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Endoscopic submucosal dissection for the treatment of early Barrett's neoplasia: long-term outcomes of a prospective multicenter study

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Abstract

Background Endoscopic submucosal dissection (ESD) allows for *en bloc* endoscopic resection of T1 esophageal adenocarcinoma arising on Barrett's esophagus (BE). Although the safety of the procedure is well established, the oncological adequacy of the procedure and the long-term follow up of the patients have not been prospectively studied.

Methods We conducted a prospective, multicenter study involving 9 French and Belgian centers. We included patients treated with ESD for a visible endoscopic lesion of more than 15mm documented with dysplasia, with a 3-year follow up. The primary endpoint was the histologically complete resection rate for adenocarcinoma and high-grade dysplasia (HGD).

Results A total of 141 patients were included in the study between December 2016 and January 2019. The R0 resection rate was 85% for adenocarcinoma and HGD, and 81% for invasive adenocarcinoma. The complication rate was 17%, of which 5% were early complications and 12% were late complications, mainly esophageal strictures. During a median follow-up length of 36.3 months, recurrence was observed in 15% of the patients and was endoscopically manageable in 44%. Eight patients (6%) underwent esophagectomy for a high-risk adenocarcinoma. Overall, 14 patients (12%) died during follow up, 3 of them (2.5%) from esophageal adenocarcinoma.

Conclusion Endoscopic resection by ESD is a safe and effective technique to treat T1 esophageal adenocarcinoma, allowing avoidance of esophagectomy in 94% of the patients.

Keywords Barrett's esophagus, esophageal adenocarcinoma, early esophageal neoplasia, endoscopic submucosal dissection

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Conflict of Interest: None

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Introduction

Barrett's esophagus (BE), occurs in about 1% of the adult western population, and in 7% of patients reporting gastroesophageal reflux symptoms [1]. It is the main risk factor for esophageal adenocarcinoma. The annual incidence of high-grade dysplasia (HGD) or adenocarcinoma in BE ranges from 0.1-0.4% [2-4].

Over the last 3 decades, esophagectomy, the historical treatment for T1 adenocarcinoma [5-7], has been replaced by endoscopic resection [8]. Most data on endoscopic resection pertain to endoscopic mucosal resection. Endoscopic submucosal dissection (ESD) allows for *en bloc* resection of

T1 cancers and preneoplastic lesions of the digestive tract, regardless of their size. Although its benefit in terms of oncological outcomes is well established for T1 esophageal squamous cell carcinoma and gastric adenocarcinoma [9], data on ESD for esophageal adenocarcinoma are scarce. Our aim was to report the oncological adequacy, in terms of the histologically complete (or R0) resection rate and long-term oncologic outcomes, of patients treated with ESD for early esophageal adenocarcinoma.

Patients and methods

Study population and inclusion criteria

We conducted a prospective, multicenter study including 9 centers in France and Belgium, with a 2-year enrolment period and a 3-year follow-up period. Participating centers were tertiary centers with extensive experience in ESD—at least 100 ESD procedures per operator—performed throughout the digestive tract. We included patients aged 18-90 years, with BE longer than 2 cm, and a visible endoscopic lesion of more than 15 mm, documented with dysplasia and treated by ESD. Patients with a history of endoscopic therapy for BE, thoracic radiotherapy, esophageal or gastric resection, esophageal strictures, or esophageal varices were excluded. Endoscopic evaluation was conducted in the referral center, completed by endoscopic ultrasonography and CT scan in the case of an endoscopically suspected T2 lesion (Paris 0-Is or 0-III lesion).

Endoscopic procedures

Diagnostic endoscopy was performed using a high-definition gastroscope equipped with narrow-band imaging and dual focus, or blue-laser imaging with magnification. The use of a distal attachment cap or 2% acetic acid chromoendoscopy was optional. All ESDs were performed under general anesthesia with endotracheal intubation and CO_2 insufflation. The choice of ESD knives and the techniques of resection (circumferential incision, tunnel, pocket technique, clip and line traction) was left to the operators. If more than 75% of the esophageal circumference was resected, prevention of esophageal stricture through oral steroid therapy was implemented according to the Yamaguchi protocol [10]. Long-term double-dose proton-pump inhibitors were prescribed following the procedure. Follow-up endoscopies were performed at 3 months, 12 months and 36 months, in addition to the endoscopic procedures needed for the eradication of residual BE.

The indication for additional treatment (surgery or chemoradiotherapy) after ESD was based on histopathological findings, including the presence of high-risk features, such as submucosal invasion, lymphovascular invasion, poor differentiation or positive deep resection margins.

Management decisions were discussed in multidisciplinary team meetings at each participating center, and were made on a case-by-case basis. No standardized treatment algorithm was applied across centers.

Study endpoints

The primary endpoint was the rate of histologically complete (R0) resection for adenocarcinoma and high-grade dysplasia. R0 resection was defined as lateral and deep resection margins clear of adenocarcinoma or high-grade dysplasia.

The secondary outcomes were: *en bloc* resection rate, R0 resection rate for adenocarcinoma, R0 resection rate for low-grade dysplasia, adverse event rate graded according to the AGREE classification [11], overall and recurrence-free survival at 1 and at 3 years, and rate of complete remission of intestinal metaplasia at 1 year and 3 years. Recurrent tumors were defined as the presence of adenocarcinoma in residual BE, termed local resection if located on the resection scar, metachronous (and local) if located on the residual BE, and distant if located in the lymph node or distant organs. We also aimed to identify factors associated with esophageal strictures, such as the circumferential extension of the resection, the preventive administration of corticosteroid therapy, and the center.

Definitions

Early recurrence was defined as recurrence detected at the first follow-up endoscopy performed at 3 months after ESD. Late recurrence was defined as recurrence detected at the 12-month follow-up endoscopy or thereafter.

High-risk adenocarcinoma was defined by the presence of at least 1 of the following features: submucosal invasion >500 μm, lymphovascular invasion, poor differentiation or positive vertical resection margin. Low-risk adenocarcinoma was defined as intramucosal or sm 1 (<500 μm infiltration of the submucosa) well differentiated adenocarcinoma, without lymphovascular invasion and with a negative vertical resection margin.

The depth of invasion for intramucosal adenocarcinoma was classified as follows: m1, limited to the *lamina propria*

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mucosae; m2, the superficial *muscularis* mucosae; m3, the layer in between the superficial and deep *muscularis* mucosae; and m4, the deep *muscularis* mucosae.

The depth of invasion for submucosal invasion was classified as sm1 when the depth of invasion was less than 500 μm, and sm2 when the depth of invasion was equal to or greater than 500 μm.

Statistical analysis and ethical aspects

Statistical analyses were performed using GraphPad Software (GraphPad Software Inc., San Diego, CA). Results are expressed as mean (± standard deviation) in case of a normal distribution of variables, and median (interquartile range [IQR] 25-75%) for variables with a skewed distribution, or as absolute numbers and percentages. The univariate analysis to identify factors associated with esophageal strictures was performed using Jamovi software (The jamovi project, 2024. *jamovi* Version 2.5 [Computer Software]. Retrieved from https://www.jamovi.org). Survival analyses were performed using the Kaplan–Meier method.

Patients' written informed consent was obtained before their inclusion in the study. The study received approval from an Ethics Advisory Committee (Comité de Protection des Personnes CPP Île-de-France, 03/10/2016, reference Am7872-1-3340). The study was registered under the following numbers (NCT02583087 and EudraCT: 2015-004700-27).

Results

Patients' characteristics

A total of 141 patients at 9 centers were treated with ESD for a visible lesion suspicious for neoplasia within a BE between December 2016 and January 2019. The mean number of patients per center was 15.7 (Supplementary Table 1).

The patients' characteristics are presented in Table 1. The mean age was 68±10 years, and 89% (126/141) were men. Pre-resection biopsies indicated adenocarcinoma in 52% (74/141) of the lesions. The median follow-up time was 36.3 months (IQR 36-48.5 months). Sixteen patients were lost to follow up. The study flowchart is presented in Fig. 1.

Procedural characteristics

The mean procedure time was 72±43 min, the mean size of the endoscopic resection was 25±12.5 mm, and the mean duration of the hospital stay was 2.7±2 days.Thirty-eight patients received post-endoscopic stricture prevention with oral steroids. All 141 lesions in 141 patients were resected en bloc. The detailed endoscopic procedural characteristics are presented in Table 2.

Table 1 Patients' characteristics

Characteristics	n=141
Age (mean±SD), years	68±11
Male sex, n (%)	126 (89)
ASA score (mean±SD)	2±0.8
Anticoagulant or antiplatelet therapy, n (%)	43 (30)
Preoperative histology, n (%)	
Low-grade dysplasia	12 (9)
High grade dysplasia/*in situ* carcinoma	55 (39)
Adenocarcinoma	74 (52)
Barrett's segment length (median, IQR), cm	
Circumferential extent (C)	2 (0-7)
Maximal extent (M)	4 (2-8)
Follow up (median, IQR), months	36.3 (36-48.5)

SD, standard deviation; IQR, interquartile range

Table 2 Endoscopic procedural characteristics (n=141)

Endoscopic procedural characteristics	Results
Procedure duration (mean±SD), min	72±43
Size of the endoscopic resection (mean±SD), mm	25±12.5
Circumferential extent of the lesion (median, IQR), % of the circumference	50 (40-60)
Paris classification of resected lesions, n (%)	
0-Is	14 (10)
0-IIa	53 (38)
0-IIb	21 (15)
0-IIc	6 (4)
0-IIb+IIc or 0-IIa+IIc	47 (33)
ESD knife used, n (%)	
Flush knife 1.5 mm	16 (11)
Dual knife J 1.5 mm	97 (69)
Hybrid knife	28 (19)
Hospital admission, (mean±SD), days	2.7±2
En bloc resection, n (%)	141 (100)

SD, standard deviation; IQR, interquartile range; ESD, endoscopic submucosal dissection

Adverse events

No periprocedural perforation occurred. Sixteen (11%) periprocedural bleedings were recorded, but were not regarded as adverse events, as they were all successfully managed during the procedure with hemostatic forceps or through-the-scope clips.

There was no delayed perforation. Early (<48 h) adverse events included 2 cases of aspiration pneumonia, treated with antibiotics, and 5 delayed bleedings. Of the 5 bleedings, 3 required endoscopic hemostasis, 1 required red blood cell transfusion, while 1 patient was only admitted to the hospital for clinical and biological monitoring.

Late (>30 days) adverse events were all post-endoscopic esophageal strictures. There were 17/141 (12%) esophageal strictures, 3 among the 38 patients who had stricture prevention (3/38 patients, 8%), and 14 among the patients

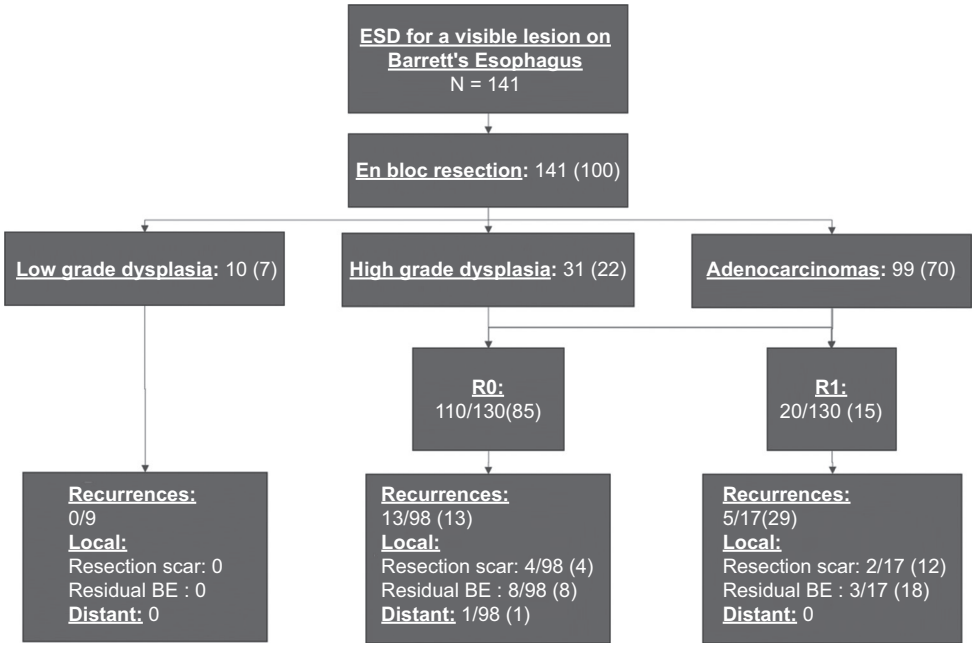


Figure 1 Flow chart of the study patients
ESD, endoscopic submucosal dissection; BE, Barrett's esophagus

without stricture prevention (14/103, 14%). The univariate analysis revealed that esophageal stricture was statistically significantly associated with the proportion of esophageal circumference resected (χ^2=11.2, df=1, P<0.001), but not with the use of corticosteroid therapy (χ^2=0.15, df=1, P=0.698), or the treatment center (χ^2=11.1, df=8, P=0.195).

According to the AGREE classification, adverse events were graded as I, II, and IIIA (mainly esophageal strictures requiring dilatation) in 1.5%, 1.5%, and 14% of patients, respectively. No grade IIIB, IV, or V adverse events were observed.

Histological analysis

Out of 141 lesions, there were 99 (70%) invasive adenocarcinomas, 31 (22%) lesions with high-grade dysplasia or *in situ* carcinoma, 10 (7%) lesions with low-grade dysplasia, and 1 (0.7%) hyperplastic lesion. Of the 99 adenocarcinomas, 80 (81%) had an R0 resection for invasive carcinoma. The R0 resection rate was 85% (110/130) for HGD and carcinoma and 86% (121/140) for any dysplasia and carcinoma.

Overall, there were 35/99 (36%) high-risk esophageal adenocarcinomas, and 64/99 (64%) low-risk adenocarcinomas. Other histological characteristics are presented in Table 3. Of the 35 high-risk adenocarcinomas, 17 were R0.

Table 3 Histological analysis of the resected specimens. Percentages may not sum to 100% due to rounding

Histological characteristics	n (%)
Histological analysis, n (%)	
Low-grade dysplasia	10 (7)
High-grade dysplasia (HGD)	31 (22)
Adenocarcinoma	99 (70)
Infiltration depth	19 (19)]
m2	
m3 or m4	47 (47)
Submucosal cancer (T1b)	27 (27)
Sm1	8 (8)
Sm2	19 (19)
Differentiation grade	
Well differentiated (low grade)	90/99 (91)
Poorly differentiated (high grade)	9/99 (9)
Lymphovascular invasion	11/99 (11)
High-risk adenocarcinomas	35/99 (36)
Low-risk adenocarcinomas	64/99 (64)
Histological quality of the endoscopic resection, n (%)	
R0 resection for invasive carcinoma	80/99 (81)
R0 resection for HGD and carcinoma	110/130 (85)
R0 resection for dysplasia and carcinoma	121/140 (86)

Additional oncological treatments after ESD

After the initial resection, 4 patients underwent esophagectomy and 6 received chemoradiotherapy, as adjuvant or salvage treatment following histological analysis of the resection specimen. The indications for the additional treatment, follow up and status at 36 months are shown in Supplementary Table 2.

During the follow-up period, 4 additional esophagectomies, 3 chemoradiotherapies, and 3 chemotherapies were performed as treatments for cancer recurrence or as an adjuvant or salvage treatment for a cancer recurrence initially managed by ESD. In total 8 esophagectomies (6%), 9 chemoradiotherapies (6%), and 3 chemotherapies (2%) were performed.

Of the 8 esophagectomies, 3 were performed as a salvage treatment following the initial ESD in patients with R1 resection (pT1aN1, pT1bN0, pT1bN0), and 1 was performed as an adjuvant treatment for a high-risk esophageal adenocarcinoma (pT0N0). Three esophagectomies were performed for recurrent adenocarcinomas during follow up (pT1bN1, HGD, pT1aN0), and 1 was an adjuvant treatment after a second ESD performed for a local recurrence at 3 months, which had not eradicated the disease by 12 months (pT1aN2). The patient who underwent this treatment developed distant metastases by 36 months, despite the surgery, and died from esophageal adenocarcinoma.

Of the 9 chemoradiotherapy treatments, 6 were administered as adjuvant or salvage treatment following the initial ESD in patients with R1 resection or a high-risk esophageal adenocarcinoma, 2 were for recurrent adenocarcinomas, and 1 was salvage treatment after the submucosal dissection for a local cancer recurrence at 3 months, which had not eradicated the disease by 12 months.

Eradication of the residual BE

Overall, 91 (64.5%) patients received BE ablation therapy, 74 (52.5%) with radiofrequency ablation and 17 (12%) with argon plasma coagulation.

The median (IQR) size of the BE segment changed from C2 (0-7) M4 (2-8) at baseline to C0 (0-0) M0 (0-1) at 36 months. The complete remission rate of intestinal metaplasia was 64% at the end of the endoscopic follow up. Fifteen patients underwent endoscopic mucosal resection during follow up, mainly for the treatment of residual dysplastic BE, and 13 new ESDs were performed. Of these 13 ESDs, 5 showed dysplastic lesions, and 8 recurrent adenocarcinomas.

Early oncological outcomes

At 3 months, we recorded 10/141 (7%) recurrences of adenocarcinoma. Five lesions were metachronous lesions, located outside the resection area, and 5 were located on the resection scar. Of the 5 patients with a recurrence on the resection scar, 3 patients had R1 resections on the index ESD. Of these 10 recurrences, 7 were managed by a second ESD, 1 by an esophagectomy (pT1bN1), and 2 by chemoradiotherapy. Of the 7 patients treated by ESD, 4 never experienced cancer recurrence. Among the 3 remaining patients, 1 underwent surgery at 12 months for a further recurrence, developed metastases at 36 months, and died at 47 months. Another underwent chemoradiotherapy at 12 months for recurrence and died of unrelated causes at 36 months. The last patient developed metastases at 12 months, was treated with chemotherapy, and was still alive at 36 months.

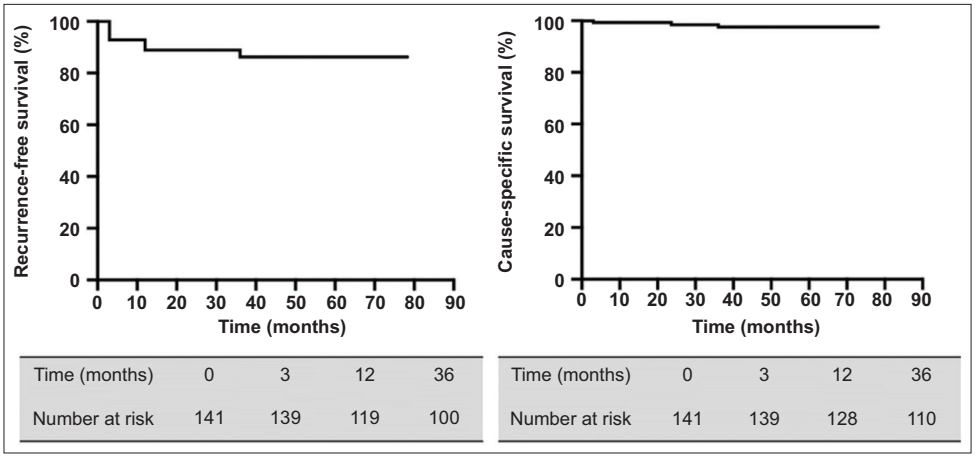
Late oncological outcomes

Sixteen patients were lost to follow up, 7 were unable to continue the follow-up protocol because of another pathology (squamous cell carcinoma of the tonsil, loss of autonomy, cerebrovascular stroke, dementia), and 14 patients died, 3 from esophageal adenocarcinoma. One of these 3 patients had a high-risk adenocarcinoma, with 2 poor histoprognostic factors on the initial resection specimen, and had received adjuvant chemoradiotherapy. However, he experienced a local recurrence at 12 months that was not amenable to endoscopic resection; he received palliative treatment with an esophageal stent, and died 1 month later. The second patient had a high-risk adenocarcinoma, with 1 poor histoprognostic factor on the resection specimen, and had tumor recurrence at 3 months on the residual BE. This second lesion was treated with a second ESD, but persistent adenocarcinoma was found on the residual BE, leading to an esophagectomy. However, metastatic recurrence was diagnosed at 36 months, and the patient died 47 months after inclusion. The last patient had a high-risk adenocarcinoma with a positive vertical margin and had received adjuvant chemoradiotherapy. He died 24 months after inclusion from adverse events following esophageal stenting for a local recurrence.

Among the 17 patients with high-risk adenocarcinoma resected with R0 margins, 4 received additional oncological treatment (surgery or chemoradiotherapy). Among these patients, 2 (50%) experienced a recurrence within 3 years following resection, resulting in a 3-year recurrence-free survival rate of 50% in this group. In comparison, among the 13 patients under simple surveillance without additional treatment, 4 (31%) experienced a recurrence, resulting in a 3-year recurrence-free survival rate of 69% in this group. Overall, the 3-year recurrence-free survival rate for high-risk adenocarcinomas resected with R0 margins was 65% (11/17) in all patients, compared with 69% (9/13) in patients managed with surveillance alone and 50% (2/4) in those who received additional oncological treatment.

After a mean follow up of 39±17 months, a total of 18 esophageal cancer recurrences were recorded, including 8 late recurrences, in addition to the 10 early recurrences already observed. Among these 8 late recurrences, 1 was located at the resection scar, which was initially a high-grade dysplasia with a histologically complete endoscopic resection. Six patients presented a recurrence on the residual BE. The last patient developed a distant metastatic recurrence, consisting of a bone metastasis diagnosed at 36 months, without evidence of residual esophageal tumor at follow-up endoscopy. The initial lesion was a poorly differentiated adenocarcinoma with submucosal invasion of 160 μm, lymphovascular invasion, and a histologically complete (R0) resection. More information about the recurrent esophageal adenocarcinomas is provided in Table 4.

Recurrence-free survival and cause-specific survival curves were generated using the Kaplan-Meier method (Fig. 2). Of the 18 recurrences, 8 were completely managed by



Time (months)	0	3	12	36
Number at risk	141	139	119	100

Time (months)	0	3	12	36
Number at risk	141	139	128	110

Figure 2 Kaplan-Meier curves showing recurrence-free survival and cause-specific survival with number of patients at risk shown below the curves

Table 4 Three-year follow up after endoscopic resection by ESD of an early esophageal adenocarcinoma (n=141)

Follow-up parameters	n, (%) or median (IQR)
Residual Barrett's length (median, IQR), cm	
Circumferential extent (C)	0 (0-0)
Maximal extent (M)	0 (0-1)
Recurrence of esophageal adenocarcinoma - n (%)	18/141 (13)
Early recurrences	10/141 (7)
Endoscopically manageable	4
Not endoscopically manageable	6
Late recurrences	8/141 (6)
Endoscopically manageable	4
Not endoscopically manageable	3
Metastatic	1
R0 resection initially	13/110 (12)
Resection scar	4
Residual BE	8
Metastatic	1

ESD, endoscopic submucosal dissection; IQR, interquartile range; BE, Barrett's esophagus

endoscopy without the need for adjuvant or rescue treatments. Five patients required chemoradiotherapy, 4 underwent esophagectomy, and 2 received chemotherapy. The initial histological characteristics, time to recurrence, management of recurrence, and follow-up data for all recurrences are presented in Supplementary table 3.

Thirteen of the 18 recurrences had an initial R0 endoscopic resection. However, of these 13 recurrences, 8 were located on the residual BE, and may have corresponded to different tumors from the initial one. Of the remainder, 4 were on the scar site and 1 was a distant recurrence.

Discussion

In this study, we demonstrated that ESD achieved histologically complete resection of invasive esophageal adenocarcinoma in 81% of patients, with no procedure-related mortality and no severe adverse events. These outcomes are in line with the findings of 2 major studies on the subject (AGREE IV and V), which reported 64-100% *en bloc* resection rates, 62-87% rates of histologically complete resection of invasive adenocarcinoma, 72-85% for invasive adenocarcinoma, 39-65% for adenocarcinoma and high-grade dysplasia, and 0% severe adverse events [12-18]. To our knowledge, this study is the first prospective multicenter documentation of these results, confirming the feasibility, efficacy and safety of ESD for this indication.

These data question the role of surgery in the management of T1 adenocarcinoma of the esophagus. Indeed, endoscopic resection allowed esophagectomy to be avoided in 94% of patients. First, 6 of the 7 patients undergoing endoscopic surveillance, with deep R1 resection as the only risk factor for recurrence, did not have residual carcinoma at the 3-month follow-up endoscopy. This is an additional argument that the R1 factor alone may not be sufficient to suggest an additional esophagectomy, and that early endoscopic surveillance is crucial, as already suggested by others [16]. It has to be noted that none of the 3 patients with a histologically complete resection of high-risk adenocarcinoma treated with adjuvant esophagectomy presented with disease recurrence. However, the number of patients is small, and the experience of salvage esophagectomy for patients with recurrent adenocarcinoma, with 25% (1/4) cancer-related mortality, demonstrates that surgery may not be the best treatment option for aggressive disease, even at an early stage.

Considering the morbidity and mortality of esophagectomy and the 7% (11/141) mortality rate from non-adenocarcinoma-related causes in our study, the indications for additional esophagectomy after ESD of a T1 adenocarcinoma should be carefully weighed.

Besides surgery, radiotherapy or chemoradiotherapy have been proposed as adjuvant treatments following the resection of high-risk early esophageal cancer, mainly squamous cell carcinoma [19], and more rarely for adenocarcinoma [20]. Overall, 9 patients received chemoradiotherapy, 3 for high-risk adenocarcinoma, 3 for deep R1 resection and 3 for recurrent disease. Although the small patient numbers and the

heterogeneity of the treatment protocols prevent the drawing of robust conclusions, only 1 of the patients who was a high-risk R0 resection at inclusion treated with chemoradiotherapy developed distant recurrence, and no severe treatment toxicity was reported.

The 3-year recurrence-free survival rate for high-risk adenocarcinomas resected with R0 margins was 65% (11/17) in all patients, compared with 69% (9/13) in patients managed with surveillance alone and 50% (2/4) in those who received additional oncological treatment. These results question the benefit of any of the currently available adjuvant treatments following endoscopic resection in terms of recurrence-free survival. The role of adjuvant immunotherapy remains to be determined in this specific clinical situation.

Paradoxically, our study brings into question the importance of R0 resection for BE associated neoplasia: first, as mentioned above and reported by others [16], deep R1 resection often did not equate to residual adenocarcinoma in the esophagus, probably because of coagulation artifacts on the resection specimen; second, 3 patients developed local recurrence of adenocarcinoma on the resection scar despite initial R0 resection, underlining the major sampling bias of any histological study; third, 11 patients had local recurrence on the residual BE, highlighting the importance of ablation of the residual BE, or at least of close endoscopic surveillance, even in frail and elderly patients.

Our work demonstrated the safety of ESD, among a large number of western centers, without any grade IV or V adverse events, and no surgery for adverse events. The most significant adverse event was esophageal stricture, recorded in 14% of patients, and requiring endoscopic balloon dilatation. Like others, we observed that a greater circumferential extent of the resection was associated with a higher likelihood of stricture [21,22]. In contrast, no significant association was observed between the use of corticosteroid therapy and esophageal stricture, indicating that corticosteroid therapy did not significantly influence the occurrence of stricture in our sample. Moreover, the analysis of hospital centers did not reveal a statistically significant association with esophageal strictures, meaning that the possibly different generator settings and different use of section or coagulation during ESD are not likely to significantly affect the rate of post-ESD esophageal strictures.

Beside the heterogeneity of the post ESD treatment protocols (esophagectomy, chemoradiotherapy, management of residual BE or recurrent lesions), and a selection bias towards more advanced lesions, the main limitation of our study lies in the 16 patients lost to follow up. A possible explanation is that these patients do not feel sick, often do not realize that they were treated for cancer, and do not understand the need to pursue endoscopic surveillance after a first normal follow-up endoscopy. This calls for better informing of patients by endoscopists about the diagnosis of early esophageal cancer and its implications. Notably, 11 of the 16 patients lost to follow up had histologically complete resection of a low-risk adenocarcinoma.

ESD allows *en bloc* resection of T1 esophageal adenocarcinomas in over 90% of patients, with an acceptable safety profile, allowing esophagectomy to be avoided. These results, recorded prospectively across a large number of centers and operators, justify the use of this technique to resect visible lesions larger than 15 mm suspected of cancer, or when endoscopic mucosal resection is technically impossible. Systematic ablation of BE after endoscopic resection, along with the development of adjuvant medical therapy following endoscopic resection, could reduce the rates of local and distant recurrences.

Summary Box

What is already known:

- Endoscopic resection is standard for early Barrett's neoplasia
- Data on the long-term outcomes of endoscopic submucosal dissection (ESD) are limited
- The safety of ESD in Barrett's neoplasia is well established
- The oncological adequacy of the procedure has yet to be studied

What the new findings are:

- ESD is a safe treatment for T1 esophageal adenocarcinoma in France, allowing more than 90% of patients to avoid esophagectomy
- ESD is indicated for lesions larger than 15 mm suspected of cancer
- Systematic ablation of Barrett's esophagus could reduce the rate of local recurrence

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Supplementary material

Supplementary Table 1 Inclusions per center

Center	Number of patients (=n)
Cochin Hospital - Paris	24
Jean Mermoz Private Hospital - Lyon	37
Edouard Herriot University Hospital - Lyon	30
Rennes University Hospital	18
Nantes University Hospital	12
Limoges University Hospital	11
Brussels University Hospital	4
Bordeaux University Hospital	3
Nice University Hospital	2

Supplementary Table 2 Additional treatments before 3 months after histological analysis of the first ESD

Patient	Additional treatment	Indication	Further recurrence	Treatment of recurrence	Status at 3 years
Patient 1	Esophagectomy (pT0N0)	LVI, Sm2	No		Alive
Patient 2	Chemoradiotherapy	LVI, Sm2	Yes, M12, on the residual BE	ESD	Non cancer related death
Patient 3	Esophagectomy (pT1aN1)	R1	No		Alive
Patient 4	Esophagectomy (pT1bN0)	R1	No		Alive
Patient 5	Chemoradiotherapy	LVI, G3	Yes, M36 metastatic	Chemotherapy	Alive
Patient 6	Chemoradiotherapy	Deep R1, LVI, G3	No		Non cancer related death
Patient 7	Chemoradiotherapy	Deep R1	Yes, M3 residual BE	Further RCT	Death related to adenocarcinoma M36
Patient 8	Esophagectomy (pT1bN0)	Deep R1, G3	No		Alive
Patient 9	Chemoradiotherapy	LVI, Sm2, G3	No		Death related to adenocarcinoma
Patient 10	Chemoradiotherapy	Deep R1	No		Alive

LVI, lymphovascular invasion; Sm2, deep (>500µm) submucosal invasion; R1, histologically incomplete resection; ESD, endoscopic submucosal dissection; BE, Barrett's esophagus; M3: 3 months; M12: 12 months; M36: 36 months

Supplementary Table 3 Follow up and management of recurrences

Patient	Initial histology	Initial BE	Vertical margins	Lateral margins	Complementary treatment	Time of recurrence	Location of recurrence	Type of management	Residual BE at M36	Status at M36
1	HGD	C2M4	R0	R0	RF	M3	Resection scar	ESD	C0M0	Recurrence at M12 treated with chemoradiotherapy. Died of other causes at M36
2	HRA	C4M6	R1	R0	RF	M3	Residual BE	ESD	C0M2	No other recurrence
3	HRA	C4M5	R1	R0	RF	M12	Residual BE	ESD	C0M0	No other recurrence
4	HRA	C7M8	R0	R0	CR	M12	Residual BE	Esophageal stent	NA	Died at M12
5	HRA	COM2	R0	R0	RF	M3	Residual BE	ESD	NA	Recurrence at M12 treated with esophagectomy. Metastasis at M36 and died at M47.
6	LRA	C4M5	R0	R0	RF	M12	Residual BE	EMR	C0M1	No other recurrence
7	HRA	C14M14	R0	R0	RF	M36	Residual BE	Chemoradiotherapy	C11M13	Alive at M36
8	HRA	C7M8	R0	R0	RF	M3	Resection scar	ESD	C3M3	No other recurrence
9	HGD	C8M10	R0	R0	RF	M12	Resection scar	ESD	C3M0	No other recurrence
10	HRA	C14M15	R0	R0	CR	M36	Metastatic	Chemotherapy	NA	Alive at M36
11	LRA	C2M3	R0	R0	RF	M3	Resection scar	ESD	C0M0	No other recurrence
12	HGD	C8M8	RO	R0	RF	M36	Residual BE	Esophagectomy	C9M9	Alive at M36
13	HRA	C6M8	R1	R0	CR	M3	Residual BE	Chemoradiotherapy	C5M5	Died at M24 after esophageal stent
14	LRA	C18M18	R0	R0	RF	M12	Residual BE	Esophagectomy	C0M0	Alive at M36
15	HRA	C5M9	R0	R0	RF	M3	Resection scar	Chemoradiotherapy	C0M1	Alive at M36
16	HRA	C9M12	R1	R1	RF	M3	Resection scar	ESD	C4M8	Metastasis at Ml2 and received chemotherapy. Alive at M36
17	HRA	C8M9	R0	R0	RF	M3	Residual BE	Esophagectomy	C0M0	No other recurrence
18	HRA	C2M4	R0	Ra	RF	M3	Residual BE	ESD	C0M0	No other recurrence

HRA, high-risk adenocarcinoma; LRA, low-risk adenocarcinoma; HGD, high-grade dysplasia; BE, Barrett's esophagus; RF, radiofrequency ablation; CR, chemoradiotherapy; ESD, endoscopic submucosal dissection