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Bleeding following Endoscopic Submucosal Dissection for Early Gastric Cancer in Surgically Altered Stomach

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Bleeding · Endoscopic submucosal dissection · Early gastric cancer · Surgically altered stomach

Abstract
Introduction: Few studies have focused on bleeding following endoscopic submucosal dissection (ESD) in surgically altered stomach. We aimed to reveal the bleeding risk in surgically altered stomach following ESD for early gastric cancer (EGC). ***Methods:*** We enrolled patients with ESD for EGC at 33 institutions between 2013 and 2016. In study 1, we evaluated bleeding risk following ESD in surgically altered stomach, compared with whole stomach. In study 2, we evaluated factors associated with bleeding following ESD in patients with surgically altered stomach. ***Results:*** Of 11,452 patients, 445 patients had surgically altered stomach with the bleeding rate following ESD of 4.9%. In study 1, the bleeding risk in surgically altered stomach was not significant (odds ratio [OR], 1.37; 95% confidence interval [CI], 0.87–2.17) in the multivariate logistic regression analysis. No significant results were obtained when the surgically altered stomach was subdivided into various types. In study 2, the multivariate logistic regression analysis revealed that independent risk factors for bleeding following ESD were ischemic heart disease (OR, 7.52; 95% CI, 2.00–28.25) and P2Y12 receptor antagonist (OR, 4.81; 95% CI, 1.21–19.14). ***Discussion/Conclusion:*** In this nationwide study, we found that the bleeding risk of surgically altered stomach following ESD for EGC did not significantly differ from that of whole stomach. The risk factors for ESD in patients with surgically altered stomach were ischemic heart disease and P2Y12 receptor antagonist.

Introduction

Endoscopic resection for early gastric cancer (EGC) has been accepted as a minimally invasive treatment [1–4], and it achieves a favorable prognosis regardless of its curability [5–7]. Compared with endoscopic mucosal resection, endoscopic submucosal dissection (ESD) is advantageous because it allows en bloc resection for precise histopathological evaluation regardless of lesion size and configuration, resulting in a lower local recurrence rate [3, 8].

For patients with EGC in the remnant stomach or gastric conduit, the role of ESD may be more important because a surgical approach, in which total gastrectomy is generally selected [9], is highly invasive and impairs the postoperative quality of life. Meanwhile, although many studies have investigated bleeding following gastric ESD in patients with whole stomach [10–12], few studies have focused on bleeding following ESD in patients with surgically altered stomach. A recent systematic review reported the bleeding rate following gastric ESD in patients with surgically altered stomach as 5.3% [13], but the details of bleeding following ESD in such patients (e.g., difference in the bleeding risk among various types of surgically altered stomach, risk factors for bleeding) remain unclear. Furthermore, no studies directly compared the bleeding risk between surgically altered and whole stomach under similar baseline characteristics. All previous studies were single-institution studies with relatively small numbers of cases [14–21], which may have made it difficult to clarify the details of bleeding following gastric ESD in patients with surgically altered stomach.

Recently, we conducted a nationwide multicenter retrospective study to establish a prediction model for bleeding following ESD for EGC (BEST-J score) in patients with whole stomach [22]. This study included over 10,000 cases, and several findings about bleeding following ESD have been clarified by using this database [23–28]. However, these studies did not include patients with surgically altered stomach and, thus, no findings about surgically altered stomach have been clarified in this database. The aim of the present study was to reveal the bleeding risk of surgically altered stomach following ESD for EGC.

Materials and Methods

Patient Selection and Data

This is a sub-analysis of a recent multicenter retrospective study [22]. This study included patients who experienced ESD for EGC at 33 institutions in Japan between November 2013 and October 2016. Among them, patients who did not meet the exclusion criteria were enrolled in the present study. The exclusion criteria were as follows: (i) ESD was not completed, (ii) follow-up duration was less than 28 days following ESD, (iii) the ulcer was closed or covered with polyglycolic acid sheets and fibrin glue following ESD, (iv) clinical data were not available due to patient refusal, (v) photodynamic therapy following ESD was performed, and (vi) invasion of the muscularis propria or deeper tissue was observed pathologically (Fig. 1). In the present study, all terminology and classification of tumor size, macroscopic type, histological type, and depth of tumor invasion were in accordance with the Japanese classification of gastric carcinoma [29]. The present study was conducted according to the guidelines of the Declaration of Helsinki and was approved by each institution's review board.

ESD Procedure

ESD was performed according to a standard technique at all institutions, and the details of the ESD procedures have been described elsewhere [30]. After excision of the lesion, electrocoagula-

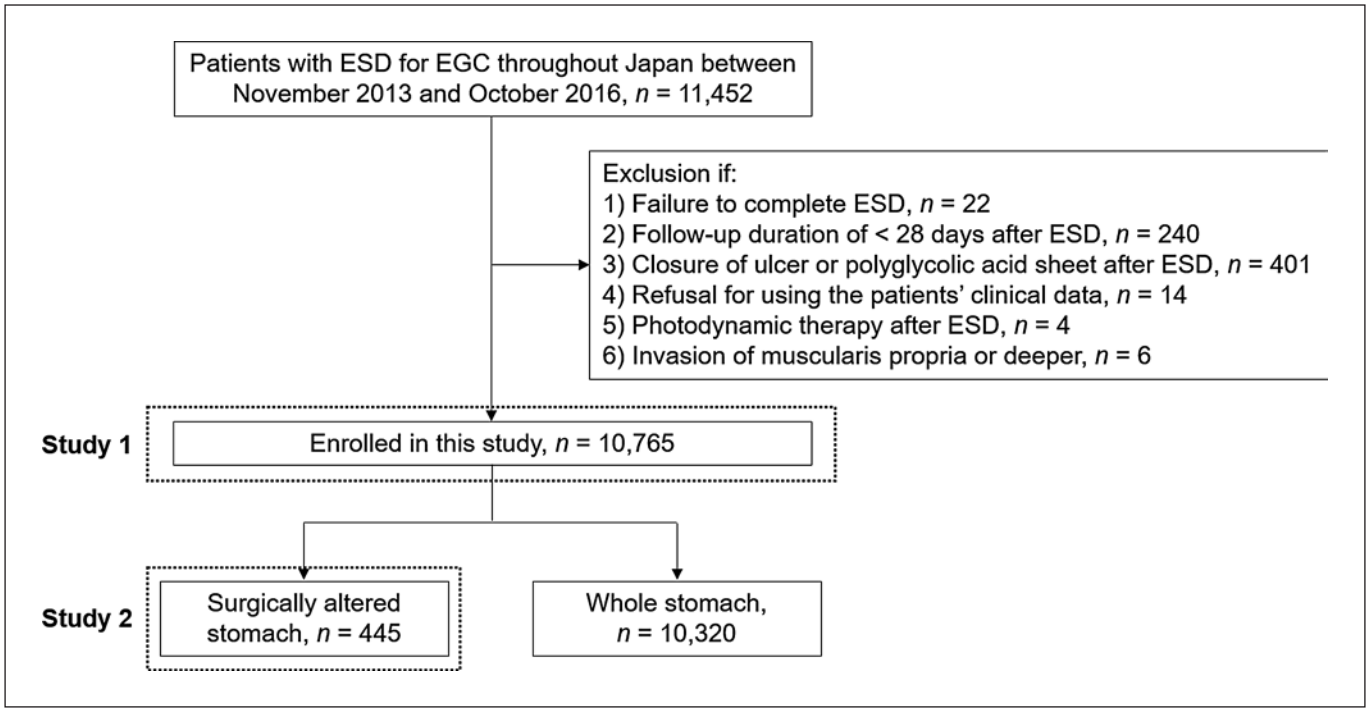

Fig. 1. Flowchart of the patient enrollment. EGC, early gastric cancer; ESD, endoscopic submucosal dissection.

tion and/or clipping was performed on the exposed vessels at the ulcer bed of ESD for the purpose of preventing postoperative bleeding. During and following ESD, proton-pump inhibitor, potassium-competitive acid blocker, or histamine-2 receptor antagonist was administered to all patients according to the selection of each doctor. Based on the Japanese guidelines available in Japan since 2012 [31], the clinicians decided whether antithrombotic agents should be temporarily stopped or not, and whether heparin bridging therapy should be conducted or not. Scheduled second-look endoscopy depended on the institution.

Study 1: Comparison of the Bleeding Risk following ESD for EGC between Surgically Altered and Whole Stomach

We evaluated the bleeding risk following ESD for EGC in surgically altered stomach compared with whole stomach. Furthermore, the bleeding risk following ESD in each type of surgically altered stomach (gastric remnant after distal gastrectomy [DG], that after proximal gastrectomy [PG], gastric conduit, and others), with reference to whole stomach, was evaluated. Bleeding following ESD was defined as active bleeding confirmed by emergent endoscopy, which was performed due to hematemesis, melena, and progression of anemia (>2 g/dL decrease of hemoglobin), until 28 days following ESD.

Study 2: Application of BEST-J Score and Factors Associated with Bleeding following ESD for EGC in Patients with Surgically Altered Stomach

First, the BEST-J score was applied to patients with surgically altered stomach, and its discriminative ability for bleeding following ESD was evaluated. Subsequently, factors associated with bleeding following ESD were examined in such patients. Candidate factors were age ≥75 years, male sex, ischemic heart disease, liver cirrhosis, chronic kidney disease (CKD) with hemodialysis, aspirin, P2Y12 receptor antagonist (P2Y12RA), cilostazol, warfarin, direct oral anticoagulant (DOAC), discontinuation of antithrombotic agents (each kind of agents), heparin bridging therapy, replacement of antiplatelet agents, type of surgically altered stomach (gastric remnant after PG, gastric conduit, and others, compared with gastric remnant after DG), multiple tumors, lower third in tumor location, tumor size >30 mm, undifferentiated type, tumor invasion into submucosa ≥500 μm (SM2), ulceration, ESD procedure time >120 min, piecemeal resection, and second-look endoscopy. Lower third in tumor location was defined as the center of the tumor in gastric antrum, irrespective of the type of surgically altered stomach.

Statistical Analyses

Categorical variables were summarized as the count and proportion, and categorical data were compared using the χ^2 test. The threshold for significance was $p < 0.05$. All statistical analyses were performed using SPSS version 23.0 for Windows software (IBM Corp., Armonk, NY, USA).

In study 1, bleeding risk of surgically altered stomach, compared with whole stomach following ESD was evaluated using the logistic regression model. The risk was adjusted by 22 variables in the adjusted model 1: age ≥75 years, male sex, comorbidities (ischemic heart disease, liver cirrhosis, and CKD with hemodialysis), antithrombotic therapy (aspirin, P2Y12RA, cilostazol, warfarin,

Table 1. Baseline characteristics of the enrolled patients

	Surgically altered stomach (*n* = 445)	Whole stomach (*n* = 10,320)	*p* value
Age ≥75 years, *n* (%)	193 (43.4)	4,184 (40.5)	0.237
Sex, *n* (%)			
Male	380 (85.4)	7,660 (74.2)	<0.001
Female	65 (14.6)	2,660 (25.8)	
Comorbidities, *n* (%)			
Ischemic heart disease	14 (3.1)	730 (7.1)	0.001
Liver cirrhosis	5 (1.1)	192 (1.9)	0.363
CKD with hemodialysis	3 (0.7)	155 (1.5)	0.222
Antithrombotic therapy, *n* (%)			
Aspirin	28 (6.3)	981 (9.5)	0.023
P2Y12RA	17 (3.8)	460 (4.5)	0.629
Cilostazol	12 (2.7)	236 (2.3)	0.519
Warfarin	10 (2.2)	326 (3.2)	0.330
DOAC	12 (2.7)	253 (2.5)	0.753
Interruption of antithrombotic agents, *n* (%)			
One kind of agent	52 (11.7)	1,215 (11.8)	0.836
Two kinds of agents	6 (1.3)	181 (1.8)	
Three kinds of agents	0 (0.0)	10 (0.1)	
Heparin bridging	16 (3.6)	429 (4.2)	0.618
Replacement of antiplatelet agents	4 (0.9)	121 (1.2)	0.820
Lesion, *n* (%)			
Multiple tumors	41 (9.2)	1,294 (12.5)	0.042
Lower third in tumor location	66 (14.8)	4,688 (45.4)	<0.001
Undifferentiated type	34 (7.6)	506 (4.9)	0.011
Tumor size >30 mm	37 (8.3)	1,217 (11.8)	0.026
SM2	38 (8.5)	655 (6.3)	0.071
Ulceration (scar)	55 (12.4)	977 (9.5)	0.045
Procedure, *n* (%)			
Procedure time >120 min	113 (25.5)	1,886 (18.3)	<0.001
Piecemeal resection	9 (2.0)	61 (0.6)	0.002
Second-look endoscopy	303 (68.1)	7,384 (71.6)	0.119
Type of surgically altered stomach			
Gastric remnant after DG	276 (62.0)	–	–
Gastric remnant after PG	45 (10.1)	–	
Gastric conduit	79 (17.8)	–	
Others	45 (10.1)	–	

CKD, chronic kidney disease; DG, distal gastrectomy; DOAC, direct oral anticoagulant; PG, proximal gastrectomy; P2Y12RA, P2Y12 receptor antagonist; SM2, submucosal invasion ≥500 μm from the muscularis mucosa.

DOAC, discontinuation of antithrombotic agents, heparin bridging therapy, and replacement of antiplatelet agents), lesion characteristics (multiple tumors, lower third in tumor location, tumor size >30 mm, undifferentiated type, SM2, and ulceration), and procedures (ESD procedure time >120 min, piecemeal resection, and second-look endoscopy). Risk of each type of surgically altered stomach was also adjusted by 22 variables in the adjusted model 2.

In study 2, the discriminative ability for bleeding following ESD was evaluated by the C-statistic. Factors associated with bleeding following ESD in patients with surgically altered stomach were evaluated using the logistic regression model. Variables with $p < 0.05$ in the univariate analysis were entered into the multivariate model.

Result

Baseline Characteristics and the Bleeding Rates

Of the total of 11,452 patients who experienced ESD for EGC, we excluded 687 patients who met the exclusion criteria. Among these enrolled patients, the numbers of patients with surgically altered and whole stomach were 445 and 10,320, respectively (Fig. 1). Patients with surgically altered stomach consisted of 276 patients with gastric remnant after DG, 45 with that after PG, 79 with gastric conduit, and 45 with others (Table 1). The bleeding

Table 2. Risk of bleeding following ESD for EGC in patients with surgically altered stomach compared with whole stomach

	Crude		Adjusted model 1[a]		Adjusted model 2[a]	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Whole stomach	1 (Reference)		1 (Reference)			
Surgically altered stomach	1.05 (0.68–1.62)	0.842	1.37 (0.87–2.17)	0.176		
Whole stomach	1 (Reference)				1 (Reference)	
Gastric remnant after DG	0.99 (0.57–1.75)	0.983			1.42 (0.79–2.57)	0.240
Gastric remnant after PG	1.96 (0.70–5.50)	0.200			1.89 (0.64–5.54)	0.249
Gastric conduit	0.79 (0.25–2.53)	0.695			0.96 (0.29–3.17)	0.940
Others	0.94 (0.23–3.87)	0.926			1.21 (0.28–5.21)	0.795

CKD, chronic kidney disease; CI, confidence interval; DG, distal gastrectomy; DOAC, direct oral anticoagulant; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; OR, odds ratio; PG, proximal gastrectomy; P2Y12RA, P2Y12 receptor antagonist; SM2, submucosal invasion ≥500 μm from the muscularis mucosa. [a] Adjusted by age ≥75 years, male sex, ischemic heart disease, liver cirrhosis, and CKD with hemodialysis, aspirin, P2Y12RA, cilostazol, warfarin, DOAC, interruption of antithrombotic agents, heparin bridging therapy, replacement of antiplatelet agents, multiple tumors, lower third in tumor location, tumor size >30 mm, undifferentiated type, SM2, ulceration, ESD procedure time >120 min, piecemeal resection, and second-look endoscopy.

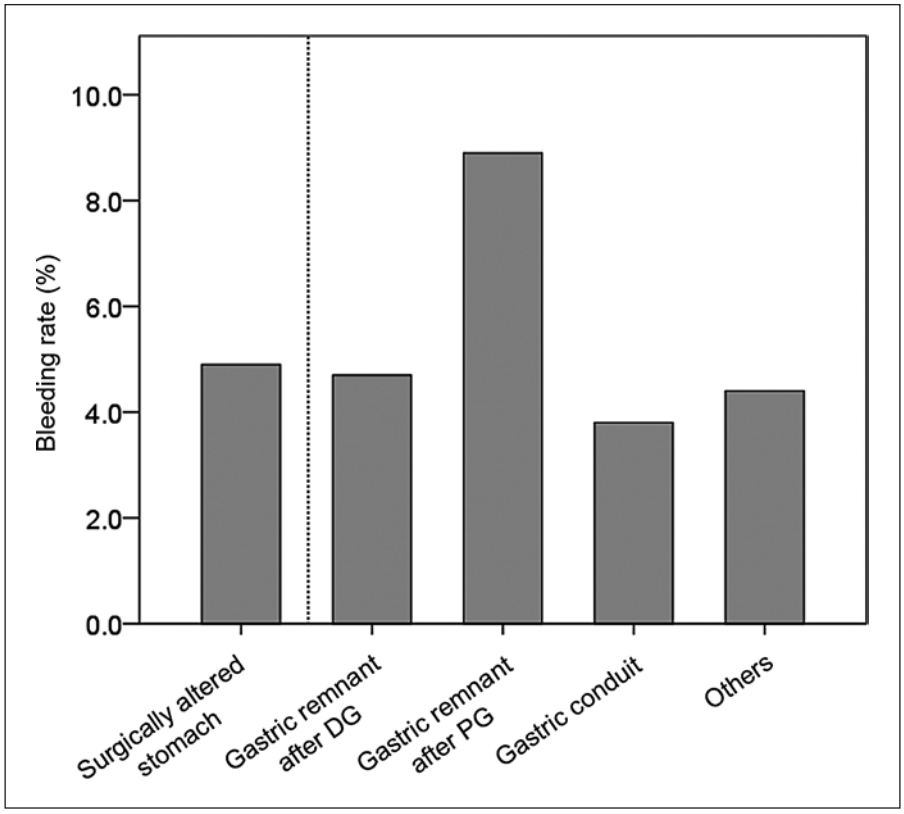

Fig. 2. The bleeding rate following ESD for EGC in patients with surgically altered stomach. The bleeding rate following ESD for EGC was 4.9% in patients with surgically altered stomach. In detail, the bleeding rates in those with gastric remnant after DG, that after PG, gastric conduit, and others were 4.7%, 8.9%, 3.8%, and 4.4%, respectively, the difference of which was not significant ($p = 0.622$). DG, distal gastrectomy; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; PG, proximal gastrectomy.

rate following ESD for EGC was 4.9% in patients with surgically altered stomach (Fig. 2). In detail, the bleeding rates in patients with gastric remnant after DG, that after PG, gastric conduit, and others were 4.7%, 8.9%, 3.8%, and 4.4%, respectively, the difference of which was not statistically significant ($p = 0.622$).

Study 1: Comparison of the Bleeding Risk following ESD for EGC between Surgically Altered and Whole Stomach

We conducted two multivariate analyses. In the adjusted model 1, the bleeding risk of surgically altered stomach following ESD for EGC, with reference to whole

Table 3. Distribution of points and bleeding rates in the BEST-J score

Risk score				Risk classification			
Total points	patients (n = 445)	bleeding (n = 22)	bleeding rate (95% CI), %	risk categories	patients (n = 445)	bleeding (n = 22)	bleeding rate (95% CI), %
0	275	12	4.4 (2.3–7.5)	Low risk	385	16	4.2 (2.4–6.7)
1	110	4	3.6 (1.0–9.0)				
2	30	1	3.3 (1.4–3.5)	Intermediate risk	30	1	3.3 (0.1–17.2)
3	18	2	11.1 (1.4–34.7)	High risk	25	2	8.0 (1.0–26.0)
4	7	0	0.0 (0.0–41.0)				
5	3	2	66.7 (9.4–99.2)	Very high risk	5	3	60.0 (14.7–94.7)
6	2	1	50.0 (1.3–98.7)				

CI, confidence interval.

stomach, was not significant (odds ratio [OR], 1.37; 95% confidence interval [CI], 0.87–2.17) (Table 2). When each type of surgically altered stomach was included in the multivariate model (adjusted model 2), no significant results were also acquired (Table 2).

Study 2: Application of BEST-J Score and Factors Associated with Bleeding following ESD for EGC in Patients with Surgically Altered Stomach

Table 3 shows the bleeding rates in the risk score and classification of the BEST-J score after applying the BEST-J score for patients with surgically altered stomach. The bleeding rates following ESD in the low-, intermediate-, high-, and very high-risk categories were 4.2%, 3.3%, 8.0%, and 60.0%, respectively. The C-statistics of the risk score and classification in the BEST-J score for bleeding following ESD were 0.57 (95% CI, 0.43–0.71) and 0.58 (95% CI, 0.45–0.72), respectively, which indicates modest discriminative ability.

The results of univariate and multivariate logistic regression analyses for factors associated with bleeding following ESD for EGC in patients with surgically altered stomach are presented in Table 4. In the univariate analysis, significant factors for bleeding following ESD for EGC in patients with surgically altered stomach were ischemic heart disease, P2Y12RA, and warfarin. Regarding the type of surgically altered stomach, the risk of gastric remnant after PG, gastric conduit, and others for bleeding, with reference to gastric remnant after DG, was not statistically significant. Multivariate analysis showed that independent risk factors for bleeding following ESD in patients with surgically altered stomach were ischemic heart disease (OR, 7.52; 95% CI, 2.00–28.25) and P2Y12RA (OR, 4.81; 95% CI, 1.21–19.14) (Table 4). Warfarin tended to be associated with bleeding (OR, 3.74; 95% CI, 0.63–22.26), but it did not reach statistical significance (p = 0.147).

The relationship between bleeding following ESD and each status of P2Y12RA was also investigated. In the result, the bleeding rates in the interruption, replacement to aspirin/cilostazol, and continuation of P2Y12RA were 9.1% (1/11), 33.3% (1/3), and 33.3% (1/3), respectively.

Discussion/Conclusion

Despite the fact that many studies have investigated and discussed bleeding following gastric ESD in patients with whole stomach [10–12, 32], few studies have evaluated the details of bleeding following gastric ESD in patients with surgically altered stomach, mainly due to the small numbers of cases in previous studies [14–21]. Thus, the present study evaluated it using the data of a large-scale multicenter study.

The present study included some clinical implications. First, we revealed that the bleeding risk of surgically altered stomach following ESD for EGC was not significant, compared with whole stomach. Similar results were obtained when surgically altered stomach was subdivided into various types. Furthermore, the bleeding risk of various types of surgically altered stomach, with reference to gastric remnant after DG, was not significant. In surgically altered stomach, bile reflux to the gastric remnant is frequently observed in cases with DG [33]. It has been reported that bile acids and pancreatic proteolytic enzymes can damage the gastric mucosa [33, 34]; however, we found that its influence on the incidence of bleeding events following ESD may be small.

Second, the discriminative ability of the BEST-J score, which had been developed from patients with whole

Table 4. Risk factors of bleeding following ESD for EGC in patients with surgically altered stomach

	Crude		Adjusted	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age				
≥75 years	1.60 (0.68–3.80)	0.282		
Sex				
Male	1.75 (0.40–7.67)	0.458		
Ischemic heart disease				
Yes	9.18 (2.63–32.09)	0.001	7.52 (2.00–28.25)	0.003
Liver cirrhosis				
Yes	–	–		
CKD with hemodialysis				
Yes	–	–		
Aspirin				
Yes	0.70 (0.09–5.39)	0.731		
P2Y12RA				
Yes	4.61 (1.22–17.43)	0.024	4.81 (1.21–19.14)	0.026
Cilostazol				
Yes	1.78 (0.22–14.47)	0.588		
Warfarin				
Yes	5.19 (1.03–26.03)	0.045	3.74 (0.63–22.26)	0.147
DOAC				
Yes	1.78 (0.22–14.47)	0.588		
Discontinuation of antithrombotic agents				
Each kind of agents	1.60 (0.65–3.93)	0.306		
Heparin bridging therapy				
Yes	2.92 (0.62–13.74)	0.175		
Replacement of antiplatelet agents				
Yes	6.67 (0.67–66.84)	0.107		
Type of surgically altered stomach				
Remnant after PG	1.97 (0.61–6.35)	0.254		
Gastric conduit	0.80 (0.22–2.88)	0.731		
Others	0.94 (0.21–4.32)	0.938		
The number of tumors				
Multiple	1.60 (0.45–5.65)	0.466		
Tumor location				
Lower-third	1.75 (0.62–4.91)	0.291		
Tumor size				
>30 mm	2.63 (0.84–8.21)	0.097		
Tumor differentiation				
Undifferentiated	1.22 (0.27–5.46)	0.793		
Tumor depth				
SM2	1.08 (0.24–4.79)	0.924		
Ulceration[a]				
Positive	1.22 (0.27–5.46)	0.793		
ESD procedure time[a]				
>120 min	1.73 (0.70–4.23)	0.233		
Resection type				
Piecemeal	2.47 (0.30–20.67)	0.404		
Second-look endoscopy				
Yes	0.81 (0.33–1.98)	0.646		

CKD, chronic kidney disease; CI, confidence interval; DOAC, direct oral anticoagulant; EGC, early gastric cancer; ESD, endoscopic submucosal dissection; OR, odds ratio; PG, proximal gastrectomy; P2Y12RA, P2Y12 receptor antagonist; SM2, submucosal invasion ≥500 μm from the muscularis mucosa. [a] There were 2 and 1 missing cases in ulceration and ESD procedure time, respectively.

stomach [22], for bleeding was not satisfactory in surgically altered stomach. The C-statistics of the risk score and classification in the BEST-J score were 0.57 and 0.58, respectively, which were lower than 0.70 that is considered sufficient to make clinically useful individual predictions [35]. Thus, caution is needed for applying the BEST-J score for patients with surgically altered stomach.

Subsequently, we evaluated the risk factors for bleeding following ESD for EGC in patients with surgically altered stomach. Among the candidate variables, ischemic heart disease and P2Y12RA were significant risk factors. Regarding ischemic heart disease, a previous systematic review revealed cardiopathy (ischemic heart disease in most studies) as one of the risk factors for bleeding following ESD, mainly in patients with whole stomach [36]. However, this systematic review showed that its risk is most probably associated with the use of antithrombotic agents [36]. In the present study, when adjusted by all antithrombotic agents, the risk of ischemic heart disease remained significant (data not shown). Thus, this factor itself may have a potential risk for bleeding in patients with surgically altered stomach. Although the mechanism is unclear, clinicians should pay attention to the bleeding risk in such patients. Meanwhile, P2Y12RA is a well-known risk factor for bleeding following ESD in patients with whole stomach [22, 37]. Then, should P2Y12RA be interrupted before ESD? Although the bleeding rate in patients with P2Y12RA was lower in interruption than in replacement with aspirin/cilostazol or continuation, interruption may lead to thromboembolism [32]. Considering the more serious condition in thromboembolism [31], interruption of P2Y12RA may not be recommended in the current status; however, it is difficult to make a definite conclusion from this study and further studies are required.

The strength in the present study is that this study included the largest number of cases. Indeed, the number of patients with surgically altered stomach is over three times larger than that in the largest study to date [18]. This enabled us to perform a multivariate analysis of risk factors for bleeding following ESD for EGC in patients with surgically altered stomach.

This study has several limitations. First, this is a retrospective style, which may include a potential bias. Second, we did not investigate whether the lesion was on the suture line/anastomotic site or not. Although no significant results on bleeding following ESD were shown in the previous study [18], this location may have a potential to be a confounding factor for the risk of bleeding. Third, despite the largest cohort to date, the sample size is still not large enough, which led to relatively wide 95% CIs in the multivariate logistic regression analysis. However, our study results are likely significant because this is the first analysis of the details of bleeding following ESD for EGC in patients with surgically altered stomach by using the data of a multicenter cohort. Fourth, the type of acid-suppressive agents was not evaluated in this study. Although it was proven that the type affected the bleeding risk following gastric ESD [38, 39], the methods of administrating acid-suppressive agents were not controlled and various patterns were shown. Thus, it was difficult to evaluate the relationship between the type of acid-suppressive agents and bleeding risk. Lastly, CKD with hemodialysis, which was proven to be a risk factor for bleeding following ESD in whole stomach [22], could not be calculated in the analysis of risk factors for bleeding in patients with surgically altered stomach due to the very small number of cases of this disease.

In conclusion, the bleeding risk of surgically altered stomach following ESD for EGC did not significantly differ from that of whole stomach. Furthermore, we first found that the risk factors for ESD in patients with surgically altered stomach were ischemic heart disease and P2Y12RA. These findings may provide some insights in this field.

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Statement of Ethics

This study protocol was reviewed and approved by the Ethics Committee of Tohoku University Graduate School of Medicine (2018-1-48) (including approval of Ethics Committee for the University of Tokyo by central Ethics Committee of Tohoku University Graduate School of Medicine), the Ethics Committee of the Cancer Institute Hospital (2018-1163), the Institutional Review Board of Shizuoka Cancer Centre (T30-15-30-1-3), the Ethics Committee of Toranomon Hospital (1683), the Institutional Review Board of Ishikawa Prefectural Central Hospital (1131), Ethical Committee of Osaka City University Graduate School of Medicine (4089), the Ethics Committee of Fukushima Medical University (30101), the Ethics Committee of the Jikei University School of Medicine for Biomedical Research (30-170 [9191]), the Ethical Committee on Clinical Investigation of Kobe University Hospital (180126), the Institutional Review Board of Tonan Hospital (338), Research Ethics Committee of Wakayama Medical University (2018-2384), the Ethics Committee of Ehime University Graduate School of Medicine (1807001), the Ethics Committee of Ehime Prefectural Central Hospital (No. 30-25), the Ethics Committee of Osaka General Medical Center (30-S03-004), the Ethics Committee of Hirosaki University Graduate School of Medicine (2018-1079), the Ethics Committee of Fukui Prefectural Hospital (18-15), Institutional Review Board Yamaguchi University Hospital (H30-058), Research Ethics Committee of the Graduate School of Medicine and School of Medicine, Chiba University (3189), Osaka City General Hospital Research Ethics Review Board (1805018), the Institutional Review Board of Toyonaka Municipal Hospital (2018-04-04), Ethics Committee of Nagasaki University Hospital (18091014), Hospital Ethics Committee Juntendo University Hospital (18-097), Osaka University Clinical Research Review Committee (18056), Shiga University of Medical Science Research Ethics Committee (R2018-029), Kansai Rosai Hospital IRB (18D046g), Institutional Review Board for Ethics in Clinical Study of Saitama Medical Centre, Saitama Medical University (1940), the Ethics Committee of National Centre for Global Health and Medicine (NCGM-G-002554-00), the Ethics Committee of Kanazawa University School of Medicine (2018-043-2823), the Ethics Committee of the University of Tsukuba (H30-107), the Ethics Committee of Gunma University Graduate School of Medicine (HS2018-102), the Ethics Committee of Shuto General Hospital (H30-5), and the Institutional Review Board of National Hospital Organization Hakodate National Hospital (H30-0514003). The need for obtaining informed consent from each patient was waived via the opt-out method on each participating institution's website. Informed consent of ESD was obtained from all patients before the procedure in accordance with the institutional protocol.

Conflict of Interest Statement

Mitsuhiro Fujishiro declared that he received lecture honoraria from Takeda Pharmaceutical, EA Pharma, and Nihon Pharmaceutical, and his department received research grants from HOYA Pentax, EA Pharma, Eisai, Taiho Pharmaceutical, AbbVie GK, Nippon Kayaku, Chugai Pharmaceutical, Gilead Sciences, KYORIN Pharmaceutical, and Mitsubishi Tanabe Pharma outside the submitted work.

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Author Contributions

Conception and design; analysis and interpretation of data; and drafting of the manuscript: Hiroyuki Odagiri and Waku Hatta; acquisition of data: Hiroyuki Odagiri, Waku Hatta, Yosuke Tsuji, Toshiyuki Yoshio, Yohei Yabuuchi, Daisuke Kikuchi, Shigetsugu Tsuji, Yasuaki Nagami, Takuto Hikichi, Masakuni Kobayashi, Yoshinori Morita, Tetsuya Sumiyoshi, Mikitaka Iguchi, Hideomi Tomida, Takuya Inoue, Tatsuya Mikami, Kenkei Hasatani, Jun Nishikawa, Tomoaki Matsumura, Hiroko Nebiki, Dai Nakamatsu, Ken Ohnita, Hiroya Ueyama, Yoshito Hayashi, Mitsushige Sugimoto, Shinjiro Yamaguchi, Tomoki Michida, Tomoyuki Yada, Yoshiro Asahina, Toshiaki Narasaka, Shiko Kuribayashi, Shu Kiyotoki, and Katsuhiro Mabe; critical revision of the manuscript: Haruhisa Suzuki and Mitsuhiro Fujishiro; statistical analysis: Waku Hatta; study supervision: Mitsuhiro Fujishiro, Atsushi Masamune, and Shu Hoteya. All authors listed have contributed substantially to the design, data collection and analysis, and editing of the manuscript.

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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