

Title

Endoscopic Submucosal Dissection of Colitis related dysplasia

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Abstract

Background and Study aims: Endoscopic Submucosal Dissection (ESD) offers en bloc resection of the lesion allowing precise pathologic assessment and would be possible in ulcerative colitis patients. However the chronic inflammation may increase the procedural risks and reduce complete resection rate. The aim of this study was to assess feasibility and to consider the factors contributing to the technical difficulty in ESD for UC.

Patients and Methods: Multicenter experiences in ESD for UC were retrospectively analyzed by reviewing endoscopic videos, pictures, report and clinical notes.

Results: Thirty two dysplastic lesions (British 23 and Japanese 9 patients) were included. The lesions were macroscopically flat or with subtle extension macroscopically in 30 (94%) with median size 33mm (range 12-73mm), locating in distal colon including 1 on pouch anastomosis. Submucosal fibrosis and adipose deposition was observed in 31(97%) and 13(41%), respectively. Enbloc resection was possible in 29/32cases (91%). One patient had delayed bleeding. Advanced pathology was observed in 11 cases(35%). Recurrence was not observed except one case (median 33 months range 6-76 months), however 3 patients developed metachronous lesions.

Conclusions: ESD is feasible for UC dysplasia without an increased rate of complications. Submucosal fibrosis and fat deposition were frequently observed contributing to technical complexity. Careful and intensive follow up should be organized for detecting metachronous lesions.

Key Points

- ESD of dysplastic lesions in UC is feasible but technically demanding due to ongoing or previous background inflammation, submucosal fibrosis and adipose deposition.
- Some UC related lesions are subtle in morphology and en bloc excision is preferred to minimize risk of recurrence and optimize the pathological specimen.
- High numbers of advanced histopathology are seen. Some cancer invasion is focal therefore en bloc resection with deep submucosal dissection is warranted.
- Development of metachronous lesions is relatively commonly observed hence meticulous and intensive endoscopic surveillance is imperative.

Introduction

Patients with long-standing extensive ulcerative colitis (UC) have an increased risk of developing colorectal cancer, although risks seen in population based studies are lower than those seen in data from tertiary centers^{12 3456}. Recent international guidelines have focused on improving detection of dysplasia through the use of chromoendoscopy to help highlight flat and subtle lesions. Guidelines now recommend that resection of circumscribed dysplasia and continued colonoscopic surveillance is a reasonable strategy in patients with ulcerative colitis ⁷⁸⁹. Data post resection of polypoid dysplasia suggest that future colorectal cancer risk may be as low as 5 cancers per 1000 patient years follow up¹⁰. The introduction of chromoendoscopy in recent years may mean that dysplasia detected in the current era is less advanced than previously and is more safely managed by endoscopic resection with close endoscopy follow up¹¹.

The data for cancer risk after resection of non-polypoid dysplasia (Paris 0-II, "flat") in colitis is extremely limited ¹². Resection is technically possible using standard or enhanced endoscopic mucosal resection (EMR) techniques, but there are concerns about the risk of recurrence and poor quality, fragmented, pathological specimens. Optimal resection should therefore be en bloc with clear margins, but this can be difficult to achieve with conventional EMR in colitis due to background inflammation making lesion edge detection challenging and leading to submucosal fibrosis that impairs adequate lifting.

Endoscopic Submucosal Dissection (ESD) has been proposed for these lesions in colitis ¹³ with a limited number of successful cases reported; however, fibrosis underneath lesions associated with inflammation in the colitis segment can contribute to technical difficulties of what is already a very technically demanding technique¹⁴. In this study, we examine the safety, feasibility and efficacy of ESD for dysplastic lesions in UC, and consider the factors may contribute to technical difficulties.

Methods

Three centers experiences in ESD for UC were retrospectively analyzed by reviewing endoscopic videos, pictures, report and clinical notes. Some information was obtained from the ESD database which all institutions recorded lesion characteristics, dissection time and specimen size routinely. The video was evaluated in 26/32 cases (81%) with fast forward mode and occasional normal play speed only if necessary. If the video was not available, the evaluation was done with all endoscopic pictures in 6/32(19%). The review of the endoscopic videos or images was performed by the each original endoscopist.

Formal ethical committee approval was not required for the UK sites as this was considered a service evaluation, with only anonymised collection of routinely available clinical data, but each site sought and received local research and development department approval. This study was carried out in accordance with the Helsinki Declaration. (R&D reference number SE16/024 at St Mark's Hospital and 160053 at Kobe University).

Study population

From January 2009 to Jan 2016, dysplastic lesions in a colitis affected segment, especially lesions deemed unresectable with a conventional snare resection including EMR, were prospectively referred for ESD. They were either (i) Large lesions >20mm (ii) Lesions with subtle peripheral extension (iii) Residual or recurrent tumors following the previous treatment or (iv) suspected T1 lesions.

Exclusion criteria were as follows: (i) multiple dysplasias, (ii) a lesion with severely inflamed background mucosa (iii) dysplasia with no demarcation line i.e. non-circumscribed

In case of not well circumscribed lesions, biopsies were taken from the surrounding mucosa to exclude invisible dysplasia during the UC surveillance colonoscopy prior to endoscopic resection.

ESD

The procedures were performed by three colonoscopists (N.S. in St Mark's Hospital n=21, J.E. in John Radcliffe Hospital n=2 and T.T. in Kobe University Hospital n=9). Single-channel gastroscopes (GIF 240 and 260, Olympus Co, Ltd, Tokyo Japan) or colonoscopes (CF 240AI and PCF 260AI, Olympus Co.) were used. The distal attachment (Olympus Co) , ST hood (Fujinon Optical Co, Ltd, Tokyo, Japan) was mounted at the tip of a colonoscope for the stabilization of the views and for the further counter traction.

Conscious sedation with a combination of intravenous Midazolam or Precedex and Pethidine or Fentanyl was used in all cases. Hyoscine butyl-bromide was given as an antispasmodic to all patients who did not have contraindications.

Prior to the endoscopic removal, these lesions were carefully assessed with dye-spray and image enhanced endoscopy including structure enhancement, narrowed spectrum endoscopy (Narrow band imaging, NBI), especially for assessing the flat lateral extension. If there was subtle extension, mucosal markings were placed around the lesion.

ESD technique

Initial submucosa injection was done with hyaluronic acid solution.(Sigmaviscs, Hyaltech Ltd, Livingston, United Kingdom and Mucoup, Johnson & Johnson KK, Tokyo, Japan). Flush knife non-tipped or ball-tipped (1.5mm or 2mm in length)(Fujinon Optical Co) with a high frequency automated electrosurgical generator (Erbotom ICC 200, ERBE VIO200S or VIO 300; ERBE Elektromedizin Ltd, Tübingen, Germany) in Endocut Effect 2 for mucosal incision or forced coagulation 35-45W were used for submucosal dissection. Soft coagulation (Effect 5-7, 80-100W) was used for coagulation of vessels with tip of flush knife or hemostatic forceps (Coagrasper, Olympus Ltd, Japan)¹⁵

Our standard ancillary devices were Flush knife BT and distal attachment (Olympus Co) but in case of extensive severe fibrosis, these were changed to non-tipped Flush knife and short ST

hood.

The standard technical approach to the lesions was conventional resection in which the incision was started from anal side with straight viewing and dissection was made towards to the oral side. The pocket creation method was sometimes applied for larger lesion with moderated fibrosis. Position changes was used to facilitate counter traction or to shift fluid pool during the procedures.

Sub mucosal findings

Submucosal fibrosis was classified into none, mild/moderate or severe. Adipose deposition in submucosa layer was also assessed and classified into none, mild (up to upper half of submucosa) or severe (more than half to whole submucosa).

Average speed of ESD from the point of submucosal injection to the detachment of lesion flap was measured as cm^2/min considering the lesion area as an ellipsis. Adverse events were categorized as intra or post-procedural (up to 14 days). Complications were ascertained either when the patient attended for the post procedural appointment or via telephone 1 week post procedure.

Histopathology analysis

Specimens were stretched on foam, fixed in formalin, cut into 2-mm thick slices, and stained with hematoxylin and eosin. Complete (R0) resection definition was applied to en bloc resection with tumor-negative lateral and vertical margins at histology. Curative resection definition was defined an R0 resection with submucosal invasion less than 1000 μm without lymph vascular involvement.

Follow-up

If curative resection was confirmed, surveillance colonoscopy was planned at 6-month intervals. Otherwise, the site check was performed in 3months post procedure. If recurrence or residual was detected, the patients were treated with further endoscopic or surgical resection.

Results

A total of 33 UC patients with 33 suspected dysplastic lesions were enrolled. One case with poor bowel preparation, subsequently the quality of endoscopic pictures were suboptimal for evaluation, was excluded. For the majority of the cases (28/32), minimal lesion biopsies had been taken during the prior surveillance colonoscopy. Patient demographic and lesion characteristics were shown in Table1.

Nineteen lesions (59%) were greater than 20mm, and 13 lesions (41%) were less than 2cm in size. Of these thirteen lesions less than 20mm in size, 11 cases of the lesions had subtle peripheral extension and two lesions were suspected for T1 lesion.

The result of ESD was shown in Table2. Submucosal fibrosis was observed in the majority of cases (none 1, mild / mod 26, severe 5) and adipose tissue deposition was observed in 41% of the cases (mild 6, severe 7).

En bloc resection was possible in 29/32 cases (91%). Failure of en bloc resection was due to patient intolerance (2), severe fibrosis and extensive adipose deposition (1). R0 resection was confirmed pathologically in 23 out of 29 cases with en bloc resection (79%).

Histology showed four T1 cancer (two sm1 invasion including one with venous invasion, two with sm2/3 invasion), high grade dysplasia(7), low grade dysplasia(19) and regenerative atypia(2).

In relation to adverse events, one patient had delayed bleeding on day3 post procedure, which did not require any further medical treatment.

Follow up

Four patients including two T1, one invisible dysplasia and one mild dysplasia in the patient with a preference for surgery received panproctocolectomy afterwards. In the surgically resected specimens, no residual dysplastic tissue was seen apart from the case with invisible dysplasia. One patient was lost follow up and two elderly patients died from other causes. At the first follow up one patient had tiny recurrence (3mm) that was further treated endoscopically. No recurrence at the site was observed in the rest of patients (n=26) who had further follow up at a median of 33 months (range 6-76). However 3 of the patients developed

metachronous dysplastic lesions at 14, 23 and 32 months, respectively. These three patients were offered panproctocolectomy.

Discussion

Recent advantages of image enhanced endoscopy including structure enhancement, narrowed spectrum endoscopy enables us to more accurately visualize, localize and diagnose UC related dysplastic lesions¹⁶¹⁷. Therefore from clinical perspective, the endoscopic resectability of a lesion is more important than whether it is thought to be a sporadic adenoma or a dysplasia-associated lesion¹⁷¹⁸.

Now that consensus seems to have been reached on the acceptability of endoscopic resection for circumscribed areas of dysplasia followed by close endoscopic surveillance in management of UC related lesion¹⁹, we need to consider the special circumstances of how to comprehensively resect such lesions.

ESD appears an ideal technique to provide an en bloc resection specimen with background mucosa as a negative margin which would allow the omission of background biopsies to check for adjacent nonvisible dysplasia. On the other hand, ESD is known as a technically demanding procedure and furthermore submucosa fibrosis from previous or ongoing inflammation could impede tissue separation in IBD patients²⁰. ESD for flat dysplasias in UC was firstly reported with limited number of 9 patients with R0 resection rate of 80%. Severe and extensive fibrosis was the factor contributing to the failed ESD¹³

In our series, our R0 resection rate was similar to this previously reported study. Retrospectively, non R0 resection was due to cancer invasion and also partly due to resection very close to the lesion especially at the edge of subtle extension. However, the completeness of resection was later confirmed at the follow up in the majority of cases.

Scarring of the submucosa was highly prevalent seen in 97% of the lesions. Adipose tissue deposition in submucosa layer also was often observed at the rate of 41%. Technically this adipose deposition impaired vision during ESD²¹ and made submucosal dissection more challenging, needing to meticulously target under this. If adipose tissue occupied the majority of submucosal layer, the ability to recognize and find resectable submucosa was extremely narrowed, requiring more meticulous targeting of the plane in submucosal dissection, which greatly contributed to the longer operation time. Our procedure time was obviously slower

than those from non UC cases reported previously ²². Also from the technical viewpoint, dissection with Endocut was mandatory for the effective cutting of adipose tissue.

Submucosal fat deposition was reported to be observed as high as 61% of the UC patients on CT evaluation. ²³. Therefore we suggest that extra procedure time should be warranted in ESD for UC patients. In our series, there were 5 cases with a procedure time longer than 2 hours, in which 3 cases had severe fibrosis, and in 2 cases adipose tissue replaced the whole submucosal layer.

Given the difficulty is assessing non-polypoid lesions, en bloc ESD resection appeared a potentially helpful option as 94% of the lesions had subtle aspects of morphology categorized as IIa, IIb or LST-NG (Laterally spreading tumor non granular type) . Mucosal marking and incision under direct vision enhanced R0 resection. Moreover the en bloc specimen allowed for precise histological evaluation, which was important in our cases as advanced histology was observed only as small foci. One of our T1 case had venous invasion, which could have been missed if only the shallow submucosal layer was resected with conventional EMR technique, even the snare had been able to capture whole lesion laterally.

Understanding longstanding UC patients are high-risk cohort of developing cancers, in our series 3 (12%) of the long term follow up patients developed metachronous dysplasias. Strict and meticulous surveillance should be organized.

Our study has limitations. First, there could be interobserver bias especially in the scoring fibrosis as three endoscopists assessed their own ESD findings. Second all our dysplastic lesions in this study were located distally therefore the findings shown in this study need to be confirmed for proximal lesions.

In conclusion, ESD for UC dysplastic lesion was feasible and is recommended as an optimal treatment for en bloc excision and precise histological evaluation. The safe resection of dysplasia in UC can be achieved by highly trained endoscopic team with more time allowed for

treating fibrosis and targeting of the narrower resectable plane due to adipose tissue deposition.

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Table1

Sex		M18: F 14
Age, median (range),y		65(49-86)
UC duration, median (range),y		20 (1-41)
Lesion location, no (%)		
	Rectum	22 (69%)
	Recto-sigmoid junction	4 (12%)
	Sigmoid colon	5 (16%)
	Pouch- anasotmois	1 (3%)
Size, no(%)		
	<20mm	13 (41%)
	20mm=/ <	19 (59%)
Morphology, no (%)		
	0-Is	2 (6%)
	0-Is+IIa	4 (13%)
	0-IIa	3 (9%)
	0-IIb	1 (3%)
	0-IIa+IIb	8 (25%)
	0-IIa+IIc	1 (3%)
	LST-G*	8 (25%)
	LST-NG**	5 (16%)
Background inflammation, no (%)		
	none	14 (44%)
	mild	15 (47%)
	moderate	3 (9%)
Background visible scar, no (%)		
	none	13 (41%)
	mild/moderate	18 (56%)
	severe	1 (3%)

LST-G*: Laterally spreading tumor –Granular type

LST-NG**: Laterally spreading tumor- Non granular type

Table2

Procedure time, mean (range) mins	87(6-290)
Speed of ESD (cm ² /min), mean/median	0.073/0.065
Submucosal fibrosis	
0	1 (3%)
1	26 (81%)
2	5 (16%)
Fat deposition	
0	19 (59%)
1	6 (19%)
2	7 (22%)
Histology	
LGD	19 (59%)
HGD	7 (22%)
cancer (T1)	4 (13%) (two sm1, two sm2/3)
regenerative atypia	2 (6%)

Figure legend

Figure 1. Examples of adipose tissue deposition

After mucosal incision, adipose tissue was observed in submucosal layer (1a).

During the submucosal dissection, fat filtration was observed upto half of the submucosal layer in this case (2b). In this case, adipose tissue occupied whole submucosal layer (1c).

Figure2. This 15mm lesion in the rectum of a 78-year-old female patient with ulcerative colitis was selected for ESD. Back ground mucosa was granular and the lesion was recognized flat nodule, Paris 0-IIa, at 9oclock position (2a). Appeared more solid presenting Paris 0-IIa under chromoendoscopy(2b). 35x20mm resection sample contained 15mm flat lesion(2c). En bloc excision was achieved with ESD(2d-a), the histology showed tiny focus of invasion (2d-b).