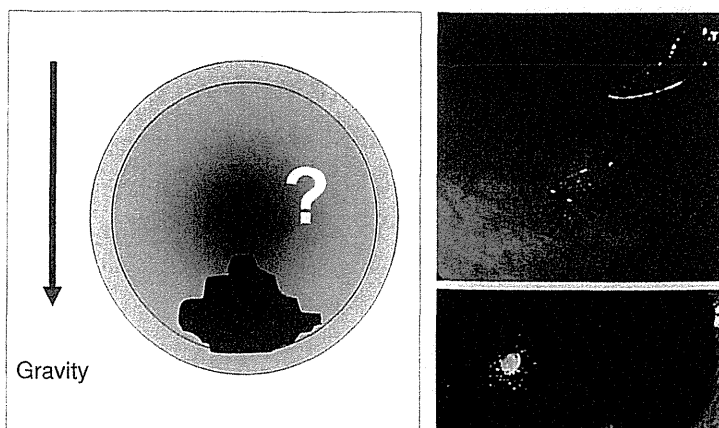
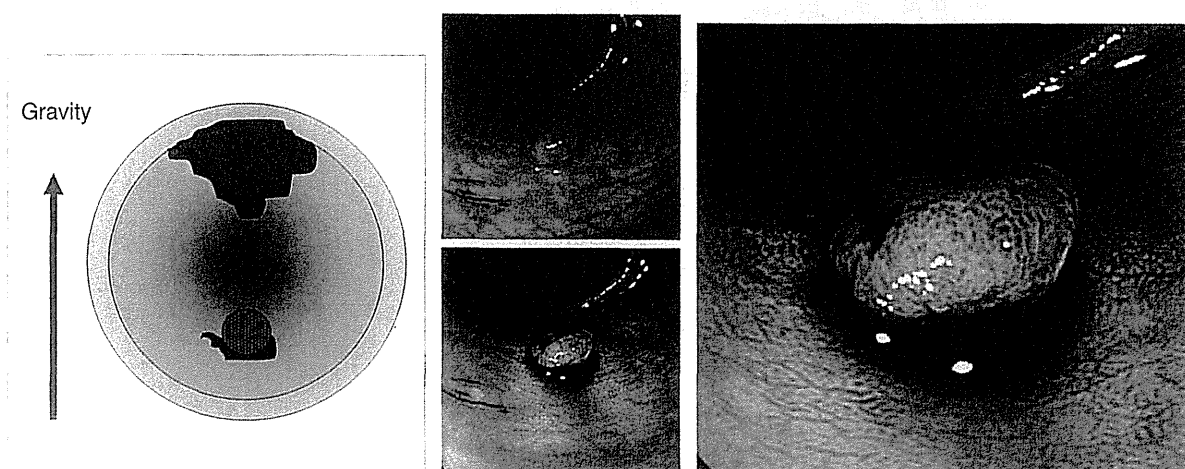


一 燥をそは方スよ

子鏡けに、察つ変



**図7 重力方向と病変の位置関係**  
 重力方向に病変が位置している場合、色素散布はかえって病変観察の妨げになり、治療の妨害にもなる。



**図8 重力方向と病変の位置関係**  
 重力と反体側に患者体位を変換することで、観察治療環境が劇的に改善することが多いので、画面を平面的に捉えるだけでなく、常に立体的な感覚で内視鏡をアプローチしていく必要がある（平面の認識から立体の認識へ）。

## おわりに

内視鏡挿入は、大腸内視鏡のすべてではなく観察・治療の出発点にすぎないということを忘れてはならない。軸保持短縮法にて短時間で確実に挿入できて初めて、拡大内視鏡観察などの詳細な病変の観察や、難しい病変の内視鏡治療を行うことができるのである。以前、ある雑誌に“盲腸まで5分をめざして”という特集が組まれた。5分をめざすことは内視鏡医にとって重要なことだが、患者にとって苦痛であったり、病変を見逃すようでは意味がなくなる。あらゆる問題をクリアしたうえでの5分を可能にするためにも日々愛日の精神を忘れず内視鏡に携わっていくことが必要だと思う。かつてベテランの内視鏡医いわく“日常何気なく見ている所見でも、見るひとの立場によって石にも玉にもなる。不断の内視鏡に対する気迫が1年、5年と月日の積み重ねを経ると、人によっては驚くほど

の差となってゆく—中略—内視鏡が見せてくれる所見の一つ一つに感激し、それを記憶しさらに先を目指してほしい”（電子コロノスコピー、南江堂、1993より抜粋）。挿入法は師匠によって異なる。胃内視鏡の挿入で blind だと危険だという先生もいる。正論であるが、かつてその方法で事故のない人もいた。要はセンスと、最初に教えた人がいかに内視鏡を持つ心を伝えるかであろう。方法論だけではない。

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## 10. 画像強調観察 (IEE) (4) AFI

松田尚久, 中島 健, 斎藤 豊

近年, 大腸癌は癌死亡の主要な原因の一つとなっており, その前癌状態と考えられる腺腫性ポリープを, 内視鏡により早期に発見し摘除することが癌予防の観点からも重要となっている. 大腸内視鏡画像の高精細化や内視鏡診断学の進歩などにより, 大腸腺腫の診断能は向上したものの, 依然として大腸内視鏡での腺腫性ポリープの見落としが24%に存在するといわれている<sup>1)</sup>. また, インジゴカルミンによる色素散布法により, 大腸病変の描出能は向上するが, 全大腸に色素を散布することは効率の良い検査法とはいえず, 簡便に大腸腫瘍をスクリーニングできるような機器の開発が望まれてきた. 現在, 大腸内視鏡による腫瘍性病変発見の効率化を目的として, さまざまな画像強調観察法が開発され臨床応用されるに至り, 従来用いられてきた色素散布法よりも簡便にスクリーニングできるようになりつつある.

自家蛍光内視鏡システム (Autofluorescence Imaging system; AFI, オリンパスメディカルシステム社製) は, 画像強調観察法の一つであり, 蛍光物質の投与を行わずに組織の変性過程に従って発生する内因性蛍光物質の自家蛍光が減弱する特性を利用した診断技術であり, 肺癌診療における気管支鏡検査に対しても応用されている. 消化管領域においても, その有用性が報告されつつあり, 本稿では AFI システムとその有用性に関する研究の紹介と今後の課題について解説する.

### AFI 画像の原理

粘膜組織に青色光を照射すると, 内因性の生体分子から緑色の蛍光が発せられる (自家蛍光) ことが知られていたものの, 通常の CCD で検出することは困難であった. そこで, 通常 CCD に加え, AFI 専用の超高感度 CCD をスコープに搭載することでそれを検出可能にしたものが AFI システムである. 腫瘍組織においては, 腫瘍による粘膜の厚みや非腫瘍との組織構築の相違など複数の因子によって, 励起光や自家蛍光が吸収され蛍光強度が減弱することが知られている. オリンパス社製 AFI システムでは, 光源から発せられた白色光を, 回転フィルターを通して青色励起光 (390~470 nm) と緑色光 (540~560 nm) に分光して順次照射し, 自家蛍光画像と緑の反射光画像を取得する. 取得した自家蛍光画像はモニター画像の G チャンネルに, 緑色反射光は R・B チャンネルに割り当て, プロセッサー内で合成して疑似カラー表示をする. これにより, 正常組織は明るい緑色に, 自家蛍光の減弱した腫瘍組織では, マゼンタ調に表示されコントラストを強調している. さらに, 現行型の AFI システムでは, 自家蛍光画像に血液成分を反映する緑領域の反射光を合成することで, 血液成分が青色調に表示され, 表面構造や血管の情報が加味された自家蛍光画像が得られるようになっている. また, 通常内視鏡 (白色光) と AFI 画像の切り替えは, スコープ (CF-FH260AZI) のグリップ部についているボタンを押すだけで瞬時に行うことが可能であり, 操作性も従来型に比べ向上している.

## AFIによる大腸ポリープ拾い上げ診断能の評価

通常白色光（以下，WL）とAFI観察各々における，大腸ポリープ拾い上げ診断能を前向きに比較検討することを目的に，当院にてpilot studyを行った<sup>2)</sup>．167名の対象患者を，AFI先行群（83名）とWL先行群（84名）の2群にランダムに分け，盲腸→上行結腸→横行結腸の右半結腸を，1名の経験のある内視鏡医がmodified back-to-back法で観察し，各々の観察法での検出病変を比較した．対象者の背景および検査動機，腸管前処置の程度は両群間に差はなく，両群とも80%以上の症例において良好な前処置での観察が可能であった．

検出されたポリープの総数は，AFI観察で100病変，WL観察では73病変であり，AFI観察で有意に多かった．また，AFI先行群で病変を見落としした確率は30%，WL先行群では49%と，AFI先行群のほうが有意にポリープの見落としが少なかった．また，腫瘍性病変に限っても，AFI観察で92病変，WL観察では69病変が検出され，AFI観察で有意に多かった．なお，有意差はなかったが，AFI観察ではWL観察に比べて平坦かつ小さな（5mm以下）病変が多く検出される傾向にあった（図1）．以上より，AFIはWLに比べて，右半結腸においてより多くの大腸ポリープを検出していた．また，ある程度の大きさや丈の高さがある病変については，WLでも十分に検出が可能であるが，WLでは検出できない病変に対しても，AFIは診断に有用である可能性が考えられた．

一方，上堂らは，AFI観察はWL観察と比べ大腸ポリープ拾い上げ診断能において有意な差を認めなかったと報告している<sup>3)</sup>．64名を対象とした本研究では，AFI観察群とWL

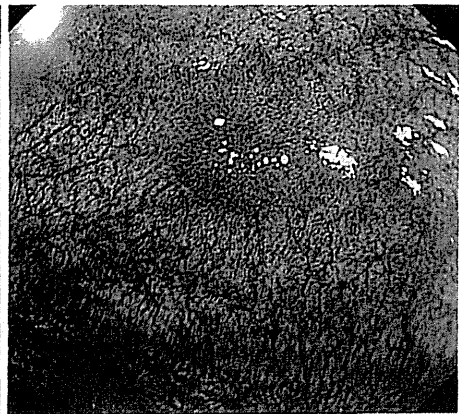
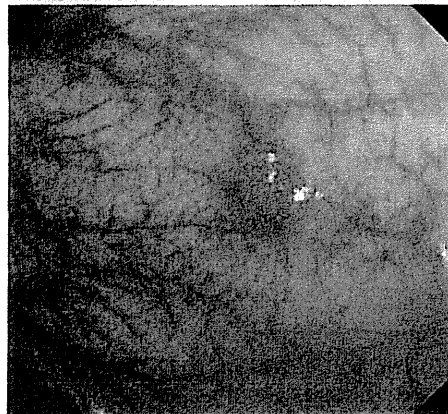
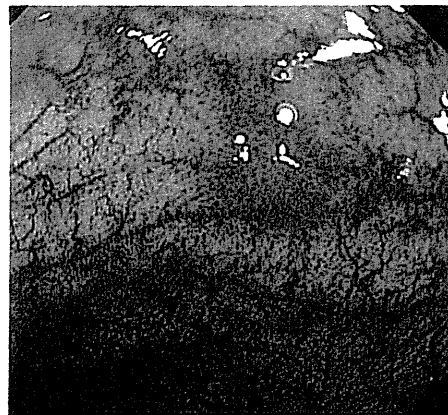


図1 内視鏡像（横行結腸4mm，II a，腺腫）

- a：通常白色光
- b：AFI
- c：NBI

a |  
b | c

観察群とに無作為に割り付け、各観察法で検査し異常所見をすべて記録した。次に、直腸まで観察・抜去した時点でほかの検査医に交替してスコープを遠位S状結腸まで再挿入し、そこからもう一つの観察法で検査し異常所見を拾い上げた。64例中28例にポリープを70個認め、各観察法で発見したポリープ数はWL観察57個（感度64%：95%信頼区間54～75%）、AFI観察が58個（感度65%：95%信頼区間55～76%）と、ポリープ拾い上げ診断能に差はなかった。しかし、同施設におけるその後の追加研究では、AFIに先端フード（TH）を組み合わせて使用することで、大腸腫瘍性病変に対する拾い上げ診断能が大きく向上した。2010年「Gastrointestinal Endoscopy」誌に、TakeuchiらがAFI/WLとTHとを組み合わせた前向き比較試験（RCT）の結果として報告している<sup>4)</sup>。この研究では、対象561名を無作為に4群（WL単独、WL+TH、AFI単独、AFI+TH）に振り分け、全大腸における腫瘍性病変の発見頻度を比較した。その結果、AFI+TH群でWL単独群と比べ、有意に良好な腫瘍性病変発見率を示した〔腫瘍性病変発見率（95%信頼区間）：1.96（1.50～2.43）vs 1.19（0.93～1.44）〕。また、AFI単独群においても、腫瘍性病変発見率（95%信頼区間）は1.36（1.07～1.65）とWL単独群よりも良好な成績であった。

## AFIによる大腸病変の質的診断

大腸病変の腫瘍・非腫瘍の鑑別は、日常臨床において非常に重要である。色素拡大内視鏡によるpit観察は非常に有用なmodalityであり<sup>5)</sup>、さらに、近年NBI拡大観察による微細血管観察に基づく診断もpit観察に匹敵するだけの成績として報告され<sup>6)</sup>、世界的にも注目されつつある。同様に、AFIでも質的診断がこれらのmodalityのように高精度に診断可能か否かは、AFIの大腸内視鏡検査における位置づけを考えるうえで、注目すべきところであり、いくつかの臨床試験が報告されている<sup>7),8)</sup>。われわれのpilot studyでは、AFIで発見された病変のうち、92%が腫瘍性病変であったことから質的診断にも有用である可能性はあるが、この点についてはさらなる検討が必要である。現在、当院を研究事務局として全国5施設における多施設共同研究（略称：AFI STUDY）が行われており、その解析結果が待たれる。

## 症例呈示

### 【症例1】（図2）

盲腸の15mm大Ⅱa（LST-G）病変である。AFIでは、病変全体が一様にマゼンタ調を呈しており、コントラストも良好に描出されている。病理組織診断では、well differentiated adenocarcinoma, low grade atypia, in adenoma, pMであった。

### 【症例2】（図3）

直腸の45mm大Ⅰs+Ⅱa（LST-G）病変である。AFIでは、腫瘍性病変の内部にマゼンタ調を呈さずグリーン調を呈する部分が介在する。病理組織診断では、well differentiated adenocarcinoma, low grade atypia, in adenoma, pMであった。

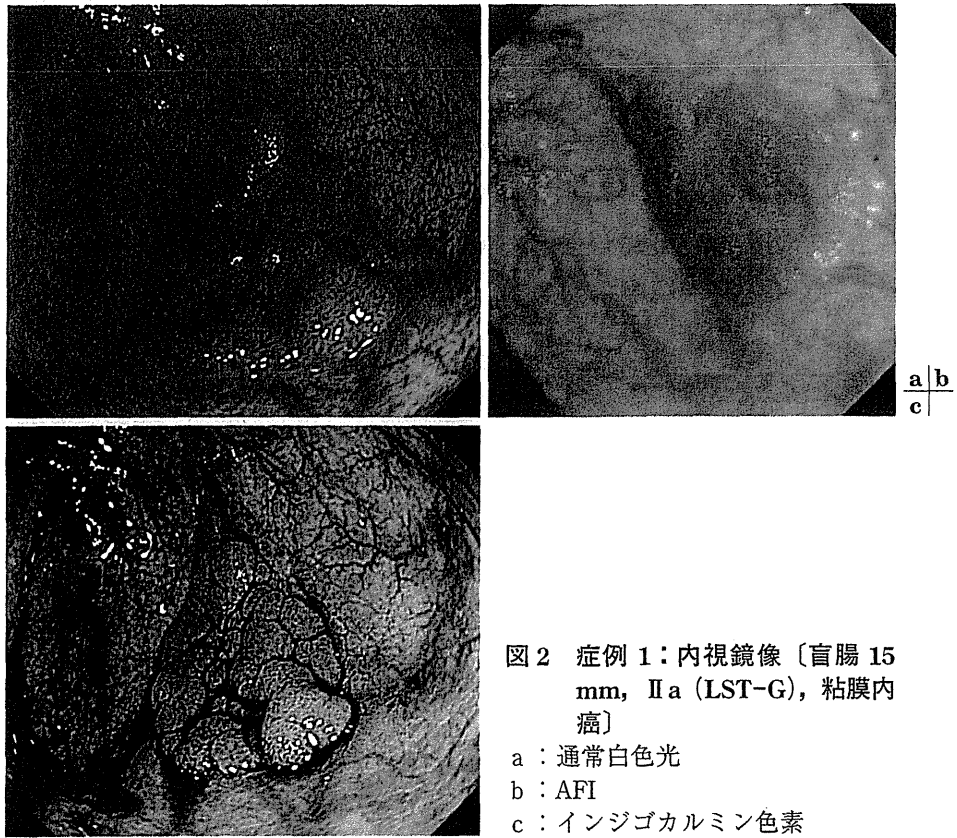


図2 症例1:内視鏡像〔盲腸15 mm, IIa (LST-G), 粘膜内癌〕

a : 通常白色光  
b : AFI  
c : インジゴカルミン色素

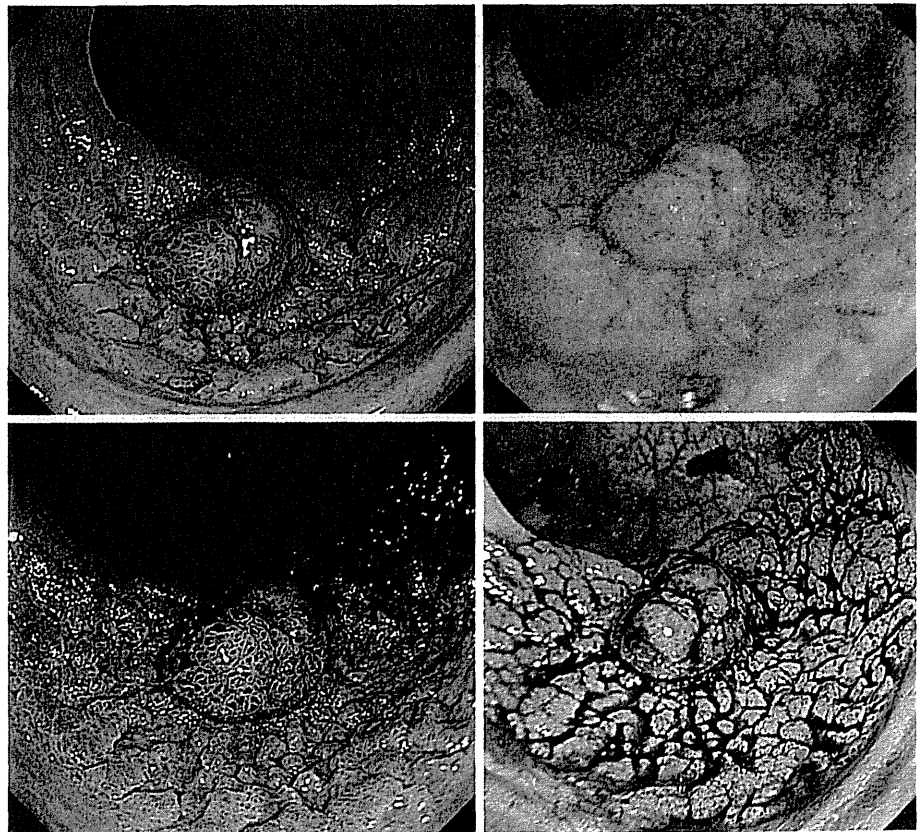


図3 症例2:内視鏡像〔直腸Rb, 45 mm, Is+IIa (LST-G), 粘膜内癌〕

a : 通常白色光, b : AFI, c : NBI, d : インジゴカルミン色素



## おわりに

AFI 観察は、小さく平坦な病変に対する拾い上げに有用である可能性が十分あるが、その臨床的意義と質的診断能については、依然として議論の余地のあるところである。今後、“Image-Enhanced Endoscopy ; IEE” として統一されたその他の新しい画像強調観察法 (NBI ; Narrow Band Imaging, FICE ; Flexible spectral Imaging Color Enhancement など) との比較検討も必要である。また、現行型の AFI 機種は従来型と比べてスコープの操作性や画質などは向上しているものの、未だスクリーニング内視鏡検査としては十分とは言い難く、今後さらなる機器の開発・改善が期待される。

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## 血管透見

[大腸]

斎藤 豊

血管透見像の消失する病変として、主として炎症と腫瘍が挙げられる。

腫瘍のなかでも、発見の難しい表面型腫瘍を拾い上げるためには、発赤、出血斑、血管透見像の限局的な消失や途絶、光沢の変化、ひだの変形などに注意することが重要である。とくに表面型腫瘍のきわめて早期の段階では血管透見像の消失以外、所見を呈さないことがあり注意を要する。最近では画像強調内視鏡の一つである Narrow Band Imaging (NBI) の有用性が注目されている。

血管透見の消失する病変としては、腫瘍以外に、炎症性疾患（潰瘍性大腸炎、クローン病、感染性腸炎、虚血性腸炎、静脈硬化性大腸炎、非特異性炎症性疾患など）が挙げられる。腫瘍との鑑別点は、単発（腫瘍）か多発（炎症）か、さらには領域性の有無、有（腫瘍）無（炎症）といった点である。

## 炎症性疾患

### 1. 潰瘍性大腸炎 (UC)

粘膜はびまん性に侵され、血管透見像は消失し、粗糙、細顆粒状を呈し易出血性である。この像は活動期、寛解期ともに認められ、UC 診断のよりどころとなる。

### 2. クロウン病 (CD)

縦走潰瘍や敷石像 (cobblestone appearance) が特徴的所見であるが、これらの所見を欠く不整形潰瘍やアフタのみからなる CD の場合に、内視鏡診断が困難な場合がある。この潰瘍は大小深浅に関係なく、周囲粘膜に炎症を欠く (discrete ulcer) という特徴を有する。

### 3. 感染性腸炎

感染性腸炎は表層上皮の破壊による急性炎症であり、生検にて粘膜の構造が保たれ、間質の急性炎症が増加している。病変範囲の分布は原因により異なり、病変の配列が不規則で背景粘膜は正常である。

- ① 細菌性腸炎 (サルモネラ, カンピロバクター, 腸炎ビブリオ, 病原性大腸菌, 結核など)
- ② ウイルス (ロタウイルス, 腸管アデノウイルス, サイトメガロウイルスなど)
- ③ 寄生虫, 原虫 (アメーバ)

### 4. アメーバ赤痢

アメーバ赤痢では直腸と回盲部に所見を認めることが多く、大小不同の不整な潰瘍が多発する。潰瘍周辺には発赤、びらんが存在する。急性期の潰瘍は周囲粘膜の発赤、浮腫が強く、タコイボ様の形態を示す。また、潰瘍底に吹き出すようなクリーム状の黄白色苔が



本症に特徴的である。しばしば潰瘍性大腸炎との鑑別が困難な場合もあるが、本症では介在粘膜の血管透見像は良好なことが多く、このような所見を十分に拾い上げることが鑑別に重要である。

## 5. 虚血性腸炎

下行結腸およびS状結腸に好発し、縦走潰瘍、および腸管の浮腫が特徴的である。軽症では、粘膜の発赤、充血、浮腫、びらんを呈するのみの場合もある。

## 6. 静脈硬化性大腸炎

比較的まれな疾患で、日本からの報告例しかない。右半結腸に好発し、特徴的な青紫色粘膜と潰瘍びらんを呈する。右側結腸壁および上腸管膜静脈領域などの静脈に硝子化と石灰化を伴う虚血性病変である。

## 7. アミロイドーシス

種々の原因によって各種臓器の細胞外に特異な蛋白であるアミロイド物質が沈着し、組織や臓器の機能異常をきたす疾患である。消化管では胃と直腸に沈着頻度が高く、血管拡張増生、血管透見像低下を認める。

## 過形成性ポリープ

過形成性ポリープにおいても表面型腫瘍同様、血管透見の低下にて認識されることがある。腺腫との鑑別は色調、表面正常から比較的容易であるが、発赤調の過形成性ポリープや、large hyperplastic polyp は腺腫と誤診されやすい。このようなポリープの鑑別には拡大内視鏡およびNBIが有用である。

## 腫瘍性病変

血管透見の低下は、表面型腫瘍の拾い上げ診断に有用である。

腺腫、早期癌：基本的にはⅡa、Ⅱb、Ⅱcなどの表面型腫瘍の発見に重要である。

木庭らの報告によると、内視鏡的粘膜切除術（EMR）が施行された表面型大腸腫瘍148病変（Ⅱa：89、Ⅱa+Ⅱc：26、Ⅱb：6、Ⅱc：27）の発見時の通常内視鏡写真の見直し診断において、隆起型病変では、凹凸の変化としての隆起が高率であり、一方ⅡbやⅡcでは凹凸の変化よりも色調の変化としての淡い発赤や血管透見像消失が発見の際の重要な内視鏡所見と考えられた。さらに、prospectiveに検討した結果、平坦陥凹型腫瘍の発見に際して、領域性のある類円形の淡い発赤とそれに伴う血管透見像消失が、拾い上げ診断の重要な内視鏡指標と考えられた。また淡い発赤などの所見はNBI観察でより容易に拾い上げられる可能性がある。

類円形発赤と鑑別を要するものとして地図状発赤が挙げられるが、地図状発赤は横行結腸に好発し、領域性に乏しく赤みが強いなどの特徴があり挿入時のアーチファクトによるものが多いと考えられた。

## まとめ

大腸表面型腫瘍の内視鏡的存在診断指標として、平坦陥凹型においては、血管透見像消失に伴う淡い発赤の変化が重要である。さらに、このような微細な変化のみでしか拾い上げられない病変も存在することを肝に銘じ、内視鏡医は細心の注意をはらって検査を施行すべきである。また今後は、このような病変に対してはNBI診断が有用となる可能性もある。

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## Treatment strategy for recurrent or residual colorectal tumors after endoscopic resection

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### Abstract

**Background** Piecemeal resection of colorectal neoplasms is associated with a higher risk of recurrent or residual tumors, but nearly all such cases can be cured by additional endoscopic resection (ER). Although the adoption of endoscopic submucosal dissection (ESD) for colorectal neoplasm is continuing, the safety of this treatment for recurrent or residual tumors has not been fully assessed. We evaluated salvage therapy for the treatment of recurrent or residual tumors, and propose an endoscopic treatment strategy for these tumors.

**Methods** This retrospective study was conducted for 60 consecutive patients who had with locally recurrent or residual tumor after ER between January 2004 and October 2005. Endoscopic treatment strategy, treatment results, complications and clinical outcomes were recorded.

**Results** Among 69 lesions in 60 patients, 67 were treated endoscopically, whereas 2 required surgical treatment. Of these 67, 87% (58/67) were resected by endoscopic mucosal resection (EMR) and 13% (9/67) by ESD. En bloc resection rate was 39% (23/58) in the EMR group and 56% (5/9) in the ESD group. One limitation of this study is that it was a single-center retrospective analysis.

**Conclusions** ESD is safe and effective for the treatment of recurrent or residual colorectal tumors. However, because of its technical difficulty, the en bloc resection rate is lower than that for the treatment of nonrecurrent lesions.

**Keywords** Colonoscopy · Endoscopic submucosal dissection · Recurrent or residual tumor

### Abbreviations

ER	Endoscopic resection
EMR	Endoscopic mucosal resection
EPMR	Endoscopic piecemeal mucosal resection
ESD	Endoscopic submucosal dissection
TEM	Transanal endoscopic microsurgery
HGD	High grade dysplasia

Thanks to its minimal invasiveness, relative safety, and cost-effectiveness, endoscopic mucosal resection (EMR) is now widely used for the treatment of colorectal tumors. However, because of the limitations in snare size and the technical difficulty of en bloc resection, it is not used to treat lesions larger than 20 mm in diameter [1], which are instead resected by using endoscopic piecemeal mucosal resection (EPMR). A method newly developed in Japan called endoscopic submucosal dissection (ESD) does allow the en bloc resection of larger lesions; however, because of its technical difficulty in the colorectum, its use for cancers at these sites is not high [2–5, 20].

The risk of residual tumor with EPMP (2.7–27.2%) is greater than that with en bloc resection [6, 16]. Moreover, complete retrieval of all specimens and histological determination of the depth of cancer invasion in EPMP are

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sometimes difficult [6–13]. It has been speculated that additional endoscopic treatment can achieve complete remission in most recurrent or residual tumors, but methods and safety in the treatment of these tumors have not been fully assessed. We evaluated salvage endoscopic therapy for the treatment of recurrent or residual tumors. We also propose an endoscopic treatment strategy for these tumors.

## Patients and methods

We retrospectively analyzed a database of all patients who underwent endoscopic treatment, including transanal endoscopic microsurgery (TEM), at our institution from January 2004 to October 2005 and identified all cases of local recurrent or residual tumors.

Sixty-nine colorectal tumors in 60 patients fulfilled the criteria of this study. In all, 67 lesions underwent endoscopic treatment, whereas two other patients who did not receive appropriate endoscopic surveillance required surgical treatment because the recurrent lesions were endoscopically diagnosed as invasive cancer. Of the 67 lesions, 58 were treated by EMR, and 9 that were technically difficult to remove by EMR were treated by ESD (Fig. 1). With regard to the initial treatment, 47 of the 58 EMR-treated lesions were residual or recurrent tumors treated at our and 9 other hospitals, and 4 of the ESD lesions were treated at our hospital and 5 at other hospitals.

## Clinical indication of endoscopic treatment

Evidence regarding the clinical indications for endoscopic treatment is growing. First, it has been reported that intramucosal colorectal cancers show no lymph node metastasis. Second, some reports have revealed that lesions with submucosal invasion limited to less than 1,000  $\mu\text{m}$  without lymphovascular invasion or a poorly differentiated component do not involve lymph node metastasis. Moreover, the depth of invasion of colorectal neoplasms can be

predicted using pit pattern analysis with magnifying chromoendoscopy. Endoscopic treatment for colorectal lesions is therefore based on the conventional endoscopic and pit pattern findings of a noninvasive pattern [14]. With regard to endoscopic management after resection, follow-up colonoscopy is required only for the observation of treatment sites after endoscopic resection for high-grade dysplasia/intramucosal cancer, which also is the case with adenoma. In contrast, borderline cases (i.e., invasion depth of approximately 1,000  $\mu\text{m}$ ) or EPMP cases, in which the histology of the tumor cannot be precisely assessed, require extensive assessment (e.g., CT scan, abdominal ultrasonography, tumor markers) to determine the presence of metastatic disease.

## Treatment strategy and techniques

### EMR

In this study, several endoscopic procedures were used in the EMR group, including hot biopsy, snare polypectomy, and conventional EMR. These methods were chosen according to the size and endoscopic features of the polyp. Hot biopsy forceps are suitable for the excision of adenomas up to 5 mm in size, and snare polypectomy for pedunculated or semipedunculated polyps larger than 6 mm. Indications for EMR include flat-type adenomas, including those with severe dysplasia, as well as early colorectal cancers diagnosed as having a noninvasive pattern by magnifying chromoendoscopy [14]. Conventional EMR procedures were performed using the well-recognized general method of tangential submucosal injection of normal saline or glycerol.

### ESD

Candidates for ESD were large lesions >20 mm that were technically unsuitable for conventional EMR due to the presence of extensive submucosal fibrosis. The technique has been standardized for early gastric cancer and is described in detail elsewhere [15]. For ESD of colorectal neoplasms, we developed a bipolar needle knife (B-knife) (Zeon Medical Inst., Tokyo, Japan), in which the electric current is localized to the needle tip, and an insulation-tipped knife (IT-knife), which allows safe dissection (Olympus Co, Tokyo, Japan).

ESD is performed as follows. Glycerol and sodium hyaluronate acid are first injected into the submucosal layer under the tumor. Initial incision of the mucosa is made with the B-knife outside the lesion edge on the elevation caused by the submucosal injection. After completion of a circumferential incision, additional submucosal injection of the same solution is made before submucosal dissection to

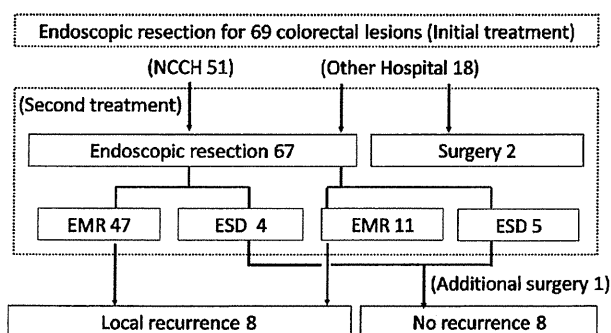


Fig. 1 Follow-up of 69 colorectal lesions after initial treatment

prevent perforation. The IT knife or B-knife is then used to dissect the submucosal layer (Fig. 2).

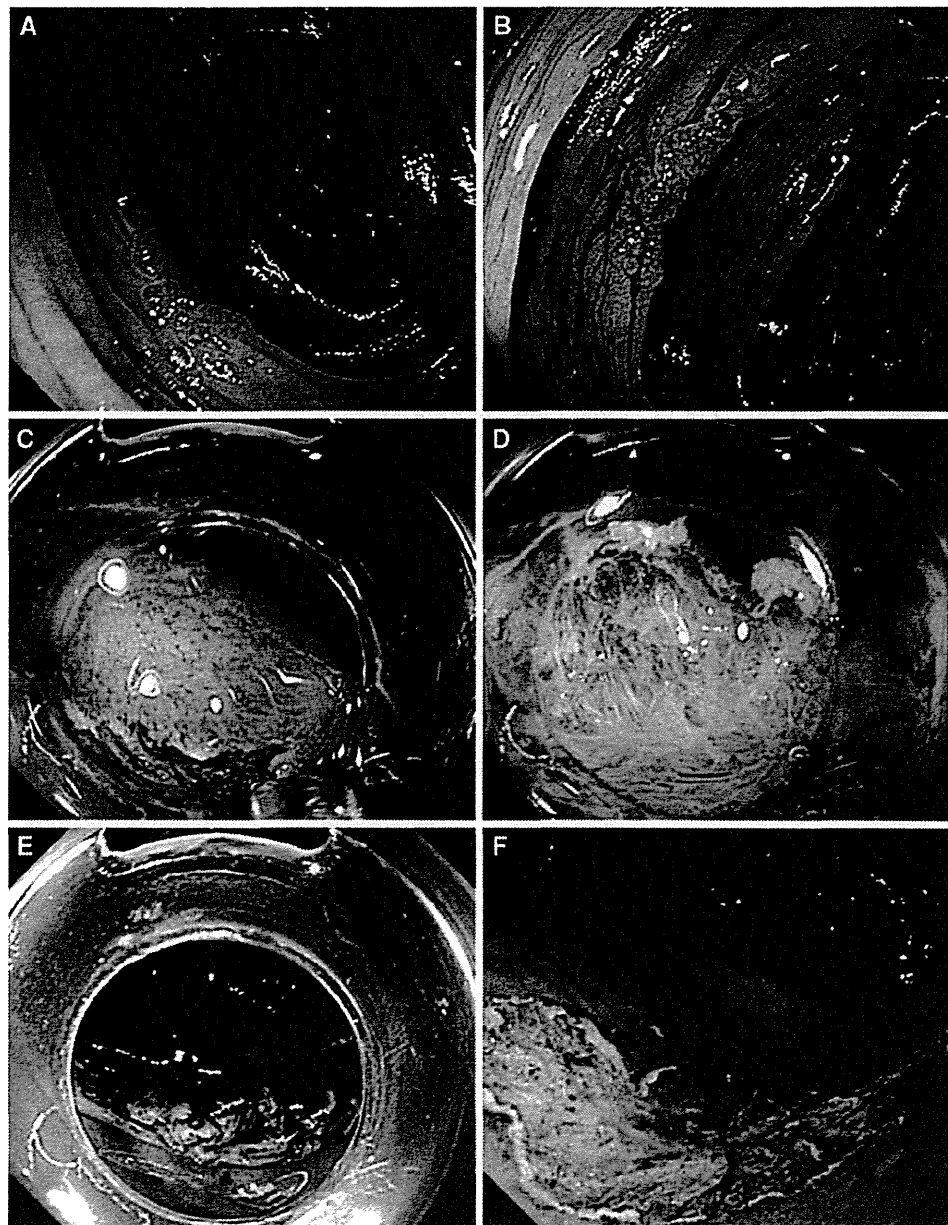
### Sedation

ESD procedures in our hospital are performed under conscious sedation in an endoscopy room. Intravenous injections of 2–3 mg of Midazolam and 15 mg of pentazocine are administered in all cases. An additional 2 mg of midazolam is given as necessary at the endoscopist's discretion.

### Pathological evaluation

We defined resections as en bloc (namely, resection of the tumor in one piece) or piecemeal, in which the lesion was removed in multiple fragments. All resected specimens were fixed in 10% buffered formalin. En bloc specimens and, where possible, larger piecemeal specimens were further cut into 2-mm-wide slices. The fragments or slices were embedded in paraffin, cut into 3- $\mu$ m sections, stained with hematoxylin–eosin, and microscopically examined for histologic type by pathologists specializing in gastrointestinal pathology.

**Fig. 2** **A** Conventional image of a sigmoid colon, flat-type (0-IIa), high-grade dysplasia. **B** Chromoendoscopy image using indigo carmine. **C** Circumferential incisions were made into the adjacent mucosa using the bipolar needle knife (ball tip type) to permit submucosal access. **D** After initial dissection, dense fibrotic bands were seen beneath the center of the lesion. **E** After submucosal dissection, a snaring technique was applied to achieve final dissection. **F** En bloc resection was achieved without complications



### Statistical analysis

Comparisons were performed with the Pearson  $\chi^2$  or the Fisher exact test for categorical data. All tests were two-sided, and  $P < 0.05$  was considered statistically significant. Analysis was performed with Statview statistical software (Statview Software version 5.0; Abacus Concepts, Berkeley, CA).

### Ethical considerations

Written, informed consent was obtained from all patients who underwent colonoscopy examination and any form of treatment.

## Results

Treatment results, complications, and clinical outcomes are summarized in Table 1. Lesions in the ESD group was significantly larger than those in the EMR group ( $P = 0.001$ ). There was no statistically significant difference in the rates of en bloc and piecemeal resection between the two groups.

### En bloc resection rate

ESD led to en bloc resection in 5 of 9 lesions (56%)—a higher rate than the 23 of 58 lesions (39%) in EMR group, despite the significantly larger tumor size in the ESD group. Nevertheless, this difference between the groups was not statistically significant (Table 1).

### Complications

One perforation (2%) occurred in the EMR group. This perforation was small and was successfully treated

**Table 1** Treatment results and complications, and clinical outcomes in 67 cases of recurrent or residual colorectal tumor after mucosal or submucosal endoscopic resection

	EMR ( $n = 58$ )	ESD ( $n = 9$ )
Mean tumor size (mm)	$7.8 \pm 6.4^*$	$25.3 \pm 19.6$
En bloc or piecemeal		
En bloc resection	23 (39)	5 (56)
Piecemeal resection	35 (61)	4 (44)
Complications		
Perforation	1 (2)	0 (0)
Bleeding	1 (2)	1 (11)
Rate of recurrence	8 (14)	0 (0)

Data are means  $\pm$  standard deviations or numbers with percentages in parentheses

\*  $P = 0.001$

endoscopically using endoclips. One patient in each group developed bleeding. All bleeding episodes were successfully treated using endoclips or coagulation.

### Clinical outcomes

We reviewed all patients who underwent endoscopic resection for recurrent lesions at 6 months after surgery. No cases of recurrent or residual lesions were seen in the ESD group compared with eight recurrences (14%) from lesions treated by EMR (Fig. 1). Most cases of recurrence were intramucosal neoplasm and were treated with additional conventional EMR or coagulation. All patients with recurrence achieved complete remission.

### Comparison of pathological characteristics between initial and recurrent or residual tumors

Of the total of 67 initial lesions, 21% (14/67) were adenomas, 58% (39/67) were high-grade dysplasia (HGD), and 4% (3/67) were submucosal cancer invading as far as the superficial layer of the submucosa (SM1:  $<1,000 \mu\text{m}$ ). In contrast, for recurrent or residual lesions, among cases in which the initial lesion was adenoma, 71% (10/14) were adenomas and 29% (4/14) were HGD; whereas among cases in which the initial lesion was carcinoma, 54% (28/52) were adenomas, 19% (10/52) were HGD, and 2% (1/52) were invasive submucosal cancer without distant or lymph-node metastasis (Table 2).

## Discussion

In this study, we found that ESD is a safe and effective treatment for recurrent or residual colorectal tumors. However, because of the technical difficulty of this procedure, the en bloc resection rate is lower than that in the treatment of nonrecurrent lesions. These findings provide further evidence for the clinical usefulness of ESD in a variety of conditions and sites.

Among the benefits of ESD, this procedure is suitable for use in endoscopic salvage procedures for recurrent lesions.

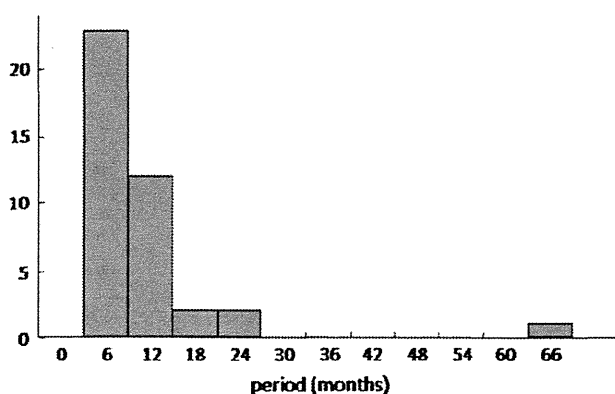
**Table 2** Pathological characteristics of initial and recurrent or residual lesions

Initial lesions	Recurrent or residual lesions			
	Adenoma	HGD	SM Ca.	Unknown
Adenoma	10	4	0	0
HGD	25	10	1	3
SM Ca.	3	0	0	0
Unknown	7	4	0	0



Furthermore, appropriate colonoscopic surveillance allows the achievement of complete cure by repeated conventional endoscopic treatment (hot biopsy, EMR, argon plasma coagulation, etc), even for recurrent or residual tumors.

These benefits emphasize the importance of a suitable follow-up period [16], which is currently considered to be 6 months after EPMR. In our study, most (88%) lesions recurring after initial treatment were diagnosed at the first follow-up colonoscopy within 6 to 12 months (Fig. 3). Surveillance at an inappropriate interval after EPMR, in contrast, would hamper the achievement of remission by conventional endoscopic treatment for almost all recurrent or residual tumors. Until recently, treatment for such lesions (i.e., those >20 mm or with severe fibrosis) was limited to surgical therapy. In our case series, however, the ESD technique enabled complete resection in these cases. Improvements in endoscopic devices and instruments have decreased complication rates with ESD, such as perforation, and after gradual evolution the technique is now widely accepted for the management of large colorectal neoplasms in Japan. The B-knife, for example, has been designed so that the high-frequency current sent to the muscle layer is reduced, enabling better control and greater endoscopist safety, whereas the return current from the knife toward the sheath tip results in greater patient safety [16–20]. However, because of its technical difficulty, longer procedure time, and increased risk of complications, it is not yet in universal use. Moreover, repeat endoscopic resection for recurrent tumor after endoscopic treatment or TEM is markedly difficult because of the development of submucosal fibrosis at the site of the previous treatment [21]. In this study, five of the nine lesions that underwent ESD (56%) were performed by en bloc resection. Although satisfactory, this rate is nevertheless lower than that in our previous series of patients who underwent ESD for primary colorectal cancer (168/200 patients; 84%) [20]. We consider that the technical difficulty of ESD makes its broad



**Fig. 3** Time between initial treatment and the detection of residual or recurrent tumor

application to recurrent or residual tumor unfeasible, although not impossible. The treatment of these lesions is likely best performed using simple EMR and requires a proper surveillance interval after EPMR. In several previous reports [23–25], incomplete endoscopic resection for submucosal cancer was associated with an increased risk of rapid growth of residual tumor. Accurate histopathological evaluation of the resected specimen is therefore crucial to determine a surveillance strategy.

An important unanswered question is the clinicopathological features of recurrent or residual tumor. Several previous studies assumed that residual tumor cells had acquired greater malignancy after EMR, and the development of residual cancer after EMR or polypectomy has been described [22–25]. In one study, 11.4% of local recurrent tumors after EPMR consisted of HGD, even though the excised specimens were diagnosed as benign adenomas [26]. However, none of these cases revealed any evidence of invasive cancer in the locally recurrent tumor, or distant or lymph node metastasis.

Although the present results indicate the acceptability of additional endoscopic treatment after EPMR for adenoma, objections may arise in the case of carcinoma. Upon histopathological comparison of the initial and recurrent tumors in our series, the recurrent or residual tumors were mainly adenoma, and the histological grade of atypia did not increase in almost any case, even when the initial treatment was HGD. This can be explained as follows: almost all lesions of colorectal neoplasm, especially LST-G, were cancer in adenoma, and local recurrence or residual tumor might have resulted from incomplete resection at the initial treatment, i.e., positive resection margins. On this basis, very few residual or recurrent tumors may present a serious clinical problem.

Several limitations of our study warrant mention. First, ESD in the colon can presently be performed by expert colonoscopists in only a limited number of specialized hospitals, and broader application in general centers may be difficult. Second, this was a retrospective study conducted at a single institution, and the validity of this treatment for recurrent or residual tumors requires confirmation in multicenter trials.

In conclusion, this study suggests that ESD may be effective in salvage therapy for the treatment of residual or recurrent tumors. Operator skill requirements are high, however, and widespread application is presently difficult. The achievement of complete remission after endoscopic piecemeal resection is dependent on suitable surveillance procedures.

**Disclosures** Taku Sakamoto, Yutaka Saito, Takahisa Matsuda, Shusei Fukunaga, Takeshi Nakajima, and Takahiro Fujii have no conflicts of interest or financial ties to disclose.

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## GASTROENTEROLOGY

**Comparing endoscopic submucosal dissection with transanal resection for non-invasive rectal tumor: A retrospective study**Shinsuke Kiriya<sup>\*,†,‡</sup>, Yutaka Saito<sup>\*</sup>, Takahisa Matsuda<sup>\*</sup>, Takeshi Nakajima<sup>\*</sup>, Yumi Mashimo<sup>\*</sup>, Henry KM Joeng<sup>\*,§</sup>, Yoshihiro Moriya<sup>¶</sup> and Hiroyuki Kuwano<sup>†</sup>

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**Key words**

endoscopic mucosal resection, endoscopic submucosal dissection, early rectal cancer, non-invasive rectal tumor, transanal endoscopic microsurgery, transanal resection.

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Part of this manuscript was presented at 14th United European Gastroenterology Week (UEGW 2006) in Berlin, Germany.

**Abstract**

**Background and Aim:** Endoscopic submucosal dissection (ESD) is an alternative to transanal resection (TAR) in treating rectal adenomas, intramucosal cancers, and superficial submucosal cancers. The purpose of this study is to compare the clinical efficacy between ESD and TAR for non-invasive rectal tumors.

**Methods:** Between January 1998 and December 2006, 85 patients with preoperative diagnosis of non-invasive rectal tumors were treated by ESD or TAR. En-bloc resection, local recurrence, complication, procedure time, and hospital stay were evaluated retrospectively using a prospectively-completed database.

**Results:** Mean resection sizes were 40 mm and 39 mm in diameter for the ESD and TAR groups, respectively. En-bloc resections with a negative resection margin were achieved in 67% (35/52) of the ESD group, which was significantly higher than the 42% (14/33) in the TAR group. Sixty-three lesions were diagnosed as curative resection, histopathologically. There was no local recurrence in the ESD group, but five local recurrences developed in the TAR group. Two rectal perforations, one minor delayed bleeding, and one subcutaneous emphysema in the ESD group were successfully managed conservatively. There were one minor delayed bleeding and two anesthesia-related complications in the TAR group. The ESD group had a shorter hospital stay than the TAR group (4.9 days vs 7 days), but a longer procedure time (131 min vs 63 min).

**Conclusion:** ESD was more effective than TAR in treating non-invasive rectal tumors, with a lower recurrence rate and shorter hospital stay.

**Introduction**

Early rectal cancers are now detected more often, therefore local excision with minimal invasiveness and excellent clinical outcome are feasible treatment options. Transanal resection (TAR) and transanal endoscopic microsurgery (TEM) are well-developed surgical procedures for local excision in the rectum and are now widely accepted for managing early-stage rectal cancer. However, high local recurrence rates and severe complications have been reported for both procedures.<sup>1-4</sup>

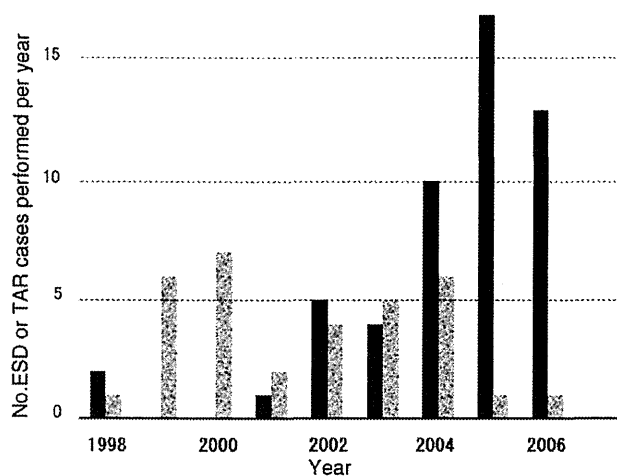
Endoscopic submucosal dissection (ESD) technique was introduced for non-invasive colorectal neoplastic lesions (adenoma, intramucosal cancer, and superficial submucosal cancer), especially in the rectum as an alternative of TAR as early as 1998.<sup>5,6</sup> The major advantage of ESD is being able to perform en-bloc resections for lesions  $\geq 20$  mm.

The aim of this retrospective study was to compare the result of ESD with TAR in treating non-invasive rectal tumors, which were unsuitable for conventional endoscopic mucosal resection (EMR).

**Methods**

Between January 1998 and December 2006 at National Cancer Center Hospital in Japan, a total of 85 rectal adenomas, intramucosal cancers (Tis), and superficial submucosal cancers (T1sm1) in 85 patients were treated by either ESD or TAR after informed written consent.

Before 2003, the indications for TAR were lesions unsuitable for conventional EMR or tumors spreading to the dentate line. Starting from 2003, TAR was performed for only eight lesions in our hospital when it was not difficult to assess the tumor margin, based on the judgement of a consultant surgeon. From 2003 onwards, we introduced ESD as the standard treatment for large



**Figure 1** Historical changes between endoscopic submucosal dissection and transanal resection for a lower rectal tumor. ■, ESD; ▨, TAR.

non-invasive rectal tumors and those spreading to the dentate line (Fig. 1).

Data were analyzed using a prospectively-completed database and pathological reports, with respect to en-bloc resection rate, local recurrence rate, early and late complications, histological diagnosis, procedure time, and length of hospital stay in both groups. This study was performed in accordance with the 1989 revised Helsinki Declaration.

### ESD procedure

ESD were carried out with a high-magnification endoscope (PCF-Q240ZI or GIF-Q240Z, Olympus Medical Systems, Tokyo, Japan) with CO<sub>2</sub> insufflation.<sup>7</sup> All ESD were performed under conscious sedation. For those lesions spreading to the dentate line, we used a local injection of lidocaine solution (0.5%) to reduce anal pain.

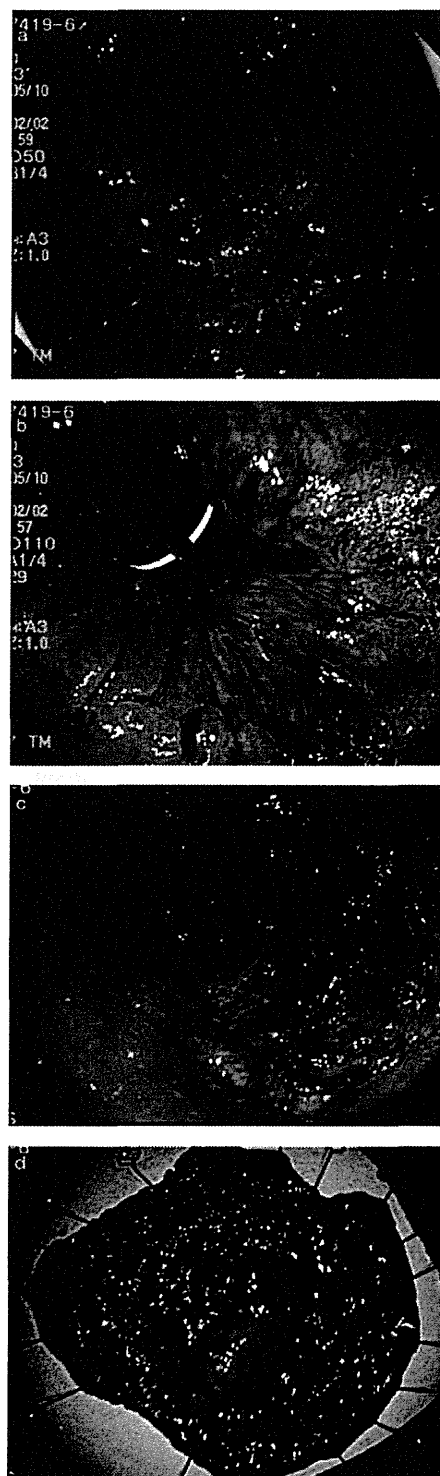
Each ESD procedure was performed according to the following steps (Fig. 2): (i) 0.4% indigo carmine dye was sprayed; (ii) glycerol and sodium hyaluronic acid were injected into the submucosal layer; (iii) an initial cut was made with a bipolar current needle knife (B-knife; XEMEX, Tokyo, Japan);<sup>8</sup> (iv) complete a circumferential incision; (v) submucosal dissection was performed using the B-knife and an insulation-tipped knife (IT knife; KD-610L, Olympus Medical Systems, Japan).

### TAR procedure

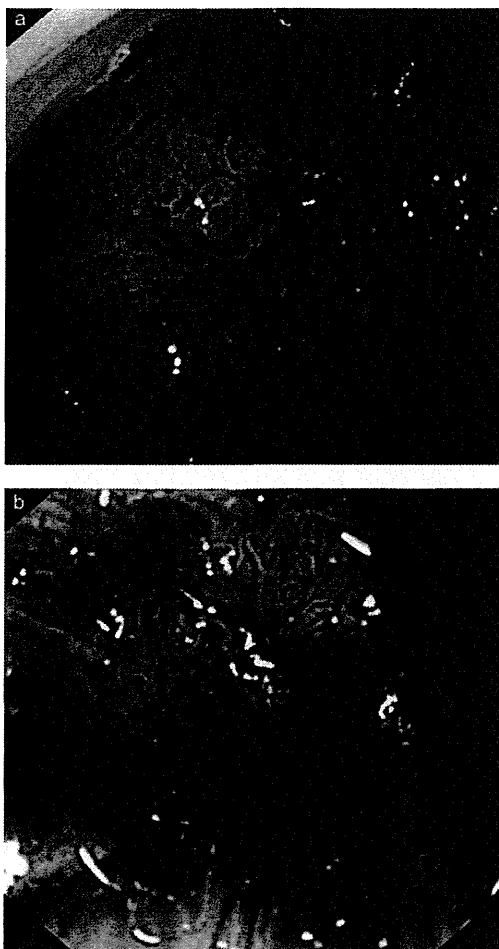
TAR were performed under general or spinal anesthesia, with patients assuming the prone jack knife position or lithotomy position. No indigo carmine dye was applied. Normal saline solution with epinephrine was injected into the submucosal layer. In the case of suspected submucosal deep invasion, a full-thickness excision, including muscularis propria, would be performed (Fig. 3).

### Assessment of procedures and histopathology

ESD procedure times were measured from the initial insertion of the endoscope to its removal following resection of the tumor;



**Figure 2** Representative endoscopic submucosal dissection case. (a) Large 0-Is-IIa lesion located in the lower rectum; (b) margins delineated using 0.4% indigo carmine dye spraying; (c) area of rectum following en-bloc resection; (d) resected specimen was 100 mm in diameter, and histological examination revealed well-differentiated adenocarcinoma with tumor-free resected margin.



**Figure 3** Representative transanal resection case. (a) Large 0-Ia lesion located in the lower rectum; (b) tumor spread to anal canal.

while TAR procedure times were measured from the initial incision to the completion of resection and hemostasis, as determined by the individual surgeons. The lateral and vertical margins of specimens resected by ESD and TAR were examined macroscopically for any tumor involvement by endoscopists or surgeons.

An en-bloc R0 resection was successfully achieved when both the lateral and vertical margins of a specimen were free of neoplasm, with resection in one piece. Specimens with deep submucosal (> 1000  $\mu$ m from the muscularis mucosae) invasion, lymphatic invasion, vascular involvement, or histologically poorly-differentiated component were diagnosed as non-curative.<sup>9</sup> Histological diagnosis was based on the Japanese classification of cancer of the colon and rectum,<sup>10</sup> and the Vienna classification.<sup>11</sup>

### Endoscopic and other modality follow up

All patients with curative resection were examined endoscopically 6 months after their original treatment. Indigo carmine dye was sprayed on the previously-resected areas, and high-magnification views were obtained to check for the existence of any recurrence

for all patients. One or two biopsies were performed as indicated, with recurrent neoplastic disease identified as type-IIIa, -IIIb, -IV, or -V pit patterns (neoplastic pattern) using high-magnification chromocolonoscopy, according to the criteria established by Kudo and Fujii.<sup>12,13</sup> When a type I or II pit pattern (non-neoplastic pattern) was identified using high-magnification chromocolonoscopy, no biopsy was performed, as there was no evidence of recurrence.<sup>13</sup> Patients with intramucosal cancer and adenoma did not require computed tomography (CT) scan on follow up. Curative resection cases with superficial submucosal invasion (T1sm1) were followed up by annual abdominal and pelvic CT scan.

### Statistical analysis

Statistical differences were analyzed using the  $\chi^2$ -test or *t*-test with a *P*-value less than 0.05, considered as statistically significant. Calculations were made using SPSS version 8.0 for Windows (SPSS Japan, Tokyo, Japan).

## Results

### Patient characteristics and lesion clinical features

A total of 85 patients were recruited into the study. Fifty-two patients were treated by ESD, and 33 patients were treated by TAR (Table 1). The mean lesion size was 40 mm and 39 mm in diameter for the ESD and TAR groups, respectively. Eleven lesions in the ESD group were located in the upper rectum (Ra; oral side from the middle transverse fold of rectum), 37 in the lower rectum (Rb; anal side from the middle transverse fold of the rectum), and four extended from the Rb to the anal canal (Rb-P). In comparison, none (0%) of the lesions in the TAR group was located in the Ra, 22 lesions were in the Rb, and 11 were in the dentate line (Rb-P).

Histological results of adenoma/intramucosal carcinoma (Tis)/T1sm1/deep submucosal carcinoma (T1sm2) were 9/26/6/11 in the ESD group and 2/18/2/11 in the TAR group, respectively.

The mean procedure time of the ESD group was significantly longer than that of the TAR group (131 vs 63 min, *P* < 0.001). The mean length of hospital stay in the ESD group was significantly shorter than that of the TAR group (4.9 days vs 7 days, *P* < 0.001).

### Histopathological results and local recurrence rates

The macroscopically-clear resection margin rates of ESD and TAR were 100% (Table 2). En-bloc resection with the microscopically-clear resection margin (En-bloc R0 resection) was successfully achieved in 67% of the ESD group, which was significantly higher than the 42% in the TAR group (*P* < 0.001).

### Clinical results in the curative resection subgroup

After histological examination, 11 ESD and 11 TAR were found to have deep submucosal invasion, including one TAR with lymphovascular involvement. These 11 ESD and 11 TAR patients

**Table 1** Patient characteristics and lesion clinical features

	Endoscopic submucosal dissection	Transanal resection	<i>P</i> -value
No. lesions	52	33	
Age (Mean (SD)), years	61 ± 11	64 ± 13	NS
Tumor size, mm	40 ± 21	39 ± 24	NS
Location			
Ra/Rb/Rb-P	11/37/4 (21/71/8%)	0/22/11 (0/67/33%)	< 0.001
Macroscopic type			
Sessile/flat/recurrent	4/44/4 (8/84/8%)	17/16/0 (52/48/0%)	NS
Histological depth			
Adenoma/Tis/T1sm1/T1sm2	9/26/6/11 (17/50/12/21%)	2/18/2/11 (6/55/6/33%)	NS
Procedure time, min (mean ± SD)	131 ± 100	63 ± 54	< 0.001
Hospital stay, days	4.9 ± 0.8	7.0 ± 3.0	< 0.001

NS, not significant; Ra, oral side from the middle transverse fold of rectum; Rb, anal side from the middle transverse fold of the rectum; Rb-P, oral side from the middle transverse fold of rectum to the anal canal; SD, standard deviation; T1sm1, submucosal invasion < 1000 µm; T1sm2, submucosal invasion > 1000 µm; Tis, intramucosal.

**Table 2** Comparison of clinical results

	Endoscopic submucosal dissection	Transanal resection	<i>P</i> -value
Macro clear resection rate <sup>‡</sup>	100% (52/52)	100% (33/33)	NS
En-bloc resection rate			
All	88% (46/52)	85% (28/33)	NS
Sessile	100% (4/4)	94% (16/17)	NS
Flat	91% (40/44)	75% (12/16)	NS
Recurrent	50% (2/4)	—	
En-bloc R0 resection rate <sup>‡</sup>			
All	67% (35/52)	42% (14/33)	< 0.001
Sessile	100% (4/4)	65% (11/17)	NS
Flat	66% (29/44)	19% (3/16)	< 0.005
Recurrent	50% (2/4)	—	

<sup>‡</sup>Macroscopically-clear resection margin; <sup>‡</sup>en-bloc and negative resection margin. NA, not applicable; NS, not significant.

received additional surgical procedure or chemoradiotherapy. Sixty-three lesions, including 41 lesions treated by ESD and 22 lesions treated by TAR, were diagnosed as curative resections (Table 3). Among the patients who received curative resection, en-bloc R0 resection was successfully achieved in 78% of the ESD group, which was significantly higher than the 27% in the TAR group ( $P < 0.001$ ). There was no recurrence for all these en-bloc R0 resection cases in the ESD group (26 flat lesions, 4 sessile lesions, and 2 recurrent lesions after other resections) over a median follow-up period of 60 months.

In the remaining nine cases of ESD, seven were resected in one piece, but the lateral margins of the resection specimen were histologically positive for neoplastic components, and two cases were resected in two pieces. These nine ESD resections were all flat lesions, but there was also no local recurrence in any of these cases over a median follow-up period of 35 months.

In comparison, six cases of TAR achieved en-bloc R0 resections. In the other 16 cases of TAR, 11 cases were resected in a single piece, but the lateral margins were histologically positive for neoplastic components. These 11 TAR cases were all flat

lesions, and three of them developed local recurrences. The other five cases of TAR were resected as piecemeal, and recurrences were present in two of these five lesions.

The overall local recurrence rate was 23% ( $P < 0.01$ ) in the TAR group cases over a median follow-up period of 55 months. The median time interval of local recurrence was 12 months after TAR. All five local recurrences in the TAR group underwent additional treatment: two proceeded with ESD, two repeated TAR, and one received low anterior resection with lymph node dissection. Curative resections were achieved in all five local recurrent cases.

### Complications

Three kinds of complications occurred in the ESD group, including rectal perforations in two patients, minor delayed bleeding in one patient, and one case of subcutaneous emphysema. All four patients were successfully managed by conservative means, using endoclips without the need of blood transfusion or any additional procedure. In comparison, two kinds of complications occurred in the TAR group, including one case of delayed bleeding after the