



Short Report

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 an increased risk of developing colorectal cancer due to chronic inflammation. Endoscopic submucosal dissection [ESD] allows removal of non-invasive neoplastic lesions in the colon, but few data are available on its efficacy in UC patients.

Methods: Data from consecutive UC patients diagnosed with visible dysplastic lesions in the colon who underwent ESD were evaluated. The *en bloc* removal, R0 resection and complication rates were calculated. Local recurrence and metachronous lesions during follow-up were identified. A systematic review of the 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. The *en bloc* resection rate was 100%, and the R0 resection rate was 96.2%. Bleeding occurred in seven [13.2%] patients, and perforation in three [5.6%] cases, all treated at endoscopy. No recurrence was observed, but two metachronous lesions were detected. Data from six other studies [three Asian and three European] were available. By pooling data, *en bloc* resection was successful in 88.4% [95% confidence interval [CI] = 83.5–92] of 216 lesions and in 91.8% [95% CI = 87.3–94.8] of 208 patients. 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] rate for patients. No difference between European and Asian series was noted.

Conclusions: This pooled data analysis indicated 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

1. Introduction

Ulcerative colitis [UC] is an idiopathic, long-lasting inflammatory bowel disease that is increasing in incidence in Western countries.¹ UC patients are at an 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, tailored endoscopic surveillance and treatment of dysplasia in UC patients are recommended by the ECCO guidelines.⁵

First introduced in Japan 20 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 *en bloc*, margin-negative resection [R0], and curative resection, thus avoiding surgery in a definite proportion of patients.⁶ In addition, ESD overcomes the limits of endoscopic mucosal resection [EMR] by removing neoplastic lesions larger than that feasible by EMR and with a coexisting 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 the procedure. However, to date, only a few data are available on the removal of superficial neoplastic lesions in the colon of UC patients by using ESD. We therefore report here our case series and performed a systematic review of the literature with pooled data analysis aiming to improve knowledge on the advantages and limits of this endoscopic approach.

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 in two tertiary referral centres, were prospectively collected in a specific database. This included demographic, endoscopic, histological and clinical data. Regarding our clinical practice, all visible dysplastic lesions detected in UC patients with a diameter ≥ 10 mm were treated with ESD, whenever not fitting the endoscopic approach [large ulcerated lesions, presence of invasive cancer at previous histology, technical difficulty] or when 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 us to overcome the limitations of EMR 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. 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 The resection was considered curative when non cancer was detected at histology on the removed lesion. Two expert operators, trained at the National Cancer Center Hospital in Tokyo, performed all ESDs under conscious or deep sedation with propofol, as appropriate. The ESD was performed following a 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, defined as dysplastic lesion detected in

another colon site during follow-up, were calculated. All patients were informed about the advantages and disadvantages of the endoscopic procedure, as well as on potential complications, and they signed an informed consent for both the procedure and anonymously using data for scientific purposes. Because 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 magnified-virtual chromoendoscopy for suspected dysplastic areas as reported elsewhere,^{10,11} were treated for visible lesions on colonic mucosa by ESD. The median duration of UC was 17 years [range: 10–25] and extensive colitis was present in 30 patients [56.6%]. A scar was observed in eight [15.1%] cases because of a previous EMR attempt in other hospitals. The *en bloc* resection was successful in all cases [100%]. R0 resection was successful in 51 [96.2%] patients, while in the remaining two [3.7%] cases it was not achieved because of the degree of F2 fibrosis. 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 one [1.8%] and negative for dysplasia in one [1.8%] patient. There were no mucosal or submucosal invasive carcinomas within the post-resection specimens, so ESD was curative in all R0 cases. Submucosal fibrosis was present in 29 [54.7%] lesions [F1: 21; F2: eight]. Bleeding was observed in seven [13.2%] patients, all successful treated by endoscopic clipping, whilst perforation occurred in three [5.6%] patients, two treated by endoscopic clipping and the other with the clip and loop method.¹² 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, two metachronous lesions of HGD were identified in two patients [32 and 37 years], at 24 and 36 months of follow-up, and both underwent surgery.

3. Literature Review

A 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 five or more patients were considered. A total of 14 citations were identified, and the full papers were retrieved. The references of the identified studies were also evaluated to search for potential missing publications. Following evaluation, those reviews without original data [N = 3], case reports [N = 3], Japanese language [N = 1] and not pertinent [N = 1] were excluded, with the remaining six studies meeting inclusion criteria.^{13–18} By cumulatively considering data, including our case series, there were a total of 208 patients with 216 treated lesions, including three Asian and four European studies [Table 1]. There was a slight prevalence of males [M/F = 1.39] and the median age was >60 years in all, and there was a 59.6% prevalence of extensive colitis. The median of duration disease ranged from 7 to 20 years in the different studies.

In total, *en bloc* resection was successful in 191 ESD procedures, corresponding to 88.4% (95% confidence interval [CI] = 83.5–92) of 216 lesions and 91.8% [95% CI = 87.3–94.8] of 208 patients. 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]

Table 1. Data of available studies on colonic endoscopic submucosal dissection procedures performed in ulcerative colitis [UC] patients

Author	Smith LA ¹³	Iacopini P 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]; years	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]
Extensive 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]
<i>En bloc</i> 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]; months	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.

rate for patients. According to the operator, *en 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] 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] of 84 lesions treated by Asian endoscopists, without a statistically significant difference between groups. The median diameter of removed lesions in the different studies varied from 15 to 35 mm [range: 8–73]. Submucosal fibrosis was detected in 104 [77.1%; 95% CI = 69.3–83.3] of 135 lesions [five 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 was observed in only eight [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 an 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 improved 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 a few case series are currently available, so that information is fragmentary, and a pooled data analysis would be useful.

Our study has 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, information on more than 200 patients was collected, suggesting that this information might be considered consistent. We found that patients with UC colitis and non-invasive neoplastic lesions are predominantly males, have extensive colitis, and have a median age of around 60 years. Overall, the data showed that ESD for removal of neoplastic lesions is feasible in UC patients, with technical success greater than 88%, despite the high prevalence of fibrosis in the colon of these patients. Moreover, the procedure is curative in more than two-thirds of patients. When coupling these results with the acceptably low incidence of complications (<10%), also safely managed at endoscopy in the majority of cases, ESD can be considered a suitable tool for removal non-invasive neoplastic lesions on colonic mucosa of selected UC patients. 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} However, 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 of 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 studies considered here, ESD can be considered to be curative only in selected UC patients. Unfortunately, the predictive factors of recurrence remain unclear so that further prospective studies are needed to identify those patients who might better benefit from endoscopic treatment. Thus, scheduled, long-term follow-up is mandatory in these patients and, in the absence of contraindications, surgery remains the option of choice.⁵

Our data found a similar level of performance between European and Asian operators, and further technical improvements could be promoted. A limitation is that ESD in Western countries is

still performed only at selected centres, and increased implementation is desirable.

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

In conclusion, this pooled-data analysis has shown 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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Conflict of Interest

All authors declare no conflicts of interest.

Author Contributions

R.M. conceived the study. R.M. and G.G. performed all endoscopic procedures. D.A.T., D.C. and U.G. collected patient data and performed the literature search. L.R.B. performed pathological evaluations. A.Z. and R.C. 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.

References

- Burisch J, Jess T, Martinato M, Lakatos PL, ECCO-EpiCom. The burden of inflammatory bowel disease in Europe. *J Crohns Colitis* 2013;7:322–37.
- Harbord M, Eliakim R, Bettenworth D, et al. Third European evidence-based consensus on diagnosis and management of ulcerative colitis. Part 2: current management. *J Crohns Colitis* 2017;11:769–84.
- Mescoli C, Albertoni L, D'incà R, Rugge M. Dysplasia in inflammatory bowel diseases. *Dig Liver Dis* 2013;45:186–94.
- Shah SC, Itzkowitz SH. Management of inflammatory bowel disease-associated dysplasia in the modern era. *Gastrointest Endosc Clin N Am* 2019;29:531–48.
- Annese V, Beaugerie L, Egan L, et al.; ECCO. European evidence-based consensus: inflammatory bowel disease and malignancies. *J Crohns Colitis* 2015;9:945–65.
- Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T, et al. Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015;47:829–54.
- Hurlstone DP, Sanders DS, Atkinson R, et al. Endoscopic mucosal resection for flat neoplasia in chronic ulcerative colitis: can we change the endoscopic management paradigm? *Gut* 2007;56:838–46.
- Matsumoto A, Tanaka S, Oba S, et al. Outcome of endoscopic submucosal dissection for colorectal tumors accompanied by fibrosis. *Scand J Gastroenterol* 2010;45:1329–37.
- Manta R, Galloro G, Pugliese F, et al. Endoscopic submucosal dissection of gastric neoplastic lesions: an Italian, multicenter study. *J Clin Med* 2020;9:E737.
- Matsumoto T, Kudo T, Jo Y, Esaki M, Yao T, Iida M. Magnifying colonoscopy with narrow band imaging system for the diagnosis of dysplasia in ulcerative colitis: a pilot study. *Gastrointest Endosc* 2007;66:957–65.
- Esaki M, Kubokura N, Kudo T, Matsumoto T. Endoscopic findings under narrow band imaging colonoscopy in ulcerative colitis. *Dig Endosc* 2011;23[Suppl 1]:140–2.
- Sakamoto N, Beppu K, Matsumoto K, et al. “Loop Clip”, a new closure device for large mucosal defects after EMR and ESD. *Endoscopy* 2008;40[Suppl 2]:E97–8.
- Smith LA, Baraza W, Tiffin N, Cross SS, Hurlstone DP. Endoscopic resection of adenoma-like mass in chronic ulcerative colitis using a combined endoscopic mucosal resection and cap assisted submucosal dissection technique. *Inflamm Bowel Dis* 2008;14:1380–6.
- Iacopini F, Saito Y, Yamada M, et al. Curative endoscopic submucosal dissection of large nonpolypoid superficial neoplasms in ulcerative colitis (with videos). *Gastrointest Endosc* 2015;82:734–8.
- Suzuki N, Toyonaga T, East JE. Endoscopic submucosal dissection of colitis-related dysplasia. *Endoscopy* 2017;49:1237–42.
- Kinoshita S, Uraoka T, Nishizawa T, et al. The role of colorectal endoscopic submucosal dissection in patients with ulcerative colitis. *Gastrointest Endosc* 2018;87:1079–84.
- Yang DH, Kim J, Song EM, et al. Outcomes of ulcerative colitis-associated dysplasia patients referred for potential endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2019;34:1581–9.
- Matsumoto K, Oka S, Tanaka S, et al. Long-term outcomes after endoscopic submucosal dissection for ulcerative colitis-associated dysplasia. *Digestion* 2019;1–11. doi:10.1159/000503341 [Epub ahead of print].