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Endoscopic submucosal dissection for superficial premalignant and malignant epithelial neoplasms of the digestive tract: a real-life experience in Italy

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Abstract. – OBJECTIVE: Endoscopic submucosal dissection (ESD) is a technique for en bloc resection of neoplastic lesions of the digestive tract. Endoscopic submucosal dissection was developed in Asia, and data from Western countries are scarce. Our study aimed to assess the efficacy and safety of ESD for resection of superficial premalignant and malignant epithelial neoplasms in a tertiary center in Italy.

PATIENTS AND METHODS: All patients with gastrointestinal lesions who underwent ESD between January 2013 and December 2018 in our center were retrospectively evaluated. Technical success, en bloc, R0, curative resection, and complication rates were assessed.

RESULTS: A total of 107 lesions (stomach, no.=41; rectum, no.=32; colon, no.=28; esophagus, no.=5; duodenum, no.=1) were resected by ESD in 93 patients. Endoscopic submucosal dissection was technically successful in 99.1% (106/107) of lesions. Among the 90 superficial premalignant and malignant epithelial neoplasms, en bloc, and R0 resection rates were 97.8% (no.=88) and 75.6% (no.=68), respectively. Major complications occurred in 9.3% (10/107) of cases: 4 (3.7%) were perforations and 6 (5.6%) were major bleedings. All complications, but two which needed surgery, were managed endoscopically.

CONCLUSIONS: Our study shows that ESD is a feasible, effective, and safe technique in a Western country.

Key Words:
Endoscopic submucosal dissection, Superficial neoplasms, Digestive tract.

Introduction

Endoscopic submucosal dissection (ESD) is an endoscopic technique for the *en bloc* resection of superficial premalignant and malignant neoplasms of the digestive tract. This technique was developed to resect early gastric cancer in Asia, but was subsequently expanded to esophagus, duodenum, colon, and rectum[1-3]. The main advantage of ESD over endoscopic mucosal resection (EMR) lies in its capability to resect *en bloc* even larger lesions, thus allowing a precise histological evaluation of resection margins and staging[4,5]. Furthermore, *en bloc* resection is associated to a lower recurrence rate[4,5]. However, ESD needs advanced endoscopic skills, has a long learning curve, and higher rates of adverse events[1,6,7]; this is why its use is recommended in high-volume tertiary centers[3].

Most part of the evidence supporting ESD as a treatment modality for superficial premalignant and malignant gastrointestinal lesions comes from Eastern countries[8,9], whereas the ESD experience in Europe and USA is still scarce. Indeed, a recent meta-analysis including 97 studies and 17,483 patients on 18,764 colorectal ESDs showed that its efficacy was significantly reduced in Western countries[10].

Further data on the performance of ESD in Western countries would help to improve our knowledge on the feasibility, efficacy, and safety of this technique.

Therefore, the aim of this study was to assess the efficacy and safety of ESD for resection of superficial premalignant and malignant epithelial neoplasms in a tertiary center in Italy.

Patients and Methods

All patients with gastrointestinal lesions who underwent ESD between January 2013 and De-

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cember 2018 in our center were retrospectively evaluated. Lesions included neoplastic esophageal lesions, gastric dysplastic/malignant lesions according to expanded indications[3], and duodenal or colorectal neoplasms without endoscopic features of deep submucosal invasion and unsuitable for *en bloc* EMR. Symptomatic sub-epithelial lesions or lesions with inconclusive diagnosis were also considered for ESD. Subjects were excluded if they were < 18 years of age or if the endoscopic or pathologic report were not available. The study protocol was carried out according to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) and was approved by the Ethical Committee (Code 153/2019/Oss/AOUBo) on March 20th, 2019.

Endoscopic Submucosal Dissection Technique

All the ESDs were performed by a single endoscopist who is highly experienced in therapeutic endoscopy. Esophageal and gastric lesions were first marked around with closed-tip Dual-Knife. A solution of 1:100,000 diluted adrenaline and indigo carmine in a plasma expander was used for submucosal lifting. Mucosal incision was performed with 1.5 mm Dual-Knife. Dual-Knife, insulated tip (IT)-2 or IT-nano knives (Olympus®, Tokyo, Japan) were used for submucosal dissection, defining the "standard" ESD. "Hybrid" ESD was defined when the mucosal incision was followed by snare resection. After dissection, hemostasis was performed with a Coagrasper (Olympus®, Tokyo, Japan) whenever necessary, and the defects were closed with through-the-scope clips.

After esophageal, gastric or duodenal ESD, patients started a regimen comprising intravenous omeprazole 40 mg b.i.d. and *nil per os* for 24 hours, switching to oral pantoprazole 40 mg b.i.d. and liquid diet for the following 3 days. Patients progressively returned to a normal diet and maintained pantoprazole for 8 weeks.

Histopathology

ESD specimens were sent for the histopathological assessment with pins on a cork plate, fixed in formalin. Sectioning at 2 mm intervals was performed to assess lateral and vertical margins. All the specimens were evaluated by two experienced gastrointestinal pathologists.

Outcomes

The ESD was considered to be a technical success if the target lesion was removed. *En bloc* resection was defined when the lesion was resected in a single specimen. R0 resection was met when histopathological evaluation showed no residual neoplasia in both lateral and deep margins; otherwise, R1 resection was defined. Curative resection was defined when the lesion was resected *en bloc*, and the histological evaluation met (1) R0 resection, (2) neoplastic tissue limited to the mucosa or reaching the superficial part of the submucosa according to the organ of interest (i.e., SM1), and (3) low-risk criteria (i.e., no lymphovascular invasion, well-differentiated type).

Adverse Events

Major and minor complications were routinely recorded. Perforation and bleeding were considered as major complications when they required additional diagnostic and/or therapeutic procedures, or when they significantly prolonged or aggravated the patient's in-hospital stay. In details, bleeding was considered a major adverse event when not endoscopically managed, or when requiring red blood cells transfusion. Minor complications included severe abdominal pain, micro-perforation that occurred during the procedure and was successfully managed by endoscopy, and fever.

Statistical Analysis

Patients' demographic features were reported as descriptive statistics. Continuous variables were expressed with mean and standard deviation (SD) or median and interquartile range (IQR), whereas categorical variables were reported as absolute and relative percentages.

The *en bloc*, R0, and curative resection rates were assessed according to the site of ESD lesions along the digestive tract. We assessed the risk of R0 and curative resection in the different sites of digestive tract in comparison with the stomach, calculating odds ratios (OR) with 95% confidence interval (CI) by univariate logistic regression. All the statistical analyses were conducted using Stata software version 15 (StataCorp LP, College Station, TX, USA).

Results

A total of 93 patients (n. 55, 51.4% males; mean age, 68.9 years, standard deviation, 11.2) with 107 lesions underwent ESD between January 1st, 2013 and December 31st, 2018 in our center. Of the 107 lesions, 5 (4.7%) lesions were located in the

esophagus, 41 (38.3%) in the stomach, 1 (0.9%) in the duodenum, 28 (26.2%) in the colon, and 32 (28.9%) in the rectum. Table I shows site and size of lesions treated with ESD. According to the Paris classification, 10 (9.4%) lesions were type 0-Ip, 19 (17.8%) type 0-Is, 38 (35.4%) type 0-IIa, 16 (14.9%) type 0-IIb, 5 (4.7%) type 0-IIc, and 19 (17.8%) type 0-IIa+IIc.

At histology, 90 (84.1%) out 107 lesions were superficial premalignant and malignant epithelial neoplasms: 35 (32.8%) were low-grade dysplasia, 30 (28.1%) high-grade dysplasia, 6 (5.6%) intra-mucosal cancers, 9 (8.4%) SM1 cancers, 8 (7.5%) SM2 cancers, 1 (1%) SM3 cancer, and 1 (1%) serrated lesion. Table II shows the histological characteristics of the 90 superficial premalignant and malignant epithelial lesions by site. Of the remaining lesions, 9 (8.4%) were neuroendocrine tumors (NET), 4 (3.7%) hyperplastic polyps, 2 (1.9%) inflammatory polyps, 1 (1%) GIST, and 1 (1%) lipoma.

Of the 107 lesions, 92 (86%) underwent standard ESD and 15 (14%) hybrid ESD. Endoscopic submucosal dissection was technically successful in 99.1% (106/107) of lesions; in one case in the transverse colon, ESD was not fully accomplished and resection was completed with EMR.

In the 90 superficial premalignant and malignant epithelial lesions, the overall *en bloc*, R0 and curative resection rates were 97.8% (no. = 88), 75.6% (no. = 68), and 72.2% (no. = 65), respectively. The *en bloc* resection was very high in all sites: 100% in esophagus (5/5) and stomach (28/28), 96.4% (27/28) in the colon and 96.6% (28/29) in the rectum. In the stomach, both R0 and curative resection rates were 78.6% (22/28); in the colon, both R0 and curative resection rates (75%, 21/28) were similar to those in the stomach (OR 0.82, 95%CI 0.24-2.84). In the rectum, the R0 resection rate (72.4%, 21/29) was similar to the stomach, whereas the curative resection rate (65.5%, 19/29) was slightly lower (OR 0.52, 95%CI 0.16-1.69) (Table III).

Table I. Site and size of lesions of the digestive tract.

Baseline characteristics	Lesions (no. = 107)
	no. (%)
Site	
Esophagus	5 (4.7)
Stomach	41 (38.3)
Duodenum	1 (0.9)
Colon	28 (26.2)
Rectum	32 (29.9)
Size, median mm (inter-quartile range)	
Esophagus	20 (10-40)
Stomach	20 (5-50)
Duodenum	15 (-)
Colon	25 (10-70)
Rectum	33 (9-100)

Surgery was performed in 10 (11.1%) out of 90 superficial premalignant and malignant epithelial neoplasms due to non-curative resection; in details, 8 (72.7%) cases were SM2C, 1 (9.1%) case was SM3C, and 1 (9.1%) case was R1 in vertical margin in an SM1C.

Of the 90 ESD lesions, 61 underwent at least one follow-up endoscopy with a median follow-up of 9 months (IQR 4-15). Recurrence was found in 9.8% (6/61) of lesions; 5 recurrences were managed endoscopically, and one underwent surgery. Recurrence rate was higher (no. 2, 20%) in the 10 lesions with R1 resection; of the two recurrences, one was managed endoscopically and one surgically.

Complications occurred in 22 (20.5%) out of the 107 ESD lesions; major complications occurred in 10 (9.3%) cases, 4 (3.7%) were per-

Table II. Histology of superficial premalignant and malignant epithelial neoplasms (no. 90) by site.

Histology	Esophagus (no. = 5)	Stomach (no. = 28)	Colon (no. = 28)	Rectum (no. = 29)
	no. (%)	no. (%)	no. (%)	no. (%)
Low-grade dysplasia	–	14 (35.1)	13 (46.5)	8 (25)
High-grade dysplasia	1 (25)	4 (10)	9 (32.1)	16 (50)
Intra-mucosal cancer	–	6 (14.6)	–	–
SM1 cancer	3 (60)	2 (5)	2 (7.1)	2 (6.3)
SM2 cancer	1 (25)	2 (5)	2 (7.1)	3 (9.4)
SM3 cancer	–	–	1 (3.6)	–
Serrated lesion	–	–	1 (3.6)	–

SM1, superficial part of submucosa. SM2, mid-third of submucosa. SM3, deeper part of submucosa.

Table III. R0 resection rate and curative resection rate of endoscopic submucosal dissection of epithelial premalignant and malignant neoplasms (n. 90) by site.

	R0 resection	Odds Ratio (95% CI)	Curative resection	Odds Ratio (95% CI)
	no. (%)		no. (%)	
Esophagus (no.=5)	4 (80)	1.00 (0.10-11.67)	3 (60)	0.41 (0.06-3.03)
Stomach (no.=28)	22 (78.6)	Ref.	22 (78.6)	Ref.
Colon (no.=28)	21 (75)	0.82 (0.24-2.84)	21 (75)	0.82 (0.24-2.84)
Rectum (no.=29)	21 (72.4)	0.72 (0.21-2.41)	19 (65.5)	0.52 (0.16-1.69)

CI, confidence interval.

forations, and 6 (5.6%) major bleedings. Three perforations were in the rectum and one in the stomach, whereas three major bleedings developed in the stomach, two in the colon, and one in the rectum. Two patients (1.8%) underwent a successful emergency surgery for perforation, one in the stomach and one in the rectum, whereas 8 (7.5%) were managed endoscopically. Minor complications occurred in 12 (11.2%) cases, including severe abdominal pain in 6 cases (5.6%), micro-perforation in 4 (3.7%) cases, and fever in 2 (1.9%) cases; severe abdominal pain occurred in the stomach (no. 2), colon (no. 3), and esophagus (no. 1), whereas micro-perforation occurred in three cases in the colon and in one case in the rectum.

Discussion

This study showed that ESD was a feasible and safe technique in real-life practice in a tertiary center in Italy; in fact, technical success was obtained in 99% of lesions and major complications occurred in only 9% of cases. We found that ESD was successful in achieving *en bloc*, R0, and curative resection in at least three-quarters of lesions.

In the stomach, R0 and curative resection were achieved in about 80% of cases. Our data are slightly better to those reported in another study in Italy; Petruzziello et al[11] showed R0 and curative resection rates of about 65% in 70 ESD gastric lesions. In our center, the efficacy of ESD in terms of curative resection rate seems to be similar to that reported in Eastern series[12]; Oda et al[12] reviewed the efficacy of ESD in 945 patients with a total of 1033 early gastric cancers reporting a curative resection rate of 83%. However, our results may be affected by the small sample size. As regards non-curative ESD, the need for surgery has been questioned, as R1 resection was not strongly associated with an increased risk of lymph node metastasis[13]. Furthermore, a large Japanese multicenter study including 1969 patients with non-curative ESD for early gastric cancer found that the disease-specific survival at three years was not different between the 1064 subjects who underwent radicalizing surgery and the 905 who were followed-up without surgery, being more than 95% in the two groups[14]. It should also be pointed out that sometimes the margins of lesions can be damaged during ESD due to technical issues, thus leading to an overestimation of R1 resections. Indeed, the 2016 Japanese guidelines on gastric ESD[1] stated that in some cases of non-curative resection of predominantly differentiated-type lesions, when the only non-curative factor is piecemeal or *en bloc* resection with positive horizontal margins (i.e., horizontal R1), surgical radicalization is not the only option, as the patient can be strictly followed-up after informed consent. In our study, it is worth noting that only one patient had a recurrence, which was managed endoscopically.

In our study, the performance of ESD in the colon in terms of R0 and curative resection (around 75%) was similar to the stomach, whereas curative resection rate in the rectum was slightly lower (65%). Our findings are consistent with other studies carried out in Western countries[10,15,16]; a recent meta-analysis including 101 studies with 18,764 colorectal ESDs reported in Western countries similar R0 and curative resection rates, around 70%[10]. In line with our research and other series[17], this meta-analysis showed a slightly reduced performance of ESD in rectal lesions[10]; the lower curative resection rate of ESD in the rectum in Western countries has been partially explained by the fact that rectal lesions are usually approached by endoscopists soon after the training period. However, in our study the median size of rectal lesions (32 mm) was larger than in the stomach (20 mm) and in the colon

(25 mm), and this may also explain the reduced curative resection rate of ESD in the rectum. Our data confirm that the performance of ESD in the rectal lesions in Western countries is lower than in Asia, where reported curative resection rate is around 85%[10]. Nevertheless, our study would suggest caution on the overuse of ESD for removing lesions in the colon and rectum; we found that SM1 cancer was present only in 7% (4/57) of colorectal lesions, in line with a meta-analysis showing 8% of SM1 cancer in 11,260 colorectal ESDs[18].

ESD can be considered a relatively safe technique when performed in real-life practice in a tertiary Western endoscopic center. Indeed, major complications occurred in less than 10% of cases (perforation 3.7%, major bleeding 5.6%); notably, all cases of major complications, but 2 cases of perforation that needed surgery, were managed endoscopically. This investigation is in line with previous reports showing major complications in around 8% of cases of ESD (perforation 5%, bleeding 3%)[9,10].

There are several limitations. The main limitation was the small sample size, in particular for, the different types of lesions localized in different sites of the digestive tract. In addition, the retrospective design is very likely to have included several known and unknown bias that may have affected our results. Furthermore, follow-up endoscopies were not retrieved in about one-third of patients and, in addition, the median follow-up was very short; therefore, the recurrence rate of lesions after ESD reported in our study may be underestimated. Finally, all the ESDs were performed by a single operator, impairing the external application of our findings.

Conclusions

Our study indicates that ESD is a feasible, effective, and safe endoscopic technique for the treatment of superficial pre-malignant and malignant neoplasms of the digestive tract in real-life in Western country. However, a European multicenter prospective study, including a large sample of patients aimed to better define the indication, performance, and safety of ESD in Western countries is needed.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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