



Comparison of a submucosal and subserosal approach in ICG-guided laparoscopic lymphadenectomy in gastric cancer patients: long-term outcomes of a phase 3 randomized clinical trial

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Background: Previous studies have demonstrated similar short-term efficacy between subserosal (SSA) and submucosal (SMA) approaches for ICG injection in gastric cancer (GC). This study aims to compare the long-term oncological outcomes of these two injection methods for lymph node (LN) tracing in ICG-guided laparoscopic gastrectomy.

Materials and methods: This study was a phase 3, open-label, randomized clinical trial (FUGES-019). A total of 266 patients with resectable gastric adenocarcinoma (cT1-4a, NO/+, MO) were enrolled. We report predefined long-term secondary outcomes, including three-year actual overall survival (OS), three-year actual disease-free survival (DFS), and recurrence patterns.

Results: Of the 266 participants, 259 patients were included in the per-protocol analysis: 129 in the SSA group and 130 in the SMA group. The actual OS in the SSA group (87.6%) was comparable to that in the SMA group (90.8%, $P = 0.41$), as were the 3-year actual DFS rates (SSA: 82.9% vs. SMA: 88.5%, log-rank $P = 0.19$). Per-protocol analysis confirmed the equivalence of the SSA compared with the SMA. The most common type of recurrence was multiple site metastasis (11 of 259 [4.24%]), with no differences in recurrence types across cancer stages. Further stratified analysis based on pT, pN staging, tumor size, and BMI showed no significant differences between the two groups.

Conclusion The 3-year outcomes of the FUGES-019 trial confirm the equivalence of SSA and SMA in ICG-guided laparoscopic lymphadenectomy for GC, supporting the previous short-term findings. The subserosal approach can be recommended for ICG administration based on clinical considerations.

Keywords: disease-free survival, gastric cancer, ICG injection approach, overall survival, recurrence patterns

Introduction

Gastric cancer (GC) is the fifth most common cancer globally and is particularly prevalent in East Asia^[1]. Despite advancements in

multimodal treatments – including surgery, chemotherapy, and targeted therapies – radical gastrectomy with complete lymphadenectomy remains the mandatory backbone of treatment^[2–5]. Indocyanine green (ICG) near-infrared fluorescent imaging has proven effective and safe for lymph node (LN) mapping across several malignancies^[6–8], including GC^[9–13]. Successful visualization of LNs during surgery depends on the accurate injection of ICG, which is typically performed through the submucosal or subserosal layer around the tumor. The application of ICG fluorescence imaging technology enables better observation of perigastric lymphatic pathways and distribution of LNs^[14,15].

Precise tracer injection around the tumor is crucial for effective LN identification. Previous studies^[9,12,16] have suggested that the preoperative submucosal approach (SMA), performed the day before surgery, can accurately visualize LNs and considerably increase the number of LNs retrieved without adding complications. However, the success of SMA injections relies on the endoscopist's skill. Alternatively, the subserosal approach (SSA) effectively traces perigastric LNs but requires injection from the outside of the gastric wall as the tumor location is identified during surgery^[17–21]. SMA involves preoperative endoscopic injection, which can ensure precise lymph node mapping but may increase patient discomfort due to the additional procedure. In contrast, SSA enables direct intraoperative injection, eliminating

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the need for preoperative endoscopy and potentially improving surgical efficiency. These differences in procedural approaches could significantly impact patient experiences and optimize surgical workflows, emphasizing the importance of tailoring the injection method to clinical scenarios.

Both SMA and SSA are effective for ICG-guided laparoscopic lymphadenectomy. The gastric surgery study group (FUGES) conducted a prospective randomized controlled trial (FUGES-019) to compare the efficacy and safety of SSA and SMA in ICG injection for LN tracing during laparoscopic gastrectomy. We previously reported that subserosal injection of ICG was comparable to submucosal injection in terms of the number of retrieved LNs, LN non-compliance rates, and postoperative complications^[22]. Both approaches were equally accurate in detecting LNs. Additionally, SSA offers better operational convenience and imposes lower economic and psychological burdens on patients compared to SMA^[22].

However, short-term advantages may not necessarily translate into long-term efficacy. Decisions regarding the clinical adoption of new technology should consider both short-term effects and long-term oncological outcomes. The efficacy of different ICG injection modalities, including long-term safety outcomes, should be evaluated at 3 years or more post-surgery. Accordingly, we report the prespecified survival endpoints from the randomized FUGES-019 study, including 3-year overall survival (OS), 3-year disease-free survival (DFS), and recurrence patterns as long-term oncologic outcomes.

Methods

Study design

This FUGES-019 trial was a phase III, parallel, open-label, randomized controlled trial conducted at a tertiary gastric cancer center in China (registered on <https://www.clinicaltrials.gov>, identifier NCT: NCT04219332). The study was initially designed as a non-inferiority trial to demonstrate that the effectiveness of ICG injection via SSA is comparable to SMA in lymph node retrieval and to compare the effects of these approaches on various secondary long-term survival outcomes (see Supplementary Digital Content online for determination of the equivalence margin). This trial was conducted in accordance with the principles of the 1964 Declaration of Helsinki. All procedures were approved by the Institutional Review Board of the Fujian Medical University Union Hospital (IRB number 2019YF045-01). The approved study protocol is provided in Supplementary Digital Content 1, <http://links.lww.com/JS9/D879>. Written informed consent was obtained from all the participants. This study adhered to the Consolidated Standards of Reporting Trials (CONSORT) reporting guidelines^[23].

Participants

The inclusion criteria were (1) age 18–75 years, (2) primary gastric adenocarcinoma, and (3) tumor stage cT1–cT4a, N0/+, or M0 based on preoperative evaluation. The exclusion criteria were (1) a history of upper abdominal surgery, gastrectomy, or endoscopic dissection and (2) linitis plastica. Patients were excluded if they had enlarged or bulky regional LNs with a diameter greater than 3 cm on preoperative imaging, a history of allergy to iodine agents, or a history of previous gastrectomy,

endoscopic mucosal resection, or endoscopic submucosal dissection. Patients with a history of upper abdominal surgery were excluded to avoid potential challenges posed by anatomical alterations, such as adhesions or fibrosis, which could complicate lymph node mapping and dissection. These structural changes may reduce the accuracy of lymph node marking and increase the risk of intraoperative complications, including bleeding, adhesions, or organ injury. Such complications could confound the study results and interfere with the evaluation of the safety and effectiveness of the two injection methods. Detailed inclusion and exclusion criteria are provided in Table S1 <http://links.lww.com/JS9/D878>. The first patient was enrolled on 31 December 2019 and the last on 27 October 2020.

Randomization and masking

Eligible participants were randomly assigned to receive ICG injections via either SSA or SMA at a 1:1 ratio. We used SAS software, version 9.4 (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 (F.F.L.) was appointed to extract random numbers retained prior to patient randomization. Patients were then randomly assigned in a 1:1 ratio to either the ICG group or the non-ICG group. To addressing potential biases from differences in surgical techniques, a stratified random block design was used, with each researcher as a factor. The assigned injection method was disclosed to the surgeon only on the day of surgery in the operating room. Although blinding surgeons and participants in surgical trials is challenging, surgeons did not participate in postoperative follow-up assessments. The pathologists and outcome analysts were blinded to patient information and outcomes throughout the study.

Procedures

In the SSA group, patients received subserosal ICG injections 20 minutes before lymph node dissection during surgery. If a pT3 or pT4 tumor invades the serosal layer or involves any of the six predetermined injection points, as specified in the study protocol, subserosal injection of ICG was performed in non-invasive areas adjacent to the original injection points. In the SMA group, patients underwent submucosal ICG injection around the tumor on endoscopy 1 day before the surgery (Fig. 1). Specific dosage and injection methods are detailed in the study protocol and previous publications^[22]. The extent of lymphadenectomy was determined according to the *Japanese gastric cancer treatment guidelines 2014 (ver. 4)*^[24]. Surgeon adherence to protocols was assessed through quality control procedures. Additionally, surgeons attended refresher training sessions to ensure familiarity with the protocol and any updates.

The eighth edition of the UICC/AJCC staging system was used for gastric cancer staging. Postoperative adjuvant chemotherapy was recommended for patients with pathological stage II or more advanced disease stages. Adjuvant chemotherapy based on tegafur gimeracil oteracil potassium capsules (S-1) or 5-fluorouracil was administered within 4–6 weeks after curative resection.

Objectives and end points

Our primary objective was to demonstrate noninferior surgical and oncologic outcomes for SSA vs SMA in ICG-guided

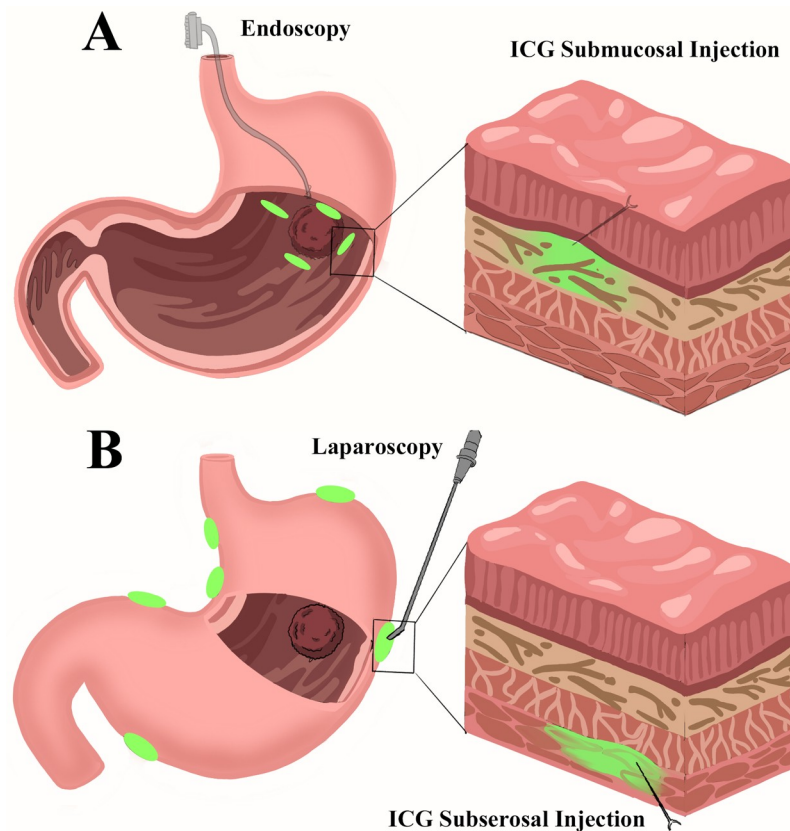


Figure 1. Procedure performed in SMA and SSA groups. (A) Laparoscopic subserosal ICG injections 20 min before lymph node dissection during surgery. (B) Endoscopic submucosal ICG injection around the tumor on endoscopy 1 day before the surgery.

laparoscopic gastrectomy. The primary end point was the **total number of retrieved LNs**, which have been previously reported. Secondary end points include the 3-year overall survival (OS) rate, disease free survival (DFS) rate, and recurrence pattern.

OS was defined as the time from surgery to death from any cause or to the last follow-up, and DFS was defined as the time from surgery to recurrence, death from any cause, or the last follow-up. The recurrence evaluation time point corresponds to the follow-up updated time. Local-regional recurrence was defined as clinically confirmed tumor recurrence within the residual stomach, anastomotic site, or surgical site of the LNs. Multiple-site recurrence was defined as recurrence at two or more metastatic sites simultaneously, including the peritoneum, liver, lungs, bones, brain, distant lymph nodes, or other hematogenous sites. Other-site recurrence encompassed locations other than the liver (e.g., lungs, bones, brain, and adrenal glands), distant lymph nodes, and sites not clearly specified.

A minimum postoperative follow-up of 36 months was required for each patient. All patients underwent tumor assessments every 3 months for the first 2 years postoperatively and every 6 months thereafter. Routine follow-up measures included (1) physical exams and blood tests for CEA, CA12-5, and CA19-9 every 3 months for the first 2 years and subsequently every 6 months. (2) Abdominal and pelvic CT scans were performed every 6 months for the initial 3 years and annually thereafter. (3) Annual postoperative upper gastrointestinal endoscopy was performed. Patients suspected of recurrence

were advised to undergo PET/CT. Recurrence was determined based on the medical history, physical examination, imaging assessments, cytology, or tissue biopsy. Symptom assessment during follow-up included timely evaluation of signs such as abdominal masses, weight loss, or possible concurrent intestinal obstruction indicative of recurrence.

Sample Size

The primary evaluation index in this study was the total number of retrieved LNs in each group. The calculation was based on clinical data from a study by Chen QY *et al.*^[25], which reported that the total number of retrieved lymph nodes in patients undergoing SMA-guided lymphadenectomy was 50.5, with a standard deviation (SD) of 15.9. Preliminary results indicated that the total number of lymph nodes retrieved using the SSA method was 49.2, with an SD of 9.8. A non-inferiority margin of 10 lymph nodes was established, considering that SSA would be deemed inferior if the total number of lymph nodes retrieved was 10 fewer than that retrieved using SMA. The actual difference in retrieved lymph nodes was estimated to be no more than 5. Using this margin of 10, a 1:1 parallel design, a one-sided type I error (alpha) of 0.025, and a target power of 80%, the required sample size was calculated to be 111 patients per group, totaling 222 patients. Accounting for a 20% dropout rate, the final sample size was determined to be 266 participants, with 133 patients per group.

Statistical analysis

The FUGES-019 study was designed with a power of 80% and a significance level of 5% to detect differences in primary endpoints. No formal sample size calculation was performed for secondary outcomes. All patients adhered to the established treatment plan without switching to an alternative, and no surgical methods or group assignments were altered. Baseline data and validity analyses were conducted on a per-protocol (PP) basis, excluding those who withdrew consent preoperatively or who had unresectable GC detected intraoperatively or ICG contamination. No outlier data were observed. Missing data levels were assessed for each variable. In this study, missing data were managed according to predefined criteria. Multiple imputations were planned if the proportion of missing data exceeded 5%. However, no missing data were observed during the collection of general clinical information or survival follow-up. For recurrence site data in Table 3, nine cases were classified as “missing completely at random” (MCAR), as their occurrence was independent of other variables or participant characteristics. These cases were categorized as “other or uncertain sites” for analysis to preserve the integrity of the dataset. Continuous variables were transformed into binary categories (see online Supplementary Digital Content, <http://links.lww.com/JS9/D879>). Categorical data are presented as numbers and percentages and were compared using the Pearson χ^2 test.

The 3-year OS and DFS rates were calculated using the Kaplan-Meier method, and the log-rank test was used to determine significance. Hazard ratios (HRs) comparing the SMA and SSA groups were estimated using Cox regression after confirming the proportional hazards assumption. Two approaches were employed: the Schoenfeld residuals test, which examined the independence of residuals from time, and graphical methods, where Schoenfeld residuals were plotted against time to visually assess the assumption. Both methods indicated that the proportional hazards assumption was reasonably satisfied. Further details on the verification process can be found in Supplementary Digital Content 2 (<http://links.lww.com/JS9/D879>).

Multivariate Cox regression analyses were performed to evaluate the effect of ICG injection types on survival after adjusting for clinicopathological covariates that were significantly associated with outcomes in univariate analyses. Factors with a P -value < 0.05 in the univariate analysis were included in further multivariate analysis. All-cause mortality was treated as a competing event for recurrence. Cumulative incidence in the context of competing risks was calculated, and competing-risk survival regression was conducted as an alternative to Cox regression.

All data analyses were performed using the SPSS statistical software (version 25.0; SPSS Inc.) and R software (version 4.2.2; R Foundation for Statistical Computing, see online Supplementary Digital Content <http://links.lww.com/JS9/D879>). Statistical analysis was performed from October to December 2023.

Results

Baseline characteristics

A total of 266 patients were randomized into the two treatment groups between 31 December 2019 and 27 October 2020. Following randomization, one participant from each group was withdrawn due to intraoperative ICG contamination.

Additionally, one participant in the SMA group withdrew consent, and four participants (three from the SSA and one from the SMA group) were excluded because of intraoperative findings of tumor spread or implant metastasis, rendering them ineligible for analysis. Thus, 3-year outcomes were analyzed in 129 patients in the SSA group (88 males [68.2%], 41 females [31.8%]) and 130 patients in the SMA group (87 males [66.9%], 43 females [33.1%]) (Fig. 2). Baseline characteristics were well-balanced between groups, with no significant differences observed in clinical and pathological factors, including age, sex, BMI, ECOG score, tumor features, staging, and treatment-related factors (all $P > 0.05$) (Table 1). The median follow-up was 40.0 (38.0–45.0) months, with 40.0 months in the SSA group and 39.0 months in the SMA group.

Overall survival

During the 3-year follow-up, 28 patient deaths resulted in actual OS rates of 87.6% (16/129) in the SSA group and 90.8% (12/130) in the SMA group, with no significant difference (log-rank $P = 0.41$, Fig. 3A). Univariable Cox regression analysis indicated associations between age, tumor size, pT stage, pN stage, and OS ($P < 0.05$). In multivariable Cox regression analysis, pT3/4 stage and pN + stage emerged as independent risk factors for 3-year OS (P all < 0.05) (Table 2), while the injection method was not a significant factor affecting the 3-year OS.

Disease-free survival

The 3-year actual DFS rate did not differ significantly between the SSA and SMA groups (SSA vs. SMA = 82.9% vs. 88.5%, log-rank $P = 0.19$, Fig. 3B). Univariable Cox regression analysis showed associations between DFS and age, tumor size, pT stage, pN stage, and adjuvant chemotherapy (P all < 0.05). Further multivariable regression analysis identified pT3/4 and pN + stages as independent risk factors for 3-year DFS (P all < 0.05) (Table 2), while the injection method did not affect the 3-year DFS.

Survival outcomes in non-fluorescent lymph node stations

Based on different LNs visualizations, the SSA and SMA groups showed similar survival outcomes. In the group with ≤ 1 non-fluorescent LN stations, comprising 30.2% of the SSA group and 30.8% of the SMA group, no statistically significant differences were observed in the 3-year OS and 3-year DFS [OS: SSA vs. SMA = 87.2% vs. 95.0%, $P = 0.23$; DFS: SSA vs. SMA = 82.1% vs. 92.5%, $P = 0.17$]. For the group with > 4 non-fluorescent LN stations, it was 6.2% in the SSA group and 15.4% in the SMA group, with no significant differences in the 3-year OS and 3-year DFS [OS: SSA vs. SMA = 87.5% vs. 90.0%, $P = 0.81$; DFS: SSA vs. SMA = 87.5% vs. 90.0%, $P = 0.82$]. For the group with two non-fluorescent LN stations (22.3% in SSA and 29.5% in SMA) and the group with 3–4 non-fluorescent LN stations (34.1% in SSA and 31.5% in SMA), no statistical differences were found in the 3-year OS and 3-year DFS between the SSA and SMA groups. Stratified analysis based on total and distal gastrectomy showed no significant differences in the 3-year OS and 3-year DFS between the SSA and SMA groups across different categories of non-fluorescent LN stations (Table S2 <http://links.lww.com/JS9/D878>).

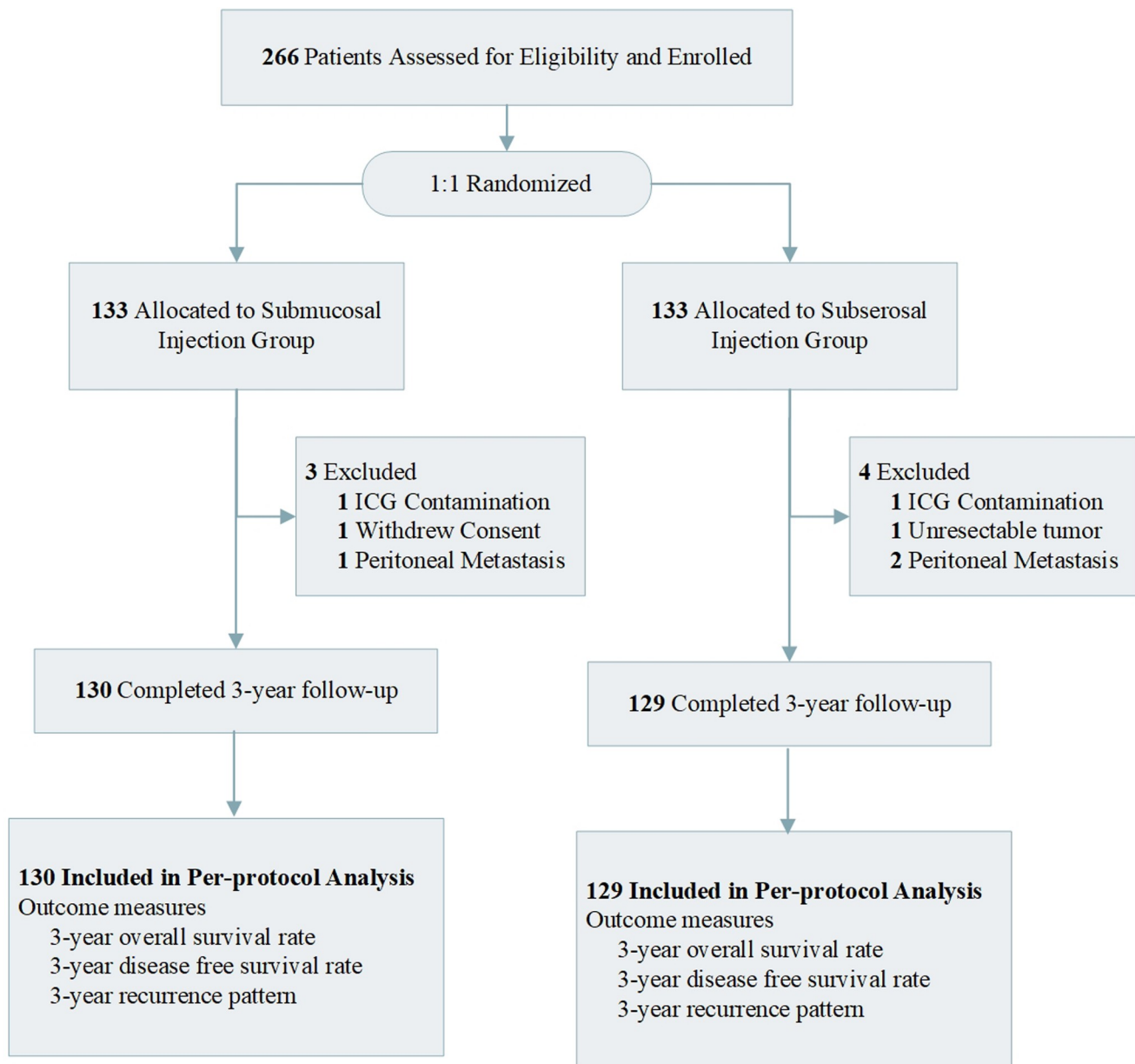


Figure 2. Study flowchart.

Recurrence pattern

During the 3-year follow-up, recurrence rates did not show a statistically significant difference between the SSA and SMA groups (SSA vs. SMA = 21/129 vs. 14/130, $P = 0.19$) (Table 3). The most common recurrence type was multi-site metastasis [SSA vs. SMA = 5 (3.9%) vs. 6 (4.6%), $P = 0.82$]. There were no significant differences in the rates of local recurrence [SSA vs. SMA = 2 (1.6%) vs. 1 (0.8%), $P = 0.19$], peritoneal metastasis [SSA vs. SMA = 4 (3.1%) vs. 2 (1.5%), $P = 0.54$], liver metastasis [SSA vs. SMA = 3 (2.3%) vs. 3 (2.3%), $P = 0.97$], and other or uncertain site metastasis [SSA vs. SMA = 7 (5.4%) vs. 2 (1.5%), $P = 0.11$]. There was no significant difference in the 3-year cumulative recurrence rates between the SSA and SMA groups [SSA vs. SMA = 21 (83.7%) vs. 14 (89.2%), $P = 0.19$] (Fig. 3C).

Subgroup analysis

In the stratified analysis of 141 patients with T3/4 stage disease, there were no significant differences in the 3-year actual OS rates [SSA vs. SMA = 76.8% vs. 83.3%, $P = 0.33$] and 3-year DFS rates [SSA vs. SMA = 71.0% vs. 79.2%, $P = 0.25$] between the SSA and SMA groups (Fig.S1 <http://links.lww.com/JS9/D878>). Post-operative recurrence rates were 24.6% in the SSA group and 16.7% in the SMA group (Table S3 <http://links.lww.com/JS9/D878>), and the cumulative recurrence rates showed no notable differences (Fig.S2 <http://links.lww.com/JS9/D878>). Among the 118 patients with T1/2 stage disease, both the SSA and SMA groups had 100% 3-year actual OS rates, and the 3-year actual DFS rates were 96.7% for SSA and 100% for SMA, without significant differences (Fig.S1C <http://links.lww.com/JS9/D878>, $P = 0.16$).

Table 1
Baseline and postoperative characteristics of the SMA and SSA groups.

Characteristics	Participants, No. (%)			P-value
	All (n = 130)	SMA (n = 130)	SSA (n = 129)	
Age, year				0.73
≤65	168 (64.9)	83 (63.8)	85 (65.9)	
>65	91 (35.1)	47 (36.2)	44 (34.1)	
Sex				0.82
Female	84 (32.4)	43 (33.1)	41 (31.8)	
Male	175 (67.6)	87 (66.9)	88 (68.2)	
BMI, kg/m ²				0.85
≤25	206 (79.5)	104 (80.0)	102 (79.1)	
>25	53 (20.5)	26 (20.0)	27 (20.9)	
ECOG				0.89
0	214 (82.6)	107 (82.3)	107 (82.9)	
1	45 (17.4)	23 (17.7)	22 (17.1)	
Tumor location				0.53
Lower	143(55.2)	71(55.4)	71(55.0)	
Middle	68(26.3)	31(31.8)	37(28.7)	
Upper	48(18.5)	27(20.8)	21(16.3)	
Tumor size, cm				0.27
≤4	158 (79.2)	75 (57.7)	46 (64.3)	
>4	101 (20.8)	55 (42.3)	83 (35.7)	
Type of gastrectomy				0.50
Total	123 (47.5)	59 (45.4)	64 (49.6)	
Distal	136 (52.5)	71 (54.6)	65 (50.4)	
Type of reconstruction				0.24
Billroth I	15 (5.8)	5 (3.8)	10 (7.8)	
Billroth II	121 (46.7)	66 (50.8)	55 (42.6)	
Roux-en-Y	123 (47.5)	59 (45.4)	64 (49.6)	
Pathological type				0.76
Undifferentiated	147 (56.8)	75 (57.7)	72 (55.8)	
Differentiated	112 (43.2)	55 (42.3)	57 (44.2)	
cT stage (AJCC8th)				0.87
T1	87 (33.6)	41 (31.5)	46 (35.6)	
T2	35 (13.5)	19 (14.6)	16 (12.4)	
T3	84 (32.4)	42 (32.4)	42 (32.6)	
T4a/T4b	53 (20.5)	28 (21.5)	25 (19.4)	
cN stage (AJCC8th)				0.50
N0	109 (42.1)	52 (40.0)	57 (44.2)	
N +	150 (57.9)	78 (60.0)	72 (55.8)	
cTNM stage (AJCC8th)				0.78
I	81 (31.3)	38 (29.3)	43 (33.3)	
II	68 (26.3)	35 (26.9)	33 (25.6)	
III	110 (42.5)	57 (43.8)	53 (41.1)	
pT stage (AJCC8th)				0.59
T1	86 (33.2)	39 (30.0)	47 (36.4)	
T2	32 (12.4)	19 (14.6)	13 (10.1)	
T3	91 (35.1)	48 (36.9)	43 (33.3)	
T4a/T4b	50 (19.3)	24 (18.5)	26 (20.2)	
pN stage (AJCC8th)				0.94
N0	110 (42.5)	52 (40.0)	58 (45.0)	
N1	51 (19.7)	27 (20.8)	24 (18.6)	
N2	43 (16.6)	23 (17.7)	20 (15.5)	
N3	55 (21.2)	28 (21.5)	27 (20.9)	
pTNM stage (AJCC8th)				0.77
I	95 (36.7)	46 (35.7)	49 (38.0)	
II	70 (27.0)	34 (26.2)	36 (27.9)	
III	94 (36.3)	50 (38.5)	44 (34.1)	
Adjuvant chemotherapy				0.65
No	102 (39.4)	53 (40.8)	49 (38.0)	
Yes	157 (60.6)	77 (59.2)	80 (62.0)	

(Continues)

Table 1
(Continued).

Characteristics	Participants, No. (%)			P-value
	All (n = 130)	SMA (n = 130)	SSA (n = 129)	
No. of non-fluorescent station				0.09
≤1	79 (30.5)	40 (30.8)	39 (30.2)	
2	67 (25.9)	29 (22.3)	38 (29.5)	
3–4	85 (32.8)	41 (31.5)	44 (34.1)	
>5	28 (10.8)	20 (15.4)	8 (6.2)	

Abbreviations: SMA: submucosal approach; SSA: subserosal approach; 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 performance status; cT, clinical T; cN, clinical N; pT, pathological T; pN, pathological N.

In the stratified analysis based on pN staging, among the 110 patients with N0 staging, there were no differences in the 3-year actual OS rates [SSA vs. SMA = 100% vs. 98.1%, $P = 0.29$] and 3-year DFS rates [SSA vs. SMA = 98.3% vs. 98.1%, $P = 0.93$] between the SSA and SMA groups. For 149 patients with N + staging, there were no differences in the 3-year actual OS rates [SSA vs. SMA = 77.5% vs. 85.9%, $P = 0.19$] and 3-year DFS rates [SSA vs. SMA = 70.4% vs. 82.1%, $P = 0.09$] between the SSA and SMA groups (Fig.S3 <http://links.lww.com/JS9/D878>). Postoperative recurrence rates were 28.2% for SSA and 16.7% for SMA (Table S4 <http://links.lww.com/JS9/D878>), and there was no significant difference in cumulative recurrence rates between N0 and N + staging (Fig.S4 <http://links.lww.com/JS9/D878>).

In the stratified analysis based on tumor size, among 158 patients with tumors ≤4 cm, there were no differences in the 3-year actual OS rates and 3-year DFS rate between the SSA and SMA groups (Fig.S5 <http://links.lww.com/JS9/D878>). Postoperative recurrence rates and cumulative recurrence rates were similar between the two groups (Table S5 <http://links.lww.com/JS9/D878> and Fig.S6A <http://links.lww.com/JS9/D878>). Similarly, the 3-year actual OS rates and 3-year DFS rates between the SSA and SMA groups showed no significant differences among the 101 patients with tumors >4 cm (Fig.S5 <http://links.lww.com/JS9/D878>). The postoperative recurrence rates and cumulative recurrence rates were comparable between the two groups (Table S6 <http://links.lww.com/JS9/D878> and Fig.S6B <http://links.lww.com/JS9/D878>).

In the stratified analysis based on BMI, among 206 patients with preoperative BMI ≤25 kg/m², there were no differences in the 3-year actual OS rates and 3-year DFS rate between the SSA and SMA groups (Fig.S7 <http://links.lww.com/JS9/D878>). Postoperative recurrence rates and the cumulative recurrence rates were not significantly different between the SSA and SMA groups (Table S7 <http://links.lww.com/JS9/D878> and Fig.S8A <http://links.lww.com/JS9/D878>). Among the 53 patients with a preoperative BMI>25 kg/m², no significant differences were found in the 3-year actual OS rates and 3-year DFS rate (Fig.S7 <http://links.lww.com/JS9/D878>). Postoperative recurrence rates and cumulative recurrence rates were also similar between the two groups (Table S8 <http://links.lww.com/JS9/D878> and Fig. S8B <http://links.lww.com/JS9/D878>).

In all stratified analyses, no significant differences were observed in the 3-year actual OS, 3-year actual DFS, or recurrence patterns between the SMA and SSA groups.

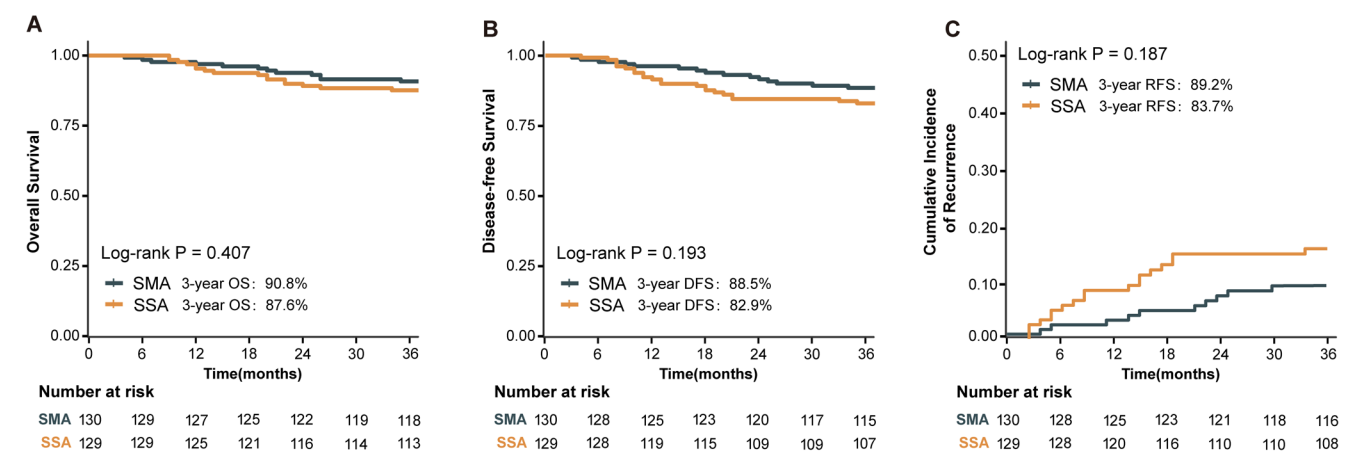


Figure 3. Kaplan-Meier curves comparing 3-year overall survival (A), 3-year disease-free survival (B), and cumulative incidence of first recurrence (C) between the SMA and SSA groups.

Discussion

Comparison of SMA and SSA in LN retrieval efficiency

To the best of our knowledge, the FUGES-019 study is the first randomized trial comparing the effectiveness of SSA and SMA in ICG-guided laparoscopic lymphadenectomy for gastric cancer. The 3-year follow-up results showed no significant differences in the actual OS and DFS rates between the two groups. The similar recurrence patterns indicate equivalence between the two methods. These findings suggest that SSA is a feasible and effective approach for ICG injection in laparoscopic lymphadenectomy, comparable to SMA.

Previous studies have confirmed that maximal LN dissection with the standard scope improves long-term survival in patients with GC^[26–29]. Given the complex lymphatic drainage of the stomach, ICG fluorescence enhances tissue penetration^[25,30]. This leads to more accurate identification of lymph nodes and the lymphatic network within hypertrophic adipose tissues, showing great potential for D2 lymphadenectomy^[12,31,32]. It facilitates lymph node dissection in radical gastrectomy, allowing the retrieval of more lymph nodes without increasing complications or surgical time, ultimately improving the prognosis of GC patients^[18,33,34]. The application of ICG in GC is in full swing.

Safety profile and complications

Enhancing the operability and convenience of ICG application is crucial for its widespread adoption. Thus, comparing the efficacy of different ICG injection methods holds essential clinical significance. SMA involves injecting ICG at four points around the tumor, similar to the traditional SSA method, which also uses four injection points around the tumor from outside the serosa^[35]. But the traditional SSA four-point injection method is difficult to determine the injection site without intraoperative tumor localization, especially in cases of early gastric cancer. Therefore, we utilized a modified SSA injection method, namely Huang's subserosal hexa-points maneuver. This method is based on the lymphatic drainage around the stomach and the principles of standard D2 lymph node dissection^[16,36,37]. It involves

injecting ICG at six points along the greater and lesser curvatures of the stomach to visualize lymphatic drainage, not just around the tumor, thus achieving the ICG fluorescence effectively.

Although these two injection methods differ conceptually, previous studies^[17,19,38] have shown that the injection site of tracers should not be limited to the mucosal layer but should also consider the lymphatic drainage pathways of the serosal layer. Injecting ICG into the submucosa around the tumor is presumed to disperse similarly to the subserosal layer injection^[39–41], and lymphatic vessels in the gastric mucosal layer are interconnected with those in the serosal layer through the intermuscular lymphatic network, leading to an assumption of no difference in LN navigation between the SMA and SSA. For early GC or advanced GC that has not invaded the serosa, submucosal injection through endoscopy is preferable. However, apart from alleviating the anxiety and discomfort caused by additional preoperative gastroscopy examinations^[42], the SSA offers several additional advantages. First, the SSA method performed by surgeons independently reduces the risk of ICG contamination and minimizes potential complications caused by inexperienced endoscopists. Second, optimal fluorescence via SSA injection is achieved approximately 20 minutes. During the waiting period for ICG imaging, surgeons can perform sequential surgical procedures, such as essential omental separation and perigastric adhesion separation without extending the overall surgical duration^[23,43]. More importantly, the SMA method requires coordination between surgeons and endoscopists, while SSA reduces dependence on multidisciplinary collaboration, making it particularly advantageous in settings with limited endoscopic expertise. By simplifying workflows and optimizing resource allocation, SSA is well-suited for community hospitals and high-volume centers alike. The cost-effectiveness of SSA further supports its broader adoption. By eliminating the need for endoscopic equipment and consumables, SSA reduces healthcare costs while improving accessibility in resource-constrained environments. Its simplicity and efficiency make it a practical option for both advanced surgical centers and rural hospitals, where economic considerations and workflow optimization are critical.

Table 2
Univariable and multivariable Cox regression analyses of risk factors for survival.

Characteristics	Overall survival				Disease-free survival			
	Univariable model		Multivariable model		Univariable model		Multivariable model	
	HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P- value	HR (95% CI)	P- value
Group								
SMA	Ref				Ref			
SSA	1.37 (0.65–2.90)	0.41			1.54 (0.80–2.97)	0.20		
Age, year								
≤ 65	Ref		Ref		Ref		Ref	
>65	2.15 (1.02–4.52)	0.04	1.71 (0.81–3.59)	0.16	2.31 (1.21–4.41)	0.01	1.83 (0.95–3.51)	0.07
Sex								
Female	Ref				Ref			
Male	0.53 (0.25–1.11)	0.09			0.76 (0.39–1.47)	0.41		
BMI, kg/m ²								
≤25	Ref				Ref			
>25	1.06 (0.43–2.61)	0.90			0.75 (0.31–1.79)	0.51		
Tumor location								
Lower	Ref				Ref			
Middle	0.82 (0.32–2.12)	0.69			0.68 (0.29–1.59)	0.37		
Upper	1.41 (0.58–3.47)	0.45			1.32 (0.61–2.88)	0.49		
Tumor size, cm								
≤4	Ref		Ref		Ref		Ref	
>4	5.08 (2.16–11.95)	<0.0001	1.85 (0.78–4.37)	0.16	4.03 (2.00–8.15)	<0.001	1.77 (0.84–3.70)	0.13
Type of reconstruction								
Billroth I/II	Ref				Ref			
Roux-en-Y	1.61 (0.82–3.15)	0.16			1.75 (0.97–3.17)	0.07		
Pathological type								
Differentiated	Ref				Ref			
Undifferentiated	0.75 (0.36–1.58)	0.45			0.78 (0.41–1.49)	0.45		
pT stage (AJCC8th)								
T1/2	Ref		Ref		Ref		Ref	
T3/4	5.20 (2.89–1272.04)	0.008	4.32 (2.16–68.63)	<0.001	16.40 (3.94–68.21)	<0.001	6.18 (1.30–29.27)	0.02
pN stage (AJCC8th)								
N0	Ref		Ref		Ref		Ref	
N +	21.92 (2.98–161.35)	0.002	5.38 (1.71–40.88)	0.004	14.51 (3.49–60.32)	<0.001	5.72 (1.25–26.16)	0.03
Adjuvant chemotherapy								
No	Ref				Ref		Ref	
Yes	2.07 (0.88–4.86)	0.10			2.12 (1.00–4.49)	0.050	0.67 (0.31–1.46)	0.31

HR: hazard ratio; CI: confidence interval; SMA: submucosal approach; SSA: subserosal approach; AJCC: American Joint Committee on Cancer; ECOG: Eastern Cooperative Oncology performance status; BMI: body mass index (calculated as weight in kilograms divided by height in meters squared); pT: pathological T; pN: pathological N.

But both SMA and SSA possess unique advantages, and the selection should be based on the clinical scenario and surgeon expertise. The choice of the injection method should consider tumor staging. SMA is particularly beneficial for early-stage cancers where accurate lymph node mapping is critical. In contrast, SSA offers are more practical for mid-to-late-stage or complex tumors, where broader lymph node visualization is necessary, and technical simplicity becomes a priority in challenging cases. Additionally, surgeons should assess their own experience and evaluate patient-specific factors comprehensively to select the most appropriate method and achieve the best surgical outcomes.

Oncological outcomes of SMA and SSA

However, most published studies comparing the efficacy of subserosal and submucosal ICG injections are retrospective analyses^[16,19,44,45]. New technologies are frequently adopted in

surgical oncology subspecialties before randomized studies are done to confirm their safety and efficacy. Given the significant advantages of ICG-guided lymph node dissection in gastric cancer treatment, our center conducted the first prospective FUGES-019 study to provide sufficient evidence supporting the equivalence of subserosal injection to traditional submucosal injection. Preliminary findings from the FUGES-019 study indicate that the performance of subserosal and submucosal ICG injections is comparable in terms of LN fluorescence, but the former is more conducive to surgical procedures and does not impose additional economic and psychological burdens on patients. However, evaluating the effectiveness and safety of a medical technology requires comprehensive consideration of both short-term and long-term results. Here, we present the 3-year survival results of the FUGES-019 study, which demonstrated comparable long-term oncological outcomes between the SMA and SSA groups. While OS and DFS are influenced by lymphadenectomy completeness, they are also affected by factors like preoperative

Table 3
Frequencies of causes of first recurrence and death within 3 years after surgery in SMA and SSA groups.

Events	Group- No. (%)		Risk difference ^a	Hazard ratio ^b	95% CI	P-value ^c
	SMA (n = 130)	SSA (n = 129)				
Recurrence ^d	14 (10.8)	21 (16.3)	-0.055	1.57	0.80–3.09	0.19
Local	1 (0.8)	2 (1.6)	-0.008	2.13	0.19–23.45	0.54
Peritoneum	2 (1.5)	4 (3.1)	-0.016	2.10	0.38–1.47	0.39
Liver	3 (2.3)	3 (2.3)	0	1.04	0.21–5.14	0.97
Multiple sites ^e	6 (4.6)	5 (3.9)	0.007	0.87	0.27–2.85	0.82
Other or uncertain sites	2 (1.5)	7 (5.4)	-0.039	3.66	0.76–17.63	0.11
All-cause death ^g	12 (9.3)	16 (12.4)	-0.031	1.37	0.65–2.90	0.41
Gastric cancer	11 (8.5)	15 (11.6)	-0.031	1.40	0.64–3.05	0.40
Other causes ^h	1 (0.8)	1 (0.8)	0	1.02	0.06–16.32	0.99

^aExcept for all-cause death, the risk difference was calculated by subtracting the cumulative incidence in the first 3 years of the SMA group from that of the SSA group in presence of competing events; for all-cause death, the risk difference was calculated by subtracting the 3-year overall survival rate of the SMA group from that of the SSA group.

^bExcept for all-cause death: competing-risks survival regression was used to derive the hazard ratio, 95% CI, and P-value. For total recurrence, all-cause death was the competing event; for the specific types of recurrence, other types of recurrence and death were the competing events; for gastric cancer cause of death, other causes of death were the competing events and vice versa. Univariable Cox regression was used for all-cause death. SMA group is the reference group.

^cP value for the hazard ratios.

^dRefers only to first-time recurrence, even though patients can have recurrence at multiple times.

^eIncludes patients who have recurrence simultaneously in 2 or more metastatic sites, including peritoneum, liver, lung, bone, brain, distant lymph node, or other hematogenous metastatic sites.

^fIncludes hematogenous recurrence at sites other than liver (i.e. lung, bone, brain, adrenal gland), recurrence at distant lymph node, and recurrence at uncertain sites.

^gPost hoc exploratory outcomes.

^hIncludes other cancers, diseases other than cancer, unintentional injuries, and unknown causes
 HR: hazard ratio; CI: confidence interval; SMA: submucosal approach; SSA: subserosal approach.

treatment and initial diagnosis. Multivariate Cox regression analyses, incorporating clinical and pathological factors (e.g., pT and pN staging, tumor size, and preoperative treatment) revealed that OS and DFS were primarily associated with tumor pathological staging, rather than ICG injection methods. Additionally, survival outcomes under different LN fluorescence conditions were also comparable between the SSA and SMA groups.

Lymph node metastasis is a critical factor in gastric cancer staging and postoperative therapy, with previous studies confirming that higher numbers of retrieved lymph nodes correlate with improved survival rates^[26,46,47]. ICG-guided lymph node dissection enhances the accuracy and completeness of lymphadenectomy by visualizing lymphatic pathways, potentially reducing the risk of postoperative metastasis and improving long-term outcomes^[48,49]. Our study, the first prospective RCT comparing SSA and SMA, found no significant differences in OS or DFS between the two methods during the 3-year follow-up, indicating comparable oncologic outcomes and supporting the broader adoption of SSA in clinical practice. These findings align with the need for comprehensive evaluation of both short- and long-term outcomes, as short-term benefits of new techniques do not always translate into long-term efficacy. For example, although minimally invasive surgery (MIS) for early cervical cancer was widely adopted based on short-term advantages, RCTs later revealed inferior DFS and increased mortality compared to open surgery^[50–52]. Similarly, robotic-assisted radical cystectomy showed no significant differences in recurrence rates or cancer-specific survival compared to open procedures despite initial perceived advantages^[53–56]. By demonstrating equivalent long-term outcomes for SSA and SMA, our study validates SSA as a safe and effective alternative for ICG-guided lymph node dissection in gastric cancer surgery. These results also provide a valuable reference for ongoing and future prospective studies, such as CLASS-11 (NCT04593615) and 3D-4K-ICG (NCT06161207), to

further optimize individualized treatment strategies and enhance surgical standardization.

There is consensus that the performance of lymphadenectomy is significantly impacted by factors such as BMI, gastrectomy extent, the extent of lymphadenectomy, tumor size, and tumor staging^[27,57]. Subgroup analysis based on these factors revealed comparable 3-year OS and DFS rates between the SMA and SSA groups. Furthermore, whether injected submucosally or subserosally, the primary role of ICG is to assist surgeons in precisely identifying the location of LNs during gastrectomy, thus facilitating accurate LN dissection. Both injection methods fundamentally operate through the same mechanism – ICG near-infrared fluorescent imaging – to achieve this goal. Therefore, provided that LNs are effectively retrieved, there may be no significant impact on the long-term survival results.

Moreover, both SMA and SSA groups exhibited similar recurrence rates and patterns, and subgroup analyses also showed no significant differences in recurrence patterns between the two groups. The comparable recurrence patterns observed between SSA and SMA may be explained by similar lymphatic drainage pathways and effective lymph node clearance achieved by both methods. Studies have shown that lymphatic vessels in the gastric mucosa and subserosa are interconnected through the intermuscular lymphatic network, enabling ICG to effectively mark lymphatic pathways regardless of the injection layer^[17,19]. Additionally, the modified SSA injection technique used in this study, employing six key points along the gastric curvatures, ensures comprehensive lymph node visualization within the D2 lymphadenectomy range, offering outcomes comparable to SMA^[17,58–60]. However, the recurrence process in gastric cancer is influenced by factors beyond lymph node dissection, including the tumor microenvironment, multi-route lymphatic drainage, and micro-metastases, which can spread via hematogenous, serosal, or distant pathways^[16,36]. Tumor heterogeneity and micro-metastatic foci further contribute to recurrence risks,

independent of the injection method^[61,62]. These intrinsic biological factors likely play a dominant role in recurrence outcomes, highlighting the need for further research to explore strategies targeting these mechanisms. Despite the similarities in recurrence patterns, SSA's practical advantages, including broader lymphatic coverage and procedural simplicity, may make it a preferable choice in complex or advanced cases.

By comprehensively comparing the lymph node mapping, cost-effectiveness, and survival outcomes, the FUGES-019 study provides evidence for the standardized application of ICG-guided lymphadenectomy, promoting the practical use of this technology and bringing better treatment outcomes to gastric cancer patients.

Study limitations

This study has some limitations. As the study was conducted at a high-volume single center in China with Asian patients, our findings may not be generalizable to other centers; thus, cautious interpretation of these results is required. However, conducting clinical trials entails substantial manpower, material, and time costs. Analyzing different study endpoints at different stages of research can explore clinical phenomena while avoiding research waste. The study was designed as a non-inferiority trial focused on lymph node retrieval, with OS and DFS reported as secondary endpoints to provide additional insights into long-term outcomes. Larger, multi-center studies are needed to validate these findings and draw more definitive conclusions. But this study is currently the only prospective RCT comparing the SSA and SMA methods and evaluating their long-term prognostic outcomes. This comparison can provide scientific evidence for ongoing prospective studies utilizing the SSA injection method and offer valuable references for future clinical research. Additionally, this study was conducted in an institution with extensive experience in minimally invasive gastric cancer surgery; we speculate that for novice laparoscopic gastric cancer surgeons, the learning curve for intraoperative ICG subserosal injection remains unclear, which could potentially influence their preference for injection methods. Moreover, since neoadjuvant treatment may induce lymphoid tissue fibrosis and alter the anatomical conditions of the primary tumor, this study excluded patients receiving neoadjuvant treatment. As the first prospective RCT comparing SSA and SMA, we aimed to minimize potential confounding factors and ensure consistency within the study population. While this approach enhanced the interpretability of the results, it limits the applicability of the findings to this growing subset of gastric cancer patients. Further studies are needed to evaluate the efficacy of ICG-guided techniques in patients receiving neoadjuvant therapy.

In conclusion, the long-term oncological outcomes of the FUGES-019 trial support the equivalence of SSA and SMA in ICG injection during laparoscopic radical gastrectomy. These findings indicate that SSA is a viable option for ICG-guided laparoscopic lymphadenectomy in gastric cancer, provided the procedure is performed by qualified surgeons.

Ethical approval

The study was approved by the Institutional Review Board at the Fujian Medical University Union Hospital (2019YF045-01).

Consent

Participants were informed of the study's purpose, procedures, potential risks and benefits, and their right to withdraw from the study at any time without penalty. Data collected were kept confidential and used solely for research purposes. Patients signed informed consent regarding publishing their data.

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Author's contribution

C.M.H. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Q.Z., Z.X.S.-G., and Z.L. contributed equally to this work and should be considered co-first authors. Concept and design: Q.Z., C.H.Z., Q.Y.C., and C.M.H. Acquisition, analysis, or interpretation of data: Q.Z., Z.X.S.-G., Z.L., Z.N.H., and P.L. Drafting of the manuscript: Q.Z., Z.X.S.-G., Z.L., Q.Y.C., and C.M.H. Statistical analysis: Q.Z., Z.X.S.-G., Z.L., Q.Y.C., and C.M.H. Administrative, technical, or material support: Z.N.H., H.G.W., J.Y.C., Q.H., J.X.W., P.L., J.W.X., C.H.Z. Supervision: Q.Z., Q.Y.C., and C.M.H.

Conflicts of interest disclosure

The authors declare that they have no competing interests.

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