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Endoscopic Submucosal Dissection for visible dysplasia treatment in ulcerative colitis patients: cases series and systematic review of literature.

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Abstract

Background and Aims: Ulcerative colitis (UC) patients are at increased risk of developing colorectal cancer due to chronic inflammation. Endoscopic submucosal dissection (ESD) allows removal of non-invasive neoplastic lesions in colon, but only few data are available on its efficacy in UC patients.

Methods: Data of consecutive UC patients diagnosed with visible dysplastic lesions in the colon who underwent ESD were evaluated. The *en bloc* removal, R0 resection and complications rates were calculated. Local recurrence and metachronous lesions during follow-up were computed. Systematic review of literature with pooled data analysis was performed.

Results: A total of 53 UC patients (Age: 65 years; range 30-74; M/F: 31/22), underwent ESD procedure. The *en bloc* resection rate was 100%, and the R0 resection was 96.2%. Bleeding occurred in 7 (13.2%) patients, and perforation in 3 (5.6%) cases, all treated at endoscopy. No recurrence was observed, whilst 2 metachronous lesions were detected. Data of other 6 studies (4 Asian and 3 European) were available. By pooling data the *en bloc* resection was successful in 88.4% (95% CI = 83.5-92) out 216 lesions and 91.8% (95% CI = 87.3-94.8) out of208 patients. The R0 resection was achieved in 169 ESDs, equivalent to a 78.2% (95% CI = 72.3-83.2) rate for lesions and 81.3% (95% CI = 75.4-86) for patients. No difference between European and Asian series was noted.

Conclusions: This pooled-data analysis pointed out that ESD is a suitable tool for safely and properly removing non-invasive neoplastic lesions on colonic mucosa of selected UC patients.

Key Words: Endoscopic submucosal dissection; Ulcerative colitis; dysplasia; colorectal cancer.

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1. Introduction

Ulcerative colitis (UC) is an idiopathic, long-lasting inflammatory bowel disease whose incidence is increasing in Western countries.[1] UC patients are at increased risk of developing colorectal cancer (CRC), varying with the extent and duration of the disease.[2] Indeed, chronic inflammation of colonic mucosa predisposes to the onset of dysplasia (i.e. non-invasive neoplasia),[3] which is a precursor of invasive cancer.[4] Therefore, a tailored endoscopic surveillance and treatment of dysplasia in UC patients are recommended by the ECCO guidelines.[5]

First introduced in Japan twenty years ago, endoscopic submucosal dissection (ESD) is an established method to accurately treat large, superficial neoplastic lesions, through the gastrointestinal mucosa.[6] Indeed, ESD allows performing *en bloc*, margin-negative resection (R0), and curative resection, thus avoiding surgery in a definite quote of patients.[6] In addition, ESD overcomes the limits of Endoscopic Mucosal Resection (EMR) in removing neoplastic lesions larger than that feasible by EMR and with a coexistent fibrotic tissue, as frequently occurs in UC patients.[7] Therefore, ESD might be considered as an appropriate therapeutic option for UC patients with lesions fitting for the procedure. However, to date, only few data are available on the removal of superficial neoplastic lesions in the colon of UC patients by using ESD. We therefore reported our case series and performed a systematic review of literature with pooled data analysis aiming to improve knowledge on the advantages and limits of this endoscopic approach.

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2. Case series

Data of consecutive UC patients, diagnosed with superficial neoplastic lesions, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) on colonic mucosa who underwent ESD procedure in two tertiary referral centers, were prospectively collected in a specific database. This included demographic, endoscopic, histological and clinical data. As for our clinical practice, all visible dysplastic lesions detected in UC patients with a diameter ≥10 mm were treated with ESD, whenever not fitting for the endoscopic approach (large ulcerated lesions, presence of invasive cancer at previous histology, technical difficulty) or multiple lesions were present, and these patients underwent surgery. ESD treatment in patients with ongoing endoscopic moderate-to-severe active UC was postponed at remission.

We performed ESD because it allows to overcome EMR limitation in UC patients.[7] For all procedures colonoscopes (CF-HQ 190L/I, Evis Exera III or CF-Q 180 AL/I, Evis Exera II; Olympus Comp.) or gastroscopes (GIF-HQ190, GIF-Q180; Olympus Comp.) for distal lesions were used. The technical success was calculated based on the *en bloc* removal of neoplastic tissue, and the R0 resection when both lateral and vertical margins were found to be free at histology. Free margin was defined as at least 2 mm distance from the lesion to the margin in the resected specimen. Fibrosis at histology was graded as absent (F0), mild (F1), and severe (F2).[8] Two expert operators, trained at National Cancer Center Hospital in Tokyo, performed all ESDs under conscious or deep sedation with propofol, as appropriate. The ESD was performed following standard technique described elsewhere.[9] The rate of complications (major bleeding and perforation) associated with the procedure was registered. Local recurrence, defined as detection of dysplastic or neoplastic tissue at the scar, and occurrence of metachronous lesions,

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defined as dysplastic lesion detected in another colon site during follow-up, were calculated. All patients were informed about advantages and disadvantages of endoscopic procedure, as well as on potential complications, and they signed an informed consent for both the procedure and anonymously using data for scientific purpose. Since no experimental drugs were administered, no additional costs or procedures for the patients were required, no identification of patients was allowed, and no funds were received, our Investigational Review Board waived formal review and approval, deeming the study to be an extension of existing clinical practice.

Between April 2009 and January 2020, a total of 53 UC patients (median age: 65 years; range 30-74; M/F: 31/22), endoscopically studied by indigo carmine chromoendoscopy and magnify-virtual chromoendoscopy for suspected dysplastic areas as reported elsewhere,[10,11] were treated for visible lesions on colonic mucosa by ESD removal. The median of UC duration was 17 years (range: 10-25) and extensive colitis was present in 30 patients (56.6%). A scar was observed in 8 (15.1%) cases because of a previous attempt of EMR in other Hospitals. The *en bloc* resection rate was successful in all the cases (100%). The R0 resection rate was successful in 51 (96.2%) patients, whilst in the remaining 2 (3.7%) cases it was not achieved because of the F2 fibrosis degree. In these patients the resection was completed by a subsequent piecemeal EMR. At histological examination of resected lesions LGD was present in 37 (69.8%) cases, HGD in 14 (26.4%), indefinite for dysplasia in 1 (1.8%), and negative for dysplasia in another (1.8%) patient. There were no mucosal or submucosal invasive carcinomas within the post-resection specimens, so that ESD was curative in all R0 cases. Submucosal fibrosis was present in 29 (54.7%) lesions (F1: 21; F2: 8). Bleeding was observed in 7 (13.2%) patients, all successful treated by endoscopic clipping, whilst perforation occurred in 3

(5.6%) patients, two treated by endoscopic clipping and the other with clip and loop method.[12] The endoscopic follow-up control was scheduled at 3, 6, and 12 months for the first year, and thereafter each 12 months. At follow-up (median 37 months, range: 6-60) no recurrence was observed. Nevertheless, 2 metachronous lesions of HGD were identified in 2 patients (32 and 37 years), at 24 and 36 months follow-up, and both underwent to surgery.

3. Literature review

Systematic review of literature was performed in PubMed on May 21, 2020 by searching for 'ulcerative colitis and ESD', with language limited to English. Only case series with ≥5 patients were considered. A total of 14 citations were identified, and the full paper were retrieved. The references of the identified studies were also evaluated to searching for potential missing publications. Following evaluation, reviews without original data (N = 3), case reports (N = 3), Japanese language (N = 1) and not pertinent (N = 1) were excluded, whilst the remaining 6 studies meet inclusion criteria.[13-18] By cumulatively considering data, including our case series, there were a total of 208 patients with 216 treated lesions, including 4 Asian and 3 European studies (Table 1). There was a slight prevalence of males (M/F = 1.39) and the median age was >60 years in all, but one study, with a 59.6% prevalence of extensive colitis. The median of disease duration was ranging from 7 to 20 years in different studies.

The *en bloc* resection was successful in 191 ESD procedures, corresponding to 88.4% (95% CI = 83.5-92) on 216 lesions and 91.8% (95% CI = 87.3-94.8) on 208 patients. The R0 resection was achieved in 169 ESDs, equivalent to a 78.2% (95% CI = 72.3-83.2) rate for lesions and 81.3% (95% CI = 75.4-86) for patients. According to the operator, the *en*

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bloc resection and R0, respectively, were achieved in 113 (86.9%; 95% CI = 80-91.7) and 107 (82.3%; 95% CI = 74.8-87.9) out of 130 lesions treated by European endoscopists, and in 78 (92.9%; 95% CI = 85.3-96.7) and 62 (73.8%; 95% CI = 63.5-82) out of 84 lesions treated by Asian endoscopists, without a statistically significant difference between groups. The median diameter of removed lesions in different studies varied from 15 to 35 mm (range: 8-73). Submucosal fibrosis was detected in as many as 104 (77.1%; 95% CI = 69.3-83.3) out of 135 lesions (5 studies). The overall rate of complications was 9.6% (95% CI = 6.3-14.4), including 6.7% bleedings and 2.9% perforations, all managed at endoscopy. At follow-up, lesion recurrence on the scare was observed in only 8 (3.8%; 95% CI = 2-7.4) patients, and a metachronous lesion developed in 13 (6.2%; 95% CI = 3.7-10.4) cases.

4. Discussion

UC patients are at increased risk of developing CRC through the inflammation-dysplasia-carcinoma sequence.[4,5] Therefore, there is a window of opportunity to reduce CRC development by identification and treatment of dysplastic lesions. The introduction of ESD allowed to improve endoscopic removal of non-invasive neoplasia in these patients, overcoming the limits of EMR in removing fibrotic tissue frequently present in the colon of UC patients.[8] Unfortunately, only data of few case series are currently available, so that information is fragmentary, and a pooled data analysis would be useful.

Our study provided some clinically relevant information on the role of endoscopic treatment for non-invasive neoplastic lesions on colonic mucosa in UC patients. By considering our case series and data available in the literature, more than 200 patients were collected, so that the information might be considered consistent. We found that

patients with UC colitis and non-invasive neoplastic lesions are predominantly males, have extensive colitis, and the median age was around 60 years. Overall, data showed that ESD for neoplastic lesions removal is feasible in UC patients, with technical success higher than 88%, despite the high prevalence of fibrosis in the colon of these patients. Moreover, the procedure is curative in more than two third of patients. When coupling these results with the acceptably low incidence of complications (<10%), also safely managed at endoscopy in the majority of cases, the performance of ESD is surely considerable. Indeed, a longer hospital stay, a wider incidence of adverse events, and a higher overall cost were reported following surgical proctocolectomy in these cases.[17,18] On the other side, patients treated with endoscopy remain at risk of developing both recurrence and metachronous lesions (10% in our review). Indeed, chronic inflammation of the colon creates a 'field effect', whereby any part of the colon that is currently, or was previously, inflamed is at risk for neoplastic transformation.[4] When considering the rate of local recurrence (3-14%), of metachronous lesions (4-71%) and need for additional surgery (2-57%), observed in the relatively short follow-up reported in the considered studies, the ESD could be considered eventually curative only selected UC patients. Unfortunately, predictive factors of recurrence are still unclear so that further prospective studies are needed to identify those patients who might better benefit of endoscopic treatment. Thus, a scheduled, long-term follow-up is mandatory in these patients and, in the absence of contraindications, surgery still remains the option of choice.[5]

Our data found a similar performance between European and Asians operators, suggesting the Western endoscopists achieved a considerable skill, albeit a further technical improvement could be promoted. A limitation is that ESD procedure in Western countries is still performed only in selected centers, so that an implementation is desirable.

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Moreover, well-designed prospective studies are necessary to establish the real role of ESD in the treatment of colonic neoplastic lesions in patients with UC, with particular consideration on long-term follow-up. In the meantime, referral of UC patients with neoplastic lesions amenable for ESD to specialized centers should be considered.

In conclusion, this pooled-data analysis pointed out that ESD is a suitable tool for safely and properly removing non-invasive neoplastic lesions on colonic mucosa in selected UC patients, as long as an appropriate and long-term follow-up is performed.

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Conflicts of Interest

All authors declared no conflicts of interest.

Author Contributions

RM conceived the study. RM and GG performed all endoscopic procedures. AT, DC and UG collected data of patients and performed literature research. LRB performed pathological evaluations. AZ and RC performed data analysis and wrote the first draft. All contributors revised the manuscript, were involved in the conception of the study, and have approved the final manuscript.

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19. **Table 1**. Data of available studies on colonic ESD procedures performed in ulcerative colitis patients.

Author	**Smith LA**[13]	**Iacopini F** [14]	**Suzuki N**[15]	**Kinoshita S**[16]	**Yang DH**[17]	**Matsumoto K**[18]	**Our series**
Country/year	UK 2008	Italy/Japan 2015	UK/Japan 2017	Japan 2018	Korea 2019	Japan 2019	Italy 2020
Age; median (range); yrs	54 (26-72)	62 (35-69)	65 (49-86)	62 (38-83)	60 (31-68)	64 (31-71)	65 (30-74)
Male/female	35/32	4/5	18/14	18/7	10/5	5/2	31/22
UC duration; median (range); yrs	11 (2-22)	13 (9-22)	20 (1-41)	19 (1-37)	14 (2-21)	7 (14-86)	17 (10-25)
Extentive colitis; (%)	NA	6 (67)	NA	19 (76)	6 (40)	4 (67)	30 (56.6)
Number of lesions	67	10	32	25	15	12	53
Lesion size, Median (range); mm	19±12*	33±12*	33 (12-73)	35±17*	19 (10-43)	15 (8–35)	34 (20-50)
En bloc resection; (%)	52 (78)	8 (80)	29 (90.1)	25 (100)	14 (93.3)	10 (83)	53 (100)
R0 resection; (%)	49 (73.1)	7 (70)	23 (71.8)	19 (76)	12 (80)	8 (67)	51 (96.2)
Fibrosis (F0/F1/F2)	NA	1/2/7	1/26/5	0/25/0	5/8/2	NA	24/21/8
Bleeding; (%)	7 (10)	1 (10)	1 (3)	0	0	0	7 (13.2)
Perforation; (%)	2 (3)	0	0	1 (4)	0	0	3 (5.6)
Follow-up; median (range) mo	18 (6-36)	24 (6-72)	33 (6-76)	21 (8-80)	25 (5-65)	180 (105–271)	37 (6-60)
Local recurrence; (%)	5 (7)	0	1 (3)	0	2 (14.3)	0	0
Metachronous; (%)	0	0	3 (9)	1 (4)	2 (14.3)	5 (71)	2
Additional surgery (%)	1 (1.5)	1 (9)	4 (12.5)	5 (20)	2 (14.3)	4 (57)	2

* Mean ± SD. NA: not available.