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Endoscopic resection for residual oesophageal neoplasia after definitive chemoradiotherapy

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ABSTRACT

Definitive chemoradiation is the recommended treatment for locally advanced, irresectable oesophageal cancer and a valid alternative to neoadjuvant chemoradiotherapy (CRT) with surgery in oesophageal squamous cell cancer (OSCC) patients. In case of locoregional recurrence, salvage treatment can be considered in fit and resectable patients. Salvage surgery is a valid option but associated with significant morbidity. Therefore, for tumors confined to the mucosa or submucosal layers endoscopic resection is a good and less-invasive alternative. Over the last decade several case-series have demonstrated a high technical success rate of endoscopic treatment after definitive CRT. In this review we summarize the clinical outcomes and challenges of endoscopic treatment of early recurrence after definitive CRT in oesophageal cancer.

1. Practice points

- Salvage treatment can be considered in oesophageal cancer patients with local or persistent disease after definitive chemoradiation
- Local recurrence rates are lower for ESD compared to EMR and therefore is ESD is the recommended technique
- Technical success rates of ESD with en-bloc resection for local recurrence after definitive chemoradiation in oesophageal squamous cell cancer (OSCC) patients are between 92 and 100 %
- Curative resection with EMR and ESD can be achieved in 58–100 %
- ESD has an acceptable risk profile with 0–3 % early adverse events and a 13–23 % stricture rate

2. Introduction

Definitive chemoradiotherapy (CRT) is a potential curative treatment option in the treatment of oesophageal cancer in cases of surgically unresectable cancers, too high surgical risks because of significant comorbidities or unwillingness to undergo surgery [1–4].

There is, however, a proportion of patients that show residual or recurrent disease after definitive CRT. In most cases the site of recurrence or residual disease is located at the primary tumor site [5,6] and referred to as local failure. Local failure is reported up to 40–60 % of cases [7,8]. Because patients with residual or recurrent disease have a very poor prognosis, salvage surgery is considered in a subgroup of patients that are medically fit enough to undergo major surgery [9,10]. In oesophageal squamous cell carcinoma (OSCC), current guidelines even consider an upfront salvage approach instead of primary oesophagectomy [4]. Even though salvage surgery is feasible, it is more complex and associated with higher morbidity and mortality rates compared to primary surgery or surgery after neoadjuvant chemoradiotherapy (CRT) [9–11].

Endoscopic resection has been described as a salvage treatment for local failures with residual or recurrent OSCC limited to the mucosal and submucosal layers in the absence of metastasis. The fact that most recurrences originate from the primary tumor site make endoscopic resection feasible [5,12]. Over the last decade, several case-series have been published initially on endoscopic mucosal resection (EMR) as salvage treatment, and with the field progressing also on endoscopic submucosal dissection (ESD) as salvage therapy [13–20]. In this review we will outline the current evidence for endoscopic salvage treatment for local recurrence of oesophageal cancer after definitive chemotherapy and provide practical considerations for selecting patients for endoscopic resection.

3. Salvage treatment after definitive chemoradiotherapy

Definitive CRT is the option of choice in oesophageal cancer patients

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with locally irresectable disease, or who are too frail or with significant comorbidity [4]. OSCC generally has a better response rate to CRT than oesophageal adenocarcinoma (OAC) with 5-year survival rates of 58 % for OSCC and 48 % for OAC in neoadjuvant treated patients [21]. Therefore, in OSCC the additional value of surgery has been frequently questioned, and besides in locally advanced disease might also serve as salvage option in patients with locoregional disease, which is endorsed by the recent ESMO guidelines [4]. Stahl et al. showed in a randomized controlled trial (RCT) for patients with locally advanced OSCC that CRT with surgery provided better locoregional control than CRT alone (2-year progression-free survival (PFS) 64.3 % vs 40.7 %, P = 0.003)), but at a cost of treatment related mortality of respectively 12.8 % versus 3.5 %, leading to a comparable 2-year overall survival (OS, 39.9 % vs 35.4 %, P = 0.007) [22]. Equivalent results were obtained by Bedenne et al., who compared induction chemotherapy with high dose definitive CRT (total 66Gy) to neoadjuvant CRT (46Gy) with surgery, and while local control rates were higher in the surgical arm than in the definitive CRT arm (66.4 % versus 57 %, P = 0.44), the 2-year overall survival was lower in the surgery group, 34 % vs 40 % in the definitive CRT group [23]. The recent long-term results of the SCOPE-1 trial affirmed these high survival rates in OSCC patients after dCRT, with current improved RT techniques the 3-year OS was 47.8 %, demonstrating that definitive CRT is a viable alternative for surgery in OSCC patients [24].

This cost-benefit balance between surgical mortality but better locoregional control might turn favorable if surgery is kept as salvage option when locoregional control fails. In a large multicenter analysis of patients treated with surgery for persistent or recurrent oesophageal cancer after definitive CRT (N = 308) compared to neoadjuvant treated patients with planned surgery (N = 540), OS and disease-free survival (DFS) were similar (respectively 43.3 % v 40.1 %; P = 0 0.542 and 39.2 % v 32.8 %; P = 0.232) [25]. This was a mixed cohort of OAC and OSCC patients, but the majority had OSCC, around 63–65 %. Complications rates were slightly higher in the salvage surgery group, with a higher anastomotic leak rate (17.2 % v 10.7 %; P = 0.007) and surgical site infection, however in-hospital mortality was similar [25]. A recent single center retrospective analysis of patients treated with planned oesophagectomy (N = 964) versus salvage oesophagectomy (N = 173) reported a higher rate of serious complications (33 % vs. 17 %; $P < 0.0001$), which were mostly serious pulmonary complications (27 % vs. 14 %; $P < 0.0001$), while anastomotic leaks were equivalent in both groups. In a multivariate analysis salvage oesophagectomy was a significant factor for a higher risk of postoperative complications (HR 2.10 (1.37–3.21), P = 0.001) [26], and in this study the 5-year OS was higher for planned oesophagectomy compared to patients treated with salvage oesophagectomy for residual or recurrent disease (45 % versus 25.2 %). However, the relatively high number of OAC cases (71–89 %) in this study should be taken into account, and there was a relative long time span of the study in which techniques, especially for RT, have improved [26]. A recent published systematic review and meta-analysis of 23555 patients treated with planned oesophagectomy compared to 2227 salvage oesophagectomies, confirms the data of the above mentioned studies. Salvage oesophagectomy involves a higher complication risk compared to planned surgery (anastomic leak 20.6 % vs 14.5 %, P < 0.001, pulmonary complications 37.1 % vs 24.2 % (P < 0.001)), but 5-year survival stays comparable with an OS of 39.2 % for salvage surgery compared to 42.6 % for planned surgery (P = 0.28) [9]. Thus, despite the higher complication risk which should be taken along in the decision making, salvage oesophagectomy should be taken into consideration after definitive CRT in OSCC patients.

Whether salvage endoscopic resection can replace salvage oesophagectomy for early stage recurrence has not been investigated in head-to-head trials. However since endoscopic resection can achieve the same goal of local control in case of early stage disease, at the compromise of less morbidity, the current evidence supports salvage endoscopic treatment as primary choice in patients with suspected stage T1a-b recurrence [13,16,19,20].

Before the introduction of ESD, several groups have published on salvage EMR after CRT. Although feasible, local recurrence rates after EMR are relatively high of 18–38 % [27–29], and a lower en-bloc resection rate can be achieved compared to ESD. In a large case-serie of 67 EMR's and five ESD's, en-bloc resection rates were 51 %, and the recurrence rate was reasonable 38 % of which 18 % were local recurrence [30]. Yet, last year Nakajo et al. published a single center retrospective comparison between 56 patients treated with salvage EMR and 40 patients treated with salvage ESD for recurrent OSCC after dCRT. En-bloc resection rates were 95 % versus 63 % for ESD versus EMR, with one perforation in the ESD group compared to no major complications after EMR. Moreover, the 3-year local recurrence rate was significantly lower in the ESD group versus the EMR group (5 % versus 27 %, p = 0.027) [14], suggesting ESD is superior to EMR for local control, although it should be noted that this was not a randomized trial. ESD also achieved higher recurrence-free (RFS) and overall survival (OS) rates compared to EMR (3-year RFS 86 % vs 48 % (P < 0.001), OS (91 % vs 72 % P = 0.0026)). These data are in line with the European Society of Gastrointestinal Endoscopy (ESGE) guidelines for primary OSCC lesions: they recommend ESD above EMR based on similar evidence as higher en-bloc and curative resection rates and lower recurrence rates [31]. For small lesions (<10 mm) en-bloc resection might be achieved with EMR, but given the 13–53 % pT1b tumors in salvage endoscopic resection [16,19,20], radical resection of the deep resection margin is more likely with ESD. Therefore, ESD should be preferred above EMR for salvage endoscopic resection.

The current literature proves that salvage ESD for OSCC is a viable option after CRT with a high technical success rate and acceptable risk profile comparable to standard ESD in treatment-naive patients [32]. Several small single-center case series have been published, mostly from Japan [13,17,20,33] and more recently also in a multicenter Western retrospective cohort [15]. En-bloc resection rates are high, 92–100 %, in patients with residual or recurrent disease, with radical resection rates between 58 and 100 % (Table 1). Two series included also ESDs of metachronous lesions within the irradiation field with comparable outcomes and high en-bloc resection rates of 80–100 % [13,18]. Curative resection, generally defined as free deep and lateral margins, and no lymphovascular invasion, was achieved in 47–68.4 % [15–17]. The reason for this wide variation among the studies was mostly lymphovascular invasion [16,17], or due to defining T1b tumors as non-curative [18]. In the study of Al-Kaabi, the horizontal and vertical margin were free in only 61 % and 85 %, but this cohort involved 11 EMR's [15].

Long-term outcomes show overall lower local recurrence rates for ESD than recurrence rates for EMR, between 0 and 21 % (Table 1), and relatively high overall survival rates. Overall and disease specific survival rates are difficult to compare due to the heterogeneity in treatments applied after salvage ESD, varying from palliative chemotherapy to local strategies including second salvage ESD or photodynamic therapy (PDT) [19,20]. Takeuchi et al. reported a 3-year OS of 74 % after salvage ESD (and 5-year around 60 %), however no information on any subsequent therapy was given [16]. These rates are comparable to two larger case-series of 30 and 51 cases with a 3-year OS of 75 %, and disease-specific survival (DSS) rate of 82–87 % [19,20]. In both these studies, patients received variable treatments for recurrence after ESD such as chemotherapy, repeat ESD, argon plasma coagulation (APC) or PDT. In the study of Al-Kaabi et, the only report of Western data, these numbers seemed lower, OS 52 %, and DFS of 79 %, however as previously mentioned the cohort consisted of both EMR and ESD's in patients with OAC and OSCC [15]. In Fig. 1 we show two examples from our experience who were successfully treated with ESD after CRT (see Fig. 1).

The literature regarding ESD for OAC tumors after definitive CRT is scarce. The recently published case-series of Al Kaabi et al. is the only study who included 9 OAC cases treated with either EMR or ESD(15). DFS seemed higher in the OAC patients compared to the OSCC patients (median, 100 % vs 54 %, P = 0.03), however a multivariate analysis

Table 1
Overview of case-series of salvage endoscopic therapy after definitive CRT.

First author	Year	N, type of cancer	Type of endoscopic resection	Succes rate	En-bloc rate	Local recurrence rate (FU in months)	Adverse Events	Type of endoscopic resected lesion	Invasion depth	Prior treatment
Al-Kaabi et al.	2021	35 OSCC 9 OAC	11 EMR 24 ESD	Radical 58 % Curative 47 %	ESD 92 % EMR 46 %	44 % (24 m)*	Early: 0 Late: 4 strictures	Recurrent: 52 % Residual: 32 % Unknown: 16 %	M1-3 60 % Sm1-3 23 %	Various, at least 84 % CRT
Takeuchi et al.	2013	19 OSCC	ESD	Radical: 94.7 % Curative: 68.4 %	100 %	0 % (55 m)	0	Recurrent: 79 % Residual: 21 %	Ep-LPM: 47 % MM/SM1 21 % SM2 32 %	RT or CRT (min 50Gy)
Koizumi et al.	2014	12 OSCC	ESD	Radical: 100 % Curative: 50 %	92 %	3/12 metachronous lesion treated with 2nd ESD	Early: 0 Late: 2 strictures	Recurrent 100 %	EP-LPM: 58 % MM: 8 % SM2: 33 %	dCRT (60Gy)
Nakajo et al.	2018	69 OSCC	ESD	Residual: 93 % Metachronous 100 %	Residual 93 % Metachronous 100 %	4 % (18 m)	0	Residual: 51 % Metachronous: 49 %	EP-LPM 70 % MM 13 % SM2 13 %	(d)CRT (min 50Gy)
Kagawa et al.	2018	10 OSCC	ESD	Curative: 60 %	80 %	0 % (12 m)	0	Recurrent: 30 % Residual: 30 % Metachronous: 40 %	EP-LPM 80 % MM 20 %	dCRT (60Gy)
Kimura et al.	2021	30 OSCC	ESD	Radical: 58 %	94 %	17 % (51 m)	Early: 1 perforation Late: 7 strictures	Recurrent: 82 % Residual: 18 %	EP-LPM 40 % MM 24 % SM2 33 %	CRT (min 50Gy)
Shiota et al.	2023	77 OSCC	(26 PDT) 51 ESD	Radical ESD 95 %	ESD 95 %	ESD 21 % (FU 41 m)	ESD Early: 0 % Late: 7.1 % strictures	unknown	ESD EP-LPM: 83 % MM/SM1 14 % SM2 3 %	CRT (min 50Gy)

Radical resection: without positive horizontal or vertical margins; Curative resection: no.
Curative resection: no positive horizontal and vertical margins, and no lymphovascular invasion. Radical resection: no positive margins.
OSCC: oesophageal squamous cell cancer, OAC: oesophageal adenocarcarcinoma EMR: endoscopic mucosal resection, ESD: endoscopic submucosal dissection, FU: follow-up, EP-LPM: epithelium-lamina propria, MM: muscularis mucosa, SM: submucosal, RT: radiotherapy, CRT: chemoradiotherapy, dCRT: definitive chemo-radiotherapy.
* no differences between ESD or EMR.

could not be completed due to the low number of included patients.

Initially ESD after definitive CRT was proposed with caution, since it was believed that endoscopic salvage treatment was more difficult due to post-radiation fibrosis. However, in two series salvage ESD after definitive CRT was directly compared to treatment-naive patients who underwent primary treatment with ESD, with good outcomes [13,18]. En-bloc resection rates were slightly higher in the treatment-naive ESD patients, 92–98 % compared to 80–93 % in the salvage ESD patients, and curative resection rates were respectively 73–83 % versus 60–63 % [13, 18]. One study specifically analyzed fibrosis levels in all specimens and showed that the ten CRT treated ESDs had a higher percentage of fibrosis in the lamina propria, muscularis mucosae and submucosa compared to non-CRT ESD (N = 59) [18]. Nevertheless severe fibrosis of the submucosa was only observed in one of the ten cases and the en-bloc resection rate was 80 %. Although the fibrosis rate might be higher after CRT and the ESD might be more challenging, the high level of technical success implicate ESD is feasible, and with the high survival rates and low complication profile ESD is still favorable above surgery.

4. A shifting paradigm

Previously patients treated with dCRT received no standardized follow-up since treatment options were limited in case of recurrence, with only palliative radio- or chemotherapy available. Salvage oesophagectomy changed this course, and patients fit and willing to undergo subsequent surgery receive follow-up according to local protocols with often radiological imaging and/or endoscopies. With the evidence accumulating for salvage ESD after definitive CRT, at least in OSCC standardized follow-up needs to be considered for patients treated with curative intent and fit enough to undergo subsequent treatment. In the current literature most centers follow close endoscopic monitoring every three months, and similar intervals are given for radiological imaging (Table 2). To allow endoscopic intervention, timely detection in an early stage is pivotal. Hence an endoscopic evaluation at least carried out every 3 months in the first year seems reasonable. In Fig. 2 we suggest a possible follow-up scheme.

Not only patients treated with definitive CRT will benefit from close endoscopic monitoring. The finalized SANO-2 trial is evaluating if an active surveillance approach is non-inferior to the standard of care of neoadjuvant treatment followed by direct oesophagectomy, and the final results of the trial are expected soon [34]. These patients are currently already under strict endoscopic monitoring, with initial endoscopies every six weeks, and endoscopic ultrasound (EUS) after 12 weeks [35]. Patients under long-term follow-up with only early local recurrence (<T2) at the primary tumor site without distant metastasis might benefit from initial salvage ESD, with the option of oesophagectomy remaining.

5. Summary

Since a proportion of oesophageal cancer patients have residual or recurrent disease after definitive CRT, salvage treatment is endorsed in

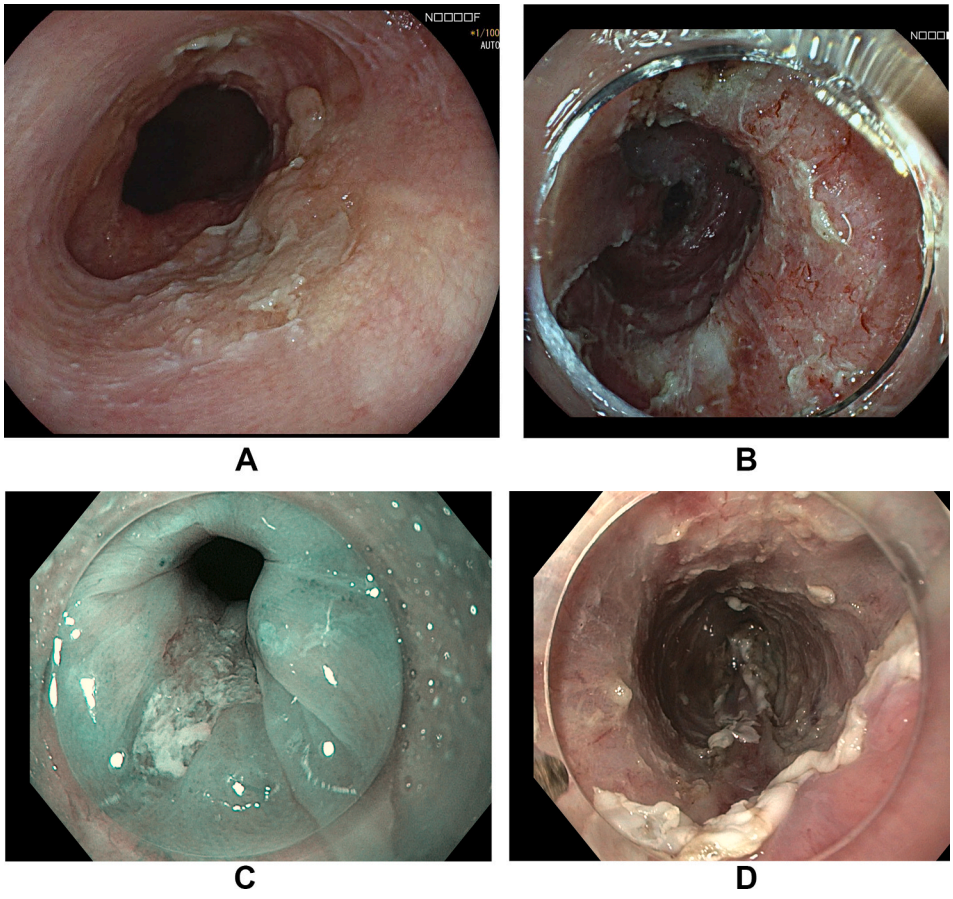

Fig. 1. ESD of OAC case and OSCC case
A-B: representative images are given of a patient previously treated with definitive chemoradiation for a cT2N1M0 OAC due to comorbidity. Three years later patients is anemic and endoscopy shows an ulcer at the previous tumor site with biopsies positive for OAC. The 20 mm lesion is resected en bloc with ESD without complications, and final pathology diagnosis reveals a pT1bsm1 tumor without lymphovascular invasion and free lateral and deep resection margins. No signs of recurrence have been detected 2 months after.
C-D: images are shown of a patient who presented with a cT2N0M0 hypopharynx tumor and cT2N0M0 OSCC just below the upper oesophageal sphincter and was initially treated with chemoradiation (41.4Gy). Four months after completion a 10 mm recurrent lesion was seen at endoscopy. A 90 % circumferent ESD was performed without complications and revealed high grade dyplasia. A post-ESD stricture was treated successfully with balloon dilatations and kneedle knife incicions. Patient remains disease free 3 years after.

Table 2
Summary of follow-up schemes after definitive CRT and after ESD for residual/recurrent oesophageal cancer.

	Imaging	Endoscopy	Follow-up after ESD
Takeuchi et al.	No follow-up	No follow-up	Endoscopy 3-monthly first year, 6-monthy thereafter, CT every 4–6 months
Koizumi et al.	Follow-up with CT, no scheme provided	FU with endoscopy, no scheme provided	Endoscopy after 2 and 6 months, thereafter 6-monthly
Nakajo et al.	No follow-up	No follow-up	Endoscopy 3, 6, and 12 months, 6 monthly thereafter. CT every 6 months
Kagawa et al.	No follow-upn	No follow-up	Endoscopy every 6-months
Hombu et al.	3-months first 2 year, 6-montly afterwards	Montly until complete respons Complete repons: 3-montly 2 years Afterwards: 6-montly	Endoscopic examinations and CT were carried out at 3, 6, and 12 months after salvage ER, and every 6 months thereafter
Shiota et al.	No follow-up	No follow-up	Every 3–4 months endoscopy, yearly CT

clinical practice. Surgical treatment is considered in fit and resectable patients, but is associated with high morbidity. For recurrent or metachronous early stage OSCC, endoscopic resection is a valid alternative. ESD is the preferred technique, due to the higher en-bloc resection rate and lower locoregional recurrence rate. Although results are early with no randomized trials available, case-series report high technical success with en-bloc resection of 92–100 % and good long-term clinical outcomes with local recurrence rates between 0 and 21 % and 3-year OS around 75 %. Fibrosis levels might be higher and the procedure more complex, but the high technical success rate and low complication rate of 0–3 %, prove ESD is a valid alternative as salvage treatment to surgery. Whether ESD could also be suitable for OAC has yet to be determined, while technically this should be feasible, different tumor biology might influence long-term outcomes. Furthermore, the gastroenterologist might encounter this dilemma more frequent if active surveillance becomes a standard choice for oesophageal cancer. Lastly, since early detection is crucial to allow early endoscopic intervention, standardized follow-up would need to be incorporated in patients willing and eligible for salvage treatment.

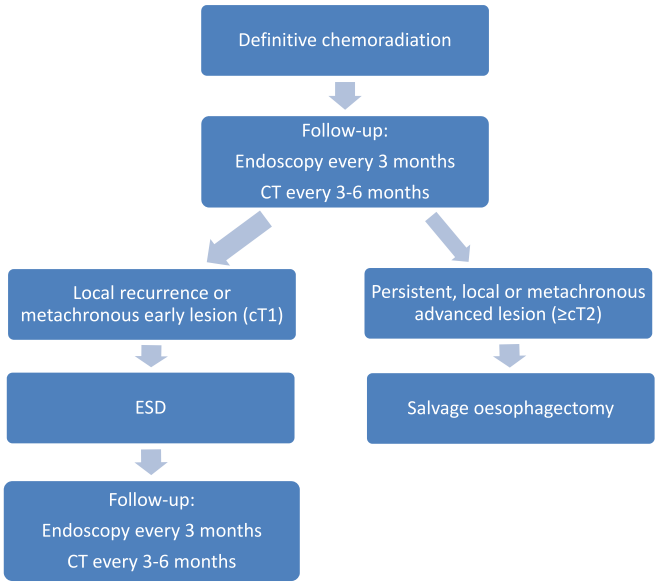

Fig. 2. Proposed diagram for clinical management after definitive CRT for OSCC patients fit for subsequent therapy
OSCC: oesophageal squamous cell cancer, CRT: chemoradiotherapy.

6. Research agenda

- Set-up a multicenter internationally database to monitor outcomes of salvage ESD after definitive CRT in both OSCC and OAC patients.
- Develop a standardized follow-up scheme after definitive chemo-radiation in oesophageal cancer patients
- Investigate if ESD can become part of an active surveillance approach instead of direct oesophagectomy after neoadjuvant CRT in oesophageal cancer

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article.

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