ORIGINAL ARTICLE

The Clinical Value of Fluorescent Lymphography with Indocyanine Green During Robotic Surgery for Gastric Cancer: a Matched Cohort Study

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Abstract

Background Near-infrared (NIR) fluorescence imaging with indocyanine green (ICG) has been recently introduced for lymphatic mapping in several tumors. We aimed at investigating whether this technology may improve the intraoperative visualization of lymph nodes during robotic gastrectomy for gastric cancer.

Methods Between June 2014 and June 2018, a total of 94 patients underwent robotic gastrectomy with D2 lymph node dissection for gastric cancer. In 37 patients, ICG was injected endoscopically into the submucosal layer around the tumor the day before surgery. After propensity score matching, the results of these 37 patients were compared with the results of 37 control patients who had undergone robotic gastrectomy without ICG injection.

Results Among the 37 patients within the ICG group, no adverse events related to ICG injection or intraoperative NIR imaging occurred. After completion of D2 lymph node dissection, no residual fluorescent lymph nodes were left in the surgical field. A mean of 19.4 ± 14.7 fluorescent lymph nodes was identified per patient. The mean total number of harvested lymph nodes was significantly higher in the ICG group than in the control group (50.8 vs 40.1, $P = 0.03$). In the ICG group, 23 patients had metastatic lymph nodes. The accuracy, sensitivity, and specificity of ICG fluorescence for metastatic lymph nodes were 62.2%, 52.6%, and 63.0%, respectively.

Conclusion Our study indicates that NIR imaging with ICG may provide additional node detection during robotic surgery for gastric cancer. Unfortunately, this technique failed to show good selectivity for metastatic lymph nodes.

Keywords Near-infrared fluorescence · Indocyanine green · Lymph node · Robotic gastrectomy · Gastric cancer

Introduction

Minimally invasive surgery, including laparoscopic and robotic approaches, has emerged as a valid option for the treatment of gastric cancer, especially in the East and for patients with early-stage tumors.[1] However, the oncological efficacy of minimally invasive techniques for the treatment of advanced gastric cancer is still controversial. In particular, some concerns have been raised regarding the possibility of carrying out an adequate D2 lymphadenectomy during minimally invasive surgery since lymph node dissection along the great vessels is considered to be technically demanding.[2,3] We hypothesized that a technique that allows intraoperative identification of draining lymph nodes from the primary tumor would help the surgeon to perform a complete lymphadenectomy

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even during a minimally invasive procedure, such as robotic-assisted gastrectomy.

Indocyanine green (ICG) is a diagnostic reagent that emits fluorescence after stimulation using a laser beam or near-infrared (NIR) light at a wavelength ≥ 820 nm. The emitted ICG fluorescence is detected using specifically designated scopes and camera.[4] Most commonly, ICG is intravenously administered where it binds to plasma proteins (albumin) and from the bloodstream, it is transported to the liver and excreted via the bile into the duodenum. Because of these properties, ICG is considered an ideal compound for both delineation of the extra-hepatic biliary tree and assessment of tissue perfusion during gastro-intestinal surgery.[5,6] Furthermore, ICG has the property of lymphatic tropism and after submucosal or subserosal injection, it can follow the lymphatic vessels and accumulate in the lymph nodes. It has been reported[7] that lymphatic vessels and lymph nodes containing ICG particle can be easily distinguished from surrounding fatty tissue using an infrared-ray technology system. In addition, ICG deposition and fluorescence imaging are characteristically found for prolonged periods of time in the lymph nodes (> 3 days).

Near-infrared imaging with ICG has been recently introduced as a safe intraoperative technology for lymphatic mapping in several tumors, such as gynecological, urological, and esophageal tumors.[8–10] This technique under laparoscopic view has also emerged as a promising tool for sentinel lymph node mapping and dissection during early gastric cancer treatment.[7,11–13] The use of ICG has been found to offer some advantages in lymph node visualization over other modalities employing radioisotopes (e.g., [99m]Technetium radiocolloid) or vital dye tracers (e.g., methylene blue, patent blue) which are currently known to provide the best sensitivity and specificity for sentinel lymph node mapping.[14] On the contrary, the potential role and significance of fluorescent lymphography with ICG during surgery for advanced gastric cancer has not been completely investigated yet. In fact, only preliminary and heterogeneous studies with either laparoscopic[15] or robotic NIR technologies[16,17] have been previously published on this issue and the reported results are not definitive.

In the present study, we analyzed the hypothesis that robot-assisted NIR imaging with ICG could be used as an intraoperative lymphatic tracer method that allows detection of lymph nodes and facilitates a more complete lymphadenectomy during gastrectomy.

Materials and Methods

Study Design and Data Collection

Using a prospectively collected gastric cancer database, we identified 94 patients who underwent robotic surgery for gastric cancer between June 2014 and June 2018 at the Center for Oncologic Minimally Invasive Surgery of the University of Florence, Italy. All the robotic gastrectomies were performed by a single experienced surgeon (F.C.). From January 2016, we started a study protocol to investigate the potential utility of intraoperative NIR imaging with ICG during robotic surgery for gastric cancer. A total of 37 patients were enrolled in the study. The results of this study were compared with those of 37 matched patients who had undergone robotic gastrectomies without the use of ICG. Patient pairing was done according to age, gender, body mass index (BMI), type of gastrectomy (subtotal or total), and tumor stage by using an automated matching procedure in the SAS® software (version 8.2; SAS Institute, Inc., Cary, NC, USA).

All patients underwent preoperative upper digestive endoscopy with gastric biopsy and computed tomography of the abdomen and chest. Patients with history of iodide or seafood allergy and preoperative or intraoperative diagnosis of enlarged/bulky lymph nodes and M1 or T4 lesions (i.e., with distant metastases, local invasion of peritoneum, spleen or pancreas) were excluded from the study. All patients had been thoroughly informed about the study and gave their written consent for the investigation in compliance with the Helsinki Declaration and in accordance with the ethical committee of our University Hospital, Azienda Ospedaliero-Universitaria Careggi (Florence, Italy).

The characteristics of patients, such as age, gender, BMI, ASA class, co-morbidities, history of abdominal surgery, perioperative chemotherapy, surgical outcomes (operative time, conversion to open procedure, postoperative morbidity and mortality, length of hospital stay), and pathological results, were examined.

The extent of gastric resection, subtotal or total, was determined according to tumor localization, classified as upper, middle, and lower third of the stomach. All patients received a D2 lymphadenectomy according to the lymph node classification of the Japanese Gastric Cancer Association.[18]

Surgical Technique

All patients underwent either curative distal or total gastrectomy with D2 lymph node dissection using a da Vinci Si Surgical System (Intuitive Surgical, Sunnyvale, CA, USA). Robotic distal gastrectomy was performed as previously described.[19] In total gastrectomy, the same procedures for lymph node dissection were performed as for subtotal gastrectomy, but with the inclusion of a complete dissection of the left greater omentum, division of short gastric vessels (lymph node station n. 4a), dissection of lymph nodes along the distal splenic artery (n. 11d), and dissection of left cardiac lymph nodes (n. 2). The distal esophagus was transected with a linear stapler and a Roux-en-Y intracorporeal linear side-to-side esophagojejunal anastomosis was performed. The specimen was pulled out through the umbilical port and either an

intracorporeal or extracorporeal jejunum-jejunostomy was constructed with a linear stapler.

Endoscopic ICG Injection and Intraoperative NIR Imaging

In 37 study patients, a 0.2% (1.25 mg/ml) ICG solution was gently injected into the submucosa layer with approximately 0.5 ml into the four quadrants around the tumor under endoscopic examination. The dye was injected 1 day before surgery. The specific dose of ICG and the method and timing of ICG injection were chosen on the basis of our previously published recommendations.[20] Intraoperative NIR imaging with ICG was carried out with a near-infrared camera system (Firefly Fluorescence Imaging Scope; Intuitive Surgical, Sunnyvale, CA) built into the robotic platform. Lymph nodes which had taken up ICG appeared as green spots emitting clear fluorescence[20] and were defined as the fluorescent nodes (FNs). During surgery, the surgeon switched on the NIR mode before and after dissection at each lymph node station. At the end of lymphadenectomy, the dissected areas were rechecked and any residual FNs or fluorescent tissue were additionally removed. The removed surgical specimens were accurately examined on the back table to retrieve, with the help of the robotic camera, all the FNs that were not identified intraoperatively. Location and fluorescence status were recorded for all the lymph nodes before they were sent for pathological analysis. In particular, the dissected lymph nodes were grouped into five gastric lymphatic basins along the main arteries as previously described by Kinami et al.[21]: left gastric artery (l-GA), right gastric artery (r-GA), right gastroepiploic artery (r-GEA), left gastroepiploic artery (l-GEA), and posterior gastric artery (p-GA). The l-GA area consisted of lymph node stations 1, 2, 3, 7, and 9. The r-GA area consisted of stations 5, 8a, 8p, and 12a. The r-GEA consisted of stations 4d and 6. The l-GEA consisted of stations 4sa and 4sb. The pGA consisted of stations 10, 11p, and 11d.

Pathological Analysis

Clinicopathological findings such as tumor location and size, tumor differentiation, depth of gastric wall invasion, lymph node metastasis, and stage distribution were reviewed according to the Japanese gastric carcinoma classification[18] and the 7th edition of AJCC/TNM tumor staging.[22] Tumors were also classified according to Lauren's histotype, i.e., intestinal, diffuse, or mixed. All dissected lymph nodes were examined histologically one slice per node and stained with H&E.

Statistical Analysis

Continuous variables were reported as mean value and standard deviation or absolute number and percentage, unless stated otherwise. A one-tailed ANOVA was used for analysis of parametric data and Pearson's X^2 test was used for discrete data. A $P < 0.05$ was considered statistically significant. All statistical analyses, including propensity score matching, were performed by using the SPSS software package (SPSS, Inc., Chicago, IL, USA).

For patients in the ICG group, the accuracy, sensitivity, and specificity were calculated according to the number of lymph nodes, the fluorescent, and metastasis condition of lymph nodes. The formulas were as follows: accuracy = number of (metastatic FNs + non-metastatic non-FNs)/number of all lymph nodes; sensitivity = number of metastatic FNs/number of (metastatic FNs + metastatic non-FNs); specificity = number of non-metastatic non-FNs/number of (non-metastatic non-FNs + non-metastatic non-FNs).

Results

After propensity score matching, 74 pairs of ICG and control patients were selected for final analysis. The group of patients with ICG included 22 males and the median age was 72.2 ± 9.8. The control group included 26 males and the median age was 72.4 ± 8.9. No statistically significant differences were observed between the two groups according to age, gender, BMI, ASA class, comorbidities, number of prior abdominal operations, perioperative chemotherapy, and tumor location (Table 1).

The operative and short-term clinical outcomes are shown in Table 2. There were no significant differences between the ICG and control groups with respect to extent of gastrectomy, conversion to open surgery, operative time, postoperative complications, and length of hospital stay. There were no deaths up to 30 days after surgery in either group.

Pathology analyses of all patients were reviewed by one pathologist (L.N.) skilled in upper gastrointestinal tumors. There were no significant differences in tumor size, grade of differentiation, and Lauren's histotype between the two groups (Table 3). Resection margins were negative in all patients. There were no significant differences in number of pathological T and N categories, tumor stage distribution, and number of metastatic lymph nodes examined between the two study groups (Table 3). The overall mean number of lymph nodes retrieved in the ICG group was significantly higher than that in the control group (40.1 ± 23.0 versus 50.8 ± 17.1, $P < 0.03$) (Table 3). At least 15 lymph nodes were examined in all patients in the ICG group and in 34 patients (91.8%) in the control group. More than 30 lymph nodes were retrieved from 35 patients (94.5%) in the ICG group and from only 26 patients (70.2%) in the control group.

Within the ICG group, there were no patients with intraoperative complications related to application of NIR imaging or adverse events attributable to endoscopic injection of ICG. In

Table 1 Clinicopathological characteristics of the ICG and control groups

	Control group (n = 37)	ICG group (n = 37)	P value
Age (years, mean ± SD)	72.4 ± 8.9	72.2 ± 9.8	0.93
Gender (%)			0.64
Male	21 (57.7)	22 (59.5)	
Female	16 (43.3)	15 (40.5)	
BMI (kg/m², mean ± SD)	23.2 ± 3.04	23.3 ± 3.07	1.00
ASA (%)			0.83
Class I	1 (2.7)	2 (5.4)	
Class II	24 (64.9)	23 (62.2)	
Class III	12 (32.4)	12 (32.4)	
Comorbidities (%)			0.23
Cardiac	11 (29.7)	12 (32.4)	
Renal	1 (2.7)	0 (0)	
Endocrine	6 (16.3)	4 (10.8)	
Gastro-intestinal	3 (8.1)	2 (5.4)	
Pulmonary	3 (8.1)	1 (2.7)	
Neurological	0 (0)	2 (5.4)	
Other	7 (18.9)	12 (32.4)	
Previous abdominal surgery (%)	14 (37.9)	14 (37.9)	0.74
Perioperative chemotherapy (%)	2 (5.4)	2 (5.4)	1.00
Tumor location (%)			1.00
Lower third	20 (54.0)	23 (62.2)	
Middle third	11 (29.7)	10 (27.0)	
Upper third	6 (16.3)	4 (10.8)	

Table 2 Operative and short-term clinical outcomes of the ICG and control groups

	Control group (n = 37)	ICG group (n = 37)	P value
Extent of gastrectomy (%)			0.18
Subtotal gastrectomy	25 (67.6)	30 (81.1)	
Total gastrectomy	12 (32.4)	7 (18.9)	
Conversion (%)	0 (0)	0 (0)	1.00
Operative time (min, mean ± SD)	321.2 ± 77.8	293.1 ± 61	0.05
Postoperative complications (%)			1.00
Total	5 (13.5)	5 (13.5)	
Respiratory	2 (5.4)	3 (8.1)	
Duodenal leak	1 (2.7)	1 (2.7)	
Anastomotic bleeding	1 (2.7)	0 (0)	
Occlusion	1 (2.7)	1 (2.7)	
Length of hospital stay (days, mean ± SD)	10.9 ± 3.8	10.0 ± 3.8	0.34
Mortality (%)	0 (0)	0 (0)	1.00

situ detection of fluorescence at the site of the gastric tumor was achieved in all cases. Dye diffusion to at least one lymph node was observed in 36 patients with a success rate of 97.2%. No residual FNs were left in the surgical field after completion of D2 lymph node dissection in all patients. The total number of retrieved lymph nodes was 1881 and the mean number of examined lymph nodes per patient was 50.8 (range, 23–110). We identified 719 FNs for a mean of 19.4 (SD, ± 14.7) lymph nodes per patient (range, 0–59). The distribution of fluorescent and non-fluorescent lymph nodes within the five lymph node basins is shown in Fig. 1. All lymph node basins contained 8 or more FNs. In particular, the highest numbers of both total lymph nodes and FNs were retrieved in the l-GA basin (583 and 262, respectively). The histopathological analysis indicated that 23 (62.1%) patients had metastatic lymph nodes. The total number of metastatic lymph nodes was 150 for a mean of 4.0 lymph nodes per patient (Table 3). Of the 150 metastatic lymph nodes, 79 (52.6%) were fluorescent. The accuracy, sensitivity, and specificity of ICG fluorescence for metastatic lymph nodes were 62.2%, 52.6. %, and 63.0%, respectively (Table 4).
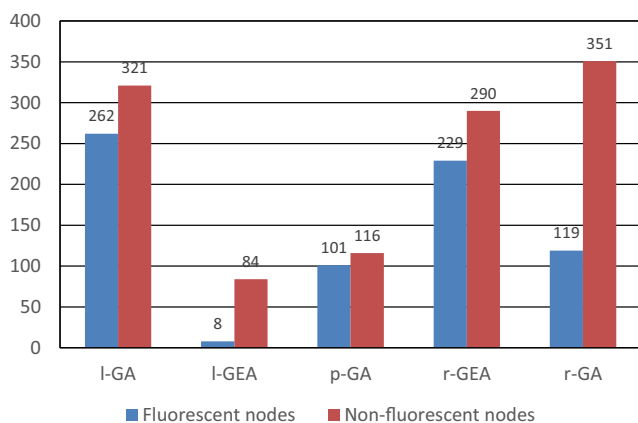
Discussion

One crucial step in gastric cancer surgery is lymphadenectomy since the removal of an adequate number of lymph nodes has been shown to improve the accuracy of staging, regional disease control, and patient survival.[23–26] In the present study, we sought to evaluate the clinical value of NIR imaging with ICG for real-time intraoperative identification of lymph nodes during robotic surgery for gastric cancer. Our results show no significant differences between patients who did and did not receive ICG with respect to their clinicopathological features and perioperative outcomes. Interestingly, we found that the mean number of total harvested lymph nodes in the ICG group was higher than that in the group without ICG. It is noteworthy that the mean number of examined lymph nodes in the control group was 40.1, that is much higher than the recommended number (i.e., 25) for adequate D2 lymphadenectomy[27] and for proper nodal staging (i.e., 16).[22] Therefore, it seems plausible that fluorescent lymphatic mapping with ICG can actually help the surgeon to remove residual lymph nodes that cannot be identified with the naked eye even after a complete D2 lymphadenectomy. Alternatively, the increase in the number of retrieved lymph nodes may be the result of more accurate harvesting from the resected specimens by means of NIR visualization, since this technique permits the identification of even very small lymph nodes that are difficult to distinguish from fatty tissue by manual palpation. Unfortunately, the lack of some pathological data on the localization of retrieved lymph nodes in the control group did not permit us to compare the number of examined lymph nodes according to each lymph node basin in the two study groups.

Table 3 Histopathologic characteristics of the ICG and control groups

	Control group (n = 37)	ICG group (n = 37)	P value
Tumor size (cm, mean ± SD)	3.9 ± 2.19	3.8 ± 1.9	0.94
Grade of differentiation (%)			0.12
Well differentiated	3 (8.1)	7 (18.9)	
Moderately differentiated	23 (62.2)	23 (62.2)	
Poorly differentiated	11 (29.7)	7 (18.9)	
Lauren classification (%)			0.79
Intestinal	20 (54.1)	21 (56.7)	
Diffuse	5 (13.5)	5 (13.5)	
Mixed	12 (32.4)	11 (29.7)	
Depth of invasion (%)			0.10
T1	7 (18.9)	6 (16.2)	
T2	5 (13.5)	11 (29.7)	
T3	25 (67.6)	20 (54.1)	
Lymph node metastasis (%)			0.16
N0	14 (37.9)	14 (37.9)	
N1	10 (27.0)	8 (21.6)	
N2	4 (10.8)	6 (16.2)	
N3	9 (24.3)	9 (24.3)	
Tumor stage (%)			0.60
Stage I	12 (32.4)	12 (32.4)	
Stage II	5 (13.5)	9 (24.3)	
Stage III	20 (54.1)	16 (43.3)	
No. of metastatic lymph nodes (mean ± SD)	4.4 ± 6.8	4.0 ± 5.4	0.75
No. of harvested lymph nodes (mean ± SD)	40.1 ± 23.0	50.8 ± 17.1	0.03

Table 4 Number of total lymph nodes, metastatic lymph nodes, and fluorescent lymph nodes in the ICG group

	Metastatic	Non-metastatic
Total	150	1731
Fluorescent lymph nodes	79	640
Non-fluorescent lymph nodes	71	1091

cancer.[7,11–13,28,29] On the other hand, the possible value of ICG as a tracer for intraoperative lymphography with the aim of carrying out a more complete and thorough lymphadenectomy is still uncertain and has been addressed only by three previously published studies. Lan et al.[17] compared 14 and 65 patients who underwent robotic gastrectomy with or without ICG fluorescence, respectively. They did not find any significant differences in the total number of lymph nodes retrieved in the two groups, but all the metastatic lymph nodes were found in the lymph node stations which showed fluorescence signals. In 9 out of their 14 patients, ICG was injected intraoperatively into the subserosa around the tumor. We believe that submucosal injection of ICG solution under endoscopic guidance at four sites around the tumor the day before surgery provides a better visualization of lymph nodes when compared with intraoperative subserosal ICG injection. It is most likely that, with intraoperative subserosal injection, the dye does not have enough time to spread into the lymphatic vessels and deposit into all draining lymph nodes. Furthermore, the endoscopic submucosal injection of ICG, unlike the subserosal approach, avoids any potential lymphatic disruption that can occur with intraoperative dissection and permits direct visualization of the lesion at the time of surgery.

Kim et al.[15] investigated the value of intraoperative (15 min before dissection) submucosal injection of ICG in 15 patients who underwent laparoscopic pylorus-sparing gastrectomy and in 15 patients who underwent laparoscopic distal gastrectomy. They found that fluorescent imaging with ICG may provide additional lymph node detection especially in the infra-pyloric area.

At the time of writing of the present manuscript, Kwon et al.[30] published the first comparative, cross-matched study addressing the value of fluorescent-guided lymphadenectomy during robotic gastrectomy. They analyzed the results obtained from 40 patients who underwent robotic gastrectomy with preoperative (1 day before surgery), submucosal injection of ICG and compared these results with those of 40 control patients who underwent the same procedure without ICG injection. They found that the mean number of overall lymph nodes harvested was higher in the ICG group than in the historical controls (48.9 vs 35.2, respectively), with a significantly greater number of lymph nodes retrieved at stations 2, 6, 7, 8, and 9. Therefore, these findings are consistent with our

The efficacy of NIR imaging with ICG has been previously proven for sentinel lymph node mapping and dissection especially in Asian countries where a significant proportion of patients are diagnosed with early-stage gastric

Fig. 1 Distribution of fluorescent and non-fluorescent lymph nodes within the five lymph node basins. l-GA, left gastric artery; l-GEA, left gastroepiploic artery; p-GA, posterior gastric artery; r-GEA, right gastroepiploic artery; r-GA, right gastric artery

results and confirm that NIR lymphography with ICG can facilitate effective visualization of draining lymph nodes and allows assessment of the thoroughness of the lymphadenectomy intraoperatively. However, one limitation of the study by Kwon et al.[30] is the enrollment of patients with early-stage disease (35 patients with T1 tumors and 5 patients with T2 tumors) with a low incidence of lymph node metastases (only 5 patients with one metastatic lymph node each). As a consequence, the authors were not able to determine metastatic lymph node–specific sensitivity or specificity of FNs.

In our present study, 23 out of 37 patients were N positive with a total of 150 metastatic lymph nodes retrieved. Our preliminary results seem to indicate that ICG fluorescence in gastric cancer has low diagnostic value for metastatic lymph nodes: in fact, the accuracy, sensitivity, and specificity for this purpose were far less than 90%. Moreover, the number of retrieved metastatic lymph nodes was similar in the two study groups. However, our findings are not surprising in light of previous studies on sentinel lymph node detection in early gastric cancer. The most common cause of a false negative result in sentinel node mapping has been reported to be an obstructed lymphatic vessel by cancer cells or a massive cancerous invasion of the lymph node.[14] In such cases, the administered tracer cannot accumulate into the positive lymph node and migrate into second tier nodes. This is the reason why sentinel node technique is not considered feasible in gastric tumors ≥ T2 that are associated with high risk for metastatic lymph nodes. Therefore, neoplastic permeation of lymphatic vessels and massive infiltration of lymph nodes may explain the poor selectivity of ICG for metastatic lymph nodes in our 23 N-positive patients.

The present study had some limitations. First of all, we used the propensity score matching method to identify the two study groups so as to overcome the limitations due to the non-randomized, retrospective nature of the trial. Secondly, our study includes only a small patient sample and was conducted in a single academic institution, thus enrolling only one experienced surgeon and pathologist. Future large-sized multi-institutional prospective randomized trials are needed to truly determine the clinical impact of intraoperative lymphatic mapping with ICG fluorescence on gastric cancer surgery.

Conclusion

The results of the present study should be interpreted with caution because of its retrospective nature. However, our findings suggest that intraoperative lymphatic mapping with ICG can help the surgeon to identify those lymph nodes left behind by observation with the naked eye and assess the thoroughness of the lymphadenectomy during robotic gastrectomy, thus increasing the number of examined lymph nodes and improving tumor staging. Unfortunately, NIR imaging with ICG failed to show good selectivity for metastatic lymph nodes.

Compliance with Ethical Standards

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