



Universiteit
Leiden
The Netherlands

Consensus conference statement on the general use of near-infrared fluorescence imaging and indocyanine green guided surgery: results of a modified Delphi study

Dip, F.; Boni, L.; Bouvet, M.; Carus, T.; Diana, M.; Falco, J.; ... ; Rosenthal, R.J.

Citation

Dip, F., Boni, L., Bouvet, M., Carus, T., Diana, M., Falco, J., ... Rosenthal, R. J. (2022). Consensus conference statement on the general use of near-infrared fluorescence imaging and indocyanine green guided surgery: results of a modified Delphi study. *Annals Of Surgery*, 275(4), 685-691. doi:10.1097/SLA.0000000000004412

Version: Publisher's Version

License: [Creative Commons CC BY-NC-ND 4.0 license](https://creativecommons.org/licenses/by-nc-nd/4.0/)

Downloaded from: <https://hdl.handle.net/1887/3566978>

Note: To cite this publication please use the final published version (if applicable).

Consensus Conference Statement on the General Use of Near-infrared Fluorescence Imaging and Indocyanine Green Guided Surgery

Results of a Modified Delphi Study

Fernando Dip, MD,*† Luigi Boni, MD,‡ Michael Bouvet, MD,§ Thomas Carus, MD,¶ Michele Diana, MD,|| Jorge Falco, MD,** Geoffrey C. Gurtner, MD,†† Takeaki Ishizawa, MD, PhD,‡‡ Norihiro Kokudo, MD, PhD,‡‡ Emanuele Lo Menzo, MD,† Philip S. Low, PhD,§§ Jaume Masia, MD,¶¶ Derek Muehrcke, MD,|||| Francis A. Papay, MD,*** Carlo Pulitano, MD, PhD,††† Sylke Schneider-Korath, MD,‡‡‡ Danny Sherwinter, MD,§§§ Giuseppe Spinoglio, MD,¶¶¶ Laurents Stassen, MD, PhD,||||| Yasuteru Urano, PhD,¶¶¶¶ Alexander Vahrmeijer, MD,**** Eric Vibert, MD, PhD,†††† Jason Warram, MD,‡‡‡‡ Steven D. Wexner, MD, PhD (Hon),† Kevin White, MD, PhD,§§§§ and Raul J. Rosenthal, MD†✉

Background: In recent decades, the use of near-infrared light and fluorescence-guidance during open and laparoscopic surgery has exponentially expanded across various clinical settings. However, tremendous variability exists in how it is performed.

Objective: In this first published survey of international experts on fluorescence-guided surgery, we sought to identify areas of consensus and non-consensus across 4 areas of practice: fundamentals; patient selection/preparation; technical aspects; and effectiveness and safety.

Methods: A Delphi survey was conducted among 19 international experts in fluorescence-guided surgery attending a 1-day consensus meeting in Frankfurt, Germany on September 8th, 2019. Using mobile phones, experts were asked to anonymously vote over 2 rounds of voting, with 70% and 80% set as a priori thresholds for consensus and vote robustness, respectively.

Results: Experts from 5 continents reached consensus on 41 of 44 statements, including strong consensus that near-infrared fluorescence-guided surgery is both effective and safe across a broad variety of clinical settings, including the localization of critical anatomical structures like vessels, detection of tumors

and sentinel nodes, assessment of tissue perfusion and anastomotic leaks, delineation of segmented organs, and localization of parathyroid glands. Although the minimum and maximum safe effective dose of ICG were felt to be 1 to 2 mg and >10 mg, respectively, there was strong consensus that determining the optimum dose, concentration, route and timing of ICG administration should be an ongoing research focus.

Conclusions: Although fluorescence imaging was almost unanimously perceived to be both effective and safe across a broad range of clinical settings, considerable further research remains necessary to optimize its use.

Keywords: consensus, Delphi survey, fluorescence-guided surgery, indocyanine green

(Ann Surg 2022;275:685–691)

Over the past few decades, with the birth and growth of minimally invasive surgical techniques that utilize advanced optoelectronic instruments, numerous different tools have been

From the *Hospital de Clinicas Buenos Aires, University of Buenos Aires, Buenos Aires, Argentina; †Cleveland Clinic Florida, Weston, FL; ‡Department of Surgery, Fondazione IRCCS - Ca' Granda - Ospedale Maggiore Policlinico University of Milan, Milan, Italy; §University of California San Diego, La Jolla, CA; ¶Elisabeth-Krankenhaus Thüine, Germany; ||IHU Strasbourg, Institute of Image-Guided Surgery and IRCAD, Research Institute against Cancer of the Digestive System, Strasbourg, France; **University Hospital Das Clinicas, Buenos Aires, Argentina; ††Stanford University School of Medicine, Stanford, CA; ‡‡National Center for Global Health and Medicine, Tokyo, Japan; §§Purdue University, West Lafayette, IN; ¶¶Clinica Planas, Barcelona, Spain; ||||Flagler Hospital, St. Augustine, FL; ***Cleveland Clinic, Lerner College of Medicine at Case Western Reserve University, Cleveland, OH; †††Royal Prince Alfred Hospital, Sydney, Australia; ‡‡‡Klinikum Südstadt Rostock, Rostock, Germany; §§§Maimonides Medical Center, Brooklyn, NY; ¶¶¶FPO Candolo Institute for Cancer Research and Treatment I.R.C.C.S., Turin, Italy; |||||Maastricht University Medical Center, Maastricht, The Netherlands; ****Leiden University Medical Center, Leiden, The Netherlands; ††††Centre Hépatobiliaire, Hôpital Paul Brousse, Villejuif, France; ‡‡‡‡University of Alabama at Birmingham, Birmingham, AL; §§§§ScienceRight Research Consulting London, Ontario, Canada; and ¶¶¶¶The University of Tokyo, Tokyo, Japan.

✉rosentr@ccf.org.

Funding: Diagnostic Green; Intuitive; Medtronic; Olympus; Quest Medical Imaging; Stryker. Each provided unrestricted grants for the International Society for Fluorescence Guided Surgery (ISFGS) Advisory Board meeting, Frankfurt, Germany, September 8, 2019, during which the Delphi consensus was discussed. Diagnostic Green also funded accommodations and meals.

Disclaimer: None of the industry sponsors were actively involved in any process of the Delphi consensus or drafting, review, or revision of the manuscript.

All companies are sponsors/Corporate Council members of the International Society for Fluorescence Guided Surgery (ISFGS). All authors are members of the ISFGS Advisory Board.

Disclosures: R.J.R.: Consultant: Diagnostic Green, Medtronic; Stock-Holder: Medica Simulation; K.W.: Consultant: Diagnostic Green; F.D.: Consultant: Diagnostic Green, Medtronic; S.D.W.: Royalties and consulting fees Intuitive, Medtronic, Karl Storz; Consulting fees: Stryker L.S.: Previous research grant Storz GmbH; Member, Diagnostic Green Advisory Board; L.B.: Consultant, Karl Storz; A.V.: No relevant financial disclosures; D.S.: No relevant financial disclosures; E.L.: No relevant financial disclosures; M.B.: Consultant, Stryker; S.S.-K.: No relevant financial disclosures; M.D.: No relevant financial disclosures; T.C.: No relevant financial disclosures; G.S.: No relevant financial disclosures; N.K.: Research Grant, Hitachi; Paid Lecturer, Eisai Co; D.M.: No relevant financial disclosures; J.W.: No relevant financial disclosures; T.L.: No relevant financial disclosures; Y.U.: No relevant financial disclosures; E.V.: No relevant financial disclosures; P.L.: Founder and stockholder: On Target Laboratories Inc; G.G.: No relevant financial disclosures; J.F.: No relevant financial disclosures; J.M.: No relevant financial disclosures; F.P.: No relevant financial disclosures; C.P.: No relevant financial disclosures.

The authors report no conflicts of interest.

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Copyright © 2020 The Author(s). Published by Wolters Kluwer Health, Inc.
ISSN: 0003-4932/20/27504-0685
DOI: 10.1097/SLA.00000000000004412

developed and tested to facilitate surgeons' visualization of essential anatomical structures in the operating room. Among these tools is near-infrared fluorescence-guided intraoperative imaging, which is currently being tested and used across an ever-expanding range of clinical settings, with the 2 goals of enhancing patient outcomes and increasing patient safety.^{1–5}

Indocyanine green (ICG) is a fluorophore that responds to near-infrared irradiation (NIR), absorbing light from 790 to 805 nm and remitting it with an excitation wavelength of 835 nm.⁶ Pioneering research on ICG fluorescence imaging initially emerged almost 50 years ago via the introduction of applied ophthalmic angiography.⁷ Roughly 3 decades later, intraoperative fluorescent imaging made its first foray into endoscopic surgery on the liver and biliary tree.¹ Since then, the use of fluorescence imaging, and ICG in particular, has expanded exponentially.⁵ This included surgery to detect tumors and sentinel lymph nodes involving the breast,^{8–10} lungs,^{11,12} liver,^{13,14} colon,¹⁵ stomach,¹⁶ and pelvis^{17–19} to assess tissue perfusion involving the viscera^{13,20–23} and in plastic surgery, including face transplants,^{24–29} to identify anastomotic leaks,^{13,22,30–33} and to locate small glands such as the parathyroid glands during thyroid and parathyroid resections.³⁴ Despite its rapidly expanding utilization, tremendous variability exists in the dose, concentration, and administration of ICG during fluorescence-guided surgery, as well as in numerous other technical aspects of its use. Questions also persist regarding whether or not it should still be considered experimental during discussions with patients, if and when its use should be considered contraindicated, and other issues not yet addressed in clinical trials.

Our primary objectives with the present study were to assess current practices with respect to the use of fluorescence imaging, with and without ICG, and to identify areas of consensus among an international panel of surgeons who are well-recognized and published experts in the field of NIR ICG fluorescence guided surgery. For these purposes, we employed a modified Delphi survey approach to permit anonymous voting and, thereby, potentially reduce voter bias that might be caused by peer pressure. The Delphi technique and numerous variants of this technique have been gaining increasing popularity and credence as a way to achieve consensus and identify areas of nonconsensus among experts across a wide variety of health and non-health-related fields.³⁵

METHODS

A modified Delphi study was conducted at a consensus meeting of the International Society for Fluorescence Guided Surgery (ISFGS) in Frankfurt Germany on September 8th, 2019, in accordance with guidelines published by Keeney et al.³⁵

Over the summer of 2019, a general survey was sent, by email, to all Advisory Board members of the ISFGS to enlist their assistance generating questions and areas of interest for the upcoming survey. Twelve of the 27 Advisory Board members responded and sent questions and/or lists of areas of interest. From these responses, a Delphi Round 1 survey was generated that consisted of 10 questions pertaining to demographics and general surgical practices, and 45 questions or statements pertaining to the general use of fluorescence imaging, with and without ICG. At the meeting, one of these 45 latter items was dropped because, after discussion, its meaning was deemed sufficiently unclear to render responses difficult to interpret. The 44 remaining questions or statements to be voted upon were divided into 4 modules: fundamentals of fluorescence imaging with ICG (n = 12 questions); patient selection and preparation (n = 6); technical aspects of fluorescence imaging and ICG use (n = 8); and indications for and effectiveness of fluorescence imaging with ICG (n = 18). Of the 44 items voted upon, 29 were statements and 15 were

questions; 29 had a binary response option, of which 26 were agree versus disagree, whereas 15 had ≥ 3 response options. All statements and questions were pilot tested on 2 board members (F.D., R.R.) who had not submitted questions, then edited for language by a professional English-language medical science editor with expertise in the development and orchestration of Delphi surveys (K.W.).

To be considered an expert, each panel member had to be an appointed Advisory Board member of the ISFGS and have extensive experience in the performance of fluorescence-guided surgery, plus/minus a sizeable publication record in its use, and be appointed to the board by existing board members. All voting members also had to be fluent in both spoken and written English and physically attend the consensus meeting in Frankfurt for its full duration.

Voting was conducted electronically on the voters' cell phones or other hand-held devices, linked to the polling software Sli.do, with statements/questions displayed on a large screen in PowerPoint. Before voting in each round, voters were given the option of asking questions of clarity. Voting commenced only after all questions of clarity were answered and the moderator announced the start of voting. From that moment, attendees had 30 seconds to vote, after which all further voting was blocked. Only statements/questions for which consensus was not reached were again asked in Round 2, after which, all voting was terminated. Immediately before Round 2 voting, and on an item-by-item basis, the results of Round 1 were displayed for all voters to see.

Based upon published guidelines,³⁵ an a priori decision was made to consider 70% agreement between voters to be evidence of consensus, and 80% participation in voting on each particular question evidence of a robust vote. To reduce the risk of agreement bias, some statements were worded favorably and others unfavorably toward fluorescence imaging and/or ICG.

RESULTS

Ultimately, 20 of the 27 Advisory Board members of ISFGS attended the consensus meeting in Frankfurt. Since one of these 20 members was a nonsurgeon (K.W.), the final expert panel of voters consisted of 19 individuals, including 7 from Europe, 6 from North America, 4 from Asia-Pacific, and 2 from South America. Countries represented included 6 from the United States of America (USA), 3 from Japan, 2 each from Germany and France, 2 from Argentina, and 1 each from the Netherlands, Italy, and Australia. Further characteristics of the sample are summarized in Table 1. Note that 17 of 19 had academic appointments, and that, although 1 expert reported having not used ICG in the past year, he/she had extensively employed fluorescence imaging for guidance during surgery. Among the 19 respondents, only 2 reported having ever observed an adverse reaction to ICG, both of which were mild systemic allergic reactions.

All 19 eligible voters voted on every single item but 3 (Tables 2–5), 1 on which 18 (94.7%) voted, and 2 on which 17 (89.5%) voted, meaning that the results for all 44 items were considered robust [$\geq 80\%$ (n ≥ 16) of eligible voters voting]. Consensus of at least 70% was reached for 41 (93.2%) of the 44 items, 39 in Round 1 and 2 in Round 2. The 2 items for which consensus was reached in Round 2, after open discussion, were: “Using fluorescence technology, with or without ICG, increases, decreases or has no effect on the overall cost of a patient's peri- and postoperative care” with which the percentage who agreed rose from 63% to 100%; and “What is the maximum safe dose of ICG: < 5 mg, 5 mg, 10 mg, > 10 mg, or other?,” for which the percentage selecting “>10mg” increased from 56.3% to 88.2%.

Statements for which consensus was reached included all 12 items in the module on fundamentals of fluorescent-guided surgery, 4 of 6 in the module on patient selection and preparation, all 8 items in

TABLE 1. Demographics and Practice Characteristics of the Expert Panel

Characteristic	n	%
Total sample	19	100.0
Location of practice		
Europe	7	36.8
North America	6	26.3
Asia-Pacific	4	21.1
South America	2	10.5
Type of practice		
Academic	17	89.5
Nonacademic	2	10.5
Years in practice		
<10	2	10.5
10–20	6	31.6
>20	11	57.9
Years performing FGS		
<5	3	15.8
5–10	7	36.8
>10	9	47.4
No. of FGS procedures per month		
<5	3	15.8
5–10	7	36.8
>10	9	47.4
% Of surgeries fluorescence-guided		
<10%	5	26.3
10%–29%	3	15.8
30%–49%	6	31.6
≥50%	5	26.3
% Of surgeries fluorescence-guided using ICG		
<10%	0	0.0
10%–50%	2	10.5
51%–99%	4	21.1
100%	12	63.2
Surgical area of expertise		
Cancer	6	31.6
Colorectal	4	21.1
Endocrine	1	5.3
Hepatobiliary	4	21.1
Plastics	2	10.5
Other	2	10.5

FGS indicates fluorescence-guided surgery.

the module on technical aspects of fluorescence imaging and ICG use, and 17 of 18 in the module on indications for and effectiveness of fluorescence imaging with ICG. Among the 26 statements for which experts were asked to agree or disagree, agreement was the consensus vote for 20 (76.9%).

Among the 41 statements/questions on which consensus was reached, the range of consensus was from 100% (on 10 items) to a low of 72.2% (13/18 voters). The 10 items for which 100% consensus was reached were: “In general, the use of fluorescence-guidance during surgery should be considered very safe” (selected response = agree); “In general, the use of ICG during fluorescence-guided surgery should be considered very safe” (agree); “Using fluorescence technology, with or without ICG, increases, decreases or has no effect on the overall cost of a patient’s peri- and postoperative care” (decreases); “Fluorescence imaging technology has the potential to dramatically facilitate many surgical procedures” (agree); “Fluorescence imaging technology has the potential to significantly enhance patient outcomes” (agree); “In general, fluorescence imaging is an important tool for the evaluation of tissue perfusion” (agree); “Over the next decade, do you see the role of fluorescence-guided surgery in clinical practice increasing, decreasing or remaining the same?” (increasing); “Over the next decade, do you see the role of fluorescence-guided surgery in clinical research increasing, decreasing or remaining the same?” (increasing); “Fluorescence imaging, with and without ICG, is useful for training surgical residents” (agree); and “Fluorescence imaging, with and without ICG, is useful for surgical quality control” (agree).

Consensus could not be reached for 3 items: “Patients undergoing a procedure using fluorescence technology should generally be asked to give informed written consent,” a statement with which the percentage agreeing declined from 63% to 59% from Round 1 to Round 2; “Patients undergoing a procedure using ICG should generally be asked to give written informed consent,” with which the percentage agreeing declined from 53% to 46%; and “At what stage of training should doctors be taught about fluorescence imaging: medical school or residency?,” for which the percentage selecting medical school rose only slightly, from 47% to 55% over the 2 rounds.

DISCUSSION

When assessing the results of any Delphi survey, it is important to appreciate that these results do not necessarily indicate truth; what they demonstrate is the degree of consensus that can be reached in the opinions of field experts. This said, the expert panel selected

TABLE 2. Module I: Fundamentals of Fluorescent Imaging With ICG

Statement/Question	# Votes	Response	% Consensus
In general, the use of fluorescence-guidance during surgery should be considered very safe.	19	Agree	100
In general, the use of ICG during fluorescence-guided surgery should be considered very safe.	19	Agree	100
Using fluorescence technology, with or without ICG, increases, decreases or has no effect on the overall cost of a patient’s peri- and postoperative care.	19	Decreases	100
Fluorescence imaging, with and without ICG, should be part of routine surgical practice.	19	Agree	94.7
In general, the use of ICG should be considered experimental.	19	Disagree	94.7
Using fluorescence technology increases/decreases the overall risk of a patient’s perioperative care.	19	Decreases	89.7
In general, fluorescence-guided surgery should be considered experimental.	19	Disagree	84.2
Using fluorescence technology appreciably increases the overall direct monetary cost of a procedure.	19	Disagree	84.2
Cost is a significant barrier to using near-infrared (NIR) technology.	19	Disagree	84.2
In general, using ICG increases/decreases the overall risk of a patient’s postoperative care.	19	Decreases	79.0
Using fluorescence technology appreciably increases the overall risk of a procedure.	19	Disagree	77.8
Using ICG appreciably increases the overall direct monetary cost of a procedure.	19	Disagree	73.7

TABLE 3. Module II — Patient Selection and Preparation

Statement/question	# votes	Response	% consensus
Prior to administering ICG, patients should be asked if they are allergic to iodine.	19	Agree	89.5
Patients undergoing a procedure using fluorescence technology should be provided specific preoperative information about this technology.	19	Agree	73.7
Patients undergoing a procedure using ICG should be provided specific preoperative information about the drug.	19	Agree	73.7
What adverse reaction should be reported to clinicians and patients as the most common?	18	All are very uncommon	72.2
Patients undergoing a procedure using fluorescence technology should generally be asked to give informed written consent.		No consensus	
Patients undergoing a procedure using ICG should generally be asked to give written informed consent.		No consensus	

for the current survey was comprised of widely acknowledged leaders in the field of fluorescence-guided surgery, all having published research in the field, and 17 of 19 having academic appointments. All are highly versed in the literature currently published on fluorescence-guided surgery and the use of ICG, and this is reflected in their voting, particularly with respect to the effectiveness and safety of fluorescence imaging and ICG use.

Our 19 voting experts agreed, with 84% to 100% consensus, that fluorescence imaging ICG was useful for the visualization of critical anatomical structures such as arteries and veins, the assessment of tissue perfusion, the detection of cancerous lesions, the localization of sentinel lymph nodes, the visualization of segmented organs such as the lungs and liver, and the detection of small organs such as the parathyroid glands. They also agreed, with 100% consensus, that both fluorescence imaging and the use of ICG should be considered very safe. Considerable published evidence exists that agrees with this, documenting both the effectiveness and safety of fluorescence technology and ICG across a wide range of settings and disciplines, including several studies each documenting its usefulness detecting tumors and sentinel lymph nodes in patients with breast,^{8–10} lung, liver,^{13,14} colon,¹⁵ stomach,¹⁶ and pelvic^{17–19} cancer; assessing tissue perfusion involving both viscera^{13,20–23} and in plastic surgery^{24–29}; identifying anastomotic leaks, particularly

during gastrointestinal surgery^{13,22,30–32}; and locating the parathyroid glands during thyroid and parathyroid resections, so as to avoid inadvertent damage or resection and resultant post-operative hypocalcemia.³⁴ This includes the recent publication of numerous meta-analyses, all of which have demonstrated either superiority of ICG relative to alternatives, or equivalence with advantages such as, cost and ease of use.^{16–19,31,32,36–44} To date, however, the only published randomized clinical trial documenting the effectiveness of fluorescence imaging with ICG is one which assessed its use identifying extrahepatic biliary structures in patients undergoing laparoscopic cholecystectomies⁴⁵; in this study, which involved 639 patients randomly assigned to undergo laparoscopic cholecystectomy either under white light or under NIR light after peripheral ICG administration, 7 different vital extrahepatic biliary structures, including the cystic and common bile duct, were 2.3 to 3.6-fold as likely to be visualized before gallbladder resection with ICG under NIR light. In addition, there were no allergic or other serious adverse reactions to ICG, and the only 2 instances of bile duct injury, widely considered the most serious adverse event resulting from laparoscopic cholecystectomy, occurred in the white light only group.

With further respect to safety using ICG with NIR light, several meta-analyses and larger clinical trials have assessed this issue. This includes a recent meta-analysis evaluating its use in the

TABLE 4. Module III — Technical Aspects of Fluorescence Imaging and ICG Use

Statement/Question	# votes	Response	% consensus
In general, how important is the dose of ICG that is administered: important, not important, or depends on the situation	17	Important	94.7
In general, how important is the timing of ICG administration: important, not important, or depends on the situation?	19	Important	94.7
One major research priority should be clinical trials to identify the optimum dose and concentration of ICG administration.	19	Agree	94.7
One major research priority should be clinical trials to identify the optimal timing of ICG administration.	19	Agree	94.7
In general, how important is the concentration of ICG that is administered: important, not important, or depends on the situation?	19	Important	89.5
In general, how important is the length of time to wait after the administration of ICG to view the anatomy under near-infrared (NIR) light (e.g. to visualize tissue perfusion, sentinel lymph nodes, glandular structures): important, not important, or depends on the situation?	19	Important	89.5
What is the minimum effective dose of ICG for fluorescence imaging: 1–2 mg, 3–4 mg, 5 mg, or > 5 mg?	19	1–2 mg	89.5
What is the maximum safe dose of ICG: < 5mg, 5 mg, 10 mg, > 10 mg, or other?	17	>10 mg	88.2

TABLE 5. Module IV—Indications for and Effectiveness of Fluorescence Imaging With ICG

Statement/Question	# votes	Response	% consensus
Fluorescence imaging technology has the potential to dramatically facilitate many surgical procedures.	19	Agree	100
Fluorescence imaging technology has the potential to significantly enhance patient outcomes.	19	Agree	100
In general, fluorescence imaging is an important tool for the evaluation of tissue perfusion.	19	Agree	100
Over the next decade, do you see the role of fluorescence-guided surgery in clinical practice increasing, decreasing or remaining the same?	19	Increasing	100
Over the next decade, do you see the role of fluorescence-guided surgery in clinical research increasing, decreasing or remaining the same?	19	Increasing	100
Fluorescence imaging, with and without ICG, is useful for training surgical residents.	19	Agree	100
Fluorescence imaging, with and without ICG, is useful for surgical quality control.	19	Agree	100
Fluorescence imaging technology has the potential to dramatically alter the way that many surgical procedures are performed.	19	Agree	94.7
In general, fluorescence imaging is an important tool for the visualization of vital anatomical structures such as arteries and veins.	19	Agree	94.7
Not just surgery residents, but residents in other medical fields should learn about fluorescence imaging?	19	Agree	89.5
In general, fluorescence imaging is an important tool for the visualization of cancerous lesions.	19	Agree	89.5
In general, fluorescence imaging is an important tool for the visualization of sentinel lymph nodes.	19	Agree	89.5
In general, which of the following is more effective as a visualization tool during surgery: ICG or a blue dye?	19	ICG	89.5
In general, fluorescence imaging is an important tool for the visualization of segmented organs such as the liver and lungs.	19	Agree	88.9
In general, fluorescence imaging is an important tool for the visualization of glands like the parathyroid and pituitary.	19	Agree	84.2
In general, from a patient standpoint, which of the following is less problematic as a visualization tool during surgery: ICG or a blue dye?	19	ICG	73.7
In general, from a technical standpoint, which of the following is less problematic as a visualization tool during surgery: ICG or a blue dye?	19	ICG	73.7
At what stage of training should doctors be taught about fluorescence imaging: medical school or residency?		No consensus	

detection of hepatic tumors,⁴⁶ in which 6 studies incorporating 587 patients were analyzed; in this study, complication rates were lower in the fluorescence-guided versus standard white light hepatectomy group, and no serious reactions to ICG were reported. In another large nonrandomized study involving 847 women with clinically node-negative breast cancer undergoing sentinel lymph node assessments, again no allergic or any other serious adverse reactions to ICG were reported.⁴⁷ Similarly, no complications related to ICG were noted in a recently published meta-analysis of 17 studies encompassing 1059 patients with pelvic cancers.¹⁹ Meanwhile, in a meta-analysis in which the use of ICG plus NIR light was compared against white light assessing free flap perfusion post mastectomy across 5 studies encompassing 902 patients, the overall complication rate was statistically lower with the former.³⁸

Among the several purposes that Delphi surveys serve is the potential to address issues that otherwise would never be addressed, or would be highly impractical to address, within the context of a clinical or other experimental study. Such issues addressed in this general survey of fluorescence-guided surgery and ICG use include those related to patient selection and preparation. For example, the experts surveyed agreed that patients should be preoperatively screened for iodine or shellfish allergies before receiving ICG, and should be provided with information specific to fluorescence technology and ICG, but they could not agree on whether or not fluorescence technology or ICG-specific informed written consent should be obtained from patients. In discussion, the rationale for not

voting for written informed consent, among those who voted thus, lay in the unanimously perceived high degree of safety associated with both NIR light and ICG.

Another issue for which limited data exist is the issue of cost. Among our panel, cost was not considered to be a barrier to the use of ICG. This result is in line with the results of a recently published survey that was conducted among 51 minimally invasive surgeons who attended the 4th International Congress of Fluorescence-Guided Surgery in Boca Raton, Florida in February 2017, among whom only 7% perceived cost to be a barrier to using fluorescence imaging.⁴⁸ In that same survey, however, almost two-thirds of respondents (64%) cited access to the imaging equipment to be a barrier. Our panel also reached consensus that fluorescence imaging, with or without ICG, does not increase the overall direct monetary costs of procedures or the overall perioperative costs of care. Upon discussion, the sentiment was widely expressed that any additional cost related to the dose and administration of ICG was likely offset by the reduction in procedural times and complications that arise from its use. This sentiment is strongly supported by the one clinical trial assessing cost that has been conducted, in which the use of NIR fluorescence cholangiography, using ICG, was compared with radiographic intraoperative cholangiography (IOC) during laparoscopic cholecystectomy (LC), with respect to that rate of successful completion of the imaging procedure, time for completion, and cost.⁴⁹ In this prospective, comparative trial, 43 patients (22 males, 21 females) underwent LC using both NIR fluorescence cholangiography and

IOC, and the former was found to have a slightly higher rate of completion, albeit, not statistically significant (43 vs 40/43; $P = 0.08$), as well as a markedly reduced time to completion (43 vs 429 seconds, $P < 0.001$), and vastly reduced cost (\$14.10 vs \$778.43, $P < 0.001$).

Yet another vital, and oftentimes overlooked, purpose of Delphi surveys is that they help to identify questions requiring further research, particularly in areas in which consensus cannot be reached. Our experts failed to achieve consensus for only 3 statements, pertaining to the issues of informed written consent, for both fluorescence imaging and, specifically, ICG, and when initial exposure to fluorescence-guided procedures should commence within a physician's training: during or after medical school. Moreover, although there was consensus as to what should be considered the minimal-effective and maximum safe dose of ICG to administer, one question that asked specifically about the most useful dose had to be eliminated because there was agreement across the panel both that the most effective dose had not yet been determined and that the optimum dose likely varied between clinical settings. In discussion between rounds regarding the issue of informed consent, it was clear that the roughly 50% to 60% who felt specific consent was needed, whether for fluorescence imaging or ICG, felt so not because either was unsafe, but for medicolegal reasons, and that even a single favorable randomized clinical trial for the most common indications would almost certainly render both consent issues moot. Moreover, in subsequent, procedure-specific Delphi surveys that have been conducted (not yet published), consensus has consistently been reached that failure to obtain informed consent, due to patient incapacity or language issues, should not be considered an absolute contraindication to using either fluorescence imaging or ICG.

With respect to technique, fluorescence imaging with ICG is a relatively straight-forward process: the dye is administered, and sometime later its presence is visualized under NIR light. Other than enhancing the surgeon's visualization of certain targeted anatomical structures and whatever impact that has upon the surgery, it otherwise does not alter the operation's technical components. Differences arise, however, in deciding on the route of ICG administration and, more often, the dose, concentration, and timing of ICG administration. In our own meta-analysis on ICG use compared to the use of technetium-99 lymphoscintigraphy or blue dye for the detection of sentinel lymph nodes in patients with primary cutaneous melanoma, the dose of ICG administered ranged from 0.2 to 10 mg.⁵⁰ That being said, among our panel, there was 95% consensus that both the dose and timing of ICG administration was important, and 90% consensus that the concentration of ICG was important. There also was 95% consensus that current major research priorities should be to document the most effective dose and concentration of ICG and timing of ICG administration in each setting in which it is used.

Finally, when and which physician trainees should be taught about fluorescence imaging was asked. Although there was consensus that not only surgery residents, but residents in other medical fields should learn about this new technology, there was no consensus as to whether this should occur during medical school or afterwards, even after 2 rounds of voting.

As mentioned at the outset of this discussion, the present study has clear limitations, among them the inherent limitations of all studies that rely on expert opinions. In no way do they replace the need for well-designed and well-conducted clinical trials. In addition, in this particular survey, there might be the issue of voter-selection bias, given that all voting experts were Advisory Board members of a society that actively promotes fluorescence-guided surgery. However, the members of the panel were highly diverse in geographic location (spanning five continents), years in practice, years using fluorescence imaging,

surgical specialty, and the extent to which they use fluorescence imaging in their practice. In addition, as board members, they were extremely well-read and published in the area of fluorescence-guided surgery, which should be considered a strength.

CONCLUSIONS

In this survey of 19 international experts in fluorescence-guided surgery, the use of fluorescence imaging, with or without ICG, was considered both highly effective and very safe across a broad range of clinical fields and settings. Further research is necessary to optimize the dose and concentration of ICG and the route and timing of ICG administration. Although the panel no longer considered fluorescence imaging experimental, no consensus could be reached as to whether or not patients should be asked to provide written informed consent specific to its use, or when physician trainees should first be exposed to this new technology.

ACKNOWLEDGMENTS

The authors thank Diagnostic Green for its financial support with the consensus meeting in Frankfurt. The authors also thank Olympus, Medtronic, Stryker, Intuitive Surgery, and Quest Diagnostics for their support.

REFERENCES

1. Alander JT, Kaartinen I, Laakso A, et al. A review of indocyanine green fluorescence imaging in surgery. *Int J Biomed Imaging*. 2012;2012:940585.
2. D'Hallewin MA, Bezdetnaya L, Guillemin F. Fluorescence detection of bladder cancer: a review. *Eur Urol*. 2002;42:417–425.
3. Mizrahi I, Wexner SD. Clinical role of fluorescence imaging in colorectal surgery—a review. *Expert Rev Med Devices*. 2017;14:75–82.
4. Mondal SB, Gao S, Zhu N, et al. Real-time fluorescence image-guided oncologic surgery. *Adv Cancer Res*. 2014;124:171–211.
5. Zelken JA, Tufaro AP. Current trends and emerging future of indocyanine green usage in surgery and oncology: an update. *Ann Surg Oncol*. 2015;22(suppl 3):S1271–S1283.
6. Fox I, Wood E. Indocyanine green: physical and physiologic properties. *Proc Staff Meet Mayo Clin*. 1960;7:13.
7. Kusano M, Kokudo N, Toi M, et al. *ICG Fluorescence Imaging and Navigation Surgery*. Tokyo: Springer Japan; 2016.
8. Niebling MG, Pleijhuis RG, Bastiaannet E, et al. A systematic review and meta-analyses of sentinel lymph node identification in breast cancer and melanoma, a plea for tracer mapping. *Eur J Surg Oncol*. 2016;42:466–473.
9. Sugie T, Ikeda T, Kawaguchi A, et al. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: a meta-analysis. *Int J Clin Oncol*. 2017;22:11–17.
10. Zhang X, Li Y, Zhou Y, et al. Diagnostic performance of indocyanine green-guided sentinel lymph node biopsy in breast cancer: a meta-analysis. *PLoS One*. 2016;11:e0155597.
11. Okusanya OT, Hess NR, Luketich JD, et al. Infrared intraoperative fluorescence imaging using indocyanine green in thoracic surgery. *Eur J Cardiothorac Surg*. 2018;53:512–518.
12. Pischik VG, Kovalenko A. The role of indocyanine green fluorescence for intersegmental plane identification during video-assisted thoracoscopic surgery segmentectomies. *J Thorac Dis*. 2018;10(suppl 31):S3704–S3711.
13. Baiocchi GL, Diana M, Boni L. Indocyanine green-based fluorescence imaging in visceral and hepatobiliary and pancreatic surgery: state of the art and future directions. *World J Gastroenterol*. 2018;24:2921–2930.
14. Terasawa M, Ishizawa T, Mise Y, et al. Applications of fusion-fluorescence imaging using indocyanine green in laparoscopic hepatectomy. *Surg Endosc*. 2017;31:5111–5118.
15. Emile SH, Elfeki H, Shalaby M, et al. Sensitivity and specificity of indocyanine green near-infrared fluorescence imaging in detection of metastatic lymph nodes in colorectal cancer: systematic review and meta-analysis. *J Surg Oncol*. 2017;116:730–740.
16. Skubleny D, Dang JT, Skulsky S, et al. Diagnostic evaluation of sentinel lymph node biopsy using indocyanine green and infrared or fluorescent imaging in gastric cancer: a systematic review and meta-analysis. *Surg Endosc*. 2018;32:2620–2631.

17. Aoun F, Albisinni S, Zanaty M, et al. Indocyanine green fluorescence-guided sentinel lymph node identification in urologic cancers: a systematic review and meta-analysis. *Minerva Urol Nefrol.* 2018;70:361–369.
18. How JA, O'Farrell P, Amajoud Z, et al. Sentinel lymph node mapping in endometrial cancer: a systematic review and meta-analysis. *Minerva Ginecol.* 2018;70:194–214.
19. Wu Y, Jing J, Wang J, et al. Robotic-assisted sentinel lymph node mapping with indocyanine green in pelvic malignancies: a systematic review and meta-analysis. *Front Oncol.* 2019;9:585.
20. Hayami S, Matsuda K, Iwamoto H, et al. Visualization and quantification of anastomotic perfusion in colorectal surgery using near-infrared fluorescence. *Tech Coloproctol.* 2019;23:973–980.
21. Keller DS, Ishizawa T, Cohen R, et al. Indocyanine green fluorescence imaging in colorectal surgery: overview, applications, and future directions. *Lancet Gastroenterol Hepatol.* 2017;2:757–766.
22. Santi C, Casali L, Franzini C, et al. Applications of indocyanine green-enhanced fluorescence in laparoscopic colorectal resections. *Updates Surg.* 2019;71:83–88.
23. Shapera E, Hsiung RW. Assessment of anastomotic perfusion in left-sided robotic assisted colorectal resection by indocyanine green fluorescence angiography. *Minim Invasive Surg.* 2019;2019:3267217.
24. Green JM 3rd, Sabino J, Fleming M, et al. Intraoperative fluorescence angiography: a review of applications and outcomes in war-related trauma. *Mil Med.* 2015;180(3 suppl):37–43.
25. Lee BT, Matsui A, Hutteman M, et al. Intraoperative near-infrared fluorescence imaging in perforator flap reconstruction: current research and early clinical experience. *J Reconstr Microsurg.* 2010;26:59–65.
26. Malagon-Lopez P, Carrasco-Lopez C, Garcia-Senosiaín O, et al. When to assess the DIEP flap perfusion by intraoperative indocyanine green angiography in breast reconstruction? *Breast.* 2019;47:102–108.
27. Nguyen JT, Ashtate Y, Buchanan IA, et al. Face transplant perfusion assessment using near-infrared fluorescence imaging. *J Surg Res.* 2012;177:e83–e88.
28. Piwkowski C, Gabryel P, Gasiorowska L, et al. Indocyanine green fluorescence in the assessment of the quality of the pedicled intercostal muscle flap: a pilot study. *Eur J Cardiothorac Surg.* 2013;44:e77–81.
29. Varela R, Casado-Sanchez C, Zarbakhsh S, et al. Outcomes of DIEP flap and fluorescent angiography: a randomized controlled clinical trial. *Plast Reconstr Surg.* 2020;145:1–10.
30. Grosek J, Tomazic A. Key clinical applications for indocyanine green fluorescence imaging in minimally invasive colorectal surgery. *J Minim Access Surg.* 2020;16:308–314.
31. Blanco-Colino R, Espin-Basany E. Intraoperative use of ICG fluorescence imaging to reduce the risk of anastomotic leakage in colorectal surgery: a systematic review and meta-analysis. *Tech Coloproctol.* 2018;22:15–23.
32. Ladak F, Dang JT, Switzer N, et al. Indocyanine green for the prevention of anastomotic leaks following esophagectomy: a meta-analysis. *Surg Endosc.* 2019;33:384–394.
33. Shen R, Zhang Y, Wang T. Indocyanine green fluorescence angiography and the incidence of anastomotic leak after colorectal resection for colorectal cancer: a meta-analysis. *Dis Colon Rectum.* 2018;61:1228–1234.
34. Fanaropoulou NM, Chorti A, Markakis M, et al. The use of Indocyanine green in endocrine surgery of the neck: a systematic review. *Medicine (Baltimore).* 2019;98:e14765.
35. Keeney S, Hasson FHM. *The Delphi Technique in Nursing and Health Research.* Chichester, UK: Wiley-Blackwell; 2011.
36. He M, Jiang Z, Wang C, et al. Diagnostic value of near-infrared or fluorescent indocyanine green guided sentinel lymph node mapping in gastric cancer: a systematic review and meta-analysis. *J Surg Oncol.* 2018;118:1243–1256.
37. Imboden S, Mereu L, Siegenthaler F, et al. Oncological safety and perioperative morbidity in low-risk endometrial cancer with sentinel lymph-node dissection. *Eur J Surg Oncol.* 2019;45:1638–1643.
38. Liu EH, Zhu SL, Hu J, et al. Intraoperative SPY reduces post-mastectomy skin flap complications: a systematic review and meta-analysis. *Plast Reconstr Surg Glob Open.* 2019;7:e2060.
39. Moghissi K, Dixon K. Image-guided surgery and therapy for lung cancer: a critical review. *Future Oncol.* 2017;13:2383–2394.
40. Slooter MD, Eshuis WJ, Cuesta MA, et al. Fluorescent imaging using indocyanine green during esophagectomy to prevent surgical morbidity: a systematic review and meta-analysis. *J Thorac Dis.* 2019;11(suppl 5):S755–S765.
41. Ulain Q, Han L, Wu Q, et al. Indocyanine green can stand alone in detecting sentinel lymph nodes in cervical cancer. *J Int Med Res.* 2018;46:4885–4897.
42. Vecchia A, Antonelli A, Hampton LJ, et al. Near-infrared fluorescence imaging with indocyanine green in robot-assisted partial nephrectomy: pooled analysis of comparative studies. *Eur Urol Focus.* 2019;6:505–512.
43. Wu Y, Zhu W, Xu D, et al. Indocyanine green-assisted internal limiting membrane peeling in macular hole surgery: a meta-analysis. *PLoS One.* 2012;7:e48405.
44. Xiong L, Gazyakan E, Yang W, et al. Indocyanine green fluorescence-guided sentinel node biopsy: a meta-analysis on detection rate and diagnostic performance. *Eur J Surg Oncol.* 2014;40:843–849.
45. Dip F, LoMenzo E, Sarotto L, et al. Randomized trial of near-infrared incisionless fluorescent cholangiography. *Ann Surg.* 2019;270:8.
46. Qi C, Zhang H, Chen Y, et al. Effectiveness and safety of indocyanine green fluorescence imaging-guided hepatectomy for liver tumors: a systematic review and first meta-analysis. *Photodiagnosis Photodyn Ther.* 2019;28:346–353.
47. Sugie T, Kinoshita T, Masuda N, et al. Evaluation of the clinical utility of the icg fluorescence method compared with the radioisotope method for sentinel lymph node biopsy in breast cancer. *Ann Surg Oncol.* 2016;23:44–50.
48. Dip F, Sarotto L, Roy L, et al. Incisionless fluorescent cholangiography (IFC): A survey of surgeons on procedural familiarity, practices and perceptions [submitted for publication].
49. Dip FD, Asbun D, Rosales-Velderrain A, et al. Cost analysis and effectiveness comparing the routine use of intraoperative fluorescent cholangiography with fluoroscopic cholangiogram in patients undergoing laparoscopic cholecystectomy. *Surg Endosc.* 2014;28:1838–1843.
50. Dip F, Falco J, Lo Menzo E, et al. Indocyanine green fluorescence for sentinel lymph node detection in primary cutaneous melanoma: a comparative, systematic review of the literature [submitted].