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別紙１

厚生労働科学研究費補助金

がん臨床研究事業

離島をモデルとした新しい対策型大腸がん検診システムの構築とその実現に向けた研究－新島STUDYに関する研究

平成22年度　総括研究報告書

研究代表者　松田　尚久

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別紙2

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厚生労働科学研究費補助金（がん臨床研究事業）
総括研究報告書

離島をモデルとした新しい対策型大腸がん検診システムの構築とその実現に向けた研究－新島 STUDY

研究代表者　松田 尚久（国立がん研究センター中央病院 医長）

研究要旨

わが国では，1992 年より 40 歳以上の成人を対象とした免疫学的便潜血反応（2 日法）による大腸がん検診が行われているが，その受診率は男性：27.5%，女性：22.7%（H19 年：国民生活基礎調査）と低く，都道府県別格差が大きい．とくに離島が抱える大腸がん検診の問題が深刻化している．東京都新島村（人口：3,068 人，1,384 世帯）における大腸がん検診は，平成 18 年：23.9%，平成 21 年：12.8%，平成 22 年：約 12%とその受診率の低下が顕著であり，大腸内視鏡検査施行医がいない現状も相俟って要精検者（便潜血陽性者）に対する精査が十分に施行されていない．本研究では，離島（新島村）をモデルに「内視鏡検査による大腸がん検診受診率 50%以上」を達成目標とし，個人登録下でのアンケート調査及び内視鏡検査結果に基づいた大腸がんリスクの層別化と，目標に向けた適正な個人勧奨のあり方について検証を行う．

池松弘朗：国立がん研究センター東病院医員
角川 康夫：国立がん研究センター がん予防検診研究センター医員
九嶋 亮治：国立がん研究センター医長
小林 望：栃木県立がんセンター 画像診断部医長
寶澤 篤：山形大学大学院医学系研究科 公衆衛生学講座講師
堀田 欣一：佐久総合病院医長

A．研究目的

本研究の目的は，日本における258の指定有人離島（人口42.9万人，関係市町村数：110）における理想的な地域大腸がん検診モデルの確立を目指し，科学的根拠に基づいた検診体制を構築するための臨床研究を策定することにある．本研究では，新島村をモデルに「内視鏡検査による大腸がん検診受診率50%以上」の目標達成として計画する啓発活動（パンフレット作成・講演会）の有効性評価と，検診非受検者に対して行う6か月ごとのリコール（反復受診勧告）による受診率向上効果を明らかにする．実際には，東京都新島村をモデルとし，大腸がん検診対象者中40～79歳の男女約1,400名に対して啓発活動後に検診としての全大腸内視鏡検査の案内を行い，文書による本研究参加の応諾が得られた者に対して，全例大腸内視鏡検査を計画する．

B．研究方法

新島村住民で，平成 23 年度大腸がん検診の対象者中 40～79 歳の男女約 1,400 名に対して，検診としての全大腸内視鏡検査（TCS）の案内状を送付する．この時点で，文書による本研究参加の応諾が得られた者に対して，全例 TCS を計画する（参加同意が得られない住民及び 80 歳以上の方につ

いては，例年通りの免疫学的便潜血検査：FOBTを推奨)．また，上記いずれの検査も受検しなかった対象者に対しては，初回呼びかけ後6か月の期間を利用して，大腸がん検診の重要性とTCS及びFOBTのメリット・デメリット等について，パンフレット送付と地域での講演会を通じて普及啓発活動を行った後に案内状を再送付（リコール）し，検診受診を再度呼びかける．

また，新島村住民すべてを対象としたアンケート調査（大腸がん検診受検・非受検理由および大腸がんリスクに関する食生活等の生活習慣・がん家族歴・既往歴・身体所見：BMI等の調査）を行う．また検診受検者については，検診結果に基づいた個別のフォローアップ方法（推奨される検査間隔およびその方法）についての情報提供を行う．

（倫理面への配慮）

本研究への参加同意が得られた島民のデータについては，新島事務局（新島村さわやか健康センター）にて管理するが，TCS及びFOBT検査結果については匿名化した形でデータセンター（メディカルリサーチサポート）が集中管理する．そこでは，データアクセスする者をID/パスワード認証を用いて限定し，ファイアウオール整備により不法アクセスを防ぐことによりセキュリティ対策を行う．データセンター，新島事務局、中央事務局（国立がん研究センター）の施設責任者は，研究のために作成されたデータセットまたは資料を研究終了後も保管する．いずれの参加者も個人情報保護法を遵守する．

C．研究結果

研究初年度（H22 年度）は，本研究グループ（消化管内視鏡医・病理医・公衆衛生の専門医及び新島村担当者）の編成と研究実施計画書（プロトコール）作成ならびに「平成23年度新島村大腸がん検診」の実施に向けての必要機器・物品の選定納入作業を進めた．現地，新島村では「さわやか健康センター」での大腸がん検診（内視鏡検査を推奨）実施に向け，内視鏡機器および洗浄機，内視鏡ファイリングシステム，便潜血検査機器の搬入を開始した．併せて，島民に対する啓発活動に際に用いる各種「パンフレット」の作成が完了し印刷作業に入っている．来年度（H23 年度）は，実際に大腸がん検診対象者：約 1,400 名に対する啓発活動と検診希望調査を実施する．

尚，本研究のプライマリー・エンドポイントを大腸がん検診受診率，セカンダリ・エンドポイントとして，リコールによる大腸がん検診受診率向上効果，大腸内視鏡検診の安全性評価（偶発症発生率），アンケート調査結果（検診受検動機），内視鏡介入群における大腸がん抑制効果（追跡調査）と設定した．

D．考察

本研究は，離島における将来の大腸がん検診体制の在り方を提案するための臨床研究として立案した．内視鏡検査の受検機会が乏しい地域に対して，内視鏡専門医が直接出向き，検診の重要性に関する啓発活動と検診としての大腸内視鏡検査の機会を提供することにより，どの程度の検診受診率向上と大腸がん罹患率の抑制が得られるか，また非受検者に対するリコール（反復受診勧告）による受診率向上が得られるか否か

についての検証が可能である.

E. 結論

離島という人口動態の把握が比較的容易なコミュニティを対象とするため，研究データの信憑性は高く，今後長期的な検討（予後調査等）を行う上でも質の高い研究となるものと確信する．また，地域における患者支援という視点で考えた場合，島を離れず一度の内視鏡検査で大腸がん検診を完遂できることは，受検者のみならず関係市町村にとっても将来的に非常に大きなメリットとなると考えられる．本研究のモデルとなる新島村での研究成果に基づき，将来的にはその他の離島関係市町村における内視鏡介入型の新しい対策型大腸がん検診システムの構築が期待できる.

F. 健康危険情報

報告すべき事項なし.

G. 研究発表

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H．知的財産権の出願・登録状況（予定を含む）

出願・登録なし．今後申請の予定なし．

別紙４

研究成果の刊行に関する一覧表

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INDICATIONS FOR ENDOSCOPIC RESECTION OF COLORECTAL POLYPS AND SURVEILLANCE GUIDELINES

PREVALENCE AND CLINICOPATHOLOGICAL FEATURES OF NONPOLYPOID COLORECTAL NEOPLASMS: SHOULD WE PAY MORE ATTENTION TO IDENTIFYING FLAT AND DEPRESSED LESIONS?

TAKAHISA MATSUDA,[1] YUTAKA SAITO,[1] KINICHI HOTTA,[2] YASUSHI SANO[3] AND TAKAHIRO FUJII[4]

[1]*Endoscopy Division, National Cancer Center Hospital,* [4]*TF Clinic, Tokyo,* [2]*Department of Gastroenterology, Saku Central Hospital, Nagano and* [3]*Sano Hospital, Kobe, Japan*

Flat and depressed (nonpolypoid) colorectal lesions have been described for over two decades by Japanese investigators. These neoplastic lesions are typically smaller than polypoid ones and can be more difficult to identify during screening colonoscopy. In particular, depressed type colorectal lesions are usually small in size, with a number of studies showing them to be at greater risk for developing high-grade dysplasia or submucosal invasive cancer. It has also been suggested that they may follow a different carcinogenic pathway to flat elevated or protruding adenomas. This paper summarizes recent data of nonpolypoid colorectal neoplasms from Western and Asian countries.

Key words: Japan Polyp Study, nonpolypoid colorectal neoplasm, screening colonoscopy.

INTRODUCTION

Colorectal neoplasms have traditionally been classified in Western countries as sessile or pedunculated. However, in 1983 the Japanese Research Society for Cancer of the Colon and Rectum also recognized the existence of flat adenomas.[1] In 1985 Muto *et al.* described small 'flat adenomas' as lesions <10 mm in size, flat-elevated, sometimes showing a central redness, and with a significant rate of high-grade dysplasia.[2] In regard to depressed lesions, the first reports of depressed (IIc) type colorectal neoplasms were published in 1977 by Kariya *et al.*[3] Following this, IIc type cancers were thought to be a unique 'Japanese phenomenon' until 1993 when Kudo *et al.*[4] reported their depressed type cancer series and classification. Several studies suggested that flat and depressed lesions may behave differently to sessile or protruding lesions, leading more frequently to high-grade dysplasia or submucosal invasive cancer. Since then, many studies have focused on the clinicopathological characteristics of flat and depressed lesions, so-called 'nonpolypoid' colorectal neoplasms.

In 1998, Fujii and Rembacken *et al.* demonstrated depressed lesions in an English population.[5] In this study, 68 adenomas were identified in 47 of 208 patients undergoing colonoscopy: 40% of these adenomas were nonpolypoid. In 2001, Saitoh *et al.* reported the prevalence of nonpolypoid colorectal lesions in North America while Tsuda *et al.* also reported these lesions in Sweden.[6,7] Although initial reports from the Western world suggested a lower frequency of nonpolypoid lesions than in the Japanese series[8] the implementation of chromoendoscopy performed by specialists trained by Japanese experts has improved the detection of such lesions in Western countries.

For screening colonoscopy to become more effective in reducing the incidence and mortality of colorectal cancer, it is important for endoscopists to recognize both polypoid and nonpolypoid colorectal cancer precursors. Left undetected, nonpolypoid colorectal neoplasms may evolve into invasive cancer within a few years following an assumedly normal colonoscopy.[9] This report is intended to provide an overview of the current understanding of the prevalence and clinicopathological features of nonpolypoid colorectal neoplasms.

PREVALENCE AND CLINICOPATHOLOGICAL FEATURES OF NONPOLYPOID COLORECTAL NEOPLASMS

Recent data from Western and Asian countries

In 2000, Rembacken *et al.* reported data from the UK (Table 1).[10] In this prospective study, 1000 consecutive patients attending routine colonoscopy were examined for flat or depressed lesions. Three hundred and twenty-one adenomas and six Dukes' A adenocarcinomas were identified: 204 (62.4%) were polypoid and 37.6% (123) were nonpolypoid lesions. Among all nonpolypoid lesions, the incidence of cancer was 3.3%. However, it was markedly higher in the depressed lesions (50%; 2/4). The authors concluded that the polyp-carcinoma hypothesis prompts colonoscopists to search only for polypoid lesions when screening for cancer, and many early colorectal neoplasms may therefore be missed. Adding to this data are results from

Correspondence: Takahisa Matsuda, Endoscopy Division, National Cancer Center Hospital, Tokyo 104-0045, Japan. Email: tamatsud@ncc.go.jp

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Table 1. Prevalence of non-polypoid colorectal neoplasms (data from Western and Asian countries)

	No. neoplastic lesions and incidence of Ca (M/SM)					
	All polypoid lesions		All nonpolypoid lesions (0-IIa, IIb, IIc)		Depressed lesions (all IIc)	
	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)
Rembacken *et al.*, UK [10] (*n* = 327/1000 pts)	204 (62.4)	2 (1.0)	123 (37.6)	4 (3.3)	4 (1.2)	2 (50.0)
Parra *et al.*, Spain [11] (*n* = 490/1300 pts)	376 (76.7)	10 (2.7)	114 (23.3)	8 (7.0)	3 (0.6)	2 (66.6)
Soetikno *et al.*, USA [13] (*n* = 1535/1819 pts)	1308 (85.2)	13 (1.0)	227 (14.8)	15 (6.6)	18 (1.2)	6 (33.3)
Chiu *et al.*, Taiwan [14] (*n* = 5682/12 731 pts)	4653 (81.9)	79 (1.7)	1029 (18.1)	60 (5.8)	39 (0.7)	20 (51.3)

Ca, cancer; M, mucosal invasive cancers; SM, submucosal invasive cancers.

a 2006 Spanish study by Parra *et al.* who reported a review of 1300 consecutive colonoscopic examinations.[11] A total of 490 polyps were adenomas and 150 were hyperplastic; 114 (23.3%) adenomas were flat (three were flat-depressed) whereas 376 (76.7%) were protruding. The diameter of flat and protruding adenomas was 9.2 ± 7.9 mm and 7.0 ± 5.9 mm, respectively ($P < 0.001$). This paper concluded that flat adenomas represent nearly one-quarter of all colorectal neoplastic polyps, their most frequent location being the right colon, and that they bear a higher risk of malignancy than protruding adenomas, especially for the flat-depressed type. From the USA, one study analyzed and reclassified 933 surgically removed sessile adenomas described in the National Polyp Study (NPS) and found no difference between polypoid and flat adenomas with respect to high-grade dysplasia or invasive cancer.[12] However, Soetikno *et al.* recently reported the prevalence and clinicopathological features of nonpolypoid colorectal neoplasms.[13] This was a cross-sectional study at a Veteran's Hospital in California with 1819 patients undergoing elective colonoscopy. Among all neoplasms (*n* = 1535) detected, 14.8% were classified as nonpolypoid lesions (*n* = 227, flat: 209, depressed: 18). Overall, nonpolypoid colorectal neoplasms were more likely to contain malignant cells (odds ratio, 9.78; 95% confidence interval, 3.93–24.4) than polypoid lesions, irrespective of the size. The depressed type had the highest risk (33.3%) of cancer. Moreover, Chiu *et al.* recently reported on the prevalence and characteristics of nonpolypoid colorectal neoplasms from Taiwan.[14] This study included 12 731 asymptomatic Chinese subjects (8372 of whom were average-risk subjects) who underwent screening colonoscopy. Nonpolypoid colorectal neoplasm was detected in 4.3% of asymptomatic and 4.2% of average-risk subjects. The prevalence of depressed lesions was 0.18% in both asymptomatic and average-risk subjects. This paper concluded that these findings may lead to modification of screening and prevention strategies for colorectal cancer. Meanwhile, Goto and Oda *et al.*[15] estimated that depressed (IIc), so-called de novo cancer might comprise up to 22.9% of early colorectal cancers (18.6% in men and 27.4% in women) in a cohort of 14 817 Japanese subjects.

Data from National Cancer Center Hospital, Tokyo

Subjects and methods

Between January 1998 and April 2003, a total of 6638 colorectal neoplasms in 3952 patients (men: 2800, women: 1152, mean age [standard deviation]: 63.4 years [9.9]) were treated endoscopically or surgically at the National Cancer Center Hospital, Tokyo. To clarify the importance of nonpolypoid colorectal neoplasms, we classified all lesions into three groups (group A: polypoid [Ip, Isp, Is]; group B: flat [IIa, laterally spreading tumor]; group C: depressed [IIc, IIa+IIc]) based on macroscopic identification during colonoscopy (Fig. 1). In addition, to clarify the clinical importance of flat lesions we further divided these lesions into three groups based on lesion size (Fig. 2).

Results

There were 4471 (67.4%) and 2167 (32.6%) polypoid and nonpolypoid colorectal neoplasms, respectively (Table 2). Among all nonpolypoid lesions, there were 178 (2.7%) depressed lesions, of which 109 (61.2%) were diagnosed as high-grade dysplasia (intramucosal cancer) or submucosal invasive cancer. On the other hand, the incidence of intramucosal cancer or submucosal invasive cancer was 15.4% and 18.9% in polypoid and nonpolypoid lesions, respectively.

Histopathological assessment of all lesions identified 5538 (83.4%) lesions as adenoma (low-grade dysplasia), 851 (12.8%) intramucosal cancer (high-grade dysplasia), and 249 (3.8%) submucosal invasive cancers (Table 3). The prevalence of cancers in our data was extremely high (16.6%) compared to other reports. We considered that this imbalance was related to the specific characteristics of our cancer center being a national referring hospital.

Among the lesions diagnosed as adenoma or intramucosal cancer, the prevalence of depressed lesions was 1.2–1.5%. In contrast, depressed type submucosal cancers were identified in 38.6% (96/249) of subjects. The prevalence of depressed lesions was relatively low compared to polypoid or flat

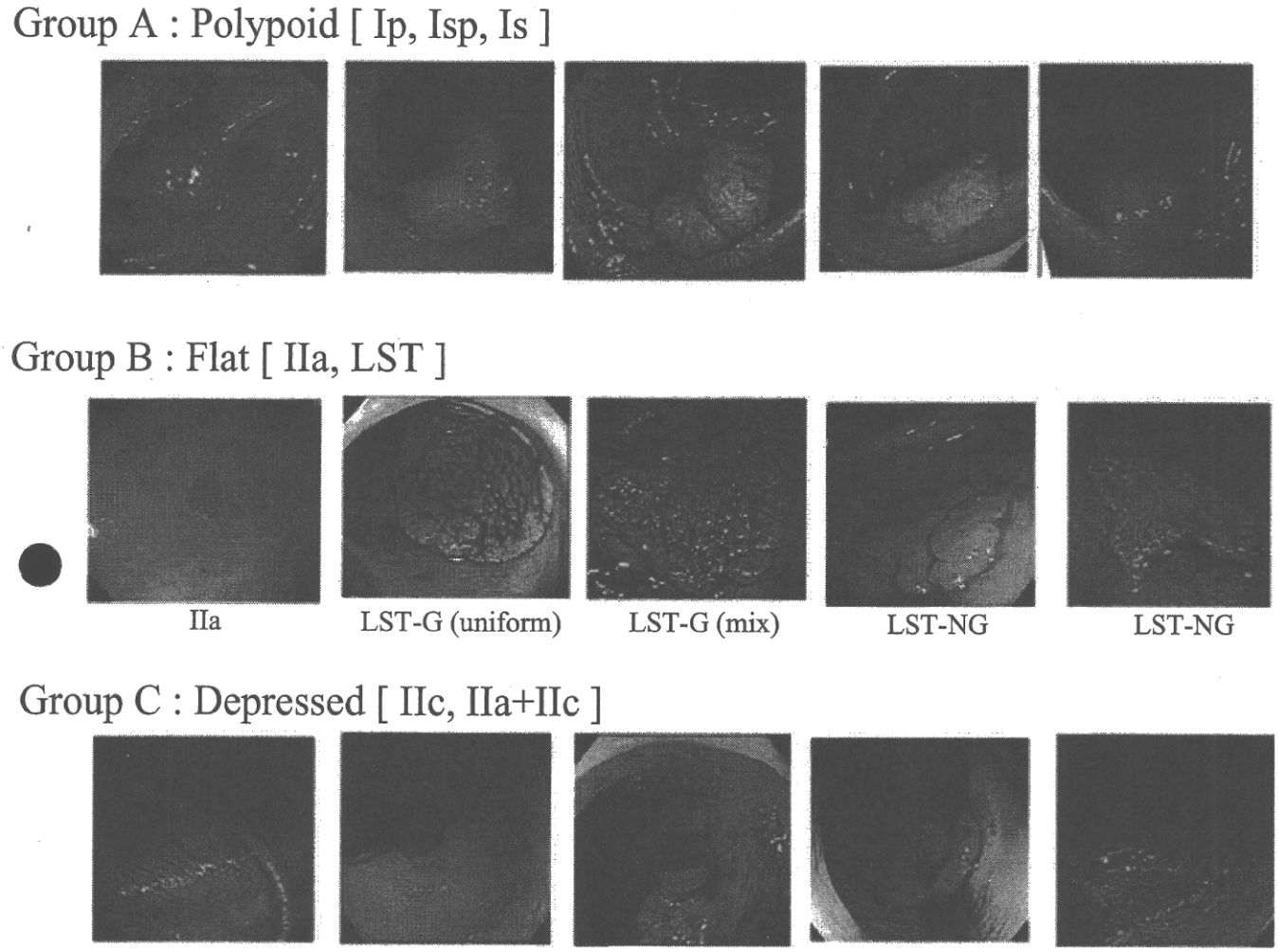

Fig. 1. Prevalence and malignant potential of flat and depressed lesions. LST, laterally spreading tumor (a flat elevated lesion ≥10 mm); LST-G, LST granular; LST-NG, LST non-granular.

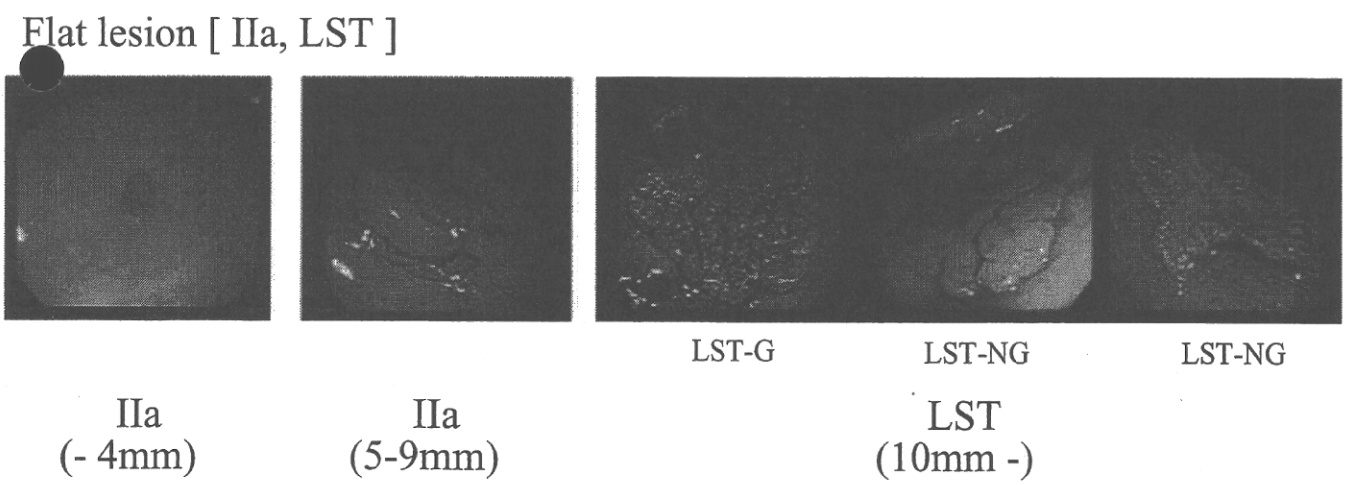

Fig. 2. Flat lesion (IIa, laterally spreading tumor [LST]). LST-G, LST granular; LST-NG, LST non-granular.

Table 2. Prevalence of non-polypoid colorectal neoplasms (National Cancer Center Hospital [NCCH], Tokyo, 1998–2003)

	No. neoplastic lesions and incidence of Ca (M/SM)					
	All polypoid lesions		All nonpolypoid lesions (0-IIa, IIb, IIc)		Depressed lesions (all IIc)	
	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)	No. lesions (%)	No. lesions with Ca (%)
NCCH (n = 6638/3952 pts)	4471 (67.4)	690 (15.4)	2167 (32.6)	410 (18.9)	178 (2.7)	109 (61.2)

Ca, cancer; M, mucosal invasive cancers; SM, submucosal invasive cancers.

Table 3. Relationship between macroscopic type and histopathological findings (National Cancer Center Hospital [NCCH], Tokyo, 1998–2003)

	Macroscopic type	Adenoma (LGD)	Intramucosal cancer (HGD)	Submucosal invasive cancer
Polypoid	Ip	360	224	25
4471 (67.4%)	Isp	1053	232	40
	Is	2368	122	47
Flat	IIa	1550	96	11
1989 (29.9%)	LST	138	164	30
Depressed	IIc	26	5	13
178 (2.7%)	IIa + IIc	43	8	83
Total: 6638 lesions		5538 (83.4%)	851 (12.8%)	249 (3.8%)

HGD, high-grade dysplasia; LGD, low-grade dysplasia; LST, laterally spreading tumor, (granular and non-granular).

Table 4. Relationship between lesion size and clinicopathological findings (1989 flat lesions, National Cancer Center Hospital, Tokyo, 1998–2003)

Size	Location (C/A/T: D/S: R)*	Adenoma (LGD)	M-SM Ca (HGD-submucosal invasive cancer)
- 4 mm (830)	508:288:34 (61%:35%:4%)	828 (99.8%)	2 (0.2%)
5–9 mm (706)	387:276:43 (55%:39%:6%)	657 (93.1%)	49 (6.9%)
10 mm - (453)	260:111:82 (57%:25%:18%)	203 (44.8%)	250 (55.2%)
Total: 1989 lesions	1155:675:159 (58%:34%:8%)	1688 (84.9%)	301 (15.1%)

C, cecum; A, ascending; T, transverse; D, descending; S, sigmoid; R, rectum.

lesions (2.7% *vs* 67.4%, 32.6%), however, the incidence of cancer among depressed lesions was significantly higher than that of the other groups.

Regarding flat lesions, there were 830 small (<5 mm), 706 intermediate (5–9 mm) and 453 large (≥10 mm; laterally spreading tumor) lesions (Table 4). As for tumor location, there were 1155 lesions (58%) in the proximal colon, 675 (34%) in the distal colon and 159 (8%) rectal lesions. Among the lesions diagnosed as small, intermediate and large flat lesions, the incidence of cancers (intramucosal cancer or submucosal invasive cancer) was 0.2% (2/830), 6.9% (49/706) and 55.2% (250/453), respectively. Therefore, laterally spreading tumor lesions are undoubtedly clinically more important than small ones.

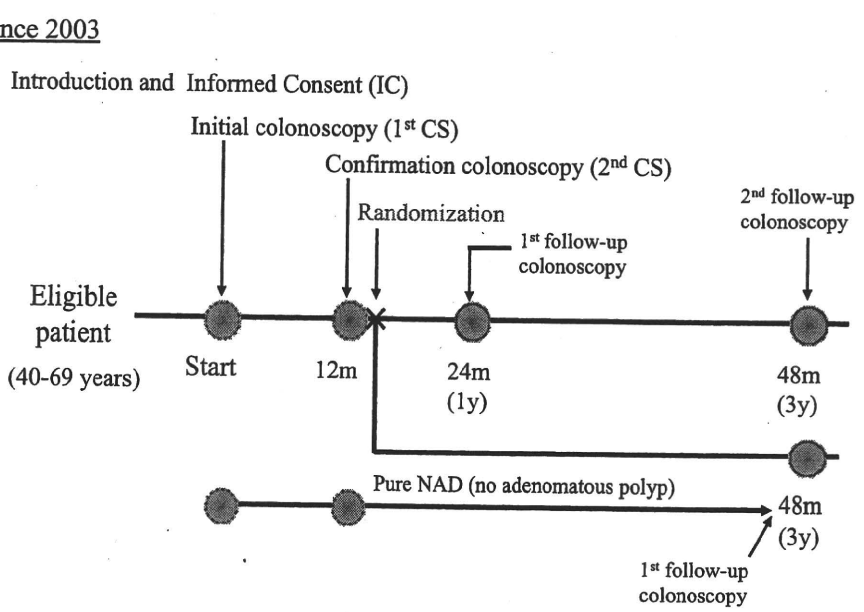

Fig. 3. Schematic overview of the Japan Polyp Study.

CONCLUSION

Although the nonpolypoid (especially depressed type) colorectal neoplasms may be regarded as occurring infrequently, they belong to a distinct subset that demonstrates greater biological aggressiveness, given the high prevalence of intramucosal or submucosal cancers. The detection and diagnosis of the nonpolypoid colorectal neoplasm presents both a challenge and an opportunity. Gastroenterologists need to meet the challenge and become proficient in the endoscopic recognition of these lesions in order to reduce the incidence and mortality from colorectal cancer. Consequently, large-scale prospective data need to be collected to further define the epidemiology and biology of nonpolypoid colorectal neoplasms in all populations. The Japan Polyp Study is a multicenter randomized controlled trial that was initiated in 2003 (Fig. 3).[16] It is prospectively evaluating follow-up surveillance strategies for Japanese populations after complete removal of all polyps, and nonpolypoid colorectal neoplasms, detected by high-resolution chromoendoscopy. The Japan Polyp Study is intended to continue until 2011, and the final step of the randomization process and complete histopathological assessment are ongoing. The clinical significance of nonpolypoid lesions (especially depressed type lesions) in Japan will become clear in this prospective study.

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Assessment of Likelihood of Submucosal Invasion in Non-Polypoid Colorectal Neoplasms

Takahisa Matsuda, MD, PhD[a,*],
Adolfo Parra-Blanco, MD, PhD[b], Yutaka Saito, MD, PhD[a],
Taku Sakamoto, MD[a], Takeshi Nakajima, MD, PhD[a]

KEYWORDS

- Non-polypoid colorectal neoplasm • Submucosal cancer
- Lymph node metastasis • Endoscopic diagnosis
- Magnifying chromoendoscopy

Endoscopic mucosal resection (EMR) is indicated to treat intramucosal colorectal carcinoma because the risk of lymph node metastasis is nil.[1,2] Surgery is indicated to treat submucosal invasive cancers (cancer cells invading through the muscularis mucosa into the submucosal layer but not extending into the muscularis propria) because of the 6% to 12% risk of lymph node metastasis.[3–7] However, there is increasing evidence to suggest that lesions with submucosal invasion lower than 1000 μm, without lymphovascular invasion and without poor differentiation, also have a minimal risk of lymph node metastasis[8] and can be cured by EMR alone. It is therefore important to be able to distinguish neoplasms that are candidates for EMR from those that will require surgery, because EMR of lesions containing massive submucosal invasive cancer is associated with the risk of bleeding and perforation and is unlikely to be curative.

Current endoscopes have high-resolution imaging that provides clear, vivid, and detailed features of the detected lesions. When combined with image enhancement, high-magnification endoscopy can provide a detailed analysis of the morphologic architecture of mucosal crypt orifices (ie, pit pattern) in a simple and quick manner.[9,10] As such, magnifying chromoendoscopy has been shown to be effective for the differential

[a] Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan
[b] Department of Gastroenterology, Central University Hospital of Asturias, Celestino Villamil s/n, 33006 Oviedo, Principado de Asturias, Oviedo, Spain
* Corresponding author.
E-mail address: tamatsud@ncc.go.jp

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diagnosis between colorectal neoplastic and non-neoplastic lesions and determination of the depth invasion of colorectal cancers. The authors highlight methods to assess depth of invasion of non-polypoid colorectal cancers based on a review of the literature and our experience at National Cancer Center Hospital in Japan.

IMPORTANCE OF ESTIMATION OF SUBMUCOSAL INVASION

In Japan, findings of deep submucosal invasion (≥1000 μm), and/or lymphovascular invasion, and/or poorly differentiated adenocarcinoma in the histopathology of an EMR specimen would lead to consideration for surgery. Though lymphovascular invasion and poorly differentiated adenocarcinoma components are impossible to predict before resection, the vertical depth of invasion of submucosal cancers can be estimated based on the morphologic appearance at the time of endoscopy.

However, estimation of submucosal invasion requires more than the measurement of the lesion size. Small colorectal neoplasms are historically believed to have a lower malignancy potential than large ones, and several authors have reported that the malignant potential of early colorectal cancer increases with size.[11–13] Although this observation may be true for adenomatous lesions, the data for submucosally invasive carcinomas are conflicting. In the authors' own large study involving 583 lesions, they found that that small submucosal cancers (≤10 mm, n = 120) had a similarly aggressive behavior and malignant potential as the larger ones (>10mm, n = 463); the risks of lymph node metastasis were similar (small: 11.2%, large: 12.1%, $P = .85$), lymphovascular invasion (small: 21.7%, large: 27%, $P = .23$), and poorly differentiated adenocarcinoma components (small: 10%, large: 17.1%, $P = .06$).[7] They also described that small submucosal cancers were more likely to have non-polypoid growth (NPG) type[14] than the larger lesions (68.3% vs 46.0%, $P<.0001$). In this retrospective study, the rate of EMR used as an initial treatment was 33.4% (195/583). EMR was more often used to resect the small lesion rather than the large lesion group (51.6% vs 28.7%, $P<.0001$). However, they were surprised to find that there were no differences in the positive rate of cut margins in both groups (17.7% vs 19.5%, $P = .81$). This result implies that EMR should not be easily applied to small colorectal lesions when they appear to be submucosally invasive because of its risk of complication and the concept of no-touch isolation.[15]

ESTIMATION OF SUBMUCOSAL INVASION USING BARIUM ENEMA, ENDOSCOPIC ULTRASONOGRAPHY, AND NONLIFTING SIGN

Barium Enema

The superiority of barium enema over colonoscopy is summarized by Tsuji and colleagues[16] as follows: (1) Barium enema is able to describe the shape of the lesion that is difficult for colonoscopy to observe because of its location. (2) In the case of a large lesion in which it is difficult to endoscopically observe the whole lesion, barium enema can describe the entire shape of the lesion and obtain information on the oral side more easily. (3) The size and location of lesions can be assessed more objectively. (4) The degree of deformity of the lateral view enables the clinician to diagnose the depth of invasion more easily.

The authors retrospectively compared the diagnostic accuracy of colonoscopy and barium enema for submucosal colorectal cancers at 2 National Cancer Centers (Tokyo, Kashiwa) in 2001.[17] One hundred eighty-six (polypoid [Ip, Is]: 117, non-polypoid [IIa, IIa+IIc, IIc, laterally spreading tumor (LST)]: 69) lesions were examined in this study, and the authors investigated the accuracy rate of the lesion's depth by 2 modalities (**Fig. 1**). The colonoscopic accuracy rate was superior to that of the barium enema study

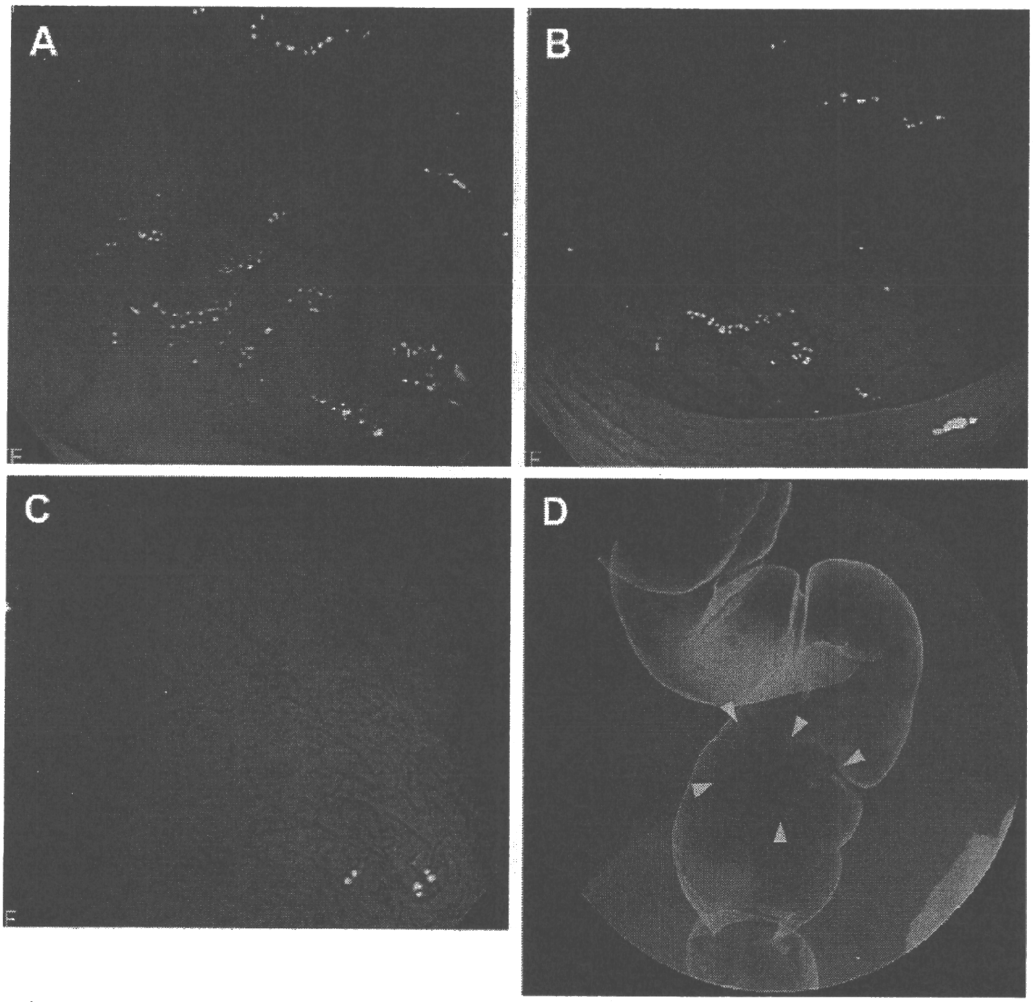

Fig. 1. (*A*) Conventional view, (*B*) Conventional view with indigo carmine dye, (*C*) Magnifying view with crystal violet staining, (*D*) Barium enema image.

(80.1% vs 69.7%, $P = .04$). This result is obtained not only in polypoid lesions (71.8% vs 60.3%, $P = .09$) but also in non-polypoid colorectal lesions (94.2% vs 83.7%, $P = .07$). As a result, the authors concluded that it is sufficient to diagnose the depth of endoscopic resectable early colorectal cancer by colonoscopy alone. However, when selecting surgical management, barium enema or computed tomographic colonography should also be performed to precisely delineate the location of the lesion.

Endoscopic Ultrasonography

Data on the utility of high-frequency endoscopic ultrasonography (EUS) in the management of the malignant colorectal polyp are conflicting. Some authors have reported the usefulness of EUS, particularly the advantages of high-frequency ultrasound (HFUS) to diagnose the invasion depth of early colorectal cancer.[18–21] Hurlstone and colleagues[20] conducted a prospective study to compare the 2 modalities (HFUS vs magnifying chromoendoscopy). They found that HFUS was superior to magnifying chromoendoscopy for determination of depth invasion (93% vs 59% accuracy, respectively [$P<.0001$]). Matsumoto and colleagues[21] also concluded that the negative predictive value of probe-EUS for deep invasion was higher than that of magnifying chromoendoscopy (90.9% vs 54.1%, respectively [$P<.01$]) in the population studied (prevalence deep submucosal invasion 56%).

In contrast, Fu and colleagues[22] have recently reported that magnifying chromoendoscopy is as accurate as EUS for preoperative staging of early colorectal cancer (87% vs 75%, $P = .0985$). Subgroup analysis was also done for polypoid and nonpolypoid lesions. For polypoid lesions, the respective overall diagnostic accuracies of magnifying colonoscopy and EUS were 88% and 72% ($P = .0785$), and for nonpolypoid lesions, 85% and 79% ($P = .7169$). HFUS requires additional training and equipment and can be time-consuming to use.

Nonlifting Sign

Observation of the lesion during and after submucosal saline injection is a simple but important method to assess the potential for deeply invasive cancer. Lesions may not lift because of desmoplastic reaction, invasion from the lesion itself, or submucosal fibrosis from prior biopsy, cautery, ink injection for marking, or ulceration.

Several studies have reported the diagnostic operating characteristics of the nonlifting sign: the positive predictive value of the nonlifting sign is approximately 80%. Originally, Uno and colleagues[23] described this terminology in 1994. Kobayashi and colleagues[24] also reported the verification of the nonlifting sign as one modality of depth diagnosis for colorectal cancers. The nonlifting sign had a sensitivity of 61.5%, a specificity of 98.4%, a positive predictive value of 80%, a negative predictive value of 96%, and an accuracy of 94.8%. In contrast, endoscopic diagnosis using magnifying chromoendoscopy of deeper infiltration had a sensitivity of 84.6%, a specificity of 98.8%, a positive predictive value of 88%, a negative predictive value of 98.4%, and an accuracy of 97.4%. Statistically significant differences were found in terms of sensitivity ($P = .031$) and accuracy ($P = .039$). In spite of the simplicity of such a technique, nonlifting sign could not reliably predict deeper cancerous invasion when compared with endoscopic diagnosis.

ESTIMATION OF SUBMUCOSAL INVASION USING CONVENTIONAL AND MAGNIFYING CHROMOENDOSCOPY

Conventional Colonoscopy

New diagnostic modalities such as endoscopic ultrasonography using miniprobe and magnifying chromoendoscopy are reported to be useful for the depth diagnosis of early colorectal cancers. However, these modalities are relatively expensive and time-consuming. Therefore, if invasion depth could be diagnosed with only conventional colonoscopy, it would be more cost-effective and convenient.

Saitoh and colleagues[25] reported that characteristic colonoscopic findings obtained by a combination of videocolonoscopy and chromoendoscopy are clinically useful for determination of the invasion depth of depressed-type colorectal cancers. In this report, characteristic colonoscopic findings, (ie, [1] expansion appearance, [2] deep depression surface, [3] irregular bottom of depression surface, and [4] folds converging toward the tumor) are needed for surgical operation. According to their results, the invasion depth of depressed-type early colorectal cancers could be correctly determined in 58 of 64 lesions (91%) by using these findings.

Data from National Cancer Center Hospital, Tokyo

To clarify the clinically important characteristic colonoscopic findings, the authors reviewed all conventional colonoscopic images of non-polypoid submucosal colorectal cancers treated endoscopically or surgically between 1999 and 2003. There were 123 non-polypoid submucosal colorectal cancers (IIa, LST: 34; IIc, IIa+IIc, Is+IIc [NPG type]: 89) as shown in **Table 1**. In this retrospective review, 7 characteristic colonoscopic findings, (1) tumor size, (2) white spots (chicken-skin appearance), (3)

Table 1
Clinicopathologic characteristics of non-polypoid submucosal cancers

	IIa, LST	IIc, IIa+IIc, Is+IIc
Number of lesions	34	89
Tumor size (mean±SD, mm)	25.4±18.2	15.3±6.8
Histopathologic diagnosis		
SM-superficial (<1000 μm)	19 (56%)	16 (18%)
SM-deep (≥1000 μm)	15 (44%)	73 (82%)
Location		
Right colon	14 (41%)	31 (35%)
Left colon	9 (27%)	23 (26%)
Rectum	11 (32%)	35 (39%)

Abbreviation: SM, submucosal.

redness, (4) firm consistency, (5) expansion, (6) fold convergence, and (7) deep depressed area (**Fig. 2**), were evaluated for association with submucosal deep invasion and then compared with histopathologic results.

Among all the non-polypoid submucosal colorectal cancers, white spots (chicken-skin appearance), redness, firm consistency, and deep depressed area were significantly associated with an increased risk of submucosal deep invasion according to univariate analysis (**Table 2**).

Magnifying Chromoendoscopy

Magnifying chromoendoscopy is a standardized validated method that facilitates detailed analysis of the morphologic architecture of colonic mucosal crypt orifices (pit pattern) in a simple and efficient manner. However, magnifying colonoscopes are still rarely used in endoscopy units. Unrecognized necessity and lack of

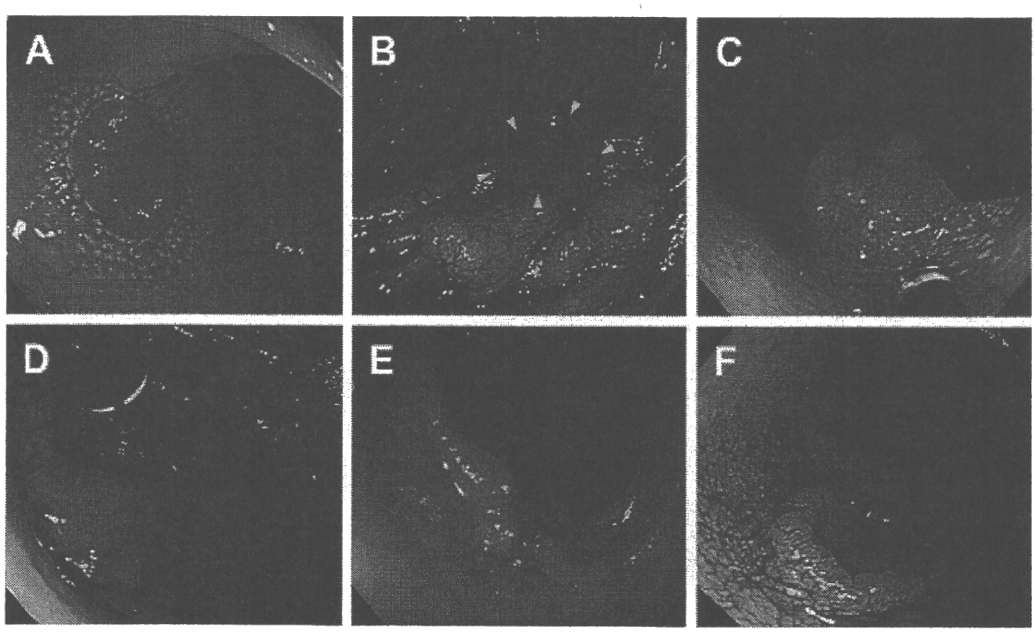

Fig. 2. Six characteristic colonoscopic findings: (*A*) white spots (chicken-skin appearance), (*B*) redness, (*C*) firm consistency, (*D*) expansion, (*E*) fold convergence, and (*F*) deep depressed area.