

Long-term survival after endoscopic resection for early gastric cancer in the remnant stomach: comparison with radical surgery

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Abstract

Background Endoscopic resection (ER) has recently become standard treatment, even for early gastric cancer (EGC) in the remnant stomach. We aimed to compare long-term survival after ER versus radical surgery for EGC in the remnant stomach.

Methods We retrospectively compared overall and cause-specific survival of patients who had undergone ER or radical surgery for EGC in the remnant stomach from 1998 to 2012.

Results During the study period, 32 patients with intramucosal (M), two with shallow submucosal (SM1) and eight with deep submucosal (SM2) cancers had undergone ER (ER group) whereas six with M and seven with SM2 cancers had undergone surgery (surgery group). All patients were followed up for a median of 60 months; during follow up, 15 patients died, including three in the ER group with SM2 cancer who died of gastric cancer. The overall 5-year survival rates of M-SM1 and SM2 cancer patients in the ER and surgery groups were 89%, 48%, 80%, and 67%, respectively ($P=0.079$). The disease-specific 5-year survival rates of M-SM1 and SM2 cancer patients in the ER and surgery groups were 100%, 48%, 100%, and 100%, respectively ($P=0.000$). Operation time and hospital stay were significantly shorter in the ER than the surgery group ($P<0.001$). Grade 2 perforation occurred in two patients in the ER group and Grade 3 anastomotic leakage in two patients in the surgery group.

Conclusion ER provides excellent outcomes, comparable with those of radical surgery, in patients with M-SM1 gastric cancer in the remnant stomach; however, patients with SM2 cancer require radical surgery.

Keywords Early gastric cancer in the remnant stomach, long-term outcomes, endoscopic muosal resection, endoscopic submucosal dissection

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Introduction

Gastric cancer is the fourth most common cancer and the third most common cause of cancer death worldwide [1]. In Japan, encouragement of screening examination and development of accurate endoscopic diagnostic techniques has increased the rate of detection of early stage gastric cancer, with a resultant improvement in prognosis of gastric cancer patients [2]. Because of these patients' prolonged survival, the incidence of gastric cancer arising in the remnant stomach is now reportedly increasing [3,4].

Endoscopic resection (ER), including endoscopic mucosal resection (EMR) [5] and endoscopic submucosal dissection (ESD) [6], has been developed in Japan; these are now widely recognized techniques for treating early gastric cancer (EGC). The Japanese gastric cancer treatment guidelines [7] state that the absolute indications for ER is differentiated intramucosal

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Conflict of Interest: None

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cancer ≤20 mm in size without ulceration, harboring very small possibility of lymph node metastasis, and thus suitable for *en bloc* resection. The expanded indications include: 1) differentiated intramucosal cancer >20 mm in size without ulceration; 2) differentiated intramucosal cancer ≤30 mm with ulceration; and 3) undifferentiated intramucosal cancer ≤20 mm without ulceration [7]. Good outcomes of ER for the above-listed lesions have been reported [8-10]. Recently, favorable 3-year or 5-year cause-specific survival rates after ER for EGC in the remnant stomach have also been reported [11,12]. However, no published studies have compared the long-term outcomes of ER and surgical resection in patients with EGC in the remnant stomach. The aim of this study was to evaluate and compare these long-term outcomes.

Patients and methods

This retrospective cohort study was performed in a referral cancer center. Consecutive patients with EGC in the remnant stomach who had undergone ER or surgical resection between January 1998 and December 2012 were identified from the Osaka Medical Center for Cancer and Cardiovascular Diseases' prospectively maintained database. The study protocol was approved by the Ethics Committee in our hospital.

In this study, all terminology and classification of tumor size, macroscopic type, histological type and depth of tumor invasion is according to the Japanese classification of gastric carcinoma [13]. Depth of tumor invasion was classified as mucosa (M), shallow submucosa (SM1, tumor invasion within 0.5 mm of the muscularis mucosa), and deep submucosa (SM2, tumor invasion 0.5 mm or more beyond the muscularis mucosa).

This manuscript was prepared according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [14].

Endoscopic procedures

ER was performed by EMR or ESD. EMR was performed with a two-channel videoendoscope (GIF-2T200, 2T-240 or 2TQ-260M, Olympus Medical Systems, Tokyo, Japan) for small (≤ 10 mm) polypoid lesions using the strip biopsy method [15]. ESD was performed using an insulation-tipped diathermic knife (IT knife, Olympus) [6] or IT knife-2 (Olympus) for large (>10 mm) polypoid or superficial lesions. Physiologic saline was used as the injection solution for EMR, and 10% glycerin solution (Glyceol, Chugai Pharmaceuticals, Tokyo, Japan) or 0.4% sodium hyaluronate (MucoUp, Johnson & Johnson K.K., Tokyo, Japan) for ESD. Intelligent Cut and Coagulation 200 or VIO300D (ERBE, Tubingen, Germany) electrosurgical units were used to generate high-frequency electric currents.

Definition of EGC in the remnant stomach

In this study, EGC in the remnant stomach was defined as cancer that had developed *de novo* in the remnant stomach; residual or recurrent tumors from the initial gastric surgery were excluded.

Measured outcomes

Outcomes of the ER and surgery groups, including operation time, complication rate, overall survival rate, and disease-specific survival rate, were compared. In the ER group, operation time was measured from the insertion of the endoscope to the stomach until its withdrawal. We routinely take at least one picture at the esophago-gastric junction before scope insertion to the stomach and at least one picture of post-ESD ulcer just before scope withdrawal from the stomach, thus the operation time in the ER group was calculated according to time of a clock appeared on the endoscopic image. In the surgery group, operation time was measured from beginning to make a skin incision until the end of skin closure by reference to operation record in which every operation procedure and time were documented. Complications were graded according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.0 [16]. Whether patients had died by the end of June 2013 was ascertained from the medical records or the Hospital Cancer Registry of the Osaka Medical Center for Cancer and Cardiovascular Diseases. For patients who were not currently visiting our institution, this information was requested by mail questionnaires or telephone interviews with their families or referring physicians. Survival was investigated according to depth of tumor invasion. Depth of tumor invasion was categorized as M-SM1 or SM2 according to the curative criteria in the Japanese gastric cancer treatment guidelines [7].

Post-operative follow up

After ER or surgery, patients were scheduled for follow-up esophagogastroduodenoscopy every 12 months. Computed tomography of the chest and abdomen was performed every 12 months in patients with SM2 cancer.

Statistical analysis

Numerical data were compared using Mann-Whitney's U-test, and categorical data were compared using the χ^2 or Fisher's exact probability tests as appropriate. Cumulative overall and disease-specific survivals were estimated using the Kaplan-Meier method and compared using the log-rank test. Computer software SPSS version 11.0 (SPSS, Chicago, IL, USA) was used for all analyses.

Results

From January 1998 to December 2012, 83 patients (male/female=72/11, median age 70 years) with gastric cancer in the remnant stomach were treated at the Osaka Medical Center for Cancer and Cardiovascular Diseases. Of these patients, 48 were treated by ER and 35 by surgery. In the ER group, three patients whose tumors had invaded the deep submucosa and one whose resection had been incomplete underwent additional surgery. One patient whose resected specimen could not be retrieved and one patient whose tumor had invaded the muscularis propria were excluded, leaving 32 patients with M, two with SM1 and 8 with SM2 cancers for analysis. Eight of the patients with SM2 cancer in the ER group were not candidates for surgery because of comorbidities and old age ($n=4$) or because they refused surgery ($n=4$). Two of these eight SM2 cancer patients received photodynamic therapy after they had undergone ER. In the surgery group, 26 patients whose cancers were invading the muscularis propria or deeper were excluded; thus, data of six patients with M and seven with SM2 cancers were analyzed (Fig. 1). In the ER group, 27 patients were treated by EMR and 15 by ESD. The reason for and type of primary operation and tumor characteristics are presented in Table 1.

Procedure-related outcomes

The operation time was significantly shorter for ER than for surgery (46 vs. 260 min, respectively, $P<0.001$). The hospital stay was significantly shorter in the ER group than in the surgery group ($P<0.001$). There was no statistically significant difference in nutritional status

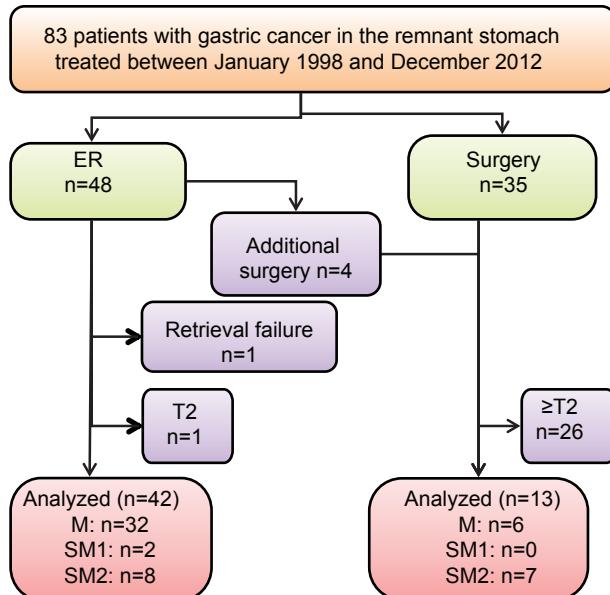


Figure 1 Flow diagram of patients who underwent remnant gastric endoscopic resection (ER) or radical surgery

between the groups 1 year after the procedure. In the ER group, two perforations occurred during the procedure and were managed conservatively by endoscopic clipping. On the other hand, in the surgery group, anastomotic leakage occurred in two cases and both required surgical intervention (Table 2).

Survival data

All 55 patients (42 in the ER and 13 in the surgery group) were followed up for a median (range) of 43.5 (6-159) months. In the ER group, 12 patients died, three of them of gastric cancer. In the surgery group, three patients died, none of them of gastric cancer. The 3- and 5-year overall survival rates in the ER group were 85.7% and 81.8%, respectively, and in the

Table 1 Patient characteristics

	ER	Surgery
Number of patients	42	13
Gender (Male/female)	40/2	12/1
Median age (years old, range)	71.5 (54-89)	69 (39-76)
Reasons of previous operation (%)		
Gastric cancer	35 (83)	9 (69)
Gastric ulcer	4 (12)	2 (23)
Others	3 (5)	2 (8)
Type of previous operation (%)		
Distal gastrectomy	28 (66)	6 (46)
Billroth-I	7 (17)	5 (38)
Billroth-II	3 (7)	1 (8)
Roux-en-Y	4 (10)	1 (8)
Proximal gastrectomy		
Tumor location		
Lessor curvature	13	5
Posterior wall	11	3
Anterior wall	6	3
Greater curvature	11	3
Median tumor size (mm, range)	10 (3-48)	23 (5-48)
Macroscopic type		
0-I	4	3
0-IIa	22	0
0-IIa+IIc	1	0
0-IIc	15	8
0-IIc+IIa	0	1
0-IIc+III	0	1
Histologic type (%)		
Differentiated	40 (93)	10 (77)
Undifferentiated	3 (7)	3 (23)
Depth of tumor invasion (%)		
M	32 (76)	6 (46)
SM1 (SM≤500 μm)	2 (5)	0
SM2 (SM>500 μm)	8 (19)	7 (54)
Method of endoscopic resection (%)		
EMR	27 (64)	
ESD	15 (36)	

ER, endoscopic resection; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; M, mucosal; SM, submucosal

surgery group 87.5% and 75 %, respectively ($P=0.602$, Fig. 2). The 3-year and 5-year cause-specific survival rates in the ER group were 94.1% and 89.8%, respectively, whereas those in the surgery group were 100% and 100%, respectively ($P=0.334$, Fig. 3).

The 3-year cause-specific survival rates of patients with M-SM1 and SM2 cancers were 100% and 47.6% in the ER group, respectively, and 100% and 100% in the surgery group, respectively ($P=0.000$, Fig. 4). In the ER group, three patients with SM2 cancer (38%) died of gastric cancer recurrence. Two of these three patients underwent endoscopic photodynamic therapy for residual lesions and the other was followed without treatment. They developed distant metastases 6, 12, and 39 months later, and died 13, 24, and 41 months after ER (Table 3).

Table 2 Procedure-related outcomes

	ER (n=42)	Surgery (n=13)	P-value
Median operation time (min, range)	46 (7-416) (n=34)	260 (170-483) (n=9)	<0.001
Median hospital stay (days, range)	8 (3-18)	26 (19-40)	<0.001
Adverse events (NCI-CTCAE grade)			
Grade 1	0	0	
Grade 2	2 (perforation)	0	
Grade 3	0	2 (anastomotic leakage)	
Grade 4	0	0	
Grade 5	0	0	
Changes of nutritional status after one year			
Total protein (g/dL)	+0.34	-0.02	0.17
Albumin (g/dL)	-0.11	+0.05	0.09

ER, endoscopic resection

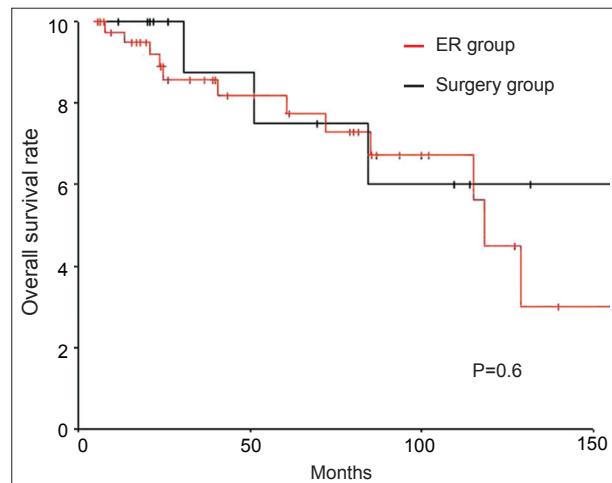


Figure 2 Overall survival of patients in endoscopic resection (ER) and surgery groups

Metachronous EGC developed in four patients in the ER group at a median (range) follow-up time of 34.5 (16-48) months; three of these patients underwent ER and the other one surgical resection.

Discussion

The present study thoroughly investigated the short- and long-term outcomes of 55 patients who had undergone ER or surgery for EGC in the remnant stomach.

The presence of lymph node metastasis is recognized as a strong adverse influence on EGC patients' prognoses [17]. Sasako *et al* reported post-surgery 5-year cancer-specific survival rates of patients with mucosal cancer of 99.3% [18]. Therefore, if the expected rate of lymph node metastasis is

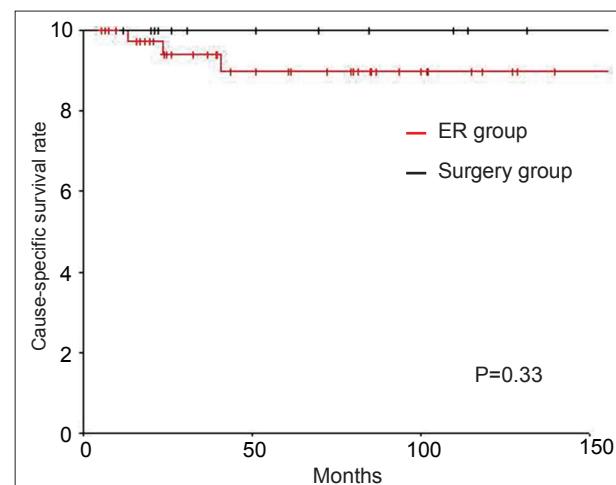


Figure 3 Cause-specific survival of patients in endoscopic resection (ER) and surgery groups

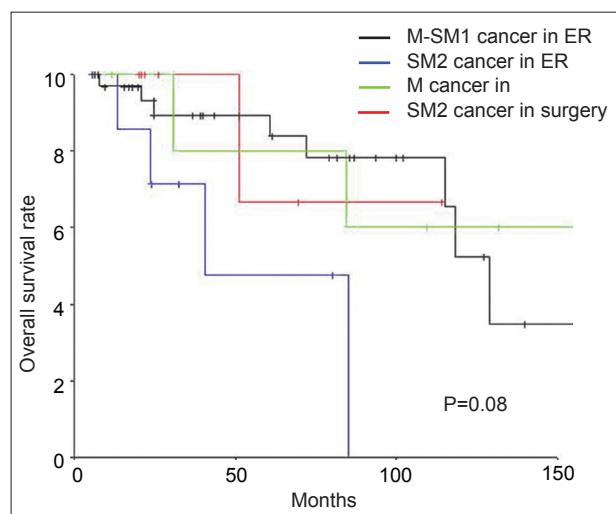


Figure 4 Cause-specific survival of patients with M-SM1 and SM2 cancers in endoscopic resection (ER) group

Table 3 Clinical features and outcomes of patients who died of gastric cancer after endoscopic resection

Case	Age (years old)	Gender	Reason of previous operation	Tumor characteristics					Method of ER	Resection	Recurrence	Time until distant metastasis (months)	Additional treatment for recurrence	Time until death of gastric cancer (months)
				Size (mm)	Macroscopic type	Histological type	Depth	Lympho-vascular involvement						
1	63	M	Gastric cancer	20	0-IIa	Differentiated	SM2	(-)	EMR	Piecemeal	Liver, Lymph node	12	Surgery Chemotherapy	24
2	89	M	Gastric ulcer	15	0-I	Differentiated	SM2	(-)	EMR (+PDT)	En bloc	Local, Bone	6	Chemoradiotherapy	13
3	83	M	Gastric ulcer	12	0-I	Differentiated	SM2	(-)	EMR (+PDT)	En bloc	Local, Peritoneum	39	Chemotherapy	41

EMR, endoscopic mucosal resection; PDT, photodynamic therapy

less than 1%, the survival rate after local treatment with ER could theoretically be an equivalent ($\geq 99\%$) to surgery for gastric mucosal cancer. Recently, Choi *et al* reported [19] that none of 17 patients (6 with absolute indications and 11 with expanded indications for ER) who underwent total gastrectomy for EGC in the remnant stomach had lymph node metastasis. They suggested that the indications for ER for primary gastric cancer might also apply to EGCs in the remnant stomach. In support of their findings, in this study, the overall and disease-specific 5-year survival of patients with M and SM1 cancer in the ER group were similar to those of patients in the surgery group, whereas some patients who had cancer SM2 invasion died from gastric cancer after having undergone only endoscopic treatment. These results justify applying the indications for ER described in the Japanese gastric cancer treatment guidelines to EGCs in the remnant stomach.

In this study, the survival of patients with M and SM1 cancer in the ER group was as good as that of those in the surgery group: The 5-year disease-specific survival rates were both 100%. Therefore, it could be said that surgical treatment of patients with intramucosal cancer in the remnant stomach is excessive because it involves longer operation times and hospital stays and is accompanied by more severe adverse events than ER. It is often more difficult to perform ER in the remnant stomach than in the normal stomach because, in the former, dissection of fibrotic submucosa at the surgical suture line or anastomotic site in the limited space of the remnant stomach is sometimes required [12,20]. However, surgery on the remnant stomach is also more difficult than that on the normal stomach because of adhesions and reconstruction of adjacent organs [19,21].

Gotoda *et al* studied 5,265 EGC patients who had undergone surgical resection and reported that the rate of lymph node metastasis in those with SM2 cancer was 23.7% [22]. The Japanese gastric cancer treatment guidelines consider SM2 invasion as not curative with ER and recommend additional surgical resection [7]. However, ER is sometimes performed in elderly patients or those with severe comorbidities because of their poor surgical risk. In particular, when regional lymph nodes have been dissected during the previous gastric surgery, the rate of lymph node metastasis is expected to be lower than that for normal stomachs. However, in our study, three of eight

patients with SM2 cancer who did not undergo additional surgery because of comorbid disease or poor performance status died of gastric cancer. Although this is a difficult decision to make when the patients' condition is poor, our findings have convinced us that radical surgery is necessary in patients with SM2 cancer, even when it is in the remnant stomach.

In this study, the durations of surgical procedure and hospital stay differed significantly between the ER and surgery groups. On the other hand, contrary to our expectations, there was no significant difference in nutritional status between the two groups. Although several previous studies have reported that malnutrition is one of the major postoperative complications of total gastrectomy [23-25], in our study there was no difference in serum total protein and albumin concentrations after total resection of the remnant stomach. Although multiple factors, such as changes in digestive physiology, damage to the mechanisms at the gastroesophageal junction, bacterial overgrowth or short intestinal transit time, are considered to cause malnutrition after total gastrectomy [26-28], no studies have reported data on nutritional status after total gastrectomy of the remnant stomach.

This study has several limitations. First, because it was a retrospective, nonrandomized study, there were biases in background physical status: ER tends to be recommended for elderly patients or those with serious comorbidities, which may have influenced the overall survival rate. A prospective randomized trial is the best means of controlling for such biases; however, random allocation of surgery and ER is unrealistic because treatment-related adverse effects are extremely different. Therefore, it is important to accumulate more retrospective data to further investigate which procedure is superior. Second, our study sample was small because surgical treatment for EGC in the remnant stomach has rarely been performed since the introduction of ESD. However, complete follow up was achieved in all patients in this study. In long-term cohort studies, the follow-up rate is important for reliability. Despite the small sample size, we believe the quality of the data warrant serious consideration of our findings.

In conclusion, the long-term outcomes of ER for M-SM1 gastric cancer in the remnant stomach were as excellent as those of radical surgery. However, if pathological examination identifies SM2 cancer, the resection should be considered noncurative and the risk of metastasis high.

Summary Box

What is already known:

- If gastric cancer in the remnant stomach is diagnosed at an early stage, it can be cured by radical surgery
- Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) have been developed in Japan and are widely recognized as techniques for treating early gastric cancer
- Recently, favorable long-term outcomes have been reported for EMR and ESD of early gastric cancer in the remnant stomach

What the new findings are:

- The long-term outcomes of endoscopic resection (ER) for M-SM1 early gastric cancer in the remnant stomach are excellent
- The operation time and hospital stay is significantly shorter for ER for early gastric cancer in the remnant stomach than for surgery; however, there is no significant difference in nutritional status
- In patients who are suspected to have SM2 invasive early gastric cancer in the remnant stomach, our findings indicate that radical surgery is necessary

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