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Performance of endoscopic submucosal dissection for undifferentiated early gastric cancer: a multicenter retrospective cohort

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Key words

Endoscopy Upper GI Tract, Precancerous conditions & cancerous lesions (displasia and cancer) stomach, Endoscopy Upper GI Tract, Endoscopic resection (ESD, EMRc, ...), Endoscopy Upper GI Tract

received 19.1.2023
accepted after revision 31.5.2023
accepted manuscript online 2.6.2023

Bibliography

Endosc Int Open 2023; 11: E673–E678
DOI 10.1055/a-2105-1934
ISSN 2364-3722

Georg Thieme Verlag KG, Rüdigerstraße 14, 70469 Stuttgart, Germany

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Additional material is available at https://doi.org/10.1055/a-2105-1934

ABSTRACT

Background and study aims Undifferentiated early gastric cancer (UD-EGC) represents an extended indication for endoscopic submucosal dissection (ESD) based on the existing guidelines. This study evaluated the prevalence of UD-EGC recurrence after ESD, and potentially implicated risk factors.

Patients and methods Data from 17 centers were collected retrospectively including demographics, endoscopic and pathological findings, and follow-up data from UD-EGC cases treated by ESD. Patients with incomplete resection or advanced disease were excluded. Descriptive statistics quantified variables and calculated the incidence of recurrence. Chi-square test was applied to assess any link between independent variables and relapse; significantly associated variables were inserted to a multivariable regression model.

Results Seventy-one patients were eligible, with 2:1 female to male ratio and age of 65.8 ± 11.8 years. Mean lesion size was 33.5 ± 18.8 mm and the most frequent histological subtype was signet ring-cells UGC (2:1). Patients were followed-up every 5.6 ± 3.7 months with a mean surveillance period of 29.3 ± 15.3 months until data collection. Four patients (5.6%) developed local recurrence 8.8 ± 6.5 months post-ESD, with no lymph node or distal metastases been reported. Lesion size was not associated with recurrence (P = 0.32), in contrast to lymphovascular and perineural invasion which were independently associated with local recurrence (P = 0.006 and P < 0.001, respectively).

Conclusions ESD could be considered as the initial step to manage UD-EGC, providing at least an "entire-lesion" biopsy to guide therapeutic strategy. When histology confirms absence of lymphovascular and perineural invasion, this modality could be therapeutic, providing low recurrence rates.

Introduction

Undifferentiated early gastric cancer (UD-EGC) represents a distinct malignant entity of stomach, not significantly associated with *Helicobacter pylori* infection, consisting of two pathological subtypes: poorly differentiated adenocarcinoma and signet-ring cell carcinoma [1] Therapeutic approach and management are challenging for clinicians and endoscopists, as UD-EGC is characterized by more aggressive behavior even in early stages, compared with differentiated adenocarcinomas. Current data support that increased diameter, superficial ulceration, deep invasion, and lymphovascular invasion are associated with high recurrence and lymph node metastases rates, thus radical resection is required [1, 2, 3, 4, 5].

Endoscopic submucosal dissection (ESD) has been established as a treatment mainstay for EGC. ESD is indicated to treat EGC for, among other things, histological subtype, with UD-EGC considered an expanded indication according to the European Society of Gastrointestinal Endoscopy (ESGE). More specifically, ESGE recommends considering endoscopic management only if the UD-EGC is < 20 mm in diameter, without ulceration, and it can be curative only for mucosal cancer if no lymphovascular invasion is present [6]. The Japanese Gastroenterological Endoscopy Society suggests that ESD is absolutely indicated for non-ulcerated UD-EGC ≤ 20 because the risk of lymph node metastasis in the absence of ulceration and lymphovascular invasion is 2.8% [95% confidence interval (CI): 1.0%-6.0%] [7].However, when the cumulative size of undifferentiated components exceeds 20 mm on histology, resection is not considered curative [7]. Although lesion size is used as a factor to guide the decision to proceed or not with ESD, these recommendations are based on low-moderate quality of data.

This multicenter study aimed to answer this question by evaluating recurrence rates for UD-EGC after ESD, with respect to established and potential risk factors to guide patient selection for endoscopic management.

Patients and methods

Study design

Seventeen centers around the globe participated in this retrospective multicenter study by providing their records from 2008 to 2022. The study was structured based on the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines (Supplementary Table 1) [8]. A predefined protocol, which conformed to the ethical guidelines of the last revision of Declaration of Helsinki and complied with Good Clinical Practice Guidelines [9, 10], was centrally approved by the Scientific Committee of the main coordinating center, and was the reference for all involved centers. Patient anonymity was ensured and the data received were de-identified.

Patients

Adult patients (≥ 18 years old), ineligible or unwilling to undergo surgery, who underwent ESD for UD-EGC, with complete en-block excision, defined as clear margins in the pathology specimen, were enrolled in this study. Exclusion criteria included patients who underwent surgery after UD-EGC diagnosis, those with metastatic disease, synchronous or previous malignancy, incomplete resection (positive vertical or lateral margins in histology), indefinite or missing data and absent follow up.

Data collection

Cases fulfilling the eligibility criteria were recruited. The eligibility of the included cases was evaluated by AP. The following variables were retrieved: 1) demographics (age at diagnosis, sex, race); 2) endoscopic features of the lesion (location, size, superficial morphology, and electronic chromoendoscopy findings of demarcation line, corkscrew vessels, absent microsurface pattern in magnification); 3) duration of ESD; 4) complications (intraprocedural bleeding, perforation); 5) histologic findings (size of specimen, UD-EGC subtype, and submucosal, lym-

phovascular, perineural or vascular invasion); 6) presence of *H. Pylori* infection, defined as positive gastric histology, rapid-urease, C13 urea breath or stool antigen test; 7) duration and frequency of follow up; and 8) need for adjuvant chemotherapy after ESD recurrence-metastasis.

An Excel file (Microsoft Excel for Mac 2019, Microsoft Corporation, Redmond, Washington, United States) with predetermined available variable values was created and shared with the involved centers. All data were stored on a secure server.

Outcomes

The primary endpoint of the current study was the recurrence rate for UD-EGC after initial treatment with ESD. Secondary outcomes included assessment of potential risk factors associated with recurrence, determination of the time of recurrence, and assessment of ESD-related adverse events.

Statistical analysis

Data analysis was performed using the Statistical Package for Social Science Software for Windows (IBM SPSS Statistics, Version 28.0. Armonk, New York, United States: IBM Corp). Continuous variables are presented as mean (± standard deviation) and categorical variables are shown as percentages. Recurrence after ESD over time was calculated according to the Kaplan-Meier method. The log-rank test was be performed for analysis. Univariable models were used to investigate individual associations between independent variables and recurrence, while in the multivariable Cox regression, all variables were inserted to assess their relationship with recurrence over time. Hazard ratios (HRs) and their 95% CIs were derived from each variable coefficient in the final model. $P \leq 0.05$ (two tailed) was considered statistically significant.

Results

After applying the inclusion/exclusion criteria, 71 patients were eligible to our analysis (Supplementary Fig. 1). ▶ **Table 1** summarizes the main characteristics of our sample. The female to

▶ **Table 1** Main characteristics of the UD-EGC cohort.

Variable	N (or mean ± SD)	%
Gender		
Female	44	62
Male	27	38
Age	65.8 (±11.8)	
Race		
White	40	56.3
Asian	17	23.9
Hispanic	12	16.9
African	2	2.8
Tumor size (endoscopy, mm)	33.5 (±18.8)	
Tumor size (histology, mm)	39.6 (±22.0)	
Tumor location		
Cardia	7	9.9
Fundus	8	11.3
Corpus	26	36.6
Antrum	15	21.1
Incisura	15	21.1
Surface (white light)		
Ulcerated	3	4.3
Scar deformity	6	8.6
Erythema	8	11.4
Discoloration	10	14.3
Nodularity	19	27.1
Depression	24	34.3
Chromoendoscopy		
Demarcation line (yes)	42	59.2
Corkscrew vessels (yes)	23	32.4
Absent microsurface pattern (yes)	36	50.7
H.pylori infection		
Previous	19	26.8
Active	5	7
Indicative biopsy before ESD (yes)	52	73.2
Histological subtype		
Poorly differentiated	25	35.2
Signet-ring cell	46	64.8
Submucosal Invasion (yes)	16	22.5
Lymphovascular invasion (yes)	7	9.9
Perineural invasion (yes)	3	4.8
Vascular invasion (yes)	4	5.6
Depth of invasion		
Mucosa	55	77.4
sm1	7	9.9
> sm1	9	12.7
ESD duration (mins)	113.1 (±74.9)	
Complications		
Intraprocedural bleeding	9	12.7
Perforation	5	7
Follow-up intervals (months)	5.6 (±3.7)	
Follow-up duration (months)	29.3 (±15.3)	

UD-EGC, undifferentiated early gastric cancer; ESD, endoscopic submucosal dissection.

▶ **Table 2** Associations between potential risk factors and UD-EGC recurrence.

		Univariate analysis (Chi-square)		Multivariate analysis (Cox regression model)	
Variable	**Cases of recurrence**	**Chi-square value**	***P* value**	**Hazard ratio**	***P* value**
Size (mm)		28.8	0.319	1.04	0.26
Size (> 20 mm)	3	0.001	0.971	0.07	0.28
Subtype (poorly differentiated)	3	2.9	0.086	0.34	0.40
Submucosal invasion	2	2.8	0.92	2.49	0.64
Lymphovascular invasion	2	7.7	0.006	4.88	0.44
Vascular invasion	1	2.9	0.084	3.89	0.43
Perineural invasion	2	19.3	< 0.001	24.6	0.06

UD-EGC, undifferentiated early gastric cancer.

male ratio was 2:1 and the mean age was 65.8 ± 11.8 years. The majority of patients were White (40; 56.3%), followed by Asians (17; 23.9%), and Hispanics (12; 16.9%), whereas only two Africans were included.

The most frequent site of UD-EGC in this cohort was the gastric corpus 36.6% (26/71), followed by the antrum and incisura, each 42.2%. Eight lesions were resected from fundus and seven from the cardia. The mean size of the tumors, as assessed by the endoscopists, was 33.5 ± 18.8 mm, with 70.4% > 20 mm. Considering mucosal features under white light, 34.3% had a depression, whereas about one-fourth had a nodular surface. The main chromoendoscopic descriptions included a demarcation line between the lesion and the surrounding mucosa in 59.2%, corkscrew vessels in 32.4%, and absent microsurface pattern after using magnification in 50.7%. Interestingly, in 73.2% of cases, the endoscopists had a histology result from UD-EGC before the procedure.

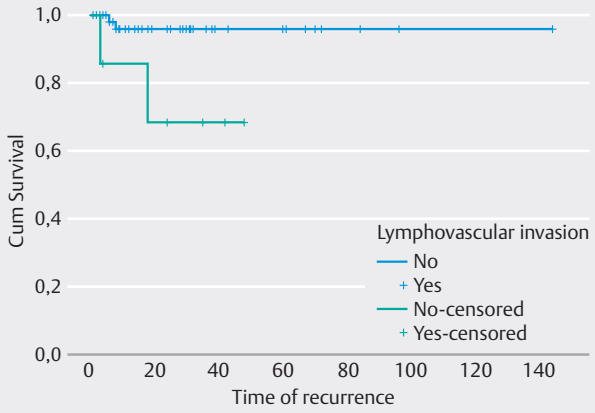
The mean ESD duration was 113.2 ± 74.9 minutes and in 19.7% of procedures a complication was recorded: 12.7% (9/71) intraprocedural bleeding and 7.0% (5/71) perforation. Complications were associated with male sex (P = 0.024) and the lesion location (cardia or fundus, P = 0.024). The mean size of the resected specimens, measured by the pathologists, was 39.6 ± 22.0 mm. The vast majority of patients (65.7%) had a negative work-up for *H. pylori* infection, 26.8% had a history of eradication, and five patients had an active infection. Regarding UD-EGC subtypes, the ratio of signet-ring cell type to poorly differentiated cancer was almost 2:1. Sixteen tumors (22.5%) invaded the submucosa, and the level of invasion was at least sm1 in nine of them (12.7%). Vascular, lymphovascular, and perineural invasions were detected in 5.6%, 9.9%, and 4.8%, respectively.

After resection, 10 patients (14.9%) received adjuvant chemotherapy, based on their preference and fitness for surgery, after adopting an individualized approach. The mean follow-up duration was 29.3 ± 15.3 months (median: 20 months) and patients were followed up every 5.6 ± 3.7 months. Local recurrence was recorded in four cases (5.6%), 8.8 ± 6.5 months post-ESD, with no lymph node or distal metastasis been reported. Three of the recurrencies were detected at the site of the previous resection and one was a metachronous UD-EGC. Lesion size (42 ± 17.9 mm) was not associated with recurrence (P = 0.32), even when a diameter of 20 mm was considered as a cut-off size (P = 0.97). Similarly, chi-square test investigating the association between depth of invasion and recurrence did not reveal any statistical significance (P = 0.14), although two of the lesions invaded the submucosa. In contrast, lymphovascular and perineural invasion were independently associated with recurrence (P = 0.006 and P < 0.001, respectively) and coexisted in two of the four recurrent lesions, whereas vascular invasion did not reach significance (P = 0.084) (▶ **Table 2**). Based on the presence of lymphovascular and perineural invasion, a Kaplan-Meier curve revealed a significantly earlier recurrence with regard to both variables. Patients with lymphovascular invasion developed recurrence < 20 months after resection (P = 0.012) (▶ **Fig. 1**), as did those with perineural invasion (P< 0.001) (▶ **Fig. 2**). Multivariable Cox regression did not reveal any statistically significant association between included variables and recurrence.

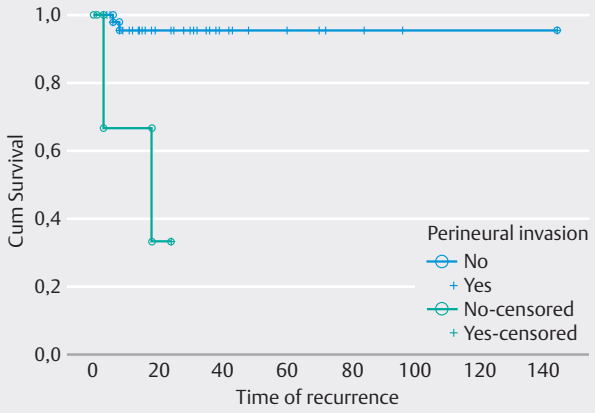
Discussion

This multicenter study, not limited to a specific subpopulation or region, is the first that indicates that the size of UD-EGC is not associated with recurrence after ESD, thus supporting the approach that endoscopic assessment of UD-EGC cannot predict the outcomes of endoscopic resection, and further management should be based on histology. More specifically, the mean size of the resected tumors was 33.5 ± 18.8 mm, greater than the threshold of 20 mm suggested by ESGE. Nevertheless, the recurrence rate in our cohort was 5.6%, similar to other studies, and it was not associated with lesion diameter [11]. In contrast, pathological confirmation of lymphovascular or perineural invasion was strongly associated with recurrence.

To date, multiple variables have been assessed to provide a reliable predictor of UD-EGC recurrence after endoscopic treat-



▶ **Fig. 1** Kaplan-Meier curve presenting the time of recurrence of UD-EGC with regard to lymphovascular invasion.



▶ **Fig. 2** Kaplan-Meier curve presenting the time of recurrence of UD-EGC with regard to perineural invasion.

ment. Among them, size and lymphovascular invasion have been the most commonly recorded [6]. The impact of size on recurrence was not significant in our study ($P = 0.32$), although lymphovascular ($P = 0.006$) and perineural invasion were significant ($P < 0.001$). Perineural invasion has not been investigated as a predictive factor for recurrence in ESD studies for UD-EGC. Nevertheless, it is known to represent an independent risk factor for recurrence, even after surgical resection ($P = 0.011$) and is associated with worse survival (HR = 1.69, 95%CI:1.38–2.06) [12, 13, 14]. The use of nonsteroidal anti-inflammatory drugs also has been incriminated in EGC recurrence, albeit in an isolated and mixed cohort of EGC [15]. Yang et al [16] developed a predictive model based on retrospective data, including tumor site in the stomach, thus suggesting that the more proximal the tumor is the higher possibility of non-curative ESD (odds ratio [OR] 1.45; 95% CI: 1.03–2.04). They included this variable, and the size of the resected tumor (diameter of 10–20 mm [OR = 2.40; 95% CI: 1.54–3.73], and 20 mm [OR 14.00; 95% CI 6.81–28.77]) into a model to predict curative ESD with an area under the curve (AUC): 0.720 (95% CI 0.673–0.766). Nevertheless, this model was targeted to endoscopic prediction of curative resection, with regard to the current definition of cure, and does not predict recurrence [6]. In our study, most recurrencies were diagnosed in patients with a primary lesion located in the incisura, although that did not reach significance compared to other sites ($P = 0.33$).

As previously mentioned, the gold standard modality for treating UD-EGC is surgery. Most studies have assessed the efficacy of ESD in the spectrum of expanded indications with regard to UD-EGC [17, 18, 19]. Huh et al [18] meta-analyzed five Korean studies comparing ESD with surgery and found a higher rate of recurrence after ESD, although cases with incomplete primary resection were included (44.4% had complete resection beyond the existing criteria), thus impacting the result. Our study excluded cases with remnant malignant lesion or unclear margins, as that was an independent risk factor for recurrence. Li et al [11], in a retrospective study, compared ESD with surgery for UD-EGC in lesions > 20 mm. Both choices provided similar survival rates, although ESD was associated with increased recurrence compared to surgery [HR = 5.2 (95% CI: 1.0–25.8, $P = 0.045$)], thus warranting long-term follow-up. Similarly, a recent meta-analysis compared surgery with curative ESD, defined as en bloc, R0 resection, ≤ 20 mm, intramucosal cancer, and absence of lymphovascular invasion, and both approaches provided comparable overall survival, although ESD was associated with shorter disease-free survival and increased recurrence [19].

All of the recurrencies in present study were recorded during the first 18 months after resection. However, the duration of follow-up varied among cases, thereby hindering a clear estimation of the long-term outcomes in our cohort. A larger cohort of 198 patients showed that the mean time of recurrence was 4.5 years (range: 3.1–5.4) after ESD, although it included cases of metachronous cancer [15]. To date, there is no standardized follow-up interval for these patients, and the approach varies among centers. Endoscopy every 3 to 6 months for the first year, followed by biannual reassessment for 2 to 3 years and then annual follow up, is a general pattern [15, 20]. Based on our results, this practice seems efficient for diagnosing early recurrence, although given the potential for late metachronous lesions, extension of biannual follow up to 5 years post-ESD seems reasonable. Nevertheless, the necessity for long-term and frequent endoscopies and the increased worry about recurrence should be taken into account before selecting ESD, as it could impact patient quality of life (QoL) and the health care system. On the other hand, those treated with surgery seem to experience more impaired QoL, due to fatigue, nausea/vomiting, loss of appetite, diarrhea, pain, reflux, eating restrictions, anxiety, taste impairment, and poor body image [21].

This study has some limitations. First, the retrospective single-arm design limits the ability to generalize the results. However, prospective and comparative studies in this field are difficult to organize, especially in western countries, where the guidelines for UD-EGC management suggest ESD as a potential choice in lesions < 20 mm. Because the centers that were included comply with these recommendations, our sample size

was also limited, which may have affected the resulted association of some variables with the recurrence, at least considering the multivariate regression analysis. The absence of a predefined protocol to describe the lesions resulted in variability in endoscopic reports, mainly histology descriptions. Further pathological findings, for example, blurring muscularis mucosae or cumulative size of undifferentiated foci inside the entire lesion or inside a mixed-type gastric cancer, could also have been assessed as predictors of recurrence if the data were adequate. Finally, the follow-up approach was not uniform between centers, with regard to duration and the intervals, thus providing limited value for the long-term therapeutic results of ESD.

Conclusions

To conclude, ESD for UD-EGC, even "non-curative" based on the current recommendations, seems to have a role in the management algorithm, at least as a diagnostic tool for whole-lesion biopsy in marginal cases. In this study, lymphovascular and perineural invasion, but not lesion size, were associated with recurrence, thus implying a potential benefit even for patients with larger lesions. This observation, however, needs further evaluation in larger studies with longer follow-up, assessing more variables.

Conflict of Interest

The authors declare that they have no conflict of interest.

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