

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2021.10.1012

Journal of GHR 2021 June 21; **10(3)**: 3531-3536
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

CASE REPORT

Effectiveness of Indocyanine Green Fluorescence in Gastric Adenosquamous Carcinoma with Hepatic Metastases

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Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

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Received: May 16, 2021

Revised: May 23, 2021

Accepted: May 25, 2021

Published online: June 21, 2021

ABSTRACT

Gastric adenosquamous carcinoma is a rare-, mixed-type gastric cancer, that consists of both glandular and squamous cells. Herein, we present a case of a 92-year-old Japanese female transferred to our hospital due to syncope and anorexia. Multiple hepatic tumors were detected on abdominal computed tomography, and esophagogastroduodenoscopy revealed a submucosal tumor at the distal gastric antrum. Hence, submucosal and intravenous injections of indocyanine green (ICG) were performed preoperatively 3 days before surgery and intraoperatively, respectively. ICG fluorescence was detectable in the gastric tumor although no fluorescence signal was observed in the hepatic tumors. In the case described here, ICG fluorescence imaging served as a useful technique for securing surgical margins during gastric tumor resection.

Key words: Gastric adenosquamous carcinoma; Hepatic metastases; Indocyanine green fluorescence

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Ono H, Kusano M, Yokoyama H, Yoshida H, Fukushima H, Kawakami M, Okamura M, Aoki T, Asakage N, Nagashima K, Danjo Y, Hayashi H, Nishihara H, Shimizu Y, Shimamura T. Effectiveness of Indocyanine Green Fluorescence in Gastric Adenosquamous Carcinoma with Hepatic Metastases. *Journal of Gastroenterology and Hepatology Research* 2021; **10(3)**: 3531-3536 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3149>

INTRODUCTION

Gastric adenosquamous carcinoma (ASC) is an exceedingly rare tumor, that accounts for only 0.14-1.9% of all gastric cancer cases^[1-6] and mostly affects Asians^[2,4-6]. Primary gastric ASC exhibits faster

tumor progression and a poorer prognosis than does the typical gastric adenocarcinoma (AC)^[7], with its 5-year survival rate of 0-22%^[1,3,6,8,9]. This type of cancer proves to be very aggressive in the majority of cases and is already at an advanced stage at the time of diagnosis with lymph node and hepatic metastases.

Indocyanine green (ICG) is a water-soluble dye that has been safely employed for over half a decade to test cardiac and hepatic functions and, more recently, detect sentinel nodes in gastrointestinal cancer surgery^[10-12]. For these reasons, we evaluated the usefulness of preoperative endoscopic tattooing with ICG injection for the localization of gastric lesions during laparotomy. Here, we report a case of a 92-year-old Japanese female with multiple hepatic tumors who underwent surgery for gastric ASC. Submucosal and intravenous ICG injections were administered preoperatively 3 days prior to surgery and intraoperatively, respectively. While the hepatic tumors emitted no fluorescence, ICG fluorescence was detected in the gastric tumor. We could determine the range of gastric tumor resection under ICG fluorescence guidance.

CASE REPORT

A 92-year-old Japanese female was transferred to Seiwa Memorial Hospital in June 2017 from another hospital because of syncope and anorexia. She had a body mass index of 20.5 kg/m², and a body temperature of 36.7°C. Physical examination was remarkable for dementia. Laboratory findings were as follows: white blood cells, 6,300/ μ L; red blood cells, 433 \times 10⁴/ μ L; C-reactive protein, 0.27 mg/dL; carcinoembryonic antigen, 2.1 ng/mL; and carbohydrate antigen 19-9, 6.0 U/mL. Abdominal computed tomography revealed multiple hepatic tumors. Esophagogastroduodenoscopy, which was performed due to her anorexia, showed a gastric submucosal tumor at the distal antrum. The duodenum could not be examined owing to gastric obstruction. ICG, as a tattooing agent, was injected into the submucosal layer of the stomach in the following manner. First, 25 mg of powdered ICG (Diagnogreen; Daiichi Sankyo Co., Ltd., Tokyo, Japan) was dissolved in 5 mL of sterile water. Then, injections of 0.3 mL/time of ICG through a 23-gauge injection needle were given by an experienced endoscopist in the endoscopy room 3 days prior to laparotomy. Tattooing was performed close to the lesion in 3 triangles (Figure 1-A, B). Standard laparotomy was conducted after obtaining informed consent. After all surgical lights were turned

off, image acquisition was initiated using a photodynamic eye (PDE) infrared camera (Hamamatsu Photonics Co., Hamamatsu, Japan) with infrared light irradiation at a wavelength of 760 nm under fluorescent lighting. The mechanism behind fluorescence measurement is that injected ICG molecules are promptly bound to the globulin fractions in serum proteins; when they are excited by 760 nm infrared light, fluorescence with a peak wavelength of 845 nm is generated, which can then be captured via a charge-coupled device camera with a light-emitting diode sensitive to near-infrared light. We utilized the PDE camera to observe lesions during the laparotomy. Intraoperatively, intravenous ICG was injected at a dose of 0.5 mg per kg of body weight as part of a routine hepatic functional test, and hepatic lesions were observed using the PDE camera. ICG fluorescence was detected in the gastric tumor, whereas no fluorescence signal was observed in the hepatic tumors. With the help of ICG fluorescence imaging, we could determine the range of gastric tumor resection (Figure 2-A,B,C). Macroscopically, the gastric tumor (type 1) was 56 \times 39 mm in size, with a luminous region measuring 33 mm width found adjacent to the tumor (Figure 3-A,B). Of the 7 resected lymph nodes, 6 were positive for ICG fluorescence and 2 contained carcinomatous cells (Figure 4). The gastric tumor was composed of 2 components (Figure 5), which were histopathologically diagnosed as AC and squamous cell carcinoma (SCC). Finally, a definitive diagnosis of pathological stage IV gastric ASC (T3N1M1) was established according to the tumor-node-metastasis classification of malignant tumors (Figure 6). The patient died of gastric cancer 2 months postoperatively.

DISCUSSION

Gastric ASC, which was first reported by Rolleston *et al.* in 1905^[13], consists of both AC and SCC components, with the latter constituting more than a quarter of the tumor^[14]. In the majority of gastric ASC cases, the tumor is already at an advanced stage when diagnosed^[5]. Early gastric ASC extending to the mucosa and submucosa is so rare that only 10 cases-including the one presented herein-have been reported since its first description by Samejima *et al.* in 1974^[6,15,16]. Five of these cases died of gastric cancer; 4, liver metastasis; and 1, distant lymph node metastasis. Compared to the excellent prognosis of the common type of early gastric AC with a 5-year survival rate of about 90%^[17], the prognosis of early gastric ASC is extremely poor.

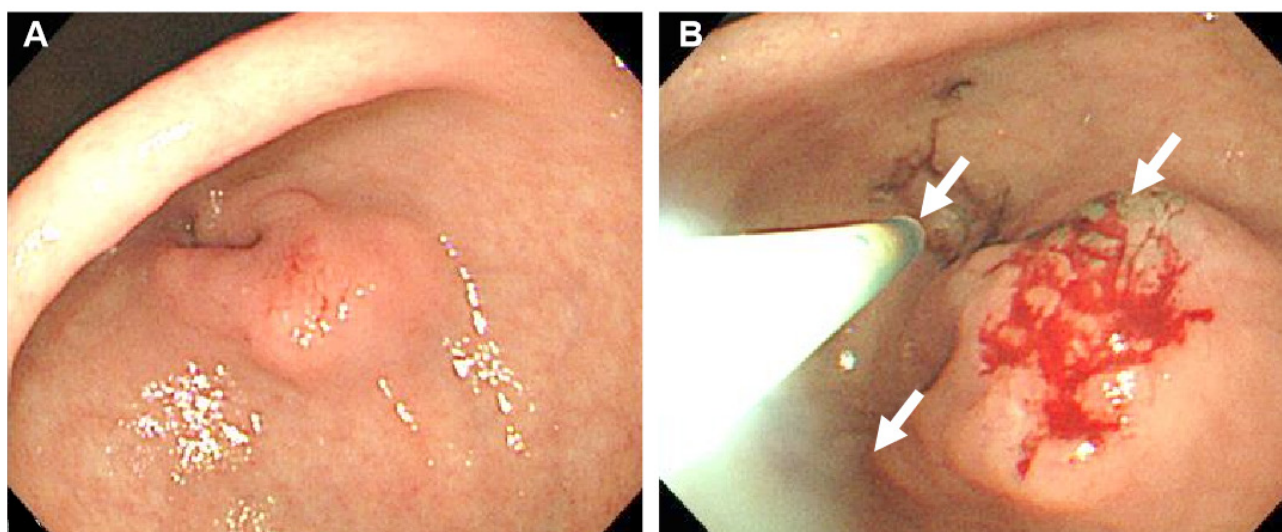


Figure 1 Esophagogastroduodenoscopy revealed a submucosal tumor at the distal antrum (A). Indocyanine green was injected into the submucosa around the tumor 3 days prior to surgery (arrows) (B).

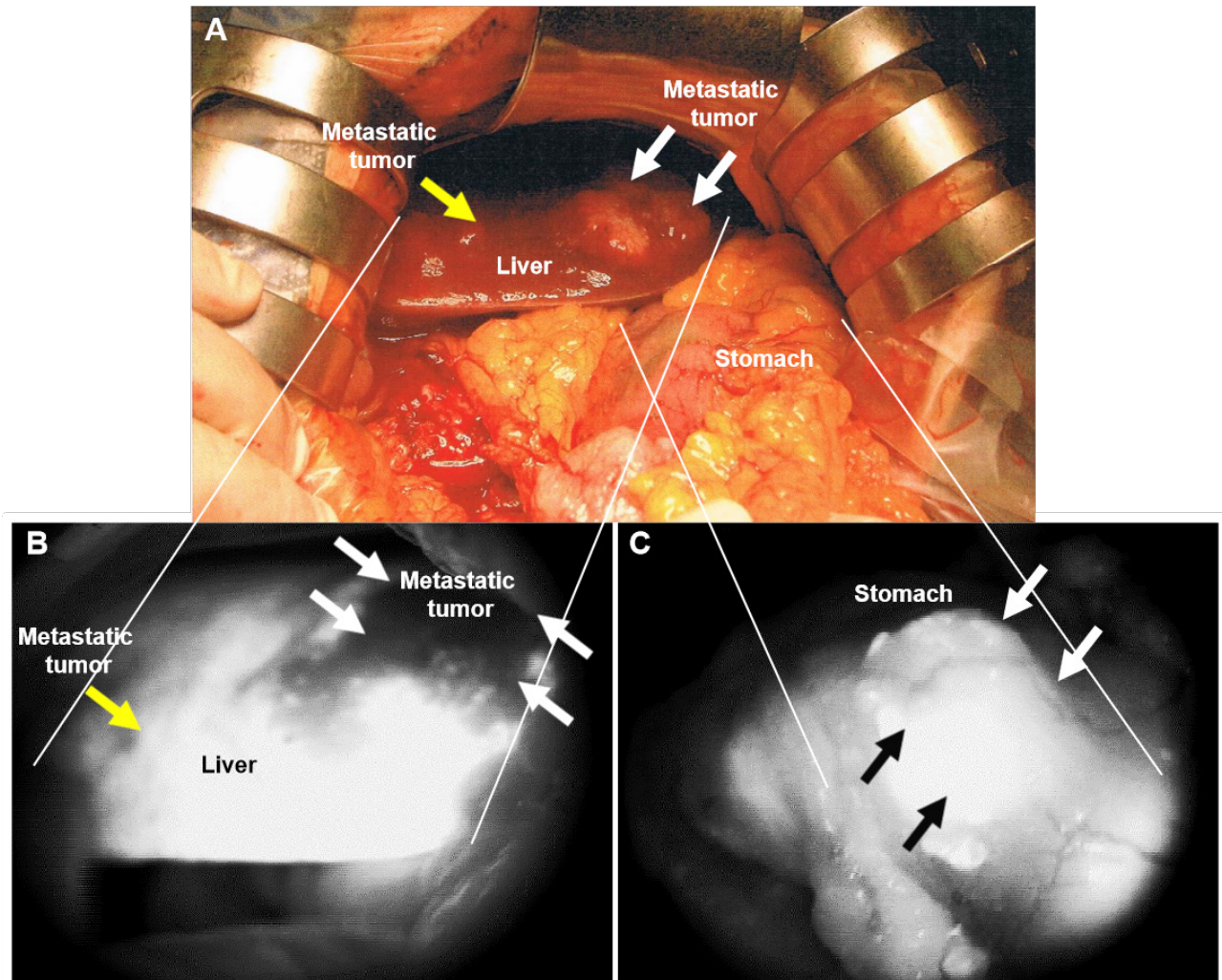


Figure 2 Standard laparotomy. Arrows indicate hepatic metastases (A). Hepatic tumors exhibited no fluorescence signal (arrows), but ICG fluorescence was detected in the intact hepatic surface (B). ICG fluorescence was observed in the gastric tumor (arrows) (C).

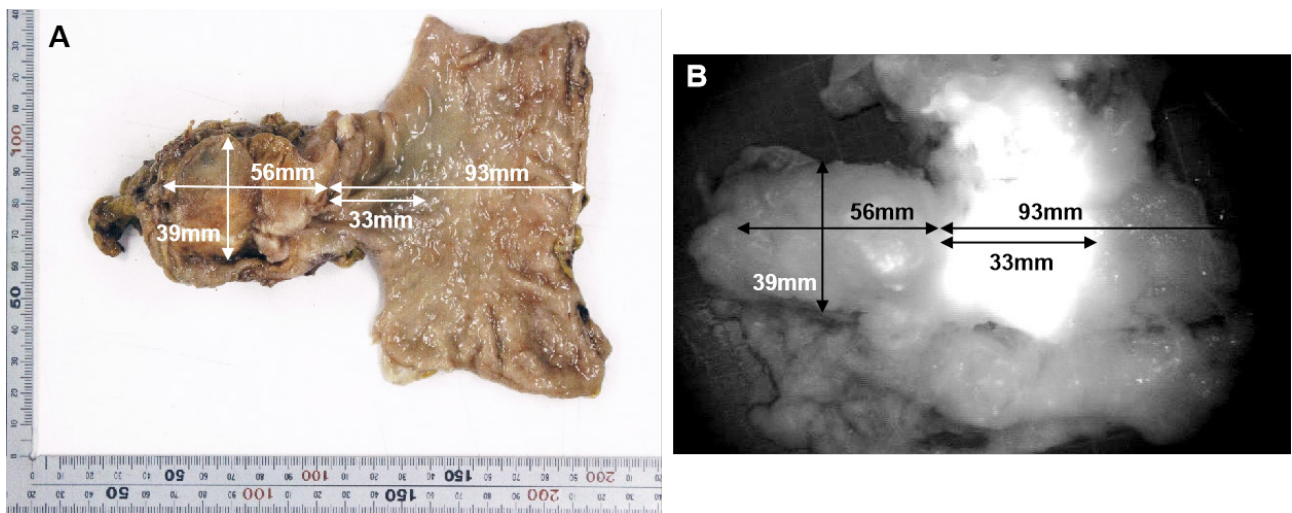


Figure 3 Macroscopically, the gastric tumor (type 1) was 56×39 mm in size (A). A luminous region measuring 33 mm in width was observed adjacent to the tumor after surgery (B).

The present case report is very significant in that it underscores the distinct possibility of gastric ASC being very aggressive and fatal even when detected at an early stage.

The histogenesis of ASC still remains unclear although 5 hypotheses have been put forward to explain its origin: (1) metaplastic transformation of AC, (2) cancerization of metaplastic squamous cells, (3) cancerization of ectopic squamous epithelium, (4) collision between AC and SCC; and (5) stem cell differentiation toward both cell lines^[1,18-25]. It has been found that most of the SCC component is located at an invasive site, whereas the AC component

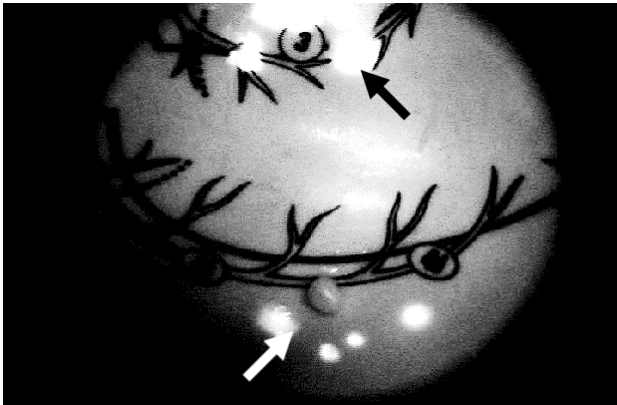


Figure 4 Of the 7 resected lymph nodes, 6 were positive for ICG fluorescence and 2 contained carcinomatous cells (arrows).

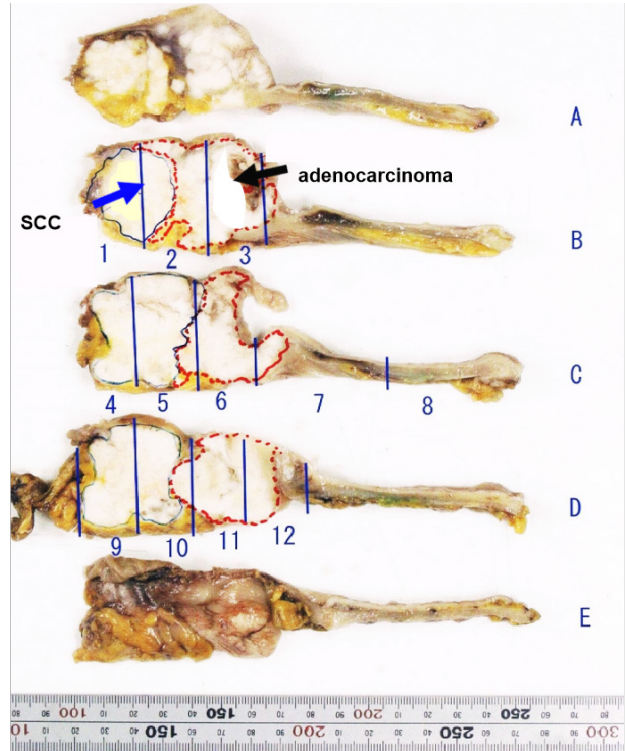


Figure 5 Macroscopically, the resected gastric tumor consisted of both adenocarcinomatous and squamous cell components.

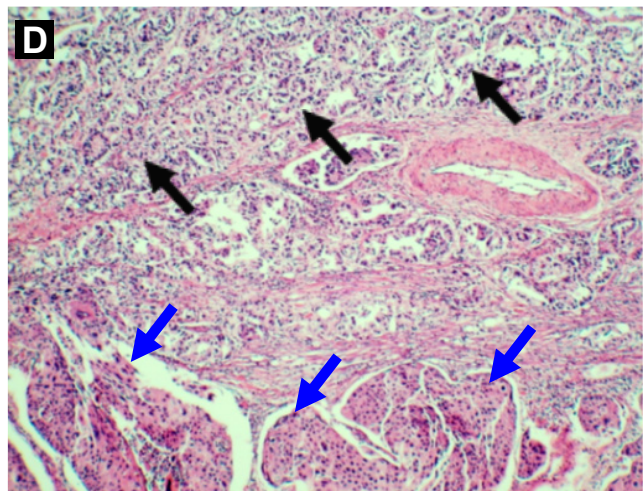
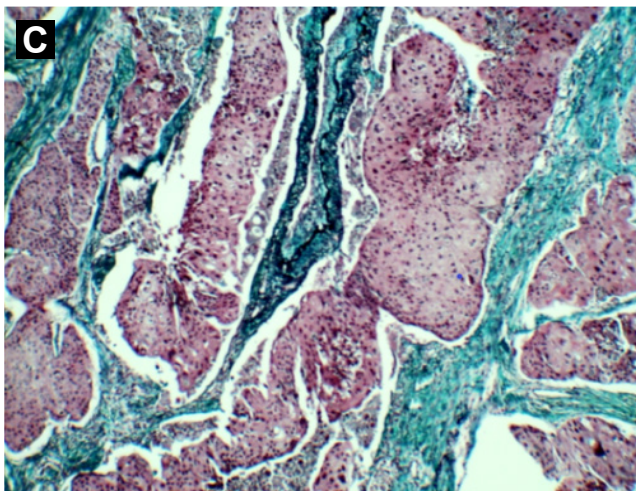
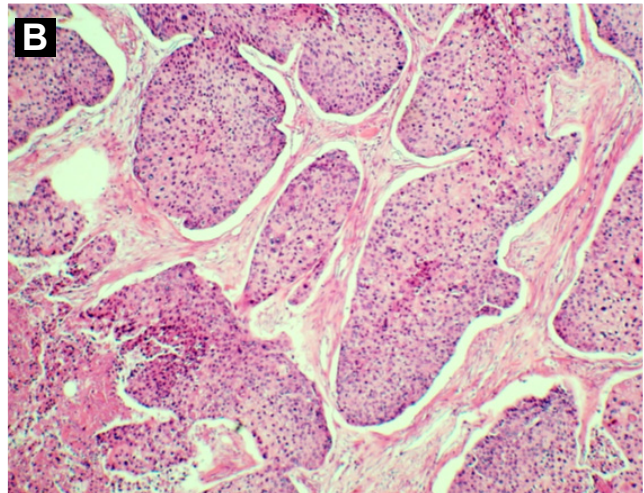
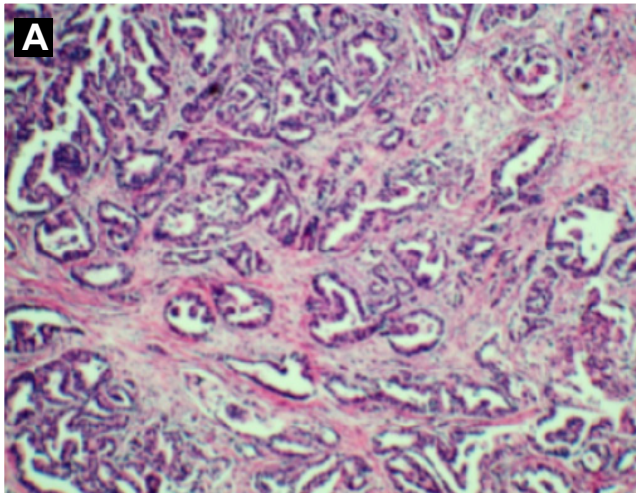


Figure 6 Microscopy of the gastric lesions revealed adenocarcinoma (tub 2) hematoxylin and eosin (H.E) stained sections ($\times 200$) (A), squamous cell carcinoma H.E stained sections ($\times 200$) (B), and SCC elastic masson stained ($\times 200$) (C). Postoperative histopathological examination of H.E stained sections revealed adenocarcinoma (black arrows) and SCC (blue arrows), leading to a diagnosis of gastric adenosquamous carcinoma ($\times 100$) (D).

resides in the mucosal region adjacent to the SCC component. Therefore, many authors now believe that the squamous neoplastic component results from metaplastic changes in the AC component.

Radical resection represents the optimal treatment for localized lesions without distant metastases. However, no standard adjuvant therapy strategy for gastric ASC has been established thus far. Moreover, although chemotherapy has been reported to be effective in patients with gastric ASC^[26], there is no consensus on its optimal strategy. Radiotherapy could also be used as an adjuvant treatment option, given that the SCC component of gastric ASC has been shown to be sensitive to radiotherapy^[27].

Kusano *et al.* demonstrated that, compared to gross macroscopic color perception, ICG fluorescence imaging might help improve the rate of tumor detection in gastrointestinal surgery and could therefore serve as a novel approach to gastric marking^[12,28]. Additionally, they suggested that fluorescence imaging offers high sensitivity in determining tumor location even though black or green staining cannot be seen by white light. One of the disadvantages of this technique is that ICG fluorescence can hardly be detected under normal room lighting; thus, room lighting should be minimized during imaging, which makes it difficult to continue the surgical procedure. Furthermore, the use of ICG fluorescence in endoscopic tattooing still requires additional information such as the volume of ICG solution and the timing of ICG injection.

Aoki *et al.*^[29] showed the near-infrared ICG fluorescence imaging system to be a novel and reliable intraoperative technique for the identification of hepatic segments and subsegments in patients undergoing anatomical hepatectomy for malignant liver tumors. Ishizawa *et al.*^[30] reported that ICG fluorescence imaging allowed for highly sensitive, real-time identification of small, and grossly unidentifiable liver cancers, thereby improving the accuracy of hepatectomy and operative staging. They classified the fluorescence patterns of liver tumors into 3 categories, *viz.*, total, partial, and rim; while total- and partial-type fluorescence patterns were chiefly detected in hepatocellular carcinoma, the metastases of colorectal cancer mainly exhibited rim-type fluorescence as a result of biliary excretion disorders in the surrounding noncancerous liver tissues compressed by the tumors. The hepatic lesions in our case displayed rim-type fluorescence as they were metastatic lesions originating from gastric cancer (Figure 2B).

CONCLUSION

Here, we demonstrated the simple, safe, and effective use of ICG fluorescence imaging in a case of gastric ASC, which is a rare type of gastric cancer. ICG fluorescence signal was not observed in the patient's hepatic metastases, but her gastric cancer displayed fluorescence, which helped us determine the resection range of the tumor. Nevertheless, the use of ICG fluorescence in endoscopic tattooing still requires further research regarding the volume of ICG solution and the timing of ICG injection.

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