Gastric Cancer (2019) 22:558–566
https://doi.org/10.1007/s10120-018-0889-8

ORIGINAL ARTICLE

# Long-term outcome of endoscopic submucosal dissection for early gastric cancer in patients with severe comorbidities: a comparative propensity score analysis

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Received: 31 July 2018 / Accepted: 22 October 2018 / Published online: 31 October 2018


## Abstract

**Background** Recently, endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) has been performed on patients with severe comorbidities because it is less invasive, although little is known regarding long-term outcomes. This study aimed to assess the long-term outcomes of ESD for patients with severe and non-severe comorbidities.

**Methods** We enrolled 1081 patients who underwent ESD for EGC between February 2004 and June 2013. Based on the American Society of Anesthesiologists Physical Status (ASA-PS) classification, we defined patients with severe and non-severe comorbidities as ASA-PS 3 and 1/2, respectively. We retrospectively compared the overall survival, risk factors for mortality, and adverse events between these two groups using propensity score matching and inverse probability of treatment weighting.

**Results** A total of 488 patients met the eligibility criteria. After matching, the ASA-PS 3 group showed a significantly shorter survival than the ASA-PS 1/2 group (5-year overall survival rate, 79.1 vs. 87.7%; $p < 0.01$). In addition, only the ASA-PS 3 group had a significant risk factor for mortality using both the Cox analysis [hazard ratio (HR), 2.56; 95% confidence interval (CI) 1.18–5.52; $p = 0.02$] and the IPTW method (HR, 3.14; 95% CI 1.91–5.14; $p < 0.01$). There was no significant difference in adverse events after matching between the two groups ($p = 0.21$).

**Conclusions** The long-term outcome of gastric ESD for patients with severe comorbidities was worse than for those with non-severe comorbidities. Further studies will be necessary to determine if ESD is truly warranted in these patients.

**Keywords** Endoscopic submucosal dissection · Early gastric cancer · Long-term outcome · American Society of Anesthesiologists Physical Status · Propensity score analysis

## Introduction

Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) has been widely accepted. Consequently, many studies [1–7] have reported favorable short- and long-term outcomes for gastric ESD. In addition, ESD has also been performed on patients with severe comorbidities, such as liver cirrhosis or renal dysfunction, as well as in elderly patients because it is less invasive [8, 9]. Some studies [10, 11] have also reported on the long-term outcome of gastric ESD for patients with severe comorbidities.

The American Society of Anesthesiologists (ASA) has advocated the ASA Physical Status (ASA-PS) classification as a means of evaluating the pre-operative general status [12]. It was reported that increases in the ASA-PS predicted significant increases in not only adverse events, but also post-operative mortality [13]. This study revealed that the long-term surgical outcome for patients with severe comorbidities, who were categorized as ASA-PS 3, was unfavorable. In a different study, no significant differences of adverse events associated with ESD, such as delayed bleeding and

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perforation, among ASA-PS 1, 2, and 3 patients, were observed [14]. The long-term outcome of ESD for ASA-PS 3 patients with EGC has not been determined. A previous study [10] reported that no significant difference regarding the long-term outcome of ESD for EGC was observed for ASA-PS groups 2 and 3 patients aged ≥ 85 years. Another study [11] reported that the prognosis of patients with severe comorbidities was poor, regardless of age. However, they were retrospective non-randomized studies, where baseline patient characteristics were not adjusted.

Therefore, we investigated the long-term outcomes of patients in ASA-PS groups 1/2 and 3 who underwent ESD for EGC. We used a pseudo-randomized method with propensity score analysis to prove our hypothesis that ESD on ASA-PS group 3 patients results in a worse prognosis than on ASA-PS group 1/2 patients.

## Patients and methods

### Patients and study design

This retrospective cohort study was conducted in the Department of Gastroenterology, at Osaka City University Hospital, Japan. Enrollment included a total of 1081 consecutive patients who underwent ESD for EGC, between February 2004 and June 2013, with follow-ups until July 2016. We compared the outcomes of 2 groups: patients who had severe and non-severe comorbidities. Based on the ASA-PS classification [15], ASA-PS 1 and 2 were defined as normal healthy patients and those with mild systemic disease, i.e., mild diseases only without substantive functional limitations (such as well-controlled hypertension, diabetes mellitus (DM), and mild lung disease, among others), respectively. Patients with severe systemic disease were classified as ASA-PS 3, i.e., those with substantive functional limitations (such as poorly controlled hypertension or DM, coronary artery disease (CAD), cerebrovascular accident (CVA), chronic obstructive pulmonary disease (COPD), active hepatitis, or end-stage renal dysfunction). Therefore, patients with severe comorbidities were classified as ASA-PS 3, and those with non-severe comorbidities as ASA-PS 1/2.

When the patients had multiple treatments for different lesions, the first lesion treated or the largest lesion was defined as the representative lesion. According to the histologic criteria for endoscopic resection in the 2014 Japanese gastric cancer treatment guidelines [16], all lesions were pathologically evaluated.

Exclusion criteria were: (1) patients who had a history of surgical gastrectomy because a remnant stomach could affect long-term outcomes, (2) patients who were diagnosed with a non-curative resection because of the risk of lymph node metastasis and recommendations for additional surgical treatments, (3) patients with a history of another malignancy potentially influencing long-term outcomes, (4) patients with missing data, and (5) patients who discontinued their outpatient follow-up program within 3 years since routine monitoring could influence their outcomes. This study's protocol was approved by the ethics committee of the Osaka City University Graduate School of Medicine (No. 3486).

### ESD

All procedures were performed using a single-channel upper GI endoscope (GIF-Q260J, Olympus, Tokyo, Japan) under intravenous sedation. The EGC margin was identified by chromoendoscopy using an indigocarmine dye or with narrow-band imaging magnified endoscopy. An insulation-tipped diathermic knife (KD-611L, Olympus, Tokyo, Japan) and a needle knife (KD-1L-1; Olympus, Tokyo, Japan) were used with an electrosurgical generator (ICC 200 or VIO300D, ERBE Elektromedizin GmbH, Tübingen, Germany). After marking and submucosal injection, a circumferential mucosal incision and submucosal dissection were performed. We defined perforation as an endoscopically visible hole in the gastric wall exposing the peritoneal cavity or free air on an abdominal radiography or computed tomography (CT). We defined delayed bleeding as hemorrhage shown by hematemesis and/or melena, and hemoglobin drop > 2 g/dL that required endoscopic hemostasis or transfusion after ESD.

### Pathologic examination

The resected specimens were fixed, sliced at 2-mm intervals, and stained with hematoxylin and eosin. Pathologists examined the specimens microscopically. Based on the Japanese classification of gastric carcinoma [17], histologic types including differentiated or undifferentiated adenocarcinoma, size, invasion depth, lateral and vertical margins, and lymphovascular involvement were assessed. We defined absolute histologic criteria for a curative resection as: en bloc resection, free lateral and vertical margins, no lymphovascular involvement, and differentiated mucosal cancer ≤ 2 cm in size without ulceration. We also defined expanded histologic criteria for a curative resection as follows: en bloc resection, free lateral and vertical margins, no lymphovascular involvement, and one of the following: (1) differentiated mucosal cancer > 2 cm in size without ulceration, (2) differentiated mucosal cancers ≤ 3 cm in size with ulceration, (3) differentiated minute submucosal cancers within 500 mm of the muscularis mucosa and ≤ 3 cm in size, and (4) undifferentiated mucosal cancer ≤ 2 cm in size without ulceration. The histological outcome that did not meet the above criteria was defined as a non-curative resection.

### Follow-up

Annual surveillance endoscopy was performed to detect metachronous lesions. Contrast-enhanced CT and tumor marker checkups were performed to detect metastases twice a year for patients with expanded histologic criteria for curative resections. The data were retrospectively collected using the medical records at the latest follow-up. If the medical records were incomplete, the follow-up data were collected by a phone interview.

### Outcome assessment

The main outcome was overall survival with the risk for mortality being the secondary outcome. We also evaluated adverse events (perforation and delayed bleeding).

### Statistical analysis

Categorical variables are presented as a mean ± standard deviation (SD) and were evaluated using the Chi-squared or the Fisher exact test, and continuous variables are presented as the median plus interquartile range (IQR) using unpaired *t* tests. A propensity score matching analysis was performed to reduce the effects of selection bias and potential confounding factors between each group by mathematically refashioning an observational study into a randomized study [18–22]. A propensity score-matched cohort was created by matching ASA-PS 1/2 and ASA-PS 3 patients (a 1:1 match) by using a greedy matching technique. Using clinical knowledge, we selected 13 variables that could potentially be confounding factors (Table 1). Using c-statistics, the model was evaluated for reliability by the Hosmer–Lemeshow test for goodness of fit and for validity using receiver operating characteristic (ROC) curves. After matching, crude comparisons of the matched cohorts were performed using the Mantel–Haenszel Chi-squared test or the McNemar test for binary data and paired *t* tests. The variables that could influence mortality were used to create a propensity score by the Cox proportional hazard model. The risk for mortality was estimated by calculating the hazard ratio (HR) and the 95% confidence interval (CI). Long-term outcomes were assessed by the log-rank test and the Kaplan–Meier method. Absolute standardized differences (ASD) were calculated for evaluating the matching effectiveness. Additionally, the inverse probability of treatment weighting (IPTW) method was performed to evaluate the sensitivity of the results by estimating propensity scores used to weigh individual observations [22–24]. The IPTW method, which is one of the approaches used to adjust the confounding factor, has the advantage of evaluating causal effects without reducing sample size. The statistical analyses were performed using IBM® SPSS® software, version 23.0 for Windows (IBM Corporation, Armonk, NY, USA). All of the statistical tests were two-sided, and a value of $p < 0.05$ was considered statistically significant.

## Results

### Baseline characteristics of patients

Of the 1081 patients with EGC treated by ESD, 48 patients with histories of surgical gastrectomy and 154 patients with non-curative resection were excluded. The remaining 879 met the criteria for a curative resection including absolute and expanded indications after pathological assessment (Fig. 1). Among these, 391 patients were excluded due to histories of other malignant neoplasms, missing data, or short follow-up periods (less than 3 years), resulting in a total of 488 patients eligible for this study. The ASA-PS 1/2 group contained 375 of these patients and 113 patients were placed in the ASA-PS 3 group. Age, sex, and antithrombotic drug use differed significantly in the baseline characteristics between both groups before matching. After matching, no factor significantly differed in the baseline characteristics of the 89 matched pairs of patients (Table 1). Among the patients with ASA-PS 3, 13 had pulmonary disease (COPD or interstitial pneumonia), 46 had cardiovascular disease (CAD, CHF, valvular disease, implanted pacemaker, or others), 13 had hepatic disease (liver cirrhosis), 30 had cerebrovascular disease (CVA or intracranial arterial stenosis), and 15 had renal disease (chronic renal failure), including 10 with chronic hemodialysis. Among them, 24 patients (27.0%) had multiple comorbidities that corresponded to ASA-PS 3.

### Long-term outcomes of the study subjects

Through the follow-up period, no disease-specific mortality was observed in either group. The 5-year overall survival rates before matching were 94.0, 89.0, and 81.8% for ASA-PS groups 1, 2, and 3, respectively (Fig. 2a). Before matching, 48 and 34 patients died in the ASA-PS groups 1/2 and 3, respectively, compared with 15 and 29 patients after matching. The causes of deaths before and after matching are shown in Table 2. Before matching, the 5-year overall survival rates in ASA-PS groups 1/2 and 3 were 90.7 and 81.8%, during a median follow-up period of 77.3 (IQR 53.2–97.9) and 67.8 (IQR 52.8–97.7) months, respectively. After matching, the 5-year overall survival rates in ASA-PS groups 1/2 and 3 were 87.7 and 79.1%, during a median follow-up period of 76.8 (IQR 51.1–92.5) and 67.8 (IQR 51.3–93.1) months, respectively. Both before and after matching, the ASA-PS 1/2 group showed a significantly longer survival than the ASA-PS 3 group ($p < 0.01$ and $< 0.01$, Fig. 2b, c).

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

| | Before matching ($n=488$) | | | | After matching ($n=178$) | | | |
|---|---|---|---|---|---|---|---|---|
| | ASA-PS ½ ($n=375$) | ASA-PS 3 ($n=113$) | $p$ value | ASD | ASA-PS ½ (n=89) | ASA-PS 3 ($n=89$) | $p$ value | ASD |
| Age | 68.2 ± 9.3 | 72.0 ± 8.7 | < 0.01 | 0.42 | 70.7 ± 9.1 | 71.1 ± 9.0 | 0.70 | 0.04 |
| Sex | | | | | | | | |
| Female | 110 (29.3) | 22 (19.5) | 0.04 | 0.23 | 25 (28.1) | 18 (20.2) | 0.27 | 0.19 |
| Male | 265 (70.7) | 91 (80.5) | | | 64 (71.9) | 71 (79.8) | | |
| Hypertension | | | | | | | | |
| Yes | 140 (37.3) | 51 (45.1) | 0.10 | 0.16 | 38 (42.7) | 40 (44.9) | 0.88 | 0.04 |
| DM | | | | | | | | |
| Yes | 51 (13.6) | 23 (20.4) | 0.10 | 0.18 | 17 (19.1) | 18 (20.2) | 1.00 | 0.03 |
| Antithrombotic drug | | | | | | | | |
| Yes | 18 (4.8) | 43 (38.1) | < 0.01 | 0.89 | 17 (19.1) | 19 (21.3) | 0.48 | 0.05 |
| Indication | | | | | | | | |
| Absolute | 217 (57.9) | 67 (59.3) | 0.83 | 0.03 | 55 (61.8) | 54 (60.7) | 1.00 | 0.02 |
| Expanded | 158 (42.1) | 46 (40.7) | | | 34 (38.2) | 35 (39.3) | | |
| Location | | | | | | | | |
| Upper third | 56 (14.9) | 20 (17.7) | 0.38 | 0.08 | 15 (16.9) | 16 (18.0) | 0.48 | 0.03 |
| Middle third | 160 (42.7) | 40 (35.4) | | 0.15 | 25 (28.1) | 31 (34.8) | | 0.14 |
| Lower third | 159 (42.4) | 53 (46.9) | | 0.09 | 49 (55.0) | 42 (47.2) | | 0.16 |
| Tumor diameter (mm), ± SD | 17.4 ± 10.6 | 17.0 ± 10.3 | 0.74 | 0.04 | 17.7 ± 11.5 | 17.0 ± 10.5 | 0.68 | 0.06 |
| Endoscopic appearance | | | | | | | | |
| Flat or depressed | 182 (48.5) | 60 (53.1) | 0.65 | 0.09 | 42 (47.2) | 46 (51.7) | 0.67 | 0.09 |
| Elevated | 193 (51.5) | 53 (46.9) | | | 47 (52.8) | 43 (48.3) | | |
| Procedure time (min), ± SD | 79.5 ± 57.3 | 78.6 ± 56.5 | 0.88 | 0.02 | 68.8 ± 49.1 | 76.4 ± 55.0 | 0.34 | 0.15 |
| Histology | | | | | | | | |
| Differentiated | 368 (98.1) | 111 (98.2) | 1.00 | 0.01 | 86 (96.6) | 88 (98.9) | 0.62 | 0.16 |
| Undifferentiated | 7 (1.9) | 2 (1.8) | | | 3 (3.4) | 1 (1.1) | | |
| UL | | | | | | | | |
| Negative | 320 (85.3) | 99 (87.6) | 0.54 | 0.07 | 80 (89.9) | 79 (88.8) | 1.00 | 0.04 |
| Positive | 55 (14.7) | 14 (12.4) | | | 9 (10.1) | 10 (11.2) | | |
| Invasion depth | | | | | | | | |
| M | 348 (92.8) | 104 (92.0) | 0.84 | 0.03 | 84 (94.4) | 82 (92.1) | 0.75 | 0.09 |
| SM1 | 27 (7.2) | 9 (8.0) | | | 5 (5.6) | 7 (7.9) | | |

*ESD* endoscopic submucosal dissection, *M* tumor confined to the mucosa, *SM1* penetration of submucosal layer less than 500 μm from the muscularis mucosa, *UL* ulceration finding, *DM* diabetes mellitus, *ASA-PS* American Society of Anesthesiologist Physical Status, *ASD* absolute standardized difference, *SD* standard deviation

## The risk factors for mortality

In the Cox proportional hazard analysis (Table 3), ASA-PS 3, age, and location (Upper third) were significantly associated with shorter survival before matching (HR, 2.85, 1.06, 0.50; 95% CI 1.83–4.44, 1.03–1.09, 0.27–0.91; $p < 0.01$, < 0.01, 0.02, respectively). After matching, only ASA-PS 3 was significantly associated with shorter survival (HR, 2.56; 95% CI 1.18–5.52; $p = 0.02$). The influence of ASA-PS 3 on mortality remained robust after adjustment for age and sex; age, sex, and indication; age, sex, indication, hypertension, and DM; and age, sex, indication, hypertension, DM, location, ulceration (UL), endoscopic appearance, tumor diameter, histology, invasion depth, antithrombotic drug, and procedure time, with the HR for each adjustment category being 2.92, 3.04, 3.39, and 4.47, respectively (Table 4). Furthermore, by using the IPTW method, the ASA-PS 3 also increased mortality (HR, 3.14; 95% CI 1.91–5.14; $p < 0.01$) (Table 5).

## Evaluation of propensity score matching

A propensity score-matched cohort was generated and assigned to the ASA-PS 1/2 or 3 group (Table 1). The

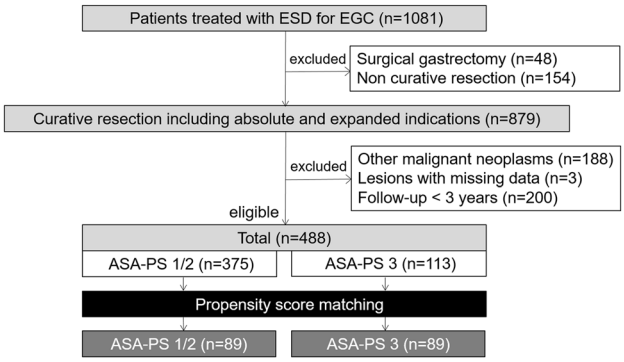


**Fig. 1** Diagram of the study design. *ESD* endoscopic submucosal dissection, *EGC* early gastric cancer, *ASA-PS* American Society of Anesthesiologist Physical Status

propensity score model was well calibrated (Hosmer–Lemeshow test, $p = 0.80$), and discriminated between the two groups ($c$ statistic = 0.76). All treated patients were matched to the closest control within a 0.19 absolute standardized difference (ASD) of the logit of the estimated propensity score.

### Adverse events of the study subjects

The adverse events before and after matching are shown in Table 2. Before matching, total adverse event rates in ASA-PS groups 1/2 and 3 were 4.3 and 10.6%, respectively ($p = 0.01$). On the other hand, total adverse event rates after matching in the ASA-PS groups 1/2 and 3 were 5.6 and 12.4%, respectively ($p = 0.21$). Except for one patient with a delayed perforation who required emergency surgery in the ASA-PS group 3 before matching, most patients were managed with endoscopic and conservative treatments. No procedure-related mortality was observed in either group 30 days after treatment.

## Discussion

We showed that the long-term survival of patients with severe comorbidities who underwent gastric ESD was significantly shorter than that of those with non-severe comorbidities, although no disease-specific or treatment-related mortalities were observed. We also demonstrated that ASA-PS 3 was an independent risk factor for overall mortality adjusted for other confounding factors using propensity score matching and IPTW methods. To the best of our knowledge, this is the first report which demonstrates the long-term outcomes of gastric ESD for patients with severe and non-severe comorbidities who were categorized according to the ASA-PS classification using propensity score analysis.

Shorter survival in the ASA-PS 3 group compared to the ASA-PS 1/2 group might be caused by exacerbation of their comorbidity which had been present before ESD. Before matching ($p < 0.01$, Table 2), the number of deaths which might be caused by exacerbation of comorbidity in the ASA-PS 3 group (13 cases, 41.9%) was significantly higher than those in the ASA-PS 1/2 group (2 cases, 4.5%). After matching, the mortalities caused by exacerbation of comorbidity

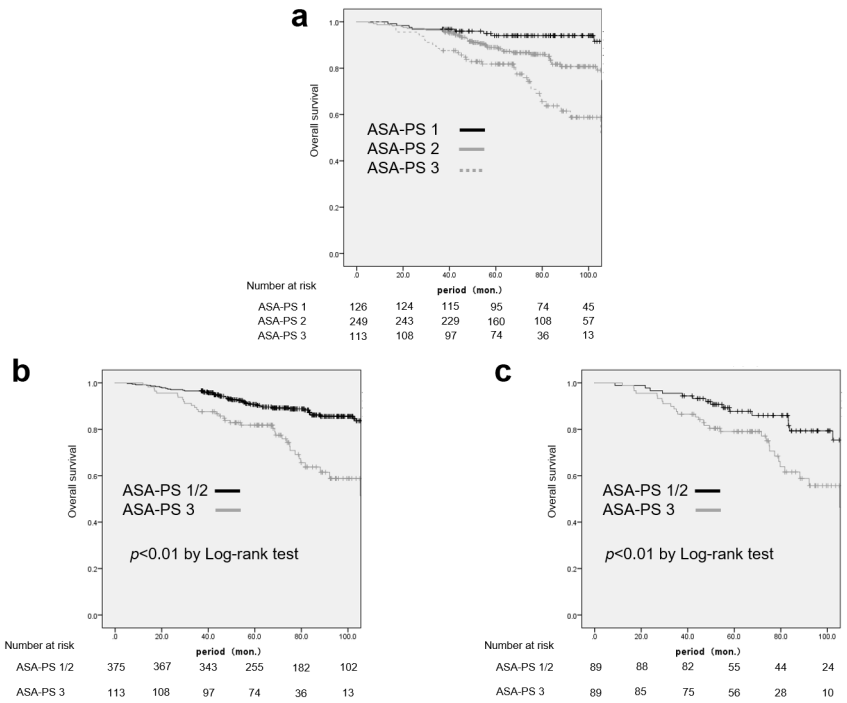


**Fig. 2** **a**–**c** Comparison of long-term outcome of ESD. **a** Overall survival in each ASA-PS score before matching. **b** Overall survival between ASA-PS 1/2 and 3 before matching. **c** Overall survival between ASA-PS 1/2 and 3 after matching. *ASA-PS* American society of Anesthesioloist Physical Status

**Table 2** The cause of death and adverse events before and after propensity score matching

| | Before matching ($n=488$) | | After matching ($n=178$) | |
|---|---|---|---|---|
| | ASA-PS 1/2 ($n=375$) | ASA-PS 3 ($n=113$) | ASA-PS 1/2 ($n=89$) | ASA-PS 3 ($n=89$) |
| Causes of death, *n* [*n*][a] | 48 [*2*] | 34 [*13*] | 15 [*0*] | 29 [*11*] |
| Pulmonary disease | 8 [*0*] | 6 [*2*] | 2 [*0*] | 5 [*2*] |
| Cardiovascular disease | 3 [*0*] | 5 [*3*] | 1 [*0*] | 4 [*1*] |
| Hepatic failure | 2 [*2*] | 6 [*4*] | 0 [*0*] | 5 [*4*] |
| Cerebrovascular disease | 3 [*0*] | 4 [*3*] | 0 [*0*] | 4 [*3*] |
| Other types of cancers (after ESD) | 18 [*0*] | 6 [*0*] | 5 [*0*] | 4 [*0*] |
| Renal failure | 1 [*0*] | 2 [*1*] | 0 [*0*] | 2 [*1*] |
| Other diseases | 9 [*0*] | 2 [*0*] | 4 [*0*] | 2 [*0*] |
| Unknown | 4 [–] | 3 [–] | 3 [–] | 3 [–] |
| Adverse events, *n* (%) | 16 (4.3) | 12 (10.6) | 5 (5.6) | 11 (12.4) |
| Delayed bleeding | 13 (3.5) | 8 (7.1) | 4 (4.5) | 8 (9.0) |
| Perforation | 3 (0.8) | 4 (3.5) | 1 (1.1) | 3 (3.4) |

Other cancers were detected during the follow-up period after ESD, although patients with history of another malignancy before ESD were excluded

*ASA-PS* American Society of Anesthesiologist Physical Status, *pulmonary disease* (pneumonia, interstitial pneumonia, respiratory failure), *cardiovascular disease* (heart failure, ischemic heart disease, aortic dissection), *cerebrovascular disease* (hemorrhage, infarction), *Other types of cancers (after ESD)* (colon, lung, liver, bile duct), *other diseases* (esophageal varix rupture, acute peritonitis, hypoglycemia, senility, accident)

[a]The number of patients who contracted each disease as a comorbidity on treatment and died of the same disease

in the ASA-PS 3 group were also significantly higher than those in the ASA-PS 1/2 group (42.3 vs. 0%, $p<0.01$).

This study demonstrated that the 5-year overall survival rate (79.1%) in the ASA-PS 3 group was significantly worse than that (87.7%) in the ASA-PS 1/2 group after matching. The prognoses of the patients who were successfully treated for EGC were reported favorable [25]. However, a poorer prognosis is anticipated in patients with severe comorbidities even if successful treatment is achieved. Recently, results similar to ours were reported [8, 10, 11]. One multicenter retrospective cohort study [8], using propensity score analysis, demonstrated that 5-year overall survival rates of patients with liver cirrhosis was 60.0%, which was significantly lower than that of patients without liver cirrhosis (91.0%). Our study also revealed that 80% of patients with liver cirrhosis died from hepatic failure. Iwai et al. [11], reported that the Charlson comorbidity index, which was used to evaluate death risk associated with comorbidities, influenced the overall survival of both elderly and non-elderly patients. Our study demonstrated similar results using the ASA-PS classification by adjusting the baseline characteristics using a propensity analysis with a larger sample size. However, another retrospective study [10] revealed that no significant difference was observed in 5-year overall survival rates among patients aged ≥ 85 years between groups ASA-PS 2 and 3.

It is unclear if treating EGC would improve the prognosis of patients with severe comorbidities. A previous report [26] described that the 5-year overall survival rate in patients who were not treated for EGC was 62.8%. We previously reported that the 5-year overall survival rates of ASA-PS 3 patients with expanded indication differentiated-type EGC who underwent surgery or ESD were 69.9 or 85.3%, respectively [22]. Although no conclusions can be drawn on the basis of these results, ESD might improve the long-term prognosis for EGC in patients with severe comorbidities.

A previous study [14] has reported that there was no significant difference in adverse events associated with ESD, such as delayed bleeding and perforation, among each ASA-PS group. In the present study, a slightly higher rate (10.6%) of adverse events associated with ESD in ASA-PS group 3 was observed; however, it was lower than what we previously reported [22] for patients with surgical gastrectomy (24.4%). Moreover, no mortality associated with adverse events was observed. In terms of adverse events, ESD might be an acceptable treatment for EGC in patients with severe comorbidities when compared to surgical resection.

The present study has three important strengths. First, this study has sufficient median follow-up duration, 77.3 months in ASA-PS group 1/2 and 67.8 months in ASA-PS group 3, compared with previous studies (33.4–64.0 months) [8, 10, 11]. Secondly, this study also has a large sample size when

**Table 3** The risk factors for mortality by crude Cox proportional hazards analysis before and after propensity score matching

| | Before matching ($n=488$) | | | | After matching ($n=178$) | | | |
|---|---|---|---|---|---|---|---|---|
| | *n* | Case (%) | Crude HR (95% CI) | *p* value | *n* | Case (%) | Crude HR (95% CI) | *p* value |
| ASA-PS | | | | | | | | |
| ASA-PS 1/2 | 375 | 48 (12.8) | 1.00 | | 89 | 15 (16.9) | 1.00 | |
| ASA-PS 3 | 113 | 34 (30.1) | 2.85 (1.83–4.44) | < 0.01 | 89 | 29 (32.6) | 2.56 (1.18–5.52) | 0.02 |
| Age (continuous, per 10 years old) | 488 | 82 (16.8) | 1.06 (1.03–1.09) | < 0.01 | 178 | 44 (24.7) | 1.03 (0.96–1.10) | 0.41 |
| Sex | | | | | | | | |
| Female | 132 | 20 (15.1) | 1.00 | | 43 | 11 (25.6) | 1.00 | |
| Male | 256 | 62 (17.4) | 0.83 (0.50–1.37) | 0.46 | 135 | 33 (24.4) | 2.00 (0.50–8.00) | 0.33 |
| Hypertension | | | | | | | | |
| No | 297 | 46 (15.5) | 1.00 | | 100 | 25 (25.0) | 1.00 | |
| Yes | 191 | 36 (18.8) | 1.37 (0.88–2.12) | 0.16 | 78 | 19 (24.4) | 1.50 (0.61–3.67) | 0.37 |
| DM | | | | | | | | |
| No | 414 | 65 (15.7) | 1.00 | | 143 | 32 (22.4) | 1.00 | |
| Yes | 74 | 17 (23.0) | 1.51 (0.88–2.57) | 0.13 | 35 | 12 (34.3) | 2.33 (0.60–9.02) | 0.22 |
| Antithrombotic drug | | | | | | | | |
| No | 427 | 70 (16.4) | 1.00 | | 142 | 37 (26.1) | 1.00 | |
| Yes | 61 | 12 (19.7) | 1.41 (0.76–2.61) | 0.27 | 36 | 7 (19.4) | 0.84 (0.37–1.88) | 0.67 |
| Indication | | | | | | | | |
| Absolute | 284 | 45 (15.8) | 1.00 | | 109 | 24 (22.0) | 1.00 | |
| Expanded | 204 | 37 (18.1) | 1.10 (0.71–1.71) | 0.66 | 69 | 20 (29.0) | 1.00 (0.32–3.10) | 1.00 |
| Location | | | | | | | | |
| Upper third | 76 | 18 (23.7) | 1.00 | | 31 | 8 (25.8) | 1.00 | |
| Middle third | 200 | 27 (13.5) | 0.50 (0.27–0.91) | 0.02 | 56 | 14 (25.0) | 0.41 (0.07–2.34) | 0.32 |
| Lower third | 212 | 37 (17.5) | 0.63 (0.36–1.11) | 0.11 | 91 | 22 (24.2) | 0.67 (0.16–2.92) | 0.60 |
| Tumor diameter (mm) | 488 | 82 (16.8) | 1.01 (0.99–1.03) | 0.26 | 178 | 44 (24.7) | 1.01 (0.97–1.06) | 0.60 |
| Endoscopic appearance | | | | | | | | |
| Flat or depressed | 243 | 46 (18.9) | 1.00 | | 88 | 25 (28.1) | 1.00 | |
| Elevated | 245 | 36 (14.7) | 0.78 (0.50–1.21) | 0.26 | 90 | 19 (21.1) | 0.67 (0.27–1.63) | 0.37 |
| Procedure time (min) | 488 | 82 (16.8) | 1.00 (0.99–1.01) | 0.94 | 178 | 44 (24.7) | 1.00 (0.99–1.01) | 0.63 |
| Histology | | | | | | | | |
| Differentiated | 479 | 80 (16.7) | 1.00 | | 174 | 42 (24.1) | 1.00 | |
| Undifferentiated | 9 | 2 (22.2) | 1.19 (0.29–4.85) | 0.81 | 4 | 2 (50.0) | 1.00 (0.06–16.0) | 1.00 |
| UL | | | | | | | | |
| Positive | 419 | 73 (17.4) | 1.00 | | 159 | 41 (25.8) | 1.00 | |
| Negative | 69 | 9 (13.0) | 0.71 (0.35–1.41) | 0.33 | 19 | 3 (15.8) | 0.60 (0.14–2.51) | 0.48 |
| Invasion depth | | | | | | | | |
| M | 452 | 77 (17.0) | 1.00 | | 166 | 42 (25.3) | 1.00 | |
| SM1 | 36 | 5 (13.9) | 0.83 (0.33–2.04) | 0.83 | 12 | 2 (16.7) | 0.50 (0.05–5.51) | 0.57 |

*ESD* endoscopic submucosal dissection, *M* tumor confined to the mucosa, *SM1* penetration of submucosal layer less than 500 μm from muscularis mucosa, *ASA-PS* American Society of Anesthesiologist Physical Status, *UL* ulceration finding, *DM* diabetes mellitus, *ASD* absolute standardized difference, *HR* hazard ratio, *CI* confidence interval

compared to previous reports [8, 10, 11]. Thirdly, we demonstrated that the ASA-PS group 3 was an independent risk factor for overall mortality and resulted in shorter patient survival when adjusted for other confounding factors using propensity score matching and IPTW methods.

Our study also had the following limitations. First, this is a retrospective, quasi-randomized study in a single center. A larger multicenter study should be conducted to evaluate the long-term outcome of ESD for EGC in patients with severe comorbidities. However, we adjusted for confounding factors which could have influenced the relationship between long-term outcomes and ASA-PS by using propensity-matched analyses to adjust for selection bias. The propensity score matching method was used to evaluate statistically causal

**Table 4** Univariate and multivariate Cox proportional hazard ratios of mortalities for ASA-PS group 3 compared with ASA-PS group 1/2 after propensity score matching

| | After matching | |
|---|---|---|
| | HR (95% CI) | *p* value |
| Unadjusted | 2.56 (1.18–5.52) | 0.02 |
| Adjusted for age, sex | 2.92 (1.18–7.25) | 0.02 |
| Adjusted for age, sex, indication | 3.04 (1.20–7.74) | 0.02 |
| Adjusted for age, sex, indication, hypertension, DM | 3.39 (1.13–10.14) | 0.03 |
| Adjusted for age, sex, indication, hypertension, DM, location, UL, endoscopic appearance, tumor diameter, histology, invasion depth, antithrombotic drug, procedure time | 4.47 (1.10–18.27) | 0.04 |

*ASA-PS* American Society of Anesthesiologists Physical Status, *DM* diabetes mellitus, *UL* ulceration finding, *HR* hazard ratio, *CI* confidence interval

**Table 5** Propensity score-matched and weighted hazard ratios of mortalities for ASA-PS group 3 compared with ASA-PS group 1/2

| | HR (95% CI) | *p* value |
|---|---|---|
| Before PS matching | 2.37 (1.26–4.43) | 0.01 |
| After PS matching | 2.56 (1.18–5.52) | 0.02 |
| IPTW | 3.14 (1.91–5.14) | < 0.01 |

*PS* Propensity score, *IPTW* Inverse probability of treatment weighting, *HR* hazard ratio, *CI* confidence interval

effects free from potentially confounding effects [19, 20, 27]. In addition, the IPTW method was also used to assess the sensitivity of the results and indicated that the results were qualitatively similar to those of the matching analysis [22–24, 28]. The application of both methods could clarify the robustness that ASA-PS 3 was an independent risk factor of mortality. Secondly, approximately 20% of the patients discontinued their outpatient follow-up program within 3 years. Early censored cases could have affected the long-term outcomes because the actual outcome (mortality or survival) of censored cases is unknown. Therefore, we excluded patients with short follow-up durations though this exclusion could lead to selection bias. However, similar rates of patients with ASA-PS 3 were observed between the enrolled (23.2%; 113/488) and excluded patients (23.0%; 46/200) in our study. Therefore, similar results might also be expected in the excluded patients with ASA-PS 3. In previous reports regarding the long-term outcomes in patients with severe comorbidities [8, 10, 11], those with a short observation period were included in the Kaplan–Meier curves. However, the 5-year survival rates in our study may be more accurate because of its longer follow-up duration compared with those in other studies.

In conclusion, the long-term outcome of gastric ESD for patients with severe comorbidities was worse than those with non-severe comorbidities resulting in sub-optimal long-term survival. Additional studies will be necessary to evaluate gastric ESD in patients with severe comorbidities.

**Funding** No funders and grants.

## Compliance with ethical standards

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

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

**Informed consent** Informed consent or a substitute for such consent was obtained from all patients before inclusion in our study.

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