Indocyanine Green Fluorescence Imaging for Sentinel Node Mapping in Gastric Cancer

Yusuke Tajima*, Masahiko Murakami, Kimiyasu Yamazaki, Takashi Kato and Mitsuo Kusano

Division of Gastroenterological & General Surgery, Department of Surgery, School of Medicine, Showa University, Tokyo, Japan

Abstract: *Background:* Indocyanine green (ICG) fluorescence imaging has recently been reported as a new method for sentinel node (SN) mapping in several types of cancers. In this study, we determined the feasibility and accuracy of SN mapping guided by ICG fluorescence imaging in gastric cancer.

Methods: Our series consisted of 84 patients with gastric cancer who had undergone standard gastrectomy with lymphadenectomy. Intraoperative SN mapping guided by ICG fluorescence imaging was conducted using a charge-coupled device camera with a light-emitting diode as the light source and a cut filter as the detector.

Results: The detection rate and mean number of SNs were 97.6% and 7.5, respectively. The accuracy and false-negative rates were 91.5% and 33.3%, respectively. The false-negative result was significantly associated with an intraoperative tracer injection, larger number of cT-stage and pT-stage (P = 0.0012, P = 0.0003, and P = 0.0062, respectively). Lymph node metastasis outside the lymphatic basins was never found in 59 patients with cT1-2 stage gastric cancer who had received preoperative ICG injection.

Conclusions: ICG fluorescence imaging-guided SN mapping with preoperative ICG injection can be useful for predicting the metastatic status in the lymph nodes in gastric cancer.

Keywords: Gastric cancer, sentinel node, indocyanine green (ICG), fluorescence imaging.

INTRODUCTION

Indocyanine green (ICG) has excitation and fluoresce wavelengths in the near-infrared range when it binds to plasma proteins. It is well known that near-infrared light can deeply penetrate living tissues. ICG fluorescence imaging thus could have the advantage of being compatible with the biochemical characteristics of living tissues [1]. Recently, an intraoperative imaging system based on the fluorescence characteristics of ICG has been developed for evaluating blood and lymphatic flows during surgery, e.g., during coronary bypass surgery, neurovascular surgery, organ transplantation and for sentinel node (SN) mapping in breast and gastrointestinal cancers [2-6].

The SN is defined as the first lymph node that receives drainage from a primary tumor. Since Morton *et al*. [7] first demonstrated the concept of SNs in a feline model, and later in a clinical study involving patients with breast cancer and melanoma, the clinical significance of the SN concept has been one of the hot topics in the field of surgical oncology [7-9]. Several investigators have reported that SN navigational surgery (SNNS) may allow minimally invasive surgery with individualized lymphadenectomy and improve the postoperative function and patients' quality of life in several cancers, including gastric cancer [10-19].

*Address correspondence to this author at the Division of Gastroenterological & General Surgery, Department of Surgery, School of Medicine, Showa University, 1-5-8, Hatanodai, Shinagawa-ku, Tokyo 142-8666, Japan; Tel: 81-3-3784-8541; Fax: 81-3-3784-5835;
E-mail: surgery@med.showa-u.ac.jp

A dye- guided or radio-guided method, or a combination of both, has been used conventionally for SN mapping in gastric cancer [10-19]. While the dye-guided method is convenient and safe, fast transit of the dye is one of the limitations of this method. In addition, the dye-guided method also offers only poor tissue contrast, which makes detection of SNs in deep, dark anatomical regions, such as the abdomen, rather difficult [10-15,17]. The radio-guided method has been demonstrated to be highly accurate for detecting SNs, however, the lymphatic vessels cannot be visualized. The high radioactivity at the primary injection site also interferes with intraoperative detection of nearby lymph nodes [12,15-17]. We have recently reported the clinical usefulness of ICG fluorescence imaging, which allows highly sensitive imaging-guided intraoperative SN mapping in gastrointestinal cancers [6,19]. We report here the results of our experience with SN mapping guided by ICG fluorescence imaging in gastric cancer.

MATERIALS AND METHODS

Patients

Our series consisted of 84 patients with gastric cancer who had undergone gastrectomy at Showa University Hospital (Tokyo, Japan). The procedures for this study were approved by the ethics committee of our university, and written informed consent was obtained from each of the patients before he/she was included in this study. Table **1** shows the clinicopathological characteristics of the patients assessed according to the Japanese classification of gastric cancer [20]. The patients were clinically diagnosed before surgery based on fiberscopic gastrointestinal endoscopy,

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double contrast gastrography, ultrasonography, and CT. All patients underwent curative gastrectomy with standardized lymphadenectomy according to the Guidelines of the Japan Gastric Cancer Association [21]. The mean number of dissected lymph nodes was 34.7 ± 18.5 per a patient. None of the patients had received any preoperative radio- and/or chemotherapy. Two patients having gastric cancer with invasion into the submucosal layer had undergone endoscopic mucosal resection before gastrectomy.

Table 1. Patients Characteristics

Gender	
Male	44
Female	40
Mean age ± standard deviation (yr)	67.6 ± 10.5
Tumor location	
upper third of the stomach	30
middle third of the stomach	41
lower third of the stomach	13
cT-number	
cT1	63
cT2	14
cT3	5
pT-number	
pT1	54
pT2	21
pT3	9
Lymph node metastasis	
Negative	63
Positive	21
Gastrectomy	
total (laparoscopic)	16 (2)
proximal (laparoscopic)	3 (3)
distal (laparoscopic)	52 (24)
pylorus preserving (laparoscopic)	13 (11)

T1, indicates invasion of mucosa or submucosa; T2, invasion of muscularis propria or subserosa; T3, invasion of serosa.

For the histopathological examinations, serial 5-mm-thick tissue sections of the entire tumor were prepared from the resected specimens fixed with 10% buffered formalin, embedded in paraffin and stained with hematoxylin and eosin (H&E). All dissected lymph nodes were examined histologically one slice per node stained with H&E. Clinicopathologic findings such as gender, age, tumor location, macroscopic type, tumor size, histologic-type, depth of invasion, and lymph node metastasis were reviewed according to the Japanese classification of gastric cancer [20].

Intraoperative SN Mapping Guided by ICG Fluorescence Imaging

A 0.5% ICG solution (Diagnogreen 0.5%; Daiichi Pharmatical, Tokyo, Japan) was injected into the submucosa endoscopically (1-3 days prior to the operation) or subserosa intraoperatively at 4 sites (0.5 ml each) around the tumor. In this study, surgeons in charge selected either preoperative or intraoperative ICG injection according to their preference. ICG fluorescence imaging was carried out using an Infrared Camera System (PDE-2; Hamamatsu Photonics, Hamamatsu, Japan)[5,6,19,22]. The light source of the ICG fluorescence imaging system was a light-emitting diode (LED) that emitted light at a wavelength of 760 nm, and the detector was a charge-coupled device (CCD) camera with a cut filter used to filter out light with wavelengths below 820 nm [5,6,19,22].

After the dissection of the lesser omentum and greater omentum, SN mapping guided by ICG fluorescence imaging through a laparotomy incision at the upper abdomen (through a 4- to 7-cm-long minilaparotomy incision during laparoscpy-assisted gastrectomy). Lymph nodes taking up ICG appeared as round spots emitting clear fluorescence and were defined as the SNs (Fig. **1**). The SNs were dissected out from the surrounding connective tissue. All the fluorescent lymph nodes were regarded as representing the SNs in this study.

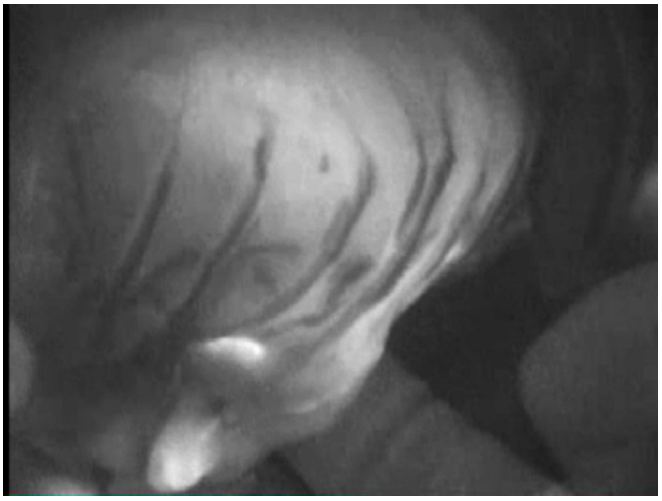


Fig. (1). SN mapping guided by ICG fluorescence imaging. Lymphatic vessels draining the tumor and round sentinel nodes were visualized by their bright fluorescence.

Lymphatic Basins

Based on the location of the SNs, the gastric lymphatic compartments (lymphatic basins; LBs) draining the tumor were divided into the following five directions along the main arteries: left gastric artery, right gastric artery, right gastroepiploic artery, left gastroepiploic artery and posterior gastric artery as described previously by Miwa *et al.* [11] and Kinami *et al.* [23]. The left gastric artery area consisted of lymph node stations 1, 3 and 7. The right gastric artery

area consisted of stations 5 and 8a. The right gastroepiploic artery area consisted of stations 4d and 6. The left gastroepiploic artery area consisted of stations 4sa and 4sb. The posterior gastric artery consisted of station 11p.

Statistical Analysis

The data were analyzed with the chi-square test or Fisher's exact test. The level of significance was set at $P < 0.05$.

RESULTS

There were no patients with complications or adverse events after the ICG injection in this study. The lymphatic vessels draining the main tumor and SNs were clearly visualized through bright fluorescence (Fig. **1**). Even SNs that were not green in color by the naked eye examination could be easily and clearly visualized by ICG fluorescence imaging (Fig. **2**). At least one SN was detected in 82 (97.6%) of the 84 patients. The mean number of SNs was 7.5 ± 6.5 per a patient and that of LBs was 1.9 ± 0.8 per a patient. The accuracy and false-negative rates were 91.5% (75/82 cases) and 33.3% (7/21 cases), respectively.

Table **2** shows a comparison between the 7 patients with the false-negative results and 75 other patients. The false-negative result was significantly associated with an intraoperative tracer injection, larger number of cT-stage and pT-stage ($P = 0.0012$, $P = 0.0003$, and $P = 0.0062$, respectively). No significant association was found between false-negative results and extent of gastrectomy, type of surgery, tumor location, tumor size, histologic type, number of SN, number of LB, or the presence of preoperative endoscopic mucosal resection.

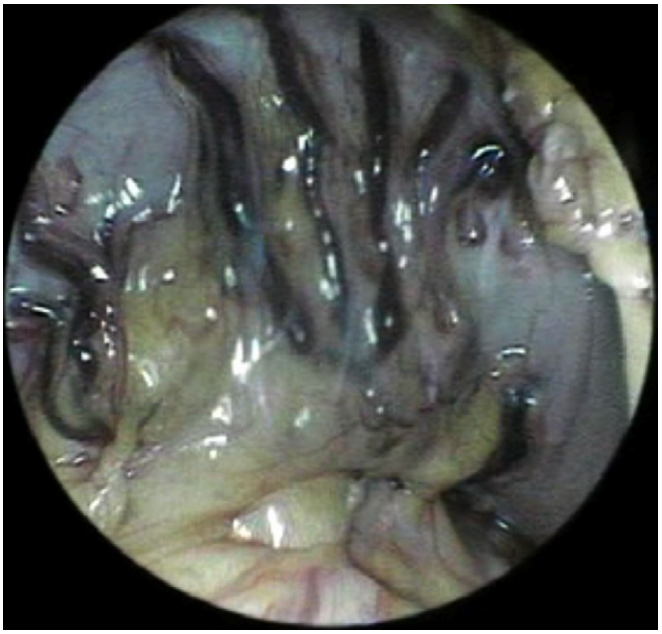
Table **3** shows the clinicopathological features of 7 patients showing the false-negative results. Among these 7 patients, there were 1 patient with preoperative ICG injection and 6 patients with intraoperative ICG injection. There were 2 patients with cT1- (pT1-) stage cancer, 2 patients with cT2- (pT2-) stage cancer, and 3 patients with cT3- (pT3-) stage cancer. Metastatic lymph nodes were within the LBs in 4 of 7 patients with the false-negative result (Case 1, 2, 3, and 4). However, lymph node metastasis outside the LBs was recognized in 3 patients (Case 5, 6, and 7).

Table **4** shows the risk of the lymph node metastasis outside the LBs according to the timing of tracer injection, metastatic status in SNs, and cT-stage. The risk of lymph node metastasis outside the LBs was 0% in 59 patients with cT1-2 stage gastric cancer who had received preoperative ICG injection. However, lymph node metastasis outside the LBs was found in 5 (21.7%) of 23 patients with cT1-3 gastric cancer who had received intraoperative ICG injection. A significant difference in the risk of lymph node metastasis outside the LBs was observed between the two groups ($P = 0.0012$).

DISCUSSION

ICG fluorescence imaging allows highly sensitive real-time imaging-guided SN mapping in gastric cancer [5,6,19]. Lymphatic vessels and SNs even in dense fat, which were not visible as green in color to the naked eye, could also be easily and clearly visualized through the bright fluorescence of ICG. Tracer deposition for prolonged periods of time in the lymphatic vessels and lymph nodes (more than 3 days) are the specific characteristics of ICG fluorescence imaging. Accordingly, both preoperative and intraoperative tracer injection are available in ICG fluorescence imaging. These could be the advantages of ICG fluorescence imaging-guided SN mapping as compared with those using other methods reported previously, such as dye- and radio-guided methods [10-17].

(**A**)



(**B**)

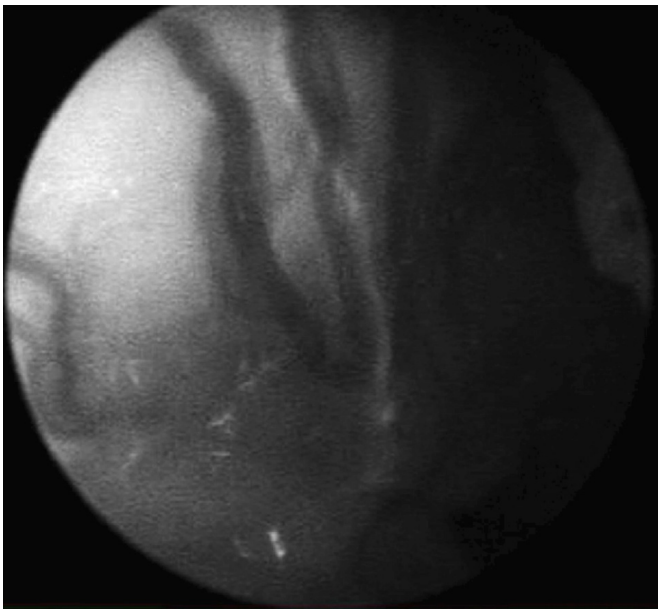


Fig. (2). A comparison between examination with the naked eye and ICG fluorescence imaging. ICG fluorescence imaging (**B**) makes it easy to distinguish the primary tumor and lymphatic flows containing ICG particles from the surrounding tissue, compared with observation with the naked eye (**A**).

Table 2. Comparison Between 7 Patients with False-Negative Results and 75 Other Patients

		Patients with False-Negative Results (n = 7)	Other Patients (n = 75)	P - Value
ICG injection	preoperative	1 (1.7%)	59 (98.3%)	0.0012
	intraoperative	6 (27.3%)	16 (72.7%)	
Extent of gastrectomy	distal	5 (9.8%)	46 (90.2%)	N.S.
	proximal	0 (0)	3 (100%)	
	total	2 (14.3%)	12 (85.7%)	
	pylorus preserving	0 (0)	12 (100%)	
Type of surgery	open	6 (14.0%)	37 (86.0%)	N.S.
	laparoscopy	1 (2.6%)	38 (97.4%)	
Location	upper third of the stomach	0 (0)	13 (100%)	N.S.
	middle third of the stomach	4 (10.0%)	36 (90.0%)	
	lower third of the stomach	3 (10.3%)	26 (89.7%)	
Tumor size (mm)	40 >	3 (5.6%)	51 (94.4%)	N.S.
	40 <	4 (14.3%)	24 (85.7%)	
Histologic-type	Differentiated-	1 (3.6%)	27 (96.4%)	N.S.
	undifferentiated-	1 (3.7%)	26 (96.3%)	
	mixed-	5 (18.5%)	22 (81.5%)	
cT-number	cT1	2 (3.2%)	60 (96.8%)	0.0003
	cT2	2 (14.3%)	12 (85.7%)	
	cT3	3 (50.0%)	3 (50.0%)	
pT-number	pT1	2 (3.8%)	51 (96.2%)	0.0062
	pT2	2 (9.5%)	19 (90.5%)	
	pT3	3 (37.5%)	5 (62.5%)	
Number of SN	6 >	6 (13.6%)	38 (86.4%)	N.S.
	6 <	1 (2.6%)	37 (97.4%)	
Number of LB	1	3 (13.0%)	20 (87.0%)	N.S.
	2	3 (7.5%)	37 (92.5%)	
	3-4	1 (5.3%)	18 (94.7%)	
Preoperative	absent	6 (7.5%)	74 (92.5%)	N.S.
endoscopic resection	present	1 (50.0%)	1 (50.0%)	

ICG, indocyanone green, T1, indicates invasion of mucosa or submucosa; T2, invasion of muscularis propria or subserosa; T3. invasion of serosa; SN, sentinel node; LB, lymphatic basin; N.S., not significant.

Table 3. Clinicopathological Features of 7 Patients with False-Negative Results

Case	ICG Injection	cT-Number	pT- Number (Depth of Invasion)	Location of SN (LB)	Location of Metastatic Lymph Node (LB)
1	preoperative	cT1	pT1 (SM)	0/3 (#3.4sb,4d,6,7,8a; RGA, LGA, RGEA, LGEA)	1/46 (#3; LGA)
2	intraoperative	cT1	pT1 (SM)	0/10 (#3,4d,6; LGA, RGEA)	1/25 (#6; RGEA)
3	intraoperative	cT2	pT2 (MP)	0/2 (#5,6; RGA, RGEA)	3/36 (#5,6; RGA, RGEA)
4	intraoperative	cT2	pT2 (SS)	0/5 (#3,4sb,4d,6; LGA, RGEA, LGEA)	16/43 (#3,4d,6; LGA, RGEA)
5[a]	intraoperative	cT3	pT3 (SE)	0/2 (#4d,6; RGEA)	1/22 (#3; LGA)
6[a]	intraoperative	cT3	pT3 (SE)	0/1 (#3; LGA)	4/21 (#3,6,7,8a; RGA, LGA, RGEA)
7[a]	intraoperative	cT3	pT3 (SE)	0/6 (#4d; RGEA)	5/55 (#3; LGA)

[a]Cases with metastasis outside lymphatic basins (LBs); ICG, indocyanine green; T1, indicates invasion of mucosa or submucosa; T2, invasion of muscularis propria or subserosa; T3, Invasion of serosa; SN, sentinel node; LB, lymphatic basin; RGA, right gastric artery area; LGA, left gastric artery area; RGEA, right gastroepiploic artery area; LGEA, left gastroepiploic artery area.

The most important clinical implication of the SN mapping is the possibility of less invasive surgery in SN-negative cases. For minimally invasive treatments based on SN mapping, accurate prediction of the status of lymph node metastasis is crucial. Our results in this study revealed acceptable results in accuracy and false-negative rates. Especially, the accuracy rate in cT1 stage cancer patients was 96.8%. Therefore, ICG fluorescence imaging-guided SN mapping could be useful for predicting the metastatic status in the lymph nodes and enhancing the intraoperative staging accuracy for such patients. However, false-negative cases have been recognized to a certain extent in the previous studies and ours [9-17,19]. The common cause of a false-negative result has been considered to be an obstructed

Table 4. Risk of Lymph Node Metastasis Outside LBs According to the Timing of Tracer Injection, Metastatic Status in SNs, and cT-Stgae

	Patients without Metastasis in SNs	Patients with Metastasis in SNs	Total
Preoperative ICG injection			
cT1	0% (0/47)	0% (0/6)	0% (0/53)
cT2	0% (0/3)	0% (0/3)	0% (0/6)
cT3	0% (0/0)	0% (0/0)	0% (0/0)
total	0% (0/50)	0% (0/9)	0% (0/59)[a]
Intraoperative ICG injection			
cT1	0% (0/7)	50.0% (1/2)	11.1% (1/9)
cT2	0% (0/6)	50.0% (1/2)	12.5% (1/8)
cT3	60.0% (3/5)	0% (0/1)	50.0% (3/6)
total	16.7% (3/18)	40.0% (2/5)	21.7% (5/23)[a]

[a] P = 0.0012; LB, lymphatic basin; SN, sentinel node; ICG, indocyanien green; T1, indicates invasion of mucosa or submucosa; T2, invasion of muscularis propria or subserosa;T3. invasion of serosa.

lymphatic vessel due to massive cancerous invasion. In such cases, the administered tracer cannot migrate into the initial SNs and escapes to the second echelon or false SNs [11,23,24]. The risk of the false-negative result has been reported to be much higher in advanced stage cancers than in early gastric cancers [9-17,19]. In this study, cT- and pT-number were also strongly associated with the false-negative results in SN mapping guided by ICG fluorescence imaging. A larger number of cT- and pT-number might be correlated with the higher risk of lymphatic vessel obstruction due to massive cancerous metastasis. Therefore, relatively early stage of gastric cancer might be a good indication for SN mapping by ICG fluorescence imaging.

In this study, preoperative ICG injection into the submucosal layer was superior in terms of the accuracy. We previously reported that the mean number of SNs was significantly higher in the preoperative ICG injection group than in the intraoperative ICG injection group (9.9 *vs* 4.1)[19]. It is suggested that the ICG particles binding with plasma proteins might spread out widely from the injection site through lymphatic vessels with time. Additionally, we frequently experienced ICG fluorescence leakage from injured lymphatic vessels during SN mapping in patients with intraoperative ICG injection of the previous study [19]. Widespread distribution of blighting ICG fluorescence covered over the surgical field made further observation difficult. Such phenomenon could be also associated with a lower mean number of SNs in patients with intraoperative ICG injection although that might reflect the highly sensitivity of ICG fluorescence leakage. However, in this study, number of SN was not significantly associated with false-negative results. Especially early stage of tumor is not always palpable from the serosal side during intraoperative SN mapping and accurate tracer injection around the tumor by the intraoperative subserosal approach is, therefore, difficult [15,19]. Such technical factors might affect the results of SN mapping. Based on our data of this study, we speculate that preoperative ICG injection might be a more preferable procedure for accurate tracer injection around the tumor and, as a result, for accurate prediction of metastatic status in the lymph nodes.

Reduced lymphadenectomy for patients with gastric cancer according to the basis of results of SN mapping should be performed as carefully as possible without increasing the risk of the not-resected residual tumors and recurrence after surgery since the prognosis of patients with T1-2 stage gastric cancer who undergo standard lymphadenectomy is favorable [25]. However, a false-negative finding was recognized even in patients with early gastric cancer. It has been reported that each gastric cancer has its own LBs in which metastasis can occur [11,23,24]. Kinami *et al*. [23] analyzed the pattern of lymph node metatsasis using a large number of gastric cancer patients received SN mapping by blue dye- and radio-guided methods. They advocated the progression pattern of lymph node metastasis in gastric cancer as follows; nodal metastasis occurred in SNs first, spread to non-SNs within the LBs next, and rarely extended outside the LBs. In this study, lymph node metastasis in 4 of 7 patients with false-negative results were within the LBs. The risk of lymph node metastasis outside the LBs was also significantly lower in preoperative ICG injection group than in intraoperative ICG injection group. Lymph node metastasis outside the LBs was never found in cT1-2 stage cancer patients who had received preoperative ICG injection. Therefore, the LB is regarded as the most important lymphatic area in which lymph node metastasis frequently develops and lymphadenectomy should be performed. Our observations in this study suggest that it might be useful to apply the LB concept to SN mapping guided by ICG fluorescence imaging with preoperative ICG injection in cT1-2 stage gastric cancer.

In conclusion, this study shows that ICG fluorescence imaging allows highly sensitive image-guided intraoperative SN mapping in gastric cancer. ICG fluorescence imaging-guided SN mapping with preoperative ICG injection can be useful for predicting the metastatic status in the lymph nodes in gastric cancer.

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