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# Long-term clinical outcomes of endoscopic vs. surgical resection for early gastric cancer with undifferentiated histology

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## Abstract

**Background** The efficacy of endoscopic submucosal dissection (ESD) for undifferentiated early gastric cancer (UD EGC) is controversial due to the relatively high risk of lymph node metastasis. We compared long-term clinical outcomes of UD EGC between ESD and surgical resection groups.

**Methods** We retrospectively reviewed the medical records of patients with UD EGC treated by either ESD or surgical resection between January 2007 and December 2014. Long-term clinical outcomes were compared between the two groups in terms of survival.

**Results** A total of 1147 patients were enrolled with median follow-up duration of 59.1 months. ESD and surgical resections were performed in 126 and 1021 patients respectively. Additional surgery was performed in 22 patients after ESD. There were no significant differences in overall survival [total, $p = 0.641$; propensity score matching (PSM), $p = 0.330$; expanded criteria, $p = 0.512$]. Although the disease-free survival rate was lower in ESD group because of the higher rate of metachronous cancer development (total, $p < 0.001$; PSM, $p = 0.001$), the difference was not significant in the group within expanded criteria ($p = 0.071$).

**Conclusions** ESD could be a comparable treatment option with surgical resection for UD EGC within expanded criteria in terms of long-term survival. It is mandatory to establish a meticulous indication of ESD for UD EGC considering the risk of lymph node metastasis.

**Keywords** Endoscopic submucosal dissection · Undifferentiated · Early gastric cancer · Survival rate

Nowadays, endoscopic submucosal dissection (ESD) has been established as one of the primary treatment modalities for early gastric cancer (EGC) replacing the role of conventional surgery [1–3]. Thanks to the widespread use of screening endoscopy and its technical advances, the proportion of early stage of gastric cancer which can be a candidate for ESD has increased in Korea [4]. With growing interest

for quality of life and technical advances of endoscopic treatment, ESD has widened its indication of endoscopic resection of EGC. Conventionally, endoscopic resection for EGC was indicated only for differentiated intramucosal cancer within 2 cm of diameter without ulcer to avoid risk of lymph node metastasis. In 2000, expanded criteria of ESD for EGC were introduced by large-scale retrospective review of surgical cases: (1) differentiated intramucosal cancer larger than 2 cm, without ulcer, (2) differentiated intramucosal cancer no larger than 3 cm, with/without ulcer, (3) differentiated cancer no larger than 3 cm, with $\leq 500$ μm depth of submucosal invasion, or (4) undifferentiated intramucosal cancer $\leq 2$ cm without ulceration [5]. Subsequent studies have reported excellent long-term outcomes of ESD in the expanded criteria. One study showed equivalent complete resection and 5-year survival rates between ESD and surgery in cases within expanded criteria [2]. Another study revealed no difference in the survival rate between ESD and surgery in EGC with submucosal invasion [6].

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Although the number of cases with undifferentiated histology in the retrospective study was too small to confirm the negligible risk of lymph node metastasis in the expanded criteria [5], a follow-up study suggested that undifferentiated intramucosal cancer ≤ 2 cm showed no risk of lymph node metastasis, [7]. Nonetheless, several studies have reported lymph node metastasis in ESD cases of undifferentiated EGC (UD EGC) < 2 cm [8, 9], and there are still debates on whether UD EGC could be safely treated with ESD without risk of lymph node metastasis or not. Therefore, this study was designed to compare long-term outcome between ESD and surgery in UD EGC, particularly within expanded criteria, ultimately to reappraise validity of ESD in UD EGC.

## Patients and methods

### Patients

We retrospectively analyzed the patients who underwent either ESD or surgical resection for UD EGC in Seoul National University Hospital in Korea between January 2007 and December 2014. Inclusion criteria were as follows: patients older than 20 years; early gastric cancer; undifferentiated histology including poorly differentiated adenocarcinoma, signet ring cell carcinoma (poorly cohesive carcinoma), or mucinous adenocarcinoma; no evidence of lymph node metastasis or distant metastasis in preoperative computed tomography (CT) and endoscopic ultrasonography (EUS). Exclusion criteria were as follows: patients who had been treated for gastric cancer previously; patients who had other cancers within 5 years before or after diagnosis of EGC; patients whose survival data were unable to be obtained.

This study was approved by the Institutional Review Board of the Seoul National University Hospital (IRB No. 1607-013-773), complying with the declaration of Helsinki. Patient consent was not obtained due to the retrospective nature of this research.

### ESD and surgery

Treatment modality was determined according to the findings of conventional endoscopy, EUS, and abdominal CT, and pathology of biopsy specimen. ESD was indicated when pre-procedural clinical diagnosis was well or moderately differentiated adenocarcinoma confined to mucosa, with ≤ 2 cm of size by endoscopic measurement, without evidence of distant or lymph node metastasis on abdominal CT or EUS. However, some patients who were clinically over the above criteria also underwent ESD due to extremely old age, poor performance or high co-morbidity. Among ESD patients, those who were found to have undifferentiated histology in

the final diagnosis were included in the ESD group of this study. Also, those who had surgery for EGC and found to have undifferentiated histology were included in the surgery group. Those who showed the histology beyond expanded criteria or incomplete resection in final pathology after ESD were recommended to receive additional surgical resection. Such cases were included in ESD group for the analysis of baseline characteristics, and in surgery group for survival or recurrence. However, those cases were not included in the survival or recurrence analysis after propensity score matching (PSM). Patients underwent endoscopy at 6, 12, and 24 months after ESD or surgery, and then annually.

### Histopathology

The specimens were evaluated with sections of 2 mm and 4 mm thickness after ESD and surgical resection respectively, under staining with hematoxylin and eosin. Poorly differentiated adenocarcinoma, signet ring cell carcinoma (poorly cohesive carcinoma), and mucinous adenocarcinoma were classified as undifferentiated histology. When more than one type of histology co-exists, the predominant type was chosen. Stage was evaluated with AJCC 7th TNM staging system.

### Definitions

Expanded criteria in UD EGC were as follows: intramucosal tumor, histologically UD EGC without ulcer, and size ≤ 2 cm. Tumor location was categorized into upper, middle, and lower third. Metachronous cancer was defined as a newly developed cancer in previously uninvolved area in the stomach more than 1 year after ESD/surgery. Synchronous cancer was defined as a newly detected cancer other than the primary one in the stomach within 1 year after ESD/surgery or simultaneously at the primary resection. Local recurrence was defined as a newly developed cancer at the site of primary resection, such as at ESD scar or surgical anastomosis site. Recurrence was defined to include local recurrence, metachronous cancer, and distant metastasis. Synchronous cancer was not considered as recurrence. Complete resection was defined as resection without margin involvement of tumor, lymphovascular invasion, or perineural invasion.

Overall survival (OS) was defined as the period from the date of ESD/surgery until death. Mortality data by 29th February 2018 were obtained from the Korean Ministry of Public Administration and Security. Disease-specific survival (DSS) was defined as the period between the date of ESD/surgery and the date of gastric cancer-related death. Disease-free survival (DFS) was defined as the period from the date of ESD/surgery until the date when local recurrence, metachronous cancer, or distant metastasis was first detected. Distant metastasis-free survival (DMFS) was

defined as the period from the date of ESD/surgery until the date when distant metastasis was first found.

## Statistical analysis

PSM analysis was used to avoid selection bias. Propensity scores were calculated using the logistic regression model for the following covariates: Charlson co-morbidity index (CCI) (0, 1, 2, 3, or more) [10], size group (2 cm or less, over 2 cm), depth of invasion [lamina propria, muscularis mucosa, submucosa < 500 μm (SM1), submucosa > 500 μm (SM2)]. Propensity score was used to match ESD and surgery groups at 1:4 ratio with caliper < 0.05.

Chi-square test or Fisher's exact test was used to compare categorical variables and Student's t-test was used for continuous variables. For multivariable analysis, logistic regression analysis was performed. Survival outcomes were analyzed using the Kaplan–Meier method, and Cox model was used for survival analysis. Factors were examined by multivariable Cox regression analysis for their effects on survival. Analyses were performed using the Statistical Package for the Social Sciences, version 23.0 for Windows (SPSS, Seoul, Korea) and R 3.1.0. A $p$ value < 0.05 was considered to be statistically significant.

## Results

### Clinicopathological characteristics

Between 2007 and 2014, 1279 patients who were finally diagnosed as UD EGC were reviewed. Among them, 111 patients with other cancers, 11 patients whose survival status was unknown, and 10 patients who were previously treated for gastric cancer were excluded. The remaining 1147 patients were included in this study. Among them, 126 and 1021 were initially treated with ESD and surgery respectively. After 1:4 PSM, we compared 102 patients from ESD group and 372 patients from surgery group (Fig. 1).

Overall, the patients in ESD group were older (69.9 ± 12.0 vs. 54.7 ± 11.9, $p < 0.001$), and had higher CCI (CCI 2: 26.2% vs. 19.8%; CCI 3 or above: 30.2% vs. 16.4%, $p < 0.001$) than those in surgery group (Table 1). In ESD group, lesions were more frequently located in lower third (51.6% vs. 29.4%, $p < 0.001$), showed smaller tumor size (24.0 ± 11.8 vs. 27.0 ± 17.0, $p = 0.010$), and less frequent depressed type (69.0% vs. 77.2%, $p = 0.010$) than those in surgery group. SM2 invasion (15.9% vs. 30.7%, $p = 0.005$) and ulcer (3.2% vs. 9.8%, $p = 0.015$) were less frequently involved in ESD group than in surgery group. The patients within expanded criteria were more frequent in ESD group than in surgery group (38.9% vs. 27.5%, $p = 0.008$). Lateral or deep margin involvement with tumor was more common in ESD group than in surgery group (22.2% vs. 0.3%, $p < 0.001$). After PSM, ESD and surgery

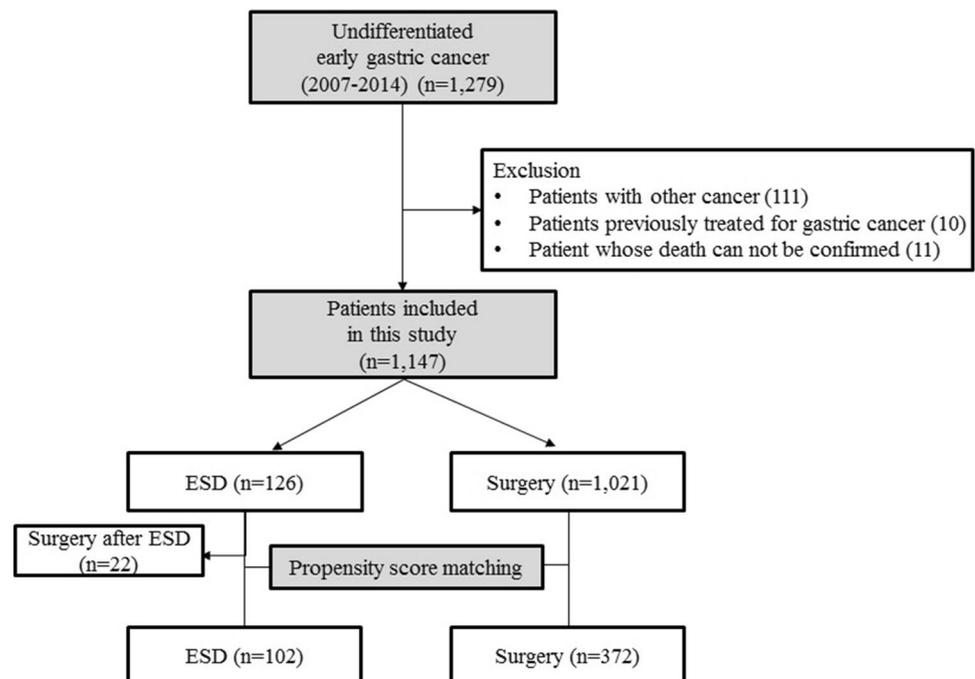**Fig. 1** Study flow chart showing patient enrollment

**Table 1** Clinicopathological characteristics before and after propensity score matching

| | Overall | | | Propensity score matching | | |
|---|---|---|---|---|---|---|
| | ESD N = 126 | Surgery N = 1021 | p value | ESD N = 102 | Surgery N = 372 | p value |
| Age, mean (SD), years | 59.9 (12.0) | 54.7 (11.9) | < 0.001 | 59.8 (12.2) | 58.5 (11.1) | 0.311 |
| Sex M | 66 (52.4) | 484 (47.4) | 0.291 | 50 (49.0) | 175 (47.0) | 0.723 |
| CCI, n (%) | | | < 0.001 | | | 0.770 |
| 0 | 19 (15.1) | 347 (34.0) | | 17 (16.7) | 71 (19.1) | |
| 1 | 36 (28.6) | 305 (29.9) | | 28 (27.5) | 115 (30.9) | |
| 2 | 33 (26.2) | 202 (19.8) | | 27 (26.5) | 95 (25.5) | |
| 3 or above | 38 (30.2) | 167 (16.4) | | 30 (29.4) | 91 (24.5) | |
| Location | | | < 0.001 | | | 0.015 |
| Lower third | 65 (51.6) | 300 (29.4) | | 48 (47.1) | 124 (33.3) | |
| Middle third | 56 (44.4) | 620 (60.7) | | 52 (51.0) | 223 (59.9) | |
| Upper third | 5 (4.0) | 101 (9.9) | | 2 (2.0) | 25 (6.7) | |
| Size, mean (SD), cm | 24.0 (11.8) | 27.0 (17.0) | 0.010 | 22.4 (11.1) | 24.6 (16.0) | 0.111 |
| ≤ 2.0 | 59 (46.8) | 450 (44.1) | 0.558 | 53 (52.0) | 190 (51.9) | 0.993 |
| > 2.0 | 67 (53.2) | 571 (55.9) | | 49 (48.0) | 176 (48.1) | |
| Gross morphology | | | 0.010 | | | 0.769 |
| Elevated | 15 (11.9) | 54 (5.3) | | 6 (5.9) | 16 (4.3) | |
| Flat | 24 (19.0) | 179 (17.5) | | 22 (21.6) | 77 (20.7) | |
| Depressed | 87 (69.0) | 788 (77.2) | | 74 (72.5) | 279 (75.0) | |
| Ulcer | 4 (3.2) | 100 (9.8) | 0.015 | 4 (3.9) | 28 (7.5) | 0.199 |
| Depth of invasion | | | 0.005 | | | 0.256 |
| Lamina propria | 48 (38.1) | 336 (32.9) | | 45 (44.1) | 189 (50.8) | |
| Muscularis mucosa | 45 (35.7) | 270 (26.4) | | 42 (41.2) | 118 (31.7) | |
| Submucosa ≤ 500 μm | 13 (10.3) | 102 (10.0) | | 9 (8.8) | 30 (8.1) | |
| Submucosa > 500 μm | 20 (15.9) | 313 (30.7) | | 6 (5.9) | 35 (9.4) | |
| Lymphovascular invasion | 17 (13.5) | 93 (9.1) | 0.115 | 6 (5.9) | 18 (4.8) | 0.670 |
| Perineural invasion | 1 (0.8) | 25 (2.4) | 0.349 | 1 (1.0) | 6 (1.6) | 1.000 |
| Histology | | | 0.001 | | | 0.063 |
| Adenocarcinoma P/D | 64 (50.8) | 391 (38.3) | | 48 (48.0) | 132 (35.5) | |
| Signet ring cell carcinoma | 59 (46.8) | 625 (61.2) | | 53 (52.0) | 239 (64.2) | |
| Mucinous adenocarcinoma | 3 (2.4) | 5 (0.5) | | 0 (0.0) | 1 (0.3) | |
| Any margin involvement | 28 (22.2) | 3 (0.3) | < 0.001 | 14 (13.7) | 1 (0.3) | < 0.001 |
| Lateral margin involvement | 15 (11.9) | 3 (0.3) | < 0.001 | 11 (10.8) | 1 (0.3) | < 0.001 |
| Deep margin involvement | 12 (9.5) | 0 (0.0) | < 0.001 | 3 (2.9) | 0 (0) | 0.010 |
| Expanded criteria | 49 (38.9) | 281 (27.5) | 0.008 | 48 (47.1) | 150 (40.3) | 0.222 |
| Follow-up duration, median months (IQR) | 65.9 (48.9–97.4) | 58.3 (42.3–72.0) | 0.001 | 63.1 (43.5–93.7) | 53.3 (39.4–68.6) | 0.006 |

*ESD* endoscopic submucosal dissection, *SD* standard deviation, *CCI* Charlson co-morbidity index, *P/D* poorly differentiated

groups showed similar clinicopathological characteristics except for margin involvement with tumor, which was still more frequent among ESD group than among surgery group (13.7% vs. 0.3%, $p < 0.001$). In overall and after PSM, median follow-up duration was longer in ESD group than in surgery group (overall: 65.9 vs. 58.3 months, $p = 0.001$; PSM: 63.1 vs. 53.3 months, $p = 0.006$).

## Lymph node and distant metastasis

Lymph node metastasis was found in 99 patients among 1043 patients in surgery group (9.5%). Among them, 92 cases were beyond expanded criteria and 7 within expanded criteria. In multivariable logistic regression analysis, tumor size > 2 cm, submucosal invasion > 500 μm,

**Table 2** Multivariable analysis for lymph node metastasis among those who had primary surgery or additional surgery after primary ESD

|  | Odds ratio (95% CI) | p value |
|---|---|---|
| Charlson co-morbidity index |  |  |
| 0 | Reference | Reference |
| 1 | 0.79 (0.43–1.43) | 0.428 |
| 2 | 0.70 (0.37–1.33) | 0.272 |
| 3 or above | 0.52 (0.26–1.04) | 0.062 |
| Gross morphology |  |  |
| Elevated | Reference | Reference |
| Flat | 0.79 (0.30–2.09) | 0.641 |
| Depressed | 0.69 (0.33–1.46) | 0.332 |
| Ulcer | 0.42 (0.17–1.06) | 0.067 |
| Size |  |  |
| ≤ 2 cm | Reference | Reference |
| > 2 cm | 2.18 (1.28–3.70) | 0.004 |
| Depth of invasion |  |  |
| Lamina propria | Reference | Reference |
| Muscularis mucosa | 0.78 (0.30–1.99) | 0.595 |
| Submucosa ≤ 500 μm | 2.36 (0.94–5.94) | 0.067 |
| Submucosa > 500 μm | 4.65 (2.26–9.57) | < 0.001 |
| Histology |  |  |
| Adenocarcinoma P/D | Reference | Reference |
| Signet ring cell carcinoma | 0.93 (0.57–1.50) | 0.753 |
| Mucinous adenocarcinoma | 0.31 (0.03–3.04) | 0.312 |
| Lymphovascular invasion |  |  |
| Negative | Reference | Reference |
| Positive | 4.59 (2.63–8.00) | < 0.001 |

*ESD* endoscopic submucosal dissection, *CI* confidence interval, *P/D* poorly differentiated

and lymphovascular invasion were found as independent risk factors for lymph node metastasis (Table 2).

Among those within expanded criteria, 7 patients were found to have lymph node metastasis (Table 3). They all had flat or depressed lesions larger than 1 cm. Among them, 1 patient developed distant lymph node metastasis 31 months after primary radical surgery, and died 14 months after refusal of additional treatment.

Distant metastasis occurred in 7 patients in surgery group. Primary lesions of them were beyond expanded criteria except for one. Among them, 3 patients had initial lymph node metastasis.

## Local recurrence, synchronous, and metachronous cancer

Local recurrence occurred in 4 patients after ESD and 1 after surgery (overall, 3.8% vs. 0.1%). The 4 recurrences in ESD group all developed after incomplete ESD with lateral margin involvement with tumor without additional

**Table 3** Profiles of patients with lymph node metastasis among those within expanded criteria

|  | Age | Sex | Charlson co-morbidity index | Location | Size (cm) | Gross type | Ulcer | Histology | Depth of invasion | Lymphovascular invasion | N stage* |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 62 | M | 2 | Upper | 1.1 | Flat | None | Adenocarcinoma P/D | Lamina propria | None | 1 |
| 2 | 59 | M | 1 | Lower | 1.2 | Flat | None | Signet ring cell carcinoma | Lamina propria | None | 1 |
| 3 | 57 | M | 1 | Lower | 2.0 | Depressed | None | Adenocarcinoma P/D | Muscularis mucosa | None | 1 |
| 4 | 42 | F | 0 | Middle | 2.0 | Depressed | None | Signet ring cell carcinoma | Lamina propria | None | 3a |
| 5 | 57 | F | 1 | Upper | 1.6 | Depressed | None | Adenocarcinoma P/D | Lamina propria | None | 1 |
| 6 | 34 | F | 0 | Middle | 1.6 | Depressed | None | Signet ring cell carcinoma | Muscularis mucosa | None | 2 |
| 7 | 57 | M | 1 | Lower | 1.6 | Flat | None | Signet ring cell carcinoma | Lamina propria | None | 1 |

*P/D* poorly differentiated

*AJCC 7th TNM staging

treatment, and the recurrent cancers were treated with either surgery or endoscopic ablation with argon plasma coagulation. The other one developed as anastomosis site recurrence after post-ESD additional surgery. Although primary ESD revealed SM2 invasion and both lateral and deep resection margin involvement with tumor, subsequent surgery showed no residual lesion. This patient died of distant metastasis 1 year after the re-operation for recurrence.

Synchronous cancer was found in 4 patients (3.2%) among ESD group and 34 (3.3%) among surgery group. All lesions except one in ESD group were found simultaneously at the primary resection. One was found 3 months after the primary ESD, and was also removed by salvage ESD. However, 15 cases in surgery group were preoperatively unsuspected and incidentally found from the resected specimens. Synchronous lesions were mostly found in nearby locations.

In multivariable analysis among PSM patients, treatment modality was not shown to be associated with detection of synchronous cancer under adjustment with histology of major lesion (OR 0.77, 95% CI 0.26–2.27, $p = 0.633$). On the other hand, mucinous adenocarcinoma in major lesion was shown to be associated with synchronous cancer (OR: 15.00 with reference to signet ring cell carcinoma, 95% CI 2.73–82.42, $p = 0.002$), while poorly differentiated adenocarcinoma was not (OR: 1.95 with reference to signet ring cell carcinoma, 95% CI 1.00-3.80, $p = 0.052$).

Overall, metachronous cancer developed in 12 patients, including 7 after ESD (6.7%) and 5 after surgery (0.5%), of which 6 cases were treated with surgery and 5 cases with ESD. The remaining 1 lost to follow-up. One of them whose initial stage was IIB, T1aN3bM0, with large primary lesion of 28 mm in size had metachronous cancer 4 years after primary surgery and adjuvant chemotherapy, who died of distant metastasis 1 year later. In multivariable analysis, ESD was highly associated with metachronous cancer under adjustment with follow-up duration and histology of primary lesion (OR: 12.71, 95% CI 3.81–42.35, $p < 0.001$).

## Survival analysis

The 5-year OS rate was 96.8% and 98.2% in ESD and surgery groups, respectively, and 96.8% and 98.9%, respectively, after PSM, and the difference was not significant before and after PSM [hazard ratio (HR): 1.25, 95% confidence interval (CI): 0.49–3.23, $p = 0.641$ before PSM; HR: 1.75, 95% CI 0.57–5.40, $p = 0.330$ after PSM] (Fig. 2A, B) (Table 4). The 5-year DSS rate was 100% in ESD group and 99.7% in surgery group, and both 100% in ESD and surgery groups after PSM. Among total 37 deaths, only 7 were gastric cancer-related, and one of them occurred in ESD group. This patient lost to follow-up after ESD for UD EGC beyond expanded criteria, and the resection was found to be incomplete with both lateral and deep margin involvement

with tumor. Among the 6 gastric cancer-related deaths in surgery group, 3 initially had SM2 invasion, 2 had regional lymph node metastasis, and 1 had large lesion of 7.5 cm. All of them had initial lesions larger than 2 cm in size. No gastric cancer-related death occurred in those within expanded criteria. The 5-year DFS rate was 88.6% and 99.3% in ESD and surgery groups respectively, and 89.5% and 99.5% after PSM (Table 4). The DFS rate was significantly lower in ESD group than in surgery group before and after PSM (HR: 8.85, 95% CI 3.78–20.71, $p < 0.001$ before PSM; HR: 14.27, 95% CI 3.07–66.31, $p = 0.001$ after PSM) (Fig. 2C, D). The 5-year DMFS rate was 100% in ESD group and 99.3% in surgery group, and 100% in ESD group and 99.5% in surgery group after PSM.

In multivariable Cox regression analysis, treatment option was not significantly related with OS (HR for ESD over surgery: 1.12, 95% CI 0.41–3.05, $p = 0.831$) under adjustment with CCI, gross morphology, ulcer, size, depth, histology, and N stage (Table 5).

We also performed subgroup analysis among those within expanded criteria. The numbers of patients within expanded criteria were 48 in ESD group and 282 in surgery group. In this subgroup, 5 deaths and 1 distant metastasis occurred in the surgery group, and metachronous cancer occurred in 2 patients in the ESD group. Among them, the 5-year OS rate was 100% in ESD group and 98.5% in surgery group, and OS did not show any significant difference between the two groups (HR: 0.04, 95% CI $2.00 \times 10^{-6}$–770.94, $p = 0.512$) (Fig. 2E). The 5-year DSS rate was 100% in ESD group and 99.6% in surgery group. The 5-year DFS rate was 97.6% and 99.6% in ESD and surgery groups respectively, of which the difference was not statistically significant (HR: 9.57, 95% CI 0.83–110.82, $p = 0.071$) (Fig. 2F). The 5-year DMFS rate was 100% and 99.6% in ESD and surgery groups respectively.

## Discussion

Since ESD was introduced as a novel treatment modality for EGC, a continuously growing number of patients are undergoing ESD procedures, supported by numerous reports presenting its sufficient efficacy and safety [11, 12]. Although conventional endoscopic resection was not indicated for UD EGC, expanded criteria have introduced the possibility of curative ESD for UD EGC in limited indication. However, it is difficult to predict accurate depth of invasion or chances of regional lymph node metastasis prior to decision of treatment modality. Although CT scan and/or EUS can support the pre-procedural diagnosis, it is still difficult to detect lymph node micrometastasis or predict depth of tumor invasion accurately with these imaging modalities [13, 14]. Furthermore, UD EGC has been known to have high risk of
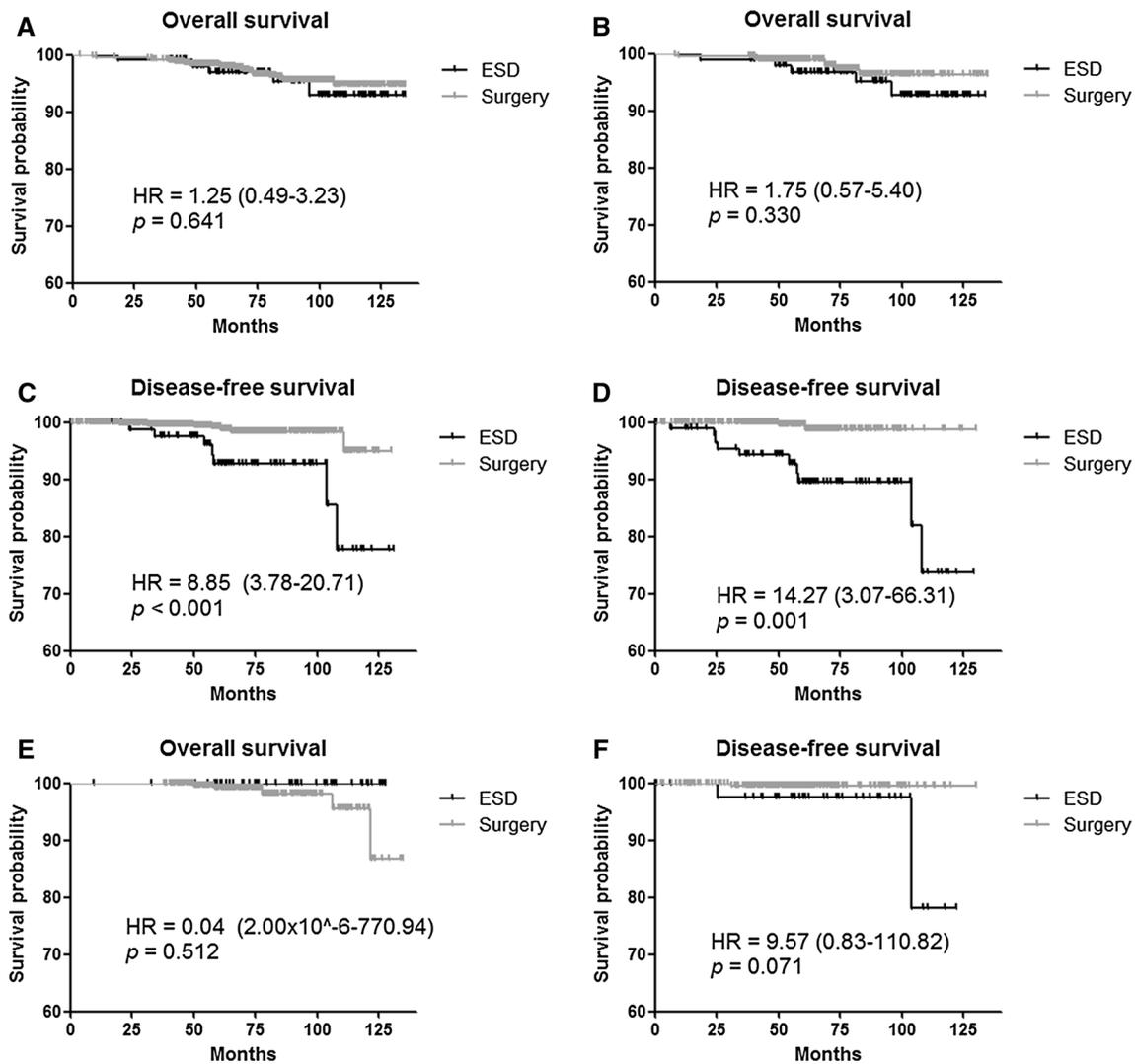
**Fig. 2** Kaplan–Meier curves comparing ESD and surgery groups: **A** Overall survival in total; **B** Overall survival in propensity score matched patients; **C** Disease-free survival in total; **D** Disease-free survival in propensity score matched patients; **E** Overall survival among those within expanded criteria; **F** Disease-free survival among those within expanded criteria

**Table 4** Numbers of events and survival rates

| | Overall | | Propensity score matching | | Expanded criteria | |
|---|---|---|---|---|---|---|
| | ESD ($n=104$) | Surgery ($n=1043$) | ESD ($n=102$) | Surgery ($n=372$) | ESD ($n=48$) | Surgery ($n=282$) |
| Death (%) | 5 (4.8) | 32 (3.1) | 5 (4.9) | 8 (2.2) | 0 (0.0) | 5 (1.8) |
| Disease specific death (%) | 1 (0.1) | 6 (0.6) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.4) |
| Distant metastasis (%) | 0 (0.0) | 7 (0.7) | 0 (0.0) | 1 (0.3) | 0 (0.0) | 1 (0.4) |
| Metachronous cancer (%) | 7 (6.7) | 5 (0.5) | 6 (5.9) | 1 (0.3) | 2 (4.2) | 0 (0.0) |
| Local recurrence (%) | 4 (3.8) | 1 (0.1) | 4 (3.9) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| 5-year OS rate (SE) | 96.8 (1.8) | 98.2 (0.4) | 96.8 (1.8) | 98.9 (0.5) | 100 | 98.5 (0.7) |
| 5-year DSS rate (SE) | 100 | 99.7 (0.2) | 100 | 100 | 100 | 99.6 (0.4) |
| 5-year DFS rate (SE) | 88.6 (3.6) | 99.3 (0.3) | 89.5 (3.6) | 99.5 (0.5) | 97.6 (2.4) | 99.6 (0.4) |
| 5-year DMFS rate (SE) | 100 | 99.3 (0.3) | 100 | 99.5 (0.5) | 100 | 99.6 (0.4) |

*ESD* endoscopic submucosal dissection, *5Y* 5-year, *OS* overall survival, *DSS* disease-specific survival, *SE* standard error, *DFS* disease-free survival, *DMFS* distant metastasis-free survival

**Table 5** Multivariable Cox regression analysis for overall survival

|  | Hazard ratio (95% CI) | *p* value |
|---|---|---|
| Charlson co-morbidity index | | |
| 0 | Reference | Reference |
| 1 | 1.26 (2.99–5.33) | 0.752 |
| 2 | 1.46 (0.34–6.21) | 0.609 |
| 3 or above | 16.12 (5.01–51.80) | < 0.001 |
| Gross morphology | | |
| Elevated | Reference | Reference |
| Flat | 2.66 (0.66–10.74) | 0.171 |
| Depressed | 1.52 (0.47–4.87) | 0.486 |
| Ulcer | < 0.01 | 0.978 |
| Size (cm) | 0.49 (0.07–3.63) | 0.482 |
| ≤ 2 | Reference | Reference |
| > 2 | 1.80 (0.84–3.90) | 0.133 |
| Depth of invasion | | |
| Lamina propria | Reference | Reference |
| Muscularis mucosa | 0.66 (0.25–1.76) | 0.406 |
| Submucosa ≤ 500 μm | 0.66 (0.19–2.27) | 0.507 |
| Submucosa > 500 μm | 0.92 (0.35–2.41) | 0.865 |
| Histology | | |
| Adenocarcinoma P/D | Reference | Reference |
| Signet ring cell carcinoma | 0.72 (0.36–1.48) | 0.375 |
| Mucinous adenocarcinoma | 1.92 (0.23–16.16) | 0.550 |
| N stage (AJCC 7th) | | |
| N0 | Reference | Reference |
| N1 | 1.24 (0.34–4.47) | 0.747 |
| N2 | 4.49 (1.20–16.80) | 0.026 |
| N3a | 16.07 (1.71–150.73) | 0.015 |
| N3b | 25.01 (2.77–225.54) | 0.004 |
| Treatment | | |
| Surgery | Reference | Reference |
| ESD | 1.12 (0.41–3.05) | 0.831 |

*CI* confidence interval, *P/D* poorly differentiated *ESD* endoscopic submucosal dissection

lymph node metastasis [7, 15–19], and because of its laterally growing nature underneath the epithelium [20, 21], it is even more difficult to decide whether to perform ESD or not. A previous study showed that ESD in UD EGC was more likely to be incomplete than in differentiated EGC and tumor size discrepancy between pretreatment evaluation and measurement after resection was higher in UD EGC [22]. Nevertheless, recent studies about ESD in UD EGC reported relatively favorable short-term outcomes in terms of tolerable complete resection and complication rates [23–27]. Therefore, comparing its long-term outcome with surgical resection has been needed to clarify the righteousness of performing ESD in UD EGC.

In this study, ESD showed comparable OS with surgery in UD EGC, which was not different after PSM as well as adjustment with multiple factors. DFS was lower in ESD group because of the high rate of metachronous cancer, which was similar to previous retrospective studies comparing ESD with surgery in UD EGC [28, 29]. However, these studies enrolled only those within expanded criteria and have not evaluated the outcomes of recurrences or gastric cancer-related deaths. In our study, all the recurrences detected in surveillance after ESD were well treated with repeated ESD or surgery. There was no gastric cancer-related death in ESD group even beyond expanded criteria except one case. The one gastric cancer-related death occurred in a patient who lost to follow-up after incomplete ESD. Among those within expanded criteria, there were no differences in OS, DSS, DFS, and DMFS between the two groups. This result implies that ESD can be a comparable treatment modality for UD EGC with surgery in terms of long-term outcomes.

As the general fear for ESD in UD EGC is mainly because of its relatively high rate of lymph node metastasis, we reviewed lymph node metastasis from surgical specimens. In this review, we found lymph node metastasis in about 10% among the patients over 1,000. Risk factors for lymph node metastasis were found to be size > 2 cm, submucosal invasion, and lymphovascular invasion, which were similar to what has been already known. Noteworthy is that there were 7 patients with lymph node metastasis with lesions within expanded criteria. Histological review revealed that all of them had flat or depressed type of lesions larger than 1 cm. Considering that one out of them had N3a lymph node metastasis and finally had fatal outcome, limiting the expanded criteria to 1 cm in size, especially for flat or depressed lesions might be worthy of being considered. Similar to this result, several previous researches have suggested to lower the size indication for UD EGC to avoid risk of lymph node metastasis [30–33]. Therefore, tumor size within 1 cm in UD EGC may be recommendable for ESD in terms of long-term outcome.

The overall recurrence rate after ESD was as high as about 10% in this study. However, among 48 patients who had complete resection for lesions within expanded criteria, the recurrence rate was 4%, which is similar to previous researches [34, 35]. All the local recurrences and metachronous cancers after ESD were treated either endoscopically or surgically and no further recurrence developed. There was no distant metastasis after ESD in this study except for one case beyond expanded criteria who lost to follow-up after incomplete ESD. However, in surgery group, one patient within expanded criteria showed distant metastasis and died of it, which revealed that even surgery might not guarantee a cure of UD EGC. Although it has been claimed that ESD should not be an alternative to surgery in UD EGC because ESD might miss hidden micro-metastasis into lymph node which could not be found in pre-procedural imaging modalities and induce

fatal outcome [9], even surgery could not avoid the risk of recurrence perfectly. Considering the comparable long-term outcome and better quality of life, ESD can be a suitable alternative for selected UD EGC with continuous regular follow-up with meticulous endoscopic surveillance.

In this study, ESD was shown to be highly associated with metachronous cancer. This is originated from totally remained gastric mucosa saved from the minimally invasive procedure [28, 29]. However, all the metachronous cancers after ESD were well treated with salvage treatment. One fatal case with metachronous cancer developed after surgery, which was initially shown to have N3b lymph node metastasis with large primary lesion of 28 mm. Meanwhile, the detection rate of synchronous cancer was similar between ESD and surgery. It means that most synchronous cancers developed at nearby location with each other, as synchronous cancers in this study were detected simultaneously with the primary lesion except for only one. However, there was one patient with far apart synchronous cancers detected in total gastrectomy: one in the fundus and the other in the antrum. Moreover, the antral lesion was unsuspected in preoperative endoscopic evaluation. In case of the other way around, the second lesion may have been missed. Although there were no unsuspected synchronous cancers detected in ESD, unexpected lesions accounted for about 44% of synchronous cancers in surgery group. When compared with our previous study including ESD for all histologic types of EGC, current results showed a lower synchronous tumor rate (3.1% vs. 5.8%) and a higher metachronous tumor rate (6.7% vs. 4.3%) [36]. In this study, synchronous lesions in UD EGC might be missed and detected later as metachronous lesions. Interestingly, mucinous adenocarcinoma was highly associated with synchronous cancer and deep submucosal invasion even in small lesions. Previously, a study reported a relatively low 5-year DSS in mucinous adenocarcinoma compared with signet ring cell carcinoma [37]. Thus, more meticulous endoscopic evaluation before ESD in UD EGC would be needed, especially for mucinous adenocarcinoma.

This study has fundamental limitation of its retrospective nature. However, we employed PSM analysis to overcome its possible selection bias. After PSM, the differences in possible confounding factors were minimized, and both groups showed similar baseline characteristics. Also, the relatively small number of ESD subjects compared with surgery subjects was another limitation. However, applying proportional PSM in this study could have improved the comparability in analysis. Another limitation is that the evaluation of lymphovascular invasion may include uncertainty. The difference in the thickness of the section of resected specimens in both groups might have affected the pathologic evaluation. In addition, the frequency of lymphovascular invasion may be underestimated without immunostaining. However, we believe that what matters is that this did not induce any poorer long-term outcome among ESD group.

In conclusion, ESD was demonstrated as a comparable treatment modality with surgery for UD EGC in expanded criteria just as in differentiated EGC in terms of long-term efficacy. However, current expanded criteria seem to have possibility to miss hidden lymph node metastasis and induce unfavorable outcome. Therefore, limiting the indication down to 1 cm in size criteria along with excluding mucinous adenocarcinoma might be suitable to avoid the risk of recurrence. Also, meticulous regular surveillance endoscopy after ESD should be followed for possible metachronous tumor development. It would be mandatory to establish more precise indication criteria for ESD in UD EGC with sufficient evidence considering the risk of lymph node metastasis.

## Compliance with ethical standards

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