Original Article

Analysis of safety and efficacy of laparoscopic radical gastrectomy combined with or without indocyanine green tracer fluorescence technique in treatment of gastric cancer: a retrospective cohort study

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Background: An adequate resection margin and lymph node dissection are important factors for successful radical gastrectomy. The presence of near-infrared camera imaging with indocyanine green (ICG) gives new insight into radical gastrectomy. Laparoscopic radical gastrectomy with ICG is still in its initial stages and requires more evidence-based medical research. The aim of the present study was to evaluate the safety and availability of lymph node dissection and precise gastrectomy for gastric cancer patients undergoing radical resection under laparoscope with ICG, in the hope of providing evidence of application of ICG tracer fluorescence technique in radical gastrectomy.

Methods: A retrospective cohort study was performed with 56 patients who underwent laparoscopic radical gastrectomy. The patients were categorized into the ICG (n=18) or the non-ICG (n=38) group based on whether preoperative endoscopic mucosal ICG injection was performed. Their clinical characteristics (age, tumor size, location, TNM stage and so on) were compared as baseline data. Perioperative outcomes (blood loss, time of first intestinal exhaust, early or long-term complications and so on) were used to assess safety. The status of lymph node dissection and tumor localization were analyzed to testify efficacy. SPSS version 26.0 was used for the statistical analysis.

Results: There was no difference in clinical data at baseline. From the safety point of view, there was no difference in perioperative outcomes (operative time, blood loss, time of first intestinal exhaust and so on) between the two groups (all P>0.05). From the efficacy point of view, the number of lymph nodes <5 mm (21.84±1.86 *vs.* 16.24±2.10, P<0.001), the total number of lymph nodes (34.61±5.87 *vs.* 29.92±5.27, P=0.004), the number of lymph nodes dissected in perigastric regions (groups 1–7, 22.89±3.64 *vs.* 20.29±3.00, P=0.007), and the number of lymph nodes in extraperigastric regions (groups 8–12, 11.72±3.06 *vs.* 9.61±3.18, P=0.022) were greater in ICG group compared with non-ICG group. In ICG group, the average vertical distances between the top and bottom of the fluorescent edge and neoplastic edge were 2.65±0.58 and 2.67±0.65 cm, respectively. Fluorescent edge pathology was negative.

Conclusions: ICG fluorescence could be conducive to lymph node dissection and precise gastrectomy in laparoscopic radical gastrectomy.

Keywords: Indocyanine green (ICG); radical gastrectomy for gastric cancer; laparoscope; fluorescence imaging

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Introduction

China has the highest incidence of gastric cancer, accounting for over 40% of new cases worldwide (1). Surgical treatment should be the first consideration for the treatment of gastric cancer. Precise tumor location and radical lymph node resection play a crucial role in the staging and final treatment of gastric cancer (2). Laparoscopy has been gradually applied in radical gastrectomy for gastric cancer, and has been shown to be safe and feasible (3). However, due to both tactile and visual influences, it is difficult to determine the most appropriate surgical margin according to the location of the tumor. Lymph nodes in adipose tissue are at risk of potential metastasis, but are difficult to find during surgery. Therefore, research should focus on how to effectively, accurately, and safely remove tumors and lymph nodes.

Indocyanine green (ICG) fluorescence imaging in endoscopic minimally invasive surgery can identify sentinel lymph node (SLN) localization of non-small cell lung cancer and breast cancer (4,5). Compared with other dyes, ICG excitation light has higher tissue penetration, and can more accurately identify tumors and lymph nodes in hypertrophic adipose tissues in laparoscopic fluorescence imaging (6,7). The minimally invasive treatment of gastric cancer patients, guided by ICG fluorescence imaging, has recently attracted much attention. Intraoperative near-infrared fluorescence imaging after preoperative injection of ICG around the tumor provides surgeons with effective visualization of lymphatic anatomy. Initially, this technology was applied to the SLN localization of early gastric cancer. Most current studies have explored the application value of ICG in the SLN localization of early gastric cancer and the evaluation of anastomotic blood supply (8-12). The application of ICG fluorescence laparoscopy in radical gastrectomy is still in the preliminary clinical stages, although there have been single-center, large-sample randomized clinical trials. The study found that ICG could noticeably improve the number of lymph node dissections and reduce lymph node noncompliance without increased complications in D2 lymphadenectomy and had its own limitations including requirement of research support from other centers and lack of exploration of precise gastrectomy (13). Therefore, our research is necessary. The aim of the present study was to analyze the safety and availability of lymph node dissection and precise gastrectomy for gastric cancer patients undergoing radical resection under laparoscope with ICG. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-508/rc).

Methods

Participants

A retrospective cohort study was used in the present study. The inclusion criteria were as follows: (I) patients with pathological tissues taken under endoscope and confirmed as gastric malignant tumor; (II) patients with an American Society of Anesthesiology grade <3 and an Eastern Cooperative Oncology Group score <1; (III) enhanced computed tomography or other examinations did not find tumor metastasis to surrounding adjacent tissues, nor metastasis to distant tissues, such as the thoracic cavity or abdominal cavity, or distant lymph node metastasis/enlargement; (IV) laparoscopic proximal, distal, or total gastrectomy plus D2 lymphatic excision; and (V) patients with complete perioperative clinicopathological outcome data. Exclusion criteria were as follows: (I) history of previous upper abdominal surgical trauma, previous endoscopic mucosal dissection intervention, or a history of rejection to laparoscopic resection; (II) preoperative neoadjuvant therapy; (III) patients with intraoperative distant metastasis and unsuccessful radical gastrectomy for gastric cancer; and (IV) laparotomy or second operation for recurrence of gastric cancer.

Based on the above criteria, 56 patients were enrolled from March 2019 to December 2020 (40 males and 16 females). Patients were divided into the ICG group and non-ICG group (18 cases in the ICG group and 38 cases in the non-ICG group) based on the surgical procedure. Differences in baseline data between the 2 groups were not statistically significant and were comparable, as shown in *Table 1*. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the Second Affiliated Hospital of Harbin Medical University (No. KY2021-225). All patients provided signed informed consent.

Preoperative preparation for ICG

Patients in the ICG group received gastroscopic submucosal injection 1 day before surgery and were informed of the related risks. ICG for 25 mg injection was dissolved in sterilized water for injection at a concentration of 1.25 mg/mL.

Table 1 Comparative analysis of clinical data between the 2 groups

Indicators	Non-ICG	ICG	χ^2 test/*t*-test/Z	P value
Sex, n (%)			0.295	0.587[a]
Male	28 (73.7)	12 (66.7)		
Female	10 (26.3)	6 (33.3)		
ASA, n (%)			0.047	0.829[a]
2	33 (86.8)	16 (88.9)		
3	5 (13.2)	2 (11.1)		
ECOG, n (%)			0.004	0.948[a]
0	25 (65.8)	12 (66.7)		
1	13 (34.2)	6 (33.3)		
Tumor size (cm), n (%)			0.125	0.724[a]
<3	15 (39.5)	8 (44.4)		
≥3	23 (60.5)	10 (55.6)		
cN stage, n (%)			0.924	0.336[a]
0	20 (52.6)	7 (38.9)		
N+	18 (47.4)	11 (61.1)		
pN stage, n (%)			0.151	0.698[a]
0	19 (50.0)	10 (55.6)		
N+	19 (50.0)	8 (44.4)		
Tumor location, n (%)			–0.499	0.618[b]
Upper	4 (10.5)	2 (11.1)		
Middle	4 (10.5)	3 (16.7)		
Lower	30 (78.9)	13 (72.2)		
cT stage, n (%)			–0.186	0.852[b]
1	17 (44.7)	8 (44.4)		
2	4 (10.5)	2 (11.1)		
3	6 (15.8)	4 (22.2)		
4a	11 (28.9)	4 (22.2)		
pT stage, n (%)			–0.177	0.860[b]
1	17 (44.7)	8 (44.4)		
2	6 (15.8)	3 (16.7)		
3	6 (15.8)	4 (22.2)		
4a	9 (23.7)	3 (16.7)		
AJCC stages, n (%)			–0.455	0.649[b]
1	16 (42.1)	9 (50.0)		
2	8 (21.1)	3 (16.7)		
3	14 (36.8)	6 (33.3)		
Tumor differentiation degree, n (%)			–0.159	0.873[b]
Low	14 (36.8)	7 (38.9)		
High	9 (23.7)	4 (22.2)		
Age, years, mean ± SD	60.42±8.09	59.11±5.72	0.617	0.540[c]
BMI, kg/m^2, mean ± SD	22.72±3.08	23.68±3.19	–1.071	0.289[c]

Table 1 *(continued)*

Table 1 *(continued)*

[a], χ^2-test; [b], rank sum test; [c], *t*-test with 2 independent samples. ICG, indocyanine green; ASA, American Society of Anesthesiology; ECOG, Eastern Cooperative Oncology; AJCC, American Joint Committee on Cancer; BMI, body mass index; SD, standard deviation.

After endoscopy, the needle was injected around the lesion to the submucosa, and 0.5 mL ICG mixture was injected at 4 points. After the injection, the mucosal lifting sign (+) was seen, and the mucosal color turned green. Four titanium clips were positioned at the injection sites.

Surgical method

All patients received standard laparoscopic-assisted radical gastrectomy (following the 5th edition of the Japanese Guidelines for Gastric Cancer Treatment) (14). In the ICG group, the intraoperative switching between natural light and green fluorescence mode of fluorescence laparoscopy was determined by the operator. The green-stained edges of the masses were marked with electrocoagulation hooks, and all the developed lymph nodes were dissected intraoperatively. The duodenum was separated from the pyloric ring at the lower 2 fingers, and cut off and closed at the proximal end, 5 cm from the tumor. If the green-stained edge of the ICG group exceeded the established tangent line, the green-stained edge prevailed. The specific procedure of Billroth II + Braun kiss or Roux-en-Y anastomosis was performed at the surgeon's discretion.

Postoperative specimen handling

After the operation, the specimen was fully flattened, and the vertical distance between the fluorescence edge and the tumor edge was measured by specialized personnel to observe whether the fluorescence edge was included in the resection edge. The fluorescence edge and the tumor resection edge were sent for examination. In strict accordance with the 5th edition of the Japanese Guidelines for the Treatment of Gastric Cancer (14), the removed lymph nodes were sorted, lymph node size was measured, and the lymph nodes were classified and marked according to groups and stations, and submitted for examination.

Observation outcome index

Intraoperative and postoperative indicators

Intraoperative and postoperative indicators included the resection scope of gastric malignant tumors (distal or total gastrectomy was determined according to tumor size and location), gastrointestinal reconstruction method (Billroth II + Braun anastomosis or Roux-en-Y anastomosis), operation duration, patient blood loss, time of first intestinal exhaust, time of first intake of water, length of postoperative hospital stay, early postoperative and long-term complications. Early postoperative complications were defined as various complications during hospitalization, mainly caused by intraoperative related operations, containing hemorrhage caused by incomplete intraoperative vascular ligation, leakage of digestive fluid at the reconstruction site or stump, poor emptying of food and digestive fluid, and pulmonary diseases. Postoperative long-term complications were surgically related symptoms after discharge without discomfort, including gastroesophageal reflux, bile reflux, anemia, malnutrition, diarrhea.

Related indicators of resected specimens

Related indicators of resected specimens included the total number of lymph nodes removed, pathologically positive number, lymph nodes <5 mm, lymph nodes >5 mm, and the vertical distance between fluorescence edge and tumor edge. Considering the small sample size, specific differences in lymph nodes of each group could not be fully explored, so lymph nodes dissected were divided into groups 1–7 for perigastric regions and groups 8–12 for extraperigastric regions (relatively complex intraoperative anatomical areas) to compare.

Follow up

Patients were followed up 6 months after surgery to determine the long-term complications according to the above and provide treatment accordingly. We followed up weekly by telephone. Considering the small sample size, we compared the complications as a whole rather than individually.

Statistical analysis

Data were statistically analyzed using SPSS 26.0 (IBM, Armonk, NY, USA). Shapiro-Wilk test method was used to test the normality of continuous variables. *T*-test was used to compare the differences of normal distribution indicators, rank sum test (non-parameter method) was used to compare the differences of non-normal distribution indicators, and P values were taken as two-sided. Two independent samples were checked by *t*-test to compare differences in measurement data between the non-ICG group and ICG group. Rank sum test was used to compare and analyze differences in rank variables between the non-ICG group and ICG group; χ^2-test was used to compare differences in classification variables between the 2 groups. P<0.05 was considered statistically significant.

Results

Comparison and analysis of operative and postoperative indexes

There were no significant differences in surgical method, gastrointestinal anastomosis, operation duration, intraoperative blood loss, time of first intestinal exhaust, time of first intake of water, and postoperative hospital stay between the non-ICG group and the ICG group (all P>0.05) (*Table 2*). One patient in the non-ICG group developed abdominal hematoma (a recent complication) 6 days after surgery and underwent a second operation to remove the hematoma and staunch the blood. No other patient developed early- or long-term clinically relevant problems.

Comparative analysis of differences in lymphatic dissection

The number of lymph nodes <5 mm in the ICG group (21.84±1.86) was greater than that in the non-ICG group (16.24±2.10, P<0.001). More lymph nodes were removed in the ICG group (34.61±5.87) than in the non-ICG group (29.92±5.27, P=0.004). The number of lymph nodes in the ICG group (22.89±3.64) was greater than that in the non-ICG group (20.29±3.00, P=0.007). More lymph nodes were removed in the ICG group (11.72±3.06) than in the non-ICG group (9.61±3.18, P=0.022). There was no statistical

Table 2 Comparison and analysis of operative and postoperative indicators

Indicators	Non-ICG	ICG	χ^2 test/*t*-test/Z	P value
Surgical method, n (%)			0.149	0.700[a]
TG	15 (39.5)	6 (33.3)		
DG	23 (60.5)	12 (66.7)		
Reconstruction, n (%)			0.196	0.658[a]
Billroth II + Braun	15 (39.5)	6 (33.3)		
Roux-en-Y	23 (60.5)	12 (66.7)		
Exhaust (days), M (P_{25}, P_{75})	2.00 (2.00, 3.00)	2.50 (2.00, 3.00)	–0.985	0.324[b]
First oral intake (days), M (P_{25}, P_{75})	5.00 (5.00, 6.00)	5.00 (5.00, 6.00)	–0.049	0.961[b]
Length of postoperative hospital stay (days), M (P_{25}, P_{75})	8.00 (7.00, 12.00)	8.00 (7.00, 10.25)	–0.374	0.709[b]
Operative time (min), mean ± SD	288.16±40.99	290.83±30.69	–0.246	0.807[c]
Intraoperative bleeding (mL), mean ± SD	116.05±33.73	117.22±38.36	–0.116	0.908[c]

[a], χ^2-test; [b], rank sum test; [c], *t*-test with 2 independent samples. ICG, indocyanine green; TG, total gastrectomy; DG, distal gastrectomy; SD, standard deviation.

difference in pathologically positive lymph nodes between the 2 groups (P>0.05) (*Table 3*). Pathologically positive lymph nodes accounted for 9.3% of the total number of lymph nodes in the ICG group and 9.1% in the non-ICG group.

Vertical distance between fluorescence edge and mass edge

The vertical distance between the fluorescence edge and upper and lower mass edges in the ICG group was 2.65±0.58 and 2.67±0.65 cm, respectively. In addition, the intraoperative fluorescence edge was found to include the edge of the tumor and was smaller than the resection edge of the tumor. The postoperative fluorescence edge and resection edge were pathologically negative.

Comparative analysis of differences in lymphatic dissection

There were statistically significant differences in the number of lymph nodes <5 cm, the total number of lymph nodes, and the number of lymph nodes in groups 1–7 and 8–12 between the non-ICG group and the ICG group. The number of lymph nodes <5 mm (P<0.001), the number of total lymph nodes (P<0.01), the number of lymph nodes in groups 1–7 (P<0.01), and the number of lymph nodes in groups 8–12 (P<0.05) in the ICG group were higher than those of the non-ICG group. Differences are shown in *Figures 1-4*.

Discussion

In the present study, all 56 patients underwent gastric cancer resection with minimally invasive surgery. Of these, 18 patients underwent surgery guided by ICG near-infrared imaging. Postoperative results showed that tumors in all resected specimens were located in the central part, according to fluorescence green staining, and none of the tumor edges exceeded the fluorescence edge. The vertical distance between the tumor edge and fluorescence edge was 2.65±0.58 and 2.67±0.65 cm, respectively. No positive results were found in fluorescence edge pathology. The actual resection range of the ICG group was consistent with that of the non-ICG group, and the fluorescence green-stained edges were all within the resection edges. These findings indicate that ICG can accurately locate the tumor in radical gastrectomy. Patients in the ICG group and non-ICG group were treated with gastric malignant tumor resection and D2 lymph node dissection. ICG fluorescence laparoscopy was conducive to increasing the number of lymph node dissected. For lymph nodes <5 mm, ICG fluorescence imaging also has significant advantages. However, lymph nodes >5 mm showed no significant difference between the 2 groups. The comparison of lymph nodes in groups 1–7 and 8–12 during the operation showed that the ICG group also had obvious advantages, with more lymph nodes in both groups. There were no significant differences in pathologically positive lymph nodes. There

Table 3 Comparison and analysis of differences in lymphatic dissection

Indicators	Non-ICG	ICG	*t*-test	P value
Diameter <5 mm, mean ± SD	16.24±2.10	21.84±1.86	−9.842	<0.001
Diameter ≥5 mm, mean ± SD	13.68±3.37	12.67±4.21	0.972	0.335
Total lymph nodes, mean ± SD	29.92±5.27	34.61±5.87	−2.997	0.004
Lymph nodes (+), mean ± SD	2.71±4.27	3.22±6.28	−0.340	0.735
Groups 1–7 lymph nodes, mean ± SD	20.29±3.00	22.89±3.64	−2.822	0.007
Groups 1–7 lymph nodes (+), mean ± SD	1.58±2.74	1.61±2.79	−0.041	0.968
Groups 8–12 lymph nodes, mean ± SD	9.61±3.18	11.72±3.06	−2.356	0.022
Groups 8–12 lymph nodes (+), mean ± SD	1.19±2.18	1.61±3.58	−0.531	0.598

(+), pathologically positive lymph nodes. ICG, indocyanine green; SD, standard deviation.

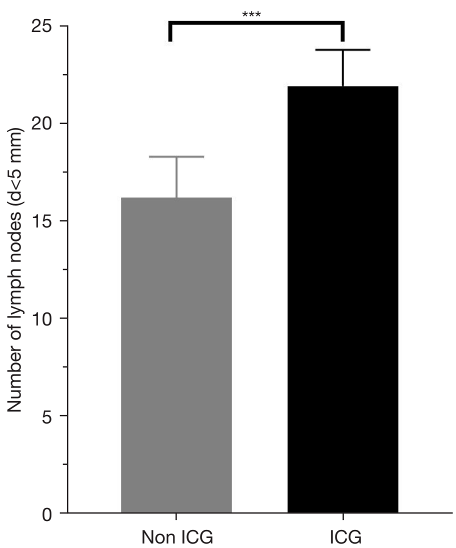

Figure 1 Comparison of the number of lymph nodes <5 mm. ***, P<0.001. ICG, indocyanine green.

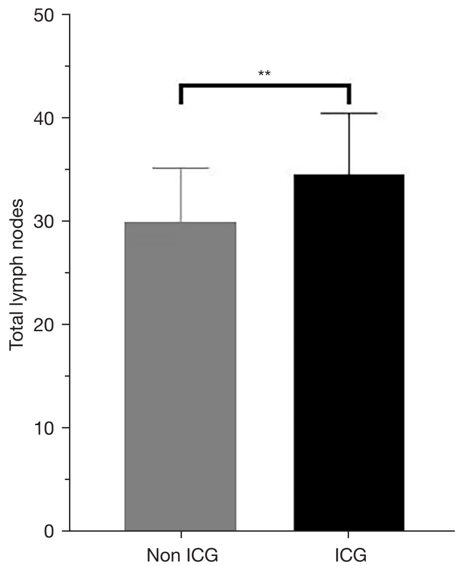

Figure 2 Comparison of total number of lymph nodes. **, P<0.01. ICG, indocyanine green.

were no significant differences in clinical baseline data and intraoperative and postoperative clinical indicators between the 2 groups, confirming that ICG fluorescence-based laparoscopic radical gastrectomy is safe and feasible.

Surgery is the primary treatment option for stomach cancer. However, there are 2 main challenges in the complete resection of gastric cancer. First, the accurate localization of the tumor, and second, the discovery of more lymph nodes during surgery (15). In early open surgery, the location of the tumor was dependent on visual observation or tactile detection. With the continuous development of endoscopic surgery, the safety and effectiveness of minimally invasive treatment for gastric cancer has been recognized, but it has also resulted in more challenges to radical gastrectomy surgery for gastric cancer. Early-stage tumors were not found to invade the serosal membrane, which reduced visualization during laparoscopy. The accurate localization of tumor margins is an important issue that warrants further research. Intraoperative gastroscopy can determine the location of the tumor in real time, but this method inevitably increases the operation time and anesthesia time, and usually requires the cooperation of the internal gastroenterologist (16). Preoperative placement of a metal clip at the edge of the tumor through a digestive

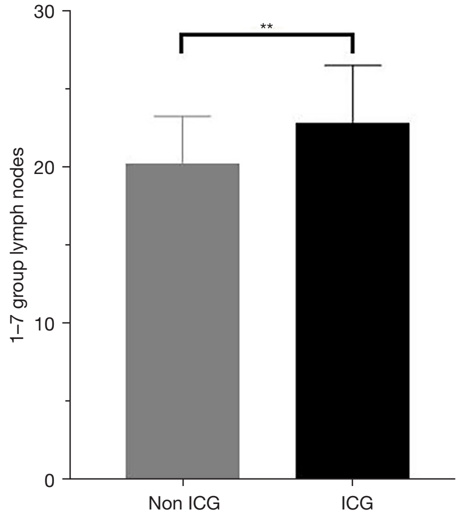

Figure 3 Comparison of total number of lymph nodes in groups 1–7. **, P<0.01. ICG, indocyanine green.

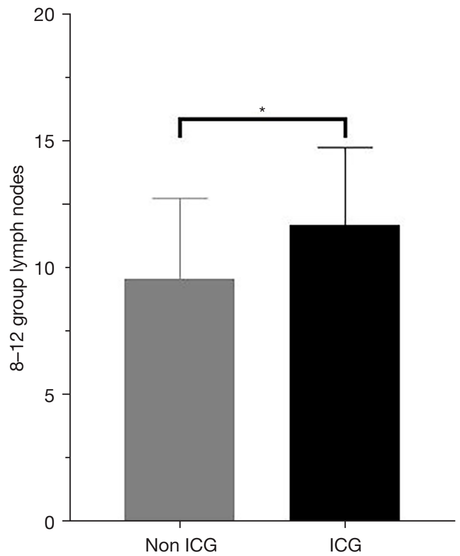

Figure 4 Comparison of total number of lymph nodes in groups 8–12. *, P<0.05. ICG, indocyanine green.

endoscope will result in the metal clip coming off. In clinical application, we found that the use of carbon nanoparticles for preoperative labeling has the risk of puncturing the surgical field contaminated by the serosal membrane, which is the same as the use of Indian ink for intraoperative staining, as has been reported in a previously published study (17). ICG fluorescence laparoscopy has been applied in gastrointestinal surgery in recent years. Several studies have found that, in gastric cancer surgery, preoperative smaller doses of ICG injection in the submucosa around the tumor are conducive to clear imaging of tumor location intraoperatively, and indicate that ICG fluorescence laparoscope could be used to determine the accurate position of intraoperative tumors (18-20). These studies support the findings of the present study. Another advantage of ICG fluorescence imaging is that, even if preoperative labeling fails, there will not be contamination of the surgical field, and the white light mode of fluorescence laparoscopy can also provide an routine operation. For patients with incomplete or excessive staining, we successfully performed conventional laparoscopic radical gastrectomy for gastric cancer, and included these patients in the non-ICG group.

Lymphatic metastasis is the main route of gastric malignant tumor metastasis. Similarly, pathologically positive lymphatic metastasis is one of the main evaluation indexes for the life span of patients with gastric malignant tumors (21). The American Joint Committee on Cancer proposed that radical gastrectomy for gastric cancer requires resection of >15 lymph nodes for accurate postoperative staging (22). Relevant studies have shown that the number of lymph nodes removed during gastric malignant tumor resection can, to a large extent, accurately determine disease progression and influence the choice of successive medication (23-26). Therefore, in radical gastrectomy for gastric cancer, adequate lymph node dissection is necessary. However, due to the complex gastric perivascular lymphatic anatomy, minimally invasive treatment itself is difficult, especially in patients with a high body mass index, as small lymph nodes are hidden in the hypertrophic adipose tissue, and thorough lymph node dissection is a challenge. The application of ICG near-infrared imaging can provide the surgeon with a clearer lymphatic network, which is helpful during surgery. In the present study, the team doctor from gastrointestinal surgery found that ICG fluorescence imaging was conducive to faster and more accurate dissection of lymph nodes, but found that, there was no obvious difference in operation time with near-infrared imaging, which was in contrast with the findings of Ushimaru *et al.* (27). Patients in the ICG group experienced more lymph nodes excisions, which led to relative prolongation of operation time. In their experimental study, Liu *et al.* found that ICG fluorescence labeling could significantly increase the number of lymph node resections and the number of lymph node resection in groups 8–12 in radical gastrectomy of gastric cancer (19). This was confirmed in the studies of Pang *et al.*, Zhong *et al.*, and Tu *et al.* (28-30). In the present study, near-infrared imaging was also found to be helpful to increase the number of lymph node resections in groups 1–7, which was supported by Chen *et al.*'s findings in their prospective randomized controlled study (13). The main reason is that, after routine lymph node resection, the missing lymph nodes that have not been removed can often be found in fluorescence mode. However, in our study, near-infrared imaging was not found to be more helpful for lymph node dissection in groups 8–12 compared with groups 1–7. This finding was not consistent with the surgical experience of our surgeons from gastrointestinal surgery, in which near-infrared imaging was conducive to lymph node removal in complex anatomical areas in actual surgeries. These results could be related to the fact that there were few samples included in our study and differences between groups were not fully explored. We also found that large lymph nodes with potential metastasis (empirically judged) were not green at the time of resection, and such lymph nodes were more likely to be pathologically positive. According to our analysis, this could be more likely to be caused by emboli blocking lymphatic vessels and obstructing lymphatic drainage. A study has found that ICG fluorescence imaging has obvious advantages in lymph node dissection <5 mm, which could be due to the fact that small lymph nodes are more likely to be hidden in fat tissue and are difficult to identify by conventional laparoscopy; lymph node dissection solely based on surgical experience is likely to result in small lymph nodes being missed (19). Previously published studies, as well as the present study, failed to find evidence to confirm the high selectivity of ICG fluorescence imaging in pathologically positive lymph nodes during radical gastrectomy (29,31). In the present study, the positive lymph node rate was 9.3% in the ICG group and 9.1% in the non-ICG group. The difference was not significant, but it further confirmed that ICG could increase the number of lymph nodes detected, and also detect more metastatic lymph nodes (29,32,33). The low selectivity could be related to the non-specific binding fluorescence dyes of ICG and the complexity of gastric lymphatic drainage, which also provides a direction for the further development of ICG fluorescence laparoscopy.

To achieve satisfactory intraoperative fluorescence imaging of tumors, a number of issues need to be resolved. First, we need to design biologic dyes with non-easy degradation and stability in vivo. Second, we need to ensure that the biologic dye has good biocompatibility and specific tumor-targeting effects. Third, the fluorescent dye injection method should be considered based on the complexity of the stomach lymphatic drainage. It has been noted that nanocarriers, such as liposomes and polymer micelles, have been widely used in drug-delivery carriers. Lipid micelles have the advantages of biocompatibility, stability, and non-toxicity. The tripeptide sequence [arginine-glycine-aspartate [(RGD)] ligand can specifically bind with αvβ3 integrin, which can be specifically expressed in malignant gastric tumor cells (34). Modified by RGD and encapsulating ICG, micelle has a specific targeting effect and significant biocompatibility for gastric tumor-bearing mice, which provides a further research strategy for complete resection of gastric cancer (35). In their study, Shao *et al.* provided a biocompatible theranostic nanoparticle with enhanced tumor-targeting ability for accurate near-infrared imaging in gastric cancer (36). Cai *et al.* used the carbon nanozonal tracer method in radical gastrectomy for gastric cancer, and found that, compared with the traditional tracer method, the former method had a longer staining time and higher lymph node black staining rate (37). Chen *et al.*, however, found that ICG administered by subserosal injection was comparable with ICG administered by submucosal injection for lymph node tracing in gastric cancer (38). This could provide further support for the application of ICG injection.

This clinical study has some limitations, including the low number of participants and non-prospective randomization. The number of lymph nodes dissected in each group could not be compared individually, but could only be divided into groups 1–7 and 8–12 for a wide range of comparisons.

In conclusion, although ICG fluorescence imaging technology cannot be solely relied on for the radical treatment of gastric cancer, ICG fluorescence laparoscopy can accurately locate the tumor, easily identify small lymph nodes, and effectively improve the number of lymph nodes dissected, which has important significance for the prognosis of gastric cancer and is worthy of further study and discussion.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-508/rc

Data Sharing Statement: Available at https://jgo.amegroups.

com/article/view/10.21037/jgo-22-508/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-508/coif). 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics board of the Second Affiliated Hospital of Harbin Medical University (No. KY2021-225). All patients provided signed informed consent.

References

1. Feng RM, Zong YN, Cao SM, et al. Current cancer situation in China: good or bad news from the 2018 Global Cancer Statistics? Cancer Commun (Lond) 2019;39:22.
2. Gao K, Wu J. National trend of gastric cancer mortality in China (2003-2015): a population-based study. Cancer Commun (Lond) 2019;39:24.
3. Hu Y, Huang C, Sun Y, et al. Morbidity and Mortality of Laparoscopic Versus Open D2 Distal Gastrectomy for Advanced Gastric Cancer: A Randomized Controlled Trial. J Clin Oncol 2016;34:1350-7.
4. Yamashita S, Tokuishi K, Anami K, et al. Video-assisted thoracoscopic indocyanine green fluorescence imaging system shows sentinel lymph nodes in non-small-cell lung cancer. J Thorac Cardiovasc Surg 2011;141:141-4.
5. Valente SA, Al-Hilli Z, Radford DM, et al. Near Infrared Fluorescent Lymph Node Mapping with Indocyanine Green in Breast Cancer Patients: A Prospective Trial. J Am Coll Surg 2019;228:672-8.
6. Jeremiasse B, van den Bosch CH, Wijnen MWHA, et al. Systematic review and meta-analysis concerning near-infrared imaging with fluorescent agents to identify the sentinel lymph node in oncology patients. Eur J Surg Oncol 2020;46:2011-22.
7. Yin R, Ding LY, Wei QZ, et al. Comparisons of ICG-fluorescence with conventional tracers in sentinel lymph node biopsy for patients with early-stage breast cancer: A meta-analysis. Oncol Lett 2021;21:114.
8. Miyashiro I, Kishi K, Yano M, et al. Laparoscopic detection of sentinel node in gastric cancer surgery by indocyanine green fluorescence imaging. Surg Endosc 2011;25:1672-6.
9. Takeuchi H, Kitagawa Y. New sentinel node mapping technologies for early gastric cancer. Ann Surg Oncol 2013;20:522-32.
10. He M, Jiang Z, Wang C, et al. Diagnostic value of near-infrared or fluorescent indocyanine green guided sentinel lymph node mapping in gastric cancer: A systematic review and meta-analysis. J Surg Oncol 2018;118:1243-56.
11. Huh YJ, Lee HJ, Kim TH, et al. Efficacy of Assessing Intraoperative Bowel Perfusion with Near-Infrared Camera in Laparoscopic Gastric Cancer Surgery. J Laparoendosc Adv Surg Tech A 2019;29:476-83.
12. Huang Y, Pan M, Chen B. A Systematic Review and Meta-Analysis of Sentinel Lymph Node Biopsy in Gastric Cancer, an Optimization of Imaging Protocol for Tracer Mapping. World J Surg 2021;45:1126-34.
13. Chen QY, Xie JW, Zhong Q, et al. Safety and Efficacy of Indocyanine Green Tracer-Guided Lymph Node Dissection During Laparoscopic Radical Gastrectomy in Patients With Gastric Cancer: A Randomized Clinical Trial. JAMA Surg 2020;155:300-11.
14. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2018 (5th edition). Gastric Cancer 2021;24:1-21.
15. Wang FH, Zhang XT, Li YF, et al. The Chinese Society of Clinical Oncology (CSCO): Clinical guidelines for the diagnosis and treatment of gastric cancer, 2021. Cancer Commun (Lond) 2021;41:747-95.
16. Kawakatsu S, Ohashi M, Hiki N, et al. Use of endoscopy to determine the resection margin during laparoscopic gastrectomy for cancer. Br J Surg 2017;104:1829-36.
17. Singh S, Arif A, Fox C, et al. Complication after pre-operative India ink tattooing in a colonic lesion. Dig Surg 2006;23:303.
18. Tanaka C, Kanda M, Funasaka K, et al. Detection of indocyanine green fluorescence to determine tumor location during laparoscopic gastrectomy for gastric

cancer: Results of a prospective study. Asian J Endosc Surg 2020;13:160-7.
19. Liu M, Xing J, Xu K, et al. Application of Near-Infrared Fluorescence Imaging with Indocyanine Green in Totally Laparoscopic Distal Gastrectomy. J Gastric Cancer 2020;20:290-9.
20. Yoon BW, Lee WY. The oncologic safety and accuracy of indocyanine green fluorescent dye marking in securing the proximal resection margin during totally laparoscopic distal gastrectomy for gastric cancer: a retrospective comparative study. World J Surg Oncol 2022;20:26.
21. Jin C, Jiang Y, Yu H, et al. Deep learning analysis of the primary tumour and the prediction of lymph node metastases in gastric cancer. Br J Surg 2021;108:542-9.
22. Amin MB, Greene FL, Edge SB, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin 2017;67:93-9.
23. Smith DD, Schwarz RR, Schwarz RE. Impact of total lymph node count on staging and survival after gastrectomy for gastric cancer: data from a large US-population database. J Clin Oncol 2005;23:7114-24.
24. Desiderio J, Sagnotta A, Terrenato I, et al. Long-term survival of patients with stage II and III gastric cancer who underwent gastrectomy with inadequate nodal assessment. World J Gastrointest Surg 2021;13:1463-83.
25. Hu Q, Pan S, Guo Z. A novel pN3 gastric cancer staging system with superior prognostic utility based upon the examination of over 31 lymph nodes: a propensity score-matching analysis. BMC Gastroenterol 2021;21:352.
26. Shannon AB, Straker RJ 3rd, Keele L, et al. Lymph Node Evaluation after Neoadjuvant Chemotherapy for Patients with Gastric Cancer. Ann Surg Oncol 2022;29:1242-53.
27. Ushimaru Y, Omori T, Fujiwara Y, et al. The Feasibility and Safety of Preoperative Fluorescence Marking with Indocyanine Green (ICG) in Laparoscopic Gastrectomy for Gastric Cancer. J Gastrointest Surg 2019;23:468-76.
28. Pang HY, Liang XW, Chen XL, et al. Assessment of indocyanine green fluorescence lymphography on lymphadenectomy during minimally invasive gastric cancer surgery: a systematic review and meta-analysis. Surg Endosc 2022;36:1726-38.
29. Zhong Q, Chen QY, Huang XB, et al. Clinical implications of Indocyanine Green Fluorescence Imaging-Guided laparoscopic lymphadenectomy for patients with gastric cancer: A cohort study from two randomized, controlled trials using individual patient data. Int J Surg 2021;94:106120.
30. Tu RH, Lin JX, Zhang LP, Zheng CH, et al. Application value of indocyanine green fluorescence imaging in lymphadenectomy of laparoscopic radical gastrectomy for gastric cancer. Zhonghua Xiao Hua Wai Ke Za Zhi 2019;18:466-71.
31. Park JH, Berlth F, Wang C, et al. Mapping of the perigastric lymphatic network using indocyanine green fluorescence imaging and tissue marking dye in clinically advanced gastric cancer. Eur J Surg Oncol 2022;48:411-7.
32. Lee S, Song JH, Choi S, et al. Fluorescent lymphography during minimally invasive total gastrectomy for gastric cancer: an effective technique for splenic hilar lymph node dissection. Surg Endosc 2022;36:2914-24.
33. Jung MK, Cho M, Roh CK, et al. Assessment of diagnostic value of fluorescent lymphography-guided lymphadenectomy for gastric cancer. Gastric Cancer 2021;24:515-25.
34. Böger C, Warneke VS, Behrens HM, et al. Integrins αvβ3 and αvβ5 as prognostic, diagnostic, and therapeutic targets in gastric cancer. Gastric Cancer 2015;18:784-95.
35. Shao J, Zheng X, Feng L, et al. Targeting Fluorescence Imaging of RGD-Modified Indocyanine Green Micelles on Gastric Cancer. Front Bioeng Biotechnol 2020;8:575365.
36. Shao J, Liang R, Ding D, et al. A Smart Multifunctional Nanoparticle for Enhanced Near-Infrared Image-Guided Photothermal Therapy Against Gastric Cancer. Int J Nanomedicine 2021;16:2897-915.
37. Cai YQ, Liang YX, Yu SY, et al. Clinical value of carbon nanoparticles tracer in gastric cancer surgery to increase the number of lymph nodes retrieval. Zhonghua Wei Chang Wai Ke Za Zhi 2020;23:984-9.
38. Chen QY, Zhong Q, Li P, et al. Comparison of submucosal and subserosal approaches toward optimized indocyanine green tracer-guided laparoscopic lymphadenectomy for patients with gastric cancer (FUGES-019): a randomized controlled trial. BMC Med 2021;19:276.

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