Review of early endoscopic findings in patients with local recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma

Yoichi Yamamoto[1,2], Tomohiro Kadota[1], Yusuke Yoda[1], Keisuke Hori[1], Ken Hatogai[3], Takashi Kojima[3], Satoshi Fujii[4], Tetsuo Akimoto[2,5], Tomonori Yano[1]

[1]Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan.

[2]Course of Advanced Clinical Research of Cancer, Juntendo University Graduate School of Medicine, Tokyo, Japan

[3]Department of Gastroenterology and Oncology, National Cancer Center Hospital East, Kashiwa, Japan.

[4]Division of Pathology, Exploratory Oncology Research & Clinical Trial Center, National Cancer Center, Kashiwa, Japan

[5]Department of Radiation Oncology, National Cancer Center Hospital East, Kashiwa, Japan

Corresponding author: Tomohiro Kadota, M.D. Ph.D.

Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, 6-5-1, Kashiwanoha, Kashiwa, Chiba 277-8577, Japan

E-mail: tkadota@east.ncc.go.jp

Phone: +81-4-7133-1111

Fax: +81-7134-6865

Abstract

Backgrounds: Local recurrence after definitive chemoradiotherapy, if diagnosed early, can be cured by salvage endoscopic therapy, which allows organ preservation and contributes to maintaining patient quality of life. This study aimed to investigate early endoscopic findings of local recurrence in post-definitive chemoradiotherapy patients.

Methods: Between January 2008 and June 2012, 17 esophageal squamous cell carcinoma patients with no metastasis but local recurrence after definitive chemoradiotherapy were enrolled. We attempted to find endoscopic hallmarks suggestive of local recurrence by comparing pre- and post-local recurrence diagnostic images. The influence of follow-up schedule on chosen salvage therapy type was also investigated.

Results: Endoscopic local recurrence findings included eight submucosal tumors, five ulcers, and four erosions. Upon review of prior images, findings suggestive of local recurrence were detected in seven patients, including six submucosal tumors and one erosion, all of which were smaller than 10 mm. These lesions had changed morphologically at local recurrence diagnosis: three submucosal tumors had become larger and three submucosal tumors and one erosion had changed to ulcers. Of 12 patients with cT1 at local recurrence, four (33%) underwent follow-up endoscopy within 1 month of local recurrence findings and

11 patients (92%) were treated with salvage endoscopic therapy.

Conclusions: Endoscopists should be aware that SMTs or erosions, even those smaller than 10 mm, can indicate local recurrence after complete response to definitive chemoradiotherapy. Follow-up endoscopy should be performed within 1–2 months if findings suggestive of local recurrence are observed on prior endoscopy, even when biopsy results are negative.

Key words: Chemoradiotherapy; Esophageal squamous cell carcinoma (ESCC); Endoscopic therapy

Introduction

Definitive chemoradiotherapy (dCRT) is widely accepted as a standard treatment for unresectable esophageal squamous cell carcinoma (ESCC). Some of the advantages of dCRT are organ preservation (in the form of marginal efficacy) and high complete response (CR) rates (60–80%) [1, 2]. However, local recurrence (LR) often occurs after CR (10–20%) [3, 4]. Salvage esophagectomy is recommended for patients with these LRs, and the reported 3-year survival rates are about 30–40% [5, 6]. However, salvage esophagectomy is a highly invasive treatment with high rates of complications and postoperative mortality (10–15%), and the quality of life is low in patients due to organ loss [6-9].

Recently, endoscopic therapies, including endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), and photodynamic therapy (PDT), have been reported as less invasive and effective salvage treatments for a select group of patients with LR limited to T1 or T2 depth invasion [10-14]. Moreover, salvage endoscopic therapy is associated with good long-term survival results following the achievement of CR after PDT or curative resection after EMR/ESD due to organ preservation [15-19]. However, indications for endoscopic salvage therapy are often limited, and in general, LR lesions at the primary tumor site expand rapidly [20]. Therefore, careful follow-up evaluation using

endoscopy is very important for patients after dCRT so that the onset of salvage endoscopic therapy, if required, is not delayed.

In a previous study, Tu et al. reported that the endoscopic findings of histologically confirmed LR after dCRT include the appearance of submucosal tumors (SMTs), flat erosions, and SMTs with superficial ulcers [21]. Although endoscopic follow-up was performed focusing on these findings, some lesions were detected as advanced recurrence lesions. These lesions were not suitable for salvage endoscopic therapy because endoscopy was not performed earlier because biopsy results were negative. To detect LR within the timeframe that allows salvage endoscopic therapy, early endoscopic diagnosis of LR should be made, even in the absence of histological confirmation.

The aim of the present retrospective study was to investigate the early endoscopic findings of LR in patients who achieved CR following dCRT for ESCC, but later developed histologically-confirmed LR.

Materials and Methods

Patients

Patients with pathologically diagnosed ESCC who underwent dCRT as an initial treatment

at the National Cancer Center Hospital East between January 2008 and June 2012 were enrolled in this study. The inclusion criteria were as follows: (i) clinical stage I–III or stage IV because of metastasis in nonregional lymph node before dCRT and (ii) development of local recurrence without lymph node and distant metastasis after achieving CR with dCRT. Patients who did not undergo any endoscopic evaluation or who had not been followed-up with endoscopy for 6 months or a longer period after achieving CR were excluded.

Clinical staging before dCRT was in accordance with the 6th Union for International Cancer Control-Tumor-Node-Metastasis classification [22] using endoscopy and contrast-enhanced computed tomography (CT) scans of the neck, chest, and abdomen. Positron emission tomography, contrast barium esophagography, and endoscopic ultrasound were carried out as necessary.

Follow-up examination

At 1–2 months post dCRT, the primary lesion was monitored by endoscopy at 4-week intervals. CR at the primary site was considered only when all the following criteria were met [23]: (i) disappearance of the tumor lesion, (ii) disappearance of the ulcer, and (iii) negative biopsy results.

Follow-up endoscopy was initially scheduled after 1 month of achieving CR. Subsequently, follow-up endoscopy for LR detection was scheduled at 2–3-month and 4–6-month intervals for the first and second or more years, respectively. LR at the primary site was defined when all the following criteria were met: (i) newly developed lesions such as SMTs, erosions, ulcers, or any other tumor findings were detected at the primary lesion site (Fig. 1) and (ii) histologically-proven viable cancer cells at the primary site on biopsy.

Study design

In this study, all consecutive endoscopic images of the primary tumor taken between the time of CR and LR were retrospectively compared. Early endoscopic findings of LR were defined as abnormal endoscopic findings suggestive of LR detected on pre-LR images at the primary tumor site existed before dCRT. These findings were confirmed by three endoscopists (YYA, TK, and TY). Subsequently, the different types of salvage therapy used to treat the LR based on these endoscopic findings were investigated.

Indication criteria for salvage therapy

The salvage therapy for LR includes endoscopic therapy (EMR, ESD, or PDT), surgery,

and palliative therapy (chemotherapy or best supportive care). The choice of the therapy was based on the criteria mentioned below. In addition, patients' physical status and requests were taken into consideration in determining an appropriate salvage therapy.

In cases of no lymph-node or distant metastasis, salvage therapy was indicated according to invasion depth and size of the LR. The indication criteria for salvage EMR/ESD were as follows [12, 16]: (1) invasion depth limited to the submucosal layer on endoscopic findings and (2) the lesion did not have deep ulceration. The indication criteria for salvage PDT were as follows [13, 14, 20]: (1) invasion depth limited to within the shallow muscle layer on endoscopic findings, (2) no indication for salvage EMR/ESD (ulceration or fibrosis caused by radiation, invasion depth, size, or circumference), (3) circumference of lesion less than three-quarters of the esophagus, and (4) patient refusal to undergo salvage surgery or physical condition not suitable for surgery. The other cases with resectable LR were recommended for salvage surgery.

Moreover, resectable cases of lymph node metastasis were also considered suitable for salvage surgery. The unresectable cases, including simultaneous distant metastasis patients, were treated with systemic chemotherapy or optimal supportive care.

Ethical considerations

This study was a retrospective study at a single institution and the protocol was approved by the institutional review board of the National Cancer Center in May 2018 (2018-052). This study was performed in accordance with the ethical standards of the World Medical Association Declaration of Helsinki. All data were collected from medical records.

Results

Patients and clinicopathological characteristics

During this study period, 182 patients with ESCC underwent dCRT (Fig. 2). Of those patients, 95 achieved CR and the remaining 87 patients did not achieve CR post-dCRT. In total, 14 of 95 patients were excluded because they did not undergo any follow-up endoscopy or had not been followed-up with endoscopy for 6 months or a longer period. Among 81 patients, 42 patients developed recurrence, and 17 patients who had LR without metastasis were enrolled in this study.

The characteristics of 17 patients who had LR are shown in Table 1. Among these patients, 16 were male and one was female, and the median age was 66 years (range: 55–81 years). Regarding the clinical T stage before dCRT, four patients had cT1, 12 had cT3, and one had

cT4. Nine patients received 50.4 Gy irradiation and the other eight patients received 60.0 Gy irradiation. All patients received a 5-fluorouracil (5-FU)-based regimen in the dCRT procedure. The median duration from starting dCRT to achieving CR was 3 months (range: 2–9 months).

Endoscopic findings at LR

The characteristics of the lesions are shown in Table 2. Post LR diagnosis, the endoscopic findings revealed SMTs in eight lesions (47%), ulcers in five lesions (29%), and erosions in four lesions (24%). The median duration from achieving CR to the detection of the LR was 6 months (range: 1–54 months).

In eight lesions with endoscopic findings indicating SMTs, the median size was 10 mm (range: 5–20 mm) and invasion depth was cT1b in six lesions and cT2 or deeper in two lesions. In five lesions with endoscopic findings indicating ulcers, the median size was 15 mm (range: 15–25 mm) and the invasion depth was cT1b in two lesions and cT2 or deeper in three lesions. In four lesions with endoscopic findings indicating erosions, the median size was 15 mm (range: 6–20 mm) and the invasion depth was cT1a in all four lesions.

The median interval from the previous follow-up endoscopy to the detection of LR was 3

months (range: 1–14 months) (Table 3). In patients with SMTs, the median endoscopy intervals of patients with cT1b and patients with cT2 or deeper were 3 months (range: 1–5 months) and 4 months (range: 3–5 months), respectively. In patients with ulcers, the median endoscopy intervals of patients with cT1b and patients with cT2 or deeper were 3.5 months (range: 1–6 months) and 4 months (range: 3–6 months), respectively. In patients with erosions, the median endoscopy interval of patients with cT1a was 3 months (range: 1–14 months).

Early endoscopic findings before LR

A review of the endoscopic images taken prior to LR diagnosis in 17 patients revealed that early endoscopic findings suggestive of LR could be detected in seven patients (41%) on pre-LR images (Fig. 3). These detections included SMTs in six lesions and erosion in one lesion.

In six lesions with SMT and cT1b, only three lesions showed early endoscopic findings of LR. There findings were smaller SMTs (median size: 5 mm, range: 3–7 mm). In two lesions with SMTs and cT2 or deeper, early endoscopic findings of LR could not be detected. In two lesions with ulcers and cT1b invasion depth, early endoscopic findings of LR was detected only in one lesion (SMT: 7 mm). In all three lesions with ulcers and cT2 or deeper, early

endoscopic findings of LR could be detected. There findings were SMTs in two lesions and erosion in one lesion (median size: 5 mm, range: 3–5 mm). In four lesions with erosions and cT1a, early endoscopic findings of LR were not detected. Additionally, early endoscopic findings of LR were identified in three of eight patients (38%) with SMTs and four of five patients (80%) with ulcers.

Following salvage therapy for LR

Of the 17 patients with LR, 11 patients (65%) were treated with salvage endoscopic therapy (six with EMR/ESD and five with PDT). Five patients (29%) were treated with surgery and the remaining one patient (6%) underwent palliative therapy (Table 3). Based on endoscopic findings, five of eight (63%) patients with SMTs, two of five (40%) with ulcers, and four of four (100%) with erosions underwent salvage endoscopic therapy. Moreover, based on the clinical T stage characterization, 11 of 12 patients with cT1 were treated with salvage endoscopic therapy and no patients with cT2 or deeper were treated with salvage endoscopic therapy.

No complications were detected post-salvage surgery. Moreover, no patients required re-operation and there were no post-operative deaths (Supplementary Tables 1 & 2). An

anatomic leakage did occur in one patient, which was addressed with antibiotic treatment and dietary management.

No perforations, bleeding, death, or other complications related to salvage endoscopic therapy occurred. Esophageal stricture occurred in one patient treated with PDT, which was addressed with repeated endoscopic balloon dilatation.

Discussion

LR after dCRT in patients with ESCC is a major medical issue. However, if LR is diagnosed at an early T stage (T1–2), patients have a good chance of being cured with organ preservation using salvage endoscopic therapy. This study showed that it is important to acknowledge that SMTs and erosions at the primary site, including lesions smaller than 10 mm, may be early signs of LR. It is particularly important to monitor lesions endoscopically, and to perform post dCRT follow-up endoscopy within a short interval (1–2 months), if findings suggestive of LR are observed on prior endoscopy, even when biopsy results are negative.

Our findings suggest that salvage endoscopic therapy is used less frequently in patients with ulcers (40%) as compared to those with SMTs (63%) or erosions (100%). Furthermore, small SMTs and erosions appear to be early findings of ulceration. In addition, the size of SMTs or

erosions at LR diagnosis was usually larger than 10 mm (five of eight patients with SMTs and three of four patients with erosions), and the size of SMTs or erosions on early endoscopic findings suggestive of LR was smaller than 10 mm in all patients (six of six patients with SMTs and one of one patient with erosion). Although Tu et al. reported that SMTs, erosions and ulcers were indicative of LR post dCRT [21], the size and other changes on endoscopic findings remained unknown. Our study suggests that small SMTs or erosions could be early indications of LR, even in the absence of histological confirmation, and thus should be monitored judiciously for LR detection.

To detect LR post-CR, ordinary follow-up endoscopy was performed at 2–3-month and 4–6-month intervals for the first and second or more years, respectively. In 12 patients with definitive cT1 LR, four patients underwent follow-up endoscopy within a short timeframe (1 month). The other eight patients underwent follow-up endoscopy according to the ordinary schedule. In five patients with cT2 or deeper, all patients underwent follow-up endoscopy according to the ordinary schedule. In this study, salvage endoscopic therapy was performed only on patients with stage cT1. Therefore, a follow-up endoscopy at short intervals (1–2 months) should be performed when the endoscopic findings are suggestive of LR. This will allow detection of LR at an early T stage and the opportunity to perform salvage endoscopic

therapy will not be missed.

Esophagectomy is generally recommended for patients with salvage treatment failure, however, severe complications, including anastomotic leakage, respiratory disorders, and treatment-related mortality, have been frequently reported [5-9]. Furthermore, salvage esophagectomy is associated with a decrease in health-related quality of life and overall life expectancy [24]. On the other hand, salvage endoscopic therapies such as EMR, ESD, and PDT can preserve organs and they have low complication rates. Previous studies have reported that postoperative mortality and severe complications, such as perforation and bleeding, are rare following EMR and ESD, and that the treatment-related death rate following PDT using porfimer sodium has been reported to be as low as 1.8%, mostly due to esophageal-aortic fistula [10-19]. In this study, there were no occurrences of postoperative mortality, however, one severe complication (anatomic leakage) did occur in one patient who underwent salvage esophagectomy. To improve a patient's indication for less-invasive salvage endoscopic therapy, it is important to carefully observe and detect small SMTs and erosions on endoscopic findings.

Our study had several limitations. First, this was a retrospective study undertaken at a single institution. Second, this study only focused on patients who developed histologically

confirmed LR. Lesions in patients with no LR, but similar early endoscopic findings of LR, were not investigated. Third, there were various endoscopic follow-up intervals in this study. Therefore, additional studies with a prospective design and larger cohort are necessary to confirm the early endoscopic findings of LR.

In summary, earlier detection of LR post dCRT enables patients to be treated with less invasive endoscopic treatments. Endoscopic findings, including SMTs and erosions less than 10 mm in size suggestive of LR, should be monitored frequently at 1–2-month intervals, even when biopsy results are negative.

Human Rights Statement and Informed Consent

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study.

Conflicts of Interest Statement

Yoichi Yamamoto, Tomohiro Kadota, Yusuke Yoda, Keisuke Hori, Ken Hatogai, Takashi Kojima, Satoshi Fujii, Tetsuo Akimoto, and Tomonori Yano declare that they have no conflict

of interest.

References

1. Kato H, Sato A, Fukuda H, et al. A phase II trial of chemoradiotherapy for stage I esophageal squamous cell carcinoma: Japan Clinical Oncology Group Study (JCOG9708). Jpn J Clin Oncol. 2009;39:638–43.
2. Kato K, Muro K, Minashi K, et al. Phase II study of chemoradiotherapy with 5-fluorouracil and cisplatin for Stage II-III esophageal squamous cell carcinoma: JCOG trial (JCOG 9906). Int J Radiat Oncol Biol Phys. 2011;81:684–90.
3. Kato K, Nakajima T, Ito Y, et al. Phase II study of concurrent chemoradiotherapy at the dose of 50.4 Gy with elective nodal irradiation for Stage II–III esophageal carcinoma. Jpn J Clin Oncol. 2013;43:608–15.
4. Du D, Song T, Liang X, et al. Concurrent chemoradiotherapy with elective lymph node irradiation for esophageal cancer: a systemic review and pooled analysis of the literature. Dis Esophagus. 2017;30:1–9.
5. Watanabe M, Mine S, Nishida K, et al. Salvage esophagectomy after definitive chemoradiotherapy for patients with esophageal squamous cell carcinoma: who really benefits from this high-risk surgery? Ann Surg Oncol. 2015;22:4438–44.
6. Tachimori Y, Kanamori N, Uemura N, et al. Salvage esophagectomy after high-dose

chemoradiotherapy for esophageal squamous cell carcinoma. J Thorac Cardiovasc Surg. 2009;l37:49–54.

7. Swisher SG, Wynn P, Putnam JB, et al. Salvage esophagectomy for recurrent tumors after definitive chemotherapy and radiotherapy. J Thorac Cardiovasc Surg. 2002;l23:175–83.
8. Miyata H, Yamasaki M, Takiguchi S, et al. Salvage esophagectomy after definitive chemoradiotherapy for thoracic esophageal cancer. J Surg Oncol. 2009;100:442–46.
9. Chao YK, Chan SC, Chang HK, et al. Salvage surgery after failed chemoradiotherapy in squamous cell carcinoma of the esophagus. Eur J Surg Oncol. 2009;35:289–94.
10. Makazu M, Kato K, Takisawa H, et al. Feasibility of endoscopic mucosal resection as salvage treatment for patients with local failure after definitive chemoradiotherapy for stage IB, II, and III esophageal squamous cell cancer. Dis Esophagus. 2014;27:42–9.
11. Saito Y, Takisawa H, Suzuki H, et al. Endoscopic submucosal dissection of recurrent or residual superficial esophageal cancer after chemoradiotherapy. Gastrointest Endosc. 2008;67:355–9.
12. Nakajo K, Yoda Y, Hori K, et al. Technical feasibility of endoscopic submucosal dissection for local failure after chemoradiotherapy or radiotherapy for esophageal squamous cell carcinoma. Gastrointest Endosc. 2018;88:637–46.

13. Yano T, Muto M, Minashi K, et al. Photodynamic therapy as salvage treatment for local failures after definitive chemoradiotherapy for esophageal cancer. Gastrointest Endosc. 2005;62:31–6.

14. Yano T, Kasai H, Horimatsu T, et al. A multicenter phase II study of salvage photodynamic therapy using talaporfin sodium (ME2906) and a diode laser (PNL6405EPG) for local failure after chemoradiotherapy or radiotherapy for esophageal cancer. Oncotarget. 2017;8:22135–44.

15. Hattori S, Muto M, Ohtsu A, et al. EMR as salvage treatment for patients with locoregional failure of definitive chemoradiotherapy for esophageal cancer. Gastrointest Endosc. 2003;58:65–70.

16. Yano T, Muto M, Hattori S, et al. Long-term results of salvage endoscopic mucosal resection in patients with local failure after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Endoscopy. 2008;40:717–21.

17. Koizumi S, Jin M, Matsuhashi T, et al. Salvage endoscopic submucosal dissection for the esophagus-localized recurrence of esophageal squamous cell cancer after definitive chemoradiotherapy. Gastrointest Endosc. 2014;79:348–53.

18. Takeuchi M, Kobayashi M, Hashimoto S, et al. Salvage endoscopic submucosal

dissection in patients with local failure after chemoradiotherapy for esophageal squamous cell carcinoma. Scand J Gastroenterol. 2013;48:1095–101.

19. Hatogai K, Yano T, Kojima T, et al. Salvage photodynamic therapy for local failure after chemoradiotherapy for esophageal squamous cell carcinoma. Gastrointest Endosc. 2016;83:1130–9.
20. Zenda S, Hironaka S, Taku K, et al. Optimal timing of endoscopic evaluation of the primary site of esophageal cancer after chemoradiotherapy or radiotherapy: a retrospective analysis. Dig Endosc. 2009;21:245–51.
21. Tu CH, Muto M, Horimatsu T, et al. Submucosal tumor appearance is a usual endoscopic predictor of early primary-site recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma. Dis Esophagus. 2011;24:274–8.
22. Wittekind C, Asamura H, Sobin LH. TNM Atlas, 6th ed. New Jersey: Wiley-Blackwell; 2014.
23. Tahara M, Ohtsu A, Hironaka S, et al. Clinical impact of criteria for complete response (CR) of primary site to treatment of esophageal cancer. Jpn J Clin Oncol. 2005;35:316–23.
24. Semenkovich TR, Meyers BF. Surveillance versus esophagectomy in esophageal cancer

patients with a clinical complete response after induction chemoradiation. Ann Transl Med. 2018;6:81.

Figure legends

Figure 1: Endoscopic findings of local recurrence lesions

A: The white arrow represents the SMT

B: The white arrow represents the ulcer

C: The white arrow represents erosion

SMT, submucosal tumor

Figure 2: Flow diagram of patients following dCRT

dCRT, definitive chemoradiotherapy; CR, complete response

Figure 3: The results of retrospective review of local recurrence lesions

Upper images: Early findings of local recurrence with retrospective review

The white arrows represent the early endoscopic findings of local recurrence.

Lower images: Definitive findings of local recurrence with positive biopsy result

The white arrows represent the definitive endoscopic findings of local recurrence.

First images on the left: SMT has become larger SMT

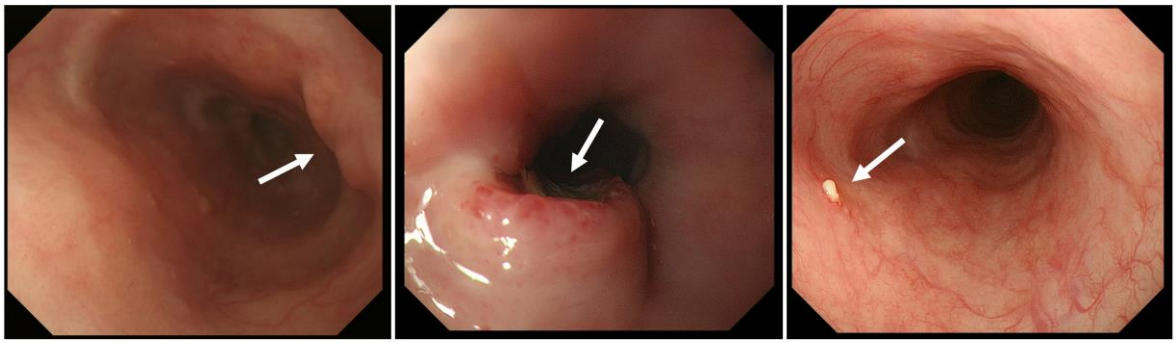
Second image on the left: Early findings could not be detected

Middle image and second image on the right: SMT has changed to ulcer

First image on the right: Early findings could not be detected

LR, local recurrence; SMT, submucosal tumor

Figure1



(A) SMT (B) Ulcer (C) Erosion

Figure2

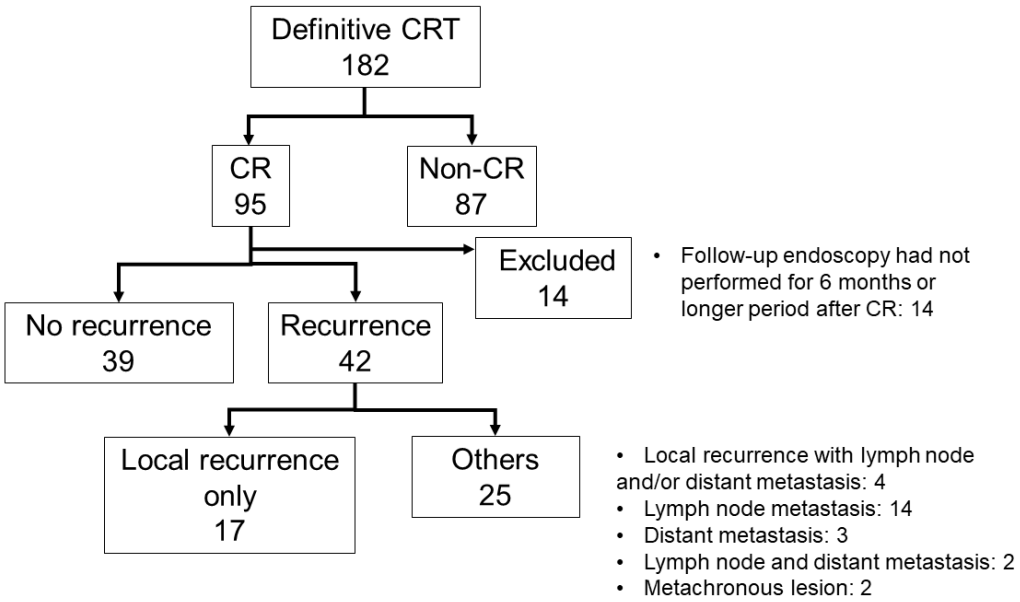


Figure3

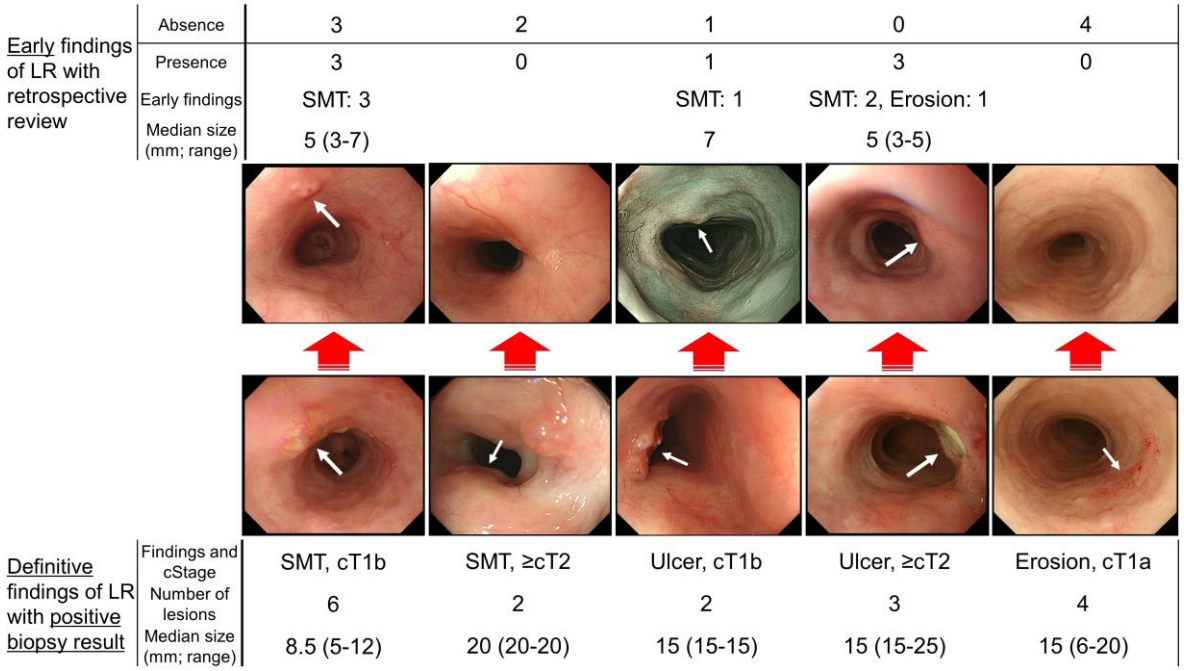

Early findings of LR with retrospective review
Absence
3
2
1
0
4
Presence
3
0
1
3
0
Early findings
SMT: 3
SMT: 1
SMT: 2, Erosion: 1
Median size (mm; range)
5 (3-7)
7
5 (3-5)
Definitive findings of LR with positive biopsy result
Findings and cStage
SMT, cT1b
SMT, ≥cT2
Ulcer, cT1b
Ulcer, ≥cT2
Erosion, cT1a
Number of lesions
6
2
2
3
4
Median size (mm; range)
8.5 (5-12)
20 (20-20)
15 (15-15)
15 (15-25)
15 (6-20)

Table 1: Patient characteristics

Characteristics	Number of patients
Sex, male/female	16/1
Age, years, median (range)	66 (55–81)
Tumor location	
Ce/ Ut/ Mt/ Lt/ Ae	0/ 6/ 6/ 5/ 0
Clinical T stage (UICC 6th edition)	
1/ 2/ 3/ 4	4/ 0/ 12/ 1
Clinical N Stage (UICC 6th edition)	
0/ 1	7/ 10
Clinical M stage (UICC 6th edition)	
0/ 1a/ 1b	13/ 2/ 2
Clinical stage (UICC 6th edition)	
I/ IIA/ IIB/ III/ IVA/ IVB	4/ 3/ 0/ 6/ 2/ 2
Radiation dose	
50.4 Gy/ 60.0 Gy	9/ 8
Chemotherapy regimen	
5-FU+CDDP/ S-1+CDDP/ 5-FU+CDGP/ 5-FU	9/ 3/ 2/ 3
Duration from starting CRT to achieving CR, months, median (range)	3 (2–9)

Ce, cervical esophagus; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; Ae, abdominal esophagus; UICC, Union International Centre le Cancer; 5-FU, 5-fluorouracil; CDDP, cisplatin; CDGP, nedaplatin

Table 2: Endoscopic findings at local recurrence

Endoscopic findings	Number of lesions	Number of lesions in each cT stage at local recurrence			Size of lesion, mm, median (range)	Duration to local recurrence from CR, months, median (range)
		cT1a	cT1b	≥cT2		
SMT	8 (47%)	0	6	2	10 (5–20)	5 (1–37)
Ulcer	5 (29%)	0	2	3	15 (15–25)	8 (1–47)
Erosion	4 (24%)	4	0	0	15 (6–20)	14 (1–54)
Total	17	4	8	5	15 (5–25)	6 (1–54)

SMT, submucosal tumor; CR, complete response

Table 3: Following salvage therapy for local recurrence

Endoscopic findings at local recurrence	Each cT stage at local recurrence	Interval to local recurrence from the latest endoscopy, months, median (range)	Salvage therapy for local recurrence			Total number of lesions
			Endoscopic therapy (EMR/ESD, PDT)	Surgery	Palliative therapy	
SMT	cT1b	3 (1–5)	5 (2, 3)	1	0	6
SMT	≥cT2	4 (3–5)	0	2	0	2
Ulcer	cT1b	3.5 (1–6)	2 (0, 2)	0	0	2
Ulcer	≥cT2	4 (3–6)	0	2	1	3
Erosion	cT1a	3 (1–14)	4 (4, 0)	0	0	4
		3 (1–14)	11 (6, 5)	5	1	17

SMT, submucosal tumor; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PDT, photodynamic therapy

Supplementary Table 1: Cases in which early endoscopic findings suggestive of local recurrence were detected on prior images

Case No.	Clinical stage	cT stage	Tumor location	Chemotherapy regimen	Radiation dose (Gy)	Early endoscopic findings before local recurrence	Size (mm)	Biopsy	Interval of next endoscopy (months)	Endoscopic finding at local recurrence	Duration from CR to local recurrence (months)	Size (mm)	Depth	Therapy after local recurrence	Complication of therapy
1	III	3	Mt	5-FU+CDDP	50.4	SMT	5	Y	5	SMT	8	12	cT1b	PDT	None
2	I	1	Mt	5-FU+CDDP	60	Erosion	5	Y	4	Ulcer	18	15	cT2	Surgery	Anatomic leakage
3	IVA	3	Ut	5-FU+CDDP	60	SMT	5	Y	3	Ulcer	6	15	≥cT2	Surgery	None
4	III	3	Mt	5-1+CDDP	50.4	SMT	3	Y	1	SMT	4	5	cT1b	EMR	None
5	III	4	Ut	5-FU+CDDP	60	SMT	7	N	6	Ulcer	47	15	cT1b	PDT	Esophageal stricture
6	III	3	Mt	S-1+CDDP	50.4	SMT	7	Y	3	SMT	8	10	cT1b	PDT	None
7	III	3	Ut	S-FU	60	SMT	3	N	6	Ulcer	8	25	≥cT2	Palliative therapy	None

CR, complete response; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; SMT, submucosal tumor; 5-FU, 5-fluorouracil; CDDP, cisplatin; EMR, endoscopic mucosal resection; PDT, photodynamic therapy

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Supplementary Table 2: Cases in which early endoscopic findings suggestive of local recurrence could not be detected on prior images

Case No.	Clinical stage	cT stage	Tumor location	Chemotherapy regimen	Radiation dose (Gy)	Early endoscopic findings before local recurrence	Interval of next endoscopy (months)	Endoscopic finding at local recurrence	Duration from CR to local recurrence (months)	Size (mm)	Depth	Therapy after local recurrence	Complication of therapy
1	IIA	3	Mt	5-FU+CDGP	50.4	No findings	3	SMT	6	10	cT1b	Surgery	None
2	IIA	3	Ut	5-FU	50-4	No findings	3	SMT	2	7	cT1b	PDT	None
3	IIA	3	Lt	5-1+CDDP	50.4	No findings	1	Erosion	1	6	cT1b	EMR	None
4	III	3	Lt	5-FU+CDDP	50.4	No findings	3	Erosion	54	20	cT1a	ESD	None
5	I	1	Ut	5-FU+CDDP	50.4	No findings	1	SMT	1	7	cT1b	EMR	None
6	IVB	3	Lt	5-FU+CDDP	60	No findings	5	SMT	37	20	≥cT2	Surgery	None
7	IVB	3	Lt	5-FU+CDDP	60	No findings	14	Erosion	22	15	cT1a	ESD	None
8	1	1	Mt	5-FU	50.4	No findings	3	Erosion	6	15	cT1a	EMR	None
9	IVA	3	Ut	5-FU+CDDP	60	No findings	3	SMT	3	20	≥cT2	Surgery	None
10	I	1	Lt	5-FU+CDGP	60	No findings	1	Ulcer	1	15	cT1b	PDT	None

CR, complete response; Ut, upper thoracic esophagus; Mt, middle thoracic esophagus; Lt, lower thoracic esophagus; SMT, submucosal tumor; 5-FU, 5-fluorouracil; CDDP, cisplatin; CDGP, nedaplatin; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; PDT, photodynamic therapy

Review of early endoscopic images in patients with local recurrence after definitive chemoradiotherapy for esophageal squamous cell carcinoma, Esophagus, Yoichi Yamamoto, Tomohiro Kadota, Yusuke Yoda, Keisuke Hori, Ken Hatogai, Takashi Kojima, Satoshi Fujii, Tetsuo Akimoto, and Tomonori Yano; Department of Gastroenterology and Endoscopy, National Cancer Center Hospital East, Kashiwa, Japan; tkadota@east.ncc.go.jp