

## Role of Endoscopic Clipping for Determining the Resection Line for Tumors Located in the Middle or Upper Corpus of the Stomach: Experience with 100 Gastrectomies for Early Gastric Cancer

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**Abstract.** *Background: The efficacy and limitations of pre-operative endoscopic clipping for determining the resection line in patients with early gastric cancer remain unclear. Materials and Methods: Subjects comprised 100 patients with early gastric cancer (33 females, 67 males; mean age, 60.5 years; range, 33-84 years) who underwent pre-operative endoscopic clipping for lesions located in the middle or upper corpus of the stomach. The results of endoscopic clipping for a selection of appropriate surgical procedures were investigated. Results: Distal gastrectomy was performed in 94 patients, the mean length between the lesion and proximal surgical margin of the resected stomach being  $28.9 \pm 18.0$  mm (mean  $\pm$ SD). The surgical margin was eventually free of tumor in all patients. In 5 patients, clips were considered to be placed inadequately, and all 5 tumors were macroscopically depressed or flat and  $>40$  mm in size. Conclusion: Pre-operative endoscopic clipping represents a safe and reliable procedure to determine the resection line for tumors located in the middle or upper corpus of the stomach for treatment of early gastric cancer. During surgical resection, frozen section examination of the proximal cut end is recommended for patients with tumors that are macroscopically depressed or flat and  $>40$  mm in size, or that display a macroscopically unclear proximal margin.*

Distal gastrectomy can preserve not only the proximal portion of the stomach, but also the esophago-cardiac function. This procedure is, thus, superior to total

gastrectomy with respect to post-operative quality of life (QOL) of patients with gastric cancer (1,2). In general, lesions located at the lower corpus or more distal portions of the stomach can be completely resected through distal gastrectomy for early gastric cancer (EGC), even if the exact location of the tumor is unclear. Although distal gastrectomy may also be preferable for patients with lesions located in the middle or upper corpus of the stomach, determining the resection line during gastrectomy to preserve a tumor-free surgical margin is difficult. Total gastrectomy is therefore often selected. Accurate diagnosis of tumor location and spread is essential to reduce the extent of gastrectomy for patients with such tumors.

Endoscopic clipping has seen wide use in a variety of fields for the endoscopic treatment of gastro-intestinal diseases (3-7). This technique has also recently been applied to intra-operative assessment of unpalpable tumors in the esophagus or stomach, to determine tumor location and appropriate surgical procedure (8-10). However, the efficacy and limitations of this technique for patients with EGC located in the middle or upper corpus of the stomach remain unclear, when attempting minimally invasive and function-preserving surgery. The present study evaluated the role of endoscopic clipping for determining the resection line in a large number of EGC patients with such lesions.

### Materials and Methods

*Patients.* From September 1996 to December 2003, a total of 647 patients with EGC underwent gastric resection at Kitasato University East Hospital, Japan. During this period, pre-operative endoscopic clipping was performed for some patients to determine the proximal resection line by identifying the exact site of the tumor intra-operatively, according to the following criteria. (i) The proximal lesion is considered as representative, if multiple tumors are present in the stomach. (ii) The proximal margin of the lesion is located in

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*Key Words:* Early gastric cancer, endoscopic clipping, surgery.

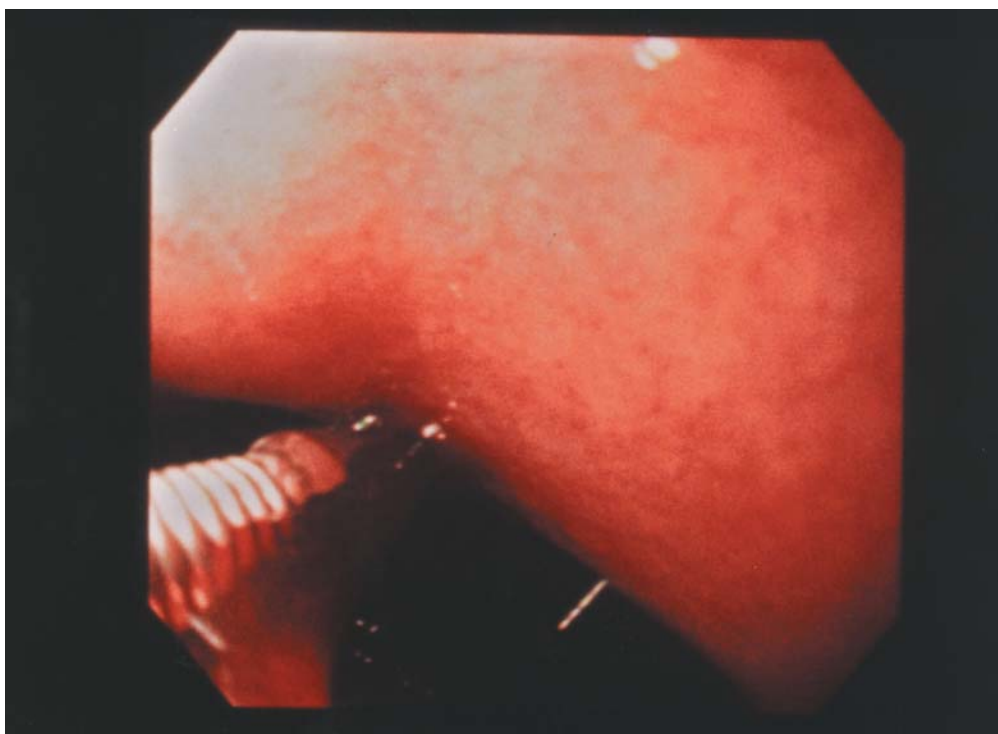


Figure 1. Pre-operative endoscopic clipping for early gastric cancer. Three clips were placed at sites proximal to the lesion (middle corpus of stomach).



Figure 2. Macroscopic findings from resected stomachs after distal gastrectomy. The resected stomach was opened along the greater curvature. Right margin of specimen corresponds to proximal cut end. A shallow depressive lesion (type IIc early gastric cancer) is located on the posterior wall of the middle corpus of the stomach, and 3 clips remained at proximal sites outside the lesion.

Table I. Pathological features of 100 tumors for which pre-operative endoscopic clipping was performed in patients with early gastric cancer.

Factors	No. of patients (N=100)	
Tumor diameter (mm)	≤20	39
	≤40	31
	≤60	16
	>60	14
Main site of tumor	Lesser curvature	39
	Posterior wall	39
	Anterior wall	11
	Greater curvature	11
Macroscopic type	Elevated (N=11)	
	IIa*	4
	IIa+IIc	5
	IIa+IIb	2
	Depressed (N=87)	
	IIc	68
	IIc+III	12
	IIc+IIb	5
	IIc+IIa	2
	Flat (N=2)	
IIb	1	
IIb+IIa	1	
Microscopic type	Differentiated	48
	Undifferentiated	50
	Adenoma**	2
Depth of invasion	Mucosa*	63
	Submucosa	37

\* Two adenomas were included.

\*\* Two patients with adenoma had concomitant early gastric cancer distal to these tumors.

the middle or upper corpus of the stomach on pre-operative endoscopy. (iii) The lesion is diagnosed pre-operatively as EGC or benign tumor combined with EGC. A total of 129 patients fulfilled the above criteria. Of these, 100 patients (77.5%, 33 females, 67 males; mean age, 60.5 years; range, 33-84 years), who underwent pre-operative endoscopic clipping, were enrolled in the present study. Multiple gastric tumors were present in 13 patients, including 9 double EGCs, 2 triple EGCs and 2 with adenoma and EGC.

**Endoscopic clipping.** Before the operation (range, 1-34 days before surgery; mean 4.3 days before surgery), endoscopic clips (HX-600-090, Olympus, Japan) were placed at proximal sites outside the lesion to determine the resection line as described in previous reports (9,10). Endoscopic clipping was performed in 93 patients within 7 days before surgery. All patients had eaten meals until one day before surgery, and the clips remained in all patients at the time of surgery. No complications involving endoscopic clipping were observed. The endoscopic view after clipping is shown in Figure 1. Endoscopic biopsies were usually taken from the proximal normal site of the lesion (just oral to the clips), except for in some patients in whom the proximal margin of the lesion could be determined macroscopically.

Table II. Results of endoscopic clipping and surgical treatment in 100 patients with early gastric cancer.

Factors	No. of patients (N=100)	
No. of clips	2	49
	3	45
	≥4	6
No. of endoscopic biopsies*	0	26
	1	15
	2	38
	≥3	21
Histology of endoscopic biopsy	No cancerous tissue	70
	Cancer	4
Intra-operative histological examination of proximal cut end**	Performed (N=78)	
	Negative	77
	Positive***	1
	Not performed (N=22)	22
Operation	Total gastrectomy***	6
	Distal gastrectomy	94
Distance to proximal surgical margin (mm)	≤20	44
	21-40	38
	>40	18

\* Biopsy taken from site oral to clips.

\*\* Histological examination of oral margin of resected stomach near lesion.

\*\*\* Total gastrectomy performed due to cancer infiltration to oral margin of resected stomach after distal gastrectomy in 1 patient.

**Surgical procedure and pathological examination.** During the operation, the stomach wall was carefully palpated and the locations of clips in the stomach were detected before gastrectomy. The resection line was determined so as to preserve >2 cm distance between clips and the proximal surgical cut end. Gastrectomy was then performed. Total gastrectomy was performed when the planned resection line reached the gastric cardia. After gastric resection, surgical specimens were immediately transferred to the pathology department. The stomach was opened along the lesser or greater curvature, and the lesion and surgical margin were examined macroscopically. Macroscopic findings for the resected stomach after distal gastrectomy are shown in Figure 2.

Additional histopathological frozen section examination of the proximal cut end adjacent to the lesion was performed in 78 patients according to the judgment of pathologists, and findings were provided to surgeons intra-operatively. Pathological findings were classified according to the Japanese Classification of Gastric Carcinoma (11). The type of gastric resection, tumor diameter, tumor location, macroscopic type, microscopic type (differentiated type, well- or moderately-differentiated tubular adenocarcinoma; undifferentiated type, poorly-differentiated adenocarcinoma or signet ring cell carcinoma), depth of tumor invasion, distance

Table III. Clinicopathological features of 5 patients in whom endoscopic biopsy or intra-operative histological examination identified cancer in the surgical margin.

No.	Age (Gender)	Tumor diameter (mm)	Main site of tumor	Macroscopic type	Microscopic type	Depth of invasion	No. of clips	No. of cancerous specimens / No. of biopsy specimens	Cancer infiltration to surgical margin*	Operation	Distance to proximal surgical margin (mm)
1	57 (Male)	120	Posterior wall	IIC+IIb	Differentiated	Submucosa	3	3/3	Negative	Distal gastrectomy	12
2	61 (Female)	45	Lesser curvature	IIC	Undifferentiated	Submucosa	2	1/2	Negative	Distal gastrectomy	12
3	56 (Male)	78	Posterior wall	IIC	Differentiated	Submucosa	4	4/4	Negative	Total gastrectomy	70
4	67 (Male)	77	Lesser curvature	IIC	Undifferentiated	Submucosa	2	1/3	Negative	Distal gastrectomy	20
5	67 (Female)	65	Lesser curvature	IIb+IIa	Differentiated	Mucosa	3	0/1	Positive	Total Gastrectomy**	60

\* Intra-operative histological examination using frozen section of the oral margin of the resected stomach near the lesion.

\*\* Total gastrectomy performed due to cancer infiltration to the oral margin of the resected stomach after distal gastrectomy.

between lesion and proximal surgical margin, histology of biopsy specimen and histology of the oral margin of the resected stomach as determined intra-operatively, were reviewed from clinical and pathological records.

## Results

The pathological features of the 100 tumors for which pre-operative endoscopic clipping was performed are presented in Table I. The mean tumor diameter was 34.2±26.6 mm (mean±SD), and 40 tumors were >40 mm in diameter. Most tumors (n=78) were located at the lesser curvature or posterior wall of the stomach. A total of 89 tumors were macroscopically depressed, and 50 tumors were microscopically undifferentiated. Invasion to the submucosal layer was noted in 37 tumors.

The results of endoscopic clipping and surgical treatment in 100 patients are presented in Table II. A total of 258 clips was used, with 2-3 clips placed in 94 patients (mean, 2.6 clips/patient; range, 2-5 clips/patient). A total of 162 endoscopic biopsies were taken from 74 patients (mean, 2.2 biopsies/patient; range, 1-6 biopsies/patient), and cancer was found in 4 of these patients (5.4%). While intra-operative histological examination of the proximal cut end was performed in 78 patients, cancer infiltration to the surgical margin was observed in only one of these patients (1.3%). Total gastrectomy was performed in 6 patients (initial treatment because planned resection line reached the gastric cardia, n=5; additional resection of remaining

proximal stomach after distal gastrectomy due to histological cancer infiltration of surgical margin, n=1). No residual cancer was found histologically in the remaining proximal stomach in the patient who underwent additional resection. The mean distance between the lesion and surgical margin was 28.9±18.0 mm, and the proximal surgical margin was finally tumor-free in all patients.

The clinicopathological features of 5 patients, in whom endoscopic biopsy or intra-operative histological examination of the proximal margin identified cancer, are presented in Table III. In 4 patients, cancer was found in endoscopic biopsies, but distal gastrectomy was performed in 3 patients (75.0%) after confirming the absence of cancer infiltration to the proximal surgical margin. In the remaining patient, cancer infiltration was found in the proximal margin, although pre-operative endoscopic biopsy had identified no cancer. In these 5 patients, the clips were considered to have been placed within the cancerous lesion, and all tumors were macroscopically depressed or flat and displayed a diameter >40 mm.

## Discussion

Long-term survival for patients who undergo gastric resection for EGC is excellent, and EGC is now considered a curable disease that can be controlled by local management (12-18). Consequently, our attention has recently been directed toward improving the post-operative QOL in patients using minimally invasive or function-

preserving surgery (19-24). Among the various options, reducing the extent of gastric resection represents a simple, but important, strategy for achieving that goal.

Exact determination of the tumor site and spread is essential for determining the resection line and reducing the extent of gastric resection in EGC surgery. However, accurate identification of the tumor position is sometimes difficult, and such tumors are often not palpable during surgery, given the characteristic inconsistent morphology and pattern of superficial spread in mucosal or submucosal layers of the stomach wall (25,26). In the present study, 5 patients underwent total gastrectomy before intra-operative pathological examination, and histological cancer infiltration to the proximal margin of the resected stomach was found in only one patient (no residual cancer was histologically identified following additional resection of the remaining stomach in this patient) from among 94 patients who underwent distal gastrectomy. Stepwise endoscopic biopsy is often used to diagnose tumor spread pre-operatively. However, correlating sites of biopsies and the resection line is difficult using this method. These findings suggest that endoscopic clipping is valuable for selecting an appropriate surgical procedure and determining the resection line for tumors located in the middle or upper corpus of the stomach.

Two methods may improve the diagnosis for tumor location and spread. One is pre-operative endoscopic biopsy from macroscopically normal sites outside the lesion (proximal to clips), as clips are considered to be placed in the proximal region outside the lesion, if endoscopic biopsy specimens are free of cancer. The other is intra-operative histological frozen section examination of the proximal surgical margin. However, routine application of these procedures to EGC surgery is relatively time-consuming and expensive.

Although endoscopic biopsy taken from sites oral to the clips revealed carcinoma in 4 patients, 3 of them were able to undergo distal gastrectomy after confirming a clear result on frozen section examination of the proximal cut end. Conversely, frozen section examination of the proximal cut end identified carcinoma in one patient, whereas pre-operative endoscopic biopsy had shown no cancerous tissues. Thus, clips were placed within the lesion in 5 patients displaying larger (>40 mm), depressed or flat lesions, indicating that endoscopic clipping is not always placed adequately due to the nature of EGC. These findings suggest that pre-operative endoscopic biopsy from sites proximal to the lesion may not contribute to decision-making for the resection line. Frozen section examination of the proximal cut end is not always necessary, but is indicated for patients with a large (>40 mm) and macroscopically depressed or flat tumor, or tumors displaying a macroscopically unclear proximal margin.

In conclusion, pre-operative endoscopic clipping is a safe and reliable procedure to determine the resection line in patients with lesions in the middle or upper corpus of the stomach. Pre-operative endoscopic biopsy taken from sites proximal to the lesion is not useful. During gastric resection, frozen section examination of the proximal cut end is recommended for patients with large (>40 mm) and macroscopically depressed or flat tumors, or tumors with a macroscopically unclear proximal margin.

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