電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

質問３．
内視鏡切除後に上部内視鏡検査を受けられていない理由は何ですか？○をつけて下さい。

１．転居し、かかりつけの病院に行けなくなった。

２．大きな病気になった。

３．忙しかった。

４．その他　　[　　]

質問４．
ヘリコバクター・ピロリ菌について、○をつけて下さい。

１．感染歴あり　　→　付問４．へ

２．感染歴なし　　→　質問５．へ

３．不明（検査未施行）　→　質問５．へ

付問４．　　除菌治療の有無について、○をつけて下さい。

１．除菌施行　→　付問５．へ

２．除菌未施行　→　質問５．へ

付問５．　　A. 除菌治療開始日は？　　平成　　年　　月　　日頃

B. 除菌治療の成否について、○をつけて下さい。

１．除菌成功

２．除菌失敗

３．不明（判定未施行）

質問５．
内視鏡切除を行った後に、新たな大きな病気にかかりましたか？（風邪などの軽い病気は除きます。）○をつけて下さい。

４．はい　　→　付問６．へ

５．いいえ　　→　質問６．へ

付問６．　新たな大きな病気について、すべて記入して下さい。
（記入しきれない場合、裏面にご記入下さい。）

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

A. いつ頃からですか？　　平成　　年　　月　　頃

B. 病名は　＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. その病気でかかっている（かかっていた）病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

質問６．
アンケート記入は、ご本人が行いましたか？代理の方が行いましたか？○をつけて下さい。

１．ご本人

２．代理の方　→　付問７．へ

付問７．　残念ながら患者さんがお亡くなりになったために、代理の方が記入された場合、下記にお答えください。

A. いつ亡くなられましたか？　平成　年　月　日

B. その原因の病名は（もし、おわかりになればご記入下さい）

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

C. お亡くなりになった病院はどちらですか？
わかる範囲でお答え下さい。

＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿病院

住所＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

電話番号＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿

担当医＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿＿先生

以上

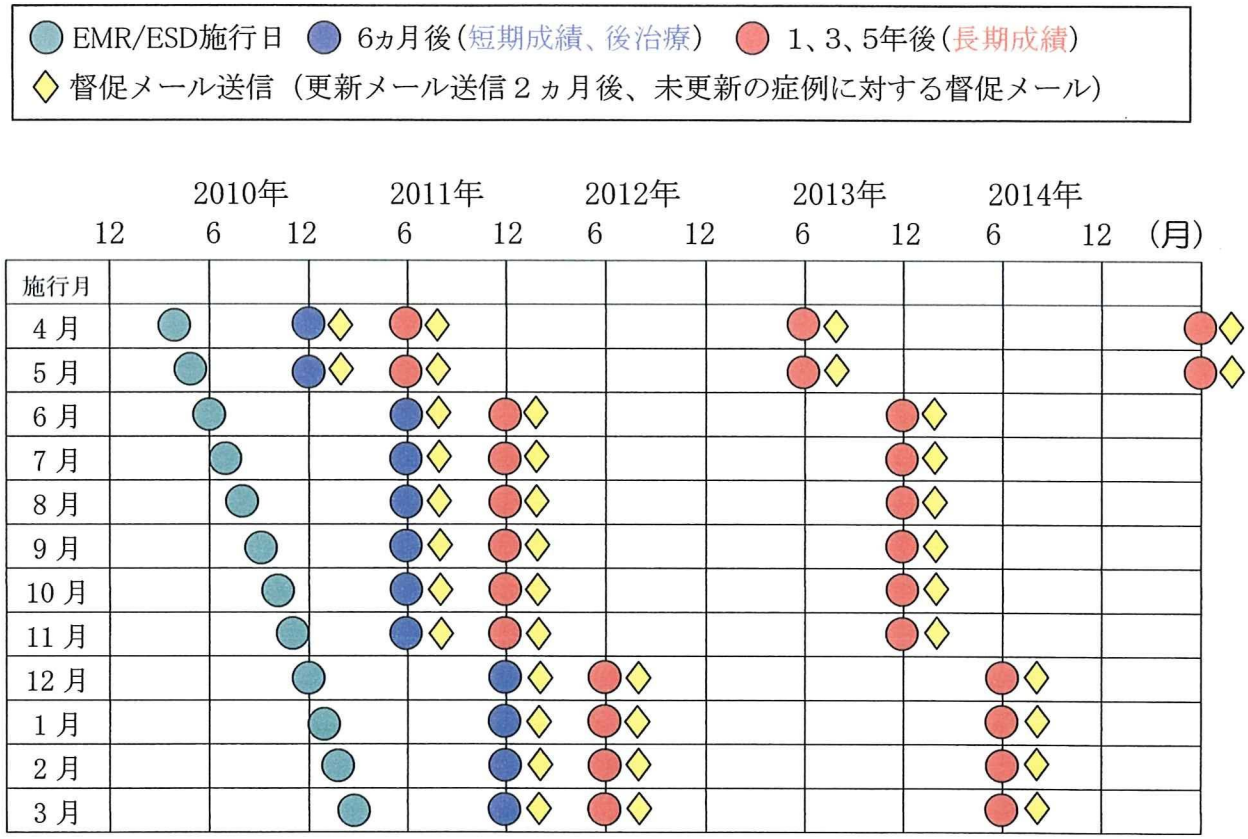
ご協力いただき、有り難うございました。

（資料5）：「自動Eメール送信機能」のシェーマ

内視鏡切除施行より 6 ヶ月後の C. 短期成績、D. 後治療の更新登録、1、3、5 年後の E. 長期成績の更新登録時期を１ヶ月以上経過して更新登録されていない症例について、年 2 回（6 月、12 月）各登録施設における登録代表者および当該登録担当医師に対し、更新登録を促すＥメールを送信する。

さらに、Ｅメール送信して２ヶ月経過しても未更新の症例に対し、再度督促Ｅメールを送信する。

これらの機能は、サーバ上で自動的・定期的に実行される。



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Original article

Endoscopic resection of early gastric cancer treated by guideline and expanded National Cancer Centre criteria

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Background: Criteria for endoscopic resection in patients with early gastric cancer (EGC) have been expanded recently by the National Cancer Centre (NCC). This study compared long-term outcomes in patients with EGC who underwent endoscopic treatment according to guideline criteria with those treated according to expanded criteria.

Methods: Baseline and outcome data from patients undergoing curative endoscopic resection for EGC between January 1999 and December 2005 were collected from electronic medical records. Survival time hazard ratios and 95 per cent confidence intervals were calculated using the Cox proportional hazards model.

Results: Of 1485 patients who had a curative resection, 635 (42·8 per cent) underwent resection according to traditional criteria and 625 (42·1 per cent) according to expanded criteria. There was no significant difference in overall survival between the groups.

Conclusion: Patients who have treatment following the expanded criteria have similar long-term survival and outcomes to those treated according to guideline criteria.

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Introduction

In Japan, endoscopic mucosal resection (EMR) has been the treatment of choice for small early gastric cancer (EGC) for the past two decades[1,2]. Owing to the technical limitations of EMR, traditional indications for endoscopic resection of EGC according to the Gastric Cancer Treatment Guidelines of the Japanese Gastric Cancer Association (JGCA) were restricted to resection of small intramucosal EGCs (smaller than 20 mm) with intestinal-type histology and no ulceration.

The low risk of lymph node involvement in EGC confined to the superficial layers of the submucosa indicated that cure can be achieved by local resection, even of lesions larger than 20 mm, as long as the lesion is removed *en bloc*[3]. Endoscopic submucosal dissection (ESD) has become established as a technique that allows *en bloc* resection regardless of size. Revised criteria were proposed by the National Cancer Centre (NCC) in Tokyo (from January 1999) to expand the indications for endoscopic treatment and avoid unnecessary radical surgery, which until recently was the 'gold standard' for larger lesions[4,5].

This study compared the long-term outcome of patients with EGC who underwent endoscopic treatment based on either guideline of JGCA criteria or expanded NCC criteria.

Methods

Consecutive patients who had endoscopic resection for EGC between January 1999 and December 2005 were studied. Informed consent was obtained from all patients in accordance with the institutional protocol. The procedure was carried out under conscious sedation using a combination of midazolam and pentazocine. Patients who were assessed histologically as having had a non-curative resection owing to positive lateral margins and/or deep submucosal invasion, regardless of positive vertical margins and/or lymphatic–vascular infiltration and/or diffuse-type histology, and those who had undergone endoscopic

resection as a palliative treatment for advanced cancer were excluded.

Curability was based on the histological criteria for curative endoscopic resection (*Table 1*) according to the Japanese Classification of Gastric Carcinoma[6]. Pathological assessment of the resected specimen included: size, location, macroscopic appearance, presence of ulceration, histological type, depth of invasion, lymphatic and vascular involvement, and resection margin status. Tumours smaller than 20 mm without ulceration were included in the JGCA criteria group and those larger than 20 mm in the NCC expanded criteria group. Patients with multiple EGCs were analysed as a separate group.

Baseline and outcome data were collected from electronic medical records. Incomplete and missing data were retrieved from different sources such as telephone contact with patients, family and referring physicians, and checked with statistical data kept by the local government registry.

All patients with curative resection who met JGCA criteria were followed up by annual upper gastrointestinal surveillance endoscopy to identify local recurrence and/or metachronous gastric cancer. Patients who met NCC criteria were additionally followed by thoracic and abdominal computed tomography and/or endoscopic ultrasonography every 6 months. Patients were followed from the date of first treatment until 31 July 2007.

Statistical analysis

Survival time was calculated as the interval between the date of the first treatment and the date of death or the last date confirmed as alive for survivors. Survival curves were calculated using the Kaplan–Meier method. To compare overall survival by treatment method, a Cox proportional hazards model was used to estimate hazard ratios and 95 per cent confidence intervals (c.i.). Age, sex and past history of cancer were included as co-variables in the multivariable analyses. All P values reported are two sided and $P < 0{\cdot}050$ was considered statistically significant.

Table 1 Histological criteria for curative endoscopic resection

Factors for no risk of lymph node metastasis
Intestinal-type histology
No lymphatic or vascular infiltration
Intramucosal cancer regardless of tumour size without ulcer finding or intramucosal cancer less than 30 mm in size with ulcer finding or minute submucosal invasive cancer (sm1) less than 30 mm in size
Factors for resection margin
Tumour-free horizontal margin
Tumour-free vertical margin

Statistical analyses were performed with SAS® software version 9.1 (SAS Institute, Cary, North Carolina, USA).

Results

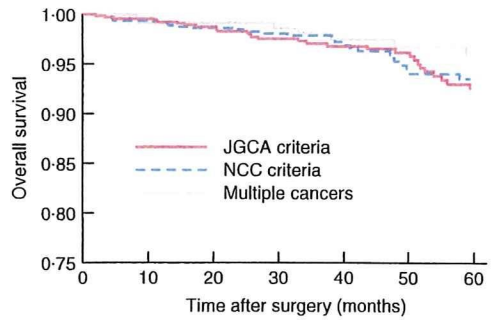
Some 1786 lesions were resected curatively among 1485 patients; 635 patients (42·8 per cent) were treated according to the guideline of JGCA criteria and 625 (42·1 per cent) in accordance with the expanded NCC criteria; 225 patients (15·2 per cent) had multiple EGCs with both criteria. Baseline characteristics by treatment allocation are shown in *Table 2*.

Follow-up was complete for all 1485 patients, with a median observation period of 44·1 months. During follow-up, 77 patients died (5·2 per cent). Only one patient treated according to JGCA criteria died from metachronous invasive gastric cancer, which was detected 5 years later. Locally recurrent gastric cancer was found in another patient who underwent piecemeal endoscopic resection. This patient underwent ESD for local recurrence 18 months after the first endoscopic resection and was alive with no evidence of recurrence after 57 months. There was

Table 2 Baseline patient characteristics by treatment group

	JGCA criteria ($n = 635$)	NCC criteria ($n = 625$)	Multiple cancers ($n = 225$)
Mean age (years)	66·4	66·5	68·6
Men	479 (75·4)	505 (80·8)	180 (80·0)
Past history of cancer	154 (24·3)	87 (13·9)	95 (42·2)
Mean tumour size (mm)	10·8	23·8	12·4

JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre.



No. at risk							
JGCA criteria	635	631	584	455	346	264	186
NCC criteria	625	621	559	433	314	242	156
Multiple cancers	225	223	210	180	156	126	89

Fig. 1 Survival by treatment group. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre

Table 3 Hazard ratio for all-cause mortality according to treatment group

	No. of deaths	5-year survival rate (%)	Hazard ratio	
			Crude	Adjusted*
JGCA criteria	36	92·4	1·00	1·00
NCC expanded criteria	31	93·4	0·93 (0·57, 1·50)	1·10 (0·67, 1·81)
Multiple cancers	10	95·6	0·63 (0·31, 1·26)	0·46 (0·23, 0·94)

Values in parentheses are 95 per cent confidence intervals. JGCA, Japanese Gastric Cancer Association; NCC, National Cancer Centre. *Multivariable Cox proportional hazards model, adjusted for age, sex and past history of cancer.

no significant difference in the rate of local and/or systemic recurrence between the JGCA and the NCCH groups.

Survival curves are shown in *Fig. 1*. The 5-year survival rate was 92·4 per cent in the JGCA group, 93·4 per cent in the NCCH group and 95·6 per cent among those with multiple cancers. There was no significant difference in overall survival (*Table 3*). In multivariable analysis, the hazard ratio for survival of patients in the NCC group compared with those in the JGCA group was 1·10 (95 per cent c.i. 0·67 to 1·81).

Discussion

Radical surgery with complete removal of first- and second-tier lymph nodes is accepted as a standard treatment for patients with EGC. A 5-year survival rate of around 90 per cent has been achieved in oriental and Western patients[7–9]. In patients with cancer limited to the mucosa, the incidence of lymph node metastasis is less than 3 per cent. This risk increases to 20 per cent when the cancer invades the submucosa[10].

Radical surgery may not be not the optimal treatment approach in all patients with EGC because it carries a significant risk of morbidity and mortality, and is associated with a significant reduction in quality of life[11–13]. Patients with no risk of lymph node metastasis can be treated safely by endoscopic resection[14].

Accepted indications for EMR of ECG have been (1) well differentiated elevated cancers less than 2 cm in diameter and (2) small (maximum 1 cm) depressed lesions without ulceration. These indications were established because of the technical limitations of EMR. In larger lesions, EMR has a high risk of recurrence as a result of incomplete resection when piecemeal EMR is used for larger lesions[15]. Specimens obtained by piecemeal EMR are difficult to analyse and there is a high risk of inadequate histological staging[16]. From a histological point of view, *en bloc* removal should be considered essential for endoscopic resection of larger lesions to ensure accurate histological staging. The treatment strategy for EGC has been revolutionized recently by the ESD procedure. This method is superior to other endoscopic techniques used for EGC as it makes *en bloc* resection possible, allowing precise histological staging and minimizing recurrence risk compared with standard EMR techniques[17].

Kojima and colleagues[18] have reviewed the outcomes of EMR from 12 major institutions in Japan. Long-term outcomes after EMR for small differentiated mucosal EGC less than 2 cm in diameter have been reported to be comparable to those following gastrectomy[19], but the long-term outcome of endoscopic resection of large EGCs has not been reported.

The present study has demonstrated that there is no difference in 5-year survival and local and/or systemic recurrence rates between patients treated according to JGCA or NCC criteria. The hazard ratio for overall survival showed no significant difference between the two groups.

Final staging can be carried out accurately only by formal histological analysis, especially with regard to potential lymphovascular infiltration. Therefore, *en bloc* resection is a prerequisite for accurate staging and prediction of a patient's risk of lymph node metastasis.

Expanded NCC criteria for patients with EGC are safe and practicable. As a result of the ability to achieve *en bloc* resection by ESD, more patients may benefit from endoscopic resection, further reducing the need for radical surgery.

Acknowledgements

The authors declare no conflict of interest.

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ORIGINAL ARTICLE—ALIMENTARY TRACT

Safe and effective sedation in endoscopic submucosal dissection for early gastric cancer: a randomized comparison between propofol continuous infusion and intermittent midazolam injection

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Abstract
Purpose Endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) generally takes longer to perform than conventional endoscopy and usually requires moderate/deep sedation with close surveillance for patient safety. The aim of this study was to compare the safety profiles and recovery scores propofol continuous infusion and intermittent midazolam (MDZ) injection as sedation for ESD.
Methods Sixty EGC patients scheduled for ESDs between August and November 2008 were included in this prospective study and randomly divided into a propofol (P-group, 28 patients) and an MDZ (M-group, 32 patients) group using an odd–even system. The P-group received a 0.8 mg/kg induction dose and a 3 mg/kg/h maintenance dose of 1% propofol using an infusion pump. All patients received 15 mg pentazocine at the start of the ESD and at 60-min intervals thereafter. We recorded and analyzed blood pressure, oxygen saturation and heart rate during and following the procedure and evaluated post-anesthetic recovery scores (PARS) and subsequent alertness scores.
Results The propofol maintenance and total dose amounts were (mean ± standard deviation) 3.7 ± 0.6 mg/kg/h and 395 ± 202 mg, respectively. The mean total dose of MDZ was 10.3 ± 4.5 mg. There were no cases of de-saturation <90% or hypotension <80 mmHg in either group. Alertness scores 15 and 60 min after the procedures were significantly higher in the P-group (4.9/4.9) than in the M-group (4.6/4.5; $p < 0.05$). The mean PARS 15 and 30 min after the ESDs were significantly higher in the P-group (9.6/9.9) than in the M-group (8.6/9.2; $p < 0.01$).
Conclusion Based on our results, the ESDs for EGC performed under sedation using propofol continuous infusion were as safe as those performed using intermittent MDZ injection. Propofol-treated patients had a quicker recovery profile than those treated with MDZ. We therefore recommend the use of continuous propofol sedation for ESD, but sedation guidelines for the use of propofol are necessary.

Keywords Endoscopic submucosal dissection · Midazolam · Propofol · Sedation

Introduction

Endoscopic submucosal dissection (ESD) reduces the risk of local recurrence following treatment for early gastric cancer (EGC) even when large and/or ulcerated lesions are involved because ESD has a higher en-bloc resection rate with a more accurate histological assessment. ESD generally takes longer than conventional endoscopic mucosal resection (EMR), and multiple doses of medications are usually required to achieve an adequate level of sedation and analgesia [1]. However, the most effective and safest sedation agent for ESD and the method by which to deliver this to the patient have not yet been clearly established.

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A lengthy and potentially uncomfortable endoscopic procedure like ESD usually requires at least moderate (conscious) sedation using a method that maintains a stable sedation level while also avoiding related complications. In addition, the guidelines from the American Society of Anesthesiology (ASA) for sedation by non-anesthesiologists recommends an accurate titration of sedation at a conscious level for patients undergoing upper endoscopy [2]. Sedation through the intermittent intravenous administration of benzodiazepine combined with an opioid often results in variable outcomes due to difficulty in maintaining stable levels of sedation [3]. The titration of such medications requires meticulous attention in adjusting the dose to be appropriate for the patient based on age, gender and medical background. Consequently, over-sedation can frequently occur in such cases [4].

Propofol is a short-acting sedative with a rapid recovery profile, and its use is associated with a number of additional advantages, including the relative ease to safely maintain a proper sedation level and a good amnesic effect. These advantages have resulted in an increased use of propofol worldwide for standard endoscopy procedures [5–7]. A study comparing patient satisfaction in terms of sedation with propofol, benzodiazepine and other agents found that patients were more satisfied with propofol [8]. A number of other studies comparing propofol with conventional sedation for gastroscopy and colonoscopy have demonstrated the benefit of propofol over such conventional sedation [9–15]. A few reports have focused on the administration of propofol for lengthy procedures, such as endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS) [16–18] but, to the best of our knowledge, there have been no studies that have compared propofol with the benzodiazepine midazolam (MDZ) as sedation for gastric ESD. The aim of this study was, therefore, to compare the safety profiles and recovery scores between propofol and midazolam (MDZ) as sedation for gastric ESD.

Methods

Patients

At total of 60 EGC patients scheduled for ESD at the National Cancer Center Hospital (NCCH) in Tokyo from August to November 2008 were included in this prospective study. Patients were excluded if they were <18 years of age and/or pregnant, had a history of sulfite, egg, soybean or propofol allergy or did not provide informed consent. Patients with an ASA physical status class of >2, severe liver disorders (liver transaminase >100 IU/l; liver cirrhosis, due to high alcohol intake), severe renal failure (serum creatinine level >2 mg/dl), severe heart disease (New York Heart Association Class III or IV), mental incompetence, systolic blood pressure (SBP) <80 mmHg and baseline oxygen saturation measured by pulse oximetry to be <90% in room air or <95% with oxygen at 2 l/min administered by nasal cannula due to smoking were also excluded. The participating patients were then divided randomly using an odd–even system based on randomly assigned hospital registration numbers into a propofol group (P-group, $n = 28$) and an MDZ group (M-group, $n = 32$). Informed consent was obtained as per institutional protocol from all patients who underwent endoscopic treatment. This study was performed in accordance with the 1989 revised Helsinki Declaration.

Personnel

All medications were administered by physicians from the endoscopy division who did not participate in the actual endoscopic procedures. At least one physician with advanced training in basic and cardiac life support was present during every ESD. An anesthesiologist was also on standby in case of an emergency, and resuscitation equipment was always present in the endoscopic room.

Medication

Local pharyngeal anesthesia was performed using an 8% topical lidocaine spray prior to intravenous administration of the sedation drugs. Patients in the P-group received a slow initial intravenous bolus of 0.8 mg/kg of 1% propofol emulsion (10 mg/ml) (Maruishi Pharmaceutical, Osaka, Japan). Additional intravenous boluses of 0.5 mg/kg of 1% propofol emulsion were administered until the patient fell asleep, as determined by a Ramsay 5–6 sedation score. After each bolus infusion, a waiting period of usually 30–60 s was observed to assess the complete effect of the drug before making a decision on the next bolus. An automatic infusion pump (Terufusion syringe pump TE-332S; Terumo Corp, Tokyo, Japan) was used to maintain a continuous infusion of 3 mg/kg/h in order to maintain the same level of sedation. The objective was to maintain a patient sedation level between moderate (patient responds properly to verbal commands either alone or accompanied by light tactile stimulation) and deep (patient cannot be easily aroused, but may respond properly to repeated or painful stimulation) [19]. When a particular patient's body mass index (BMI) was >25, sedation doses were calculated based on body weight for a BMI of 25. For elderly patients >70 years of age, the initial bolus was reduced to 0.5 mg/kg. When a patient seemed to be in discomfort or exhibited restlessness following verbal stimulation, an

additional 10 mg of propofol was given as a bolus injection and the infusion rate was increased by 1 mg/kg/h. Conversely, if an adverse event occurred, such as hypotension with SBP <80 mmHg or oxygen de-saturation <90%, the maintenance dose was reduced by 1 mg/kg/h. Propofol infusion was continued until removal of the endoscope.

In the M-group, an initial bolus of 3 mg of MDZ (Astellas Pharma, Tokyo, Japan) for patients with a body weight <50 kg and 4 mg for patients weighing ≥50 kg were administered through an intravenous catheter. Incremental doses (2 mg) were given if the patient showed signs of discomfort, restlessness or agitation or if he/she responded to verbal commands. A reversal agent of MDZ (flumazenil) was administered, if needed, according to NCCH conscious-sedation guidelines.

All patients received 15 mg of pentazocine at the start of the ESD and at 60-min intervals thereafter during the procedures as an analgesic agent. The depth of sedation was monitored by a physician not directly involved in the procedure using a 4-point somnolence score (4, fully alert; 3, awake but lethargic; 2, spontaneous eye closure, but responsive to voice; 1, responds only to shaking or prodding). Endoscopic intubation commenced once the patient reached a sedation level of 2.

Monitoring

Patients received supplemental oxygen (2 l/min) by nasal cannula in the endoscopic room as their vital signs and oxygen saturation were continuously monitored and recorded every 5–10 min using standard three-lead electrocardiogram, pulse oximetry and automatic blood pressure equipment. Chest excursion and respiratory rates were monitored visually, and consciousness levels were assessed initially after the induction of sedation and then at 20-min intervals thereafter during the procedure using the Ramsay sedation score.

Management of adverse events

Adverse events were considered to be a decline in oxygen saturation to <90% and SBP <80 mmHg. If a patient developed oxygen de-saturation <90% for longer than 10 s, supplemental oxygen was used to immediately increase the oxygen flow until the saturation level was >95%. If supplemental oxygen did not improve the patient's oxygenation condition within 3 min, the ESD procedure and sedation were interrupted to secure the airway and administer a reversal agent as necessary. In cases of hypotension, we immediately increased the rate of the intravenous drip (for example, from 100 to 150 ml/h), decreased the propofol infusion rate by 1 mg/kg/h or administered 8 mg of ephedrine by bolus intravenous injection.

Recovery phase

Vital signs (blood pressure, oxygen saturation and heart rate) were recorded immediately upon conclusion of the ESD and then at 15, 30, 60 and 120 min post-ESD. Patients were discharged from the endoscopy room 15 min after the procedure, provided their vital signs were stable. All 15-, 30- and 60-min post-procedure, post-anesthetic recovery scores (PARS; modified Aldrete score [20, 21], where 0 = under anesthesia and 10 = fully awake) were determined by the same physician. All alertness scores (five questions involving name, age, date, day and a simple calculation) were determined at 15, 30 and 60 min after each procedure by the same physician.

Statistical analysis

Category outcomes were analyzed using the Fisher exact test or the chi-square test where appropriate. Continuous outcomes were analyzed with the independent sample *t* test for normally distributed data and the Wilcoxon rank sum test for nonparametric data.

Results

Sixty patients were enrolled in this prospective study, with 28 patients randomly assigned to the P-group and 32 to the M-group. Patient characteristics for both groups are shown in Table 1. An en-bloc resection was achieved in all 60 cases, and there were no statistically significant differences between the two groups in terms of age, gender, BMI, alcohol consumption and tobacco use, tumor size, procedure time and sedation time.

All sedation inductions went smoothly with no complications. The total amount of propofol and MDZ administered to P-group and M-group patients was 395 ± 202 mg (mean ± standard deviation, SD) and 10.3 ± 4.5 mg, respectively (Table 2). The mean maintenance dose of propofol was 3.7 ± 0.6 mg/kg/h. The mean total amount of pentazocine given to the P-group and M-group patients was 25.7 ± 9.9 and 21.8 ± 7.2 mg, respectively. There were no instances of uncontrolled agitation or movement that required a delay during any of the ESD procedures and none of the patients had to be restrained while under sedation.

There were no cases of de-saturation <90% during or after any ESD and no need for intubation or ventilation. Similarly, there were no cases of transient hypotension (SBP < 80 mmHg) in either group. As a result, there were

no statistical differences between the two groups in terms of the above-mentioned parameters.

The recovery phase results are shown in Table 3. The alertness scores recorded at 15 min post-ESD were 4.9 ± 0.4 for the P-group and 4.6 ± 0.8 for the M-group ($p < 0.05$); those recorded 60 min post-ESD were 4.9 ± 0.4 and 4.5 ± 1.2, respectively ($p < 0.05$). The P-group registered higher scores for each measurement. There was a significant difference between the two groups in terms of both the PARS recorded 15 min post-ESD (P-group/M-group 9.6 ± 0.8/8.6 ± 1.5; $p < 0.01$) and 30 min post-ESD (P-group/M-group: 9.9 ± 0.3/9.2 ± 1.2; $p < 0.01$). In addition, the alertness scores recorded 30 min post-ESD and PARS recorded 60 min post-ESD were the highest in the P-group (5.0 ± 0.2 and 10.0 ± 0, respectively), although these scores were not significantly different from those of the M-group (4.8 ± 0.6 and 9.7 ± 1.0, respectively).

Table 1 Patient characteristics

Patient characteristics	Propofol	Midazolam	*p* value
Number of cases	28	32	
Mean age, years (range)	68 (49–87)	70 (48–86)	NS
Gender, male/female	22/6	27/5	NS
Body mass index	22.9 ± 3.5	22.8 ± 3.4	NS
Habit, cases (*n*)			
Alcohol			
Daily drinker	10	12	NS
Social drinker	5	9	
No drinker	13	11	
Tobacco			
Smoker	6	2	NS
Quit smoking			
40 PY<	8	7	
<40 PY	6	9	
No smoker	8	14	
Mean tumor size (mm)	19.1 ± 11.0	17.3 ± 11.4	NS
Mean procedure time (min)	85.4 ± 50.8	89.6 ± 53.1	NS
Mean sedation time (min)	117.6 ± 58.0	119.7 ± 60.7	NS

Where appropriate, values are given as the mean ± standard deviation (SD)

NS Not significant, *PY* pack-year

Discussion

To the best of our knowledge, this study is the first randomized prospective trial to compare continuous infusion propofol sedation with intermittent MDZ injection sedation administered by a gastroenterologist during an ESD for EGC. The results indicate that propofol was both effective and safe as sedation for ESD, a finding that had previously been established for other lengthy endoscopic procedures, such as ERCP and EUS [22–25]. Our study demonstrates that the induction and maintenance of sedation can be safely performed using propofol, resulting in faster overall patient recovery. The Ramsay score of 6 that we obtained in most cases also indicates the doses of propofol which we calculated were appropriate for achieving moderate to deep patient sedation.

Propofol is a short-acting sedative, with a plasma half-life of only 1–4 min, and the onset of sedation after propofol injection occurs between 30 and 60 s. Consequently, it is difficult to maintain a stable level of sedation using an intermittent propofol injection because of the rapid recovery profile. On the other hand, continuous infusion of a long-acting sedative, such as the benzodiazepines, for longer endoscopic procedures is associated not only with difficulty in maintaining stable levels of sedation but also with an increased risk of complications. Therefore, intermittent benzodiazepine injection or continuous propofol injection has recently been used for lengthy endoscopic procedures, such as ESD, requiring at least moderate sedation. However, many reports have suggested that sedation using intermittent intravenous administration of benzodiazepines often results in variable outcomes due to this known difficulty in maintaining stable levels of sedation. We therefore compared propofol continuous infusion with intermittent MDZ injection as sedation for ESD.

Propofol has been increasingly used in recent years in many gastrointestinal endoscopic procedures [26–28]. Previous studies have demonstrated that, in comparison to conventional sedation, propofol sedation is associated with a lower risk of complications and serious adverse events during standard endoscopy [29]. However, published data on the safety of propofol for prolonged procedures, such as ESD, are limited. The most important finding of such

Table 2 Use of sedation agents during the endoscopic submucosal dissection procedures

Parameters of sedation agents	Propofol ($n = 28$)	Midazolam ($n = 32$)	*p* value
Mean total dose (mg)	395 ± 202	10.3 ± 4.5	
Maintenance rate, mg/kg/h (range)	3.7 ± 0.6 (3.0–5.0)		
Mean pentazocine dose (mg)	25.7 ± 9.9	21.8 ± 7.2	NS
Adverse events (*n*)			NS
Desaturation	0	0	
Hypotension	0	0	

Where appropriate, values are given as the mean ± SD

Table 3 Scores measured during the recovery phase

Scores[a]	Propofol	Midazolam	*p* value
Alertness score			
15	4.9 ± 0.4	4.6 ± 0.8	<0.05
30	5.0 ± 0.2	4.8 ± 0.6	NS
60	4.9 ± 0.4	4.5 ± 1.2	<0.05
Post-anesthetic recovery score (PARS)			
PARS 15	9.6 ± 0.8	8.6 ± 1.5	<0.01
PARS 30	9.9 ± 0.3	9.2 ± 1.2	<0.01
PARS 60	10.0 ± 0	9.7 ± 1.0	NS

Values are given as the mean ± SD

[a] 15, 30, 60 indicate the score measured at 15, 30 and 60 min following the end of the endoscopic submucosal dissection procedure

studies to date has been that recovery from the amnesic stage of propofol sedation is faster than that with standard sedatives, such as the benzodiazepines. As is the case with therapeutic ERCP, ESD generally takes considerably more time than conventional EMR, emphasizing a common need for a sedation agent and a delivery method that better meet the technical difficulty of the procedure.

In ESD, one of risk factors for sedation complications is that the gastroenterologist, as operator, not only performs the ESD but is also responsible for the sedation throughout the procedure. Furthermore, unstable sedation using the intermittent administration of sedative drugs causes interruptions and subsequent lengthening of the procedure. Therefore, the rapid onset and offset of sedation associated with the continuous infusion of propofol decreases the risk of sedation complications and reduces the burden on the gastroenterologist during the procedure.

Our goal was to maintain a moderate to deep sedation level. Quite often, the onset of sedation is deeper at first, with the sedative effect moderating over time. Given the narrow therapeutic window of propofol, fluctuations in the depth of sedation may occur, but none of the ESD procedures in this study had to be delayed or terminated, suggesting that our dose calculations and sedation procedures were effective in addition to being safe.

In our series of patients, the alertness score and PARS 15 were evaluated in the endoscopy room 15 min after the gastric ESD has been completed; the patients were then moved from the endoscopy room to the hospital ward. The PARS were higher in the P-group than in the M-group; this was particularly evident for the initial recovery measurement conducted 15 min post- ESD. In other words, propofol patients recovered from the sedation sooner than MDZ patients, thereby making it easier to evaluate immediate endoscopic- and sedation-related complications. An immediate recovery from sedation is an important feature of safe sedation management in ESD. The higher alertness and PAR scores in the propofol group recorded 15 min post-ESD suggest the possibility of safer management of ESD using propofol. These higher scores in association with no severe adverse events during and after the ESD also suggest that propofol continuous infusion is not only associated with improved safety but also with improved usefulness.

In both groups, alertness scores recorded 30 min post-ESD were higher than those recorded 60 min post- ESD. A possible explanation for result is that the residual invasive stress of the endoscopic procedure resulted in higher alertness scores 30 min after the procedure and that the relaxation associated with the return to the ward resulted in lower alertness scores at 60 min. In other words, patients may be in a relatively over-sedated state at 15 and 60 min post-ESD. However, the alertness scores of the propofol group were significantly higher than those of the MDZ group at 15 and 60 min post-ESD, suggesting that propofol provides safer sedation management in the post-ESD period, a time when patients are liable to be over-sedated.

Propofol is a short-acting agent, although episodes of prolonged apnea requiring intubations have occurred on rare occasions. With no reversal agent available for propofol, the presence of well-trained personnel in airway rescue is mandatory, although none of the patients in either group in this study required endotracheal intubation. The results of our study confirmed that the recovery profiles for the P-group were better than those of the M-group at every measurement point.

No severe adverse events, such as de-saturation or hypotension, resulted from the administration of propofol by a non-anesthesiologist physician in this study, but the American Society for Gastrointestinal Endoscopy (ASGE) has recommended that additional training be provided for the safe administration of propofol [30]. An ASA/ASGE taskforce further recommended that non-anesthesiologists using propofol for endoscopic procedures should be trained by anesthesiologists. Propofol has a narrow therapeutic window that can result in a rapid depression of consciousness and cardiovascular function, leading to a state of general anesthesia, and there is no reversal agent. Therefore, additional training and the use of a safe infusion protocol are recommended to ensure the safe administration of propofol. The presence of an anesthesiologist and special monitoring equipment, such as an electroencephalogram [31], capnometer and target-controlled infusion system, would entail added costs and an anesthesiologist may simply not be available in some situations. Accordingly, we utilized the services of a properly trained gastroenterologist to administer the sedation agents, with satisfactory results.

The equipment used in this study to monitor the physiological parameters included a pulse oximeter, continuous electrocardiogram and automatic blood pressure monitoring

device. A number of reports have indicated that a capnometer was available during the procedure for deep sedation [32]. Although a capnometer would more readily identify a patient experiencing an apneic episode, the calculated doses of propofol used in our study never caused de-saturation requiring mechanical ventilation; therefore, pulse oximetry may be sufficient for the detection of hypoxia. However, a capnometer is a non-invasive method for measuring respiratory activity, and we are currently investigating whether carbon dioxide monitoring is desirable [33].

In this study, we used pentazocine for both groups as an analgesic agent in smaller doses that is used for general anesthesia. Only a minimum dose of an analgesic agent is needed when deep sedation is used during ESD for EGC. In addition to pentazocine, the use of other analgesic agents, such as remifentanyl, ketamine and pethidine, may be feasible [34], so further research should be conducted to ascertain the optimal combination with propofol.

In conclusion, gastroenterologist-directed and supervised sedation using propofol continuous infusion for ESD in EGC is a safe procedure. Based on our results, propofol sedation is also effective for the evaluation of patients after ESD because it has a significantly better recovery profile than conventional intermittent MDZ injection. It is therefore essential that the most suitable sedation regimen for ESD using propofol be determined as quickly as possible.

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Remarkable progress in endoscopic resection of early gastric cancer

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Endoscopic resection is accepted in many countries as a less invasive local resection of early gastric cancer with a negligible risk of lymph-node metastasis.[1,2] Endoscopic resection preserves the stomach and therefore improves patient quality of life compared with surgery. Remarkable progress has been made during the past decade because of technical improvements and an expansion of the indications for endoscopic resection. The methods vary from polypectomy to conventional endoscopic mucosal resection (EMR) to endoscopic submucosal dissection (ESD).[1,2] EMR procedures include inject and cut, strip biopsy, EMR with a cap-fitted endoscope (EMRC), endoscopic aspiration mucosectomy (EAM) and EMR with a ligating device (EMRL), whereas ESD is a relatively new endoscopic resection method that facilitates one-piece resection.

In the past, the accepted indications for endoscopic resection of early gastric cancer were a small intramucosal cancer less than 2 cm in size, having a differentiated histopathological type and without an ulcer finding.[2] Recently, the indications for endoscopic resection of early gastric cancer have been expanded, as shown in Table 1, to cover other lesions with a negligible risk of lymph-node metastasis.[2,3] These expanded indications include larger lesions and lesions with ulceration. Such lesions were previously resected by surgery because of the difficulty in effectively using EMR techniques. As a result, ESD was developed to achieve one-piece resections even for larger and ulcerative lesions.[1,2]

In volume 24 issue 6 of the *Journal of Gastroenterology and Hepatology*, Hoteya *et al.* report on the advantages of ESD for treating early gastric cancer compared to EMR.[4] The local complete resection (one-piece resection with a negative tumor margin) rate (EMR, 64%; ESD, 95%) and the curative resection rate (EMR, 60%; ESD, 83%) were significantly higher for ESD than for EMR in their study. In addition, 13 local recurrences (4.0%) were detected in the EMR group during follow up in comparison to no local recurrences in the ESD group.

One-piece resection with a negative tumor margin is optimal for endoscopic resection because it substantially reduces the risk of local recurrence. One-piece resection with a positive tumor margin and piecemeal resection both have an increased risk of local recurrence, although the thermal effect from endoscopic resection may help to prevent this. Hoteya and his colleagues demonstrated in their article that the rate of one-piece resection with a negative tumor margin was higher regardless of location in ESD compared to EMR, thus reducing the overall risk of local recurrence. Their results were similar to previously published reports.[5–8]

Table 1 Histopathological criteria for curative endoscopic resection

Early gastric cancer with negligible risk of lymph-node metastasis
Differentiated adenocarcinoma
No lymphatic or venous invasion
Intramucosal cancer regardless of tumor size without ulcer finding
or intramucosal cancer ≤ 30 mm in size with ulcer finding
or minute submucosal cancer (sm1) ≤ 30 mm in size
Resection margin
Tumor-free lateral margin
Tumor-free vertical margin

One-piece resection is also optimal because endoscopic resection is a local resection procedure without lymph-node dissection. It is therefore indicated for early gastric cancer with a negligible risk of lymph-node metastasis. The early gastric cancer criteria for a negligible risk of lymph-node metastasis are shown in Table 1. Tumor depth is one of the most important factors, but endoscopic prediction of early gastric cancer in terms of tumor depth is not always accurate, even when endoscopic ultrasonography is used.[9–11] The curability of endoscopic resection therefore must be determined histopathologically based on criteria for early gastric cancer with a negligible risk of lymph-node metastasis, as well as the resection margin (Table 1).

Endoscopic resection is considered to be non-curative if a tumor is diagnosed as having either a possible risk of lymph-node metastasis or a positive lateral margin. In fact, lymph-node metastasis has been reported among 6.3% of patients who had surgery following non-curative endoscopic resection with a possible risk of lymph-node metastasis.[12] Piecemeal resections can make it difficult to histopathologically evaluate curability, thus resulting in some findings that suggest a possible risk of lymph-node metastasis being overlooked. Without surgical treatment in such cases, there could be a risk of distant metastasis developing. It follows that histopathological staging using specimens obtained by one-piece resection is crucial with endoscopic resection so as to decide on the need for any subsequent treatment.

Hoteya *et al.* also demonstrated that there were no significant differences in complication (postoperative bleeding and perforation) rates between EMR and ESD. Endoscopic resection techniques should be safe, but endoscopic resection has been associated with an increased risk of complications such as bleeding and perforation. Although there was no reported significant difference in the perforation rate between the EMR and ESD groups, several earlier articles indicated that the risk of perforation was higher for ESD than for EMR.[2,5] It has also been reported previously that the risk of perforation is related to tumor location, size and an ulcer finding,[13,14] as has the usefulness of endoscopic closure with endoclips for gastric perforations.[14]

Whereas the rate of postoperative bleeding was similar between EMR and ESD, intraoperative bleeding occurs infrequently with EMR, but is quite common with ESD.[15] Management of intraoperative bleeding plays a critical role in achieving complete resection during ESD. Cautery is used for hemostasis during endoscopic resection because endoclips interfere with the subsequent resection.

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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.

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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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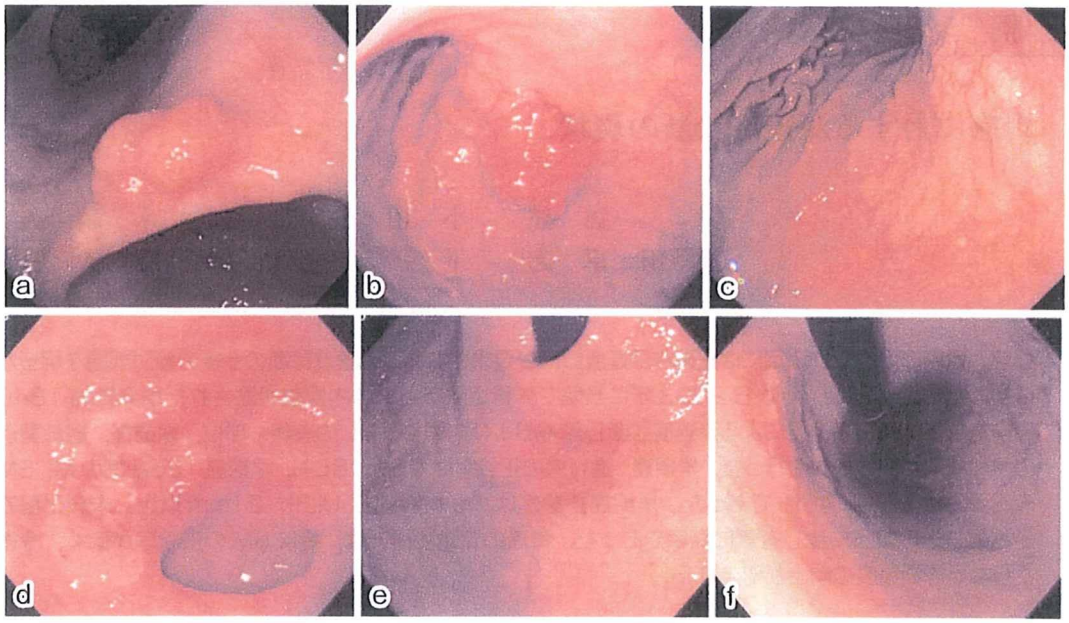

Figure 1. 通常内視鏡による深達度臨床診断 **a**：1.5cm 大のⅠ型病変で表面にくずれ・陥凹などを認めず，M と診断する． **b**：2.5cm 大，広基性のⅠ型病変で，SM と診断する． **c**：5cm 大のⅡa 型病変で表面に陥凹などを認めず，M と診断する． **d**：2.5cm 大の中心陥凹をともなう隆起性病変（Ⅱa＋Ⅱc 型）で SM と診断する． **e**：2cm 大の浅い陥凹性病変（Ⅱc 型）で，粘膜模様は保たれ，壁の厚みなどを認めず，M と診断する． **f**：2.5cm 大の陥凹性病変（Ⅱc 型）で，壁の厚みをともない SM と診断する．

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，