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ポリープ切除の大腸がん予防に及ぼす効果の評価と内視鏡検査間隔の適正化に関する前向き臨床試験に関する研究

平成２０年度～２２年度　総合研究報告書

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別紙２

目　　次

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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

本研究“ポリープ切除の大腸がん予防に及ぼす効果の評価と内視鏡検査間隔の適正化に関する前向き臨床試験：Japan Polyp Study（JPS）”は，我が国が誇る内視鏡を基盤とした初めての大規模な多施設共同前向き比較試験であり，平成15年2月より登録を開始した．平成18年12月末日（最終登録者数：3,926名）をもって登録を完了し，現在，割り付け後のフォローアップ全大腸内視鏡検査（TCS）と病理中央判定，割り付け前検査データの解析と論文化が進行中である．

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A．研究目的

大腸がんの高危険群としては，腺腫性ポリープ患者の存在が知られているが，これらに対して内視鏡的な予防介入（内視鏡摘除）を行う場合，1）微小ポリープに対する摘除の必要性，2）全大腸内視鏡検査（TCS）による精検処理能の限界，3）平均的リスク群と高リスク群における適正な検査間隔の設定，4）ポリープ摘除によるがん罹患率抑制効果の有無，など様々な要件が未解決であり，これらに対して医療経済の側面を含めた科学的な回答を得ることが急務となっている．

上記 3），4）については，米国より1993年に報告された National polyp study（NPS）の成績から，平均的リスク群では3cm以下の全ての腺腫を摘除すること（クリーンコロン）で，その後の検査間隔は3年で良いこと，さらに，一般人口や腺腫を摘除しなかった過去のデータとの比較により，76～90%の大腸がん累積罹患率の減少が期待できると結論づけられた．しかし本邦では，内視鏡検査および腸管前処置の質の違いと，本研究開始に際して行った遡及的検討結果から，表面陥凹型がんの存在を無視した NPSの結果に基づくこのガイドラインを完全には容認できないという結論に至った．本研究は，わが国の平均的リスク群に対して NPSと同質の前向き介入試験を行うことで，クリーコロンにおける適正な検査間隔を求めるとともに，欧米とは異なる日本独自の検査体制の要否（表面陥凹型大腸がん診断の意義），内視鏡的ポリープ摘除が大腸がん罹患率減少に及ぼす効果の有無とその程度を明らかにすることを目的に本臨床試験プロトコールを作成し，各研究施設（11施設）の倫理審査委員会の承認を得て，平成15年2

月より登録開始となった.

B．研究方法

【対象】40歳～69歳の健常者

【目的】大腸がん罹患の超高危険群（家族性大腸腺腫症・遺伝性非ポリポージス性大腸がん）を除く，全ての腫瘍性ポリープを摘除した対象者に対する全大腸内視鏡(TCS)の至適検査間隔期間について，1年と3年後に行う2回検査群と3年後のみに行う1回検査群とのランダム化比較試験によって評価する.

・Primary endpoint:

クリーンコロン後のIndex lesion（10mm以上の上皮性腫瘍・高度異型腺腫・がん腫）の発生割合.

・Secondary endpoint:

クリーンコロン後の全大腸腫瘍，陥凹型腫瘍，有害事象の発生割合.

尚，3年後のランダム化比較試験評価後は，浸潤がんの発生頻度，予後に関する長期経過観察から探索的検討を行う.

【除外・中止基準】

I）除外基準

1. 大腸切除の既往(虫垂切除は除く)
2. 大腸上皮性腫瘍に対する内視鏡切除の既往（既往病変について詳細な情報が確認されている場合は除外しない)
3. 炎症性腸疾患の既往，活動性感染性腸炎の現症
4. 家族性大腸腺腫症，遺伝性非ポリポージス性大腸がんの発端者または家系構成員
5. 重篤な合併症(活動性の他臓器がん)あり
6. クリーンコロン化困難例

II）中止基準

1. 1次・2次検査におけるクリーンコロン化不履行
2. 3cm以上の広基性腫瘍が存在
3. sm以深大腸がんあり
4. 炎症性腸疾患および活動性感染性腸炎
5. Total colonoscopy不可能
6. 他，本研究計画に不適格と判断される大腸疾患あり

【参加施設】：全国11施設（国立がん研究センター中央病院・国立がん研究センター東病院・藤井隆広クリニック・昭和大学横浜市北部病院・昭和大学病院・佐久総合病院・服部胃腸科・栃木県立がんセンター・静岡がんセンター・北里大学東病院・大阪成人病センター)

【サンプルサイズ】

当初，登録期間3年・目標登録者数3,000人と設定したが，1次・2次TCSにて腺腫性ポリープを有さない群が約20%認められたためサンプルサイズの再算出を行い，3,700名を最終目標登録者数に修正するプロトコール変更申請手続きを行った.

【方法】

1）文書による同意取得，2）1次TCSにより腫瘍性ポリープ全てを内視鏡摘除，データセンターに登録，3）全例1年後に再検査（2次TCS）を行い，初回検査での見逃しを含めた全ての腺腫性ポリープの摘除を行いクリーンコロンとする．その後，データセンターから2回検査群（1年と3年後の検査）と，1回検査群（3年後に検査）の割り付け情報を入手，4）経過観察中にみられるIndex lesion: IL（10mm以上の上皮性腫瘍，高度異型腺腫，がん腫）の発見割合を1回検査群と2回検査群間で比較し，クリーンコロン施行後3年間で2回検査が必要か，3年後の1回検査で十分かどうかを検証する.

尚，本研究のPrimary endpointは，ILの発見割合とし，1回検査群の3年後に発見されるIL発生割合と，1年と3年後の合計したIL発生割合の両群間の比較試験を行ない，2%以内を許容範囲とした非劣性試験である．

（倫理面への配慮）

本研究の実施に際しては，各参加施設（全国11施設）における倫理審査委員会での承認取得を前提条件とした．また，各施設にて生じる有害事象に関しては，モニタリング委員会（委員長：四国がんセンター 新海哲医師，他4名の医師より構成）を設置し，早急（72時間以内）に対処できるよう配慮している．

データ管理体制については，本研究に関する全ての試験データおよび参加患者プロファイルを匿名化し，データセンター（メディカル・リサーチ・サポート）による委託管理としている．外部からのデータ参照および抽出の防止には細心の注意を払っている．尚，本研究への参加については，十分な口頭での説明の上，文書による参加の同意を得ることを前提とした．また，患者側から試験中止の希望があった際には，患者意思を尊重し速やかに中止措置をとり，その後の診療においても患者不利益が生じないよう配慮している．

C．研究結果

現時点で，3,926 名の登録と 2,757 名の割り付け作業が完了し，2 回のクリーンコロン化とその後のフォローアップ TCS および病理中央判定が進行中である．割り付け状況は，2 回検査群（1.3 年後検査群）：1,087 名，1 回検査群（3 年後検査群）：1,079 名，腫瘍性ポリープ（-）群：591 名である．尚，平成 23 年 3 月現在，3 年後の最終 TCS 完了者数は，2 回検査群：695 名，1 回検査群：799 名，腫瘍性ポリープ（-）群：408 名の合計 1,902 名であり，2,000 名近い参加者が順調に本試験を完遂している．さらに，本試験の最終 TCS が完了した対象者については，今後約 10 年間の追跡調査を行うための再同意を文書で取得している．

現時点まで，本試験に伴う重篤な偶発症および大きな問題は生じておらず，最終的な結果が得られる平成24年まで，参加者の脱落をいかに最小限に抑えられるかが最大の課題と考えている．

本年度は，内視鏡検査におけるクリーンコロン化1年後のNew lesionの出現率（見逃し率）やInterval cancer，家族歴および成人病と発見病変との関係，クリーンコロン化に伴う内視鏡治療時の偶発症発生頻度などの解析を開始した．

また，平成 22 年度末の班会議において，今後の Outcome に関するディスカッションを行い，各種専門委員会（学術委員会・診断委員会・データベース作成管理委員会）の役割分担を再確認した．

D．考察

近年の内視鏡機器および診断・治療技術の向上にも関わらず，大腸がん罹患率・年齢調整死亡率は増加傾向にあり，その予防対策についての施策を講ずべき段階にある．わが国の検診システムは，便潜血反応によって集団から抽出された要精密検査群に対して，全大腸内視鏡検査が推奨されているが，その後に繰り返される経過観察例の増

加も相まって，検査件数は増大の一途を辿っている．また，内視鏡医の不足，検査処理能力の限界，医療費の増大などが社会問題ともなっている．

しかし，大腸がんは超高危険群（家族性大腸腺腫症，遺伝性非ポリポージス性大腸がん）を除けば，経過観察中に浸潤性大腸がんが発見されることは極めて少なく，適正な検査間隔指針の確立が求められている．本研究により，不必要な大腸内視鏡検査を減少させることが可能となり，医療経済学的に大きなメリットがあるものと考えられ，「がん対策基本法」の基本的施策に合致するものと思われる．

E．結論

【JPS 第 1 期】平成 12 年～平成 14 年：遡及的検討および JPS プロトコール作成．
【JPS 第 2 期】平成 15 年～平成 18 年：試験参加登録者数（3,700 名）の達成．
【JPS 第 3 期】平成 19 年～平成 21 年： 1 次・2 次 TCS と割り付け作業の完了および割り付け後検査・病理中央判定の遂行．

以上の達成目標を設定し，本研究を進めてきた．平成 21 年末時点で，割り付け作業が完了し，フォローアップ TCS をいかに脱落なく遂行していけるかが本研究成功の最大の課題である．平成 23 年度以降は，JPS から得られるデータをさらに国内・外に向けて発信していく．

米国の National Polyp Study (NPS)では，1,400 名程度のサンプルサイズをもって，クリーンコロン後 3 年後のフォローアップの妥当性を論じている．しかし，長年，我が国から報告してきた表面・陥凹型大腸腫瘍の重要性が，ここ数年欧米でも更に注目されるに至り，本研究の臨床的意義が高まっている．一般に内視鏡的に発見することが難しいと言われている表面・陥凹型腫瘍に対しても十分注意を払った本研究結果は，海外研究者からもその結果が期待されている．最終結果が得られる平成 24 年まで，参加 11 施設が一丸となって本研究成功に向けて尽力したい．

F．健康危険情報

報告すべき事項なし．

G．研究発表

1. 論文発表

① Matsuda T, Saito Y, Hotta K, Sano Y, Fujii T. Prevalence and clinicopathological features of nonpolypoid colorectal neoplasms: should we pay more attention to identifying flat and depressed lesions? Dig Endosc. 2010; 22; S57-62

② Matsuda T, Adolfo Parra-Blanco, Saito Y, Sakamoto T, Nakajima T. Assessment of likelihood of submucosal invasion in non-polypoid colorectal neoplasms. Gastrointest Endosc Clin N Am. 2010;20:487-96

③ Matsuda T, Gotoda T, Saito Y, Nakajima T, Conio M. Our perspective on endoscopic resection for colorectal neoplasms. Gastroenterol Clin Biol. 2010;34:367-70

④ Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Kuang-I Fu, Itoi T, Fujii T. Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection.

Surg Endosc. 2010;24:343-52
⑤ Bando H, Ikematsu H, Fu KI, Oono Y, Kojima T, Minashi K, Yano T, Matsuda T, Saito, Y, Kaneko K, Ohtsu A. A laterally-spreading tumor in a colonic interposition treated by endoscopic submucosal dissection. World J Gastroenterol. 2010;21;16:392-4
⑥ Kikuchi T, Fu KI, Saito Y, Uraoka T, Fukuzawa M, Fukunaga S, Sakamoto T, Nakajima T, Matsuda T. Transcutaneous monitoring of partial pressure of carbon dioxide during endoscopic submucosal dissection of early colorectal neoplasia with carbon dioxide insufflation: a prospective study. Surg Endosc. 2010; 24(9):2231-35
⑦ Fukuzawa M, Saito Y, Matsuda T, Uraoka T, Itoi T, Moriyasu F. Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer. World J Gastroenterol. 2010;14;16:1727-34
⑧ Ikematsu H, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y. Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms. BMC Gastroenterol. 2010 Mar 27;10(1):33
⑨ Uraoka T, Higashi R, Saito Y, Matsuda T, Yamamoto K. Impact of Narrow-Band Imaging in screening colonoscopy. Dig Endosc. 2010; 22; S54-56
⑩ Ikehara H, Saito Y, Matsuda T, Uraoka T, Murakami Y. Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy. J Gastroenterol Hepatol. 2010;25:905-12
⑪ Kakugawa Y, Kami M, Matsuda T, Saito Y, Kim SW, Fukuda T, Mori S, Shimoda T, Tanosaki R, Saito D. Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation. World J Gastroenterol. 2010 ;16:2907-12
⑫ Saito Y, Matsuda T, Fujii T. Endoscopic submucosal dissection of non-polypoid colorectal neoplasms. Gastrointest Endosc Clin N Am. 2010;20:515-24
⑬ Conlin A, Kaltenbach T, Kusano C, Matsuda T, Oda I, Gotoda T. Endoscopic resection of gastrointestinal lesions: Advancement in the application of endoscopic submucosal dissection. J Gastroenterol Hepatol. 2010;25:1348-57
⑭ Kobayashi N, Matsuda T, Sano Y. The natural history of non-polypoid colorectal neoplasms. Gastrointest Endosc Clin N Am. 2010;20:431-435
⑮ Higashi R, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, Matsuda T, Ikematsu H, Sano Y, Suzuki S, Murakami Y, Yamamoto K. Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program. Gastrointest Endosc. 2010;72:127-35
⑯ Bhandari P, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, Oda I, Gotoda T. Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: a prospective, randomized, controlled, blinded trial. Scand J Gastroenterol. 2010;45:357-61
⑰ Hotta K, Saito Y, Matsuda T, Shinohara T, Oyama T. Local recurrence and surveillance after endoscopic resection of large colorectal tumors. Dig Endosc. 2010;221:S63-8
⑱ Kishino T, Matsuda T, Sakamoto T,

Nakajima T, Taniguchi H, Yamamoto S, Saito Y. Recurrent advanced colonic cancer occurring 11 years after initial endoscopic piecemeal resection: a case report. BMC Gastroenterol. 2010 Aug 5;10:87

⑲ Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosaldissections (with video). Gastrointest Endosc. 2010;72(6):1217-25

⑳ Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, Kato K, Hamaguchi T, Shimada Y. Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer. Cancer Sci. 2010;101:1286-91

㉑ Matsuda T, Fujii T, Sano Y, et al. Five-Year Incidence of Advanced Neoplasia after Initial Colonoscopy in Japan: A Multicenter Retrospective Cohort Study. Jpn J Clin Oncol 2009;39:435-42

㉒ Matsuda T, Saito Y, Fujii T, Shimoda T, Sano Y, et al. Size does not determine the grade of malignancy of early invasive colorectal cancer. World J Gastroenterol 2009;15:2708-13

㉓ Lambert R, Kudo SE, Matsuda T, Triadafilopoulos G, et al. Pragmatic classification of superficial neoplastic colorectal lesions. Gastrointest Endosc 2009;70:1182-99

㉔ Parra-Blanco A, Matsuda T, Quintero E, et al. Validation of Fujinon intelligent chromoendoscopy with high definition endoscopes in colonoscopy. World J Gastroenterol 2009;15:5266-73

㉕ Kobayashi N, Saito Y, Matsuda T, et al. Treatment Strategy for Laterally Spreading Tumors in Japan: Before and After the Introduction of Colorectal Endoscopic Submucosal Dissection. J Gastroenterol 2009; 24: 1387-92

㉖ Takizawa K, Matsuda T, et al. Lymph Node Staging in Esophageal Squamous Cell Carcinoma: A Comparative Study of EUS vs CT. J Gastroenterol Hepatol 2009;24:1687-91

㉗ Uraoka T, Sano Y, Matsuda T, et al. Narrow-band imaging for improving colorectal adenoma detection: appropriate system function settings are required. Gut 2009;58:604-5

㉘ Chou YP, Saito Y, Matsuda T, et al. Novel diagnostic method of early squamous-cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection: a case report. Endoscopy 2009;41:283-5

㉙ Sano Y, Kaneko K, Soetikno R, et al. Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps. Gastrointest Endosc 2009;69:278-83

㉚ Hotta K, Fujii T, Saito Y, Matsuda T. Local recurrence after endoscopic resection of colorectal tumors. Int J Colorectal Dis 2009;24:225-30

㉛ Matsuda T, Saito Y, Fu KI, et al. Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate? - A pilot study. Am J Gastroenterol. 2008;103:1926-32.

㉜ Sung JJ, Sano Y, Matsuda T, et al. Asia Pacific Working Group on Colorectal Cancer. Asia Pacific consensus recommendations for colorectal cancer screening. Gut. 2008;57:1166-76.

㉝ Matsuda T, Fujii T, Sano Y, Shimoda T, et al. Efficacy of the

invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms. Am J Gastroenterol. 2008;103:2700-6.

㉞ Kudo S, Fujii T, Matsuda T, Shimoda T, et al. Nonpolypoid neoplastic lesions of the colorectal mucosa. Gastrointest Endosc. 2008;68:S3-47.

㉟ Uraoka T, Saito Y, Matsuda T, Sano Y, et al. Detectability of colorectal neoplastic lesions using a narrow-band imaging system: a pilot study. J Gastroenterol Hepatol. 2008;23:1810-5.

2. 学会発表（講演）

① Matsuda T: A polyp is found: What next? Predictors of recurrence: Japan Polyp Study (JPS). 2010, New Orleans, USA

② Matsuda T: Technique of ESD for treatment of early colonic neoplasia. 3rd Master Workshop on Novel Endoscopic Technology & ESD. 2010, Hong Kong

③ Matsuda T: Update on the Japan Polyp Study (JPS). 2010, Kuala Lumpur, Malaysia

④ Matsuda T: Japanese perspective on endoscopic resection for colorectal neoplasms. 2010, Bogota, Colombia

⑤ Matsuda T: Endoscopic diagnosis and treatment for early stage colorectal neoplasms. 2010, Beijing, China

⑥ Matsuda T: Risk of lymph node metastasis and recurrence rate in patients with pedunculated type early invasive colorectal cancer: a retrospective multicenter study. 2010, UEGW, Barcelona, Spain

⑦ Matsuda T: Submucosal colorectal cancer: Assessment and management. 2010, Marbella, Spain

⑧ Matsuda T: The Diagnosis and Treatment Strategies for the Precancerous and Early Colorectal cancer. 2009, Beijing, China

⑨ Matsuda T: Endoscopic Diagnosis and Treatment of Colorectal Neoplasms "Mucosectomy and ESD" 2009, Modena, Italy

⑩ Matsuda T: Endoscopic Diagnosis of Inflammatory Bowel Disease. Current Status and Problems in Diagnosis of Colitic Cancer/Dysplasia- With a Review of Literature 2009, Seoul, Korea

⑪ Matsuda T: New Modalities for Endoscopic Diagnosis of Pre-malignant and Malignant Colorectal Lesions. Advanced Education Course of Endoscopy- IEE (Image Enhanced Endoscopy). 2009, Taipei, Taiwan

⑫ Matsuda T: Endoscopic Diagnosis of Early Colorectal Cancer Using Newly Developed Modalities. 2009, Barcelona, Spain

⑬ Matsuda T: Colonoscopy Surveillance after Polypectomy- Comparison of NPS and JPS. 2009, Oviedo, Spain

⑭ Matsuda T: Endoscopic Resection for Early Stage Colorectal Neoplasms - EMR & EPMR: Endoscopic Piecemeal Resection. 2009, Oviedo, Spain

⑮ Matsuda T: New Endoscopy Modalities in the Diagnose of GI Cancers. 2008, Panama City, Panama.

⑯ Matsuda T: Colon Cancer: Optimizing Screening Colonoscopy and Endoscopic Treatment. GI-Hep Singapore 2008 GESS & SCRS Annual Scientific Meeting. 2008, Singapore.

⑰ Matsuda T: Flat Adenoma. 2008, Stresa, Italy.

⑱ Matsuda T, Sano Y, Oda I: Endoscopic Diagnosis of Flat and Depressed Colorectal Neoplasms. 2008, Bogota, Colombia.

⑲ Matsuda T, Sano Y, Oda I: Endoscopic Diagnosis of Nonpolypoid Colorectal Neoplasms. 2008, Santiago, Chile.

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

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsuda T, Saito Y, Hotta K, Sano Y, Fujii T.	Prevalence and clinicopathological features of nonpolypoid colorectal neoplasms: should we pay more attention to identifying flat and depressed lesions?	Dig Endosc.	22	S57-62	2010
Matsuda T, Adolfo Parra-Blanco, Saito Y, Sakamoto T, Nakajima T.	Assessment of likelihood of submucosal invasion in non-polypoid colorectal neoplasms.	Gastrointest Endosc Clin N Am.	20	487-96	2010
Matsuda T, Gotoda T, Saito Y, Nakajima T, Conio M.	Our perspective on endoscopic resection for colorectal neoplasms.	Gastroenterol Clin Biol.	34	367-70	2010
Saito Y, Fukuzawa M, Matsuda T, Fukunaga S, Sakamoto T, Uraoka T, Nakajima T, Ikehara H, Kuang-I Fu, Itoi T, Fujii T.	Clinical outcome of endoscopic submucosal dissection versus endoscopic mucosal resection of large colorectal tumors as determined by curative resection.	Surg Endosc.	24	343-52	2010
Bando H, Ikematsu H, Fu KI, Oono Y, Kojima T, Minashi K, Yano T, Matsuda T, Saito, Y, Kaneko K, Ohtsu A.	A laterally-spreading tumor in a colonic interposition treated by endoscopic submucosal dissection.	World J Gastroenterol.	;21;16:	392-4	2010
Kikuchi T, Fu KI, Saito Y, Uraoka T, Fukuzawa M, Fukunaga S, Sakamoto T, Nakajima T, Matsuda T.	Transcutaneous monitoring of partial pressure of carbon dioxide during endoscopic submucosal dissection of early colorectal neoplasia with carbon dioxide insufflatio	Surg Endosc	24(9)	2231-35	2010
Fukuzawa M, Saito Y, Matsuda T, Uraoka T, Itoi T, Moriyasu F.	Effectiveness of narrow-band imaging magnification for invasion depth in early colorectal cancer.	World J Gastroenterol.	14;16	1727-34	2010

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Ikematsu H, Matsuda T, Emura F, Saito Y, Uraoka T, Fu KI, Kaneko K, Ochiai A, Fujimori T, Sano Y.	Efficacy of capillary pattern type IIIA/IIIB by magnifying narrow band imaging for estimating depth of invasion of early colorectal neoplasms.	BMC Gastroenterol.	Mar 27;10(1)	33	2010
Uraoka T, Higashi R, Saito Y, Matsuda T, Yamamoto K.	Impact of Narrow-Band Imaging in screening colonoscopy.	Dig Endosc.	22	S54-56	2010
Ikehara H, Saito Y, Matsuda T, Uraoka T, Murakami Y.	Diagnosis of depth of invasion for early colorectal cancer using magnifying colonoscopy.	J Gastroenterol Hepatol.	25	905-12	2010
Kakugawa Y, Kami M, Matsuda T, Saito Y, Kim SW, Fukuda T, Mori S, Shimoda T, Tanosaki R, Saito D.	Endoscopic diagnosis of cytomegalovirus gastritis after allogeneic hematopoietic stem cell transplantation.	World J Gastroenterol.	16	2907-12	2010
Saito Y, Matsuda T, Fujii T.	Endoscopic submucosal dissection of non-polypoid colorectal neoplasms.	Gastrointest Endosc Clin N Am.	20	515-24	2010
Conlin A, Kaltenbach T, Kusano C, Matsuda T, Oda I, Gotoda T.	Endoscopic resection of gastrointestinal lesions: Advancement in the application of endoscopic submucosal dissection.	J Gastroenterol Hepatol.	25	1348-57	2010
Kobayashi N, Matsuda T, Sano Y.	The natural history of non-polypoid colorectal neoplasms.	Gastrointest Endosc Clin N Am.	20	431-435	2010
Higashi R, Uraoka T, Kato J, Kuwaki K, Ishikawa S, Saito Y, Matsuda T, Ikematsu H, Sano Y, Suzuki S, Murakami Y, Yamamoto K.	Diagnostic accuracy of narrow-band imaging and pit pattern analysis significantly improved for less-experienced endoscopists after an expanded training program.	Gastrointest Endosc.	72	127-35	2010

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Bhandari P, Green S, Hamanaka H, Nakajima T, Matsuda T, Saito Y, Oda I, Gotoda T.	Use of Gascon and Pronase either as a pre-endoscopic drink or as targeted endoscopic flushes to improve visibility during gastroscopy: a prospective, randomized, controlled, blinded trial.	Scand J Gastroenterol.	45	357-61	2010
Hotta K, Saito Y, Matsuda T, Shinohara T, Oyama T.	Local recurrence and surveillance after endoscopic resection of large colorectal tumors.	Dig Endosc.	22	S63-8	2010
Kishino T, Matsuda T, Sakamoto T, Nakajima T, Taniguchi H, Yamamoto S, Saito Y.	Recurrent advanced colonic cancer occurring 11 years after initial endoscopic piecemeal resection: a case report.	BMC Gastroenterol.	Aug 5;10:	87	2010
Saito Y, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D.	A prospective, multicenter study of 1111 colorectal endoscopic submucosaldissections (with video).	Gastrointest Endosc.	72(6)	1217-25	2010
Nakajima TE, Yamada Y, Hamano T, Furuta K, Matsuda T, Fujita S, Kato K, Hamaguchi T, Shimada Y.	Adipocytokines as new promising markers of colorectal tumors: adiponectin for colorectal adenoma, and resistin and visfatin for colorectal cancer.	Cancer Sci.	101	1286-91	2010
Matsuda T, Fujii T, Sano Y, et al	Five-Year Incidence of Advanced Neoplasia after Initial Colonoscopy in Japan: A Multicenter Retrospective Cohort Study	Jpn J Clin Oncol	39	435-42	2009
Matsuda T, Saito Y, Fujii T, Shimoda T, Sano Y, et al	Size does not determine the grade of malignancy of early invasive colorectal cancer	World J Gastroenterol	15	2708-13	2009

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Lambert R, Kudo SE, Matsuda T, Triadafilopoulos G, et al	Pragmatic classification of superficial neoplastic colorectal lesions	Gastrointest Endosc	70	1182-99	2009
Parra-Blanco A, , Matsuda T, Quintero E, et al	Validation of Fujinon intelligent chromoendoscopy with high definition endoscopes in colonoscopy	World J Gastroenterol	15	5266-73	2009
Kobayashi N, Saito Y, Matsuda T, et al	Treatment Strategy for Laterally Spreading Tumors in Japan: Before and After the Introduction of Colorectal Endoscopic Submucosal Dissection	J Gastroenterol	24	1387-92	2009
Takizawa K, Matsuda T, et al	Lymph Node Staging in Esophageal Squamous Cell Carcinoma: A Comparative Study of EUS vs CT	J Gastroenterol Hepatol	24	1687-91	2009
Uraoka T, Sano Y, Matsuda T, et al	Narrow-band imaging for improving colorectal adenoma detection: appropriate system function settings are required	Gut	58	604-5	2009
Chou YP, Saito Y, Matsuda T, et al	Novel diagnostic method of early squamous-cell carcinoma of the anal canal successfully resected by endoscopic submucosal dissection: a case report.	Endoscopy	41	283-5	2009
Sano Y, Kaneko K, Soetikno R, et al	Meshed capillary vessels by use of narrow-band imaging for differential diagnosis of small colorectal polyps	Gastrointest Endosc	69	278-83	2009
Hotta K, Fujii T, Saito Y, Matsuda T	Local recurrence after endoscopic resection of colorectal tumors	Int J Colorectal Dis	24	225-30	2009

別紙４

研究成果の刊行に関する一覧表

雑誌

発表者氏名	論文タイトル名	発表誌名	巻号	ページ	出版年
Matsuda T, Saito Y, Saito D. et al	Does autofluorescence imaging videoendoscopy system improve the colonoscopic polyp detection rate? - A pilot study.	Am J Gastroenterol.	103	1926-32.	2008
Sung JJ, Sano Y, Matsuda T, Chan FK. et al	Asia Pacific Working Group on Colorectal Cancer. Asia Pacific consensus recommendations for colorectal cancer screening.	Gut.	57	1166-76.	2008
Matsuda T, Fujii T, Sano Y, Shimoda T, Fujimori T. et al	Efficacy of the invasive/non-invasive pattern by magnifying chromoendoscopy to estimate the depth of invasion of early colorectal neoplasms.	Am J Gastroenterol.	103	2700-6.	2008
Kudo S, Lambert R, Fujii T, Matsuda T, Shimoda T, Hurlstone P D. et al	Nonpolypoid neoplastic lesions of the colorectal mucosa	Gastrointest Endosc.	68	S3-47	2008
Uraoka T, Saito Y, Matsuda T, Sano Y, Ikehara H, Mashimo Y, Kikuchi T, Saito D,Saito H.	Detectability of colorectal neoplastic lesions using a narrow-band imaging system: a pilot study.	J Gastroenterol Hepatol.	23	1810-5	2008

Digestive Endoscopy (2010) **22** (Suppl. 1), S57–S62 doi:10.1111/j.1443-1661.2010.00967.x

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?

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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

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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

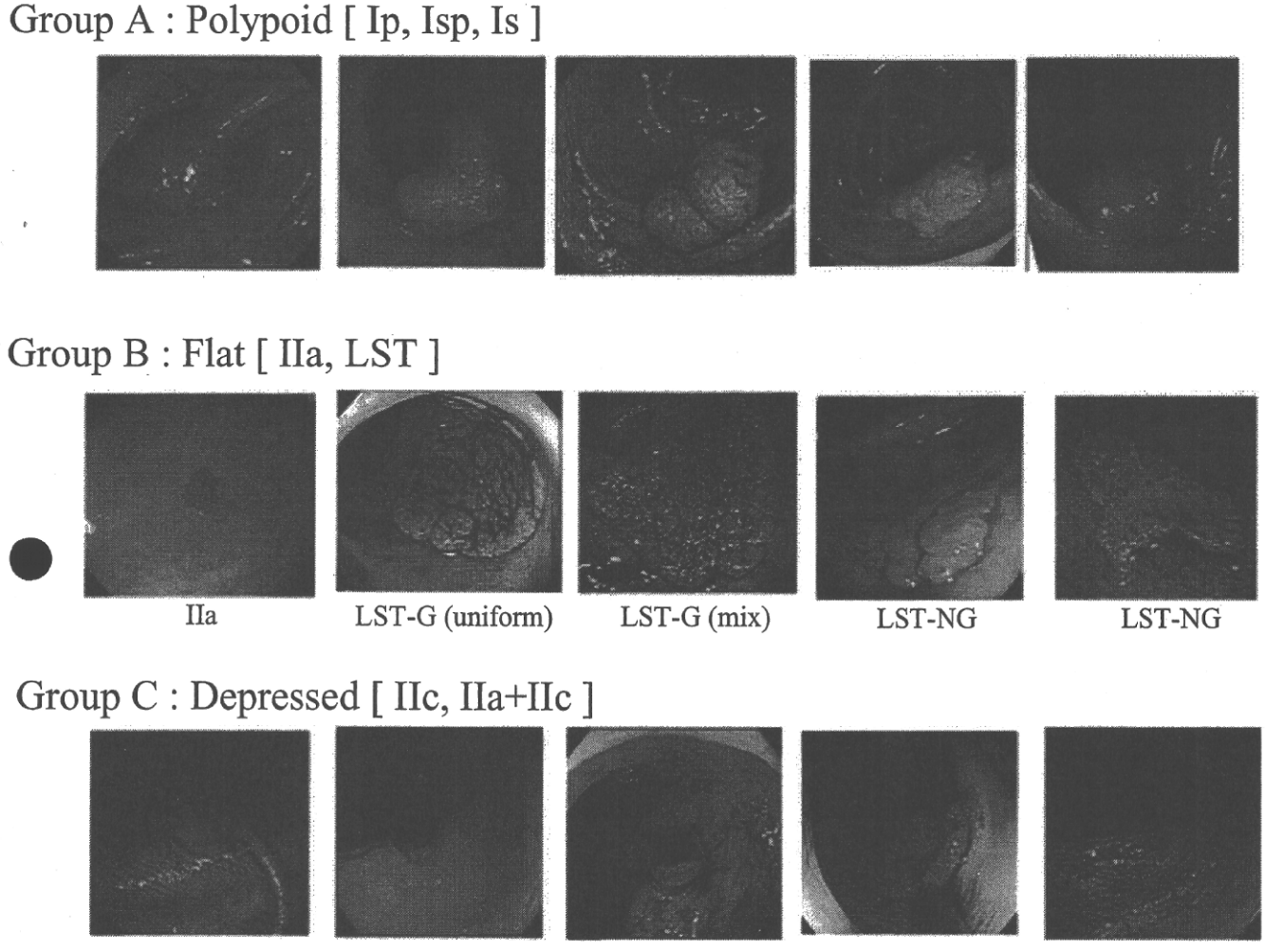

Fig. 1. Prevalence and malignant potential of flat and depressed lesions. LST, laterally spreading tumor (a flat elevated lesion ≥10 mm); LST-G, LST granular; LST-NG, LST non-granular.

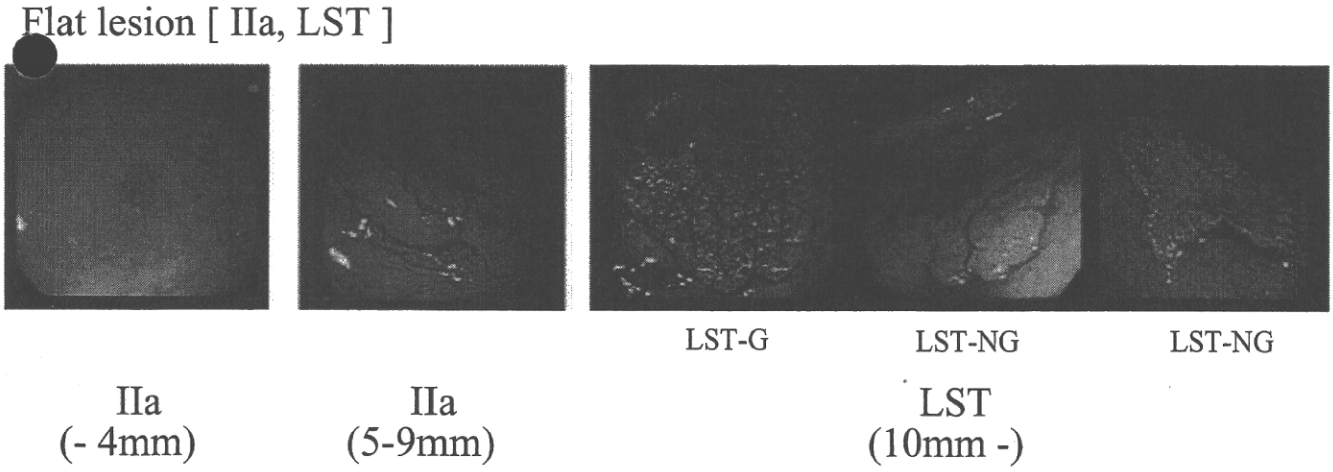

Fig. 2. Flat lesion (IIa, laterally spreading tumor [LST]). LST-G, LST granular; LST-NG, LST non-granular.

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	508:288:34	828	2
(830)	(61%:35%:4%)	(99.8%)	(0.2%)
5–9 mm	387:276:43	657	49
(706)	(55%:39%:6%)	(93.1%)	(6.9%)
10 mm -	260:111:82	203	250
(453)	(57%:25%:18%)	(44.8%)	(55.2%)
Total: 1989 lesions	1155:675:159	1688	301
	(58%:34%:8%)	(84.9%)	(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.

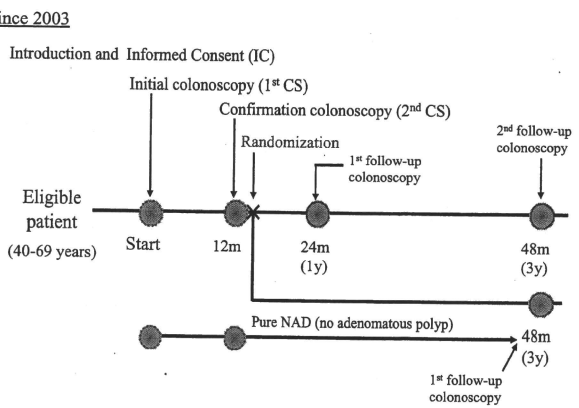

Fig. 3. Schematic overview of the Japan Polyp Study.

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.

REFERENCES

1. The Japanese Research Society for Cancer of Colon and Rectum. *General Rules for Clinical and Pathological Studies on Cancer of Colon, Rectum and Anus*, 2nd edn. Tokyo: Kanehara, 1983.
2. Muto T, Kamiya J, Sawada T *et al.* Small 'flat adenoma' of the large bowel with special reference to its clinicopathologic features. *Dis. Colon Rectum* 1985; **28**: 847–51.
3. Kariya A. A case of early colonic cancer type IIc associated with familial polyposis coli. 1977; **12**: 1359–64 (in Japanese with English abstract).
4. Kudo S. Endoscopic mucosal resection of flat depressed type of early colorectal cancer. *Endoscopy* 1993; **25**: 455–61.
5. Fujii T, Rembacken BJ, Dixon MF *et al.* Flat adenomas in the United Kingdom: are treatable cancers being missed? *Endoscopy* 1998; **30**: 437–43.
6. Saitoh Y, Waxman I, West AB *et al.* Prevalence and distinctive biologic features of flat colorectal adenomas in a North American population. *Gastroenterology* 2001; **120**: 1657–65.
7. Tsuda S, Veress B, Toth E, Fork FT. Flat and depressed colorectal tumours in a southern Swedish population: a prospective chromoendoscopic and histopathological study. *Gut* 2002; **51**: 550–5.
8. Wolber RA, Owen D. Flat adenomas of the colon. *Hum. Pathol.* 1991; **22**: 70–4.
9. Matsui T, Yao T, Iwashita A. Natural history of early colorectal cancer. *World J. Surg.* 2000; **24**: 1022–28.
10. Rembacken BJ, Fujii T, Cairns A *et al.* Flat and depressed colonic neoplasms: a prospective study of 1000 colonoscopies in the UK. *Lancet* 2000; **355**: 1211–14.
11. Parra-Blanco A, Gimeno-Garcia AZ, Nicolas-Perez D *et al.* Risk for high-grade dysplasia or invasive carcinoma in colorectal flat adenomas in a Spanish population. *Gastroenterol. Hepatol.* 2006; **29**: 602–9.
12. O'Brien MJ, Winawer SJ, Zauber AG *et al.* Flat adenomas in the National Polyp Study: is there increased risk for high-grade dysplasia initially or during surveillance? *Clin. Gastroenterol. Hepatol.* 2004; **2**: 905–11.