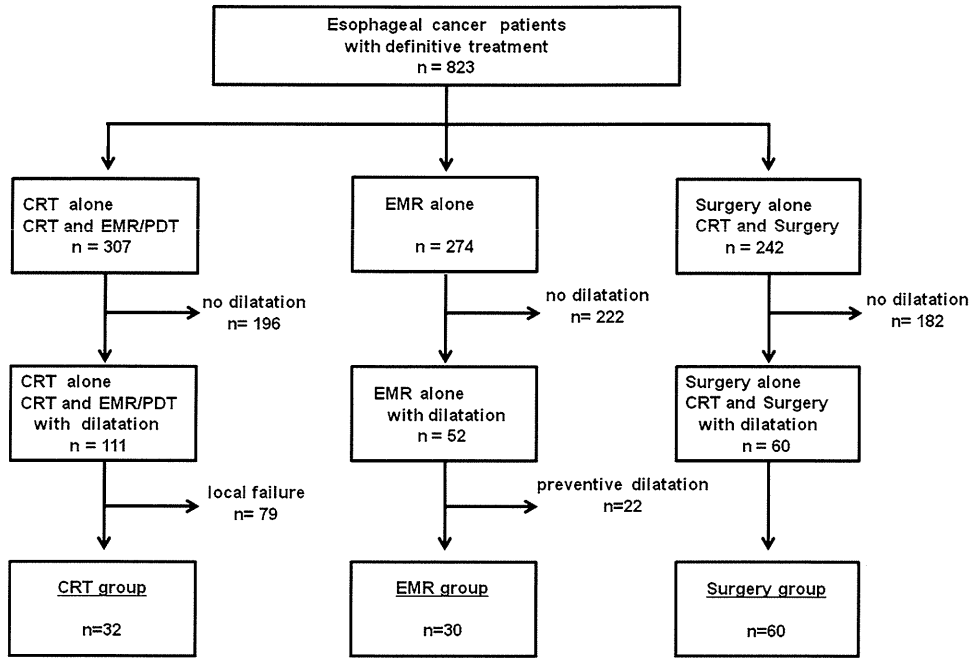

Fig. 2 Selection of patients for this study. Of 307 patients with esophageal cancer treated with CRT, 111 patients were treated with EBD for stricture. Of these 111 patients, 79 patients who had malignant stricture were excluded. In 274 patients treated with EMR, 52 patients were treated with EBD for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

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)

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.

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

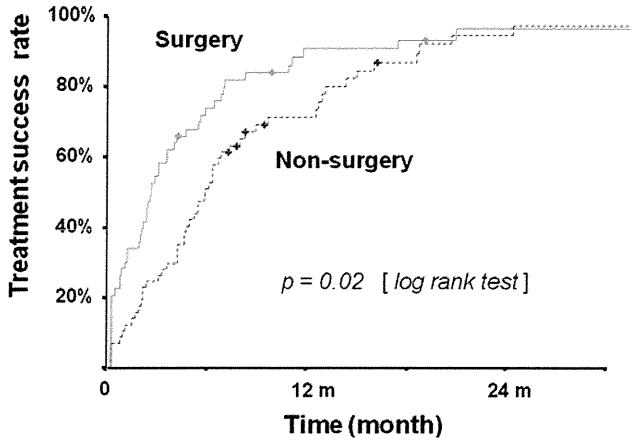

Fig. 3 Time to treatment success from the initiation of EBD in both groups of patients with esophageal cancer and dysphagia caused by benign stricture. *Red line* is surgery group and *blue line* is nonsurgery group

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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