

## Risk and Management of a Perforation Complicating an Endoscopic Resection of Superficial Gastric Cancer and Adenoma

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**Abstract:**Background and aims: An endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are standard treatments for superficial gastric neoplasms. However, a perforation is the major complication in these treatments. The objective of this study was to assess the risk and management of perforations associated with EMRs and ESDs. Patients and methods: A total of 347 patients diagnosed with superficial gastric epithelial neoplasms (350 cancers and 54 adenomas) who underwent an EMR or ESD from 1999 to 2008 were included in this study. The risk and management of gastric perforation during an endoscopic resection was retrospectively investigated. The perforation rate was evaluated divided during the first (1999–2002), second (2003–2005) and third (2006–2008) periods. The clinical outcome after perforation was assessed between the surgical group and the nonsurgical group. Results: The overall incidence of gastric perforation due to an endoscopic resection was 3.5%. The perforation rate was higher with ESD than with EMR (5.1% vs. 0%,  $p < 0.05$ ). In ESD, the perforation rate was significantly decreased in the third period in comparison to the second period (3.3% vs. 10.4%,  $p < 0.05$ ). Hospital days after the occurrence of gastric perforation were significantly lower in the nonsurgical group in comparison to the surgical group (10.7 days vs. 17.8 days,  $p < 0.05$ ). Conclusions: An ESD as well as an EMR are effective and safe treatments for superficial gastric neoplasms, although there is a minimal risk of perforation. Even if a perforation develops, nonsurgical management should still be considered.

**Key words:** Gastric cancer, Gastric adenoma, Endoscopic submucosal dissection, Endoscopic mucosal resection, Perforation, Complication

### Introduction

Minimally invasive endoscopic treatment has been considered the treatment of choice for early gastric cancer without lymph node metastasis.<sup>1)3)</sup> It is also a more cost effective alternative to surgical treatment. An endoscopic mucosal resection

(EMR) is a proven therapeutic option in the treatment of premalignant lesions and noninvasive early cancers in the stomach.<sup>4)5)</sup> However, the diameter of the lesion must be less than 20 mm to achieve an en bloc resection with conventional EMR. En bloc resection is recommended because of a lower recurrence rate. Recently, an endoscopic submucosal dissection (ESD) was developed to

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Abbreviations: ESD, Endoscopic submucosal dissection; EMR, Endoscopic mucosal resection.

Table 1. Demographic characteristics of patients

	EMR	ESD	<i>p</i> value
Patients	116	231	
Age ( years )			
Mean	71	70	N.S.
Range	48-100	46-98	
Gender			N.S.
Male	91	181	
Female	25	50	
Lesions	127	277	
Histology			N.S.
Cancer	108	242	
Adenoma	19	35	
Macroscopic type			N.S.
Elevated	57	143	
Flat	1	2	
Depressed	69	132	

overcome these difficulties and to allow en bloc resection of larger specimens, which potentially results in a lower recurrence rate and improvement of the precision of a histopathological diagnosis.<sup>6)8)</sup> An ESD does not rely on snare techniques but requires the mastering of various devices, such as an insulation-tipped needle knife (IT knife), a Hook knife, or a Flex knife for dissection of submucosal tissue.<sup>3)</sup>

In comparison to a conventional EMR, the ESD technique is more difficult and time consuming, requiring a longer learning curve.<sup>9)</sup> In addition, the problem with the ESD technique is the high risk of complications, such as perforation and bleeding. The complications during the treatment may lower the value of the modality. This study investigated the rate and management of perforation as a major complication with the ESD procedure.

#### Patients and Methods

##### *Patients*

A total of 347 patients diagnosed with 404 superficial gastric neoplasms that underwent an endoscopic resection from January 1999 to December 2008. Patients with clear invasion of the submucosa on endoscopic ultrasound or metastatic disease on computed tomography were excluded from undergoing an endoscopic resection. The 404 lesions were divided into two groups: conventional EMR methods were performed in 127 lesions (116 patients) from 1999 to 2008, and ESD were performed in 277 lesions (231 patients) from 2003 to

2008 (Table 1). There was no difference in the patient characteristics between the EMR group and the ESD group. The superficial gastric neoplasms included 350 cancers and 54 adenomas. Written informed consent was obtained from all patients before performing the endoscopic resection.

##### *EMR procedure*

Before the endoscopic resections, the lateral margin of each lesion was determined by using conventional white-light endoscopy, chromoendoscopy with indigo carmine (0.2%) and magnifying endoscopy with narrow band imaging (Olympus Optical Co, Ltd, Tokyo, Japan). An epinephrine and saline solution (1:40,000) was injected into the submucosa to elevate the lesion. For the EMR-strip biopsy technique, the lesion was retracted with the grasping forceps and snared, and then resected electrosurgically.<sup>4)</sup> For the EMR-cap technique, the lesion was aspirated, retracted with snaring, and then resected electrosurgically.<sup>10)</sup>

##### *ESD procedure*

After the determination of the margin as in an EMR, several marks were electrosurgically made with a Hook knife around the lesion. A submucosal injection with an epinephrine and saline solution (1:40,000) stained with a slight amount of indigo carmine was used to obtain sufficient lifting. An initial circumferential incision around the marks was performed, then the lesion was dissected using various knives, such as a Hook knife, an IT-knife and a Flash knife.<sup>6)11)</sup> The ESD proce-

cedure was completed when the lesion was removed.

#### Assessment of perforation

A perforation was defined as having occurred when a hole was easily recognizable by endoscopy during an ESD, or when free air was detected on a plain radiograph taken after an ESD.<sup>9)</sup> The peripheral white blood cell (WBC) count, serum C-reactive protein (CRP) and albumin level were evaluated before and after perforation. Hospital days after perforation were compared between the surgical group and the nonsurgical group.

#### Statistical analysis

Continuous variables were analyzed with the Mann-Whitney *U* test. The  $\chi^2$  test or Fisher exact test was used to compare categorical variables between the groups as appropriate. A *P* value <0.05 was considered to be statistically significant.

### Results

#### Perforation rate

A perforation was observed in 14 patients. The overall perforation rate was 3.5% (14/404). In total the rate of perforation was higher in ESDs than in EMRs (5.1% vs. 0%,  $p < 0.01$ ; Table 2). Divided into three periods, there was a significant difference between the EMR group and the ESD group in the second period (0% vs. 10.4%,  $p < 0.05$ ). In the third period, however, the perforation rate did not differ between the EMR group and the ESD group. In ESD, the perforation rate was significantly decreased in the third period in comparison to the second period (3.3% vs. 10.4%,  $p < 0.05$ ).

#### Management of gastric perforation

Endoscopic closure was possible during the procedure in 11 out of 14 patients with perforation (Fig.

1A, B, C, D). In the remaining three patients, endoscopic closure was not performed because a minimal hole could be invisible. Management of gastric perforation occurring during endoscopic resection was compared between the surgical group and nonsurgical group (Table 3). The patients' age, gender, histology, macroscopic type and endoscopic clipping did not differ between the two groups. Four patients (endoscopic clipping performed in 3 patients, not performed in 1 patient) underwent surgery at the surgeon's discretion. Ten patients received conservative management with clinical observation, an initial nil-by-mouth regimen, and intravenous proton pump inhibitor and antibiotic therapy. All of the patients with a perforation recovered uneventfully. Based on a firm proposal by endoscopists, a new protocol that nonsurgical management is preferred as long as the abdominal pain and fluid collection do not increase was established based on the consensus of both endoscopists and surgeons on November 2006. When a perforation occurred, surgical management was preferred before the establishment of the above protocol, while nonsurgical management was preferred after the new protocol was established. Thereafter, all five patients with a perforation were managed nonsurgically.

#### Clinical outcome

The peripheral WBC count, serum CRP and albumin levels prior to the perforation did not differ between the surgical group and the nonsurgical group (Table 4). The WBC and CRP did not differ between the two groups on day after perforation. One week after perforation, there was no significant difference in the WBC but there was a significant difference in CRP between the surgical group and the nonsurgical group ( $8.2 \pm 1.5$  mg/dl vs.  $1.0 \pm 0.4$  mg/dl,  $p < 0.05$ ). Hospital days after

Table 2. Risk of perforation divided into three periods

Period (Year)	EMR	ESD	<i>p</i> value
First period (1999–2002)	0/ 64 (0%)		
Second period (2003–2005)	0/ 50 (0%)	7/ 67 (10.4%)	$p < 0.05$
Third period (2006–2008)	0/ 13 (0%)	7/210 (3.3%)*	N.S.
Total (1999–2008)	0/127 (0%)	14/277 (5.1%)	$p < 0.01$

\* $p < 0.05$  compared with ESD (2003–2005)

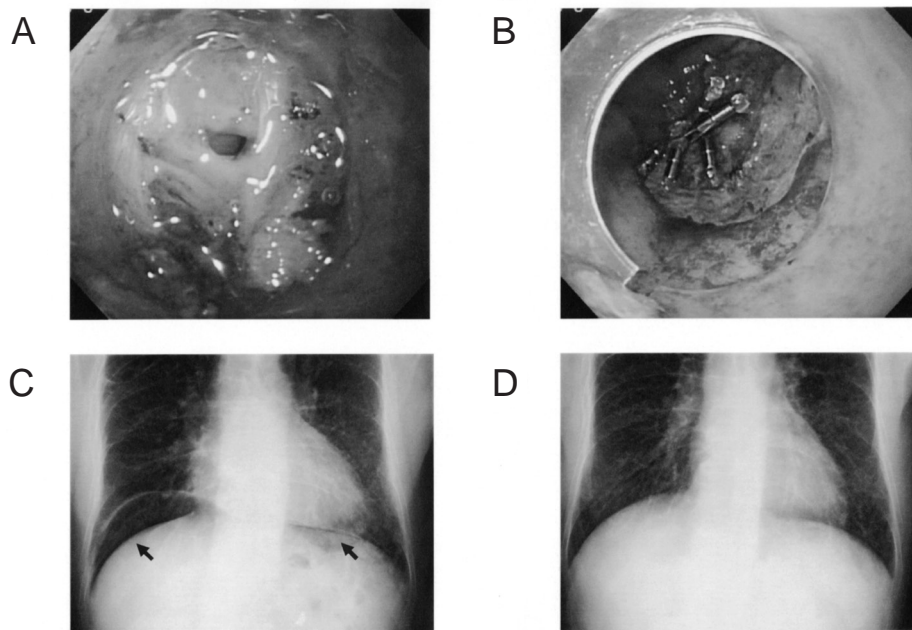


Fig. 1. Gastric perforation during ESD. A, Esophagogastroduodenoscopy shows a small perforation. B, The perforation is closed by endoscopic clipping. C, Abdominal X-ray reveals free air on the day of perforation (Arrows). D, Free air disappears 6 days later under nonsurgical management.

Table 3. Management of gastric perforation occurring at endoscopic resection

	Surgical	Nonsurgical	<i>p</i> value
Age			
Mean	66	70	N.S.
Range	56-84	56-77	N.S.
Gender			N.S.
Male	1	3	
Female	3	7	
Histology			N.S.
Cancer	4	7	
Adenoma	0	3	
Macroscopic type			N.S.
Elevated	1	7	
Depressed	3	3	
Endoscopic clipping			N.S.
Yes	3	8	
No	1	2	

perforation were significantly higher in the surgical group in comparison to the nonsurgical group (mean 17.8 days vs. 10.7 days,  $p < 0.05$ ; Table 4). No endoscopic resection-related mortality was observed.

#### Discussion

An endoscopic resection has become the treatment of choice for noninvasive early cancers and

premalignant lesions of the gastrointestinal tract to avoid unnecessary surgery with its higher morbidity and substantial mortality.<sup>15)</sup> However, a conventional EMR cannot be performed as an en bloc resection in large lesions, and even in lesions smaller than 20 mm in diameter piecemeal resection is not uncommon. The one-piece resection rate for early gastric cancers smaller than 20 mm has been reported to be 76%.<sup>12)</sup> The ESD technique has made it possible to overcome these

Table 4. Clinical outcome in patients with gastric perforation

	Surgical	Nonsurgical	<i>p</i> value
Laboratory data			
Before perforation			
WBC	4,800 ± 548	5,360 ± 352	N.S.
CRP	0.08 ± 0.03	0.2 ± 0.1	N.S.
Albumin	3.8 ± 0.1	3.8 ± 0.1	N.S.
One day after perforation			
WBC	11,000 ± 923	8,660 ± 611	N.S.
CRP	4.2 ± 1.4	3.5 ± 0.8	N.S.
One week after perforation			
WBC	6,075 ± 564	4,620 ± 426	N.S.
CRP	8.2 ± 1.5	1.0 ± 0.4	<i>p</i> < 0.05
Hospital days after perforation			
Mean	17.8	10.7	<i>p</i> < 0.05
Range	12–27	8–14	

WBD, white blood count ; CRP, C-reactive protein ; Data are shown as mean ± S.E.

problems. The clear advantage of ESD is the possibility of an en bloc resection especially for large lesions, leading to an improvement in the histopathological diagnosis and decreasing the local recurrence. However, the ESD procedure is time consuming and technically difficult, potentially leading to complications such as perforation and bleeding.<sup>5)</sup>

The present study presented a comprehensive review of perforation complicating EMR and ESD for superficial gastric cancers and adenomas. The published data have shown that the rates of a perforation during ESD range from 3.5% to 8.7%, which was higher than that occurring during an EMR.<sup>3,9,13)</sup> The current perforation rate in ESD was similar to this published data. The reason for perforation includes the size of the lesion, fibrosis, tumor location (upper portion of the stomach), repeated coagulation of bleeding points, and technical difficulty. It is therefore necessary to dissect very carefully in cases of a recurrent lesions or a lesion with an accompanying scar, because of a thin submucosal layer and hard fibrotic tissue, both of which make dissection difficult to perform without perforation. It is especially noteworthy that Oka *et al.* reported the incidence of perforation with an ESD dramatically increased to 53.8% in cases with ulceration in comparison to an EMR (2.9%)<sup>3)</sup> Therefore, ESD should be carefully performed in cases with ulceration. Multibending endoscopy can also be used to minimize the technical difficulty.<sup>14)</sup>

Peritoneal seeding has been documented after fine-needle aspiration biopsy and port-site metastasis has similarly been reported after laparoscopic surgery for malignancy.<sup>15) 16)</sup> It is possible that a defect of the gastric wall in an area containing malignant cells during endoscopic resection may lead to peritoneal seeding. However, none of the patients who had endoscopic clip closure of a gastric perforation developed peritoneal disease, indicating that peritoneal dissemination is unlikely to occur after gastric perforation during an endoscopic resection.<sup>17)</sup>

The ESD technique is more difficult and time consuming in comparison to a conventional EMR, requiring a longer learning curve.<sup>5,9)</sup> The perforation rate was decreased from 10.4% (the second period) to 3.3% (the third period) in the current study, presumably indicating a relatively sharp learning curve. One limitation of the current study was the use of different instruments and multiple endoscopists from beginners to experts for ESD over time, which makes assessment of the learning curve difficult. Approximately 40–50 procedures are necessary to fully train for this technique.<sup>5,9)</sup>

Formerly, perforations caused by an endoscopic resection necessitated emergency surgery. More recently, however, complete closure of the hole can be achieved by endoscopic procedures. Most perforations with ESD are small, so can be treated by simple endoscopic clipping.<sup>18)</sup> The omental patch method is effective even if the hole is larger.<sup>19)</sup> Additionally, treatment with intravenous antibiotics

and proton pump inhibitor and nothing-by-mouth has been shown to be successful.<sup>5)</sup> The current cases of gastric perforation were cured not only by surgical but nonsurgical treatments, and hence their clinical courses were all uneventful. In spite of the lack of any difference in general and nutritional conditions before the endoscopic procedures, there was a significant difference with regard to a decrease in CRP and hospital days, suggesting that nonsurgical management could enable an earlier recovery. Perforations could usually be treated endoscopically.<sup>5)</sup> Perforation related to ESD can no longer be regarded as an obstacle to performing ESD, because this can be completely managed by endoscopic clipping in most cases, with favorable final outcomes. More importantly, there was no mortality during the current study. Bleeding, another major complication, during ESD was more frequent but could be managed with coagulation devices, with no need for surgery and transfusion in most cases.

In conclusion, gastric perforations with ESD were identified to be few if any and the incidence decreases after a sharp learning curve. An ESD has a significant complication risk but seems to be safe under careful management. An ESD makes it possible to expand the indications to lesions of any size without ulceration, and to some lesions even with ulceration unless fibrosis is severe. Further innovations are needed to develop new techniques and devices to improve the safety of ESD. Furthermore, this treatment procedure should be performed cautiously to prevent complications, especially during the early learning period.

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