

Endoscopic Submucosal Dissection of Gastric Neoplastic lesions in Patients with liver Cirrhosis: An Analytical Systematic Review

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Abstract

Endoscopic sub mucosal dissection (ESD) is effective and safe for the removal of neoplastic lesions in the general population, but its role in patients with cirrhosis is not clear. We evaluated data on feasibility and safety of ESD for gastric lesions in cirrhotic patients. An analytical systematic review of the literature with pooled-data analysis was performed. Data of all consecutive cirrhotic who underwent ESD for gastric neoplastic lesions in a single centre were also reported. In reviewing the published literature, 68 ESD procedures for gastric neoplastic lesions have been performed in 61 cirrhotic, including 5 patients from our experience. En bloc removal and the R0 resection were successful in 88.2% and 89.7% of procedures, respectively. Post-ESD bleeding occurred in 8 (13.1%) patients, and perforation in 1 (1.6%). All patients were successfully managed by endoscopic treatment. No procedure-related death was observed. Patients with advanced cirrhosis, with either INR >1.33 and/or platelets count <105,000/mm³ should be regarded at increased risk of bleeding following ESD. ESD for gastric neoplastic lesions in cirrhosis is an effective and relatively safe procedure. Procedure-related bleeding is a frequent complication, but can be successfully managed endoscopically.

Index Terms - Endoscopic submucosal dissection, Endoscopic Mucosal Resection, Liver cirrhosis, Gastric cancer, Bleeding.

1.0 INTRODUCTION

Liver cirrhosis is a common and serious chronic disease. Indeed, chronic liver disease and cirrhosis result in about 35,000 deaths each year in the US, being the ninth leading cause of death [1]. In Italy there are over 300,000 cirrhotic [2]. These patients are at increased risk of developing gastric cancer [3, 4]; a 2.6-fold increased prevalence of gastric cancer was observed as compared to the general population [5]. Endoscopic mucosal resection (EMR) has become a standard treatment for superficial neoplastic lesions of the stomach - such as low- and high-grade gastric dysplasia and early gastric cancer - because of its reduced invasiveness as compared to surgery [6]. In addition, endoscopic submucosal dissection (ESD) has been recently introduced in Far Eastern countries to remove lesions generally not suitable for en bloc EMR treatment, such as those larger than 2.0 cm [7]. These endoscopic therapeutic approaches have been found to be effective and safe for removing neoplastic lesions of the esophagus, stomach and colon in the general population [8-10]. Moreover, potential complications of ESD, such as bleeding or perforation, may be managed by an endoscopic increased risk of procedure-related bleeding is foreseeable in cirrhotics, due to both severe clotting impairment and platelet count reduction in these patients [12]. Nonetheless, surgical treatment is associated with higher morbidity and mortality rates in cirrhotics as compared to controls [13]. Consequently, it would be important to ascertain whether endoscopic removal of superficially confined gastric neoplastic lesions in these patients is clinically relevant. To date, only scanty data are available on ESD safety in cirrhotic patients and, to our knowledge, no case reports from Western countries have been published. This study therefore performed a systematic review of the available data on this important topic, and also describes our case series on gastric neoplastic lesions removal with ESD in cirrhotic patients.

2.0 METHODS

2.1 Systematic review

The study considered all studies describing patients with cirrhosis who underwent ESD for the removal of gastric lesions. Exclusion criteria included single case reports, review articles,

position papers, editorials, commentaries, abstracts, and book chapters. If there was any suspicion of cohort overlap between studies, only the most recent study was considered for inclusion. Relevant publications were identified by MEDLINE for the period January 1999 and May 2012. Medical terms "Endoscopic submucosal dissection and cirrhosis" were used in the search, adopting "Human studies" and English language as limits. This study also hand searched the references of review articles. The full paper of all relevant studies was retrieved, and manual searches of reference lists from identified relevant papers were performed to find any additional studies that may have been missed using the above-mentioned procedure. Potential studies were initially screened based on the title and abstract by two researchers (AZ, CH). The reviewers checked whether inclusion and exclusion criteria were met and, for all papers with even a remote potential for study inclusion, the full text was retrieved and reviewed. Data extraction was independently performed by the two reviewers using predefined data extraction forms. From each report, reviewers independently abstracted: (a) number of patients included and sex distribution; (b) mean age; (c) follow-up period; (d) liver cirrhosis etiology; (e) Child-Pugh class; (f) portal hypertension signs; (g) platelets count and international normalized ratio (INR) for clotting evaluation; (h) mean lesion size; (i) lesion location; (j) en bloc resection rate; (k) R0 resection rate; (l) procedure duration; (m) complications and their management; and (n) final histology.

2.2 Case series

Data of all consecutive cirrhotics who underwent ESD for gastric neoplastic lesions in a single Centre were systematically collected. Cirrhosis was diagnosed by clinical, biochemical, endoscopic, and ultrasound findings. Liver cirrhosis was classified according to the Child-Pugh class. All patients provided written informed consent before endoscopic treatment. The ESD procedures were carried out under deep sedation by using diazepam and propofol. All endoscopies were performed by using a conventional single-channel endoscope (GIF-Q165/160T; Olympus Co, Tokyo, Japan) with a distal attachment (D-201-11804; Olympus Co, Tokyo, Japan). Endoscopic characteristics of the lesions were classified according to the Paris endoscopic classification [14], whilst histological classification was done according to the revised Vienna

classification [15].CO2 insufflations was used instead of air insufflations to reduce patient discomfort. Lesion margins were delineated before ESD using 0.4%indigo-carmine spray dye and then marked with coagulation spots few mm outside the lesion borders. A solution of HPMC (Hydroxy-propyl-methylcellulose) mixed with saline, adrenaline and a few dropsofethylene blue was used for submucosal injection, as we previously reported [16]. Circumferential incisions was made using the Hook knife (Olympus Co, Tokyo, Japan) outside the marking spots and afterwards sub mucosal dissection proceeded paying a lot of attention to provide careful preventive homeostasis to sub mucosal vessels by using the co grasper. The procedure-related outcomes, including then bloc resection rate, histologically complete resection rate (i.e. R0 resection), operation time, complication rate, and procedure-related dead was assessed in all patients. This study defined an en bloc resection as the 1-piece resection of an entire lesion as observed endoscopically. The ESD procedure was considered curative when both deep and lateral margins of removed lesions were disease-free (≥ 2 mm), and the tumor invasion in the submucosa was $<500 \mu\text{m}$. Early and late bleeding was defined as bleeding that occurred within and after 24 h from the procedure, respectively. Bleeding was presumed when haematemesis, maelena, or hemoglobin concentration decreased by more than 2 g/dl were observed. All bleeding was controlled by endoscopic treatments. Perforation was diagnosed endoscopically by direct observation of mesenteric fat just after resection or by the presence of free air on radiographs or CT images in suspected cases.

3.0 RESULTS

Initially 36 studies were identified. After a thorough review of the titles and abstracts, 15 studies were excluded because they did not comprise cirrhotic patients, 3 were single case reports, 4 studies were dealing with esophageal ESD, and 10 studies with colon ESD. A further study enrolled916 patients who underwent gastric ESD including 28cirrhotics, but results were cumulatively provided so that it was not possible to extrapolate data of cirrhotic patients [17].Therefore, 3 endoscopic series (2 Korean and 1 Japanese) dealing with ESD for gastric lesion removal in cirrhotic patients eventually satisfied inclusion criteria [18–20].There were 61 patients: 56 identified in the literature and 5unpublished cases (Table I) observed in our experience. Overall, the mean age of the patients was 64.5 years. There were 48 (78.7%) males. Liver cirrhosis was classified as Child-Pugh class A in 46 cases, class B in 13, and class Cin the remaining 2 patients. Overall, an ESD procedure was performed to remove 68 gastric lesions that were mainly located in the antrum and gastric body, whilst lesions in the fundus were infrequent (Table II). Theen bloc removal was successful in 60 (88.2%) lesions, the R0 resection was achieved in 61 (89.7%) lesions. Early gastric cancer was the most frequent removed lesion, accounting for 52.9%of all ESD performed. As far as complications, bleeding occurred in 8 (13.1%) patients. Clinical data of these patients were available for all, but 1 study [20]. In detail, cirrhotic with bleeding included 5 Child-Pugh class B and 1 class A patients. Thus, ESD-related bleeding occurred more frequently in Child-Pugh class B/C patients as compared to those in class A (5/9 vs 1/33; $p < 0.001$; Fisher's exact test).

Moreover, INR values in bleeding patients ranged from 1.33 and 1.6, and the platelet counts from 43,000 to105,000/mm³. The mean values of either INR (1.44 ± 0.1) or platelets count ($71,177 \pm 21,000/\text{mm}^3$) in these patients were lower than the mean values for the entire patient group (Table III). All these patients were managed by endoscopic treatment (clipping, epinephrine injection, electro coagulation, argon plasma coagulation). Overall, 1, (1.6%) case of gastric perforation was reported. This patient recovered by conservative treatment with nil per oral intake and intravenous administration of antibiotics. No patient required a surgical approach for complications, and no procedure-related death was reported.

Table I. Our case series.

Age	Sex	Child-Pugh class	Platelets count/mm ³	INR value	Lesion (mm)	Lesion morphology	Duration (min)	Complications	Follow-up (months)
53	M	B	57,000	1.46	30	Ila-IIb	80	Late bleeding	36
72	F	A	82,000	1.10	25	Ila	75	None	22
61	F	A	55,000	1.38	40	Ila-IIc	120	None	18
64	M	A	64,000	1.26	30	Ila-IIb	100	None	18
70	M	A	70,000	1.38	40	Ila	86	Early bleeding	24

Table II. Demographic and clinical characteristics of patients enrolled in different series.

	Choi [18]	Ogura [19]	Know [20]	Our series
Patients number	23	15	18	5
Male/Female	17/6	10/5	18/0	3/2
Mean age, yrs	61.3	69.6	64.6	64
Follow-up (Median, range) months	17.5 (2-72)	22 (12-39)	NA	22 (18-36)
Cirrhosis aetiology				
- HBV	16	0	4	1
- HCV	2	6	2	2
- Alcoholic	0	5	8	1
- Other	5	4	4	1
Child-Pugh class				
A/B/C	20/3/0	9/6/0	13/3/2	4/1/0
Mean platelets count (mm ³)	106,700	110,000	165,590	65,600
INR*	1.2±0.2	1.27 (1.1-1.76)	NA	1.31 (1.1-1.46)
Portal hypertension signs**				
- Oesophageal varices	7	7	NA	5
- Gastric varices	3	-	NA	1
- Congestive gastropathy	2	2	NA	1

*INR: International normalized ratio. **More than 1 sign may be present in the same patient.

Table III. Endoscopic characteristics of patients enrolled in different series.

	Choi [18]	Ogura [19]	Know [20]	Our series
Mean lesion size: (range) mm	14 (ND)	18 (5-34)	NA	30 (20-40)
Number of lesions removed	23	18	22	5
Lesion location				
- antrum	17	4	2	2
- body	6	10	8	3
- fundus	0	4	1	0
- not specified	0	0	11	0
Endoscopic procedure				
- En bloc (%)	19 (82.6)	16 (88.9)	20 (90.2)	5 (100)
- R0 resection	21 (91.3)	16 (88.9)	19 (86.4)	5 (100)
- Time: Mean±SD: (range) min	41±26.1	70 (10-450)	35 (NA)	101 (75-130)
- Bleeding (%)	1 (4.3)	3 (16.7)	2 (9.1)	2 (33.3)
- Perforation (%)	0	0	1 (4.5)	0
Histology				
- LGD	4	0	NA	0
- HGD	4	0	NA	2
- Early gastric cancer	15	18	NA	3
Recurrence at follow-up	None	None	NA	None

LGD: Low grade dysplasia; HGD: High grade dysplasia.

4.0 CONCLUSION

Cirrhotic patients are at increased risk of developing gastro duodenal lesions [21], including gastric cancer [3–5].Surgery in these patients is associated with high morbidity and mortality rates [13]. It is thus important to establish whether endoscopic removal of early gastric lesions is effective and safe in these patients. Indeed, although ESD for gastric neoplastic lesions has been reported to be adequately safe in the general population,

post-procedure bleeding is expected to occur more frequently in cirrhotics due to both clotting impairment and platelets count reduction [12]. By reviewing the published literature, we found 3 Asian series dealing with gastric ESD in cirrhotics [18–20]. By pooling data of these series and data of our 5 personal cases, there were 68 gastric ESDs performed in 61 cirrhotic patients. Both the en bloc removal and the R0 resection were achieved in nearly 90% of cases. This high rate of technical feasibility and clinical efficacy of ESD should discourage a first-line surgical approach for early neoplastic gastric lesions in all cirrhotics, especially when considering the high surgery related morbidity/mortality in these patients. However, a careful clinical follow-up is needed to adequately manage both early and late post-procedure bleeding which was reported to occur in 2 out of the 5 cases. Of note, such a complication was successfully managed by endoscopic approach in both cases, with no deaths reported. Overall, the bleeding rate (12.1%) calculated in the present analysis in cirrhotics would appear distinctly higher than the 1.2% bleeding rate reported in a large series of gastric ESD performed in the general population [17]. We observed that bleeding occurred more frequently in Child-Pugh class B/C cirrhotics as compared to class A patients. Moreover, data showed that all patients with bleeding episodes presented with an INR value >1.33 and/or platelets count <105,000/mm³. Therefore, while waiting for larger and better controlled studies, it could be reasonable to consider these thresholds as alerting values in order to identify those cirrhotics at increased risk of bleeding following ESD. These cut-off values are lower than the INR <1.5 and platelet counts >50,000/mm³, suggested to safely perform in cirrhotics less invasive procedure, such as liver biopsy, multiple gastric biopsies, central venous cannulation procedure, and paracentesis [12, 22]. Finally, our analysis found that the perforation rate (1.6%) following gastric ESD in cirrhotics would be similar to 2.1% reported in the general population [17].

Based on the review of the published literature and our small case series, ESD for gastric neoplastic lesions in cirrhotics appears to be an effective and relatively safe procedure. Procedure-related bleeding has been reported to be quite frequent, but it can be successfully managed by an endoscopy approach in all cases. Patients with advanced cirrhosis (stage B or C), with either INR >1.33 and/or platelets count <105,000/mm³ appear to be at increased risk of bleeding following ESD. In conclusion, the ESD for early gastric neoplastic lesions removal in cirrhotics achieved a very high R0 resection rate, preventing a more invasive, and potentially life-threatening surgical approach in these patients.

ETHICAL ISSUES

The authors declare no competing financial interest.

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