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Effective optical identification of type "0-IIb" early gastric cancer with narrow band imaging magnification endoscopy, successfully treated by endoscopic submucosal dissection

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Abstract

Background Endoscopic submucosal dissection (ESD) is currently considered the minimal invasive endoscopic treatment for early gastric cancer. Most superficial gastric neoplastic lesions are depressed type "0-IIc" (70-80%), while totally flat, classified as type "0-IIb" early gastric cancer, is rarely reported (0.4%). The aim of the present study was to assess the efficacy of narrow band imaging (NBI) magnification endoscopy in identifying type "0-IIb" early gastric cancer and ESD treatment with curative intention.

Methods Twelve of 615 (2%) patients (10 males, median 72 years), treated by ESD at our center, were diagnosed as type "0-IIb" gastric cancer. Ten had exclusively type "0-IIb", while two had combined types "0-IIb+IIc" and "0-IIa+IIb" gastric cancer. Initial diagnosis was made during screening gastroscopy, while NBI magnification endoscopy combined with indigo-carmine chromoendoscopy were also used.

Results White light endoscopy showed only superficial redness. One patient with signet-ring carcinoma showed whitish appearance. Indigo-carmine chromoendoscopy showed better visualization, while NBI magnification endoscopy revealed abnormal mucosal microsurface and microvascular findings which enabled border marking. ESD with curative intention was completed without complications. Histological examination showed complete (R0) resection, in 10 patients (83%). One patient with positive margins received additional surgery (8%). Mean procedure time was 149 (range 60-190) min. One to six years post-ESD all patients remain alive.

Conclusions ESD is considered a safe and effective curative treatment for type "0-IIb" gastric cancer, resulting in long-term disease-free survival. NBI magnification endoscopy is effective for accurate optical identification and border marking of type "0-IIb" early gastric cancer.

Keywords Endoscopic submucosal dissection, narrow band imaging magnification endoscopy, type "0-IIb" early gastric cancer

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Introduction

Endoscopic submucosal dissection (ESD), developed by Japanese investigators [1-4], has been successfully used for local, minimal invasive treatment of early gastric cancer and is considered the treatment of choice for *en bloc* resection [5-9]. Although most superficial neoplastic lesions in the stomach are depressed type "0-IIc" (70-80%), totally flat early gastric cancer, classified as type "0-IIb" is scarcely reported (9/2098, 0.4% in Paris classification [10]), because it is usually missed during routine endoscopy and misdiagnosed as chronic gastritis [1,10].

Accurate endoscopic diagnosis and precise evaluation of type "0-IIb" early gastric cancer, a fundamental prerequisite for

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Conflict of Interest: None

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endoscopic treatment, became often difficult or even impossible by standard endoscopic techniques [7,11,12]. In these cases, high suspicion from endoscopist's part, in combination with incorporation of new technologies in clinical practice may increase the diagnostic yield of early gastric cancer [11-13].

Narrow band imaging (NBI) magnification endoscopy is a relatively new imaging technique that enhances mucosal microsurface structures and microvasculature by using a short wavelength and narrow bandwidth illumination (415 nm), which has a high affinity to be absorbed by hemoglobin [11-15].

NBI magnification allows more detailed observation of mucosal architecture and improves the diagnostic capability for determining tumor margins, absolutely necessary for curable ESD [7,11-14,16,17]. According to several reports, including a recent multicenter study from Japan [7], NBI magnification improved the optical identification of early gastric cancer compared with conventional endoscopic methods [7,12,13,18-23].

In high-risk patients, every erythematous, gastritis-like lesion of the stomach should be meticulously evaluated using NBI magnification for abnormal microvascular and mucosal microsurface findings, corresponding to early gastric cancer type "0-IIb".

Endoscopic therapies became even more important for elderly patients, often poor candidates for surgery due to comorbidities [24,25]. Complete specimen for histopathology is also obtained by ESD. Horizontal and lateral margins of the endoscopic specimen, as well as lymphovascular invasion should be negative for curative (R0) resection of early gastric cancer according to the Japanese classification of gastric cancer (JCGC) [22,23]. Overlooked lateral spreading, type "0-IIb" gastric cancer be resulted in histologically incomplete endoscopic resection [11,12].

The novelty of this paper is that, although endoscopic diagnosis and treatment of early gastric cancer is widely reported, these reports mainly referred to slightly depressed or slightly elevated gastric lesions, classified as type "0-I", "0-IIc", or "0-IIa" lesions, while international experience of NBI magnification endoscopy and ESD in gastritis-like, totally flat, type "0-IIb" gastric cancer is limited [26-31].

The aim of the present study was to assess the efficacy of endoscopic identification using NBI magnification endoscopy and ESD treatment with curative (R0) intention of type "0-IIb" early gastric cancer. Secondary endpoint was to access the efficacy of endoscopic diagnosis and ESD treatment of undifferentiated, type "0-IIb", signet-ring cell early gastric cancer, which belongs to the extended criteria for ESD.

Patients and methods

From 2005 to 2011, a total of 615 patients with endoscopically and histologically proven early gastric cancer according to JCGC [22] were selected and treated by ESD in the Digestive Disease Center of Showa University, Northern Yokohama Hospital, Japan. Initial diagnosis was done during screening gastroscopy, while definite decision for ESD was made by an experienced endoscopist, based on endoscopic macroscopic and NBI magnification findings, according to Japanese Gastric Cancer Association (JCGA) guidelines [32,33].

The study was approved by the Institutional Review Board of the Showa University, Northern Yokohama Hospital. The study protocol was explained to the patients before written informed consent was obtained. This study was registered with the University Hospital Medical Information Network in Japan.

Twelve of 615 (2%) patients, 10 males, mean age 69±10.1 years, median age 72 years, age range 52-85 years, were diagnosed as type "0-IIb" early gastric cancer, according to JCGC [22] and Paris endoscopic classification of early gastrointestinal (GI) neoplasia [10]. Ten patients had purely type "0-IIb" lesions (Fig. 1-5), while two patients had combined types "0-IIb+IIc" (Fig. 6) and "0-IIa+IIb" lesions, respectively (JCGC) [22]. The patient with type "0-IIb+IIc" early gastric cancer had local recurrence after previous ESD. Clinico-pathological features of patients are shown in Table 1.

The procedures were performed by 7 skilled endoscopists under conscious sedation at the Endoscopy department in 9 (75%) patients, while 3 (25%) patients were treated under general anesthesia with intratracheal intubation. CO_2 insufflation was available during procedures to avoid pneumoperitoneum. All patients were treated at a left lateral position.

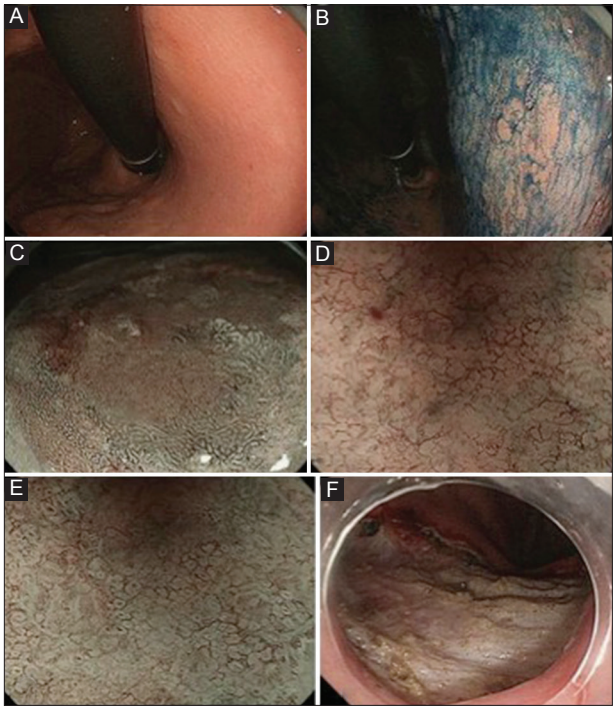

Figure 1 Type "0-IIb" gastric cancer at the middle gastric body to lesser curvature. (A) White light endoscopy except for slight redness is almost normal. (B) Indigo-carmine delineates better the lesion. (C) Narrow band imaging (NBI) low magnification shows brownish area and demarcation line. (D) NBI high magnification shows abnormal fine network pattern. (E) NBI high magnification after acetic acid spray shows abnormal small pit pattern. (F) Endoscopic submucosal dissection ulcer

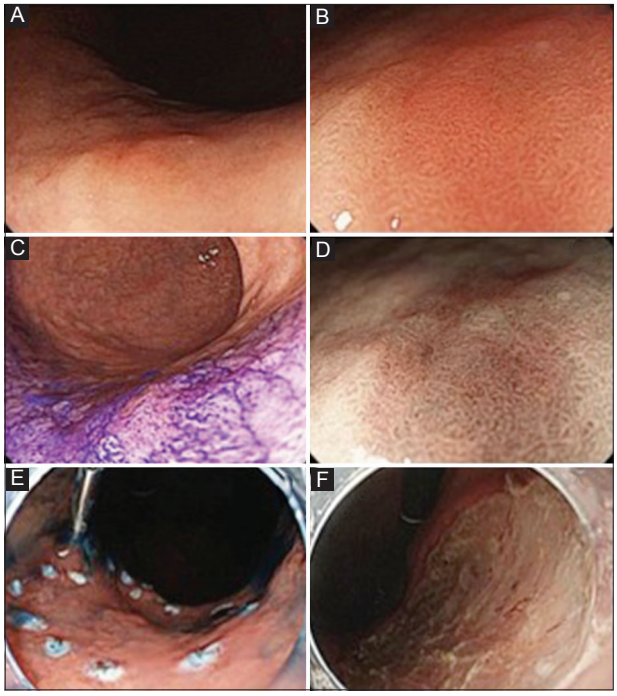

Figure 2 Type "0-IIb" gastric cancer at the posterior wall of the middle body. (A) and (B) White light endoscopy with low (A) and high (B) magnification shows slight flat redness. (C) Crystal violet staining shows better delineation of the lesion. (D) Narrow band imaging (NBI) magnification shows abnormal microsurface structure, clearly brownish area from the surrounding mucosa and demarcation line. (E) Tumor border marking with dots outside the demarcation line as evaluated by NBI magnification. (F) Endoscopic submucosal dissection ulcer

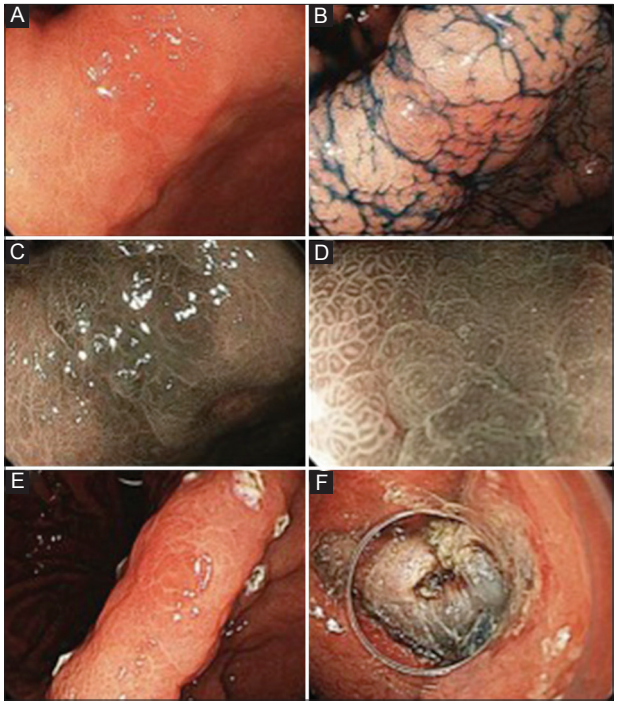

Figure 3 Type "0-IIb" gastric cancer at the gastric angulus. (A) White light endoscopy shows slight redness. (B) Indigo-carmine chromoendoscopy delineates better the lesion. (C) Narrow band imaging (NBI) low magnification shows brownish area with demarcation from the surrounding normal mucosa. (D) NBI high magnification shows abnormal microsurface pattern with clear demarcation line. (E) Tumor border marking with dots just outside the demarcation line. (F) Endoscopic submucosal dissection ulcer

A diagnostic gastroscopy was performed just before ESD, in order to re-evaluate the gastric lesion and mark the tumor borders. A high-resolution NBI magnification endoscope was used for marking. A small black hood was mounted on the tip of the endoscope to facilitate NBI.

NBI magnification supplied useful information of the mucosal pattern in all patients by enhancing mucosal microsurface and microvascular architecture, in accordance to previous reports [7,11-14,16,17]. A particular difficulty in identification the demarcation line was experienced with type "0-IIb" gastric cancers due to the nature of these totally flat gastric lesions. The abnormal NBI findings under high magnification were further classified according to previous report by Yokoyama *et al* [13]. This classification was extremely helpful in predicting the possible differentiation type (Table 3). In cases with mixed NBI magnification findings the major pattern was described.

NBI magnification imaging after acetic acid spray, additionally used upon indication, showed further specific abnormal microsurface structural findings, according to previous classification [34].

After thorough endoscopic examination, marking of the tumor borders was carried out, mainly based on NBI magnification findings. Dots were placed outside the demarcation line, according to the report by Yao *et al* [11] (Fig. 2, 3, 6 E).

ESD procedure was performed using a therapeutic endoscope. Circumferential mucosal incision and direct submucosal dissection were carried out with one of the specified knives until complete excision was achieved. Flush knife (Fujinon Corp., Omiya, Japan) and Triangle Tip Knife (TT-Knife) (Olympus Corp. Japan) were the main knives used, while a rotable Hook-Knife (Olympus Corp. Japan) was used in combination with flush knife in one patient (Table 2). Flush Knife (Fujinon Corp., Omiya, Japan), the most commonly used knife in 67% of cases, had the advantage of water injection through the knife tip to submucosal area during dissection [35].

Endoscopic hemostasis was achieved either with the knife used for the dissection or with hemostatic forceps (Coagrasper, Olympus Corp.) whenever active bleeding was noticed. Hemoclips were not used in this study.

High frequency generators (ERBE corp. Tubingen, Germany, 200ICC or V/O 300D) were used for marking, circumferential mucosal incision, submucosal dissection, and endoscopic hemostasis. Electrosurgical settings were selected according to the standard preferences and to guidelines provided by the manufacturers.

Individualized strategy was followed during ESD procedure according to location and size of the tumor. Typical sequences followed in all cases: a) peripheral marking; b) submucosal injection to lift the mucosal lesion and inflate the submucosal layer; c) peripheral incision; and d) submucosal dissection with

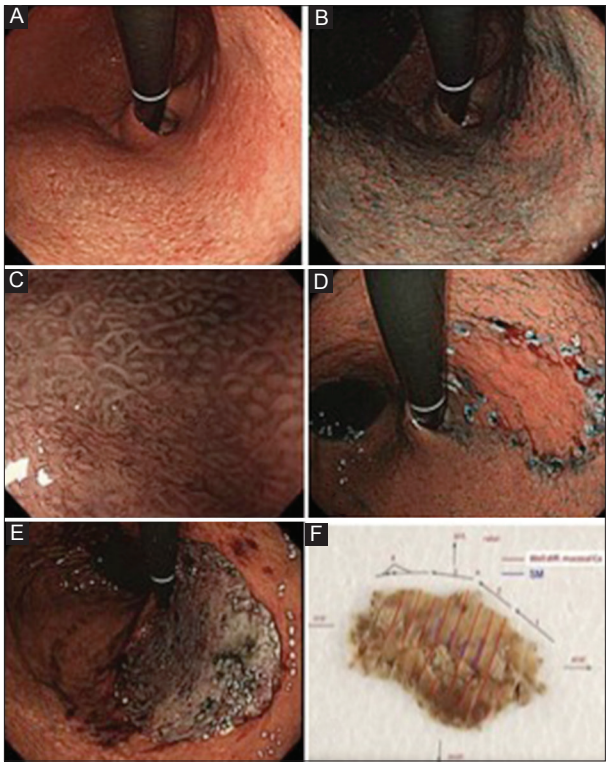

Figure 4 Type "0-IIb" gastric cancer at the upper gastric body along the lesser curvature. (A) White light endoscopy shows slight erythematous area. (B) Indigo-carmine chromoendoscopy visualizes better the tumor but still with unclear tumor borders. (C) Narrow band imaging (NBI) with high magnification shows a demarcation line between irregular (cancerous) and regular (noncancerous) mucosa. Background mucosa shows regular microvascular (open-loop) and microsurface (tubular) patterns, while cancerous mucosa shows irregular microvascular (tortuous/branched/bizarre vessels) pattern and absence of obvious microsurface pattern. (D) Circumferential marking before endocopic submucosal dissection (ESD). Dots were placed at the tumor margins, as they identified by NBI magnification imaging. (E) Post-ESD gastric ulcer. (F) ESD specimen showing horizontal and vertical (submucosal invasion) margins positive for gastric cancer

simultaneous hemostasis when needed. A 21-25-G injection needle was used for submucosal injection.

The location of the lesions was determined according to JCGC [22] as upper, middle, lower part, lesser curvature, greater curvature, anterior and posterior gastric wall (Table 1). Lesions were classified according to the largest diameter as ≤20 mm (7 patients, 58%) and >20 mm (5 patients, 42%). "Procedure time" was defined as the time from insertion of the endoscope to complete removal (Table 1).

Fixation of all specimens as well as final histopathological examination was performed according to JCGC guidelines [22]. Main pathological criteria assessed were histological type [well differentiated (tub-1); moderately differentiated (tub-2); or poorly differentiated (por)], invasion depth [horizontal (H) and vertical (V) margins], and presence or absence of lymphatic or vascular invasion.

R0 *en bloc* resection was defined as a lesion resected in a single piece with at least 1 mm of deep and lateral margins

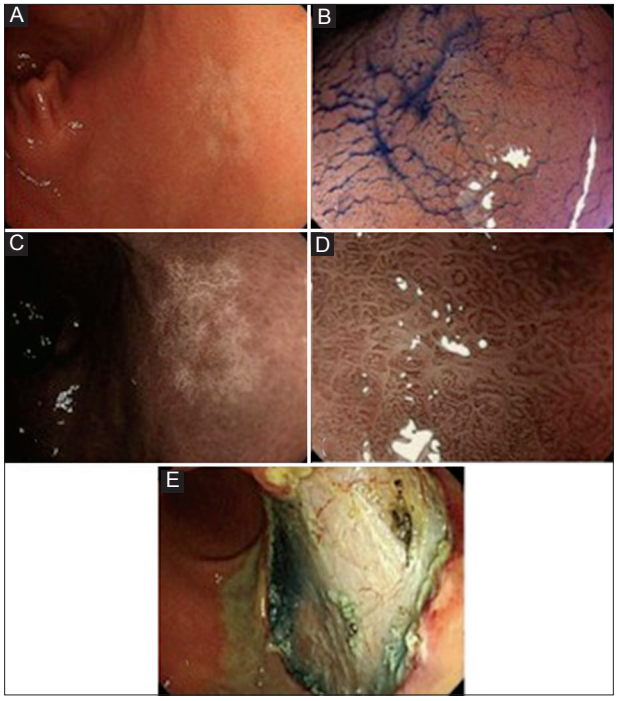

Figure 5 Type "0-IIb" early gastric signet-ring carcinoma measuring 10x9 mm. (A) White light endoscopy shows a whitish flat area typical for signet-ring carcinoma. (B) Indigo-carmine chromoendoscopy. Narrow band imaging with low (C) and high (D) magnification. (E) Endoscopic submucosal dissection ulcer

free of tumor and no lymphatic or vascular invasion. Final pathological classification included pT1a [mucosal (M) and/or upper submucosal (Sm1) cancer] corresponding to 'R0' resection, and T1b2 (Sm2 for invasive deep submucosal cancers), defined as incomplete resection according to TNM classification of JCGC [22].

Data is presented as mean ± SD, median and range. Statistical significance was evaluated by using the chi-square test as needed. P values ≤0.05 were considered as significant.

Results

In the present study conventional white light endoscopy (WLE) was unable to show specific characteristics of type "0-IIb" early gastric cancer, while in most cases a slightly erythematous, "gastritis-like" lesion was detected, difficult or even impossible to be distinguished from chronic inflammation (Fig. 1-4A, 6A). In one patient with 10x9 mm type "0-IIb" signet-ring gastric carcinoma, WLE showed a whitish appearance (Fig. 5A).

Better visualization was obtained by indigo-carmine chromoendoscopy in 8 of 12 (67%) patients (Fig. 1B, 3-5B), while it was totally normal in 4 patients (33%). Chromoendoscopy was particularly useful for delineation of combined lesions, especially for identifying the elevated element of type "0-IIa+IIb" or the depressed element of type "0-IIc+IIb" gastric cancer (Fig. 6C). However, tumor margins were unclear in most

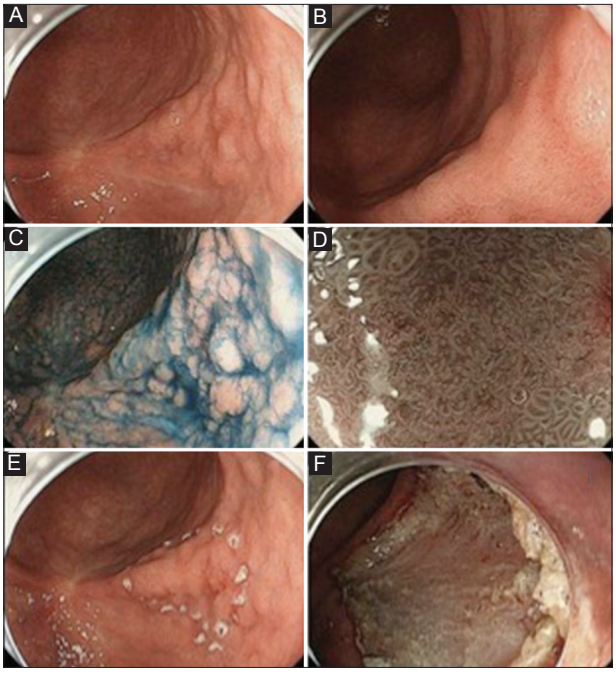

Figure 6 Combined type "0-IIc+IIb" early gastric cancer. (A, B) White light endoscopy shows slightly irregular erythematous area in the proximity of a scar from previous endoscopic submucosal dissection (ESD). (C) Indigo-carmine chromoendoscopy shows slightly better delineation of the tumor. (D) Narrow band imaging (NBI) magnification shows clearly irregular NBI microstructure and demarcation line. (E, F) Tumor marking and ESD ulcer

Table 1 Clinicopathological features of type "0-IIb" early gastric cancer.

N=12 patients	Mean±SD (range)
Age, years	69±10.1 (52-85)
Lesion size (mm)	22.6±16.8 (5-58)
ESD specimen size (mm)	41.1±16.9 (26-77)
Gender (male/female) (%)	10/2 (83% male)
Endoscopy department (conscious sedation) Operation room (intubation)	9 pts 75% 3 pts 25%
Procedure time (min) (total)	149±29.7 (60-190)
Lesion size: ≤20 mm >20 mm	 7 pts (58%) 5 pts (42%)
Tumor location • Upper body • Middle body • Lower body (total) • Antrum • Angulus	 • 2 pts (17%) • 4 pts (33%) • 6 pts (50%) • 4 pts (33%) • 2 pts (17%)
Tumor location ➢ Anterior wall ➢ Posterior wall ➢ Lesser curvature ➢ Great curvature	 ➢ 2 pts (17%) ➢ 2 pts (17%) ➢ 7 pts (58%) ➢ 1 pt (8%)

ESD, endoscopic submucosal dissection

patients (8 of 9), with "0-IIb" gastric cancer and tumor border marking was impossible based only on chromoendoscopy. Particularly, it was not feasible to detect the laterally spreading "0-IIb" element of type "0-IIa+IIb" gastric cancer.

NBI magnification endoscopy revealed abnormal findings (Fig. 1C-D, 2D, 3C-D, 4C, 5C-D, 6D), particularly irregular microvascular and mucosal microsurface pattern, in all patients and showed better optical identification of type "0-IIb" gastric cancer than both WLE and chromoendoscopy. The most common major and minor NBI patterns are shown in Table 3.

Based on the previous standardized NBI magnification classification [13], we found that: inter-lobular loop pattern (ILL)-1 (58% of cases) or fine network (17% of cases) (Fig. 1C) were the major patterns in tub-1 gastric adenocarcinomas; ILL-2 (17%) was the major pattern in tub-2; and ILL-2 combined with corkscrew pattern was identified in one patient with por gastric adenocarcinoma. These results were in accordance to the previous report by Yokoyama *et al* [13].

Moreover, NBI magnification after acetic acid spray further demonstrated specific abnormal microstructural patterns and was useful in equivocal cases (Table 3). Two main malignant NBI magnification patterns were identified after acetic acid spray, according to previous classification [34]: a) villous pattern (in 33% of cases) with fusion or increased intensity of villous structures; and b) small pit pattern (in 8% of cases) (Fig. 1E).

Demarcation line was clearly identified in all cases by NBI magnification (Fig. 1C, 2-3D, 4C, 5-6D). In combined type "0-IIa+IIb" lesion, the type "0-IIb" element was only recognized by abnormal NBI magnification findings, while demarcation line was detected as a white zone between normal metaplastic mucosa and tumorous NBI mucosal pattern. Subsequently, margin marking was feasible with dots placed outside the demarcation line (Fig. 2-3E, 4D, 6E).

ESD was completed in all patients without severe early or late complications and it is considered endoscopically complete. However, histological examination of the resected specimens showed complete (R0) resection in 10 of 12 (83%) patients, according to the strict JCGC criteria [22]. In exclusively type "0-IIb" gastric cancer, complete R0 resection was possible in 9 of 10 patients.

Table 2 Endoscopic techniques (n=12)

Instruments used	n (N=12) %
• Flush knife	8 (67)
• TT knife	4 (33)
• Hook knife	1 (8)
• Combination of knives (Flush knife+ +hook knife)	1 (8)
Hood	12 (100)
Complementary endoscopic procedures • Argon plasma coagulation	1 (8)

Table 3 NBI magnification endoscopic characteristics of type "0-IIb" gastric cancer (n=12)

	n (%)
Major NBI pattern	
• ILL1	7 (58)
• ILL2	2 (17)
• Fine network	2 (17)
• Network-like	1 (8)
Minor NBI pattern	
• ILL-1	2 (17)
• Corkscrew	3 (25)
• Network-like	1 (8)
• No minor pattern	6 (50)
NBI after acetic acid spray (major pattern)	
• Villous pattern	4 (33)
• Small pit pattern	1 (8)
• Unknown	7 (59)
NBI after acetic acid spray (minor pattern)	
• Villous pattern	1 (8)
• Small Pit pattern	2 (17)
• Unknown	9 (75)

NBI, narrow band imaging; ILL1, intra-lobular loop pattern 1; ILL2, intra-lobular loop pattern 2

Table 4 Histopathological findings of type "0-IIb" early gastric cancer (n=12)

	n (%)
Marginal tumor invasion	
• LM (+) for cancer	1 (8)
• LM (+) for adenoma	1 (8)
• VM (+) for cancer	1 (8)
• Ly (+)	0 (0)
• v (+)	0 (0)
• cUL(+)	1 (8) (IIb+IIc)
Classification (JCGC [23] and Paris [10])	Only IIb 10 pts (83) IIb+IIc 1 pt IIa+IIb 1pt } 17%
Histology	
❖ Mucosal	11 (92)
❖ Sm2	1 (8)
Outcome of patients with LM(+)	
❖ Operation post-ESD	1pt (8) No lymph node metastases
❖ Follow up only (LM+for adenoma)	1 pt (8) No recurrence
Differentiation	
❖ Well differentiated (tub 1)	8 (67)
❖ Moderately differentiated (tub 2)	3 (25)
❖ Poorly differentiated (por)	1 (8) signet-ring cell carcinoma

LM, lateral margin; VM, vertical margin; Ly, lymphovascular invasion; v, venous invasion; pUL, pathological ulceration; cUL, endoscopic ulceration; Sm2, deep submucosal invasion

Horizontal and vertical margins of ESD specimen were positive for gastric cancer in one patient with exclusive type "0-IIb" gastric cancer (Fig. 4F). The tumor was located at the upper gastric part (Fig. 4A,B), tumor size was 27x23 mm and NBI findings were suitable for fine network (main pattern) and corkscrew (minor pattern). Final histological diagnosis was tub-1 adenocarcinoma. Gastric cancer in this patient was classified as T1b2 (Sm2 invasive cancer) and he was subsequently treated by surgery. During 5-year follow up post-operation he is alive without local disease or distal metastases.

Horizontal margins were positive for gastric adenoma in another patient with combined type "0-IIc+IIb" lesion. No additional therapy was necessary, while during the 3-year follow up post-ESD he is alive with excellent quality of life without local recurrence or systemic disease.

The most common location of the type "0-IIb" early gastric cancer was the lower gastric body (50%) and lesser curvature (58%), while a less common tumor location was the upper gastric body (17%).

Mean tumor size was 22.6±16.8 mm, median 20 mm, range 5-58 mm, while in 42% of cases, lesion size was greater than 20 mm. Regarding the ESD specimen, mean size was 41.1±16.9 mm, ranging between 26-77 mm. Clinicopathological features, tumor location, and size are presented in Table 1.

In most cases one knife was used to complete the ESD. Additional argon plasma coagulation was successfully applied at the resection borders in one patient. Total mean procedure time was 149±29.7 (range 60-190) min, while no differences were found between patients treated at the Endoscopy department versus the operation room (170 vs. 150 min, P=NS).

No severe early or late complications were reported, particularly no early or late severe bleeding, no perforation and no need for repeat endoscopy. All patients recovered uneventfully after standard hospitalization in similar cases. Overall median inpatient stay was 5 days.

Histological type and tumor infiltration depth are presented in Table 4. Histopathology showed a tub-1 adenocarcinoma in 8 patients (67%), tub-2 in 3 patients (25%), and poor differentiation (signet-ring carcinoma) in 1 patient (8%).

The final histopathological results showed mucosal cancer (M) in 11 patients (92%) (T1a), while 1 patient (8%) had deep submucosal invasion (sm2, T1b2). Lymphovascular or venous invasion was not found.

Regarding the type "0-IIb" gastric signet-ring carcinoma, histological examination of the 46x39 mm ESD specimen showed a 10x9 mm M (T1a) cancer, without lymphovascular invasion [ly (-), v (-)] and with both horizontal and lateral margins negative (complete R0 resection). No other treatment was administered while the patient is still alive 3 years post-ESD, without local recurrence or distal metastases with excellent quality of life.

Finally, no additional therapy was necessary. To date, 1-6 years post-ESD, all patients remain alive with excellent quality of life and without local recurrence or systemic disease.

Discussion

Early gastric cancer usually appears as small depressed or slightly elevated area, while totally flat, type "0-IIb" gastric cancer

consists a relatively rare disease [10]. Only 2% of patients who underwent ESD for early gastric cancer during the last decade in Digestive Disease Center were finally classified as having type "0-IIb" lesions, while exclusively type '0-IIb' gastric cancer was even rarer (1.6%). In the Paris endoscopic classification [10] the totally flat early gastric cancer, classified as type "0-IIb", was reported in 9 of the 2098 patients (0.4%), while in other studies type "0-IIb" early gastric cancer was diagnosed in up to 8.7% of cases [26]. However, the frequency of "gastritis-like" early gastric cancer is higher (22/50, 44%) after *Helicobacter pylori* eradication, according to a small study [28].

Totally flat gastric cancer can be missed, not only by standard WLE but also by chromoendoscopy [7,36], because it usually appears as a non-specific, slightly erythematous mucosal lesion, resembling gastric erosion or inflammation, as it was also the case in the present study (Fig. 1-4A, 6A).

Better visualization is obtained by chromoendoscopy. However in 33% of our cases, type "0-IIb" gastric cancer was completely undetected after chromoendoscopy, while precise identification of the tumor borders was still difficult in most cases. Precise tumor border marking was impossible based only on chromoendoscopy.

While in elevated type "0-IIa" or depressed type "0-IIc" (Fig. 6C) gastric cancers chromoendoscopy effectively delineates the tumor margins, in totally flat "0-IIb" lesions, tumor borders are usually unclear. The difficulty in diagnosis may be one of the causes of the low incidence of type "0-IIb" early gastric cancer [2,7,37].

NBI magnification endoscopy showed better optical identification of type "0-IIb" gastric cancer than conventional endoscopic methods, also in accordance with previous reports [7,11-13,38]. Not only was the "0-IIb" gastric cancer identified but also the differentiation type could be predicted on the basis of specific NBI magnification mucosal and microvascular patterns [11-13,38].

Our findings also confirm a previous report regarding the 4-grade classification of NBI magnification findings in relation to gastric cancer differentiation [13]. Particularly, fine network and ILL-1 pattern were found in tub-1 adenocarcinomas, ILL-2 pattern in tub-2, while combined ILL-2 with corkscrew patterns were found in por gastric carcinoma.

Another interesting finding is the usefulness of acetic acid spray in equivocal cases, which emphasized the superficial glandular structure and enabled enhancement of endoscopic tissue characterization under NBI magnification. After acetic acid spray two main NBI magnification patterns were identified according to previous classification [34], which correspond well to the standard NBI patterns described previously [13]. The small pit pattern (Fig. 1A) corresponded to the fine network pattern, while villous pattern with fusion or increased intensity of villous structures corresponded to ILL-1. These findings were extremely helpful in distinguishing malignant from metaplastic mucosa.

Identification of demarcation line and precise marking of tumor borders, fundamental for complete ESD, was possible under NBI magnification endoscopic guidance in all patients of the present study. NBI magnification was superior to both conventional WLE and chromoendoscopy in clearly identifying the demarcation line (Fig. 1C, 2-3D, 4C, 5-6D). Margin marking was performed with dots placed outside the demarcation line, according to the report by Yao *et al* [11] (Fig. 2-3E, 4D, 6E).

ESD was completed in all patients, irrespective of tumor size, location, differentiation and all other clinicopathological factors studied. This interesting finding was a consequence of successful and accurate preoperative evaluation of "0-IIb" gastric cancer, leading to accurate selection of patients for endoscopic treatment, according to the expanded criteria of JCGC [22].

Finally, histopathological complete R0 resection was found in most of the cases (83%), according to the strict JCGC criteria [22], while no additional therapy was necessary in these patients. Only one patient (8%) with exclusive "0-IIb" gastric cancer, had deep submucosal invasion (sm2, T1b2, JCGC) [22] and was subsequently treated by surgery. He is alive, 5 years post-operation without local disease or distal metastases. In this case, histopathology of ESD specimen provided a definite biopsy, leading to final accurate curative treatment decision.

In another patient with combined type "0-IIc+IIb" gastric cancer, treated for local recurrence after previous ESD, lateral margins were positive for gastric adenoma according to JCGC [22], corresponding to low-grade intraepithelial neoplasia of the revised Vienna classification of epithelial GI neoplasia [23]. In this case, however, no additional therapy was administered and during the 3-year follow up post-, the patient is alive with excellent quality of life, without local recurrence or systemic disease.

Although por gastric adenocarcinomas are contraindicated for endoscopic treatment due to aggressive behavior and there are only relative indications according to expanded criteria for ESD (JCGC) [22], in our study curative ESD was successfully completed in a patient with type "0-IIb", signet-ring gastric carcinoma, 10x9 mm in diameter (Fig. 5A-E). In this case, WLE showed a whitish appearance of the lesion, diagnostic for signet-ring gastric carcinoma (Fig. 5A). No other additional treatments were necessary, while the patient remained alive without local recurrence or distal metastases and with excellent quality of life, during the 3-year follow up post-ESD.

Laterally spreading early gastric tumors may result in incomplete endoscopic resection and precise identification before treatment planning is of significant importance [11,14,27,31,39]. This situation was experienced in a case with combined type "0-IIa+IIb" early gastric cancer, published previously [31], where a very small "0-IIb" laterally spreading gastric cancer was identified on basis of abnormal NBI magnification findings. Complete R0 *en bloc* ESD of both tumors followed based on border marking under NBI magnification guidance [31].

In the latter case, identification of the laterally spreading "0-IIb" early gastric cancer was missed by standard endoscopic practices and was detected only by NBI magnification, as it was also reported by other studies [11]. Accurate pre-ESD evaluation is extremely important for optional, curative outcome and prevention of late recurrence [40]. Overlooked gastric lesions could be one of the possible etiologies of late recurrence after ESD for early gastric cancer however further studies are necessary [41,42].

Summary Box

What is already known:

- Most early gastric cancers appear as slightly depressed, type "0-IIc", or slightly elevated, type "0-IIa", lesions, while totally flat, type "0-IIb" early gastric cancer, particularly the pure type, is rarely reported (0.4% in Paris classification), and it is usually misdiagnosed as chronic gastritis
- Narrow band imaging (NBI) magnification improves the optical identification of early gastric cancer revealing abnormal mucosal microsurface and microvascular patterns, which have been classified, and permits endoscopic prediction of histology (differentiated versus undifferentiated) and determination of tumor margins
- Endoscopic submucosal dissection (ESD) is currently considered the standard, minimally invasive, endoscopic treatment for early gastric cancer

What the new findings are:

- NBI magnification endoscopy was superior to conventional endoscopic methods in providing accurate, real-time, optical identification of pure as well as combined, laterally spreading, type "0-IIb" early gastric cancer, while curative R0 ESD resection was feasible in the majority (83%) of cases resulting in long-term disease-free survival
- Even in one case of undifferentiated, type "0-IIb" gastric carcinoma, a relative indication for ESD, accurate endoscopic diagnosis by NBI magnification followed by curative R0 ESD resection was successfully completed
- In high-risk patients, every erythematous, gastritis-like, lesion in the stomach should be meticulously evaluated using NBI magnification for abnormal microvascular and mucosal microsurface findings, corresponding to early gastric cancer type "0-IIb"

Synchronous multiple or multifocal gastric cancers have been already reported in the literature, while synchronous or metachronous gastric cancer after initial endoscopic treatment was found in 4% and 3.3% of patients respectively, within one year after treatment [6,41-45]. In our study no local recurrence or systemic disease was reported during 1-6 years of follow up post-ESD, while all patients remain alive.

In conclusion, NBI magnification was superior to conventional endoscopic methods, not only in providing accurate and reliable real-time optical identification of pure as well as combined type "0-IIb" early gastric cancer or determining the tumor borders, but also in predicting possible tumor differentiation, and the feasibility of complete endoscopic resection.

The novelty of the present study is that, although ESD for early gastric cancer is widely reported [5-9], these reports mainly referred to slightly depressed or slightly elevated gastric lesions, classified as type "0-I", "0-IIc", or "0-IIa" lesions, while international experience of ESD in gastritis-like, totally flat, type "0-IIb" gastric cancer is limited. Our study have demonstrated, that successful curative R0 ESD was feasible in the majority of cases (83%) with type "0-IIb" early gastric cancer, resulting in long-term disease-free survival with excellent quality of life.

Even in one case of undifferentiated, type "0-IIb", signet-ring cell gastric carcinoma, a relative indication for ESD, accurate endoscopic diagnosis by NBI magnification followed by curative R0 ESD resection was successfully completed.

Although the number of our patients was low, the rarity of type "0-IIb" early gastric cancer in combination with the successful outcome after ESD, in these diagnostically and therapeutically difficult cases, made our study interesting. However, larger multicenter studies are warranted.

References

1. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006;**41**:929-942.
2. Yoshida S, Kozu T, Gotoda T, et al. Detection and treatment of early cancer in high-risk populations. *Best Pract Res Clin Gastroenterol* 2006;**20**:745-765.
3. Yamamoto H. Technology insight: endoscopic submucosal dissection of gastrointestinal neoplasms. *Nat Clin Pract Gastroenterol Hepatol* 2007;**4**:511-520.
4. Inoue H. Endoscopic mucosal resection for the entire gastrointestinal mucosal lesions. *Gastrointest Endosc Clin N Am* 2001;**11**:459-478.
5. Mori H, Kobara H, Inoue H, et al. New technique for safer endoscopic submucosal dissection using the duodenal balloon occlusion method. *J Gastroenterol Hepatol* 2012;**27**:81-85.
6. Abe N, Gotoda T, Hirasawa T, et al. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. *Gastric Cancer* 2012;**15**:70-75.
7. Ezoe Y, Muto M, Uedo N, et al. Magnifying narrowband imaging is more accurate than conventional white-light imaging in diagnosis of gastric mucosal cancer. *Gastroenterology* 2011;**141**:2017-2025 e3.
8. Isomoto H, Ohnita K, Yamaguchi N, et al. Clinical outcomes of endoscopic submucosal dissection in elderly patients with early gastric cancer. *Eur J Gastroenterol Hepatol* 2010;**22**:311-317.
9. Ono H, Kondo H, Gotoda T, et al. Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 2001;**48**:225-229.
10. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. *Gastrointest Endosc* 2003;**58**:S3-S43.
11. Yao K, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009;**41**:462-467.

12. Kiyotoki S, Nishikawa J, Satake M, et al. Usefulness of magnifying endoscopy with narrow-band imaging for determining gastric tumor margin. *J Gastroenterol Hepatol* 2010;**25**:1636-1641.
13. Yokoyama A, Inoue H, Minami H, et al. Novel narrow-band imaging magnifying endoscopic classification for early gastric cancer. *Dig Liver Dis* 2010;**42**:704-708.
14. Yao K, Iwashita A, Kikuchi Y, et al. Novel zoom endoscopy technique for visualizing the microvascular architecture in gastric mucosa. *Clin Gastroenterol* Hepatol 2005;**3**:S23-S26.
15. Gono K, Obi T, Yamaguchi M, et al. Appearance of enhanced tissue features in narrow-band endoscopic imaging. *J Biomed Opt* 2004;**9**:568-577.
16. Sumiyama K, Kaise M, Nakayoshi T, et al. Combined use of a magnifying endoscope with a narrow band imaging system and a multibending endoscope for en bloc EMR of early stage gastric cancer. *Gastrointest Endosc* 2004;**60**:79-84.
17. Nakayoshi T, Tajiri H, Matsuda K, et al. Magnifying endoscopy combined with narrow band imaging system for early gastric cancer: correlation of vascular pattern with histopathology (including video). *Endoscopy* 2004;**36**:1080-1084.
18. Hirasawa D, Fujita N, Yamagata T, et al. A case of early gastric cancer in which the degree of histological atypia was correctly predicted by magnifying endoscopy combined with narrow band imaging. *Dig Endosc* 2011;**23**(Suppl 1):92-94.
19. Soetikno RM, Gotoda T, Nakanishi Y, et al. Endoscopic mucosal resection. *Gastrointest Endosc* 2003;**57**:567-579.
20. Morita Y, Fujiwara S, Tanaka S, et al. A case of small early gastric cancer that was successfully detected by narrow band imaging magnifying endoscopy. *Dig Endosc* 2011;**23**(Suppl 1):89-91.
21. Takeuchi M, Kobayashi M, Hashimoto S, et al. Usefulness of magnifying narrow band imaging for assessing lateral tumor extent of early gastric cancer: a case report. *Dig Endosc* 2011;**23**(Suppl 1):86-88.
22. Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011;**14**:101-112.
23. Stolte M. The new Vienna classification of epithelial neoplasia of the gastrointestinal tract: advantages and disadvantages. *Virchows Arch* 2003;**442**:99-106.
24. Suzuki T, Minami H, Komatsu T, et al. Prolonged carbon dioxide insufflation under general anesthesia for endoscopic submucosal dissection. *Endoscopy* 2010;**42**:1021-1029.
25. Mori H, Kobara H, Muramatsu A, et al. Comparison of postoperative complications after endoscopic submucosal dissection: differences of insufflations and anesthesias. *Diagn Ther Endosc* 2011;**2011**:709237.
26. Ang TL, Fock KM, Teo EK, et al. The diagnostic utility of narrow band imaging magnifying endoscopy in clinical practice in a population with intermediate gastric cancer risk. *Eur J Gastroenterol Hepatol* 2012;**24**:362-367.
27. Asada-Hirayama I, Kodashima S, Goto O, et al. Factors predictive of inaccurate determination of horizontal extent of intestinal-type early gastric cancers during endoscopic submucosal dissection: a retrospective analysis. *Dig Endosc* 2013;**25**:593-600.
28. Kobayashi M, Hashimoto S, Nishikura K, et al. Magnifying narrow-band imaging of surface maturation in early differentiated-type gastric cancers after Helicobacter pylori eradication. *J Gastroenterol* 2013;**48**:1332-1342.
29. Oda I, Abe S, Kusano C, et al. Correlation between endoscopic macroscopic type and invasion depth for early esophagogastric junction adenocarcinomas. *Gastric Cancer* 2011;**14**:22-27.
30. Oka S, Tanaka S, Numata N, et al. Endoscopic diagnosis of early gastric cancer. *Nihon Rinsho* 2012;**70**:1742-1747.
31. Eleftheriadis N, Inoue H, Ikeda H, et al. Improved optical identification of laterally spreading type "0-IIb" gastric lesion with narrow band imaging magnification endoscopy. *Ann Gastroenterol* 2014;**27**:267-269.
32. Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 2011;**14**:113-123.
33. Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007;**10**:1-11.
34. Eleftheriadis N, Inoue H, Ikeda H, et al. Acetic acid spray enhances accuracy of narrow-band imaging magnifying endoscopy for endoscopic tissue characterization of early gastric cancer. *Gastrointest Endosc* 2014;**79**:712.
35. Toyonaga T, Man IM, Fujita T, et al. The performance of a novel ball-tipped flush knife for endoscopic submucosal dissection: a case-control study. *Aliment Pharmacol Ther* 2010;**32**:908-915.
36. Tajiri H, Ohtsu A, Boku N, et al. Routine endoscopy using electronic endoscopes for gastric cancer diagnosis: retrospective study of inconsistencies between endoscopic and biopsy diagnoses. *Cancer Detect Prev* 2001;**25**:166-173.
37. Wong Kee Song LM, Wilson BC. Endoscopic detection of early upper GI cancers. *Best Pract Res Clin Gastroenterol* 2005;**19**:833-856.
38. Kobayashi M, Takeuchi M, Ajioka Y, et al. Mucin phenotype and narrow-band imaging with magnifying endoscopy for differentiated-type mucosal gastric cancer. *J Gastroenterol* 2011;**46**:1064-1070.
39. Kakushima N, Ono H, Tanaka M, et al. Factors related to lateral margin positivity for cancer in gastric specimens of endoscopic submucosal dissection. *Dig Endosc* 2011;**23**:227-232.
40. Nonaka K, Arai S, Ban S, et al. Prospective study of the evaluation of the usefulness of tumor typing by narrow band imaging for the differential diagnosis of gastric adenoma and well-differentiated adenocarcinoma. *Dig Endosc* 2011;**23**:146-152.
41. Takenaka R, Kawahara Y, Okada H, et al. Risk factors associated with local recurrence of early gastric cancers after endoscopic submucosal dissection. *Gastrointest Endosc* 2008;**68**:887-894.
42. Han JS, Jang JS, Choi SR, et al. A study of metachronous cancer after endoscopic resection of early gastric cancer. *Scand J Gastroenterol* 2011;**46**:1099-1104.
43. Choi J, Kim SG, Im JP, et al. Lymph node metastasis in multiple synchronous early gastric cancer. *Gastrointest Endosc* 2011;**74**:276-284.
44. Vogel Y, Muller C, Uhl W, et al. Coexistence of multifocal gastric adenocarcinoma with signet-ring cell morphology and a gastrointestinal stromal tumour in a stomach with hp-associated gastritis. *Z Gastroenterol* 2011;**49**:201-206.
45. Naylor GM, Gotoda T, Dixon M, et al. Why does Japan have a high incidence of gastric cancer? Comparison of gastritis between UK and Japanese patients. *Gut* 2006;**55**:1545-1552.