have predictive value for sensitivity against EGFR inhibition, a newly developed CRC molecular target [51–54]. As neutralizing EGFR antibody is effective even against far-advanced CRC without K-*ras* mutation, the development of new treatments, including adjuvant chemotherapy, is eagerly anticipated. On the other hand, CRC with K-*ras* mutation proved ineffective by EGFR inhibition [53]. About 75% CRC cases with K-ras mutation had co-mutated PI3K [49] and, in such cases, downstream inhibition of both B-raf and PI3K may efficiently regulate CRC cells.

None of the rectal patients in the current study underwent radiotherapy either pre- or post-operatively, which may not represent the standard of care of rectal cancer worldwide, and perhaps would effect the outcome of the analysis. In rectal cancer, we would thus examine the K-ras mutation status and prognosis in such patients who undertake the standard therapy in the near future. Actually, we recently adopted neoadjuvant chemoradiotherapy for localized advanced rectal cancer before surgery [55,56]. Even if molecular target therapy such as anti-EGFR MoAb is used, CRC at stage IV has a dismal prognosis [51,52,57] and almost all patients will die of disease progression. That is why improving the prognosis of CRC depends upon improving treatment for curable cases, which includes adjuvant chemotherapy. The most promising treatment strategy for CRC is therefore to develop tailor-made adjuvant chemotherapy using novel indicators on the basis of oncogenic mutational profiles as in the present study.

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臨床研究 III

直腸癌に対する腹腔鏡下低位前方切除術後・早期固形食摂取の検討

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近年，結腸癌術後に早期経口摂取を開始する検討が行われており，大腸癌手術後の早期回復における役割は大きい．しかしながら，腹腔鏡下低位前方切除術において，術後早期固形食摂取を積極的に行っている報告はまだない．直腸癌に対する腹腔鏡下低位前方切除術後の早期固形食摂取の現状と安全性について検討する．

対象は腹腔鏡下低位前方切除術を施行した直腸癌20例である．術後1日目から飲水開始，術後2日目から固形食経口摂取開始予定とし，術後の飲水・摂食状況，摂食熱量，摂食後消化器症状，合併症，退院日などについて調査した．

食事経口摂取については，術後2日目に20例中18例（90%）で固形食の摂取が可能であった．早期経口摂取開始後に，誤嚥，縫合不全など，重篤な合併症を認めなかった．手術日から退院許可日までは中央値6日間で，術後在院期間は中央値9日間であった．

索引用語：ERAS，早期経口摂取，腹腔鏡下低位前方切除術

はじめに

我々の施設においては大腸癌周術期の早期回復プログラム（表1）を作成し，プログラムの一環として術後早期経口摂取を行っている．本邦においても結腸癌の術後に早期経口摂取開始の検討が行われており，大腸癌手術後の早期回復における役割は大きいと考えられる．しかしながら，腹腔鏡下低位前方切除術においては，直腸切離・吻合などの技術的困難性が存在し，高い縫合不全率の報告もあることから，一般的に術後早期経口摂取を積極的に行っている報告はまだない．

当院の直腸癌に対する腹腔鏡下低位前方切除術後の早期固形食摂取の現状と安全性について検討する事を目的とした．

対象および方法

対象は2006年8月から2008年9月までに当院にて一時的人工肛門を造設せずに腹腔鏡下低位前方切除術を施行した直腸癌20例である．20例の平均年齢は60.0歳（38～81歳），性別は男性14例・女性6例で，病変の主占拠部位は上部直腸17例・下部直腸3例であった（表2）．術前に心臓病食や腎臓病食などの特別食の摂取が必要な患者は含まれなかった．術後早期経口摂取開始の設定は，術後1日目から飲水開始，術後2日目から固形食経口摂取開始予定とした．経口摂取メニューは一般食の術後ライト食（図1）（総カロリー1,400kcal）を2日目から開始した．なお，術後ライト食とは当院独自の固形食であり，主食には「おむすび」を取り入れ，主菜には魚・肉などを用いるが，見た目の量を抑え食べやすさを工夫した食事である．ライト食を全量，摂取することで基礎代謝熱量はほぼ満たされるため，退院までライト食を継続した．ただし，患者の希望があれば一般常食に変更した．

クリニカルパスに沿って，術後2日目から全例に緩下剤（マグミット®330mg錠，1日6錠　毎食後）を投与した．主治医の判断で消化管機能改善薬を追加投与した．

退院許可規準は，(1)食事を5割以上摂取可能であること，(2) シャワー浴が可能であること，(3) 病棟外までの歩行運動が可能であること，(4)創部の自己

表 1　当院における大腸癌周術期早期回復プログラム

項目	内容
術前の炭水化物投与	術前経口補液食の実施
硬膜外麻酔法による術後鎮痛	患者自己調節鎮痛，フェンタニル硬膜外麻酔
術後の早期離床	術後 1 日目から歩行
経静脈栄養の早期終了	術後 2 日目で経静脈栄養を終了，過剰輸液回避
術後ドレーンの非留置	
胃管の非留置	術中のみ胃管を留置
明確な退院規準の設定	
術後の早期経口摂取開始	術後 2 日目から固形食開始

表 2　腹腔鏡下低位前方切除術症例の患者および手術背景因子

年齢（平均）	60.0 歳（38 ～ 81 歳）
性別（男性：女性）	14 例：6 例
BMI（平均）	22.4（15.4 ～ 32.8）
既往歴	アルコール性肝炎 1 例，内頸動脈狭窄症 1 例
	糖尿病 1 例，鬱病 1 例
病変の主占拠部位	
上部直腸：下部直腸	17 例：3 例
総合進行度（fStage）	
0：Ⅰ：Ⅱ：Ⅲ	1 例：10 例：1 例：8 例
手術時間（中央値）	270 分（159 分～ 501 分）
出血量（中央値）	20ml（0 ～ 100ml）
リンパ節郭清度（D3：D2）	8 例：12 例
再建方法	全例，自動吻合器による DST

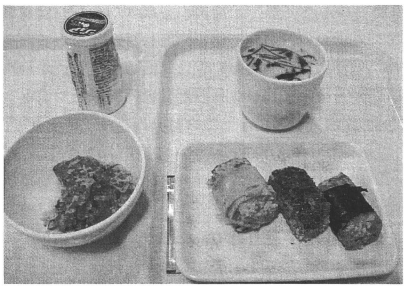

図 1　術後ライト食

管理が可能であること，(5) 37℃ 未満の体温が 2 日間以上継続していること，(6) 白血球数が正常範囲内であることのすべてを満たす事とした．

対象患者の飲水，摂食状況，摂食熱量，摂食後消化器症状，合併症，退院日などについて調査した．

結　果

飲水は全例で術後 1 日目に，誤嚥無く可能であった．食事経口摂取については，術後 2 日目に 20 例中 18 例（90%）で固形食の摂取が可能であった．術後 2 日目時点での早期経口摂取が不可能であった 2 症例は，食欲不振による摂食不能が 1 例，吻合部出血が 1 例であった．それぞれ術後 4 日目，25 日目から固形食の経口摂取を開始した．

術後 2 日目から固形食を開始した症例の排便状態は，初回排便を術後 1 日目に 3 例，術後 2 日目に 10 例，術後 3 日目に 5 例に認めた．初回排便後は 17 例で退院まで毎日排便を認めた．退院前日の排便回数は平均 3.3 回（1 から 10 回）であった．1 日以上の絶食を必要とするイレウスを 1 例に認めたが，保存的加療で軽快した．その他の消化器症状は，絶食を必要としない嘔吐を 1 例に認め，消化管機能改善薬投与後に症状は消失した．

吻合部出血のために経口摂取開始を見合わせていた症例で縫合不全を認めたため，保存的加療の後に

経口摂取を開始した．2日目からの固形食早期経口摂取を開始した症例では，誤嚥・縫合不全などの重篤な術後合併症を認めなかった．

早期経口摂取を開始した18例の術後2日目の経口摂取熱量は平均1,058kcal/日であり，20例の平均としても952kcal/日であった．経静脈栄養は術後2日目に7例，術後3日目に9例，術後5日目に2例，術後7日目に1例，術後32日目に1例，投与を終了した．

手術日から退院許可日までは中央値6日間（4から36日間）であり，術後在院期間は中央値9日間（8から40日間）であった．

考　察

近年，外科手術後入院期間の短縮や合併症発症の軽減を目的として，手術方法の工夫・麻酔および鎮痛方法の工夫・術前術後管理の工夫がなされてきている．これらの工夫を連合・結合させた総合的な早期回復プログラムは，「ERAS（enhanced recovery after surgery）プログラム」や「Fast-track プログラム」といった名称で呼ばれ，早期回復プログラムによる管理の結果，腹部手術の術後に早期回復が可能であったと報告されている[1,2]．また，結腸癌周術期に早期回復プログラムによって管理された患者は，早期退院が可能であったのみならず，術後の呼吸機能・心機能の低下も軽度であったとの報告もある[3,4]．欧米では，大腸癌周術期での従来法による管理と早期回復プログラムによる管理を比較したランダム化比較試験が既に行われ，両群間で術後合併症に差は無く，早期回復プログラム群の患者で入院期間の短縮が認められた[5,6]．一方，本邦でも手術・術後管理の進歩にともなって，術後疼痛の軽減や早期退院が可能となってきたが，周術期における早期回復プログラムの概念はまだ一般化しておらず，術前管理や栄養評価を含めた総合的な評価については今後の研究課題と考えられる[7]．当院では現在，大腸癌周術期管理の工夫として「術前の炭水化物投与」「硬膜外麻酔法による術後鎮痛」「術後早期離床」「経静脈栄養の早期終了」「術後ドレーンの非留置」「胃管の非留置」「明確な退院規準の設定」に並んで，「術後早期経口摂取開始」を加えており，当院での大腸癌周術期早期回復プログラムとしている．

術後早期の経口摂取開始については，欧米において大腸癌の術後に早期経口摂取を開始することで術後合併症の軽減が得られたことが報告され[8-11]，2006年に発表されたヨーロッパ静脈経腸栄養学会（ESPEN）ガイドラインでは消化器手術周術期においても，可能な限り絶食期間を短縮し，可能な限り早期に普通食に復帰させることを推奨している[12]．本邦においても結腸癌の術後に早期経口摂取開始の検討[13,14]が行われており，標準的なパスにおいては結腸癌術後の経口摂取開始は術後3日目から五分粥開始となっている（厚生労働省第3次対がん総合戦略研究事業・がんクリニカルパスデータベース構築に関する研究班による）．平塚ら[15]は開腹手術による結腸癌術後に早期経口摂取を行った患者で術後腸管機能回復が早く，入院期間が短縮したと述べており，縫合不全などの重篤な合併症を引きおこすことはなかった[16]．また，高橋ら[17]は直腸癌に対する開腹手術後に術後1日から粥食を開始する早期経口摂取の有効性を報告しているが，当院のような直腸癌術後の早期固形食の摂取はいまだ一般化していない．

本邦においては腹腔鏡下手術の普及とともに術後経口摂取開始時期が早期化されてきた[18]．しかしながら，腹腔鏡下低位前方切除術ではその低侵襲性・有効性が報告される一方で，技術的側面において直腸切離・吻合などの技術的困難性[19,20]が存在することや，縫合不全率についても開腹手術と同等であるとする報告[21]がある一方で，高い縫合不全率の報告もあり，一般的に直腸癌術後早期経口摂取を積極的に行っている報告はまだない．当院では開腹術による低位前方切除術後においても，早期回復プログラムとして，術後2日目からの経口摂取開始としており，その有用性を報告している[13]．我々の施設では直腸癌に対する腹腔鏡下低位前方切除術の適応をcStage 0またはIの直腸癌とし，開腹低位前方切除術の適応と患者背景は異なるものの，前述の経験から，低侵襲手術と考えられる腹腔鏡下低位前方切除術後においても少なくとも開腹手術後と同等以上の割合で術後2日目からの早期経口摂取が可能と推測し，今回の検討を行った結果，腹腔鏡下低位前方切除術後に，90％の症例で術後2日目からの固形食早期経口摂取が可能であった．

当院のプログラムでは術後の段階的食事アップではなく当初から固形食を開始している．従来法では排ガスを腸管機能回復の目安としてきたが，排ガス

は大腸機能回復の目安であり，消化管機能をすべて反映しているわけではなく，胃・小腸の運動が回復すれば，便塊を形成しにくい緩下剤投与などを併用することで，すぐに固形食の摂食が理論的には可能と考えられる[22]．術後栄養管理については，消化器手術後であっても静脈栄養を漫然と行うべきではなく，腸管の使用が可能であれば早期からの経口摂取・経腸栄養が望ましいとされている[12]．今回の検討では，早期経口摂取開始の設定を含む大腸癌周術期早期回復プログラムの適応の下で，腹腔鏡下低位前方切除術後2日目に平均1,058kcal/日の熱量の経口摂取が得られ，術後3日目までに20例中16例（80%）の症例で経静脈栄養を終了できた．また，早期経口摂取に関連すると考えられる重篤な合併症を認めず，術後入院日数は中央値9日間であった．

術後2日目の時点で食欲不振のために経口摂取を開始できなかった症例の原因は，既往症の鬱病が食欲に悪影響を及ぼした可能性や，あるいは，術後2日目からモサプリドを追加投与された後に症状が軽快した事から，消化管機能回復の遅延が食欲不振の原因であった可能性も考えられる．また，早期経口摂取を開始後に嘔吐症状があった症例は，大建中湯を投与された後に症状が軽快した．Narita ら[23]は，結腸癌の腹腔鏡下手術後の腸管機能回復にモサプリドが有効であったと報告している．当院では，現在，主治医の判断により消化管機能改善薬を投与しているが，消化管機能改善薬投与の早期回復プログラムへの導入について今後，検討予定である．

結　論

直腸癌に対する腹腔鏡下低位前方切除後には早期経口摂取が可能であり，早期摂取症例では重篤な合併症を認めなかった．

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Early Oral Nutrition in Patients with Rectal Cancer Undergoing Laparoscopic Low Anterior Resection

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BACKGROUNDS and AIMS: Early oral nutrition has been shown to accelerate recovery and decrease hospital stay after elective colonic surgery. Because the feasibility of early oral nutrition in patients with rectal cancer undergoing laparoscopic low anterior resection has not been demonstrated yet, we describe our initial results of early oral nutrition after laparoscopic rectal cancer surgery.

PATIENTS AND METHODS: Twenty consecutive unselected patients undergoing laparoscopic low anterior resection without loop ileostomy for rectal cancer by one surgeon underwent the early oral nutrition program. The patients were scheduled to drink clear liquid from postoperative day 1 and take solid food from day 2 in our program. Demographic and operative data, gastrointestinal function, calorie intake, local and general complications, mortality and hospital stay were assessed.

RESULTS AND FINDINGS: On postoperative day 2, 18 of the 20 patients (90%) tolerated solid food. General complications (aspiration, anastomotic leakage, etc.) were not seen after early initiation of oral nutrition. The median postoperative hospital stay was 9 days (4-36), and 6 days were needed to meet the discharge criteria after laparoscopic surgery. Postoperative hospital stay compared favorably to other series with traditional perioperative nutrition. Early initiation of oral nutrition was feasible in patients with rectal cancer undergoing laparoscopic low anterior resection.

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Risk Factors for Metachronous Gastric Cancer in the Remnant Stomach After Early Cancer Surgery

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Abstract
Background Early gastric cancer patients have a good prognosis after radical resection. However, if the patients have a gastric remnant after the surgery, the risk of metachronous gastric cancer remains. The aim of this study was to clarify the risk factors for metachronous gastric cancer after partial gastrectomy for early gastric cancer.
Methods Data on a series of 1281 consecutive gastrectomy patients with pathologically confirmed early gastric cancer from 1991 to 2007 in Shikoku Cancer Center were analyzed retrospectively.
Results The gastric remnants of 868 patients were periodically surveyed by endoscopic examination. Among those surveyed cases, 26 patients were diagnosed as having metachronous gastric cancer in the gastric remnant. They underwent curative resection by remnant gastrectomy ($n = 13$ patients) or endoscopic mucosal resection ($n = 13$ patients). Multivariate analysis showed that male sex, older age, submucosal invasion, and proximal gastrectomy were independent risk factors.
Conclusions Our data suggested that more intensive endoscopic follow-up is needed for the remnant stomach in patients with these risk factors to detect metachronous gastric cancer at its early stage.

Introduction

Gastric cancer is one of the most common types of solid tumor; it is estimated to be the fourth most common in terms of morbidity and the second most frequent cause of cancer death in the world [1]. To remove gastric cancers curatively, partial gastrectomy is one of the most common procedures [2]. However, if the patients have a gastric remnant after the surgery, the risk of metachronous gastric cancer remains [3, 4]. Because early gastric cancer patients have a good prognosis after curative surgery [2, 5], the incidence of metachronous gastric cancer in the remnant stomach is now problematic [3, 4, 6, 7]. For early detection and curative treatment of metachronous gastric cancer, periodic endoscopic examinations of the gastric remnant are extremely important. However, a follow-up program that is too intensive may not be of benefit to the patient. Therefore, it is necessary to clarify the risk factors of metachronous gastric cancer to develop an optimal endoscopic surveillance program. To the best of our knowledge, a multivariate analysis of risk factors has been performed for gastric remnant cancer only after peptic ulcer surgery [8–10] but never for gastric remnant cancer as a metachronous lesion following cancer surgery. In the present study, we conducted a multivariate analysis for the risk factors of metachronous gastric cancer after early cancer surgery.

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Patients and methods

A retrospective database review of a series of 1281 consecutive cases of gastrectomy for pathologically confirmed early gastric cancer from 1991 to 2007 in Shikoku Cancer Center identified 1091 patients who underwent partial gastrectomy (Fig. 1). Negative surgical margins were confirmed by pathology examination in the resected specimens of all of these patients. Following surgery, the patients were advised to undergo surveillance endoscopic examinations at short intervals—annually if possible or every 2 to 3 years as the maximum interval. Among the above-described patients, 868 patients underwent such endoscopic examinations at Shikoku Cancer Center with a follow-up time of more than 1 year after the partial gastrectomy and were included in this study.

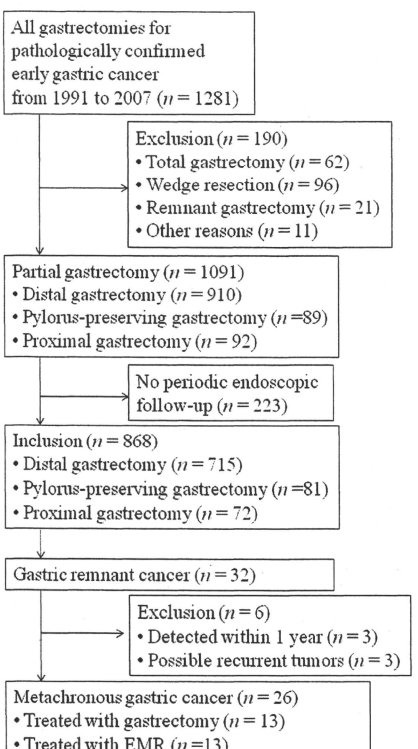

Fig. 1 Selection criteria for patients in this study. A series of 1281 consecutive gastrectomies for pathologically confirmed early gastric cancer from 1991 to 2007 was analyzed retrospectively. Of these patients, 1091 underwent partial gastrectomy and 868 had periodic endoscopic surveillance and were included in our univariate and multivariate analysis. A total of 32 patients were diagnosed as having gastric remnant cancer. Among those patients, 26 were finally diagnosed as having metachronous gastric cancer. *EMR* endoscopic mucosal resection

Early gastric cancer, defined as that invading the mucosal or submucosal layer regardless of lymph node metastasis, was classified according to the Japanese Classification of Gastric Carcinoma [11]. To exclude recurrent lesions or synchronous multiple gastric cancers from this study, metachronous gastric cancer in the remnant stomach was defined using the following criteria: (1) that curative surgery of the initial cancers had been carried out with adequate surgical margins (≥5 mm); (2) that the secondary cancers were found distant from the site of the anastomosis or the suture line; (3) that the secondary cancers were detected by endoscopic examinations >1 year after the partial gastrectomy. Any lesions detected <1 year after gastrectomy were considered to be a synchronous multiple gastric cancer that had not been detected during the first operation. Any tumors that did not meet the criteria were diagnosed as a possible recurrent tumor or a synchronous multiple cancer and were excluded from this study.

The partial gastrectomy performed on the patients in our population included three types of gastrectomy. First, distal gastrectomy, the most standard procedure for gastric cancer [2], was carried out for gastric cancer located in the middle or lower part of the stomach, with two-thirds to four-fifths of the distal stomach resected depending on the tumor location. Second, pylorus-preserving gastrectomy was performed for gastric cancer located in the middle of the stomach. Here, two-thirds of the distal stomach, except the pyloric lesion (3 cm in length) was resected [12]. Finally, proximal gastrectomy was carried out for gastric cancer located in the upper third of the stomach, in which one-third to one-half of the proximal stomach was resected depending on the tumor location [13]. Wedge resection was excluded from this study because it is not a partial gastrectomy, and the stomach after this surgery is not usually called a gastric remnant [14].

For all of the surveillance endoscopic examinations, the mucosa of the gastric remnant was carefully observed. Any suspicious lesions were biopsied and examined histologically. Follow-up time was defined as the period from the partial gastrectomy until the detection of metachronous gastric cancer by endoscopic examination or until the last endoscopic follow-up, at which point data were censored.

The cumulative prevalence of metachronous gastric cancer was calculated by the Kaplan–Meier method. Univariate and multivariate Cox proportional hazard models were used to estimate the relation of clinicopathologic characteristics and metachronous gastric cancer. The level

of significance was set at $P < 0.05$. Factors for multivariate analysis were selected by means of a forward stepwise approach using a significance level of $P < 0.10$ for entering or remaining in the model. The StatView program, version 5 (SAS Institute, Cary, NC, USA) was used for all statistical analysis.

Results

A retrospective review of our database spanning from 1991 to 2007 and containing a series of 1281 consecutive gastrectomy patients for pathologically confirmed early gastric cancer in Shikoku Cancer Center identified 1091 patients who underwent partial gastrectomy (Fig. 1). Among those patients, 868 patients underwent periodic endoscopic examinations at Shikoku Cancer Center with a follow-up time of >1 year after gastrectomy. The median follow-up time from the partial gastrectomy to the last endoscopic examination was 46 months (range 12–193 months). Most of these patients underwent distal gastrectomy ($n = 715$ patients), with the remainder having either pylorus-preserving gastrectomy ($n = 81$ patients) or proximal gastrectomy ($n = 72$ patients).

Among those cases surveyed, 32 patients were diagnosed as having a gastric remnant cancer. Using our criteria (see "Patients and methods"), 26 patients were finally diagnosed as having a metachronous gastric cancer. Of the six patients who did not meet the criteria, three had a possibly recurrent tumor and three had synchronous multiple gastric cancer.

Additional treatments for patients with metachronous gastric cancer included remnant gastrectomy for 13 patients and endoscopic mucosal resection for 13 patients. All these resections were confirmed curative by pathology examinations. The types of first gastrectomy for the patients were distal gastrectomy ($n = 18$ patients), pylorus-preserving gastrectomy ($n = 2$ patients), and proximal gastrectomy ($n = 6$ patients). The metachronous gastric cancer in the two patients who had undergone pylorus-preserving gastrectomy did not involve the preserved pyloric lesion but was in the proximal gastric remnant. The median follow-up time from the partial gastrectomy to the detection of metachronous gastric cancer was 37 months (range 13–149 months). Figure 2 shows Kaplan–Meier estimates of the cumulative prevalence of metachronous gastric cancer. The cumulative 3-year prevalence rate was estimated as 1.9%. Table 1 shows clinicopathologic characteristics of 26 metachronous gastric cancers. Most of these patients had a T1 tumor at its early stage ($n = 23$ patients), with the remainder having a T2 or T3 advanced tumor ($n = 3$ patients). Pathologic lymph node metastasis was not found in any patients who underwent remnant gastrectomy.

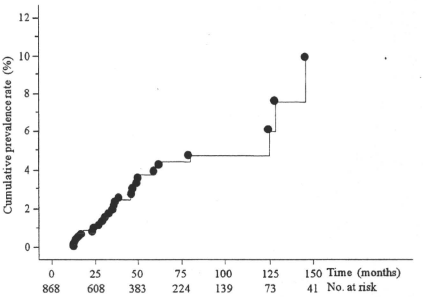

Fig. 2 Kaplan–Meier estimates of the cumulative prevalence of metachronous gastric cancer in the remnant stomach after partial gastrectomy for early gastric cancer. *Filled circles* indicate the 26 incidences of metachronous gastric cancer. The cumulative 3-year prevalence was estimated at 1.9%

Table 1 Clinicopathologic characteristics of metachronous gastric cancers: correlation with type of treatment

Factor	Total no.	Type of treatment	
		Gastrectomy	EMR
No. of patients	26	13	13
Sex			
Male	24	11	13
Female	2	2	0
Age			
≤60 years	4	3	1
>61 years	22	10	12
Histology			
Intestinal	18	5	13
Diffuse	8	8	0
Depth of invasion			
T1	23	10	13
T2	2	2	0
T3	1	1	0
Node metastasis			
Negative	13	13	–
Positive	0	0	–
Tumor size			
<30 mm	23	10	13
>31 mm	3	3	0

EMR endoscopic mucosal resection

To identify which clinicopathologic characteristics at the time of first surgery served as risk factors for metachronous gastric cancer, Cox regression analysis was performed. Upon univariate Cox regression analysis, male sex, older age, tumor location in the upper third of the stomach,

submucosal invasion, and having undergone proximal gastrectomy were significantly correlated with a higher incidence of metachronous gastric cancer (Table 2). Multivariate Cox regression analysis showed that male sex, older age, submucosal invasion, and proximal gastrectomy were significant risk factors for metachronous gastric cancer.

Table 2 Univariate and multivariate Cox regression analysis of risk factors for metachronous gastric cancer: correlation with clinicopathologic characteristics at the time of partial gastrectomy

Factors	No.	Metachronous GC	Univariate analysis		Multivariate analysis[c]	
			OR (95% CI)	*P*	OR (95% CI)	*P*
Total patients	868	26 (3.0%)	–	–	–	–
Sex						
Male	566	23 (4.1%)	1		1	
Female	302	3 (1.0%)	0.23 (0.07–0.76)	0.016	0.27 (0.08–0.89)	0.032
Age						
<60 years	338	6 (1.8%)	1		1	
>61 years	530	20 (3.7%)	2.97 (1.17–7.52)	0.022	2.83 (1.10–7.30)	0.032
Cancer history other than GC						
Negative	770	21 (2.7%)	1			
Positive	98	5 (5.1%)	1.77 (0.67–4.71)	0.250		
Synchronous multiple GCs						
Negative	788	23 (2.9%)	1			
Positive	80	3 (3.8%)	1.40 (0.42–4.66)	0.585		
Tumor location						
Upper third	83	6 (7.2%)	1			
Middle third	493	11 (2.2%)	0.27 (0.10–0.72)	0.009		
Lower third	292	9 (3.1%)	0.38 (0.14–1.07)	0.066		
Gross appearance[a]						
Protruded	172	6 (3.5%)	1			
Depressed	673	19 (2.8%)	0.76 (0.30–1.90)	0.556		
Tumor size						
<30 mm	492	14 (2.8%)	1			
>31 mm	376	12 (3.2%)	1.22 (0.56–2.65)	0.610		
Histology						
Intestinal	495	17 (3.4%)	1			
Diffuse	373	9 (2.4%)	0.66 (0.29–1.48)	0.310		
Depth of invasion						
Mucosa	469	7 (1.5%)	1		1	
Submucosa	399	19 (4.8%)	3.27 (1.38–7.81)	0.007	3.03 (1.27–7.25)	0.013
Node metastasis						
Negative	767	23 (3.0%)	1			
Positive	101	3 (3.0%)	1.14 (0.34–3.81)	0.830		
Vascular or lymphatic invasion						
Negative	647	17 (2.6%)	1			
Positive	221	9 (4.1%)	1.97 (0.87–4.43)	0.102		
Type of partial gastrectomy[b]						
Distal part	796	20 (2.5%)	1		1	
Proximal part	72	6 (8.3%)	3.95 (1.58–9.90)	0.003	3.53 (1.40–8.93)	0.008

GC gastric cancer, *OR* odds ratio, *CI* confidence intervals

[a] Flat type was included in the protruded type

[b] Pylorus-preserving gastrectomy was included in the distal part

[c] A forward stepwise approach was used to select factors for multivariate analysis

Discussion

We have previously reported that metachronous gastric cancer arose significantly more often after proximal than after distal gastrectomy [15]. In the present study, we updated our database to perform a more comprehensive multivariate analysis. As a result, we determined that the significant risk factors of metachronous gastric cancer were male sex, older age, submucosal invasion, and proximal gastrectomy. Our previous conclusion was therefore validated by the current multivariate analysis. To the best of our knowledge, this is the first report that shows the multivariate analysis of risk factors for metachronous gastric cancer in the remnant stomach after cancer surgery. Although it has been reported that the incidence of metachronous gastric cancer after partial gastrectomy for early gastric cancer is 0.6–2.9% [3, 6, 7], none of the previous studies demonstrated any risk factors for metachronous gastric cancer. The 3.0% overall incidence of metachronous gastric cancer in the present study was consistent with that in previous reports.

Most metachronous gastric cancers in the remnant stomach following cancer surgery are thought to derive from multicentric carcinogenesis, but some may be lesions that were missed at the time of diagnosis of the primary early gastric cancer [16–20]. Typically, a secondary metachronous gastric cancer develops within 10 years after the primary surgery [7]. Likewise, in this study, metachronous gastric cancer was detected in 21 (81%) cases within 5 years and in 23 (88%) cases within 10 years. In contrast, gastric remnant cancer after peptic ulcer surgery usually develops 15 years after surgery [8–10]. Multivariate analysis showed that gastric ulcer surgery (not duodenal ulcer surgery) and a long interval after the first surgery ($\geq$15 years) were independent risk factors for gastric remnant cancer after peptic ulcer surgery [9].

Among the four risk factors found in the present study, male sex and older age have been previously reported to be associated with synchronous and metachronous multiple cancers [21–24]. However, submucosal invasion of the primary cancer detected by multivariate analysis in the present study has not been reported previously. This can probably be explained by the time difference in the progression of multicentric carcinogenesis [17, 18]. The deeper primary cancer invasion means more time has passed toward the progression of multicentric carcinogenesis. If the primary cancer invades the deeper submucosal layer, tumor precursors have had more time to progress toward carcinogenesis than those whose primary cancer invades the shallower mucosal layer. The progressed tumor precursors may then arise as metachronous gastric cancers earlier on the gastric remnant mucosa.

We speculate that there are two possible explanations for the higher incidence of metachronous gastric cancer in the remnant stomach after proximal gastrectomy. One is the difference in the preserved mucosal area in the gastric remnant between the two groups. Usually, one-fifth to one-third of the proximal stomach is preserved with the distal gastrectomy or the pylorus-preserving gastrectomy [12]. In contrast, one-half to two-thirds of the distal stomach is preserved with the proximal gastrectomy [13]. Therefore, the mucosal area in the gastric remnant should be larger after the proximal gastrectomy, and the larger mucosal area may be associated with a higher incidence of metachronous gastric cancer. The other possible explanation is the difference in the incidence of metachronous gastric cancers in the upper, middle, and lower third of the stomach. We have reported that the incidence was about 17, 33, and 50%, respectively, during whole stomach endoscopic surveillance after endoscopic mucosal resection for primary early gastric cancer [16]. This result suggested that the lower third of the stomach has the foci of multicentric carcinogenesis more than the upper third of the stomach. In other words, the distal gastric remnant is more likely the source of metachronous gastric cancer development.

In the present study, 80 patients with synchronous multiple cancers underwent partial gastrectomy to remove multiple cancers at the same time. Among them, metachronous gastric cancer developed in three patients. However, having synchronous multiple gastric cancers was not a significant risk factor (Table 2). This result was unexpected because both metachronous and synchronous multiple gastric cancers are thought to derive from multicentric carcinogenesis and to have similar characteristics [25, 26]. Another unexpected result was the correlation between metachronous gastric cancer and the histologic type of primary cancer. It has been reported that the intestinal type of gastric cancer was associated with multiple gastric cancers [7, 16, 22, 25, 26]. However, the intestinal type was not selected as a risk factor either.

It has been known that Billroth II anastomosis is associated with gastric remnant cancer after distal gastrectomy for peptic ulcer because of duodenogastric reflux [9, 27]. The reconstruction method after distal gastrectomy in this study included Billroth I anastomosis (n = 617 patients), Billroth II anastomosis (n = 19 patients), and Roux-Y anastomosis (n = 79 patients). Metachronous gastric cancers arose in the gastric remnant in 15 patients after Billroth I anastomosis (2.4%), in 0 patients after Billroth II anastomosis, and in 3 patients after Roux-Y anastomosis (3.8%). There was no statistically significant difference in the prevalence rate among these three groups (data not shown).

It is well known that *Helicobacter pylori* infection in the gastric remnant after gastrectomy is associated with

metachronous gastric cancer [28–30]. Currently, *H. pylori* eradication is considered preventive therapy for metachronous gastric cancer [28, 31, 32]. Although it has been reported that prophylactic *H. pylori* eradication after endoscopic mucosal resection reduced the incidence of metachronous multiple gastric cancers in the whole stomach in a randomized controlled trial [31], it remains unclear if it can prevent the appearance of metachronous gastric cancer after partial gastrectomy. In this study, the presence of *H. pylori* infection was confirmed in the resected stomach in 20 of 26 patients (77%) who had metachronous gastric cancer at the first surgery by pathological examination (data not shown). Because none of the patients had been given *H. pylori* eradication therapy after the first surgery, the infection remained in the remnant stomach in 17 of the 20 patients at the time of the second treatment (data not shown). The relatively high incidence of *H. pylori* infection in this group may be associated with the high incidence of metachronous gastric cancer.

In this study, 21 of 23 patients who had T1 staged metachronous gastric cancer underwent yearly or biyearly endoscopic follow-up. However, three patients who had advanced T2-3 staged tumors underwent surveillance endoscopy every 3 years or at longer intervals. Therefore, yearly or biyearly endoscopic follow-up is desirable to detect metachronous gastric cancer at an early, curable stage.

Among the 26 patients, we observed 3 with all four risk factors, 11 with three risk factors, 11 with two risk factors, 1 with one risk factor, and none with no risk factor. Based on these findings, we recommend yearly or biyearly surveillance endoscopy for a gastric remnant in patients with any of these risk factors. It is also important to survey the gastric remnant periodically (more than every 3 years) even in patients with no risk factor. This is an optimal endoscopic surveillance program that we recommend.

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ノート

6. 早期大腸癌の精密画像診断 endocytoscopy

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要旨 一体型超拡大内視鏡(XCF-Q260EC1, prototype)は，通常観察，拡大観察，超拡大観察が可能となっており，超拡大観察の拡大レベルは450倍で，画像の取得深度は50 μmとされている．生体内で病理診断に極めて近い診断ができ，赤血球をはじめとする血流の流れや種々の細胞の動きを観察することができる超拡大内視鏡を，筆者らは次世代の内視鏡として位置づけている．大腸上皮性病変において超拡大内視鏡EC(endocytoscopy)分類は病理組織診断とよく相関しており，超拡大内視鏡診断の有用性が示唆される．超拡大内視鏡により，現行の内視鏡では診断困難とされる様々な問題が解決されることを期待する．

Key words : endocytoscopy pit pattern 診断 早期大腸癌 大腸EC分類 病理組織診断

はじめに

大腸内視鏡診断学の分野においては，拡大内視鏡により生体内で腫瘍表面の腺口形態(pit pattern)の観察が可能になり，非腫瘍・腫瘍の鑑別，ならびに大腸癌における深達度診断において有用であることが証明されている[1]．食道においては扁平上皮乳頭内における毛細血管のパターン診断〔IPCL(intra-epithelial papillary capillary loop)パターン分類〕により，拡大内視鏡診断の有用性が認識されている[2][3]．さらに胃においても拡大内視鏡によるdemarcation lineや異常微小血管の出現の認識が質的診断に有用であると報告されている[4]．拡大内視鏡は消化管粘膜をリアルタイムに詳細観察し，pit patternや表層の微小血管網の変化を鮮明にとらえることができ，日常臨床上その有用性が高いものであることが判明した．このような流れから，筆者らはさらに詳細な内視鏡診断を求めて，生体内で病理診断と同様に構造異型，細胞異型さらには核異型までの診断ができ，赤血球をはじめとする血流の流れ，さらには種々の細胞の動きを観察することができる超拡大内視鏡(endocytoscopy ; EC)を次世代型の内視鏡として位置づけている[5]．今後大腸内視鏡診断においては，拡大内視鏡におけるpit pattern診断とEC所見を組み合わせることでintegratedされた診断が可能になると考えている．

本稿では，既報のEC分類が，病理組織診断での異型度を念頭にEC0～EC3の大きく分けて4つに分類されていたのを改変し，非腫瘍性病変をEC1，腫瘍性病変をEC2(腺腫)，EC3(癌腫)といった3つに大別し分類したので，大腸上皮性病変におけるEC分類の有効性を報告する．

一体型超拡大内視鏡の仕様(Fig. 1, Table 1)および観察方法

一体型超拡大内視鏡(integrated EC, XCF-Q260EC1, prototype, オリンパス)は，太さ13.6 mmの硬度可変型の内視鏡で，通常観察，拡

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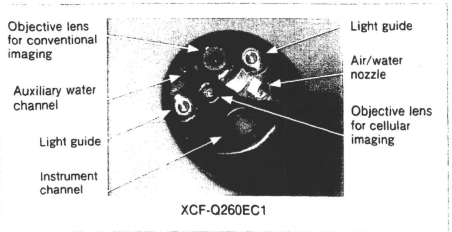

Fig. 1　一体型超拡大内視鏡.

Table 1　一体型超拡大内視鏡の仕様

先端部外径	13.6 mm
有効長	1,330 mm
拡大倍率	約 450 倍
取得深度	50 μm
取得画像範囲	300 × 300 μm

大観察，超拡大観察が可能となっている．超拡大観察における拡大レベルは 450 倍で，画像の取得深度は 50 μm とされている．超拡大観察は contact endoscopy の原理と同様で，標的粘膜にスコープ先端を軽く接触させて行う．このようにスコープ先端を直接対象病変に接触させるため，カテーテル型の超拡大内視鏡に比べ観察が容易である．さらに，一体型超拡大内視鏡にはウォータージェット機能が備わっており，病変の洗浄が容易となっている．

病変の観察は，拡大内視鏡観察と同様にウォータージェット機能や Gascon® 水を用いて病変をよく洗うことから始める．粘液の付着が強い時は，ブロナーゼを溶解させた Gascon® 水を用いる．その後，インジゴカルミン撒布やクリスタルバイオレット染色を施し拡大観察を行う．pit pattern 診断を行ったのちに，病変内で最も異型が強いと考えられた領域を中心に観察を行うが，染色としては撒布チューブを用いて 0.5〜1 % メチレンブルー染色を行う．1 分ほど経過したのち再度病変を水洗し，病変にスコープ先端を軽く接触させる．手元のボタンで EC モードに切り替えると，瞬時に EC 画像が取得される．

超拡大内視鏡 endocytoscopy (EC) 分類 (Table 2, Fig 2)

EC 画像で認識できる所見は，上皮表層における腺管の腺腔および腺腔縁（上皮遊離面に相当する）の形態，メチレンブルーにより染色される上皮細胞核の形状および染色性の濃淡である．腺腔形態，腺腔縁の形態，核形，核のメチレンブルー染色性，核の偽重層の有無および核/細胞質比の高低を判定し，EC 画像による大腸 EC 分類を行った．非腫瘍性病変を EC1 とし，腫瘍性病変を，病理組織診断での異型度を念頭に EC2，3 に分類した (Table 2)．

腫瘍性性格が示唆される中で，低異型度腺腫から粘膜内癌までの病理組織像に相当する群を EC1 (EC1a，EC1b) 群と分類した．小さく円形で腺腔が明瞭に観察され，腺腔縁は平滑であり，大きさの揃った紡錘形の核が腺腔縁から均等に放射状に配列するものを EC1a とし，正常大腸粘膜相当とした．正常粘膜とは異なり，腺腔が狭小で鋸歯状に観察され，小円形の核が緻密に配列するものを EC1b とし，過形成ポリープ相当とした．腺腔が明瞭なスリット状で，さらに腺腔縁が平滑であり，均一な紡錘形の核ないしは紡錘形に加えて類円形の核が認められ，一部に核の偽重層や核/細胞質比が高いように示唆される所見を含めて EC2 とし，低異型度腺腫から高異型度腺腫 (一部の粘膜内癌も含む) 相当とした．さらに，腺腔が不整形で，また腺腔縁が粗糙であり，メチレンの濃染する類円形の核が多数認められる所見を呈するものを EC3a とし，明らかな癌相当とした．さらに最も異型が高度な群を細胞がバラバラになり，超拡大観察で腺管構築の目立たないものを EC3b とし，浸潤癌相当とした．

EC 分類における有用性の検討

1. 対象と方法

2005 年 5 月〜2009 年 8 月の期間において当センターで内視鏡的ないし外科的に切除され，本研

Table 2　大腸 EC 分類

EC 分類	EC 画像所見	相当する病理組織診断
非腫瘍		
EC 1		
a	腺腔は円形 上皮細胞核：小円形で淡染	正常粘膜
b	腺腔は鋸歯状 上皮細胞核：小円形で淡染	過形成ポリープ
腫瘍		
EC 2	腺腔はスリット状，腺腔縁は滑 上皮細胞核：紡錘形～類円形 偽重層（＋），N/C 比（低～高）	腺腫もしくは粘膜内癌
EC 3		
a	腺腔は不整形，腺腔縁は粗 上皮細胞核：類円形で濃染核 偽重層（＋），N/C 比（高）	明らかな癌
b	腺腔不明瞭もしくは認識不可能 上皮細胞核：不整形で濃染 炎症性と思われる細胞浸潤	浸潤癌

N/C 比：核/細胞質比．

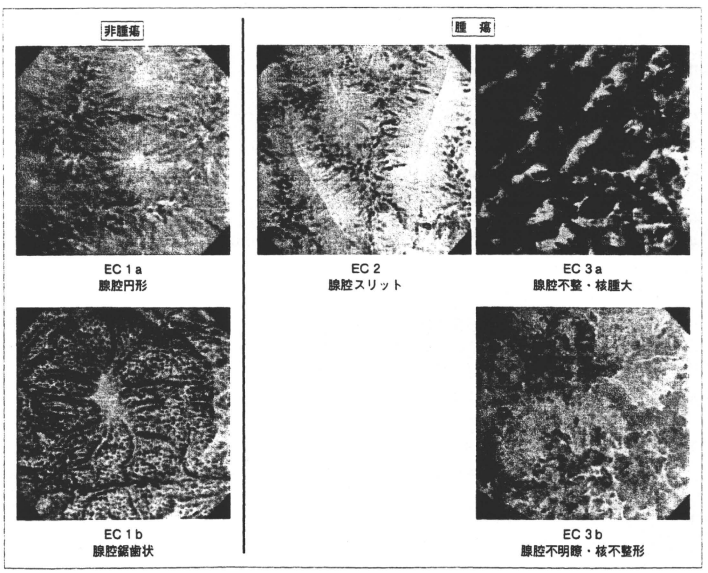

Fig. 2　EC 分類の画像．

Table 3 EC 分類による診断と pit pattern 診断との対比

Endocytoscopic diagnosis	Pit pattern						
	I	II	IIIL	IV	IIIs	VI	VN
EC 1a	9 (100 %)						
EC 1b		7 (100 %)					
EC 2			59 (59.0 %)	26 (26.0 %)		15 (15.0 %)	
EC 3a			1 (3.0 %)	3 (9.1 %)	3 (9.1 %)	24 (72.7 %)	2 (6.1 %)
EC 3b				1 (1.6 %)		24 (38.1 %)	38 (60.3 %)

Table 4 EC 分類による診断と病理組織診断との対比

Endocytoscopic diagnosis	Pathological diagnosis					
	Normal mucosa	Hyperplastic polyp	Adenoma	Cancer		
				M	SM-s	SM-m ~
EC 1a	9 (100 %)					
EC 1b		7 (100 %)				
EC 2			75 (75.0 %)	23 (23.0 %)	1 (1.0 %)	1 (1.0 %)
EC 3a			3 (9.1 %)	15 (45.4 %)	9 (27.3 %)	6 (18.2 %)
EC 3b					1 (1.6 %)	62 (98.4 %)

SM-s : Slightly invasive submucosal cancer, SM-m : Massively invasive sabmucosal cancer.

究における informed consent が得られた大腸上皮性病変 212 病変を対象とした．一体型 EC (XCF-260EC1, Olympus) を使用し，前述の観察方法にて EC 画像の観察を行った．今回は，対象症例によって得られた EC 画像を超拡大内視鏡 EC 分類にしたがって retrospective に解析し，pit pattern 診断および病理組織診断との対比を行った．

2. 結果

EC 分類と pit pattern 診断との対応を **Table 3** に示す．EC1a 群はすべて I 型 pit pattern (100 %) であった．EC1b 群はすべて II 型 pit pattern (100 %) であった．EC2 群においては，IIIL 型 pit pattern が 59 症例 (59.0 %)，IV 型 pit pattern が 26 症例 (26.0 %)，VI 型 pit pattern が 15 症例 (15.0 %) であった．EC3a 群においては，VI 型 pit pattern が 24 症例 (72.7 %) さらには VN 型 pit pattern が 2 症例 (6.1 %) であった．IIIs 型 pit pattern と診断した 3 症例においてはすべて EC3a 群であった．EC3b 群においては VI 型 pit pattern が 24 症例 (38.1 %)，VN 型 pit pattern が 38 症例 (60.3 %) であった．

EC 分類における病理組織診断の陽性的中率は **Table 4** のごとくであった．EC1a 群は正常粘膜が 9 症例 (100 %)，EC1b 群は過形成性ポリープが 7 症例 (100 %) であり，非腫瘍性病変の陽性的中率は 100 % であった．さらに EC2 群は，腺腫が 75 症例 (75.0 %)，粘膜内癌が 23 症例 (23.0 %)，SM 微小浸潤癌 1 症例 (1.0 %)，SM 深部浸潤癌が 1 症例 (1.0 %) であった．EC3a 群は腺腫が 3 症例 (9.1 %)，粘膜内癌が 15 症例 (45.4 %)，SM 微小浸潤癌が 9 症例 (27.3 %)，SM 深部浸潤癌が 6 症例 (18.2 %) であった．EC3b 群は SM 微小浸潤癌が 1 症例 (1.6 %)，SM 深部浸潤癌が 62 症例 (98.4 %) であり，EC3b 群における SM 深部浸潤癌の陽性的中率は 98.4 % であった．

症 例

患者は 60 歳，男性．スクリーニング目的で大腸内視鏡を施行した．通常観察およびインジゴカルミン撒布像 (**Fig. 3 a, b**) では，S 状結腸に 4 mm 大の発赤調の病変で，正常粘膜と明らかな段差を有する面状の陥凹局面が認識された．肉眼形態は IIc と診断した．NBI (narrow band imaging) 拡大観察像 (**Fig. 3 c**) では陥凹局面に一致して血管密度の少ない領域を認め，一見 sparse pattern の vascular pattern が観察されるが異常血管を認めず，

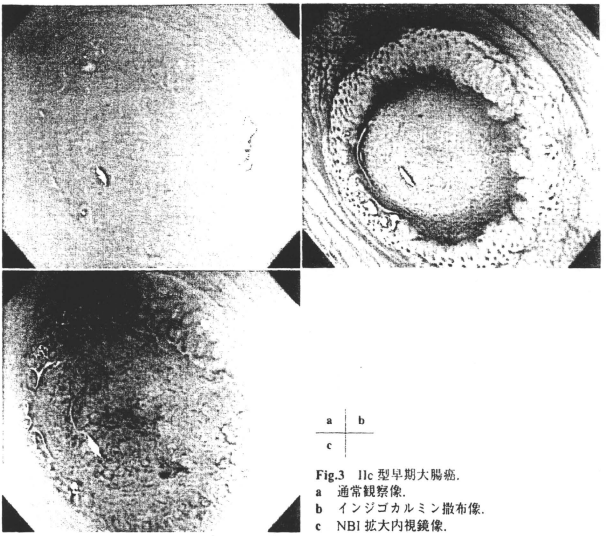

Fig.3 IIc 型早期大腸癌.
a 通常観察像.
b インジゴカルミン撒布像.
c NBI 拡大内視鏡像.

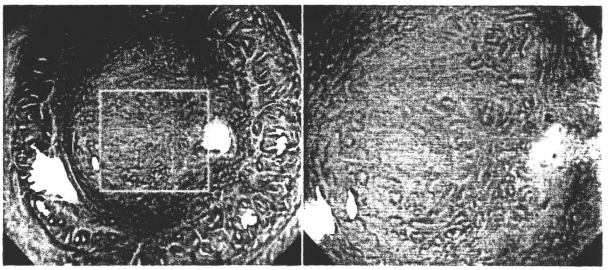

Fig.4 クリスタルバイオレット染色.
a 弱拡大像.
b 強拡大像.

network pattern と診断した．クリスタルバイオレット染色後の拡大観察（**Fig. 4**）では，大部分は細かい小型類円形の IIIs 型 pit pattern を呈していたが，中央部に大小不同の不揃いな構造があり V_I 型軽度不整と診断した．EC 所見は（**Fig. 5**），腫瘍腺管において腺腔が不整形で，メチレンブルーで濃染した腫大した核を認め，EC3a と診断した．なお，段差を伴った陥凹辺縁においては，正常腺管と腫瘍腺管の境界が明瞭に描出されていた．以上より IIc 型早期大腸癌，深達度 SM 微小浸潤までの病変と考え，内視鏡的粘膜切除術を施行した．

病理診断（**Fig. 6**）は early colon cancer，IIc，4 mm，S，tub1，sm1a（pSM 130 μm），ly0（D2-40），v0（VB），HM0，VM0 であった．

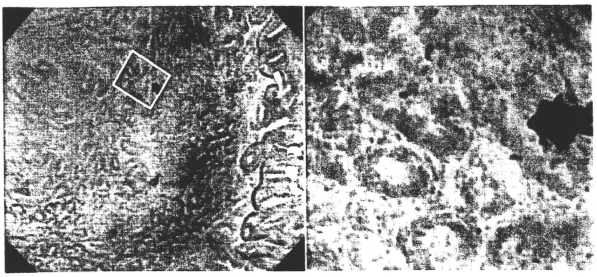

Fig.5 pit pattern と超拡大内視鏡(EC)像の対応.
a クリスタルバイオレット染色像(強拡大).
b EC像(EC3 a).

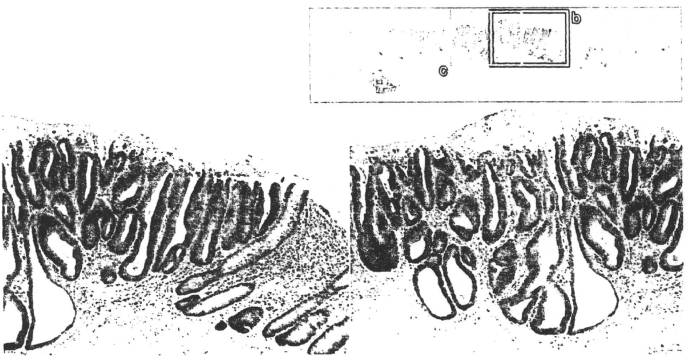

Fig.6 病理組織像.
a ルーペ像.
b 中拡大像(腫瘍辺縁部).
c 中拡大像(腫瘍浸潤部).

考 察

一体型ECは,内視鏡に一体化させることによりECとしての画角が広がるとともに,画像ファイリングへの取り込みも容易になり,消化管診断における gold standard の1つとされる生検診断,細胞診に匹敵する画像をリアルタイムに生体内で得ることが可能になった[6].ECを用いた消化管腫瘍に対する診断としては,Inoue ら[7]が食道におけるEC画像をその組織異型度によりECA (EC atypism) として分類して,病理組織をウィーン分類と対比させ,その有用性を報告している.さらに特に食道ではこれまでのECではメチレンブルー単染色による細胞観察を行っていたが,胃粘膜においては単染色では,診断可能な画像の獲得が十分ではなく,クリスタルバイオレット・メチレンブルーの2重染色などの工夫がなされ,食道と同様にECA分類がなされ,その有用性が報告されている[6].

大腸においては,Sasajima ら[8]によりカテーテル型の超拡大内視鏡による腫瘍・非腫瘍の鑑別,さらには粘膜下層浸潤癌の診断の有用性について