

## ピロリ胃炎の有無によるメリハリのある 上部消化管内視鏡検査

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**要旨** ピロリ感染のない胃粘膜から胃癌が発症することは稀である。RACや胃底腺ポリープ、胃体部の稜線上発赤、前庭部のたこいぼびらんなどの所見から、ピロリ非感染胃粘膜であると判断した場合は、胃癌を発見する可能性は極めて低い。つまり、胃癌のスクリーニングという意味では、ピロリ非感染者が急速に増えてきている現状では、ピロリ感染の有無を加味した胃癌診断は効率的である。一方、ピロリ感染胃粘膜では、胃癌診断学に基づいて慎重な観察を行わなくてはならない。その場合、年齢や性別、胃粘膜萎縮の程度などの情報から、最も起こり得そうな部位に考えられそうな組織型を想像しながら、内視鏡所見(病変)を探すスタンスは見落とさない胃癌診断には必須である。

**key words:** ヘリコバクター・ピロリ感染症、萎縮性胃炎、早期胃癌

### はじめに

ヘリコバクター・ピロリ(以下、ピロリ)の長期感染とそれから惹起される胃粘膜の萎縮が、胃癌発生の予測因子と報告されている<sup>1-4)</sup>。50歳以上の世代ではピロリ感染者が半数以上を占める(1992年時点)と発表されている<sup>5)</sup>。しかし、胃癌の年齢階級別死亡率は男女ともに1965年から減少を続けている<sup>6)</sup>。年齢調整死亡率でも、1980年と2003年の比較において男女ともにそれぞれ69.9から34.1(/100,000)、34.5から13.2(/100,000)に漸減している<sup>7)</sup>。

胃癌診断を目的にした上部消化管内視鏡検査で重

要なことは、ピロリ感染のない胃粘膜からは胃癌が発症することは極めて稀であるという報告である<sup>8)</sup>。

本稿では、この事実に基づいた効率的な胃癌発見のためのメリハリのある上部消化管内視鏡検査について述べる。

### 1. まずはピロリ菌感染のチェック

比較的若年で(今なら59歳以下くらいか)食道裂孔ヘルニアが存在しないのに逆流性食道炎を観察した時点で、「あ、ひょっとして萎縮はないかな？」くらいは考える(図1a)。その勢いで胃体上部の胃粘膜の正常や粘液の付着状態をすぐにチェックする。胃粘液が少なく、RAC(regular arrangement of collecting venules)を認め、胃底腺ポリープなど発見すれば、「まず、胃粘膜の萎縮はなさそうだ！」と考える(図1b, c)。胃癌のリスク診断は食道胃接合部の観察からすでに始まっているのである。

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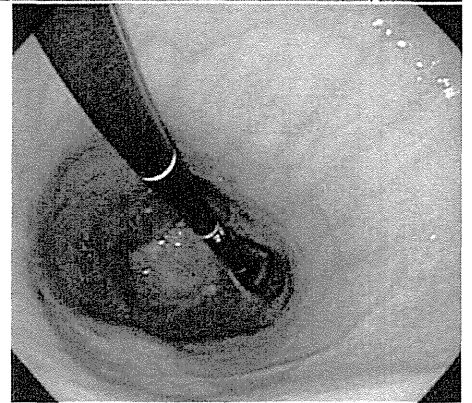
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▲図 1

- a. 逆流性食道炎
- b. RACを伴う胃体部の非萎縮胃粘膜
- c. 胃底腺ポリープ
- d. 胃体部の稜線上発赤

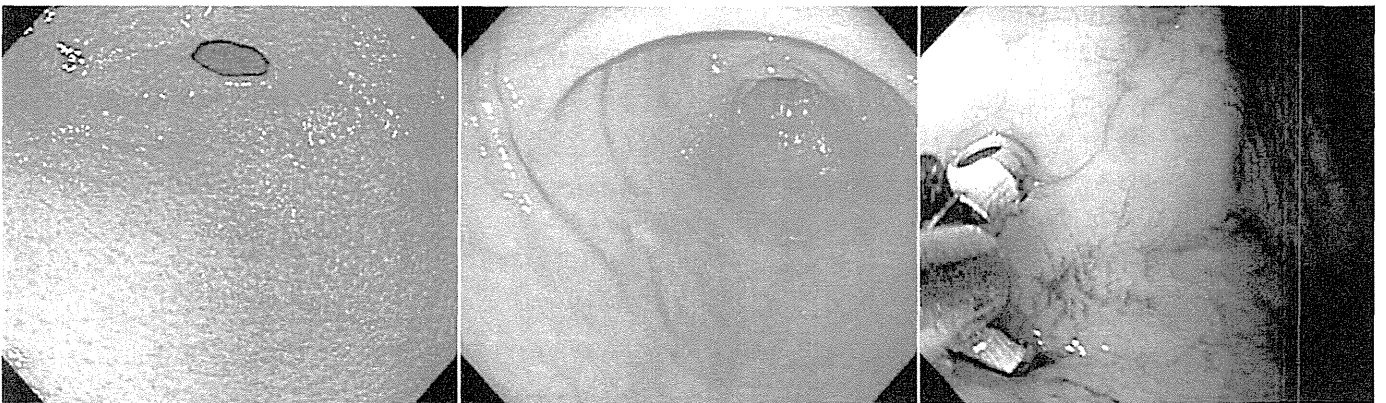
a|b|c  
d



▼図 2

- a. 鳥肌胃炎
- b. ピロリ非感染非萎縮胃粘膜内の褪色領域
- c. 近接像で内視鏡診断(4 mm, sig. 0-IIc, T1a)

a|b|c



さらにスコープを進めながら粘膜を観察することによって、幽門前庭部の胃粘膜にも萎縮がなくRACを認めた場合は、ピロリ感染の可能性は極めて低いと考えてもよい。つまり、胃癌を発見する可能性は極めて低いということになる。胃癌のスクリーニングという意味では、この時点で上部消化管内視鏡検査を終了してもよいくらいである。最近、

このタイプの胃粘膜が急速に増えてきていると実感している。

## II. でもちょっと待って！

しかし、ここで見逃してはならないのが若年者のピロリ感染と関連が注目されている“鳥肌胃炎”(nodular gastritis)である<sup>9)</sup>。20歳代・30歳代の女性

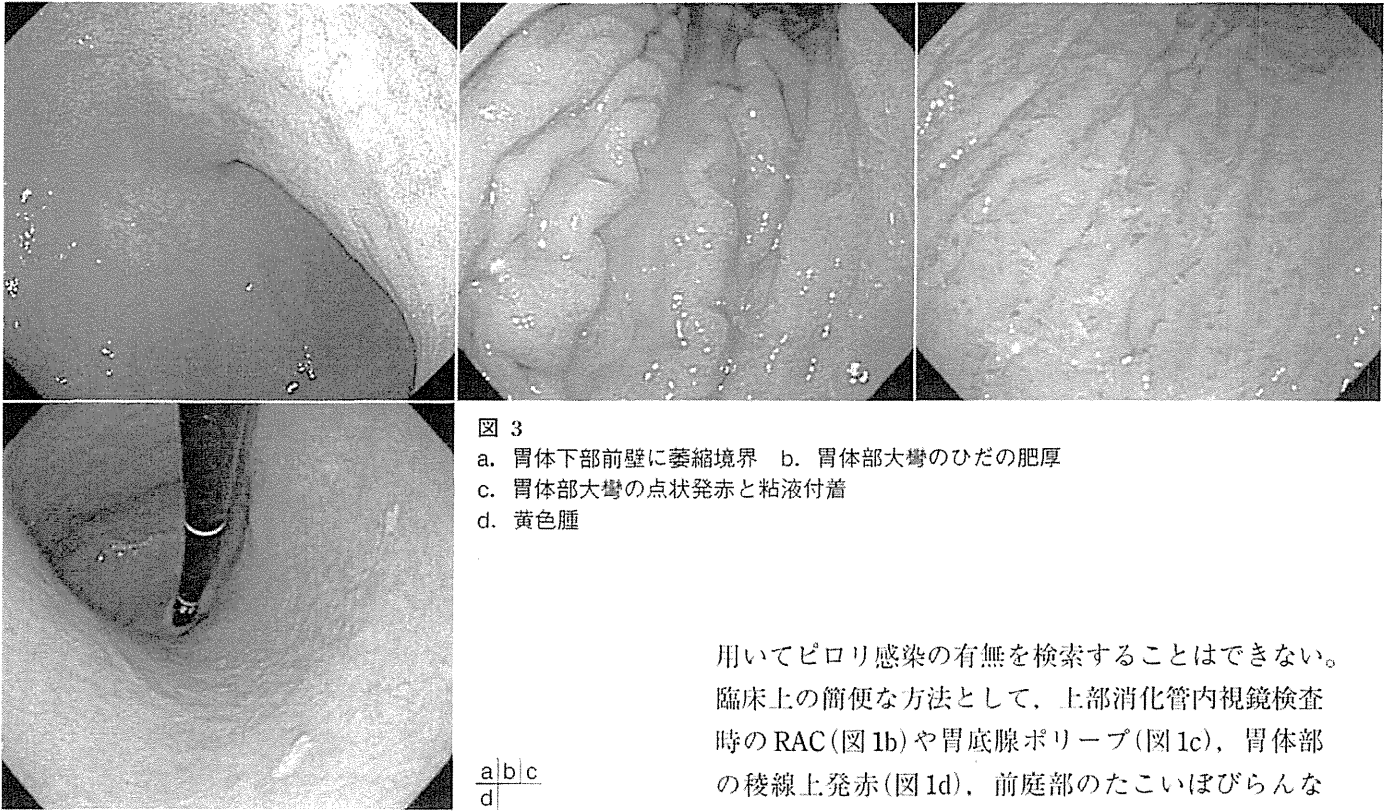


図 3  
 a. 胃体下部前壁に萎縮境界 b. 胃体部大彎のひだの肥厚  
 c. 胃体部大彎の点状発赤と粘液付着  
 d. 黄色腫

a|b|c  
 d|

に多く、組織学的に粘膜内のリンパ濾胞の増生による小顆粒状隆起の密集である。内視鏡的には鳥肌様の所見として観察される(図 2a)<sup>10)</sup>。若年者胃癌、特に未分化型腺癌のリスクを伴う粘膜変化として考えられるようになってきているので注意が必要である<sup>11-13)</sup>。

もう一つ記憶の片隅に留めておくべきことは、最近徐々にその存在が報告されつつあるピロリ非感染の胃粘膜から発生する未分化型腺癌である。非萎縮粘膜に存在する小さな褪色调の浅い陥凹である<sup>14)</sup>(図 2b, c)。胃粘膜に炎症のないピンクの背景粘膜のなかに褪色调領域として認めるため、その存在を知っていれば診断は困難ではない。

### Ⅲ. 胃粘膜萎縮を診断する

効率的な胃癌診断の第一歩は、胃粘膜の観察によってピロリ感染の有無に当たりをつけることである。スクリーニングの上部消化管内視鏡検査の前情報として、全例で尿素呼気テストや抗体検査などを

用いてピロリ感染の有無を検索することはできない。臨床上的に簡便な方法として、上部消化管内視鏡検査時の RAC(図 1b)や胃底腺ポリープ(図 1c)、胃体部の稜線上発赤(図 1d)、前庭部のたこいぼびらんなどの所見から、ピロリ非感染胃粘膜であることを予測する。逆に言えば、これらの所見がなく胃粘膜萎縮(図 3a)、胃体部大彎のひだの蛇行や肥厚(図 3b, c)、黄色腫(図 3d)、鳥肌様粘膜(図 2a)などを認めた場合は、ピロリ感染(既感染含む)胃粘膜と言える。そして、胃癌の診断において臨床的に最も重要な所見が萎縮性変化である。

### Ⅳ. 萎縮からみた胃癌診断

胃粘膜萎縮と判断した場合は、戦闘モード全開となる。胃の内視鏡検査における醍醐味がそこにある。ピロリ感染に伴う炎症性変化や萎縮性変化によってすでに軽度発赤し凹凸のある粘膜のなかから、さらに“赤い”、“白っぽい”、“凹凸の中のわずかな陥凹”を診断していくのである。その手助けとなるのが萎縮の程度である。

中等度の萎縮粘膜を背景にもつ場合は、その萎縮境界に病変が存在することが多い。特に胃角部や胃体下部後壁は漫然とした観察では見落としやすいので注意が必要である(図 4a)。また、噴門部小彎も微細な粘膜変化を見落としやすい部位なのでしっか

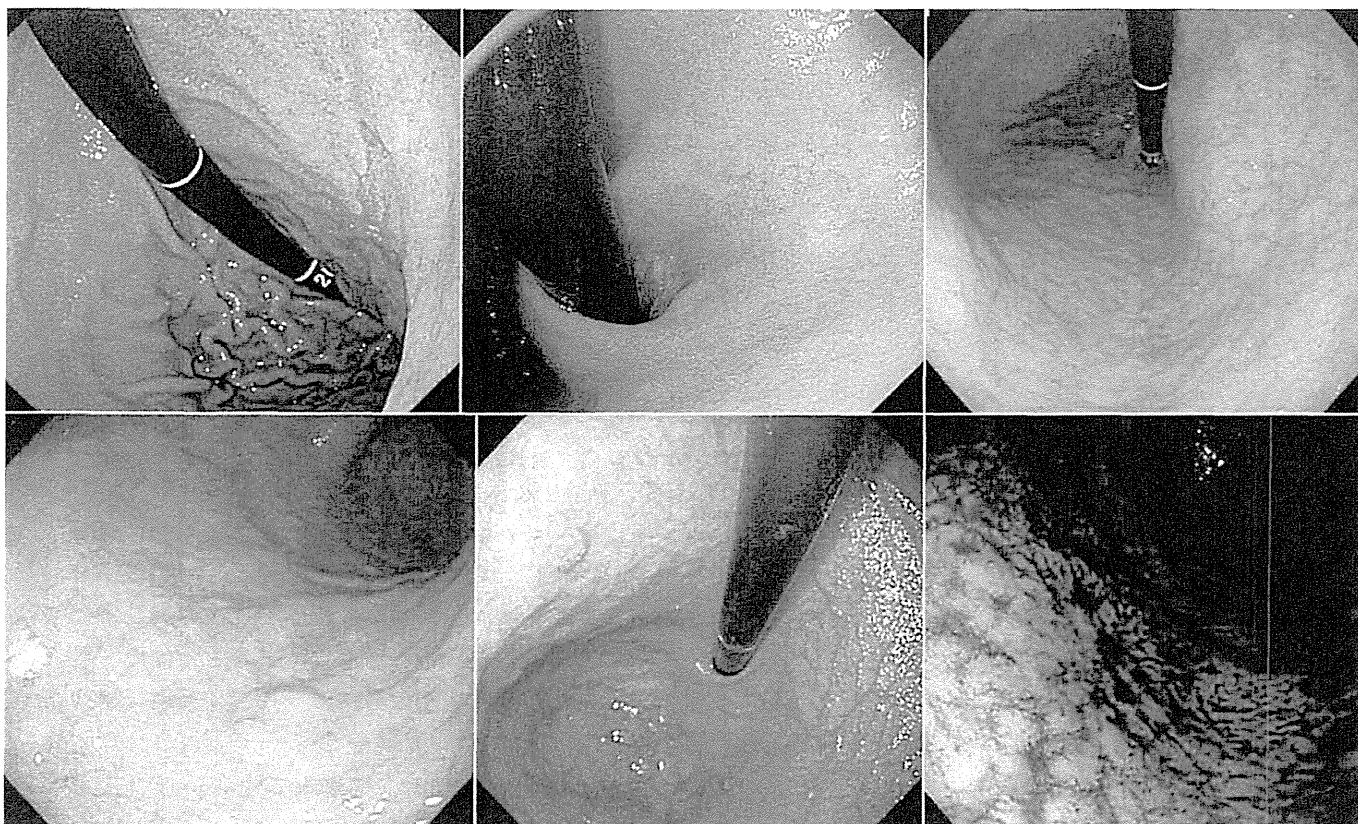


図 4

a. 胃体下部後壁の萎縮境界に存在する陥凹型早期胃癌(15 mm, sig to por, 0-II c, T1a) b. 噴門部小彎の萎縮境界に存在する褪色陥凹(4 mm, tub1, 0-II c, T1a) c. 高度萎縮胃粘膜 d. 腸上皮化生を伴う萎縮胃粘膜 e. 胃体上部後壁の高度萎縮胃粘膜に存在する軽度発赤病変(13 mm, tub1, 0-II c+II a, T1b) f. 前庭部前壁の腸上皮化生を伴う高度萎縮胃粘膜に存在する早期胃癌(15 mm, tub1, 0-II a+II c, T1b)

りと近接して観察する必要がある(図4b)。ちょっとした色調の違いや、角度を変えた観察によって、わずかな陥凹として気づくことが多い。

しかし、コンピュータシステムのように1対1の対応で診断できるほど甘くはない。自動画像システムで発赤や褪色を指摘(存在診断)することはできるであろう。しかし、同じ発赤でも背景の胃粘膜の違いによって、筆者らは所見の取り方は無意識に変えている。人間の脳は、実際の検査をしながら年齢や性別、胃粘膜萎縮の程度、炎症所見など、さまざまな情報を加味して瞬時に鑑別診断(質的診断)を行っているわけである。

高度萎縮粘膜(図4c)や腸上皮化生(図4d)を伴う胃粘膜における胃癌の診断は、困難である。わずかな色調の変化や凹凸の違いで存在に気づくのである

が、最終的には生検診断に頼らざるを得ないことも多い<sup>15)</sup>。

非萎縮粘膜であるが胃粘液が多く、ピロリ感染を完全に否定できない場合には、注意が必要である。萎縮がまだ伸展していない状態なだけであり、決して胃癌の低リスク群ではない。ピロリ感染の有無をより正確に把握することが重要である。また、このような胃粘膜では、前述したピロリ菌非感染非萎縮粘膜における観察と同様に褪色領域(多くは未分化型腺癌)を探す努力をすべきである(図5a, b)。もちろん、胃癌の診断において、スキルス(4型)胃癌を見落とさないことは言うまでもない(図5c)。

#### V. やみくもに所見を探さない!

胃癌の診断は、まずは微妙な粘膜所見を拾い上げ

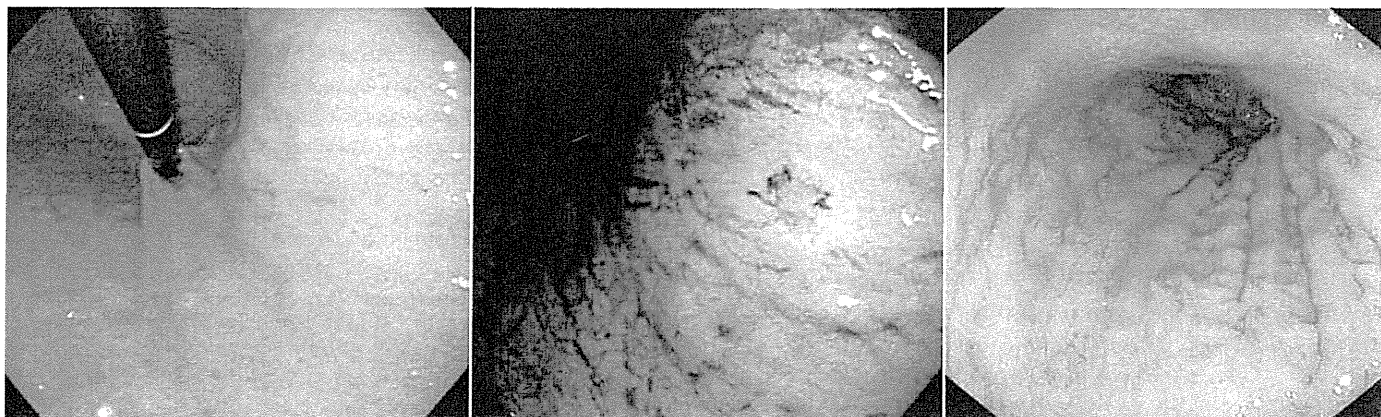


図 5

a. ピロリ感染非萎縮粘膜の褪色領域 b. インジゴカルミン散布像:浅い辺縁不整な陥凹型早期胃癌(5 mm, sig. 0-II c, T1a) c. 胃体部大嚢を中心としたひだの腫大と胃壁の肥厚(Linitis plastica: 4型胃癌)

るのであるが、やみくもに異常所見を探しても見つかるものではない。“このような病変も存在する”という認識がなければ、微細な粘膜変化に気づくことなく見落とされてしまう。

実際の胃癌の診断では、背景の胃粘膜や患者情報を基礎に、過去に見たことがある内視鏡所見(病変)を探しているのである。もちろん、いくら経験をしても初めて遭遇する所見や、過去の経験とは反する結果となる場合も多い。これらの所見(経験)を自分なりの診断の“引き出し”に分類していくのである。ただし、煩雑に引き出しに詰め込んでも探すのに一苦労で、実際の臨床では使えない。

すでに述べてきたように胃癌の診断には観察における理論がある。そのうえで、毎日の経験する所見を上手に“引き出し”に分類するのである。もちろん“引き出し”は多すぎても使えない。ただし、いかに分類するかにはセンスが必要かもしれない。

## VI. メッセージ

胃癌の診断の基本は、病変の有無を判断する存在診断、病変の良悪性などを判断する質的診断、病変の大きさや深達度を判断する量的診断、として継承

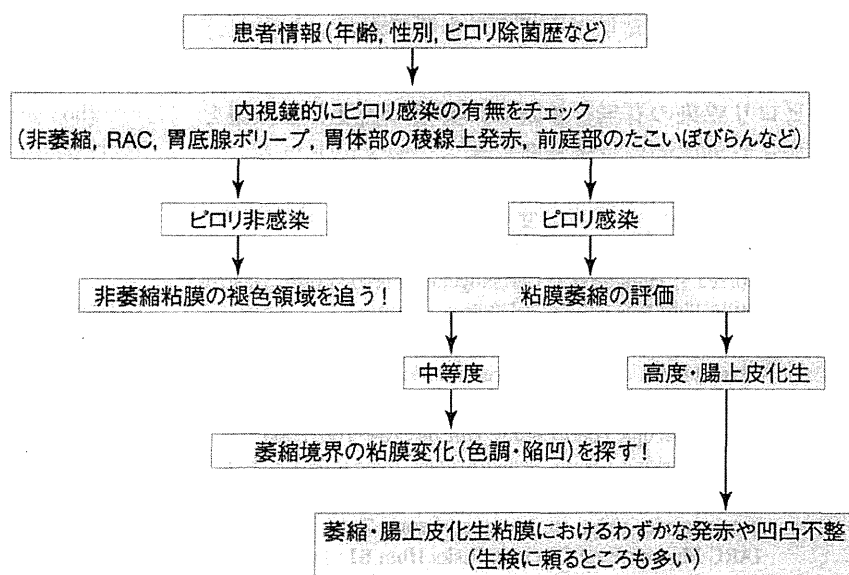


図 6 ピロリ感染と萎縮性変化を考慮した胃粘膜の観察

されてきた。しかし、存在診断がなければ何も始まらない。その最初のステップである存在診断を見落とすことなく行うためには、ただ漠然と検査するのではなく、悪性の可能性がどれほどであるか、どこが最も悪性の所見なのかなどを常に意識して検査に望むべきである。そのうえで、検査後の内視鏡所見と生検結果の見直しを行うことをクセにする。これが、存在診断のための“引き出し”を増やしていくコツである。いずれにしても、経験の浅いうちは胃内を隈なく観察することを怠ってはいけない<sup>16,17)</sup>。少し乱

暴ではあるが、ピロリ感染と胃粘膜萎縮を考慮した胃癌の診断に至るステップを示す(図6)。言うまでもないが、メリハリのある内視鏡検査とは、しっかりした知識と経験が基礎にあってこそ可能である。

### おわりに

ほとんどすべての国民がピロリ菌に感染していた胃癌の入れ食い状態の時代ならいざ知らず、今後はピロリ感染の低下に伴い、胃癌を発見する機会が急速に減っていく。ピッチャーがすべて4番バッターのつもりで投球して常に完投することは無理なのと同様に、胃癌の診断という一点で言えば、メリハリのある上部消化管内視鏡検査があってもいいのかもしれない。今までの胃癌診断学はピロリ感染胃粘膜を背景にして成り立ってきたものである。しかし、ピロリ非感染胃粘膜が大多数を占めていく今後は、ピロリ感染の有無を診断し、萎縮の程度と組織型を考えた効率的な胃癌診断もあってもよいと思う。

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### Modulated Screening Gastroscopy for Minute Gastric Cancer Based on the Status of *Helicobacter pylori* Infection

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It is well known that gastric cancer is found in *Helicobacter pylori* infected gastric mucosae during long-life times. Otherwise, it is clinically rare to encounter gastric cancer in an uninfected condition. In the past, most Japanese were exposed to *Helicobacter pylori*, which meant they ran a high risk of gastric carcinogenesis. However, recently the incidence of *Helicobacter pylori* infection is rapidly decreasing. Thus, the excessive use of gastroscopy screening for gastric cancer for all Japanese might be outdated. In order to conduct more efficient gastroscopy screening in terms of time and manpower, the status of *Helicobacter pylori* infection should be assessed

during gastroscopy. When *Helicobacter pylori* is present, diagnostic ability to find gastric cancer should be intensively concentrated on in order to avoid overlooking subtle mucosal changes on *Helicobacter pylori* infected gastric mucosae. Age, gender, level of mucosal atrophy, and status of intestinal metaplasia are very important factors for detecting gastric cancer, as well as for predicting mucosal color (reddish or discolor), tumor location (on the atrophic boarder or in the severe atrophic mucosa), macroscopic type (depressed type or elevated type), and histology type (intestinal type or diffuse type).

**key words:** *Helicobacter pylori* infection, atrophic gastritis, early gastric cancer

### Legends to Figures

- Figure 1 a. Reflux esophagitis (Grade B).  
 b. Regular arrangement of collecting venules (RAC) in the non-atrophic gastric mucosa without *H. pylori* infection.  
 c. Fundic grand polyp in the gastric body.  
 d. Superficial gastritis on the lesser curvature of the gastric body.
- Figure 2 a. Nodular gastritis.  
 b. Discolored area in the non-atrophic gastric mucosa without *H. pylori* infection.  
 c. Small early gastric cancer (4 mm, sig, 0-II c, T1a).
- Figure 3 a. Atrophic boarder of the lower gastric body.
- Figure 4 a. Depressed type early gastric cancer on the atrophic boarder of the lower gastric body (15 mm, sig to por, 0-II c, T1a).  
 b. Small discolored area on the lesser curvature of the cardia (4 mm, tub1, 0-II c, T1a).  
 c. Gastric mucosa with severe atrophy.  
 d. Atrophic change with intestinal metaplasia.  
 e. Reddish mucosa on the posterior wall of the upper gastric body (13 mm, tub1, 0-II c+II a, T1b).  
 f. Superficial gastric cancer developed from sever atrophic gastric mucosa with intestinal metaplasia (15 mm, tub1, 0-II a+II c, T1b).
- Figure 5 a. Discolored area on the lesser curvature of upper gastric body without atrophy but with *H. pylori* infection.  
 b. Shallow depressed lesion identified clearly under indigo-carmin dye (5 mm, sig, 0-II c, T1a).  
 c. Advanced gastric cancer classified into linitis plastic.
- Figure 6 Diagnostic steps for gastric cancer taking into account the status of *H. pylori* infection and the level of atrophic change.

# A multicenter validation of an endoscopic classification with narrow band imaging for gastric precancerous and cancerous lesions

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**Background and study aim:** The reliability and external validity of narrow band imaging (NBI) in the stomach have not been described consistently. The aim of the current study was to describe and estimate the accuracy and reliability of a simplified classification system for NBI in the diagnosis of gastric lesions.

**Methods:** Consecutive patients undergoing NBI endoscopy at two reference centers (n=85, 33% with dysplasia) were included in two studies. In total, 224 different areas were biopsied and recorded onto video. In the derivation study, previously described NBI features were analyzed in order to develop a simplified classification. In the validation study the accuracy and reliability of this classification were estimated among three groups of endoscopists with different levels of expertise in NBI.

**Results:** The reliability/accuracy results from the derivation study allowed the creation of a simplified NBI classification. In the validation study, “regular vessels with circular mucosa” (pattern A) was associated with normal histology (accuracy 83%; 95% confidence interval [CI] 75%–90%);

“tubulo-villous mucosa” (pattern B) was associated with intestinal metaplasia (accuracy 84%; 95CI 77%–91%; positive likelihood ratio [LR+] = 4.75); and “irregular vessels and mucosa” (pattern C) was associated with dysplasia (accuracy 95%; 95CI 90%–99%; LR+ = 44.33). The reproducibility of these patterns was high (k=0.62). “Light-blue crest” was moderately reliable (k=0.49) but specific (87%) for intestinal metaplasia. A variable vascular density (additional pattern+) was the best feature for *Helicobacter pylori* gastritis (accuracy 70%; 95CI 59%–80%) but showed only fair reliability (k=0.38). Non-experienced endoscopists presented lower agreement (k=0.6 vs. k=0.75) and accuracy (74% vs. 86%) than international experts/experienced endoscopists.

**Conclusion:** A simplified NBI classification is accurate and reliable for the diagnosis of intestinal metaplasia and dysplasia. The classification should be further assessed and validated on a per-patient assessment of NBI, and by comparing NBI with other imaging technologies.

## Introduction

Gastric adenocarcinoma is the second most lethal cancer worldwide with only a minority of gastric adenocarcinomas diagnosed in a curable and resectable form [1,2]. *Helicobacter pylori* is considered the most important risk factor for gastric cancer, by promoting a multi-step process of chronic gastritis, atrophy, intestinal metaplasia, dysplasia and, finally, intestinal-type adenocarcinoma [3]. Secondary prevention through diagnosis of premalignant lesions and early gastric cancer, and screening or follow-up of individuals at high risk, would probably be the most immediate

strategies for improving survival [4, 5]. Endoscopy examination is therefore of paramount importance. However, endoscopic evaluation of gastric mucosa correlates poorly with histological findings [6,7], and it is not surprising that ancillary techniques such as chromoendoscopy have been used for an accurate diagnosis of precancerous lesions and/or invasiveness of cancerous lesions [8–10]. Even so, for diverse reasons these methods are not very popular among endoscopists, particularly those in Western countries.

Diverse descriptions of new methods of electronic chromoendoscopy, namely high resolution with narrow band imaging (NBI), with or without magnification, have been published [11–24]. Good results have been reported for the imaging of intestinal metaplasia and cancer; however, reliability

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has seldom been evaluated, no study has included the whole spectrum of lesions, and no external validation of any defined features has been reported [25].

Thus, the aims of the current study were: to assess the reliability of previously described NBI features for gastric precancerous and neoplastic lesions; to simplify the features under a new classification; and to validate this classification on a new sample of patients and observers, and to assess the accuracy of the classification system in endoscopists with a range of NBI experience.

## Methods



### Study design and selection of patients

Patients undergoing routine upper gastrointestinal endoscopy at two hospitals in the North of Portugal (Portuguese Oncology Institute of Porto and Braga's Hospital), between September and December 2009 and between February and April 2010, were consecutively considered and included in this study after giving informed consent. Both hospitals are tertiary centers to which patients with superficial lesions are referred and treated with minimally invasive techniques [26]. Patients with chronic liver disease, psychiatric conditions, anticoagulant therapy or coagulation disorders, were excluded. The ethical committees of both hospitals approved the study.

Two studies were planned (see [Fig. e1](#), available online only):

- ▶ the first 45 patients (estimated sample of 100 videos), who were treated between September and December 2009, constituted the "derivation cohort," which provided data for a study on the reliability of previously described mucosal and vascular features of gastric mucosa using NBI [11–24]. These data were used to derive a simple NBI classification and were also subject to validity testing using histology as the reference test;
- ▶ in the second study, a "validation cohort" of 40 new patients (and a new estimated sample of 100 videos), who were assessed between February and April 2010 using endoscopic observations, provided data for the validation of the new NBI classification and assessment of the reliability of the classification within groups of endoscopists with diverse experience.

### Endoscopic procedures and selection of videos

Under pharyngeal anesthesia (85% of the patients) or deep sedation (15% of patients) all patients underwent upper gastrointestinal endoscopy using a high resolution (HR) Olympus endoscope with NBI (EVIS EXERA II video system center GIF-180; Olympus, Tokyo, Japan). Detailed observation of esophageal, gastric, and duodenal mucosa was performed and all endoscopic lesions were described accordingly. High resolution videos of low magnification ( $\times 1.5$ ) NBI endoscopy were recorded for further analysis from (subject to patient tolerance) five areas of antral, incisura, and corpus mucosa. Recordings were also made from those areas with endoscopic changes, either at high resolution white light endoscopy (HR-WLE) or at HR-NBI. A shift between the HR-WLE and HR-NBI was used to ensure the position and precision of the biopsies taken. The total number of histological samples was equal to the total number of videos recorded. From all of the procedures, 140 (derivation study) and 119 (validation study) videos of approximately 10 seconds in duration were recorded consecutively and converted into MPEG-4 files of approximately 10 MB each using iMovie (Apple Inc., Cupertino, California, USA). No area was recorded twice. Each video was labeled with a random number and transferred onto a computerized database. Of the

259 videos recorded only those showing highest quality images of mucosal morphology and in which the video observation confirmed the targeting of the biopsies were selected for use in the respective studies (124 in the derivation study and 100 in the validation study). The quality of the videos was assessed by one experienced endoscopist. The whole potential spectrum of histological lesions (no intestinal metaplasia or dysplasia [normal mucosa], presence of intestinal metaplasia, presence of dysplasia [or carcinoma], and presence of *H. pylori* irrespective of histology, excluding dysplasia) was considered for video selection, both for the derivation study and for the validation study.

### Histopathological procedures

All gastric mucosa specimens were obtained by endoscopic biopsy at each area selected for video recording, with the exception of videos recorded from superficial lesions where a whole mucosectomy specimen was obtained. Specimens were fixed in buffered formalin, processed for paraffin embedding, sectioned, and stained with hematoxylin and eosin. Gastric specimens were also evaluated for *H. pylori* infection using modified Giemsa (2%) stain. Two expert gastrointestinal pathologists, who were blind to the NBI features, made the final histological diagnosis according to the Sydney–Vienna classification [27, 28].

### Selection of endoscopists

For the derivation study (reliability assessment of previously described NBI features), three endoscopists (End1, End2, and End3) who had previous clinical experience of NBI (>50NBI gastroscopies) each assessed all of the videos; they were blinded to histology and to the evaluation of the other endoscopists. Endoscopists were instructed to evaluate the videos using previously reported mucosal and vascular features when these features were applicable to NBI with low magnification [11–24]. In order to overcome the problem of an irregular pattern being assigned different meanings and being associated with different pathologies such as *H. pylori* infection [11], intestinal metaplasia [12], and dysplasia/cancer [16, 18], the endoscopists were instructed to state the pattern as "irregular" only when they observed a complete architectural loss of the mucosal or vascular pattern (see below for definition of variables).

In the validation study, nine observers were included:

- ▶ the three experienced endoscopist observers (End1, End2, and End3) who participated in the derivation study;
- ▶ three different gastroenterologists who had not participated in the first assessment, and who had special interest in chromoendoscopy but with diverse NBI experience (<50NBI gastroscopies); these were designated non-experienced observers;
- ▶ and three international expert NBI endoscopists (from Europe, USA and Japan); these were designated the expert observers.

All of the observers classified the second set of videos after receiving a pen drive with a PowerPoint presentation (Microsoft Office 2003, Microsoft Inc., Redmond, Washington, USA), which contained the rationale of the derived classification and example videos.

### Variables

In the derivation study the following variables were included [11–24].

- ▶ Mucosal pattern: regular circular (well delineated circular/oval glands), regular tubulo-villous (well delineated tubulo or villous or ridge glandular pattern) or irregular (glandular pattern

is clearly irregular with architecture distortion with absent glandular pattern in some areas possible).

- ▶ Light blue crest (LBC): presence (yes) or not (no) of blue-whitish slightly raised areas.
- ▶ White opaque substance (WOS): presence (yes) or not (no) of white material above the mucosa that could be either well defined (regular) or not (irregular).
- ▶ Vascular pattern: regular (vessels well defined in the center or surrounding the glands) or irregular (areas with clearly anomalous vessels associated with architecture distortion of the mucosa). If there were areas where vessels were not seen clearly but without anomalous configurations they were included in the regular group.
- ▶ Vascular thickness: subjective opinion of normal/thick vessels or somewhat thin or ultrathin.
- ▶ Vascular density: high density (almost all of the glands are surrounded by reddish vessels with some areas with vessel agglomerates possible) or low density (vessels are not seen clearly surrounding all of the glands, pale colored vessels).
- ▶ Variable vascular density (VVD): presence (yes) or not (no) of alternating areas of high and low density in the same video.

To assess the reliability of these features for inclusion in the classification, each video was classified by all observers according to these NBI features and a grade for certainty was assigned. In addition, each observer was asked to make an histological diagnosis based on the NBI features and, again, to assign this diagnosis a grade of certainty. Histopathological assessment was considered to be the gold standard or reference test for accuracy estimates.

#### Statistical analysis

The Statistical Package for Social Sciences (SPSS 17.0 Package Facility, SPSS Inc., Chicago, Illinois, USA) was used for data support and analysis.

The proportion of overall agreement was the proportion of cases for which two observers agreed. The proportions of specific

agreement relative to each category was an estimation of the probability of, given that one observer makes a rating in a category, that the other observers will rate the same. The generalized formulae, for more than two observers, for the proportions of overall and specific agreement, were calculated by dividing the total number of actual agreements by the total number of possible agreements. Light's Kappa (mean of the kappa values obtained from each pair of raters) was also calculated. The nonparametric bootstrap was used to estimate the 95% confidence intervals (CIs). Strength of agreement was considered as follows: slight 0–0.2; fair 0.2–0.4; moderate 0.4–0.6; substantial 0.6–0.8; almost perfect 0.8–1.

For estimation of sample size, a target estimate standard error of 0.1 in kappa values was determined. Each video classification was compared with the histological diagnosis of the corresponding specimens (gold standard or reference test). Sensitivity, specificity, and global accuracy were estimated separately and for all nine observers combined, along with the 95% CIs. Likelihood ratios (LR) were estimated based on mean sensitivity and specificity estimates.

#### Results

##### Derivation study

##### Description of participants and videos

Patient characteristics and a description of endoscopic procedures included in the study are shown in **Table 1**. In 20% of the patients five or more biopsies were possible and in 28% four biopsies of different areas were performed. Due to the specialist nature of the institutions, a large number of endoscopic examinations were performed for dysplasia or mucosectomy (36%). This yielded a significant number of histological samples of dysplasia (n=23) and metaplasia (n=40). A total of 124 good quality videos (67 normal mucosa, 34 intestinal metaplasia, and 23 dysplasia

Patients	Total n=85	Derivation n=45	Validation n=40
Male sex, n (%)	50 (59)	28 (62)	22 (55)
Age, mean (range), years	61 (21–91)	61 (21–91)	61 (49–80)
Number of biopsies, median (range)	3 (1–6)	3 (1–5)	3 (1–6)
Indications for upper gastrointestinal endoscopy, n			
Follow-up/previous diagnosis of dysplasia	23	11	12
Dyspepsia	16	12	4
Follow-up after precursors conditions (metaplasia)	16	6	10
Follow-up after gastric mucosectomy	14	8	6
For gastric mucosectomy	11	5	6
Other (e. g. GERD)	5	3	2
Main endoscopic findings, n			
Gastric superficial lesions	21	11	10
Normal	17	13	4
Papular-erythematous gastritis	15	8	7
Gastric scar	13	6	7
Gastric irregularity	11	5	6
Erosive gastritis	8	2	6
Histological diagnosis per patient, n			
Normal mucosa (antrum and body)	21	12	9
Intestinal metaplasia antrum	22	11	11
Intestinal metaplasia corpus	14	8	6
Dysplasia (one or more areas)	28	14	14
H. pylori infection	38	21	17

GERD, gastroesophageal reflux disease.

**Table 1** Description of participants and endoscopic procedures (n=85).

**Table 2** Derivation study: correlation between features of narrow band imaging and histology; according to observer classification (End1, End2, and End3) reliability measures are estimated (proportion of agreement and specific proportions of agreement [Pa] and kappa [k]) for previously described features (n = 124).

	Histological findings, %				Observer classification <sup>1</sup> , n (%)			Reliability [95%CI]	
	Normal	Intestinal metaplasia	Dysplasia	H. pylori	End1	End2	End3	Pa	K
Mucosal pattern								0.82 [0.77–0.87]	0.71 [0.62–0.80]
Regular, circular	86	9	1	51	56 (45)	64 (52)	62 (50)	0.84 [0.78–0.89]	
Regular, tubulo-villous	12	89	3	45	39 (32)	36 (29)	39 (32)	0.73 [0.63–0.81]	
Irregular	2	2	96	4	29 (23)	24 (19)	23 (18)	0.84 [0.82–0.97]	
Light blue crest								0.89 [0.84,0.93]	0.58 [0.49,0.72]
No	95	51	97	76	106 (85)	104 (84)	101 (81)	0.93 [0.90–0.96]	
Yes	5	49	3	24	18 (15)	20 (16)	23 (19)	0.65 [0.51–0.78]	
White opaque substance								0.93 [0.89,0.97]	0.57 [0.40,0.79]
No	100	95	61	100	117 (94)	111 (89)	111 (89)	0.96 [0.94–0.98]	
Yes	0	5	39	0	7 (6)	13 (11)	13 (11)	0.64 [0.47–0.77]	
Regularity									
Regular	0	5	15	0	4	8	8		
Irregular	0	0	13	0	3	5	5		
Vascular pattern								0.96 [0.93–0.98]	0.89 [0.78–0.96]
Regular	98	98	3	96	96 (77)	100 (81)	99 (80)	0.97 [0.96–0.99]	
Irregular	2	2	97	4	28 (23)	24 (19)	25 (20)	0.91 [0.82–0.97]	
Vascular thickness								0.62 [0.56–0.68]	0.19 [0.02–0.28]
Thin or ultrathin	28	24	34	22	68 (55)	9 (7)	28 (23)	0.32 [0.22–0.41]	
Thick (normal)	72	76	66	78	56 (45)	115 (93)	96 (77)	0.74 [0.68–0.79]	
Vascular density								0.65 [0.60–0.71]	0.24 [0.13–0.36]
Low	34	38	32	43	49 (39)	36 (29)	44 (36)	0.49 [0.39–0.59]	
High (normal)	66	62	68	57	75 (61)	88 (71)	80 (65)	0.73 [0.67–0.78]	
Variable vascular density								0.61 [0.55–0.67]	0.21 [0.09–0.35]
No (normal)	61	47	0	38	55 (57)	54 (54)	56 (57)	0.66 [0.58–0.73]	
Yes	39	53	100	62	41 (43)	46 (46)	43 (43)	0.55 [0.46–0.63]	

<sup>1</sup> Endoscopists with previous clinical experience of NBI (> 50 NBI gastroscopies).

[20 high grade, 3 low grade]), 50 of which *H. pylori* positive, were recorded to accompany 140 histological samples.

#### Accuracy and reproducibility of previously described NBI features

The correlation of different NBI features with histology, the reliability measures for all described NBI features, and the presumptive histological results are shown in [Table 2](#) and [Table 3](#).

The identification of different mucosal and vascular patterns was associated with high reproducibility (Pa > 80% with k = 0.71 and k = 0.89, respectively). The identification of LBC or WOS was also associated with substantial reproducibility (Pa > 80% with k = 0.58 and k = 0.57, respectively). Conversely, other vascular features such as thickness or density had only weak to moderate reproducibility (Pa = 0.62 and Pa = 0.65 with k = 0.19 and k = 0.24, respectively).

Variable vascular density was the most accurate parameter for identification of *H. pylori* gastritis, although inter-observer agreement was only fair (Pa = 0.61 and k = 0.21).

Mucosal and vascular patterns derived from the histology results were highly valid for metaplasia and dysplasia ([Table 3](#)). The histological diagnosis proposed by the observers showed a high agreement with histological diagnosis (Pa = 0.82, k = 0.71) but only a weak to moderate agreement for *H. pylori* infection (Pa = 0.61, k = 0.21).

#### Development of a simplified classification

Using the results from the derivation study, a simplified classification of gastric lesions was established ([Table 4](#) and [Fig. 2](#)). The presence of LBC contributed but was not essential to the diagnosis of intestinal metaplasia. Also, WOS contributed to the diagnosis of dysplasia or cancer; however, it could only be considered when an irregular mucosal/vascular pattern was seen.

#### Validation study

##### Description of participants and videos

The characteristics of patients and endoscopic procedures included in the validation study are shown in [Table 1](#), and were similar to those of the derivation study. Dysplasia in previous biopsies and mucosectomy were important indications for endoscopy (45%). A total of 100 good quality videos (40 normal mucosa, 38 intestinal metaplasia, 22 dysplasia [19 high grade, 3 low grade], and 39 of which had *H. pylori*) were recorded to accompany 119 histological samples.

##### Accuracy and reproducibility of the new NBI classification

[Table 5](#) shows the correlation between NBI patterns and histological findings, inter-observer agreement, and accuracy for the different NBI patterns proposed. WOS was not evaluated because only one cancer lesion presented this feature in the validation study. The identification of the different patterns was associated with substantial reproducibility (Pa = 0.76, k = 0.62). There were no differences in the reproducibility between the experts and the experienced observers. However, the agreement between the group of experienced observers was higher when compared with the non-experienced group (k = 0.75 vs. 0.60). The identification of the LBC was associated with a moderate agreement (Pa = 0.77, k = 0.49); again, however, this agreement was better between the experienced than between the non-experienced observers (k = 0.77 vs. k = 0.40, respectively). The reproducibility of the variable vascular density NBI pattern for *H. pylori* was fair to moderate (Pa = 0.71, k = 0.38) with no differences between the groups.

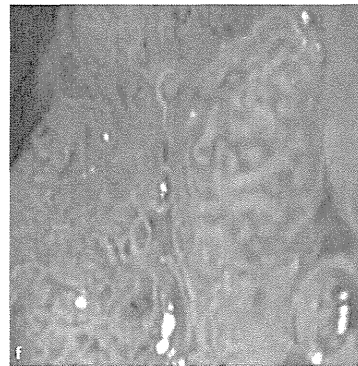
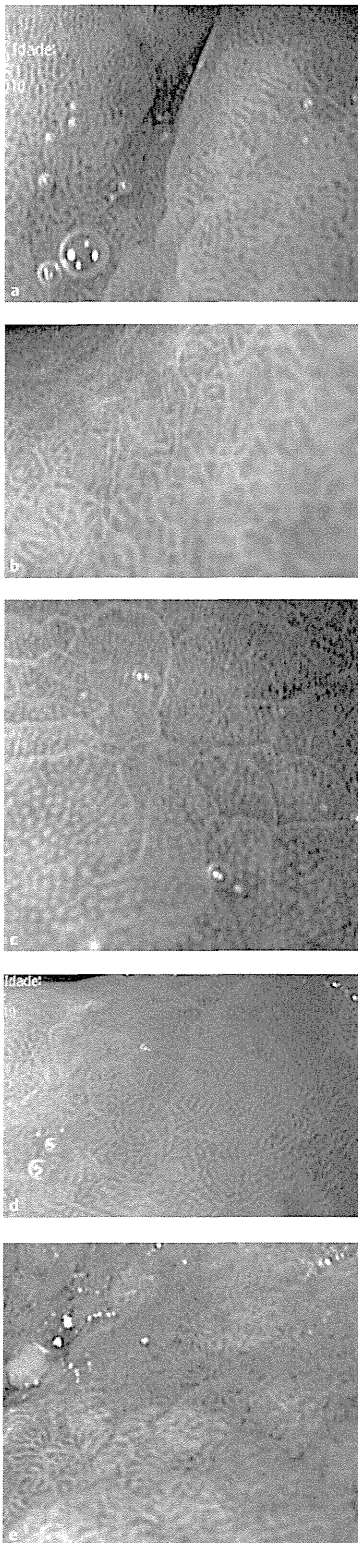
The new NBI patterns derived and proposed were highly accurate for metaplasia and, in particular, for dysplasia ([Table 5](#)). The accuracy of the patterns (A–C) was higher in the experts and experienced observers compared with the non-experienced (pat-

**Table 3** Derivation study: features on narrow band imaging with accuracy estimates for the diagnosis of the several gastric lesions.

Mucosal/vascular pattern	Outcome	Mean sensitivity (range) [95%CI]	Mean specificity (range) [95%CI]	Mean accuracy (range) [95%CI]
Regular, tubulo-villous	Intestinal metaplasia	0.89 (0.85–0.94) [0.78–1.00]	0.90 (0.88–0.95) [0.84–0.96]	0.90 (0.87–0.94) [0.85–0.95]
Irregular	Dysplasia	0.96 (0.92–1.00) [0.82–1.00]	0.98 (0.96–0.99) [0.92–1.00]	0.97 (0.97–0.98) [0.95–1.00]
Light blue crest	Intestinal metaplasia	0.48 (0.42–0.55) [0.31–0.66]	0.96 (0.95–0.97) [0.89–0.99]	0.83 (0.81–0.85) [0.77–0.90]
Variable vascular density	<i>H. pylori</i> infection	0.62 (0.45–0.69) [0.46–0.75]	0.70 (0.58–0.78) [0.56–0.82]	0.66 (0.52–0.73) [0.56–0.75]

**Table 4** Proposed classification for gastric lesions on narrow band imaging. Regular mucosal and vascular patterns favor the absence of dysplasia, ridge or tubulo-villous being found in areas with intestinal metaplasia. The light blue crest should be considered specific for intestinal metaplasia but its absence does not exclude intestinal metaplasia. A variable vascular density may favor the presence of *H. pylori* infection.

Proposed classification					
	A	B		Hp+	C
Mucosal pattern	Regular circular	Regular ridge/tubulo-villous	Light blue crest	Regular	Irregular/absent White opaque substance
Vascular pattern	Regular Thin/peripheric (body (b) or thick/central (a) vessels	Regular		Regular with variable vascular density	Irregular
Expected outcome	Normal	Intestinal metaplasia		<i>H. pylori</i> infection	Dysplasia



**Fig. 2** The simplified classification of gastric lesions using narrow band imaging. **a** Pattern Aa – regular circular/oval mucosa surrounding regular thick vessels in the center of the gland; histology showed normal antrum mucosa; **b** Pattern Aa+ – variable vascular density with areas of low (right) and high (top and center) density but with a pattern of a normal antrum; histology showed *H. pylori* gastritis. These areas of low or high density may render the visualization of narrow band imaging (NBI) features difficult, however, they should not be confused with the irregularity seen in dysplasia (f); **c** Pattern Ab – regular circular mucosa that is surrounded by regular vessels, not in the center of the gland as in the antrum; histology showed normal body mucosa. It is important to recognize that normal body and antrum mucosa have a slightly different NBI appearance; **d** Pattern B – regular ridge/tubulo-villous mucosa with regular vessels; histology showed intestinal metaplasia; **e** Pattern B+ with light blue crest – ridge mucosa with some blue-whitish slightly raised areas and a variable vascular density; histology showed intestinal metaplasia with *H. pylori* gastritis; **f** Pattern C – irregular mucosa with irregular vessels and a complete architectural loss of the mucosal and vascular pattern; this flat lesion presented high grade dysplasia.

tern A: accuracy 87% vs. 74%; pattern B: 88% vs. 76%; pattern C: 97% vs. 91%) as well as the accuracy of LBC (87% vs. 81%). There were no differences between the groups with regard to *H. pylori* pattern accuracy.

The predictive values for the classification were as follows (© **Table 6**). For the diagnosis of intestinal metaplasia using pattern B, a likelihood ratio for a positive test (presence of a certain mucosal pattern) was estimated to be 4.75 and the likelihood ratio of its absence (LR<sup>-</sup>) was 0.13. The diagnosis of intestinal metaplasia using LBC showed LR<sup>+</sup>=5.13 and LR<sup>-</sup>=0.37. Variable vascular density produced predictive values of LR<sup>+</sup>=2.53 and LR<sup>-</sup>=0.48. Importantly, pattern C presented LR<sup>+</sup>=44.33 and LR<sup>-</sup>=0.16 for dysplasia.

## Discussion



To the best of our knowledge this is the first study of reproducibility and validity of HR-NBI endoscopy for the identification of several different gastric lesions that incorporates the entire spectrum of precancerous and intestinal-type cancer lesions. The study provides significant evidence that NBI endoscopy may be a reproducible and accurate method for the diagnosis of gastric pre-neoplastic and cancer lesions. Indeed, some NBI features were very reproducible and were associated consistently with gastric lesions. Furthermore, it appears that a learning curve for the identification of these NBI features should be allowed for, as

**Table 5** Validation study: correlation between features on narrow band imaging (NBI) and histology, and reproducibility and diagnosis accuracy of the simplified NBI patterns.

	Overall reproducibility	Mucosal pattern			Variable vascular density	
		A	B	C	Light blue crest	
Observed outcome, %						
Normal		76	22	2	11	39
Intestinal metaplasia		9	89	2	68	49
Dysplasia		2	14	84	17	13
<i>H. pylori</i> infection		39	59	2	41	64
All observers [95%CI]						
Pa	0.76 [0.71–0.80]	0.75 [0.67–0.81]	0.74 [0.67–0.79]	0.81 [0.72–0.87]	0.77 [0.73–0.81]	0.71 [0.66–0.75]
k	0.62 [0.55–0.62]				0.49 [0.38–0.58]	0.38 [0.29–0.48]
Mean sensitivity (range)		0.76 (0.60–1.00) [0.63–0.89]	0.90 (0.79–1.00) [0.79–1.00]	0.84 (0.50–1.00) [0.70–0.99]	0.68 (0.56–0.82) [0.53–0.84]	0.64 (0.41–0.86) [0.49–0.80]
Mean specificity (range)		0.94 (0.83–1.00) [0.83–0.97]	0.81 (0.61–0.98) [0.72–0.91]	0.98 (0.95–1.00) [0.95–1.00]	0.87 (0.68–0.98) [0.79–0.95]	0.75 (0.56–0.95) [0.61–0.88]
Mean accuracy (range)	0.82 (0.64–0.95) [0.75–0.90]	0.83 (0.64–0.95) [0.75–0.90]	0.84 (0.67–0.95) [0.77–0.91]	0.95 (0.88–1.00) [0.90–0.99]	0.80 (0.70–0.91) [0.73–0.88]	0.70 (0.63–0.86) [0.59–0.80]
Experts <sup>1</sup> [95%CI]						
Pa	0.84 [0.78–0.90]	0.80 [0.69–0.88]	0.83 [0.77–0.89]	0.88 [0.78–0.96]	0.81 [0.75–0.86]	0.71 [0.66–0.77]
K	0.75 [0.65–0.83]				0.60 [0.47–0.72]	0.40 [0.28–0.53]
Mean sensitivity (range)		0.69 (0.62–0.76) [0.55–0.83]	0.92 (0.85–1.00) [0.83–1.00]	0.90 (0.83–0.96) [0.78–1.00]	0.72 (0.56–0.82) [0.56–0.87]	0.71 (0.57–0.86) [0.57–0.86]
Mean specificity (range)		0.95 (0.91–1.00) [0.86–0.98]	0.80 (0.79–0.82) [0.70–0.89]	0.98 (0.95–1.00) [0.95–1.00]	0.82 (0.68–0.89) [0.73–0.91]	0.73 (0.64–0.85) [0.59–0.87]
Mean accuracy (range)	0.82 (0.77–0.86) [0.74–0.89]	0.82 (0.77–0.86) [0.74–0.90]	0.84 (0.81–0.86) [0.77–0.91]	0.96 (0.94–0.99) [0.92–1.00]	0.78 (0.73–0.94) [0.70–0.86]	0.72 (0.63–0.86) [0.62–0.82]
Experienced observers <sup>2</sup> [95%CI]						
Pa	0.84 [0.78–0.89]	0.85 [0.77–0.90]	0.78 [0.69–0.86]	0.90 [0.81–0.97]	0.91 [0.86–0.95]	0.77 [0.71–0.83]
K	0.75 [0.65–0.83]				0.77 [0.62–0.88]	0.46 [0.32–0.60]
Mean sensitivity (range)		0.91 (0.79–1.00) [0.83–1.00]	0.89 (0.82–0.94) [0.79–1.00]	0.94 (0.88–1.00) [0.85–1.00]	0.67 (0.59–0.79) [0.51–0.83]	0.58 (0.41–0.68) [0.42–0.74]
Mean specificity (range)		0.95 (0.91–1.00) [0.86–0.98]	0.93 (0.83–0.98) [0.87–0.99]	0.99 (0.97–1.00) [0.96–1.00]	0.98 (0.97–0.98) [0.95–1.00]	0.81 (0.64–0.95) [0.69–0.93]
Mean accuracy (range)	0.91 (0.86–0.95) [0.86–0.97]	0.91 (0.86–0.95) [0.86–0.97]	0.92 (0.87–0.95) [0.86–0.97]	0.98 (0.95–1.00) [0.95–1.00]	0.87 (0.85–0.91) [0.81–0.94]	0.70 (0.63–0.80) [0.59–0.80]
Non-experienced observers <sup>3</sup> [95%CI]						
Pa	0.75 [0.68–0.82]	0.76 [0.65–0.84]	0.76 [0.68–0.83]	0.70 [0.56–0.82]	0.73 [0.66–0.77]	0.73 [0.67–0.79]
K	0.60 [0.48–0.71]				0.40 [0.26–0.53]	0.44 [0.31–0.57]
Mean sensitivity (range)		0.67 (0.60–0.76) [0.53–0.82]	0.87 (0.79–0.91) [0.76–0.98]	0.68 (0.50–0.83) [0.49–0.87]	0.67 (0.62–0.71) [0.51–0.83]	0.64 (0.49–0.76) [0.48–0.79]
Mean specificity (range)		0.92 (0.83–0.97) [0.85–0.99]	0.71 (0.61–0.80) [0.60–0.82]	0.98 (0.96–1.00) [0.95–1.00]	0.80 (0.74–0.92) [0.71–0.90]	0.70 (0.56–0.77) [0.56–0.84]
Mean accuracy (range)	0.74 (0.64–0.83) [0.66–0.83]	0.74 (0.64–0.83) [0.66–0.83]	0.76 (0.67–0.84) [0.68–0.85]	0.91 (0.88–0.94) [0.85–0.96]	0.76 (0.70–0.84) [0.67–0.84]	0.67 (0.66–0.72) [0.57–0.78]

<sup>1</sup> Three international experts with known interest in NBI.<sup>2</sup> The three experienced endoscopist (End1, End2, and End3) who participated in the derivation study<sup>3</sup> Three different gastroenterologists with special interest in chromoendoscopy but with diverse NBI experience (<50 NBI gastroscopies).

**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  $\times 80$ ), 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 ex-

pertise. 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]. Ezo 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

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 be 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

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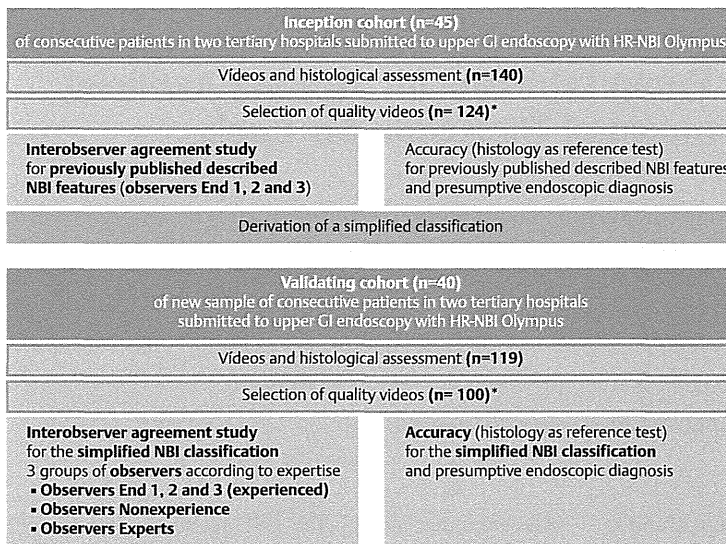


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\*estimated number of 100 for Pa and kappa confidence intervals estimates with clinical relevance

**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.

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

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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 ( $\geq 40$  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 H<sub>2</sub> receptor antagonists (H<sub>2</sub>RAs) 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 H<sub>2</sub>RA 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 H<sub>2</sub>RA 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

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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. Kaku-shima 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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