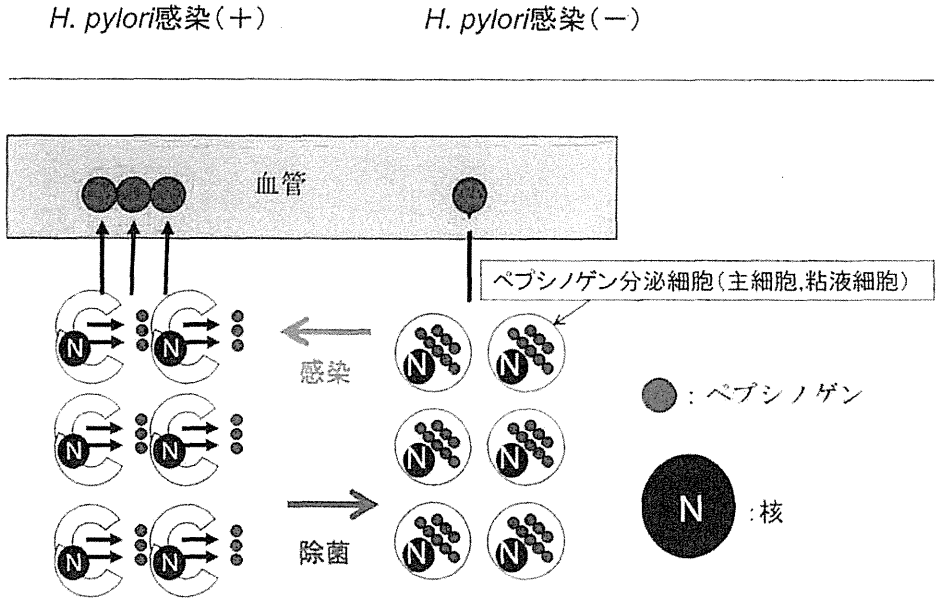


Figure 1. PG値と *H. pylori* 感染の関係.

流れる（Figure 1右）．PG I，IIを産生するPG分泌細胞は主細胞と粘液細胞である．PG値は，この血液中に分泌されたPGの数値を指す．しかしながら現在PG I，PG II値の正常値は決まっていない．

一方，PG法は，判定法の1つであり，陽性と陰性に分けられ，数値ではない．Mikiら[6]は内視鏡的な慢性萎縮性胃炎の進展をコンゴーレッドによる色素内視鏡で解析し，萎縮腺境界と血清PG I，PG II値の関係において腺境界の進展とともに，血清PG I値およびPG I/II比は段階的に低下し，両群間に高い相関があることを報告している．さらに胃粘膜萎縮の程度が強いほど胃癌になりやすいことを応用して，日本ではこのPG法が胃癌のスクリーニングとして用いられている．すなわちPG I 70ng/mL以下でかつPG I/II比が3.0以下をPG陽性とし，胃癌をおこしやすい高度萎縮性胃炎を示す．実際にPG法を用いて胃癌群を感度64%，特異度87%で同定可能と報告[7]されている．PG I 70ng/mL以下でかつPG I/II比が3.0以下以外をPG陰性としている．PG値とPG法を混同しないよう注意が必要である．このPG法とヘリコバクター抗体を組み合わせたABC法（ABC検診）が近年注目されている．

III 胃粘膜萎縮とPG値（*H. pylori* 感染状態と除菌後）

1. *H. pylori* 感染状態（除菌前）

血清PG値は胃粘膜萎縮，炎症，*H. pylori* 感染の3つの因子に影響を受けていると報告されている[8~10]．すなわち，①主細胞，副細胞を中心とする分泌細胞からのPGの血液中への分泌，さらに，②*H. pylori* 感染にともなう活動性胃炎による細胞の崩壊にともなう血液中への多くのPGの放出である．*H. pylori* 感染をすると胃粘膜に炎症がおこる．炎症にともない細胞の崩壊が生じ，PG分泌細胞からPG I，PG IIが放出される（Figure 1左）ことにより一時血清PG I，PG II値が上昇する．その後持続的な炎症の結果として胃体部の萎縮がおこるとPG分泌細胞数が減少し，結果として徐々に血清PG I，PG II値も低下する（Figure 2）．さらに先に述べたようにPG I，PG IIの胃における分布の差から，PG Iは胃体部の萎縮の影響を受けやすく，PG IIは胃幽門腺，胃体部の主細胞，さらに十二指腸腺より分泌されるため体部の萎縮の影響を受けにくい．したがって萎縮の程度が強くなればなるほど，PG Iは低下が強く，PG I/II比もsevereな胃粘膜萎縮にて低下すると報告されている[11]．実際に内視鏡的萎縮が軽度な場

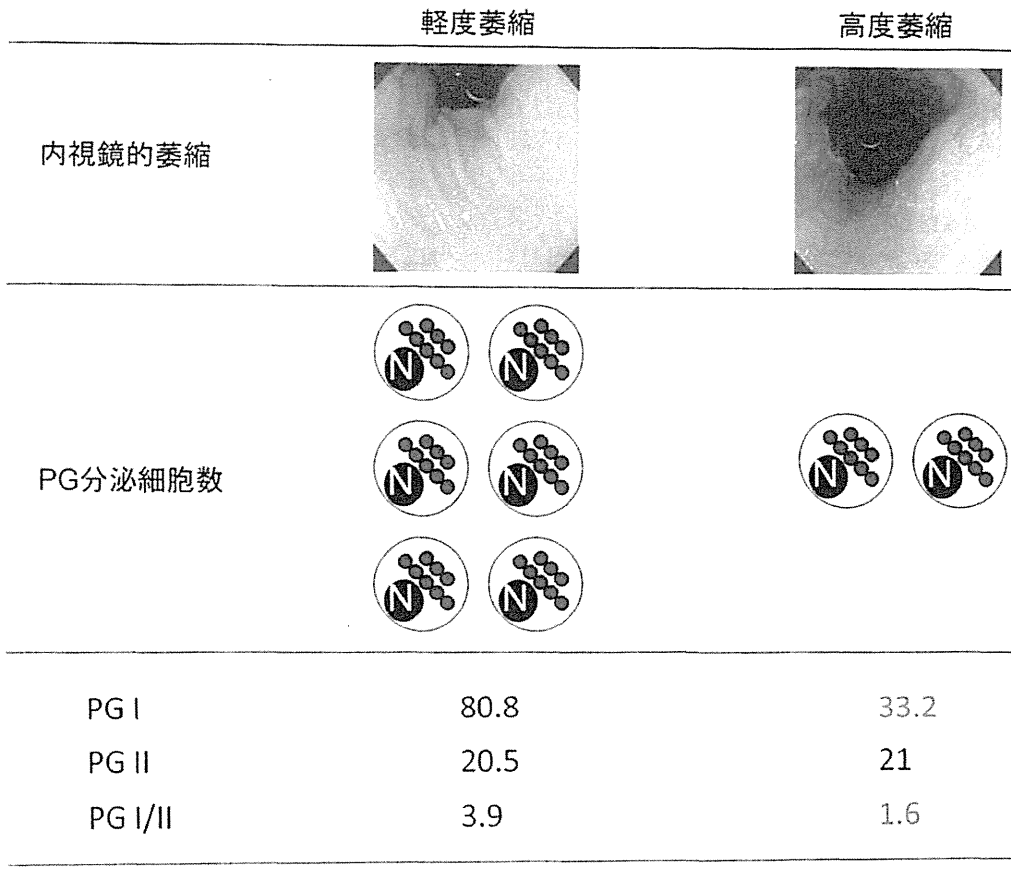


Figure 2. 萎縮性胃炎とPGの関係.

合はFigure 2左側のように，粘膜もきれい（左上段），PG分泌細胞も十分存在（左中段），PG値はI：80.8，II：20.5，さらにI/II比：3.9であるが（左下段），一方内視鏡的萎縮が強い場合，Figure 2右側のように，内視鏡的には粘膜ヒダは消失し，血管透見像が強い（右上段），PG分泌細胞数も極めて少なくなり（右中段），PG値はI：33.2，II：21，さらにI/II比：1.6と低下する（右下段）．Uritaらは，878人においてPGと腸上皮化生について検討し，腸上皮化生はPG I，PG I/II比が低いものに多く，PG I/II比3.0をカットオフ値とした場合，感度71.7%，特異度66.7%で腸上皮化生を判別可能であると報告[12]している．

2．除菌後

PG値は，除菌により炎症による細胞崩壊によるPG顆粒の放出が減少し，一般に低下する（Figure 1：除菌により左側から右側へ変化する）と考えられる．しかしながらこれまで*H. pylori*除菌後PG値がどのような経過をたどるか検討した報告は少ない．除菌後PG値が低下する報告と上昇する報告があり，一定の見解は得られていない[13]~[15]．著者ら[16]のPG I，PG II，PG I/II比およびIgGHP抗体価の除菌前後の報告を示す．PG I値に関しては除菌前61.4ng/mLから除菌成功2カ月後35.9ng/mLに低下し，除菌成功12カ月後41.5ng/mLに増加し，除菌成功24カ月後も41.9ng/mLであったと報告した（Table 1）．さらにPG値と組織学的所見を検討した症例を呈示する（Figure 3）．65歳女性，胃ポリープの患者．組織学的には除菌後も萎縮，腸上皮化生の程度には改善を認めなかった．しかしながら除菌成功24カ月後の組織像にて，一部に副細胞様の細胞の出現（Figure 3，矢印）を認めた．一方PG I値は除菌前27.4から除菌成功2カ月後14.6に低下し，除菌成功24カ月後では21.3に上昇してい

Table 1. *H. pylori* 除菌前・後の PG 値および *H. pylori* 抗体価の推移

	PG I (ng/mL)	PG II (ng/mL)	PG I/II	IgGHP antibody (U/mL)
before	61.4±37.7	23.6±12.2	2.71±1.21	94.2±85.9
2mths	35.9±18.4*	7.23±2.55*	4.98±1.92*	52.1±52.9*
12mths	41.5±23.2*	8.77±4.58*	4.80±1.49*	20.1±52.8*
24mths	41.9±19.1*	8.60±3.41*	4.84±1.22*	12.4±17.8*

*P<0.05 compared to pre-eradication.

Kawai T. et al. Aliment Pharmacol Ther 2006; 24 (suppl 4): 23-30 改変.

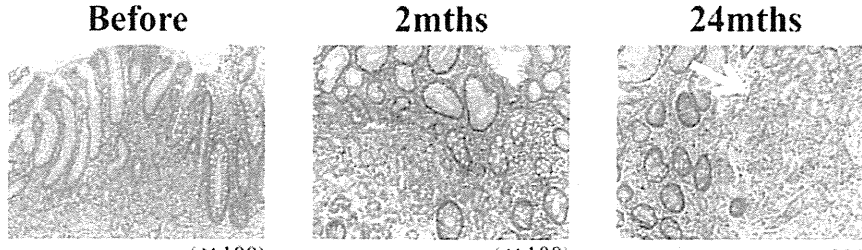
た．PG II 値は除菌成功2カ月後著明に低下し，除菌成功24カ月後ではわずかに上昇していた．PG I/II 比は除菌成功2カ月後上昇し，24カ月後はわずかに上昇した．

さらに著者ら[16]は，PG 値と組織学的萎縮との相関に関する検討をし，体部において PG 値と萎縮の間に相関が認められたと報告した．特に体中部小弯においては PG I，PG I/II 比と萎縮との間に除菌前から有意な相関が認められ，除菌成功2カ月後相関係数が大きくなった．除菌成功12カ月後は有意差を認めるも相関係数が小さくなり，除菌成功24カ月後は有意差が消失していた．これは先に述べたように除菌前には PG 値が3つの因子胃粘膜萎縮，炎症，*H. pylori* 感染の影響を受けていることに起因すると思われる[11~13]．除菌前はこの3つの因子が絡み合うことにより PG 値と組織学的萎縮の相関が弱く，除菌成功後は炎症と *H. pylori* 感染が関与しなくなり，PG 値と萎縮の相関が強くなったと推測される．すなわち除菌前は炎症，*H. pylori* 感染により主細胞からの滲出，あるいは主細胞の崩壊により血液中に多くの PG が放出されていたが，*H. pylori* 除菌に成功することにより胃粘膜の炎症性変化にともなう PG の細胞からの放出がなくなり，主細胞内から血液中に循環する PG のみとなるために除菌2カ月後 PG 値と組織学的萎縮に相関が認められたのであろう．一方除菌成功後12カ月，24カ月では，炎症と *H. pylori* 感染は認めないも，萎縮も軽度は改善し，さらに再生上皮が出現してくる．再生上皮に含まれる副細胞あるいは幼弱な主細胞などの PG 分泌細胞の出現が推測される．再生上皮からの PG 分泌にともない，PG 値と組織学的萎縮との相関が除菌成功後消失する可能性があると思われた．すなわち Updated Sydney System では萎縮性変化は，固有胃腺の変化を評価しており，この再生粘膜が出現しても副細胞あるいは幼弱な主細胞では，萎縮が改善されたと評価できない．このために，除菌後12カ月，24カ月後では，PG 値と萎縮の相関が消失してしまっている可能性がある．

IV 胃粘膜萎縮と PG 法（*H. pylori* 感染状態と除菌後）

1. *H. pylori* 感染状態（除菌前）

先に述べたように PG 法（陽性：PG I 70ng/mL 以下でかつ PG I/II 比が3.0以下）により，胃癌群を感度64%，特異度87%と効率的に検出可能[7]であるとされている．Yoshihara らは，PG 法による胃癌のスクリーニングは死亡率低下につながると報告[17]した．さらに *H. pylori* 抗体と PG 法を組み合わせた ABC 法は，本来 A 群，B 群，C 群，D 群の4群に分類される．A 群：*H. pylori* 抗体陰性・PG 陰性，B 群：*H. pylori* 抗体陽性・PG 陰性，C 群：*H. pylori* 抗体陽性・PG 陽性，D 群：*H. pylori* 抗体陰性・PG 陽性である．Watabe ら[18]は6983人を対象として，この ABC 法による胃癌の発生率を，内視鏡検査を用いて前向きに研究を行った．平均4.7年の経過観察にて，年率の胃癌発生率は，A 群：0.04%，B 群：0.06%，C 群：0.35%，D 群：0.60% と明らかな差を認め，ABC 法の有用性を報告している．さらに Yanaoka ら[19]，Mizuno ら[20]も同様に，ABC 法の胃癌ハイリスクのスクリーニングへの有用性を報告している．Watabe ら，Yanaoka ら，Mizuno らはそれぞれ1995年，1994年，1987年に登録開始（血清



PG I	**27.4**	**14.6**	**21.3**
PG II	**21**	**4.3**	**5.8**
PG I/II	**1.3**	**3.4**	**3.6**

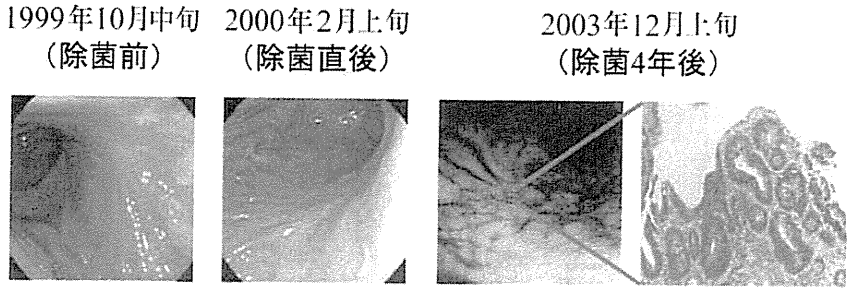
No remarkable improvement of atrophy and intestinal metaplasia was recognized histologically after *H. pylori* eradication in the lesser curvature of mid-corpus, on the other hand, PG I level decreased at 2 months after eradication, afterward PG I increased slightly.

Figure 3. 症例：65歳，女性，胃ポリープ（Kawai T, et al. Aliment Pharmacol Ther 2006; 24 (suppl 4): 23-30 改変）．

採取）された検討であり，*H. pylori* 除菌が広く行われる以前の検討である．

2．除菌後

Furutaらは1997年既に，除菌において早期（1カ月後）にPG値に変化が生じることに着目し，PG I II比の除菌前と1カ月後の変化率を用いて，除菌判定に応用し，感度100%，特異度93.1%，有用度96.2%であると報告している．すなわちPG値には除菌後早い段階から変化が生じる．そこで著者ら[21]は120人の *H. pylori* 陽性消化器疾患患者に除菌療法を行い，除菌前と除菌2カ月後のPG法の判定の変化を検討した．除菌率は全体で79.3%であった．除菌前にPG法陽性は57人であり，46人で除菌に成功し，6人は除菌不成功（脱落5人）であった．46人のPG法陽性者のうち，37人（80.4%）は除菌後2カ月後PG法陰性に変わってしまっていた．一方除菌不成功の6人は除菌2カ月後もPG法陽性のままであった．すなわちPG IIは，PG Iに比べ，胃・十二指腸に広範囲に分布しているため，Table Iに認められるように除菌により数値自体も，PG Iに比べPG IIの数値がより大きく低下する．したがってPG I/II比は，相対的に上昇し，PG法判定は，陽性から陰性になる．先に示した症例においても（Figure 3），除菌2カ月後にPG Iは14.6に低下するも，PG I/II比が3.4と上昇した．したがってこの症例も，除菌後PG法の判定が陰性に変化した．*H. pylori* 除菌後胃癌症例を提示する（Figure 4），1999年胃体上部後壁に潰瘍瘢痕を認め，IgGHP抗体は157.5と陽性，PG I：41.4，PG II：23.6，PG I/II比：1.8と，PG法陽性であり，ABC法ではC群であった．その後胃潰瘍再発予防にて，除菌療法を行い成功した．除菌後は，PG I：23.4，PG II：6.1，PG I/II比：3.9とPG法陰性となり，ABC分類では判定が危険度の低いB群となった．しかし除菌経過観察中の4年後に，潰瘍瘢痕近傍より胃癌（0-IIc）を認めた[22]．この症例も除菌後にPG法，ABC法による判定を初めて行った場合には，PG法は陰性，ABC法はB群となり胃癌の危険度は低いと判定されてしまう．Takeらの報告[23]のように除菌後も長期にわたり胃癌は発生する．PG法およびABC法の適応は，あくまでも *H. pylori* 除菌治療を受けたことのない症例のみであることを忘れないでいただきたい．実際にKudoら[24]は，2007年から2009年に発見された95の胃癌症例においてABC法にて分類し，除菌後A群からの胃癌症例の増加を報告している．



PG I	41.4	23.4	21.0
PG II	23.6	6.1	5.8
PG I/II	1.8	3.9	3.6
IgGHP	157.5	59.8	14.1
PG法判定	陽性	陰性	陰性
ABC判定	C群	B群	B群

Figure 4. *H. pylori* 除菌後胃癌発生例の内視鏡像と PG 値の経過.

おわりに

PGと萎縮性胃炎の関係について述べた．PG値は萎縮性胃炎との関係はあるも，*H. pylori* 除菌治療の影響を受ける．特にPG法（ABC法も含む）は，*H. pylori* 除菌成功後は，胃癌リスクの判定には使用は困難となる．既に健診においては30%以上の受診者が除菌済ともいわれており，今後除菌後患者さんに対する新しいPG法の基準を決めるべきである．

本論文内容に関連する著者の利益相反
：なし

文 献

1) Kimura K : Chronological transition of the fundic-pyloric border determined by stepwise biopsy of the lesser and greater curvatures of the stomach. Gastroenterology 63 : 584–592 : 1972
2) Kawai T, Yamamoto K, Fukuzawa M, et al : Helicobacter pylori infection and reflux esophagitis in young and middle-aged Japanese subjects. J Gastroenterol Hepatol 25 (suppl 1) : S80–S85 : 2010
3) Uemura N, Okamoto S, Yamamoto S, et al : Helicobacter pylori infection and the development of gastric cancer. N Engl J Med 345 : 784–789 : 2001
4) Samloff IM, Varis K, Ihamaki T, et al : Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. Gastroenterology 83 : 204–209 : 1982
5) Kodoi A, Yoshihara M, Sumii K, et al : Serum pepsinogen in screening for gastric cancer. J Gastroenterol 30 : 452–460 : 1995
6) Miki K, Ichinose M, Shimizu A, et al : Serum pepsinogens as a screening test of extensive chronic gastritis. Gastroenterol Jpn 22 : 133–141 : 1987
7) Miki K, Ichinose M, Ishikawa KB, et al : Clinical application of serum pepsinogen I and II levels for mass screening to detect gastric cancer. Jpn J Cancer Res 10 : 1086–1090 : 1993
8) Knight T, Greaves S, Wilson A, et al : Variability in serum pepsinogen levels in an asymptomatic population. Eur J Gastroenterol Hepatol 7 : 647–654 : 1995
9) Cave TR, Cave DR : Helicobacter pylori stimulates pepsin secretion from isolated rabbit gastric glands. Scand J Gastroenterol Suppl 181 : 9–14 : 1991
10) Lorente S, Doiz O, Trinidad Serrano M, et al : Helicobacter pylori stimulates pepsinogen secretion from isolated human peptic cells. Gut 50 : 13–18 : 2002
11) Kiyohira K, Yoshihara M, Ito M, et al : Serum pepsinogen concentration as a marker of Helicobacter pylori infection and the histologic grade of gastritis : evaluation of gastric mucosa by serum pepsinogen levels. J Gastroenterol 38 : 332–338 :

2003
12) Urita Y, Hike K, Torii N, et al : Serum pepsinogens as a predicator of the topography of intestinal metaplasia in patients with atrophic gastritis. Dig Dis Sci 49 : 795–801 : 2004
13) Chen TS, Tsay SH, Chang FY, et al : Effect of eradication of Helicobacter pylori on serum pepsinogen I, gastrin, and insulin in duodenal ulcer patients : a 12-month follow-up study. Am J Gastroenterol 89 : 1511–1514 : 1994
14) Ohkusa T, Miwa H, Nomura T, et al : Improvement in serum pepsinogens and gastrin in long-term monitoring after eradication of Helicobacter pylori : comparison with H. pylori-negative patients. Aliment Pharmacol Ther 20 (suppl 1) : 25–32 : 2004
15) Kokkola A, Sipponen P, Rautelin H, et al : The effect of Helicobacter pylori eradication on the natural course of atrophic gastritis with dysplasia. Aliment Pharmacol Ther 16 : 515–520 : 2002
16) Kawai T, Kawakami K, Kataoka M, et al : Correlation of serum pepsinogen with histological atrophy following successful Helicobacter pylori eradication. Aliment Pharmacol Ther 24 (suppl 4) : 23–30 : 2006
17) Yoshihara M, Hiyama T, Yoshida S, et al : Reduction in gastric cancer mortality by screening based on serum pepsinogen concentration : a case-control study. Scand J Gastroenterol 42 : 760–764 : 2007
18) Watabe H, Mitsushima T, Yamaji Y, et al : Predicting the development of gastric cancer from combining Helicobacter pylori antibodies and serum pepsinogen status : a prospective endoscopic cohort study. Gut 54 : 764–768 : 2005
19) Yanaoka K, Oka M, Yoshimura N, et al : Risk of gastric cancer in asymptomatic, middle-aged Japanese subjects based on serum pepsinogen and Helicobacter pylori antibody levels. Int J Cancer 123 : 917–926 : 2008
20) Mizuno S, Miki I, Ishida T, et al : Prescreening of a high-risk group for gastric cancer by serologically determined Helicobacter pylori infection and atrophic gastritis. Dig Dis Sci 55 : 3132–3137 : 2010
21) Kawai T, Miki K, Ichinose M, et al : Changes in evaluation of the pepsinogen test result following Helicobacter pylori eradication therapy in Japan. Inflammopharmacology 15 : 31–35 : 2007
22) 片岡幹統, 河合 隆, 川上浩平, 他 : *H. pylori* 除菌4年後に異時性早期胃癌を認めた1例. Progress of Digestive Endoscopy 66 : 54–55 : 2005
23) Take S, Mizuno M, Ishiki K, et al : The long-term risk of gastric cancer after the successful eradication of Helicobacter pylori. J Gastroenterol 46 : 318–324 : 2011
24) Kudo T, Kakizaki S, Sohara N, et al : Analysis of ABC (D) stratification for screening patients with gastric cancer. World J Gastroenterol 17 : 4793–4798 : 2011

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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[1-4]。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[5]。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[6]。年齢調整死亡率でみても，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[7]。

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[8]。

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。

Ⅰ．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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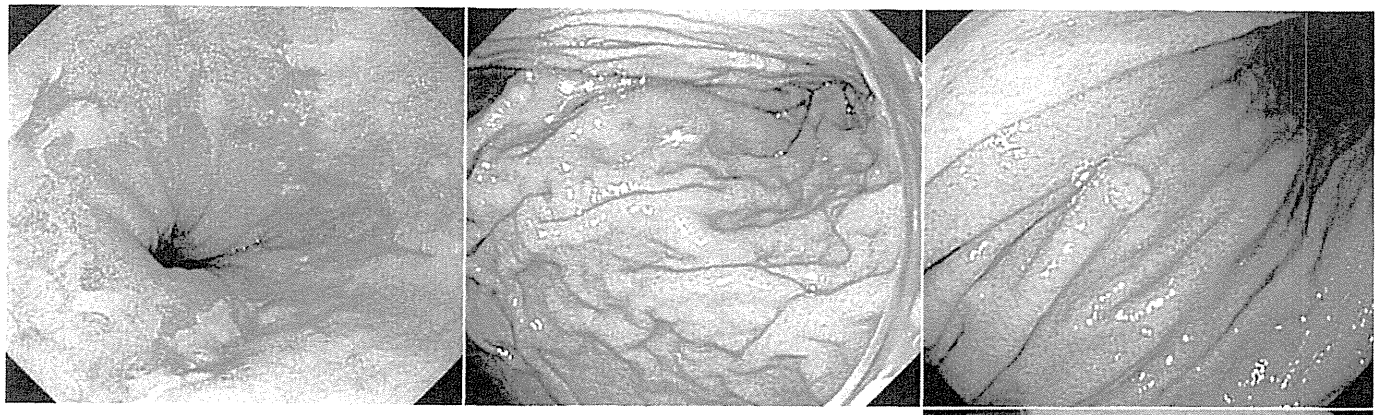
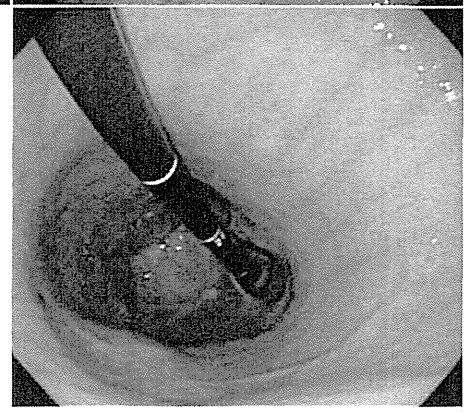


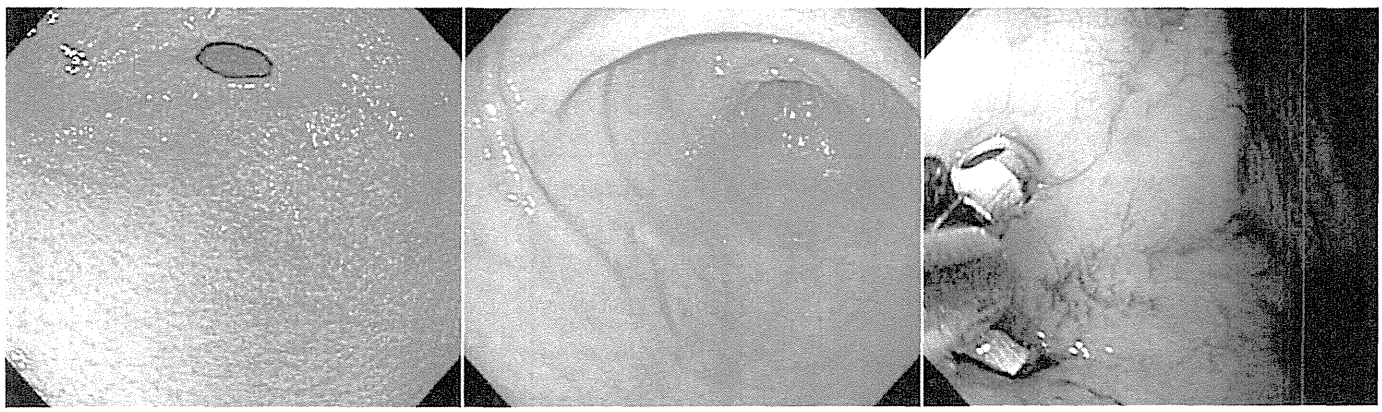
▲図 1
a．逆流性食道炎
b．RACを伴う胃体部の非萎縮胃粘膜
c．胃底腺ポリープ
d．胃体部の稜線上発赤

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[9]。20歳代・30歳代の女性

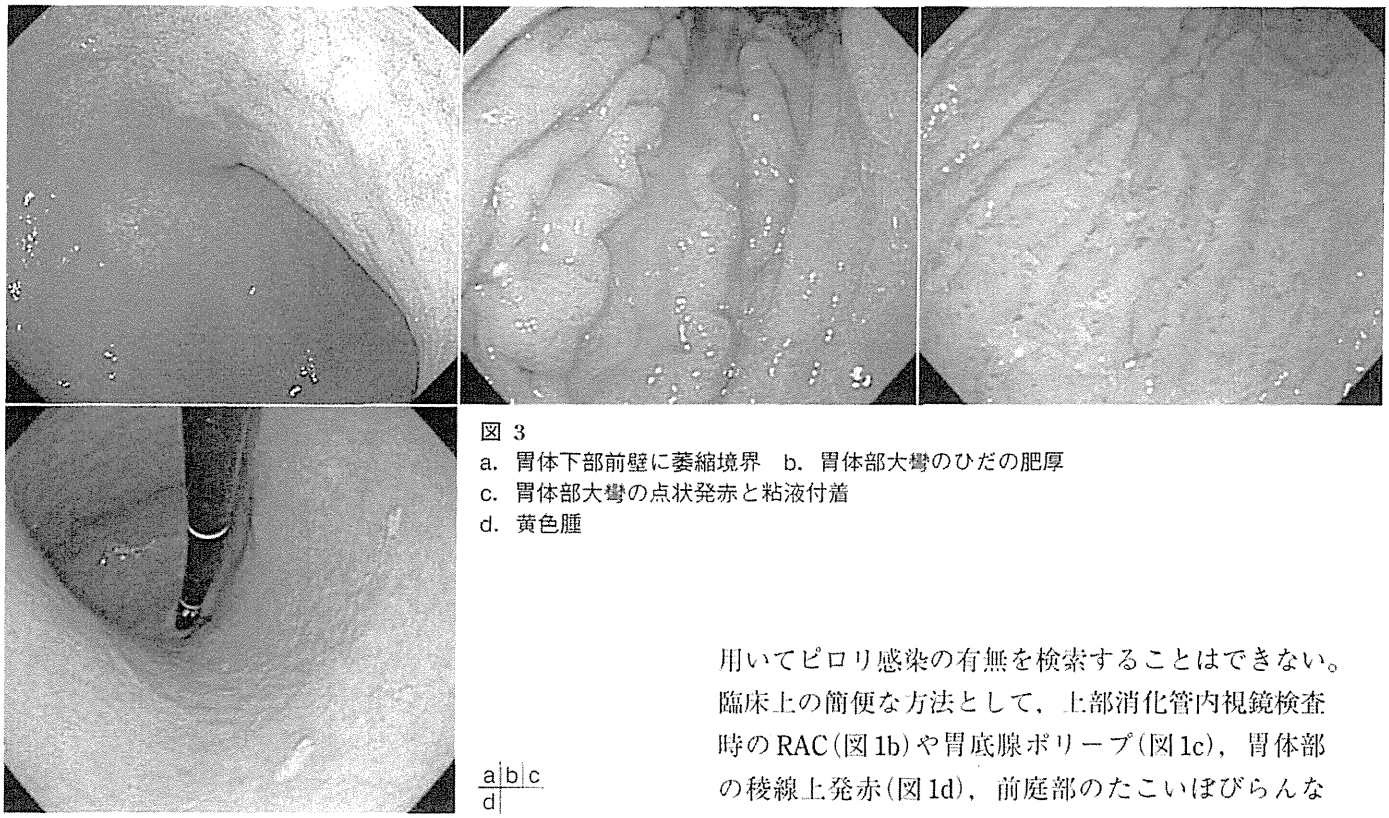


図 3
a. 胃体下部前壁に萎縮境界　b. 胃体部大彎のひだの肥厚
c. 胃体部大彎の点状発赤と粘液付着
d. 黄色腫

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**)[10]。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[11~13]。

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調の浅い陥凹である[14](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。臨床上の簡便な方法として，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に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

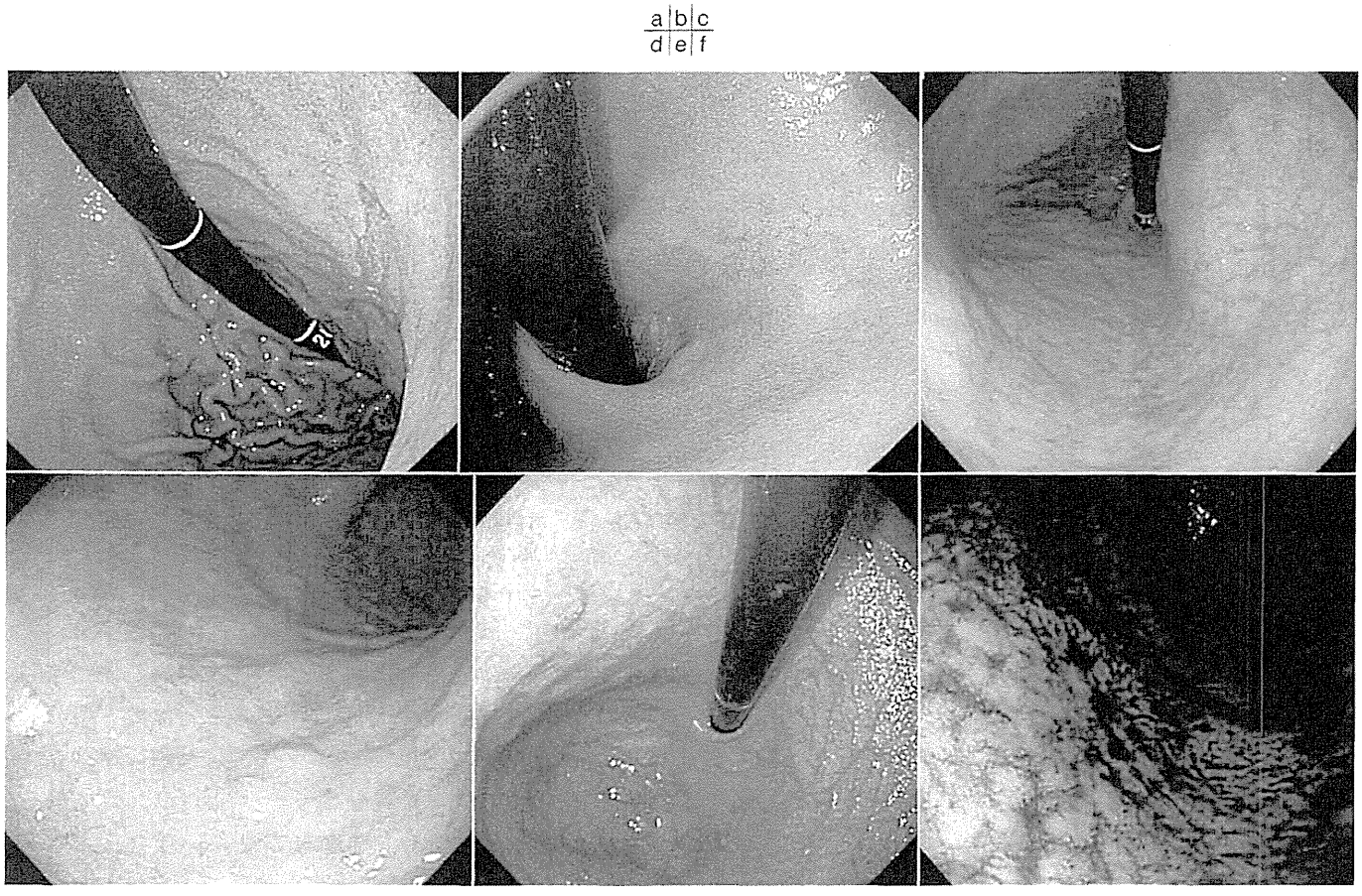


図 4
a. 胃体下部後壁の萎縮境界に存在する陥凹型早期胃癌(15 mm, sig to por, 0-Ⅱc, T1a) b. 噴門部小彎の萎縮境界に存在する褪色陥凹(4 mm, tub1, 0-Ⅱc, T1a) c. 高度萎縮胃粘膜 d. 腸上皮化生を伴う萎縮胃粘膜 e. 胃体上部後壁の高度萎縮胃粘膜に存在する軽度発赤病変(13 mm, tub1, 0-Ⅱc+Ⅱa, T1b) f. 前庭部前壁の腸上皮化生を伴う高度萎縮胃粘膜に存在する早期胃癌(15 mm, tub1, 0-Ⅱa+Ⅱc, T1b)

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[15]。

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

a|b|c

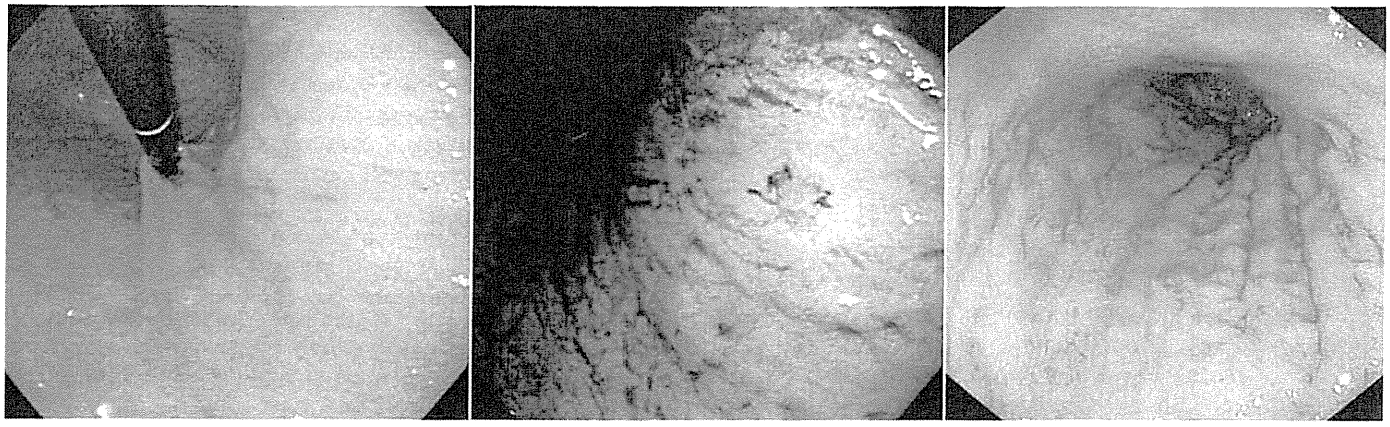


図 5

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-Ⅱc. T1a)　c. 胃体部大彎を中心としたひだの腫大と胃壁の肥厚(Linitis plastic: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。

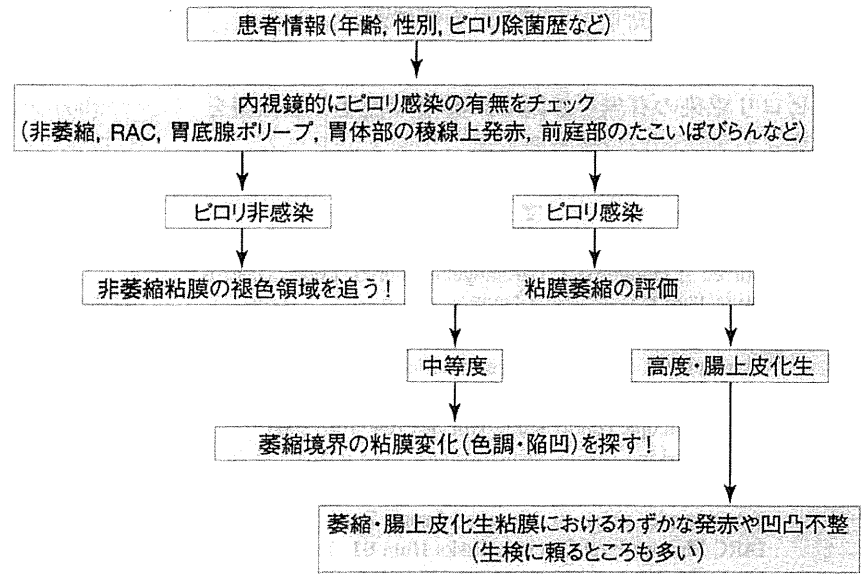


図 6　ピロリ感染と萎縮性変化を考慮した胃粘膜の観察

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しなく行うためには，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[16,17]。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。

文献

1. Correa P, Houghton J: Carcinogenesis of *H. pylori*. Gastroenterology **133**: 659-672, 2007
2. Watabe H, Mitsushima T, Yamaji Y et al: Predicting the development of gastric cancer from combining *Helicobacter pylori* antibodies and serum pepsinogen status: prospective endoscopic cohort study. Gut **54**: 764-768, 2005
3. IARC Working Group. Schistosomes, liver flukes and *Helicobacter pylori*. IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 7-14, June 1994. IARC Monogr Eval Carcinog Risks Hum **61**: 1-241, 1994
4. Ohata H, Kitauchi S, Yoshimura N et al: Progression of chronic atrophic gastritis associated with *Helicobacter pylori* infection increases risk of gastric cancer. Int J Cancer **109**: 138-143, 2004
5. Asaka M, Kimura T, Kubo M et al: Relationship of *Helicobacter pylori* to serum pepsinogens in asymptomatic Japanese population. Gastroenterology **102**: 760-766, 1992
6. 独立行政法人国立がん研究センターがん対策情報センター
7. 厚生労働省大臣官房統計情報部「人口動態統計」:がんの統計. 2005
8. Uemura N, Okamoto S, Yamamoto S et al: *Helicobacter pylori* infection and the development of gastric cancer. N Engl J Med **345**: 784-789, 2001
9. Miyamoto M: Nodular gastritis in adults is caused by *H. pylori* infection. Dig Dis Sci **48**: 968-975, 2003
10. 鎌田智有: *H. pylori* 感染と胃の結節性変化. Helicobacter Research **9**: 4-9, 2008
11. Haruma K, Komoto K, Kamada T et al: *Helicobacter pylori* is a major risk factor for gastric carcinoma in young patients. Scand J Gastroenterol **35**: 255-259, 2000
12. Miyamoto M, Haruma K, Yoshihara M et al: Five cases of nodular gastritis and gastric cancer. Dig Liver Dis **34**: 819-820, 2003
13. Kamada T, Miyamoto M, Ito M et al: Nodular gastritis is a risk factor for diffuse-type of gastric carcinoma in Japanese young patients. Gastroenterology **126**: A456, 2004
14. 平澤俊明，山本頼正，藤崎順子: ESDの適応拡大　未分化適応拡大病変の臨床像の検討. 第82回日本胃癌学会総会記事，141，2010
15. 後藤田卓志，下田忠和，藤城光弘ほか:内視鏡的に良性と診断され生検で確診された早期胃癌の特徴　特に慢性胃炎と鑑別困難な早期胃癌について. 胃と腸 **34**: 1495-1503，1999
16. 濱中久尚，南　伸弥，後藤田卓志:見落としのないスクリーニング内視鏡. 消化器内視鏡 **15**: 501-508，2003
17. 角川康夫，正田浩子，草野　央ほか:胃癌に対する内視鏡スクリーニング　私はこうしている. 胃と腸 **43**: 1225-1229，2008

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-IIc, T1a).

Figure 3 a. Atrophic boarder of the lower gastric body.
b. Edematous change of gastric folds in the gastric body.
c. Reddish spots with gastric mucous on the greater curvature of the gastric body.
d. Xanthoma on the lesser curvature 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-IIc, T1a).
b. Small discolored area on the lesser curvature of the cardia (4 mm, tub1, 0-IIc, 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-IIc+IIa, T1b).
f. Superficial gastric cancer developed from sever atrophic gastric mucosa with intestinal metaplasia (15 mm, tub1, 0-IIa+IIc, 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-carmine dye (5 mm, sig, 0-IIc, 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

Authors

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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 (×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

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

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 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[1], 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]	

[1] 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 (**Table3**). 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

Table5 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.

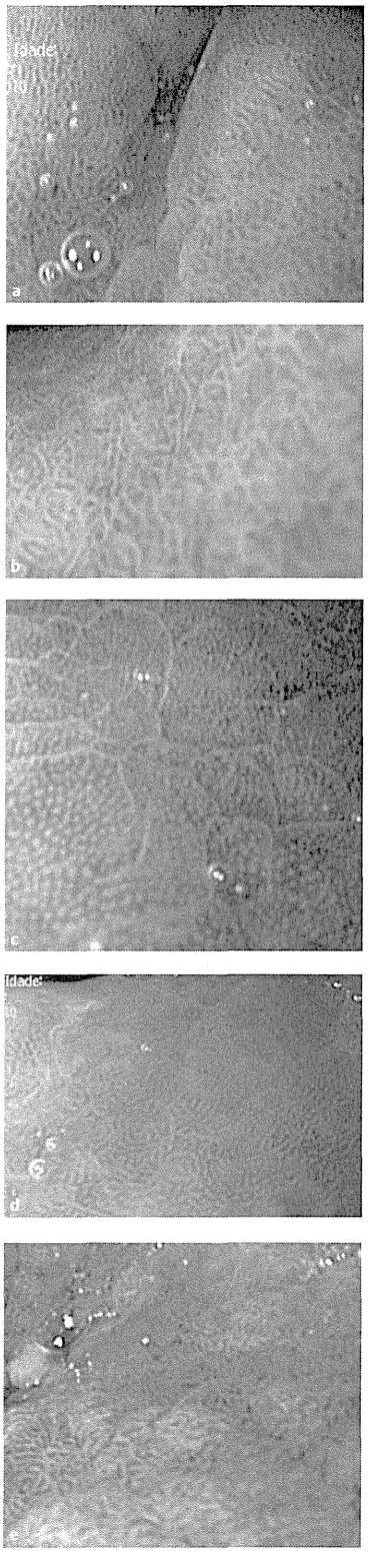
The new NBI patterns derived and proposed were highly accurate for metaplasia and, in particular, for dysplasia (**Table 5**). The accuracy of the patterns (A–C) was higher in the experts and experienced observers compared with the non-experienced (pat-

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	*H. pylori* 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		H. pylori infection	Dysplasia



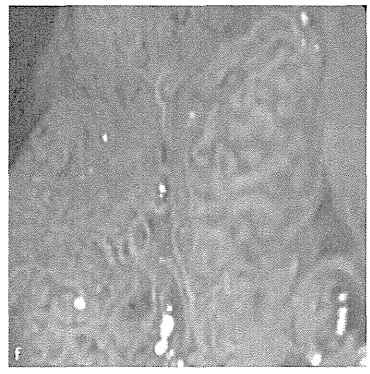


Fig. 2 The simplified classification of gastric lesions using narrow band imaging. **a** Pattern Aa – regular circular/oval mucosa surrounding regular thick vessels in the center of the gland; histology showed normal antrum mucosa; **b** Pattern Aa+ – variable vascular density with areas of low (right) 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–) was 0.13. The diagnosis of intestinal metaplasia using LBC showed LR+=5.13 and LR–=0.37. Variable vascular density produced predictive values of LR+=2.53 and LR–=0.48. Importantly, pattern C presented LR+=44.33 and LR–=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
H. pylori 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[1] [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[2] [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[3] [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]

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