JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.13016

ORIGINAL ARTICLE

Long-term outcomes after endoscopic submucosal dissection for colorectal epithelial neoplasms in patients with severe comorbidities

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Key words
American Society of Anesthesiologists Physical Status, colorectal cancer, comorbidity, endoscopic submucosal dissection, propensity score matching.

Accepted for publication 17 November 2023.

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Declaration of conflict of interest: The authors have no conflicts of interest to declare.
Author contribution: Yasuhiko Hamada contributed to the study conception and design. Yasuhiko Hamada, Yohei Ikenoyama, Yuhei Umeda, Hiroki Yukimoto, Akina Shigefuku, Yasuko Fujiwara, Tsuyoshi Beppu, Misaki Nakamura, and Noriyuki Horiki contributed to patient care and data collection. Hayato Nakagawa supervised the study. Yasuhiko Hamada wrote the first draft of this manuscript. All authors have read and approved the final manuscript.

Abstract

Background and Aim: Long-term outcomes after endoscopic submucosal dissection (ESD) for colorectal epithelial neoplasms (CENs) in patients with severe comorbidities have not been clarified; the current study aimed to examine these long-term outcomes and compared them with those in patients with non-severe comorbidities.
Methods: We included 231 patients with CENs who underwent ESD between April 2005 and March 2023. Patients with comorbidities were categorized according to the American Society of Anesthesiologists Physical Status (ASA-PS). We conducted a propensity score-matched analysis and compared long-term outcomes of the two groups after ESD for CENs.
Results: Of the 156 patients enrolled in the study, 43 and 113 had severe (ASA-PS III) and non-severe (ASA-PS I/II) comorbidities, respectively. The 1:1 propensity score analysis matched 36 patients with severe comorbidities to 36 patients with non-severe comorbidities. After matching, there was no difference in the procedural outcomes of ESD between both groups. Regarding long-term outcomes, the 5-year overall survival rates after matching in the ASA-PS I/II and III groups were 100% and 73.5%, respectively, and patients in the ASA-PS III group exhibited significantly shorter overall survival than those in the ASA-PS I/II group (hazard ratio 7.209; 95% confidence interval 1.592–32.646; $P = 0.010$). No colorectal cancer-related deaths were noted in either group.
Conclusion: Overall survival after ESD for CENs was shorter in patients with severe comorbidities than in those with non-severe comorbidities. Clinicians should carefully determine whether the benefits of CEN resection with ESD outweigh the procedural risks in patients with severe comorbidities.

Introduction

Colorectal cancer (CRC) is one of the leading causes of morbidity and mortality worldwide.[1] Consequently, CRC screening programs are recommended in many countries.[2] Endoscopic submucosal dissection (ESD) has been gradually accepted as a minimally invasive treatment option for large colorectal epithelial neoplasms (CENs).[3-5] As CRC screening programs are conducted, the number of CEN cases requiring ESD has increased. To date, several studies have reported excellent outcomes following colorectal ESD.[6-8]

Aging societies are globally observed in many countries, and the number of older patients requiring ESD for CEN with severe comorbidities is expected to increase. In this regard, several studies have reported long-term outcomes of colorectal ESD in older patients with severe comorbidities.[9-12] However, these studies did not focus on the severity of their comorbidities but on patients' age. Moreover, they were retrospective and non-randomized studies; thus, baseline patient characteristics were not adjusted. Therefore, there is limited information on the long-term outcomes after ESD for CEN in patients of all ages with severe comorbidities.

This study aimed to examine the long-term outcomes of patients with and without severe comorbidities who underwent ESD for CEN using propensity score matching.

Methods

Study design and patients. This single-center retrospective study was conducted at our institution. A total of 231 consecutive patients who underwent colorectal ESD for CEN between

April 2005 and March 2023 were included. The exclusion criteria were as follows[1]: patients in whom the tumor invasion depth was pathologically evaluated as muscular layer,[2] patients who had incomplete ESD, and[3] patients who discontinued their follow-up for more than 2 years. Patients with a short life expectancy were not excluded from the study population. When the patients had multiple treatments for different lesions, the lesions with the deepest tumor invasion depth were qualified in this study. All data were reviewed and collected from patient's medical records and responses to questionnaires collected by doctors in other hospitals.

The study was approved by the ethics committee of our institution (approval number H2021-116) and was conducted in accordance with the ethical standards of the 1964 Helsinki Declaration and its later amendments. The ethics committee approved the opt-out method for obtaining patient consent; accordingly, we posted information about this study on the institutional website and gave participants the opportunity to decline study participation.

The American Society of Anesthesiologists Physical Status classification system. The ESD outcomes between patients with severe and non-severe comorbidities were categorized according to the American Society of Anesthesiologists Physical Status (ASA-PS) classification and compared to one another.[13,14] The ASA-PS classification was used as a method to evaluate the patients' general preoperative status, and a higher ASA-PS classification reportedly predicted both adverse events and postoperative mortality.[15] Based on the ASA-PS classification,[16] patients were allocated to one of six groups according to the severity of their comorbidities. ASA-PS I patients were those who did not have a systemic disease, ASA-PS II patients had mild systemic diseases, and ASA-PS III patients had severe systemic diseases that were not life-threatening. ASA-PS ≥ IV patients were defined as those with severe life-threatening diseases that were contraindicative for colorectal ESD. Thus, in the current study, patients with ASA-PS III were classified as the group with severe comorbidities whereas patients with AS-PS I/II were classified as the group with non-severe comorbidities.

ESD procedure. For bowel preparation, 2 L of polyethylene glycol-electrolyte solution was used on the day of the procedure. All patients received scopolamine butylbromide or glucagon intravenously unless contraindicated. Intravenous sedation was performed using a combination of diazepam and pethidine according to the judgment of each endoscopist. Carbon dioxide was used for colonic insufflation instead of room air.

During the study period, various experienced endoscopists performed colorectal ESD with a Dual knife (Olympus, Tokyo, Japan). Depending on the case, we additionally used an IT knife nano (Olympus), a Hook knife (Olympus), or an SB knife Jr. (Sumitomo Bakelite, Tokyo, Japan). ESD was performed using a colonoscope (PCF-Q260AZI or PCF-H290AZI; Olympus) or an upper gastrointestinal endoscope (GIF-Q260J; Olympus). A 10% glycerin solution with epinephrine (dilution, 1:200 000) was used for submucosal injection. All procedures were performed by either expert endoscopists who had previously performed more than 30 ESD procedures or by trainee endoscopists under the supervision of expert endoscopists. ESD was performed in an inpatient setting, and hospitalization lasted 5 days after ESD if no complications were observed. All patients visited the hospital 4–5 weeks after discharge to evaluate their health condition, including adverse events within 30 days of ESD, and to explore the pathological results of ESD.

Histological assessment. The resected specimens were pinned to specimen boards, fixed in formalin, dissected into 2- to 3-mm wide slices, and stained with hematoxylin and eosin. According to the Japanese classification of cancer of the colon and rectum,[17] we evaluated the gross type, specimen size, histological type, tumor invasion depth, horizontal and vertical resection margins, degree of tumor budding, and lymphovenous invasion. The lesions were classified as adenoma, sessile serrated lesion (SSL), Tis (intramucosal cancer, corresponding to high-grade dysplasia and mucosal high-grade neoplasia as defined by the World Health Organization classification), T1a (adenocarcinoma with the submucosal invasion of <1000 μm), or T1b (adenocarcinoma with the submucosal invasion of ≥1000 μm).

Definitions. We classified the tumors based on their location in the colorectum as tumors of the cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectum. The procedure time was defined as the time from the start of the resection to the complete removal of the lesion. En bloc resection was defined as the removal of the tumor in a single piece. Complete resection was defined as en bloc resection with negative vertical margins, and curative resection was defined as complete resection without T1b carcinoma, lymphovenous invasion, tumor budding grade 2 or 3, or a poorly differentiated component.[4]

Adverse events included postoperative bleeding and perforation within 30 days of ESD. Postoperative bleeding was defined as hemorrhage after ESD requiring transfusion or intervention. We diagnosed perforation by visualization of the abdominal cavity during ESD. Local and distant recurrences were noted during the follow-up. Local recurrence was defined as the development of a tumor at the site of a previous ESD scar. Distant recurrence was defined as lymphadenopathy or detection of a cancerous lesion in another organ on computed tomography.

Salvage treatment and follow-up strategy. When resection was curative, we performed endoscopic examination and biopsy of suspicious sites at 3 and 12 months after ESD and at 12-month intervals thereafter. When resection was non-curative, we informed the patient about the need for salvage surgical resection and the associated benefits and risks. When patients opted for follow-up without salvage surgical resection, we performed computed tomography of the chest, abdomen, and pelvis every 6 months and endoscopic examination annually. However, we occasionally changed the surveillance period based on the patient's physical condition.

Study outcomes. The main outcome was the long-term survival of patients with severe comorbidities (ASA-PS III) after colorectal ESD for CENs, which was compared with that of patients with non-severe comorbidities (ASA-PS I/II). We also evaluated adverse events of colorectal ESD.

Propensity score matching. A propensity score-matched analysis was conducted to decrease the effects of selection bias and confounding factors between the ASA-PS III and I/II groups. Propensity scores were calculated using a logistic regression model. Based on our clinical knowledge and experience, the following variables were included in the model: age, sex (female or male), tumor location (rectum or colon), gross type (flat/elevated or depressed), tumor size, and invasion depth (mucosa or submucosa). Discriminatory power of the propensity score model was evaluated using the C-statistic. After the propensity scores were calculated, we conducted one-to-one nearest neighbor matching using a caliper set at 0.2. A standardized mean difference (SMD) was used to evaluate the balance of the confounding variables between the two groups after propensity score matching, and an SMD of ≤0.2 was evaluated as well-balanced.[18]

Statistical analysis. Continuous variables are presented as means (SDs) for normally distributed data and medians (interquartile range [IQR]) for non-normally distributed data. Categorical variables are expressed as numbers and frequencies. We used the Mann–Whitney *U* test to compare continuous variables and the Chi-squared or Fisher's exact test to compare categorical variables, as appropriate. The overall survival and disease-specific survival rates were estimated using the Kaplan–Meier method. The log-rank test was conducted to compare the survival curves. The Cox proportional hazard analysis examined the risk factors for mortality. All statistical analyses were performed using SPSS version 26 (IBM Corp., Armonk, NY, USA) and EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan).[19] All tests were two-sided, and a *P*-value of <0.05 denoted statistical significance.

Results

Baseline clinicopathological characteristics of all patients. The study selection process is illustrated in Figure 1. Of the 231 patients with CEN treated by ESD, 75 patients were excluded; 1 had a CEN with muscular layer invasion, 8 had incomplete ESD, and 66 discontinued their follow-up within 2 years. Therefore, 156 patients were included in the analysis.

The clinicopathological characteristics and ESD outcomes of the 156 patients are summarized in Table 1. The numbers of patients with ASA-PS I, II, and III were 38 (24.4%), 75 (48.1%), and 43 (27.6%), respectively, and the patients were predominantly male (59.0%). The median age (IQR) was 71.0 (63.0, 78.0) years, and the median tumor size (IQR) was 30.0 (25.0, 43.0) mm. The most common tumor location was the rectum (39.1%). Regarding the gross type of tumor, 96.2% were of the flat/elevated type. Lymphatic and venous invasions were observed in 1.9% and 1.3% of the cases, respectively. The en bloc, complete, and curative resection rates were 94.7%, 93.6%, and 80.8%, respectively. Salvage treatment was performed in 10 patients (6.4%): 7 had a T1b carcinoma, 2 had a lymphovenous invasion, and 1 had a vertical margin involvement. These patients had no residual tumor in the resected specimens and no recurrences during the follow-up period.

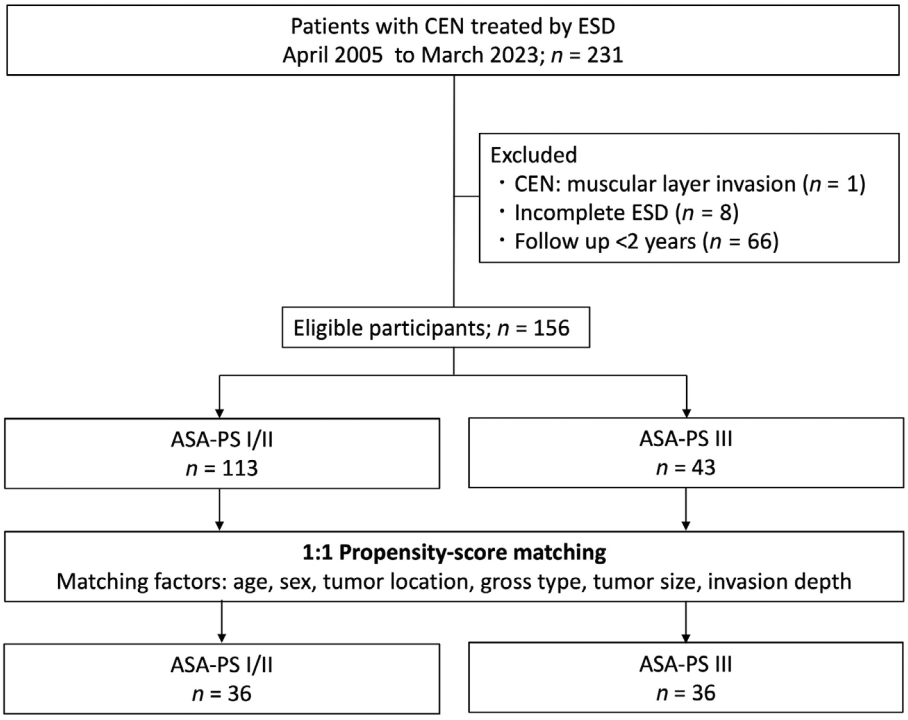

Figure 1 Study flowchart. ASA-PS, American Society of Anesthesiologists Physical Status; CEN, colorectal epithelial neoplasm; ESD, endoscopic submucosal dissection.

Table 1 Baseline clinicopathological characteristics and endoscopic submucosal dissection outcomes of all patients ($n = 156$)

Variables	
Sex, *n* (%)	
Female	64 (41.0)
Male	92 (59.0)
Age, median (IQR), years	71.0 (63.0, 78.0)
ASA-PS, *n* (%)	
Class I	38 (24.4)
Class II	75 (48.1)
Class III	43 (27.6)
Tumor size, median (IQR), mm	30.0 (25.0, 43.0)
Tumor location, *n* (%)	
Cecum	25 (16.0)
Ascending colon	27 (17.3)
Transverse colon	26 (16.7)
Descending colon	5 (3.2)
Sigmoid colon	12 (7.7)
Rectum	61 (39.1)
Gross type, *n* (%)	
Flat/elevated	150 (96.2)
Depressed	6 (3.8)
Tumor histology, *n* (%)	
Adenoma	59 (37.8)
SSL	2 (1.3)
Tis carcinoma	75 (48.1)
T1a carcinoma	11 (7.1)
T1b carcinoma	9 (5.8)
Lymphovenous invasion, *n* (%)	
Lymphatic invasion	3 (1.9)
Venous invasion	2 (1.3)
Resection type, *n* (%)	
En bloc resection	233 (94.7)
Complete resection	146 (93.6)
Curative resection	126 (80.8)
Complications, *n* (%)	
Postoperative bleeding	4 (2.6)
Perforation	11 (7.1)
Salvage treatment, *n* (%)	10 (6.4)
Follow-up period, median (IQR), months	63.8 (41.1, 82.6)

ASA-PS, American Society of Anesthesiologists Physical Status; IQR, interquartile range; SSL, sessile serrated lesion; Tis, adenocarcinoma in situ; T1a, adenocarcinoma with shallow submucosal invasion (<1000 μm); T1b, adenocarcinoma with deep submucosal invasion (≥1000 μm).

Evaluation of propensity score matching. Cohorts generated by propensity score-matched analysis were assigned to the ASA-PS I/II or III group (Table 2). Fair discrimination and good calibration were indicated by the C-statistic (0.742). In addition, the SMDs after propensity score matching were within 0.2 for all variables.

Clinicopathological characteristics before and after propensity score matching. Comparisons of the clinicopathologic characteristics between the ASA-PS I/II and III groups before and after matching are shown in Table 2. The ASA-PS I/II and III groups included 113 and 43 patients, respectively. Age significantly differed between the two groups before matching. After matching, no factors differed significantly in the baseline characteristics of the 36 matched pairs of patients.

ESD outcomes before and after propensity score matching. Comparisons of the colorectal ESD outcomes between the ASA-PS I/II and III groups before and after propensity score matching are shown in Table 3. Neither before nor after propensity score matching were there any differences in the procedural outcomes of ESD between groups. Moreover, no procedure-related mortality or worsened comorbidity was observed in either group 30 days after ESD.

Long-term outcomes of the study patients. The 5-year overall survival rate of all patients who underwent colorectal ESD was 93.2%. During the follow-up period, 15 deaths occurred. Before matching, the 5-year overall survival rates in the ASA-PS I/II and III groups were 99.0% and 77.3%, respectively (Fig. 2a). After matching, the 5-year overall survival rates in the ASA-PS I/II and III groups were 100% and 73.5%, respectively (Fig. 2b). Both before and after matching, patients in the ASA-PS I/II group showed significantly longer overall survival than those in the ASA-PS III group ($P = 0.0001$ and $P = 0.003$, respectively). During the follow-up period, no CRC-related deaths were noted (Table 4).

Risk factors of shorter overall survival. Cox proportional hazard analysis (Table 5) demonstrated that ASA-PS III, older age, and male sex were significantly associated with shorter overall survival before matching (hazard ratio [HR] 8.537, 1.091, and 4.818; 95% confidence interval [CI] 2.710–26.892, 1.025–1.163, and 1.085–21.394; $P < 0.001$, $P = 0.007$, and $P = 0.039$, respectively). After matching, only ASA-PS III was significantly associated with shorter overall survival (HR 7.209; 95% CI 1.592–32.646; $P = 0.010$).

Discussion

In this study, we demonstrated that the overall survival of patients with severe comorbidities who underwent colorectal ESD was significantly shorter than that of patients with non-severe comorbidities. We also showed that ASA-PS III was an independent risk factor for shorter overall survival after propensity score-matching to adjust for other confounding factors.

The benefits of colorectal ESD for patients with severe comorbidities include removing the tumor and preventing a decline in the patient's quality of life, which would otherwise result and lead to gastrointestinal stricture and pain caused by tumor growth. However, the risks include exacerbation of comorbidities and increased thrombosis risk associated with withdrawal of antiplatelet and anticoagulant medications during the ESD.

Previous studies have reported favorable prognoses for patients with CEN who were successfully treated with ESD.[7,20-24] However, a worse prognosis is expected in patients with severe comorbidities even if ESD is achieved successfully. A previous report demonstrated that the 5-year overall survival rates after colorectal ESD were 86.3% and 93.5% in patients aged ≥75 years and < 75 years, respectively ($P = 0.026$).[25] Another study that focused on patients aged >80 years showed

Table 2 Baseline characteristic comparisons between American Society of Anesthesiologists Physical Status (ASA-PS) I/II and III groups before and after propensity score matching

	Before matching ($n = 156$)				After matching ($n = 72$)			
Variables	ASA-PS I/II ($n = 113$)	ASA-PS III ($n = 43$)	SMD	*P*-value	ASA-PS I/II ($n = 36$)	ASA-PS III ($n = 36$)	SMD	*P*-value
Age, median (IQR), years	68.00 (59.00, 75.00)	75.00 (70.00, 81.00)	0.833	<0.001	74.50 (69.00, 79.00)	73.00 (68.00, 78.25)	0.034	1.000
Sex, *n* (%)			0.311	0.103			<0.001	1.000
Female	51 (45.1)	13 (30.2)			12 (33.3)	12 (33.3)		
Male	62 (54.9)	30 (69.8)			24 (66.7)	24 (66.7)		
Tumor location, *n* (%)			0.012	1.000			0.173	0.627
Rectum	44 (38.9)	17 (39.5)			15 (41.7)	12 (33.3)		
Colon	69 (61.1)	26 (60.5)			21 (58.3)	24 (66.7)		
Gross type, *n* (%)			0.116	1.000			<0.001	1.000
Flat/elevated	108 (95.6)	42 (97.7)			35 (97.2)	35 (97.2)		
Depressed	5 (4.4)	1 (2.3)			1 (2.8)	1 (2.8)		
Tumor size, median (IQR), mm	30.0 (25.00, 43.00)	30.5 (21.50, 40.00)	0.116	1.000	30.50 (25.00, 41.50)	28.00 (20.75, 39.25)	<0.001	1.000
Invasion depth, *n* (%)			0.260	0.283			0.094	1.000
Mucosa	96 (85.0)	40 (93.0)			32 (88.9)	33 (91.7)		
Submucosa	17 (15.0)	3 (7.0)			4 (11.1)	3 (8.3)		

IQR, interquartile range; SMD, standardized mean difference.

Table 3 Endoscopic submucosal dissection outcome comparisons between American Society of Anesthesiologists Physical Status (ASA-PS) I/II and III groups before and after propensity score matching

	Before matching ($n = 156$)			After matching ($n = 72$)		
Variables	ASA-PS I/II ($n = 113$)	ASA-PS III ($n = 43$)	*P*-value	ASA-PS I/II ($n = 36$)	ASA-PS III ($n = 36$)	*P*-value
Procedure characteristics, *n* (%)						
Procedure by trainee	6 (5.3)	3 (7.0)	0.707	3 (8.3)	2 (5.6)	1.000
Use of traction device	5 (4.4)	3 (7.0)	0.685	1 (2.8)	2 (5.6)	1.000
Procedure time, median (IQR), min	82.00 (50.00, 124.00)	73.00 (49.50, 114.50)	0.181	74.00 (52.25, 107.50)	72.50 (48.75, 114.25)	0.652
Hospitalization period, median (IQR), day	5.0 (5.00, 6.00)	5.0 (4.00, 6.00)	0.387	5.00 (4.75, 6.00)	5.00 (4.00, 6.00)	0.491
Resection type, *n* (%)						
En block resection	106 (93.8)	40 (93.0)	1.000	35 (97.2)	34 (94.4)	1.000
Complete resection	95 (84.1)	37 (86.0)	1.000	33 (91.7)	31 (86.1)	0.710
Curative resection	90 (79.6)	36 (83.7)	0.654	32 (88.9)	30 (83.3)	0.735
Adverse event, *n* (%)						
Delayed bleeding	2 (1.8)	2 (4.7)	0.305	0 (0.0)	2 (5.6)	0.491
Perforation	8 (7.1)	3 (7.0)	0.746	2 (5.6)	2 (5.6)	1.000
Lymphovenous invasion, *n* (%)	3 (2.7)	1 (2.3)	1.000	0 (0.0)	1 (2.8)	1.000
Salvage treatment, *n* (%)	9 (8.0)	2 (4.7)	0.728	1 (2.8)	2 (5.6)	1.000

IQR, interquartile range.

that the overall survival rate was higher in ASA-PS I/II patients than in ASA-PS III patients ($P = 0.0105$).[12] However, these studies did not focus on the severity of their comorbidities but on the age of the patients and did not adjust for baseline clinicopathological characteristics. Therefore, our study focused on the severity of comorbidities in patients of all ages and adjusted for baseline clinicopathological characteristics using a propensity score-matched analysis.

The main reason for the shorter overall survival in ASA-PS III patients could be attributed to causes other than CRC

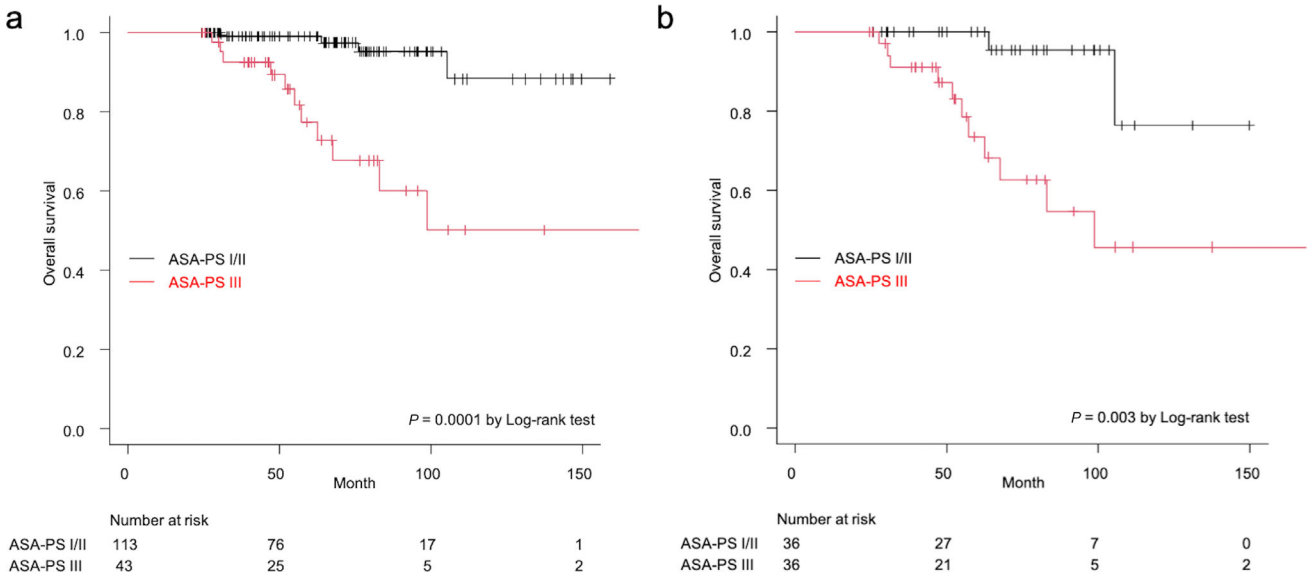

Figure 2 Comparison of long-term outcomes after colorectal endoscopic submucosal dissection. (a) Overall survival between the American Society of Anesthesiologists Physical Status (ASA-PS) I/II and III groups before matching. (b) Overall survival between the ASA-PS I/II and III groups after matching.

Table 4 Causes of death between American Society of Anesthesiologists Physical Status (ASA-PS) I/II and II groups before and after propensity score matching

	Before matching ($n = 156$)		After matching ($n = 72$)	
Causes of death, *n* (%)	ASA-PS I/II ($n = 113$)	ASA-PS III ($n = 43$)	ASA-PS I/II ($n = 36$)	ASA-PS III ($n = 36$)
All deaths	4 (100.0)	11 (100.0)	2 (100.0)	11 (100.0)
Colorectal cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other cancers[†]	3 (75.0)	3 (27.3)	1 (50.0)	3 (27.3)
Pulmonary disease	0 (0.0)	3 (27.3)	0 (0.0)	3 (27.3)
Cardiovascular disease	0 (0.0)	2 (18.2)	0 (0.0)	2 (18.2)
Cerebrovascular disease	0 (0.0)	1 (9.1)	0 (0.0)	1 (9.1)
Digestive disease	1 (25.0)	0 (0.0)	1 (50.0)	0 (0.0)
Hepatic failure	0 (0.0)	2 (18.2)	0 (0.0)	2 (18.2)

[†]Other cancers were detected during the follow-up period after colorectal endoscopic submucosal dissection.

because no CRC mortalities were noted. Instead, the mortalities could be related to the exacerbation of comorbidities, such as pulmonary, cardiovascular, and cerebrovascular diseases, that existed before colorectal ESD. Similar results were demonstrated for the long-term outcomes of gastric and esophageal ESD in patients with severe comorbidities categorized according to the ASA-PS classification.[26,27]

According to previous reports on the normal development of CRC, adenomas with an average size of 11.1 mm developed into advanced cancer in an average observation period of 64.5 months.[28] Considering this report, CEN measuring >20 mm, for which colorectal ESD is indicated, may develop into advanced cancers affecting the patient's prognosis in approximately 4–5 years. Thus, removing such lesion through ESD in patients with a life expectancy of less than 5 years is unlikely to improve the prognosis; thus, whether ESD is performed in such patients should be carefully determined. To reduce unnecessary ESD in patients with a limited life expectancy, clinicians must first determine the life expectancy based on the patient's health status. To screen patients with life expectancy that may proportionately benefit from ESD, a calculation tool using the patient's chronological age and comorbidities could be used, as previously reported.[29] Prospectively using such tools may enable clinicians to determine whether the benefits of CEN resection with ESD outweigh the procedural risks in patients with a short life expectancy.

This study has several strengths. First, to our knowledge, this is the first study to examine the long-term outcomes after colorectal ESD in patients with severe and non-severe comorbidities who were categorized according to the ASA-PS classification. Second, we adjusted for confounding factors, including age, using propensity score matching. This study provided useful data on long-term outcomes after colorectal ESD for patients with severe comorbidities. The findings of our study may assist clinicians treating patients with severe comorbidities and CEN

Table 5 Risk factors for shorter overall survival before and after propensity score matching

	Before matching ($n = 156$)				After matching ($n = 72$)			
Factor	*n*	Death case (%)	HR (95% CI)	*P*-value	*n*	Death case (%)	HR (95% CI)	*P*-value
ASA-PS								
Class I/II	113	4 (3.5)	1		36	2 (5.6)	1	
Class III	43	11 (25.6)	8.537 (2.710–26.892)	<0.001	36	11 (30.6)	7.209 (1.592–32.646)	0.010
Age	156	15 (9.6)	1.091 (1.025–1.163)	0.007	72	13 (18.1)	1.072 (0.986–1.164)	0.102
Sex								
Female	64	2 (3.1)	1		24	2 (8.3)	1	
Male	92	13 (14.1)	4.818 (1.085–21.384)	0.039	48	11 (22.9)	2.785 (0.616–12.584)	0.193
Tumor location								
Rectum	61	7 (11.5)	1		27	6 (22.2)	1	
Colon	95	8 (8.4)	0.813 (0.294–2.248)	0.689	45	7 (15.6)	0.860 (0.286–2.585)	0.788
Gross type								
Flat/elevated	150	15 (10.0)	1		70	13 (18.6)	1	
Depressed	6	0 (0.0)	0.047 (0.000–47 756.645)	0.665	2	0 (0.0)	0.047 (0.000–313 653.452)	0.703
Tumor size	156	15 (9.6)	0.997 (0.964–1.031)	0.872	72	13 (18.1)	0.991 (0.949–1.034)	0.669
Invasion depth								
Mucosa	136	12 (8.8)	1		65	11 (16.9)	1	
Submucosa	20	3 (15.0)	1.570 (0.442–5.578)	0.485	7	2 (28.6)	1.549 (0.342–7.017)	0.570

Results from univariate analysis using Cox proportional hazard.
ASA-PS, American Society of Anesthesiologists Physical Status; CI, confidence interval; HR, hazard ratio.

by clarifying whether such patients should be treated with colorectal ESD when indicated.

The present study also has some limitations. First, this was a retrospective observational study conducted at a single center; thus, prospective studies are required to evaluate the long-term outcomes of ESD for CEN in patients with severe comorbidities. However, we adjusted for confounding factors that could have influenced the relationship between long-term outcomes and ASA-PS classification using propensity score-matched analysis. The application of this method could reduce the effects of selection bias by mathematically refashioning an observational study into a randomized study. Second, the study did not evaluate other comorbidity indices such as the Charlson Comorbidity Index classification.[30] Nevertheless, scoring patient comorbidities with the ASA-PS classification is easier than with Charlson Comorbidity Index classification because only the most severe comorbidities are scored in the ASA-PS classification, and the number of items is lower in the ASA-PS classification than in the Charlson Comorbidity Index classification. Furthermore, the ASA-PS classification is known to have a significant and persistent effect on long-term survival.[31]

In conclusion, long-term outcomes after colorectal ESD were significantly worse in patients with severe comorbidities than in those with non-severe comorbidities, although no mortality due to CRC was observed. By calculating life expectancy using a patient's health status, clinicians should carefully determine whether the benefits of CEN resection with ESD outweigh the procedural risks in patients with severe comorbidities. Further studies are required to establish robust evidence on the efficacy of colorectal ESD in patients with severe comorbidities.

Acknowledgments

The authors thank the medical staff members of the Department of Endoscopy at Mie University Hospital for their contribution to this study. We would also like to thank Editage (www.editage.com) for English language editing.

Patient consent

Informed consent was obtained from all participants using the opt-out method on an institutional website.

Data availability statement. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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