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Endoscopic submucosal dissection for early esophagogastric junction adenocarcinomas: a systematic review

Paul Doumbe-Mandengue[a], Anna Pellat[a,b], Benoit Terris[b,c], Frédéric Beuvon[c], Mahaut Leconte[d], Anthony Dohan[b,e], Stanislas Chaussade[a,b], Romain Coriat[a,b], Maximilien Barret[a,b]

Cochin Hospital, Assistance Publique - Hôpitaux de Paris; Université de Paris, France

Abstract

Background Esophagogastric junction adenocarcinomas (EGJAs) include esophageal and gastric cardia adenocarcinomas (GCAs). These tumors are currently regarded as a single entity, with similar surgical and oncological therapies, although they originate from different organs. Endoscopy allows an early-stage diagnosis, where both subtypes can be differentiated. With this review we aimed to describe the outcomes of endoscopic submucosal dissection for the treatment of esophageal adenocarcinomas (EAs) and GCAs.

Methods We identified studies by screening PubMed, Embase and Web of Science. We included all 19 studies that mentioned at least one of the following criteria of interest: *en bloc*; R0 resection; local recurrences; and/or overall survival.

Results We found an *en bloc* resection rate superior to 90% for both tumors. R0 resections rates were over 60% for most EAs, vs. 83% for most GCAs. We recorded less than 13% and 20% early and late adverse events for EA, and 10% and 7% for GCA. The local recurrence rate was 8% for EA and 3% for GCA. The overall survival was over 90%.

Conclusions Endoscopic submucosal dissection is safe and effective for esophageal and GCAs. These data support the extension of the use of endoscopic submucosal dissection to all EGJAs, including early EAs.

Keywords Esophagogastric junction adenocarcinoma, Barrett's adenocarcinoma, gastric cardia adenocarcinoma, endoscopic submucosal dissection

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[a]Department of Gastroenterology and Digestive Oncology, Cochin Hospital, Assistance Publique - Hôpitaux de Paris (Paul Doumbe-Mandengue, Anna Pellat, Stanislas Chaussade, Romain Coriat, Maximilien Barret); [b]Department of Medicine, Université de Paris (Anna Pellat, Benoit Terris, Anthony Dohan, Stanislas Chaussade, Romain Coriat, Maximilien Barret); [c]Department of Pathology, Cochin Hospital, Assistance Publique - Hôpitaux de Paris (Benoit Terris, Frédéric Beuvon); [d]Department of Digestive Surgery, Cochin Hospital, Assistance Publique - Hôpitaux de Paris (Mahaut Leconte); [e]Department of Diagnostic and Interventional Imaging, Cochin Hospital, Assistance Publique - Hôpitaux de Paris (Anthony Dohan), France

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Correspondence to: Maximilien Barret, 27 rue du Faubourg Saint-Jacques, 75014 Paris, France, e-mail: maximilien.barret@aphp.fr

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Introduction

Esophageal cancer accounted for 600,000 new cases worldwide in 2020, ranking 7th and 6th in terms of incidence and cancer-related mortality, respectively [1]. There are 2 main histologic subtypes of esophageal cancer: squamous cell carcinomas (SCC) and adenocarcinomas. SCC share the same risk factors with other squamous epithelium cancers (especially cigarette smoking and heavy alcohol drinking); esophageal adenocarcinomas (EA) arise from Barrett's esophagus, a columnar epithelium harboring intestinal metaplasia, resulting from the healing of peptic esophagitis in patients with gastroesophageal reflux disease (GERD) and obesity [2]. Chronic *Helicobacter pylori* (*H. pylori*) infection is a protective factor for EA [3]. Worldwide, the most common histology is SCC, mainly because of its high incidence in Eastern Asia. On the other hand, EA represent two-thirds of esophageal cancers in western countries, and their incidence is still rising [3]. Considering the increasing frequency of risk factors for adenocarcinomas, particularly excess body fatness and GERD, it is likely that this subtype will become the most prevalent esophageal cancer in many countries [4].

Gastric cancer accounted for over 1,000,000 new cases in 2020, ranking 5th and 4th in terms of incidence and cancer-

related mortality, respectively [1]. Risk factors for gastric adenocarcinoma include atrophic gastritis and gastric intestinal metaplasia, mainly caused by chronic *H. pylori* infection, alcohol consumption, cigarette smoking and a salty diet [5]. Gastric cardia adenocarcinomas (GCAs) are increasingly prevalent among gastric cancers [6]. Although EA and GCA may share some risk factors, such as excess body fatness [2], the reported protective role of *H. pylori* infection suggests that EA and GCA might have been mixed in some studies [7].

Esophagogastric junction adenocarcinoma (EGJA) is a clinical entity encompassing adenocarcinoma arising from the lower esophagus and the proximal stomach, including the gastric cardia. Most cases are diagnosed at an advanced stage, where it is often impossible to determine whether an EGJA is an EA reaching the stomach, or a gastric adenocarcinoma invading the esophagus. As a result, surgeons and gastrointestinal oncologists frequently mix both cancer types in clinical studies [8-11]. In 1998, Siewert and Stein introduced a classification for the management of EGJA [12]. In this classification, the actual EGJA is termed Siewert type II, and extends from 1 cm above to 2 cm below the squamocolumnar junction. The quantitative and qualitative expansion of gastrointestinal endoscopy allows EGJA to be diagnosed at an early stage, where EA can be discriminated from GCA. EAs typically arise from a Barrett's esophagus, in a patient with a hiatal hernia, a GERD history or endoscopic evidence of GERD, and specific features of the esophagus surrounding the lesion at histological examination (duplication of the *muscularis mucosae*, esophageal glands, squamous epithelium between sites of columnar epithelium). GCA occurs in patients without the aforementioned features but with chronic atrophic gastritis or gastric intestinal metaplasia, and/or *H. pylori* infection.

Surgical resection is the historical and currently recommended treatment for most cases of resectable EGJA [13,14]. However, surgical resection of EGJA, by means of an esophagectomy or a gastrectomy extended to the lower esophagus, results in a severe morbidity of 29% and 19%, respectively, and a 30-day mortality of 2.4% and 5.3%, respectively [15].

Gastrointestinal endoscopy allows the resection of T1N0M0 stage tumors, also referred to as "early" or "superficial" tumors, with acceptable oncological outcomes. Furthermore, endoscopic resection shows a better safety profile, lower costs and less impairment of quality of life when compared to surgical resection [16-19]. Finally, the development of upper gastrointestinal malignancy screening programs in eastern Asia, and the surveillance of preneoplastic conditions of the upper gastrointestinal tract (gastric intestinal metaplasia and Barrett's esophagus) will lead to an increased proportion of early EGJA diagnoses.

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are the 2 modalities for endoscopic resection. ESD is more time consuming, more expensive, and takes a longer time to master, but allows for *en bloc* resection of a T1 lesion, regardless of its size and morphology. Conversely, EMR is cheap, quick, and widely performed throughout endoscopy centers, but is limited by the size of the cap and/or the electrocautery snare used (typically, EMR does not allow *en bloc* resection of lesions exceeding 15 mm in size), and the quality of the submucosal lifting of the lesion after submucosal injection, which may be impaired or absent in the case of fibrotic or ulcerated tumors. The aim of endoscopic resection for early EGJA is to obtain a curative resection, defined by a histologically complete resection with a low risk of lymph node metastasis (well differentiated tumor, absence of lymphovascular involvement, and absence of submucosal invasion below 500 μm).

The risk of lymph node metastasis increases with the depth of the tumor, as T1a tumors (i.e., tumors invading the mucosa) are not associated with lymph node metastasis [20]. On the other hand, the prevalence of lymph node metastasis in T1b tumors is higher, reaching 20% to 35% in several surgical studies [21,22]. The issue is to evaluate *a priori*, through magnifying endoscopy and biopsies, the depth of the tumor to choose between endoscopic resection and surgery.

Released in 2015, the European Society of Gastrointestinal Endoscopy guidelines advised the use of EMR for EA and ESD for gastric adenocarcinomas [23]. However, the expansion of ESD in the West has led many teams to resect EA with ESD in the last decade [24,25].

In 2021, gastrointestinal endoscopy of EGJA allows the discrimination between EA and GCA. While endoscopists advocate different treatments, oncologists and surgeons treat them as a single disease. Our aim was to review the literature on the treatment of early EGJA by a single and most advanced endoscopic technique, namely ESD. The purpose of this review was to describe the clinical and technical outcomes of ESD for the treatment of EA and GCA, searching for potential differences between EA and GCA.

Materials and methods

Search strategies

We identified studies of interest by searching 3 different databases, PubMed, Embase and Web of Science, for the period from January 1st, 2006, to April 11th, 2021. Our search was limited to studies involving human patients, written in English, with an abstract available, without regional restriction. Since our aim was to assess the differences between ESD in EA and in GCA, we conducted our search using 1 or 2 search strings per topic (esophageal ESD and gastric cardia ESD), in each database.

In PubMed, we used the following search strings to look for studies involving EA and EGJA, respectively: ("Barrett Esophagus"[Mesh] AND "Adenocarcinoma"[Mesh]) AND ("Endoscopic submucosal dissection"); ("Barrett's esophagus") AND ("endoscopic submucosal dissection"); and ("Esophagogastric Junction"[Mesh] AND "Adenocarcinoma"[Mesh]) AND ("Endoscopy"[Mesh] OR "Endoscopy, Digestive System"[Mesh] OR "Endoscopy, Gastrointestinal"[Mesh]). Similarly, in Embase

the following search strings were used: ('Barrett esophagus'/exp OR 'barrett esophagus') AND ('endoscopic submucosal dissection'/exp OR 'endoscopic submucosal dissection'); and ('gastroesophageal junction' OR (esophagogastric AND junction)) AND adenocarcinoma AND 'endoscopic submucosal dissection'. Finally, in Web of Science we used: TS ='endoscopic submucosal dissection' AND (TS='esophagus' AND TS='barrett'); and (TS='esophagogastric junction' OR TS='gastroesophageal junction') AND (TS='adenocarcinoma') AND (TS='endoscopic submucosal dissection').

Using these search strategies, studies were assessed for relevance based on their title and their abstract. We included all studies that involved EA or GCA and reported at least one clinical or histological outcome such as *en bloc* resection, R0 resection, or curative resection. Duplicates between the 3 databases were removed. Review articles, conference abstracts, editorials and case reports were not included in the analysis, but we used their information for the background and discussion. We excluded studies that dealt with EGJA without differentiating EA from GCA, and studies that included both types of Siewert II adenocarcinomas without analyzing them separately.

Finally, we accessed the full text of the remaining publications and excluded additional studies not in the scope of our study or when duplicates were found. We searched the references of each study included in the review for additional relevant publications, as well as the authors' own libraries.

Data extraction and definitions

The search strings were elaborated by PDM (Paul Doumbe-Mandengue) and MB (Maximilien Barret). PDM conducted the screening, data extraction and selection of the final articles. MB independently verified the searches. We defined *a priori* the variables of interest to be extracted from each study—characteristics of the patients and the lesions, study endpoints, clinical and histological outcomes, long-term outcomes, and adverse events—and included them in the Tables.

In all studies, EA were defined endoscopically as adenocarcinomas arising in the tubular esophagus from a visible Barrett's mucosa. Moreover, when it was described, histological features helped to define an EA when duplications of the *muscularis mucosae*, esophageal glands or squamous epithelium between sites of glandular epithelium were found. On the other hand, GCA was defined as an EGJA arising from below the squamocolumnar junction, without the previously mentioned histological features.

If the definition of an *en bloc* resection is consensual, the definitions of histologically complete (R0) and curative resection are controversial. Probst *et al*, Barret *et al* and Doumbe-Mandengue *et al*, in studies evaluating the efficacy of ESD for EA, distinguished 2 different definitions for R0 resections: cancer-free margins, and high-grade dysplasia-free margins [24,34,35]. In our work, we decided to use the outcomes of the "high-grade dysplasia-free margins" definition, in order to homogenize the results. Nagami *et al*, Shimizu *et al* and Subramaniam *et al* considered an R0 resection to be a histologically complete resection for EA [25,33,36]. All the other studies included for EA and GCA termed "R0 resection" a resection with high-grade dysplasia-free margins.

The definition of a curative resection is evolving over time, making it impossible to use a single definition for all the studies included in this work. For this variable, we therefore used the definition described in each study. In the studies assessing the clinical outcomes of EA, we found 5 different definitions in 17 publications. The most common and most recent definition, also used by the European Society of Gastrointestinal Endoscopy (ESGE), was used in 7 publications and was the following: a resection is considered curative if it is an *en bloc* and R0 resection of a well-to-moderately differentiated T1a or T1bsm1 (<500 μm) lesion, without lymphovascular invasion [25,27,30,33-36]. Other definitions encountered used a different deep submucosal invasion cutoff (200 μm) [32,37], did not mention the deep submucosal invasion [38], considered submucosal invasion, even below 500 μm, as non-curative [24,31], or used the gastric adenocarcinomas criteria [28].

In the studies assessing clinical outcomes of GCA, the definition of a curative lesion was more consensual and met the Japanese Classification of Gastric Carcinoma: intramucosal differentiated adenocarcinoma, regardless of tumor size, without ulceration; intramucosal differentiated adenocarcinoma less than 30 mm in size with ulceration; or minute submucosal differentiated adenocarcinoma (within 500 μm of the *muscularis mucosa*) less than 30 mm in size; and intramucosal undifferentiated adenocarcinoma less than 20 mm in size without ulceration.

Results

Study selection

By combining searches of our 3 databases we found 1156 hits, as shown in the PRISMA flow diagram (Fig. 1). Among these hits, automation tools—mainly language and publication type filters—from PubMed, Embase and Web of Science allowed us to exclude 375 studies. One hundred sixty-eight studies were duplicates and were removed. We excluded 576 more records after assessing 613 abstracts. Finally, we accessed the full text of 37 studies and assessed them for eligibility. Nineteen were excluded, mostly because of the absence of endoscopic criteria of interest and the absence of possible discrimination between EA and GCA. One publication was added from the authors' own library.

Of the 19 publications finally included, the majority were single-center retrospective studies. Three were multicenter and retrospective [25-27], 3 were prospective [24,28,29], and 1 was randomized controlled [30]. Thirteen of the 17 studies involving EA were conducted in western countries (France, Germany, Belgium, UK, USA), whereas only 1 study involving

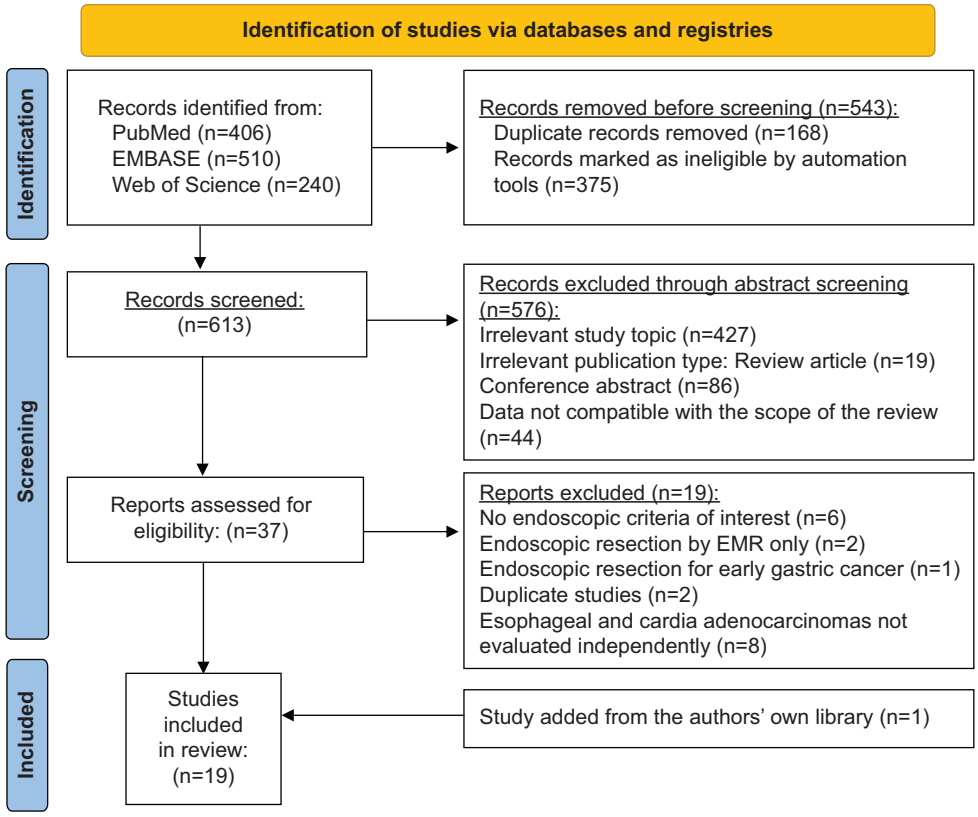

Figure 1 PRISMA 2020 flow diagram of the study selection
EMR, endoscopic mucosal resection

GCA was conducted in a western country. All the other publications were eastern Asian studies. Four studies were designed to compare EA with GCA [31-34].

Short-term outcomes

Outcomes for studies reporting on ESD for EA and GCA are presented in Tables 1 and 2, respectively. Table 3 presents the data of the 4 studies that specifically compared ESD for EA and GCA. An example of an endoscopic and a histological view of ESD for EA and GCA is presented in Fig. 2.

The mean patient's age ranged from 60-72 years in all the 19 publications included. In both EA and GCA studies, the lesion size was around 15-20 mm and the size of the resection was twice as large.

An *en bloc* resection rate superior to 95% was achieved in 12/17 (71%) studies on EA and 4/6 (67%) studies on GCA. In both types of cancer, all the lesions were resected *en bloc* when the lesion was strictly inferior to 20 mm.

The R0 resection rate was lower in EA and ranged from 39-100% vs. 83-96% in GCA. Notably, 2/17 (12%) studies for EA and 2/6 (33%) studies for GCA did not mention their R0 resection rate [32,38,39]. In the 4 studies that directly compared EA to GCA, 1 found an R0 resection rate significantly higher in the gastric cardia group (99/103 or 96.1% vs. 16/25 or 64%, P<0.05) [31], 2 found no differences [33,34], and 1 did not assess this variable but found a curative resection rate significantly higher in the gastric cardia group (71/87 or 81.6% vs. 34/55 or 61.8%, P=0.01) [32].

The curative resection rate ranged from 48% to 86% in EA and from 60-82% in GCA. In 2 studies involving 128 and 142 patients, Hoteya *et al*, as well as Osumi *et al*, found a significantly higher curative resection rate in GCA compared to EA: 48% vs. 80% (P<0.05), and 61.6% vs. 81.6% (P=0.01) respectively [31,32].

Long-term outcomes

The average duration of follow up was heterogeneous between the studies for both EA and GCA. Follow-up duration ranged from 11-42 months in studies on EA, and from 17-69 months in studies on GCA.

The recurrence rate was low, ranging from 0-19% in EA and 0-2.4% in GCA. Doumbe-Mandengue *et al* found a 19% recurrence rate for EA, as this study mixed actual local recurrences and metachronous lesions [34]. Likewise, the overall survival rate was superior to 89% in all studies but one, as Hoteya *et al* in 2013 found a 74% overall survival rate [31]. There were no statistically significant differences between gastric cardia and EA in terms of recurrence rate and overall survival rate, in the 4 studies that investigated both types of cancers.

Table 1 Outcomes of studies reporting on endoscopic submucosal dissection for esophageal adenocarcinomas

Study [ref.]	Country	Study design	Mean age (years)	Number of procedures	Proportion of LSBE (%)	Follow up (median, months)	Endpoints	Mean size of the lesion/ resection (mm)	*En bloc* resection rate (%)	R0 resection rate (%)	Curative resection rate (%)	Early adverse event rate (%)	Late adverse event rate (%)	Local recurrence rate (%)	Overall survival † (%)
Doumbe-Mandengue *et al* (2021) [34]	France	Retrospective	67	57	NM	24	Comparative outcomes vs. GCA	20/40	100	75	56	2	14	19	89
Tomizawa *et al* (2020) [26]	USA	Retrospective, multicenter	71	32	NM	16	Technical outcomes of salvage vs. first line ESD	NM/32	97	78	NM	0	4	NM	NM
Podboy *et al* (2020) [40]	USA	Retrospective	71	20	NM	14	Comparative outcomes vs. EMR	17/28	100	81	NM	0	15	5	NM
Shimizu *et al* (2018) [36]	Japan	Retrospective	64	91	21	29	Compare clinical outcomes of SSBE vs. LSBE	15/36	100	83	72	0	3	8	95
Osumi *et al* (2017) [32]	Japan	Retrospective	64	55	NP	NM	Comparative outcomes vs. GCA	15/NM	100	NM	61.6	3.6	NM	0	NM
Yang *et al* (2017) [27]	USA	Retrospective, multicenter	69	46	46	11	Evaluate safety and efficacy	NM/45	96	76	70	9	15	0	NM
Terheggen *et al* (2017) [30]	Germany	Prospective, randomized	64	20	NM	23	Comparative outcomes vs. EMR	16/29	100	59	53	0	NM	NM	NM
Subramaniam *et al* (2017) [25]	United Kingdom/ Italy/ Switzerland	Retrospective, multicenter	71	143	72	22	Safety and short-term efficacy	31/NM	91	79	66	1.4	2.1	7	93
Coman *et al* (2016) [28]	USA	Prospective	69	36	30	10	Safety and short-term efficacy	NM/49	100	81	69	3	19	0	NM

(Contd...)

Table 1 *(Continued)*

Study [ref.]	Country	Study design	Mean age (years)	Number of procedures	Proportion of LSBE (%)	Follow up (median, months)	Endpoints	Mean size of the lesion/ resection (mm)	*En bloc* resection rate (%)	R0 resection rate (%)	Curative resection rate (%)	Early adverse event rate (%)	Late adverse event rate (%)	Local recurrence rate (%)	Overall survival † (%)
Barret *et al* (2016) [35]	France	Retrospective	66	36	NM	13	Safety and short-term efficacy	NM/51	89	72.4	51.4	8	9	6.9	NM
Probst *et al* (2015) [24]	Germany	Prospective	66	87	69	24	Safety and short-term efficacy	21/39	95	73.6	72	1	9	2	96
Höbel *et al* (2015) [37]	Germany	Retrospective	64	22	NM	19	Safety and short-term efficacy	NM/44	96	82	76	13	14	6	NM
Chevaux *et al* (2015) [38]	Belgium	Retrospective	68	75	NM	20	Safety and short-term efficacy	20/53	90	NM	85	7	60	0	92
Kagemoto *et al* (2014) [41]	Japan	Retrospective	63	26	13	33	Safety and short-term efficacy	19/NM	100	85	NM	0	19	0	NM
Nagami *et al* (2014) [33]	Japan	Retrospective	61	14	7	42	Comparative outcomes vs. GCA	18/NM	100	100	86	0	0	0	100
Hoteya *et al* (2013) [31]	Japan	Retrospective	64	25	NM	34	Comparative outcomes vs. non-junctional gastric adenocarcinomas	20/NM	NM	64	48	4	NM	0	74
Neuhaus *et al* (2012) [29]	Germany	Prospective	60	30	30	17	Safety and short-term efficacy	20/25	90	39	NM	6.6	3.3	0	NM

† at the end of the follow up

NM, not mentioned; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SSBE, short-segment Barrett's esophagus (>3 cm); LSBE, long-segment Barrett's esophagus (>3 cm); GCA, gastric cardia adenocarcinoma

Table 2 Outcomes of the studies reporting on endoscopic submucosal dissection for gastric cardia adenocarcinomas

Study [ref.]	Country	Study design	Mean age (years)	Number of procedures	Follow up (median, months)	Endpoints	Mean size of the lesions/ resections (mm)	*En bloc* resection rate (%)	R0 resection rate (%)	Curative resection rate (%)	Early adverse event rate (%)	Late adverse event rate (%)	Local recurrence rate (%)	Overall survival (%) †
Doumbe-Mandengue *et al* (2021) [34]	France	Retrospective	68	19	17	Comparative outcomes vs. EA	25/50	89	83	63	5.3	5.3	0	100
Osumi *et al* (2017) [32]	Japan	Retrospective	72	87	NM	Comparative outcomes vs. EA	18/NM	100	NM	81.6	2.3	NM	2.3	NM
Gong *et al* (2016) [19]	Korea	Retrospective	66	88	69	Safety and short-term efficacy	20/NM	88.6	83	60.2	9	1.2	2.4	93.2
Nagami *et al* (2014) [33]	Japan	Retrospective	65	29	42	Comparative outcomes vs. EA	13/NM	100	89.7	75.9	3.4	6.8	0	89
Hoteya *et al* (2013) [31]	Japan	Retrospective	69	103	34	Comparative outcomes vs. non-junctional adenocarcinomas	21.8/NM	NM	96	80	4	NM	0	94
Hirasawa *et al* (2010)[39]	Japan	Retrospective	69	58	37	Safety and short-term efficacy	20.3/37.7	100	NM	79	5	2	0	91

†: at the end of the follow-up period
NM, not mentioned; EA, esophageal adenocarcinoma

Figure 2 Endoscopic and histological presentations of esophageal and gastric cardia adenocarcinomas. (A) Endoscopic presentation of a Paris 0-IIa esophageal adenocarcinoma. The black arrows show the limits of the lesion. (B) Endoscopic presentation (in retroflex vision) of a large Paris 0-Is gastric cardia adenocarcinoma. The black arrows show the demarcation lines of the lesion. (C) Histopathological assessment of an esophageal adenocarcinoma, hematoxylin-eosin-saffron. The scale is indicated at the bottom of the image. The black arrow shows glands in intestinal and glandular metaplasia, while the grey arrow shows a squamous mucosa, corresponding to a normal esophageal mucosa between the metaplastic mucosa and the adenocarcinoma. The black star indicates the esophageal adenocarcinoma. (D) Histopathological assessment of the gastric cardia adenocarcinoma shown in panel B, hematoxylin-eosin-saffron. The scale is indicated at the bottom of the image. (E) Histopathological assessment of the esophageal adenocarcinoma shown in panel C, hematoxylin-eosin-saffron. The scale is indicated at the bottom of the image. The black arrow shows the duplication of the *muscularis mucosa*, typical of a Barrett's esophagus. The black star shows the submucosal invasion of the esophageal adenocarcinoma. (F) Histopathological assessment of the esophageal adenocarcinoma shown in panels B and D, hematoxylin-eosin-saffron. The scale is indicated at the bottom of the image. The black arrow shows a superficial mucosa in high-grade dysplasia, extending to the submucosa. The black star shows cystic glands in the submucosa, corresponding to the adenocarcinoma invading the submucosa

Adverse events

The early rate of adverse events, mainly large bleeding and perforations, was less than 8% for EA, except for one study (13% in a study by Höbel *et al* [37]). We recorded at most 6% adverse events in GCA.

The late adverse events were mostly explained by strictures and delayed bleedings. Of the 15 studies that assessed late adverse events after the resection of EA, 6 found a late adverse events rate ranging between 0% and 5% [25,26,29,33,36], 2 found between 5% and 10% [24,35], 6 between 10% and 20% [27,28,34,37,40,41], while 1 reported a 60% late adverse events rate [38]. The 4 studies designed to compare EA to GCA

Table 3 Outcomes of the studies comparing ESD for esophageal and gastric cardia adenocarcinomas

Study [ref.]	Mean age (years)	Number of ESD	Follow up (median, months)	Mean size of the lesions	*En bloc* resection rate	R0 resection rate	Curative resection rate	Early adverse events	Late adverse events	Local recurrence rate (%)	Overall survival † (%)
Doumbe-Mandengue *et al* (2021) [34]	67/68	57/19	24/17	20/25**	100/89	88/83	67/63	2/5.3	14/5.3	19/0	89/100
Osumi *et al* (2017) [32]	64/72	55/87	NM/NM	15.2/17.8**	100/100	NM/NM	61.6/81.6**	3.6/2.3	NM/NM	0/2.3	NM/NM
Nagami *et al* (2014) [33]	61/65	14/29	42/42	18/13	100/100	100/89.7	86/75.9	0/3.4	0/6.8	0/0	100/89
Hoteya *et al* (2013) [31]	64/69	25/103	34/34	20/21.8	NM/NM	64/96**	48/80**	4/4	NM/NM	0/0	74/94

Each line compares EA to GCA (EA/GCA)
†: at the end of the follow up
**: P<0.05
NM, not mentioned; EA, esophageal adenocarcinoma; GCA, gastric cardia adenocarcinoma; ESD, endoscopic submucosal dissection

did not find any significant differences between early or late adverse events in these 2 types of cancer.

Discussion

This review aimed to describe the clinical and histological outcomes of ESD for EA and GCA. We found a high *en bloc* resection rate, superior to 95% for most EAs and GCAs: this result strongly supports the use of ESD for early EGJA. R0 and curative resection rates were also high and seemed superior in GCA.

The local recurrence rate was low, less than 8% for EA and 3% for GCA. The trend for a higher recurrence rate in EA, although not statistically significant in the 4 studies directly assessing this variable, could be explained by the fact that ablative treatments of the remaining Barrett's esophagus might not have been performed in all patients with Barrett's adenocarcinoma, as recommended after an endoscopic resection [23].

The overall survival was high, superior to 90% in almost all studies. Despite a heterogeneous length of follow up, it highlights that early EGJA have high overall survival, stressing the importance of providing the most effective and oncologically adequate endoscopic treatment, without significant morbidity, because the patients' life expectancy is longer.

Hoteya *et al*, in 2013, found a relatively low (74.3%) overall survival rate in patients treated with ESD for an EA, with a median follow up of 34 months [31]. This rate was not significantly different from the 94.3% survival rate in patients treated with ESD for GCA, but the trend for a lower survival rate in this study was mainly explained by a significantly lower curative resection rate (48% vs. 80%, P<0.05). The authors explained that difference by a subsquamous infiltration of the tumors, making it difficult to define the resection margins.

Studies included in our work were heterogeneous in several aspects. First, there were 12 single-center retrospective studies, 3 multicenter retrospective studies, 3 prospective studies, and 1 randomized controlled study. Moreover, 71% of studies assessing EA were conducted in western countries, whereas 83% of studies assessing GCA were conducted in eastern Asia. The primary endpoints of the studies included, presented in Table 1 and Table 2, were also heterogeneous. Furthermore, R0 resections and curative resections followed different definitions, depending on the authors and on the date of publication. For these reasons, we considered that the characteristics of the studies were too diverse to perform a meta-analysis, according to SWiM guidelines [42].

Many other studies conducted to evaluate the follow up of ESD-treated patients found a high 5-year survival rate, and a low local or metastatic recurrence rate [43-45]. This explains the trend towards broadening the criteria for curative resection. For T1 lesions, EMR is recommended for early EA, whereas ESD is recommended for early gastric adenocarcinomas, including GCA. It is explained in the ESGE guidelines, released in 2015, that reasons to favor EMR over ESD are the safety and efficacy of EMR and the risks of ESD. Indeed, in a large single-center retrospective study including more than 1000 consecutive patients with intramucosal EA treated by EMR, Pech *et al* found a 96.3% rate of complete remission of neoplasia and 91.5% 5-year overall survival [46]. Even after an incomplete resection by EMR, radiofrequency ablation can efficiently complete the treatment, also on intramucosal adenocarcinoma, as found by Haidry *et al* in 2015 [47]. Likewise, in an international multicenter retrospective study evaluating the safety of EMR for early EA in 3827 endoscopic resections, Belghazi *et al* found a 0.4% perforation rate and 0.9% post-procedural bleedings [48]. Finally, the only randomized controlled study comparing

EMR to ESD in EA did find significant differences in terms of endoscopic and histological outcomes (R0 resection rate of 59% vs. 12%, curative resection rate of 53% vs. 12%); but the overall survival and local recurrence rates were not statistically different.

Nevertheless, in the study by Pech *et al*, all submucosal adenocarcinomas were excluded from the analysis, which artificially increases the efficacy of EMR. Among patients who were *a priori* eligible for endoscopic resection (i.e., early Barrett's neoplasia), 222/1603 (14%) had a submucosal lesion (T1bsm1, sm2 or sm3) [46]: although intramucosal adenocarcinomas are more common, the safety and efficacy of EMR for the treatment of submucosal EA has yet to be demonstrated. Moreover, in the hands of experienced teams, ESD is a safe technique. In our work, we found an early adverse event rate below 10% in EA and 5% in GCA. In 2021, in a large systematic review and meta-analysis, Han and Sun found no differences between ESD and EMR for EA in terms of bleedings, perforations, or postoperative strictures [49]. In addition, in this meta-analysis, ESD for EA was associated with fewer local recurrences than EMR, especially in the subgroup that included lesions larger than 20 mm [49]. Moreover, Abe *et al* conducted in 2019 a retrospective analysis of 372 patients who underwent ESD or EMR for superficial EGJA, and found favorable long-term outcomes (disease-specific survival over 90%, 5-year cumulative incidence of local recurrence of 13% for EMR and 0.5% for ESD, P<0.01) [44]. The advantages of ESD are the *en bloc* resection, which is more frequently achieved than in EMR [30], the ability to treat T1bsm1 lesions, and the more accurate histological analysis: in 2020, Podboy *et al* found that EMR for EA led to pathologic uncertainty and the inability to reach a definitive diagnosis in 13/31 (42%) EMR vs. 0/20 ESD [40].

This review is the first to our knowledge to describe separately the endoscopic and oncological outcomes of the 2 subtypes of early EGJA. The strength of our work relies on its exhaustiveness, with the screening of 3 databases and 1156 articles. Limitations are mainly due to the retrospective nature of the included studies. Moreover, a lot of studies were excluded because they assessed EGJA as a single entity instead of separating EA from GCA. These data support the extension of the use of ESD for early EA, as it is already recommended for early SCC and early gastric adenocarcinomas including early GCAs.

In summary, in this study, we aimed to review the literature on the treatment of early EGJA by ESD, separating tumors arising from the esophagus and tumors arising from the gastric cardia, and assessing clinical and histological outcomes. We found a high *en bloc* resection rate in the 2 subtypes (more than 90%). R0 and curative resection rates were high, with reasonable early and late adverse events (less than 13% and 20% early and late adverse events for EA, and 10% and 7% for GCA). The overall survival was superior to 90% in both types of adenocarcinoma. In conclusion, ESD seems safe, effective in the short and long term for both subtypes. These data suggest the absence of difference between outcomes of ESD in EA and GCA, supporting a broader use of ESD for the treatment of all EGJAs.

Summary Box

What is already known:

- A large part of early esophagogastric junction adenocarcinomas (EGJAs) can be managed endoscopically
- Endoscopic submucosal dissection (ESD) is recommended for early gastric adenocarcinomas and early esophageal squamous cell carcinomas
- Endoscopic mucosal resection is recommended for early esophageal adenocarcinomas (EAs)

What the new findings are:

- ESD seems effective in the short and long term for early EA and gastric cardia adenocarcinomas (GCAs), with an overall survival rate superior to 90% in almost all studies
- For experienced teams, ESD seems safe, with reasonable early and late adverse events: less than 13% and 20% for EA, and 10% and 7% for GCA, respectively
- ESD should be recommended for all EGJAs

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