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The efficacy of intraoperative indocyanine green fluorescence angiography in gastric cancer operation after living donor liver transplantation: A case report

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ABSTRACT

INTRODUCTION: The incidence of *de novo* malignancies after organ transplantation is increasing. We herein report a patient who developed gastric cancer after living donor liver transplantation (LDLT) and splenectomy. Intraoperative indocyanine green (ICG) fluorescence angiography immediately after gastrectomy was useful for evaluating the blood supply into the remnant stomach in this patient.

PRESENTATION OF CASE: A 69-year-old woman underwent LDLT and splenectomy for end-stage liver disease. Gastric cancer was found by an endoscopic examination eight years after LDLT. Although total gastrectomy was considered due to previous splenectomy, we decided to intraoperatively evaluate the flow of the remnant stomach using ICG fluorescence. After ligation of the left gastric artery and transection of the stomach with a sufficient proximal margin from the tumor, intraoperative ICG fluorescence angiography showed abundant intramural blood flow of the remnant stomach. We were able to preserve the proximal stomach with confidence and she recovered smoothly after the operation without any signs of acute rejection.

CONCLUSION: Intraoperative ICG fluorescence angiography may be helpful for evaluating the blood flow in the remnant stomach during surgery for *de novo* gastric cancer after LDLT.

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1. Introduction

Transplantation is the only effective method for treating organ failure. The number of organ transplantation has increased rapidly, and advance in immunosuppressant therapy and surgical procedures has markedly improved the long-term survival of patients after transplantation. However, *de novo* malignancy after organ transplantation has become a major issue affecting the long-term survival of recipients. The recent research has confirmed that *de novo* malignancy is the second leading cause of death in transplant recipients who survive at least 1-year after transplantation [1].

De novo gastric cancer is one of these malignancies and there are several reports concerning with its treatment such gastrectomy [2–6]. Although surgery are the mainstay treatments for *de novo* gastric cancer just as with malignancy that develops in the general population [6,7], there are some issues to be considered when gastrectomy would be attempted especially after liver transplantation: Severe postoperative adhesion and anatomical rearrangement due

to vessel reconstruction could lead to vascular injuries. Moreover, if splenectomy was performed with liver transplantation, a dissection between the stomach and splenic hilum might impair a blood supply to the stomach and insufficient blood supply to remnant stomach after gastrectomy is one of risks of anastomotic leakages and gastric necrosis. As these perioperative severe complications could easily place patients at lethal condition because of the perioperative immunocompromised condition due to the administration of immunosuppressive agents, evaluation of blood supply into the remnant stomach is crucial issue.

We herein report a patient who developed gastric cancer after living donor liver transplantation (LDLT) and splenectomy. Intraoperative indocyanine green (ICG) fluorescence angiography immediately after gastrectomy was useful for evaluating the blood supply both into the remnant stomach.

This case report has been reported in line with the SCARE 2018 criteria [8].

2. Case report

A 77-year-old woman was admitted to our hospital for surgical treatment for gastric cancer. She had a history of LDLT and simulta-

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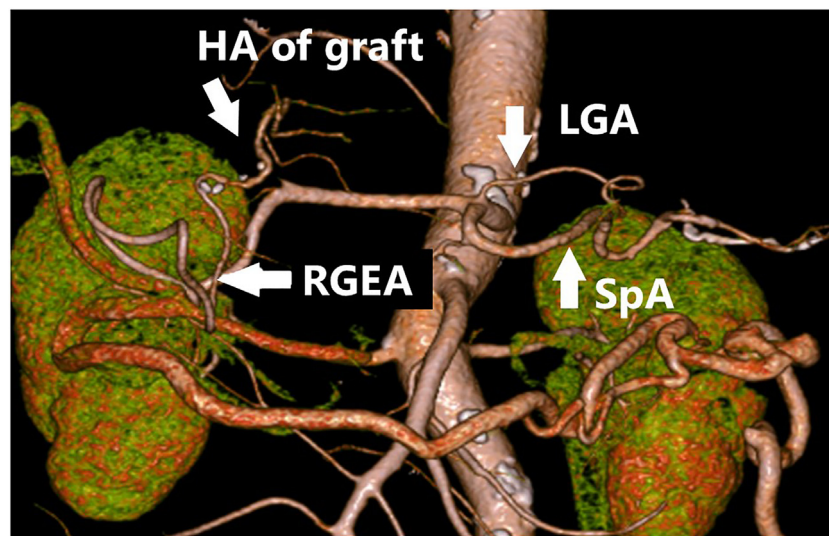


Fig. 1. Three-dimensional computed tomography (CT) showing vessels around the stomach. The arrow indicates the left gastric artery (LGA), the right gastroepiploic artery (RGEA) anastomosed to the right hepatic artery in the right lobe of the liver graft (HA of graft). We only found small branches divided from the splenic artery (SpA) due to the history of splenectomy.

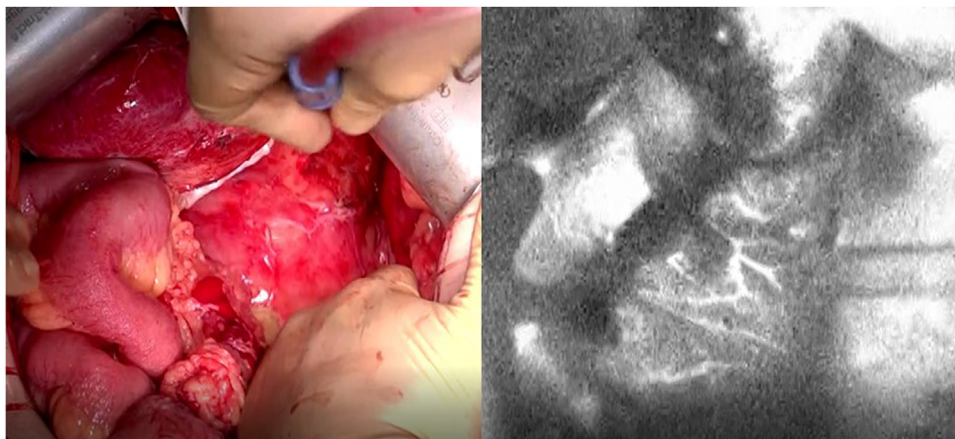


Fig. 2. ICG (3 mL) was administered intravenously at a concentration of 2.5 mg/mL. Intraoperative indocyanine green (ICG) fluorescence angiography showed abundant intramural blood flow of the remnant stomach in about 20 s.

neous splenectomy due to hepatitis C virus (HCV)-related cirrhosis with hepatocellular carcinoma (HCC) and antiviral treatment for eradication of HCV eight years ago. She had no significant family history and psychosocial history. Postoperative immunosuppressive treatment with Mycophenolate Mofetil and Tacrolimus had been continued, and there were no signs of rejection or any problems on routine monitoring of parameters, including the liver function.

The patient had undergone annual gastroscopy after transplantation, but no pathological findings had been found until gastroscopy performed eight years after transplantation showed ulcerative lesion with an irregular raised margin located in the lower portion of the stomach. A histological examination of the biopsied specimen revealed moderately differentiated adenocarcinoma. Her biochemistry, blood count and tumor markers, including α -fetoprotein (AFP), carcinoembryonic antigen (CEA), and carbohydrate antigen (CA19-9), were within normal ranges.

Endoscopic ultrasonography implied that the depth of cancer invasion was limited to the submucosal layer of the gastric wall. Contrast-enhanced computed tomography (CT) revealed no swollen lymph nodes around the stomach. No distant metastasis and no recurrence of HCC were identified. Three-dimensional CT (3D-CT) demonstrated the left gastric artery and main truncus

of the splenic artery, but robust short gastric arteries was absent due to the previous splenectomy procedure. Instead, only small branches divided from the splenic artery were detected in the greater curvature of the stomach. In addition, the right gastroepiploic artery was anastomosed to the right hepatic artery of the transplanted liver as feeding vessels (Fig. 1).

Under the diagnosis of *de novo* gastric cancer after LDLT, gastrectomy with lymph node dissection was planned, and we preoperatively discussed the ideal procedure for this patient. Distal gastrectomy with lymph node dissection of the left gastric lesion was considered the most curative approach from an oncological perspective. However, there was concern about whether or not the remnant stomach could be safely preserved without the development of ischemia after ligation of the left gastric artery. We therefore decided to intraoperatively evaluate the flow in the remnant stomach using ICG fluorescence, and if an insufficient blood flow was observed, we planned to perform total gastrectomy.

No peritoneal dissemination was recognized on laparotomy, but severe adhesion between the grafted left lobe of the liver and the stomach was encountered. The grafted liver was enlarged due to regeneration, occupying the left upper part of the abdominal cavity, and the omental stalk, including the right gastroepiploic artery, ran across the dorsal side of the stomach. After careful exfoliation

around the right gastroepiploic artery in order to minimize tissue manipulation, the anal side of the stomach was divided 2 cm proximal to the pyloric ring using a linear stapling device. Following ligation of the left gastric artery and vein with lymph node dissection, the stomach was transected with a sufficient proximal margin from the tumor.

The remnant stomach showed no ischemic manifestation, but whether or not the extragastric arteries, such as the posterior gastric artery, had been preserved was impossible to confirm due to the severe adhesion around the remnant stomach. Intraoperative ICG fluorescence angiography was performed via injection of ICG at a concentration of 2.5 mg/mL to visualize the blood flow and vascular distribution in the remnant stomach. After injecting the ICG solution, abundant intramural blood flow of the remnant stomach was confirmed in about 20 s (Fig. 2).

Reconstruction was performed with Roux-en-Y gastrojejunostomy via the antecolic route, and an intestinal feeding tube was inserted into the distal bowel. The duration of the operation was 484 min. and blood loss was 6,000 mL.

A histopathological examination of the resected stomach revealed moderately differentiated adenocarcinoma with subserosal invasion. There was no lymph node metastasis, and the tumor was staged as pT3N0M0. Immunosuppressive agents were administered through the nasal feeding tube the day after the operation. The patients recovered smoothly after operation without any signs of acute rejection. She was discharged from the hospital three weeks after the operation. Following the gastric surgery, same dose of immunosuppressive agent prescribed before the surgery was used. One year and three months after gastrectomy, however, multiple liver metastases and local recurrence developed despite her taking one year of adjuvant chemotherapy and she died one year and eight months after gastrectomy.

3. Discussion

The incidence of *de novo* gastric cancer after liver transplantation is reported to range from 0.1% to 1%, with a standard incidence ratio (SIR) of 0.6–11.35 worldwide [9–16]. In Japan, Miyazaki et al. reported 19 cases of *de novo* gastric cancer among 4226 cases of liver transplantation [16]. The development of *de novo* gastric cancer is induced by various factors, such as long-lasting immunosuppressive treatment and a pre-transplant condition including complication with metabolic and infectious diseases. Infection with *Helicobacter pylori* (HP) is a strong etiology underlying the development of gastric cancer in the general population, but from the perspective of geographical characteristics, there seems to be little correlation between the reported prevalence of HP and SIR of *de novo* gastric cancer after liver transplantation [17]. Thus far, only limited data are available regarding risk factors of *de novo* gastric cancer after liver transplantation.

Curative treatment should be considered even for gastric cancer after transplantation if the performance status and cardiopulmonary function of each patient are considered medically fit [6,7]. The guideline of the Japanese Research Society for Gastric Cancer recommends distal gastrectomy with dissection of lymph nodes around the stomach and left gastric artery as a radical operation for gastric cancer with submucosal invasion [18]. Special precautions must be taken in cases with anatomical changes resulting from previous transplantation, such as in the hepatic hilum and hepatogastric regions, which contain reconstructive vessels and the bile duct. Therefore, it is important to accurately assess the anatomical information preoperatively in order to avoid iatrogenic injury of these structures. In the present case, 3D-CT was useful for demonstrating the structure of the feeder artery of the right gastroepiploic artery flowing into the grafted liver. However, we were unable to confirm the presence of a potential feeding artery for the

remnant stomach after gastrectomy. Theoretically, total gastrectomy should have been selected for this patient, since she had a history of splenectomy.

Splenectomy is performed for splenic malignant lymphoma, hematological disease such as idiopathic thrombocytopenic purpura and hypersplenism. It is also performed simultaneously during LDLT for the improvement of graft outcomes by reducing the portal pressure [19]. Splenectomy also performed for prevention of thrombocytopenia in antiviral treatment for HCV like in our patient. In this procedure, the splenic artery is often ligated. As this artery is essential for maintaining the blood supply to the proximal stomach, in cases of gastrectomy in patients with a history of splenectomy, there is some concern of ischemic necrosis of the remnant stomach or leakage at the anastomosis. These infectious complications are particularly lethal for patients under immunosuppressive treatment, like the present patient.

Recently, the usefulness of intraoperative indocyanine green (ICG) fluorescence angiography has been reported in various situation. Takahashi et al. used ICG fluorescence in visualization of the blood flow in the remnant stomach after the completion of distal pancreatectomy in a patient with prior distal gastrectomy [20]. Yamana et al. also assessed the blood flow of the cancer-bearing gastric tube after clamping the gastroepiploic artery, and they performed subtotal gastrectomy with preservation of these vessels because the flow of gastric tube was insufficient [21].

We therefore used intraoperative ICG fluorescence angiography in order to evaluate the blood flow in the remnant stomach after distal gastrectomy. Although a preoperative evaluation was unable to detect the robust vessels feeding the upper portion of the stomach, such as the recurrent branches of the left inferior phrenic artery and/or descending branches of the esophageal artery, intraoperative ICG revealed a rich blood flow into the remnant stomach. Potential mechanisms underlying the successful preservation of the blood flow are as follows: The collateral blood flow via small branches of the splenic artery might have played an important role in our patient. There is also the possibility that during a long interval after the previous surgery, small supplemental vessels might be fertilized from adjacent tissues. In addition, the intramural capillary networks in cooperation with the extragastric arterial blood supply may have helped compensate for the loss of blood flow from the left gastric artery.

Adjuvant chemotherapy after curative gastrectomy is recommended in order to prevent postoperative recurrence [22,23]. Our patient has received adjuvant chemotherapy of S1 without any adverse events and no deterioration of the liver function, although multiple liver metastasis and local recurrence nevertheless developed. Park et al. reported that almost all patients with *de novo* malignancies after liver transplantation in Korea were able to receive aggressive cancer treatment including chemotherapy, suggesting the safety of chemotherapy [10]. However, the results remain controversial, as various drugs, including anticancer agents, may harm the liver and worsen the immunocompromised status.

Recently the safety and curability of endoscopic resection for superficial cancer has been reported provided the tumor invasion is limited to the mucosal layer. This procedure can help avoid gastrectomy, which can diminish the quality of life due to the loss of the reserve function, damage to the antireflux barrier, and dumping syndrome. Furthermore, gastrectomy is known to decrease the surface area for drug absorption, which results in the alteration of the pharmacokinetic profiles of some immunosuppressive agents [24]. Resection of the upper gastrointestinal tract can therefore cause the fluctuation of immunologic activities meant to prevent acute rejection. The early detection of *de novo* malignancy, especially in the upper gastrointestinal tract, is thus extremely important. Although the appropriate approach to postoperative surveillance for the digestive tract has yet to be clarified, routine endoscopic

examinations are recommended after liver transplantation in high-risk recipients. There is a geographic difference in the incidence of gastric cancer, so it is necessary to establish tailored surveillance programs after liver transplantation in each country. Close surveillance through endoscopy is particularly important in countries with a high prevalence of HP, such as Japan,

In conclusion, with the achievement of a long-term survival after liver transplantation, the incidence of *de novo* gastric cancer has increased. Surgeons who are not specialized in transplantation may therefore be faced with opportunities to treat malignancy in patients with a history of LDLT, often accompanied by a history of splenectomy. Intraoperative ICG fluorescence angiography may aid in evaluating the blood flow in the remnant stomach in cases of surgery for *de novo* gastric cancer after LDLT.

Declaration of Competing Interest

The authors report no declarations of interest.

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Ethical approval

The study is exempt from ethical approval in my institution.

Consent

Written informed consent was not obtained from the patient for publication of this case report, because of the patient's death and provided by next of kin.

Registration of research studies

Not applicable.

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CRedit authorship contribution statement

Wei Zhou: Conceptualization, Writing - original draft. **Kengo Kanetaka:** Conceptualization, Writing - review & editing, Supervision. **Akira Yoneda:** Writing - review & editing. **Shinichiro Kobayashi:** Writing - review & editing. **Masaaki Hidaka:** Writing - review & editing. **Susumu Eguchi:** Supervision.

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