Surgery 172 (2022) S3–S5

Contents lists available at ScienceDirect

Surgery

journal homepage: www.elsevier.com/locate/surg

Intraoperative fluorescence imaging in different surgical fields: First step to consensus guidelines

Fernando Dip, MD[a], Emanuele Lo Menzo, MD, PhD[b], Michael Bouvet, MD[c], Rutger M. Schols, MD, PhD[d], Danny Sherwinter, MD[e], Steven D. Wexner, MD, PhD (Hon)[g], Kevin P. White, MD, PhD[f], Raul J. Rosenthal, MD[b,*]

[a] *Hospital de Clínicas José de San Martín, Buenos Aires, Argentina*
[b] *Cleveland Clinic Florida, Weston, FL*
[c] *University of California San Diego, La Jolla, CA*
[d] *Maastricht University Medical Center, Maastricht, The Netherlands*
[e] *Maimonides Medical Center, Brooklyn, NY*
[f] *ScienceRight Research Consulting Services, London, Ontario, Canada*
[g] *Ellen Leifer Shulmand and Steven Shulman Digestive Disease Center, Cleveland Clinic Florida, Weston, FL*

ARTICLE INFO

Article history:
Accepted 4 April 2022

The authors of this special issue and the International Society for Fluorescence Guided Surgery (ISFGS) hope that the results of consensus surveys like the ones reported herein and those of both already-published and soon-to-be-published research will yield empirically validated guidelines to facilitate the adoption of best practices for intraoperative fluorescence imaging. We consider the surveys reported in this issue an essential step in this process. Intraoperative fluorescence imaging is novel technology that uses fluorescent light and, by doing so, allows surgeons to see more during surgical procedures. This includes enhancing the visualization of specific anatomical structures, visualizing structures located behind scar tissue or fat, and assessing whether or not certain tissues are adequately perfused to prevent complications. Some tissues, such as parathyroid and neural tissue, fluoresce spontaneously when visualized under light within a specific wavelength.[1,2] In other situations, however, a fluorescent fluorophore like indocyanine green (ICG) is employed. It was ophthalmologists—performing ophthalmic angiography using ICG under infrared light—who initially integrated intraoperative fluorescence imaging into clinical practice over 50 years ago. Since then, but especially over the past 2 decades, its use has steadily expanded into virtually every surgical field. This includes its application for localizing malignant tumors and sentinel lymph nodes (SLNs) in patients with a wide range of malignancies including cancers involving the breast, skin, head and neck, liver, lungs, and both the gastrointestinal and gynecological tracts[3]; assessing the quality of tissue perfusion in viscera[4] and during plastic surgery[5] to predict postoperative tissue viability; preventing and identifying anastomotic leaks[6,7]; reducing the risk of bile duct injuries and conversion to open surgery during laparoscopic and robotic cholecystectomies[8]; and evaluating parathyroid gland vitality during thyroidectomies and parathyroid gland resections[1,9]; among other purposes.

In some situations, fluorescence imaging is being used to locate specific anatomical structures, either because of the structure's autofluorescence (eg, parathyroid glands, adrenal glands, nerves) or because of the increased accumulation of ICG within the tissue of interest (eg, biliary ducts, liver, ureters, malignant tumors). Such increased visualization can permit structure resection or repair, as well as its protection from injury. This is especially well documented in the case of laparoscopic cholecystectomies, for which a randomized clinical trial that compared 321 patients who underwent laparoscopic cholecystectomy with near-infrared fluorescence cholangiography (NIFC) and 318 in whom it was not used, revealed that the visualization of biliary structures deemed essential to performing the procedure and preventing complications was 2.3 to 3.6-fold as high with NIFC.[10] Added to this, in a subsequently published meta-analysis that assessed the efficacy of

This article is published as part of a supplement supported by the International Society for Fluorescence Guided Surgery (ISFGS) with funding from Arthrex, Diagnostic Green, Intuitive, Medtronic, Olympus, Karl Storz Endoscopy, Stryker, and Richard Wolf.

* Reprint requests: Raul J. Rosenthal, MD, Cleveland Clinic Florida, 2950 Cleveland Clinic Blvd., Weston, FL 33331.
E-mail address: rosentr@ccf.org (R.J. Rosenthal);
Twitter: @FernandoDDip, @MichaelBouvet, @DannySherwinter, @SWexner, @RaulRosenthalMD

https://doi.org/10.1016/j.surg.2022.04.017

fluorescence imaging with ICG as a tool to protect biliary structures during laparoscopic cholecystectomies, rates for bile duct injuries and conversions to open surgery were only one-fourth and one-seventeenth as high among patients whose surgery was conducted with NIFC versus those in whom it was not.[8] With tumors, fluorescence imaging not only aids in their detection, but also facilitates resection to ensure clear margins, as observed in one prospective cohort study evaluating its use during breast cancer resections in 35 women with breast cancer, in whom the absence of fluorescence was 100% accurate predicting the absence of any residual tumor (negative predictive value = 100%).[11]

In other situations, the flow of ICG, via fluorescence angiography allows for the identification, and thus the repair or protection from injury, of vessels; closure of vascular defects (especially intracranial vascular defects); assessment of the adequacy of perfusion and, hence, the future viability of tissues, especially gastrointestinal anastomoses, plastic surgery flaps and grafts, and organ transplants; identification of vascular and gastrointestinal leaks; and identification of SLNs in patients with cancer. Numerous meta-analyses have documented clear noninferiority and sometimes even superiority of ICG fluorescence over the two other diagnostic markers commonly used—blue dye and the gold-standard approach employing technetium-99 (Tc-99) and a gamma counter—for detecting SLNs in patients with breast cancer, despite less risk, greater technical simplicity, and, in the case of Tc-99, lower costs with ICG fluorescence.[12–19] For all these reasons, and because the technology itself continues to advance, especially in terms of imaging equipment, the uses of fluorescence imaging continue to rapidly expand.

Despite these widespread applications, however, variability exists as to how and when fluorescence imaging is used, since no consensus guidelines have yet been published establishing best practices, like the optimum dose and timing of ICG administration, contraindications against its use, and how steep the learning curve is.

It was for these reasons that, in February 2019 in Frankfurt, Germany, the Advisory Board of the ISFGS, an international group of independent surgeons and scientists dedicated to performing methodologically robust basic and clinical research studying intraoperative fluorescence imaging and educating others about its use, unanimously voted to conduct a series of Delphi surveys across multiple surgical fields as a first step toward drafting consensus guidelines. The first of these surveys, on its general use, has already been published.[20] The current special edition reports the methodology and results of the next six surveys, all conducted in 2020–2021, evaluating current beliefs and practices on fluorescence imaging spanning 6 distinct surgical scenarios: (1) laparoscopic cholecystectomy; (2) anastomosis assessments and SLN mapping during colorectal surgery; (3) lymphedema surgery; (4) SLN mapping during gastric cancer surgery; (5) tissue perfusion assessments during plastic surgery; and (6) parathyroid gland protection during thyroid and parathyroid resections.

The Delphi survey methodology was adopted for each survey, both because this approach has been widely used to identify areas of consensus and nonconsensus among experts since the 1950s and has gained broad support among survey experts and because it would permit experts from around the world to express their opinions anonymously and uninfluenced by other survey participants, thereby minimizing the risk of acquiescence bias.[21] An MD-PhD level survey methodology expert with particular expertise in Delphi surveys (KPW) facilitated all facets of each survey, from survey development through data collection and analysis. Further details about Delphi survey methodology are provided in all six articles.

It is imperative, however, that both the uses and limitations of Delphi surveys are appreciated. First, they cannot and must not replace readers' reliance on well-designed, well-orchestrated clinical trials to ultimately decide whether a given therapeutic/diagnostic approach is effective and/or safe. Conversely, even randomized clinical trial (RCT) results require interpretation of their reproducibility and generalizability to other patient groups. In addition how does one interpret conflicting results between studies, when some support a given approach while others fail to do so? Increasingly, systematic literature reviews and meta-analyses have emerged to aid such interpretation. However, even these analyses are bias-prone, for reasons that include decisions regarding which studies to exclude from review, which outcome variables to evaluate and how, which statistical approaches to use, and how to rate each study's level of bias. Even using validated risk-of-bias tools—like the Cochrane Collaboration's Risk of Bias tool for RCTs and the Robins-I tool for nonrandomized trials—requires interpretation during several steps: choosing which tool(s) to use; which tool items apply/do not apply; how each potential study deficiency should be weighted to estimate its impact on bias risk; how to estimate each study's overall bias risk and categorize that overall risk; and what threshold of risk to use to exclude studies. Another limitation of most systematic reviews/meta-analyses is that between a paper's drafting and publication, additional potentially more robust studies may be published.

Another criticism of Delphi studies is that there may be inherent bias since clinicians who use a given diagnostic or therapeutic approach to such a degree that they become well-recognized experts in its use obviously must believe in its value. Conversely, one major advantage of asking panels of experts to comment on a given therapeutic or diagnostic approach is that, besides having extensive clinical experience, they are also invariably familiar with the current literature, many having actively contributed to it, and are, thereby, perhaps best equipped to interpret it.

Delphi studies also have several uses and advantages that even the most robustly designed RCTs or meta-analyses lack. Among them is the ability, not generally available within clinical trials, to assess different technical aspects of procedures, such as different doses and times of ICG administration, the use of different imaging equipment, and how such equipment is used including different camera angles and distances. Expert panels also can identify potential advantages and, perhaps even more importantly, limitations of given approaches and areas that require further improvement and research. All six Delphi surveys reported in this special issue purposely addressed all of these technical domains as predominant components to identify areas requiring further empirical study. The authors of this special issue and the ISFGS hope that the results of consensus surveys like the ones reported herein and those of both already-published and soon-to-be-published research will yield empirically validated guidelines to facilitate the adoption of best practices for intraoperative fluorescence imaging. We consider the surveys reported in this issue an essential step in this process.

Funding/Support

Diagnostic Green; Intuitive; Medtronic; Olympus; Karl Storz; Stryker: Each provided unrestricted grants for the ISFGS Advisory Board meeting, Frankfurt, Germany, September 8, 2019, during which the Delphi consensus was discussed. Diagnostic Green also funded accommodations and meals. Diagnostic Green, Medtronic, Karl Storz, Stryker, Arthrex, and Richard Wolf provided additional financial support to ISFGS for this publication.

Conflict of interest/Disclosure

Michael Bouvet: Consultant for Stryker; Danny Sherwinter: Ownership interest, Brainchild Surgical Device; Raul Rosenthal:

Consulting fees from Medtronics, Arthrex, Diagnostic Green and Ethicon. Advisory Board Member Axon Imaging Technologies. Stock Holder: Hechtech / Medicad Simulation, Germany; Steven Wexner: consulting fees for consulting from Stryker, Medtronic, Intuitive, and Olympus and Royalties for intellectual property license from Intuitive and from Karl Storz.

Acknowledgments

All authors are members of the ISFGS Advisory Board. 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 ISFGS.

References

1. Dip F, Falco J, Verna S, et al. Randomized controlled trial comparing white light with near-infrared autofluorescence for parathyroid gland identification during total thyroidectomy. *J Am Coll Surg*. 2019;228:744–751.
2. Dip F, Bregoli P, Falco J, White KP, Rosenthal RJ. Nerve autofluorescence in near-ultraviolet light markedly enhances nerve visualization in vivo. *Surg Endosc*. 2022;36:1999–2005.
3. Zeng HC, Hu JL, Bai JW, Zhang GJ. Detection of sentinel lymph nodes with near-infrared imaging in malignancies. *Mol Imaging Biol*. 2019;21:219–227.
4. 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.
5. Liu EH, Zhu SL, Hu J, Wong N, Farrokhyar F, Thoma A. Intraoperative SPY reduces postmastectomy skin flap complications: a systematic review and meta-analysis. *Plast Reconstr Surg Glob Open*. 2019;7:e2060.
6. 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.
7. 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.
8. Dip F, Lo Menzo E, White KP, Rosenthal RJ. Does near-infrared fluorescent cholangiography with indocyanine green reduce bile duct injuries and conversions to open surgery during laparoscopic or robotic cholecystectomy? A meta-analysis. *Surgery*. 2021;169:859–867.
9. Zaidi N, Bucak E, Okoh A, Yazici P, Yigitbas H, Berber E. The utility of indocyanine green near infrared fluorescent imaging in the identification of parathyroid glands during surgery for primary hyperparathyroidism. *J Surg Oncol*. 2016;113:771–774.
10. Dip F, LoMenzo E, Sarotto L, et al. Randomized trial of near-infrared incisionless fluorescent cholangiography. *Ann Surg*. 2019;270:278.
11. Pop FC, Veys I, Vankerckhove S, et al. Absence of residual fluorescence in the surgical bed at near-infrared fluorescence imaging predicts negative margins at final pathology in patients treated with breast-conserving surgery for breast cancer. *Eur J Surg Oncol*. 2021;47:269–275.
12. Goonawardena J, Yong C, Law M. Use of indocyanine green fluorescence compared to radioisotope for sentinel lymph node biopsy in early-stage breast cancer: systematic review and meta-analysis. *Am J Surg*. 2020;220:665–676.
13. Jeremiasse B, van den Bosch CH, Wijnen M, Terwisscha van Scheltinga CEJ, Fiocco MF, van der Steeg AFW. Systematic review and meta-analysis concerning near-infrared imaging with fluorescent agents to identify the sentinel lymph node in oncology patients. *Eur J Surg Oncol*. 2020;46:2011–2022.
14. Kedrzycki MS, Leiloglou M, Ashrafian H, et al. Meta-analysis comparing fluorescence imaging with radioisotope and blue dye-guided sentinel node identification for breast cancer surgery. *Ann Surg Oncol*. 2020;28:3738–3748.
15. Mok CW, Tan SM, Zheng Q, Shi L. Network meta-analysis of novel and conventional sentinel lymph node biopsy techniques in breast cancer. *BJS Open*. 2019;3:445–452.
16. Sugie T, Ikeda T, Kawaguchi A, Shimizu A, Toi M. Sentinel lymph node biopsy using indocyanine green fluorescence in early-stage breast cancer: a meta-analysis. *Int J Clin Oncol*. 2017;22:11–17.
17. Thongvitokomarn S, Polchai N. Indocyanine green fluorescence versus blue dye or radioisotope regarding detection rate of sentinel lymph node biopsy and nodes removed in breast cancer: a systematic review and meta-analysis. *Asian Pac J Cancer Prev*. 2020;21:1187–1195.
18. Yin R, Ding LY, Wei QZ, Zhou Y, Tang GY, Zhu X. Comparisons of ICG-fluorescence with conventional tracers in sentinel lymph node biopsy for patients with early-stage breast cancer: a meta-analysis. *Oncol Lett*. 2021;21:114.
19. 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.
20. Dip F, Boni L, Bouvet M, et al. Consensus conference statement on the general use of near-infrared fluorescence imaging and indocyanine green guided surgery: results of a modified Delphi study. *Ann Surg*. 2022;275:685–691.
21. Keeney S, Hasson F, McKenna H. *The Delphi Technique in Nursing and Health Research*. Chichester, UK: Wiley-Blackwell; 2011.