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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

平成２１年度　総括研究報告書

研究代表者　松田　尚久

平成２２（２０１０）年　３月

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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が進行中である．

尾田　恭　尾田胃腸内科・内科 院長
金子和弘　国立がん研究センター東病院 医長
工藤進英　昭和大学横浜市北部病院 教授
佐野　寧　佐野病院消化器センター 院長
谷口浩和　国立がん研究センター中央病院 医員
藤井隆広　藤井隆広クリニック 理事長
堀田欣一　佐久総合病院 医長

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 21 年末現在，3 年後の最終 TCS 完了者数は，2 回検査群：397 名，1 回検査群：455 名，腫瘍性ポリープ（-）群：231 名の合計 1,083 名であり，1,000 名を越える参加者が順調に本試験を完遂している．

また，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．

最終結果の報告前に，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予定している．

また，平成 21 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再度行い，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）の役割分担を明確にした．

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 22 年度以降は，JPS から得られるデータを海外に発信していく最終段階となる.

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, 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

② 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

③ Lambert R, Kudo SE, Matsuda T, Triadafilopoulos G, et al. Pragmatic classification of superficial neoplastic colorectal lesions. Gastrointest Endosc 2009;70:1182-99

④ 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

⑤ 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

⑥ Takizawa K, Matsuda T, et al. Lymph Node Staging in Esophageal Squamous

研究成果の刊行に関する
一覧表

平成２２（２０１０）年　３月

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

研究成果の刊行物・別刷

平成２２（２０１０）年　３月

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Five-year Incidence of Advanced Neoplasia after Initial Colonoscopy in Japan: A Multicenter Retrospective Cohort Study

Takahisa Matsuda[1], Takahiro Fujii[1], Yasushi Sano[2], Shin-ei Kudo[3], Yasushi Oda[4], Masahiro Igarashi[5], Hiroyasu Iishi[6], Yoshitaka Murakami[7], Hideki Ishikawa[8], Tadakazu Shimoda[9], Kazuhiro Kaneko[2] and Shigeaki Yoshida[2]

[1]Endoscopy Division, National Cancer Center Hospital, Tokyo, [2]Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa, [3]Digestive Disease Center, Showa University, Northern Yokohama Hospital, Yokohama, [4]Hattori GI Endoscopy and Oncology Clinic, Kumamoto, [5]Division of Digestive Endoscopy, Cancer Institute Ariake Hospital, Tokyo, [6]Division of Digestive Endoscopy and Gastrointestinal Oncology, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, [7]Department of Health Science, Shiga University of Medical Science, Shiga, [8]Department of Molecular-Targeting Cancer Prevention and Epidemiology for Community Health and Medicine, Kyoto Prefectural University of Medicine, Kyoto and [9]Clinical Laboratory Division, National Cancer Center Hospital, Tokyo

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Objective: The National Polyp Study is used as the basis of recommendations for colonoscopic surveillance after polypectomy, establishing an interval of 3 years after removal of newly diagnosed adenomas. The aim of this retrospective cohort study was to estimate the incidence of advanced neoplasia after initial colonoscopy and compare the differences among risk groups.

Methods: Patients over 40 years who were referred for initial colonoscopy at six institutes were selected. They were classified into four groups based on the initial colonoscopy: A, patients without any adenoma; B, with adenomas of <6 mm only; C, with adenomas of ≥ 6 mm; D, with any intramucosal cancer. The index lesion (IL) at follow-up colonoscopy was defined as large adenoma ≥ 10 mm, intramucosal/invasive cancer.

Results: A total of 5309 patients were enrolled in this study. Overall, median follow-up period was 5.1 years. The numbers of eligible patients in the various subgroups were A, 2006; B, 1655; C, 1123; D, 525. A total of 379 ILs were newly diagnosed during follow-up colonoscopy. The cumulative incidence of ILs in each group was A, 2.6%; B, 6.7%; C, 13.4%; and D, 12.6%.

Conclusions: Patients with any adenomas >6 mm or intramucosal cancer at the initial colonoscopy have a higher risk of advanced neoplasia during follow-up colonoscopy.

Key words: colonoscopy – polyp – colorectal cancer – screening – surveillance

INTRODUCTION

Colorectal cancer (CRC) is the third most common cause of cancer mortality in Japan (1). The identification and removal of adenomatous polyps and post-polypectomy surveillance are considered to be crucial for the control of CRC (2,3). However, recommendations for post-polypectomy surveillance in Japan have not been established. In current practice, the intervals between colonoscopies after polypectomy are variable, often annual, and not based on data from randomized clinical trials.

The evolution of CRC from a precursor lesion, the adenoma, was first reported in studies by Morson (4) as the adenoma–carcinoma sequence. The introduction of colonoscopy provided an opportunity for clarifying this sequence because of its ability to examine the entire colon and remove polyps for pathological examination. The epidemiology and natural history of adenomas are not only important for choosing the optimal follow-up policy after polypectomy,

For reprints and all correspondence: Takahisa Matsuda, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. E-mail: tamatsud@ncc.go.jp

but also for evaluating endoscopic screening for colorectal adenomas and cancer. The existence of flat and depressed lesions, including some with advanced histology, has been demonstrated in multiple recent series from several countries in the West and Japan (5–8). However, the clinical significance of flat and depressed (non-polypoid) lesions and whether they actually constitute alternative pathways to CRC is still controversial (9).

In the USA, the National Polyp Study (NPS) carried out since 1980 recommended an interval of at least 3 years between the colonoscopic removal of newly diagnosed adenomatous polyps and follow-up examination (2,3,10). However, the NPS was conducted prior to recent epidemiologic studies documenting the prevalence of non-polypoid lesions in the colorectum as well as other recent studies suggesting improvements in yield at colonoscopy with slower withdrawal times (11). Thus, the Japanese style colonoscopy, which consists of a bowel preparation using polyethylene glycol (PEG) solution given in the morning on the day of colonoscopy, and techniques such as chromoendoscopy required for the diagnosis of non-polypoid neoplasia (6,12,13) were not used and may at least in part explain the discrepancy between the results of NPS and those of the recent epidemiologic studies (14,15). The aim of this multicenter retrospective cohort study was to estimate the incidence of advanced neoplasia including the prevalence of non-polypoid lesions after initial colonoscopy using the Japanese style colonoscopy and to compare the differences among risk groups of such incidences.

PATIENTS AND METHODS

Subjects and Study Design

This multicenter retrospective cohort study was coordinated by the Japan Polyp Study Workgroup (JPSWG), which was set up in 2000 in Japan. Cases of screening patients over 40 years who were referred for initial total colonoscopy at the six institutes (National Cancer Center Hospital, National Cancer Center Hospital East, Akita Red Cross Hospital, Kitasato University East Hospital, Osaka Medical Center for Cancer and Cardiovascular Diseases, Hattori GI Endoscopy and Oncology Clinic) in Japan were followed up for >3 years from 1990 to 1995. Patients who did not have a familial or personal history of familial adenomatous polyposis, hereditary non-polyposis CRC, inflammatory bowel disease, a personal history of polypectomy or invasive CRC or a sessile adenoma with a base >30 mm where a piecemeal resection or closer follow-up would have been needed were selected for this retrospective cohort study. Written informed consent for examination and treatment were obtained from all of the studied patients prior to the procedures. We retrospectively reviewed colonoscopy reports and medical records for all patients.

They were classified into four groups according to the most advanced lesion found at initial colonoscopy: Group A, patients without any adenomatous polyp; Group B, patients with adenomas of <6 mm only; Group C, patients with adenomas of ≥ 6 mm; Group D, patients with any intramucosal (M) cancer. All adenomatous polyps of >6 mm and M cancers were removed at the initial colonoscopy. The index lesion (IL) diagnosed during follow-up colonoscopy was defined as follows: large adenomatous polyp ≥ 10 mm, M cancer and invasive cancer. In this study, we analyzed the cumulative incidence of ILs at follow-up colonoscopy for each patient based on the four groups.

Endoscopic Procedures

All patients were prepared for colonoscopy by administering 2–3 l of PEG on the examination day morning. Scopolamine butylbromide (10 mg) or glucagon (0.5 mg) was administered intravenously to patients with no contraindication prior to examination to avoid bowel movements. Medium-length colonoscopes were used, and one man method colonoscopy was performed. During colonoscopy, the location and the size of all detected lesions were documented and evaluated in real time and categorized as non-neoplastic or neoplastic using chromoendoscopy or magnifying chromoendoscopy. The size of the lesions was estimated using open biopsy forceps. Those diagnosed as non-neoplastic lesions were left untreated. If lesions were identified as neoplastic, hot biopsy, snare polypectomy or EMR was performed. Basically, polyps <6 mm were removed by coagulation biopsy (hot biopsy), and flat lesions or those ≥ 6 mm were treated with loop snare polypectomy or EMR. However, diminutive adenomatous polyps <6 mm were occasionally permitted to be left untreated. Finally, all neoplastic lesions with >6 mm and M cancers were completely removed at the initial colonoscopy. If lesions were diagnosed as invasive cancer, biopsy specimen was taken and patients were referred for surgery.

Histopathological Evaluation

Resected specimens were immediately fixed in 10% buffered formalin solution and subsequently stained with hematoxylin–eosin. Experienced gastrointestinal pathologists evaluated all pathological specimens. Histopathological diagnoses were determined according to the Japanese Research Society for Cancer of the Colon and Rectum (JRSCCR) and the World Health Organization (WHO) criteria (16,17).

Statistical Analysis

The cumulative incidence of ILs during the follow-up period was described by the Kaplan–Meier method. The Kaplan–Meier curves were compared in the four groups, and the cumulative incidence at 1-year, 3-year and the maximum follow-up period was estimated, respectively. For comparison, we re-categorized the above-mentioned four groups (A, B, C, D) into two (A + B, C + D), and the

cumulative incidences for the maximum follow-up period between the two groups were compared by a log-rank test. A two-sided P value of <0.05 was considered statistically significant. When the differences of the baseline characteristics between ILs were examined, the chi-squared test was used for the proportion and t-test for continuous variables. All statistical analyses were performed with SPSS statistical software (SPSS, version 16.0J, for Windows, Tokyo, Japan).

RESULTS

Subjects and Outlines of Follow-up Colonoscopy

A total of 5309 patients, including 3328 (63%) male patients, were enrolled in this study as shown in Table 1. Eligible patients were classified into four groups as follows: Group A, 2006 (38%); Group B, 1655 (31%); Group C, 1123 (21%); and Group D, 525 (10%). The mean age was 60.2, 63.2, 63.7 and 65.1 in Groups A, B, C and D, respectively. Overall, the median follow-up period and the frequency of colonoscopy were 5.1 years and 4.1 times, respectively. There were no significant differences in the follow-up period and the number of times in each group. Moreover, the average interval of colonoscopy was 21.3, 17.2, 16.8 and 13.9 months in Groups A, B, C and D, respectively.

Incidence of IL According to Initial Colonoscopy

A total of 379 ILs were newly diagnosed during follow-up colonoscopy. In Table 2, the incidence of ILs (%) and total cases (in parenthesis) in each group were as follows: Group A, 2.6% (52); Group B, 6.7% (111); Group C, 13.4% (150); and Group D, 12.6% (66). In Groups A, B, C and D, the cumulative incidence of ILs at 1 and 3 years was 0.1/0.8%, 1.0/2.9%, 2.5/5.4% and 2.9/5.7%, respectively. When we re-categorized four groups into two, the cumulative incidence of ILs at 1 and 3 years was 0.5/1.9% and 2.7/5.6% in Group A + B (low-risk group) and Group C + D (high-risk group), respectively. A significant difference was found between the low- and high-risk groups ($P < 0.0001$) (Fig. 1).

Clinicopathological Characteristics of ILs

There were 189 (50%), 125 (33%) and 65 (17%) right-sided, left-sided and rectal ILs, respectively, as shown in Table 3. Group A revealed right-sided ILs in 24 (46%), left-sided in 15 (29%) and rectal in 13 (25%). Similarly, Groups B, C and D exhibited right-sided ILs in 59 (53%), 74 (49%) and 32 (48%), left-sided in 32 (29%), 55 (37%) and 23 (35%) and rectal in 20 (18%), 21 (14%) and 11 (17%), respectively.

Of these ILs, 197 (52%) were large adenoma $\geq$10 mm, 143 (38%) were M cancer, 20 (5%) were submucosal (SM) invasive cancer and 19 (5%) were advanced (ADV) cancer. Group A revealed a large adenoma in 28 (54%), M cancer in 13 (25%), SM cancer in 4 (8%) and ADV cancer in 7 (13%). Similarly, Groups B, C and D exhibited large adenoma in 56 (50%), 80 (54%) and 33 (50%), M cancer in 46 (41%), 59 (39%) and 25 (38%), SM cancer in 3 (3%), 6 (4%) and 7 (11%) and ADV cancer in 6 (6%), 5 (3%) and 1 (1%), respectively.

Morphologically, the macroscopic types of ILs apart from ADV cancer were 220 (58%) polypoid, 122 (32%) flat and 18 (5%) depressed lesions (Table 4). Furthermore, concerning the occurrence time of IL, there were 69 (18%), 74 (20%), 50 (13%), 89 (23%) and 97 (26%) within 1, 1–2, 2–3, 3–5 and >5 years, respectively. Group A + B revealed within 1 year occurrence in 21 (13%), 1–2 years in 23 (14%), 2–3 years in 21 (13%), 3–5 years in 44 (27%) and >5 years in 54 (33%). Group C + D exhibited within 1 year occurrence in 48 (22%), 1–2 years in 51 (24%), 2–3 years in 29 (13%), 3–5 years in 45 (21%) and >5 years in 43 (20%).

Association of Baseline Characteristics with ILs

The 379 patients diagnosed with ILs were older than those without such findings (mean age, 65.4 vs. 62.2 years; $P = 0.02$). Patients who were classified into Group C + D seemed more likely to be diagnosed with an IL than those who were classified into Group A + B (4.5% vs. 13.1%; $P = 0.04$) and men seemed more likely than women to have an IL (8.5% vs. 4.8%; $P < 0.0001$) as shown in Table 5.

Table 1. Patient characteristics and outlines of follow-up colonoscopy

	Group A	Group B	Group C	Group D	Total
Patients [no. (%)]	2006 (38)	1655 (31)	1123 (21)	525 (10)	5309
Male sex [no. (%)]	934 (47)	1145 (69)	849 (76)	400 (76)	3328 (63)
Age[a] (years)	60.2 ± 9.8	63.2 ± 9.8	63.7 ± 9.1	65.1 ± 9.2	62.4 ± 9.8
Follow-up period[b] (years)	5.2 (3.0–12.3)	5.3 (3.0–10.7)	5.0 (3.0–11.0)	4.8 (3.0–10.2)	5.1 (3.0–12.3)
Number of exam times of TCS[a]	3.8 ± 1.7	4.3 ± 1.9	4.1 ± 1.8	4.5 ± 1.7	4.1 ± 1.8
Interval of TCS[a] (months)	21.3 ± 11.5	17.2 ± 8.4	16.8 ± 9.2	13.9 ± 6.7	18.3 ± 10.0

[a]Plus-minus values are mean ± SD.
[b]Median (range).

Table 2. Cumulative incidence of index lesions after initial colonoscopy

	Cumulative incidence (%)			*n*	Total number of incidence cases
	1-year	3-year	Maximum follow-up period		
Group A	0.1	0.8	2.6	2006	52
Group B	1.0	2.9	6.7	1655	111
Group C	2.5	5.4	13.4	1123	150
Group D	2.9	5.7	12.6	525	66
Group A + B (low risk)	0.5	1.9	4.5	3661	163
Group C + D (high risk)	2.7	5.6	13.1	1648	216

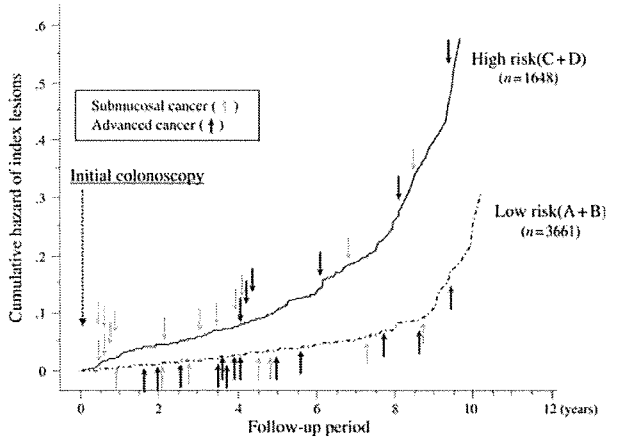

Figure 1. Comparison of cumulative incidence of index lesion and invasive colorectal cancer between risk groups.

Table 3. Clinicopathological characteristics of index lesions in each group

	Group A ($n = 52$)	Group B ($n = 111$)	Group C ($n = 150$)	Group D ($n = 66$)	Total ($n = 379$)
Location [no. (%)]					
Right colon[a]	24 (46)	59 (53)	74 (49)	32 (48)	189 (50)
Left colon[b]	15 (29)	32 (29)	55 (37)	23 (35)	125 (33)
Rectum	13 (25)	20 (18)	21 (14)	11 (17)	65 (17)
Histopathology [no. (%)]					
Adenoma (≥10 mm)	28 (54)	56 (50)	80 (54)	33 (50)	197 (52)
Intramucosal cancer	13 (25)	46 (41)	59 (39)	25 (38)	143 (38)
Submucosal cancer	4 (8)	3 (3)	6 (4)	7 (11)	20 (5)
Advanced cancer	7 (13)	6 (6)	5 (3)	1 (1)	19 (5)

[a]Cecum–transverse colon.
[b]Descending–sigmoid colon.

Table 4. Clinicopathological characteristics of index lesions in each group

	Group A ($n = 52$)	Group B ($n = 111$)	Group C ($n = 150$)	Group D ($n = 66$)	Total ($n = 379$)
Macroscopic type [no. (%)]					
Adenoma/early cancer					
Polypoid	26 (50)	52 (47)	94 (63)	48 (73)	220 (58)
Flat	18 (35)	46 (42)	44 (29)	14 (21)	122 (32)
Depressed	1 (2)	7 (6)	7 (5)	3 (5)	18 (5)
Advanced cancer	7 (13)	6 (5)	5 (3)	1 (1)	19 (5)
Occurrence time [no. (%)]					
<1 (year)	2 (4)	19 (17)	29 (19)	19 (29)	69 (18)
1–2	6 (12)	17 (15)	36 (24)	15 (23)	74 (20)
2–3	6 (12)	15 (14)	24 (16)	5 (7)	50 (13)
3–5	19 (36)	25 (23)	29 (19)	16 (24)	89 (23)
>5	19 (36)	35 (31)	32 (22)	11 (17)	97 (26)

Table 5. Association of baseline characteristics with index lesions

Baseline characteristics	Number (%)	Index lesion		*P* value
		No ($n = 4930$)	Yes ($n = 379$)	
Mean age[a] (year)		62.1 ± 9.7	65.4 ± 9.7	0.02
Age (year)				
40–49	487 (9.2)	463 (95.1)	24 (4.9)	
50–59	1640 (30.9)	1557 (94.9)	83 (5.1)	
60–69	1882 (35.4)	1737 (92.3)	145 (7.7)	
>70	1300 (24.5)	1173 (90.2)	127 (9.8)	
Sex				
Male	3328 (62.7)	3045 (91.5)	283 (8.5)	<0.0001
Female	1981 (37.3)	1885 (95.2)	96 (4.8)	
Category				
Group A	2006 (37.8)	1954 (97.4)	52 (2.6)	0.04
Group B	1655 (31.2)	1544 (93.3)	111 (6.7)	
Group C	1123 (21.1)	973 (86.6)	150 (13.4)	
Group D	525 (9.9)	459 (87.4)	66 (12.6)	

[a]Plus-minus values are mean ± SD.

Description of Patients Diagnosed with Invasive Cancer Within 3 Years

A total of 13 invasive cancers including three ADV cancers were newly diagnosed during the follow-up period within 3 years as shown in Table 6. The cancers were located in different sites; 8 out of the 13 were located at the sigmoid colon or rectum. The mean size was 14.1 ± 5.6 mm (range: 6–20 mm). Macroscopically, of these invasive cancers, six

(46%) were sessile/semi-pedunculated, five (39%) were depressed and two (15%) were flat lesions.

DISCUSSION

This is the first large multicenter retrospective cohort study to analyze the incidence of advanced neoplasia after initial colonoscopy in Japan. From our data, it is thought that patients with any adenomatous polyps of >6 mm or M cancer at the baseline colonoscopy have a higher risk of ILs rather than the other groups. Some authors have reported that patients categorized into a high-risk group, from the findings of initial colonoscopy, had high recurrence rates of colorectal adenomas. Recurrence rates dependent on adenoma characteristics have been reported as 15–60% within 3–4 years after previous endoscopic removal (3,18–21). In Japan, Yamaji et al. reported that recurrence rates of colorectal neoplasia were estimated to be 7.2% per year in those with no initial neoplasia, 19.3% per year in those with small adenomas and 22.9% per year in those with advanced lesions. However, this study was carried out in an asymptomatic patient cohort, unlike our current study, which includes both symptomatic and asymptomatic cases. For advanced colorectal lesions, the incidence rate was 0.21% per year, whereas recurrence rates in those with small adenomas and advanced lesions were 0.64% and 1.88% per year, respectively. From their study, the recurrence rates after polypectomy were elevated; however, the incidence rates in subjects with no neoplastic lesions initially were quite high (22). In contrast, Lieberman et al. (23) reported from the USA that the cumulative result represents the most advanced lesion found on any colonoscopy performed during the 5.5-year study period. Among 298 patients with no neoplasia at baseline who had follow-up evaluation, 67 (22.5%) had small tubular adenomas (<10 mm), and 2.4% had advanced neoplasia, including 1 (0.3%) patient with cancer. Basically, our results were in agreement with this report. The 5-year incidence of ILs in those with no initial neoplasia (Group A) was 2.6%, in those with small adenomas (Group B), large adenomas (Group C) and M cancers (Group D) were 6.7%, 13.4% and 12.6%, respectively. Moreover, the cumulative incidence of ILs at 1 and 3 years was 0.5/1.9% and 2.7/5.6% in Group A + B (low-risk group) and Group C + D (high-risk group), respectively. These results suggested that a surveillance colonoscopy after initial total colonoscopy should be performed at 3-year for patients without any polyps or with polyps <6 mm (low-risk group). In contrast, it should be performed at 1 year for patients with any large polyp (≥6 mm) or intramucosal cancer (high-risk group).

According to the latest guidelines from the USA, the recommendations for the surveillance interval for patients with one or two small (<10 mm) tubular adenomas with no high-grade dysplasia ranged from 5 to 10 years after baseline colonoscopy. On the other hand, patients with three or more adenomas, high-grade dysplasia, villous features or an adenoma ≥10 mm in size should have a 3-year follow-up colonoscopy (24). Lieberman et al. (23) reported that many of the interval cancers and large adenomas were discovered in the first 36 months after initial colonoscopy, raising issues about the quality of the colonoscopy. Among the 379 ILs, a total of 193 (51%) lesions, including 13 invasive cancers, were newly diagnosed within 3 years in our study, especially 7 SM cancers were detected in the first 12 months. A

Table 6. Description of 13 patients diagnosed with invasive cancer during the follow-up period within 3 years

Baseline characteristics					
Age (year)/sex	Category (group)	Months since initial colonoscopy	Location	Size/macroscopic type	Depth of lesion (T-stage)
41/M	C	4	Rectum	8 mm/Is (sessile)	SM (T1)
50/M	D	4	Sigmoid	10 mm/Is (sessile)	SM (T1)
61/M	C	6	Sigmoid	13 mm/Isp (semi-pedunculated)	SM (T1)
68/M	D	6	Sigmoid	15 mm/Isp (semi-pedunculated)	SM (T1)
68/F	C	8	Cecum	20 mm/IIa + IIc (depressed)	SM (T1)
69/F	D	9	Transverse	15 mm/IIa (LST-NG) (flat)	SM (T1)
71/M	B	11	Transverse	20 mm/IIa + IIc (depressed)	SM (T1)
67/F	A	19	Rectum	20 mm/Is (sessile)	MP (T2)
72/F	B	24	Rectum	10 mm/IIa + IIc (depressed)	MP (T2)
58/M	B	25	Ascending	6 mm/IIa + IIc (depressed)	SM (T1)
66/F	D	26	Transverse	6 mm/Is (sessile)	SM (T1)
47/M	A	30	Sigmoid	20 mm/IIa + IIc (depressed)	SS (T3)
75/M	B	32	Sigmoid	20 mm/IIa (LST-NG) (flat)	SM (T1)

SM, submucosa; LST-NG, laterally spreading tumor, non-granular; MP, muscularis propria; SS, subserosa.

diagnosis of ILs soon after complete colonoscopy shows that the procedure is not 100% sensitive in identifying prevalent neoplasia. It strongly suggests the possibility that prevalent neoplasia were missed at baseline colonoscopy. Significant miss rates of single colonoscopy, especially for small adenomas, have been estimated on the basis of back-to-back tandem colonoscopy. Rex et al. (25) reported that the miss rate for adenomas $\geq$10 mm was 6%, for adenomas 6–9 mm was 13% and for adenomas $\leq$5 mm was 27%. Similarly, in a recent study of virtual colonoscopy, conventional colonoscopy failed to detect 12% of lesions $\geq$10 mm (26).

From our data, among all ILs except ADV cancer, there were 122 (32%) flat and 18 (5%) depressed lesions. Non-polypoid colorectal neoplasms (NP-CRNs) are considered to have a high malignant potential and a high miss rate compared with polypoid ones of similar size (27–30). Soetikno et al. reported that the overall prevalence of NP-CRNs and NP-CRNs with *in situ* or SM invasive carcinoma was 9.35% and 0.82%, respectively. They also concluded that NP-CRNs were more likely to contain carcinoma (odds ratio: 9.78) than polypoid lesions, regardless of the size (30). In our study, among all 13 invasive cancers diagnosed during the 3-year follow-up period, there were seven (54%) NP-CRNs (five depressed and two flat lesions). Moreover, the mean size of these lesions was $<$15 mm in diameter. It is quite difficult to recognize such lesions compared with the polypoid ones; therefore, special attention must be paid to NP-CRNs during colonoscopy. Future advances in image-enhanced endoscopy (31), e.g. narrow band imaging (32–35), autofluorescence imaging (36,37) and chromoendoscopy (38,39), may improve the ability to detect flat and depressed lesions during colonoscopy, whereas the effect of such lesions on clinical outcomes still remains to be established.

The incidence of ILs during follow-up colonoscopy was associated with sex and age in our study. The association of advanced lesions with sex and age was not significant in previous studies (22,40,41); however, it can be concluded that ILs are more likely to develop in males and in older patients. Furthermore, we find that patients with polyps of $\geq$6 mm or with any M cancer at initial colonoscopy have a very high risk of interval advanced neoplasia during surveillance. Few studies have performed systematic follow-up of patients after curative resection of CRC (42,43). Nava and Pagana followed 240 patients for 4 years after curative resection of CRC. They detected 28 (11.7%) patients with cancer during the follow-up (43). In our high-risk group (Group C+D), 216 (13.1%) patients had ILs including 19 (1.2%) invasive cancers during the follow-up period. The chronology of this makes it more likely that these were missed lesions or followed the '*de novo* pathway' (44,45) rather than progression of the adenoma–carcinoma sequence.

There are several limitations in this study. First, this present study was a multicenter retrospective cohort study. The number of subjects was probably enough, however, a prospective study would help to overcome some of these limitations. Another point worth mentioning is that we could not investigate the main indication for colonoscopy at the time of initial examination. Therefore, subjects were not limited strictly to asymptomatic patients in this study. Actually, the prevalence of Group A, patients without any adenomatous polyp, was lower than the other study subjects (38% vs. 66%, 63%) (22,23). In addition, we could not evaluate the number of adenomas and adenomas with villous histology at initial colonoscopy. Several studies have found that individuals with either 3 or more adenomas, tubular adenoma $\geq$10 mm, villous adenoma or adenoma with high-grade dysplasia at a baseline screening colonoscopy have a similarly higher risk of advanced neoplasia within 5 years compared with patients with no polyps or 1 or 2 small ($<$10 mm) tubular adenomas. On the basis of the results of our current study, a prospective evaluation of these factors would seem logical in order to validate other international guidelines in the Japanese context. Regarding the JPS, we started to recruit the eligible patients since 2003 (46). The JPS is a multicenter randomized controlled trial designed to evaluate CRC surveillance strategies in patients who have undergone complete colonoscopies on two occasions, with the removal of all detected neoplasia by high-resolution colonoscope, including the removal of flat and depressed lesions. The JPS is intended to continue until 2011, and the last step of the randomization process and complete histopathological assessment are ongoing.

In conclusion, there is a strong relationship between the results of baseline colonoscopy and the rate of serious incident lesions during 5 years of surveillance. Patients with any adenomatous polyps of $\geq$6 mm or M cancer at the initial colonoscopy have a higher risk of advanced lesions compared with the lower risk group. Another issue is that important lesions were missed at the initial colonoscopy and detected during follow-up colonoscopy, although all examinations were performed by experts.

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Conflict of interest statement

None declared.

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Appendix

In addition to the authors listed in the author field, following are the authors who contributed equally to this study.

Kinichi Hotta: Department of Gastroenterology, Saku Central Hospital, Nagano.

Nozomu Kobayashi: Endoscopy Division, National Cancer Center Hospital, Tokyo.

Yutaka Saito: Endoscopy Division, National Cancer Center Hospital, Tokyo.

Kuang-I Fu: Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa.

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wjg@wjgnet.com
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ORIGINAL ARTICLES

Size does not determine the grade of malignancy of early invasive colorectal cancer

Takahisa Matsuda, Yutaka Saito, Takahiro Fujii, Toshio Uraoka, Takeshi Nakajima, Nozomu Kobayashi, Fabian Emura, Akiko Ono, Tadakazu Shimoda, Hiroaki Ikematsu, Kuang-I Fu, Yasushi Sano, Takahiro Fujimori

Takahisa Matsuda, Yutaka Saito, Takahiro Fujii, Toshio Uraoka, Takeshi Nakajima, Nozomu Kobayashi, Fabian Emura, Akiko Ono, Endoscopy Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Tadakazu Shimoda, Clinical Laboratory Division, National Cancer Center Hospital, Tokyo 104-0045, Japan
Hiroaki Ikematsu, Kuang-I Fu, Yasushi Sano, Division of Digestive Endoscopy and Gastrointestinal Oncology, National Cancer Center Hospital East, Kashiwa 277-8577, Japan
Takahiro Fujimori, Department of Surgical and Molecular Pathology, Dokkyo University School of Medicine, Shimotsuga, Tochigi 321-0293, Japan
Author contributions: Matsuda T, Saito Y and Fujii T contributed equally to this work; Matsuda T, Uraoka T, Nakajima T and Kobayashi N designed the research; Matsuda T, Ikematsu H, Fu KI and Sano Y performed the research; Shimoda T and Fujimori T performed the histopathology; Matsuda T, Saito Y, Emura F and Ono A wrote the paper.
Correspondence to: Takahisa Matsuda, MD, Endoscopy Division, National Cancer Center Hospital, 5-1-1 Tsukiji, Chuo-ku, Tokyo 104-0045, Japan. tamatsud@ncc.go.jp
Telephone: +81-3-35422511 Fax: +81-3-35423815
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Abstract

AIM: To clarify the clinicopathological characteristics of small and large early invasive colorectal cancers (EI-CRCs), and to determine whether malignancy grade depends on size.

METHODS: A total of 583 consecutive EI-CRCs treated by endoscopic mucosal resection or surgery at the National Cancer Center Hospital between 1980 and 2004 were enrolled in this study. Lesions were classified into two groups based on size: small (≤ 10 mm) and large (> 10 mm). Clinicopathological features, incidence of lymph node metastasis (LNM) and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

RESULTS: There were 120 (21%) small and 463 (79%) large lesions. Histopathological analysis of the small lesion group revealed submucosal deep cancer (sm: ≥ 1000 μm) in 90 (75%) cases, LVI in 26 (22%) cases, and PDA in 12 (10%) cases. Similarly, the large lesion group exhibited submucosal deep cancer in 380 (82%) cases, LVI in 125 (27%) cases, and PDA in 79 (17%) cases. The rate of LNM was 11.2% and 12.1% in the small and large lesion groups, respectively.

CONCLUSION: Small EI-CRC demonstrated the same aggressiveness and malignant potential as large cancer.

Key words: Colorectal cancer; Submucosal invasion; Lymph node metastasis; Endoscopic mucosal resection

Peer reviewers: Peter L Lakatos, MD, PhD, Assistant Professor, 1st Department of Medicine, Semmelweis University, Koranyi S 2A, Budapest H1083, Hungary; Javier San Martín, Chief, Gastroenterology and Endoscopy, Sanatorio Cantegril, Av. Roosevelt y P 13, Punta del Este 20100, Uruguay

Matsuda T, Saito Y, Fujii T, Uraoka T, Nakajima T, Kobayashi N, Emura F, Ono A, Shimoda T, Ikematsu H, Fu KI, Sano Y, Fujimori T. Size does not determine the grade of malignancy of early invasive colorectal cancer. *World J Gastroenterol* 2009; 15(22): 2708-2713 Available from: URL: http://www.wjgnet.com/1007-9327/15/2708.asp DOI: http://dx.doi.org/10.3748/wjg.15.2708

INTRODUCTION

Colorectal cancer (CRC) is the third most important cause of cancer mortality in Japan, and its incidence is gradually increasing. To reduce CRC mortality, early detection and appropriate treatment are required. In general, small lesions are suspected of having a lower malignant potential than large ones, and hence are easy to remove endoscopically. Several authors have reported that the malignant potential of early invasive colorectal cancer (EI-CRC) increases with lesion size[1-3]. Therefore, lesion size is considered to be indicative of the depth of invasion and presence of lymph node metastasis (LNM). In contrast, flat, and in particular depressed lesions, are considered to have a tendency to invade rapidly the submucosal layer, even when small[4-6]. However, clinicopathological features of small EI-CRCs have still

not been studied extensively.

The aim of this retrospective study was to clarify the clinicopathological characteristics of small and large EI-CRCs and their implications for endoscopic treatment.

MATERIALS AND METHODS

Subjects

Five hundred and eighty-three patients (374 male and 209 female) with EI-CRC that had been resected surgically or endoscopically at the National Cancer Center Hospital, between January 1980 and January 2004, were examined retrospectively. In all of these patients, cancer cells invaded through the muscularis mucosa into the submucosal layer but did not extend deeply into the muscularis propria. Eligibility also required the lesions to be macroscopically non-pedunculated (sessile, flat and depressed). Patients with synchronous advanced CRC, multiple EI-CRCs, inflammatory bowel disease, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis were excluded from the study.

Methods

All lesions were classified into two groups according to their endoscopic image size: small ($\leqslant$ 10 mm) and large (> 10 mm). Furthermore, lesions were classified into three categories (sessile, 0- I s, I s+ II a; flat, 0- II a; and depressed, 0- II c, II a+ II c, I s+ II c) according to the Paris classification[7]. Clinicopathological features, incidence of LNM and risk factors for LNM, such as depth of invasion, lymphovascular invasion (LVI) and poorly differentiated adenocarcinoma (PDA) were analyzed in all resected specimens.

Histopathology

Resected specimens were fixed in 10% formalin and examined histopathologically following hematoxylin and eosin staining. Histopathological diagnosis was based on the World Health Organization (WHO) criteria[8]. Submucosal invasion was measured from the muscularis mucosa to the deepest portion. When the muscularis mucosa could not be identified because of cancer invasion, the vertical length was measured from the surface of the lesion to the deepest portion according to Kitajima's classification[9]. Tumors with a vertical length of < 1000 μm in the submucosal layer were classified as submucosal superficial invasive cancers (sm-superficial), and lesions with a length $\geqslant$ 1000 μm were classified as submucosal deep invasive cancers (sm-deep). The tumor growth patterns were histopathologically divided into polypoid growth (PG) and non-polypoid growth (NPG) types. Shimoda *et al*[10] have reported polyp cancers with protrusions caused by intramucosal proliferation of the carcinoma or coexistent adenoma that behaved as PG type carcinoma, while flat/depressed type carcinoma without polypoid proliferation of intramucosal tumor behaved as NPG type carcinoma.

Statistical analysis

The significance of differences in proportions was assessed by the χ^2 test, Fisher's exact test and the Wilcoxon matched-pairs signed-ranks test using SPSS statistical software (SPSS for Windows , version 16.0J, Tokyo, Japan). Statistical significance was defined as $P < 0.05$.

RESULTS

A total of 583 EI-CRCs were retrospectively evaluated, with 120 (21%) small and 463 (79%) large lesions identified (Table 1). The gender ratio (male/female) was 2.4 and 1.7, and the mean age was 61.5 and 62.4 years in the small and large lesion groups, respectively. Mean size of the small and large lesions was 8.3 and 22.1 mm, respectively.

Macroscopic type, growth type and location

Macroscopic assessment of small lesions identified 51 cases as sessile (42%), 14 as flat (12%), and 55 as depressed (46%). Similarly, large lesion groups comprised 233 sessile (50%), 64 flat (14%), and 166 depressed (36%) type. PG types were identified in 32% (38/120) and 54% (250/463) of small and large lesions, respectively. In contrast, the prevalence of NPG type in the small lesion group was significantly higher than in the large lesion group (68% *vs* 46%, $P < 0.0001$). Regarding tumor location, there were 33 (27%) rectal, 56 (47%) distal colon and 31 (26%) proximal colon cancers in the small lesion group. In contrast, there were 213 (46%) rectal, 139 (30%) distal colon and 111 (24%) proximal cancers in the large lesion group. The incidence of rectal cancer in the large lesion group was significantly higher than in the small lesion group ($P = 0.02$).

LNM

Among the lesions treated surgically, the incidence of LNM was 11.2% (10/89) and 12.1% (46/381) in small and large lesion groups, respectively ($P = 0.85$) (Table 2).

Depth of invasion/LVI/PDA

Histopathological analysis of the small lesion group revealed sm-deep cancer in 90 (75%) cases, LVI in 26 (22%) and PDA in 12 (10%). Similarly, the large lesion group exhibited sm-deep cancer in 380 (82%) cases, LVI in 125 (27%), and PDA in 79 (17%). Therefore, in relation to depth of invasion, LVI and PDA, there were no significant differences between the groups.

Treatment strategy

Among the small lesion group, 62 (52%) cases were initially treated with endoscopic mucosal resection (EMR), while 58 (48%) cases were surgically resected. In contrast, among the large lesion group, 133 (29%) cases were initially treated with EMR, while 330 (71%) cases were surgically resected. Among all lesions treated by EMR, there were no differences in the rate of positive and unknown vertical and/or lateral cut margins in the small (18%, 11/62) and large lesion groups (20%, 26/133). Furthermore, among all positive cut margin cases in the small and large lesion groups, there were 11 (100%) and 18 (69%) positive vertical margin cases (Table 3, Figures 1 and 2).