

# Curative endoscopic submucosal dissection of large nonpolypoid superficial neoplasms in ulcerative colitis (with videos)

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**Background:** Endoscopic resection of superficial neoplasms in inflammatory bowel disease (IBD) is appropriate if a complete resection can be achieved. However, EMR is ineffective for large, nonpolypoid neoplasms in IBD due to submucosal fibrosis, and no data are available on the efficacy of endoscopic submucosal dissection (ESD).

**Objective:** To assess ESD feasibility and efficacy for large, nonpolypoid neoplasms in patients with IBD.

**Design:** Prospective case series.

**Setting:** Multicenter: Italian and Japanese centers.

**Patients:** Consecutive patients with long-standing ulcerative colitis and a superficial nonpolypoid neoplasm, >20 mm within the colitic mucosa.

**Intervention:** Neoplasm characterization and delineation by chromoscopy and narrow-band imaging. ESD performed according to the standard technique.

**Main Outcome Measurements:** Feasibility, safety, curative resection rates.

**Results:** Nine patients with 10 neoplasms were included (7 and 3 in the Italian and Japanese centers, respectively). Neoplasms were laterally spreading tumors—non-granular in 5 cases, in the left side of the colon in 7, had median size of 33 mm, and were associated with scar in 5 cases. Margin delineation was difficult in 5 cases. Submucosal fibrosis was present in 9 cases. ESD was en bloc with negative margins (R0) in 8 cases, and curative in 7. No endoscopic invisible dysplasia or cancer was found during the follow-up (median 24 months, range 6-72 months) at the resection site and elsewhere within the colitic mucosa.

**Limitations:** Small series.

**Conclusion:** ESD achieves curative resections in patients with IBD, but the procedure is difficult because of the high prevalence of submucosal fibrosis. Patients need to be accurately evaluated before resection and adhere to strict long-term follow-ups.

Patients with inflammatory bowel disease (IBD) have an increased risk of colorectal dysplasia and cancer that mainly occur on visible lesions,<sup>1,4</sup> and endoscopic resection is

appropriate if it is complete, with no endoscopic invisible dysplasia in the adjacent mucosa and in the colitic mucosa.<sup>1,2</sup> However, this assumption is evidence-based for

*Abbreviations:* ESD, endoscopic submucosal dissection; IBD, inflammatory bowel disease; R0, endoscopic resection with negative margins.

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selected patients with IBD and small (<10 mm) polypoid neoplasms<sup>5,6</sup> for which EMR can be en bloc and curative. EMR is actually inadequate for large (>20 mm), nonpolypoid neoplasms because of the risk of an inaccurate histologic assessment and high recurrence rates.<sup>7</sup> These drawbacks are particularly relevant in IBD lesions because of the high prevalence of submucosal fibrosis<sup>8</sup> and main causes of surgery.

Endoscopic submucosal dissection (ESD) achieves complete en bloc resections regardless of lesion size and submucosal fibrosis, and superficial neoplasms in IBD have been proposed as an absolute indication for this technique.<sup>7,9</sup> This is the first study reporting the feasibility and efficacy of ESD for curative resection of selected, large, nonpolypoid neoplasms in patients with IBD.

## METHODS

### Study population

From January 2009 to July 2014, consecutive patients with ulcerative colitis in clinical remission (Mayo total score  $\leq 2$ ), with at least a left-side extension, a >8-year disease duration, and superficial nonpolypoid neoplasms within the colitic mucosa that were  $\geq 20$  mm with no deep submucosal invasion, were prospectively referred for ESD. Exclusion criteria were as follows: endoscopic moderate-to-severe active ulcerative colitis (Mayo endoscopic subscore  $\geq 2$ ) and endoscopic invisible dysplasia in the mucosa adjacent to the neoplasm and in the colitic segment.

Deep submucosal invasion was excluded on the basis of absence of a demarcated area, fold convergence, ulceration, spontaneous bleeding, and severely irregular mucosal (type Vn) and capillary (type IIIB) patterns,<sup>10</sup> characterized by chromoendoscopy (indigo-carmin and acetic acid) and narrow-band imaging according to the Kudo and Sano classification, respectively. Magnification and cresyl violet staining were used at the Japanese center. Endoscopic invisible dysplasia was excluded by pancolonic chromoendoscopy and nontargeted biopsies.

The study was approved by the institutional review board in accordance with the Declaration of Helsinki.

### ESD

ESDs were performed by two competent endoscopists (F.I., Y.S.).<sup>7,11</sup> A small-caliber tip attachment (DH, Fujinon, Tokyo, Japan), CO<sub>2</sub> insufflation, and conscious sedation and analgesia were used. Hydroxyethyl starch or 10% glycerol with indigo-carmin and epinephrine (1:250,000) was used for submucosal injection. Mucosal incision was set to be performed 5 mm beyond the tumor margins. Mucosal incision and submucosal dissection were made with non-insulated-tip (Dual-knife, Olympus; B-knife, Xeon Medical Co, Tokyo, Japan) and insulated tip (IT nano, Olympus) knives. Hemostasis and coagulation of visible vessels

**TABLE 1. Patient and ulcerative colitis features**

|  | 9 patients |
|--|------------|
| Age, median (range), y                         | 62 (35-69) |
| Sex (male/female)                              | 4/5        |
| Ulcerative colitis duration, median (range), y | 13 (9-22)  |
| Extension: left/total, no. patients            | 3/6        |
| Mayo total score, median (range)               | 0 (0-2)    |
| Mayo endoscopic subscore, median (range)       | 0 (0-1)    |
| Previous EMR, no. patients (%)                 | 3 (33%)    |
| Morphology: 0-Is/LST                           | 2/1        |
| Size, median (range), mm                       | 15 (10-20) |
| Histology: LGD/intramucosal cancer             | 2/1        |

LST, Laterally spreading tumor; LGD, low-grade dysplasia.

were achieved by hemostatic forceps (Coagrasper, Olympus). A VAIO generator unit was used (ERBE Elektromedizin GmbH, Tübingen, Germany). Submucosal fibrosis was assessed according to a 3-point score: F0, no fibrosis; F1, mild; F2, severe.<sup>9</sup>

Operating time for resection was measured as a whole and as minute/cm<sup>2</sup>, considering the lesion area as an ellipsis. Adverse events were differentiated as intraprocedural, postprocedural (<14 days), and late (15-30 days). Resection was defined as en bloc or piecemeal if the lesion was removed in one or multiple pieces, respectively.

### Histopathology analysis

Specimens were stretched on foam, fixed in formalin, cut into 2-mm thick slices, and stained with hematoxylin and eosin. Histopathology was based on the Vienna classification.<sup>12</sup>

Complete (R0) resection definition was applied to en bloc resection with tumor-negative lateral and vertical margins at histology. Curative resection definition was applied to R0 resection with submucosal invasion <1000  $\mu$ m, absent lymphovascular involvement, good cell differentiation.

### Follow-up

Pancolonic chromoscopy with random and targeted biopsies was scheduled at 6-month intervals during the first year and then yearly. Biopsy specimens were taken at the resection site independently of endoscopic tumor presence. If dysplasia or cancer was detected, patients were reassessed for endoscopic or surgical resection.

## RESULTS

Ten neoplasms in 9 patients were referred for ESD: 7 in the Italian center, 3 in the Japanese center (Table 1). Neoplasm features are reported in Table 2. A scar was observed in 5 cases because of a previous attempt at resection in 4 and multiple (n = 22) biopsies in 1. All

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