

Endoscopic Identification of Colorectal Cancer Margin by Indocyanine Green Fluorescence Imaging

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ABSTRACT

AIM: We assessed whether indocyanine green (ICG) fluorescence is effective for endoscopic tattooing in colorectal cancer surgery using a photodynamic eye (PDE) camera and fluorescent endoscope.

METHODS: Between June 2014 and February 2018, 39 patients-17 patients with early and 22 patients with advanced colorectal cancer respectively-were enrolled and underwent preoperatively colonoscopic tattooing using 0.5 mL/time ($n = 28$ cases) or 0.3 mL/time ($n = 11$ cases) of ICG three days before laparotomy or laparoscopic surgery. We observed lesions using a PDE camera or a fluorescent endoscope during laparotomy or laparoscopic surgery. Moreover, we assessed the fluorescent luminance and fluorescent size of resected lesions intra- and post-operatively, respectively. Patients' medical records and operation videos were retrospectively assessed to evaluate the visibility, duration, and adverse effects of tattooing.

RESULTS: It was possible to obtain a useful fluorescent image with ICG fluorescent labeling and to determine the resection range in all cases. No difference regarding the distance from cancer's oral margin to the ICG oral margin according to the volume of ICG (0.5 mL/time vs. 0.3 mL/time) was observed, but a significant difference concerning the distance from cancer's oral margin to the ICG oral margin between early colorectal cancer and advanced cancer was noted ($p = 0.0038$).

CONCLUSION: In our experience, the ICG fluorescence imaging system seems to be simple, safe, and effective. However, the use of ICG fluorescence in endoscopic tattooing necessitates the exploration of additional information such as the volume of the ICG solution and the timing of the ICG injection.

Key words: Colorectal cancer; Endoscopic tattooing; Fluorescent endoscope; Indocyanine green fluorescence; Photodynamic eye camera

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Abbreviations

ICG: indocyanine green; PDE: photodynamic eye; SD: standard deviation.

INTRODUCTION

Endoscopic tattooing of colorectal lesions to assist in operative localization was first described in 1975 [1]. India ink tattoos properly placed in the colorectum are long-lasting and are reported to remain contrasted; therefore, they are commonly used for colonic tattooing. However, complications such as peritonitis, pseudotumor, and abscess due to endoscopic tattooing of the colon with India ink have been reported and their true safety profile is controversial [2-5].

When using mucosal clips, the intraoperative identification of lesions as detected by endoscopy is often particularly difficult to perform during laparoscopic surgery because of the inability of surgeons to palpate the colorectum intraoperatively. Therefore, accurate localization of colorectal tumors remains of critical importance during laparoscopic surgery; among other outcomes, the lack of accurate lesion identification during laparoscopy may lead to resection of the wrong segment of the bowel [6-8].

Indocyanine green (ICG) has been described in some reports of animal models as a potential alternative to India ink [9-11]. While adverse reactions to ICG have been reported [12], this dye has also been applied safely for more than 50 years in tests of cardiac and hepatic function and, more recently, for sentinel node detection in cancer surgery [13,14]. For these reasons, we herein evaluated the usefulness of preoperative colonoscopic tattooing using the ICG injection method for the localization of colorectal lesions in laparotomy and laparoscopic surgery.

METHODS

Patients

We included 39 patients (n = 26 males, age range: 45-93 years; mean age: 71.5 ± 10.9 years) who underwent laparotomy or laparoscopic surgery between June 2014 and February 2018 at Seiwa Memorial Hospital, including 17 patients with early and 22 patients with advanced colorectal cancer, respectively. Among the 39 patients, 11 (28.2%) also had cerebrovascular disease, six also had hypertension, and three also had dementia. Chief complaints were hematochezia in eight cases, poor fecal occult blood test results in seven cases, and anemia in seven cases. During peripheral blood testing, the mean ± standard deviation (SD) values of the white blood cell count, red blood cell count, and hemoglobin concentration were 6.18 ± 2.28 × 10³/μL, 392.6 ± 71.7 × 10⁴/μL, and 12.0 ± 2.7 g/dL, respectively. Meanwhile, during biochemistry testing and tumor marker assessment, the mean ± SD values of albumin, carcinoembryonic antigen, and carbohydrate antigen 19-9 were 4.1 ± 0.7 g/dL, 5.4 ± 8.9 ng/mL, and 58.9 ± 223.8 U/mL, respectively (Table 1). Patients' medical records and operation videos were retrospectively assessed to evaluate the visibility, duration, and adverse effects of tattooing. This study was performed according to the principles of the Declaration of Helsinki and approval was given by the ethics committee of Seiwa Memorial Hospital (approval no. SMH 2014-01). Written informed

consent was obtained from all included patients.

Protocol for ICG injection

We accessed the colorectal cancer by transporting the endoscope through the oral side. The ICG injection method was used to inject tattooing agents into the submucosal layer of the colorectum. First, 25 mg of powdered ICG was dissolved in 5 mL of sterilized water. Then, using a 23-gauge injection needle, 0.5 mL or 0.3 mL/time of ICG (Diagnogreen; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was injected by one of three veteran endoscopists in the endoscopy room three days prior to laparotomy or laparoscopic colorectal surgery. Tattooing was performed circumferentially close to the lesion in all four quadrants.

Operative procedure

After the surgical lights were turned off, image acquisition was initiated using a photodynamic eye (PDE) infrared camera (Hamamatsu Photonics Co., Hamamatsu, Japan), with infrared light at a wavelength of 760 nm emitted under room fluorescent lighting. The mechanism behind fluorescence measurement is that injected ICG molecules are promptly bound to the globulin fractions in serum proteins. When excitation light of 760 nm is irradiated, fluorescence with a peak wavelength of 845 nm will be emitted. This process is captured by a charge-coupled device (CCD) camera with a light-emitting diode (LED) having sensitivity in the near-infrared wavelength range. We observed lesions using the PDE camera

Table 1 Characteristics of patients with colorectal cancer.

| | | | |
|------------------------------|------------------------|--------------------------------|----|
| Age (yr), median (range) | 71.0 (45-93) | Type of tumors | |
| Gender (male) | 26 (66.7) | 0-I, II, Ila+Iic | 13 |
| Underlying disease | | Laterally splendid tumor (LST) | 4 |
| Cerebrovascular disease | 11 (28.2) | type 1 | 2 |
| Hypertension | 6 (15.4) | type 2 | 16 |
| Dementia | 3 (7.7) | type 3 | 2 |
| Diabetes mellitus | 3 (7.7) | type 4 | 2 |
| Hyperlipidemia | 3 (7.7) | Histopathologic type | |
| Old myocardial infarction | 2 (5.1) | tub1 | 13 |
| Chief complaint | | tub2 | 14 |
| Hematochezia | 8 (20.5) | others | 12 |
| Positive FOBT | 7 (17.9) | pStage | |
| Anemia | 7 (17.9) | stage 0 | 1 |
| Peripheral blood test | | stage I | 16 |
| WBC (×10 ³ /μL) | 6.18 ± 2.28 (3.2-13.3) | stage II | 13 |
| RBC (×10 ⁴ /μL) | 392.6 ± 71.7 (234-513) | stage IIIa | 5 |
| Hb (g/dL) | 12.0 ± 2.7 (4.9-15.7) | stage IIIb | 2 |
| Biochemistry test | | stage IV | 2 |
| Albumin (g/dL) | 4.11 ± 0.7 (2.1-5.2) | Operative procedure | |
| CEA (ng/mL) | 5.4 ± 8.9 (0.7-48.1) | Rt.-hemicolectomy | 5 |
| CA19-9 (U/mL) | 58.9 ± 223.8 (5-1340) | Lt.-hemicolectomy | 3 |
| Region of tumors | | Partial colectomy | 13 |
| Cecum | 4 | Low arterial resection | 7 |
| Ascending colon | 5 | Hartmann operation | 1 |
| Transverse colon | 8 | Mile's operation | 3 |
| Descending colon | 3 | Others | 7 |
| Sigmoid colon | 6 | Laparoscopic surgery | 9 |
| Rectum | 13 | Laprotomy | 30 |

Peripheral blood test and Biochemistry test are demonstrated as mean ± SD, and numbers in parenthesis are shown as range. Gender, Underlying disease, and Chief complaint in parenthesis are shown as percentage. FOBT; fecal occult blood test

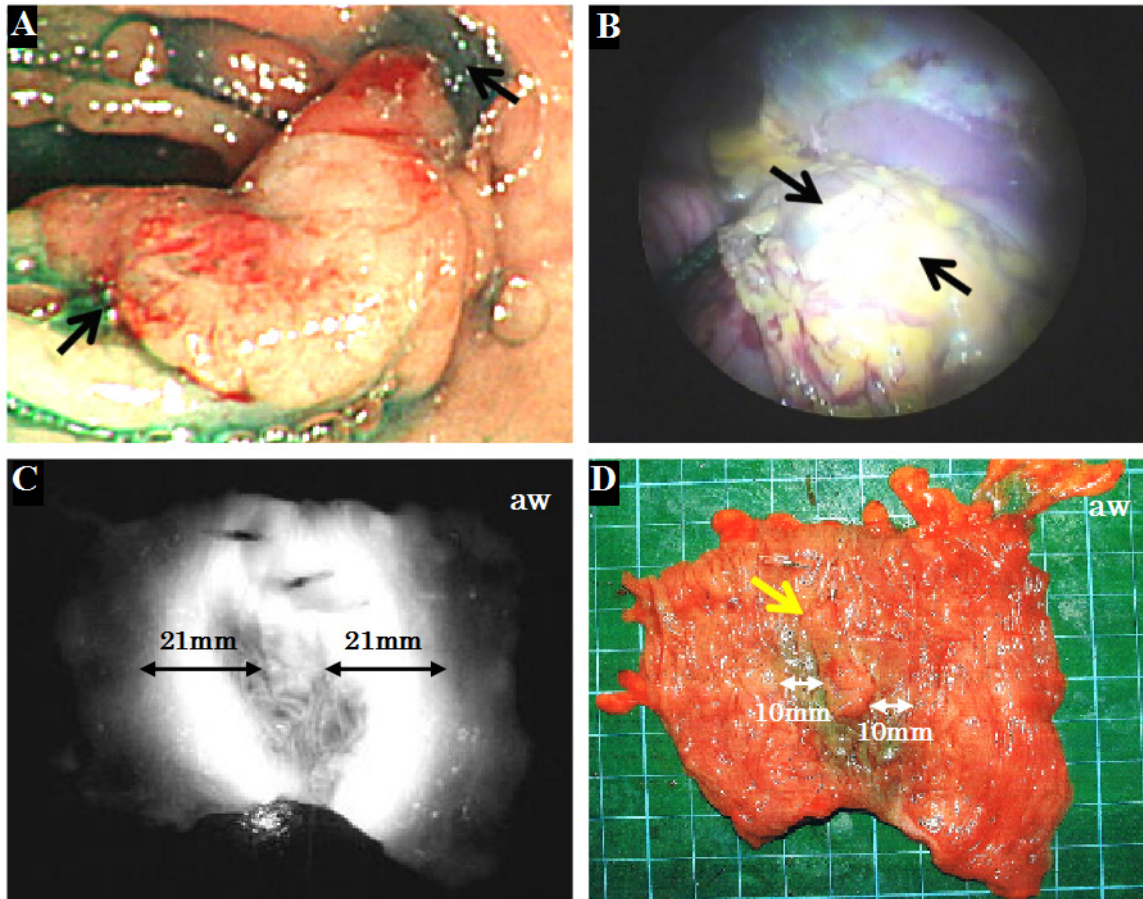


Figure 1 (A) Colonoscopy revealed an elevated lesion in the transverse colon. Black arrows indicate the ICG injections. (B) ICG fluorescence was observed to be emitting from the serosa lesions during laparoscopic surgery (black arrows). (C) ICG fluorescent luminance was apparent at the resected lesion. The luminance was located 21 mm apart from the tumor. (D) The resected tissue. The green color was observable 10 mm away from the tumor. Yellow arrow indicates the tumor, which measured 23 × 10 mm in size.

during a laparotomy but used a fluorescent endoscope (Shinkoukouki Co., Tokyo, Japan) during laparoscopic surgery. We observed the fluorescent luminance intraoperatively and the fluorescent size of resected lesions postoperatively.

Statistical analysis

ICG volume (0.5 mL or 0.3 mL/time) and colorectal cancer stage (early or advanced) in each group were compared using the *t*-test. Values were expressed as mean ± SD. A difference was considered to be statistically significant when the *p*-value was less than 0.05. All statistical evaluation was carried out using the Statistical Package for the Social Sciences version 20 software (IBM Corporation, Armonk, NY, USA).

RESULTS

Laparoscopic surgery was performed in nine cases, involving transverse and sigmoid colonic partial resections in five cases, right-hemicolectomy in two cases, cecal resection in one case, and high anterior resection of the rectum in one case. Separately, laparotomy was performed in 30 cases, involving partial colectomy in eight cases, hemicolectomy in six cases, low anterior resection in seven cases, cecal resection in four cases, Mile’s operation in three cases, and other procedures (Table 1). In all cases, the lesions of tumors were able to be easily and clearly visualized by ICG fluorescence imaging intraoperatively from the serosa lesions. The fluorescent luminance and fluorescent size of resected lesions could be observed postoperatively in all cases.

Table 2 Relationship as distance from cancer’s oral margin to ICG oral margin, and from cancer’s anal margin to ICG anal margin between volume of ICG (0.5mL/time) and ICG (0.3mL/time).

| | Volume of ICG (0.5mL/time) (N = 28) | Volume of ICG (0.3mL/time) (N = 11) | P value |
|------------------------------------------------------------|-------------------------------------|-------------------------------------|---------|
| Distance from cancer’s oral margin to ICG oral margin (mm) | 15.9 ± 6.7 (5-30) | 17.7 ± 8.9 (4-28) | 0.302 |
| Distance from cancer’s anal margin to ICG anal margin (mm) | 16.5 ± 5.8 (6-27) | 14.7 ± 6.0 (5-25) | 0.227 |

Distances from cancer’s oral margin to ICG oral margin, and from cancer’s anal margin to ICG anal margin are demonstrated as mean±SD, and numbers in parenthesis are shown as range.

Table 3 Relationship as distance from cancer’s oral margin to ICG oral margin, and from cancer’s anal margin to ICG anal margin between early colorectal cancer and advanced colorectal cancer.

| | Early colorectal cancer (N = 17) | Advanced colorectal cancer (N = 22) | P value |
|------------------------------------------------------------|----------------------------------|-------------------------------------|---------|
| Distance from cancer’s oral margin to ICG oral margin (mm) | 12.4 ± 4.7 (4-21) | 18.9 ± 7.6 (5-30) | 0.004 |
| Distance from cancer’s anal margin to ICG anal margin (mm) | 16.5 ± 7.1 (5-27) | 15.6 ± 5.0 (8-25) | 0.345 |

Distances from cancer’s oral margin to ICG oral margin, and from cancer’s anal margin to ICG anal margin are demonstrated as mean±SD, and numbers in parenthesis are shown as range.

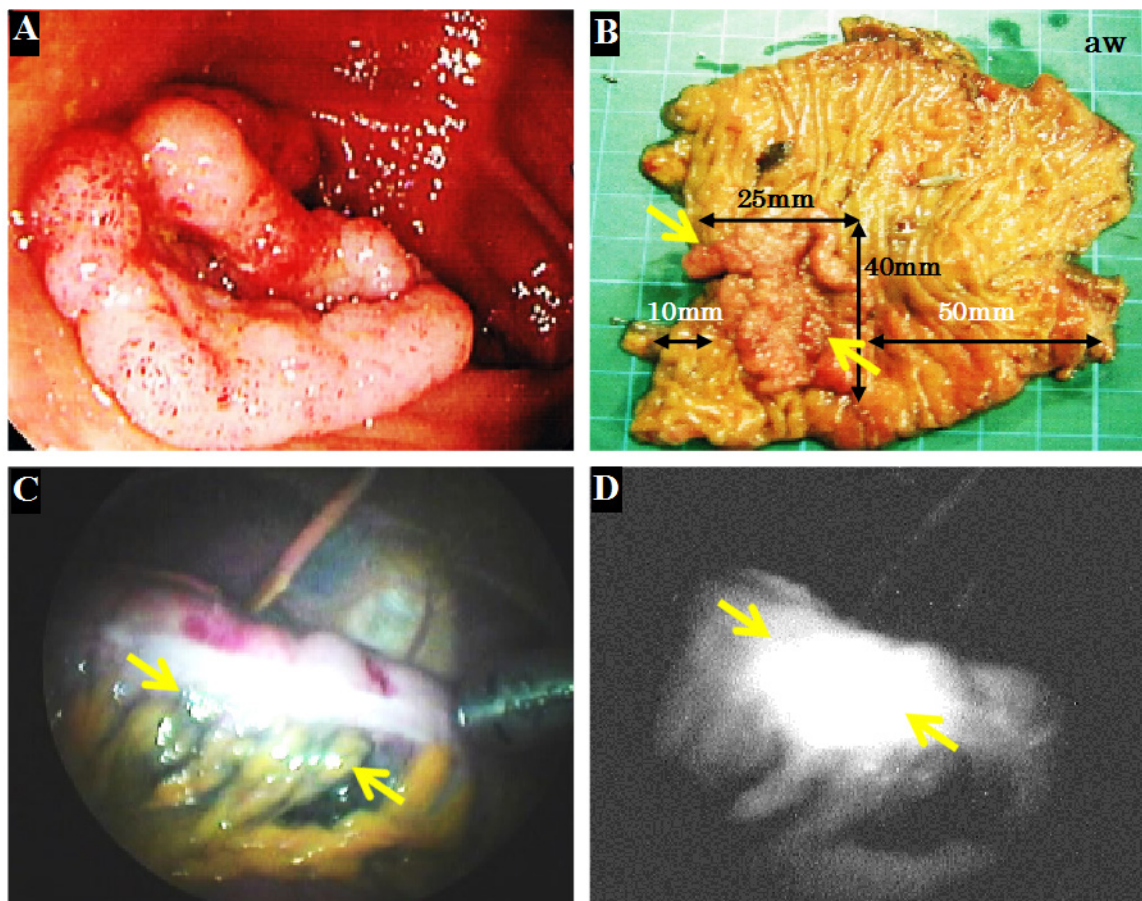


Figure 2 (A) Colonoscopy revealed a LST in the transverse colon. (B) The resected lesion is shown (yellow arrows). The LST measured 40 × 25 mm in size. (C) The green color was apparent during laparoscopic surgery (yellow arrows). (D) ICG fluorescent luminance was observed to be emitting from the serosa lesion during laparoscopic surgery (yellow arrows).

There was no difference observed concerning the distance from the cancer’s oral margin to the ICG oral margin and from the cancer’s anal margin to the ICG anal margin between volume the ICG volume groups (0.5 vs. 0.3 mL/time) (Table 2). Similarly, no difference regarding the distance from the cancer’s anal margin to the ICG anal margin between early and advanced colorectal cancer cases was noted, but a significant difference in the distance from the cancer’s oral margin to the ICG oral margin between the early and advanced cancer groups was apparent ($p = 0.0038$) (Table 3).

We henceforth highlight four of the cases with colorectal cancer included in this study. In the first case, a 60-year-old female had a type 0-IIa tumor at the transverse colon measuring 25 × 12 mm in size. The depth was reflected by mucosal invasion, classification was TisN0M0, and staging was pStage 0 (Figure 1). The second case involved a 72-year-old female with a laterally splendid tumor (LST) located at the transverse colon. This tumor was 40 × 25 mm in size, its depth was reflected by mucosal invasion, its classification was TisN0M0, and its staging was pStage 0 (Figure 2). In the third case, an 88-year-old male had a type 2 tumor located at the transverse colon measuring 35 × 30 mm in size. The depth was reflected by subserosal invasion, its classification was T3N0M0, and its staging was pStage II (Figure 3). Finally, in the fourth case, a 67-year-old male had a type 4 tumor at the rectum measuring 60 × 58 mm in size, with a depth reflected by serosal invasion, a classification of T3N0M0, and a staging of pStage II (Figure 4).

DISCUSSION

The injection of a dye into the colorectal wall is the most commonly

used and effective technique for marking colorectal lesions prior to resection. Some tattooing agents including India ink, ICG, methylene blue, indigo carmine, and toluidine blue have been evaluated in animals, but only India ink and ICG remained visible for up to 48 hours after tattooing^[9,15,16]. Several experimental studies comparing ICG and India ink for colonic tattooing in animals reported that India ink is superior to ICG because of its greater visibility and longer duration^[10,11]. However, a longer duration is not always necessary for surgical resection. To date, endoscopic tattooing using ICG in 12 patients was visible at 36 hours after injection and resulted in only minimal inflammation^[16]. In another study of 39 patients, Miyoshi et al. reported that the ICG marking was clearly observed in all 29 patients who underwent surgery within eight days. However, at nine days or later, the staining was clearly seen in only two of the 10 remaining patients and the markings in three patients were undetectable^[17]. Clinically relevant complications of tattooing are considered to be rare^[18]. Fu et al^[19], reported the rate of India ink leakage into the peritoneal cavity to be 1.8%, which is comparable with that reported by Miyoshi et al. in their ICG series (1/39 patients; 2.6%)^[17].

In their research, Kusano et al. explored ICG fluorescence imaging in gastrointestinal surgery^[20,21]; importantly, these authors revealed that the use of fluorescence imaging with ICG may improve the detection rate of tumors as compared with when using gross macroscopic color perception and constitute a new method of colorectal marking. Kusano et al. additionally suggested that fluorescence imaging offers high sensitivity in the determination of tumor location even though black or green staining cannot be seen by white light. As the only disadvantage, it was difficult to observe

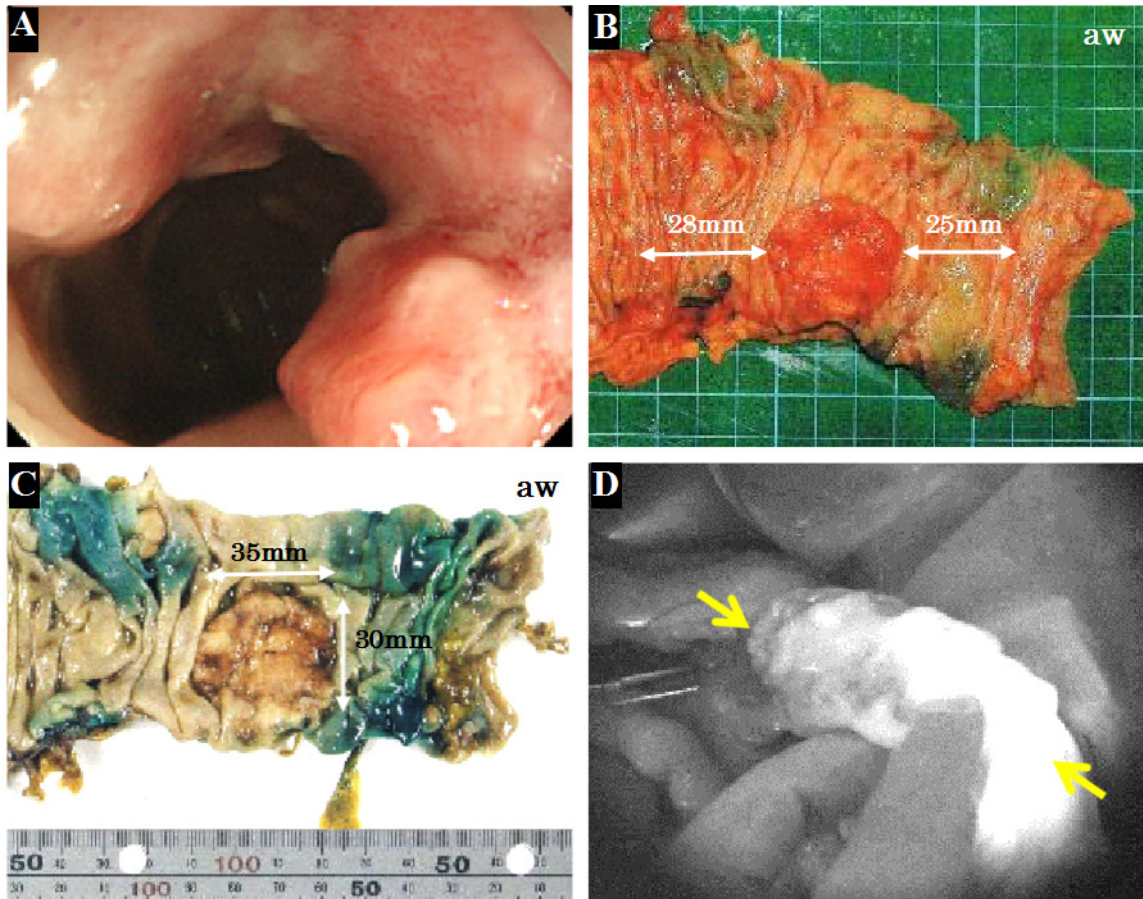


Figure 3 (A) Colonoscopy revealed a type 2 tumor in the transverse colon. (B) The resected tissue is shown. Green coloring was observable 28 mm and 25 mm away from the tumor. (C) The resected lesion was apparent after formalin fixation. The tumor was 35 × 30 mm in size. Four green-colored points were observable around the tumor. (D) ICG fluorescence was intraoperatively noted. The lines of resection were decided between the oral and anal wedges according to ICG fluorescent luminance (yellow arrows).

ICG fluorescence in room light; in this situation, ICG fluorescence could instead only be recognized when the room light was turned off, which made it difficult to conduct the surgery. Furthermore, the use of ICG fluorescence in endoscopic tattooing still requires additional information such as the volume of the ICG solution and the timing of the ICG injection. It may be believed that the fluorescent luminance and fluorescent size of resected lesions are not apparent.

In our study, the distance from the cancer's oral margin to the ICG oral margin between the early and advanced cancer groups showed a significant difference ($p = 0.0038$) (Table 3). Resection end of oral wedge of advanced cancers, which compared to early cancers takes longer, because advanced cancers may crawl under the mucous membrane. We think that it may become longer because it is possible to leave enough an intestinal canal for a long oral wedge.

Meanwhile, there was no difference in the distance between the cancer's oral margin and the ICG oral margin and between the cancer's anal margin and the ICG anal margin between the different volumes of ICG (0.5 and 0.3 mL/time) (Table 2). Usually, it is thought that the distance at a volume of ICG of 0.3 mL/time would be shorter than that associated with a volume of 0.5 mL/time. The fluorescence range is most lying about the amount, but it is affected by the depth of the injection, the speed of the injection, and the time of observation, and the difference in this study may not have been statistically significant.

In 2012, the HyperEye Medical System (Mizuho Medical Co., Ltd., Tokyo, Japan) was developed, which can simultaneously detect color and near-infrared rays and can be used under room light. This

method shows that abdominal surgery guided by this technology is feasible under room light^[22]. In addition to the development of optical devices such as HyperEye Medical System, ICG is one of the most commonly used fluorophores in near-infrared fluorescence-guided techniques. But, it also has some disadvantages, such as limited photostability, a moderate fluorescence quantum yield, a high plasma protein binding rate, and undesired aggregation in aqueous solution. In addition, ICG does not specifically target tumor cells. However, one way to exploit the capabilities of ICG is to develop high-performance near-infrared nanocomplexes formulated with ICG, and it is interpreted to mean that the development of nanoparticle of ICG will require the development of target supplies with high tumor affinity in the future^[23].

CONCLUSION

The described ICG fluorescence imaging approach seems to be simple, safe, and effective. However, the use of ICG fluorescence in endoscopic marking requires that additional information such as the volume of the ICG solution and the timing of the ICG injection should be gathered to ensure optimal outcomes.

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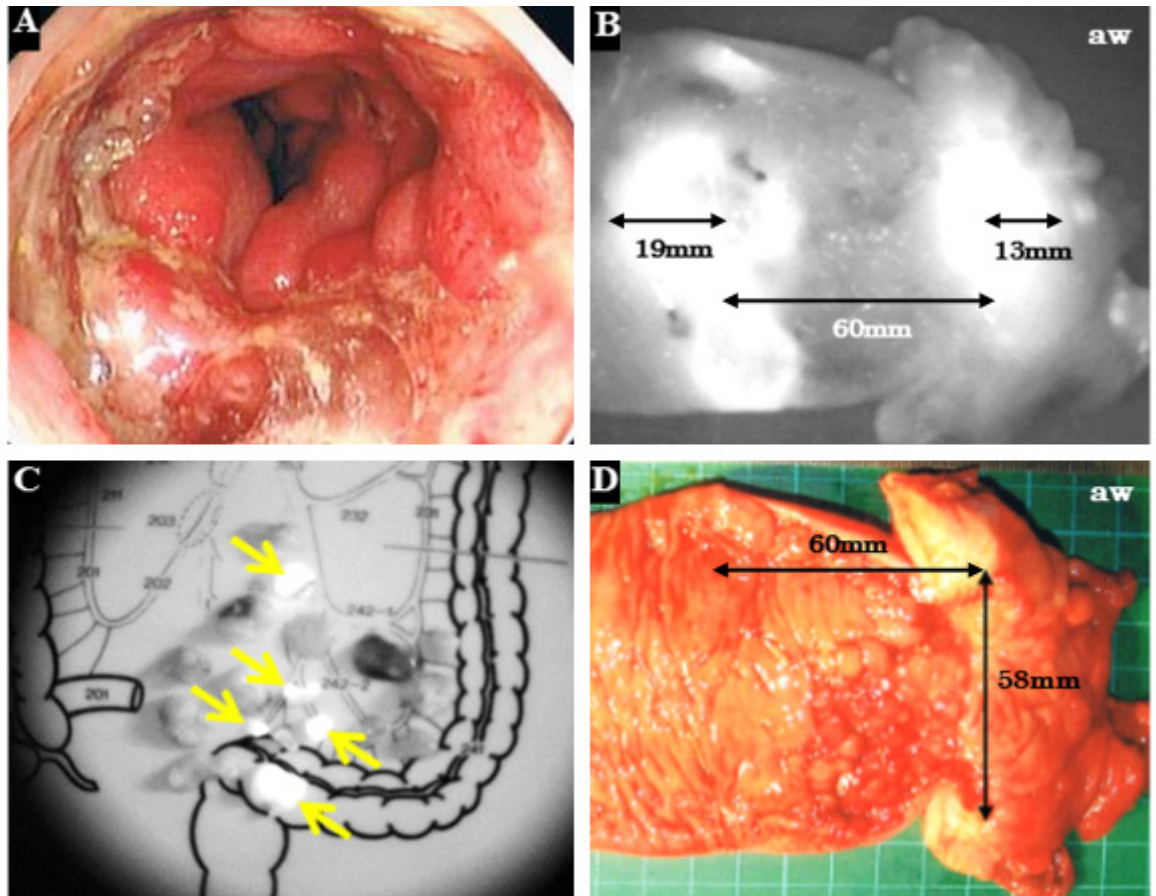


Figure 4 (A) Colonoscopy revealed a type 4 tumor in the rectum. (B) The resected lesions were marked by ICG fluorescence postoperatively. At the oral wedge, the luminance was located 19 mm away from the tumor, while, at the anal wedge, the luminance was present 13 mm away from the tumor. (C) The resected lymph nodes were revealed; five of 18 lymph nodes were positive with ICG fluorescent luminance (yellow arrows), but carcinoma cells were not detected in any of the five lymph nodes. (D) The tumor was 60 × 58 mm in size. The green coloring was not observable around the tumor under room light.

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