Minor oozing can be controlled by cautery using cutting devices such as the needle knife, IT knife, Hook knife or Flex knife. Cautery using hemostatic forceps is suitable for arterial bleeding.[15]

The number of early gastric cancer patients undergoing endoscopic resection is increasing in Japan because of the expanded indications and technical improvements mentioned above. Consequently, the actual number of complications associated with endoscopic resection has also increased. Thus, endoscopists must now be aware of both the risk factors and the rate of complications as well as how to effectively treat such complications.

Early detection is essential for carrying out endoscopic resection. Japan has had a well-organized mass-screening program for gastric cancer as part of its public health services since the mid-1960s.[16] This program has, however, most often used gastrophotofluorography which has comparatively poor resolution so that sensitivity for early-stage cancer was low (39%), albeit sensitivity for advanced cancer was high (92%).[17] Recently, the development of video endoscopy has had a substantial impact on improving early diagnosis, and early gastric cancer now accounts for nearly 50% of all gastric cancers treated at major medical facilities in Japan.[18,19] In fact, most cases (78%) of early gastric cancer at our hospital between 2001 and 2003 were detected by endoscopy.[20]

The use of endoscopy for mass screening nationwide would be impractical and difficult, because of its low cost-effectiveness and the lack of a sufficient number of endoscopists. An alternative mass-screening approach has been proposed using endoscopy after the identification of high-risk subjects.[21] An initial screening test would be carried out using combination assays of serum *Helicobacter pylori* antibody and pepsinogen, followed by endoscopic examination of those individuals determined to be high-risk subjects. Such a strategy might also prove useful for the detection of early gastric cancer in other countries where the ratio of early gastric cancer to all gastric cancer cases is still low.

Finally, Hoteya and his colleagues also reported that the rate of one-piece resection with a negative tumor margin did not differ significantly between EMR and ESD for lesions $\leq$ 5 mm in diameter. Such lesions can therefore be treated by either EMR or ESD. The precise method of resection is less important because the primary aim of endoscopic resection as a local resection procedure is to achieve one-piece resection with a negative tumor margin. In other words, alternative resection methods that may be developed in the future, such as a full-thickness resection procedure, could eventually replace ESD for the local resection of early gastric cancer.

References

1 Soetikno R, Kaltenbach T, Yeh R, Gotoda T. Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J. Clin. Oncol.* 2005; **23**: 4490–8.
2 Gotoda T. Endoscopic resection of early gastric cancer. *Gastric Cancer* 2007; **10**: 1–11.
3 Gotoda T, Yanagisawa A, Sasako M *et al.* Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 2000; **3**: 219–25.
4 Hoteya S, Iizuka T, Kikuchi D, Yahagi N. Benefits of endoscopic submucosal dissection according to size and location of gastric neoplasm, compared with conventional mucosal resection. *J. Gastroenterol. Hepatol.* 2009; **24**: 1102–6.
5 Oda I, Saito D, Tada M *et al.* A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262–70.
6 Oka S, Tanaka S, Kaneko I *et al.* Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest. Endosc.* 2006; **64**: 877–83.
7 Watanabe K, Ogata S, Kawazoe S *et al.* Clinical outcomes of EMR for gastric tumors: historical pilot evaluation between endoscopic submucosal dissection and conventional mucosal resection. *Gastrointest. Endosc.* 2006; **63**: 776–82.
8 Shimura T, Sasaki M, Kataoka H *et al.* Advantages of endoscopic submucosal dissection over conventional endoscopic mucosal resection. *J. Gastroenterol. Hepatol.* 2007; **22**: 821–6.
9 Sano T, Okuyama Y, Kobori O, Shimizu T, Morioka Y. Early gastric cancer. Endoscopic diagnosis of depth of invasion. *Dig. Dis. Sci.* 1990; **35**: 1340–4.
10 Seto Y, Shimoyama S, Kitayama J *et al.* Lymph node metastasis and preoperative diagnosis of depth of invasion in early gastric cancer. *Gastric Cancer* 2001; **4**: 34–8.
11 Yanai H, Matsumoto Y, Harada T *et al.* Endoscopic ultrasonography and endoscopy for staging depth of invasion in early gastric cancer: a pilot study. *Gastrointest. Endosc.* 1997; **46**: 212–16.
12 Oda I, Gotoda T, Sasako M *et al.* Treatment strategy after non-curative endoscopic resection of early gastric cancer. *Br. J. Surg.* 2008; **95**: 1495–500.
13 Oda I, Gotoda T, Hamanaka H *et al.* Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig. Endosc.* 2005; **17**: 54–8.
14 Minami S, Gotoda T, Ono H, Oda I, Hamanaka H. Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery. *Gastrointest. Endosc.* 2006; **63**: 596–601.
15 Oda I, Ikehara H, Yokoi C, Matsuda T, Bhandari P. How to cope with complication throughout the gastrointestinal tract. In: Conio M, Siersema P, Repici A, Pomchon T, eds. *Endoscopic Mucosal Resection*. Oxford: Blackwell Publishing, 2008; 196–211.
16 Yanaoka K, Oka M, Mukoubayashi C *et al.* Cancer high-risk subjects identified by serum pepsinogen tests: outcomes after 10-year follow-up in asymptomatic middle-aged males. *Cancer Epidemiol. Biomarkers Prev.* 2008; **17**: 838–45.
17 Nishizawa M. [Present status and prospect for cancer screening.] *J. Gastroenterol. Mass. Surv.* 1993; **78**: 100–3. (In Japanese)
18 Nakamura K, Ueyama T, Yao T *et al.* Pathology and prognosis of gastric carcinoma. Findings in 10,000 patients who underwent primary gastrectomy. *Cancer* 1992; **70**: 1030–7.
19 Shimizu S, Tada M, Kawai K. Early gastric cancer: its surveillance and natural course. *Endoscopy* 1995; **27**: 27–31.
20 Suzuki H, Gotoda T, Sasako M, Saito D. Detection of early gastric cancer: misunderstanding the role of mass screening. *Gastric Cancer* 2006; **9**: 245–53.
21 Miki K. Gastric cancer screening using the serum pepsinogen test method. *Gastric Cancer* 2006; **9**: 245–53.

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原　著

胃癌に対する深達度診断の現状

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要旨：胃癌の治療方針決定には正確な深達度診断が要求される．深達度診断の今後の検討課題を明らかにするために，2001年から2003年に当院で外科切除あるいは内視鏡切除された単発胃癌1846例を対象に，通常内視鏡による深達度診断正診率および肉眼型，ULの有無，部位，腫瘍径，組織型別の早期癌誤診例の検討を行った．早期癌，進行癌の正診率は95%，86%，早期癌1258例のM，SMの正診率は85%，46%であった．早期癌誤診例はIIa+IIc型，UL+，21mm以上，未分化型でそれぞれ他の因子に比し有意に高率であった．胃癌の深達度診断は，特にSMの正診率が低く，今後さらなる診断精度の向上が望まれる．

索引用語：胃癌，深達度診断，内視鏡診断

緒　言

胃癌に対する治療方針の決定に際しては，正確な深達度診断が必要である．たとえば，外科手術における定型手術あるいは縮小手術の選択にはT1とT2の鑑別，内視鏡切除の適応決定には，MとSMとの鑑別が重要となる[1)]．内視鏡による胃癌の深達度診断は，これまで多くの検討が行われてきたが[2)~5)]，いまだ十分とはいい難い．また，超音波内視鏡[6)]に加えて，近年では拡大内視鏡[7)]，狭帯域フィルター内視鏡（Narrow Band Imaging；NBI）など特殊光観察[8)]も用いられ，その診断精度の向上が期待されている．そこで今回われわれは，今後さらに発展すると思われる拡大内視鏡，特殊光観察時代に向けての検討課題を明らかにするために，当院において拡大内視鏡，特殊光観察導入以前の症例を対象に，通常内視鏡による胃癌の深達度診断の現状を検討した．

I　対象と方法

2001年から2003年までの3年間に国立がんセンター中央病院で外科的に胃切除あるいは内視鏡切除が施行された単発胃癌1846症例を対象に以下の検討を行った．対象の年齢中央値は64歳（26～93），性別は男/女；1301/545であった．検討1として，内視鏡による臨床診断（c）と切除後病理診断（p）より深達度診断正診率の検討を行った．内視鏡による臨床診断（c），特にMとSMとの診断は，2001年の小野らの報告[4)]に基づき，胃癌取扱い規約による肉眼型[9)]ごとに診断した．具体的には，I型は2cm以下ではM，2cmを超えかつ広基性や表面にくずれ・陥凹をともなう場合にSMと診断した（Figure 1a，b）．IIa型は基本的にMであるが，大小不同の結節が目立つ，中心陥凹がある，表面にびらん・発赤をともなう場合はSMとした（Figure 1c，d）．陥凹型では，著明な発赤，ひだ先端の融合，壁の厚み，陥凹内隆起，粘膜表面の無構造化，辺縁粘膜下腫瘍様隆起はSM（もしくはSM以深）を示唆する所見とした（Figure 1e，f）．また，陥凹型では

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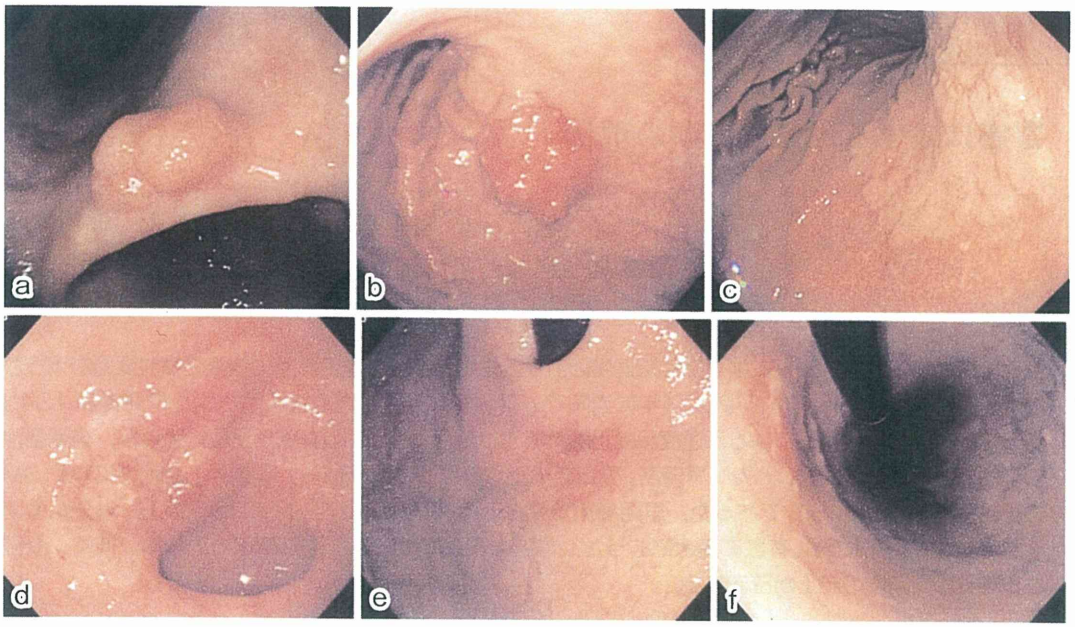

Figure 1. 通常内視鏡による深達度臨床診断 **a**：1.5cm 大のⅠ型病変で表面にくずれ・陥凹などを認めず，M と診断する． **b**：2.5cm 大，広基性のⅠ型病変で，SM と診断する． **c**：5cm 大のⅡa 型病変で表面に陥凹などを認めず，M と診断する． **d**：2.5cm 大の中心陥凹をともなう隆起性病変（Ⅱa＋Ⅱc 型）で SM と診断する． **e**：2cm 大の浅い陥凹性病変（Ⅱc 型）で，粘膜模様は保たれ，壁の厚みなどを認めず，M と診断する． **f**：2.5cm 大の陥凹性病変（Ⅱc 型）で，壁の厚みをともない SM と診断する．

大きさも深達度と相関している（2cm 以上では約半数で SM）ことを考慮した．また，実際の内視鏡検査は内視鏡経験 3 年以上の複数の内視鏡医によって行い，全対象症例の内視鏡による臨床診断（c）は，内視鏡部，放射線診断部，外科，病理部の合同によって術前に毎週開催される症例検討会により最終決定した．切除後病理診断（p）は，内視鏡切除の病理報告書，外科的胃切除の病理報告書よりデータを採取し，内視鏡切除後に追加外科的胃切除を施行した場合は最深の深達度とした．検討 2 として，早期胃癌における誤診例を肉眼型，UL 有無，部位，腫瘍径，組織型別に検討した．検討に際して，肉眼型はⅠ・Ⅱa 型，Ⅱa＋Ⅱc 型，Ⅱc・Ⅱb 型に，UL 有無は UL＋と UL－に，部位は U 領域，M 領域，L 領域に，腫瘍径は 10mm 以下，11～20mm，21mm 以上に，組織型は優勢な組織像に従い分化型，未分化型に大別し[9]，それぞれの因子における誤診率および浅読みあるいは深読みに関する内訳を検討した．

各因子別の誤診率は，χ^2検定を用い，$p<0.05$ を有意差ありと判定した．

Ⅱ 結 果

【検討 1】深達度診断の正診率

対象期間中の日常臨床において，内視鏡による臨床診断は，概ね cM，cSM，cMP-SS，cSE と診断されていた．SM の臨床診断（cSM）は cSM1 と cSM2 に亜分類されていなかった．早期癌と進行癌の鑑別では p 早期癌，p 進行癌の正診率はそれぞれ 95%，86% であった（Table 1）．

早期癌 1258 症例のうち pM は 836 症例，pSM は 422 症例であった．pM 836 症例の正診率は 85% で，14% が cSM に，1% が cMP 以上に深読みされていた．pSM の正診率は 46% で，42% は cM と浅読み，12% は cMP 以上に深読みされていた（Table 2）．

pSM 422 症例のうち，pSM1 は 155 症例，pSM2 は 267 症例であった．Table 3 に示すように pSM1 のうち cSM と臨床診断された症例は 30% で，

Table 1. 早期癌と進行癌の診断

		臨床診断	
		c 早期癌	c 進行癌
病理診断	p 早期癌	95% (1199/1258)	5% (59/1258)
	p 進行癌	14% (84/588)	86% (504/588)

Table 2. M と SM の診断

		臨床診断		
		cM	cSM	cMP
病理診断	pM	85% (714/836)	14% (112/836)	1% (10/836)
	pSM	42% (177/422)	46% (196/422)	12% (49/422)

Table 3. SM1 と SM2 の診断

		臨床診断		
		cM	cSM	cMP
病理診断	pSM1	65% (100/155)	30% (47/155)	5% (8/155)
	pSM2	29% (77/267)	56% (149/267)	15% (41/267)

65% は cM と診断されていた．pSM2 では，56% が cSM に臨床診断され，29% が cM と浅読み，15% が cMP 以上に深読みされていた．

【検討 2】早期胃癌における誤診例の検討

Table 4 に肉眼型，UL 有無，部位，腫瘍径，組織型別の早期胃癌誤診例を示している．肉眼型別の誤診率は II a+II c 型で 36% と他の I・II a 型，II c・II b 型に比し有意に高率であった ($p<0.05$)．I・II a 型では pSM を cM と浅読みした例が多く，II a+II c 型と II c・II b 型では浅読みと深読みともに分布していた．

UL の有無別には UL+で UL−に比し誤診率が 37% と有意に高率であった ($p<0.01$)．UL−では浅読みした例が多く，UL+では浅読みと深読みともに分布していた．

部位別には，U 領域で他の M 領域，L 領域より誤診率が高率であったが，有意差は認めなかった．また，U 領域，M 領域では浅読みした例が多く，L 領域では深読みした例が多かった．

腫瘍径別には，誤診率は 21mm 以上で 37% と他の 10mm 以下，11〜20mm に比し有意に高率であった ($p<0.01$)．また，10mm 以下，11〜20 mm では浅読みした例が多く，21mm 以上では深読みした例が多かった．

組織型別には，分化型 22% に比し未分化型で 42% と誤診率が有意に高率であった ($p<0.01$)．誤診例の内訳をみると分化型では浅読みした例が多く，未分化型では深読みした例が多かった．また，分化型のうち，中分化型管状腺癌 (34%：37/110, $p<0.01$) と乳頭腺癌 (42%：5/12, $p<0.05$) の誤診率は，高分化型管状腺癌 (20%：160/789) の誤診率に比し有意に高率であった．

III 考　察

近年，治療技術の向上にともなって，早期胃癌に対する縮小手術，内視鏡切除は広く普及してきているが，その治療方針決定には正確な深達度診断が要求される．誤診例のうち，深読みは，縮小手術や内視鏡切除で根治可能な病変を過剰に治療する原因となる．一方，術前に浅読みされ縮小手術や内視鏡切除が行われた場合，根治的治療とし

Table 4. 肉眼型，UL有無，部位，腫瘍径，組織型と誤診例

	誤診率			
	pSMをcMと浅読み	pSMをcMP以上と深読み	pMをcSM以上と深読み	計
肉眼型				
Ⅰ・Ⅱa（n = 236）	15%（35）	4%（9）	0.4%（1）	19%（45）
Ⅱa＋Ⅱc（n = 125）	20%（25）	12%（15）	4%（5）	36%（45）
Ⅱc・Ⅱb（n = 897）	13%（117）	3%（25）	13%（116）	29%（258）
ULの有無				
UL－（n = 762）	15%（112）	3%（26）	3%（26）	22%（164）
UL＋（n = 496）	13%（65）	5%（23）	19%（96）	37%（184）
部位				
U領域（n = 230）	23%（53）	4%（10）	5%（12）	33%（75）
M領域（n = 407）	16%（64）	1%（6）	7%（27）	24%（97）
L領域（n = 621）	10%（60）	5%（33）	13%（83）	28%（176）
腫瘍径				
10mm以下（n = 275）	6%（15）	0.4%（1）	1%（3）	7%（19）
11～20mm（n = 357）	19%（66）	0.8%（3）	8%（29）	28%（98）
21mm以上（n = 626）	15%（96）	7%（45）	14%（90）	37%（231）
組織型				
分化型（n = 911）	15%（137）	3%（24）	5%（41）	22%（202）
未分化型（n = 347）	12%（40）	7%（25）	23%（81）	42%（146）
計（n = 1258）	14%（177）	4%（49）	10%（122）	28%（348）

て不十分な治療につながる可能性がある．

定型手術あるいは縮小手術の選択において，深達度に関しては，T1（早期癌）あるいはT2以上（進行癌）の鑑別が問題となる[1]．今回の検討において，早期癌と進行癌の正診率は95%と86%であり，当院の1997年から2001年までの検討[4]の成績（95%と85%）と比し大きな向上はなかったが，臨床的に妥当な成績と考えられた．

内視鏡切除の適応決定には，MとSMとの鑑別が重要となる．今回の検討において，Mの正診率は85%と1997年から2001年までの検討[4]の成績（84%）とほぼ同様であったが，SMの正診率は46%で，1997年から2001年までの検討[4]の成績（66%）と比べ20%低下していた．そのうち，pSMをcMに浅読みしたのが42%，pSMをcMP以上に深読みしたのが12%と，1997年から2001年までの検討[4]の成績（20%と14%）に比し浅読みが高率であった．これは内視鏡切除が内視鏡的粘膜切除術（EMR）[10)~12)]から内視鏡的粘膜下層剥離術（ESD）[13)~16)]の時代へと移り変わり，正確な病理学診断が可能となり，pMをcSM以上と深読みすることによる過剰な治療（ESDで根治可能な病変を手術する）を防ぐため，ESDを診断的側面として利用しているためと思われる．つまり，当院では①生検で分化型，②cM，③UL－病変は腫瘍径に制限なし，UL＋病変は腫瘍径30mm以下をESD前の適応基準とし，ESD後にTable 5に示す治癒切除基準に基づき病理評価を行い，追加の外科的切除の必要性を判断している．ESD前の適応基準のうち，特に②のcMに関しては，pMをcSM以上と深読みすることにより過剰な治療となることを防ぐため，明らかなcSM所見のない場合はcMと判断し，診断的意義を含めたESDを行っているためと推測される．早期癌の誤診例の内訳において，pMをcSM以上と深読みした症例が，ESDの対象となり得る分化型において未分化型に比し少なかったことも上記を示唆していると考えられる．また，ESDの対象が多く含まれるUL－，小さな症例において深読みした症例が少なかったことも同

Table 5. ESD 治癒切除基準

1. 分化型腺癌
2. 脈管侵襲陰性
3. M 癌，UL −
or M 癌，UL +，腫瘍径 30mm 以下
or SM1 癌，腫瘍径 30mm 以下，浸潤部低分化型腺癌成分陰性
4. 水平断端陰性，垂直断端陰性

様に上記を示唆していると考えられる．実際に当院外科的胃切除例で，結果的に胃癌学会ガイドラインの EMR 適応基準内[1]であった症例の頻度は，EMR 時代には 3.8%（52/1369）であったのに対し，ESD 時代には 0.2%（2/954）に減少していた[17]．

以上のように，pM を cSM 以上と深読みすることによる過剰な治療を防ぐため，pSM を cM と浅読みした症例が増加していたと推測されるが，ESD 自体を診断過程の 1 つのモダリティーととらえると臨床的には許容されると考える．しかし，一方でそのような浅読み症例で ESD 後に仮に適切な追加外科的胃切除が行われない場合は，根治的治療として不十分な治療となる可能性がある．実際に当院で内視鏡切除後，結果的に非治癒切除であった 226 症例のうち，約 35% は追加外科的胃切除が行われていなかった[18]．その理由の半数は手術リスクや他臓器癌などであったが，残りの半数は患者選択であった[18]．ESD 後結果的に非治癒切除となった場合の外科的胃切除の必要性については，ESD 前より十分に説明しておく必要があると思われる．そのほか，ESD 偶発症の可能性，コストの観点からも本来的には内視鏡診断により M と SM の鑑別が行われ，適切な治療へと適応が決定されることがより望ましいことはいうまでもなく，超音波内視鏡，拡大内視鏡，特殊光観察も含め，今後の改善が必要である．

近年，外科手術例における検討[19]より，Table 5 に示すように分化型の SM1 癌も腫瘍径 3cm 以下，浸潤部低分化型腺癌成分なし，脈管侵襲なしであれば，リンパ節転移が 0%（95% 信頼区間：0〜2.5%）であり，内視鏡切除にて根治可能な病変として扱われつつある．しかし，SM1 に対する確立された内視鏡診断基準はないため，日常臨床においては cSM1 と積極的に臨床診断しているのではなく，cM あるいは cSM と臨床診断しているのが現状である．今回対象の pSM1，pSM2 別の検討（Table 3）によると，pSM1 病変は 65% において cM，30% で cSM と，pSM2 病変の cM が 29%，cSM が 56% であった成績とは異なり，臨床的には cM と判断されていることが多かった．しかし，pSM1 病変の cM が 65%，cSM が 30%（Table 3）は，pM 病変の cM が 85%，cSM が 14%（Table 2）の成績とも相違があり，pSM1 病変の臨床診断は，pM 病変と pSM2 病変の臨床診断の中間に位置していた．SM1 に対する内視鏡診断基準を持たない現状においても，結果的にこのように pM と pSM2 の中間に pSM1 が位置していたことは，SM1 の内視鏡診断基準を作成できる可能性があることを示唆している．拡大内視鏡や特殊光観察を含め，今後の検討に期待したい．

早期胃癌における誤診例の検討により，肉眼型，UL 有無，部位，腫瘍径，組織型ごとにそれぞれの因子ごとにその誤診率や浅読みが多い病変，深読みが多い病変の内訳が明らかになった．この点に関しても，拡大内視鏡や特殊光観察を含めた，さらなる検討が必要である．

結　語

内視鏡的診断学および機器の進歩した現時点においても，胃癌に対する深達度診断成績はいまだ十分とはいえず，その課題が浮き彫りとなった．通常内視鏡，超音波内視鏡に加えて，近年では有用性が期待されている拡大内視鏡や特殊光観察も含め，今後のさらなる検討が必要である．

文 献

1) 日本胃癌学会：胃癌治療ガイドライン，第2版，金原出版，東京，2004
2) 広門一孝，岡部治弥，吉田隆亮，他：胃癌深達度診断―主として内視鏡診断客観化の立場から．胃と腸 4；327–337：1969
3) 八尾恒良，藤原 侃：病理組織構築との対比よりみた早期胃癌診断の問題点―深達度診断を中心に．Gastroenterol Endosc 18；200–201：1976
4) 小野裕之，吉田茂昭：内視鏡像からみた深達度診断．胃と腸 36；334–340：2001
5) 八尾恒良，田邊 寛，長浜 孝，他：胃の陥凹型SM癌の病理組織構築と対比した内視鏡所見―pSM2癌診断のための観察方法と診断限界．胃と腸 43；1109–1125：2008
6) 長南明道，三島利之，安藤正夫，他：超音波内視鏡からみた深達度診断．胃と腸 36；341–350：2001
7) 丹羽康正，北畠秀介，宮原良二，他：拡大内視鏡による癌の深達度診断．胃と腸 42；747–751：2007
8) 加藤正之，仲吉 隆，斉藤彰一，他：狭帯域フィルター内視鏡（Narrow Band Imaging：NBI）システム併用拡大内視鏡観察による早期胃癌の深達度診断．Gastroenterological Endoscopy 46（Suppl）；664：2004
9) 日本胃癌学会：胃癌取扱い規約，第13版，金原出版，東京，1999
10) Tada M, Murakami A, Karita M, et al：Endoscopic resection of early gastric cancer. Endoscopy 25；445–450：1993
11) Inoue H, Takeshita K, Hori H, et al：Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. Gastrointest Endosc 39；58–62：1993
12) Tanabe S, Koizumi W, Kokutou M, et al：Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. Gastrointest Endosc 50；819–822：1999
13) Oyama T, Kikuchi Y：Aggressive endoscopic mucosal resection in the upper GI tract-Hook knife EMR method. Min Invas Ther & Allied Technol 11；291–295：2002
14) Yamamoto H, Kawata H, Sunada K, et al：Successful en-bloc resection of large superficial tumors in the stomach and colon using sodium hyaluronate and small-caliber-tip transparent hood. Endoscopy 35；690–694：2003
15) Yahagi N, Fujishiro M, Kakushima N, et al：Endoscopic submucosal dissection for early gastric cancer using the tip of an electrosurgical snare (thin type). Dig Endosc 16；34–38：2004
16) Oda I, Gotoda T, Hamanaka H, et al：Endoscopic submucosal dissection for early gastric cancer：Technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 17；54–58：2005
17) 小田一郎，後藤田卓志，濱中久尚，他：胃ESDのコツと治療成績，今後の可能性．消化器内視鏡 17；583–590：2005
18) Oda I, Gotoda T, Sasako M, et al：Treatment strategy after non-curative endoscopic resection of early gastric cancer. Br J Surg 95；1495–1500：2008
19) Gotoda T, Yanagisawa A, Sasako M, et al：Incidence of lymph node metastasis from early gastric cancer：estimation with a large number of cases at two large centers. Gastric Cancer 3；219–225：2000

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Endoscopic diagnosis of gastric cancer invasion depth

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Accurate endoscopic diagnosis of gastric cancer invasion depth is essential in making a proper treatment strategy decision. We investigated the accuracy of diagnostic depth invasion in 1846 gastric cancers resected by surgery or endoscopy from 2001 to 2003 at our hospital. Diagnostic accuracy was 95% for early cancer and 86% for advanced cancer; and 85% for mucosal cancer and 46% for submucosal cancer. The rate of diagnostic inaccuracy was significantly higher in IIa+IIc type than in other macroscopic types; and lesions with UL than without UL; lesions >20mm and those ≤20mm; as well as in undifferentiated type than in differentiated type, respectively. Endoscopic diagnosis of gastric cancer invasion depth was not always accurate and improved diagnosis for submucosal cancer in particular is necessary.

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Original article

Pilot study to assess the safety of local lidocaine injections during endoscopic submucosal dissection for early gastric cancer

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Abstract

Background. **In Japan, endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) is performed by endoscopists on patients under sedation. There is an increased risk of anesthesia-related complications due to the higher sedative doses required during lengthier ESDs, so we sought to determine whether a local pain control method could safely reduce such doses.**

Methods. **Twenty EGC patients enrolled in this study received local lidocaine injections during ESDs at our hospital (lidocaine group; LG). Electrocardiography, heart rate, oxygen saturation, and blood pressure were monitored during and after the ESDs, along with the doses of midazolam and pentazocine. Pain assessments were recorded for LG patients on the day of their ESDs and the following day.**

Results. **The mean volume of lidocaine injection solution was 55.4 ml and the mean dose of lidocaine was 236 mg (range, 100–300 mg). The mean size of the resected specimens was 39.3 mm and mean procedure time was 66.0 min. There were no lidocaine-related complications, and electrocardiography, heart rate, oxygen saturation and blood pressure measurements were normal. In comparison to 157 consecutive patients (control group; CG), who had similar characteristics and had undergone ESDs previously with submucosal injections of conventional normal saline solution, the mean ± SD pentazocine dose of 15.8 ± 10.3 mg in the LG was significantly lower ($P < 0.01$) than the dose of 23.1 ± 9.5 mg in the CG, and none of the LG patients complained of abdominal pain on the day of their ESDs, whereas such pain was reported by 17% (27/157) of the CG.**

Conclusion. **Local lidocaine injections into the submucosal layer were safe when administered during ESDs performed on EGC patients under sedation.**

Key words Lidocaine · Endoscopic submucosal dissection (ESD) · Early gastric cancer · Local anesthesia · Submucosal injection

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Introduction

Although endoscopic submucosal dissection (ESD) is less invasive for early gastric cancer (EGC) than gastrectomy, the classical open surgical procedure, some ESD patients suffer considerable postoperative pain. Localized pain both during and after ESD for large EGCs is probably caused by ulcer defects and/or electrical thermal burns extending from the submucosal (sm) layer to the serosa.

There is a problem not only with pain management but also with sedation management during the ESD procedure. In a previous report, 41% of ESDs took longer than 1 h [1]. As a result of such increased procedure times, therefore, higher doses of sedative drugs such as midazolam have become necessary, and endoscopists performing ESDs must be even more careful about the depth of patient sedation, because deep sedation can occur during endoscopic procedures [2]. Because there is an increased risk of anesthesia-related complications with the higher sedative drug doses required during lengthier ESDs, we decided to determine whether a local pain control method could safely reduce such doses.

By controlling localized pain during ESD, we thought that it might be possible to reduce the dose of the sedative drug administered during the actual procedure. In addition, administering local analgesia for pain during ESD would amount to providing preemptive analgesia for patient pain that might otherwise be experienced the day after the procedure [3].

Local anesthesia is commonly used in surgery, including laparoscopic surgery [4, 5], but there have been no previous reports on the use of lidocaine for local pain control either during or after ESD. This study intended to assess the safety of local lidocaine injections into the sm layer of EGC lesions in controlling localized pain both during and subsequent to ESD procedures performed on patients under sedation.

Patients and methods

Patients

A total of 20 EGC patients were enrolled in this study (lidocaine group; LG) between September 2005 and April 2007 at the National Cancer Center Hospital in Tokyo, Japan. These subjects were scheduled for gastric ESDs based on endoscopic mucosal resection (EMR) guideline criteria [6, 7] and had their given informed consent before undergoing the procedures. Patients with: (1) an allergy to lidocaine or other amide-type local anesthesia; (2) severe liver disease, heart disease, or renal dysfunction; (3) a gastric or duodenal ulcer; (4) atherosclerotic disease; (5) hyperthyroidism; or (6) an American Society of Anesthesiologists (ASA) physical status higher than class 2 were excluded from the study. This study was performed in accordance with the Helsinki Declaration as revised in 1989.

ESD procedures

ESDs were performed following a standard protocol, and procedure times were recorded for all LG patients. Lesion margins were delineated beforehand by using 0.2% indigo-carmine dye spraying. After the marking dots were made with a needle knife (KD-1L-1; Olympus Medical Systems, Tokyo, Japan), 0.5% lidocaine solution was injected into the sm layer to lift the lesion. A circumferential incision in the mucosa was then completed using the needle knife, an insulation-tipped knife (IT knife; KD-610L, Olympus) [7–10], and a high-frequency current electrical generator (ICC 200; ERBE, Tubingen, Germany) and, finally, the thickened sm layer was dissected using the same two endoscopic knives.

Injection solutions

As previously noted, we used 0.5% lidocaine solution consisting of 10 ml of Xylocaine Polyamp 1%, containing 100 mg of lidocaine hydrochloride (HCl; AstraZeneca, Osaka, Japan), 9.7 ml of normal saline, 0.2 ml of 0.4% indigo-carmine dye, and 0.1 ml of 0.1% epinephrine (Table 1) for the LG in this study. The maximum volume of 0.5% lidocaine solution per LG patient was 60 ml, which contained 300 mg of lidocaine HCl [11–13].

For the purpose of lifting an EGC lesion, the lidocaine injection solution was injected into the sm layer under and around the lesion, as determined by the endoscopist, using a 23-gauge needle injection catheter (NM-200L-0423; Olympus). Once the needle was inserted into the sm layer, the endoscopist's assistant would aspirate the syringe, particularly for those patients suffering from hypertension or diabetes mellitus, thereby creating negative pressure. If no blood reflex appeared, the assistant would begin injecting the solution and would stop when the lesion was sufficiently lifted and became slightly blue in color, with the total volume of the injection solution being recorded at that time.

Patient monitoring during and following ESD procedures

Electrocardiography, heart rate, oxygen saturation, and blood pressure were automatically monitored during and after each ESD; lidocaine-related complications were recorded, as were any complications resulting from the ESD itself, such as a perforation. In addition, the patient's white blood cell count and C-reactive protein level were checked on the first day following the ESD.

Sedation during ESDs

All ESDs on LG patients were performed following standard sedation procedures. Sedation was induced with 0.06 mg/kg of midazolam. Incremental 2-mg doses of midazolam were given if a patient demonstrated signs of discomfort, restlessness, or agitation, or responded to verbal commands. When additional midazolam was ineffective, 15 mg of pentazocine was infused as an analgesic agent. Each patient received oxygen by nasal cannula from the start of the ESD for a maximum period of 3 h after the procedure.

Table 1. Composition of injection solutions

	Lidocaine solution	Conventional solution
1% Lidocaine (ml) (Lidocaine 100 mg/10 ml)	10	0
Normal saline (ml)	9.7	19.7
0.4% Indigo-Carmine (ml)	0.2	0.2
0.1% Epinephrine (ml)	0.1	0.1
Lidocaine concentration (%)	0.5	0
Maximum lidocaine injection	300 mg/60 ml	

Table 2. Results

	Lidocaine group (LG)
Number	20
Sex	
Male	16
Female	4
Injection solution	
Mean injection volume (ml)	55.4
Lidocaine, mg	236
(range)	(100–300)
Laboratory data (day 1)	
Mean +/– SD white blood cell count	8700 ± 2100
C-Reactive protein (g/dl)	0.8 ± 0.7
Abnormality in monitoring	
Electrocardiography	0
Heart rate	0
Oxygen saturation	0
Blood pressure	0
Complications	
Lidocaine-related	
Intoxication	0
Convulsion	0
Arrhythmia	0
Respiratory	0
Perforation	0

In assessing the necessity for sedative drugs, we retrospectively compared the doses of midazolam and pentazocine during ESDs performed on the 20 LG patients with the doses used in 157 other consecutive EGC patients who had previously received conventional sm injections during ESDs, as a historical control group (control group; CG). The ESDs in the CG patients, whose clinical characteristics matched those of the LG patients, had been performed between January and August 2005, with the patients under sedation, as these CG patients also met the EMR guideline criteria. Their conventional sm injections consisted of a solution of 19.7 ml of normal saline, 0.2 ml of 0.4% indigo-carmine dye, and 0.1 ml of 0.1% epinephrine (Table 1).

Evaluation of abdominal pain after ESD

In evaluating the efficacy of pain control, a written questionnaire about the absence or presence of abdominal pain (no pain, mild pain without painkiller, or severe pain with painkiller) was distributed to each patient in the LG, to be completed on the day of the ESD after the procedure, and on the next day. We then proceeded to retrospectively determine the absence or presence of abdominal pain for each CG patient at the same two points in time as those in the LG, based on complete medical records. Finally we also identified those patients in each group who either received a painkiller (pain [+]) or did not receive a painkiller (pain [–]) after their procedures.

Statistical analysis

Values for all variables in this study are expressed as means ± SD. In comparing baseline characteristics between the two groups, we used a *t*-test for continuous variables, with the χ^2 or Fisher test for dichotomous variables. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) program (SPSS, version 8.0 for Windows; Tokyo, Japan). The P values were two-sided, and $P < 0.05$ determined statistical significance.

Results

The mean volume of lidocaine injection solution was 55.4 ml and the mean dose of lidocaine was 236 mg (range, 100–300 mg; Table 2). There were no electrocardiography, heart rate, oxygen saturation, or blood pressure abnormalities recorded, nor were there any episodes of lidocaine intoxication, including respiratory depression or hypotension, convulsion, or arrhythmia, such as cardiovascular collapse or bradycardia. The mean ± SD white blood cell counts and C-reactive protein values on the first post-procedure day were 8700 ± 2100 cells/mm^3 and 0.8 ± 0.7 g/dl, respectively.

Pain evaluation in comparison with historical control group

In our comparison of LG patients with the CG as a historical control, there were no significant differences

Table 3. Comparison with historical control

	Lidocaine group	Control group	*P* value
Number	20	157	
Age, years (mean ± SD)	69.4 ± 7.2	66.7 ± 9.4	NS
Resection size, mm (mean ± SD)	39.3 ± 11.6	36.3 ± 8.3	NS
Sedating agents			
Midazolam, mg (mean ± SD)	9.7 ± 3.2	10.3 ± 4.6	NS
Pentazocine, mg	15.8 ± 10.3	23.1 ± 9.5	<0.01
Procedure time (min)	66.0 ± 36.9	61.0 ± 30.7	NS
Post-ESD pain			
Day 0			
Pain (–)	20 (100%)	130 (83%)	
Pain (+)	0	27 (17%)	<0.05
Day 1			
Pain (–)	18 (90%)	95 (61%)	
Pain (+)	2 (10%)	62 (39%)	<0.05

NS, not significant

in clinicopathological characteristics between the two groups. The mean ± SD size of the resected specimens was 39.3 ± 11.6 mm in the LG and 36.3 ± 8.3 mm in the CG, while the mean ± SD ages were 69.4 ± 7.2 years and 66.7 ± 9.4 years, respectively (Table 3). The mean ± SD doses of midazolam were 9.7 ± 3.2 mg and 10.3 ± 4.6 mg in the LG and CG, respectively (difference not significant [NS]), but the mean ± SD dose of pentazocine in the LG was significantly lower than that in the CG, at 15.8 ± 10.3 mg and 23.1 ± 9.5 mg, respectively ($P < 0.01$).

All of the LG patients completed the questionnaires regarding the absence or presence of abdominal pain on the day of the ESD following the procedure, as well as the next day. None of the LG patients complained of abdominal pain immediately following their ESDs, whereas abdominal pain that required a painkiller occurred in 17% (27/157) of the CG patients ($P < 0.05$). On the day after their ESDs, 2 (10%) of the LG patients complained of abdominal pain requiring a painkiller, whereas abdominal pain that necessitated a painkiller occurred in 39% (62/157) of the CG patients ($P < 0.05$).

Discussion

Based on the results of this pilot study, local lidocaine injection into the sm layer was demonstrated to be safe during ESDs for EGC patients under sedation. The safety and efficacy of lidocaine as preemptive analgesia has already been assessed and proven in the surgical field, particularly with respect to laparoscopic surgery, and it is now commonly accepted that local anesthesia is effective during certain surgical procedures, and it is used accordingly [14–17]. Although lidocaine has generally been associated with a number of adverse reactions, such as respiratory depression, hypotension, convulsion, and arrhythmia, including cardiovascular collapse and bradycardia [18], there were no such complications observed in the present study. All the results related to complications, as well as the laboratory data, indicated that local lidocaine injection into the sm layer could be used safely during ESDs for EGCs performed under sedation.

ESD produces higher rates of en-bloc resections and tumor-free margins compared to conventional EMR. As a result, it has been proposed as the gold standard treatment for EGC, because it facilitates more accurate histological assessment and reduces the risk of tumor recurrence [19–21]. At the present time, the indications for ESD are in the process of being expanded; this will make it possible for even more EGC patients to be successfully treated without having to undergo open surgery.

ESD for large tumors is usually a prolonged procedure requiring higher doses of sedative and pain-control drugs such as midazolam and pentazocine, but there have been no published reports as yet addressing the problem of epigastric pain associated with ESDs. In our study, patient abdominal discomfort was considerably lower in the LG, most likely because of the immediate local anesthesic effect of lidocaine, as evidenced by the significantly lower mean total dose of pentazocine.

Preemptive analgesia is defined as preventing or reducing the memory of nociceptive stimuli in the central nervous system, utilizing analgesic methods performed prior to such nociceptive stimuli, with a resultant decrease in the need for postoperative analgesics. Recent research on postoperative pain control has led to the development of the concept of preemptive analgesia, in which pain management begins at the preoperative stage so as to decrease the severity of pain in the postoperative period, by applying analgesic methods

before the onset of nociceptive stimuli [13, 22–24]. Based on this conceptual approach, local anesthesia can also have a preemptive analgesic effect, so it is likely that in the LG patients in our study the lidocaine injections had elevated their pain thresholds after completion of their ESDs. This, in turn, resulted in these patients not complaining of abdominal pain on the day of their procedures, and having fewer pain-related comments and milder pain on the day after the procedure.

The mean dose of midazolam required in the LG was lower than that in the CG, although the difference was not statistically significant, but the mean dose of pentazocine in the LG was significantly lower than that in the CG. This suggests that local lidocaine injection could reduce the amount of pentazocine required by locally controlling a patient's pain perception, thus resulting in less patient movement and fewer delays in the ESD caused by such movement. Fewer delays and less time spent administering sedative and pain-control drugs during a lengthier ESD procedure, combined with an actual reduction in the doses of such drugs, could reduce the risk of respiratory and other drug-related complications caused by oversedation.

In our study, none of the LG patients reported any abdominal pain on the day of their ESDs, indicating the probable effectiveness of local lidocaine injections for pain control during and immediately after ESD. Given lidocaine's characteristic feature of controlling pain for a only a short period, its local injection into the sm layer appears to be an effective method for pain management during and immediately following ESD, but further investigation of other longer-acting local analgesics is recommended.

Our investigation was a small pilot study of a lidocaine-treated group that was retrospectively compared to a considerably larger historical control group. A randomized control study will be necessary in the future to reliably assess the effectiveness of the particular technique that we have described. While the assessment and measurement of pain are very important considerations for both patients and physicians, pain tolerance varies greatly among patients, so further investigation will be required in accordance with the basic philosophy of preemptive analgesia.

In conclusion, local lidocaine injections into the sm layer during ESDs in EGC patients under sedation are safe. This study indicated that such lidocaine injections have a beneficial effect on local pain control during ESDs and in the immediate post-procedure period.

References

1. Oda I, Gotoda T, Hamanaka H, Eguchi T, Saito Y, Matsuda T, et al. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. Dig Endosc 2005;17:54–8.
2. Patel S, Vargo JJ, Khandwala F, Lopez R, Trolli P, Dumot JA, et al. Deep sedation occurs frequently during elective endoscopy with meperidine and midazolam. Am J Gastroenterol 2005;100: 2689–95.
3. Karaaslan D, Sivaci RG, Akbulut G, Dilek ON. Preemptive analgesia in laparoscopic cholecystectomy: a randomized controlled study. Pain Pract 2006;6:237–41.
4. Goldstein A, Grimault P, Henique A, Keller M, Fortin A, Darai E. Preventing postoperative pain by local anesthetic instillation after laparoscopic gynecologic surgery: a placebo-controlled comparison of bupivacaine and ropivacaine. Anesth Analg 2000;91: 403–7.
5. Einarsson JI, Sun J, Orav J, Young AE. Local analgesia in laparoscopy: a randomized trial. Obstet Gynecol 2004;104:1335–9.
6. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma — 2nd English edition. Gastric Cancer 1998;1: 10–24.
7. Gotoda T, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. J Gastroenterol 2006;41:929–42.
8. Gotoda T, Kondo H, Ono H, Saito Y, Yamaguchi H, Saito D, et al. A new endoscopic mucosal resection (EMR) procedure using an insulation-tipped diathermic (IT) knife for rectal flat lesions. Gastrointest Endosc 1999;50:560–3.
9. Gotoda T. Endoscopic diagnosis and treatment for early gastric cancer. Cancer Review: Asia-Pacific 2004;2:17–37.
10. Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, et al. Endoscopic mucosal resection for treatment of early gastric cancer. Gut 2001;48:225–9.
11. Polk JW, Bailey AH. Topical anesthesia for endoscopy; evaluation of prilocaine (Citanest), a new local anesthetic. Dis. Chest 1967;51:293–7.
12. Mather LE, Tucker GT, Murphy TM, Stanton-Hicks MD, Bonica JJ. The effects of adding adrenaline to etidocaine and lignocaine in extradural anaesthesia. II: Pharmacokinetics. Br J Anaesth 1976;48:989–94.
13. Garwood S, Reeder M, Mackenzie IZ, Guillebaud J. Tubal surface lidocaine mediates pre-emptive analgesia in awake laparoscopic sterilization: a prospective, randomized clinical trial. Am J Obstet Gynecol 2002;186:383–8.
14. Smith G. Intraperitoneal administration of analgesia: is this practice of any utility? Br J Anaesth 2002;89:535–7.
15. Elhakim M, Elkott M, Ali NM, Tahoun HM. Intraperitoneal lidocaine for postoperative pain after laparoscopy. Acta Anaesthesiol Scand 2000;44:280–4.
16. Carbonell AM, Harold KL, Mahmutovic AJ, Hassan R, Matthews BD, Kercher KW, et al. Local injection for the treatment of suture site pain after laparoscopic ventral hernia repair. Am Surg 2003;69:688–91.
17. Zullo F, Pellicano M, Cappiello F, Zupi E, Marconi D, Nappi C. Pain control after microlaparoscopy. J Am Assoc Gynecol Laparosc 1998;5:161–3.
18. Sweetman SC, Blake PS, McGlashan JM, Neathercoat GC, Parsons AV. Lidocaine. In: Martindale: the complete drug reference. 35th ed. London/Chicago: Pharmaceutical Press; 2006. p. 1702–6.
19. Rembacken BJ, Gotoda T, Fujii T, Axon ATR. Endoscopic mucosal resection. Endoscopy 2001;33:709–18.
20. Soetikno RM, Gotoda T, Nakanishi Y, Soehendra N. Endoscopic mucosal resection. Gastrointest Endosc 2003;57:567–79.
21. Eguchi T, Gotoda T, Oda I, Hamanaka H, Hasuike N, Saito D. Is endoscopic one-piece mucosal resection essential for early gastric cancer? Dig Endosc 2003;15:113–6.
22. Kedek A, Derbent A, Uyar M, Bilgen C, Uyar M, Kirazli, et al. Pre-emptive effect of ibuprofen syrup and lidocaine infiltration on post-operative analgesia in children undergoing adenotonsillectomy. J Int Med Res 2005;33:188–95.

23. Homer JJ, Swallow J, Semple P. Audit of pain management at home following tonsillectomy in children. J Laryngol Otol 2001;115:205–8.
24. Wu CT, Yett CC, Yu JC, Lee MMS, Tao PL, Ho ST, et al. Preincisional epidural ketamine, morphine and bupivacaine combined with epidural and general anaesthesia provides pre-emptive analgesia for upper abdominal surgery. Acta Anasthesiol Scand 2000;44:63–8.

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Original article

Analysis of the color patterns of early gastric cancer using an autofluorescence imaging video endoscopy system

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Abstract

Background. **Using a novel autofluorescence imaging video endoscopy system (AFI), tumors in the esophagus and the colon appeared purple in a green background, but the color patterns of early gastric cancer (EGC) were found to vary. Factors associated with these patterns remain unknown. The aims of the present study were to classify the color patterns of EGCs and to investigate the correlation between the patterns and clinicopathological features.**

Methods. **A total of 107 EGCs that had been evaluated by AFI endoscopy, prior to endoscopic or surgical resection, were included. The color patterns of EGCs in AFI images and the association between tumor color and clinicopathological factors were evaluated. These factors included tumor morphology, location, size, background color, histological type, depth of invasion, lymphatic or vessel permeation, and ulceration.**

Results. **The color patterns of EGCs were classified into the following four groups: purple tumors in a green background (52%); green tumors with a purple margin in a green background (21%); green tumors in a purple background (17%); and purple tumors in a purple background (10%). Univariate analysis showed that macroscopic type, histological type, ulceration, and background AFI color were significantly associated with tumor color, whereas multivariate analysis revealed that macroscopic type was the only independent contributor to tumor color.**

Conclusion. **The present study has enabled a clearer understanding of the significance of tumor color in relation to the AFI imaging of EGCs. Recognition of the color patterns in AFI images should help in the diagnosis of EGCs.**

Key words Autofluorescence endoscopy · Early gastric cancer · Atrophic gastritis · Tumor color patterns

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Introduction

Early diagnosis and treatment can improve the prognosis of gastric cancers. Despite the progressive development of endoscopic modalities [1], the early detection of superficial neoplasms during routine esophagogastro-duodenoscopy (EGD) remains difficult because there are few morphological changes that differentiate malignant from nonmalignant lesions. Moreover, although treatments such as endoscopic mucosal resection [2] or endoscopic submucosal dissection (ESD) [3] are widely performed for the local resection of EGCs in Japan, accurate diagnosis of tumor extent is sometimes difficult because EGCs occasionally have flat or isochromatic tumor extensions. Chromoendoscopy can increase diagnostic yields in relation to the detection and delineation of flat tumors, by the enhancement of morphological features [4]. However, this modality is not widely used in clinical practice because its deployment can result in substantial prolongation of routine endoscopic examinations. Consequently, easier and more efficacious endoscopic modalities for diagnosing EGC are needed.

An autofluorescence imaging videoendoscopy (AFI) system produces real-time pseudocolor images from the computed detection of autofluorescence emitted by endogenous fluorophores (collagen, nicotinamide, adenine dinucleotide, flavin, and porphyrins) due to excitation by light. The system can identify lesions, including malignancies, by detecting differences in tissue fluorescence properties, and can thus reveal early-stage cancers that are not detectable by conventional white-light endoscopy [2].

In a previous study, when we investigated the diagnostic ability of an AFI system for early-stage cancers in the digestive tract, we discovered that tumors in the

esophagus and the colon appeared purple in a green background [5]. However, the color pattern of EGCs in the AFI images varied among tumors. The factors associated with these color variations were not investigated at that time [5]. The aims of the present study were to evaluate the endoscopic appearance of EGCs in AFI images and to investigate the clinicopathological factors associated with different tumor colors.

Patients and methods

Study sample

Since September 2003, the data of patients who have visited our endoscopy unit at Osaka Medical Center for Cancer and Cardiovascular Diseases, and who have undergone AFI, have been recorded consecutively in a database that is maintained prospectively and regularly updated. The input clinicopathological data were compiled according to the *Japanese classification of gastric carcinoma* protocol [6]. From this database, patients with EGC who presented between June 2004 and January 2006 were retrieved and their main tumors were included in the study. Patients with a history of gastrectomy were excluded. If a patient had multiple lesions, the largest one was selected for analysis. Approval from the Institutional Review Board at our medical center was obtained for this study.

A total of 127 consecutive patients with EGC who underwent AFI for pretherapeutic evaluation were identified from the database. Seven patients with a history of gastrectomy and one patient who transferred to another hospital were excluded. Among the 119 EGC lesions in the 119 patients involved in the study, AFI images were insufficient for evaluation in 10 lesions, and 2 lesions could not be classified. Therefore, a final total of 107 lesions were analyzed in this study.

Endoscopic procedure

The AFI system used in this study consisted of a light source (CLV-260SL; Olympus Medical Systems, Tokyo, Japan), a processor (CV-260SL; Olympus), a video monitor, and a video endoscope (EVIS-FQ260Z; Olympus) that was equipped with two charged-coupled devices (CCDs) that were available with autofluorescence and white-light modes. In the autofluorescence mode, blue excitation light (395–475 nm) to induce autofluorescence and green light (540–560 nm) to capture green reflection images were sequentially emitted from the light source through a rotation filter. A cut filter that was placed with the lens was used to permit only light with wavelengths between 490 and 625 nm to intensify the CCD for the AFI mode [7]. All examinations were performed by a single endoscopist (N.U.) who had 4 years' experience with autofluorescence endoscopy and 14 years' experience with conventional endoscopy.

Five minutes before the examination, patients ingested a mixture of a mucolytic agent, 20000 U pronase (Pronase MS; Kaken Pharmaceutical, Tokyo, Japan), a defoaming agent, 80 mg dimethylpolysiloxane syrup (Gascon Drops; Kissei Pharmaceutical, Matsumoto, Japan), and 1 g sodium bicarbonate diluted in 100 ml of tap water. After the application of topical anesthesia, the endoscope was gently inserted into the stomach. First, the color of the background mucosa and tumors were evaluated under AFI observation, and at least four AFI images of each tumor were taken from various viewing angles. After that, the tumors were thoroughly investigated by conventional white-light endoscopy. This was followed by 0.04% indigo carmine chromoendoscopy. Images obtained from the white-light endoscopy and chromoendoscopy were recorded. All images were digitally stored on an image server (Solemio Endo; Olympus).

Analysis of color patterns of EGC

Two endoscopists (M.K. and N.U.) reviewed the recorded AFI images, and the color patterns were classified into the following four types on the basis of tumor and background color: (1) a purple tumor on a green background (P/G type); (2) a green tumor on a green background (G/G type); (3) a green tumor on a purple background (G/P type); and (4) a purple tumor on a purple background (P/P type). When a tumor was located on a background color border, the color which surrounded more than half of the circumference of the tumor was designated as a background color.

The association between tumor color in the AFI images and a range of clinicopathological factors was investigated. These factors included: tumor size (≤2 cm or >2 cm), location (upper, middle, or lower third), macroscopic type (elevated or depressed), histological type (differentiated or undifferentiated), and depth of invasion (mucosal or submucosal); the presence or absence of vessel invasion; and background AFI color. For the factors that had a significant association on univariate analysis, multivariate analysis was performed to assess the strength and independence of the association. The macroscopic type of the tumor was determined under chromoendoscopic observation. Types 0I, 0IIa, and 0IIa+IIc were classified as elevated type. Types 0IIc and 0IIc+IIa were classified as depressed type. Type 0IIb (flat) and type 0III (excavated) were not found in the present study sample.

Statistical analysis

Stat View version 5.0 (SAS Institute, Cary, NC, USA) was used for data analysis. The χ^2 test and Fisher's exact probability test, when appropriate, were used for univariate analysis of the association between tumor AFI color and clinicopathological factors. Logistic regression analysis was performed for multivariate analysis. A P value of less than 0.05 was considered to be statistically significant.

Results

AFI color patterns of early gastric cancers

The characteristics of the EGCs are detailed in Table 1. The distribution of the color patterns of the EGCs observed in AFI images is shown in Fig. 1. The P/G- and G/P-type tumors could be easily identified due to clear differences in color (Figs. 2 and 3). For G/G type tumors, both the tumor and the background mucosa color were green. However, the tumors usually had a purple margin and could therefore be differentiated from the background mucosa (Fig. 4). For both G/P- and G/G-type tumors, purple nodules were sometimes seen inside the green tumors. P/P-type tumors exhibited a color similar to that of the background mucosa and could only be recognized by their shape.

Table 1. Clinical characteristics of the study subjects

Number of patients	119
Mean age (years)	70 (9)[a]
Sex (%)	Men: 77
	Women: 23
Treatment (%)	Endoscopy: 86
	Surgery: 14
Location (%)	U: 29
	M: 44
	L: 27
Mean tumor size (mm)	21.4 (15.0)
Macroscopic type (%)	0I: 3
	0IIa: 42
	0IIa+IIc: 3
	0IIc+IIa: 3
	0IIc: 49
Histological type (%)	Pap: 3
	Tub1: 73
	Tub2: 16
	Por: 4
	Sig: 4
Depth of invasion (%)	Mucosal: 79
	Submucosal: 21
Vessel invasion (%)	Absent: 91
	Present: 9
Ulceration (%)	Absent: 87
	Present: 13
Tumor AFI color (%)	Purple: 56
	Green: 34
	Not evaluable: 10
Background AFI color (%)	Purple: 28
	Green: 72

AFI, autofluorescence imaging videoendoscopy; U, upper third; M, middle third; L, lower third; Pap, papillary adenocarcinoma; Tub1, well-differentiated tubular adenocarcinoma; Tub2, moderately differentiated tubular adenocarcinoma; Por, poorly differentiated adenocarcinoma; Sig, signet-ring cell carcinoma

[a] Numbers in parentheses are SDs

Factors associated with AFI tumor color

Univariate analysis showed that macroscopic type, histological type, the presence of ulceration, and background AFI color were significantly associated with tumor color (Table 2). However, when multivariate analysis was used to further assess these factors, only macroscopic type was independently associated with tumor color (Table 3).

Discussion

In the present study, we found that EGCs in AFI images could be classified according to the tumor and background color, and that the factor most strongly associated with tumor color was the macroscopic type. In AFI images, almost all tumors with an elevated appearance (elevated type) were purple, while most of the tumors with a depressed appearance (depressed type) were green. Although endogenous fluorophores exist in both the mucosa and the submucosa, collagen in the submucosa discharges a strong green autofluorescence [8]. AFI images differ according to the autofluorescence properties of the tissue, and the intensity of light, in particular, affects the AFI color. Areas with strong autofluorescence appear bright green and areas with weak autofluorescence appear purple or greenish-

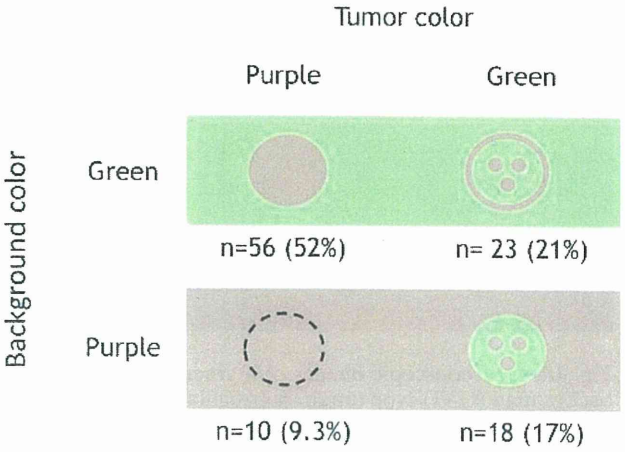

Fig. 1. Color patterns and prevalence of early gastric cancers in autofluorescence imaging videoendoscopy (AFI)

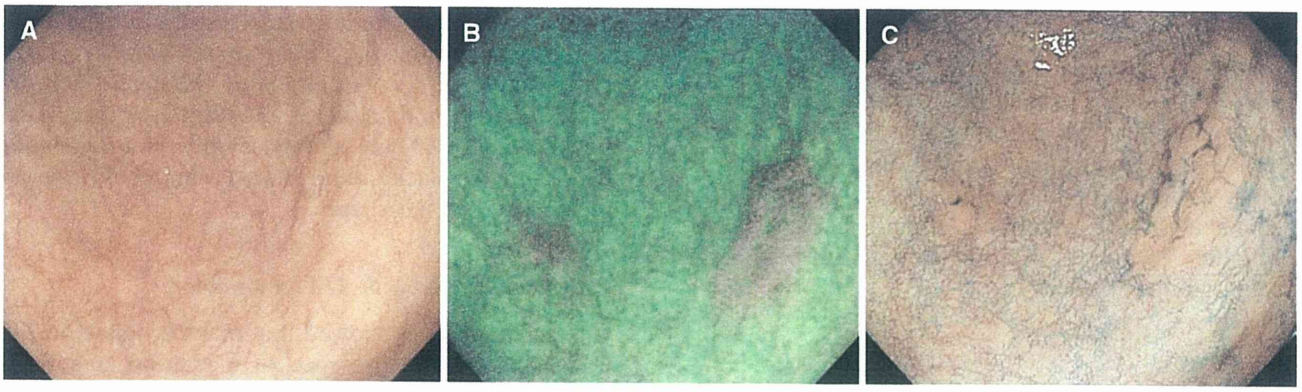

Fig. 2A–C. Endoscopic images of a purple tumor on a green background (P/G)-type tumors. **A** Conventional white-light image showing a slightly elevated tumor. However, its extent is unclear. **B** AFI image depicting the tumor as purple areas in a green background. **C** Image of two elevated tumors with contrasting topography visualized using chromoendoscopy with indigo carmine. The tumor was identified as a differentiated adenocarcinoma and removed endoscopically

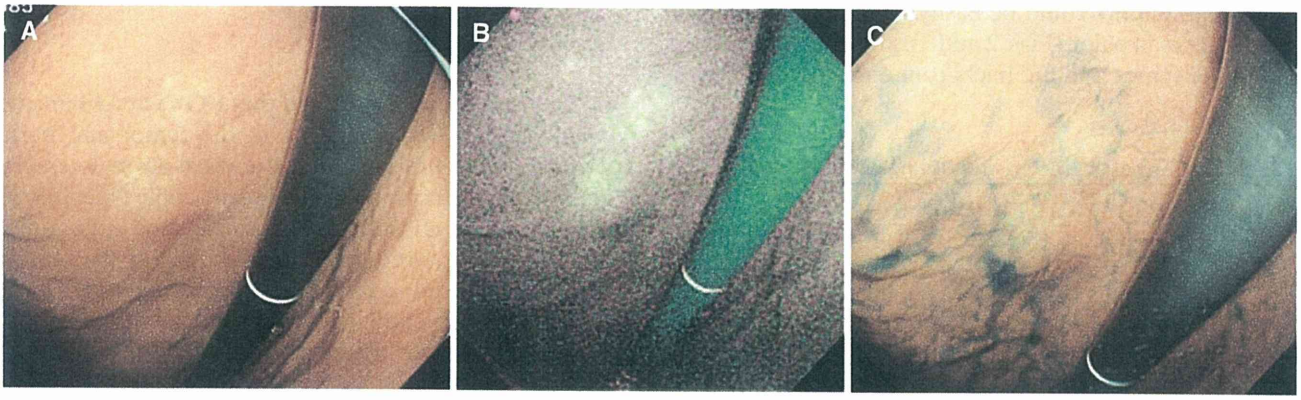

Fig. 3A–C. Endoscopic images of a green tumor on a purple background (G/P)-type tumor. **A** Image obtained using white-light endoscopy. Tumors appear as vague whitish areas. **B** AFI image showing the tumors as green areas in a purple background. **C** Image obtained using chromoendoscopy and showing a shallow depressed tumor located in the lower gastric body. An endoscopically resected specimen revealed undifferentiated adenocarcinoma confined to the mucosa

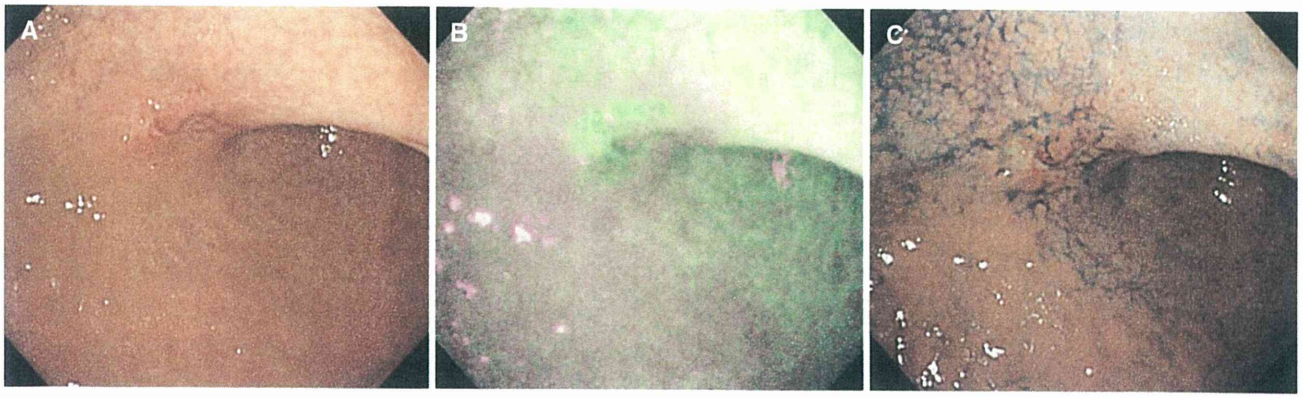

Fig. 4A–C. Endoscopic images of a green tumor on a green background (G/G)-type tumor. **A** Irregular reddish mucosa in the anterior wall of the lower gastric body. **B** AFI image. The tumor appears as a green area with a purple margin. A purple nodule is located in the center of the lesion. The tumor was located in an area adjacent to the purple-colored background mucosa, but was mostly surrounded by green background that indicated areas with chronic atrophic fundal gastritis. **C** Chromoendoscopic image revealing a depressed-type tumor with a central nodule. This tumor was identified histologically as a well-differentiated tubular adenocarcinoma

Table 2. Univariate analysis of factors associated with the color of lesions in AFI images

	No. of green tumors	No. of purple tumors	*P* value
Location			
Upper third	10	17	0.088
Middle third	24	26	
Lower third	7	23	
Size			
<20 mm	19	37	0.328
≥20 mm	22	29	
Macroscopic type			
Elevated	4	51	0.000
Depressed	37	15	
Histological type			
Differentiated	33	65	0.001
Undifferentiated	8	1	
Depth of invasion			
Mucosal	36	48	0.065
Submucosal	5	18	
Vessel invasion			
Absent	32	57	0.147
Present	9	9	
Ulceration			
Absent	32	62	0.018
Present	9	4	
Background color in AFI image			
Green	23	56	0.001
Purple	18	10	

Table 3. Multivariate analysis of factors associated with green tumor color in AFI images

	Odds ratio (95% CI)	*P* value
Macroscopic type		
Elevated	1	
Depressed	24.9 (7.12–87.3)	0.000
Background color		
Green	1	
Purple	2.56 (0.62–9.09)	0.144
Histological type		
Differentiated	1	
Undifferentiated	2.54 (0.26–2.43)	0.419
Ulceration		
Absent	1	
Present	1.00 (0.22–4.55)	0.999

CI, confidence interval

purple. Therefore, we speculate that the elevated-type tumor reduces autofluorescence from the submucosa and thus appears purple in AFI images, and that most of the depressed-type tumors do not affect autofluorescence intensity because they are thin and therefore appear green. In contrast to colon or esophageal tumors, most EGCs have been found to be of a depressed macroscopic type [9]. Therefore, their color would be green, which is uncommon in other regions of the digestive tract.

Histological type and background AFI color were two factors that were found to be significantly associated with tumor color on univariate analysis. However, this association did not prove to be the case on multivariate analysis. We believe that there are a number of reasons for this. With regard to morphology, although differentiated-type EGCs have the appearance of both elevated- and depressed-type tumors, undifferentiated-type EGCs are mostly of the depressed type [10]. As for the background color, the color of the gastric body mucosa is closely related to the grade of atrophic fundal gastritis [11]. The normal fundic mucosa looks purple, whereas abnormal mucosa with gastritis appears green. Our chromoendoscopic investigation showed that undifferentiated-type EGCs were likely to develop in the areas adjacent to, or sometimes inside, the normal fundic mucosa [12], which appears purple in AFI images. The undifferentiated EGCs are likely to be of the depressed type and, therefore, look green. By contrast, differentiated-type EGCs that are often of the elevated type frequently look purple and develop in areas with atrophic fundal gastritis or in the pyloric mucosa [12]. The pyloric mucosa appears green in AFI images.

In P/G- and G/P-type tumors, we found that the tumor profile was well delineated in the AFI images. We compared the diagnostic ability of AFI, white-light endoscopy, and chromoendoscopy for the extent of the EGC lesions. It was found that the accuracy of AFI was not as good as that of chromoendoscopy, but that it was better than white-light endoscopy [5]. Mucosal thickening or edema caused by ulceration and scarring looked purple, mimicking the tumor color. In some cases, this led to the misdiagnosis of tumor extent. Consequently, AFI may not be suitable for the evaluation of lesions with ulceration or scars. We believe, therefore, that chromoendoscopy is still necessary for pretreatment examination, although AFI would be a useful adjunct in routine EGD, because it does not require a troublesome dye spraying procedure and is less time-consuming.

Our study had several limitations. Patients with EGC who were referred for endoscopic resection accounted for more than 80% of our study subjects. Therefore, our study may not reflect the ECG profile in the actual population. In other words, the majority of the ECGs evaluated in our study were small, elevated, and differentiated types of mucosal EGCs. To correct for such bias in the analysis of factors associated with tumor color, we performed multivariate analysis. This revealed that the strongest independent correlation was between tumor color and macroscopic type.

The incidence of the P/P-type tumor was relatively low as compared with that of the other types of EGC tumor. For tumor types where the tumor color and background color differed, such as was the case with the

P/G and G/P types, the tumor was clearly delineated. However, for tumors that had a color similar to that of the background mucosa, it was sometimes difficult to identify them by their color. Although G/G-type tumors were frequently associated with a purple rim or central nodules, and were recognized by their color, P/P-type tumors were the most difficult to recognize. As a consequence, it is possible that some of these tumors were missed in the screening process using AFI.

In conclusion, the present study has enabled a clearer understanding of the significance of tumor color in relation to the AFI imaging of EGCs. The color pattern of the EGCs was classified into four types and their color appeared to be primarily associated with the macroscopic type of the tumor. Recognition of these color patterns should facilitate a clearer interpretation of endoscopic findings in relation to AFI diagnosis.

References

1. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon: November 30 to December 1, 2002. Gastrointest Endosc 2003;58:S3–43.
2. Uedo N, Iishi H, Tatsuta M, Ishihara R, Higashino K, Takeuchi Y, et al. Long term outcomes after endoscopic mucosal resection for early gastric cancer. Gastric Cancer 2006;9:88–92.
3. Takeuchi Y, Uedo N, Iishi H, Yamamoto S, Yamamoto S, Yamada T, et al. Endoscopic submucosal dissection with insulated-tip knife for large mucosal early gastric cancer: a feasibility study (with videos). Gastrointest Endosc 2007;66:186–93.
4. Ohkawa A, Miwa H, Namihisa A, Kobayashi O, Nakaniwa N, Ohkusa T, et al. Diagnostic performance of light-induced fluorescence endoscopy for gastric neoplasms. Endoscopy 2004;36: 515–21.
5. Uedo N, Iishi H, Tatsuta M, Yamada T, Ogiyama H, Imanaka K, et al. A novel videoendoscopy system by using autofluorescence and reflectance imaging for diagnosis of esophagogastric cancers. Gastrointest Endosc 2005;62:521–8.
6. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma, 2nd English edition. Gastric Cancer 1998;1: 10–24.
7. Uedo N, Iishi H, Ishinhara R, Higashino K, Takeuchi Y. Novel autofluorescence videoendoscopy imaging system for diagnosis of cancers in the digestive tract. Dig Endosc 2006;18(Suppl 1): S131–6.
8. Izuishi K, Tajiri H, Fujii T, Boku N, Ohtsu A, Ohnishi T, et al. The histological basis of detection of adenoma and cancer in the colon by autofluorescence endoscopic imaging. Endoscopy 1999; 31:511–6.
9. Everett SM, Axon AT. Early gastric cancer in Europe. Gut 1997; 41:142–50.
10. Fujishiro M, Oka M, Yahagi N, Nakamura M, Kakushima N, Kodashima S, et al. Correlation of serum pepsinogens and gross appearances combined with histology in early gastric cancer. J Exp Clin Cancer Res 2006;25:207–12.
11. Inoue T, Uedo N, Ishihara R, Kawaguchi T, Kawada N, Chatani R, et al. Autofluorescence imaging videoendoscopy in the diagnosis of chronic atrophic fundal gastritis. J Gastroenterol 2009. doi:10.1007/s00535-009-0150-7.
12. Tatsuta M, Okuda S, Taniguchi H, Tamura H. Gross and histological types of early gastric carcinomas in relation to the acid secreting area. Cancer 1979;43:317–21.