J Gastric Cancer. 2017 Jun;17(2):145-153
https://doi.org/10.5230/jgc.2017.17.e17
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Original Article

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Real-time Vessel Navigation Using Indocyanine Green Fluorescence during Robotic or Laparoscopic Gastrectomy for Gastric Cancer

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Received: Apr 13, 2017
Revised: May 8, 2017
Accepted: May 22, 2017

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Funding
This study was supported by a grant from the National R&D Program for Cancer Control,

ABSTRACT

Purpose: Identification of the infrapyloric artery (IPA) type is a key component of pylorus-preserving gastrectomy. As the indocyanine green (ICG) fluorescence technique is known to help visualize blood vessels and flow during reconstruction, we speculated that this emerging technique would be helpful in identifying the IPA type.
Materials and Methods: From August 2015 to February 2016, 20 patients who underwent robotic or laparoscopic gastrectomy were prospectively enrolled. After intravenous injection of approximately 3 mL of ICG (2.5 mg/mL), a near-infrared fluorescence apparatus was applied. The identified shape of the IPA was confirmed by examining the actual anatomy following infrapyloric dissection.
Results: The mean interval time between ICG injection and visualization of the artery was 22.2 seconds (range, 14–30 seconds), and the mean duration of the arterial phase was 16.1 seconds (range, 9–30 seconds). The overall positive predictive value (PPV) of ICG fluorescence in identifying the IPA type was 80% (16/20). The IPA type was incorrectly predicted in four patients, all of whom were obese with a body mass index (BMI) of more than 25 kg/m^2.
Conclusions: Our preliminary results indicate that intraoperative vascular imaging using the ICG fluorescence technique may be helpful for robotic or laparoscopic pylorus-preserving gastrectomy.

Keywords: Stomach neoplasms; Laparoscopy; Indocyanine green; Fluorescence

INTRODUCTION

The performance of laparoscopic gastrectomy is increasing in combination with function-preserving surgery due to the increased incidence of early gastric cancer in Korea and Japan [1,2]. Since the extent of gastric resection is modified in function-preserving gastrectomy, remnant gastric function can be preserved as much as possible and the post-gastrectomy syndrome can be milder than that following conventional gastrectomy [3-6].

Laparoscopy-assisted pylorus-preserving gastrectomy (LAPPG) provides definitive clinical benefits, such as good nutritional status, fewer complications, and a lower incidence of

Ministry of Health and Welfare, Republic of Korea (1320270). The funding source had no role in the design of this article and will not have any role in its execution or publication.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

This study was presented at Korean International Gastric Cancer Week 2016 (KINGCA Week 2016) and awarded as one of the best poster presentations.

postoperative gallbladder stones compared with laparoscopy-assisted distal gastrectomy [7,8]. However, it has not gained in popularity owing to postoperative delayed gastric emptying and the technical difficulty of infrapyloric lymph node dissection.

From the technical viewpoint, preservation of the infrapyloric artery (IPA) is essential to achieving a successful LAPPG. A recent study reported the anatomical characteristics of the IPA, including classification according to its origins and the incidence of each type [9]. However, preservation of the IPA remains challenging because the IPA is poorly identifiable in preoperative imaging studies and tactile sensation is limited during laparoscopic surgery.

Recently, indocyanine green (ICG) fluorescence imaging technology has been applied to detect sentinel lymph nodes in gastric cancer and to visualize blood flow during vascular surgery or esophageal reconstructive surgery [10-15]. This emerging technique might be helpful in identifying the origin and shape of a vessel during a laparoscopic gastrectomy procedure, such as LAPPG. Thus, this pilot study was performed to evaluate the feasibility of the ICG fluorescence imaging technique in identifying the IPA type during robotic or laparoscopic gastrectomy. As an ancillary study, we also applied this technique to aid the identification of an accessory splenic artery in order to evaluate whether it was helpful to minimize unintended surgical insults such as inferior splenic infarction after ligation of the left gastroepiploic artery (LGEA).

MATERIALS AND METHODS

Patients

This study was approved by the Institutional Review Board of Ajou University Hospital (IRB No. AJIRB-MED-DE1-15-011). Patients with gastric cancer were prospectively enrolled in this study after informed consent was obtained. Patients with a history of allergic reaction to ICG, those in whom poor excretion of ICG was expected such as those with liver cirrhosis, and those who underwent palliative surgery were excluded. From August 2015 to February 2016, 20 patients who underwent robotic or laparoscopic gastrectomy for gastric cancer were enrolled in this study. In a subgroup analysis, the patients were divided into an obese group (body mass index [BMI] $\geq$25 kg/m^2; n=10) and a non-obese group (BMI <25 kg/m^2; n=10) according to the World Health Organization (WHO) definition of obesity in the Asia-Pacific region [16].

Identification of vessel shapes using near-infrared fluorescence

Before identification of the IPA, the right gastroepiploic vein was ligated and a small part of the right gastroepiploic artery (RGEA) was exposed. Then, 3 mL of ICG was administered intravenously at a concentration of 2.5 mg/mL. Firefly™ fluorescence imaging technology of the Da Vinci Si robotic platform (Intuitive Surgical Inc., Sunnyvale, CA, USA) was applied during robotic surgery, and the Storz Spiel Full HD D-Light P ICG technology (KARL STORZ GmbH & Co. KG, Tuttlingen, Germany) was introduced for laparoscopic surgery.

The shapes of the IPA were classified into 3 types according to its origins as follows: 1) a distal type with the IPA originating from the anterior superior pancreaticoduodenal artery, 2) a caudal type with the IPA originating from the RGEA, and 3) a proximal type with the IPA originating from the gastroduodenal artery [9]. The IPA types visualized by ICG fluorescence were compared with the actual vessel anatomies after infrapyloric dissection during the operations. Procedural times were also measured, such as the interval time from ICG injection to arterial visualization, and the arterial phase time during which the artery was visualized and identifiable from adjacent organs prior to venous visualization.

A similar procedure was conducted to visualize an accessory splenic artery originating from the LGEA following identification of the left gastroepiploic vessels, in which the same amount of ICG was injected intravenously and a near-infrared fluorescence apparatus was applied. The presence of an accessory splenic artery, the interval time, and the arterial phase time were all evaluated.

Statistical analysis

Statistical analysis was performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The Mann-Whitney U test was applied for the subgroup analyses. A P-value <0.05 was considered statistically significant.

RESULTS

Patient characteristics

Of the 20 patients, 14 underwent robotic gastrectomy and 6 underwent laparoscopic gastrectomy. Fifteen patients (75.0%) underwent subtotal gastrectomy and 5 (25.0%) underwent total gastrectomy. The mean age of the patients was 57.3 years, and the male to female ratio was 2.6:1. The mean BMI was 24.4 kg/m^2, and 10 patients (50.0%) had a BMI of more than or equal to 25 kg/m^2 (**Table 1**). No adverse effects such as an allergic reaction were observed in all cases.

Appearances of IPAs visualized by ICG fluorescence

The appearances of the visualized vessels are shown in **Fig. 1**. In the distal type, 2 separated fluorescent streams were well visualized simultaneously at the beginning of the arterial phase. The IPA was visualized at the pancreas head, with the left side adjacent to the RGEA. In the caudal type, a fluorescent stream of the RGEA was divided into 2 streams. In the proximal type, the duodenum was first visualized with small vessels around it just before the arterial phase, and then the RGEA was solely visualized.

Table 1. Patient demographics

Characteristics	Values
No. of patients	20
Age (yr)	55.9±16.7
Sex (male:female)	14:6
BMI (kg/m^2)	24.4±3.8
<25	10 (50.0)
≥25	10 (50.0)
Approach	
Robot	14 (70.0)
Laparoscopy	6 (30.0)
Extent of resection	
Distal gastrectomy	15 (75.0)
Total gastrectomy	5 (25.0)

Values are presented as number of patients (%) or mean ± standard deviation.
BMI = body mass index.

 https://doi.org/10.5230/jgc.2017.17.e17

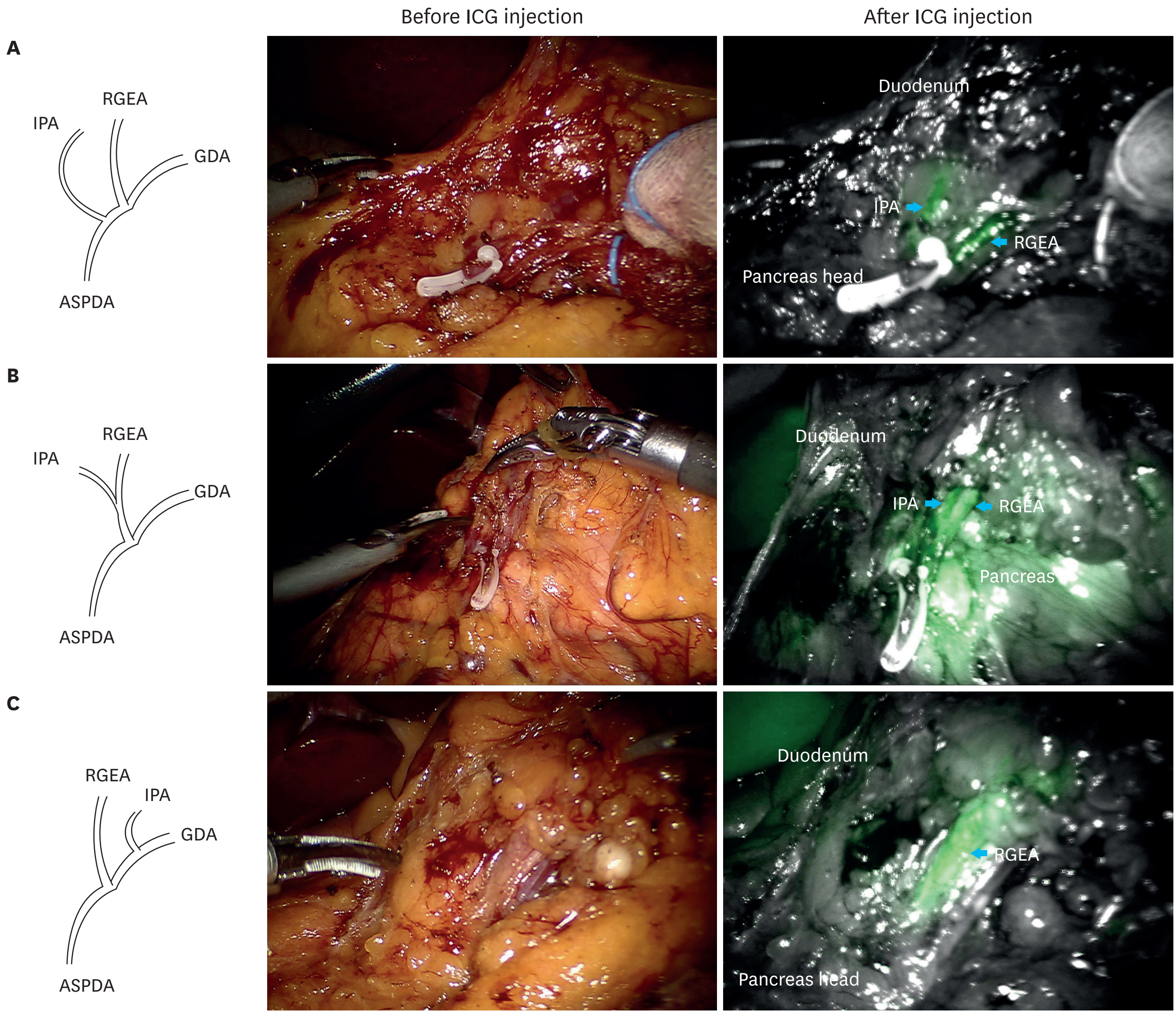

Fig. 1. ICG fluorescence images of various IPA types and an accessory splenic artery. (A) In the distal type, 2 separated fluorescent streams (blue arrows) arise from the pancreas head. (B) In the caudal type, a stream is divided into 2 (blue arrows) at the RGEA. (C) In the proximal type, the duodenum is slightly visualized without any vessel visualization, and then the RGEA is solely visualized (blue arrow).
IPA = infrapyloric artery; RGEA = right gastroepiploic artery; GDA = gastroduodenal artery; ASPDA = anterior superior pancreaticoduodenal artery; ICG = indocyanine green.

Positive predictive value (PPV) of ICG fluorescence for IPA classification

The interval time was defined as the time from ICG injection to arterial visualization, and the arterial phase time was defined as the time from arterial visualization to venous visualization. The mean interval time was 22.2 seconds (range, 14–30), and the mean arterial phase time was 16.1 seconds (range, 9–30). The mean total procedural time was 38.5 seconds (range, 24–57); therefore, the entire procedure for identifying the IPA type required less than one minute.

In 16 patients (80.0%), the visualized IPA type was coincident with the real vessel anatomy. Two of 9 assumed distal types were proximal types upon examination of the actual anatomy, and 2 of 7 assumed caudal types were actually the distal or proximal type. Thus, the PPV of

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Table 2. The PPV of ICG fluorescence for the IPA type

IPA types		ICG fluorescence			PPV
		Distal	Caudal	Proximal	
Real anatomy	Distal	7	1	0	7/8 (87.5)
	Caudal	0	5	0	5/5 (100.0)
	Proximal	2	1	4	4/7 (57.1)
PPV		7/9 (77.8)	5/7 (71.4)	4/4 (100)	16/20 (80.0)

Values are presented as number (%).
ICG = indocyanine green; IPA = infrapyloric artery; PPV = positive predictive value.

Table 3. Comparison of ICG fluorescence outcomes between obese and non-obese patients

Characteristics	Obese* (BMI ≥25 kg/m²)	Non-obese (BMI <25 kg/m²)	P-value
No. of patients	10	10	-
PPV	6/10 (60.0)	10/10 (100.0)	0.087
Interval time† (sec)	23.2 (18–28)	21.2 (14–30)	0.315
Arterial phase† (sec)	18.3 (10–30)	14.0 (9–20)	0.190
Total procedural time† (sec)	40.9 (30–57)	36.2 (24–47)	0.353

Values are presented as number of patients (%) or mean (range).
ICG = indocyanine green; BMI = body mass index; PPV = positive predictive value; WHO = World Health Organization.
*The WHO definition of obesity in the Asia-Pacific region; †Mann-Whitney U test was applied.

the classification was 77.8% for the distal type, 71.4% for the caudal type, and 100% for the proximal type. However, with respect to the actual anatomy, the PPV of the proximal type classification (57.1%) was lower than that of the other types (**Table 2**).

In 4 patients, we failed to predict the actual IPA type, and all of these patients had a BMI of more than 25 kg/m² (**Table 3**). However, there was no difference in procedural times between the obese and non-obese subgroups.

ICG fluorescence for identifying an accessory splenic artery

In 12 patients, the feasibility of using ICG fluorescence to identify an accessory splenic artery of the LGEA, which is frequently injured during gastrectomy (**Table 4**), was evaluated. Six patients were identified to have an accessory splenic artery and the origins of each of them were easily identified (**Fig. 2**). After the use of ICG fluorescence, no splenic infarction was observed following ligation of the left gastroepiploic vessels in all cases. Regarding the procedural times, the mean interval time, arterial phase time, and total procedural time were 19.9, 11.5, and 31.5 seconds, respectively. These times were significantly shorter than the measured times for the IPA (19.9 vs. 22.1 seconds, P=0.034; 11.5 vs. 15.9 seconds, P=0.010; 31.5 vs. 38.8 seconds, P=0.003).

Table 4. Outcomes of the identification of an accessory splenic artery from the LGEA

Characteristics	Values
No. of patients	12
Visualization by ICG fluorescence	
Identified	6 (50.0)
Not identified	6 (50.0)
Splenic infarction after ligation of the LGEA	0
Measured time (sec)	
Interval time	19.9 (10–26)
Arterial phase	11.5 (6–17)
Total procedural time	31.5 (18–41)

Values are presented as number of patients (%) or mean (range).
ICG = indocyanine green; LGEA = left gastroepiploic artery.

https://doi.org/10.5230/jgc.2017.17.e17

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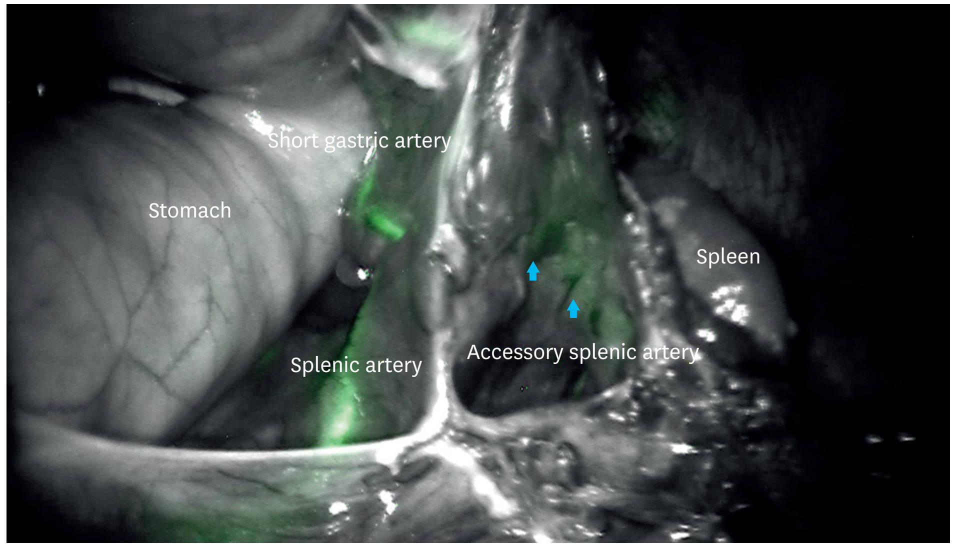

Fig. 2. An accessory splenic artery (blue arrows) from the LGEA.
LGEA = left gastroepiploic artery.

DISCUSSION

Gastric cancer surgery is evolving from empirically based to real-time navigated operations along with advances in imaging devices. Currently, a robotic surgical platform is a representative assembly for real-time surgical imaging via the TilePro™ (Intuitive Surgical Inc.) and Firefly™ technologies (Intuitive Surgical Inc.). TilePro™ is a type of multi-input display mode that allows preoperative computed tomography (CT) images to be integrated into the robotic surgical console, enabling surgeons to see both the CT images and the surgical view simultaneously during the operation. Kim et al. [17] reported 12 cases of image-guided robotic gastric cancer surgery using TilePro™ and 3D-reconstructed vascular images. In a recent study, Firefly™ was applied to the harvesting of lymph nodes for lymphadectomy as an adjunct to the identification of relevant lymph node basins in real time during robotic gastrectomy [18].

Recently, near-infrared fluorescence imaging technology has been integrated into laparoscopic systems by some manufacturers, and a few investigators have attempted to apply this emerging technology to gastric surgery. Miyashiro et al. [19] first reported the laparoscopic detection of sentinel nodes in gastric cancer surgery using ICG fluorescence. Rino et al. [13] used ICG fluorescence imaging to visualize the blood supply route to the reconstructed stomach during esophagectomy. However, these were preliminary studies with small sample sizes; thus, further studies and more evidence are required to verify its wide application in clinical practice.

Similarly, we conducted this pilot study to determine the adjunct role of ICG fluorescence in gastric surgery. To the best of our knowledge, this study is the first to evaluate the feasibility of intraoperative ICG fluorescence imaging in the identification of the shape and origin of small vessels, which are unpredictable based on preoperative imaging studies. Our results showed that the IPA type was identified correctly in 80% of cases, with a procedural time of less than one minute. We believe that this technology may be helpful for reducing operative time and blood loss, especially for surgeons who are inexperienced in LAPPG or for novices who are inexperienced in laparoscopic infrapyloric dissection, which is the most difficult and

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time-consuming procedure in laparoscopy-assisted distal gastrectomy [20]. However, further studies are needed to validate the potential role of intraoperative ICG fluorescence imaging.

In the present study, we also applied this technique in 10 patients for the detection of an accessory splenic artery, as an ancillary study. An accessory splenic artery arises from the left gastroepiploic vessel and enters the inferior part of the spleen, which is frequently unintentionally injured following ligation of the LGEA. Even though inferior splenic infarction is rarely symptomatic and has no clinical significance, we assumed that the ICG fluorescence technique would be helpful to minimize this kind of unintended surgical insult. In addition, we were curious as to whether the procedural times would vary according to the location of the target arteries. In the present study, we were able to easily identify the presence or absence of an accessory splenic artery by applying ICG fluorescence, and the ligation level of the left gastroepiploic vessels was able to be determined such that no splenic infarction occurred. Furthermore, we found that the procedural times, including the interval and arterial phase times, differed according to the location of the vessel. The interval and arterial phase times were significantly shorter for the left gastroepiploic vessels than for the right gastroepiploic vessels. These findings might be helpful for researchers who are considering the use of ICG fluorescence for vessel navigation due to the rapid transit time of ICG.

There are several limitations in the present study. First, this study was only performed in patients who underwent laparoscopic subtotal or total gastrectomy, and not those who underwent LAPPG, because it was designed as a pilot study to evaluate whether this technique was applicable to the identification of small vessels during surgery. Therefore, a further study of patients undergoing LAPPG is necessary to confirm our preliminary results. Second, the fluorescence apparatus used in this study has a limitation: the fluorescence spectra are optimized only for ICG. Near-infrared light can penetrate human tissues to a depth of 2–4 cm; however, it is greatly influenced by the overlying tissue thickness [21-24]. This is true for the excitation and emission wavelengths of ICG; therefore, a penetration depth of only several millimeters with low fidelity can be achieved [21,25,26]. In future studies, this shortcoming of near-infrared fluorescence should be improved and other fluorophores should be developed for the wide application of near-infrared fluorescence in clinical practice.

Based on our experience, real-time vessel navigation using ICG fluorescence during laparoscopic gastrectomy was proven feasible with minimal added complexity. Our preliminary results indicate that intraoperative vascular imaging using the ICG fluorescence technique is useful for identifying the shapes and origins of small vessels such as the IPA and an accessory splenic artery. Its use may enable the performance of successful robotic or laparoscopic pylorus-preserving gastrectomy, with a reduction in unintended intraoperative injuries such as inferior polar infarction of the spleen during laparoscopic gastrectomy.

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