Brief Report

Lymph node mapping with near-infrared fluorescence imaging during robotic surgery for gastric cancer: a pilot study

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Abstract: Lymphadenectomy for gastric cancer is considered to be technically difficult to perform in conventional laparoscopic surgery. The robotic system has been introduced to overcome some of these technical limitations of laparoscopy. The daVinci robotic platform allows near-infrared fluorescence imaging (NIFI) with indocyanine green (ICG) to be integrated into the surgical field. This pilot study aimed at investigating whether the use of NIFI with ICG may improve the intraoperative visualization of lymph nodes and help to identify complete lymph node removal during robotic gastrectomy. Fourteen patients underwent robotic distal gastrectomy with D2 lymph node dissection for gastric cancer. A 0.2% ICG solution was injected into the submucosa endoscopically at four sites around the tumor. Fluorescence imaging with ICG was carried out with a robotic infrared camera system. Fluorescent lymph nodes were both dissected out intraoperatively and isolated in the dissected specimen with the help of the robotic camera. Eight males and 6 females were enrolled in the study. No adverse effects of the ICG were observed. The mean total number of examined lymph node was 43.3 (range, 27–78). The mean number of fluorescent lymph nodes was 19.4 (range, 1–36). Seven patients were found to have metastatic lymph nodes: in 3 patients, all the metastatic lymph nodes were fluorescent, in 3 they were non-fluorescent and in 1 patient they were both fluorescent and non-fluorescent. NIFI is a promising method of lymphatic mapping during robotic gastrectomy and may provide a valuable adjunct for identification of complete D2 lymphadenectomy.

Keywords: Near infrared fluorescence; indocyanine green (ICG); lymph node; robotic gastrectomy; gastric cancer

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Introduction

Laparoscopic surgery has emerged as a valid option for treatment of gastric cancer during the last two decades, especially in the East and for patients with early-stage tumors (1). In the Western world, minimally invasive surgery for gastric cancer has not garnered similar popularity and this is mainly due to the lower incidence of early gastric cancer and the complexity of the laparoscopic procedure (2,3).

Gastrectomy with D2 lymphadenectomy, i.e., lymph node dissection along the great vessels, is considered to be technically demanding to perform in laparoscopy (4-6). Robotic surgery has been introduced to overcome the technical difficulties of traditional laparoscopy: magnified 3D imaging and articulating instruments with a greater range of motion can help the surgeon to perform complex surgical steps during radical gastrectomy, such as an accurate lymph node dissection and intracorporeal anastomoses (7-9). Moreover, the daVinci Si robotic platform (Intuitive

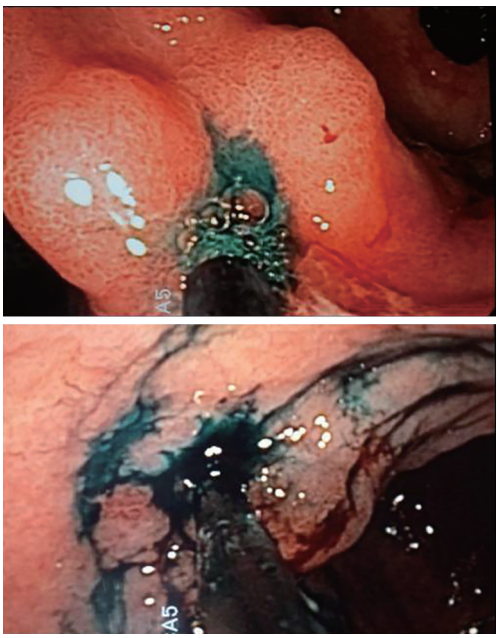

Figure 1 Preoperative submucosal injection of indocyanine green into the four quadrants around the tumor under endoscopic view.

Surgical Inc., Sunnyvale, CA, USA) is equipped with a near-infrared fluorescence imaging (NIFI) system which allows intraoperative imaging with indocyanine green (ICG) (10). This technology has emerged as a promising intraoperative procedure for lymphatic mapping in gynecological (11), urological (12) and esophageal (13) cancers. In early gastric cancer, NIFI has already been used to identify the sentinel lymph node and thus modulate lymphadenectomy during minimally invasive surgery (14,15).

We hypothesized that robot-assisted NIFI with ICG could be developed for intraoperative lymph node visualization during gastric surgery with the specific aim to help the surgeons to perform a complete D2 lymphadenectomy.

Material and methods

Patients

Fourteen patients diagnosed with gastric adenocarcinoma and scheduled to undergo robotic gastrectomy were enrolled between January and October 2016 at the Center of Oncologic Minimally Invasive Surgery (COMIS), University of Florence, Florence, Italy. 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 pre- or intraoperative diagnosis of M1 or T4 lesions (i.e., with distant metastases, local invasion of peritoneum, spleen or pancreas), were excluded from the study. None of the patients had received any preoperative radiotherapy and/or chemotherapy. 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).

Endoscopic and surgical technique

A 0.2% ICG solution was injected into the submucosa layer with 0.5 mL into the four quadrants around the tumor under endoscopic examination as previously described by Tajima *et al.* (14) (*Figure 1*). The dye was injected 1 day before surgery. All patients underwent curative distal gastrectomy with D2 lymph node dissection. The robotic procedures were performed by one surgeon (F.C.) as previously described (16). Intraoperative fluorescence imaging with ICG was carried out with a near-infrared camera system (Firefly Fluorescence Imaging Scope; Intuitive Surgical, Sunnyvale, CA, USA) built into the robotic platform. Lymph nodes which had taken up ICG appeared as green spots emitting clear fluorescence (*Figure 2*) and were defined as the fluorescent nodes (FNs). The FNs were intraoperatively dissected from the surrounding fatty tissue and pulled out through the assistant 12 mm trocar. The lymph nodes removed with the surgical specimens were isolated from the surrounding tissues on the back table and examined to determine, with the help of the robotic camera if they also exhibited fluorescence. Location and fluorescence status were recorded for all the lymph nodes before they were sent for pathological analysis. Particularly, the dissected lymph nodes were grouped into five gastric lymphatic basins along the main arteries as previously described by Kinami *et al.* (17): 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.

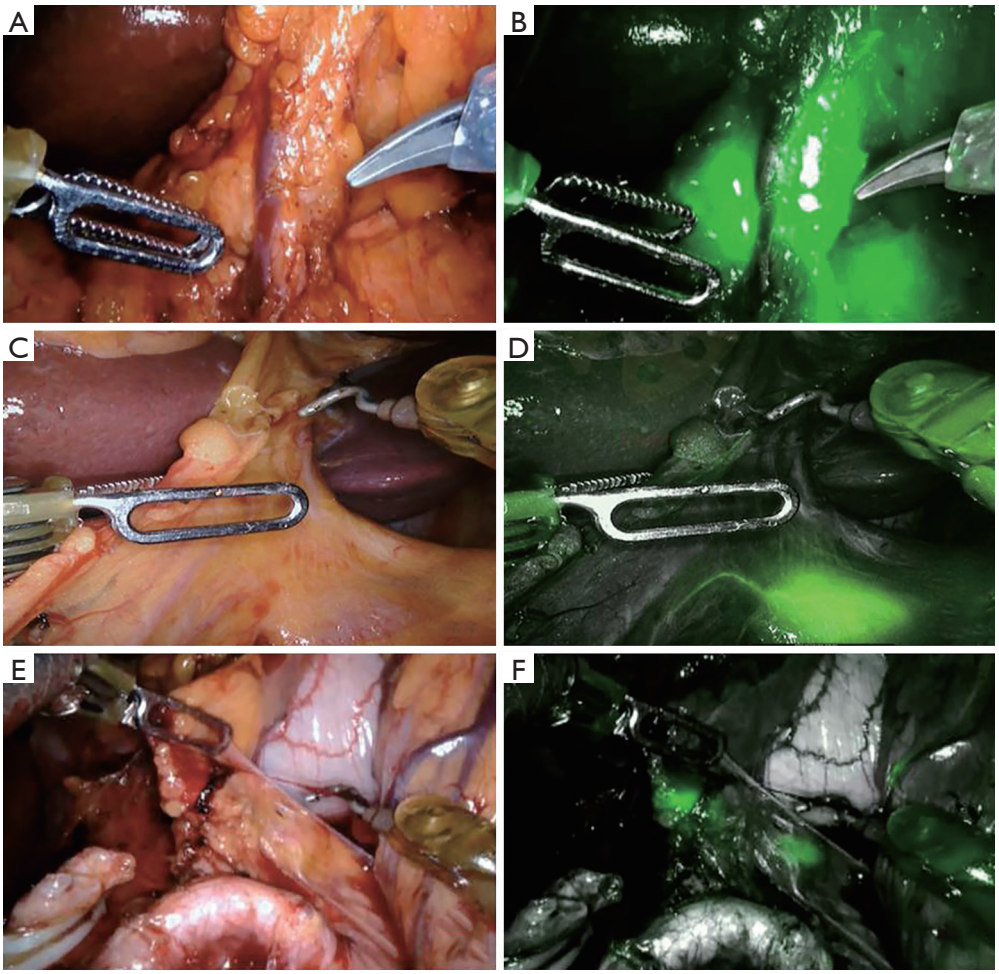

Figure 2 Lymph node dissection during robotic gastrectomy: aspects of station 6 without (A) and with near-infrared fluorescence imaging (B), station 8a without (C) and with near-infrared fluorescence imaging (D) and station 11p without (E) and with near-infrared fluorescence imaging (F).

Pathological analysis

Clinicopathological findings such as tumor location, histotype, tumor differentiation, Lauren classification, depth of invasion, lymph node metastasis and stage distribution were reviewed according to the Japanese gastric carcinoma classification (18). All dissected lymph nodes were examined histologically one slice per node and stained with H&E.

Results

Fourteen patients (8 males and 6 females) were enrolled in the study. Their median age was 76 years (range, 49–81 years) and mean BMI was 25.2 kg/m^2. Patients' clinicopathological characteristics are shown in *Table 1*. There were no patients with complications or adverse events after ICG injection in this pilot study. All patients underwent a robotic distal gastrectomy with standardized D2 lymphadenectomy. *In situ* detection of NIFI at the site of the gastric tumor was achieved in all cases. The mean total number of retrieved and examined lymph nodes was 43.3 (range, 27–78) (*Table 2*). The mean number of FNs was 19.4 (range, 1–36) (*Table 2*). Dye diffusion to lymph nodes was observed in all the patients (*Table 2*). No ICG staining was observed in those lymph nodes (namely station 2, 4sa, 10 and 11 d) for which dissection is not suggested during distal gastrectomy. Patient 11 had only one FN retrieved,

Table 1 Clinicopathological characteristics of patients undergoing robotic distal gastrectomy

Characteristics	Patients (N=14)
Gender (male/female)	8/6
Age (year) [median, range]	76 [49–81]
BMI (kg/m^2) [median, range]	25.2 [23–30]
Tumor location (%)	
Middle third	7 (50.0)
Lower third	7 (50.0)
Lauren classification (%)	
Intestinal	8 (57.2)
Diffuse	1 (7.1)
Mixed	5 (35.7)
Tumor differentiation (%)	
Well differentiated	4 (28.6)
Moderately differentiated	7 (50.0)
Poorly differentiated	3 (21.4)
Tumor size (cm) (mean ± SD)	3.8±2.1
Stage distribution (%)	
I	6 (42.9)
II	5 (35.7)
III	3 (21.4)

and this was most likely due to the pathological finding of massive infiltration of the submucosa (linitis plastic) that might have occluded the lymphatic vessels and prevented ICG diffusion. The histopathological analysis indicated that 7 patients had metastatic lymph nodes: all the metastatic lymph nodes were fluorescent in 3 patients, they were non-fluorescent in 3 and both fluorescent and non-fluorescent in 1 (*Table 2*). The distribution of lymph nodes and their metastatic/fluorescent status within the five lymphatic basins are shown in *Table 3*. It is of interest that in patients n. 1 and 6, the metastatic non-fluorescent lymph nodes were found within the lymphatic basins which were marked by at least one FN (*Table 3*).

Discussion

Adequate lymph node sampling during radical gastrectomy is crucial for proper staging of patients with gastric cancer. In this pilot study, we evaluated the feasibility and safety of a novel application of NIFI with ICG for real-time intraoperative mapping of lymph nodes during robotic surgery for gastric cancer. ICG is a diagnostic reagent that has excitation and fluorescence wave-lengths in the near-infrared range. Nimura *et al.* (19) have reported that lymphatic vessels and lymph nodes containing ICG particle can be easily distinguished from surrounding fatty tissue using 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).

An intraoperative imaging system based on NIFI with ICG has already been proposed for sentinel lymph node mapping in early gastric cancer (14,15,20,21). To our knowledge, this is the third pilot trial designed to visualize intraoperatively the lymphatic pathways draining gastric tumors using NIFI with ICG without the purpose of sentinel lymph node retrieval. Herrera-Almario *et al.* (22) used this technique in 29 patients who had undergone robotic resection for gastric adenocarcinoma: they demonstrated the safety and feasibility of the procedure and stated that it could be a valuable adjunct for overall lymph node retrieval. They found that a mean of 29 lymph nodes were examined and, in all cases, at least 5 lymph nodes were seen along the main nodal compartments. Lan *et al.* (23) 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. Our preliminary study confirmed the feasibility and safety of the procedure and interestingly, we found a higher number of lymph nodes in the surgical specimens than the other two previously published studies, with a mean of 43.3. We hypothesize that this advantage was due to the different method of dye injection. In the study by Herrera-Almario (22), ICG was injected intraoperatively into the subserosa around the tumor in all their 31 patients whereas the same method was adopted in 9 out of the 14 patients investigated by Lan *et al.* (23). It is most likely that, with subserosal injection, the dye did not have enough time to spread into the lymphatic vessels and deposit in 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

Table 2 Characteristics of lymphadenectomy specimens according to fluorescence and metastatic status

Pt n.	TNM	Total examined LNs	Fluorescent LNs (%)	Fluorescent metastatic LNs	Non-fluorescent metastatic LNs
1	T1N2	42	35 (83.3)	0	3
2	T1N0	60	34 (56.6)	0	0
3	T2N1	47	36 (76.5)	1	0
4	T2N0	49	34 (69.3)	0	0
5	T2N0	44	5 (11.3)	0	0
6	T3N1	27	5 (18.5)	0	1
7	T2N0	49	23 (46.9)	0	0
8	T3N3	78	31 (39.7)	7	7
9	T1N0	53	8 (15.0)	0	0
10	T1N0	34	12 (35.2)	0	0
11	T3N3	27	1 (3.7)	0	7
12	T2N2	45	7 (18.4)	5	0
13	T2N2	63	36 (57.1)	4	0
14	T2N0	27	5 (18.5)	0	0
Overall (mean ± ESM)		43.3±3.7	19.4±3.8	1.2±0.6	1.2±0.6

dissection and permits direct visualization of the lesion at the time of surgery. Other important limitations of subserosal injection are the potential intraoperative leakage of ICG with spoiling of the near infrared view and the difficulty to identify tumor location from the outside of the stomach without intraoperative localization of the tumor, especially in the cases of early gastric cancer.

We found that the most important factor in determining the image quality during intraoperative fluorescence imaging is the dosage of ICG injection. In our very first cases, not considered in the present study, we injected 1 mL of 0.2% ICG solution into the four quadrants around the tumor but the patients had a dissemination of the fluorescence signal in the omentum, mesocolon and pancreatic surface. We obtained a better quality of fluorescence imaging by reducing the ICG dosage to 0.5 mL.

Importantly, the mean value of retrieved and examined lymph nodes in the present study was even higher than that we found in a group of patients who were operated on by robotic distal gastrectomy without intraoperative ICG-NIFI (43.3 *vs.* 39.1, respectively) between June 2014 and September 2015 (16).

We also found that metastatic disease was present in FNs in 4 out of our 7 patients classified as N+, whereas metastatic non-fluorescent lymph nodes were found within lymphatic basins with fluorescence signals in 2 other cases. These findings confirmed those reported by Lan *et al.* (23) and suggest that intraoperative lymphatic mapping with ICG fluorescence has the potential to improve the likelihood of an adequate lymphadenectomy by identifying those lymphatic basins that most likely contain metastatic disease.

In conclusion, we recognize that this pilot trial includes only a small patient sample and that future trials are needed to truly determine the impact of intraoperative lymphatic mapping with ICG fluorescence on gastric cancer surgery. However, our preliminary results suggest that this technique is feasible and can help the surgeon to have a real-time visual reference of the lymph nodes during dissection along the main gastric vessels, thus adding a potentially valuable adjunct to perform a complete D2 lymphadenectomy.

Table 3 Distribution of harvested lymph nodes and their metastatic/fluorescence status within the five lymphatic basins

Pt n.	Tumor location	Tumor size (cm)	Left GA		Left GEA		Posterior GA		Right GEA		Right GA	
			Fluorescent	Non	Fluorescent	Non	Fluorescent	Non	Fluorescent	Non	Fluorescent	Non
1	Middle	2	6	2	0	0	9	1	18	1	2	3 (3)
2	Middle	2.5	15	6	0	0	0	0	3	19	16	1
3	Lower	4	18	0	0	1	8	0	7 (1)	2	3	8
4	Lower	4	9	7	0	0	8	0	5	5	12	3
5	Lower	2.5	3	7	0	0	0	5	2	12	0	15
6	Lower	5.5	2	10	0	0	0	2	2	9	1	1 (1)
7	Middle	4	11	10	0	0	2	1	5	4	5	11
8	Lower	8	7	5	0	5	0	8	13 (3)	6 (3)	11 (4)	23 (4)
9	Middle	2	1	24	0	0	0	4	7	6	0	11
10	Lower	5	5	6	0	0	0	0	7	10	0	6
11	Middle	7	0	18 (5)	0	2	0	1 (1)	5	1 (1)	0	0
12	Lower	2.5	0	16	0	0	0	5	5 (4)	8	2 (1)	9
13	Middle	1	12	0	0	0	5 (1)	2	11 (3)	6	8	19
14	Middle	2.5	0	1	0	0	0	0	5	1	0	20

GA, gastric artery; GEA, gastroepiploic artery; ( ) : number of metastatic lymph nodes.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ales.2018.03.13). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee(s) and with the Helsinki Declaration (as revised in 2013). 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).

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