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がん臨床研究事業

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

平成22年度～24年度 総合研究報告書

研究代表者 松田 尚久

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松田 尚久

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（総合）研究報告書

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

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研究要旨

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

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A. 研究目的

本研究の目的は、日本における258の指定有人離島（人口42.9万人、関係市町村数：110）における理想的な地域大腸がん検診モデルの確立を目指し、科学的根拠に基づいた検診体制を構築するための臨床研究を策定することにある。本研究では、新島村をモデルに「内視鏡検査による大腸がん検診受診率50%以上」の目標達成として計画する啓発活動（パンフレット作成・講演会）の有効性評価と、検診非受診者に対して行う6か月ごとのリコール（反復受診勧告）による受診率向上効果を明らかにする。実際には、東京都新島村をモデルとし、大腸がん検診対象者中40～79歳の男女約1,600名に対して啓発活動後に検診としての全大腸内視鏡検査の案内を行い、文書による本研究参加の応諾が得られた者に対して、全例大腸内視鏡検査を計画する。

B. 研究方法

新島村住民で、平成23年度大腸がん検診の対象者中40～79歳の男女約1,600名に対して、検診として

の全大腸内視鏡検査（TCS）の案内状を送付する。この時点で、文書による本研究参加の応諾が得られた者に対して、全例TCSを計画する（参加同意が得られない住民及び80歳以上の方については、例年通りの免疫学的便潜血検査：FOBTを推奨）。また、上記いずれの検査も受検しなかった対象者に対しては、初回呼びかけ後6か月の期間を利用して、大腸がん検診の重要性とTCS及びFOBTのメリット・デメリット等について、パンフレット送付と地域での講演会を通じて普及啓発活動を行った後に案内状を再送付（リコール）し、検診受診を再度呼びかける。また、新島村住民すべてを対象としたアンケート調査（大腸がん検診受検・非受検理由および大腸がんリスクに関する食生活等の生活習慣・がん家族歴・既往歴・身体所見：BMI等の調査）を行う。また検診受検者については、検診結果に基づいた個別のフォローアップ方法（推奨される検査間隔およびその方法）についての情報提供を行う。

（倫理面への配慮）

本研究への参加同意が得られた島民のデータについては、新島事務局（新島村さわやか健康センター）にて管理するが、TCS及びFOBT検査結果については匿名化した形でデータセンター（メディカルリサーチサポート）が集中管理する。データセンター、新島事務局、中央事務局（国立がん研究センター）の施設責任者は、研究のために作成されたデータセットまたは資料を研究終了後も保管する。いずれの参加者も個人情報保護法を遵守する。

### C. 研究結果

第1期検診(H23)に加え第2期(H24)では、新たに317名が本研究に参加し大腸がん検診を受検した[第1-2期合計:783名(うち、全大腸内視鏡検査:TCS受検者614名;一部、重複あり);全検診対象者の約47%]。今年度の検査種別内訳は、TCS+FOBT:167名、TCS単独:101名、FOBT単独:49名であった。今年度新たに86名に要治療病変(5mm以上の腫瘍性病変)を、さらにその中には29名のIndex lesion(10mm以上の腫瘍あるいは内視鏡的に癌が疑われる病変)保有者を認めた。第1-2期合わせると、延べ571名がFOBT、614名がTCS検診を受検し、182名(TCS受検者の約30%)に治療対象となる5mm以上の腺腫性ポリープを、83名(約13%)に10mm以上の腺腫あるいは癌が疑われる病変を認めたことになる。現在、これらの対象者については、当院を中心に保険診療下に内視鏡治療が進行中である。研究期間内の目標として掲げた検診受診率50%にはわずかに及ばなかったものの、現時点ですでに3例のSM(粘膜下層)浸潤癌と18例のM(粘膜内)癌が発見され、その治療が完了している。

また、全島民を対象としたアンケート調査(受検・非受検理由等)が完了し、検診対象者の約7割にあたる約1,100名からの回答が得られた。現在、その最終集計・解析作業が進行中である。

### D. 考察

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

### E. 結論

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

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G. 知的所有権の取得状況

出願・登録なし。今後申請の予定なし。

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## Assessment of the validity of the clinical pathway for colon endoscopic submucosal dissection

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### Abstract

**AIM:** To determine the effective hospitalization period as the clinical pathway to prepare patients for endoscopic submucosal dissection (ESD).

**METHODS:** This is a retrospective observational study which included 189 patients consecutively treated by ESD at the National Cancer Center Hospital from May 2007 to March 2009. Patients were divided into 2 groups; patients in group A were discharged in 5 d and patients in group B included those who stayed longer than 5 d. The following data were collected for both groups: mean hospitalization period, tumor site, median tumor size, post-ESD rectal bleeding requiring urgent endoscopy, perforation during or after ESD, abdominal pain, fever above 38 °C, and blood test results positive

for inflammatory markers before and after ESD. Each parameter was compared after data collection.

**RESULTS:** A total of 83% (156/189) of all patients could be discharged from the hospital on day 3 post-ESD. Complications were observed in 12.1% (23/189) of patients. Perforation occurred in 3.7% (7/189) of patients. All the perforations occurred during the ESD procedure and they were managed with endoscopic clipping. The incidence of post-operative bleeding was 2.6% (5/189); all the cases involved rectal bleeding. We divided the subjects into 2 groups: tumor diameter  $\geq 4$  cm and  $< 4$  cm; there was no significant difference between the 2 groups ( $P = 0.93$ ,  $\chi^2$  test with Yates correction). The incidence of abdominal pain was 3.7% (7/189). All the cases occurred on the day of the procedure or the next day. The median white blood cell count was  $6800 \pm 2280$  (cells/ $\mu$ L;  $\pm$  SD) for group A, and  $7700 \pm 2775$  (cells/ $\mu$ L;  $\pm$  SD) for group B, showing a statistically significant difference ( $P = 0.023$ ,  $t$ -test). The mean C-reactive protein values the day after ESD were  $0.4 \pm 1.3$  mg/dL and  $0.5 \pm 1.3$  mg/dL for groups A and B, respectively, with no significant difference between the 2 groups ( $P = 0.54$ ,  $t$ -test).

**CONCLUSION:** One-day admission is sufficient in the absence of complications during ESD or early post-operative bleeding.

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**Key words:** Clinical pathway; Colon; Complication; Endoscopic submucosal dissection; Hospitalization period; Rectum

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## INTRODUCTION

Conventional laparotomy is the standard treatment for early colon cancer. Subsequently, endoscopic mucosal resection (EMR) was developed for small polyps<sup>[1]</sup>. Analysis of surgically resected specimens revealed that in cases of early colon cancer with a depth of invasion of < 1000  $\mu$ m into the submucosal layer (SM 1), no lymphatic invasion, no vascular involvement, or without a poorly differentiated adenocarcinoma component, curative resection can be obtained by endoscopic treatment<sup>[2,3]</sup>.

Endoscopic submucosal dissection (ESD) is an advanced technique, compared with EMR, by which higher *en-bloc* resection and lower rates of tumor recurrence are achieved when treating large tumors > 20 mm in diameter<sup>[4-11]</sup>.

In our institution, gastric ESD has been performed since 1996, and in 2002, a clinical pathway (CP) was introduced to standardize this form of intervention. This CP included a set period of hospitalization to prepare patients and to determine any sign of post-procedure complications. The efficacy of the CP in gastric ESD was then reported<sup>[12]</sup>. A similar CP was introduced for colon ESD, which involves a 5 d hospital admission, including a 1 d pre-procedure for bowel preparation. In this study, we examined the appropriateness of this hospitalization period as the CP to prepare patients for ESD and to determine any sign of post-procedure complications.

## MATERIALS AND METHODS

In our institution, colon ESD was introduced in 2007, and the CP was implemented in May 2007. All 189 consecutive patients who had colon ESD from May 2007 to March 2009 were included in this study. All used data were recorded in the ESD database.

Patients were divided into 2 groups: group A included patients who were discharged in 5 d and group B included patients who stayed longer than 5 d. The following data were collected for both groups: mean hospitalization period, tumor site, median tumor size, post-ESD rectal bleeding requiring urgent endoscopy, perforation during or after ESD, abdominal pain, fever above 38 °C, and blood test results positive for inflammatory markers before and after ESD.

Perforation during colon ESD was diagnosed when the abdominal cavity could be observed owing to injury of the muscle layer. Cases with no perforation, but with a deep separation of the submucosal layer, enabling the

endoscopist to observe the muscle layer directly were recorded as "exposure of the muscle layer". Late-onset bleeding was defined as the occurrence of rectal bleeding after ESD, if confirmed by urgent endoscopy. Abdominal pain was defined as the presence of tenderness following examination by a physician or by patient request for analgesia. Late-onset perforation was defined as the finding of free air on abdominal computed tomography or plain X-ray, performed owing to the complaint of abdominal pain. All complications were defined in advance and recorded in the ESD database.

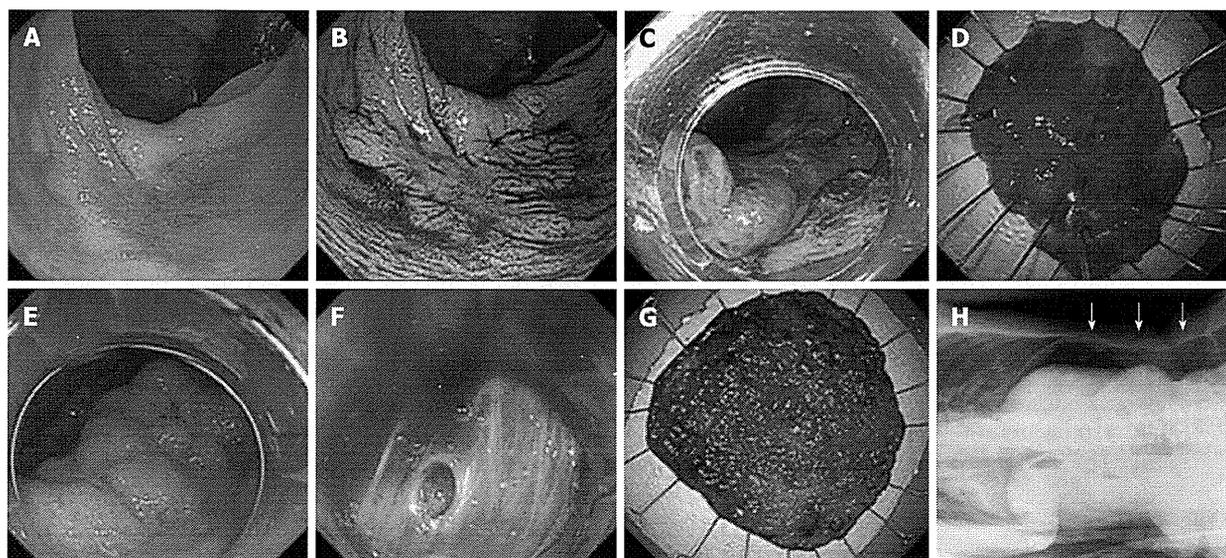
Patients are admitted 1 d before the procedure at noon, and receive a low-fiber diet for lunch and dinner. For bowel preparation on the day of ESD, patients drink 3000 mL of intestinal lavage fluid [polyethylene glycol; (PEG)] over a period of 2 h in the morning. Then, the ward nurse checks their stools. If the bowel preparation is poor, patients will drink an additional 500 mL to 1000 mL of PEG. Otherwise, no food or drink is allowed on the day of the procedure or the following day. The procedure starts in the afternoon after achieving successful bowel preparation. We provide prophylactic antibiotic (cefmetazole 1.0 g, intravenously) just before the procedure.

In general, the ESD procedure is performed using a bipolar needle knife (Xeon Medical Co., Tokyo, Japan), insulation-tipped (IT) knife (Olympus Co., Tokyo, Japan), HemoStat-Y (bipolar forceps for hemostasis, PENTAX, Tokyo, Japan), water jet scope (Olympus Co.), distal attachment (short ST hood, Fujifilm Co., Tokyo, Japan)<sup>[13]</sup>, and a CO<sub>2</sub> insufflation system (Olympus Co.) for all patients. The high-frequency wave device used is ICC200 (ERBE, Tübingen, Germany); to set the output power, an Endo Cut 50 W/Forced 40 W bipolar needle knife/IT knife is used; a bipolar 25 W is used for the HemoStat-Y.

Conscious sedation is performed to allow positional changes to patients during the procedure. Sedation with midazolam and pentazocine is usually started with 2 mg and 15 mg doses intravenously, respectively, and if required, additional dosing will be provided perioperatively based on the operator's assessment. Hyoscine butylbromide (Buscopan) (10 mg, intravenously) is administered immediately before the procedure and another 10 mg can be given later if needed.

The morning after the ESD, routine peripheral blood and biochemistry tests are performed. Providing there are no signs or symptoms of complications, patients will start to drink water on day 1 and have meals (rice porridge) on day 2. Patients can only walk to the restroom as they should maintain bed rest the whole day of the ESD procedure. On the next day, they can walk within the hospital ward. If there is no concern with the clinical progression, patients are allowed home on day 3. Patients are instructed to refrain from ingesting alcohol or performing exercise during the first week after hospital discharge.

The ESD procedure is performed by 6 endoscopists, all of whom began performing colon ESD after first experiencing gastric ESD cases.



**Figure 1** Case without complications and with perforation. A: Tumor located in the ascending colon; B: Image of dye spraying (indigo carmine). The macroscopic type is 0-IIa (LST-NG). The size is 35 mm; C: Treatment by endoscopic submucosal dissection (ESD); D: *En-bloc* resection was performed; E: Tumor located in the cecum. The macroscopic type is 0-IIa (LST-G). The size is 65 mm; F: Perforation occurred during ESD. It was closed by endoscopic clipping; G: *En-bloc* resection was performed by ESD; H: Prominent free air was observed in the abdominal cavity with the patient lying on the left side. The free air is indicated in the Figure by an arrow. LST-NG: Laterally spreading tumors-non-granular; LST-G: Laterally spreading tumors-granular.

**Table 1** Results of the patients reviewed

|                                                 | Group A           | Group B   | Total or average |
|-------------------------------------------------|-------------------|-----------|------------------|
| Number                                          | 156               | 33        | 189              |
| Average hospitalization period (d)              | 4.94              | 6.67      | 5.81             |
| Location of lesion                              |                   |           |                  |
| Colon (%)                                       | 108 (69.2)        | 23 (70.0) | 131 (69.0)       |
| Rectum (%)                                      | 48 (30.8)         | 10 (30.3) | 58 (31)          |
| Median size of lesion (mm)                      | 34.5              | 35        | 35               |
| Hemorrhage (%)                                  | 1 (0.6)           | 4 (12.1)  | 5 (2.6)          |
| Perforation (%)                                 | 1 (0.6)           | 6 (18.2)  | 7 (3.7)          |
| Abdominal pain (%)                              | 2 (1.3)           | 5 (15.2)  | 7 (3.7)          |
| Fever > 38.0 °C (%)                             | 2 (1.3)           | 2 (6.1)   | 4 (2.1)          |
| WBC (cells/ $\mu$ L; median)                    | 6800 <sup>a</sup> | 7700      | 7000             |
| Hemoglobin level change pre-/post-ESD > 2.0 (%) | 5 (3.2)           | 1 (3.0)   | 6 (3.2)          |
| CRP (mg/dL; mean)                               | 0.4 <sup>b</sup>  | 0.5       | 0.4              |

<sup>a</sup> $P = 0.023$ , <sup>b</sup> $P = 0.54$  vs group B. ESD: Endoscopic submucosal dissection; CRP: C-reactive protein; WBC: White blood cell.

## RESULTS

### Case presentations

**Case without complications:** This is the case of a 74-year-old male patient. The tumor was of the macroscopic type, grade 0-IIa laterally spreading tumors-non-granular (LST-NG) with a diameter of 35 mm, located in the ascending colon. *En-bloc* resection was achieved by ESD. The total length of hospital stay was 5 d. Histological examination revealed a well-differentiated adenocarcinoma, low-grade atypia with no lymphatic-vascular invasion, and the lateral and horizontal margins were negative. Curative resection was achieved (Figure 1).

**Case with perforation:** This is the case of a 58-year-old

female patient. The tumor was of the macroscopic type, grade 0-IIa laterally spreading tumors-granular (LST-G) with a diameter of 65 mm, located in the cecum. *En-bloc* resection was achieved by ESD. A small perforation occurred during the ESD, which was closed by endoscopic clipping immediately after submucosal dissection around the perforation site. Abdominal X-ray showed a small amount of free air, but no abdominal pain was reported or high-grade fever (suggesting peritonitis) observed, so the patient was managed conservatively and stayed for a total of 10 d in the hospital. Histological examination revealed a well-differentiated adenocarcinoma, low-grade atypia with no lymphatic-vascular invasion, and the lateral and horizontal margins were negative. Curative resection was achieved and no surgical treatment was necessary (Figure 1).

Of all the patients, 83% (156/189) could be discharged from the hospital on day 3 post-ESD (group A). On the other hand, the remaining 17% (33/189) of patients required prolonged hospitalization (group B) (Table 1). Complications were observed in 12.1% (23/189) of patients. Perforation was the most commonly observed complication, occurring in 3.7% (7/189) of patients. All the perforations occurred during the ESD procedure and none were of late-onset. They were managed with endoscopic clipping and no patient required surgical intervention. Six out of 7 patients with perforations (86%) were required to stay for more than 5 d.

The incidence of post-operative bleeding was 2.6% (5/189); all the cases involved rectal bleeding. Five cases required hemostatic intervention and 3 of them were inpatient admissions. The period of hospitalization needed to be prolonged for 4 out of the 5 (80%) cases. Two patients had to be re-admitted to undergo emergency

endoscopy due to bleeding which occurred after hospital discharge (post-discharge days 4 and 6); however, bleeding did not recur after that.

To analyze the rates of late-onset bleeding and tumor size, we divided the subjects into 2 groups: one with a tumor diameter < 4 cm (118 patients) and the other with a tumor diameter  $\geq$  4 cm (71 patients). The incidence of post-ESD bleeding was compared. The rates were 5.6% (4/71) for a tumor diameter < 4 cm and 4.2% (5/118) for a tumor diameter  $\geq$  4 cm. There was no significant difference between the 2 groups ( $P = 0.93$ ,  $\chi^2$  test with Yates correction).

The incidence of abdominal pain was 3.7% (7/189). All the cases occurred on the day of the procedure or the next day. Of all the patients who had abdominal pain, 70% (5/7) stayed for more than 3 d post-procedure, based on the attending physician's assessment. The most common causes of delayed discharge from the hospital were late-onset bleeding and social reasons (7 patients each). Other complications were as follows: perforation (6 patients), exposure of the muscle layer (6 patients), abdominal pain (5 patients), fever (2 patients), and increased inflammatory reaction (1 patient).

Serum inflammatory markers were also assessed. On the day after ESD, the median white blood cell (WBC) count was  $6800 \pm 2280$  (cells/ $\mu$ L;  $\pm$  SD) for group A, and  $7700 \pm 2775$  (cells/ $\mu$ L;  $\pm$  SD) for group B, showing a statistically significant difference ( $P = 0.023$ ,  $t$ -test). The mean C-reactive protein (CRP) values the day after ESD were  $0.4 \pm 1.3$  and  $0.5 \pm 1.3$  mg/dL for groups A and B, respectively, with no significant difference between the 2 groups ( $P = 0.54$ ,  $t$ -test).

## DISCUSSION

The introduction of the CP for colon ESD was demonstrated to be useful for maintaining the safety of ESD and post-procedure care<sup>[12,14-16]</sup>. Seventy-nine percent of the patients were discharged on day 3 post-procedure; they had no complications or adverse events requiring medical attention. Three percent had complications, but they did not need to stay any longer. One percent of patients were readmitted 1 week post-procedure due to bleeding.

Looking at the breakdown of the 17% of patients with CP deviation (those who stayed for more than 5 d), it was observed that most cases were due to social reasons. Taking the above into consideration, we conclude that, in the absence of complications during ESD or early post-operative bleeding, the period of admission can be safely shortened to 1 d. However, we have to consider patients' circumstances and traveling requirements. Patients certainly need to be educated before ESD on appropriate ways of responding if symptoms of complications (particularly post-operative bleeding) occur. They may need to be advised to stay in a hotel nearby if they live far away from the endoscopy center. We have no local evidence that inpatient preparation is better than outpatient prepara-

tion. However, to avoid failure of the procedure, and patient dissatisfaction, we have included 1 d hospital stays for these reasons within our CP, particularly since the cost is very low here in Japan. On the other hand, reports from the United States and the United Kingdom have shown no differences between inpatient and outpatient preparation, and the latter situation may even be preferable<sup>[17]</sup>. Therefore, a 1 d admission for bowel preparation may not be necessary under all conditions. Omitting this admission would minimize the cost of the procedure.

As mentioned previously, the indications for colon ESD are 0-Is+IIa (LST-G) exceeding 30 mm, LST-NG exceeding 20 mm, IIc and non-lifting sign positive intramucosal lesions, and residual recurrent lesions that cannot be resected by EMR<sup>[18]</sup>. This is because the rate of SM invasion of LST-NG lesions is comparatively high, and 27% of them are multifocal invasions, making it difficult to identify the region of invasion before the procedure. Thus, accurate pathological evaluation by reliable *en-bloc* resection is necessary<sup>[3]</sup>. In LST-G, 84% of cases of SM invasion are in the macro-nodular area, and if the same area can be resected *en-bloc*, endoscopic piecemeal mucosal resection (EPMR) is also allowed. However, with a 0-Is+IIa (LST-G) exceeding 30 mm, if EPMR is eventually performed, there is the possibility that the pathological assessment of the macro-nodular component will be inaccurate; such lesions are also treated by ESD as a relative indication.

The bowel preparation for colon ESD at our institution consists of domperidone (10 mg) and mosapride citrate hydrate (15 mg) administered with 3000 mL to a maximum of 4000 mL of PEG. This is a more rigorous bowel preparation than that used for conventional colonoscopy. This is to ensure a good field of view during ESD and to prevent diffuse peritonitis due to the discharge of fecal fluid in case perforation occurs<sup>[19]</sup>.

Currently, there are no fixed guidelines for antibiotics that can be administered prophylactically in colon ESD. In the field of gastroenterological surgery, there is evidence that prophylactic administration of antibiotics is useful in the prevention of wound infection, and broad-spectrum antibiotics are commonly used immediately before surgery. In the field of therapeutic endoscopy of the colon, Ishikawa *et al.*<sup>[20]</sup> reported that if the high risk of infectious endocarditis and bacteremia are considered, the administration of antibiotics depended on the type of treatment procedure. This report was on conventional snare polypectomy and hot biopsy. With colon ESD, the risk of perforation is slightly higher than in the above procedures; therefore, we considered it appropriate to provide some form of prophylactic treatment. However, as changes in WBC and CRP level are minimal, there is the possibility that such treatment can be omitted.

We consider the bipolar system (B-knife), which is mainly used in the colon ESD procedure, to be safe<sup>[21]</sup>. Although the monopolar system is available as a backup, the IT-knife with an insulated tip that enhances safety is being used<sup>[22,23]</sup>. In other institutions, there are those that

mainly use a dual-knife (Olympus Co.) with the monopolar system. Differences between such devices can create differences in the rate of complications and the method of post-ESD management.

The colon ESD performed at our institution has the indications mentioned above and is discussed in the context of the CP. The purpose of this study was to investigate the appropriateness and effectiveness of the 5 d hospitalization period, including 1 d for bowel preparation, as the CP to prepare patients for ESD and to determine any sign of post-procedure complications. However, the attending physician mainly judged the prolongation of the hospitalization period. Although there is no particularly clear standard, the attending physician usually orders the prolongation under any of the following circumstances: (1) when complications, such as perforation and bleeding, are observed; (2) when an ablation on the intrinsic muscle layer at the time of ESD is judged as invasive; and (3) when there may be problems with blood sampling or physical findings the following day. It became clear that in such a case, the time to restart ingestion of water and food was commonly prolonged. At our institution, the incidence of post-ESD bleeding following gastric ESD is approximately 5% and the CP for gastric ESD is 7 d (patients discharged on day 5 after ESD). With the introduction of the CP for colon ESD, the incidence of post-ESD bleeding was lower than gastric ESD bleeding; thus, the period of hospitalization was set at 5 d and safety could be maintained for many patients. The lesions, method and bowel preparation in colon ESD differ according to the institution; therefore, the risks of complications during and after ESD are likely to differ. Hereafter, to stratify the risks in the CP, addition of the status after resection (complete suturing) and the site of the lesion (rectum or colon) as parameters should increase safety.

### Limitations

There is no doubt that a 5 d hospitalization period may not be possible in many countries for financial reasons. A randomized control trial would be the best method to evaluate the necessity of post-procedure hospital admission. However, we would like to share our findings from this retrospective observational study which confirm the safety of discharging ESD patients without any complications 1 d after the procedure.

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### COMMENTS

#### Background

Conventional laparotomy is the standard treatment for early colon cancer.

Subsequently, endoscopic mucosal resection (EMR) was developed for small polyps. Analysis of surgically resected specimens revealed that in cases of early colon cancer with a depth of invasion of < 1000  $\mu\text{m}$  into the submucosal layer (SM 1), no lymphatic invasion, no vascular involvement, or without a poorly differentiated adenocarcinoma component, curative resection can be obtained by endoscopic treatment.

#### Research frontiers

Endoscopic submucosal dissection (ESD) is an advanced technique, compared with EMR, by which higher *en-bloc* resection and lower rates of tumor recurrence are achieved when treating large tumors > 20 mm in diameter.

#### Innovations and breakthroughs

This is a retrospective observational study which included 189 patients consecutively treated by ESD at the National Cancer Center Hospital from May 2007 to March 2009. The following data were collected for both groups: mean hospitalization period, tumor site, median tumor size, post-ESD rectal bleeding requiring urgent endoscopy, perforation during or after ESD, abdominal pain, fever above 38  $^{\circ}\text{C}$ , and blood test results positive for inflammatory markers before and after ESD. Each parameter was compared after data collection.

#### Applications

The lesions, method and bowel preparation in colon ESD differ according to the institution; therefore, the risks of complications during and after ESD are likely to differ. Hereafter, to stratify the risks in the clinical pathway, addition of the status after resection (complete suturing) and the site of the lesion (rectum or colon) as parameters should increase safety.

#### Peer review

The paper covers an important topic related to the ESD procedure: the length of the hospital stay and the quality of the monitoring of the patient after the procedure. The clinical problem is well exposed, the picture is impressive and the paper opens a new area of discussion on colonic ESD.

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# EMR-ESD del colon-retto: il punto di vista degli endoscopisti orientali

■ La resezione mucosa endoscopica (EMR) è una tecnica mini-invasiva per il trattamento delle lesioni del colon-retto in fase iniziale e senza potenziale invasivo. L'elevata frequenza di recidiva locale dopo EMR *piecemeal* per le lesioni di grandi dimensioni, è considerato un grave problema. Al contrario, la dissezione endoscopica della sottomucosa (ESD) consente la resezione *en bloc*, a prescindere dalle dimensioni della lesione. Pertanto, è indispensabile conoscere le caratteristiche endoscopiche delle lesioni in fase early per un efficace trattamento.

■ Endoscopic mucosal resection is a minimally invasive technique for effective treatment of early stage colorectal lesions with no invasive potential. The high frequency of local recurrence after EMR for large lesions, however, is considered a serious problem. In contrast, endoscopic submucosal dissection allows *en bloc* resection, irrespective of the lesion's size. Therefore, it is indispensable to have knowledge of early stage colorectal lesions and understanding the key to success for safe EMR.

■ **Parole chiave:** resezione mucosa endoscopica (EMR), dissezione endoscopica sottomucosa (ESD), neoplasia del colon-retto, tumori a diffusione laterale (LST)

■ **Key words:** *endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), colorectal neoplasm, laterally spreading tumor (LST)*

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## Introduzione

Il cancro coloretale è la terza causa di mortalità per cancro in Giappone (1). La diagnosi e la rimozione del tumore in fase iniziale e delle lesioni precancerose sono considerati i più importanti fattori per il controllo del cancro del colon-retto (2). La resezione mucosa endoscopica (EMR) è ormai una tecnica consolidata per il trattamento delle neoplasie coloretali in fase precoce (3-6); tuttavia, l'elevata incidenza di recidiva locale dopo EMR di lesioni di grandi dimensioni è un problema rilevante (7,8). Per evitarlo, gli endoscopisti giapponesi hanno sviluppato una nuova tecnica che permette la resezione *en bloc* di lesioni del colon-retto di grandi dimensioni. Questa tecnica, nota come dissezione endoscopica sottomucosa (ESD), inizia con l'iniezione nella sottomucosa, seguita dalla dissezione in corrispondenza dei bordi laterali e nello strato di sottomucosa finché la lesione non viene rimossa in un unico pezzo. Nonostante i lunghi tempi richiesti dalla procedura e la maggiore percentuale di complicanze, la ESD presenta un alto tasso di resezione *en bloc* rispetto alla EMR (9-11). La ESD consente una resezione *en bloc* della lesione, indipendentemente dalle sue dimensioni. In principio, la ESD è stata ampiamente usata per trattare lesioni

del tratto gastrointestinale superiore, in particolare dello stomaco, perché la resezione *en bloc* garantisce la conservazione dell'organo e permette una più accurata diagnosi istopatologica (12,13). In Giappone, dal 2006 l'assicurazione copre la ESD eseguita per il trattamento del cancro gastrico precoce e dal 2008, anche la ESD per il trattamento di lesioni neoplastiche superficiali dell'esofago. Pertanto, questa tecnica è considerata il "gold standard" per l'asportazione endoscopica dei tumori maligni del tratto gastrointestinale superiore. Tuttavia l'impiego dell'ESD per le lesioni del colon-retto (14-20), non è ancora pienamente affermata come metodo terapeutico standard per le lesioni del colon-retto per i seguenti motivi: i tumori del colon hanno caratteristiche patologiche e organo-specifiche (ad esempio sequenza adenomacarcinoma) che differiscono radicalmente da quelle dei tumori esofagei e gastrici. In Giappone, dall'aprile 2012 la ESD coloretale per le lesioni di grandi dimensioni sarà rimborsata dall'assicurazione medica.

Questo articolo riassume i più recenti dati del database del National Cancer Center Hospital di Tokyo sulle neoplasie del colon-retto, le indicazioni per la resezione *en bloc*, e la prevalenza delle lesioni delle neoplasie del colon-retto in fase iniziale.

È importante, quindi, capire quali lesioni dovrebbero essere asportate *en bloc* e quali possono invece essere resecate con la tecnica *piecemeal*.

## Criteri per la resezione endoscopica

La EMR è indicata per il trattamento del cancro coloretale intramucoso in quanto il rischio di metastasi linfonodali è assente (21,22).

L'intervento chirurgico è indicato per il trattamento di tumori che invadono la sottomucosa a causa del rischio del 6%-12% di metastasi linfonodali (23-27). I dati di letteratura finora pubblicati, tuttavia, evidenziano come le lesioni con invasione della sottomucosa <1.000 micron senza invasione linfovaskolare (linfatica e/o venosa) e in caso di tumori non scarsamente differenziati hanno un rischio minimo di metastasi linfonodali (28) e possono essere trattate con la EMR.

Tuttavia, l'invasione linfovaskolare e la componente adenocarcinomatosa scarsamente differenziata sono impossibili da prevedere prima della resezione e la profondità di invasione della sottomucosa può essere solo stimata sulla base dell'aspetto morfologico durante l'endoscopia.

È quindi molto importante essere in grado di distinguere tumori che sono candidati per la EMR da quelli che richiedono un intervento chirurgico.

## Stato attuale e limitazioni della mucosectomia del colon

La EMR è una tecnica minimamente invasiva per l'efficace trattamento di lesioni coloretali in fase iniziale senza rischio di metastasi linfonodali. Sono state descritte diverse tecniche di EMR [ad esempio: strip biopsy (iniezione, sollevamento e taglio) EMR con cappuccio, EMR con legatura]. Il metodo "iniezione, sollevamento e taglio" è semplice e sicuro ed è ampiamente utilizzato per le neoplasie del colon-retto. Le lesioni che non si sollevano durante l'iniezione sottomucosa non sono generalmente candidate per la resezione con EMR. A causa delle dimensioni delle anse, dei cappucci o dei dispositivi di legatura, queste tecniche di EMR non possono essere utilizzate per rimuovere *en bloc* lesioni di diametro maggiore di 20 mm. Questa limitazione impedisce la precisa valutazione istopatologica ed aumenta il rischio di recidiva locale. La resezione di lesioni di grandi dimensioni intramucose o con invasione superficiale della sottomucosa (<1.000 micron) è tecnicamente possibile; tuttavia, alcuni studi hanno dimostrato che il rischio di recidiva locale è del 2.7% - 23.5% (10,29,30). Frequenze variabili sono state riportate da diversi centri, probabilmente correlate alle tecniche di resezione e dall'esperienza nel giudicare una minima quantità di tumore residuo al termine della resezione stessa. Tuttavia, è stato dimostrato che quasi tutte le recidive locali non rappresentano un grave problema, trattandosi per lo più di lesioni adenomatose sviluppatasi dal margine della lesione primaria e che possono essere trattate con un'ulteriore resezione endoscopica, se viene effettuato un attento follow-up (10,29,31). L'intervallo adatto per la colonscopia di sorveglianza dopo EMR *piecemeal* è ancora controverso (generalmente 2-6 mesi) (32).

## Diagnosi endoscopica della profondità e indicazione per la resezione en bloc

La stima della profondità di invasione del cancro prima del trattamento è cruciale per decidere la strategia terapeutica. Diverse modalità diagnostiche come l'ecoendoscopia (EUS) con mini-sonda e la cromoendoscopia con magnificazione, si sono dimostrate utili per la diagnosi della profondità delle lesioni coloretali. La cromoendoscopia con magnificazione è un metodo validato che facilita, in modo semplice ed efficace, l'analisi dettagliata dell'architettura morfologica della mucosa colica con gli orifici delle cripte (pit pattern). La classificazione clinica del pit pattern (invasiva e non invasiva)

tabella 1: relazione tra la dimensione della LSTs e il tasso di invasione della sottomucosa. National Cancer Center Hospital, Tokyo, 1998-2006

|                                       | 10 mm -          | 20 mm -           | 30 mm -          | 40 mm -           | Total             |
|---------------------------------------|------------------|-------------------|------------------|-------------------|-------------------|
| Ila (LST-G*):<br>LST-G, tipo uniforme | 0/115<br>(0%)    | 0/70<br>(0%)      | 1/31<br>(3.2%)   | 0/13<br>(0%)      | 1/229<br>(0.4%)   |
| Is+Ila (LST-G):<br>LST-G, tipo misto  | 4/72<br>(5.6%)   | 6/70<br>(8.6%)    | 9/65<br>(13.8%)  | 25/114<br>(21.9%) | 44/321<br>(13.7%) |
| Ila (LST-NG**)                        | 12/246<br>(4.9%) | 24/106<br>(22.6%) | 11/33<br>(33.3%) | 8/17<br>(47.0%)   | 55/402<br>(13.7%) |

\*LST-G: diffusione del tumore lateralmente, tipo granulare

\*\*LST-NG: diffusione del tumore lateralmente, tipo non-granulare

utilizzando la cromoendoscopia con magnificazione è stata originariamente descritta da Fujii, allo scopo di discriminare tra invasione intramucosa-sottomucosa superficiale ed invasione sottomucosa profonda (33). La presenza di un pattern non invasivo definito dalla cromoendoscopia con magnificazione, è il requisito necessario per il trattamento endoscopico non invasivo (34). Un pit pattern caratterizzato da cripte irregolari e distorte è suggestivo di invasione profonda della sottomucosa (> 1.000 micron). Le indicazioni per la resezione *en bloc* (35), che si basano su ampie analisi clinico-patologiche, sono: LST di tipo non-granulare (LST-NG) di diametro > 20 mm e un LST granulare (LST-G) di diametro > 30 mm.

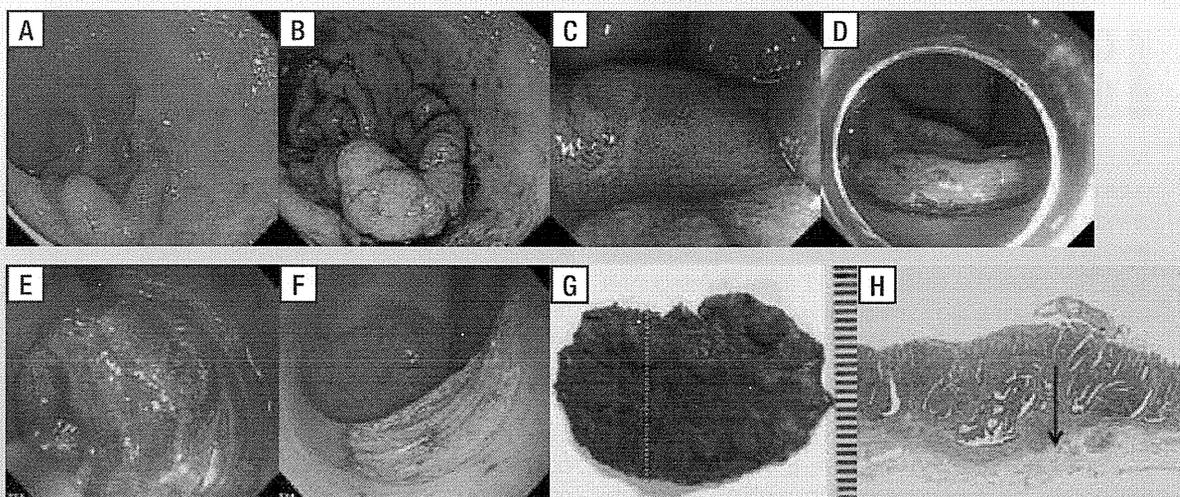
Entrambe queste lesioni hanno un alto tasso di invasione della sottomucosa (tabella 1) (36). In particolare, gli LST-NG di diametro > 20 mm sono tecnicamente difficili da rimuovere completamente, anche con EMR e pertanto queste lesioni sono una "indicazione assoluta per la resezione *en bloc*". Al contrario, gli LST-G di diametro > 30 mm sono considerati una "indicazione relativa per la resezione *en bloc*". Inoltre, grandi tumori villosi, lesioni recidive e lesioni residue intramucose con "non lifting sign" dopo EMR sono candidati potenziali per l'ESD.

knife) (Xeon Medical Co) (37) o un ago con la punta isolata (IT-Knife) (Olympus), insufflazione con anidride carbonica (CO<sub>2</sub>) invece di aria ambiente per ridurre il fastidio al paziente (10,38,39). I margini della lesione sono delineati prima di eseguire la dissezione, spruzzando con un catetere spray, una soluzione di indaco-carminio allo 0,4%. Dopo l'iniezione di Glicerolo (10% glicerolo e il 5% fruttosio in soluzione fisiologica) (40) e acido ialuronico nella sottomucosa (41), viene effettuata un'incisione circonferenziale utilizzando il B-knife, quindi la dissezione sottomucosa viene eseguita utilizzando sia il B-knife, che l'IT-knife (figura 1). Recentemente, alcune lesioni del colon-retto selezionati di 20-40 mm di diametro vengono asportate utilizzando la tecnica della mucosectomia con incisione circonferenziale (Circumferential endoscopic mucosal resection [CEMR]) (42). La CEMR viene effettuata utilizzando un B-knife e un'ansa diatermica. Dopo l'iniezione del glicerolo nella sottomucosa, viene effettuata un'incisione circonferenziale e la lesione viene asportata con un'ansa diatermica. Nel nostro studio, abbiamo effettuato 24 CEMR di lesioni di 20-40 mm di diametro; in 8 pazienti con lesioni di diametro maggiore di 35 mm non è stato possibile eseguire una resezione *en bloc* (CEMR completa). Questi dati suggeriscono che la CEMR è più adatta per la resezione di lesioni di diametro compreso tra 20 e 30 mm.

## ESD/CEMR

La ESD è senza dubbio uno dei metodi ideali per la resezione *en bloc*. Al National Cancer Center Hospital di Tokyo, le ESD sono principalmente eseguite utilizzando un *needle-knife* bipolare (B-

figura 1: dissezione endoscopica coloretale della sottomucosa (ESD)



### Procedure della dissezione endoscopica coloretale della sottomucosa (ESD)

(A,B) lesione localizzata nel retto (Ra) di 30 mm, Ila+Iic. (C) La Cromoendoscopia con magnificazione ha rivelato un pattern non-invasivo. (D,E) Dopo l'iniezione nello strato della sottomucosa di glicerolo e acido ialuronico, viene eseguita un'incisione circonferenziale usando l'ago bipolare (B-knife) la dissezione sottomucosa viene effettuata usando sia il B-knife che l'ago con la punta isolata (IT knife). (F) Letto della lesione (base d'impianto) dopo la resezione "en bloc". (G) "pezzo" istologico resecato "en bloc" (H) L'istopatologia ha rivelato un cancro sottomucoso superficiale (SM: 800 µm senza invasione linfovaskolare, negativo il margine di resezione).

**Decorso clinico:** A tutt'oggi non si sono osservate recidive in un follow-up di 3 anni dopo l'ESD e senza nessun intervento chirurgico aggiuntivo