Table 6 Estimates of predictive values.

Outcome	Feature	LR+	Positive predictive value, %				LR–	Negative predictive value, %			
			1%	10%	20%	50%		1%	10%	20%	50%
Intestinal metaplasia											
	B pattern	4.75	5	34	54	83	0.13	0.10	1	3	11
	Light blue crest	5.13	5	36	56	84	0.37	0.40	4	8	27
Dysplasia											
	C pattern	44.33	31	83	92	98	0.16	0.20	2	4	14

LR, likelihood ratio

expertise is associated with a more precise identification of the lesions and a more accurate diagnosis.

The main limitations to the study were the fact that NBI features were not compared with HR-WLE and that some gastric lesions that can present dysplasia, such as erosions or ulcers, were not included. Also not included were some gastric pathologies that are associated with increased cancer risk, such as autoimmune gastropathy (pernicious anemia) or Ménétrier disease. Therefore, the results should be regarded as applicable to patients with precancerous conditions and intestinal Lauren-type gastric adenocarcinoma. In addition, as low grade dysplasia was observed in only six lesions it cannot be accurately stated that the classification will be applicable equally to low grade dysplasia and high grade dysplasia/intramucosal adenocarcinoma. Also, diffuse-type adenocarcinomas were not included in the current study.

Other studies have provided interesting results on the role of NBI for the detection of gastric pre-neoplastic and cancer lesions [11–24]. However, there are several aspects of the previous studies that must be borne in mind. The definitions of the NBI features were different between the studies, only one study evaluated the reproducibility of some NBI features, and no single study included the whole spectrum of gastric lesions in the same classification or evaluation [25]. Moreover, almost all of the data come from Japan, and therefore applicability to Western countries is uncertain. Another consideration is that almost all of the previous studies used NBI with high magnification (up to ×80), which is not practical in clinical routine as these endoscopes are not available in most centers, at least not in Western countries.

To our knowledge, only three other studies have attempted to identify *H. pylori* gastritis. Alaboudy et al. [23] was the only study that used NBI without magnification; however, the NBI patterns in this study were complex and no reproducibility analysis of these complex patterns was undertaken. Bansal et al. [11] associated irregularity of mucosal and vascular patterns and a low vascular density to *H. pylori* gastritis. However, they did not define irregularity, nor was any reproducibility analysis undertaken, and a low number of patients was included. Tahara et al. [19] associated *H. pylori* gastritis to different patterns with enlarged pits and increased density of irregular vessels. However, again, no reproducibility analysis was done and in neither of these studies was dysplasia considered. This is important because, in our opinion, the "irregularity" described by those studies is clearly different from the irregularity that is present in cancer lesions. To overcome this problem in the current study, irregularity and the different patterns described in previous studies was defined as "variable vascular density," which did indeed show a positive association with *H. pylori* gastritis; however, the reproducibility of this feature on NBI was relatively low and independent of expertise. The results from all of the studies suggest that, even though NBI may be superior to WLE for the identification of *H. pylori* gastritis, NBI (at least without magnification) does not replace other diagnostic tests (e.g. histology) that are clearly more sensitive, specific, and reproducible.

In the case of intestinal metaplasia identification, however, the existing evidence suggests that NBI may be an important tool. Indeed, the two studies by Bansal and Tahara associated a tubulovillous mucosal pattern to intestinal metaplasia with great accuracy [11, 19]. These results were confirmed in the present study, with 92% accuracy of this mucosal pattern for the diagnosis of metaplasia by experienced observers. Uedo et al. [21] suggested that the finding of LBC with NBI is also very accurate for intestinal metaplasia; reproducibility of this finding was not evaluated in the study. In the current study, however, LBC was not very sensitive for metaplasia (68% global sensitivity), though it was specific (87% global specificity). Nevertheless, at least when using a low magnification and the Olympus EXERA system (Uedo used high magnification and the LUCERA system), it appears that a tubulovillous mucosal pattern is more consistently associated and in a more reproducible manner with metaplasia.

Evaluation of dysplasia/cancer using NBI has been performed in several studies. Initial studies have also attempted to establish NBI patterns that could help to predict the degree of tumor differentiation [13,18,20]. Despite some positive results, the authors concluded that NBI was not able to replace histology for tumor differentiation [18]. In these studies, however, the authors did not evaluate which NBI features could help to differentiate between benign and dysplastic lesions. Some authors suggest that "adenoma" may have an NBI pattern resembling pattern B in the current study [20,22], but the precise histological diagnosis of the lesions was not provided in previous studies and it is likely that they presented foci of low grade dysplasia in the context of extensive intestinal metaplasia. In contrast, Kaise et al. [16] evaluated NBI criteria for cancer diagnosis in gastric depressed lesions. They concluded that irregular vascular and mucosal patterns were very specific for cancer, although sensitivity was low and reproducibility only moderate. These relatively modest results may be because cancer lesions were compared only with a particular benign lesion – gastric erosions. Indeed, the same group of authors using the same criteria for dysplasia but evaluating different suspicious lesions found that the sensitivity and specificity of magnification endoscopy NBI for the diagnosis of dysplasia were >90% [29]. Ezoe et al. [14] obtained similar results using similar NBI criteria. In the current study, the accuracy of irregular mucosal and vascular patterns, considered as a complete architecture distortion, was evaluated for the diagnosis of gastric dysplasia in the context of all benign lesions and using only low

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magnification. The results were very impressive, showing not only that these NBI criteria are very accurate for the diagnosis of dysplasia, similar to the study of Kato et al. [29], but also that they allow dysplasia diagnosis in a very reproducible manner. Taking all of the evidence together, it can be suggested that this pattern irregularity with NBI appears to be a good method for the diagnosis of gastric dysplasia, at least for high grade dysplasia.

What is the clinical utility of all these aspects? The current study is not a comparative study of NBI with WLE, it is not possible to state whether or not NBI is better than WLE for the diagnosis of gastric lesions. However, comparing the current results with those from other studies that used HR-WLE [30–32] NBI appears to be clearly superior to WLE for the diagnosis of these types of gastric lesions. More importantly, Kaise et al. [16], Ezoe et al. [14], and Kato et al. [29] compared WLE with NBI for the diagnosis of cancer and concluded that the accuracy of NBI is significantly superior to WLE. Recently, Cappelle et al. [12] compared the yield of NBI to WLE in the surveillance of patients with a previous history of intestinal metaplasia or dysplasia. They used the same NBI system as in the current study and similar definitions; however, *H. pylori* gastritis was not considered and no reproducibility analysis was done. Capelle et al. showed that NBI was better than routine WLE for the diagnosis of intestinal metaplasia and dysplasia. Taking all of these data together, we can say that NBI may help to select suspicious areas for biopsy and probably replace the random biopsy method with a biopsy strategy directed to the suspicious areas of metaplasia and/or dysplasia. Moreover, NBI can also help to delineate gastric lesions for endoscopic gastric resection. Indeed, Kadowaki et al. [15], using similar NBI criteria for dysplasia, have shown that NBI is better than WLE for early cancer demarcation recognition.

Another aspect that is relevant to the current study is the fact that endoscopists with more NBI experience and expertise recognize NBI patterns with more agreement and with more diagnostic accuracy. This is important as it reflects a learning curve for this new technology and suggests that even highly experienced endoscopists should undergo training before using NBI in clinical routine. Moreover, data are presented as range of expected values for accuracy. These results may therefore help endoscopists to judge the accuracy of their diagnosis when NBI is used for the assessment of gastric lesions in clinical practice.

Using likelihood ratios, it was possible to estimate the predictive values of this classification in different scenarios (◎ **Table 6**). For reference centers in countries with a high prevalence of precancerous and cancerous lesions, as in Portugal and Eastern European countries, this classification will able to confirm/predict the presence of dysplasia (post-test probability or positive predictive values of 83%–98%) and to exclude both intestinal metaplasia and dysplasia within centers of low prevalence countries (negative predictive value lower than 1%). Further studies of a per-patient assessment of utility in such specific settings, namely by comparing NBI with WLE or other technologies are needed.

In conclusion, HR-NBI endoscopy is an efficacious technique for the characterization of gastric intestinal metaplasia and, in particular, dysplasia. Irregularity of vascular/mucosal pattern is identified in a reproducible manner and it is consistently associated with gastric dysplasia. HR-NBI endoscopy may be an important tool for the early diagnosis of gastric pre-neoplastic and neoplastic lesions and for therapeutic procedures.

Competing interests: None

Institutions

[1] Department of Gastroenterology, Portuguese Oncology Institute of Porto, Porto, Portugal
[2] Department of Physiology, Cardiovascular Research and Development Unit, Porto Faculty of Medicine, Porto University, Porto, Portugal
[3] CINTESIS/Biostatistics and Medical Informatics, Faculty of Medicine, Porto University, Porto, Portugal
[4] Department of Gastroenterology, Hospital de Braga, Braga, Portugal
[5] Department of Gastroenterology, Centro Hospitalar do Porto, Porto, Portugal
[6] Surgical Sciences Research Domain, Life and Health Sciences Research Institute (ICVS), School of Health Sciences, University of Minho, Braga, Portugal
[7] Department of Gastroenterology, Hospital de São João, Porto, Portugal
[8] Department of Gastroenterology, Portuguese Oncology Institute of Coimbra, Coimbra, Portugal
[9] Department of Pathology, Portuguese Oncology Institute of Porto, Porto, Portugal
[10] Department of Gastroenterology, Academic Medical Center, Amsterdam, The Netherland
[11] Division of Gastroenterology and Hepatology, Veterans Affairs Medical Center, Kansas City, Missouri, USA
[12] Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan
[13] Department of Pathology and Molecular Immunology, Institute of Biomedical Sciences Abel Salazar, University of Porto, Porto, Portugal

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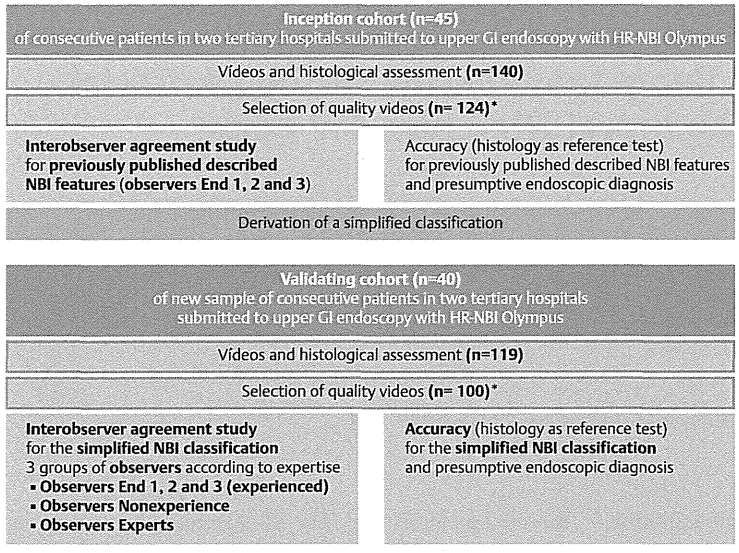

*estimated number of 100 for Pa and kappa confidence intervals estimates with clinical relevance

Fig. e1 Two studies were planned: 1) a consecutive sample of 45 patients (yielding an estimated sample of 100 videos), observed across two tertiary hospitals between September and December 2009, constituted the "derivation cohort," which provided data for a reliability study of previously described mucosal and vascular features using high resolution narrow band imaging (HR-NBI) in gastric mucosa [11–24]. These features were used to develop a simplified NBI classification, which also considered validity measures (using histology as the reference test); 2) a "validation cohort" of 40 new patients (and a new estimated sample of 100 videos) was assessed between February and April 2010; endoscopic observations were used to validate the new NBI classification and assess the reliability of the classification within groups of endoscopists with diverse experience.

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EDITORIAL

Optimal Duration of Proton Pump Inhibitor for Healing Artificial Ulcers After Endoscopic Submucosal Dissection for Early Gastric Cancer

Takuji Gotoda

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To determine the optimal duration of proton pump inhibitor (PPI) treatment for artificial gastric ulcers caused by endoscopic submucosal dissection (ESD), Lee et al. [1] investigated 333 patients who underwent ESD, utilizing a retrospective analysis ($n = 221$) and prospective randomized validation ($n = 112$). The patients with 8-week PPI administration had significantly greater healing of large ESD defects (≥40 mm) than those with 4-week PPI administration (83.3 vs. 42.6%, $p < 0.01$). Therefore, they concluded that 8-week courses of PPI administration should be recommended to treat ESD-induced ulcers larger than 40 mm.

Endoscopic resection allows complete histological staging of the cancer, and is superior to biopsy for diagnosing superficial gastrointestinal neoplasia [2]. Endoscopic mucosal resection (EMR) has been widely established as a safe and reasonable procedure for superficial gastrointestinal neoplasia [3, 4]. However, the tumors are frequently removed in fragments [5, 6], and specimens obtained by such piecemeal resection render pathological staging inaccurate [7]. This is a major factor leading to the high risk of recurrence when this technique is used on larger lesions [8].

T staging using EUS is reportedly accurate in only 80–90% of cases [9, 10]. Hence, the final staging can only be done through a formal histological analysis of en bloc resected material [11]. The ESD technique has been rapidly gaining popularity in Japan and Korea, the countries with the highest incidence of gastric cancer, primarily because of the ability to remove large early gastric cancer (EGC) en bloc [12]. Furthermore, expanded criteria for endoscopic resection have been proposed based on a large study of surgically resected gastric cancers that revealed particular conditions of mucosal cancers with little risk of lymph node metastasis [13]. Recently, many large EGC lesions have been removed by ESD, resulting in large artificial ulcers.

Endoscopic resection is safe, effective, and applicable to a wide variety of clinical situations. However, ESD may cause large and deep defects after the procedure. Green et al. [14] and Berstad [15] have shown that the intragastric pH should be 6.0 or above to allow platelet aggregation and prevent disaggregation. PPIs and histamine H2 receptor antagonists (H2RAs) are generally administered for the treatment of ESD-related ulcers. In standard EMR, artificial ulcers were thought to heal faster and to recur less often than peptic ulcers [16]. Lee et al. [17] reported that at least 4 weeks of PPI administration was required to close even small ulcers after EMR. Yamaguchi et al. [18] found no significant difference between the effect of PPI and that of H2RA for small ulcers caused by ESD and EMR.

In contrast, Ye et al. [19] reported that active ulcers remained at a higher incidence after 4 weeks of H2RA treatment than after PPI administration in ESD-/EMR-induced ulcers with an approximate size of 10 mm. Uedo et al. [20] reported that 8 weeks of PPI administration was sufficient to prevent re-bleeding from ESD defects smaller than 20 mm. Oh et al. [21] reported that the size of the initial defect affects the rate of ulcer healing at 4 weeks of PPI administration post-ESD. Kakushima et al. [22] reported that 4 weeks of PPI administration was not

T. Gotoda (✉)
Department of Gastroenterology and Hepatology,
National Center for Global Health and Medicine,
Tokyo, Japan
e-mail: tgotoda@hosp.ncgm.go.jp

T. Gotoda
Department of Gastroenterology and Hepatology,
Tokyo Medical University, Tokyo, Japan

sufficient, and 8 weeks of administration was required to obtain satisfactory results for larger ulcers after ESD.

Very recently, Imaeda et al. [23] assessed the effects of PPI and H2RA for the prevention of bleeding and the promotion of ulcer healing after ESD, and compared the cost-effectiveness of these two drugs. In this study, although two of the 62 patients (3.2%) in the PPI group and three of the 61 patients (4.9%) in the H2RA group showed bleeding after ESD, there was no significant difference between the two treatment groups. The ulcer-healing rate was 93.5% (58/62) in the PPI group and 93.4% (57/61) in the H2RA group. The total cost of treatment with the antisecretory agent from the day of the ESD to day 56 after the ESD was 13,212 yen for PPI and 5,841 yen for H2RA. The authors concluded that H2RA appears to have a high cost effectiveness in the prevention of bleeding and in the promotion of ulcer healing after ESD for superficial gastric neoplasia.

The optimal dose of PPI for the treatment of artificial ulcers after ESD has not yet been established. Gastric peptic ulcer healing rates using half-dose PPI were reported to be significantly better than those seen when using a standard dose of H2RA [24]. However, there had been no study using half-dose PPI for treating artificial ulcers after ESD. Kawano et al. [25] evaluated the possibility of reducing the dose of PPI from 30 mg (standard-dose) to 15 mg (half dose), and examined ulcer healing, prevention of bleeding, and quality of life. In this study, 91 patients with gastric mucosal neoplasms were enrolled. All patients who underwent ESD were given a standard dose of a PPI daily during the first week, after which they were randomly assigned to either the standard-dose or half-dose group. The stage of ulcers, ulcer reduction ratios, and scores on the Gastrointestinal Symptom Rating Scale did not differ at 28 and 56 days between the groups. The costs of PPI for the half-dose group and standard-dose group were 7,326.5 and 11,698.4 yen, respectively. The authors concluded that a reduced dose of PPI after 1 week of ESD was equivalent in treatment performance to the standard dose regimen, and was less expensive.

Kato et al. [26] recently indicated that combination therapy of a PPI with rebamipide, a mucosa-protective anti-ulcer drug, was more effective than the PPI alone for treating ulcers larger than 20 mm within 4 weeks after ESD. Fujiwara et al. [27] also reported that combination treatment with a PPI plus rebamipide improved healing rates at 8 weeks for patients with ESD-derived artificial ulcers, and appeared to be particularly effective for patients with severe atrophic gastritis. These studies demonstrate the efficacy of a combination of PPI with rebamipide in comparison to PPI alone for early healing of large-sized defects after ESD. These effects may mitigate the limitation of single drug PPI therapy in terms of both the ulcer size and the drug administration period after ESD. Kakushima et al. [28] showed that the infection status of *Helicobacter pylori* and the extent of gastric atrophy do not affect ulcer healing when treating with a combination therapy of sucralfate and PPI at 8 weeks after ESD.

There is no doubt about the significant advantages of ESD as a minimally invasive but curative treatment for EGC. However, the sufficient doses of PPI or H2RA, including combination therapies, for ESD-induced artificial ulcers are not yet established. Eight-week PPI (standard dose) administration is an effective treatment that should be widely applied for complete, rapid, and definitive healing of large artificial defects caused by ESD.

As for future investigations, we should clarify whether the eradication of *Helicobacter pylori* should be undertaken before ESD to aid in the healing of artificial ulcers and/or prevent delayed bleeding. Lee et al. have also excluded patients currently using aspirin and/or anticoagulant agents. Elderly patients have a higher frequency of using aspirin and/or anticoagulant drugs, however, and the increased chance of delayed bleeding from ESD-related artificial ulcers these drugs can create might be more detrimental than the beneficial effects these drugs can provide in elderly patients. We should determine the proper timing of PPI drug withdrawal, and the proper dose and optimal duration of PPI (or H2RA) treatment in this era of an aging society.

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ORIGINAL ARTICLE

Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older

Nobutsugu Abe · Takuji Gotoda · Toshiaki Hirasawa · Shu Hoteya · Kenji Ishido · Yosuke Ida · Hiroyuki Imaeda · Eiji Ishii · Atsushi Kokawa · Chika Kusano · Tadateru Maehata · Satoshi Ono · Hirohisa Takeuchi · Masanori Sugiyama · Shinichi Takahashi

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Abstract
Background Little information is available on the long-term outcomes of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) in patients of advanced age (≥80 years).
Methods A multicenter study was conducted at 10 Japanese institutions concerning their results for ESD. Data on 440 patients of advanced age (≥80 years) with EGC (470 lesions) were collected and reviewed. Early and long-term outcomes of ESD were assessed. We compared the overall survival rates between 3 patient groups, those with curative ESD, additional surgery after noncurative ESD, and nonsurgical follow-up after noncurative ESD.
Results Bleeding and perforation rates were 3.2 and 2.8%, respectively. Curative ESD was achieved in 366 of the 470 lesions (77.9%). Of the 104 patients with noncurative ESD, 12 patients (11.5%) underwent additional surgery and 91 patients (87.5%) were followed without surgery. The 5-year survival rate in the patients with nonsurgical follow-up after noncurative ESD (66.7%) was significantly lower than that in the patients with curative ESD (80.3%, $p = 0.0001$). There was no significant

N. Abe (✉) · H. Takeuchi · M. Sugiyama
Department of Surgery, Kyorin University School of Medicine, 6-20-2 Shinkawa, Mitaka, Tokyo 181-8611, Japan
e-mail: abenbtg@ks.kyorin-u.ac.jp

T. Gotoda · C. Kusano
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

T. Hirasawa
Endoscopy Division, Cancer Institute Hospital, Tokyo, Japan

S. Hoteya
Department of Gastroenterology, Toranomon Hospital, Tokyo, Japan

K. Ishido
Department of Gastroenterology, Kitasato University East Hospital, Kanagawa, Japan

Y. Ida · H. Imaeda
Division of Gastroenterology, Department of Internal Medicine, School of Medicine, Keio University, Tokyo, Japan

H. Imaeda
Department of General Internal Medicine, Saitama Medical University, Saitama, Japan

E. Ishii
Department of Gastroenterology, Kameda Medical Center, Chiba, Japan

A. Kokawa
Department of Gastroenterology, Yokohama City University Medical Center, Kanagawa, Japan

C. Kusano
Department of Endoscopy, National Cancer Center Hospital, Tokyo, Japan

T. Maehata
Department of Gastroenterology and Hepatology, Internal Medicine, St Marianna University School of Medicine, Kanagawa, Japan

S. Ono
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan

S. Takahashi
The Third Department of Internal Medicine, Kyorin University School of Medicine, Tokyo, Japan

difference in the 5-year survival rates between the patients with curative ESD and those with surgery after noncurative ESD (100%, $p = 0.21$), nor was there a difference in these rates between the patients with surgery after noncurative ESD and those with nonsurgical follow-up after noncurative ESD ($p = 0.061$). None of the patients developed cancer recurrence after curative ESD, and none developed cancer recurrence following the additional surgery after noncurative ESD. In the patients with curative ESD and in those with surgery after noncurative ESD, the cumulative observed survival was better than the expected survival for the general population of similar age and gender.
Conclusions ESD is safe for the treatment of EGC in patients 80 years of age or older. Both curative ESD and additional surgery after noncurative ESD may contribute to the extension of life expectancy.

Keywords Early gastric cancer · Endoscopic submucosal dissection (ESD) · Elderly · Multicenter study

Introduction

Early gastric cancer (EGC), which is associated with a 5-year-survival rate of 90%, is diagnosed in more than 50% of patients with gastric cancer in Japan [1]. As the general population ages, larger numbers of elderly patients with EGC will be candidates for endoscopic resection.

Endoscopic submucosal dissection (ESD) is widely recognized as a safe and effective treatment of EGC [2–5], even in aged or high-risk patients [6–10]. However, little information is available on the long-term outcomes of ESD in a large number of elderly patients. To evaluate these outcomes, a retrospective multicenter study was conducted at 10 Japanese institutions concerning their results for ESD in patients of advanced age (≥80 years).

Patients and methods

Patients and indications for ESD

Ten Japanese institutions participating in this study were selected from major centers with accumulated experience in ESD for EGC (Table 1). This study was carried out with the approval of the institutional review board of each institution.

EGC is defined as a lesion confined to the mucosa or submucosa regardless of the presence or absence of lymph node metastasis, according to the *Japanese classification of gastric carcinoma* established by the Japanese Gastric Cancer Association [11]. We collected data of 440 patients who had undergone ESD for EGC (470 lesions) between August 2001 and July 2009 and who were able to be followed for more than 2 years after the ESD (also included are the data of the patients who died for some reason within 2 years after the ESD) (Table 1). Data on clinicopathological characteristics and early and long-term outcomes were collected and analyzed in July 2010, according to the ethical guidelines for epidemiological research proposed by the Ministry of Education, Culture, Sports, Science and Technology of Japan and the Ministry of Health, Labour and Welfare of Japan.

The indications for ESD were basically determined on the basis of the presence or absence of nodal metastasis [12–14] and on the basis of the criteria for endoscopic resection proposed in the *Treatment guidelines for gastric cancer in Japan* [15]. The indication criteria are listed in

Table 1 Participating institutions and numbers of patients (lesions)

Institutions	Number of patients (lesions)
1. Department of Gastroenterology, Toranomon Hospital, Tokyo	17 (17)
2. Department of Gastroenterology, Kitasato University East Hospital, Kanagawa	42 (45)
3. Department of Internal Medicine, School of Medicine, Keio University, Tokyo	17 (17)
4. Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo	22 (22)
5. Department of Gastroenterology, Yokohama City University Medical Center, Kanagawa	73 (75)
6. Endoscopy Division, Cancer Institute Hospital, Tokyo	30 (30)
7. Department of Gastroenterology and Hepatology, St Marianna University School of Medicine, Kanagawa	58 (58)
8. Department of Endoscopy, National Cancer Center Hospital, Tokyo	124 (142)
9. Department of Surgery, Kyorin University School of Medicine, Tokyo	27 (31)
10. Department of Gastroenterology, Kameda Medical Center, Chiba	30 (33)
Total	440 (470)

Table 2 Indication criteria for endoscopic submucosal dissection (ESD)

1. Differentiated-type mucosal cancer without ulceration
2. Differentiated-type mucosal cancer with ulceration and up to 3 cm in diameter
3. Undifferentiated-type mucosal cancer without ulceration and up to 2 cm in diameter
4. Differentiated-type minute submucosal cancer (SM1) without ulceration and smaller than 3 cm in diameter

Table 2. This study also included patients who had not met these criteria (for various reasons) and who had undergone ESD.

Clinicopathological characteristics

The location of the tumor was classified as upper, middle, and lower stomach according to the *Japanese classification of gastric carcinoma* established by the Japanese Gastric Cancer Association [11]. Macroscopic type was divided into elevated type and depressed and/or flat type.

Early outcomes

The early outcomes (bleeding and perforation rates, procedure-related mortality, and curability) were assessed. Bleeding was defined based on clinical evidence of bleeding with occurrence of melena and/or hematemesis, or by confirmation of blood or coagulated blood in the stomach and bleeding spots by endoscopy. Perforation was confirmed endoscopically during the procedure and/or by the presence of free air on plain abdominal radiographs after the ESD. Procedure-related mortality was defined as death due to complications such as perforation or bleeding within 30 days after the ESD.

Curability was assessed histologically, on the basis of the indication criteria for ESD, tumor margin status, and the presence or absence of lymphovascular invasion, as curative and noncurative. When a tumor was within the indication criteria with tumor-free margins and absence of lymphovascular invasion, the curability was defined as curative. When histological evaluation was difficult, or revealed that a lesion was outside the indication criteria and/or that it had a positive margin or lymphovascular invasion, the curability was defined as noncurative.

Long-term outcomes

Patient survival was estimated in three patient groups, those with curative ESD, additional surgery after noncurative ESD, and nonsurgical follow-up after noncurative ESD. We compared the overall survival rates between these 3 patient groups. Expected patient survival was computed for persons of similar age, gender, and calendar year of birth based on cohort life tables constructed for Japan [16].

Table 3 Patient and tumor characteristics

Parameters	No. of patients ($n = 440$) or tumors ($n = 470$)
Age, years, mean (range)	82 (80–93)
Sex ratio (M/F)	314/126
Tumor location	
Upper third	101 (21.5%)
Middle third	153 (32.6%)
Lower third	216 (45.9%)
Macroscopic type	
Elevated	232 (49.4%)
Depressed and/or flat	238 (50.6%)

Table 4 Early outcomes of ESD

	No. of patients ($n = 440$) or tumors ($n = 470$)
Bleeding	15 (3.2%)
Perforation	13 (2.8%)
Procedure-related death	0 (0%)
Curability[a]	
Curative resection	366 (77.9%)
Noncurative resection	104 (22.1%)

[a] When a tumor was within the indication criteria, with tumor-free margins, the curability was defined as curative. When histological evaluation was difficult, or, revealed that a lesion was outside the indication criteria and/or that it had a positive margin, the curability was defined as noncurative

Statistical analysis

Patient survival was estimated using the Kaplan–Meier method. Differences were considered significant when $p < 0.05$.

Results

Early outcomes

The patients' clinicopathological characteristics are shown in Table 3. The patients were 314 men and 126 women with a mean age of 82 years (range 80–93 years).

Bleeding and perforation rates were 3.2 and 2.8%, respectively (Table 4). Although no deaths related to ESD occurred, one patient died of a cardiac event during the

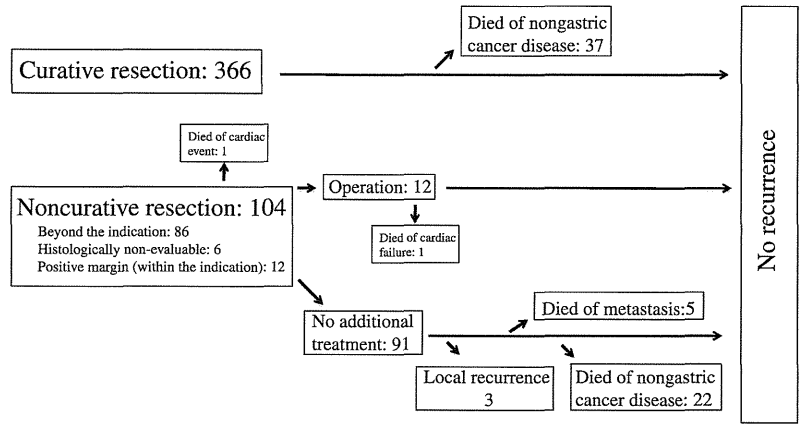

Fig. 1 Clinical outcomes of endoscopic submucosal dissection (ESD)

hospital stay (on post-ESD day 10). The complication rate (bleeding and perforation) was similar to those in other reports [2–10], showing that ESD was mostly safely performed even in the elderly. Curative ESD was achieved in 366 of 470 lesions (77.9%). Of the 104 patients with noncurative ESD, 12 patients (11.5%) underwent additional surgery, and the remaining 91 patients (87.5%) were followed without surgery (Fig. 1). One patient died of cardiac failure after the additional surgery during the hospital stay.

Long-term outcomes

The overall median follow-up period was 41 months (range 2–99). Of the 366 patients with curative ESD, 37 patients (10.1%) died of nongastric cancer disease, and none of the remaining 329 patients (89.8%) developed cancer recurrences (Fig. 1). Of the 104 patients with noncurative ESD, none of the 11 patients who underwent additional surgery developed cancer recurrences. Of the 91 patients with nonsurgical follow-up after noncurative ESD, three patients (3.3%) developed local recurrence, and five (5.5%) and 22 (24.2%) patients died of gastric cancer metastasis and nongastric cancer disease, respectively. None of the remaining 61 patients (67%) developed cancer recurrences.

The median follow-up period in the patients with curative ESD, surgery after noncurative ESD, and nonsurgical follow-up after noncurative ESD was 38.5, 44, and 33 months, respectively. The overall 5-year survival rates in these three groups were 80.3%, 100% (excluding one patient who died of cardiac failure after the surgery), and 66.7%, respectively (Fig. 2). The 5-year survival rate in the patients with nonsurgical follow-up after noncurative ESD was significantly lower than that in the patients with curative ESD ($p = 0.0001$). There was no significant difference in the 5-year survival rates between the patients

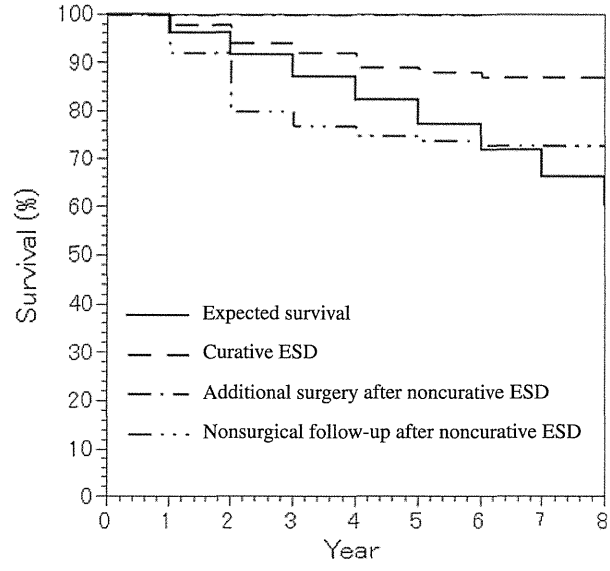

Fig. 2 Observed patient survival in each group, and expected survival. The expected survival was based on that of persons of similar age, gender, and calendar year of birth, using life tables for death from all causes for Japan [15]

with curative ESD and those with surgery after noncurative ESD ($p = 0.21$), nor was there a significant difference in the 5-year survival rates between the patients with surgery after noncurative ESD and those with nonsurgical follow-up after noncurative ESD ($p = 0.061$). In the patients with curative ESD and those with surgery after noncurative ESD, the cumulative observed survivals of 80.3, 100, and 65% at 5 years after ESD were better than the expected survival for the general population of similar age and gender. In the patients with nonsurgical follow-up after noncurative ESD, the cumulative observed survival of 66.7 and 65% at 5 years after ESD was comparable to the expected value for the general population of similar age and gender.

Discussion

According to the fiscal 2008 statistics published by the Ministry of Health, Labour and Welfare, the mean life spans in Japan for men and women, respectively, were 79 and 86 years, and the mean life expectancies at the age of 80 years were 8 and 11 years for men and women, respectively [16]. With the coming of such a superaging era, endoscopic treatment has been increasingly performed for EGC in the elderly, and it has been established as a safe and minimally invasive technique [6–10]. However, only one report has been published on the long-term outcomes of endoscopic treatment for EGC in a large number of patients of advanced age [17]. Moreover, the natural history of EGC has been poorly clarified. Therefore, whether EGC affects the prognosis of patients of advanced age, regardless of the presence or absence of a therapeutic intervention, has not been fully clarified. With these features as a background, the present retrospective multicenter study was carried out to determine the early and long-term outcomes of ESD in the elderly (age 80 years or older) and to clarify the validity of ESD.

In the examination of long-term outcomes, the patients with curative ESD did not show cancer recurrence, and were only followed up after ESD. Although 12.8% of the patients in this group died of nongastric cancer disease, the overall survival rate of this group was better than the expected survival rate of the general population. This finding suggests that the active implementation of ESD will contribute to the extension of life expectancy even in patients of advanced age with EGC when a lesion fulfills the indication criteria for endoscopic treatment, as Kusano et al. [17] have recently demonstrated. However, in the present study, the elderly patients who received endoscopic examination, therapy, and/or additional surgery could have been healthier and could have had a better performance status than the general elderly population. Thus, we should pay special attention to this potential selection bias in the present study.

In clinical practice, when an ESD specimen is diagnosed as being beyond the indication criteria for endoscopic treatment on the basis of histopathological analysis, we often face the problem of deciding whether additional surgery should be performed; this choice is faced in younger patients as well as in patients of advanced age. In patients of advanced age, however, the appropriate surgical treatment should be selected considering background factors such as the presence or absence of dementia or chronic comorbidities, and the use of anticoagulation agents, as well as considering the decrease in the patient's quality of life after the surgery. In addition, the fact that death from nongastric cancer disease reduces the survival rate in patients of advanced age compared with that in younger patients should be considered.

In the present study, 87.5% of the 104 patients with noncurative ESD did not undergo additional surgery but were only followed up. Of these, 24.2% died of nongastric cancer disease, and inevitably, a considerable number of patients (5.5%) died of cancer metastasis. Background factors such as the presence or absence of dementia or chronic comorbidities, and the use of anticoagulation agents, were not considered in this study. Therefore, there might have been a bias because the group with nonsurgical follow-up after noncurative ESD would have included many patients with difficulties in undergoing surgery or those who were assessed as having a higher risk of death from nongastric cancer disease even before the ESD. It is presumed that many such patients were followed up because of factors unique to the elderly that cannot be quantified in numerical terms. However, the patients who underwent additional surgery after noncurative ESD did not develop recurrence. Moreover, nongastric cancer death was not found in such patients. Therefore, it may be desirable to perform additional surgery when possible after noncurative ESD, although in the present study there might also have been a bias because the patients in the group with additional surgery after noncurative ESD did not have a risk of death from nongastric cancer disease. In fact, Kusano et al. [17] have recently shown that additional surgery following noncurative endoscopic resection improved survival in elderly patients. On the other hand, in the present study, because the overall survival rate (66.7%) in the patients with nonsurgical follow-up after noncurative ESD was similar to the expected survival rate (65%) of the general population, it is possible that local control provided by ESD alone may be significant even in such patients. A prospective study of the followed-up patients is necessary to establish the significance of ESD in these patients. However, such a clinical investigation has major ethical issues because the lesions that do not meet the indication criteria for endoscopic treatment have a possibility of lymph node metastasis and are therefore beyond the indication for endoscopic resection in the first place. In the meantime, it is necessary to select the appropriate treatment for the individual patient in clinical practice, to accumulate cases of patients whose lesions are outside the criteria for endoscopic treatment who are only followed up after ESD, and to conduct a retrospective multiple-case study of the cases thus accumulated.

In conclusion, ESD is safe for the treatment of EGC in patients 80 years of age or older. Both curative ESD and additional surgery after noncurative ESD may contribute to the extension of life expectancy. However, careful follow-up after noncurative ESD (namely, ESD only) can be one of the options in patients of advanced age who have difficulties in undergoing surgery or who are assessed as having a high risk of death from nongastric cancer disease.

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ORIGINAL ARTICLE

Depth-predicting score for differentiated early gastric cancer

Seiichiro Abe · Ichiro Oda · Taichi Shimazu · Tetsu Kinjo · Kazuhiro Tada · Taku Sakamoto · Chika Kusano · Takuji Gotoda

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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

S. Abe · I. Oda (✉) · T. Kinjo · K. Tada · T. Sakamoto · C. Kusano · T. Gotoda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ioda@ncc.go.jp

T. Shimazu
Epidemiology and Prevention Division, Research Center for Cancer Prevention and Screening, National Cancer Center, Tokyo, Japan

C. Kusano · T. Gotoda
Department of Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

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

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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

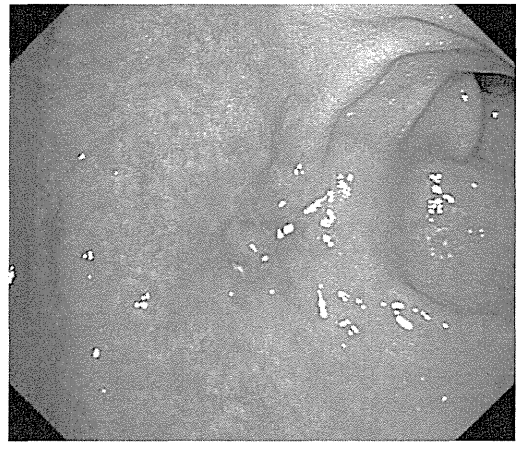

Fig. 1 Remarkable redness: endoscopic picture shows unusual redness inside the lesion

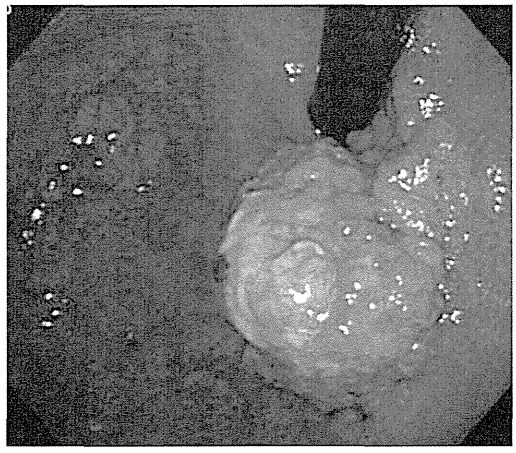

Fig. 2 Uneven surface: nodular mucosa can be seen

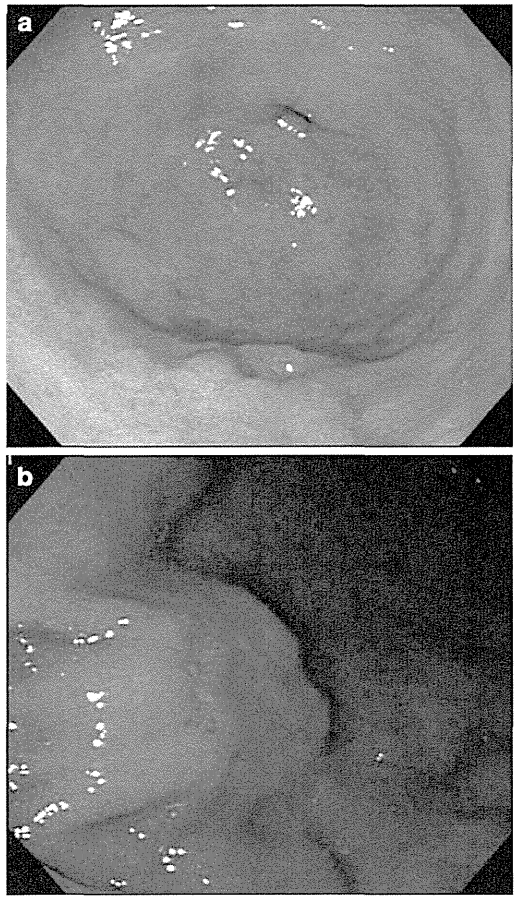

Fig. 3 **a** Margin elevation: endoscopic picture of surrounding elevation. **b** Margin elevation: endoscopic picture of submucosal tumor like component can be demonstrated from the view with a limited amount of air insufflation

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.

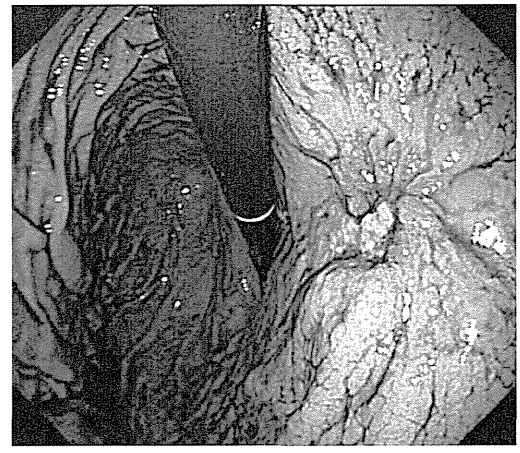

Fig. 4 Ulceration: endoscopic picture of ulceration

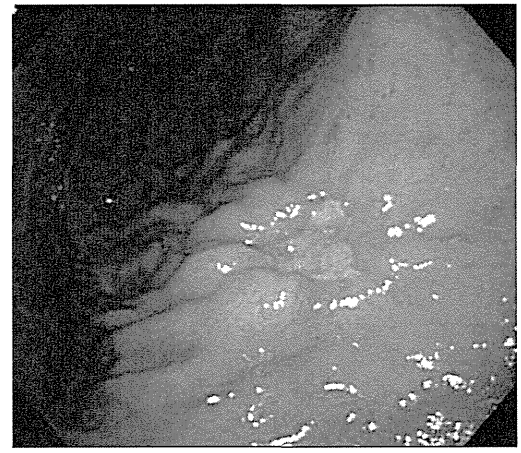

Fig. 5 Enlarged folds: thickened or merged folds can be seen toward the inside of the lesion

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).

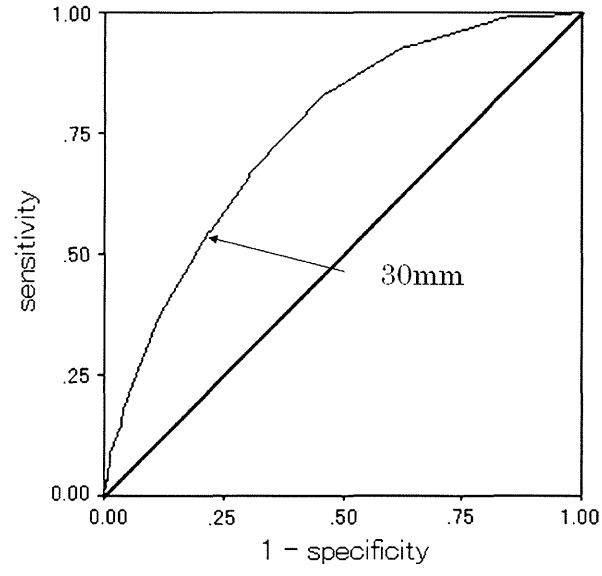

Fig. 6 Receiver operating characteristic curve for tumor size and the sensitivity of submucosal cancers ≥500 μm in depth (SM2): the *arrow* (30-mm diameter) shows the cutoff point between intramucosal and minute submucosal <500 μm in depth (M-SM1) and SM2 cancers

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

Table 3 Multivariate logistic regression analysis

	β-coefficient	Odds ratio (95% CI)	p value
Margin elevation	7.838	6.221 (3.938–9.825)	<0.0001
Tumor size (more than 30 mm)	6.570	4.937 (3.066–7.951)	<0.0001
Remarkable redness	3.411	2.087 (1.367–3.186)	0.0006
Uneven surface	3.343	2.306 (1.413–3.764)	0.0008

CI confidence interval

Evaluated items in multiple logistic regression analysis were followed: tumor size more than 30 mm, macroscopic type (IIa + IIc), remarkable redness, uneven surface margin elevation, ulceration and enlarged folds. Only the statistically significant items are listed in the table

Table 4 Proposed depth-predicting score

Factor	Points	
	Present	Absent
Margin elevation	2	0
Tumor size (more than 30 mm)	2	0
Remarkable redness	1	0
Uneven surface	1	0

83.7–88.8%), and 81.1% (95% CI 78.5–83.8%), respectively (Fig. 7).

Finally, we applied the suggested DPS model to the 211 validation lesions without any histological information. When we considered 3 points or more as SM2, the sensitivity, specificity, and accuracy of the proposed DPS, assigned by the three endoscopists, were 29.7–45.9, 93.1–93.7, and 82.5–84.8%, respectively. When we divided the validation group into "IIa" and "IIc/IIa + IIc", the sensitivity, specificity, and accuracy were 50.0–83.3, 92.6–96.3, and 91.7% (by all three endoscopists) for IIa lesions and 25.8–38.7, 92.5–93.3, and 78.8–82.1% for IIc/IIa + IIc lesions (Table 5).

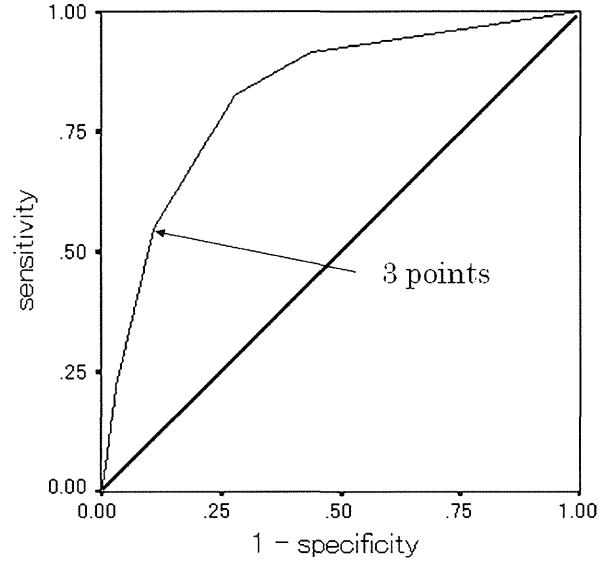

Fig. 7 Receiver operating characteristic curve for depth-predicting score (DPS) and the sensitivity of SM2: the *arrow* (3 points) shows the cutoff point between M-SM1 and SM2

Table 5 Diagnostic sensitivity and specificity by depth-predicting score according to macroscopic type in the validation group

	IIa	IIc/IIa + IIc	Total
Endoscopist 1			
Sensitivity	50.0% (3/6)	25.8% (8/31)	29.7% (11/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	78.8% (119/151)	82.5% (174/211)
Endoscopist 2			
Sensitivity	83.3% (5/6)	38.7% (12/31)	45.9% (17/37)
Specificity	92.6% (50/54)	93.3% (112/120)	93.1% (162/174)
Accuracy	91.7% (55/60)	82.1% (124/151)	84.8% (179/211)
Endoscopist 3			
Sensitivity	50.0% (3/6)	35.8% (11/31)	37.8% (14/37)
Specificity	96.3% (52/54)	92.5% (111/120)	93.7% (163/174)
Accuracy	91.7% (55/60)	80.8% (122/151)	83.9% (177/211)

Discussion

Patients' quality of life is one of the most important issues in EGC treatment, because the prognosis of EGC is favorable [13]. Differentiating endoscopically resectable M-SM1 gastric cancers from surgically resectable SM2 lesions is of great significance, given the low risk of lymph node metastases with the former. In conventional endoscopic diagnosis for these EGCs, however, endoscopists have had to empirically estimate the depth of invasion, as no objective criteria existed.

The first aim of this retrospective study was to analyze the differences in conventional endoscopic features between M-SM1 and SM2 EGCs. We found that tumor size more than 30 mm, margin elevation, uneven surface, and remarkable redness were significantly associated with an increased risk of SM2 invasion according to logistic regression analysis.

There have been few reports about the usefulness of conventional endoscopy for predicting depth of invasion. The overall accuracy rates for determining depth of invasion of EGCs were between 63 and 73% by non-objective criteria [11, 14, 15]. Namieno et al. [16] concluded that

macroscopic appearance, histological differentiation, and tumor size were associated with submucosal invasion. However, they did not analyze the morphologic features of the tumors.

Although we used endoscopy in the present study, EUS can also show the depth of invasion clearly. The introduction of high-frequency thin probes has allowed target scanning with high resolution under endoscopic control [8, 9]. In spite of some excellent accuracy data [17], there have been no significant differences between EUS and endoscopy in terms of depth accuracy [14].

Considering the need for simple and objective diagnosis, we proposed an endoscopic determination for the depth of invasion of differentiated EGCs by the DPS described here, based on our analysis of the derivation group. The DPS could be used to determine an appropriate treatment strategy for the validation group with 82.5–84.8% accuracy. Based on macroscopic type, the accuracy for elevated lesions tended to be better than that for the depressed and combined lesions.

Although specificity was good in steering M-SM1 cancers toward endoscopic treatment, low sensitivity was a weak point of the DPS. Selected endoscopic features may not reflect microscopic SM2 invasion. Also, each variable was considered as only either present or absent. If the significance of each finding had been taken into consideration, the sensitivity and accuracy of the score may have increased. However, this would have complicated the DPS, and was therefore not done.

EUS could be omitted for lesions with a DPS of less than 2 points and endoscopic resection performed, except for large ulcerative lesions more than 30 mm in diameter. Lesions with a DPS of 3 points or more may be considered as candidates for additional EUS, potentially providing more precise prediction. By using this simple diagnostic model, appropriate treatment strategies can be determined for differentiated M-SM1 EGCs, while saving time and cost as compared to EUS being done for all cases.

The limitation of this investigation was the retrospective design at a single institution. Further research in a prospective study is needed to investigate the utility of the DPS in combination with EUS for lesions with a DPS of 3 points or greater.

In conclusion, the proposed DPS may be useful in making treatment decisions for differentiated M-SM1 EGCs.

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ORIGINAL ARTICLE

Clinical impact of a strategy involving endoscopic submucosal dissection for early gastric cancer: determining the optimal pathway

Satoru Nonaka · Ichiro Oda · Teruo Nakaya · Chika Kusano · Haruhisa Suzuki · Shigetaka Yoshinaga · Takeo Fukagawa · Hitoshi Katai · Takuji Gotoda

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Abstract
Background Endoscopic submucosal dissection (ESD) is a technique developed to enable the endoscopic resection (ER) of large and ulcerative neoplastic lesions that were previously unresectable using conventional endoscopic mucosal resection (EMR). We investigated the clinical outcomes of ER of early gastric cancer (EGC) before and after the introduction of ESD, with particular attention to surgery and its potential consequences.
Methods We reviewed 2,785 consecutive surgical patients with EGC and 2,469 consecutive lesions treated by ER with curative intent between 1990 and 2005. The study was divided into an EMR period (1990–1999) and an ESD period (2000–2005). We analyzed the clinical outcomes of endoscopic and surgical resections and defined 'potentially avoidable surgery' as cases of surgery performed for lesions curable by ER.
Results The rate of potentially avoidable surgery was 3.8% (52/1,369) in the EMR period and 0.2% (3/1,416) in the ESD period ($P < 0.001$). For ER patients, the rate of overall non-curative ER was 36.9% (154/417) in the EMR group and 17.0% (348/2,052) in the ESD group ($P < 0.001$). The rate of non-curative ER for lesions defined as having 'positive or difficult to estimate horizontal margins only' decreased significantly, from 26.1% (109/417) in the EMR group to 1.4% (29/2,052) in the ESD group ($P < 0.001$). Conversely, the rate of non-curative ER for lesions defined as having 'possible lymph node metastasis' significantly increased in the ESD group (15.5%; 319/2,052) compared to that in the EMR group (10.8%; 45/417) ($P < 0.01$).
Conclusions The application of a pathway involving ESD resulted in a significant decrease in the rate of potentially avoidable surgery, highlighting the advantages associated with performing ESD.

Keywords Early gastric cancer · Lymph node metastasis · Endoscopic submucosal dissection · Potentially avoidable surgery · Non-curative endoscopic resection

Abbreviations

ER	Endoscopic resection
EGC	Early gastric cancer
EMR	Endoscopic mucosal resection
ESD	Endoscopic submucosal dissection
sm2	Submucosal deep invasion
sm1	Submucosal superficial invasion

Introduction

Therapeutic endoscopic resection (ER) has been performed for early gastric cancer (EGC) since the mid 1980s and is now accepted as the standard treatment for those patients with negligible risk of lymph node metastasis [1–8]. The conventional method by which EGCs were removed was by endoscopic mucosal resection (EMR). The limitations

S. Nonaka · I. Oda (✉) · T. Nakaya · C. Kusano · H. Suzuki · S. Yoshinaga · T. Gotoda
Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
e-mail: ioda@ncc.go.jp

C. Kusano · T. Gotoda
Gastroenterology and Hepatology, National Center for Global Health and Medicine, Tokyo, Japan

T. Fukagawa · H. Katai
Gastric Surgery Division, National Cancer Center Hospital, Tokyo, Japan

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