

## Endoscopic resection for undifferentiated early gastric cancer

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**Background and Objective:** Endoscopic resection (ER) has become an important curative option for early gastric cancer (EGC). However, the application of ER for undifferentiated EGC remains controversial. The aim of this study was to evaluate the clinicopathologic outcomes of ER performed in undifferentiated EGC with special reference to histopathologic subtypes to examine the feasibility of ER in undifferentiated EGC.

**Design and Setting:** Retrospective, single-center study.

**Patients:** From January 2001 to April 2007, 58 lesions in 58 patients with undifferentiated EGC (17 poorly differentiated adenocarcinoma; 41 signet-ring cell carcinoma) were treated by ER at Severance Hospital, Seoul, Korea.

**Main Outcome Measurements:** The therapeutic efficacy of ER was assessed according to en bloc resection, histologic complete resection (CR), lateral or vertical cut end-positive (including submucosal invasion), and recurrence rates in 3- to 65-month follow-up periods.

**Results:** The en bloc resection and CR rates were 84.5% and 67.2%, respectively. The en bloc and CR rates in poorly differentiated were 82.4% and 58.8%, whereas those in signet-ring cell were 85.4% and 70.7%, respectively. There were no significant differences between poorly differentiated and signet-ring cell. However, all (100%) of the histologic incomplete resections in poorly differentiated were vertical cut end-positive, whereas 83.3% of these resections in signet-ring cell were lateral cut end-positive. The recurrence rate was 5.1% in CR during the follow-up period.

**Limitations:** Retrospective, short-term follow-up period.

**Conclusions:** ER may be a feasible local treatment for undifferentiated EGC if CR can be achieved. However, a different approach is necessary between poorly differentiated and signet-ring cell before ER to prevent incomplete resection. (*Gastrointest Endosc* 2009;69:e1-e9.)

Endoscopic resection (ER) has become one of the main treatment options for early gastric cancer (EGC). In general, the application of ER has been limited to EGC with differentiated histopathologic features, without submucosal extension, that is smaller than 2 cm and not associated

*Abbreviations:* APC, argon plasma coagulation; CR, histologically complete resection; EGC, early gastric cancer; EMR-C, EMR with cap technique; EMR-P, EMR by snare after circumferential precutting; ER, endoscopic resection; ESD, endoscopic submucosal dissection; MSI, microsatellite instability; TND, tubule neck dysplasia.

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with ulceration.<sup>1,2</sup> However, Gotoda et al<sup>1</sup> demonstrated that undifferentiated EGC did not reveal the presence of lymph node metastasis in selected cases. These large-scale data suggested that ER may be a curative treatment option in selected cases of undifferentiated EGC, and ER has since been used in treatment of undifferentiated EGC.

Undifferentiated adenocarcinoma in the Japanese classification<sup>3</sup> lacks gland formation and includes poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma as in the World Health Organization classification. Signet-ring cell is a unique subtype of mucin-producing adenocarcinoma characterized by abundant intracellular mucin accumulation and a compressed nucleus displaced toward one extremity of the cell. Mucinous carcinoma has abundant extracellular mucin. Poorly differentiated and mucinous adenocarcinoma

have been associated with higher rates of lymph node metastasis than have other histologic types, whereas signet-ring cell in EGC exhibits a relatively lower rate of lymph node metastasis than does non-signet-ring cell.<sup>4-7</sup> Although biologic behavior may be different among histopathologic subtypes in undifferentiated EGC, various treatment strategies have been applied to undifferentiated EGC indiscriminately, especially ER. Therefore, we performed a retrospective analysis of the clinicopathologic outcomes of ER in undifferentiated EGC with special reference to histopathologic subtypes to examine the feasibility of ER in undifferentiated EGC.

## PATIENTS AND METHODS

### Study subjects

From January 2001 to April 2007, 58 lesions in 58 patients (26 men and 32 women, age range 26-81 years, mean age 55 years) with undifferentiated EGC (17 poorly differentiated, 41 signet-ring cell) were treated by ER at Severance Hospital, Yonsei University College of Medicine, Seoul, Korea. All lesions were limited to the mucosa estimated by EUS without concomitant ulcerations. The tumor size measured by EUS was  $\leq 20$  mm before ER.<sup>8</sup> The patients had no clinical, ultrasonographic, or CT evidence of lymph node or distant metastasis. The tumor locations were categorized by longitudinal axis and cross-sectional circumference of the stomach. That is, the longitudinal axis of the stomach was divided into 3 sections (upper third containing the fundus, cardia, and upper body; middle third containing the mid body, lower body, and angle; and lower third containing the antrum and pylorus) and the cross-sectional circumference into 4 sections (lesser curvature, posterior wall, greater curvature, and anterior wall). For this study, endoscopic findings of the tumors were classified by predominant type according to the classification system of the Japanese Research Society for Gastric Cancer. Furthermore, the protruded type and superficial elevated type were classified into the elevated type. The superficial flat type was classified into the flat type, and the superficial depressed type and excavated type were classified into the depressed type on the basis of a previous study.<sup>9</sup>

All the patients chose to receive ER for EGC and gave written informed consent after explanation of possible procedure-related risks, complications, and alternative surgical options.

To compare ER with surgery, the age-, sex-, and histopathologic-matched surgical control group within the same time period was used.

### Methods of ER

The ER methods included in this study consisted of conventional EMR (including the injection-and-cut technique and EMR with cap technique [EMR-C]), EMR by snare after

### Capsule Summary

#### What is already known on this topic

- Undifferentiated early gastric cancer is not generally considered an indication for endoscopic resection because it has an increased risk of lymph node metastasis.

#### What this study adds to our knowledge

- In a retrospective single-center study of 58 patients with undifferentiated early gastric cancer, endoscopic en bloc and complete resection rates in poorly differentiated lesions were 82.4% and 58.8%, whereas those in signet-ring cell cancers were 85.4% and 70.7%, respectively.

circumferential precutting with a knife (EMR-P), and endoscopic submucosal dissection (ESD).<sup>10-13</sup> Chromoscopy with indigo carmine (0.2% solution) was performed before ER when it was necessary to define the extent of the lesion more accurately.

In the injection and cut technique, diseased mucosa was resected with a snare loop after injection of the underlying submucosa has been completed.<sup>10</sup> EMR-C was performed with a transparent cap with a prelooped snare on its distal tip. The diseased mucosa was suctioned into the cap, and then a snare loop was closed to cut the mucosa.<sup>10</sup> In ESD, the target lesion was first carefully examined and marked with a coagulation current from the tip of a knife approximately 5 mm around the margin of the tumor.<sup>12</sup> The entire marked area was then elevated by submucosal injection.<sup>12</sup> Cutting along the outside of the margins was done with a knife while the lesion was still elevated. Dissection along the submucosal plane was then performed with an insulation-tipped knife.<sup>12</sup>

### Assessment of therapeutic efficacy

The therapeutic efficacy of ER was assessed according to the en bloc resection, histologic complete resection (CR), and recurrence rates in the follow-up period. The definition of CR in this study was (1) no cancer cell exposure to any cut end and the line between normal tissue and the portion denatured by burning, regardless of whether en bloc resection or multifragment resection had been performed and (2) intramucosal lesion, including lamina propria and muscularis mucosa.<sup>14</sup> Incomplete resection was defined as an end-positive lateral or vertical cut (including submucosal invasion).<sup>14</sup>

### Statistical analysis

The  $\chi^2$  test was used to test for associations among various categorical variables, and the *t* test was used for noncategorical variables. Multivariate logistic regression analysis was used to assess the relationship among the factors that affect complete resection.  $P < .05$  was considered to

**TABLE 1. Clinical characteristics of undifferentiated EGC**

Characteristics	No. of patients (%)			P value
	Total	Poorly differentiated	Signet-ring cell	
Location				
Upper third	1 (1.7)	0 (0)	1 (2.4)	.212
Mid third	33 (56.9)	7 (41.2)	26 (63.4)	
Lower third	24 (41.4)	10 (58.8)	14 (34.2)	
Anterior wall				
Great curvature	17 (29.3)	2 (11.7)	15 (36.6)	.137
Posterior wall	10 (17.2)	2 (11.7)	8 (19.5)	
Lesser curvature	16 (27.6)	6 (35.4)	10 (24.4)	
Gross type				
Depressed	15 (25.9)	5 (29.4)	10 (24.4)	.138
Flat	18 (31.0)	2 (11.8)	15 (36.6)	
Elevated	25 (43.1)	10 (58.8)	16 (39.0)	
Size (cm)*				
≤ 1	21 (36.2)	6 (35.3)	15 (36.6)	.495
> 1, ≤ 2	33 (56.9)	11 (64.7)	22 (53.7)	
> 2	4 (6.9)	0 (0)	4 (9.7)	
ER method				
Conventional EMR	17 (29.3)	5 (29.4)	12 (29.3)	.571
EMR-P	9 (15.5)	4 (23.5)	5 (12.2)	
ESD	32 (55.2)	8 (47.1)	24 (58.5)	

EGC, Early gastric cancer; ER, endoscopic resection; EMP-P, EMR by snare after circumferential precutting.

\*Dimension measured in endoscopically resected specimen.

indicate statistical significance. All analyses were performed with SPSS version 12.0 (SPSS, Chicago, Ill).

## RESULTS

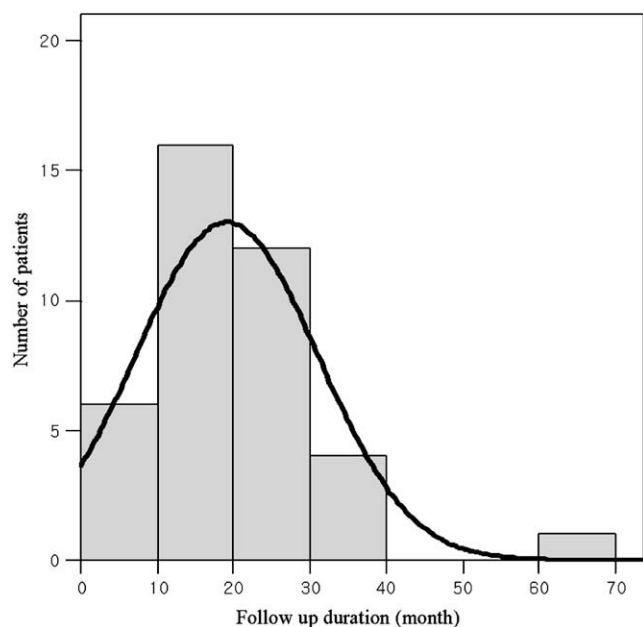
### Clinical and endoscopic characteristics of the lesions

A total of 58 lesions with undifferentiated EGC (17 [29.3%] poorly differentiated; 41 [70.7%] signet-ring cell) were treated by ER. The mean size of the lesions was  $13.3 \pm 6.5$  mm ( $\pm$ SD). The predominant endoscopic gross types of lesions were depressed (15/58, 25.9%), flat (18/58, 31.0%), and elevated (25/58, 43.1%) without concomitant ulcerations. The elevated type was more common in poorly differentiated histologic findings, whereas the non-elevated gross type (flat and depressed type) was more common in signet-ring cell findings, although the difference was not statistically significant. Chromoscopy was performed in 79.3% of the cases (10 cases [58.8%] in poorly differentiated, 36 cases [87.8%] in signet-ring

cell). The most commonly used ER technique was ESD (32/58: 55.2%). There were no significant differences between poorly differentiated and signet-ring cell according to the clinical characteristics of the lesions (Table 1).

### Therapeutic efficacies of ER

The overall en bloc resection and CR rates were 84.5% (49/58) and 67.2% (39/58), respectively. The en bloc and CR rates were 82.4% (14/17) and 58.8% (10/17) in poorly differentiated cases, whereas they were 85.4% (35/41) and 70.7% (29/41) in signet-ring cell cases, respectively. There were no statistically significant differences between poorly differentiated and signet-ring cell in the en bloc resection or CR rates ( $P > .05$ ). However, all cases of incomplete resection in poorly differentiated cases were vertical-cut end-positive, whereas 83.3% (10/12) in signet-ring cell cases were lateral-cut end-positive ( $P < .01$ ). The recurrence rate was 5.1% (2/39) in CR cases during the 3- to 65-month follow-up periods (median 16.0 months) (Fig. 1). The



**Figure 1.** The follow-up duration of completely resected patients ( $n = 39$ ). The mean ( $\pm$ SD) duration was 19.0 ( $\pm$  12.0 months).

therapeutic efficacies of ER are summarized in Table 2. There were no factors significantly related to CR (Table 3).

### Clinical outcomes after ER

The overall clinical outcomes after ER are summarized in Figure 2. The recurrent or incompletely resected lesions were successfully treated by salvage operation (11/21, 52.4%) or endoscopic retreatment (7/21, 33.3%). In operated cases (9/19, 47.4%) among the incomplete resections, 4 cases (4/9: 44.4%) had residual cancer cells in surgical specimens, and 1 case (1/9, 11.1%) had lymph node metastasis.

Figure 3 shows the clinical courses after ER with special reference to histopathologic subtypes. In the poorly differentiated group, none of the CR cases had local recurrence. Most of the incompletely resected cases (6/7, 85.7%) underwent surgery, and 1 case (1/6, 16.7%) showed the presence of lymph node metastasis histopathologically. In the signet-ring cell group, 2 cases (2/29, 6.9%) among the CR cases showed local recurrence. Recurrence was seen in the previous ER site in 1 case and in a location remote from the original ER site in the other. Seven cases (7/12, 58.3%) of incomplete resection were retreated endoscopically, such as with ER or argon plasma coagulation (APC), and 1 case (1/7, 14.3%) showed local recurrence. Three (25.0%) of the incompletely resected cases underwent surgery, and 2 cases had residual cancer cells in surgical specimens without lymph node metastasis. Table 4 summarizes the characteristics of the cases showing local recurrence.

### ESD versus surgery

There was no significant difference in the recurrence rate between the ESD-treated group ( $n = 32$ ) and the

**TABLE 2. Therapeutic efficacies for ER**

Therapeutic efficacies	No. of patients (%)			P value
	Total	Poorly differentiated	Signet ring cell	
En bloc resection	49 (84.5)	14 (82.4)	35 (85.4)	.773
Complete resection	39 (67.2)	10 (58.8)	29 (70.7)	.540
Incomplete resection	19 (32.8)	7 (41.2)	12 (29.3)	
Lateral cut end (+)	10 (52.6)	0 (0)	10 (83.3)	<.001
Vertical cut end (+)	9 (47.4)	7 (100)	2 (16.7)	
Recurrence, no.(%)	4 (6.9)	0 (0)	4 (9.8)	.310
In CR	2 (5.1)	0 (0)	2 (6.9)	
In incomplete resection	2 (10.5)	0 (0)	2 (16.7)	

ER, Endoscopic resection; CR, histologically complete resection.

age-, sex-, and histopathologic-matched surgical control group ( $n = 32$ , 8 poorly differentiated; 24 signet-ring cell) within the same time period in our institution (ESD-treated group, 3.1% [1/32] vs surgery group, 0.0%;  $P = 1.000$ ). The follow-up duration was not different between the 2 groups (ESD-treated group,  $17.1 \pm 9.1$ ; surgery group,  $17.5 \pm 6.2$ ;  $P = .848$ ).

### Complications

Bleeding was noted in 8 cases (8/58, 13.8%). Most bleeding occurred during the procedure (6 cases) or within 24 hours (2 cases). There were no cases of delayed bleeding. Most of the bleeding was minor and did not require a transfusion, and the bleeding was controlled endoscopically in all cases. More bleeding was seen in the ESD group than in the EMR cases (conventional EMR and EMR-P), but the difference was not statistically significant ( $P = .276$ ). Bleeding complications developed in 2 EMR cases and in 6 ESD cases.

There was 1 case of perforation (1.7%) in this study. The patient was successfully treated conservatively with endoscopic clipping without open surgery. There were no treatment-related or cancer-related deaths during the follow-up period.

### DISCUSSION

One critical factor in selecting ER for the treatment of EGC would be accurate evaluation of the presence of

**TABLE 3. Relationship between clinicopathologic factors and histologically complete resection**

Clinicopathologic factors	Complete resection, no. (%)	Incomplete resection, no. (%)	P value
Location	0 (0)	1 (5.3)	.317
Upper third			
Mid third	22 (56.4)	11 (57.9)	
Lower third	17 (43.6)	7 (36.8)	
Gross type	12 (30.8)	3 (15.8)	.070
Depressed			
Flat	14 (35.9)	4 (21.0)	
Elevated	13 (33.3)	12 (63.2)	
Size (cm)*	16 (41.0)	5 (26.3)	.847
≤1	21 (53.9)	12 (63.2)	
>1, ≤2			
>2	2 (5.1)	2 (10.5)	
Pathology	10 (25.6)	7 (36.8)	.225
Poorly differentiated	29 (74.4)	12 (63.2)	
Signet-ring cell			
Resection type	34 (87.2)	15 (78.9)	.833
En bloc			
Piecemeal	5 (12.8)	4 (21.1)	
ER method	11 (28.2)	6 (31.6)	.338
Conventional EMR			
EMR-P	5 (12.8)	4 (21.0)	
ESD	23 (59.0)	9 (47.4)	

ER, Endoscopic resection; EMR-P, EMR by snare after circumferential precutting; ESD, endoscopic submucosal dissection.

\*Dimension measured in endoscopically resected specimen.

These studies suggested that ER may be a curative option for undifferentiated EGC in selected cases. However, to our knowledge, there have been no previous studies regarding the outcomes of ER for undifferentiated EGC. Therefore, we evaluated the clinicopathologic outcomes of undifferentiated EGC after ER. Furthermore, signet-ring cell in EGC has been shown to harbor distinct biologic behaviors, different from other histologic entities in undifferentiated EGC.<sup>5,6,19,20</sup> Therefore, we compared the clinical outcomes of ER between poorly differentiated and signet-ring cell cases.

The overall CR rate was 66.1% in the current study, which was lower than that of differentiated EGC in other studies.<sup>13,21,22</sup> However, the recurrence rate in CR cases (5.1%) was comparable to those in other studies in differentiated EGC.<sup>13,21</sup> Furthermore, comparing the ER group (limited to the ESD method) with the age- and sex-matched surgery group retrospectively, the recurrence rate was not different between the 2 groups with a similar follow-up period. However, the results of comparison with surgery in undifferentiated EGC should be validated by long-term follow-up.

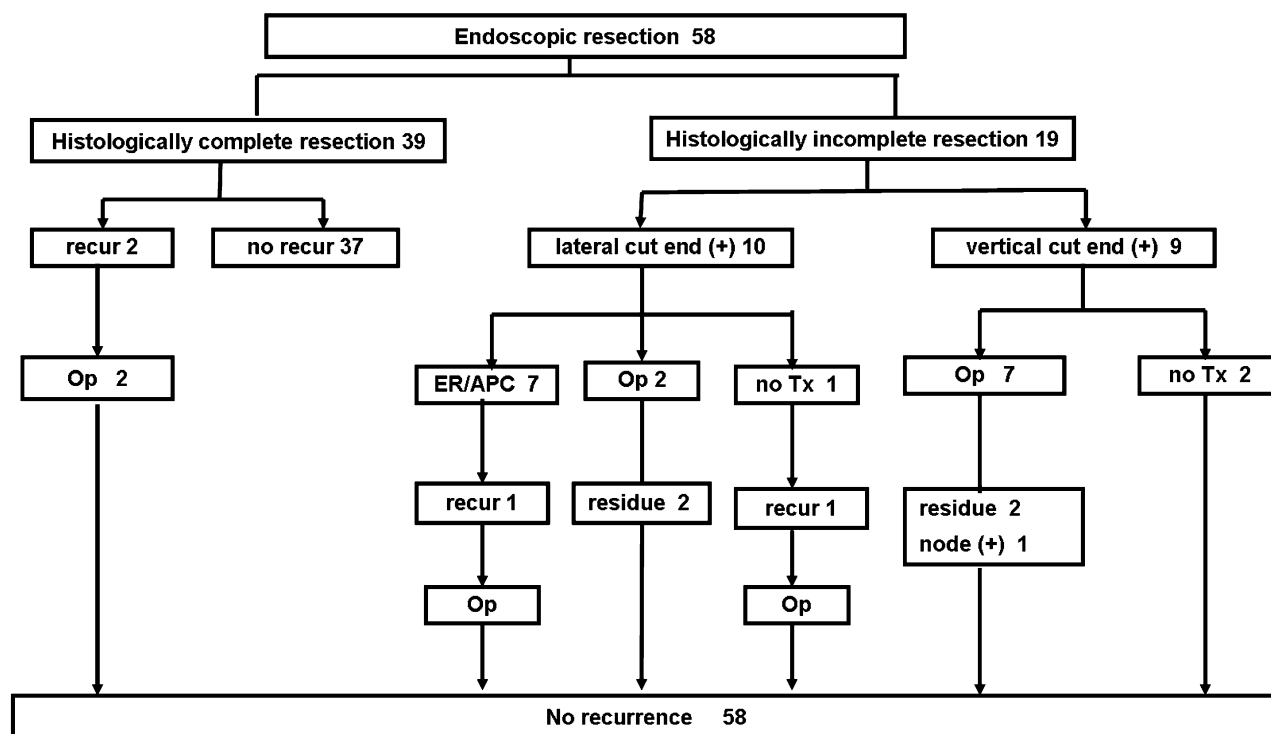
In the current study, the ESD method did not affect the complete resection rate compared with conventional EMR or EMR-P. This result might be derived from the size criteria of our study. The size of lesions in this study was limited to ≤20 mm by pretreatment staging. Therefore, the merit of ESD could not be shown by our data. Furthermore, resection type (en bloc or piecemeal resection) did not also affect the complete resection rate or recurrence rate in our study. However, piecemeal resection still has several problems, such as difficulty in exact evaluation of tumor margin and high possibility of local tumor recurrence.<sup>23,24</sup>

In this study, elevated gross morphologic features had a higher probability of incomplete resection than other gross types with borderline significance. It is difficult to explain the reasons in our study. The relationship between gross morphology and incomplete resection in undifferentiated adenocarcinoma should be demonstrated by large-scale data.

The results of the current study indicated that a different approach may be necessary for CR between poorly differentiated and signet-ring cell cases, although both are undifferentiated carcinomas. In our study, all cases (100%) of incomplete resection in poorly differentiated cases were vertical-cut end-positive (including submucosal invasion), whereas 83.3% in signet-ring cell cases were lateral-cut end-positive.

In the incomplete resection of poorly differentiated EGC, ER after pretreatment staging by EUS and CT was performed in all cases. Although pretreatment evaluation of the depth of invasion by EUS revealed that the lesions were confined to the mucosa, the final pathologic depth of invasion was the submucosa in these cases. These observations suggested that pretreatment evaluation for

lymph node metastasis.<sup>15</sup> Undifferentiated EGC is not generally considered an indication for ER because even intramucosal undifferentiated carcinoma may demonstrate a higher probability of lymph node metastasis (4.2%) than intramucosal differentiated histopathologic features (0.4%).<sup>1</sup> However, Gotoda et al<sup>1</sup> demonstrated that none of the cases of intramucosal undifferentiated EGC without ulceration less than 20 mm in size were associated with positive lymph nodes. These large-scale data suggest that ER can be used for curative treatment in selected cases of undifferentiated EGC. There have been several reports regarding the risk factors of lymph node metastasis in undifferentiated EGC.<sup>8,15-18</sup>



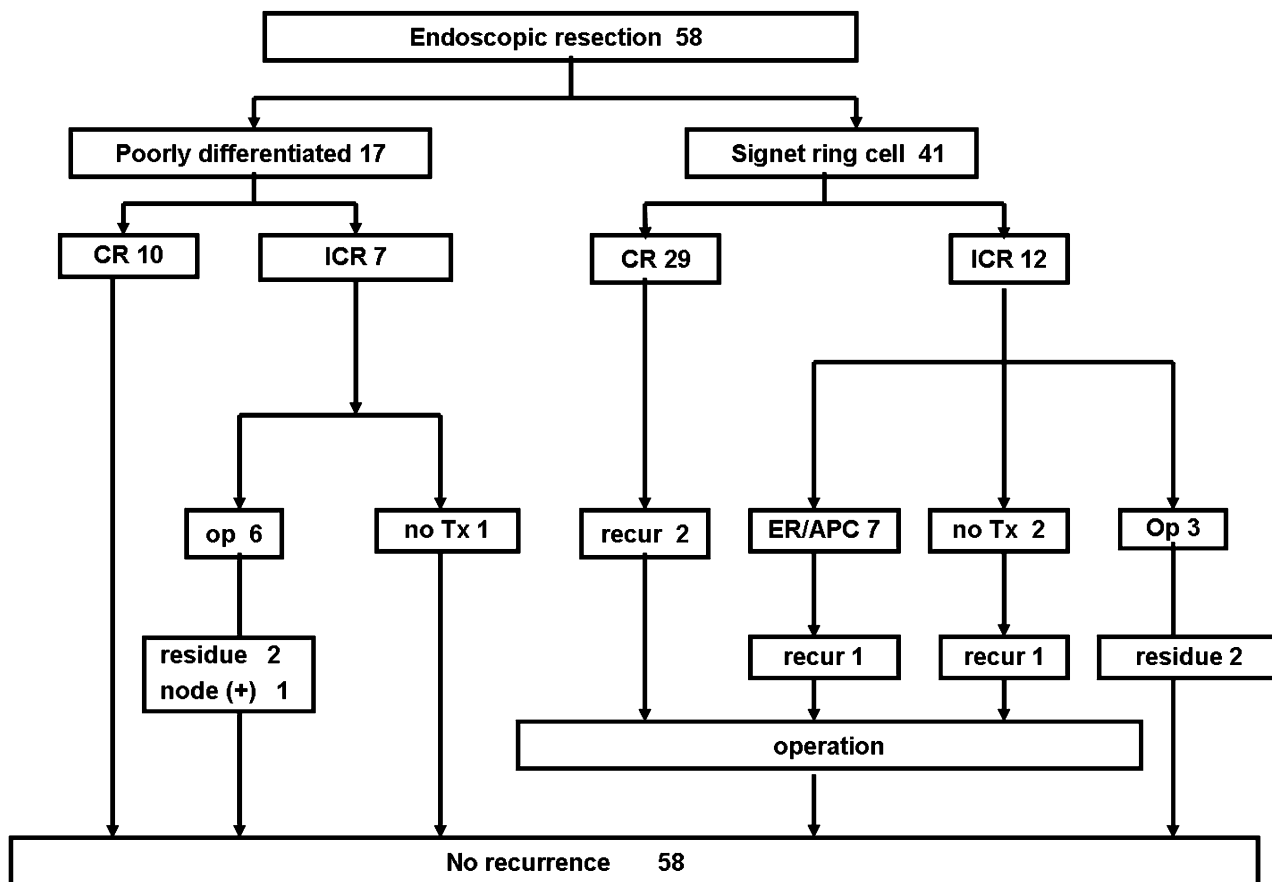
**Figure 2.** Overall clinical courses after ER for undifferentiated EGC. The number in the boxes indicates the number of cases.

the depth of invasion by EUS may have a high chance of underestimation in poorly differentiated EGC, consistent with our previous study in which we found that the histologic features of poorly differentiated cases were significantly associated with understaging the invasion depth in multivariate analysis.<sup>25</sup> Therefore, the possibility of underestimation by EUS should be considered before ER in poorly differentiated EGC. Strict EUS criteria for submucosal invasion should be established to avoid underestimating the T staging for CR in poorly differentiated EGC. Park et al<sup>18</sup> suggested that lesions confined to the mucosa or with minimal submucosal infiltration ( $\leq 500$  mm) could be considered for curative ER because of the very low risk of lymph node metastasis in poorly differentiated EGC. However, a poorly differentiated histologic diagnosis was significantly associated with underestimation of the depth of invasion in our previous study,<sup>25</sup> and therefore minimal submucosal infiltration by pretherapeutic T staging in poorly differentiated EGC cannot exclude the possibility of deeper submucosal infiltration. Thus, the criteria for ER in the study of Ha et al may be problematic for clinical application before ER. The decision to perform ER in EGC has been based on surgical data to evaluate the risk of lymph node metastasis. However, actual problems for ER cannot be considered only on the basis of surgical data. Thus, data of ER in undifferentiated EGC will be important for its application in undifferentiated EGC.

It was not possible to evaluate the accuracy of N staging by EUS because not all cases underwent surgery. However,

a metastatic lymph node was found after surgery in 1 poorly differentiated case among the 10 operated cases because the cutoff level was positive, although no metastatic lymph nodes were detected by pretherapeutic EUS. Previously, Hamada et al<sup>26</sup> reported that undifferentiated gastric cancer had a lower detection rate for metastatic lymph nodes by EUS than did differentiated gastric cancer. Although it is not clear that a poorly differentiated histologic diagnosis was also related to inaccurate N staging by EUS in our study, similar to the study of Hamada et al,<sup>26</sup> the accuracy of N staging by pretherapeutic EUS is important in poorly differentiated EGC for treatment success and cancer recurrence. ESD and laparoscopic lymph node dissection can provide accurate assessment of the potential presence of lymph node metastasis.<sup>27</sup>

Although almost all the incompletely resected cases among signet-ring cell cases were lateral cut end-positive, the gross circumferential margins of the ER were usually estimated about 5 to 10 mm from the lesion. Thus, a further method for estimation of gross margins in signet-ring cell cases is important for precise pretherapeutic staging. In the current study, chromoscopy was performed in most signet-ring cell cases (36/41, 87.8%). Thus, another technique for establishing the precise extent of the lesion is necessary, such as narrow-band imaging or autofluorescence and refluorescence imaging. Bhunchet and Shibata<sup>28</sup> proposed that fluorescein electronic endoscopy could detect and determine the extent of EGC that is not evident with routine endoscopy and also suggested



**Figure 3.** Clinical courses after ER in special reference to histopathologic subtypes of undifferentiated EGC. The number in the boxes indicates the number of cases. *ICR*, Histologically incomplete resection.

that rapid stump diagnosis on the basis of a pit pattern could prevent cancer remnants on the stumps just after ER. These 2 methods may represent a breakthrough for establishing the optimal margins in signet-ring cell EGC, although this should be validated in further studies.

Our results also suggest that endoscopic estimation of the gross margin in lesions may underestimate the true histopathologic margins in signet-ring cell EGC. There is no doubt that this possibility should be premised on the optimal technique of ER. This discrepancy between the endo-

scopic and pathologic margins of the lesion may be derived from the different origins of the signet-ring cell from other gastric adenocarcinomas.<sup>29</sup> Tubule neck dysplasia (TND) may be a precursor lesion of signet-ring cell. TND can spread upward toward the foveolar surface and possibly downward to the gastric glands.<sup>29</sup> Thus, the gastric mucosa of the signet-ring cell EGC may show a largely intact surface epithelium, despite cancer cells residing in the lamina propria. Therefore, grossly normal gastric mucosa surrounding the lesion in ER could contain cancer cells beneath the

**TABLE 4. Cases of local recurrence**

Sex	Age (y)	Initial location	Gross type	Size (mm)*	Patho	LVI	ER method /result	Recur site /duration (mo)	Re-Tx (stage)
F	45	Upper/ LC	Elevated	13	Signet	No	EMR/ en bloc, lateral (+)	ER site/4	Op (T2N0)
M	51	Mid/ GC	Flat	6	Signet	No	EMR/ en bloc, lateral (+)	Other site/24	OP (T1aN0)
M	56	Lower/ GC	Flat	2	Signet	No	EMR/ en bloc, CR	ER site/3	Op (T1aN0)
F	54	Lower/ AW	Depressed	20	Signet	No	ESD/ en bloc, CR	Other site/1	Op (T2N2)

LC, Lesser curvature; GC, greater curvature; AW, anterior wall; LVI, lymphovascular invasion; Op, operation; ER, endoscopic resection; CR; histologically complete resection; ESD, endoscopic submucosal dissection; Patho, pathology; Re-Tx, retreatment.

\*Dimension measured in endoscopically resected specimen.

epithelium. Further studies regarding methods of judging the optimal margins for ER in signet-ring cell EGC are necessary to achieve good rates of CR.

In the current study, half the cases of local recurrence developed in different locations from the previous ER site, although the number of cases was small (2 cases). One recurrence was found 1 month after ER. This case was regarded as a recurrence despite the short-term follow-up because the recurrent lesion was not located in a site remote from the previous ER lesion. The pathologic type of all cases of recurrence in new sites was signet-ring cell, which may be one of the defining characteristics of this type of carcinoma. A previous study suggested that microsatellite instability (MSI) high is associated with the multiplicity of gastric cancer.<sup>30</sup> However, signet-ring cell is a representative MSI-negative cell type. Therefore, studies to determine another marker for multiplicity in signet-ring cell would be helpful in deciding on a treatment strategy in signet-ring cell EGC, such as ER or surgical resection.

The cases of recurrence also suggest the importance of a follow-up protocol for undifferentiated EGC after ER. All cases of local recurrence were signet-ring cell, and in half these cases recurrence occurred in a location remote from the original site of ER. Thus, the evaluation of local recurrence may be especially important in follow-up protocols for signet-ring cell by shortening the follow-up interval for endoscopy or increasing the number of biopsies at the previous ER site.

In contrast, there was no local recurrence in poorly differentiated cases during the follow-up period, and long-term follow-up was necessary. This observation suggests that the evaluation for distant metastasis (eg, lymph node metastasis) is more important in poorly differentiated cases. It may be important to evaluate lymph node metastasis in poorly differentiated cases during follow-up protocols, such as for routine follow-up in standard EUS. This follow-up strategy is also important because the currently available diagnostic tools for recognizing lymph node metastases are inadequate.<sup>31</sup>

Strategies for additional treatment for incompletely resected lesions are not well established. However, when a vertical-cut end is positive, radical surgery for additional treatment is mandatory. In the current study, the vertical-cut end-positive lesions were treated by salvage operation, except in 2 cases because the patients refused further treatment. The lateral-cut end-positive lesions were treated by salvage operation or endoscopic retreatment, such as ER or APC. In the operated cases, among those with incomplete resection, 44.4% had residual cancer cells in surgical specimens, and 11.1% were positive for lymph node metastasis. Among the cases with a positive vertical-cut end, 28.6% had residual cancer cells in surgical specimens, and 14.3% were positive for lymph node metastasis. Although, among the cases with a positive lateral-cut end, 100% had residual cancer cells in surgical specimens, and

0% had lymph node metastasis. However, 14.3% of cases with a positive lateral-cut end showed recurrence after local additional treatment during follow-up. Thus, surgical resection may be preferable rather than local treatment for additional management in incompletely resected undifferentiated EGC. However, large-scale data are needed for the proposal of proper treatment strategies after incomplete resection of undifferentiated EGC.

In conclusion, ER may be a feasible local treatment for undifferentiated EGC if CR can be achieved. However, a different approach is necessary between poorly differentiated and signet-ring cell before ER to prevent incomplete resection. However, our study has several limitations such as being retrospective, having limited follow-up, and containing different ER techniques. Thus, our results should be validated by prospectively well-designed, long-term follow-up studies. Furthermore, the different clinical outcomes after ER between poorly differentiated and signet-ring cell cases should be validated by large-scale data, respectively.

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