Clinical outcomes of endoscopic resection for undifferentiated intramucosal early gastric cancer larger than 2 cm

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Abstract

Background This study investigated the long-term clinical outcomes of endoscopic resection (ER) for undifferentiated-type (UD) early gastric cancer (EGC), with tumor size > 2 cm as the only non-curative factor.

Methods From among 1123 patients who underwent ER for UD EGC at 18 tertiary hospitals in Korea between 2005 and 2014, we identified 216 patients with UD intramucosal EGC > 2 cm, which was completely resected, with negative resection margins, and absence of ulceration and lymphovascular invasion. The patients were divided into the additional surgery ($n=40$) or observation ($n=176$) groups, according to post-ER management and were followed up for a median duration of 59 months for recurrence and 90 months for overall survival.

Results Lymph node (LN) or distant metastasis or cancer-related mortality was not observed in the surgery group. In the observation group, two (1.1%) patients developed LN or distant metastasis with a 5-year cumulative risk of 0.7%, and one (0.6%) patient died of gastric cancer. The 5- and 8-year overall survival rates were 94.1% and 89.9%, respectively, in the observation group and 100.0% and 95.2%, respectively, in the surgery group (log-rank $P=0.159$). Cox regression analysis did not reveal an association between the observation group and increased mortality.

Conclusion The risk of LN or distant metastasis was not negligible, but as low as 1% for patients undergoing non-curative ER for UD EGC, with tumor size > 2 cm as the only non-curative factor. Close observation may be an alternative to surgery, especially for older patients or those with poor physical status.

Keywords Stomach neoplasms · Undifferentiated-type histology · Endoscopic mucosal resection · Treatment outcome · Lymph node metastasis

Introduction

Endoscopic resection (ER) is currently recommended for patients with early gastric cancer (EGC) with a negligible risk of lymph node (LN) metastasis [1, 2]. The indications for ER include undifferentiated-type (UD) intramucosal EGC of size ≤ 2 cm without ulceration or lymphovascular

invasion (LVI) [3]. Instrumental and technical advancements, such as the development of endoscopic submucosal dissection (ESD), have enabled resection of larger tumors. Consequently, ER for UD cancer often results in complete resection of UD intramucosal EGC > 2 cm in size with negative resection margins and absence of ulceration and LVI. For this non-curative ER with tumor size > 2 cm as the only non-curative factor, additional surgical resection with LN dissection is still recommended. However, patients often refuse additional surgery and prefer follow-up without additional treatment due to various reasons, such as old age, underlying illness, or fear of surgical adverse events [4–7]. Several previous studies have reported that patients undergoing non-curative ER for UD EGC with tumor size > 2 cm as the only non-curative factor may be at low risk of LN metastasis [4, 8].

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Although many surgical studies reported that the risk of LN metastasis was significantly higher for tumors sized > 2 cm than for tumors sized ≤ 2 cm [3, 9–13], Hirasawa et al. reported the estimated risk of LN metastasis for UD intramucosal EGC > 2 cm in size in the absence of ulceration and LVI [3]. The LN metastasis rate was 3.9% (16/411) for tumors > 2 cm in size and 1.9% (3/162) for tumors sized 2.1–3.0 cm. A recent surgical study by Horiuchi et al. reported that the rate of LN metastasis in pure UD intramucosal tumors sized 2.1–4.0 cm without ulceration and LVI was 0% [0/54, 95% confidence interval (CI), 0–6.1%] [14]. The LN metastasis rate may be lower for patients treated with ER because the aforementioned data were based on surgically resected EGCs that were serially sectioned into 4–5 mm thick slices. In the pathological examination for endoscopically resected EGC, the width of the section is 2 mm; consequently, small submucosal invasion, ulceration, or LVI can be detected [15]. To date, no study has reported on the risk of LN or distant metastasis after ER for UD intramucosal EGC > 2 cm. Therefore, in this nationwide multicenter cohort study, we investigated the long-term clinical outcomes of ER for UD intramucosal EGC, with tumor size > 2 cm as the only non-curative factor. We also examined the outcomes in patients with tumors measuring 2.1–3.0 cm and in those with pure UD tumors measured 2.1–4.0 cm.

Materials and methods

Patients

The present retrospective nationwide multicenter cohort study was conducted at 18 tertiary hospitals in six geographical areas in Korea. The study was approved by the ethical committee of each participating hospital and conducted in accordance with the guidelines of the Declaration of Helsinki.

We screened consecutive patients, who received ER for UD EGC at the participating hospitals between January 1, 2005 and December 31, 2014 ($n = 1124$). For the present study, we identified patients with UD intramucosal EGC with tumor size > 2 cm that was completely resected en bloc with negative resection margins and absence of ulceration and LVI after excluding patients who met the following exclusion criteria (Fig. 1): history of gastric cancer ($n = 43$); multiple gastric cancers ($n = 23$); and lost to follow-up after the initial ER ($n = 37$). Among the remaining 1021 patients, 354 (32.7%) patients who received curative ER were excluded. Of the 667 patients with non-curative ER beyond the expanded criteria, 300 patients with submucosal invasive cancer were also excluded. Among the 367 patients with intramucosal EGC, 151 patients with one or more other

non-curative factors were further excluded (piecemeal resection, $n = 17$; positive horizontal margin, $n = 100$; positive vertical margin, $n = 9$; ulceration, $n = 33$; and LVI, $n = 19$). Finally, 216 patients with tumor size > 2 cm as the only non-curative factor were assessed. Radical surgery with LN dissection was recommended for all included patients. The patients who underwent additional surgical resection constituted the additional surgery group ($n = 40$), while those who refused surgery and were followed up without further treatment constituted the observation group ($n = 176$).

The electronic medical records of each patient were reviewed for data extraction. Data on age, sex, American Society of Anesthesiologists (ASA) physical status classification class, tumor location, size, macroscopic appearance, and histology, and ER method were collected at baseline. One physician at each hospital ensured completeness of the data collected. Two authors (H.J.Y and Y.I.K) independently cleared and validated the collected data and then compared them.

Endoscopic procedure

Before ER, patients routinely underwent upper endoscopy with chromoendoscopy using indigo carmine dye, as well as narrow-band imaging if available. If endoscopist deemed it necessary, endoscopic ultrasound and forceps biopsies around the lesion were additionally conducted. ER was indicated for EGC with expanded indication at most institutions and with absolute indication at some institutions according to the guidelines [2]. ER for EGC with out-of-indication was performed only in exceptional cases as a diagnostic ER [16].

Endoscopic mucosal resection (EMR) or ESD was performed during ER. The procedure was performed under sedation. Initially, the lesion was visualized using white-light endoscopy with chromoendoscopy and circumferential markings were generated outside the lesion. Image-enhanced endoscopy and magnification were selectively used, according to the study center protocols. A submucosal injection of normal saline mixed with epinephrine (0.01 mg/mL) with or without indigo carmine was administered. For EMR, a snare was used with or without circumferential incision. For ESD, after routine circumferential incision of the lifted mucosa, the submucosal layer was dissected using an insulation-tipped knife or other knives. All bleeding or non-bleeding visible vessels were coagulated using hemostatic forceps or coagulation probes.

Histopathological examination

The ER specimens were fixed in formalin, embedded in paraffin blocks, serially sectioned into 2 mm thick slices, and then stained with hematoxylin and eosin. The histological type was classified according to the Japanese guidelines

Fig. 1 Flow diagram of the patient selection process. *EGC* early gastric cancer, *ER* endoscopic resection, *LVI* lymphovascular invasion, *UD* undifferentiated-type

[2, 15]. Accordingly, UD cancer was defined as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma and differentiated-type cancer was defined as well- or moderately differentiated adenocarcinoma or papillary adenocarcinoma. In the current study, we further sub-classified UD cancer into pure UD cancer, defined as cancer containing only undifferentiated components, and mixed UD cancer, defined as cancer with a quantitatively predominant UD component and a component of differentiated-type cancer [14]. The depth of tumor invasion, presence of ulceration and LVI, and horizontal and vertical resection margins were also evaluated.

Follow-up

Follow-up endoscopic evaluation was conducted at 1–3 months after ER or additional surgery. Regular surveillance with upper endoscopy and abdominal computed tomography was performed annually or biannually for the

first 3 years and then annually until at least 5 years after the initial ER [2, 17].

Recurrence of primary cancer was evaluated as local, regional LN, or distant metastasis. Local recurrence was defined as the presence of a tumor on the previous ER scar. Recurrence of a new lesion detected at a previously uninvolved site was defined as either synchronous or metachronous recurrence, depending on the time interval between the diagnosis of the new lesion and the initial treatment (≤ 1 year or > 1 year, respectively).

Overall survival was defined as the time elapsed between the initial endoscopic treatment and death from any cause or censoring. Disease-specific survival was defined as the time between the initial endoscopic treatment and death from gastric cancer. The survival status was determined from the medical records and claims data of the Korean National Health Insurance Service (NHIS). Korea has the single-payer universal healthcare insurance system [18]. Virtually all Koreans are covered by NHIS. The disqualification of insurance occurs by death or emigration [19]. Because it

was thought that the patients who underwent non-curative ER for EGC were unlikely to emigrate, disqualification of health insurance was considered indicative of mortality and maintenance of insurance on the date of screening (October 30, 2018) was considered indicative of censoring [20]. The cause of death was classified as gastric cancer, other, or unknown. When mortality was presumed based on the claims data, the cause of death was recorded as unknown.

Statistical analysis

Intergroup differences were evaluated with Student's *t* test or Mann–Whitney *U* test for continuous variables and Pearson's chi-square test or Fisher's exact test for categorical variables. Survival data were analyzed using the Kaplan–Meier method and compared between groups with the log-rank test. Adjusted analyses of the survival data were performed using Cox regression analysis. Because the cause of death was not determined in several patients, we estimated disease-specific survivals in the combinations where patients who had died more than six months after the last hospital visit, each had died of gastric cancer, or other cause, and also using the data from medical records only. We pre-specified two subgroups within the observation group that were expected to have a very low risk of LN metastasis, namely the group with tumors sized 2.1–3.0 cm and group with pure UD cancer sized 2.1–4.0 cm. We also evaluated the clinical outcomes in these subgroups. SPSS (version 21.0; SPSS Inc., Chicago, IL, USA) was used for statistical analyses, and values of $P < 0.05$ were considered significant.

Results

Patients

The patients with UD intramucosal EGC > 2 cm in size with complete resection and absence of ulceration and LVI constituted 32.4% (216/667) of the overall non-curative ER cohort and 58.9% (216/367) of the non-curative intramucosal cancer cohort (Fig. 1). In the preoperative evaluation, 18.5% (40/216) patients were diagnosed as intramucosal UD EGC > 2 cm in size without ulceration (Supplementary Table 1). Among the included patients, only 18.5% (40/216) underwent radical surgery with LN dissection, 21 patients underwent total gastrectomy, and others underwent distal gastrectomy.

Significant differences were not observed between the surgery and observation groups with respect to the mean age of the patients (mean age $\pm$ standard deviation: 57.6 ± 10.0 vs. 60.3 ± 12.5 years) and proportion of male patients (60.0% vs. 57.4%; Table 1). However, the ASA physical status class was significantly better in the surgery group than in the

observation group ($P = 0.005$). With respect to the tumor-related factors, the tumor size was 2.1–3.0 cm in 61.1% (132/216) patients. A higher incidence of mixed UD cancer (32.5% vs. 3.4%, $P < 0.001$) and elevated tumor appearance (35.0% vs. 11.4%, $P < 0.001$) was found in the surgery group than in the observation group. Significant differences in tumor location, size, histology, and resection method were not observed between the groups.

Recurrence

Table 2 summarizes the clinical outcomes after ER. The surgical pathology of the patients in the surgery group revealed absence of LN metastasis. During a median follow-up duration of 59.2 [interquartile range (IQR) 41.7–83.9] months, recurrence was not observed in the surgery group. In contrast, in the observation group, two patients (1.1%, 95% CI 0–2.7%) experienced LN or distant metastasis. One patient (79/M), who initially had a 2.9 cm signet ring cell carcinoma with a poorly differentiated adenocarcinoma component, developed metastasis to the LNs, lungs, and bones 31 months after ER. He was managed with only supportive care because of his old age and died of gastric cancer. The other patient (44/M), who had a 2.4 cm signet ring cell carcinoma, developed locally recurrent cancer 77 months after ER and was treated with R0 surgical resection. The pathological outcome was poorly differentiated adenocarcinoma with proper muscle invasion and regional LN metastasis. The 5-year cumulative risk of developing LN or distant metastasis was 0.0% in the surgery group and 0.7% (95% CI 0–1.4%) in the observation group (log-rank $P = 0.474$; Fig. 2a).

In the observation group, three additional cases of local recurrence without LN metastasis were observed. They were detected at 5.5, 6.9, and 9.6 months after ER and were curatively treated with surgery ($n = 2$) or ESD ($n = 1$), without further recurrence during the follow-up period. Among the four patients with local recurrence, including the patient with LN metastasis, three patients had UD cancer and one patient had moderately differentiated adenocarcinoma. Eleven other patients showed 12 synchronous or metachronous recurrences; of these, UD histology was noted in four cancers. Among the 11 patients, 10 patients were treated with curative ESD ($n = 5$) or R0 surgical resection ($n = 5$); however, two other patients underwent non-curative ER and were then followed up without further recurrence (Supplementary Table 2).

Overall survival

During a median follow-up period of 90.1 months (IQR 63.5–108.6), only one patient died in the surgery group compared to 16 patients in the observation group (Table 2).

Table 1 Baseline characteristics of the included patients

	Overall (<i>n</i> = 216)	Surgery (<i>n</i> = 40)	Observation (<i>n</i> = 176)	<i>P</i> value
Age, years, mean (SD)	59.8 ± 12.1	57.6 ± 10.0	60.3 ± 12.5	0.210
Male sex, <i>n</i> (%)	125 (57.9)	24 (60.0)	101 (57.4)	0.763
ASA class, <i>n</i> (%)				0.005
I	137 (43.4)	33 (82.5)	104 (59.1)	
II	73 (33.8)	7 (17.5)	66 (37.5)	
III–IV	6 (2.8)	0 (0.0)	6 (3.4)	
Location of tumor, <i>n</i> (%)				0.206
Upper	88 (40.7)	21 (52.5)	67 (38.1)	
Middle	119 (55.1)	17 (42.5)	102 (58.0)	
Lower	9 (4.2)	2 (5.0)	7 (4.0)	
Tumor size, cm, median (IQR)	2.8 (2.4–3.6)	3.0 (2.4–3.6)	2.8 (2.4–3.6)	0.465
2.1–3.0 cm, <i>n</i> (%)	132 (61.1)	23 (57.5)	109 (61.9)	
3.1–4.0 cm, <i>n</i> (%)	47 (21.8)	10 (25.0)	37 (21.0)	
4.1–5.0 cm, <i>n</i> (%)	23 (10.6)	4 (10.0)	19 (10.8)	
5.1–6.0 cm, <i>n</i> (%)	10 (4.6)	3 (7.5)	7 (4.0)	
6.1–7.0 cm, <i>n</i> (%)	4 (1.9)	0 (0.0)	4 (2.3)	
Macroscopic appearance, <i>n</i> (%)				< 0.001
Elevated	34 (15.7)	14 (35.0)	20 (11.4)	
Depressed/flat	182 (84.3)	26 (65.0)	156 (88.6)	
Histology, <i>n</i> (%)				0.230
PD	137 (63.4)	30 (75.0)	107 (60.8)	
SRC	78 (36.1)	10 (25.0)	68 (38.6)	
Mucinous	1 (0.5)	0 (0.0)	6 (0.6)	
Mixed UD cancer, <i>n</i> (%) ^a	19 (8.8)	13 (32.5)	6 (3.4)	< 0.001
Resection method, <i>n</i> (%)				0.157
EMR	4 (1.9)	2 (5.0)	2 (1.1)	
ESD	212 (98.1)	38 (95.0)	174 (98.9)	

ASA American Society of Anesthesiologists, EMR endoscopic mucosal resection, ESD endoscopic submucosal dissection, IQR interquartile range, PD poorly differentiated adenocarcinoma, SD standard deviation, SRC signet ring cell carcinoma, UD undifferentiated-type

^aMixed UD cancer was defined as cancer with a quantitatively predominant UD component and a component of differentiated-type cancer

Table 2 Summary of clinical outcomes

	Surgery (<i>n</i> = 40)	Observation (<i>n</i> = 176)	<i>P</i> value
Recurrence, <i>n</i> (%)	0 (0.0)	16 (9.1)	0.047
Follow-up duration, months, median (IQR)	59.2 (50.7–83.9)	59.2 (39.1–84.0)	1.000
Local recurrence	0 (0.0)	4 (2.3) ^a	1.000
Regional lymph node or distant metastasis	0 (0.0) ^b	2 (1.1) ^a	1.000
Synchronous recurrence ^c	0 (0.0)	3 (1.7)	1.000
Metachronous recurrence ^c	0/39 (0.0)	8/169 (4.7)	0.357
Mortality, <i>n</i> (%)	1 (2.5)	16 (9.1)	0.208
Follow-up duration, months, median (IQR)	88.9 (70.8–115.0)	90.1 (62.7–108.5)	1.000
Gastric cancer	0 (0.0)	1 (0.6)	
Other cause	0 (0.0)	9 (5.1)	
Unknown cause	1 (2.5)	6 (3.4)	

IQR interquartile range

^aOne patient developed both local recurrence and regional lymph node metastasis

^bIncludes lymph node metastasis in surgical specimen

^cSynchronous and metachronous recurrence was defined as recurrence of a new lesion detected at a previously uninvolved site during follow-up ≤ 1 year versus > 1 year after the initial treatment, respectively

Fig. 2 (a) Cumulative risk of developing lymph node or distant metastasis, and (b) overall survival according to treatment after non-curative endoscopic resection

The 5- and 8-year overall survival rates were 100.0% and 95.2%, respectively, in the surgery group and 94.1% and 89.9%, respectively, in the observation group (log-rank $P = 0.159$; Fig. 2b). The results of the univariate and multivariate analysis of the possible risk factors for mortality are shown in Table 3. In the adjusted Cox regression model, age [hazard ratio (HR) 1.14; 95% CI 1.07–1.21; $P < 0.001$], male sex (HR 3.29; 95% CI 1.04–10.39; $P = 0.042$), and ASA class III–IV (HR 8.14; 95% CI 1.78–37.18; $P = 0.007$) were identified as the independent risk factors for mortality. The observation group was not independently associated with increased mortality (HR 1.91; 95% CI 0.23–16.01).

The cause of death in the observation group was gastric cancer in only one (0.6%) patient; other causes, nine patients; and unknown causes, six patients. One patient in the surgery group also died of unknown cause. Five of seven deaths from unknown causes occurred less than six months from

the last hospital visit, and thus were considered deaths from other causes. The disease-specific survivals were evaluated in the four combinations where the other two patients each had died of gastric cancer or other causes (Supplementary Fig. 1) and also using the data from the medical records only (Supplementary Fig. 2). In the observation group, the 5- and 8-year disease-specific survival rates ranged 98.7–99.4% and 97.8–99.4%, respectively. These rates were not significantly different from 100.0% after 5 and 8 years of follow-up in the surgery group (all log-rank $P > 0.05$).

Clinical outcomes in the pre-specified subgroups

There were 109 patients with tumors sized 2.1–3.0 cm and 141 patients with pure UD cancer sized 2.1–4.0 cm in the observation group. Because the aforementioned two patients who developed LN or distant metastasis had a 2.9-cm signet ring cell with a poorly differentiated adenocarcinoma component and a 2.4-cm signet ring cell carcinoma, respectively, they belonged to both subgroups. Consequently, the clinical outcomes, including LN or distant metastasis and overall survival, were essentially unchanged in these subgroups, compared to the overall observation group (Supplementary Table 3).

Discussion

In this study, we investigated the clinical outcomes of ER for UD intramucosal EGC > 2 cm that was completely resected with negative resection margins and absence of ulceration and LVI. Of the 176 patients in the observation group, two (1.1%) patients developed LN or distant metastasis with a 5-year cumulative risk of 0.7%, and one (0.6%) of them died of gastric cancer. In contrast, LN or distant metastasis or cancer-related mortality was not detected in the surgery group. Overall survival was not significantly different between the two groups, and the observation group was not significantly associated with increased mortality in the adjusted analysis.

To date, several cohort studies have reported the clinical outcomes of ER for patients with UD EGC [21–25]. However, the clinical outcomes of patients with UD EGC with tumor size > 2 cm as the only non-curative factor of ER have not been evaluated in detail. This may be important in clinical practice because these cases accounted for approximately one-third of the overall non-curative ER cases and two-thirds of the non-curative intramucosal cancer cases in our cohort. While some physicians consider this group of patients to be at low risk of LN metastasis [8], this notion has not been supported by sufficient evidence. To the best of our knowledge, this study is the first study to report the long-term outcomes after ER for patients with UD intramucosal

Table 3 Univariate and multivariable analyses for mortality

Covariates	Univariate analysis		Multivariable analysis	
	HR (95% CI)	<i>P</i> value	HR (95% CI)	<i>P</i> value
Age, years	1.14 (1.07–1.20)	<0.001	1.14 (1.07–1.21)	<0.001
Sex		0.097		0.042
Female	1		1	
Male	2.59 (0.84–7.93)		3.29 (1.04–10.39)	
ASA class		0.001		0.008
I	1		1	
II	3.40 (1.14–10.15)	0.028	1.07 (0.30–3.78)	0.919
III–IV	17.33 (4.11–73.20)	<0.001	8.14 (1.78–37.18)	0.007
Location of tumor		0.195		
Middle/lower	1			
Upper	1.88 (0.72–4.90)			
Tumor size, cm	1.03 (0.990–1.07)	0.151		
Histology		0.875		
SRC	1			
Non-SRC	1.08 (0.40–2.93)			
Additional treatment		0.191		0.550
Surgery	1		1	
Observation	3.85 (0.51–29.02)		1.91 (0.23–16.01)	

ASA American Society of Anesthesiologists, *CI* confidence interval, *HR* hazard ratio, *SRC* signet ring cell carcinoma

EGC > 2 cm in size with negative resection margins and absence of ulceration and LVI.

In our study, the estimated rate of LN or distant metastasis was 1.1% (95% CI 0–2.7%) as a simple proportion and 0.7% (95% CI 0–1.4%) as the 5-year cumulative probability. The rate of LN metastasis in patients with UD intramucosal EGC > 2 cm in size was 3.3–7.6% in previous surgical studies [3, 9–14]. However, only two studies have reported that the rates of LN metastasis in the absence of both ulceration and LVI were 3.9% (16/411; 95% CI 2.0–5.7%) and 3.4% (4/118; 95% CI 0.8–6.7%) [3, 14]. The rate in our study is lower than the aforementioned rates. This may be because small submucosal invasion, ulceration, or LVI—that would have been missed on pathological examinations of surgical specimens—was detected during our pathological examinations of the ER specimens, and cancer patients with those findings were excluded. Moreover, these rates were also lower than the rate of LN metastasis for the entire patients undergoing non-curative ER, which was 5.1–12.2% after additional surgery [4, 6–8, 26]. In overall patients of our study, the rate of LN metastasis was 7.1% (20/281) in additional surgery after non-curative ER. Thus, UD intramucosal EGC > 2 cm in size may be associated with a low risk of LN metastasis in patients with non-curative ER, unless they present with ulceration or LVI. This group of patients cannot be categorized as being at “minimal” risk of LN metastasis. Furthermore, LN or distant metastasis or gastric cancer-related death was not noted in the surgery group, although

we acknowledge that the sample size was small. Therefore, our results suggest that surgical resection with LN dissection should still be recommended as the standard treatment for non-curative ER of UD EGC, even though tumor size > 2 cm was the only non-curative factor. Close follow-up without surgery may be an alternative for the selected patients who refuse to undergo surgery.

The overall survival rate was lower in the observation group than in the surgery group, but the difference was not statistically significant. Furthermore, the observation group had significantly poorer baseline physical status than the surgery group. Consequently, in multivariate analysis, the observation group was not associated with increased mortality. Old age, male sex, and ASA class III–IV were significantly associated with overall mortality. In addition, the disease-specific survival in the observation group, which was at least 97.8% after 8 years of follow-up, was favorable and not inferior to the surgery group. Therefore, close observation may be recommended for patients with these risk factors.

Our results may not lead directly to recommendations for ER of intramucosal UD EGC with tumor size > 2 cm without ulceration in preoperative diagnosis. Among the overall 1,021 patients, 102 patients had UD EGC > 2 cm without ulceration in preoperative evaluation (Supplementary Table 1). ER for these patients resulted in curative resection in 11.8% (12/102) and non-curative resection with tumor size > 2 cm as the only non-curative factor in 39.2% (40/102). Thus, it may be difficult to recommend ER

because of low curative resection rate. However, for patients with abovementioned risk factors, 51% possibility of either curative resection or non-curative resection with tumor size > 2 cm ‘only’ may not negligible, and ER may be carefully considered.

It was interesting that four patients showed local recurrence, including one patient with LN metastasis, because the initial ER specimens had shown negative horizontal and vertical margins. It is unclear whether these recurrent lesions were derived from the primary cancer or from a new lesion that developed near the primary lesion. The higher incidence of UD histology in cancer with local recurrence (3/4) than in cancer with synchronous or metachronous recurrence (4/12) may indicate that these lesions are not simply new lesions residing in a nearby location. It is possible that the patients with local recurrence may have had residual cancers with false-negative margins because of the infiltrative growth patterns at the time of initial ER. Diffuse-type gastric cancer was more likely to show local recurrence after R0 surgical resection [27]. Thus, the risk of local recurrence in patients with negative margins for UD histology should be elucidated in studies in the future. Our results suggest that ER sites should be meticulously evaluated in patients who were followed up without surgery.

In our study, we pre-specified two subgroups within the observation group that were hypothesized to have a very low risk of LN metastasis. We selected the subgroups of patients with tumors sized 2.1–3.0 cm and those with pure UD cancer sized 2.1–4.0 cm because the rates of LN metastasis were 1.9% (3/162, 95% CI 0–4.0%) and 0.0% (0/59, 95% CI 0–6.1%), respectively, in previous studies [3, 14]. However, we could not find sufficient evidence to suggest that these subgroups are at minimal risk of LN metastasis because the two patients with LN or distant metastasis were from these subgroups. Further studies are required to determine whether there may be a group of patients at minimal risk of LN metastasis within the patient cohort with UD intramucosal EGC > 2 cm in size.

The strengths of this study are its large sample size that allowed the selection of a group of patients with tumor size > 2 cm as the only non-curative factor among those who underwent non-curative ER for UD EGC and the long-term follow-up duration that helped us detect rare events of LN or distant metastasis in this cohort. However, several limitations should also be acknowledged. First, our study was a retrospective study based on the review of medical records. Second, the curative resection rate was low, and the rates of submucosal invasion and positive horizontal margin were high in our overall patients (Supplementary Table 1). These were mainly because the patients who were not diagnosed as UD EGC before ER or diagnosed as UD EGC with out-of-indication were included in the study. In the patients with UD EGC

clinically within expanded criteria, the rates of submucosal invasion and positive horizontal margin were similar to previous studies [21, 22]. Nevertheless, the curative resection rate (51.0%) in these patients were still lower than 61.4% from a previous systematic review [28], which may indicate limited accuracy of preoperative evaluations. Nevertheless, this might not affect the current study results because our results were based on the final pathological outcomes after ER. Third, although the use of claims data provided us with long-term information on overall survival, the disqualification of insurance could have occurred by emigration, not by death. However, in this case, the overall survival rates would be higher than the estimates in the current analysis, especially in the observation group. In addition, we could not determine the cause of death for several patients; thus, the incidence of gastric cancer-related death may have been higher than that reported here.

In conclusion, the risk of LN or distant metastasis was not negligible, but as low as 1% in patients undergoing non-curative ER for UD EGC, with tumor size > 2 cm as the only non-curative factor. Additional surgical resection with LN dissection is the standard treatment, but close observation without surgery may be an alternative for old patients, male patients or those with poor physical status.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human rights statement and informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions.

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