Long-term survival after endoscopic resection versus surgery in early gastric cancers

Authors

Young-Il Kim^{*}, Young-Woo Kim^{*}, Il Ju Choi, Chan Gyoo Kim, Jong Yeul Lee, Soo-Jeong Cho, Bang Wool Eom, Hong Man Yoon, Keun Won Ryu, Myeong-Cheorl Kook

Institution

Center for Gastric Cancer, National Cancer Center, Goyang, Korea

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Bibliography

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Corresponding author II Ju Choi, MD PhD

Center for Gastric Cancer, National Cancer Center 323 Ilsan-ro Ilsandong-gu Goyang Gyeonggi 410–769 Korea Fax: +82-31-9201127 cij1224@hanmail.net **Background and study aim:** Endoscopic resection for early gastric cancers that meet the expanded indication is considered to be an investigational treatment. The study aim was to evaluate longterm outcomes of endoscopic resection compared with surgery for early gastric cancers meeting the expanded indication.

Methods: We retrospectively reviewed data from patients who underwent endoscopic resection or surgery for gastric cancers meeting the expanded indication between 2001 and 2009. Overall survival rate was the primary outcome; gastric cancer recurrence rates and complication rates were secondary outcomes.

Results: Among 457 patients included, 165 underwent endoscopic resection and 292 surgery, with median follow-up duration of 58.6 months. The 5-year overall survival rates were 97.5% and 97.0% for endoscopic resection and surgery, respectively; Kaplan–Meier analysis showed no significant difference (P=0.425). The 5-year gas-

tric cancer recurrence rate was higher for endoscopic resection than for surgery (4.8% vs. 0.3%; P<0.001) mainly because of metachronous cancers which developed only in the endoscopic resection group (9/165, 5.5%). Most of the metachronous cancers (88.9%) were curatively treated with endoscopic resection. Early complication rates were similar between the groups (P= 0.557), but the endoscopic resection group had more grade III or higher complications according to the Clavien–Dindo classification compared with the surgery group (4.8% vs. 1.4%, P=0.026). Late complications occurred only following surgery (4.8%, P=0.004), and most (92.9%) were grade III or higher.

Conclusions: Endoscopic resection may be an optimal alternative to surgery for gastric cancers that meet the expanded indication criteria, because of a comparable long-term overall survival rate.

Introduction

In Korea, among patients with gastric cancer a high proportion are diagnosed at an early stage owing to cancer screening programs [1, 2]. For early gastric cancer (EGC), gastrectomy with lymph node dissection has long been the standard treatment [3]. The reported long-term outcomes following surgery are excellent, with 5-year overall survival of more than 92% [4,5]. Endoscopic resection, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), is now widely performed to treat EGC without lymph node metastasis [6,7]. It is a standard treatment for EGCs that meet the absolute indication for endoscopic resection (namely, intramucosal differentiated-type cancer

* These two authors contributed equally to this work.

≤2 cm in size without ulcerative findings) [3]. The expanded indication for endoscopic resection was proposed based on the zero risk for lymph node metastasis found from the pathology results from EGC patients who underwent surgery [8]. Owing to the rapid improvement in techniques and devices for ESD, complete resections are possible in such EGC lesions. Recent studies have reported favorable long-term outcomes for EGCs that meet the expanded indication [9], with 5-year overall survival rates of 93.4% to 97.2% [10–12], comparable to those of EGCs meeting the absolute indication [12–14].

To date, the validity of the expanded indication for endoscopic resection remains controversial; several recent reports suggest that lymph node metastasis may occur even with EGCs that meet the expanded indication [15-17]. Therefore, endoscopic resection is still considered an investigational treatment for EGC lesions that meet the expanded indication [3]. In this study, we evaluated the longterm outcomes of endoscopic resection in comparison with those of surgery for EGCs that meet the expanded indication.

Methods

Study population and data collection

We prospectively collected clinicopathological data using the medical records of patients who underwent endoscopic resection or surgery for EGC at the National Cancer Center, Korea. The inclusion criteria were as follows: (i) age \geq 20 years, (ii) newly diagnosed EGC without previous treatment; (iii) EGC meeting the expanded indication criteria for endoscopic resection (criterion I, intramucosal tumor, differentiated type histologically, without ulcerative findings, and size \geq 2 cm; criterion II, intramucosal tumor, differentiated type, with ulcerative findings, and size \leq 3 cm; criterion III, submucosal invasion less than 500 µm (sm1), differentiated type histology, and size \leq 3 cm); (iv) no lymphovascular invasion, and (v) follow-up duration of more than 1 year. This study was approved by the institutional review board of the National Cancer Center, Korea (NCC2014-0006).

All patient data related to baseline demographics, endoscopic findings, pathology results, and treatment results were obtained from our database. Tumor stage was determined according to the 7th edition of the International Union Against Cancer/American Joint Committee on Cancer classification system [18].

Treatment methods

After the diagnostic work-up, which included esophagogastroduodenoscopy with biopsy and computed tomography (CT) of the abdomen, all EGC cases were thoroughly reviewed in multidisciplinary conferences before and after the treatment. When EGC lesions appeared to meet the expanded indication, patients and their family members were fully advised regarding the choice between endoscopic resection and surgery, because endoscopic resection for these lesions is still an investigational treatment.

All endoscopic resection procedures were performed by experienced gastroenterologists. EMR was carried out as an endoscopic resection method until April 2004. After the introduction of ESD devices in April 2004, endoscopic resection procedures were performed using the ESD technique. Detailed procedures for endoscopic resection have been described in a previous study [19]. For patients who underwent surgery, radical gastrectomy with lymph node dissection was performed by experienced surgeons. The reconstruction methods were Billroth I or II for subtotal gastrectomy, and Roux-en-Y esophagojejunostomy for total gastrectomy. Patients were provided with full consultation and then given the choice of open or laparoscopic surgery. The extent of lymph node dissection was more than D1 + beta, based on the recommendations of the Japanese Gastric Cancer Association [3].

Pathological evaluation

Specimens resected by endoscopic resection and surgery were fixed in 10% formalin for pathological evaluation. All specimens were sliced serially (at 2-mm intervals for endoscopic resection specimens and at 4-mm intervals for surgical specimens), embedded in paraffin blocks, and stained with hematoxylin and eosin. Lymph nodes were prepared for pathological evaluation. A single pathologist specializing in gastric cancer (M.-C.K.) performed the pathological evaluation. Histological tumor subtypes were classified on the basis of the World Health Organization classification of gastric cancer [20]. Well-differentiated and moderately differentiated tubular adenocarcinoma as well as papillary adenocarcinoma were considered to be differentiated-type, whereas poorly differentiated adenocarcinoma, signet ring-cell carcinoma, and mucinous adenocarcinoma were considered to be undifferentiated-type [21]. When the tumor had a mixture of differentiated and undifferentiated types, the tumor was classified according to the major component of the tumor (50% or more) [20].

Follow-up surveillance

After endoscopic resection and surgery, esophagogastroduodenoscopy was performed at 3 and 12 months, and then annually. In the endoscopic resection group an additional esophagogastroduodenoscopy was done at 6 months. Abdominal CT was carried out annually. At every follow-up esophagogastroduodenoscopy, the presence of local recurrence in the remnant stomach was evaluated and biopsy specimens were obtained at the endoscopic resection scar to check for local recurrence, as well as from any lesion suspected of being metachronous gastric cancer. In the present study, 3-year and 5-year adherence rates to the followup surveillance were 87.8% and 53.8%, respectively, and there were no significant differences in surveillance rates between the two treatment groups.

Outcome assessment

Overall survival was the primary endpoint of this study. Both patient survival status and cause of death were obtained from the medical records or from the claim database of the Korean National Health Insurance Corporation. Follow-up data on deaths and recurrences until December 2012 were obtained.

Secondary outcomes included gastric cancer recurrence rates, and treatment-related complications. Overall survival was evaluated on the basis of death from any cause. Metachronous gastric cancer was defined as a new cancer at a previously uninvolved site in the remnant stomach occurring more than 1 year after treatment.

Complications within 30 days of endoscopic resection or surgery were defined as early complications, and those occurring beyond 30 days after the treatment were defined as late complications. Complications were also classified according to the Clavien-Dindo classification [22], comprising five grades as follows: grade I, any deviation from the normal postoperative course, without the need for pharmacological treatment or surgical, endoscopic, or radiological interventions; grade II, requiring pharmacological treatment with drugs other than those allowed for grade I complications, requiring blood transfusions, or total parenteral nutrition; grade IIIa, requiring surgical, endoscopic, or radiological intervention not under general anesthesia; grade IIIb, requiring interventions as described for Grade IIIa but under general anesthesia; grade IV, life-threatening complication requiring intermediate care/intensive care unit management; grade V, death.

For patients who underwent endoscopic resection, short-term treatment outcomes were compared according to the endoscopic resection method, including en bloc resection and curative resection rates, according to the guidelines [3].



Statistical analysis

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Continuous variables are given as mean \pm standard deviation or as median with interquartile range (IQR). Comparisons of categorical variables were done using the chi-squared or Fisher's exact tests, and those of continuous variables were done using the Student *t* test or the Mann–Whitney *U* test. A curve for overall survival was estimated using the Kaplan–Meier method and compared using the log-rank test. Gray's test was used to compare gastric cancer-specific death and recurrence rates, which had competing risks of death without recurrence [23].

Multivariate Cox proportional hazards model analyses were performed using the estimated propensity scores to reduce bias [24]. The propensity scores were estimated from the logistic regression model by including variables that could affect outcomes after treatment: age, sex, co-morbid disease, criteria of expanded indication, and tumor characteristics including location, size, and histologic type. In model I, a multivariate analysis was performed after adjusting estimated propensity scores, age, sex, and indication for esophagogastroduodenoscopy that led to the EGC diagnosis. In model II, a propensity score-matched multivariate analysis was performed. For this analysis, patients in the endoscopic resection group were matched in a one-to-one ratio to those in the surgery group using identical propensity scores. A multivariate analysis using the Fine–Gray regression model [25] was performed for cancer recurrence with competing risks.

All data were analyzed using STATA 12.1 (Stata, College Station, Texas, USA) or SAS version 9.3 (SAS, Cary, North Carolina, USA). *P* values less than 0.05 were considered to be statistically significant.

Results

Demographic and baseline clinicopathological characteristics

A detailed flowchart summarizing this study is shown in **•** Fig. 1. Baseline characteristics of all included patients and propensity score-matched patients are presented in **•** Table 1. During the study period, 165 patients underwent endoscopic resection and 292 underwent surgery for EGCs that met the expanded indication, and they were included in the analysis. The median followup was 58.6 months (IQR 39.2–61.9 months). In the surgery group, total gastrectomy was performed in 36 patients (12.3%), and subtotal gastrectomy in 256 (87.7%), with 128 patients (43.8%) having laparoscopic surgery and 164 (56.2%) having open surgery.

Patients in the endoscopic resection group were older and had smaller tumor sizes than those in the surgery group. The distribution of the expanded indication criteria in the included patients was different between the two treatment groups (*P*<0.001): the endoscopic resection group had a higher rate of criterion I, and a lower rate of criterion II, than did the surgery group. Other demographic and baseline clinicopathological characteristics including sex, co-morbid disease, symptoms at the time of diagnostic esophagogastroduodenoscopy, and tumor location, histology, and morphology were not different between the two groups. In 157 pairs of propensity score-matched patients, no demographic or baseline clinicopathological characteristics differed between the treatment groups (**> Table 1**).

Comparisons of baseline characteristics and short-term outcomes according to endoscopic resection method

Of 165 endoscopic resection patients, 18 (10.9%) underwent EMR and 147 (89.1%) underwent ESD. Tumor size was larger in the ESD group than in the EMR group. However, there were no significant differences in other baseline characteristics, including age, sex, tumor location, histologic type of tumor, and expanded indication criteria (**D Table e2**, available online only).

Table 1 Endoscopic resection versus surgery in early gastric cancer (EGC): patient demographics and baseline clinicopathological characteristics.

	All patients			Propensity score-matched patients			
	Endoscopic resection (n = 165)	Surgery (n=292)	P value	Endoscopic resection (n = 157)	Surgery (n=157)	P value	
Age, median (IQR), years	62 (54 – 70)	60 (52 – 68)	0.049	62 (54–69)	62 (53 – 69)	0.624	
Sex, n (%)			0.930			0.591	
Male	122 (73.9)	217 (74.3)		119 (75.8)	123 (78.3)		
Female	43 (26.1)	75 (25.7)		38 (24.2)	34 (21.7)		
Comorbid disease, n (%)			0.108			0.981	
Diabetes mellitus	17 (10.3)	27 (9.2)		17 (10.8)	18 (11.5)		
Hypertension	20 (12.1)	48 (16.4)		20 (12.7)	17 (10.8)		
Coronary artery disease	3 (1.8)	8 (2.7)		3 (1.9)	2 (1.3)		
Chronic liver disease	8 (4.8)	35 (12.0)		8 (5.1)	10 (6.4)		
Chronic pulmonary disease	14 (8.5)	17 (5.8)		13 (8.3)	12 (7.6)		
Indication for the diagnostic esophago-			0 1941			0 315 ¹	
No symptoms (screening)	122 (73.9)	199 (68.2)	0.154	117 (74 5)	109 (69 4)	0.515	
Clinical symptoms	43 (26.1)	93 (31.9)		40 (25 5)	48 (30.6)		
Enigastric discomfort	22 (13 3)	63 (21.6)		20 (12 7)	31 (19.8)		
Dyspensia	14 (8 5)	18 (6 2)		14 (8 9)	9(57)		
Nausea	2 (1 2)	2 (0 7)		1 (0.6)	1 (0.6)		
Weight loss	2(1.2)	5(1.7)		2 (1.3)	3 (1.9)		
Gastrointestinal bleeding	3(1.8)	5(17)		3(19)	4(2.6)		
Criteria of expanded indication n (%)	5(1.0)	5(1.7)	< 0.001	5(1.5)	1 (2.0)	0.832	
l: mucosa (m) no ulceration (UI (-))			01001			0.002	
and size > 2 cm	118 (71.5)	190 (65.1)		115 (73.3)	114 (72.6)		
II: mucosa (m), ulceration (UL(+)),							
and size ≤ 3 cm	12 (7.3)	60 (20.5)		12 (7.6)	15 (9.6)		
III: submucosa (sm1) and size ≤ 3 cm	35 (21.2)	42 (14.4)		30 (19.1)	28 (17.8)		
Location of tumor, n (%)			0.899			0.802	
Upper third	10 (6.1)	21 (7.2)		10 (6.4)	13 (8.3)		
Middle third	24 (14.5)	42 (14.4)		23 (14.7)	21 (13.4)		
Lower third	131 (79.4)	229 (78.4)		124 (79.0)	123 (78.3)		
Size of tumor, mean ± SD, cm	2.5 ± 0.9	3.0 ± 1.2	< 0.001	2.6 ± 0.9	2.6 ± 0.9	0.836	
Histology of tumor ² , n (%)			0.061			0.279	
Differentiated type only	156 (94.5)	261 (89.4)		148 (94.3)	143 (91.1)		
Mixed with undifferentiated type	9 (5.5)	31 (10.6)		9 (5.7)	14 (8.9)		
Morphology of tumor, n (%)			0.581			0.516	
Elevated	38 (23.0)	74 (25.3)		37 (23.6)	42 (26.8)		
Flat or depressed	127 (77.0)	218 (74.7)		120 (76.4)	115 (73.3)		
Follow-up duration, median (IQR), months	49.2 (36.7 – 62.5)	59.3 (42.3 - 61.4)	0.018	49.2 (36.8 - 62.0)	59.2 (42.3 - 62.1)	0.033	

IQR, interquartile range; SD, standard deviation

¹ P values for comparison between patients without symptoms and those with symptoms

² Differentiated type denotes papillary, well-differentiated, or moderately differentiated adenocarcinoma; undifferentiated type denotes poorly differentiated adenocarcinoma or signet ring-cell carcinoma.

Patients in the ESD group had higher en bloc resection rates (97.3% vs. 77.8%, P=0.005) than those in the EMR group. Patients who underwent ESD had also higher curative resection rates than those in the EMR (90.5% vs. 61.1%, P=0.003) (• **Table e2**).

Comparisons of survival rates and gastric cancer recurrence rates

The 5-year overall survival rates were 97.5% in the endoscopic resection group and 97.0% in the surgery group; Kaplan–Meier analysis showed no significant difference in overall survival between the two treatment groups (P=0.425; **• Fig.2a**). The 5-year cumulative incidence rates of gastric cancer-specific death were 0% in the endoscopic resection group and 0.3% in the surgery group; Gray's test revealed no statistically significant difference (P=0.452). In the surgery group, one 65-year-old male patient had recurrence with multiple liver and bone metastases at

18 months after total gastrectomy with D2 lymph node dissection. The patient refused chemotherapy, and died at 22 months after surgery.

The cumulative incidence rate of gastric cancer recurrence was higher in the endoscopic resection group than in the surgery group (5-year cumulative incidence rate: endoscopic resection 4.7% vs. surgery 0.3%; P<0.001, Gray's test) (**•** Fig.2b). Metachronous gastric cancer occurred in 9 of 165 patients (5.5%) who underwent endoscopic resection (12.6 cases per 1000 person-years, 5-year cumulative incidence rate of 4.8%). Thus, patients in the endoscopic resection group had a higher rate of metachronous gastric cancer than those in the surgery group, who never developed metachronous gastric cancer (P<0.001).

All the metachronous gastric cancers in the endoscopic resection group occurred as EGCs without lymph node metastasis. The characteristics of the metachronous gastric cancers are presented



Fig.2 Comparisons between endoscopic resection and surgery groups of long-term outcomes for early gastric cancers that met the expanded indication criteria for endoscopic resection: **a** Kaplan–Meier curve for overall survival; **b** cumulative incidence rate of gastric cancer recurrence.

in • Table e3 (available online only). All nine cases were treated again with endoscopic resection. This was curative in eight patients whose metachronous cancer remained within the expanded indication for endoscopic resection; in one patient, at endoscopic resection, the lesion was found to have invaded the submucosa to a depth of 1000 µm. Therefore, metachronous gastric cancer did not affect overall survival. As mentioned above, the only case of gastric cancer recurrence in the surgery group was a distant metastasis.

Subgroup analyses according to each expanded indication criteria also revealed no differences in overall survival between the two treatment groups (**•** Fig. 3).

Multivariate analyses for overall mortality and cancer recurrence

Using the propensity score adjustment method (model I), the covariates for the analyses were age, sex, indication for esophago-gastroduodenoscopy, and estimated propensity score (**•** Table 4).



Fig. 3 Comparisons of overall survival between endoscopic resection and surgery groups with early gastric cancer, according to each expanded indication criterion for endoscopic resection. **a** Criterion I: intramucosal tumor, differentiated type histologically, without ulcerative findings, and size > 2 cm; **b** criterion II: intramucosal tumor, differentiated type histologically, with ulcerative findings, and size $\leq 3 \text{ cm}$; **c** criterion III: submucosal invasion $< 500 \,\mu\text{m}$, and differentiated type histologically, size $\leq 3 \,\text{cm}$. **P* values were calculated using the log-rank test.

 Table 4
 Endoscopic resection versus surgery in early gastric cancers that met the expanded indication for endoscopic resection: multivariate analyses for overall mortality and gastric cancer recurrence.

	n	Overall mortality ¹			Cancer recurrence ¹		
		aHR	95 %CI	P value	aHR	95 %CI	P value
Model I. Propensity score adjustment ²	457						
Treatment method							
Surgery		1.00		0.514	1.00		0.014
Endoscopic resection		0.70	0.24-2.03		16.96	1.76-163.41	
Indication for the diagnostic esophagogastroduodenoscopy							
No symptoms (screening)		1.00		0.663	1.00		0.226
Presence of symptoms		1.22	0.50-3.01		2.36	0.59-9.50	
Propensity score ³		0.33	0.04-3.13	0.338	3.06	0.17-56.78	0.452
Model II. Propensity score matching ⁴	314						
Treatment method							
Surgery		1.00		0.475	1.00		0.035
Endoscopic resection		0.67	0.23-2.00		11.33	1.19-107.66	

aHR, adjusted hazard ratio; 95%CI, 95% confidence interval.

¹ Cox regression hazard model for overall mortality and Fine–Gray regression model for cancer recurrence after treatments were used.

² Hazard ratio adjusted for age, sex, and propensity score.

³ Propensity score was estimated from age, sex, co-morbidity, distribution of criteria for expanded indication, and tumor size, histologic type, and location.

⁴ Hazard ratio adjusted for age, sex, and indication for EGD.

The adjusted hazard ratio (aHR) for overall mortality was 0.70 in the endoscopic resection group, which was not significantly different from the surgery group (P=0.514). However, the aHR for gastric cancer recurrence for the endoscopic resection group was 16.96 and significantly higher compared with the surgery group (P=0.014).

In the propensity score matching analysis (model II), overall mortality was not significantly different between the endoscopic resection and surgery groups (aHR in endoscopic resection group, 0.67; P=0.475) (• Table 4). Using this model, the aHR for gastric cancer recurrence for the endoscopic resection group (aHR 11.33; P=0.035) was also significantly higher compared with the surgery group. Thus, both propensity score-adjusted and score-matched models led to the same conclusion that the overall survival rate in the endoscopic resection group was not compromised despite frequent gastric cancer recurrence.

Early and late complications

The complications that occurred in both treatment groups are summarized in • **Table 5**. Overall, complications occurred in 38 of the study patients (9 patients [5.5%] in the endoscopic resection group and 29 patients [9.9%] in the surgery group; P=0.096). Although early complication rates were not different between the two treatment groups (P=0.557), the endoscopic resection group had Clavien–Dindo grade III or higher complications more frequently than the surgery group (4.8% vs. 1.4; P=0.026). In the endoscopic resection group, 7 cases of post-procedural bleeding and 1 case of perforation required endoscopic treatment (grade IIIa complication). In the surgery group, three endoscopic closures for anastomosis leakage (grade IIIa) and one surgical repair for wound dehiscence (grade IIIb) were needed.

In contrast, late complications occurred only in patients in the surgery group (4.8%, P=0.004). Most of these complications were grade III or higher (92.9%, 13/14 cases), including 6 anastomosis site strictures treated by endoscopic balloon dilation (grade IIIa), 3 incisional hernias and 3 intestinal obstructions that required surgical intervention (grade IIIb), and 1 death (grade V). A 71-year-old woman, who had undergone total gastrectomy for EGC 22 months previously, died after emergency

surgery for strangulated small bowel caused by postoperative adhesion.

In the subgroup analysis, the total complication rate was higher in patients undergoing open surgery (13.4%, 22/164 patients) than in those undergoing laparoscopic surgery (5.5%, 7/128 patients; P=0.024). However, there were no statistically significant differences according to the surgical treatment method in terms of early or late complication rates or in severity as assessed using the Clavien–Dindo classification.

Discussion

Until now, there has been no randomized study directly comparing long-term outcomes of endoscopic resection and surgery for EGCs, and only two retrospective studies have compared longterm outcomes between these two treatment modalities. Chiu et al. showed that 3-year survival rates were 94.6% in patients who underwent ESD and 89.7% in those who underwent surgery, which was not significantly different between the two treatment groups [26]. However, in that study, only 43% of the patients who underwent ESD had severe dysplasia or adenocarcinoma, whereas the remaining 57% of patients had mild to moderate dysplasia. Furthermore, it was not known whether the EGCs met the absolute or the expanded indications for endoscopic resection. Choi et al. also reported that the overall survival of patients who underwent EMR was comparable to that of patients who underwent surgery, with 5-year overall survival rates of 93.6% in the EMR group and 94.2% in the surgery group, respectively [27]. This study was also limited: only the EMR procedure was evaluated; most of the EGCs probably met the absolute indication for endoscopic resection; and in about 10% of the patients the EGC was histologically undifferentiated-type. In contrast to those studies, we included only patients with differentiated-type adenocarcinomas that strictly met the expanded indication, and we found that long-term outcomes after endoscopic resection were comparable to those of surgery.

With the introduction of ESD, it was possible to successfully achieve en bloc and curative resection for EGC lesions meeting

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	Endoscopic resection (n = 165)	Surgery ¹ (n=292)	P value ²	Surgery		
				Laparoscopic (n = 128)	Open (n=164)	P value ²
Early complications ³ , n (%)						
Bleeding	8 (4.8)	0(0)		0 (0)	0(0)	
Perforation	1 (0.6)	1 (0.3)		0 (0)	1 (0.6)	
Pneumonia	0 (0)	11 (3.8)		3 (2.3)	8 (4.9)	
Wound problem	0 (0)	4(1.4)		1 (0.8)	3 (1.8)	
lleus	0 (0)	2 (0.7)		1 (0.8)	1 (0.6)	
Intra-abdominal abscess	0 (0)	2 (0.7)		0 (0)	2 (1.2)	
Total	9 (5.5)	20 (6.8)	0.557	5 (3.9)	15 (9.2)	0.079
Clavien–Dindo classification for early complications, n (%)						
Grade I	0 (0)	4(1.4)		2 (1.6)	2(1.2)	
Grade II	1 (0.6)	12 (4.1)		3 (2.3)	9 (5.5)	
Grade IIIa	8 (4.8)	3 (1.0)		0 (0)	3 (1.8)	
Grade IIIb	0 (0)	1 (0.3)		0 (0)	1 (0.6)	
Grade IV	0 (0)	0(0)		0 (0)	0(0)	
Grade V	0 (0)	0(0)		0 (0)	0(0)	
≥ Grade III	8 (4.8)	4(1.4)	0.026	0 (0)	4 (2.4)	0.075
Late complications ³ , n (%)						
Anastomosis stricture	0 (0)	6 (2.1)		2 (1.6)	4 (2.4)	
Intestinal obstruction	0 (0)	3 (1.0)		0 (0)	3 (1.8)	
Incisional hernia	0 (0)	3 (1.0)		0 (0)	3 (1.8)	
Wound problem	0 (0)	1 (0.3)		1 (0.8)	0 (0)	
lleus	0 (0)	1 (0.3)		0 (0)	1 (0.6)	
Total	0 (0)	14 (4.8)	0.004	3 (2.3)	11 (6.7)	0.083
Clavien–Dindo classification for late complications, n (%)						
Grade I	0 (0)	0(0)		0 (0)	0(0)	
Grade II	0 (0)	1 (0.3)		0 (0)	1 (0.6)	
Grade IIIa	0 (0)	7 (2.4)		3 (2.3)	4 (2.4)	
Grade IIIb	0 (0)	5 (1.7)		0 (0)	5 (3.1)	
Grade IV	0 (0)	0(0)		0(0)	0(0)	
Grade V	0 (0)	1 (0.3)		0(0)	1 (0.6)	
≥ Grade III	0 (0)	13 (4.5)	0.006	3 (2.3)	10 (6.1)	0.123

¹ Five patients in the surgery group had both early and late complications (4 open and 1 laparoscopic surgery).

² Chi-squared test.

³ Complications occurring within 30 days after endoscopic resection or surgery are defined as early complications, and those occurring beyond 30 days as late complications.

the expanded indication [6], and therefore, surgical treatment for such lesions is less frequent [28]. However, an important limitation of endoscopic resection is that the expanded indications are based on the retrospective analyses of the final pathological results after the procedure [8]. Additional long-term follow-up studies are needed because of the potential risk of lymph node metastasis [29]. Recent studies have reported distant lymph node metastases in patients with EGC lesions that met the expanded indication, with rates of 0.2% to 15% according to each criterion [15,16]. Furthermore, lymph node metastasis occurs even after curative resection of EGC lesions that met criteria for endoscopic resection, although the rates were quite low [9,13]. Thus, there is a need for well-designed prospective randomized studies that evaluate the outcomes of endoscopic resection, in comparison with those of surgery, for EGCs that meet the expanded indication.

A major concern related to endoscopic resection is the occurrence of metachronous cancer. The annual incidence of metachronous cancers after endoscopic resection has been reported to be 4% [30]; in other studies, metachronous cancers occurred at 14.1 – 14.7 cases per 1000 person-years in patients who received *Helicobacter pylori* eradication and at 29.7 – 40.5 cases per 1000 person-years in those who did not [31,32]. In our study, only the endoscopic resection group developed metachronous cancers, at a rate of 12.6 cases per 1000 person-years which is similar to the incidence after *H. pylori* eradication in previous studies. In multivariate analyses the endoscopic resection group had a higher aHR for cancer recurrence compared with the surgery group. However, metachronous cancers were usually detected at the EGC stage and could be successfully treated by repeated endoscopic resection. Therefore after endoscopic resection, patients with EGC lesions that met the expanded criteria require careful follow-up surveillance to detect metachronous cancers. In patients who underwent surgery, further interventions in-

cluding surgery or endoscopic procedures have been needed because of major complications such as bleeding, ischemic or perforated viscera, anastomosis site stricture, or intestinal obstruction after surgery [33, 34]. In the present study, early complication rates were comparable in both groups, but late complications after 30 days of treatment occurred only in the surgery group. Among patients who underwent surgery, 2% of patients needed additional surgical treatments and 2% needed endoscopic treatment for anastomosis site strictures occurring as late complications. Furthermore, one patient in the surgery group died after surgery for a severe late complication of small-bowel strangulation caused by postoperative adhesion. Patients who underwent endoscopic resection had no late complications, and all early complications in the group such as bleeding and perforation were successfully managed by endoscopic procedures as previously reported [35]. In addition, mortalities associated with open or laparoscopic surgery have been reported at rates between 0.6% and 3.3% [36–39]. Our results suggest that endoscopic resection might be safer and may reduce the occurrence of late complications and potential mortality that are associated with surgery.

This study has the following limitations. First, it is retrospective, and the choice of endoscopic resection or surgery was not based on randomization. To reduce or overcome this limitation, we performed multivariate analyses for comparing long-term outcomes between the two treatment groups using propensity score adjustment and matched models. Although a multivariate analysis was done, there were significant differences between the two groups at baseline, specifically, larger size of tumor and more frequent ulceration in the surgery group. These differences may have negatively biased outcomes against the surgery group. Nevertheless, both groups showed excellent long-term outcomes. Second, the numbers for each criterion of the expanded indication were small, and comparisons could not be done for each criterion. Third, the duration of follow-up was different for the two treatment groups. EMR was not recommended for gastric cancers with the expanded indication. Thus, before April 2004, a higher proportion of patients underwent surgery compared with EMR, which resulted in a difference in the follow-up duration. Lastly, patients who had follow-up periods of less than 1 year were excluded because of this short-term follow-up, and they were significantly older than those included in the final analysis, although there were no significant differences in other baseline characteristics. Therefore, potential selection bias cannot be ignored.

In conclusion, endoscopic resection might be a good alternative to surgery for EGCs that meet the criteria for the expanded indication, because of the comparable long-term overall survival rate and lower incidence of late complications. However, because metachronous gastric cancers after endoscopic resection can occur more frequently in the conserved stomach, careful surveillance after treatment and further evaluation of long-term outcomes is needed.

Competing interests: None

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▼

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Tables e2 and e3

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Correction

S. Halpern et al. Comparison of adenoma detection and miss rate between a novel balloon colonoscope and standard colonoscopy: a randomized tandem study. Endoscopy 2015; 47: 238–244 DOI 10.1055/s-0034-1391437

The authors have requested the following changes:

- Page 240, "Study End Points", second paragraph, line 17–18, the sentence
- "The ratio of balloon colonoscopy additional adenoma detection to the standard colonoscopy miss rate is a measure of the adenoma detection..."

was corrected to

"The ratio of balloon colonoscopy additional adenoma detection to the miss rate is a measure of the adenoma detection..."

Page 241 "Per-lesion adenoma detection and miss rates", third paragraph, line 3 – 5, the sentence
"The ratio of balloon colonoscopy additional adenoma detection to the standard colonoscopy miss rate was 10.8 (81%/7.5%)."
was corrected to

"The ratio of balloon colonoscopy additional adenoma detection to the miss rate was 10.8 (81%/7.5%)."