

RAPID COMMUNICATION

## Treatment of gastric remnant cancer post distal gastrectomy by endoscopic submucosal dissection using an insulation-tipped diathermic knife

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### Abstract

**AIM:** To evaluate the effectiveness of endoscopic submucosal dissection using an insulation-tipped diathermic knife (IT-ESD) for the treatment of patients with gastric remnant cancer.

**METHODS:** Thirty-two patients with early gastric cancer in the remnant stomach, who underwent distal gastrectomy due to gastric carcinoma, were treated with endoscopic mucosal resection (EMR) or ESD at Sumitomo Besshi Hospital and Shikoku Cancer Center in the 10-year period from January 1998 to December 2007, including 17 patients treated with IT-ESD. Retrospectively, patient backgrounds, the one-piece resection rate, complete resection (CR) rate, operation time, bleeding rate, and perforation rate were compared between patients treated with conventional EMR and those treated with IT-ESD.

**RESULTS:** The CR rate (40% in the EMR group vs 82% in the IT-ESD group) was significantly higher in the IT-ESD group than in the EMR group; however, the operation time was significantly longer for the IT-ESD group ( $57.6 \pm 31.9$  min vs  $21.1 \pm 12.2$  min). No significant differences were found in the rate of underlying cardiopulmonary disease (IT-ESD group, 12% vs EMR group, 13%), one-piece resection rate (100% vs 73%), bleeding rate (18% vs 6.7%), and perforation rate (0% vs 0%) between the two groups.

**CONCLUSION:** IT-ESD appears to be an effective treatment for gastric remnant cancer post distal gastrectomy because of its high CR rate. It is useful for histological confirmation of successful treatment. The

long-term outcome needs to be evaluated in the future.

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**Key words:** Remnant stomach; Distal gastrectomy; Gastric cancer; Endoscopic mucosal resection; Insulation-tipped diathermic knife

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### INTRODUCTION

Distal gastrectomy has been widely accepted as a standard operation for early stage gastric cancer. Gastric cancer of the proximal gastric remnant is now increasing in Japan. Nozaki *et al*<sup>[1]</sup> described that the gastric remnants of 457 cases post distal gastrectomy due to gastric cancers were surveyed periodically by endoscopic examination, and 10 patients (2.2%) were diagnosed as having gastric remnant cancer within 12 years. Endoscopic submucosal dissection (ESD) techniques using a variety of knives, such as the insulation-tipped diathermic knife (IT-knife), hook knife, needle knife, or flex knife, have been developed in Japan<sup>[2-10]</sup> and high one-piece resection rates have been reported for the treatment of mucosal malignancies<sup>[3,11-17]</sup>. The remnant stomach post distal gastrectomy has narrow spaces. Thus, in this condition, it is more difficult to completely resect gastric remnant cancer by endoscopic technique than from an unoperated stomach. Few reports have described the results of ESD using an insulation-tipped diathermic knife (IT-ESD) for gastric remnant cancer. The purpose of this study was to evaluate the effectiveness of IT-ESD for patients with gastric remnant cancer post distal gastrectomy.

## MATERIALS AND METHODS

### Patients

We retrospectively reviewed the records of post distal gastrectomy patients with gastric remnant cancer, who underwent distal gastrectomy for the treatment of gastric cancer, admitted to Sumitomo Besshi Hospital and Shikoku Cancer Center between January 1998 and December 2007. Patients admitted during this period were divided into a conventional endoscopic mucosal resection (EMR) group and into a IT-ESD group according to the endoscopic resection method. Since 2000, the IT-knife procedure has been used instead of the conventional EMR for the treatment of gastric remnant cancer. Patient backgrounds, the one-piece resection rate, complete resection (CR) rate, operation times, bleeding rate, and perforation rate were compared between the groups. Patients with severe underlying disease, such as heart disease, respiratory disease, liver disease, or bleeding tendency, were excluded from the indication of ESD in our institute; however, no patients had severe underlying disease in this study. Patients taking drugs to promote bleeding, such as ticlopidine, aspirin, or warfarin, underwent ESD after a fixed term of drug discontinuance. All patients fulfilled the following criteria in this study: diagnosed as having mucosal gastric carcinoma by endoscopic findings or endoscopic ultrasonography, a biopsy specimen obtained from the lesion revealed differentiated adenocarcinoma, without ulceration of the lesion, no residual/local recurrence lesion after endoscopic treatment and the diameter of the lesion was up to 30 mm. The performance status (PS) of each patient was less than 2 on the Eastern Cooperative Oncology Group (ECOG) scale. IT-ESD was performed under informed consent. Two highly skilled endoscopists familiar with EMR and ESD performed endoscopic resection in this study.

### EMR technique

Conventional EMR was performed with a 2-channel endoscope<sup>[16,18]</sup>. The mucosa around the lesion was marked with coagulation current, and saline containing 0.0025% epinephrine was injected until the mucosa around or under the lesion was raised. Grasping forceps was passed through the loop of the conventional polypectomy snare, and an area near the lesion was grasped with the forceps to elevate the lesion. Then the snare was opened and the lesion was strangled. The specimen was completely resected by electric current application.

### IT-ESD technique

IT-knife was developed by Hosokawa and Yoshida in 1994 in Japan<sup>[19]</sup>. IT-knife has a ceramic ball at the top of the incising needle knife<sup>[11,12,19-21]</sup> to prevent perforation of the gastric wall. IT-ESD was performed as previously described using a single-channel endoscope<sup>[3,12,14,17,22]</sup>. Marks were made at several points along the outline of the lesion with a coagulation current, and saline containing 0.0025% epinephrine was injected just outside the marks to prevent perforation until the mucosa around the lesion was raised. A circumferential incision in the mucosa just outside the marks was made using an IT-knife, with a safe lateral margin, and the submucosal tissue under the circumcised

area was abraded with it. The specimen was then either completely resected using the IT-knife, or finally removed using a conventional polypectomy snare if it was attached only to a pedicle (Figure 1).

### Histological assessment

A gastrointestinal pathologist evaluated the ESD specimens with special attention to the depth of tumor invasion, and the lateral and deep margins of the excision. Resected specimens were cut into 2 mm slices according to the Japanese Classification of Gastric Carcinoma<sup>[23]</sup> and evaluated as to whether cancerous glands were present or absent at the margin of each slice.

### Definition of complete and incomplete resection

When one-piece resection could be performed, it was easy to evaluate the completeness of the resection histologically. The efficacy of resection was determined according to the completeness of the resection: when the tumor was resected as a single piece, contained within the mucosal layer, and when the margin was definitely free of tumorous glands, resection was considered to be complete. Multifragment resections were defined as incomplete when tumorous glands were present in 2 or more fragments histologically, even if endoscopically the lesion had been completely removed. If the lateral margin of the lesion could not be evaluated histologically because of the effects of the electrosurgical current or mechanical damage, the resection was defined as being incomplete.

### Complications

Bleeding and perforation were two major complications of ESD. Bleeding (delayed bleeding) was defined as clinical evidence of bleeding as hematemesis or melena at 1 d-10 d after ESD and requiring endoscopic treatment.

### Statistical analysis

Values are expressed as the mean  $\pm$  SD. Statistical analysis was performed using the unpaired Student's *t*-test and the chi-square test. A *P* value of  $< 0.05$  was considered significant.

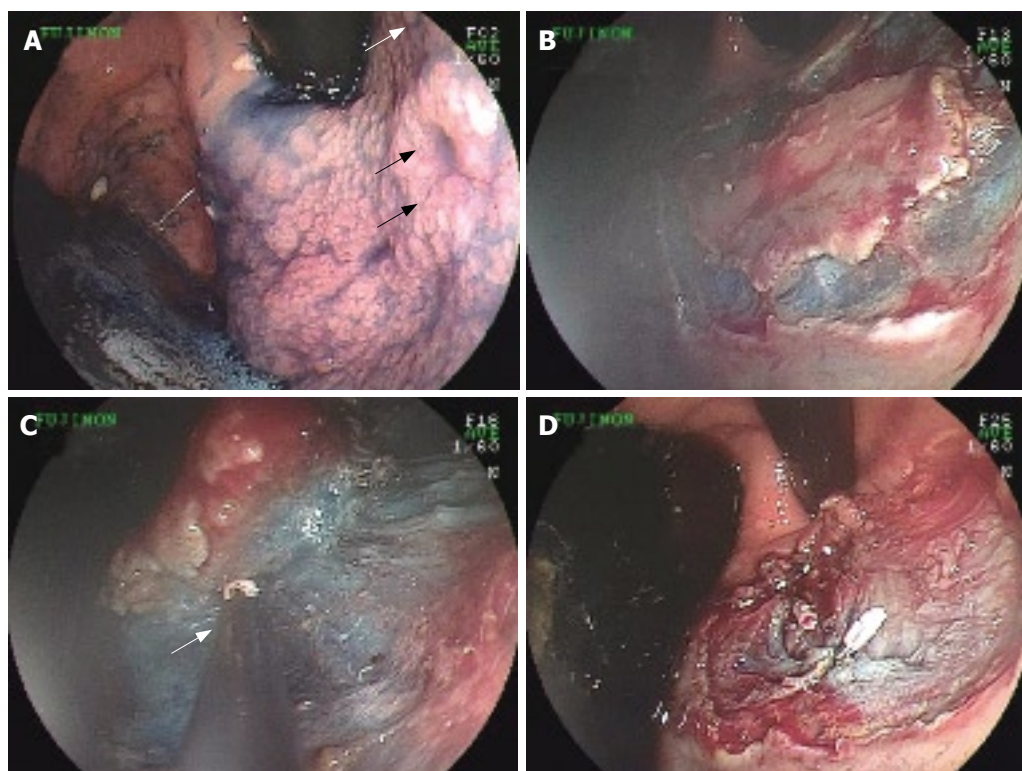
## RESULTS

### Clinicopathological features of the tumors

Concerning tumor location and gross type, no significant differences were found between patients included in the EMR ( $n = 15$ ) and those included in the IT-ESD ( $n = 17$ ) group (Tables 1 and 2, and Figure 2).

### Patient backgrounds

The mean age was  $68.3 \pm 9.2$  years (range, 46-80 years) in the EMR and  $73.1 \pm 5.4$  years (range, 64-84 years) in the IT-ESD group. The mean size of the lesion was  $12.7 \pm 2.9$  mm and  $15.5 \pm 5.6$  mm in the in the EMR and the IT-ESD group, respectively, with no significant difference between the two groups. No significant differences were found in the rate of underlying cardiopulmonary disease between the two groups [2 patients (13%) in the EMR group and 2 patients (12%) in the IT-ESD group] nor in



**Figure 1** The procedure of endoscopic submucosal dissection using an insulation-tipped diathermic knife (IT-ESD). **A:** A IIc lesion (black arrows) is seen near the suture line (white arrow) in the remnant stomach; **B:** Completion of IT-knife cutting around the lesion with a safe lateral margin; **C:** Abrasion of the submucosal tissue under the circumcised area with IT-knife (white arrow); **D:** the tumor is completely resected with IT-knife.

**Table 1** Tumor characteristics of patients in the ESD and EMR groups

	ESD group	EMR group
<i>n</i>	17	15
Location of the tumor (%)		
Posterior wall	4 (23.5)	3 (20)
Anterior wall	4 (23.5)	2 (13)
Lesser curvature	6 (35)	6 (40)
Greater curvature	3 (18)	4 (27)
Gross type of the tumor (%)		
Superficial depressed type	11 (65)	10 (67)
Superficial elevated type	6 (35)	5 (33)

the number of patients receiving anticoagulant therapy [one patient (6.7%) in the EMR group *vs* one patient (5.9%) in the IT-ESD group].

#### Evaluation of resected specimens and clinical outcomes

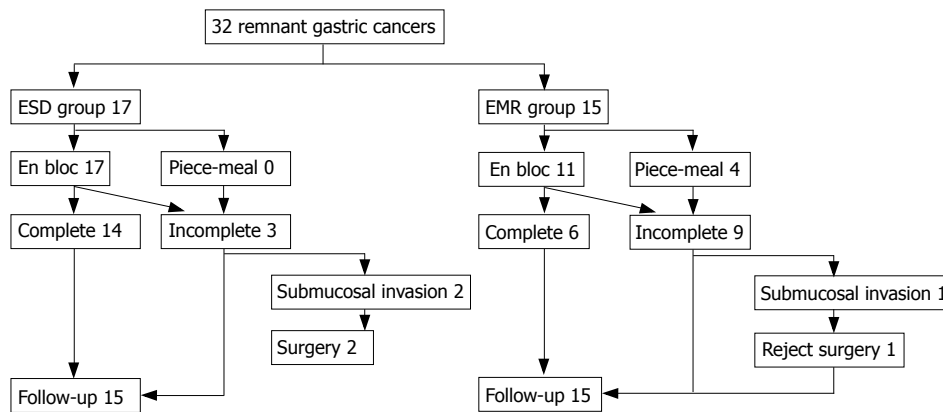
There was no significant difference in the one-piece resection rate among the groups (73% in the EMR group *vs* 100% in the IT-ESD group). The CR rate was significantly higher in the ESD group (40% in the EMR group *vs* 82% in the IT-ESD group). The mean operation time was 21.1 min  $\pm$  12.2 min for the EMR group and 57.6 min  $\pm$  31.9 min for the IT-ESD group. There were 4 cases of bleeding after endoscopic resection: one (6.7%) in the EMR group and 3 (18%) in the IT-ESD group, but no patient needed further surgery. All 3 patients with delayed bleeding developed clinical signs of hematemesis or melena 1 or 2 d after ESD. No patient developed hematemesis or melena later than 3 d after ESD. There was no severe delayed bleeding with a need for transfusion. Perforation

**Table 2** Characteristics and results of clinical data of patients in the ESD and EMR groups

	ESD group (tumor size: 10-26 mm)	EMR group (tumor size: 10-18 mm)	<i>P</i>
<i>n</i>	17	15	
Mean age (yr)	73.1 $\pm$ 5.4	68.3 $\pm$ 9.2	NS
Mean size of the lesion (mm)	15.5 $\pm$ 5.6	12.7 $\pm$ 2.9	NS
Frequency of the cardiopulmonary underlying disease (%)	12	13	NS
Frequency of the anticoagulant therapy (%)	5.9	6.7	NS
One piece resection rate (%)	100	73	NS
Complete resection rate (%)	82	40	< 0.05
Operation time (min)	57.6 $\pm$ 31.9	21.1 $\pm$ 12.2	< 0.001
Complications			
Rate of bleeding (%)	18	6.7	NS
Rate of perforation (%)	0	0	NS
Depth of invasion (mucosa:submucosa)	15:2	14:1	

NS: Not significant.

occurred in none of the patients. Twelve patients were judged as having incomplete resection in both groups. The margin of the fragment was positive for tumor or the lateral margin of the lesion could not be evaluated because of the effects of the electrosurgical current in 5 patients (four in the EMR group and one in the IT-ESD group). These five patients did not undergo additional laser or surgical therapy, although they have remained under close periodic observation. Three patients (one in the EMR group and two in the IT-ESD group) were judged as having submucosal invasion and two underwent total gastrectomy



**Figure 2** Clinical courses after endoscopic submucosal dissection (ESD) and conventional endoscopic mucosal resection (EMR) for remnant gastric cancers.

of the remnant stomach with regional lymph nodes dissection (additional surgery). The remaining case (in the EMR group) refused surgery and has been under close periodic observation. A total of 30 patients who did not undergo additional surgery were followed by endoscopy in both groups at least every year after treatment. The mean follow-up period was 2135 d (range 180-3285 d). There were no local recurrences after CR in the 20 patients in both groups and one patient resulting in incomplete resection in the IT-ESD group during that period. Only one patient in the EMR group resulted in piece-meal resection had a local recurrence 2 years after EMR and underwent additional EMR therapy.

## DISCUSSION

EMR has become a standard treatment for intramucosal gastric cancer because it is less invasive for patients compared with surgical resection<sup>[24-28]</sup>. To achieve cure by EMR, one-piece resection is optimal for all lesions because it may reduce the local recurrence rate<sup>[10,29]</sup>. IT-ESD is a useful new endoscopic mucosal resection (EMR) method, which has recently become widespread in Japan due to its high one-piece resection rates<sup>[3,11,13,15-17]</sup>. Few reports have described the results of IT-ESD for gastric remnant cancers in comparison with the usual strip biopsy method (conventional EMR).

Although PS for all patients was less than 2, and no patients had severe underlying diseases or severe complications in both groups, the CR rate was higher and operation time was longer in the IT-ESD group. In the present study, the one-piece resection rate and CR rate were high for over 10 mm lesions in the IT-ESD group. In contrast, the CR rate was low in the EMR group. In the unoperated stomach, it is easier to remove a tumor larger than 10 mm in diameter with IT-ESD than with the usual strip biopsy method<sup>[11,22]</sup>. The reason why the one-piece resection rate and CR rate were high in the IT-ESD group in our study might be as follows: we adequately abraded the submucosal tissue under the lesion before snaring, and in more than half of the patients in this study, direct dissection of the submucosal layer was carried out with an IT-knife until complete removal had been achieved<sup>[14,17]</sup>. The reason why the CR rate was low in the EMR group (under the condition of a remnant stomach) may be owing to the

difficulty of handling a polypectomy snare in the narrow space of the remnant stomach. In the IT-ESD method, the narrow space of the remnant stomach also makes IT-ESD procedures difficult; however, if the surgeon cuts around the lesion with a safe lateral margin, frequent CR is expected with the IT-ESD method. We speculated that it was difficult to ensure a safe lateral margin by snaring in the EMR technique because there were more patients with positive lateral margin in the EMR group (4/15) than in the IT-ESD group. Our study proved that the CR rate was significantly higher in the IT-ESD group, and IT-ESD was useful for gastric remnant cancers post distal gastrectomy that were larger than 10 mm in diameter, although it took longer.

The circulatory and respiratory states did not worsen in any patient during IT-ESD even if with underlying diseases or a long operation time. We should pay particular attention to patients with hypertension or anticoagulation therapy before or during ESD because they are related to bleeding during IT-ESD and the operation time<sup>[14]</sup>. The good result in the IT-ESD group in this study might be due to the small number of patients having anticoagulation therapy. The operation time for IT-ESD was significantly longer than that of conventional EMR. The reasons why IT-ESD took longer than conventional EMR in this study might be as follows: complicated operation of the IT-knife for abrasion of the submucosal tissue, a high frequency of bleeding, and narrow space of the remnant stomach.

As for complications, the delayed bleeding frequency was 18% (3/17) in the IT-ESD group, which was higher than in Onozato *et al.*<sup>[30]</sup> who reported it as 7.6%, although the total number of patients enrolled in this study was small. However, there were no problems due to delayed bleeding in this study in the IT-ESD group because we prevented delayed bleeding by follow-up endoscopic examination according to the clinical pathway<sup>[3]</sup>. It is necessary to pay particular attention to perforation with the ESD technique<sup>[13]</sup> because Ohkuwa *et al.*<sup>[11]</sup>, Miyazaki *et al.*<sup>[13]</sup>, Ono *et al.*<sup>[20]</sup>, and Fujishiro *et al.*<sup>[31]</sup> reported that the incidence of perforation with IT-ESD is 5%-11.5%. We think that the risk of perforation with the ESD technique on a remnant stomach is higher than with the usual strip biopsy method on an unoperated stomach.

In conclusion, the CR rate was significantly higher in the IT-ESD group than in the EMR group, although the

operation time was significantly longer in the IT-ESD group. Our study proved that IT-ESD was an effective treatment for gastric remnant cancer post distal gastrectomy, and is useful for histological confirmation of successful treatment, although the long-term outcome should be evaluated in the future.

## COMMENTS

### Background

Endoscopic submucosal dissection (ESD) is a useful new endoscopic mucosal resection (EMR) method, which has recently become widespread in Japan due to its high one-piece resection rates. Gastric cancer of the proximal gastric remnant is now increasing in Japan. The aim of this study was to evaluate the effectiveness of ESD using an insulation-tipped diathermic knife (IT-ESD) for the treatment of patients with gastric remnant cancer post distal gastrectomy.

### Research frontiers

It is still uncertain whether conventional EMR or IT-ESD results in better clinical outcome in the treatment of gastric remnant cancer post distal gastrectomy. Further investigations on a larger scale to compare the efficacy and safety of conventional EMR vs IT-ESD should be conducted.

### Innovations and breakthroughs

In this article we analyze if IT-ESD is superior to conventional EMR in the complete resection rate in 32 patients with gastric remnant cancer post distal gastrectomy.

### Applications

This study serves as a reminder to readers of the management of mucosal remnant gastric cancer post distal gastrectomy with IT-ESD. Because of its high complete resection rate, IT-ESD may be worth trying as the first therapy for treating patients with mucosal remnant gastric cancer post distal gastrectomy.

### Peer review

It is an interesting initial series comparing conventional EMR to IT-ESD in the treatment of gastric remnant cancer post distal gastrectomy. The study presents novel findings.

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