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Endoscopic submucosal dissection versus endoscopic mucosal resection for type 0-II superficial gastric lesions larger than 20 mm

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Abstract

Background Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are increasingly used for the treatment of superficial gastrointestinal neoplasia. However, the limits and the indications for each technique are still debated. Our retrospective study aimed to compare these techniques in patients with gastric flat lesions larger than 20 mm without the non-lifting sign.

Methods Between January 2013 and July 2016, a total of 36 patients with early gastric flat lesions larger than 20 mm and without the non-lifting sign were resected by ESD and were followed up by endoscopy. As a control group, 40 EMR cases from our database were matched. *En bloc* and curative resection were compared between the two groups according to histological assessment, tumor size, recurrence, complication rate, and procedure time. A Kaplan-Meier comparison was performed for both groups with a log-rank test to compare the survival curves; the chi-square test was employed for other parameters.

Results *En bloc* resection rate and curative resection rate were significantly higher in the ESD group than in the EMR group. Procedure time was significantly longer in the ESD group. No significant differences were found in the recurrence and complication rates, although the former were higher in the EMR group and the latter in the ESD group. Survival curves were similar for both groups.

Conclusions Our retrospective analysis seems to confirm a clear advantage for ESD over EMR in removing early superficial gastric neoplasm. Although ESD has expanded the endoscopic resectability of endoscopic gastric lesions, EMR may still be considered one of the therapeutic options for flat gastric lesions without the non-lifting sign.

Keywords Early gastric cancer, endoscopic submucosal dissection, endoscopic mucosal resection

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Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are increasingly used for the treatment of gastrointestinal neoplasia [1-3]. In contrast to Japan and other Asian countries, few data are available in western countries, especially with regard to long-term outcomes. Despite its efficacy, EMR is sometimes associated with local recurrences, especially when larger lesions are removed in a piecemeal manner [4]. In piecemeal-resected specimens, histological assessment sometimes becomes difficult, because of the effects of tissue burning on the lesion. EMR has other limitations, such as lesions with the non-lifting sign [5]. Conversely, ESD is a new endoluminal therapeutic technique involving the use of cutting devices that allow a

larger resection of the tissue over the *muscularis propria* of the gastrointestinal tract; this technique was developed in Japan for the *en bloc* removal of early-stage gastrointestinal tumors, including large lesions and positive non-lifting sign lesions. ESD is considered a substantial advance in therapeutic endoscopy; its main advantage is its higher *en bloc* resection rate due to submucosal dissection with a direct view, using a special electrosurgical knife. Because of these special features, ESD offers a possible advantage in terms of an enhanced cure rate and a more accurate histopathological assessment. However, the procedure is known to have several disadvantages, including greater technical difficulty, a longer learning curve, a longer procedural time, and a higher risk of related complications, including perforation and bleeding, compared to conventional EMR [5-7]. For these reasons, according to the European guidelines, endoscopic resection (ER) by the ESD technique should be reserved for lesions larger than 20 mm or those that have the non-lifting sign [8].

Although the ESD technique may allow a better and more complete resection, piecemeal resection of larger lesions by EMR may achieve a high cure rate, while reducing the procedure time and risks related to the procedure. Current guidelines [8] are mainly derived from the Japanese experience, but few studies have compared the pros and cons of ESD vs. EMR in western countries for early-stage gastric lesions. Therefore, the present matched case-control study was performed to clarify whether ESD is more effective than EMR for treatment of type 0-II gastric flat lesions larger than 20 mm in the absence of the non-lifting sign.

Patients and methods

Patient characteristics and selection criteria

Between January 2013 and July 2016, 36 patients referred to the Endoscopic Unit of Luigi Sacco Hospital in Milan for type 0-II gastric flat lesions larger than 20 mm and without the non-lifting sign were treated with ESD. All the data from these patients were entered into a prospectively completed database. As a control group, 40 patients were retrospectively and randomly selected from a larger group of 138 patients who had undergone EMR between January 2008 and June 2016 and were matched with each studied ESD-patient for age (± 5 years), sex (male/female), lesion size (± 5 mm), and histology (adenoma/early cancer) (Tables 1, 2, and 3).

The follow-up clinical information was collected until the end of June of 2017, established as the closing date of the study.

Preoperative assessment

To assess the depth of the lesion and the absence of local lymph node involvement, all patients underwent endoscopy with narrow-band imaging and chromoendoscopy with acetic acid plus indigo carmine, biopsy and endoscopic ultrasound before the enrolment. Such screening is needed to judge preoperatively whether a gastric lesion is non-lifting or not. The endoscopic morphology of superficial lesions (type 0-II) was assessed according to the Paris endoscopic classification of superficial neoplastic lesions of the gastrointestinal tract [9].

In our experience, we never switch from EMR to ESD when the non-lifting sign becomes clear during an EMR procedure, because of the difficulty in recognizing the submucosal layer after the coagulation induced by EMR. We switch patients with uncompleted EMR to surgery, if they are eligible.

Table 1 Characteristics of patients

Characteristic	EMR	ESD	P
No. of lesions	40	36	
Age (years), mean±SD	63.7±12.3	65±15	0.886
Sex (M/F)	22/18	20/16	0.942

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

Table 2 Lesion size and procedure time in the two study groups

Treatment	Mean±SD	
	Lesion size (mm)	Procedure time (min)
EMR (n=40)	26.5±4	24.6±14.6
ESD (n=36)	25.3±3	96.7±51.3
P	0.929	0.007

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

Table 3 Histological distribution of lesions

Histology	EMR (n=40)	ESD (n=36)	P
Noninvasive low-grade neoplasm	12 (30%)	16 (44.4%)	0.197
Noninvasive high-grade neoplasm	20 (50%)	15 (41.7%)	0.472
SM1	7 (17.5%)	1 (2.8%)	<0.037
SM2	-	1 (2.8%)	0.289
Carcinoid tumor	1 (2.5%)	3 (8.3%)	0.261

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; SM1, submucosal invasion <500 µm from the muscularis mucosae; SM2, submucosal invasion >500 µm from the muscularis mucosae

Exclusion criteria

Patients with involvement of the submucosal layer during the preoperative assessment and patients with the non-lifting sign during the procedure were excluded from the study.

Patients' consent

Written informed consent was obtained from all patients before the ER was performed.

Follow up clinical evaluation

All patients underwent follow-up endoscopy with chromoendoscopy and a re-biopsy of the area where ER was performed at three-monthly intervals during the first semester and then at six-monthly intervals to assess for local recurrences.

ER techniques

Lesions predicted to be noninvasive neoplasms and carcinomas *in situ* were removed by ER. All treatments were performed with the patients under intravenous sedation with midazolam and pethidine. ER was performed using either ESD or EMR and was completed after total removal of the unstained lesion. EMR was performed according to the conventional technique [7]. Submucosal solution (NaCl plus adrenaline 1:10,000, indigo carmine 4 mg, and glycerol 10%) was injected with a needle into the submucosa beneath the lesion. A high-frequency electrosurgical snare (Olympus Medical, Singapore) was passed through the channel and the lesion was captured and strangulated using the snare; a forced coagulation current was then applied to cut it.

According to the standard process [7], ESD was developed as follows: a mucosal cut was made outside the marking dots using the endocut mode. Immediately after the mucosal incision, a deep cut of the submucosa was made using the endocut mode, while submucosal dissection in the deep layer was performed mainly using the swift coagulation mode. Glyceol® (Chugai Pharma, Japan) was used as the submucosal injection agent. As ESD knives we used mainly a dual knife, Coagrasper hemostatic forceps with soft coagulation mode at 80 W, and a short-type as distal attachment.

The electrosurgical units for both procedures included a VIO 300 D (ERBE, Tubingen, Germany).

Histological evaluation and assessment of therapeutic efficacy

The histological assessment of resected specimens was based on the revised Vienna classification of epithelial neoplasia [10,11]: category 1, no neoplasia; category 2, indefinite for neoplasia; category 3, low grade adenoma/dysplasia; category 4, noninvasive high-grade neoplasia (including high-grade dysplasia and intramucosal carcinoma); and category 5, invasive carcinoma.

A curative resection was achieved when both the lateral and vertical margins of the specimen were assessable and free of atypical cells, when there was no lymphatic invasion, vascular involvement, poorly differentiated component or submucosal invasion deeper than 500 μm from the *muscularis mucosae* [12,13].

Lesions histopathologically diagnosed as low/high-grade dysplasia, noninvasive neoplasia, or carcinoma with minute submucosal (SM) invasion, without features indicative of high pathological risk, were regarded as curative because they had no risk of lymph node metastasis. In contrast, lesions histopathologically diagnosed as carcinoma with deep SM invasion were considered as non-healing, and these patients were referred for additional surgery, including nodal dissection. Lesions with non-evaluable margins for artificial coagulation were evaluated for further treatment during the follow up. Non-free margins were considered to be specimens with positive cancer cells at the edge of the specimen, suggesting incomplete resection of the tumor.

Statistical analysis

SPSS 22.0 software was used for the statistical analysis. Randomization of patients in the matched control group was based on a single sequence of random assignments after controlling all the matching factors in the analysis. A Kaplan-Meier cumulative survival analysis was performed for the two groups of patients who underwent EMR or ESD. A log-rank test was employed to compare the survival curves, with the null hypothesis being that there was no difference in the overall survival distributions between the two groups. Despite the small sample size for the other parameters considered we expressed all data as mean ± SD and performed a statistical comparison between the two treatment groups using the chi-square test. Values are reported as percentages and numbers. Statistical significance was set at the $P<0.05$ level.

Results

Histological characteristics of lesions

A total of 76 endoscopic specimens were analyzed; the mean lesion size was similar in the EMR and ESD groups (P=NS; Table 2). We found that 37% of the lesions were noninvasive low-grade neoplasms, 46% were noninvasive high-grade neoplasms, and 12% were adenocarcinomas, including 1.5% unexpectedly deep invasive SM cancers.

More specifically, as shown in Table 3, the lesions in the EMR group included 12 noninvasive low-grade neoplasms, 20 noninvasive high-grade neoplasms, 7 adenocarcinomas, and 1 carcinoid tumors. Among ESD-removed lesions, we found that 16 were noninvasive low-grade neoplasms, 15 noninvasive high-grade neoplasms, 2 adenocarcinoma, and 3 carcinoid tumors.

Procedure time

The mean procedure time was significantly longer for ESD than for EMR (data with mean values and P values are summarized in Table 2).

En bloc and curative resection rate

The *en bloc* and curative resection rates were significantly higher for ESD than for EMR ($P<0.05$).

In the EMR group, the *en bloc* resection rate was 23/40 (57.5%), and the procedure was judged curative in 24 patients (60%). In 16 patients the procedure was considered non-curative: in 3 patients because of non-free margins and in 13 patients because of non-evaluable margins.

The *en bloc* resection rate in ESD was 33/36 (91.6%) and a curative resection was achieved in 31 patients (86.1%). In 5 patients the procedure was considered non-curative, because of deeper submucosal invasion in 1 patient, failure to achieve disease-free margins in 2 patients, and non-evaluable margins in 2 patients.

In both groups, patients with non-free margins or deep invasion underwent early surgery, while patients with non-evaluable margins were evaluated during the follow up. All data are summarized in Table 4.

Survival, follow up, and recurrences

The survival rates at 40 months for patients who underwent EMR and ESD were 100% and 94%, respectively. There was no statistically significant difference in survival rates between the groups (log-rank χ^2-test 2.241, P=0.134).

The mean duration of follow up was 23.5 (range 11-43) months for both groups. Within three months after the procedure, all patients who did not undergo early surgery (n=69; EMR n=37; ESD n=32) underwent endoscopy to evaluate the residual disease. In addition, in these patients, a follow up including endoscopy with chromoendoscopy was performed every six months to evaluate recurrences. As shown in Table 4, *en bloc* and curative resection rates were significantly higher in the ESD group. In this group a significantly higher accuracy of margin definition was achieved. Recurrences were slightly more common in the EMR group; however, this difference did not reach statistical significance.

In the EMR group there were 3 patients with local recurrences (all in the subgroup with non-evaluable margins): 2 of them were successfully treated by additional EMR and 1 by surgical resection. In contrast, at the time of writing there has been no recurrence in the ESD group; however, this difference was not statistically significant (Table 4).

Surgical treatments and complications

In each group, 3 patients needed early surgery because of non-free margins or deeper invasion. One case of surgical treatment for complications was registered in the ESD group. During the follow up, only one patient in the EMR group needed surgery for disease recurrence.

Perforation and bleeding represented the major complications related to ER [14,15]. In the ESD group, perforation occurred in 2 patients and 1 patient needed emergency surgery because of delayed perforation (Table 4); the other patient was managed using endoscopic clipping without salvage surgery. Bleeding occurred in 2 other patients and both were treated endoscopically. No perforation occurred in the EMR group, while postoperative bleeding was observed in 1 patient and treated endoscopically. Blood transfusion was not required for any patient.

Discussion

ER is an effective alternative to surgery for the management of early gastric tumors [16]. In Japan, ER represents the gold standard for the treatment of early gastric neoplasms [1-3] and several studies from the Japanese experience have evidenced that ESD can overcome the technical limitations of the EMR technique, such as piecemeal resection for flat lesions larger than 20 mm, achieving a higher *en bloc* resection rate [4,5,17]. Despite the small sample size, our study seems to confirm that ESD is significantly better than EMR in terms of *en bloc* resection rate, curative resection rate and recurrences.

The major advantage of this technique is indeed the lower rate of recurrence, due to the possibility of controlling the depth, size, and shape of the resection, achieving an accurate dissection of the submucosal layer and a complete removal of the lesion. However, to achieve these results ESD is significantly more time-consuming and requires more expertise. In addition, our results showed that the survival rate was similar in the EMR and ESD groups (Fig. 1) and only a small percentage of patients treated by EMR required definitive surgical treatment. According to current guidelines [8], EMR should be reserved for the resection of non-depressed flat lesions smaller than 20 mm, while ESD should be performed to remove larger or flat lesions with the non-lifting sign, defining the field in which the benefits from ESD outweigh its difficulties and risk-related complications.

Although ESD allows the endoscopic treatment of non-lifting lesions, a complete resection by EMR may be obtained for lesions larger than 20 mm in a high percentage of patients. Since specialized training and adequate experience, after an appropriate learning curve, appear to be necessary

Table 4 Outcomes

Treatment	*En bloc* resection	Curative resection	Non-free margins	Non-evaluable margins	Recurrences	Deeper invasion	Complications requiring surgery	Surgery
EMR	23 (57.5%)	16 (40%)	3 (7.5%)	13 (32.5%)	3 (8.1%)	0 (0%)	0 (0%)	4 (10%)
ESD	33 (91.6%)	30 (86.1%)	3 (8.3%)	2 (5.5%)	0 (0%)	1 (2.6%)	1 (2.6%)	4 (11%)
P	<0.008	<0.032	0.898	0.0028	0.083	0.529	0.529	0.888

EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection

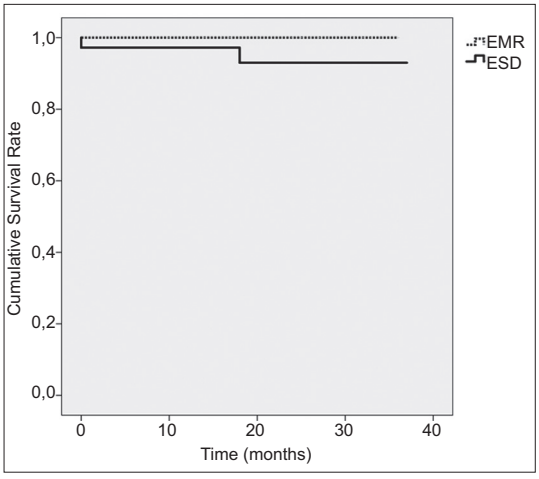

Figure 1 Kaplan Meier cumulative survival curves
EMR, endoscopic mucosal resection; ESD, endoscopic submucosal resection

before approaching ESD, this technique has not been widely adopted [7]. Our results suggest that large flat lesions without the non-lifting sign may be treated by EMR, achieving a good rate of complete resections, even in a piecemeal manner.

Since the goal of the ER is not to remove lesions in *en bloc* fashion, but to reduce gastrointestinal cancer-related death, EMR may be safely used for larger lesions, reserving ESD for non-lifting neoplasms or early cancer with evidence of involvement of the *muscularis mucosae* or superficial submucosal layer.

The limit of piecemeal resection is the lower accuracy of the histological evaluation. However, our study showed that, even though the margins were not evaluable in 32.5% of patients undergoing piecemeal EMR, only 8.1% showed a recurrence of disease during the follow up. In our setting, a high percentage of the lesions were dysplastic, without adenocarcinoma-positive cells, limiting the evaluation of risk associated with piecemeal resection. However, the low prevalence of adenocarcinoma in our patients may depend on the selection of lesions without the non-lifting sign, which are less likely to be more advanced, and our data may support the hypothesis that the non-lifting sign more than size may influence the choice of ER technique. The limitations of our study are all consequences of the relative small experience of ESD in western countries, the monocentric and retrospective nature of the study, the relatively small sample size, and the short mean time of follow up.

However, the small number of patients is partly the result of the exclusion of all lesions with the non-lifting sign and the lower incidence of gastric neoplasms compared to eastern countries. Despite these limitations, our data seem to confirm that ESD is better than EMR for removing early gastric neoplasms. Indeed, the ESD technique has enlarged the scenario of therapeutic options for endoscopic resectable lesions, reducing the number of surgical interventions in favor of a wider diffusion of this technique. ESD is usually viewed as more challenging than EMR and has a limited diffusion among endoscopic centers; for this reason, EMR may still be considered one of the therapeutic options for flat gastric lesions without the non-lifting sign.

Summary Box

What is already known:

- Endoscopic resection is an effective alternative to surgery in the management of early gastric tumors and in Japan represents the gold standard of treatment
- Although endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are increasingly used to treat patients with early gastric neoplasms in western countries, the indications for each technique and the relative advantages are still being debated and need to be defined
- ESD is considered as a substantial advance in therapeutic endoscopy. However, the procedure is known to have some disadvantages, such as greater technical difficulty, increased risk of related complications, and requires a longer procedure time
- Few studies have compared the pros and cons of ESD vs. EMR in western countries for the treatment of early gastric tumors

What the new findings are:

- Our retrospective analysis seems to confirm a possible advantage of ESD when compared to EMR in removing early superficial gastric neoplasms
- Our study seems to confirm that ESD is significantly better than EMR in terms of *en bloc* resection rate, curative resection rate, and recurrence rate
- In the ESD group, a significantly higher accuracy of margin definition was achieved

Some controversial issues remain when the resection by EMR is piecemeal and the histological evaluation of margins is unclear. Indeed, it appears that in the worst scenarios, with piecemeal resection and non-evaluable margins, the risk of recurrence is still high (in our experience 8.1%), also considering that more curative techniques, such as ESD or surgery, are available.

Since the biology of gastric neoplasms, as well as the epidemiology and natural history of these tumors, may differ between western and eastern countries [18,19], further large multicenter studies are needed to better define the precise role of EMR vs. ESD in treating gastric neoplasms.

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