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Safety and Efficacy of Indocyanine Green Tracer-Guided Lymph Node Dissection During Laparoscopic Radical Gastrectomy in Patients With Gastric Cancer
A Randomized Clinical Trial

Qi-Yue Chen, MD; Jian-Wei Xie, PhD; Qing Zhong, MD; Jia-Bin Wang, PhD; Jian-Xian Lin, PhD; Jun Lu, PhD; Long-Long Cao, MD; Mi Lin, MD; Ru-Hong Tu, MD; Ze-Ning Huang, MD; Ju-Li Lin, MD; Hua-Long Zheng, MD; Ping Li, PhD; Chao-Hui Zheng, PhD; Chang-Ming Huang, MD

IMPORTANCE The application of indocyanine green (ICG) imaging in laparoscopic radical gastrectomy is in the preliminary stages of clinical practice, and its safety and efficacy remain controversial.

OBJECTIVE To investigate the safety and efficacy of ICG near-infrared tracer-guided imaging during laparoscopic D2 lymphadenectomy in patients with gastric cancer.

DESIGN, SETTING, AND PARTICIPANTS Patients with potentially resectable gastric adenocarcinoma (clinical tumor stage cT1-cT4a, N0/+, M0) were enrolled in a prospective randomized clinical trial at a tertiary referral teaching hospital between November 2018 and July 2019. Patients were randomly assigned to the ICG group or the non-ICG group. The number of retrieved lymph nodes, rate of lymph node noncompliance, and postoperative recovery data were compared between the groups in a modified intention-to-treat analysis. Statistical analysis was performed from August to September 2019.

INTERVENTIONS The ICG group underwent laparoscopic gastrectomy using near-infrared imaging after receiving an endoscopic peritumoral injection of ICG to the submucosa 1 day before surgery.

MAIN OUTCOMES AND MEASURES Total number of retrieved lymph nodes.

RESULTS Of 266 participants randomized, 133 underwent ICG tracer-guided laparoscopic gastrectomy, and 133 underwent conventional laparoscopic gastrectomy. After postsurgical exclusions, 258 patients were included in the modified intention-to-treat analysis, which comprised 129 patients (86 men and 43 women; mean [SD] age, 57.8 [10.7] years) in the ICG group and 129 patients (87 men and 42 women; mean [SD] age, 60.1 [9.1] years) in the non-ICG group. The mean number of lymph nodes retrieved in the ICG group was significantly more than the mean number retrieved in the non-ICG group (mean [SD], 50.5 [15.9] lymph nodes vs 42.0 [10.3] lymph nodes, respectively; $P < .001$). Significantly more perigastric and extraperigastric lymph nodes were retrieved in the ICG group than in the non-ICG group. In addition, the mean total number of lymph nodes retrieved in the ICG group within the scope of D2 lymphadenectomy was also significantly greater than the mean number retrieved in the non-ICG group (mean [SD], 49.6 [15.0] lymph nodes vs 41.7 [10.2] lymph nodes, respectively; $P < .001$). The lymph node noncompliance rate of the ICG group (41 of 129 patients [31.8%]) was lower than that of the non-ICG group (74 of 129 patients [57.4%]; $P < .001$). The postoperative recovery process was comparable, and no significant difference was found between the ICG and non-ICG groups in the incidence (20 of 129 patients [15.5%] vs 21 of 129 [16.3%], respectively; $P = .86$) or severity of complications within 30 days after surgery.

CONCLUSIONS AND RELEVANCE Indocyanine green can noticeably improve the number of lymph node dissections and reduce lymph node noncompliance without increased complications in patients undergoing D2 lymphadenectomy. Indocyanine green fluorescence imaging can be performed for routine lymphatic mapping during laparoscopic gastrectomy, especially total gastrectomy.

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Video and Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Authors: Chao-hui Zheng, PhD (wwkzch@163.com), and Chang-Ming Huang, MD (hcmlr2002@163.com), Department of Gastric Surgery, Fujian Medical University Union Hospital, No. 29 Xinquan Rd, Fuzhou 350001, Fujian Province, China.

Radical lymphadenectomy can significantly improve the long-term survival and accuracy of the tumor staging of patients with gastric cancer.[1-6] The retrieval of more lymph nodes has gradually become the current requirement among surgeons.[5,7,8]

Since Kitano et al[9] reported the use of laparoscopic distal gastrectomy for patients with gastric cancer in 1994, laparoscopic radical gastrectomy has been widely used in clinical practice.[10-12] Today, lymphadenectomy is often performed without the aid of visual instruments according to the surgeon's experience. However, owing to the complex vascular anatomy of and lymphatic drainage around the stomach, it remains a substantial challenge for surgeons, especially newly trained surgeons, to dissect enough lymph nodes efficiently and accurately without increasing surgery-related complications. With the advent of minimally invasive surgery, surgeons continue to explore how to conveniently and accurately perform real-time lymph node navigation using laparoscopic guidance to conduct systematic and sufficient lymph node dissection.

As a new surgical navigation technique, indocyanine green (ICG) near-infrared (NIR) fluorescent imaging has achieved satisfactory results in the localization of sentinel lymph nodes in patients with breast cancer, non-small cell lung cancer, and other cancers.[13-16] With the successful application of ICG fluorescence imaging technology in laparoscopic devices, NIR imaging has enabled better tissue penetration and can more accurately identify lymph nodes in hypertrophic adipose tissues than other dyes in visible light.[17,18] Indocyanine green fluorescence imaging-guided minimally invasive treatment in patients with gastric cancer has become the new direction for exploration.[19]

At present, the application of ICG in laparoscopic lymphadenectomy for patients with gastric cancer is in the preliminary stages. Most of the studies conducted were small-sample retrospective studies that evaluated sentinel lymph nodes[20,21] and anastomotic blood flow.[22] Studies within the past decade have reported different results regarding whether the use of ICG can assist surgeons in performing safe and effective lymphadenectomy.[23-25] Kwon et al[26] conducted only a prospective single-arm study that analyzed 40 patients who underwent robotic gastrectomy after peritumoral injection of ICG.

Therefore, there remains a lack of high-level evidence-based large-sample randomized clinical trials to evaluate the safety, efficacy, and feasibility of ICG-guided laparoscopic D2 lymphadenectomy in patients with gastric cancer worldwide. This clinical trial aimed to assess the efficacy of lymph node harvest and perioperative safety during laparoscopic ICG-guided radical gastrectomy for patients with gastric cancer. It also aimed to promote the standardization of NIR imaging in the laparoscopic resection of gastric cancer and to establish a reference for the application of ICG imaging in the radical resection of digestive tract cancer.

Key Points

Question Can indocyanine green tracer-guided lymph node dissection during laparoscopic radical gastrectomy in patients with gastric cancer efficiently harvest more lymph nodes than conventional lymph node dissection?

Findings In this randomized clinical trial of 266 patients with gastric adenocarcinoma, more retrieved lymph nodes and lower lymph node noncompliance were observed in patients in the indocyanine green group compared with those in the non–indocyanine green group, with a comparable recovery process.

Meaning Indocyanine green can help surgeons harvest more lymph nodes than conventional lymph node dissection and reduce lymph node noncompliance in patients with gastric cancer who undergo D2 lymphadenectomy, and indocyanine green fluorescence imaging can be used for routine lymphatic mapping during laparoscopic gastrectomy, especially total gastrectomy.

Methods

This phase 3 parallel open-label randomized clinical trial was conducted at Fujian Medical University Union Hospital, an institution affiliated with Fujian Medical University that performs more than 800 gastrectomies annually in patients with gastric cancer. The primary end point was the total number of retrieved lymph nodes. The secondary end points were diagnostic sensitivity and specificity, postoperative recovery course, morbidity and mortality rates, and 3-year disease-free survival rate. The clinical trial protocol is available in Supplement 1. This study was approved by the institutional review board of Fujian Medical University Union Hospital. Written informed consent was obtained from all patients.

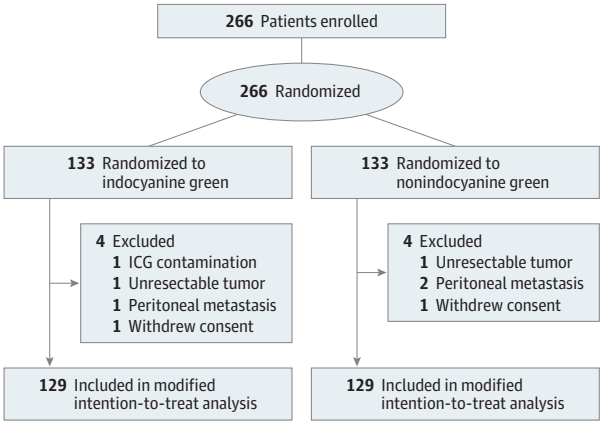
Patients were eligible to participate if they were aged 18 to 75 years and had (1) primary gastric adenocarcinoma; (2) a tumor stage of cT1 to cT4a, N-/+, M0 at the preoperative evaluation; (3) no direct metastasis; (4) a performance status of 0 or 1 on the Eastern Cooperative Oncology Group scale (score range: 0-5, with the lowest score indicating fully active and the highest score indicating dead); and (5) a Society of Anesthesiology score of class 1, 2, or 3. Some of the exclusion criteria were (1) pregnant or breastfeeding; (2) severe mental disorder; (3) history of previous upper abdominal surgery, gastrectomy, endoscopic mucosal resection, endoscopic submucosal dissection, or rejection of laparoscopic resection; and (4) enlarged or bulky regional lymph node with a diameter of more than 3 cm as measured by preoperative imaging (a full list of inclusion and exclusion criteria is available in eTable 1 in Supplement 2). **Figure 1** illustrates the patient flow through the trial.

Randomization and Interventions

We used SAS software, version 9.2 (SAS Institute), to generate serial numbers ranging from 001 to 266 that corresponded with the patients' intervention assignments. After confirming that patients met the inclusion criteria, an investigator (M.L.) was appointed to extract random numbers that were retained before patients were randomly assigned on a 1:1 ratio to either the ICG group or the non-ICG group.

Patients in the ICG group underwent endoscopic injection of ICG 1 day before surgery (**Video 1**). The ICG powder (Dandong Yichuang Pharmaceutical Co) was dissolved in 1.25

Figure 1. Study Flowchart



mg/mL of sterile water. Approximately 0.5 mL of the prepared solution, containing 0.625 mg of ICG, was injected along the submucosa of the stomach at 4 points around the primary tumor, for a total volume of 2 mL.

We used the NOVADAQ fluorescence surgical system (Stryker) equipped with the fluorescence mode to obtain NIR fluorescent images in the ICG group. A simple finger click can change a visible light into NIR images (infrared imaging, green fluorescence, and color-segmented fluorescence) without the need to change any equipment; because the surgical system contains a module for fluorescence imaging, the surgeon could turn on the NIR mode during lymph node (LN) dissection. Surgeons can choose any fluorescent mode at any time according to the situation (**Video 2**).

Surgical Quality Control

Lymphadenectomies were performed by the same group of surgeons (C.-H.Z. and C.-M.H.), and another group of surgeons reviewed the unedited videos of participants' lymphadenectomies once a week using a sample survey for standardization and quality control (eTable 2 in Supplement 2). The extent of gastric resection for distal or total gastrectomy was determined based on the tumor location, as indicated in the Japanese guidelines.[5] Sequences of lymph node dissection were routinely performed as described elsewhere.[27,28] Lymph node dissection at station 10 was performed as a selective dissection[29-31] when (1) the primary tumor was located in the upper-middle part of the stomach and was invading the greater curvature, (2) preoperative imaging suggested splenic lymph node enlargement, or (3) lymph nodes at station 10 emitted fluorescence signals under the NIR mode.

In the ICG group, after completing all lymph node dissections, a routine imaging of the surgical area was performed to determine the presence of any residual fluorescent lymph nodes. When residual lymph nodes containing fluorescence were detected in the dissected area, a complementary dissection was performed (**Video 3**). If fluorescent lymph nodes were detected outside the planned dissection areas (stations 10 and 14v), excessive dissection beyond the scope of D2 lymph node dissection was performed.

Outcome Measurements

Based on the definition of lymph node stations in the Japanese classification guidelines,[32] lymph node–bearing soft tissue was separated from the resected specimens in vitro. In the ICG group, under direct NIR imaging, lymph nodes displaying fluorescence were retrieved from each station (**Video 4**). Lymph node stations that displayed fluorescence were classified as fluorescent stations, and lymph nodes that displayed fluorescence at the fluorescent stations were classified as fluorescent lymph nodes (**Figure 2**). Surgeons (J.-W.X. and Q.Z.) examined all specimens, which were immediately sent to the pathology department. All pathological examinations were performed in a standard manner.[32]

The lymph node dissection rate was determined by the number of patients in whom a lymph node station was harvested divided by the total number of patients who required retrieval in the corresponding lymph node station. Lymph node noncompliance was defined as the absence of lymph nodes that should have been excised from more than 1 lymph node station. Major lymph node noncompliance was defined as more than 2 intended lymph node stations that were not removed.[33,34]

Current guidelines suggested that at least 16 regional lymph nodes should be removed pathologically, and the removal of 30 or more nodes was desirable.[35,36] The reference numbers 16 and 30 were used.

Morbidity and mortality were assessed within 30 days after surgery. Postoperative complications were graded according to the Clavien-Dindo classification.[37]

Sample Size and Statistical Analysis

In this study, the total number of retrieved lymph nodes was considered to be the main effectiveness evaluation index. The mean total number of retrieved lymph nodes from the control groups of 4 previous studies was 32.9.[38-41] The current analysis was based on an α value of .05, a power of 80%, and a margin delta of 15%, revealing that a minimum of 107 patients should be included per group. Given an expected dropout rate of 20%, each group needed to include at least 133 patients, for a total of 266 participants. The sample size was calculated using nQuery Advisor software, version 7.0 (Statistical Solutions, Ltd). Statistical analysis was performed from August to September 2019.

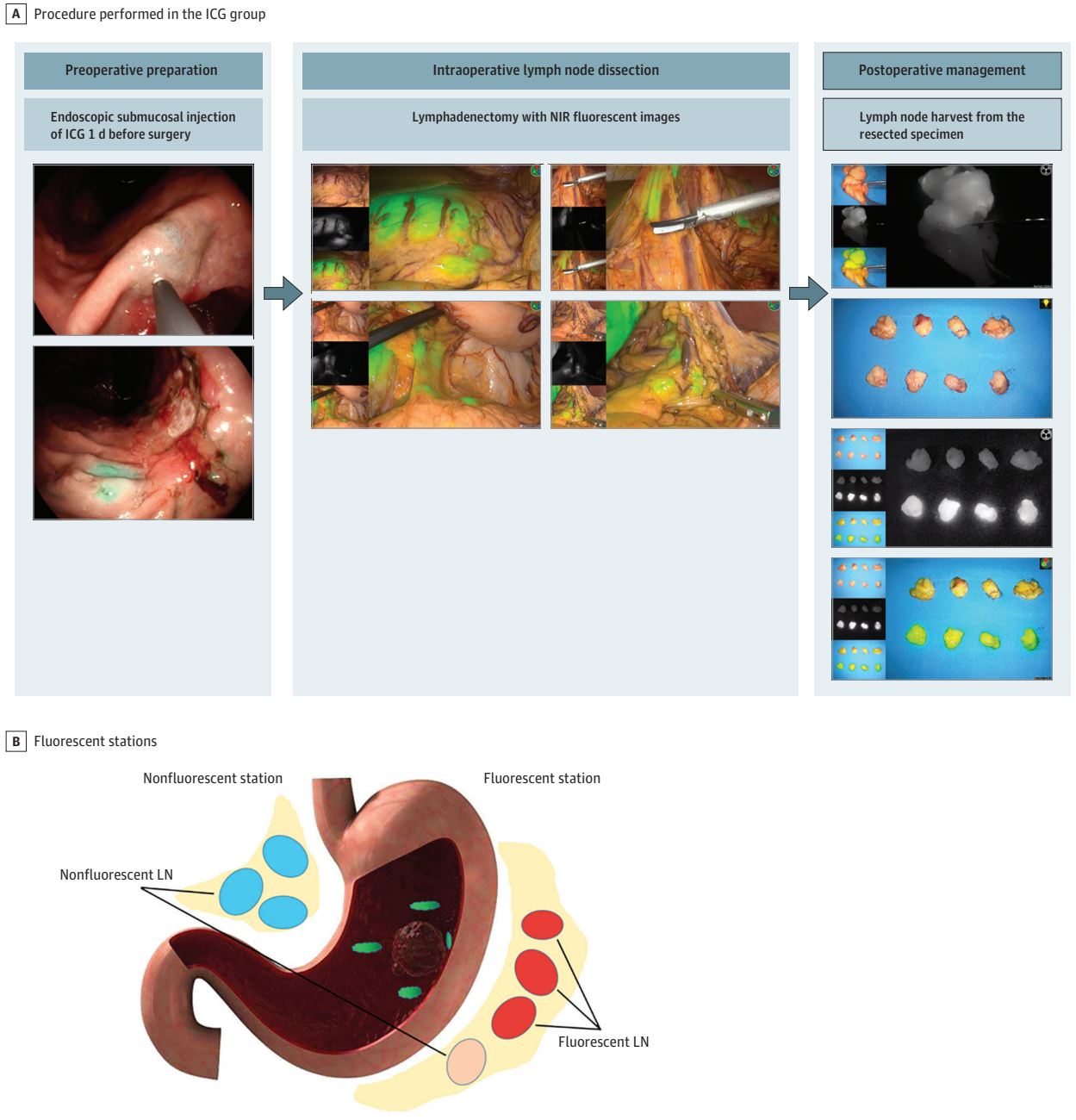
The modified intention-to-treat group excluded patients who had been randomized and met the postrandomization exclusion criteria. Continuous variables were expressed as mean (SD) and categorical variables as numbers. The differences between the groups were assessed using a *t* test or χ^2 test, as appropriate. All tests were 2-sided with a significance level of $P < .05$. All data were analyzed using SPSS statistical software, version 19.0 (SPSS Inc), and the R software environment, version 3.5.3 (R Foundation for Statistical Computing).

Results

Baseline Characteristics

A total of 266 patients were randomized to either the ICG group or the non-ICG group from November 19, 2018, to

Figure 2. Procedures Performed in ICG Group and Illustration of Fluorescent Lymph Nodes and Stations



ICG indicates indocyanine green; LN, lymph node; and NIR, near-infrared.

July 13, 2019. Of those, 133 patients in the ICG group underwent ICG tracer-guided laparoscopic gastrectomy, and 133 patients in the non-ICG group underwent conventional laparoscopic gastrectomy. After surgery, 4 patients were excluded from the ICG group (1 with ICG contamination, 1 with an unresectable tumor, 1 with peritoneal metastasis, and 1 who withdrew from the study), and 4 patients were excluded from the non-ICG group (1 with an unresectable tumor, 2 with abdominal metastases, and 1 who withdrew from the study). After these exclusions, 258 patients were included in the modified intention-to-treat analysis, which comprised 129 patients (86 men and 43 women; mean [SD] age, 57.8 [10.7] years) in the ICG group and 129 patients (87 men and 42 women; mean [SD] age, 60.1 [9.1] years) in the non-ICG group (**Table 1**).

The baseline characteristics of participants were generally balanced, with the exception of the distribution of tumor sites, type of surgical procedures, and reconstruction methods across groups (Table 1). A stratified analysis by surgical procedure indicated that the clinicopathological

Table 1. Basic Characteristics of ICG and Non-ICG Groups

Characteristic	No. (%)		*P* Value
	ICG (n = 129)	Non-ICG (n = 129)	
Age, y	57.8 (10.7)	60.1 (9.1)	.07
BMI	23.2 (3.2)	22.8 (3.1)	.26
Sex			
Male	86 (66.7)	87 (67.4)	.90
Female	43 (33.3)	42 (32.6)	
ECOG performance status			
0	114 (88.4)	113 (87.6)	.85
1	15 (11.6)	16 (12.4)	
Tumor location			
Upper	33 (25.6)	66 (51.2)	<.001
Middle	21 (16.3)	14 (10.9)	
Lower	75 (58.1)	49 (38.0)	
Surgical procedure			
Distal gastrectomy	71 (55.0)	43 (33.3)	<.001
Total gastrectomy	58 (45.0)	86 (66.7)	
Reconstruction method			
Billroth I	9 (7.0)	4 (3.1)	.002
Billroth II	62 (48.1)	39 (30.2)	
Roux-en-Y	58 (45.0)	86 (66.7)	
Histology			
Differentiated	75 (58.1)	90 (69.8)	.05
Undifferentiated	54 (41.9)	39 (30.2)	
Lymphovascular invasion			
Negative	66 (51.2)	73 (56.6)	.38
Positive	63 (48.8)	56 (43.4)	
Size, cm			
≤3	64 (49.6)	50 (38.8)	.08
>3	65 (50.4)	79 (61.2)	
cT stage			
cT1	35 (27.1)	29 (22.5)	.65
cT2-cT3	68 (52.7)	70 (54.3)	
cT4a	26 (20.2)	30 (23.3)	
cN stage			
cN0	60 (46.5)	54 (41.9)	.45
cN+	69 (53.5)	75 (58.1)	
pT stage			
pT1	42 (32.6)	39 (30.2)	.52
pT2-pT3	68 (52.7)	64 (49.6)	
pT4a	19 (14.7)	26 (20.2)	
pN stage			
pN0	54 (41.9)	55 (42.6)	.57
pN1	24 (18.6)	16 (12.4)	
pN2	20 (15.5)	18 (14.0)	
pN3a	19 (14.7)	26 (20.2)	
pN3b	12 (9.3)	14 (10.9)	
AJCC stage			
I	50 (38.8)	41 (31.8)	.43
II	33 (25.6)	33 (25.6)	
III	46 (35.7)	55 (42.6)	
Metastatic LNs	5.6 (11.2)	5.7 (8.9)	.94

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ECOG, Eastern Cooperative Oncology; ICG, indocyanine green; LN, lymph node.

Table 2. Number of Retrieved Lymph Nodes in ICG and Non-ICG Groups

Variable	Mean (SD)		*P* Value
	ICG (n = 129)	Non-ICG (n = 129)	
Total retrieved LNs	50.5 (15.9)	42.0 (10.3)	<.001
≥30	129 (100.0)	113 (87.6)	<.001
<30	0	16 (12.4)	
Surgical procedure			
Distal gastrectomy	49.2 (15.5)	39.8 (10.1)	<.001
Total gastrectomy	52.1 (16.2)	43.1 (10.2)	<.001
BMI			
<24	51.8 (17.2)	43.4 (9.9)	<.001
≥24	48.6 (13.6)	39.0 (10.6)	<.001
Sex			
Male	49.8 (16.7)	41.4 (10.1)	<.001
Female	51.8 (14.1)	43.2 (10.5)	.002
Histological type			
General	51.3 (17.0)	42.0 (9.9)	<.001
Special	48.1 (11.7)	42.2 (12.0)	.07
Histology			
Differentiated	50.0 (17.8)	41.8 (10.3)	<.001
Undifferentiated	51.2 (12.8)	42.6 (10.2)	<.001
cT stage			
cT1	49.0 (16.6)	39.3 (10.3)	.008
cT2-cT3	49.1 (12.3)	42.8 (10.5)	.001
cT4a	56.0 (21.6)	42.9 (9.3)	.004
cN stage			
cN0	49.0 (13.6)	39.5 (10.4)	<.001
cN+	51.7 (17.6)	43.8 (9.8)	<.001
pT stage			
pT1	48.7 (15.1)	39.8 (10.3)	.003
pT2-pT3	51.5 (16.9)	43.2 (10.4)	.001
pT4a	50.9 (13.9)	42.5 (9.6)	.02
pN stage			
pN0	47.2 (12.5)	39.8 (10.7)	.001
pN+	52.9 (17.6)	43.7 (9.6)	<.001
AJCC stage			
I	47.8 (14.1)	39.3 (10.3)	.002
II	51.1 (20.6)	42.4 (10.5)	.03
III	53.0 (13.4)	43.8 (9.9)	<.001
LN confined to D2 lymphadenectomy	49.6 (15.0)	41.7 (10.2)	<.001
Surgical procedure			
Distal gastrectomy	48.5 (13.7)	39.8 (10.1)	<.001
Total gastrectomy	50.9 (16.3)	42.7 (10.2)	.001

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); ICG, indocyanine green; LNs, lymph nodes.

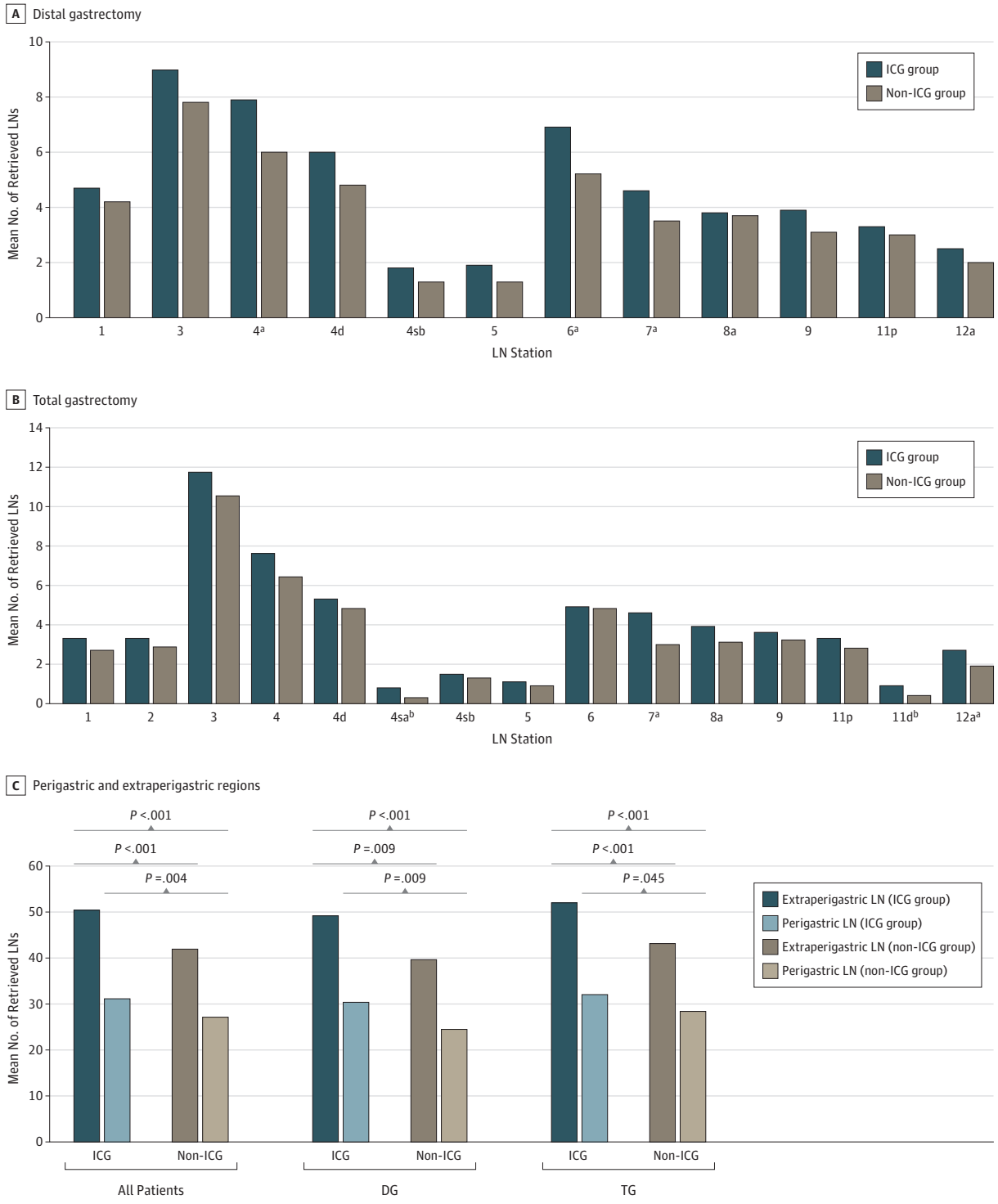
features were comparable between the 2 groups (eTable 3 in Supplement 2).

Lymph Node Dissection

The mean (SD) total number of retrieved lymph nodes in the ICG group was 50.5 (15.9), which was significantly more than the number retrieved in the non-ICG group (mean [SD], 42.0 [10.3]; $P < .001$; **Table 2**). For patients who underwent distal gastrectomy, the mean (SD) number of retrieved lymph nodes in the ICG group was 49.2 (15.5), which was more than the 39.8 (10.1) lymph nodes retrieved in the non-ICG group ($P < .001$). For patients who underwent total gastrectomy, the mean (SD) number of retrieved lymph nodes in the ICG group was 52.1 (16.2), which was also more than the number retrieved in the non-ICG group (mean [SD], 43.1 [10.2]; $P < .001$). A stratified analysis indicated that the mean total number of lymph node dissections in the ICG group was significantly higher than those of the non-ICG group, regardless of the cT, cN, pT, or pN stage (**Figure 3**).

For distal gastrectomy, the number of lymph node dissections in the ICG group was higher than that of the non-ICG group in the same lymph node station, especially in stations

Figure 3. Total Retrieved Lymph Nodes (LNs) in ICG and Non-ICG Groups by Lymph Node Station



A, Distal gastrectomy. ICG indicates indocyanine green. B, Total gastrectomy. ICG indicates indocyanine green. C, Perigastric and extraperigastric regions. Perigastric lymph nodes at stations 1, 2, 3, 4, 5, and 6; extraperigastric lymph nodes at stations 7, 8, 9, 11, and 12a. DG indicates digital gastrectomy; TG, total gastrectomy.

[a] $P < .05$.

[b] $P < .001$.

4, 6, and 7 (Figure 3). For total gastrectomy, the number of lymph node dissections in the ICG group was higher than that of the non-ICG group in the same lymph node station, especially in stations 4sa, 7, 11d, and 12a.

In the ICG group, a mean (SD) total number of 27.3 (13.0) fluorescent lymph nodes was detected, which was significantly more than the mean (SD) total number of 23.2 (14.1) nonfluorescent lymph nodes detected ($P = .01$). The mean number of lymph nodes retrieved from the fluorescence stations was significantly higher than the mean number retrieved from the nonfluorescence stations, regardless of the resection method (for distal gastrectomy, mean [SD], 5.27 [4.03] vs 2.16 [2.96] lymph nodes, respectively; for total gastrectomy, mean [SD], 4.89 [4.56] vs 2.04 [2.60] lymph nodes, respectively; $P < .001$ for both comparisons; eFigure 1 in Supplement 2).

Dissection Extent

We divided the lymph nodes into perigastric regions (stations 1-6) and extraperigastric regions (stations 7-9, 11, and 12a). The number of perigastric and extraperigastric lymph node dissections in the ICG group was significantly higher than the number of dissections the non-ICG group (Figure 3C). Moreover, the mean (SD) total number of retrieved lymph nodes in the ICG group was 49.6 (15.0) within the scope of D2 lymphadenectomy, which was significantly more than the total number of 41.7 (10.2) retrieved lymph nodes in the non-ICG group ($P < .001$).

Regardless of whether distal gastrectomy or total gastrectomy was performed, the ICG group underwent a significantly greater mean number of lymph node dissections than the non-ICG group based on the D2 criteria (for distal gastrectomy, mean [SD], 48.5 [13.7] vs 39.8 [10.1] dissections, respectively; $P < .001$; for total gastrectomy, mean [SD] 50.9 [16.3] vs 42.7 [10.2], respectively; $P = .001$).

Lymph Node Noncompliance

Among patients who underwent distal gastrectomy, the lymph node dissection rates in the ICG group were not significantly higher than those in the non-ICG group in each station (eFigure 2 in Supplement 2). For patients who underwent total gastrectomy, the lymph node dissection rates in the 4sa, 11d, and 12a stations of the ICG group were significantly higher than those in the non-ICG group.

The comparison of lymph node noncompliance between the 2 groups indicated that, among total patients, the lymph node noncompliance rate of the ICG group (41 of 129 patients [31.8%]) was lower than that of the non-ICG group (74 of 129 patients [57.4%]; $P < .001$; eFigure 2C in Supplement 2). A stratified analysis showed that, for total gastrectomy, the lymph node noncompliance rate of the ICG group (24 of 58 patients [41.4%]) was lower than that of the non-ICG group (58 of 86 patients [67.4%]; $P = .002$). For distal gastrectomy, the lymph node noncompliance rate in the ICG group (17 of 71 patients [23.9%]) was lower than that of the non-ICG group (16 of 43 patients [37.2%]), although this difference did not achieve statistical significance ($P = .13$).

The effect of the ICG intraoperative lymph node tracer on the degree of lymph node noncompliance was further analyzed (eTable 4 in Supplement 2). We found that, in patients who underwent total gastrectomy, the major noncompliance (ie, more than 2 intended lymph node stations not removed) of the ICG group (13 of 58 patients [22.4%]) was significantly lower than that of the non-ICG group (34 of 86 patients [39.5%]; $P = .03$). In patients who underwent distal gastrectomy, the major noncompliance rates were comparable in the ICG group (6 of 71 patients [8.4%]) and the non-ICG group (5 of 43 patients [11.7%]; $P = .75$).

Lymph Node Metastasis

A comparison of the number of metastatic lymph nodes between the 2 groups indicated that the number of metastatic lymph nodes in each station in the ICG group was not significantly higher than the number in the non-ICG group, regardless of the resection method (eTable 5 in Supplement 2). An analysis of the relationship between the fluorescence lymph nodes and metastatic lymph nodes retrieved in the ICG group indicated that the diagnostic sensitivity and specificity of fluorescence and metastatic lymph nodes were 410 of 728 nodes (56.3%) and 2669 of 5785 nodes (46.1%), respectively (eTable 6 in Supplement 2).

Metastasis was observed in 5 of 24 patients (20.8%) from the ICG group with lymph nodes at station 10, with 14 patients (58.3%) having a fluorescent-positive station 10; 16 of the 69 retrieved lymph nodes (23.2%) from station 10 metastasized. Metastasis was observed in 3 of 9 patients (33.3%) from the ICG group with a fluorescent-positive station 14v; 5 of the 43 retrieved lymph nodes (11.6%) from station 14v metastasized.

Surgical Outcomes

No significant differences between the ICG and non-ICG groups were observed in intraoperative blood loss (51.5 mL vs 54.3 mL, respectively; $P = .86$) and operative time (196.1 minutes vs 190.4 minutes, respectively; $P = .33$; eTable 7 in Supplement 2). The postoperative recovery process was comparable. There were no significant differences in time to first flatus, time to ambulation, time to first liquid intake, and postoperative hospital stay between the 2 groups. Further stratification indicated that the postoperative recovery process in the 2 groups was comparable, whether the patients underwent total or distal gastrectomy (eTable 8 in Supplement 2). We excluded 1 patient whose adipose tissue could not be distinguished from lymph nodes owing to leakage caused by mistakenly injecting ICG into the abdominal cavity under endoscopic guidance. No complications related to the endoscopic injection of ICG were observed, and no delayed complications associated with NIR imaging of the ICG injection were found.

No significant differences were found between the ICG and non-ICG groups regarding the incidence (20 of 129 patients [15.5%] vs 21 of 129 patients [16.3%], respectively; $P = .86$) or severity of postoperative complications within 30 days after surgery (eTable 7 in Supplement 2).

Discussion

In contrast to the study performed by Kwon et al,[26] our study used a large sample of patients with stage cT1 to cT4a cancer, including those with advanced gastric cancer, and

we performed a detailed analysis of the number of lymph node dissections, the number of metastatic lymph nodes, and the rate of lymph node noncompliance. Regardless of whether the dissected lymph nodes metastasized, complete perigastric lymphadenectomy is important for the accurate staging of tumors, the selection of subsequent treatment, and the improvement of prognosis.[1,2,42,43] Theoretically, ICG fluorescence imaging-guided radical gastrectomy for gastric cancer has the characteristics of in vivo and real-time imaging[13,44,45]; it allows surgeons to closely observe the physiological condition of perigastric lymph nodes and accurately locate lymph nodes, which has certain advantages. However, studies have reported various results regarding whether ICG can increase the number of lymph nodes retrieved during laparoscopic gastrectomy. Kim et al[24] suggested that, in laparoscopic surgery, the application of ICG can increase the detection rate of lymph nodes. Similarly, Kwon et al[26] reported that ICG-guided surgery had a similar incidence of postoperative complications to conventional surgery and that ICG-guided surgery is effective in retrieving more lymph nodes than conventional surgery. However, Lan et al[23] reported that, compared with the non-ICG group, the number of total retrieved lymph nodes in the ICG group did not improve.

In addition to the selection bias of retrospective studies and the differences in inclusion criteria, we believe that the differences in ICG injection methods, times, and concentrations were also factors in the inconsistent results. Therefore, this randomized clinical trial not only strictly followed the standards of randomized clinical trials in selected patients and made the general data comparable, it also developed methods with regard to the standard use of ICG. From the preoperative injection and intraoperative photography to the postoperative sorting of lymph nodes, we adopted a unified standard and documented the process by recording images. Through early exploration, we found that, compared with intraoperative subserosal injection of ICG, preoperative submucosal injection of ICG under endoscopic guidance was easier to control and saved time, and it was less likely to cause intraoperative leakage of ICG into the surgical field or to interfere with the operation by straying into blood vessels.[23] The endoscopic injection of ICG 1 day before surgery may cause discomfort to the patient and is likely to increase the corresponding risk. However, this study showed that preoperative endoscopic injection is safe and feasible, and the application of ICG does not increase the incidence of complications.

To increase dissections of all metastatic lymph nodes, a certain number of normal lymph nodes may also be removed during ICG-guided lymphadenectomy, and there is no inherent benefit in removing normal lymph nodes. Nevertheless, it has been reported that a greater number of lymph node dissections for patients with node-negative gastric cancer may provide survival benefit by reducing potential micrometastases and lymphatic invasion.[46-50] Therefore, long-term follow-up is also needed to assess whether an excess number of lymph node dissections among patients receiving ICG will be beneficial in the future. Furthermore, this study was conducted at an institution with extensive experience in gastric cancer surgery.[27,51] We speculate that, for newly trained gastric surgeons, laparoscopic ICG-guided radical gastrectomy may provide greater assistance.

Further analysis indicated that the total number of lymph nodes detected in the ICG group remained significantly higher than the total number detected in the non-ICG group within the range of standard D2 lymphadenectomy stipulated by the current Japanese gastric cancer treatment guidelines (excluding stations 14v and 10).[52] Because ICG can emit NIR light around a wavelength of 840 nm after excitation, the tissue penetration depth of enhanced fluorescence ranges from 0.5 cm to 1.0 cm.[53] The outline and boundary of perigastric lymph nodes can be clearly displayed by NIR through high-definition laparoscopy. Because of the different rates of ICG uptake in diverse tissues, high-definition laparoscopy can effectively distinguish lymphoid tissue from perigastric blood vessels, fat, pancreatic tissue, and other tissues. It allows the surgeon to confidently and accurately perform lymph node dissection within the specified range without increasing the incidence of complications.

In the ICG group, our results indicated that the number of retrieved fluorescent lymph nodes was significantly higher than the number of retrieved nonfluorescent lymph nodes. In other words, the surgeon can dissect more lymph nodes in the same station with similar operation time using NIR fluorescent imaging. Notably, we found that the lymph node metastasis rate in patients with fluorescent station 14v was as high as 30%, which was significantly higher than the rate reported in previous studies,[54,55] one of which was focused on the potential use of ICG imaging in the dissection of station 14v.

Previous studies have reported that lymph node noncompliance has substantial consequences for the long-term survival of patients with gastric cancer.[33,56,57] Therefore, our study also focused on assessing whether the use of ICG can reduce the rate of lymph node noncompliance during laparoscopic radical gastrectomy. To measure the noncompliance of lymph nodes, we undertook standard D2 resection, as previous clinical trials also indicated a high noncompliance rate. A Dutch clinical trial[33] reported noncompliance rates as high as 81.6% during D2 lymphadenectomy, and the D2 lymph node noncompliance rate was 58.9% in the CRITICS clinical trial.[58] In the COACT 1001 study,[59] the noncompliance rate of the laparoscopic distal gastrectomy group was 47%. A previous retrospective study[34] showed that the noncompliance rate was 50.9% in the distal gastrectomy group and 59.8% in the total gastrectomy group. Through the use of an ICG tracer, the noncompliance rate in our study was 23.9% in the distal gastrectomy group and 41.4% in the total gastrectomy group, which was a much lower incidence than previously reported.

As shown in the videos of the present study, by using ICG imaging in addition to lymphadenectomy, the surgeon can also assess the completeness of lymph node dissection and dissect residual lymph nodes, thereby effectively reducing lymph node noncompliance. Our results indicated that, for total gastrectomy, ICG imaging could significantly reduce the lymph node noncompliance rate. Compared with total gastrectomy, D2 lymphadenectomy of distal gastrectomy was less difficult and decreased the rate of lymph node station dissection; hence, even for the non-ICG group, intraoperative lymph node compliance was easier to achieve. For distal gastrectomy, use of the

ICG tracer decreased lymph node noncompliance, although this decrease did not achieve statistical significance.

Limitations

This study has limitations. First, only patients from a single center were included, and the results of long-term follow-up were not available. Theoretically, lymph node dissection under NIR guidance is a more accurate method, decreasing tumor spread in lymph nodes during dissection and possibly increasing long-term survival. However, the accuracy of ICG imaging technology needs to be confirmed by multicenter studies.

Second, in this study, no patients in the ICG group achieved fluorescence with all retrieved lymph nodes, and only 56.3% of metastatic lymph nodes displayed fluorescence in this group. Similar to previous studies,[21,60,61] ICG fluorescence could not accurately indicate metastatic lymph nodes, and some false negative rates have been reported in these studies. This inaccuracy may have been owing to the obstruction of lymphatic vessels by cancer cells or a massive cancerous invasion of the lymph node. In such cases, the administered tracer cannot accumulate in the positive lymph nodes.[62] We believe that with the continuous use of ICG imaging in clinical practice and technological innovation, this technology will improve in accuracy.

Third, the study included all potential tumor sites of patients with gastric cancer. Therefore, a few variables, such as tumor location, may have been unevenly matched. The literature has also reported that, in randomized clinical trials, uneven stratification of individual variables may be the result of an occasional small probability event.[63,64] For example, the HELOISE[65] and PHOENIX-GC[66] clinical trials also appeared to not be completely comparable at baseline. Although the proportion of patients in the 2 groups who underwent total gastrectomy or distal gastrectomy differed, a stratified analysis indicated that similar results were obtained, regardless of the resection method.

Conclusions

This study indicated that, without any increase in operating time and complications, the use of ICG can guide surgeons to efficiently harvest more lymph nodes during laparoscopic radical gastrectomy compared with conventional lymph node dissection and effectively reduce lymph node noncompliance, especially among patients who undergo total gastrectomy, and the use of ICG has broad prospects for future applications.

ARTICLE INFORMATION

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Author Affiliations: Department of Gastric Surgery, Fujian Medical University Union Hospital, Fuzhou, China (Chen, Xie, Zhong, Wang, J.-X. Lin, Lu, Cao, M. Lin, Tu, Z.-N. Huang, J.-L. Lin, H.-L. Zheng, Li, C.-H. Zheng, C.-M. Huang); Department of General Surgery, Fujian Medical University Union Hospital, Fuzhou, China (Chen, Xie, Zhong, Wang, J.-X. Lin, Lu, Cao, M. Lin, Tu, Z.-N. Huang, J.-L. Lin, H.-L. Zheng, Li, C.-H. Zheng, C.-M. Huang); Key Laboratory of Ministry of Education of Gastrointestinal Cancer, Fujian Medical University, Fuzhou, China (Chen, Xie, Zhong, Wang, J.-X. Lin, Lu, Cao, M. Lin, Tu, Z.-N. Huang, J.-L. Lin, H.-L. Zheng, Li, C.-H. Zheng, C.-M. Huang); Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, China (Chen, Xie, Zhong, Wang, J.-X. Lin, Lu, Cao, M. Lin, Tu, Z.-N. Huang, J.-L. Lin, H.-L. Zheng, Li, C.-H. Zheng, C.-M. Huang).

Author Contributions: Drs Chen, Zhong, and Xie contributed equally to this work and should be considered first coauthors. Drs C.-M. Huang and C.-H. Zheng had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Chen, Zhong, Li, C.-H. Zheng, C.-M. Huang.
Acquisition, analysis, or interpretation of data: Chen, Xie, Zhong, Wang, Jian-Xian Lin, Lu, Cao, M. Lin, Tu, Z. Huang, Ju-li Lin, H. Zheng, C.-H. Zheng, C.-M. Huang.
Drafting of the manuscript: Chen, Zhong, Li, C.-H. Zheng, C.-M. Huang.
Critical revision of the manuscript for important intellectual content: Chen, Xie, Zhong, Wang, Jian-Xian Lin, Lu, Cao, M. Lin, Tu, Z. Huang, Ju-li Lin, H. Zheng, C.-H. Zheng, C.-M. Huang.
Statistical analysis: Chen, Xie, Zhong, Wang, Jian-Xian Lin, Lu, Cao, M. Lin, Z. Huang, Ju-li Lin, H. Zheng, Li, C.-H. Zheng, C.-M. Huang.
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Supervision: Cao, C.-M. Huang.

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