

The Healing Process of Artificial Colorectal Ulcers after Endoscopic Submucosal Dissection

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ABSTRACT

AIM: Endoscopic submucosal dissection applied to endoscopic resection of larger lesions in the gastrointestinal tract may result in the creation of large artificial ulcers. The healing process of colorectal ulcers post-endoscopic submucosal dissection is still unclear. The purpose of this study was to evaluate the healing process of colorectal ulcers post-endoscopic submucosal dissection, using endoscopy and endoscopic ultrasonography.

METHODS: Twenty patients who underwent colorectal endoscopic submucosal dissection between July 2009 and January 2011 were included in this study. Endoscopy and endoscopic ultrasonography were performed to evaluate healing of the artificial colorectal ulcers 4 weeks post-endoscopic submucosal dissection. Ten of the patients with ulcers that had not healed within 4 weeks were examined again after 8 weeks.

RESULTS: Endoscopic observation parameters included ulcer size, location and healing stage. All post-endoscopic submucosal dissection ulcers healed within 8 weeks. In ulcers healed within 4 weeks (early), the mean size of resected specimens was 31.0 mm (long-axis). In ulcers requiring more than 4 weeks to heal (late), the mean size of specimens was 47.8 mm, which was significantly different to the early healing group ($p < 0.05$). The locations of ulcers were not significantly different between the two groups. The study was limited by the small number of cases from a single center.

CONCLUSIONS: Colorectal ulcers artificially created by endoscopic submucosal dissection heal within 8 weeks, regardless of size and location. The larger specimen sizes take longer to heal.

Key words: Endoscopic submucosal dissection; Artificial ulcer; Colorectum; Endoscopic ultrasonography

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INTRODUCTION

Endoscopic mucosal resection (EMR) is a useful therapeutic technique for colorectal laterally spreading tumors, large sessile elevated-type lesions, and superficial-type neoplasms. Conventionally, the indication for EMR was a mucosal lesion with no risk of nodal metastasis. The en bloc resection of a lesion, regardless of its size, can be performed by endoscopic submucosal dissection (ESD), which was recently introduced in Japan. ESD is now gaining acceptance as the standard endoscopic resection technique for stomach neoplasms at an early stage, especially for large or ulcerative neoplasms. Recently, the ESD technique has been used for esophageal and colorectal neoplasms in some institutions. Although the healing process of artificial gastric ulcers after ESD has been reported^[1], there has been no precise study describing colorectal ulcers after ESD. Because laterally spreading tumors are resected en-bloc by ESD, additional colorectal surgery is not usually required, and so pathological findings of artificial ulcers after ESD are not generally available. Fortunately, the usefulness of endoscopic ultrasonography (EUS) for evaluating ulceration has been previously reported^[2,3]. Therefore, the aim of the present study was to evaluate the healing process of artificial colorectal ulcers after ESD, by performing EUS.

MATERIALS AND METHODS

Patients

Twenty patients, 14 men and 8 women (mean age, 69.8 years), with colorectal tumors treated by ESD from July 2009 to January 2011 were enrolled in this prospective study. All enrolled patients were carefully followed. Patients who took anticoagulative agents or non-steroidal anti-inflammatory drugs daily were excluded from the study. Patients were preoperatively diagnosed, by magnifying

observations and EUS examinations. The locations of the lesions were as follows: 4 in the cecum, 3 in the ascending colon, 3 in the transverse colon, 2 in the descending colon, 2 in the sigmoid colon, and 6 in the rectum. There were 1 case of carcinoma, 8 cases of carcinoma in adenoma and 11 cases of adenoma. For all the patients, ESD was performed by one skilled co-author (K. S). After removing the lesion, the artificial ulcer was not sutured. Any remaining vessels in the ulcer bed were coagulated with hemostatic forceps. Patients were allowed small amounts of water in bed immediately after ESD, and oral intake was allowed from the next day, unless serious complications occurred. The patients were discharged within 1 week after ESD. This study was performed according to a protocol approved by the Ethics Committee of our institution, and written informed consent about the study and follow-up was obtained from each patient.

Follow-up

At the first follow-up 4 weeks after the resection, colonoscopy and EUS were performed in the outpatient clinic. Some of the patients with open ulcers at that time returned a further 4 weeks later (8 weeks after the resection) for a further colonoscopy and EUS, after providing informed consent again. For EUS, a 20 MHz US catheter probe was used. EUS was performed by the author who evaluated the depth of the open ulcer and ulcer scars in accordance with Murakami's classification^[3]. Open ulcers consisted of three components: an ulcer crater, a hyperchoic layer at the floor of the crater, and an internal hypochoic area.

Statistical analysis

The effect of primary ulcer size on healing was evaluated. Statistical analysis was performed by the t test.

RESULTS

The average size of the resected specimen was 41.9 mm (range, 18-70 mm). In all patients, ESD was performed without serious complications. At 4 weeks, healing was observed in 7 patients, with the appearance of regenerative mucosa along the rim of the remarkably reduced ulcer. EUS also showed the healing stage of these ulcers to be UL-II. Of the 13 patients with unhealed ulcers, 10 patients underwent a further colonoscopy and EUS at 8 weeks after ESD. In the other 3 patients, further examinations were refused as they found the preparation for colonoscopy hard. At 8 weeks, the scarring stage was observed in all patients endoscopically. EUS revealed that a thickening of the wall remained after the ulcer was scarred. All post-ESD ulcers healed within 8 weeks.

In ulcers healed within 4 weeks (early healing group), the mean size of the resected specimen was 31.0 mm (long-axis). In ulcers requiring more than 4 weeks to heal (late healing group), the mean size of specimen was 47.8 mm. The mean size of the resected specimen was significantly different between the early healing group and the late healing group ($P=0.023$). However, every ulcer healed within 8 weeks, irrespective of the primary ulcer size and location.

DISCUSSION

ESD has recently been applied to the treatment of superficial colorectal tumors. Despite its longer procedure time and higher perforation rate, ESD results in higher en bloc resection and curative rates compared with EMR^[4-6].

While there are many studies describing the healing process of artificial colorectal ulcers after EMR^[7-11], only a few reports describe



Figure 1 A laterally spreading tumor existed in the rectum.

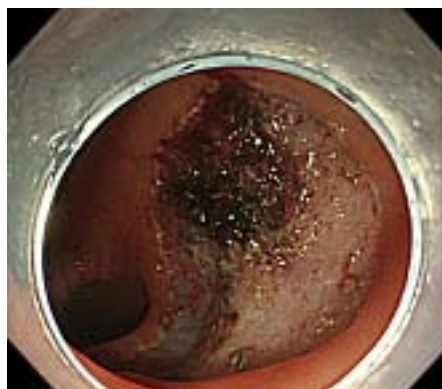


Figure 2 Endoscopic submucosal dissection was performed.



Figure 3 Endoscopy revealed the ulcer still open 4 weeks after endoscopic submucosal dissection.

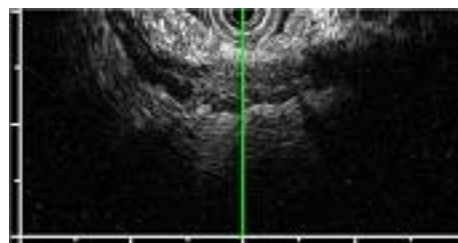


Figure 4 Endoscopic ultrasonography revealed the open ulcer.

ulcers after ESD, and these studies report healing within 6 to 8 weeks in the esophagus, stomach and colorectum^[1,12-14]. The present study showed that artificial ulcers of the colorectum after ESD healed within 8 weeks irrespective of size and location. Even though the artificial ulcer had healed endoscopically, EUS showed that the ulcer echo and the thickening of the wall still existed.

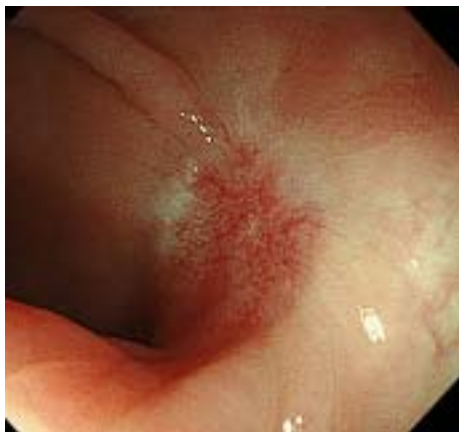


Figure 5 Endoscopy revealed ulcer scarring 8 weeks after endoscopic submucosal dissection.



Figure 6 Endoscopic ultrasonography revealed wall thickening.

There have been reports demonstrating the utility of EUS for evaluating the depth of ulceration^[2,3,15,16]. It is well known that EUS of the ulcer surface can visualize the layer structure of the ulcer. Grade UL-II ulcers involve the submucosal layer. Open ulcers consist of three components: an ulcer crater, a hyperechoic layer at the floor of the crater, and an internal hypoechoic area called an ulcer echo. Histopathologically, an ulcer echo consists of fibrosis and granulation, sonographically correlating well with the thickening of the wall^[16]. EUS revealed that the UL-II ulcer scars had convergence of the submucosal layer. As the healing progresses, the ulcer echo disappears and the thickening of the wall subsides.

Fibrosis and wall thickening were observed using EUS in all patients at 4 weeks after ESD. There was convergence of the submucosal layer in all cases of the early healing group. Among the 13 patients of the late healing group, a mucosal defect was observed as well as an ulcer crater, a hyperechoic layer and ulcer echoes at that time. Logically, artificial ulcers after ESD are UL-II ulcers, so there is no damage of the proper muscle layer. In addition, inflammation and fibrosis of the local area are less, as artificial ulcers created by ESD occur within a very short time. The thickening of the wall is associated with healing of the artificial ulcer, and there are several factors that affect this healing, such as injury of colonic wall tissue by ESD and the time of follow-up after ESD.

Interestingly, there has been a previous report of intra-abdominal adhesions induced by artificial ulceration after ESD^[17]. Pathological examination revealed the presence of inflammatory cell invasion and fibrosis formation in the deeper muscular layer in specimens resected from patients with artificial ulcerations of over 25 mm in diameter. However the formation of intra-abdominal adhesions did not appear to be associated with the interval from ESD to gastrectomy.

Further examinations are necessary to evaluate the thickening of the wall after ESD. A case report of repeat colonoscopy performed 2 months after ESD showed that only a small residual mucosal defect remained within the center of the ulcer scar^[18]. Additionally a study about ESD outcomes in cases of colorectal tumors reported that

follow-up endoscopies were principally performed 2 months after ESD to confirm artificial ulcer healing, and 6 months and 1 year after ESD to check for recurrent tumors and secondary tumors^[19,20]. Our study supports these previous studies, with respect to the timing of follow-up endoscopy.

However, there are limitations of this study - it was not a randomized study and only evaluated a small number of cases in a single center. In addition, we only performed follow-up colonoscopy and EUS at 4 weeks and 8 weeks after ESD and could not compare the EUS results with pathological findings.

In conclusion, artificial ulcers of the colorectum after ESD healed within 8 weeks.

The larger-sized artificial ulcers will take a longer time to heal. EUS can be used to predict the healing stage without pathology. This finding could be very useful for ESD follow-up, but a more detailed analysis of a larger series should be conducted in the future.

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