Table 3 Difference of patients who underwent endoscopy with/without cessation

	With cessation ($n = 724$)	Without cessation ($n = 246$)	*P*-value
Age (years)	71.9 ± 7.8	70.2 ± 8.9	NS
Gender (M : F)	532:192	183:63	NS
Number of agents			< 0.05
Single-agent	620	184	
Multi-agents	104	62	
Two agents	85	56	
Three agents	11	3	
More than four agents	8	3	
Modality			< 0.05
Esophagogastroduodenoscopy	511	194	
Colonoscopy	213	52	
Endoscopic procedures			< 0.05
Non-invasive procedures	385	204	
Biopsy	268	40	
Mucosal resection	71	2	
Prophylactic antacid agent			NS
None	377	114	
Proton pump inhibitor	170	65	
H2 receptor antagonist	81	33	
Others	96	34	

NS, Not significant.

hundred and ninety-one patients (19.7%) received warfarin as anticoagulants. The most common antiplatelet agent was aspirin in 563 patients (58.0%), followed by clopidogrel, eicosapentaenoic acid preparation, and cilostazol. Four hundred and seventy-nine patients (49.4%) received agents for peptic ulcer healing including 349 patients (36.0%) on proton pump inhibitors (24.2%) or H2 receptor antagonists (11.8%).

Proportion of pre-existing comorbidities of patients

The most common comorbidity requiring anticoagulants or antiplatelet agents was ischemic heart disease in 271 patients (27.9%), followed by cerebrovascular disturbance and arrhythmia in 216 (22.3%) and 164 patients (16.9%), respectively (Fig. 2). Among 271 patients with ischemic heart disease, 141 patients (52.1%) had undergone implantation of a mechanical stent in a coronary artery.

Cessation period

The histograms of cessation periods before endoscopy are shown in Figure 3. Most patients underwent endoscopy without cessation or after a cessation period of 6–7 days (58.5%). For further analysis, histograms of the cessation period in patients receiving warfarin, aspirin, ticlopidine, and a combination of aspirin and ticlopidine are shown in Figure 4.

Among 970 patients, valid responses were obtained from 941 patients. The cessation period after endoscopy is shown in Figure 5. Among 572 patients who underwent endoscopy without invasive procedures, 505 patients (88.3%) restarted these agents within 2 days. On the other hand, among 369 patients who underwent endoscopy with invasive procedures, 316 patients (85.6%) restarted within 4 days.

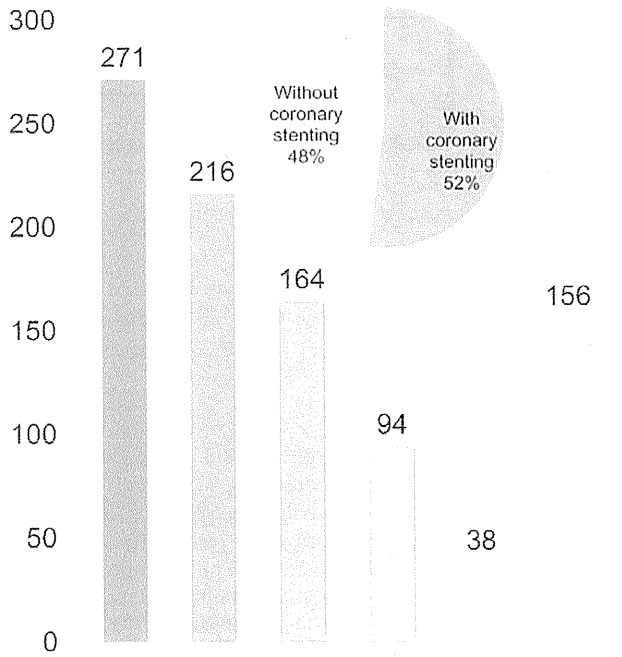

Figure 2 Comorbidities of 970 patients. ▩, ischemic heart disease; ▩, cerebrovascular disturbance; ▩, arrhythmia; ▩, peripheral vascular disturbance; ▩, valvular heart disease; ▩, other disease.

Specialty of physicians who determined cessation periods

Cessation periods before endoscopy were determined by non-gastroenterologists for 51% of patients. For 49% of patients, the cessation period before endoscopy was determined by gastroen-

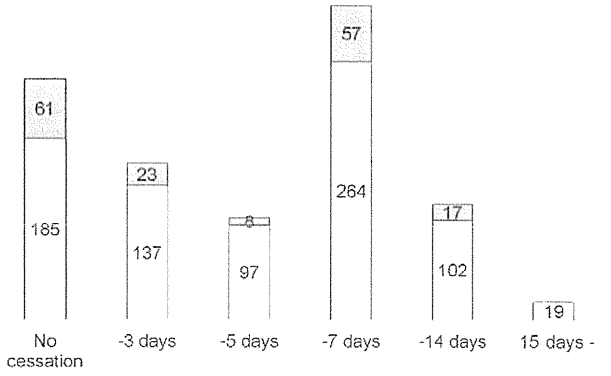

Figure 3 Cessation periods before endoscopy for 970 patients receiving single- or multi-agent therapies. ▨, multi-agent; □, single-agent.

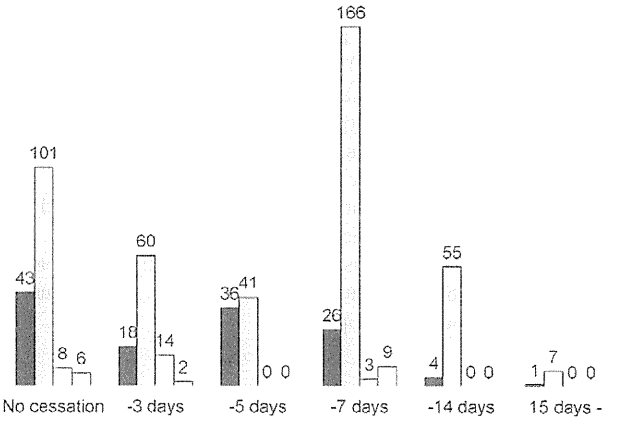

Figure 4 Cessation periods before endoscopy for patients receiving warfarin (WFR), aspirin (ASP), ticlopidine (TPD), or a combination of aspirin and ticlopidine. ■, WFR; □, ASP; □, TPD; □, ASP + TPD.

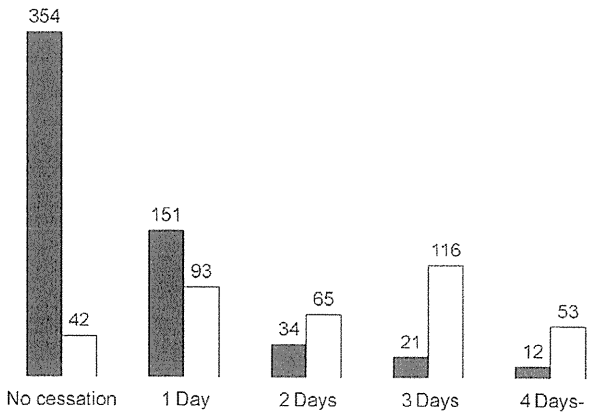

Figure 5 Cessation periods after endoscopy with or without invasive procedures for 941 patients. ■, without invasive procedure; □, with invasive procedure.

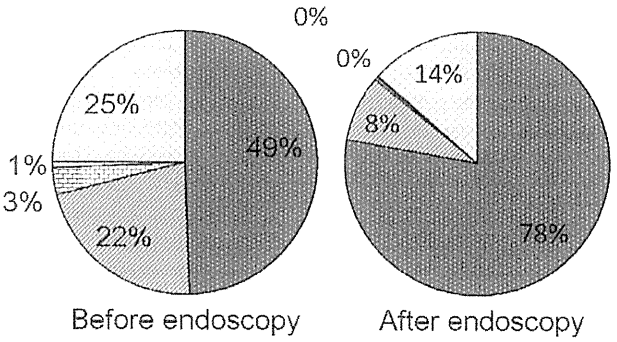

Figure 6 Specialties of doctors who determined cessation periods before and after endoscopy. ■, gastroenterology specialist; ▨, cardiology specialist; ▤, neurology specialist; ▣, orthopedic specialist; □, other specialist.

terologists (Fig. 6). By contrast, for 78% of the patients, cessation periods after endoscopy were determined by gastroenterologists, including endoscopists.

Complications

In this study, two patients experienced major complications that might be related to thromboembolic events or gastrointestinal bleeding (Table 4). One patient on warfarin for arrhythmia restarted warfarin on the third day after colonic EMR and experienced hematochezia on the fourth day. This patient underwent endoscopic clipping and recovered well. The other patient had previously undergone pacemaker implantation for arrhythmia and died due to sudden onset ventricular tachycardia on the 14th day after endoscopy without any invasive procedures. This patient continued clopidogrel during the periendoscopic period. The 95% confidence interval of the major complication rate of all patients taking these agents is estimated to be 0.0–0.7%.

Procedures without cessation

Invasive procedures were performed without cessation in 42 patients (two resections and 40 biopsies in 35 EGDs and seven CSs). Both resections were performed in CSs. Among these, no patient experienced major bleeding complications. The 95% confidence interval of the major complication rate in patients who underwent invasive procedures without cessation is estimated to be 0.0–8.4%.

Discussion

Previous studies revealed the current clinical daily practice concerning management of antithrombotics in a single but high volume endoscopy center.[11,12] Confusion in clinical daily practice might be the result of low permeation of the guideline, and the same may be true throughout Japan. Generally, absence of a unified guideline may create a confusing situation about management of antithrombotic agents during the periendoscopic period in Japan.

Table 4 Profile of patients who experienced major complications in this study

No.	Age (years)	Gender	Co-morbidity	Agents	Cessation (days)		Modality	Procedure	Complication	Treatment
					Before	After				
1	61	M	Arrythmia	WFR	5	3	CS	EMR	Hematochezia on 4th day	Clipping
2	85	M	Arrythmia	CP	0	0	EGD	No	CPA on 14th day	CPR

CP, clopidogrel; CPA, cardiopulmonary arrest; CPR, cardiopulmonary resuscitation; CS, colonoscopy; EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; WFR, warfarin.

Although the JGES guideline recommends 3 days for aspirin, 5 days for ticlopidine, and 7 days for combination therapy with both, most patients discontinued these agents for 0 or 7 days. This tendency means that most physicians order 7 days' cessation uniformly for patients with a low thromboembolic risk state. We speculate that this length of cessation was determined by considering the lifetime of the platelet. Consequently, permeation of the cessation period recommended in the JGES guideline is low. In other words, lack of evidence to support the guideline might create a low permeation because the cessation period recommended in the JGES guideline is based upon only one article.[19]

This study revealed complications in patients taking these agents during the periendoscopic period. Only one major bleeding complication was observed in this study. Although this case required endoscopic hemostasis, this case recovered well with no blood transfusion. On the other hand, the other complication was a severe and lethal cardiogenic event. Even though this case underwent endoscopy without cessation and was not finally diagnosed as a thromboembolic complication, this case demonstrates the severity of cardiogenic events that can occur in a high thromboembolic risk state. By contrast, no bleeding complications were observed among 42 patients that underwent invasive procedures without cessation even though many endoscopists might hesitate to perform invasive procedures for patients receiving antithrombotic agents as shown in Table 3.

It is difficult to conclude that thromboembolic complications can result in a more severe outcome than bleeding complications based on this study alone. However, 3 of 13 representative endoscopists at different institutions experienced thromboembolic complications during the cessation period.[10] Among them, one endoscopist experienced a lethal outcome due to thromboembolic complications although none of the 13 endoscopists experienced a lethal outcome due to bleeding complications. Furthermore, Sung JJ *et al.* recently reported that continuation of low-dose aspirin for patients with peptic ulcer bleeding may increase the risk for recurrent bleeding but reduces mortality rates.[20] Additionally, postprocedural bleeding events in the periendoscopic period are not increased in anticoagulated patients.[21] Considering the severity of thromboembolic complications during the cessation period and the absence of solid evidence for racial differences of bleeding risk and thromboembolic risk, less invasive procedures or biopsies might be feasible for Asians as the Western guidelines recommend.

This study also revealed an important clue about restart of these agents after endoscopy. In most guidelines, including the JGES guideline, restart of antithrombotic therapy is recommended shortly after endoscopy as low risks of bleeding are confirmed after endoscopy depending on procedure-specific circumstances. However, there are no solid criteria to judge restart. In this study, approximately 86% of patients who underwent invasive procedures after a cessation period restarted these agents within 4 days. Among them, 37% of patients restarted these agents on the day of or the day after endoscopy. Considering the low rate of bleeding complications in this study, restart of therapy within 4 days or sometimes within 2 days can be reasonable for outpatient procedures.

The limitation of this study is its small number of participants and low complication rate, although we conducted a multicenter study to recruit about 1000 patients. As a result, the confidence interval is too wide to evaluate safety, particularly for the complication rate in patients undergoing invasive procedures.

In summary, this multi-center study revealed a confusing clinical situation due to absence of a unified guideline in Japan. It is mandatory to establish a unified guideline based upon solid evidence in close coordination between endoscopists and non-gastroenterology physicians. Although cessation before biopsy may be dispensable for Asians or Japanese people, we need further evidence to support this proposal.

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Competing interests

This study design was discussed by participants at the 11th meeting of Tokyo Gastrology Clinical Diagnosis Conference (TGCDC), supported by Eisai Co. and the contents were partially presented at the 15th TGCDC meeting, Tokyo, Japan, on 27 August, 2010.

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Should Elderly Patients Undergo Additional Surgery After Non-Curative Endoscopic Resection for Early Gastric Cancer? Long-Term Comparative Outcomes

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OBJECTIVES: **Endoscopic resection (ER) including endoscopic submucosal dissection has been widely accepted for treatment of early gastric cancer (EGC) in Japan. Additional surgery is recommended when ER is non-curative histologically. Many elderly patients, however, do not undergo radical surgery due to comorbid disease or limited life expectancy. The aim of this study is to assess the survival outcomes of radical surgery compared with observation only in elderly patients after non-curative ER.**

METHODS: **We reviewed existing data of all elderly patients (older than 75 years) who had undergone ER for EGC at the National Cancer Center Hospital between January 1999 and December 2005. We compared the overall and disease-free survival rates between three patients groups: curative ER, non-curative ER with additional surgery, and non-curative ER without additional surgery.**

RESULTS: **In total, 428 patients underwent ER; 308 (72%) curative ER and 120 (28%) non-curative ER. Of the 120 non-curative ER patients, 38 patients (31.7%) underwent additional surgery and 82 patients (68.3%) were followed without surgery. There was no significant difference in American Society of Anesthesiologist score between three groups. Patients who did not undergo surgery tended to be older. Overall 5-year survival rates in the curative ER, non-curative ER with surgery, and non-curative ER without surgery were 85, 92, and 63%, respectively. There was no significant difference in overall and disease-free survival between patients in the curative ER and non-curative ER with surgery groups. On the contrary, a significant difference in overall and disease-free survival was evident between the curative ER and non-curative ER without surgery groups (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).**

CONCLUSIONS: **In our elderly patient cohort, additional surgery following non-curative ER improved overall and disease-free survival compared with non-surgical observation only. Thus, surgery should be considered following non-curative ER in EGC patients >75 years of age.**

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INTRODUCTION

Life expectancy in elderly patients has increased dramatically worldwide (1,2). Although surgical techniques and preoperative management have improved minimally invasive curative treatment is preferable for the elderly, particularly for early stage cancer (EGC).

Endoscopic resection (ER) has been accepted as standard treatment for EGCs that meet guideline or expanded criteria (3,4), which have a low risk of lymph node metastasis. Following ER, meticulous pathological evaluation of the resected specimen is used to stratify patient management. Patients with lesions that meet the guideline or expanded criteria are followed closely, whereas those who have had a non-curative ER are considered for additional surgery.

Gastrectomy is associated with high surgical risk for the general population. Partial or total gastrectomy is also associated with short and long-term morbidity, and mortality (5,6). Furthermore, the majority of elderly patients who are 75 years or older

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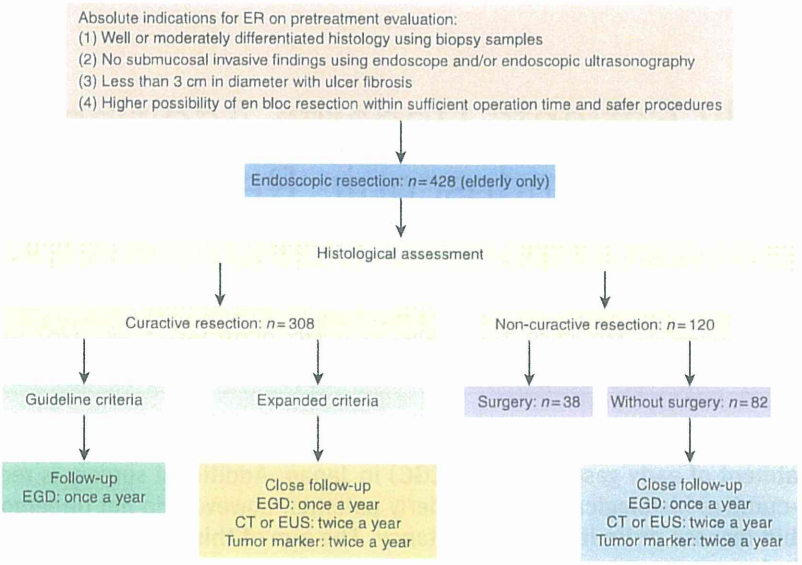

Figure 1. Flowchart of critical procedure. CT, computed tomography; EGD, endogastroduodenoscopy; ER, endoscopic resection; EUS, endoscopic ultrasonography.

have multiple diseases and functional disorders influencing daily life (7,8). In this study, we describe the long-term outcomes of ER for EGC in patients aged 75 years or older. We primarily aim to determine whether lesions beyond the guideline or expanded criteria in this elderly cohort can be treated adequately with ER alone.

METHODS

Study design

We reviewed existing data on all patients who had undergone ER for EGC at the National Cancer Center Hospital, Tokyo, between January 1999 and December 2005. Patients whose lesions did not meet criteria for ER following preoperative diagnosis were excluded. We defined elderly patients as 75 years or older (7). Elderly patients were divided into three groups: curative ER, non-curative ER with additional radical surgery, and non-curative ER without surgery. We used the American Society of Anesthesiologist (ASA) score and Charlson Index (9) as a measurement of patients overall health status, and surgical risk. All patients provided written informed consent.

Method

Starting in 1999, our institution has routinely followed a standard protocol for the ER of EGC.

Indication for ER

Indication criteria for ER—"differentiated histology," "macroscopic absence of submucosal invasive findings using endoscope and/or endoscopic ultrasonography," "lesion size- <3 cm in diameter with ulcer fibrosis," and "high probability of safe en bloc resection with short procedure duration." Patients deemed unfit for open surgery due to their general condition were also judged to be poor candidates for ER (**Figure 1**).

Historical assessment

Resection specimens were classified according to the Japanese Classification for Gastric Carcinoma (10). In this study, ER was declared curative when the specimen showed en bloc resection with margins free of cancer and if applicable, met the expanded criteria: (i) intramucosal cancer, differentiated type, no lymphatic or/and venous invasion, and no ulceration, irrespective of tumor size; (ii) intramucosal cancer, differentiated type, no angiolymphatic invasion, and tumor <3 cm in size, irrespective of ulceration findings; (iii) minimally invasive submucosal cancer (invasion depth $\leq 500\,\mu$m, sm1), differentiated type, no lymphatic or/and venous invasion, and tumor <3 cm in size.

Post ER management

All patients were followed according to our standard protocol (**Figure 1**). Surveillance upper endoscopy was performed annually. Curative cases with expanded criteria also underwent abdominal computed tomography or endoscopic ultrasonography and tumor-marker studies (carcinoembryonic antigen, CA19–9) every 6 months to exclude lymph node or distant metastasis. Patients who underwent non-curative ER and were deemed fit for surgery were referred and consented for radical resection and lymph node dissection. Patients with the non-curative ER without surgery due to physician judgment or strong patient refusal were followed up by the same protocol as patients with curative resection with expanded criteria.

Statistical analysis

Differences in patient characteristics between the three groups were examined by χ^2 test. Survival curves were calculated using the Kaplan–Meier method. To compare overall and disease-free survival among the treatment status, Cox proportional-hazards model was performed to estimate hazard ratio (HR) and 95% confidence interval (CI). The following covariates were included

in the multivariable analyses: age, sex, ASA score, past history of cancer (stratified by cancer stage), and comorbid illnesses. We also compare the overall and disease-free survival in the multivariable analyses included age, sex, and Charlson Index. All *P* values reported are two-sided, and significance level was set at $P<0.05$. All statistical analyses were performed with the SAS software version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Patient characteristics

A total of 2,012 cases (2,399 lesions) of EGC were treated endoscopically at the National Cancer Center Hospital between January 1999 and December 2005. Of these, 1,947 cases (2,331 lesions) met the indication for ER following preoperative diagnosis. In all, 428 (519 lesions) of the 1,947 cases were elderly (75 years or older). Of these cases in elderly patients, 26 lesions were treated by endoscopic mucosal resection and 493 lesions were treated by endoscopic submucosal dissection. A total of 308 elderly patients (72%, 308/428) had a curative ER and 120 patients (28%, 120/428) had a non-curative ER. Of the 120 patients with non-curative ER, 38 patients (31.7%, 38/120) underwent radical surgery and 82 patients (68.3%, 82/120) were followed without surgery.

Patient characteristics are summarized in **Table 1**. ASA score of all patients except nine was 2. In all, 312 patients (72.9%, 312/428) were Charlson Index 2, 65 patients (15.2%, 106/428) were 3, 41 patients (9.6%, 41/428) were 4, and 10 patients were over 5 (2.3%, 10/428). There was no significant difference in ASA score and Charlson Index between three groups (ASA score, $P=0.17$; Charlson Index; $P=0.33$). There was a significant difference in age and the prevalence of cardiovascular disease. Patients who did not undergo surgery tended to be older.

Reasons for not undergoing surgery in the remaining 82 patients included patients' choice ($n=29$), physicians' judgment ($n=45$) (including 10 very elderly (mean age 84 years), one with chronic renal dysfunction, one with ventilatory impairment and one with aneurysm of the thoracic aorta, concomitant cancer in other organs ($n=7$)) and unknown ($n=8$).

Table 1. **Patient characteristics**

	Curative resection	Non-curative resection with surgery	Non-curative resection without surgery
Number of patients (%)	308 (72.0)	38 (8.9)	82 (19.2)
Age, mean (s.d.)	78.8 (3.3)	76.9 (2.3)	80.1 (3.9)
Gender ratio, men: women	228:80	32:6	67:15
Concomitant disease (%)			
Cancer	59 (19.2)	3 (7.9)	13 (15.9)
Cardiovascular diseases	48 (15.6)	16 (42.1)	11 (13.4)
Diabetes	29 (9.4)	6 (15.8)	7 (8.5)
Respiratory diseases	6 (1.9)	1 (2.6)	3 (3.7)
Other diseases	15 (4.9)	2 (5.3)	6 (7.3)
ASA score (%)			
2	304 (100)	37 (100)	78 (98.7)
3	0	0	1
Missing information	4	1	3
Charlson Index			
2	232 (75.3)	25 (65.8)	55 (67.1)
3	43 (14.0)	8 (21.1)	14 (17.1)
4	25 (8.1)	4 (10.5)	12 (14.6)
5+	8 (2.6)	1 (2.6)	1 (1.2)

ASA, American Society of Anesthesiologist.

Survival

The median follow-up period in the curative ER, non-curative ER with surgery, and non-curative ER without surgery was 40.6, 43.1, and 38.1 months, respectively. Overall 5-year survival in each group was 84, 95, and 63%, respectively (**Table 2**). Using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases, there was no significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER with surgery ($n=38$). On the contrary, a significant difference in overall and disease-free survival was evident between the patients with curative ER ($n=308$) and non-curative ER without surgery ($n=82$) (HR (95% CI): 1.89 (1.08–3.28), 2.30 (1.35–3.94); **Table 2**, **Figure 2**). The multivariable analysis using Charlson Index, age, and sex shows a statistical difference in overall and disease-free survival between the patients with curative ER and non-curative ER without surgery (HR (95% CI): overall survival, 2.35 (1.36–4.05); disease-free survival, 2.76 (1.64–4.67)).

In total, 59 patients (13.8%, 54/428) died during this study period. The majority (55.9%, $n=33/59$) of deaths occurred in the curative ER group followed by the non-curative ER without surgery group (40.7%, $n=24/59$). Only two (3.4%) deaths occurred in the group who had non-curative ER with surgery. Of the 428 patients, 1.2% ($n=5$) died as a result of gastric cancer and 12.6% ($n=59/432$) died from another causes (**Table 2**). Of the five patients who died of gastric cancer, one patient died from metachronous advanced gastric cancer following curative ER of the index lesion. Four patients in the non-curative ER without surgery died from lymph node metastasis or distant metastasis. There were no deaths from cancer recurrence in the non-curative ER with surgery.

Survival according to the risk of lymph node metastasis

We divided non-curative ER groups into two groups according to the risk of lymph node metastasis: A—high risk ("positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion") and B—low risk (other reasons except high risk of lymph node metastasis such as intramucosal cancer >30 mm in size with ulcer findings and minute submucosal cancer

Table 2. **Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to curability**

	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
			HR	95% CI	HR	95% CI
Curative ER	33 (1)	84	1.00		1.00	
Non-curative ER with surgery	2 (0)	95	0.52	0.13–2.17	0.70	0.16–2.98
Non-curative ER without surgery	24 (4)	63	2.62	1.54–4.46	1.89	1.08–3.28

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

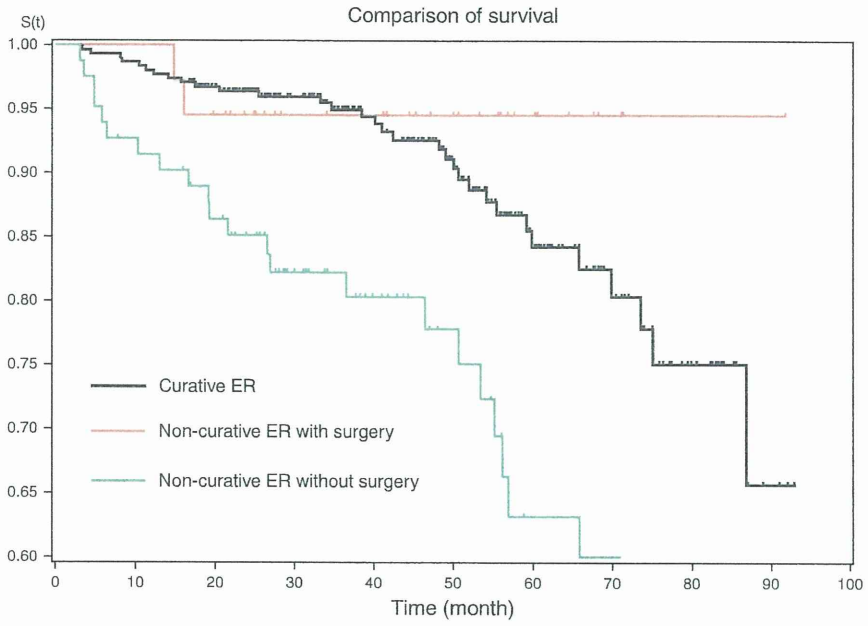

Figure 2. Survival for elderly patients (overall survival). ER, endoscopic resection.

(sm1) >30 mm in size). Among the non-curative ER patients, 29 of the 67 high-risk patients (43.3%) underwent additional surgery compared with only 9 patients of the 53 low-risk patients (17.0%). **Table 3** shows overall survival according to the risk of lymph node metastasis using ASA score, age, sex, clinical stage of cancer in past history, and past history of diseases. Overall 5-year survival rate in non-curative ER-A without surgery group was lowest (52%). There were significant difference in overall and disease-free survival between the patients with curative ER ($n=308$) and non-curative ER-A without surgery group (HR (95% CI): 3.31 (1.67–6.58), 4.26 (2.20–3.94); **Table 3**). In the multivariable analysis using Charlson Index, age, and sex, a statistical significance was evident in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery (HR (95% CI): overall survival, 4.15 (2.18–7.89); disease-free survival, 5.30 (2.85–9.84)).

DISCUSSION

Surgery continues to be the mainstay of treatment for gastric cancer—with a reported high resection rate (96%) and a low surgical complication rate (8%) even in elderly patients (11). However, 5-year survival after surgery in elderly patients varies among institutions, and is reported to be 69–74% for EGC. This is compared with 5-year survival rates of >90% in young and middle-aged patients (12). Age-related disease, in fact, is the main etiology of the relatively low survival in elderly patients. Thus, less invasive surgical treatment is desirable in the elderly, and ER is attractive in this respect.

ER targets EGC lesions that have a negligible likelihood of lymph node metastasis, estimated at <1% for intramucosal cancer and <3% for submucosal invasive cancer (4). Several recent studies have reported that endoscopic submucosal dissection can be carried out on larger lesions resulting in a high rate of cancer-free

Table 3. **Hazard ratio (HR) and 95% confidence intervals (CIs) of overall survival according to the risk of lymph node metastasis**

	Number of subject	Number of deaths (death from gastric cancer)	Five-year survival rate (%)	Crude		Multivariable adjusted[a]	
				HR	95% CI	HR	95% CI
Curative ER	308	33	84	1.00		1.00	
Non-curative ER-A with surgery	29	1 (0)	96	0.36	0.05–2.66	0.54	0.07–4.07
Non-curative ER-B with surgery	9	1 (0)	89	0.96	0.13–7.01	1.09	0.15–8.14
Non-curative ER-A without surgery	38	14 (3)	52	4.72	2.52–8.85	3.31	1.67–6.58
Non-curative ER-B without surgery	44	10 (1)	71	1.55	0.75–3.22	1.17	0.56–2.47

ASA, American Society of Anesthesiologist; ER, endoscopic resection.
[a]Adjusted for age, sex, ASA score, clinical stage of cancer in past history, and past history of diseases (cardiovascular diseases, diabetes mellitus, respiratory diseases, and others).

margin (13,14). Long-term survival of EGC patients undergoing ER with expanded criteria has been equal to those undergoing ER with original guidelines (15). Expanded criteria for ER of larger tumors may benefit elderly patients with EGC (16).

As a general rule, additional surgery should be recommended for patients when curative ER is not achieved (17), as EGC surgical outcomes are known to be excellent (11). Our study provides long-term survival data of EGC in an elderly cohort. We demonstrate the efficacy of curative ER for EGC, showing a similar 5-year survival rate among elderly patients with curative ER and non-curative ER with surgery. We found that when curative ER was not achieved, elderly patients appeared to benefit from subsequent surgical gastrectomy. Furthermore, patients who had a non-curative ER without surgery and were established to have a high risk of lymph node metastasis had the lowest overall 5-year survival rate of 52%.

It was reported that lymphovascular involvement and massive submucosal penetration had a significant association with lymph node metastasis in EGC (18). From our data, there were significant difference in overall and disease-free survival between the patients with curative ER and non-curative ER-A without surgery group. Lymphovascular involvement or massive submucosal penetration was more frequent in surgical patients than in non-surgical patients. It is likely that the physician suggested additional surgery to these patients with high risk of lymph node metastasis. Considering the patient's age and the risk of lymph node metastasis in this recommendation.

Notably, the patients with the non-curative ER without surgery did not undergo additional surgery primarily due to subjective measures. Thus, although the treating physician routinely discussed and recommended radical surgery to all patients with non-curative ER, individual factors such as comorbid disease, reason for non-curative ER, age, and patient preference ultimately influenced treatment decisions. These conditions are subjective and cannot be expressed numerically, and are an inherent limitation of our retrospective study.

In conclusion, following non-curative ER for ECG, especially with lymphovascular involvement or massive submucosal penetration, additional surgery is recommended in elderly patients.

CONFLICT OF INTEREST

Guarantor of the article: Chika Kusano, MD, PhD.

Specific author contributions: Conceptualization, data analysis, and script preparation: Chika Kusano and Motoki Iwasaki; endoscopic diagnosis and treatment: Takuji Gotoda and Ichiro Oda; data collection: Chika Kusano, Ichiro Oda, and Takuji Gotoda; critical reviewer of the paper: Ichiro Oda, Takuji Gotoda, Tonya Kaltenbach, and Abby Conlin. All authors have read and approved the submitted version of the paper.

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Potential competing interests: None.

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- Endoscopic resection (ER) has been accepted as standard treatment for early gastric cancers, which have a low risk of lymph node metastasis.
- Additional surgery with lymph node dissection should be recommended for patients when curative ER is not achieved.
- Deciding whether or not to pursue gastric surgery or not is particularly complex in elderly patients who often have comorbidities and limited life expectancy.

WHAT IS NEW HERE

- A significant difference in overall and disease-free survival was evident between the patients with curative endoscopic resection (ER) and non-curative ER without surgery (hazard ratio (95% confidence interval): 1.89 (1.08–3.28), 2.30 (1.35–3.94)).
- Overall and disease-free survival of non-curative ER with "positive lymphatic or/and venous invasion" or "submucosal deep (sm2) invasion" are lowest.
- After non-curative ER for early gastric cancer, especially with lymphovascular involvement or massive submucosal penetration in historical findings, additional surgery is necessarily even in elderly patients.

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ORIGINAL ARTICLE

Correlation between endoscopic macroscopic type and invasion depth for early esophagogastric junction adenocarcinomas

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Abstract
Background Although correlations between endoscopic macroscopic type and tumor depth have been reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas, there is no published study investigating the correlation between endoscopic macroscopic type and invasion depth for mucosal (M) and submucosal (SM) adenocarcinomas located at the esophagogastric junction (EGJ). We decided to analyze, therefore, the relationship between endoscopic macroscopic type and tumor depth for such cancers.
Methods We retrospectively reviewed 73 early EGJ adenocarcinomas (M/SM = 33/40; differentiated/undifferentiated type = 70/3) in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008. The mean age of the patients was 63.9 years (range 37–85 years) and the male/female ratio was 62:11. EGJ adenocarcinoma was defined as junctional carcinoma (type II) according to the Siewert classification.
Results We found polypoid type lesions (0-I) in 14 patients, non-polypoid type without mixed type (0-IIa, 0-IIb, or 0-IIc) in 39, and mixed type (0-IIa + IIc or 0-IIc + IIa) in 20 patients. Non-polypoid type without mixed type (31%; 12/39) lesions had a significantly lower risk for SM invasion compared to polypoid type (79%; 11/14; $p < 0.01$) and mixed type (85%; 17/20; $p < 0.01$) lesions. In polypoid type lesions, the risk of SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions (0%; 0/2 vs. 92%; 11/12; $p < 0.05$). M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$).
Conclusions Determination of endoscopic macroscopic type may be useful in accurately diagnosing early EGJ adenocarcinoma invasion depth.

Keywords Esophagogastric junction · Adenocarcinoma · Endoscopic macroscopic type · Depth of invasion

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Introduction

Accurate endoscopic diagnosis of invasion depth for gastrointestinal cancer is essential for making the proper decision on treatment strategy. The use of endoscopic resection in treating early gastrointestinal cancer has become more widespread recently. As a result, the differential endoscopic diagnosis of mucosal (M) and submucosal (SM) depth of invasion has become increasingly important for determining the indications for endoscopic resection [1–3].

Endoscopy examination is the primary modality for diagnosing gastrointestinal cancer and is also helpful in diagnosing invasion depth. Correlations between endoscopic macroscopic type and invasion depth have been

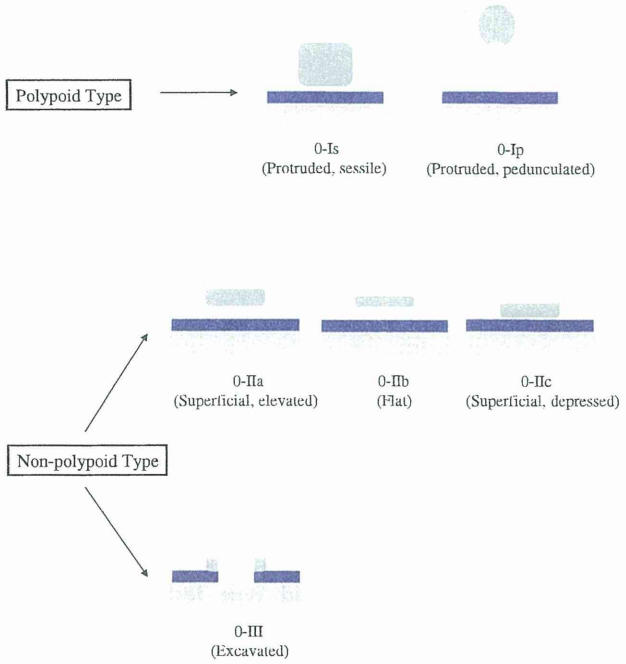

Fig. 1 Classification of endoscopic macroscopic types of early esophagogastric junction adenocarcinomas

reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas in *The Paris endoscopic classification of superficial neoplastic lesions* [4], and in an even more recent evaluation, of endoscopic macroscopic types in early Barrett's neoplasia, such correlations have also been reported [5]. There has been no previously published study, however, investigating the correlation between endoscopic macroscopic type and invasion depth for M and SM adenocarcinomas located at the esophagogastric junction (EGJ). The intention of this study was to clarify the relationship between endoscopic macroscopic type and invasion depth for such early EGJ adenocarcinomas.

Patients and methods

A total of 73 early EGJ adenocarcinomas in 73 consecutive patients treated endoscopically and/or surgically between January 2000 and December 2008 at the National Cancer Center Hospital in Tokyo, Japan, were retrospectively analyzed in this study. EGJ adenocarcinoma was defined as a junctional carcinoma (type II) according to the Siewert classification [6]. An upper gastrointestinal endoscopy examination was performed on each patient before treatment.

We reviewed the clinical records and endoscopic and pathological reports for every patient and analyzed the relationships between invasion depth of early EGJ adenocarcinomas and the following clinicopathological findings: age, gender, initial treatment, histological type, histological findings with regard to a diagnosis of Barrett's cancer, center of tumor location, tumor size, and endoscopic macroscopic type.

Table 1 Clinicopathological findings of 73 patients with esophagogastric junction adenocarcinoma

Age, mean ± SD (years)	63.9 ± 12.0
Sex (%)	
Male	62 (85)
Female	11 (15)
Invasion depth (%)	
Mucosal	33 (45)
Submucosal	40 (55)
Initial treatment (%)	
Endoscopic resection	40 (55)
Surgical resection	33 (45)
Histological type (%)	
Differentiated type	70 (96)
Undifferentiated type	3 (4)
Histological finding (%)	
Barrett's cancer	42 (58)
Non-Barrett's cancer	31 (42)
Tumor location, quarter (%)	
12:01–3 o'clock	50 (68)
3:01–6 o'clock	10 (14)
6:01–9 o'clock	3 (4)
9:01–12 o'clock	10 (14)
Tumor size, mean ± SD (mm)	20.0 ± 9.1
Endoscopic macroscopic type (%)	
0-I	14 (19)
0-IIa	8 (11)
0-IIb	1 (1)
0-IIc	30 (41)
0-IIa + IIc	17 (23)
0-IIc + IIa	3 (4)
0-III	0 (0)

SD Standard deviation

Invasion depth for early EGJ adenocarcinomas was divided into M and SM and initial treatment was divided into endoscopic resection and surgical resection. Histological type was diagnosed based on the predominant tumor pattern in the M layer and then divided into two types: differentiated type and undifferentiated type, according to the *Japanese classification of gastric carcinoma* [7]. The histological findings with regard to a diagnosis of Barrett's cancer were classified as Barrett's cancer and non-Barrett's cancer, with Barrett's cancer diagnosed whenever a tumor was continuously located on Barrett's esophagus. The center of tumor location was divided into quarters (12:01–3:00, 3:01–6:00, 6:01–9:00, and 9:01–12:00 o'clock), using

Table 2 Correlation between clinicopathological findings and invasion depth

	Invasion depth		*p* value
	Mucosal ($n = 33$)	Submucosal ($n = 40$)	
Age, mean ± SD (years)	63.3 ± 11.5	64.3 ± 12.5	NS
Sex (%)			
Male	28 (45)	34 (55)	NS
Female	5 (45)	6 (55)	
Histological type (%)			
Differentiated type	33 (47)	37 (53)	NS
Undifferentiated type	0 (0)	3 (100)	
Histological findings (%)			
Barrett's cancer	23 (55)	19 (45)	NS
Non-Barrett's cancer	10 (32)	21 (68)	
Tumor location, half (%)			
12:01–6 o'clock	28 (47)	32 (53)	NS
6:01–12 o'clock	5 (38)	8 (62)	
Tumor size, mean ± SD (mm)	14.5 ± 7.5	24.5 ± 7.7	<0.01
Endoscopic macroscopic type (%)			
Polypoid type (0-I)	3 (21)	11 (79)	<0.01*
Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc)	27 (69)	12 (31)	
Mixed type (0-IIa + IIc or 0-IIc + IIa)	3 (15)	17 (85)	<0.01*

SD Standard deviation, *NS* not significant

* Significantly different from non-polypoid type without mixed type

the forward endoscopic EGJ view. Tumor size was defined as the length of the major axis. Endoscopic macroscopic type was classified based on the Paris classification and divided into polypoid (0-I) and non-polypoid (0-IIa, 0-IIb, 0-IIc and 0-III) types (Fig. 1) [4]. A mixed type was diagnosed whenever a lesion consisted of at least two distinct endoscopic macroscopic types. Polypoid type lesions were then subdivided into sessile (0-Is) and pedunculated (0-Ip) subtype lesions.

Data were analyzed using the χ^2 test, Fisher's exact test, or Student's *t* test as appropriate. Value differences in which $p < 0.05$ were considered statistically significant.

Results

Clinicopathological findings are shown in Table 1. The mean age ± standard deviation (SD) of the patients was 63.9 ± 12.0 years and the male/female ratio was 5.64 (62:11). Relationships between clinicopathological findings and invasion depth are shown in Table 2. M lesions (mean size 14.5 ± 7.5 mm) were significantly smaller than SM lesions (24.5 ± 7.7 mm; $p < 0.01$). Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion than polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions (Table 2; see images in Figs. 2, 3, 4). When polypoid type lesions were subdivided into sessile (0-Is) and pedunculated (0-Ip) subtypes, the risk of SM invasion was significantly lower for the pedunculated subtype than for the sessile subtype (0%; 0/2 vs. 92%, 11/12; $p < 0.05$) (see images in Figs. 4, 5).

Discussion

There has been a dramatic increase in the incidence of EGJ adenocarcinomas in the United States and other Western countries over the past two decades [8–12]. It has also been reported from a large referral center in Japan that the proportion of EGJ adenocarcinomas among all gastric adenocarcinomas detected in Japanese patients has been increasing in recent years [13].

Remarkable progress has been made during the past decade in the development and refinement of endoscopic resection methods, from conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD) [14–20], which has been applied to early EGJ adenocarcinomas [21]. Consequently, accurate differential endoscopic diagnosis of M and SM invasion depth in early EGJ adenocarcinomas has become more important for determining the indications for such procedures.

Endoscopic ultrasonography (EUS) is one of the current modalities used for diagnosing tumor invasion depth. Using conventional EUS (7.5 MHz), advanced T3/T4 carcinomas can be distinguished from T1/T2 carcinomas in

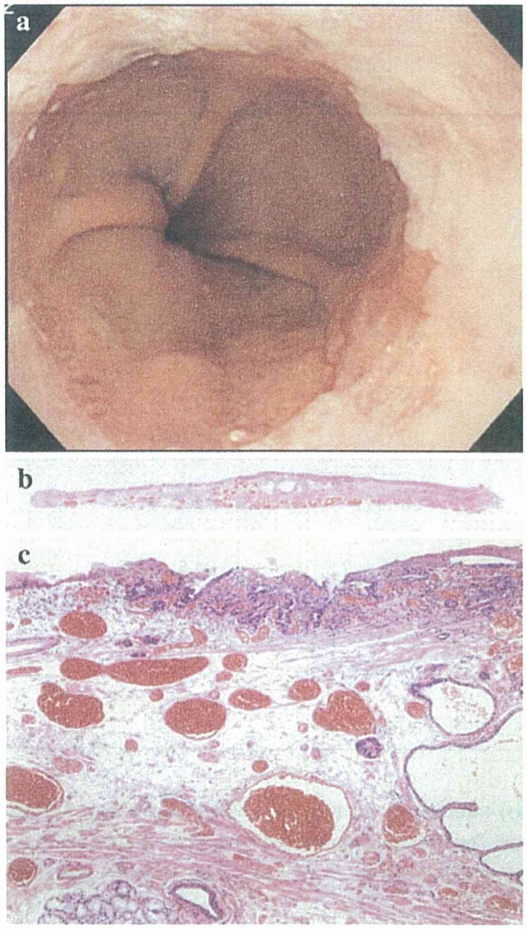

Fig. 2 **a** Endoscopic image reveals a non-polypoid type without mixed type, slightly depressed (0-IIc) lesion at the esophagogastric junction (EGJ). **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer that had spread to the subepithelial layer of the esophagus (**b** H&E, panoramic view), (**c** H&E, ×40)

more than 80% of cases; however, accurate differentiation between M and SM invasion depth is difficult [22–24]. EUS using a miniprobe (20 MHz) has reportedly demonstrated a high diagnostic accuracy of approximately 80% for differentiating between M and SM early EGJ adenocarcinomas. There was no significant difference, however, between EUS diagnostic accuracy and that of high-resolution video endoscopy [23]. Consequently, endoscopy can also be helpful in diagnosing invasion depth, but such diagnosis is subjective in nature so there is a need for objective criteria.

In the present study, we analyzed the relationship between the invasion depth of early EGJ adenocarcinomas and relevant clinicopathological findings, including endoscopic macroscopic type. We found that M lesions were

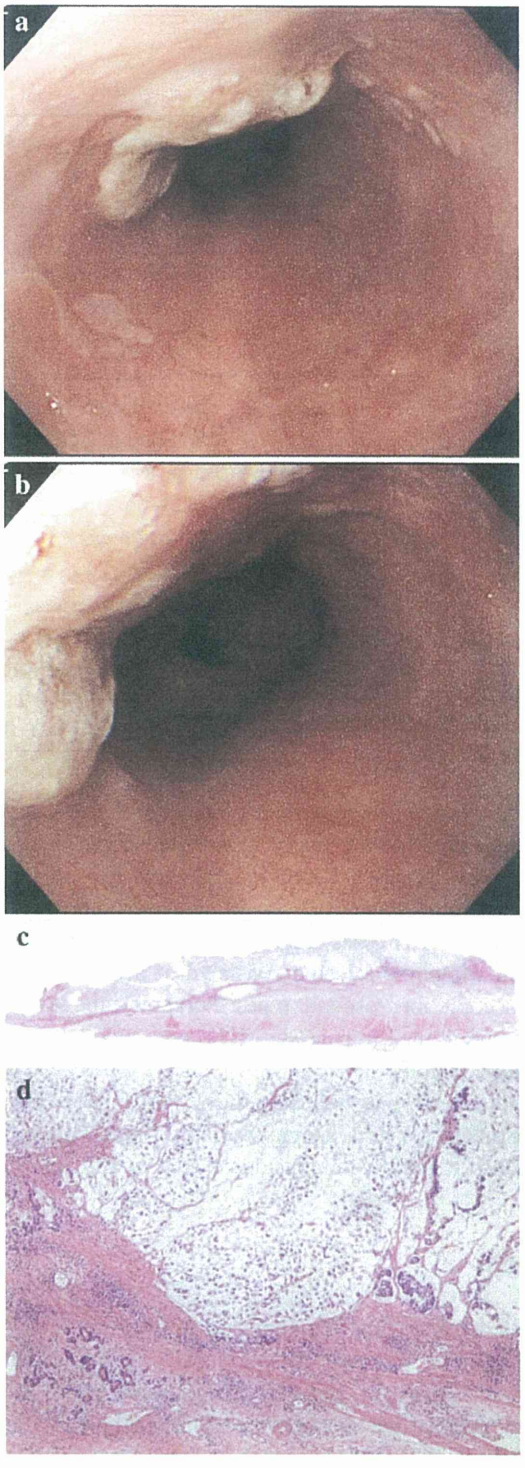

Fig. 3 **a**, **b** Endoscopic images reveal a mixed type, elevated lesion with a central depression (0-IIa + IIc) at the EGJ. **c**, **d** Histological features of the resected specimen indicate a mucinous adenocarcinoma in the mucosal layer and a poorly differentiated adenocarcinoma that had invaded the submucosal layer (**c** H&E, panoramic view), (**d** H&E, ×100)

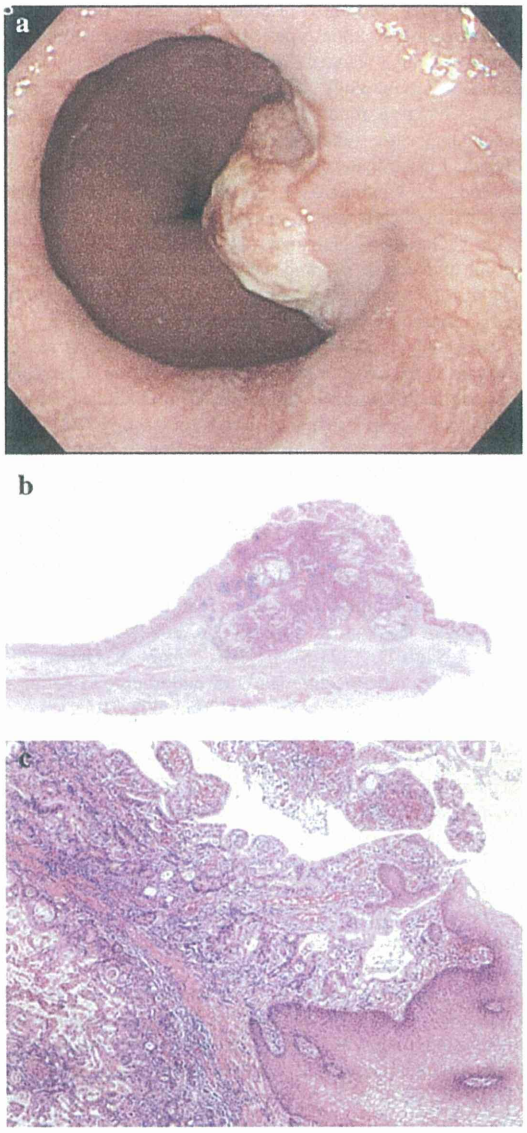

Fig. 4 **a** Endoscopic image reveals a polypoid type, sessile subtype (0-Is) lesion at the EGJ. **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma that had invaded the submucosal layer (**b** H&E, panoramic view), (**c** H&E, ×100)

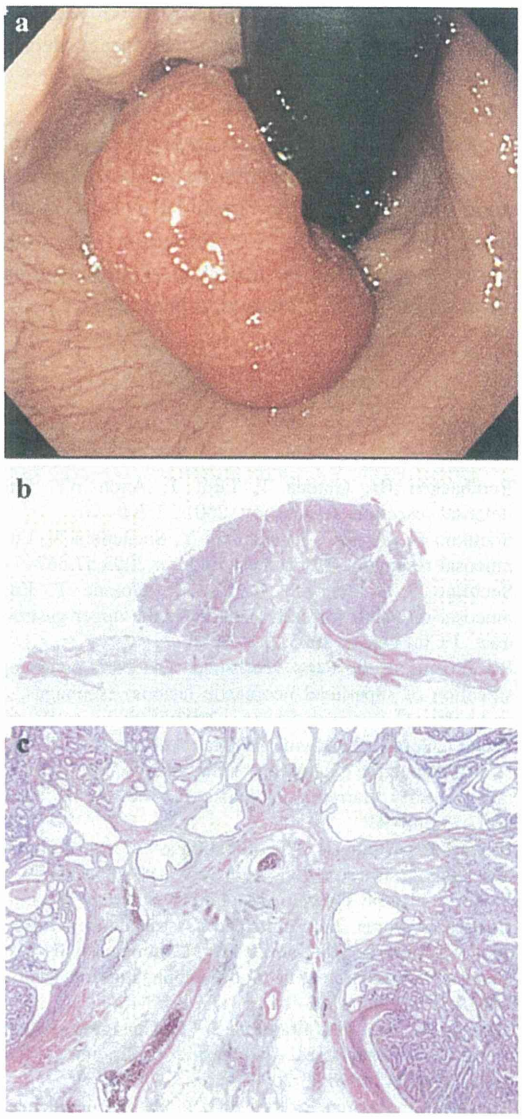

Fig. 5 **a** Endoscopic image reveals a polypoid type, pedunculated subtype (0-Ip) lesion at the EGJ. **b**, **c** Histological features of the resected specimen indicate a well-differentiated adenocarcinoma confined to the mucosal layer (**b** H&E, panoramic view), (**c** H&E, ×100)

significantly smaller than SM lesions. Non-polypoid type without mixed type (0-IIa, 0-IIb or 0-IIc) lesions had a significantly lower risk for SM invasion compared to polypoid type (0-I) and mixed type (0-IIa + IIc or 0-IIc + IIa) lesions. In the polypoid type lesions, the risk for SM invasion was significantly lower for the pedunculated subtype (0-Ip) than for the sessile subtype (0-Is) lesions. These results were similar to those in previously published reports of other gastrointestinal neoplasias [4, 5].

One limitation of the present study is that it was a retrospective investigation from a single center, with a relatively small number of reported cases, so a large prospective study will be needed to confirm our findings on the correlation of endoscopic macroscopic type with invasion depth for early EGJ adenocarcinomas. Another limitation of our study was that invasion depth for early EGJ adenocarcinomas was divided into M and SM, but SM was not further subdivided into SM1 and SM2, because the definition of SM1 for EGJ adenocarcinomas is still undecided at the present time. SM1 for gastric cancer and esophageal cancer is defined as a tumor that invades less than 500 μm and less than 200 μm, respectively, into the submucosa from the muscularis mucosa and is associated with a lower

risk of lymph-node metastasis compared with SM2 [4]. Additional investigation as to an accurate definition of SM1 and the risk of lymph-node metastasis for EGJ adenocarcinomas is also necessary.

In conclusion, this retrospective study demonstrated that there were certain correlations between endoscopic macroscopic type and invasion depth for early EGJ adenocarcinomas. As a result, determination of endoscopic macroscopic type may be useful in accurately diagnosing invasion depth for EGJ adenocarcinomas.

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ORIGINAL ARTICLE

Depth-predicting score for differentiated early gastric cancer

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Abstract
Background Intramucosal and minute submucosal (M-SM1; <500 μm in depth) differentiated gastric cancers, which have a negligible risk of lymph node metastasis, are the targets for endoscopic resection. However, there have been few reports about the endoscopic distinction between these cancers and cancers with deeper submucosal invasion (SM2; ≥500 μm in depth). The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2 cancers, and to develop a simple scoring model to predict the depth of these early gastric cancers.
Methods We analyzed 853 differentiated early gastric cancers treated endoscopically or surgically as a derivation group. Endoscopic images were reviewed to determine the relationship between depth of invasion and the following endoscopic features: tumor location, macroscopic type, tumor size, and endoscopic findings (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds). Secondly, we created a depth-predicting model based on the obtained data and applied the model to 211 validation samples.
Results On logistic regression analysis, tumor size more than 30 mm, remarkable redness, uneven surface, and margin elevation were significantly associated with deeper submucosal cancers. A depth-predicting score was created by assigning 2 points for margin elevation and tumor size more than 30 mm, and 1 point for each of the other endoscopic features. When validation lesions of 3 points or more were diagnosed as deeper submucosal cancers, the sensitivity, specificity, and accuracy as evaluated by three endoscopists were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively.
Conclusions The depth-predicting score could be useful in the decisions on treatment strategy for differentiated M-SM1 early gastric cancers.

Keywords Early gastric cancer · Depth · Diagnosis · Endoscopy

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Introduction

Endoscopic resection in patients with early gastric cancer (EGC) is less invasive and more economical than conventional surgery. The negligible incidence of lymph node metastasis in certain stages of EGC means that, in selected cases, patients can be cured with such therapies. Gotoda et al. [1] concluded that among 5265 patients who underwent gastrectomy, there was no lymph node involvement in differentiated mucosal (M) gastric cancers without lymphatic or vessel invasion when the cancers were smaller than 3 cm in diameter with ulceration, or any size without ulceration. Differentiated minute submucosal (SM1, <500 μm in depth) cancers without lymphatic or venous involvement and cancers smaller than 3 cm also showed no lymph node involvement [1]. The endoscopic submucosal dissection (ESD) technique using an insulation-tipped

diathermic knife or other endo-knives could technically achieve one-piece resection for such lesions [2–7]. It is important to distinguish M-SM1 cancers from deeper submucosal (SM2; ≥500 μm in depth) cancers, which have the possibility of lymph node metastasis, for making the proper decision on treatment strategy.

Thus, preoperative determination of the depth of invasion is important. Although the usefulness of endoscopic ultrasonography (EUS) has been reported, with this modality it is impossible to distinguish M-SM1 from SM2 definitively [8, 9]. Conventional endoscopy is the initial route of EGC detection, but there have been few reports comparing the endoscopic features of EGC stages M-SM1 and SM2. Furthermore, no objective criteria regarding the depth of invasion exist, and many endoscopists diagnose based on their own experiences. The aim of this retrospective study was to analyze the differences in the endoscopic features between M-SM1 and SM2, and to develop a simple model to predict the depth of these EGCs.

Materials and methods

Analyzed lesions and review methods

A total of 880 consecutive differentiated EGCs were treated endoscopically or surgically between 2001 and 2003 at the National Cancer Center Hospital in Tokyo. Twenty-seven lesions were excluded because precise endoscopic findings could not be depicted [eight detected in remnant stomach, six after esophagectomy, six local recurrences after endoscopic mucosal resection (EMR), five with insufficient endoscopic images, one with a tattoo, and another with an endo-clip artifact].

The remaining 853 differentiated EGCs (M 592, SM1 111, SM2 150, mean patient age of 65.6 years, 686 male and 167 female patients) were analyzed as a derivation group. An endoscopist (S.A.), experienced with more than 5000 gastroscopies, reviewed conventional endoscopic images without histological information about depth. The following characteristics were evaluated: tumor location (upper, middle, and lower), tumor size (mm), macroscopic type, and five other endoscopic findings that are widely accepted as markers of deeper submucosal invasion among Japanese endoscopists, with some minor variations (remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds) [10, 11].

Subsequently, we made a simple and practical scoring model (depth-predicting score, DPS) to distinguish M-SM1 from SM2 cancers, based on the analyzed data in the derivation group. Three endoscopists (S.A., T.K., and K.T., each experienced with more than 5000 gastroscopies) evaluated the endoscopic findings and investigated the sensitivity, specificity, and accuracy of our DPS in our validation set, consisting of 211 differentiated EGCs treated between January and June in 2000 at our hospital.

Conventional white-light endoscopy (video-endoscope Q240 or Q260; Olympus Medical Systems, Tokyo, Japan) was used for pretreatment endoscopic examination. In addition, surface details were enhanced by indigo-carmine chromoendoscopy.

Definitions

The EGC macroscopic and histological types in the enrolled patients were decided according to the *Japanese classification of gastric carcinoma* [12]. We divided the macroscopic types into three groups: IIa (elevated lesions such as 0 I, 0 IIa, and 0 I + IIa), IIc (depressed lesions such as 0 IIc, 0 IIc + III, and 0 III + IIc), and IIa + IIc (combined type, such as 0 IIa + IIc and 0 IIc + IIa). Histological type was diagnosed based on the predominant tumor pattern and then divided into two types; differentiated type and undifferentiated type. Well differentiated, moderately differentiated, and papillary adenocarcinoma were defined as differentiated type.

We described five endoscopic features in this study. Remarkable redness was defined as a reddish area similar to regenerative epithelium (Fig. 1). Nodulations in the tumor's surface were considered an uneven surface (Fig. 2). Margin elevation referred to the finding of a protruding edge surrounding the tumors, including submucosal tumor like component with a limited amount of air insufflation (Fig. 3a, b). Either a scar or an ulcerative area within the tumors was evaluated as ulceration (Fig. 4). Finally, enlarged folds included any thickened or merged convergent folds (Fig. 5).

Statistical methods

To identify the variables that were significantly more common in SM2, the endoscopic data were initially

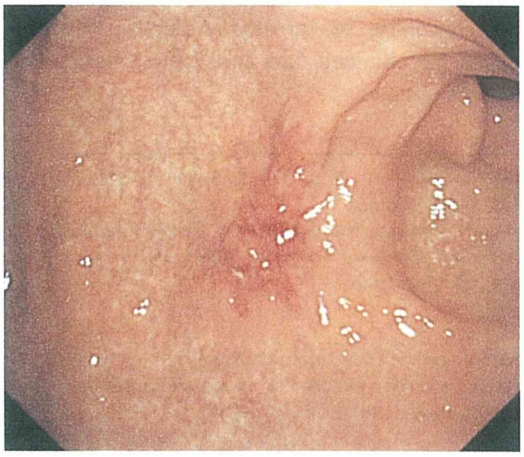

Fig. 1 Remarkable redness: endoscopic picture shows unusual redness inside the lesion

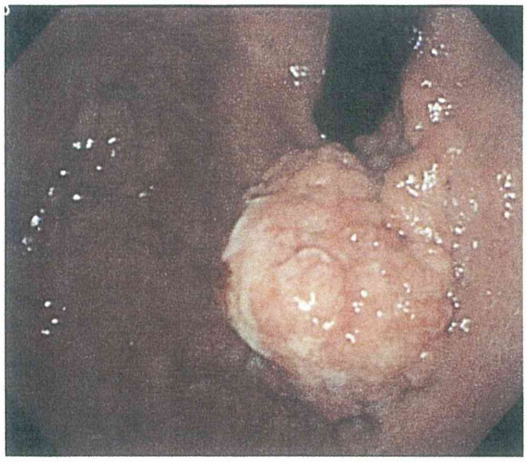

Fig. 2 Uneven surface: nodular mucosa can be seen

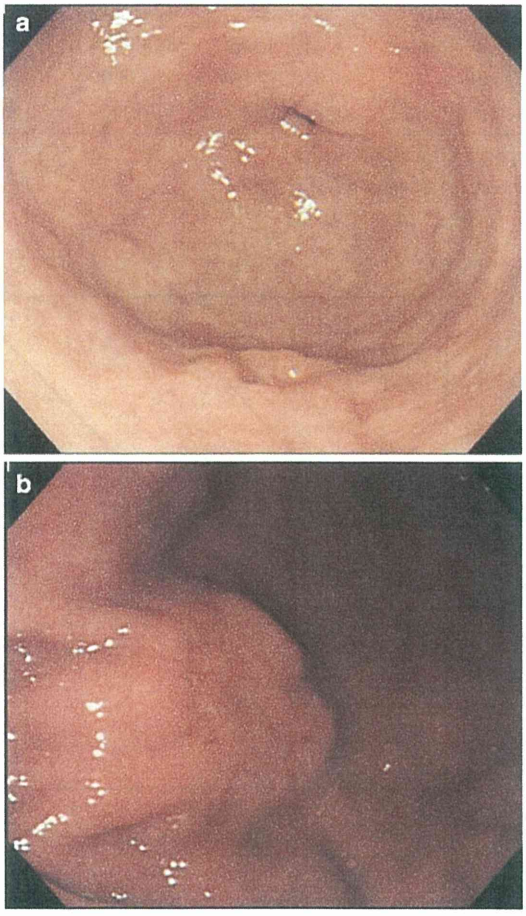

Fig. 3 **a** Margin elevation: endoscopic picture of surrounding elevation. **b** Margin elevation: endoscopic picture of submucosal tumor like component can be demonstrated from the view with a limited amount of air insufflation

evaluated with Student's t test for tumor size and the χ^2 test for other endoscopic features. We then entered the candidate variables into a logistic regression analysis.

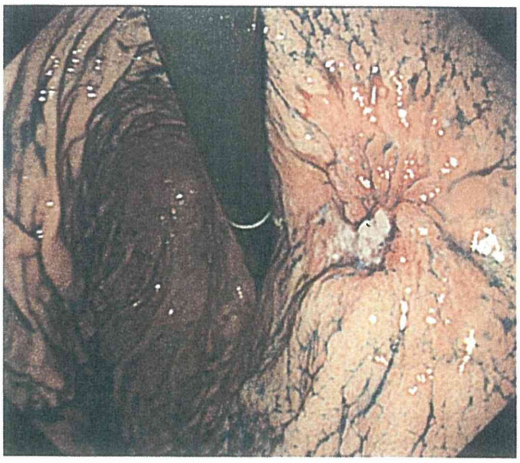

Fig. 4 Ulceration: endoscopic picture of ulceration

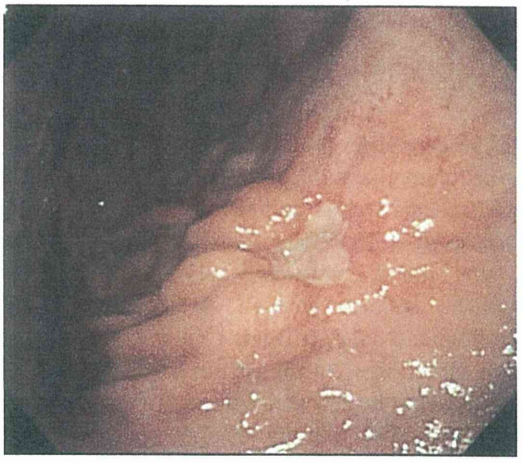

Fig. 5 Enlarged folds: thickened or merged folds can be seen toward the inside of the lesion

Endoscopic features independently and statistically associated with SM2 penetration were selected as examination items for the DPS. The relative weighting of each DPS variable was based on its β-coefficient in the logistic regression analysis. The significance level was set at 5% for each analysis. A p value of <0.05 was considered significant.

Results

Analysis of endoscopic features

Table 1 shows the histological and therapeutic characteristics of both the derivation and validation groups. There were no significant differences between the two groups in the depth of invasion, histological type, or treatment strategies.

Table 1 Histological and therapeutic characteristics

	Derivation group ($n = 853$)	Validation group ($n = 211$)	p value
Depth (M-SM1/SM2)	703/150	175/36	NS*
Histological type			
Well	732	185	NS*
Moderately	109	25	
Papillary	12	1	
Treatment			
EMR/ESD	632	171	NS*
Surgery	221	40	

M-SM1 intramucosal and minute submucosal (<500 μm in depth) cancers, *SM2* deeper submucosal (≥500 μm in depth) cancers, *well* well-differentiated adenocarcinoma, *moderately* moderately differentiated adenocarcinoma, *papillary* papillary adenocarcinoma, *EMR*, endoscopic mucosal resection, *ESD* endoscopic submucosal dissection, *NS* not significant

* χ^2 test

Table 2 Endoscopic comparison between M-SM1 and SM2 in derivation group

	M-SM1 ($n = 703$)	SM2 ($n = 150$)	p value
Location			
U	134	38	
M	257	35	NS*
L	312	77	
Tumor size (mm)			
Mean, range	19.2 (3–120)	31.6 (5–120)	<0.0001**
Macroscopic type			
IIa	178	30	
IIc	458	88	
IIa + IIc	67	32	<0.0001*
Endoscopic features			
Remarkable redness	160 (22.8%)	70 (46.7%)	<0.0001*
Uneven surface	72 (10.2%)	47 (31.3%)	<0.0001*
Margin elevation	110 (15.6%)	82 (54.7%)	<0.0001*
Ulceration	152 (21.6%)	57 (38.0%)	<0.0001*
Enlarged folds	7 (1.0%)	11 (7.3%)	<0.0001*

U upper, *M* middle, *L* lower

* χ^2 test, ** Student's t test

In the derivation group, there was no significant difference in tumor location between M-SM1 and SM2. SM2 gastric cancers were significantly larger and were characterized as IIa + IIc. According to the endoscopic features, we also found statistically significant differences in remarkable redness, uneven surface, margin elevation, ulceration, and enlarged folds (Table 2).

The tumor size cutoff was set at 30 mm with a cross point between the receiver operating characteristic (ROC) curve against SM2 and the 45° line, which represented the ROC curve of a test whose decision ability is no better than chance (Fig. 6). Tumor size more than 30 mm was determined as a variable in multivariate analysis.

In the logistic regression analysis, tumor size (more than 30 mm), macroscopic type, and endoscopic features which were significantly more common in SM2 by univariate analysis were investigated. As a result, margin elevation, tumor size (more than 30 mm), remarkable redness, and uneven surface were significantly associated with SM2 EGCs (Table 3).

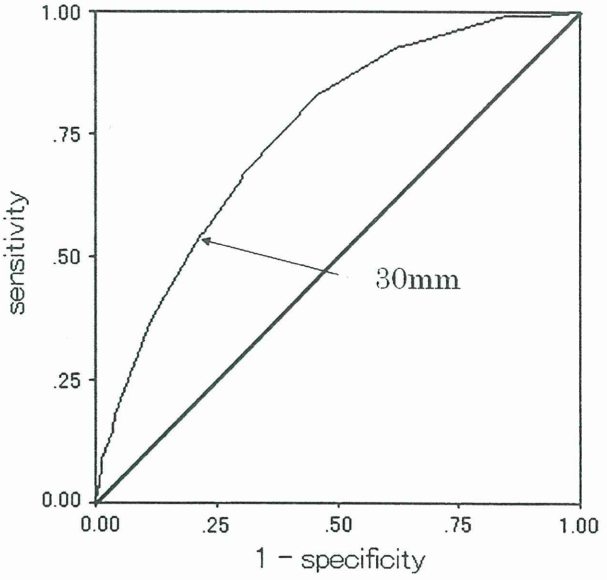

Fig. 6 Receiver operating characteristic curve for tumor size and the sensitivity of submucosal cancers ≥500 μm in depth (SM2): the *arrow* (30-mm diameter) shows the cutoff point between intramucosal and minute submucosal <500 μm in depth (M-SM1) and SM2 cancers

Establishment of depth-predicting score

The DPS was created based on the above results. One point was given for remarkable redness and uneven surface, while margin elevation and tumors more than 30 mm were scored with 2 points because the relative magnitude of the β-coefficient was roughly twice that of other variables. Thus, the range of the resulting DPS was 0–6 points (Table 4). A total of 3 points was defined as the cutoff between M-SM1 and SM2. This was done in order to balance the power for SM2 selection and minimize the population for overtreatment. The sensitivity, specificity, and accuracy of the proposed DPS were 57.3% (95% confidence interval [CI] 49.4–65.3%), 86.2% (95% CI