

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、11~20mm 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			計
	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	
肉眼型				
I・II a (n = 236)	15% (35)	4% (9)	0.4% (1)	19% (45)
II a + II c (n = 125)	20% (25)	12% (15)	4% (5)	36% (45)
II c・II b (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に示す治療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 治療切除基準

- | |
|---|
| 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、結果的に非治療切除であった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後結果的に非治療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ままでもなく、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まだ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。

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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.



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 \pm 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

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.

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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-carmin 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, Tübingen, 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-carmin 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 \pm SD white blood cell count	8700 \pm 2100
C-Reactive protein (g/dl)	0.8 \pm 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-carmin 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 \pm 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 \pm SD white blood cell counts and C-reactive protein values on the first post-procedure day were 8700 \pm 2100 cells/mm³ and 0.8 \pm 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 \pm SD)	69.4 \pm 7.2	66.7 \pm 9.4	NS
Resection size, mm (mean \pm SD)	39.3 \pm 11.6	36.3 \pm 8.3	NS
Sedating agents			
Midazolam, mg (mean \pm SD)	9.7 \pm 3.2	10.3 \pm 4.6	NS
Pentazocine, mg	15.8 \pm 10.3	23.1 \pm 9.5	<0.01
Procedure time (min)	66.0 \pm 36.9	61.0 \pm 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 \pm SD size of the resected specimens was 39.3 \pm 11.6 mm in the LG and 36.3 \pm 8.3 mm in the CG, while the mean \pm SD ages were 69.4 \pm 7.2 years and 66.7 \pm 9.4 years, respectively (Table 3). The mean \pm SD doses of midazolam were 9.7 \pm 3.2 mg and 10.3 \pm 4.6 mg in the LG and CG, respectively (difference not significant [NS]), but the mean \pm SD dose of pentazocine in the LG was significantly lower than that in the CG, at 15.8 \pm 10.3 mg and 23.1 \pm 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 anesthetic 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.

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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

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 esophago-gastro-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

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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, Matsuyama, 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.

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-

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
^aNumbers in parentheses are SDs

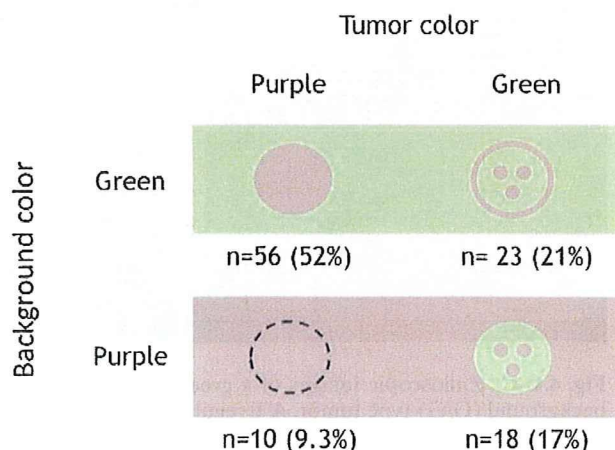


Fig. 1. Color patterns and prevalence of early gastric cancers in autofluorescence imaging videoendoscopy (AFI)

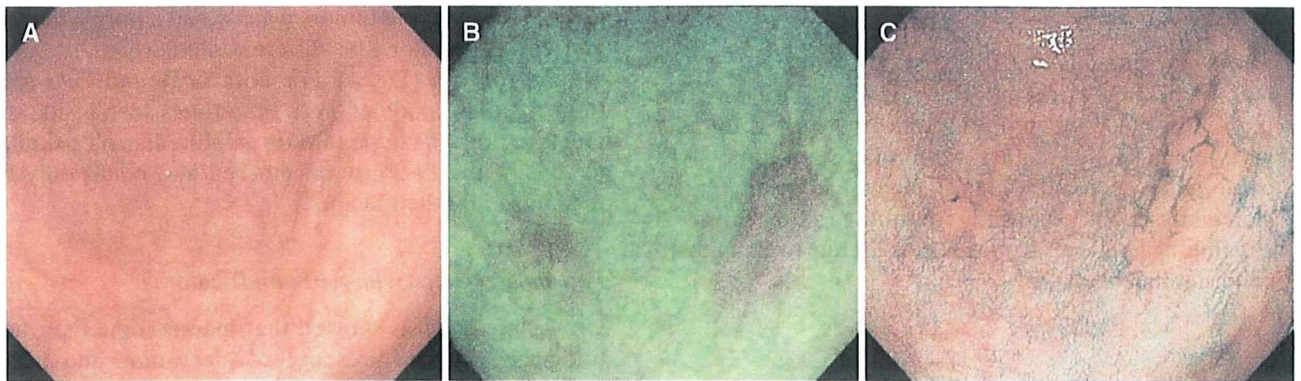


Fig. 2A–C. Endoscopic images of a purple tumor on a green background (P/G)-type tumors. **A** Conventional white-light image showing a slightly elevated tumor. However, its extent is unclear. **B** AFI image depicting the tumor as purple areas in a green background. **C** Image of two elevated tumors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

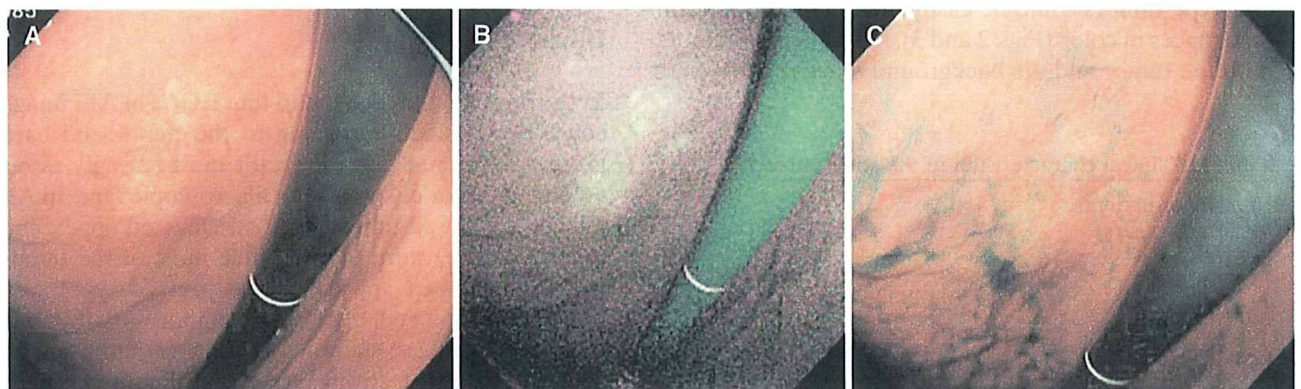


Fig. 3A–C. Endoscopic images of a green tumor on a purple background (G/P)-type tumor. **A** Image obtained using white-light endoscopy. Tumors appear as vague whitish areas. **B** AFI image showing the tumors as green areas in a purple background. **C** Image obtained using chromoendoscopy and showing 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	<i>P</i> 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)	<i>P</i> value
Macroscopic type		
Elevated	1	0.000
Depressed	24.9 (7.12–87.3)	
Background color		
Green	1	0.144
Purple	2.56 (0.62–9.09)	
Histological type		
Differentiated	1	0.419
Undifferentiated	2.54 (0.26–2.43)	
Ulceration		
Absent	1	0.999
Present	1.00 (0.22–4.55)	

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 EGC profile in the actual population. In other words, the majority of the EGCs 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 PP-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.

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Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve*

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Please see the accompany-
 ing editorial by J. J. G. H. M.
 Bergman on page 988.

Background and aim: Endoscopic submucosal dissection (ESD) is feasible as a treatment for early gastric cancer (EGC) when it is performed by an experienced endoscopist. We investigated whether it was feasible for novice endoscopists to perform ESD for EGC, and how difficult it was to learn the procedure.

Methods: This case series study was performed in a cancer referral center. Three resident endoscopists, who had already learned basic procedures, performed ESD under supervision for 30 consecutive lesions, and their procedures were analyzed. The procedure was divided for assessment into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut. An insulated-tip knife was used for mucosal incision and submucosal dissection. A total of 90 mucosal EGCs (≤ 2 cm) without ulcers or scars in 87 patients were included. Outcomes were: rates of complete resection, complications, and self-completion; operation time; learning curve; and reasons for change of supervisor as an indicator of difficulty.

Introduction

Endoscopic submucosal dissection (ESD) was developed as an advanced technique of endoscopic resection for early gastric cancer (EGC) [1,2]. It yields a higher complete resection rate than do conventional methods of endoscopic mucosal resection [3,4], and enables en bloc removal of previously unresectable lesions, such as large mucosal tumors [5] or tumors with scars [6]. Although

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Results: Among the 90 procedures, there was a good overall complete resection rate of 93%, with an acceptable complication rate of 4.4%; the complications were delayed hemorrhage in two patients, and perforations in another two patients that were repaired successfully by endoscopic clipping. The self-completion rate and operation time were significantly worse for submucosal dissection than for mucosal incision. Two of the three operators showed a flat learning curve for submucosal dissection. Difficulty with the procedure was related mainly to uncontrollable hemorrhage.

Conclusions: With appropriate supervision, gastric ESD by residents is feasible, with equivalent complete resection rates and acceptable complication rates compared with those of experienced endoscopists, although there was difficulty in achieving sufficient self-completion rates in submucosal dissection. Better control of bleeding during submucosal dissection may be a key to improving the procedure.

effective, the technique of ESD is complicated and requires considerable expertise and a prolonged operation time [7].

Previous studies have indicated that ESD for EGC is technically feasible when performed by experienced endoscopists [5]; however, its practicability for novice endoscopists and the difficulty of learning this advanced endoscopic procedure are still unclear. If we can identify the difficulties involved, we can establish a way to overcome these and reduce the time required to learn the ESD procedure.

The present study investigated the practicability of supervised residents performing ESD for EGC, and the difficulty of learning the procedure.

Endoscopist	A	B	C
Years since graduation	7	10	5
Number of EGDs performed	2000	3200	1500
Number of EMRs performed for EGC	22	18	10
Number of colonoscopies performed	800	800	250
Number of ERCPs performed	20	65	10

EGD, esophagogastroduodenoscopy; EMR, endoscopic mucosal resection; EGC, early gastric cancer; ERCP, endoscopic retrograde cholangiopancreatography.

Table 1 Profiles of three operating endoscopists.

Endoscopists	A	B	C	Total
Number of lesions	n = 30	n = 30	n = 30	n = 90
Median tumor size, mm (IQR)	15 (8.5)	15 (10.25)	13.5 (5.75)	15 (10)
Location of gastric lesions, n (%)				
Upper third	1 (3.3)	5 (17)	1 (3.3)	7 (7.8)
Middle third	13 (43)	11 (37)	14 (47)	38 (42)
Lower third	16 (53)	14 (47)	15 (50)	45 (90)
Type of tumors, n (%)				
Elevated	14 (47)	11 (37)	14 (47)	39 (43)
Depressed	16 (53)	19 (63)	16 (53)	51 (57)

IQR: interquartile range

Table 2 Characteristics of the lesions treated by ESD.

Table 3 Devices and settings of electrical surgical unit for each procedure.

Procedure	Device	ICC200	PSD60
Marking	Needle knife	Forced 20W	Forced 30W, effect 1
Mucosal incision	IT knife	Endo Cut 80 – 120W, effect 3	Endo Cut 120W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Submucosal dissection	IT knife	Forced coagulation 50W	Forced coagulation 55W, effect 2
	IT knife (fibrous submucosal tissue)	Endo Cut 80 – 120W, effect 3	Endo Cut 120W, effect 3 (Endo Cut impulse 3, Endo Cut speed 16)
Hemostasis	IT knife (small vessel)	Forced coagulation 50W	Forced coagulation 55W, effect 2
	Hemostatic forceps (large vessel)	Soft coagulation 80W	Soft coagulation 80W, effect 6

Patients and methods

This case series was performed in the endoscopic training and learning center of a tertiary cancer referral center.

Participants

A total of three endoscopists were involved in this study. They had experience of at least 1500 regular esophagogastroduodenoscopy procedures and more than 10 endoscopic mucosal resections by the strip biopsy or cap methods (Table 1). Before starting ESD, the operators participated in pre- and postoperative conferences with surgeons, gastroenterologists, radiologists, and pathologists to learn about the diagnosis and management of gastric cancer. They attended ESD procedures performed by senior doctors, as assistants, for at least 1 year, and then attended a lecture about ESD techniques, using a manual and videos, by an experienced endoscopist.

We investigated the records of 30 consecutive ESD procedures performed by each of the three endoscopists, between June 2003 and February 2005, in 87 patients (68 men, 19 women, mean age 67 years). The lesions were allocated to the three endoscopists irrespective of tumor location and size. Lesion characteristics are shown in Table 2. The indication for ESD in this study was differentiated-type mucosal EGC, without ulcers or scars, smaller than 2 cm, as described in the gastric cancer treat-

ment guidelines issued by the Japanese Gastric Cancer Association [8]. Before treatment, anticipated results, possible risks and complications, and alternative treatments including surgery and no treatment, were explained by the operator to all the patients, who gave their written informed consent. Patients who had severe organ failure or coagulopathy were excluded. The study protocol was approved by the institutional review board at our center.

ESD procedure

All procedures were performed with a videoendoscope (GIF-Q240; Olympus Medical Systems Co., Ltd., Tokyo, Japan) that was fitted with a disposable attachment (D-201-11804; Olympus) on its tip. A needle knife (KD-1L-1; Olympus), an insulated-tip (IT) knife (KD-610L; Olympus), and hemostatic forceps (Coagrasper, FD-410LR; Olympus) were used in the procedure. The Intelligent Cut and Coagulation 200 (ICC-200; Erbe Elektromedizin GmbH, Tübingen, Germany) or Power Supply Diathermy 60 (PSD-60; Olympus) was used as an electrical surgical unit; the output settings are summarized in Table 3. A solution of 2% epinephrine (Bosmin; Daiichi Pharmaceutical Co., Ltd., Tokyo, Japan) with 20% concentrated glycerin-fructose (Glyceol; Chugai Pharmaceutical Co., Ltd., Tokyo, Japan) was used for submucosal injection.

With the patient under sedation, the ESD procedure was performed as follows [6]. **Marking for removal:** The endoscope was inserted into the stomach, and the extent of the tumor was estimated under chromoendoscopic observation to determine the resection area. Marking dots were drawn circumferentially 3 mm from the tumor boundary by a needle knife. **Mucosal incision:** The epinephrine and glycerol solution was injected into the submucosa just outside the marking dots to elevate the lesion. The procedure was performed with a downward view in the antrum and a retroflex view in the corpus. A precut hole to insert the tip of the IT knife was made outside the region to be resected with the needle knife. The hole was made at the distal side of the lesion in an endoscopic view, and it needed to be sufficiently deep to reach the submucosa. The tip of the IT knife was inserted fully into the submucosa through the precut hole, and the proximal mucosa was cut continuously outside the marking dots using an Endo Cut mode. During mucosal incision, the ceramic tip was in contact with the gastric wall and was pulled with some tension. **Submucosal dissection:** Submucosal dissection was started after completion of the circumferential mucosal cut. The epinephrine and glycerol solution was injected into the submucosa to obtain sufficient mucosal elevation. The IT knife was moved laterally, with the tip continuously touching the gastric wall. Lateral movement was achieved by torquing the scope rather than by using the scope angle. Submucosal dissection was performed with the IT knife using the coagulation mode, or the Endo Cut mode if the submucosa was fibrous. **Hemostasis:** When hemorrhage was noted from small vessels, the bleeding point was coagulated with the blade of the IT knife, using forced coagulation. When hemorrhage from larger vessels was observed, the bleeding point was stopped with the hemostatic forceps using the soft coagulation mode. **Retrieval of the specimen and prevention of delayed hemorrhage:** After removal of the mucosal area, it was retrieved by grasping forceps (FG-47L-1; Olympus). The ulcer base was washed out repeatedly and any adherent clots or suspicious

protrusions were coagulated by the hemostatic forceps to avoid delayed hemorrhage. Resected specimens were sent to the department of pathology for histological assessment of completeness of resection and curability.

Assistant policy

The entire procedures were performed under the supervision of an experienced endoscopist (N.U.). The supervisor was changed under the following circumstances: (1) overtime: when time for each mucosal incision and submucosal dissection exceeded 1 hour; (2) inability to achieve hemostasis: when spurting hemorrhage could not be stopped; (3) perforation; and (4) inability to continue the procedure: when the procedure could not be continued for reasons other than inability to achieve hemostasis, or perforation. If an operator changed supervisor, the procedure was regarded as not "self-completed."

All procedures were recorded digitally on video and all events relating to the procedure were recorded on dedicated operation records.

Measured outcome parameters

Complete resection and complication rates were evaluated for assessment of feasibility. Self-completion rate, operation time, learning curve, and reasons for incompleteness were analyzed to elucidate procedural difficulties. For assessment the ESD procedure was divided into (i) mucosal incision and (ii) submucosal dissection by completion of the circumferential mucosal cut.

Complete resection was defined as en bloc resection without cancer involvement to the lateral and vertical margin of the resected specimen, as shown by histology. Complications included delayed hemorrhage and perforation, which were classified as grade 3 or 4 according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 3.0 [9]. Operation time was measured from the start of the mucosal incision until the end of tumor removal. "Self-completion" referred to a

Endoscopist	A	B	C	Total	P-value*
Complete resection, n (%)	28 (93)	28 (93)	28 (93)	84 (93)	
Complication, n (%)					
Delayed hemorrhage	1 (3.3)	1 (3.3)		2 (6.7)	
Perforation	1 (3.3)	1 (3.3)		2 (6.7)	
Self-completion, n (%)					
Mucosal incision	30 (100)	20 (67)	27 (90)	77 (86)	0.000
Submucosal dissection	23 (77)	15 (50)	16 (53)	54 (60)	
Median procedure time, minutes (IQR)					
Mucosal incision	19 (13)	23 (19)	33 (26)	23 (20)	0.000
Submucosal dissection	26 (33)	34 (28)	57 (59)	39 (38)	

*P-value for total mean procedure time and total self-completion rate of mucosal incision vs. submucosal dissection.

Procedure	A	B	C	Total (%)
Mucosal incision				
Overtime			2	2 (2)
Inability to achieve hemostasis		1	1	2 (2)
Perforation		1		1 (1)
Inability to continue procedure		8		8 (9)
Submucosal dissection				
Overtime	2	2	6	10 (11)
Inability to achieve hemostasis	1	2	2	5 (6)
Perforation	1			1 (1)
Inability to continue procedure	3	11	6	20 (22)

Table 4 Evaluated parameters for feasibility of ESD.

Table 5 Reasons for change of supervisor.