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Original Article

Endoscopic Submucosal Dissection in Iran: Preliminary Results

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ABSTRACT

Background:
Endoscopic submucosal dissection (ESD) is a novel technique for removal of early mucosal neoplasms of gastrointestinal tract. While it has been widely used in Japan and eastern Asian countries, there have been no data available from Iran. Here we report our experience with this method in a single, private, non-tertiary care, and non-referral hospital in Iran.

Materials and Methods:
Demographics, outcomes, and complications of ESD of six lesions in six patients performed at a single center during 2013-2016 were retrospectively evaluated.

Results:
The mean (range) age of the patients was 60.5 (40 - 71) years. Of them three had gastric lesions and three had rectal lesions. Two gastric lesions were HGD (High Grade Dysplasia) and one was intramucosal carcinoma. Rectal lesions were villous adenoma in one case and two T1 adenocarcinomas in two other cases. The mean (range) size of the lesions size was 3.1 cm (2.5-8 cm). Complete removal was achieved in all the patients both endoscopically and histopathologically. Microscopic perforation occurred in one case, which was managed conservatively without a need for surgical intervention. No significant late bleeding was observed. No surgery was needed either for completion of removal or control of complications. During mean follow-up of 20 months no recurrence occurred.

Conclusion:
Our first experience with ESD shows its high rate of effectiveness with acceptable complication rate and success rate. Proper patient selection and use of standard techniques and instruments are required to produce clinically acceptable outcomes for patients in need of this method to cure their early mucosal neoplasia.

Keywords: Endoscopic Submucosal Dissection, Iran, Endoscopic Piecemeal Mucosal Resection, Colon Cancer, Gastric Cancer.

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INTRODUCTION

Endoscopic resection techniques were first developed in Japan in 1969. The first report on endoscopic resection of early gastric cancer through endoscopic methods dates back to 1988(1-4). Since then it has been developed and novel devices and techniques have been developed for this purpose.

Endoscopic submucosal dissection (ESD) has been developed for en bloc resection of lesions more than 2 cm in size. The basic technique has been described widely. Shortly it consists of marking the mucosal neoplastic area to be removed, removing the lesion from

the underlying muscularis mucosae by fluid injection and cushioning, cutting the circumference of lesion and then dissecting it to be removed from muscularis propria while controlling bleeds and taking care of potential perforations through muscularis propria(5). Indications for ESD have been described and have been expanded in recent years. It can be used to remove early neoplastic lesions in upper and lower digestive tract(5). Experience with this method has been widely published from Far East but up to now there has been no published experience with this method from Iran. Here we review the first experience of this method among Iranian patients in a single, non-referral center. This case series includes data on demographics, outcomes, and complications of ESD performed on gastric and rectal lesions.

MATERIALS AND METHODS

Patient selection

ESD was performed at Mehrad General Hospital, Tehran, Iran on six patients between December 28, 2013 and August 21, 2016 by a single endoscopist (B.N.N). Informed consent was obtained from all the patients prior to the procedure. The indications in each patient were according to published guidelines(5). Therapeutic options were explained to each patient and complications were discussed.

Pre-ESD evaluation

Patients were selected for ESD during diagnostic procedures performed at the same hospital and all lesions were diagnosed during either opportunistic screening procedures of upper and/or lower digestive tract or during endoscopic evaluation of symptoms related to upper or lower gastrointestinal (GI) tract. We used Olympus HD-190 system. Single channel scopes were used. Preparation for upper endoscopies included overnight fasting and the patients had a cocktail of simethicone/N-Acetylcysteine half an hour before the procedure. Preparation for colonoscopies included one day of clear liquids before the procedure and split dose of five liters polyethylene glycol. During diagnostic and evaluative endoscopies, morphology of lesions was assessed based on Paris and Kudo classifications(6,7). All diagnostic procedures were performed under sedation and were monitored by attending anesthesiologist.

ESD technique

We used ESD technique as described in reference 5. Shortly this technique includes marking around the lesion by either APC (Argon Plasma Coagulation) or triangle ESD catheter, injecting on the rim of the lesion and cushioning, cutting through marked rim and separating lesion circumferentially from unremarkable surrounding mucosae, injecting to lift mucosae and submucosae from muscularis propria, and dissecting apart these layers. To cut the circumference of targeted area, we always used IT (Insulated Tip) knife. Hypertonic saline 5% was used for submucosal injections. In four cases we used methylene blue mixed with hypertonic saline to mark muscularis propria but in the last two cases we stopped using methylene blue. To dissect lesions we used either IT knife or flex knife. For ESD, dissection is usually begun from proximal to distal way. During the procedure, bleedings were controlled by coagrasper hemostatic forceps (Olympus Inc.). The following catheters were used for dissection: IT knife (Olympus), Flex knife (Olympus), Triangled knife (Olympus), and hook knife (Olympus). Hypertonic saline 5% was used for lifting and cushioning. ESG-100 HF (Olympus Inc.) electrosurgical unit was used for the first five cases with following modes: Cut 120 W, forced mode 40 W, effect 2 or 3. For the last case we used VIO 300 D electrosurgical unit (ERBE GmbH, Tubingen, Germany).

Pathological review

All pathological reviews were performed by three expert GI pathologists (M.R.A, S.N, and M.G.M).

Endoscopic outcomes

En bloc resection was defined as when a lesion was removed in one piece. A successful histological resection (R0) was defined as removing the lesion with clear vertical and lateral margins. Curative resection was defined as tumor-free vertical or lateral margins in a resected lesion and absence of vascular or lymphatic involvement. It was also defined by invasion < 1000 μm and < 500 μm from the muscularis mucosa in colorectal and gastric lesions, respectively(8). Significant bleeding was defined as requiring blood transfusion and repeated endoscopy after the ESD procedure. A perforation was confirmed by radiological (CT) evidence of a perforation.

Table 1: Clinical features and outcomes of ESD cases

Pt/Age/Sex	Comorbidities	Site/ Time (min)	Size/ En bloc removal	Histology	Invasion depth, lymphatic or venous permeation	R0 Resection	Complication/ Treatment	Outcome
1/75/M	none	Subcardia/240	3.5 cm /N	HGD	Intramucosal/N	Y	Perforation/ conservative, Bleeding/Coagrasper	No recurrence after 32 m
2/69/F	HTN/Dyslipidemia/NAFLD	Antrum/150	6/Y	A	Intramucosal/N	Y	Bleeding/Coagrasper	No recurrence after 6 m
3/69/M	Lung Cancer, COPD, HBV	Subcardia/180	2.5/Y	HGD	Intramucosal/N	Y	Bleeding/Coagrasper	No recurrence after 28 m
4/44/F	FAP	Rectum/120	1.6/Y	A	Less than 500 µm/N	Y	Bleeding/Coagrasper	No recurrence after 16 m
5/40/F	None	Rectum/210	2/N	Villous adenoma	Less than 500 µm/N	Y	Bleeding/Coagrasper	No recurrence after 27 m
6/73/M	CRC in past, LAR	Rectum/30	1.5/Y	A	Less than 500 µm/N	Y	Bleeding/Coagrasper	No recurrence after 18 m

abbreviations: A. Adenocarcinoma, HTN: Hypertension, NAFLD: Non-alcoholic Fatty Liver Disease, HGD: High Grade Dysplasia

Follow-up

All the patients were followed up with no lost to follow patient. Usually patients had follow-up endoscopy after 6 months and annually thereafter. Biopsy samples were taken from ESD site to look for recurrence.

RESULT

There were six lesions in the six patients. The mean (range) age of the patients was 60.5 (40-71) years (table 1). There were three gastric lesions and three rectal lesions. En bloc resection was achieved in 5 out of the 6 (83%) patients. R0 resection was achieved in all patients (100%). Significant bleeding requiring repeated endoscopy or blood transfusion did not occur. One patient underwent surgery despite R0 resection of rectal cancer, due to underlying familial adenomatous polyposis coli, but ESD was performed because the lesion was just above the dentate line and ESD helped for sphincter preservation in this case. No patient died during the follow-up and mean follow-up time was 20 months. No recurrence was observed during the follow-up. The mean (range) lesions' size was 3.1 cm (2.5 - 8 cm).

Gastric ESD

Clinical features of patients with gastric ESD

There were three gastric lesions in three patients, which were resected by ESD (figure 1). The mean (range) age in these patients was 70.3 (69 - 71) years. No patient was lost to follow-up and mean (range) follow-up time was 24 (12 - 36) months. In our case series no synchronous lesion was observed and no metachronous lesion(s) has/have been found during surveillance endoscopies. No recurrence has occurred yet. Two lesions were below cardia on the upper part of the lesser curve and one lesion was in prepyloric area toward posterior wall of the antrum. The mean (range) size of the lesions was 3 (2.5 - 3.5) cm. Histopathological examination of the ESD specimens revealed two high-grade dysplastic lesions in the lesions removed from below cardia and one intramucosal adenocarcinoma in antral lesion.

Outcomes of patients with gastric ESD

Of the three lesions removed from the patients with gastric ESD, en bloc resection was achieved in two patients and piecemeal resection was performed for one lesion. R0 resection was achieved in all. No patient required complementary surgery or adjuvant chemotherapy. No recurrence has occurred during the follow-up of these patients.

Complications in patients with gastric ESD

In our first patient with ESD, we had subdiaphragmatic air without clinical signs of perforation and sepsis. So we decided to admit the patient, manage him by ordering NPO and

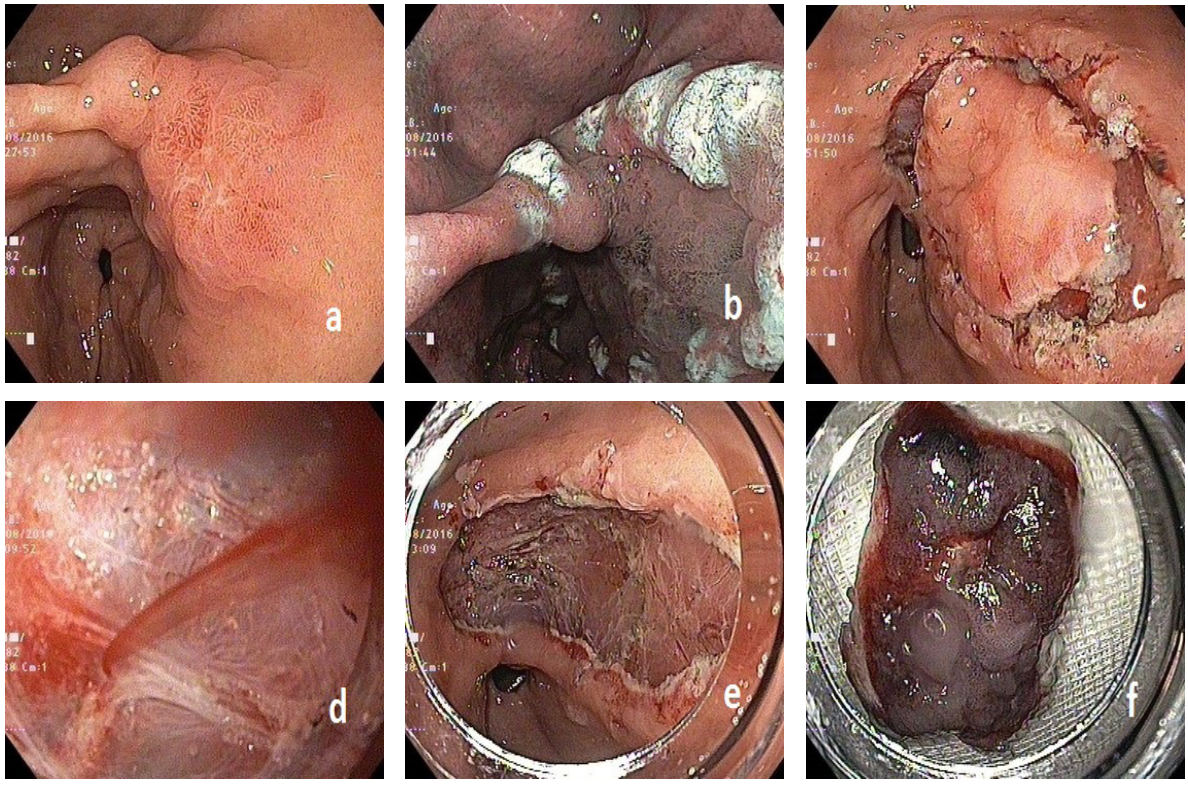

Fig.1: a. Prepyloric lesion b. Marking around c. Cutting around d. Bleeding e. After ESD f. Specimen retrieval

administering intravenous antibiotics. He had an uneventful course. Oral feeding was resumed 3 days after ESD and he was discharged from hospital without need for surgery. In the other two cases no perforation happened. Brisk bleedings requiring endotherapy occurred in all the three patients but were meticulously and completely controlled endoscopically. No significant late bleeding occurred after ESD in our cases.

ESD in rectum

There were three patients with rectal flat lesions requiring ESD. En bloc resection was achieved in one and piecemeal resection in the other two cases. R0 resection was achieved in all three. The first case of rectal ESD was due to marginal recurrence of villous adenoma after endoscopic piecemeal mucosal resection (EPMR) of villous adenoma in a young woman. As the marginal recurrence was close to anal sphincter and surgical intervention could potentially result in sphincter damage or fertility-sexual problems in a young woman, we decided to try ESD resection.

The second case had a history of rectal cancer many years before, managed by low anterior resection with low-lying anastomosis, and was found to have a flat adenocarcinoma just above the dentate line and below anastomosis. Our last case was a young woman with adenomatous polyposis coli syndrome who had a subtotal colectomy 8 years before and had numerous adenomatous polyps in the rectosigmoid area. She had a flat adenocarcinoma just above the dentate line and ESD was performed for her as a sphincter preserving procedure. She later had a complementary resection of remnant rectosigmoid parts and ileoanal J-pouch reconstruction was performed with excellent functional results.

DISCUSSION

ESD is now the current standard practice for removal of early mucosal neoplastic and pre- neoplastic lesions of GI tract and is usually used for lesions more than 2 cm in diameter. ESD has been mostly used in the

management of early gastric neoplasms. Finding these lesions is even more important than their endoscopic removal. Considering the high incidence of gastric cancer among Iranian population, it is crucial that every diagnostic upper GI endoscopy be performed not only to investigate the cause of the symptoms, but also to try to diagnose those early pre-or neoplastic lesions, which are almost always asymptomatic at the time they are limited to mucosae. This is the early window of chance that gastroenterologists have the best chance to prevent advanced cancers in their patients. The same is true for colon, esophageal, and rectal lesions. Once a suspicious area is found, decision must be made to biopsy or directly proceed to removal. Currently with high definition and high resolution endoscopes and with the aid of magnification it is possible to diagnose neoplastic lesions without the need to biopsy taking and proceed directly to removal of the lesion. This is important as every biopsy resulted in fibrosis makes later ESD removal complicated and difficult. Our suggestion is that if suspicious lesions are found and facilities for ESD removal and positive diagnosis by endoscopy without biopsy taking are not available, it is better to avoid biopsy and refer patient for detailed exam and removal in a single session. Once diagnosed, decision may be made to remove the lesion by endoscopic or minimally invasive surgery. For endoscopic removal of the lesions larger than 2 cm in diameter, there are currently two methods at hand: ESD and EPMR. EPMR technique is more prone to local recurrence and incomplete removal of large lesions. In fact, both our own experience (unpublished data that will be available in our next manuscript) and experience from other centers corroborate this notion.

Compared with EMR (Endoscopic Mucosal Resection), ESD has higher en bloc removal rate and curative resection rate but is also associated with more bleeding and perforation rates and is more time consuming. These shortcomings should be weighted before it is being used for every individual. Current improvements in minimally invasive surgical techniques make it crucial to weigh the potential risks and unwanted side effects of ESD versus its benefits and superiorities. In those patients with advanced age and severe comorbid conditions, ESD has advantages over surgical procedures. Also in those with previous abdominal surgeries in whom re-operation in the abdominal cavity is technically difficult, ESD is an option. These were the main reasons for adopting ESD in our current series. The en bloc resection rate of gastric lesions (two of three) is acceptable considering the learning curve for ESD. In fact in the very first case of ESD, we used piecemeal technique and later on with increased experience and confidence, our en bloc resection rate rose. Among rectal lesions, en bloc resection was done in two of three cases. The reason for piecemeal resection in rectal lesion was technical. That case was a recurrence of rectal villous adenoma after EPMR. Usually, performing biopsies or incomplete resections make either EMR or ESD technically difficult and challenging.

In two of our gastric cases, lesions were located on the lesser curve just below gastroesophageal junction. For these lesions, ESD has superiority over surgery as surgeons usually adopt a total gastrectomy with Roux-en-Y reconstruction, which has demanding long-term functional results for patients. Although, technically, ESD in those lesions is more difficult and scope control is a problem, it has obvious superior functional results with less patient recovery time, conserving the normal anatomy and gastric physiology.

In our series we did not have any major late bleeding. This is due to what we learnt from our experience with EMR. We do not use any methylene blue (as is recommended and used in most series) and this helps us to see exposed submucosal vessels. We use coagrasper to ablate all those visible vessels and this helps to prevent late major bleeds. Of course the size of vessel and location of ESD is important to choose the most suitable coagrasper and complementary endoscopic techniques such as water immersion and change in position also improves those technical success rates.

In conclusion, there have been many series of ESD reported from western and eastern countries. This is the first report from Iran. Both gastric and colonic lesions requiring ESD appear to be frequent in Iran although this first study was on too small number of patients to make any conclusions on this. En bloc resection and curative resection rates together with complication rates are acceptable and comparable to experience from other centers and count.

CONFLICT OF INTEREST

The authors declare no conflict of interests related to this work.

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