



Use of fluorescence imaging and indocyanine green for sentinel node mapping during gastric cancer surgery: Results of an intercontinental Delphi survey



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ABSTRACT

Background: Understanding the extent of tumor spread to local lymph nodes is critical to managing early-stage gastric cancer. Recently, fluorescence imaging with indocyanine green has been used to identify and characterize sentinel lymph nodes during gastric cancer surgery, but no published guidelines exist. We sought to identify areas of consensus among international experts in the use of

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fluorescence imaging with indocyanine green for mapping sentinel lymph nodes during gastric-cancer surgery.

Methods: In this 2-round, online Delphi survey, 27 international experts voted on 79 statements pertaining to patient preparation and contraindications to fluorescence imaging with indocyanine green during gastric cancer surgery; indications; technical aspects; advantages/disadvantages and limitations; and training and research. Methodological steps were adopted during survey design to minimize bias.

Results: Consensus was reached on 61 of 79 statements, including giving single injections of indocyanine green into each of the 4 quadrants peritumorally, administering indocyanine green on the same day as surgery, injecting a total of 1 to 5 mL of 5 mg/mL indocyanine green, injecting endoscopically into submucosa, and repeating indocyanine green injections a second time if sentinel lymph node visualization remains inadequate. Consensus also was reached that fluorescence imaging with indocyanine green is an acceptable single-agent modality for sentinel lymph node identification and that the sentinel lymph node basin method is preferred. However, sentinel lymph node dissection should be limited to T1 gastric cancer and tumors ≤ 4 cm in diameter, and further research is necessary to optimize the technique and render fluorescence-guided sentinel lymph nodes dissection acceptable for routine clinical use.

Conclusion: Although considerable consensus was achieved, further research is necessary before this technology should be used in routine practice.

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Introduction

According to 2018 global statistics, gastric cancer is the fifth most common malignancy and third most frequent cause of cancer-related death worldwide.¹ Tragically, most gastric cancer patients present after their malignancy has spread beyond the prospect of surgical cure, resulting in low long-term survival rates.² In recent years, considerable research has been published targeting the identification and proper staging of patients with earlier stage gastric cancer to increase survival rates and better tailor treatment among, at least, this subset of gastric cancer patients.^{3,4} Sentinel lymph node dissection (SLND)—or dissection of the first node(s) downstream from the primary malignancy—has long been recognized as predictive of more distant spread and, as such, also is predictive of patient survival and a tool to use to tailor further management.^{5–8} The SLND concept has been borne out in various malignancies and has become standard of care for both breast cancer and melanoma. Unfortunately, SLND in gastric cancer has presented a unique set of challenges, including variable gastric drainage and the presence of skip metastases.

Among various tools developed to enhance the localization of SLNs during gastric cancer surgery has been fluorescence imaging (FI),^{4,9,10} most commonly using the fluorophore indocyanine green (ICG), which has generally proven itself superior to other dyes not just during gastric cancer surgery¹¹ but also during the detection of SLNs in numerous other cancers, including those of breast,^{12–15} skin,¹² head and neck,¹⁴ uterine, and endometrial origin.^{16–20} During gastric cancer surgery, FI with ICG (FI+ICG) has been found not only to enhance the identification of SLNs, but also to increase the sensitivity of detecting SLNs with micrometastases^{9,10,21,22} and augment the localization of tumors and their margins.^{23–25} This said, to date, only a single randomized clinical trial (RCT) has been published evaluating the effectiveness and safety of using FI+ICG for SLN identification,²⁶ leading to questions regarding the appropriateness of its routine use.⁹ Uncertainty also remains regarding the mechanics of FI+ICG, including the optimal dose and route of administration for ICG.^{10,27}

To address the challenges, uncertainties, and variabilities of intraoperative FI across a range of surgical fields, in February 2019, members of the Advisory Board of the International Society for Fluorescence-Guided Surgery (ISFGS) convened at a consensus conference in Frankfurt, Germany,²⁸ where they decided to conduct, over the next few years, surveys to identify areas of consensus and nonconsensus within intraoperative FI among world experts across multiple surgical fields. The current paper describes

the results of our survey among world experts in the use of intraoperative FI for SLN identification during gastric cancer surgery. The study's main objective was to identify both areas of consensus among experts and areas of nonconsensus requiring further empirical study.

Methods

Expert recruitment and data collection

A Delphi survey was completed from November 2020 to April 2021, adhering to published guidelines²⁹ and coordinated by an MD-PhD-level expert (K.P.W.) in survey design and orchestration. The Delphi technique has achieved appreciable credence as a way to identify areas of consensus/nonconsensus among experts over a broad range of health- and non-health-related fields.²⁹

After the consensus conference in Frankfurt,²⁸ emails were sent to all ISFGS advisory board members asking everyone to provide a list of questions and/or issues they consider important pertaining to fluorescence-guided procedures within their surgical field. These questions/issues were employed to create Delphi surveys intended for distribution among experts within each specific field. After several iterations, the final gastric cancer SLN-detection survey consisted of 5 questions on the nature of each expert's surgical practice, followed by 79 statements for participating experts to vote upon, divided into the following 5 modules: Module 1: Patient preparation and contraindications ($n = 12$ statements); Module 2: Indications and general statements ($n = 19$); Module 3: Technical aspects ($n = 24$); Module 4: Potential advantages, disadvantages, and limitations ($n = 15$); and Module 5: Training and research ($n = 9$). Among these 79 statements, 60 had the binary response option agree/disagree, whereas 19 statements had multiple response options like never/sometimes/most times/always.

During survey development, attempts were made to minimize the risk that the survey tool itself might influence voter responses via the wording and/or order of its statements and/or response options (acquiescence bias). Such attempts included balancing the number of statements that might be perceived as favorable, unfavorable, and neither favorable nor unfavorable (non-judgmental) to FI and varying the order of the available response options, listing the most FI-agreeable option sometimes first, sometimes last, and sometimes in the middle. Whether the statements were considered favorable, unfavorable, or nonjudgmental was determined by a panel of 4 judges (D.S., F.D., R.J.R., K.P.W.) who rated the statements independently, with further discussion or altering of statements

performed, as necessary, to achieve unanimous agreement. Of the 79 consensus statements, 27 ultimately were deemed favorable, 25 unfavorable, and 27 nonjudgmental.

Potential experts were identified both by word of mouth and by generating a list of corresponding authors while reviewing all currently-published studies on FI use during gastric cancer surgery. To select expert voters, the following eligibility criteria were employed: (1) coauthorship of ≥ 1 clinical study examining FI use during gastric cancer surgery published in a peer-reviewed scientific journal; or (2) ≥ 10 years in surgical practice and 5 years using FI+ICG during gastric cancer surgery; they also had to (3) be acknowledged as an expert in FI use during gastric cancer surgery by the ISFGS advisory board, (4) be fluent in written English, (5) be willing to participate, and (6) be willing to review the manuscript's penultimate draft prior to submission for publication. This ultimately resulted in a list of 38 experts spanning 5 continents.

After this list of experts was generated, an email was sent to everyone on the list, asking them to participate in the survey and providing a link to the online survey application SurveyMonkey, with follow-up emails sent to all nonrespondents once weekly for 3 weeks, followed by an email or telephone call from the survey overseer (D.S.) to anyone who had not yet responded. Round 1 was considered complete within 1 week of the above-noted telephone calls, and all round 1 data were analyzed to identify the degree of consensus reached with each of the 79 statements. Only statements for which adequate consensus was not reached were included in the round 2 survey, to which all 38 experts again were sent an email and link, adhering to the same email, telephone, and data collection termination protocol employed for round 1. Following published Delphi survey guidelines,²⁹ along with the statements for which no round 1 consensus was achieved, round 2 participants also were informed of the percentage of participants who had selected each response option in round 1.

Data analysis

Percentage consensus—defined as the agreement between the responders rather than the agreement with any given statement—was calculated as the number of voters choosing the most commonly-selected response divided by the total number of experts voting on that particular statement, with $\geq 70\%$ consensus considered consensus. Percentage participation also was calculated for each statement, with $\geq 80\%$ participation considered necessary for consensus/nonconsensus to be considered valid. For quality control, data were analyzed using both SurveyMonkey's intrinsic data-analysis tool and Windows Excel, version 16.0 (Microsoft Corp, Redmond, WA).

Results

Voter characteristics

Twenty-seven (71.1%) of the 38 listed experts ultimately participated, among whom 15 voted in both rounds: 7 just in round 1 and 5 just in round 2, for round totals of $n = 22$ and $n = 20$, respectively. Geographically, there was almost equal distribution across Asia-Pacific, Europe, and North America, with a single respondent from South America. Further characteristics of the expert panel are summarized in Table I.

Consensus results

One of the 79 statements, which achieved 89.6% consensus, was eliminated from final analysis because its wording was felt to be potentially misleading by an independent reviewer after data

Table I
Practice characteristics of the sample

Practice characteristic	Number	Percentage
Region of practice ($N = 27$)		
Asia-Pacific	9	33.3
Europe	9	33.3
North America	8	29.6
Latin America	1	3.7
Surgical specialty ($N = 26$)		
Upper GI surgery	12	46.2
GI surgery	9	34.6
Surgical oncology	2	7.7
Hepatobiliary surgery	2	7.7
Other	1	3.8
Nature of practice ($N = 27$)		
Primarily university-based	18	66.7
Some university affiliation	4	14.8
Nonacademic	5	18.5
Years performing gastric cancer surgery ($N = 27$)		
<10 y	2	7.4
10–20 y	14	51.9
>20 y	11	40.7
Years performing fluorescence-guided surgery ($N = 27$)		
<5 y	15	55.6
5–10 y	9	33.3
>10 y	3	11.1

GI, gastrointestinal.

Table II
Overall summary of results

	Number	Percentage
Summary of statements (78 statements)		
Consensus reached	60	76.9
No consensus reached	18	23.1
Number of agree/disagree statements	59	75.6
Statements agreed with ($n = 59$), n (%)	47	79.7
Statements disagreed with ($n = 59$), n (%)	10	16.9
Statements evenly split ($n = 60$), n (%)	2	3.4
Statements worded favorably to FI/ICG or SLN mapping	26	33.3
Statements worded unfavorably to FI/ICG or SLN mapping	25	32.1
Nonjudgmental statements	27	34.6
Mean overall consensus	78.9%	
Minimum consensus	36.8%	
Maximum consensus	100.0%	
When consensus reached (60 statements)		
Consensus reached in first round	38	63.3
Consensus reached in second round	22	36.7
100% consensus reached	7	11.7
90%–99% consensus reached	9	15.0
80%–89% consensus reached	26	43.3
70%–79% consensus reached	18	30.0
Statements agreed with (consensus)	38	64.4
Statements disagreed with (consensus)	10	16.9

FI, fluorescence imaging; ICG, indocyanine green; SLN, sentinel lymph node.

collection, leaving 78 for analysis. Over 2 rounds of voting, consensus was reached on 60 of these remaining 78 statements (76.9%), 38 in the first and 22 in the second round (Table II). Valid voting, defined as $\geq 80\%$ of all the voters in a given round actually voting, was achieved for all but 1 statement (Module 3). With the 59 statements on which voters were asked to either agree or disagree, the majority of voters agreed with 47 (79.7%), although they disagreed with 10 (16.9%) and were evenly split on 2. The

Table III

Module 1—Patient preparation and contraindications

Statements voted upon	No. of votes	Voting, %	Most common response	No. of rounds	Consensus, %
Consensus reached					
Allergic reactions to ICG are extremely rare.	20	90.9	Agree	1	100
Inability to provide informed written consent is an absolute contraindication to using Fl+ICG.	20	100	Disagree	2	95.0
All patients should be asked if they are allergic to iodine, shellfish, or ICG prior to having ICG administered.	19	86.4	Agree	1	94.7
Prior to undertaking SLN dissection for clinical decision-making, patients should be informed that its use is still experimental.	21	95.5	Agree	1	90.5
Prior to undertaking SLN dissection for clinical decision-making, patients should provide written informed consent specific to its use.	22	100	Agree	1	86.4
Prior to surgery, patients should be provided with written information about the use of SLN dissection for clinical decision-making.	21	95.5	Agree	1	85.7
Inability to provide informed written consent is an absolute contraindication to using SLN dissection for clinical decision-making.	20	90.9	Agree	1	85.0
Known or suspected allergy to iodine or shellfish is an absolute contraindication to Fl+ICG.	19	95.0	Agree	2	78.9
No consensus reached					
Pregnancy is an absolute contraindication to Fl+ICG.	20	100	Agree	2	60.0
Prior to undergoing Fl+ICG, patients should provide written informed consent specific to its use.	20	100	Agree	2	55.0
Prior to undergoing Fl+ICG, patients should be provided with written information specifically addressing its use.	20	100	Agree/Disagree	2	50.0
Prior to undergoing Fl+ICG, patients should be informed that its use is still experimental.	20	100	Agree/Disagree	2	50.0

Average consensus = 77.6%.

Fl, fluorescence imaging; ICG, indocyanine green; SLN, sentinel lymph node.

overall level of consensus across the 78 statements was 78.9%; however, this percentage was appreciably lower in the first 4 modules—mean percentage consensus ranging from 76.7% for Module 3 to 78.4% for Modules 2 and 4—than the fifth, on training and research, for which the mean consensus across 9 statements was 91.6%. The percentage of statements for which consensus was reached also varied considerably among the 5 modules; 66.7%, 72.2%, 79.2%, 73.3%, and 100% for Modules 1 to 5, respectively. Total unanimity was achieved for the following 7 statements: on allergic reactions to ICG being extremely rare (Module 1); on ICG being injected around the tumor's periphery, the timing of ICG administration being important, and the need for further research to determine the optimum dose, concentration, and timing of ICG administration (Module 3); and on the use of Fl being likely to increase, both in clinical practice and research over the next decade, and the need for an RCT to determine the role of Fl for SLN identification during gastric cancer surgery (Module 5).

Survey results for all 78 statements are listed individually in **Tables III to VII**. No consensus was attainable for 4 of the 12 statements on patient preparation and contraindications against either Fl or ICG (**Table III**). Although consensus was reached that failure to obtain informed written consent is an absolute contraindication to using SLN dissection for decision-making, there was 100% agreement that using ICG without informed written consent is not. Although 95% felt that a known or suspected allergy to iodine or shellfish is an absolute contraindication to performing Fl+ICG and 86% agreement that all patients should be asked about such allergies, there also was 100% consensus that allergic reactions to ICG are extremely rare. Only 60% felt that pregnancy was an absolute contraindication. And although consensus was reached that, prior to using SLND for clinical decision-making, patients should (a) be provided with information specific to SLND, (b) be told that its use is still experimental, and (c) give informed written consent specific to SLND preoperatively, none of these 3 sentiments was expressed by even a majority of voters for Fl+ICG.

Regarding indications, consensus was reached that SLN dissection is appropriate for early-stage cancers under either 3 cm or 4 cm in diameter, even when endoscopic resection is the only management of the primary tumor, but that this only applies to T1-stage cancers and not to cancers >4 cm in diameter. The only statement for which strong ($\geq 90\%$) consensus was reached was that SLN navigation surgery could increase the applicability of local resection techniques in SLN-negative cases. The SLN basin approach was preferred over the “pick-up” method by 82% of the voters. Levels of consensus for further statements on indications for SLN identification are listed in **Table IV**.

On ICG administration (**Table V**), consensus was reached that it should be injected peritumorally; no more than 4 injections are needed, but that all 4 quadrants should be injected; it should be injected endoscopically into submucosal tissue; it should be injected on the same day as surgery; the optimum total ICG dose is 1 to 5 mL (5–25 mg); Fl+ICG is an acceptable single modality for SLN identification; and that ICG should be re-administered if adequate SLN visualization is not achieved with the first dose. There also was consensus that the dose, concentration, and timing of ICG administration are very important. On the other hand, there was 100% consensus that further research is necessary to determine the optimum dose, concentration, and timing for ICG and that Fl+ICG should only be used sometimes (as opposed to never/most times/always). There also was no consensus reached regarding the best approach to SLN identification (though almost two-thirds selected Fl+ICG alone over radiocolloid combined with either blue dye or Fl+ICG), whether ICG should be dosed on an mg/kg or absolute basis, when on the same day the ICG should be injected (though almost two-thirds selected 11 to 30 minutes before switching to near-infrared light), or how often Fl+ICG should be used as the only approach.

Regarding advantages (**Table VI**), strong consensus was reached that using Fl+ICG for SLN identification has the potential to significantly change gastric cancer surgery, but no consensus that it

Table IV

Module 2—General statements regarding and indications for sentinel lymph node identification during gastric cancer surgery

Statements voted upon	No. of votes	Voting, %	Most common response	No. of rounds	Consensus, %
Consensus reached					
SLN navigation surgery can increase the applicability of local resection techniques (eg, ESD, WR, segmental resection, NEWS, CLEAN-NET, etc) in SLN negative cases.	19	86.4	Agree	1	94.7
Cancer deposits in a sentinel lymph node <2 mm in diameter (micrometastasis) should be considered a positive node.	21	95.5	Agree	1	86.4
The SLN basin is best defined by a... (named artery area; lymph node area)	20	100	Lymph node area Disagree	2	85.0
There is a role for SLN dissection for early-stage cancers EVEN LARGER than 4 cm in diameter.	19	95.0	Disagree	2	84.2
SLN dissection only has a role in patients with T1 gastric cancer.	18	90.0	Agree	2	83.3
The best approach to SLN dissection is the... (pick-up method; SLN basin technique).	17	85.0	SLN basin	2	82.4
There is a role for SLN dissection in patients with any T-stage gastric cancer.	20	90.9	Disagree	1	80.0
A false negative rate >10% is acceptable for the clinical application of SLN navigation in gastric surgery.	19	86.4	Disagree	1	78.9
There is a role for SLN dissection for early-stage cancers <3 cm in diameter.	19	95.0	Agree	2	78.9
There is a role for SLN dissection even in cases where endoscopic resection is the only management of the primary tumor (EMR or ESD).	19	95.0	Agree	2	78.9
There is a role for SLN dissection for early-stage cancers <4 cm in diameter.	20	90.9	Agree	1	75.0
Intraoperative frozen section evaluation with H&E staining is an acceptable modality for the identification of positive SLNs in gastric cancer.	18	90.0	Agree	2	72.2
Frozen section with H&E is not enough for the diagnosis of positive SLNs and more advanced pathologic methods should be used (eg, serial sectioning, IHC, and/or PCR).	18	81.8	Agree	1	72.2
No consensus reached					
Frozen section is inadequate for identification of positive SLNs regardless of pathologic modality used (only permanent section is appropriate for clinical decision-making).	20	100	Agree	2	65.0
SLN dissection should be used for decision-making re: the extent of gastric resection (versus a standard resection schema (distal/subtotal/total) based solely on tumor location... (N, S, M, A).	19	95.0	Sometimes	2	63.2
SLN dissection should be used for decision-making regarding the extent of lymphadenectomy (versus routine D2 lymphadenectomy)... (N, S, M, A)	19	95.0	Most times	2	63.2
SLN dissection is for research purposes only and has no role in clinical practice.	19	95.0	Agree	2	63.2
There is a role for SLN dissection in patients with T1 & T2 gastric cancer.	18	90.0	Agree	2	61.1

Average consensus = 76.2%.

CLEAN-NET, combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique; EMR, endoscopic mucosal resection; ESD, endoscopic submucosal dissection; FI, fluorescence imaging; H&E, hematoxylin and eosin; ICG, indocyanine green; IHC, immunohistochemistry; NEWS, nonexposure endoscopic wall-inversion surgery; NIR, near-infrared; (N, S, M, A), never, sometimes, most of the time, always; PCR, polymerase chain reaction; SLN, sentinel lymph node; WR, wedge resection.

has already achieved that potential. There was strong consensus that FI+ICG renders SLN dissection feasible laparoscopically, and moderate (80.0%–89.9%) consensus that it improves both the accuracy and sensitivity of SLN identification, though no consensus was reached on its impact upon specificity. There was consensus that using FI+ICG does not increase operating time to an extent that would be considered a limitation and that neither regulatory issues nor the inability to identify suitable surgical candidates are limitations. Two limitations that were identified were inadequate empirical evidence supporting the use of FI+ICG to identify gastric cancer SLNs and equipment unavailability. Meanwhile, though just short of 70% (68.4%) felt that background fluorescence is a limitation, the percentage who felt that inadequate fluorescence is a limitation was lower still (58%).

Consensus was reached on all 9 statements in the module on training and research (Table VII), including unanimity regarding the increasing use of FI over the next decade, both clinically and in research. It also was perceived as useful training for both surgical and nonsurgical residents. On the other hand, consistent with calls for research in earlier modules, there was unanimous agreement that an RCT remains necessary to determine the approach's role in gastric cancer surgery, near-unanimous consensus that an international registry would be helpful, and moderate consensus regarding the need for fluorescent molecules targeting lymph node

binding sites. Eighty-nine percent of the experts felt that 11 to 25 cases are necessary to overcome the necessary learning curve.

Discussion

In the current survey, 2 main components of SLN identification were addressed—(1) the use of FI+ICG to identify SLNs and metastasis-positive SLN, and (2) the use of SLND to guide further decision-making. The survey's results suggested that experts who use FI+ICG during gastric cancer surgery felt differently about these 2 objectives. This was perhaps best illustrated by examining the voting results for statements designed to be either favorable or unfavorable to FI (judgmental statements) and comparing these results against those for statements drafted to be either favorable or unfavorable to SLND. In this comparison, whereas only 6 of 22 judgmental statements where consensus was reached were unfavorable (27%) to FI, the same was true for 7 of 14 judgmental statements (50%) about SLND, suggesting that the voters' concern regarding FI+ICG's value for detecting SLNs was not primarily with the technology's ability to identify nodes and tumor-positive nodes, but with the extent of credence the findings of SLN detection should be afforded when deciding further cancer management. Such uncertainty was further expressed by the expert panel's consensus opinions that a false-negative rate detecting nodes with

Table V

Module 3—Technical aspects of sentinel node identification during gastric cancer surgery

Statements voted upon	No. of votes	Voting, %	Most common response	No. of rounds	Consensus, %
Consensus reached					
ICG should be delivered peritumorally.	22	100	Agree	1	100
When using ICG for SLN identification, the timing of ICG administration is very important.	20	90.9	Agree	1	100
Research is necessary to determine the optimum dose and concentration of ICG and timing of administration.	22	100	Agree	1	100
Four-quadrant peritumoral injection yields OPTIMAL SLN identification.	20	90.9	Agree	1	95
When using ICG for SLN identification, the dose of ICG is very important.	19	86.4	Agree	1	94.7
When using ICG for SLN identification, the concentration of ICG administered is very important.	19	86.4	Agree	1	94.7
There is a role for sentinel BASIN imaging in gastric cancer.	19	86.4	Agree	1	89.5
Using the "pick-up method" the number of "hot" nodes that can be considered SLNs is (1 node; 2–4 nodes; >4 nodes).	18	90	2–4	2	88.9
The optimal mode of ICG administration when using it for SLN identification is (endoscopic–submucosal injection; transabdominal–subserosal injection)	22	100	Endoscopically	1	86.4
If you use radiocolloid, (99m)Tc-colloid or some other agent should be used.	14	70	99mTc	2	85.7
ICG should only be administered endoscopically (because of cross-contamination when used transabdominally).	19	95	Agree	2	84.2
The optimal timing of ICG injection prior to imaging with NIR light for SLNs is (on the same day as surgery; on the previous day).	19	95	Same day	2	78.9
There is a role for SLN basin identification to decrease the extent of LA and, thereby, the incidence of morbidity from more extensive nodal dissection at low-volume* centers.	18	81.8	Agree	1	77.8
At 5 mg/ml, the optimum dose of ICG to administer for SLN identification during gastric cancer surgery is (<1 mL; 1–5 mL; >5 mL)	22	100	1–5 mL	1	77.3
>4 injection sites are needed to obtain optimal SLN identification.	19	95	Disagree	2	73.7
If adequate visualization of SLNs is NOT achieved, the dose of ICG should be repeated.	19	95	Disagree	2	73.7
ICG and FI is an acceptable single-agent modality for SLN identification.	18	81.8	Agree	1	72.2
For gastrectomies, ICG, and FI should be used for SLN identification, either as a single agent or as part of a dual agent regimen (N, S, M, A)...	18	90	Sometimes	2	72.2
There is a role for frozen section of SLNs in deciding on the degree of lymphadenectomy in gastric cancer.	20	90.9	Agree	1	70
No consensus reached					
The dose of ICG to administer for SLN identification during gastric cancer surgery should be determined as (mg/kg; an absolute dose)	19	95	Absolute	2	68.4
The best identification of SLNs is achieved with radiocolloid + blue dye, FI+ICG, or radiocolloid + FI+ICG.	19	95	FI+ICG	2	63.2
IF given on the same day, the optimal timing of ICG injection prior to imaging with NIR light for SLNs is (<10 min before; 10–30 min before; >30 min before)	19	95	11–30 minutes	2	63.2
Relative to its use in open surgery, use of ICG and NIR technology (for SLNs) has a value in laparoscopic procedures (either as a single or dual-agent regimen) that is...	20	100	-Same	2	60
ICG and FI should be used as a SINGLE-AGENT for the identification of SLNs, never, sometimes, most times, always.	19	95	Most times	2	36.8

Average consensus = 78.4%.

99mTc, technetium-99m; FI, fluorescence imaging; ICG, indocyanine green; LA, lymphadenectomy; NIR, near-infrared; (N, S, M, A), never, sometimes, most of the time, always; SLN, sentinel lymph node.

micro-metastases >10% is unacceptable; their calls for patients to be provided with information, be required to provide informed written consent, and be told that the use of SLN dissection for clinical decision-making remains experimental (3 steps not required for either FI or ICG); and in the 64% of experts who considered SLN dissection for research purposes only and having no role in clinical practice. On the other hand, though no consensus was reached on how often SLN dissection should be used to guide the extent of lymphadenectomy, 18 of the 19 experts who voted felt it should be used either most times ($n = 12$) or always ($n = 6$), and no expert voted never.

In a recently-published meta-analysis incorporating 3,767 patients spanning 54 studies, in which FI+ICG use was compared against 4 other approaches—blue dye alone, radioisotope (RI) alone, combined RI and blue dye, and combined RI and FI+ICG—the rate of SLN detection and both the sensitivity and accuracy of cancer-positive nodes were highest when FI+ICG was used alone, at 99%, 90%, and 98%, respectively.⁹ On the other hand, across the 8

studies in which FI+ICG alone was studied, though the SLN detection rate and overall accuracy of cancer-positive nodes were consistently high, how sensitive FI+ICG was in detecting cancer-positive nodes ranged from 50% to 100% and was $\leq 75\%$ in 3 of the 8 studies. Though none of the other 4 approaches faired any better—sensitivity rates ranging from 41.7% to 100% for blue dye, 78.6% to 100% for RI, 50.0% to 100% for RI + blue dye, and 54.8% to 100% for RI + FI+ICG—in the 3 studies with sensitivity rates from 50% to 75%, FI+ICG clearly failed to meet the <10% false-negative rate our experts considered the upper limit of acceptable. Moreover, though the overall number of patients spanning the 5 treatment options was 3,767, data on the rate of SLN detection and cancer-positive node sensitivity and accuracy were available for just 513 patients using FI+ICG, and in none of these 8 studies was there any direct comparison against any other SLN-detection approach.^{5,30–36} More recently, 4 larger comparative studies have been published, 3 retrospective reviews,^{22,37,38} and 1 RCT.²⁶ In each of these 4 studies, the number of SLNs identified per patient was

Table VI

Module 4—Potential advantages, disadvantages, and limitations

Statements voted upon	No. of votes	Voting, %	Most common response	No. of rounds	Consensus, %
Consensus reached					
Fluorescent imaging for SLN identification has the potential to significantly change gastric cancer surgery practice.	19	86.4	Agree	1	94.7
Fl+ICG makes SLN dissection feasible (doable and useful) laparoscopically (as a single agent or as part of a dual-agent regimen).	21	95.5	Agree	1	90.5
Fl+ICG improves SLN accuracy over standard agents (as a single agent or as part of a dual-agent regimen).	19	86.4	Agree	1	89.5
Fl+ICG improves SLN sensitivity over standard agents (as a single agent or as part of a dual-agent regimen).	18	90.0	Agree	2	88.9
Increased operating time is a significant limitation of using Fl during gastric cancer surgery.	21	95.5	Disagree	1	85.7
Inadequate empirical evidence supporting efficacy is a major barrier to performing Fl during gastric cancer surgery.	21	95.5	Agree	1	85.7
Equipment unavailability is a major barrier to using fluorescence imaging during gastric cancer surgery.	18	90.0	Agree	2	83.3
Fluorescent molecules are needed that specifically target either lymph node (eg, tilmanocept) or tumoral binding sites before SLN identification can become standard of care for gastric cancer.	20	90.9	Agree	1	80.0
Fluorescent imaging for SLN identification is necessary for all gastric cancer surgery.	21	95.5	Disagree	1	76.2
Regulatory issues are a major barrier to using fluorescence imaging during gastric cancer surgery.	19	95.0	Disagree	2	73.7
Identifying suitable surgical candidates who might benefit from Fl is a major barrier to its use during gastric cancer surgery.	19	95.0	Disagree	2	73.7
No consensus reached					
Background fluorescence is a significant disadvantage of using Fl during gastric cancer surgery.	19	95.0	Agree	2	68.4
Fl+ICG improves SLN specificity over standard agents (as a single agent or as part of a dual-agent regimen).	18	90.0	Agree	2	66.7
Fluorescence angiography significantly impacts the way that gastric cancer surgery is performed.	18	90.0%	Agree	2	61.1
Inadequate fluorescence and the need for repeat dosing is a major limitation of Fl during gastric cancer surgery.	19	95.0%	Agree	2	57.9

Average consensus = 78.4%.

Fl, fluorescence imaging; ICG, indocyanine green; NIR, near-infrared; SLN, sentinel lymph node.

statistically greater among patients with injected versus no injected ICG; however, sensitivity rates for cancer-positive nodes ranged from 52.6%³⁷ to 100%.²² Moreover, in none of these studies or in any study within either of the 2 previously mentioned meta-analyses^{9,10} was the impact of fluorescence-guided SLN dissection on patient survival examined.

In their meta-analysis, besides examining the overall effectiveness of Fl+ICG for SLN mapping, He et al compared different approaches to ICG use and found that injecting ICG submucosally was significantly more sensitive at detecting cancer-positive nodes than sub-serosal injection (98% vs 40%),¹⁰ consistent with our experts' preference for the former. Also consistent with the consensus

Table VII

Module 5—Training and research

Statements voted upon	No. of votes	Voting, %	Most common response	No. of rounds	Consensus, %
Consensus reached					
Over the next decade, the use of Fl in surgical practice is likely to increase, decrease, or stay the same.	22	100	Increase	1	100
Over the next decade, the use of Fl in research is likely to increase, decrease, or stay the same.	22	100	Increase	1	100
A randomized clinical trial to determine the role of Fl for SLN identification in gastric cancer is needed.	21	95.5	Agree	1	100
To help answer some of the technical questions related to the use of Fl during gastric cancer surgery, an international registry would be helpful.	21	95.5	Agree	1	95.2
Fl is useful for training surgical residents about gastric cancer surgery.	20	90.9	Agree	1	90.0
Not just surgery residents, but residents in other non-surgical fields should learn about Fl.	19	95.0	Agree	2	89.5
The number of cases of Fl for SLN identification that need to be completed to overcome the learning curve is... (1–10; 11–25; >25).	18	90.0	11–25	2	88.9
There is a need for fluorescent molecules TARGETED either to LN binding sites (eg, Tilmanocept) or tumoral binding sites before SLN identification can become standard of care.	21	95.5	Agree	1	81.0
Exposure of physician trainees to Fl should begin during medical school or residency training.	20	90.9	Residency	1	80.0

Average consensus = 91.6%.

Fl, fluorescence imaging; ICG, indocyanine green; LN, lymph node; SLN, sentinel lymph node.

opinions our experts reached, He et al found that such sensitivity was considerably greater for cT1 than for either cT2 or cT3 stage tumors and speculated that ICG was being overdosed in many studies.¹⁰ Unfortunately, few studies have directly compared different doses or concentrations of ICG during SLN mapping in any surgical scenario, though concerns regarding higher doses increasing background fluorescence have been expressed.³⁹

Fluorescence imaging with indocyanine green is useful for detecting SLNs as has been demonstrated in other surgical scenarios, including breast,^{12–15} skin,¹² head and neck,¹⁴ uterine, and endometrial cancer.^{16–20} However, its usefulness for detecting SLNs in colorectal cancer is less certain, with potential reasons for this including the location of colonic sentinel lymph nodes within the fatty mesocolon and the limited penetration of fluorescent dyes into fat.⁴⁰ Similar to colorectal cancers and quite dissimilar to the relatively-straightforward lymphatic drainage typical for breast cancer and tumors originating in a limb, the lymphatic drainage patterns for stomach cancer are complex,⁴¹ which might explain the reduced confidence our experts expressed using fluorescence-guided SLN dissection as a guide to gastric cancer patient management outside of research protocols, despite clear confidence in this technology's future potential.

As with all Delphi studies, our results must be interpreted as opinions rather than empirically-derived findings. However, they are the opinions of a highly-qualified, very-diverse panel of world experts, who all are not only unquestionably more informed about and qualified to interpret relevant empirical data than almost anyone else but, in most cases, actual contributors to such research. Our results also provided insights into many issues that likely could never be included in any clinical trial unless massive, like an examination of all the potential doses and concentrations of ICG and various options for the timing and route of ICG administration. Moreover, perhaps the greatest value of Delphi studies is not where consensus is reached but where no consensus is achievable, as this provides directions for future research.

All this notwithstanding, 2 further limitations of the current study must be considered. First, although 27 experts participated in this 2-round survey—22 in round 1, 20 in round 2—only 15 participated in both rounds, which is neither ideal nor what we intended. Unfortunately, despite 3 emails followed by a personal phone call, 7 round 1 participants elected not to participate in the second round, the most common reason given being their current workload. Our decision to include 5 new experts in round 2 might also be debated. However, removing these 5 from the analysis of round 2 results changed little. Moreover, attrition is a common phenomenon among all multiple-stage surveys,⁴² and as few as 10 participants have long been deemed acceptable for Delphi surveys.⁴³

Second, we sought consensus on 2 related but disparate issues—FI's effectiveness detecting SLNs and its influences on surgical decision-making and outcomes—and contradictory conclusions were reached. Although FI was largely felt to have value for SLN detection, enthusiasm was guarded regarding its role in surgical planning and impact on patient outcomes. As such, though FI was deemed to have considerable potential, its current place in gastric cancer surgery, with respect to SLN detection, was generally perceived as limited to research protocols, at least pending the publication of more supportive results.

In conclusion, in the case of SLN detection in early gastric cancer, further research is both necessary and, given the technology's perceived potential, highly warranted.

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Conflict of interest/Disclosure

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