

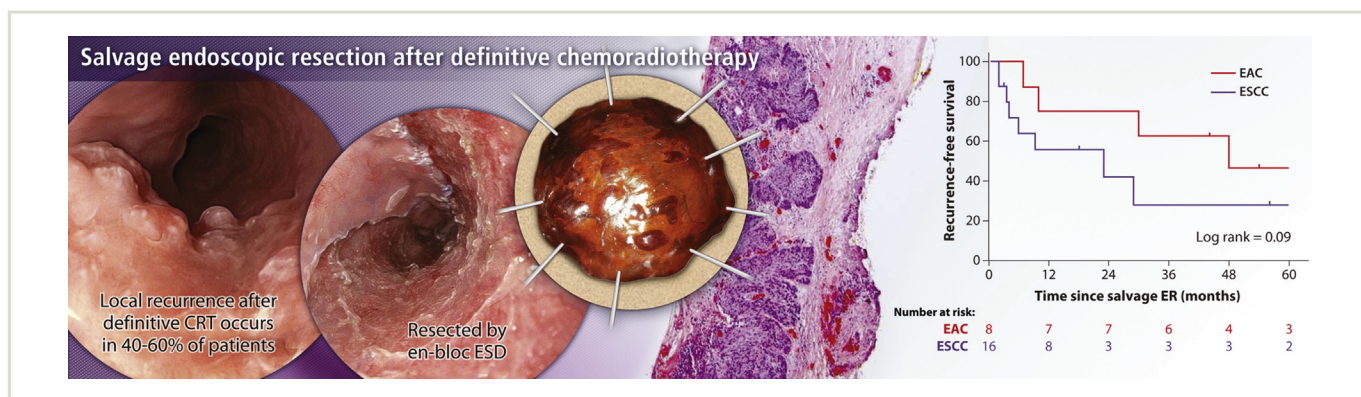


Salvage endoscopic resection after definitive chemoradiotherapy for esophageal cancer: a Western experience

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GRAPHICAL ABSTRACT



Background and Aims: Definitive chemoradiotherapy (CRT) is increasingly used as a nonsurgical treatment for esophageal cancer. In Japanese studies, salvage endoscopic resection (ER) has emerged as a promising strategy for local failure after definitive CRT. We aimed to evaluate the safety and efficacy of salvage ER in a Western setting.

Methods: Gastroenterologists from Europe and the United States were invited to submit their experience with salvage endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) after definitive CRT. Participating gastroenterologists completed an anonymized database, including patient demographics, clinicopathologic variables, and follow-up on survival and recurrence.

Results: Gastroenterologists from 10 endoscopic units in 6 European countries submitted information on 25 patients. A total of 35 salvage ER procedures were performed, of which 69% were ESD and 31% EMR. Most patients had squamous cell carcinoma (64%) of the middle or lower esophagus (68%) staged as cT2-3 (68%) and cN+ (52%) before definitive CRT. The median time from end of definitive CRT to ER was 22 months (interquartile range, 6-47). The en-bloc resection rate was 92% for ESD and 46% for EMR. During a median of 24 months (interquartile range, 12-59) of follow-up after salvage ER, 52% developed a recurrence (11 locoregional, 2 distant). The 5-year recurrence-free survival, overall survival, and disease-specific survival were 36%, 52%, and 79%, respectively. No major intra- or postprocedural adverse events, such as bleeding or perforation, were reported.

Conclusions: In carefully selected esophageal cancer patients, salvage ER is technically feasible after definitive CRT. Further prospective research is recommended to validate the safety and effectivity of salvage ER for the management of local failure. (Gastrointest Endosc 2021;93:888-98.)

(footnotes appear on last page of article)

Esophageal cancer is the sixth leading cause of global cancer-related death, responsible for 509,000 deaths in 2018.¹ In Western guidelines, neoadjuvant chemoradiotherapy (CRT) followed by esophagectomy is considered more beneficial than surgery alone for the treatment of potentially curable esophageal cancer and is currently the recommended approach.^{2,3} Patients unwilling to undergo surgical resection or with a high surgical risk because of significant comorbidities are often treated with definitive CRT.^{4,5} Although neoadjuvant CRT followed by surgical resection is considered superior to other treatment modalities, randomized controlled and population-based studies suggest comparable overall survival (OS) and quality of life for patients with esophageal squamous cell carcinoma (ESCC) treated with definitive CRT.⁵⁻⁷ Therefore, definitive CRT is increasingly accepted as a well-tolerated nonsurgical modality, especially for potentially curable ESCC.

In contrast to neoadjuvant CRT followed by esophagectomy, locoregional failure (ie, residual disease or local recurrence at the primary tumor site) after definitive CRT is a common problem. Local failure has been reported in 40% to 60% of patients,⁸⁻¹¹ with almost 90% located within the irradiation field of the esophagus.⁸ Patients with residual or recurrent disease have a very poor prognosis, with a median survival of 4 to 28 months.^{8,12} To date, no follow-up and/or treatment recommendations for locoregional failure after definitive CRT are available. When deemed medically fit, selected patients may undergo salvage surgical resection. Nonetheless, this is a high-complex procedure associated with increased postoperative morbidity and mortality.¹³

Based on the histopathologic assessment of surgical resection specimens after neoadjuvant CRT, it has been shown that most residual tumor cells can be detected in the mucosal and submucosal layers.^{14,15} This provides a rationale to consider endoscopic resection (ER) techniques, such as endoscopic submucosal dissection (ESD) or EMR, as complementary treatments for local failure after definitive CRT. For localized cT1aN0M0 cancer and in some cases of cT1bN0M0 esophageal cancer, ER is already considered a safe and effective first-line therapy.¹⁶ However, because of concerns about the effectiveness, safety, and feasibility of ER in CRT-treated patients, salvage endoscopic interventions need further study.

In a few single-center and multicenter Japanese case series, salvage ER has emerged as a promising curative treatment modality for superficial residual or recurrent ESCC after definitive CRT. This strategy seems to be associated with promising short- and long-term survival rates with no major adverse events.¹⁷⁻²⁴ Case series from outside Japan are notably limited to 1 small case report.²⁵ This study is the first international collaborative initiative to collect and investigate cases of salvage ER for local failure after definitive CRT in a Western population. The primary aim of the study is to evaluate the long-term safety and

efficacy of this endoscopic treatment strategy for local failure after definitive CRT.

METHODS

Study design and data collection

Eighty endoscopists from endoscopic centers in Europe and the United States were invited by e-mail to share their experience with salvage ER. Participating endoscopists assessed the eligibility of their cases using the provided inclusion criteria. Patients were included if they had potentially curable adenocarcinoma or squamous cell carcinoma of the esophagus or gastroesophageal junction without distant metastases (cT1-4a, any cN, cM0) and treated with definitive therapy, because they were considered not fit enough for surgery because of comorbidity or declined undergoing surgery. All patients were diagnosed with local failure after definitive therapy for which salvage EMR or ESD was performed. Definitive therapy with curative intent may have consisted of systemic chemotherapy, radiotherapy, or combinations of both modalities.

Participants were asked to complete an anonymous individual patient dataset. Details on patient-, tumor- and treatment-related characteristics, including age at diagnosis, gender, anatomic tumor location, clinical stage before definitive therapy (cTNM), type of definitive therapy, time to ER, type of ER, and whether salvage esophagectomy was performed were recorded. Participants were also asked to provide histopathologic characteristics of the ER specimen, such as histology type, grade of differentiation, depth of tumor invasion, resection technique (en bloc vs piecemeal), and completeness of the resection. Time to ER after definitive therapy, follow-up time after ER, and time to recurrence were measured in months.

All data were handled confidentially and anonymously. The study was performed in accordance with national and international codes of conduct for scientific practice. Because only anonymous patient data without identifiers were included, approval by the institutional review board was not required.

Definitions

Local failure was defined as endoscopic suspicion of a superficial residual or recurrent lesion after definitive therapy with no evidence for lymph node and distant metastases (cT1N0M0) based on CT and positron emission tomography–CT and sometimes EUS. Possible major adverse events related to ER included intraprocedural (perforation, major bleeding) and postprocedural (major delayed bleeding, mediastinitis, and stricture) adverse events. Local tumor stage (pT1) was subclassified according to depth of tumor invasion in the mucosa (m1-3) and submucosa (sm1-3): sm1 <500 μ M (ESCC, <200 μ M), sm2 <1000 μ M, and sm3 >1000 μ M. Recurrences after

ER were classified as locoregional or distant recurrence (cM1). Radical resection (R0) was defined as tumor-free horizontal and vertical margins. Radical EMR or ESD resections with a low-risk profile including well to moderate tumor differentiation and absence of lymphovascular invasion were considered curative.

Outcomes

The primary outcomes were OS, disease-specific survival (DSS), and recurrence-free survival (RFS). The secondary outcome was intra- and postprocedural adverse events related to ER.

Statistical analysis

Data were analyzed with descriptive statistics. Baseline characteristics of all patients are presented as a whole. Continuous variables are presented as mean and standard deviation or as median and interquartile range (IQR) if not normally distributed. Binary and categorical variables are presented as frequencies and percentages. Survival curves were estimated using Kaplan-Meier methods and compared by the log-rank test. Statistical analysis was performed using SPSS Statistics v25.0 (IBM Corp, Armonk, NY, USA).

RESULTS

Study population

Responses were collected from 10 endoscopic centers, including our center, in 6 countries (ie, Belgium, United Kingdom, France, Switzerland, Austria, and the Netherlands). Clinical data on 25 unique esophageal cancer patients who had undergone salvage ER procedures ($n = 35$) after definitive CRT were included. A summary of the clinicopathologic characteristics before salvage ER is presented in [Table 1](#). Most patients were men with squamous cell carcinoma of the middle or lower third of the esophagus. Before definitive therapy, 68% of patients were staged cT2-3 and half were suspected of lymph node metastases (cN+). CRT was the most frequently administered definitive therapy (84%). There was a notable variation in the chemotherapy regimens and total doses of radiotherapy used ([Table 2](#)). Nonetheless, most patients (60%) received high-dose radiotherapy with total doses of >50 Gy.

Local failure after definitive therapy

The median time from the last day of definitive therapy to salvage ER was 22 months (IQR, 6-47; range, 2-177). Local tumor lesions after definitive therapy were mostly recognized as recurrent disease (52%), followed by residual disease (32%), or unknown (16%). [Figures 1](#) and [2](#) show 2 cases of salvage EMR and salvage ESD, respectively, for a recurrent lesion after definitive therapy.

Histopathologic outcomes of salvage ER

Of the 35 salvage ER procedures, ESD was the most common procedure (69%), followed by EMR (31%; [Table 3](#)). In 27 ER procedures (77%), en-bloc resection was achieved (ESD, 92%; EMR, 46%). Based on histopathologic evaluation of the ER specimen, 60% of the tumor lesions were located in the mucosal layer (m1-3). Submucosal lesions (sm1-3) were found in 23% of the resections. Invasive tumors were mostly well to moderately differentiated tumors. Tumor-free vertical margins and horizontal margins were reported in 28 (85%) and 20 (61%) resections. Radical and curative resections were confirmed in 58% and 47%, respectively, of ER procedures. Lymphovascular invasion was found in 3 patients (9%).

ER-related adverse events

No intra- or postprocedural major bleedings or perforations were reported. During follow-up, 4 patients developed a stricture, 2 after ESD and 2 after EMR. All patients with a stricture had been treated with chemotherapy with concurrent radiotherapy.

Follow-up after salvage ER

All patients underwent at least 1 follow-up endoscopy with biopsy sampling from the resection scar and surrounding mucosa. The median follow-up time after salvage ER was 24 months (IQR, 12-59; range, 2-118). Thirteen patients (52%) developed a recurrence after salvage ER, of which 11 (44%) had locoregional recurrence only and 2 distant disease (8%; [Table 3](#)). The median time of salvage ER to the occurrence of locoregional or distant recurrence was 9.6 months (IQR, 4-29; range, 2-48). No differences in recurrence rates were seen when stratified to radicality (R0 vs R1), curative resection, and type of ER ([Supplementary Table 1](#), available online at www.giejournal.org). More recurrences, mostly locoregional, were seen after ESD compared with EMR; however, the difference did not reach statistical significance.

All patients with locoregional recurrent disease after salvage ER ($n = 11$) underwent reintervention after careful staging. Of the patients treated with a second ER procedure ($n = 8$), eventually 7 (88%) achieved complete remission (median follow-up, 43 months; IQR, 25-75). Four patients underwent ablative therapy after salvage ER: 2 radiofrequency ablations, 1 cryoablation, and 1 argon plasma coagulation.

In total, 3 ESCC patients were treated with salvage esophagectomy for locoregional recurrence. Two patients sustained a long survival after surgery: 1 had no signs of recurrence after 9 years of follow-up until death and the other died 6 years later because of an unknown second primary malignancy with metastases. The third patient died 10 months after salvage surgery of multiple hepatic and pulmonary metastases from esophageal cancer.

TABLE 1. Baseline characteristics before salvage ER

Baseline variable	Values n or median	Values % or interquartile range
Total cases	25	100
Total salvage ER procedures	35	
Age, y		
Median	71	66-76 (range, 45-78)
Gender		
Male	17	68
Female	8	32
Histology		
Adenocarcinoma	9	36
Squamous cell carcinoma	16	64
Location of tumor		
Upper third	6	24
Middle third	9	36
Lower third	8	32
Gastroesophageal junction	2	8
Clinical T stage before definitive therapy		
cT1	7	28
cT2	7	28
cT3	10	40
Unknown	1	4
Clinical N stage before definitive therapy		
cN0	9	36
cN+	13	52
cNx	3	12
Definitive therapy		
Chemotherapy	1	4
Radiotherapy	3	12
Chemoradiotherapy	21	84
Local failure		
Residual disease	8	32
Recurrent disease	13	52
Unknown	4	16
Time from end of definitive therapy to ER, mo		
Median	22	6-47 (range, 2-177)
Follow-up after salvage ER, mo		
Median	24	12-59 (range, 2-118)

ER, Endoscopic resection.

The 2 cases with distant metastases after salvage ER were both diagnosed with ESCC. At baseline both patients were suspected to have lymph node metastases. One patient (cT3N1M0) developed a local recurrence 26 months after definitive CRT for which an ESD was performed. Six months later, the patient died because of metastatic disease. In the other patient (cT1bNxM0), an ESD was performed for residual disease 3 months after definitive

high-dose radiotherapy. The patient developed distant metastases 4 months after ESD and was still alive at the last follow-up, 12 months after salvage ESD.

Survival outcome after salvage ER

At the time of survival analysis, 15 patients were still alive. Overall, the 5-year RFS, OS, and DSS were 36%, 52%, and 79%, respectively (Fig. 3A-C). In a subgroup

TABLE 2. Type of definitive therapy

Chemotherapy regimen
Cisplatin + 5-fluorouracil (n = 11)
Carboplatin + paclitaxel (n = 6)
Epirubicin + cisplatin + 5-fluorouracil (n = 1)
5-Fluorouracil + leucovorin + oxaliplatin (n = 1)
5-Fluorouracil alone (n = 1)
Carboplatin alone (n = 1)
Capecitabine + cisplatin (n = 1)
Radiotherapy dose
Total dose range, 35-60 Gy

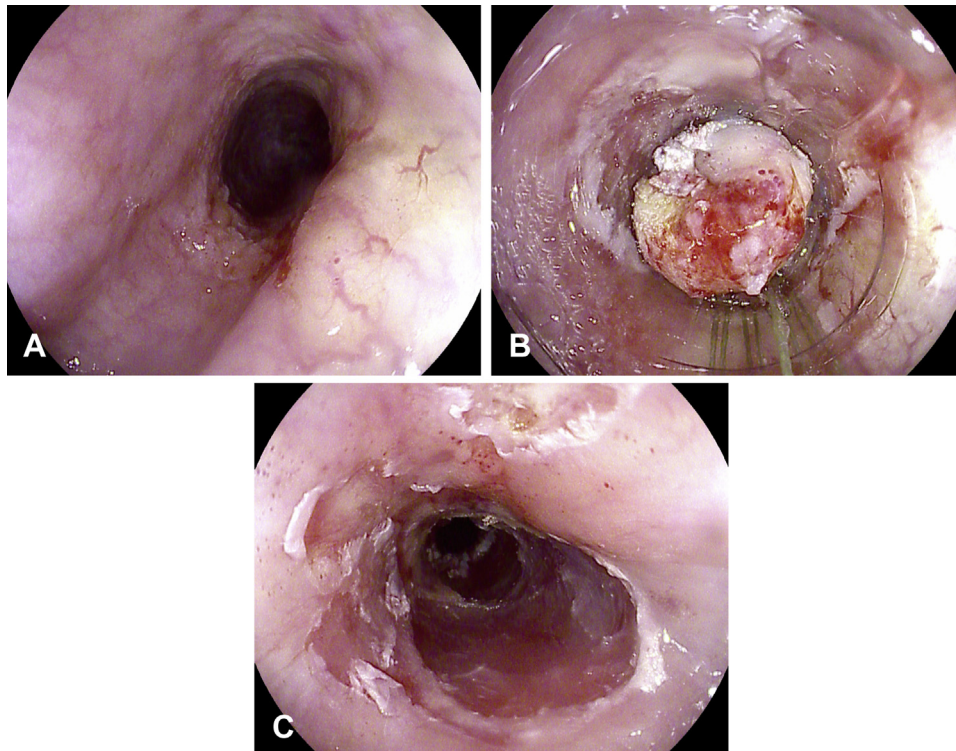


Figure 1. Endoscopic images of a patient undergoing salvage EMR. A 61-year-old woman with cT3N1 squamous cell carcinoma of the proximal esophagus was treated with carboplatin and paclitaxel combined with 50.4-Gy radiotherapy. **A**, Nine years later she developed a local recurrent lesion. Band-ligation EMR was performed (**B**), with resection of the lesion in 3 pieces (**C**).

analysis, patients with no recurrence after salvage ER had a 3-year and 5-year OS of 88% and 53% compared with 65% and 49%, respectively, in those with a recurrence (log rank $P = .36$). When comparing survival according to histologic subtype, there was a clinically relevant difference between esophageal adenocarcinoma and ESCC in RFS (5-year, 47% vs 28%; Fig. 3D), OS (5-year, 62% vs 46%; Fig. 3E), and DSS (median, 100% vs 54%; Fig. 3F). However, this survival difference was only statically significant for DSS (log rank $P = .03$). In univariable Cox regression analysis, only EMR (reference ESD; hazard ratio, 10; 95% confidence interval, 1.3-80) was associated with RFS. Comprehensive

multivariable analyses were not possible because of the low number of cases.

Discussion

This is the first Western multicenter study reporting results on the safety and efficacy of salvage ER for local failure after definitive CRT. In this exploratory case series, we found that several endoscopic centers in Europe had performed salvage EMR or ESD for residual or recurrent esophageal cancer after definitive CRT. Pooled data from these cases demonstrated good local control after salvage ER, which was associated with good survival.

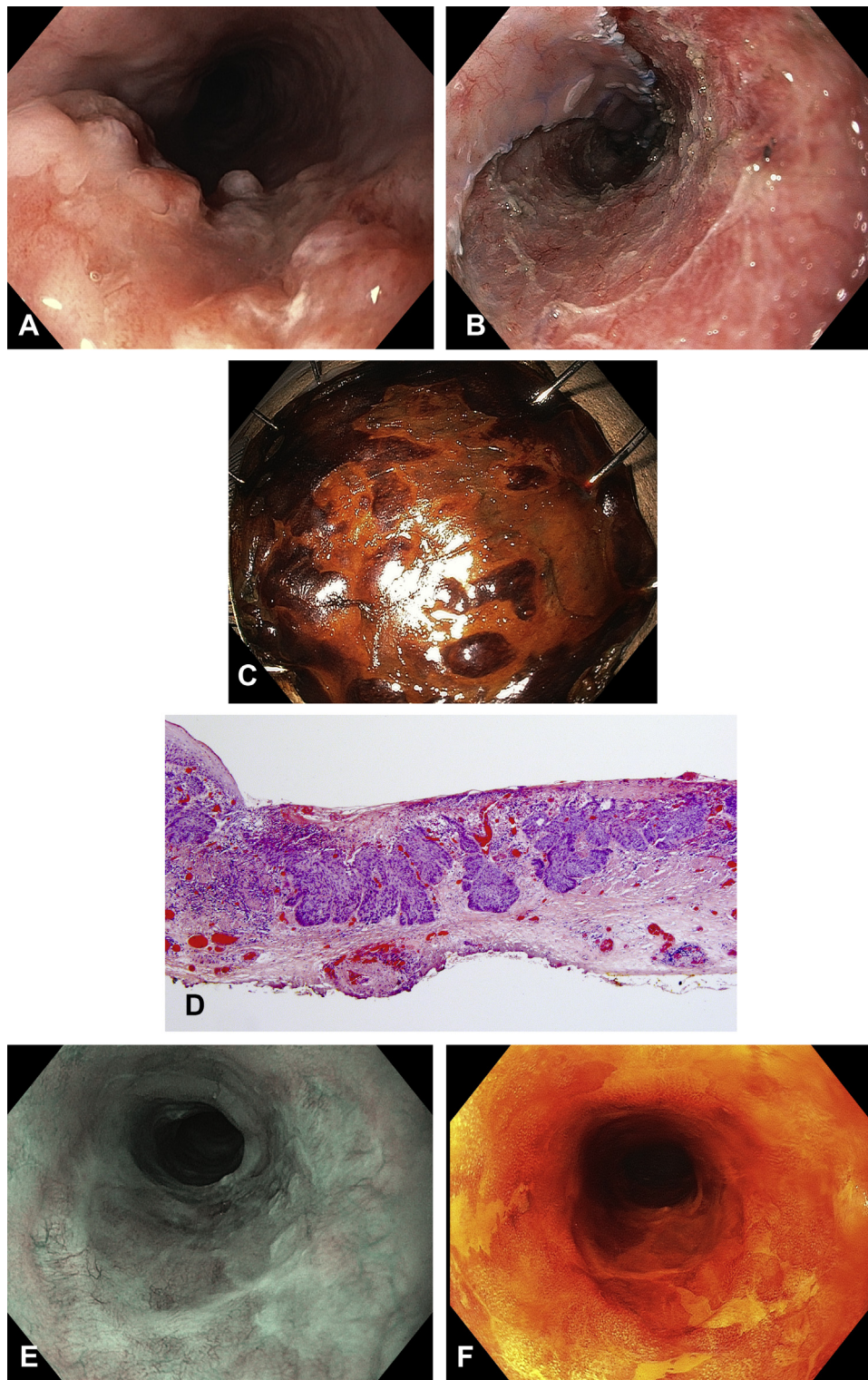


Figure 2. Endoscopic images of a patient undergoing salvage endoscopic submucosal dissection (ESD). A 63-year-old man with cT1bN1M0 cancer of the proximal esophagus was treated with carboplatin and paclitaxel combined with 49.4-Gy radiotherapy. **A**, Follow-up endoscopy 2 years after definitive chemoradiotherapy showed a recurrent cancer. **B** and **C**, The lesion was successfully resected by en-bloc ESD. **D**, Histology with H&E staining (H&E, orig. mag. $\times 40$) demonstrates the superficial submucosal invasion in the cancerous area (ypT1bSm1 [170 mm] R0 G2 LVI0). Follow-up endoscopy 4 months after ESD is shown using high magnification endoscopy with narrow-band imaging (**E**) and Lugol staining (**F**), with no signs of recurrent cancer.

TABLE 3. Baseline characteristics after salvage ER

Baseline variable	Values n or median	Values % or interquartile range
Type of salvage ER		
EMR	11	31
ESD	24	69
En-bloc resection		
Total ER	27	77
ESD	22	92
EMR	5	46
Depth of tumor invasion (pT)		
No tumor	3	9
pTis(m1)	10	29
pT1a(m2)	7	20
pT1a(m3)	4	11
pT1b(sm1)	3	9
pT1b(sm2)	1	3
pT1b(smX)	4	11
Unknown	3	9
Differentiation grade		
Well (G1)	8	23
Moderate (G2)	14	40
Poor (G3)	2	6
Undifferentiated (G4)	1	3
Unknown (Gx)	8	23
R0-VM	28	85*
R0-HM	20	61*
Radical resection (R0-VM-HM)	19	58*
Curative resection†	16	47*
Lymphovascular invasion	3	9
Time to recurrence after salvage ER, mo		
Median	9.6	4-29 (range, 2-48)
Type of recurrence after salvage ER		
Locoregional	11	44
Distant	2	8

ER, Endoscopic resection; ESD, endoscopic submucosal dissection; smX, submucosal invasion with unknown depth; Gx, differentiation grade cannot be assessed/unknown; LV0, no lymphovascular invasion; R0, radical resection; HM, tumor-free horizontal margin; VM, tumor-free vertical margin.

*Missing values excluded.

†R0-VM-HM-G1/2-LV0.

Our overall survival rates were comparable with rates from earlier published single-center case series from Japan.¹⁷⁻²⁴ The largest Japanese case series of ESCC to date (n = 72) reported a 3-year RFS, OS, and DSS of 49%, 61%, and 73%, respectively.²⁴ Table 4 provides a summary of published studies. Participating endoscopists in our study did not report any severe adverse events after salvage ER. This is in line with previous studies showing a good safety profile for salvage ER.¹⁷⁻²⁴ No patient in our case series developed a major intra- or postprocedural bleeding or perforation, which is also comparable

with rates reported after standard EMR or ESD in early-stage esophageal cancer (bleeding: EMR 3%, ESD <30%; perforation rate: EMR <1%, ESD <10%).^{26,27} Esophageal strictures were seen in 4 patients (16%) after both ESD and EMR.²⁶

In general, patients undergoing definitive CRT have limited treatment alternatives when they present with local residual or recurrent disease. Current guidelines recommend endoscopic interventions only for early esophageal cancer and for palliative management of dysphagia in patients with a short life expectancy.² Here we confirm the

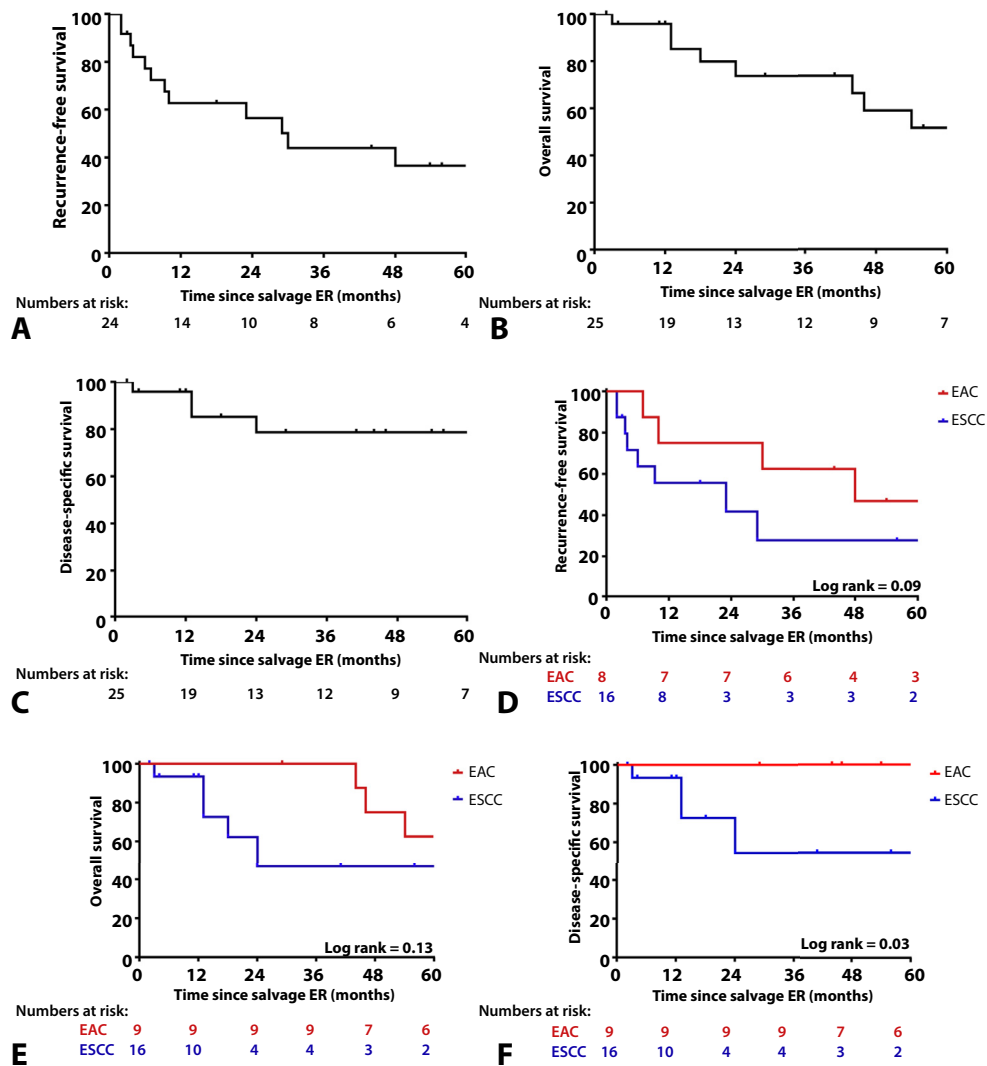


Figure 3. Kaplan-Meier analyses of all patients: recurrence-free survival (A), overall survival (B), disease-specific survival (C), and survival curves according to histology type (D-F). EAC, Esophageal adenocarcinoma; ESCC, esophageal squamous cell carcinoma.

existing evidence from Japan that ER is also technically feasible as a salvage procedure with curative intent.

Although the first salvage ER was described almost 20 years ago, Western endoscopists likely have been reluctant to perform salvage endoscopic procedures in the esophagus after definitive CRT. It is widely believed that it is more difficult to perform salvage ER with en-bloc resection and that it is associated with a higher risk of adverse events, such as bleeding or perforation.²⁸ Concerns about postradiation changes in the esophageal wall, such as chronic inflammation, tissue fibrosis, and vascular damage, may well have contributed to this belief.^{29,30} However, our data and that of others¹⁷⁻²⁴ suggest that concerns with respect to the complexity of salvage ER in the postradiation setting seem to be overrated (Table 4). The en-bloc resection rates of ESD were excellent, whereas EMRs had a relatively lower en-bloc resection rate. In 3 previous reports, about half of salvage EMRs were en-bloc re-

sections.^{17,18,20} This was not unexpected because it is well known that piecemeal EMR is usually required in the esophagus to obtain complete resection.²⁶ Submucosal fibrosis most likely may have contributed to difficulties in lifting the neoplastic lesions. Limited data are available on the procedure time of salvage ER to complement the discussion on treatment safety. Only Nakajo et al³¹ reported a significantly lower procedure time for salvage ESD compared with conventional ESD for lesions >20 mm.

In this series, we also show that repeated ER is possible in case of a recurrence after the first salvage ER. The incidence or recurrences after salvage ER have been reported to range from 16% to 59%.¹⁷⁻²³ The incidence rate of a recurrence in our study was 55%, mostly being locoregional recurrences. Nevertheless, 70% of these cases could still be managed with a successful endoscopic reintervention to sustain complete remission.

TABLE 4. Summary of studies including salvage ERs for local failure after definitive therapy

Study	Country	Method	Period	Population	No. of cases	ER type	Definitive chemoradiotherapy	Outcome
Hombu (2018) ²⁴	Japan	Retrospective single-center cohort	1998-2013	ESCC	72	EMR/ESD	5FU ± cisplatin + RT 50 Gy	Adverse events: no major AE Recurrence rate: 38% Survival: 3-year RFS, OS, and DSS were 48.9%, 61.2%, and 72.9%
Kondo (2016) ²¹	Japan	Retrospective single-center cohort	2000-2010	ESCC	37	EMR/ESD	At least RT 50 Gy ± 5FU ± platinum	Adverse events: 18.9% Recurrence rate: 59% Survival: 3-year and 5-year OS were 73% and 53%
Nakamura (2016) ²³	Japan	Retrospective single-center cohort	2001-2012	ESCC	37	EMR/ESD	Definitive chemoradiotherapy or RT	Adverse events: no major AE Recurrence rate: 49% Survival: 5-year OS was 30%
Koizumi (2014) ²²	Japan	Retrospective single-center cohort	2004-2011	ESCC	12	ESD	5FU + cisplatin + RT 60 Gy	Adverse events: no major AE Recurrence rate: 25% Survival: median OS 18 mo (range, 8-70)
Makazu (2014) ²⁰	Japan	Retrospective single-center cohort	2000-2008	ESCC	11	EMR	>50, 4 Gy RT + 5FU or s-1 + cisplatin	Adverse events: no major AE Recurrence rate: 46% Survival: 5-year OS was 42%
Takeuchi (2013) ¹⁹	Japan	Retrospective single-center case-control study	2000-2010	ESCC	19	ESD	At least 50 Gy RT ± chemotherapy	Adverse events: no major AE Recurrence rate: 16% Survival: 3-year OS was 74%
Yano (2008) ¹⁸	Japan	Retrospective single-center cohort	1998-2004	ESCC	21	EMR	5FU + cisplatin + RT 60 Gy	Adverse events: no major AE Recurrence rate: 52% Survival: 3-year and 5-year OS were 56% and 49%
Hattori (2003) ¹⁷	Japan	Retrospective single-center cohort	1996-1999	ESCC	16	EMR	5FU + cisplatin + RT 60 Gy	Adverse events: no major AE Recurrence rate: 50% Survival: 3-year OS was 56%
Noordzij (2018) ²⁵	Netherlands	Case report	—	Esophageal adenocarcinoma	2*	EMR	Carboplatin + paclitaxel	Adverse events: not reported Recurrence rate: both cases had remnant superficial lesions removed by means of ER Survival: both cases died 46 and 44 months, respectively, after achieving complete response

ER, Endoscopic resection; ESD, endoscopic submucosal dissection; AE, adverse event; DSS, disease-free survival; ESCC, esophageal squamous cell carcinoma; 5FU, 5-fluorouracil; —, not reported; Gy, gray; OS, overall survival; RFS, recurrence-free survival; RT, radiotherapy.

*Both cases also included in the present study.

Most importantly, our data from Europe suggest that salvage ER is technically feasible, at least in a subgroup of patients treated with definitive therapy. Yet, the practical feasibility of salvage ER in the future depends on two major factors. First, more validating data from large prospective, comparative studies are needed before accurate criteria for patient selection can be formulated. Second, effective application of salvage ER would impose that patients who have received definitive CRT should probably also undergo active surveillance for early detection of local residual or recurrent disease. However, considerable uncertainties exist about the diagnostic accuracy of modern imaging techniques to assess clinical response after CRT, with no clear guidelines about routinely performing restaging studies.³² Various image-, endoscopy-, and molecular-based clinical response evaluation strategies are still under investigation.³³⁻³⁵ Anticipated results from these studies will definitely provide more insights into how effective surveillance strategies should be designed.

As an alternative for salvage ER for local residual or recurrent disease after definitive CRT, salvage esophagectomy may also be considered. Despite evidence for technical feasibility in expert hands, the efficacy of salvage surgical resection is still debated.³⁶ Head-to-head comparison between salvage ER and salvage esophagectomy for local recurrence is not easily possible, because highly selected patient groups are included in both groups. Salvage ER may well have a better safety profile compared with salvage surgery for local residual or recurrent lesions after definitive CRT. It should be noted, however, that both salvage modalities might have distinct indications, because not all patients with residual or recurrent lesions are appropriate candidates for salvage ER. Tumor regression pattern analysis has shown that in some cases with mucosal or submucosal lesions, residual tumor cells could also be present in deeper esophageal wall layers.^{14,15}

This case series should be interpreted with caution because it is an exploratory study with a relatively small sample size. Multivariable logistic and Cox regression analysis was not possible because of limited patient numbers. With no clear guidelines for follow-up after definitive therapy, there may have been differences in methods of restaging across sites. Moreover, the diagnostic accuracy of restaging after CRT for the detection of lymph node and distant metastases remains uncertain. Inevitably, there were also other possible sources of bias. First, there could well be selection bias. Almost 60% of endoscopists responded to the e-mail invitation; however, this still may not be representative of all Western countries. Also, selection bias might have affected this study, because for instance no cases in which an endoscopic procedure was aborted because of deep tumor invasion or extensive fibrosis was submitted for inclusion by participating gastroenterologists. Second, because of self-reporting, the study is subject to considerable recall bias, because participating gastroenterologists may not remember or may omit some details of the included cases.

To ensure systematic and consistent data recording of case- and treatment-related information, all participants received a fixed dataset with predefined study variables. Despite its shortcomings, self-reporting is an acceptable research method for explorative studies to generate research hypothesis for future studies on the application of salvage ER in esophageal cancer.

In conclusion, this study is the first multicenter case series of salvage ER in the West. The results of this study support the suggestion that salvage ER is technically feasible after definitive CRT. In carefully selected patients, salvage EMR or ESD seems to be safe and effective nonsurgical treatment options for the management of local residual or recurrent esophageal cancer. After salvage ER, patients had a favorable long-term DSS. These findings contribute to the current literature and could help to improve the outcome of esophageal cancer patients with local failure after definitive CRT. Future prospective work is an essential next step to validate our results, to define necessary patient selection criteria for salvage ER, and to establish effective surveillance strategies after definitive therapy.

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Abbreviations: CRT, chemoradiotherapy; DSS, disease-specific survival; ER, endoscopic resection; ESD, endoscopic submucosal dissection; ESCC, esophageal squamous cell carcinoma; IQR, interquartile range; OS, overall survival; RFS, recurrence-free survival.

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SUPPLEMENTARY TABLE 1. Recurrence after salvage ER stratified into type of ER, radicality, and curative resection

		Recurrence after salvage ER			P value
		No	Locoregional	Distant	
Type of ER	ESD	6	9	2	.16
	EMR	6	2	0	
Radical ER*	Yes	7	5	2	.35
	No	5	6	0	
Curative ER†	Yes	7	5	1	.54
	No	5	6	1	

ER, Endoscopic resection; ESD, endoscopic submucosal dissection.

*Radical resection (R0) was defined as tumor-free horizontal (HM) and vertical margins (VM): R0-VM-HM.

†R0-VM-HM-G1/2-LV10.