



Long-term Outcomes of Undifferentiated-Type Early Gastric Cancer with Positive Horizontal Margins after Endoscopic Resection

Hyo-Joon Yang¹, Wan-Sik Lee², Bong Eun Lee³, Ji Yong Ahn⁴, Jae-Young Jang⁵, Joo Hyun Lim⁶, Su Youn Nam⁷, Jie-Hyun Kim⁸, Byung-Hoon Min⁹, Moon Kyung Joo¹⁰, Jae Myung Park¹¹, Woon Geon Shin¹², Hang Lak Lee¹³, Tae-Geun Gweon¹⁴, Moo In Park¹⁵, Jeongmin Choi¹⁶, Chung Hyun Tae¹⁷, Young-Il Kim¹⁸, and Il Ju Choi¹⁸

¹Division of Gastroenterology, Department of Internal Medicine and Gastrointestinal Cancer Center, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, ²Department of Internal Medicine, Chonnam National University Medical School, Gwangju, ³Department of Internal Medicine, Pusan National University School of Medicine, Busan, ⁴Division of Gastroenterology, Department of Internal Medicine, Asan Medical Center, University of Ulsan College of Medicine, ⁵Department of Internal Medicine, Kyung Hee University College of Medicine, ⁶Department of Internal Medicine, Healthcare Research Institute, Healthcare System Gangnam Center, Seoul National University Hospital, Seoul, ⁷Division of Gastroenterology, Kyungpook National University Hospital and School of Medicine, Kyungpook National University, Daegu, ⁸Division of Gastroenterology, Department of Internal Medicine, Gangnam Severance Hospital, Yonsei University College of Medicine, ⁹Department of Medicine, Samsung Medical Center, Sungkyunkwan University School of Medicine, ¹⁰Department of Internal Medicine, Korea University Guro Hospital, Korea University College of Medicine, ¹¹Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, ¹²Department of Internal Medicine, Hallym University College of Medicine, ¹³Division of Gastroenterology, Department of Internal Medicine, Hanyang University College of Medicine, Seoul, ¹⁴Division of Gastroenterology, Department of Internal Medicine, Incheon St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Incheon, ¹⁵Department of Internal Medicine, Kosin University College of Medicine, Busan, ¹⁶Department of Internal Medicine, Sanggye Paik Hospital, Inje University College of Medicine, ¹⁷Department of Internal Medicine, Ewha Womans University College of Medicine, Seoul, and ¹⁸Center for Gastric Cancer, National Cancer Center, Goyang, Korea

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Corresponding Author

Wan-Sik Lee

ORCID <https://orcid.org/0000-0002-8021-6228>

E-mail jadelook@hanmail.net

Bong Eun Lee

ORCID <https://orcid.org/0000-0003-2734-2134>

E-mail bongsul@daum.net

Background/Aims: This study examined the long-term outcomes of undifferentiated-type early gastric cancer (UD EGC) with positive horizontal margins (HMs) after endoscopic resection (ER) and compared them between additional surgery and nonsurgical management.

Methods: From 2005 to 2015, a total of 1,124 patients with UD EGC underwent ER at 18 tertiary hospitals in Korea. Of them, 92 patients with positive HMs as the only noncurative factor (n=25) or with both positive HMs and tumor size >2 cm (n=67) were included. These patients underwent additional surgery (n=40), underwent additional endoscopic treatment (n=6), or were followed up without further treatment (n=46).

Results: No lymph node (LN) metastasis was found in patients who underwent additional surgery. During a median follow-up of 57.7 months (interquartile range, 27.6 to 68.8 months), no LN or distant metastases or gastric cancer-related deaths occurred in the overall cohort. At baseline, the residual cancer rate was 57.8% (26/45) after additional surgery or ER. The 5-year local recurrence rate was 33.6% among patients who were followed up without additional treatment. The 5-year overall survival rates were 95.0% and 87.8% after additional surgery and nonsurgical management (endoscopic treatment or close follow-up), respectively (log-rank p=0.224). In the multivariate Cox regression analysis, nonsurgical management was not associated with an increased risk of mortality.

Conclusions: UD EGC with positive HMs after ER may have favorable long-term outcomes and a very low risk of LN metastasis. Nonsurgical management may be suggested as an alternative, particularly for patients with old age or chronic illness. (*Gut Liver*, Published online April 6, 2021)

Key Words: Stomach neoplasms; Undifferentiated-type histology; Endoscopic mucosal resection; Margins of excision; Lymphatic metastasis



INTRODUCTION

Endoscopic resection (ER) is accepted as a standard treatment for early gastric cancer (EGC) with a negligible risk of lymph node (LN) metastasis.¹⁻⁴ When curative resection is achieved, ER provides excellent long-term outcomes compared with surgery.⁵ However, curative ER is not always possible, and additional gastrectomy with LN dissection is recommended when the resection is considered noncurative.⁶⁻⁸ The guidelines also recommend nonsurgical management, such as additional endoscopic treatment or close observation without further treatment, as an alternative option for differentiated-type EGC in which a cancer-positive horizontal resection margin is the only noncurative factor, because of a very low risk of LN metastasis.^{2,9-11} In a previous study, no LN or distant metastasis or gastric cancer-related death occurred among 75 patients with differentiated-type EGC with a positive horizontal margin (HM) as the only noncurative factor during a median follow-up of 60 months.¹² However, no such guidelines are available on the nonsurgical management for undifferentiated EGC with positive HM after ER. A recent study of 76 patients with positive HM only demonstrated that both differentiated and undifferentiated cancers can be managed with additional endoscopic treatments.¹³ However, in that study, the median follow-up duration after endoscopic treatments ranged from 13 to 21 months. Importantly, one patient with well-differentiated cancer who underwent argon plasma coagulation (APC) for positive HM developed peritoneal seeding after 4 years of follow-up. This can be a more crucial issue for an undifferentiated-type histology. Therefore, it is important to investigate the long-term outcomes, particularly the risk of LN or distant metastasis, of undifferentiated cancers with positive HM in order to evaluate the safety of nonsurgical management in these patients.

Therefore, this nationwide multicenter cohort study aimed to examine the long-term clinical outcomes of undifferentiated-type EGC (UD EGC) with positive HM after ER, and to compare them between patients with additional surgery and those with nonsurgical management.

MATERIALS AND METHODS

1. Patients

In this retrospective cohort study, we reviewed the data of consecutive patients with UD EGC who underwent ER at 18 tertiary hospitals in six geographic areas in Korea between February 2005 and May 2015. We included patients with positive HM, which was defined as either *en*

bloc resection with cancer cells identified in the horizontal resection margins of the resected specimen or a piecemeal resection. We excluded patients with positive vertical margin, submucosal invasion, lymphovascular invasion, or ulcer. Because we aimed to evaluate long-term outcomes, we further excluded patients with a history of gastric cancer, multiple gastric cancers, and initial follow-up loss. However, patients with tumor size >2 cm were not excluded because it was reported that they had a low risk of LN metastasis.^{14,15} The baseline clinical, endoscopic, and histological data were retrospectively reviewed using the medical records. Chronic medical illness was defined as any of the following conditions: diabetes, cardiovascular disease, cerebrovascular disease, liver cirrhosis, or chronic kidney disease. One physician for each hospital was responsible for the data collection process. Two authors (H.J.Y. and Y.I.K.) independently reviewed, cleaned, and validated the overall data. The study protocol was reviewed and approved by the institutional review boards of all participating hospitals, and the requirement for informed consent was waived.

2. Endoscopic resection

Before ER, the lesion was identified with white-light endoscopy and chromoendoscopy using indigo carmine dye. Image-enhanced endoscopy was also used when available. Each patient underwent either endoscopic mucosal resection or endoscopic submucosal dissection (ESD). Several markings were made 5 mm outside the margin of the lesion, and epinephrine-containing saline solution was injected into the submucosal layer. Endoscopic mucosal resection was performed using a polypectomy snare. For ESD, after making a circumferential mucosal incision outside the markings, dissection along the submucosal plane was performed using a knife. Various knives, including IT-2 knife (Olympus, Tokyo, Japan), Flex knife (Olympus), or Dual knife (Olympus), were used according to the preference of the endoscopist.

3. Histopathological assessment

Endoscopically resected specimens were fixed in formalin and serially sectioned at 2-mm intervals to determine the presence of cancer cells in the horizontal resection margin. The histological types, tumor size, tumor invasion depth, presence of ulcer and lymphovascular invasion, and vertical resection margin were also evaluated microscopically. According to the Japanese guidelines,¹⁶ an undifferentiated-type histology was defined as poorly differentiated adenocarcinoma, signet ring cell carcinoma, or mucinous adenocarcinoma.

4. Additional treatment and follow-up

The attending physician decided the additional treatment for positive HM from among additional surgery, additional ESD, APC, and close observation without further treatment, based on the tumor burden involved in the HM and the patient's general condition. The patients were divided into the surgery group, which included those who underwent additional surgical resection, and the non-surgery group, which included those who were treated endoscopically or followed up without further treatment.

Upper endoscopy with a forceps biopsy at the ER site was conducted 3 months after the initial treatment, every 6 to 12 months for the first 3 years, and annually thereafter. Abdominal computed tomography was also performed every 6 to 12 months for the first 3 years, and then annually.^{2,17}

Local recurrence was defined as a recurrent cancer occurring at the ER site. Synchronous or metachronous recurrence was defined as a new lesion detected at a lo-

cation other than the previous ER site within or after 12 months from the initial ER, respectively. Overall survival was defined as the time from the initial ER to death from any cause. Survival status was determined from the medical records, and the cause of death was recorded as gastric cancer or other causes. The claims data of the Korean National Health Insurance Corporation were also accessed on March 2019. Disqualification of health insurance was considered to indicate death from an unknown cause, whereas maintenance of insurance was considered as censored on the date of screening.¹⁸

5. Statistical analysis

Continuous variables were compared using the Student t-test or the Mann-Whitney U test, and categorical variables were compared using the Pearson chi-square test, Fisher exact test, or linear-by-linear association test. Time-dependent variables were evaluated using the Kaplan-Meier methods and log-rank test. The Cox regression analysis

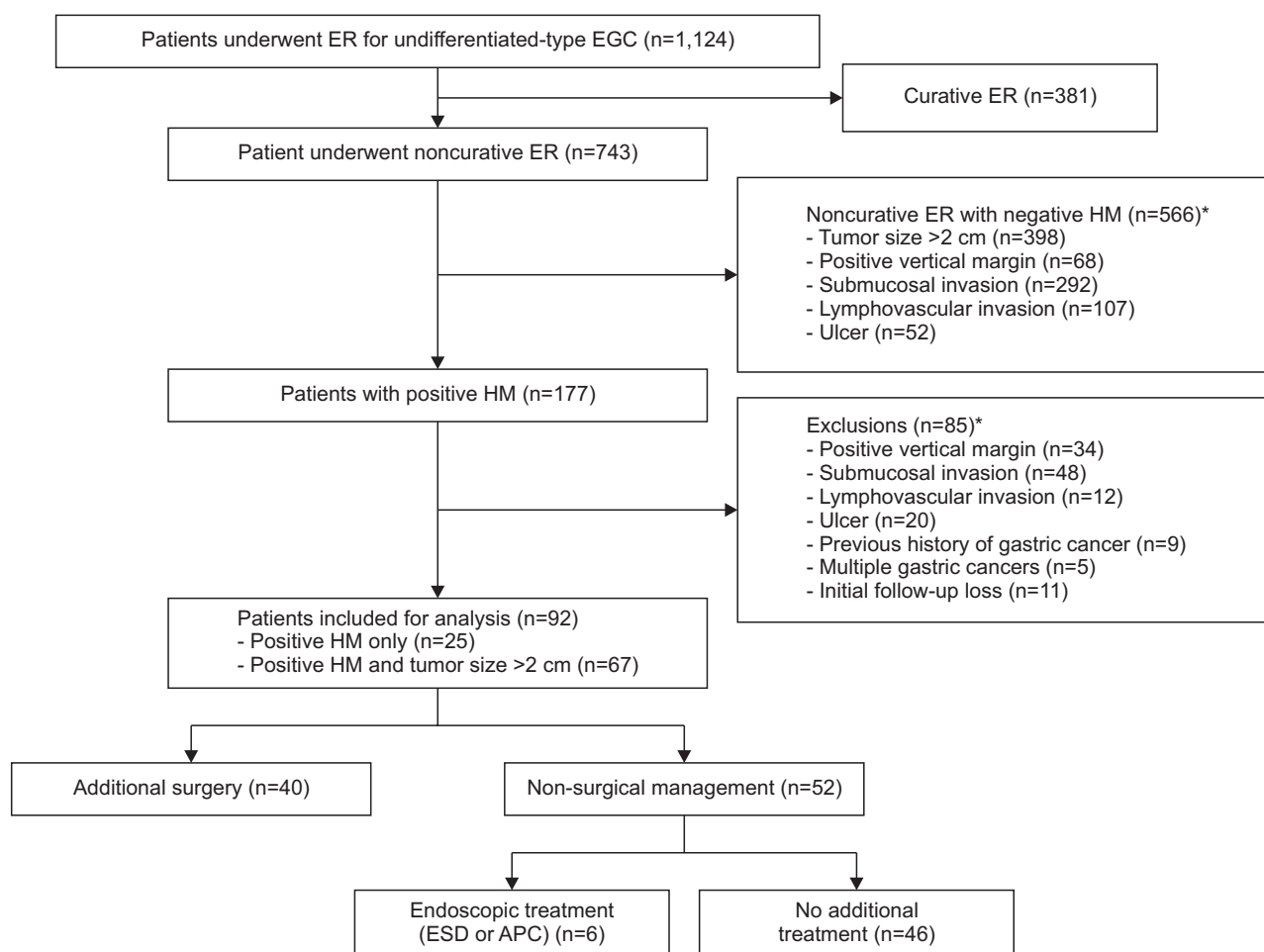


Fig. 1. Flowchart of the patients included in the analysis.

ER, endoscopic resection; EGC, early gastric cancer; HM, horizontal margin; ESD, endoscopic submucosal dissection; APC, argon plasma coagulation.

*Some patients met more than one exclusion criteria.

was also conducted for adjusted analyses of survival data. SPSS version 21.0 (SPSS Inc., Chicago, IL, USA) was used for the statistical analyses, and values of $p < 0.05$ were considered significant.

RESULTS

1. Baseline characteristics of the included patients

A total of 1,124 patients underwent ER for UD EGC, and 743 (66.0%) underwent noncurative resection (Fig. 1). Of these patients, 177 were found to have a positive HM. Eighty-five patients were excluded for one or more of the following reasons: positive vertical margin ($n=34$), submucosal invasion ($n=48$), lymphovascular invasion ($n=12$), ulcer ($n=20$), previous history of gastric cancer ($n=9$), multiple gastric cancers ($n=5$), and initial follow-up loss ($n=11$). Consequently, 92 patients with positive HM as the only noncurative factor ($n=25$) or with both positive HM

and tumor size > 2 cm ($n=67$) were included in the analysis. Of them, 40 patients in the surgery group underwent additional surgery and 52 patients in the non-surgery group were treated with ESD ($n=5$) or APC ($n=1$), or were followed up without additional treatment ($n=46$).

Table 1 presents the baseline characteristics of the included patients. The surgery and non-surgery groups were significantly different in age, type of positive HM, and tumor size. The mean age \pm standard deviation was 57.6 ± 9.1 years in the surgery group and 65.0 ± 13.8 years in the non-surgery group ($p=0.003$). No patient with piecemeal resection (0/14) and only 20.0% (5/25) of the patients with tumor size ≤ 2 cm underwent additional surgery. Meanwhile, patients with positive HM after *en bloc* resection or with larger tumor size were more likely to be treated with additional surgery (both $p < 0.05$).

Table 1. Baseline Characteristics of the Included Patients

Characteristics	Surgery (n=40)	Non-surgery (n=52)	p-value
Age, yr	57.6 \pm 9.1	65.0 \pm 13.8	0.003
Male sex	21 (52.5)	32 (61.5)	0.384
ASA class			0.813
I	22 (55.0)	32 (61.5)	
II	18 (45.0)	18 (34.6)	
III-IV	0	2 (3.8)	
Current or past smoking	11 (27.5)	14 (26.9)	0.951
Chronic medical illness*	7 (17.5)	9 (17.3)	0.985
<i>Helicobacter pylori</i> infection	21/31 (67.7)	31/48 (64.6)	0.773
Location of tumor			0.695
Upper/middle	38 (95.0)	47 (90.4)	
Lower	2 (5.0)	5 (9.6)	
Macroscopic appearance			0.240
Elevated	11 (27.5)	9 (17.3)	
Depressed/flat	29 (72.5)	43 (82.7)	
Histology			0.546
PDA	21 (52.5)	24 (46.2)	
SRC	19 (47.5)	28 (53.8)	
Resection method			0.649
EMR	3 (7.5)	2 (3.8)	
ESD	37 (92.5)	50 (96.2)	
Type of positive HM			<0.001
<i>En bloc</i> with positive HM	40 (100)	38 (73.1)	
Piecemeal resection	0	14 (26.9)	
Tumor size, cm	3.4 (1.2-6.2)	2.8 (0.6-7.0)	0.036
Tumor size, cm			0.012
≤ 2	5 (12.5)	20 (38.5)	
2-4	23 (57.5)	17 (32.7)	
> 4	12 (30.0)	15 (28.8)	

Data are presented as mean \pm SD, number (%), or median [range].

ASA, American Society of Anesthesiologists; PDA, poorly differentiated adenocarcinoma; SRC, signet ring cell carcinoma; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; HM, horizontal margin.

*Chronic medical illnesses included diabetes, cardiovascular disease, cerebrovascular disease, liver cirrhosis, and chronic kidney disease.

2. Risk of residual cancer and recurrence after positive HM

Among the 40 patients in the surgery group, LN metastasis was not noted in the surgical specimen of any patient (Table 2). However, residual cancer was detected in 65.0% (26/40) of the patients who underwent additional surgery and in 0.0% (0/5) of those who underwent additional ESD. The histological outcome of residual cancer was not available in one patient who underwent additional APC because the patient lost to follow-up after APC.

The overall follow-up duration was 57.7 months (interquartile range, 27.6 to 68.8 months) for recurrence and gastric cancer-related mortality. During the follow-up, no regional LN or distant metastasis was detected in

both groups. Further, no local, synchronous, or metachronous recurrence was found in the surgery group. On the contrary, 11 (21.2%) local recurrences and four (7.7%) synchronous or metachronous recurrences were recorded in the non-surgery group. Specifically, local recurrence occurred only in the 46 patients who were followed up without additional treatment. The cumulative risk of local recurrence was 13.8%, 20.2%, and 33.6% after 1, 3, and 5 years of follow-up, respectively (Fig. 2A). With respect to tumor size, the 5-year risk of local recurrence was 17.7% for tumor size ≤2 cm and 43.4% for tumor size >2 cm (log-rank p=0.051). The clinical course after local recurrence is presented in Fig. 2B. Patients with local recurrence were treated with surgery (n=4), ESD (n=5), or APC (n=2). The

Table 2. Summary of Clinical Outcomes

Outcome	Surgery (n=40)	Non-surgery (n=52)	p-value
Outcome of additional treatment			
Residual cancer	26 (65.0)	0/5 (0)*	-
LN metastasis	0	-	-
Recurrence			
Follow-up duration, mo	58.9 (37.9–68.4)	48.7 (15.1–69.3)	0.228
Local recurrence	0	11 (21.2)	0.002
Regional LN or distant metastasis	0	0	NA
Synchronous or metachronous recurrence [†]	0	4 (7.7)	0.130
Mortality			
Follow-up duration, mo	88.5 (67.4–112.0)	79.2 (60.0–97.3)	0.337
Gastric cancer	0	0	
Other cause	1 (33.3)	3 (37.5)	
Unknown cause	2 (66.7)	5 (62.5)	

Data are presented as number (%) or median (interquartile range).

LN, lymph node; NA, not available.

*Data were available for patients who underwent additional endoscopic submucosal dissection; [†]Synchronous recurrence and metachronous recurrence were defined as the recurrence of a new lesion detected at a previously uninvolved site during follow-up ≤1 year and >1 year after initial treatment, respectively.

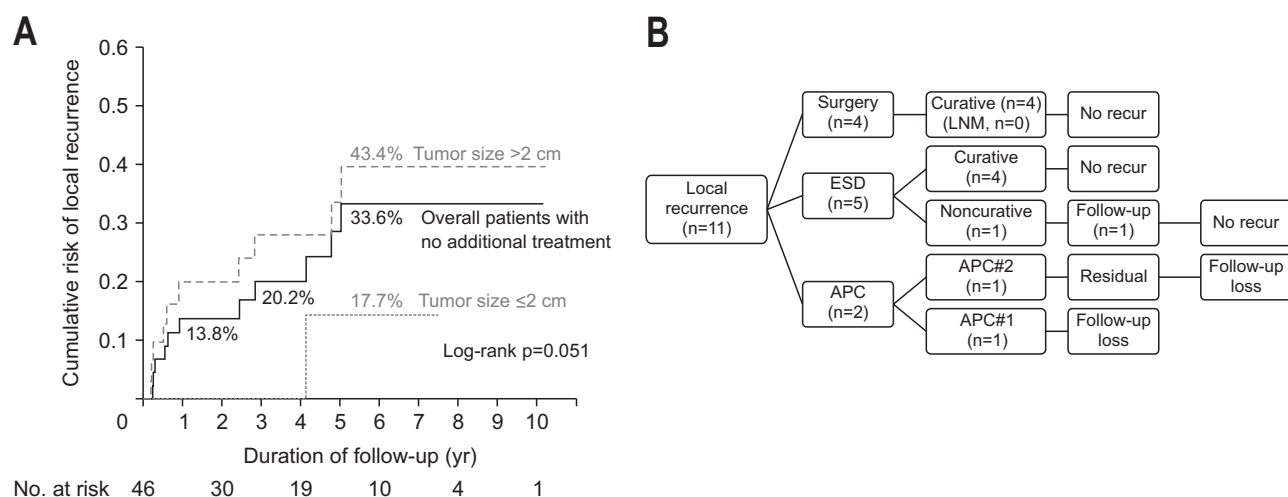
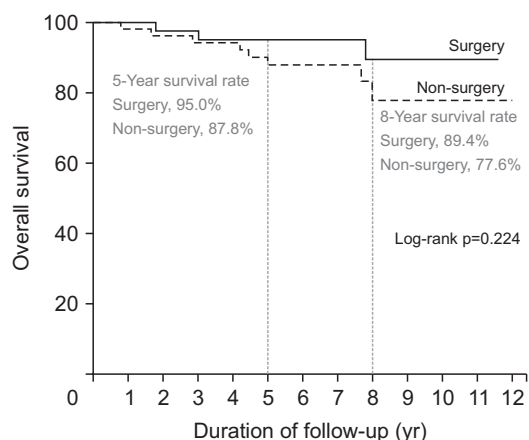


Fig. 2. (A) Cumulative risk of local recurrence in patients who were followed up without additional treatment. (B) Clinical course of patients who developed local recurrence during the follow-up period.

ESD, endoscopic submucosal dissection; LNM, lymph node metastasis; APC, argon plasma coagulation.



No. at risk	0	1	2	3	4	5	6	7	8	9	10	11	12
Surgery	40	39	37	28	16	5	0						
Non-surgery	52	50	48	32	14	8	0						

Fig. 3. Overall survival according to the management strategy of patients with positive horizontal margins after endoscopic resection.

patients did not develop further recurrence after surgery or ESD during the remaining follow-up period. However, in the two patients who treated with APC, one patient still had residual cancer after APC and another patient was not assessed for treatment outcome because of follow-up loss. Four patients with synchronous or metachronous recurrences also did not develop further recurrence after curative (n=3) or noncurative ESD (n=1).

3. Survival outcomes according to management for positive HM

During the median follow-up of 81.3 months (interquartile range, 62.7 to 106.7 months) for overall survival, no gastric cancer-related death was recorded, although two and five patients in the surgery and non-surgery groups died of an unknown cause, respectively (Table 2). The 5- and 8-year overall survival rates were 95.0% and 89.4%, respectively, in the surgery group and 87.8% and 77.6%, respectively, in the non-surgery group (p=0.224) (Fig. 3). In multivariate Cox regression analysis, age (hazard ratio [HR], 1.19; 95% confidence interval [CI], 1.07 to

Table 3. Univariate and Multivariable Analyses for Mortality

Covariate	Univariate analysis		Multivariable analysis	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age, yr	1.11 (1.04–1.17)	0.001	1.19 (1.07–1.34)	0.002
Sex		0.112		
Female	1		1	
Male	3.47 (0.75–16.06)			
Smoking		0.028		0.006
Never	1		1	
Current or past	2.80 (1.16–12.48)		8.45 (1.82–39.18)	
Chronic medical illness*		0.019		0.011
No	1		1	
Yes	4.93 (1.30–18.78)		7.27 (1.59–33.30)	
ASA class		0.275		
I	1			
II–IV	1.94 (0.59–6.38)			
<i>Helicobacter pylori</i>		0.168		
Absent	1			
Present	0.43 (0.13–4.42)			
Histology		0.340		
SRC	1			
Non-SRC	1.82 (0.53–6.22)			
Type of positive HM		0.851		
Piecemeal resection	1			
<i>En bloc</i> with positive HM	0.86 (0.19–4.01)			
Tumor size, cm		0.867		
≤2	1			
>2	0.89 (0.24–3.37)			
Additional treatment		0.236		0.401
Surgery	1		1	
Non-surgery	2.23 (0.59–8.43)		0.49 (0.09–2.61)	

HR, hazard ratio; CI, confidence interval; ASA, American Society of Anesthesiologists; SRC, signet ring cell carcinoma; HM, horizontal margin.

*Chronic medical illnesses included diabetes, cardiovascular disease, cerebrovascular disease, liver cirrhosis, and chronic kidney disease.

1.34; $p=0.002$), smoking (HR, 8.45; 95% CI, 1.82 to 39.18; $p=0.006$), and chronic medical illness (HR, 7.27; 95% CI, 1.59 to 33.30; $p=0.011$) were independently associated with mortality (Table 3). After adjustment for these variables, nonsurgical management was not associated with an increased risk of mortality (HR, 0.49; 95% CI, 0.09 to 2.61; $p=0.401$).

DISCUSSION

In the present study, we included 92 patients with UD EGC who had positive HM after ER. To our knowledge, this is the largest sample size from a nationwide multicenter cohort in Korea. We found no case of LN metastasis after additional surgery, and no LN or distant metastasis or gastric cancer-related death occurred in the overall cohort during a median follow-up of 58 months. In addition, nonsurgical management was not associated with an increased risk of overall mortality during a median follow-up of 81 months. Our findings suggest that the risk of LN metastasis may be very low in UD EGC with positive HM, and that nonsurgical management can be an alternative for these cases.

Many studies have evaluated various aspects of EGC with positive HM after ER, including predictors of positive HM,¹⁹ outcomes of additional endoscopic treatment,⁹⁻¹¹ risk factors for local recurrence,^{12,20,21} and long-term outcomes.¹² However, no or only a small number of cases of undifferentiated-type cancer were included in those studies. A recent study reported data on 76 patients with positive HM after ER, including 26 patients with UD EGC.¹³ In that study, no LN or distant metastasis was detected among patients with UD EGC. However, the study was also limited in that the follow-up duration was relatively short and patients undergoing close observation without additive treatment were not included. In our study, we included 92 patients with UD EGC with positive HM after ER and followed them up for a median of 5 years. Our study demonstrates that these patients may have a very low risk of LN metastasis, with higher credibility than previous small-sized studies. To obtain a large sample size, we also included patients with tumor size >2 cm. Although tumor size >2 cm is associated with LN metastasis in undifferentiated-type cancer,³ a more recent study suggested that the risk of LN metastasis would be low in patients with a tumor size of >2 cm as the only risk factor than in those with other risk factors.¹⁴ Therefore, our results suggest that a positive HM status with an undifferentiated-type histology after ER may not increase the risk of LN metastasis if there are no further risk factors.

In our study, the residual cancer rate was 58% (26/45) among patients who underwent additional surgery or ESD. Our results are consistent with those of previous studies that reported a 50% to 86% rate of residual cancer.^{9,13,19} The rate of local recurrence was 33.6% after 5 years of follow-up among patients who were followed up without additional treatment in our study. Although the rate was lower in patients with tumor size ≤ 2 cm (18%) than in those with tumor size >2 cm (43%), these findings are also consistent with previous results demonstrating a rate of 13% to 36%.^{9,12,13,20} Thus, our results suggest that the risk of residual cancer or local recurrence due to positive HM after ER would be similar between the undifferentiated-type histology that was observed in our study and the differentiated-type histology that was reported in previous studies.

The overall survival rates in the non-surgery group were only 88% and 78% after 5 and 8 years of follow-up. These seemed lower than those in the surgery group, which were 95% and 89% after 5 and 8 years of follow-up, respectively. However, these may not be due to gastric cancer because no metastatic disease and gastric cancer-related death occurred during 5 years of follow-up. This was supported by the results of the Cox regression analysis in which age, smoking, and chronic medical illness were independent predictors of overall survival. In fact, patients in the non-surgery group were significantly older than those in the surgery group at baseline. Therefore, these results suggest that nonsurgical management could be recommended for patients with old age or chronic illness.

ESD was previously suggested to be an effective treatment for residual or locally recurrent cancer with positive HM after ER.^{10,11,13,19} In our study, 10 patients were treated with ESD for residual cancer or local recurrence and did not experience further recurrence after ESD. On the contrary, only three patients were treated with APC. One patient underwent additional APC for positive HM before any local recurrence was detected, and the other two underwent APC after local recurrence was diagnosed. Because two patients were lost to follow-up after APC, the treatment outcome was available in only one patient in whom APC failed to eradicate recurrent cancer. Therefore, our results support the use of ESD as additive treatment for residual cancer or salvage treatment for local recurrence. However, the data from our study were not sufficient to evaluate the effectiveness of APC.

The strength of our study lies in the large sample size and long-term follow-up duration, reliably suggesting that a positive HM with undifferentiated-type histology after ER has a very low risk of LN metastasis. However, the limitation of our study was that UD EGCs >2 cm in diameter were included in addition to EGCs ≤ 2 cm. Our data

should not be interpreted to mean that UD EGCs >2 cm in diameter may be subject to ER because we did not include all patients with tumor size >2 cm. Another limitation is the retrospective design based on a medical record review and the lack of pathological slide review. Consequently, we could not measure the length of positive HM that was suggested as an important risk factor in the selection of additive treatment modality or for the prediction of local recurrence.^{12,13,20,21} However, it may be unlikely that the length of positive HM influences the long-term risk of LN or distant metastasis, which was the focus of the present study.

In conclusion, UD EGC with positive HM after ER may have favorable long-term outcomes and a very low risk of LN metastasis. Nonsurgical management such as additional endoscopic treatment or close follow-up without additional treatment may be suggested as an alternative for patients with old age or chronic illness.

CONFLICTS OF INTEREST

J.Y.A. is an editorial board member of the journal but did not involve in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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AUTHOR CONTRIBUTIONS

Study concept and design: H.J.Y., J.Y.A., J.H.K., W.G.S., I.J.C. Data acquisition: all authors. Data analysis and interpretation: H.J.Y. Drafting of the manuscript: H.J.Y. Critical revision of the manuscript for important intellectual content: all authors. Statistical analysis: H.J.Y. Obtained funding: H.J.Y., W.G.S. Administrative, technical, or material support: J.Y.A., J.H.K., W.G.S., Y.I.K., I.J.C. Study supervision: W.S.L., B.E.L.

ORCID

Hyo-Joon Yang <https://orcid.org/0000-0002-0265-672X>
Wan-Sik Lee <https://orcid.org/0000-0002-8021-6228>

Bong Eun Lee <https://orcid.org/0000-0003-2734-2134>
Ji Yong Ahn <https://orcid.org/0000-0002-0030-3744>
Jae-Young Jang <https://orcid.org/0000-0002-7930-1468>
Joo Hyun Lim <https://orcid.org/0000-0002-8437-096X>
Su Youn Nam <https://orcid.org/0000-0002-5568-7714>
Jie-Hyun Kim <https://orcid.org/0000-0002-9198-3326>
Byung-Hoon Min <https://orcid.org/0000-0001-8048-361X>
Moon Kyung Joo <https://orcid.org/0000-0001-6050-3695>
Jae Myung Park <https://orcid.org/0000-0002-1534-7467>
Woon Geon Shin <https://orcid.org/0000-0002-9851-5576>
Hang Lak Lee <https://orcid.org/0000-0002-2825-3216>
Tae-Geun Gweon <https://orcid.org/0000-0002-0884-7228>
Moo In Park <https://orcid.org/0000-0003-2071-6957>
Jeongmin Choi <https://orcid.org/0000-0001-6976-9887>
Chung Hyun Tae <https://orcid.org/0000-0002-0764-7793>
Young-Il Kim <https://orcid.org/0000-0002-2614-3419>
Il Ju Choi <https://orcid.org/0000-0002-8339-9824>

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