Dear Editor,

We thank you for the opportunity to review our editorial entitled "Don't forget Emergency Surgery! Lessons to learn from elective ICG-guided gastrointestinal interventions". We have considered the reviewers' comments and provided below a point-by-point answer to each of them. Changes have been incorporated and highlighted in the revised paper. We are grateful to the reviewers for their comments which have helped us improve the manuscript. We hope that you will find this revised version suitable for publication in your esteemed journal.

With kind regards,

Davina Perini, Jacopo Martellucci

Point-by-point response to comments

1. The paragraph "lessons to learn" has now been implemented (see point 4 below).

2. In the revision, the abstract has been enriched with concepts. However, we kept a hint to the format of the article because, in our opinion, it could be useful to the reader to better understand the intention of the paper.

3. Thank you

4-7. -- As suggested by the reviewer, we made major changes, modifying the style and the many mentions to Kalayarasan's work. Nevertheless, we would like to underline that our objective was not to criticize or diminish the worthiness of the aforementioned work and we intend to rectify this misunderstanding in the next review.

This Editorial article was an invitation for a paper addressing the current in-press article by Kalayarasan et al., according to our topical interest in ICG-guided surgery. The present editorial was written from our perspective and expressing our opinion on the in-press article we have chosen to address. Moreover, we accurately followed the guidelines for an Editorial article that can be found at: https://www.wjgnet.com/bpg/GerInfo/214. Our purpose was attracting readers to read the article in the issue by providing deeper and intriguing insights, as well as persuasive arguments. Importantly, we didn't want to merely present a conclusion; we wanted to encourage readers to develop their own critical thinking.

In conclusion, we filed our paper in accordance with reviewer's suggestions, while maintaining the format of the editorial previously provided by the editor.

-- We implemented the section titled “Lessons to learn from elective surgery” with more “lessons” from ICG elective use. We added data on how the ICG has been spread and used more and more since its beginnings, for which procedures it is currently well established, and how this can help in the particularities of emergent surgeries. In addition, the revised manuscript deepens more specific data learned from the elective use that can be applied in emergency surgery.

-- As suggested by the reviewer we have added the reference: Cassinotti E. et al; Surg Endosc. 2023 Mar;37(3):1629-1648 (reference No. 6).

-- After careful consideration, we organized our project in three main parts: (i) general topics, specifically lessons to learn (ii) cholecystectomy and (iii) intestinal ischemia. We decided to include these two sub-groups of emergency surgical conditions because they are the ICG application most frequently studied in emergency settings. Moreover, in our opinion, these are the indications that could benefit most from the development of green fluorescence in acute settings. In the review we added a brief mention to those applications of green fluorescence that are promising, but not fully recognized, and for which we have not highlighted specific "lessons" to learn from the elective setting.

-- Abbreviations are now defined upon first mention in the text.

-- In the section titled “ICG-guided emergency laparoscopic cholecystectomy: when and why?” We claim that “According to numerous studies, ICG fluorescence (…) helps to identify the biliary tree elements more precisely during LC and hence to reduce biliary lesions and conversion-to-open events, (…)”. Two paragraphs later we relate how the evidence about this specific topic is contradictory. They are not opposite because we referred to different fields of application: first elective setting, two paragraph later emergency one. We better specify this difference in the review.

-- As suggested by the reviewer, we simplified the first half of the section titled “An emergency dilemma: intestinal ischemia” in a more straightforward style. Again about this section, we did not conclude that ICG fluorescence is still not useful until qualitative measurement is more advanced: we state that ICG fluorescence in intestinal ischemia is a promising technique, but not yet exploited at its best. We decided to include this example of emergency surgical condition because - in our opinion - it is one of those fields that could benefit most from the development of green fluorescence in acute settings. Other limitations of the qualitative assessment of the intestinal viability with ICG (e.g. the fluorescence or

brightness of the green varies depending on the distance between the intestinal wall and the camera) are not mentioned because they are minor limitations that can be overcome by the operator's surgical skills and experience.

8-10 Not applicable.

11 As suggested by the reviewer we added the reference: Cassinotti E. et al; Surg Endosc. 2023 Mar;37(3):1629-1648 (reference No. 6)

12 As suggested by the reviewer, we reorganized our editorial in this way:

- we added more concepts to the abstract;
- we reduced the too many mentions of the previously published work (even in the conclusion);
- we better described the so-called "Lessons to learn";
- we better explained the conclusion of the two paragraphs: the first one is that routine ICG-guided elective LC is propaedeutic to the use of indocyanine green in challenging cases, such as acute cholecystitis and Mirizzi syndrome, when it may be a helpful - but almost adjunctive - tool; the second one concludes that ICG fluorescence in intestinal ischemia is a promising technique, but not yet exploited at its best;
- we mentioned the other emergent examples in the last paragraph that have been added; however, none of them has clear and standardized benefits rather than conventional techniques, at least in emergency surgery.

13,14 Not applicable.

LANGUAGE POLISHING REQUIREMENTS FOR REVISED MANUSCRIPTS SUBMITTED BY AUTHORS WHO ARE NON-NATIVE SPEAKERS OF ENGLISH

Further language polishing, that ensures all grammatical, syntactical, formatting and other related errors be resolved, was performed. The revised manuscript was carefully checked for the English correction with the help of a native English language speaking expert.

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TITLE

Don't forget Emergency Surgery! Lessons to learn from elective Indocyanine Green-guided gastrointestinal interventions.

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AUTHOR CONTRIBUTIONS

Perini D. and Martellucci J. contributed to this paper. Perini D. and Martellucci J. designed the overall concept; Perini D. contributed to the design of the manuscript and the writing; Martellucci J contributed to the discussion and the editing; Perini D. and Martellucci J. contributed to the review of literature.

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KEY WORDS: Indocyanine Green; Fluorescence; Navigation Surgery; Angiography; Emergency Surgery; Decision-Making

ABSTRACT

Fluorescence-based imaging has found application in several fields of elective surgery, but there is still lack of evidence in the literature about its use in emergency setting. Clinical trials have consistently shown that indocyanine green (ICG)-guided surgery can dramatically reduce the risk of postoperative complications, length of in-hospital stay and total healthcare costs in the elective setting. It is well-known that emergency surgery has a higher complication rate than its elective counterpart, therefore an impelling need for research studies to explore, validate and develop this issue has been highlighted.

The present editorial aims to provide a critical overview of currently available applications and pitfalls of ICG fluorescence in abdominal emergencies. ~~This paper provides an overview of the multiple fields of applications of indocyanine green (ICG) fluorescence in visceral and oncological surgery, discussing indications, summarizing the most recent and significant available literature, as well as giving technical notes of its use. However, in the paper, there is no mention of such treatment in emergency surgery. In the present editorial we specifically focus on ICG-fluorescence use in emergency settings and on how the~~ **Furthermore, we evidenced how the experience of ICG-fluorescence in elective surgery might be of great help in implementing its use in acute situations.**

In the first paragraph we analyzed the tips and tricks of ICG-guided cancer surgery that might be exploited in acute cases. We then deepened the two most described topics in ICG-guided emergency surgery: acute cholecystitis and intestinal ischemia, focusing on both the advantages and limitations of green-fluorescence application in these two fields.

In emergency situations, ICG fluorescence demonstrates a promising role in preventing undue intestinal resections or their entity, facilitating the detection of intestinal ischemic zones, identifying biliary tree anatomy, reducing post-operative complications, and mitigating high mortality rates. The need to improve its application still exists, therefore we strongly believe that the elective and routinary use of the dye is the best way to acquire the necessary skills for emergency procedures.

CORE TIP: ICG-fluorescence is a novel cornerstone in the era of navigation surgery with the potential for reducing perioperative complications and better postoperative outcomes. The use of indocyanine green in general surgery began in the field of oncologic surgery, and then spread to other surgical areas. The ICG-guided emergency surgery is still in its infancy

but represents a very promising scope of application. The experience of fluorescence-guided elective surgery can be of great help in implementing its use in emergency settings, increasing its application, and overcoming its limitations.

MAIN TEXT

Introduction

We read with great interest the valuable article by Kalayarasan R *et al*. (manuscript NO: 87027)[1] that depicts an overview ~~of current clinical applications and scientific literature on the use of indocyanine green (ICG) fluorescence in oncologic gastrointestinal and liver surgery.~~ of the multiple fields of applications of indocyanine green (ICG) fluorescence in visceral and oncological surgery, discussing indications, summarizing the most recent and significant available literature, as well as giving technical notes of its use. It represents a contemporary practical guide that can be a useful tool, both for daily surgical practice and for development of future research in this field.

~~Kalayarasan R *et al*.[1] focused on hepato-biliary and pancreatic, colorectal and upper GI surgery. However, we noticed that there are no direct mentions of the several implications of fluorescence-guided surgery in the emergency setting.~~ Although, to include all fields of application of ICG in surgery, a special mention of fluorescence use in abdominal emergency situations is necessary. To date, the research in this domain is nascent and fragmented, necessitating a shared effort - both from surgeons and academics - to gain an extensive knowledge about it.

It is well known that emergency surgeons operate under thought-provoking circumstances and high stress. Furthermore, intraoperative decision-making can be extremely challenging in the case of urgent surgery, as often the preoperative study of the patient is - by its own nature - inaccurate. In addition, intraoperatively, we are often faced with unexpected clinical pictures that put a strain on the surgical skills of the operator. The progress in ICG fluorescence imaging could facilitate intraoperative decision-making and empower the capacity of the surgeon to settle any possible doubts.[2] ICG-guided surgery in emergency setting plays a role not only in minimally invasive approaches, but also in conventional ones: the surgeon can use a laparoscope or a handheld optical system for near-infrared imaging during open surgery as well.[3]

The present editorial aims to highlight tips and tricks of ICG navigation in elective surgery that can be exploited in emergency context. Furthermore, our scope is to integrate recent advances in both ICG-guided oncologic and emergency surgery: these two aspects represent different sides of the same coin and the improvement of one necessarily leads to new horizons for the development of the other. Lastly, our aim is also to highlight the limits of

green fluorescence in daily surgical practice, that ~~in Kalayarasan's article[1]~~ **often** are not analyzed so punctually as its advantages.

Lessons to learn from elective surgery

Indocyanine green fluorescence is a mode of intraoperative navigation that might support the surgeon by enhanced real-time visualization of anatomical structures. It is based on the ability of a dye (indocyanine green - ICG) to emit a fluorescent signal when stimulated by a light source at a wavelength of 700-900 nm (near-infrared spectrum). Thanks to its relatively low costs, high availability, extremely high toxic dose/low reported allergic reactions, indocyanine green is the most widely used fluorescent dye in general surgery.[4] The latest equipment used for imaging in minimally invasive surgery allows surgeons to combine 4K vision with laser technology to activate fluorescence imaging. In this way it is possible to study, intraoperatively and in real time, the surgical structures, as well as their anatomical variants, and thus to guide the action of the surgeon.

Since its introduction for breast cancer sentinel node detection[5], ICG-fluorescence use showed a wide spread of its application in various areas of gastrointestinal and liver surgery and, consensually, a significant reduction of postoperative complications[6]. It can be used either in fully mini-invasive interventions or directly on the operative field during open procedures. This technology has a short learning-curve and can also be used for the training of surgical residents.

ICG fluorescence is becoming almost a game-changer in the era of navigation surgery. According to the latest EAES guidelines[6], the following well-established and recommended ICG-guided surgical procedures currently exist (strong grade of recommendation):

- the use of fluorescent cholangiography during laparoscopic cholecystectomy, whenever available, in order to improve the visualization of the biliary structures;

- the use of ICG fluorescence in colorectal surgery to assess tissue perfusion, in order to reduce the risk of anastomotic leak;

- the use of ICG fluorescence in liver surgery, in order to detect superficial liver tumors.

Since it is straightforward and does not interfere with the surgical workflow, ICG-fluorescence can be widely exploited in both elective and urgent interventions and surgeons who are skilled in its use in elective surgeries can safely apply it in urgency as well.[3,8,9]

After knowing the reported decrease of complications in elective surgery[2,4,7], we expect an even bigger impact in the emergency setting.

The crucial point is that ICG fluorescence can dramatically affect intraoperative decision-making. **This concept is perhaps more important in the acute care setting, in which the recognition of anatomical structures can be difficult by the acute inflammatory state, and the blood supply is often impaired by the underlying diseases (e.g., acute mesenteric ischemia, bowel perforation/resection, trauma). In emergency situations, ICG fluorescence demonstrates a promising role in preventing undue intestinal resections or their entity, facilitating the detection of intestinal ischemic zones, identifying biliary tree anatomy, reducing post-operative complications and mitigating high mortality rates[10]. The need to improve its application still exists, although we strongly believe that the elective and routinary use of the dye is the best way to acquire the necessary skills for emergency procedures**.

However, ICG should not be considered as a panacea to direct surgical actions, and surgeons, especially the youngest, must need to exercise their own dexterity and critical sense, based on individual skills, experience, and training.

The major pitfalls of green fluorescence are the dosage and the timing of ICG administration: arbitrary doses, sometimes distorted by patient or tissue characteristics, or uncoordinated administration, often due to operator inexperience, might lead to acquisition of false data, causing misinterpretation of the tissue perfusion. Indeed, critical points in the use of intraoperative fluorescence imaging, clearly sharpened in the emergency setting, are the low standardization and reproducibility of the results and the associated difficulty in comparing the results of the existing trials. Furthermore, little is known about the influence of hemodynamic parameters on the quantitative assessment of ICG fluorescence during surgery.

The merit of elective surgery - that we can learn for emergency contexts - is to ensure standardized settings and documentation that are essential, as they rule out most of the possible pitfalls in ICG fluorescence angiography/cholangiography.

ICG has a myriad of clinical applications, including many emerging. The ever-growing availability of imaging software that can employ this fluorophore will turn some of these applications into a standard of care.[4] To begin with, the nascent standardized evidence-

based guidelines[6] needed to be implemented and disseminated for safe adoption of ICG-fluorescence in daily surgical practice.

This editorial specifically focuses on laparoscopic cholecystectomy (LC) for acute cholecystitis and laparoscopy/laparotomy for intestinal ischemia, since they are the most common and established applications of ICG in emergency surgery. A recently published systematic literature review[10] reported benefits from using ICG for acute cholecystitis in 48% of cases (clear identification of biliary structures and a safer surgical procedure) and in almost 37% of cases that concerned the use of ICG for occlusive or non-occlusive mesenteric ischemia, ICG injection led to a modification of the surgical strategy.

Other fields of application are trauma, appendectomies, strangulated hernias, control of intestinal anastomosis and identification of the ureter in complex viscerolysis or intestinal resections[6,10]. These applications are promising, however less unanimously recognized and for which we have not highlighted specific "lessons" to learn from the elective setting.

ICG-guided emergency laparoscopic cholecystectomy: when and why?

Laparoscopic cholecystectomy is one of the most common procedures in abdominal surgery; moreover, it is performed under emergency conditions in case of acute cholecystitis. The conversion rate in elective LC is quite low, but it dramatically increases in the event of acute cholecystitis (up to 30% reported in some studies[12]). In fact, the most important risk factor for conversion to open in LC is acute cholecystitis itself: the presence of inflamed tissues could make surgical dissection difficult and might lead to improper assessment of anatomy, thus this may necessitate conversion.

The most feared complication of cholecystectomy is definitely iatrogenic injuries of bile ducts. Biliary lesions often happen when the biliary anatomy is misidentified; as misidentification of structures during LC is not uncommon, Strasberg *et al.* have advocated the concept of "critical view of safety"[13] for proper identification of the biliary anatomy to avoid biliary injury. The biliary anatomy is not easy to delineate when tissues are acutely inflamed, and that is where ICG-fluorescence comes into play. ICG is metabolized by hepatic cells and secreted to the bile, so it allows a real-time visualization of the biliary system. According to numerous studies **about elective cholecystectomy**[7,14], ICG fluorescence, applied to the "critical view of safety", helps to identify the biliary tree

elements more precisely during LC and hence to reduce biliary lesions and conversion-to-open events, which are relatively frequent in urgency.

Compared to conventional intraoperative radiographic cholangiography, ICG-cholangiography provides real-time visualization of critical structures, even before the Calot's dissection. Although fluorescence might fail to identify common bile duct stones and intrahepatic biliary anatomy, it offers the possibility to perform the procedure also in case of unavailability of traditional cholangiography (e.g., at night). This last element is essential in urgency, much more than the identification of common bile duct calculosis, which can be treated endoscopically at a later time.

As opposed to the elective setting, scientific reports on the use of ICG for acute cholecystitis are mainly retrospective studies, and the results are often contradictory. A 2023 study by Losurdo *et al.*[14] showed a reduction trend in intra- and postoperative complications, duration of surgery and length of hospital stay in urgent ICG-guided LC. However, in literature not everyone agrees with this statement. A randomized controlled trial published on *Surgical Endoscopy* in 2022[15] underlined that green fluorescence did not make any difference in conversion or complication rate, even in emergency surgery, and its routinary use in LC is questionable. This divergence of opinion is probably due to different evidence of fluorescence limits. In fact, visualization of ICG can be affected by both injection timing and amount, as well as by the edema of encountered tissues. These parameters are difficult to manage due to the nature of emergency surgery. **Moreover, the heterogeneity of the results might be linked to the experience and dexterity of the surgeon that play a decisive role in the possibility to achieve the same positive outcomes.**

Here comes the lesson we can learn from elective surgery. The use of indocyanine green in programmed surgery allows to shorten the ICG-navigation learning-curve and refine the technical details of its use, in view of urgent interventions, where time has a key-role, and it can not be consumed in attempts. In a word, routine ICG-guided elective LC is propaedeutic to the use of indocyanine green in challenging cases, such as acute cholecystitis and Mirizzi syndrome, when it may be a helpful - **but almost** adjunctive - tool.

An emergency dilemma: intestinal ischemia

Assessing bowel viability can be challenging during acute surgical procedures and the decision whether to resect an intestinal tract in an emergency setting is anything but trivial:

this represents a crucial moment that could strongly influence postoperative complications and the overall outcome of the patient, including its future quality of life. Extensive resections should be carefully considered, as removal of large segments of small bowel can result in intestinal failure for short bowel syndrome, resulting in significant morbidity and poor quality of life. If, however, the surgical approach is too conservative, leaving ischemic bowel in situ, further clinical deterioration may need reinterventions and increase the risk of death. Judging the most suitable resection margins may be difficult as a broad range of variables, including hemodynamic instability and vasopressor support, may exist. None of the intraoperative tools to assess intestinal perfusion that have been considered over past years became widely used, due to their complexity, as well as their costs: a straightforward and inexpensive intraoperative tool to test intestinal viability would be very helpful in an emergency setting.

~~In the early 80s, Bulkley *et al* compared the use of ICG, combined with doppler, to the clinical judgment to determine bowel viability after ischemic injury.[13]~~ ICG-fluorescence is a promising technique that has shown value for evaluation of adequate perfusion in gastrointestinal anastomoses in the elective setting; in the last few years, some authors reported case reports about its use as an intraoperative method to determine intestinal microcirculation in the setting of minimally invasive approaches to ischemic and injured bowel.[3,9] ~~Unfortunately, its potential added value in the acute setting has barely been studied. Despite the high mortality rate associated with mesenteric ischemia, no real progress has been made in improving the survival of those patients in the last decade.~~

As evidenced by Lim ZY *et al.* in a recently-published review[11], it can be challenging to macroscopically differentiate between reversible and irreversible ischemic bowel. Moreover, laparoscopy reduces the ability to discern signs of irreversible vascular insufficiency, such as absence of peristaltic movements, mesenteric pulsations, and discoloration of the bowel wall. Intraoperative real-time ICG-fluorescence makes it possible to detect non-viable intestine that is not apparent to white light and may be a valuable tool for the surgeon to determine whether bowel resection is necessary and to define the most appropriate resection margins.[2]

ICG fluorescence has the capacity to properly define ("to map-out") ischemic bowel areas during laparoscopic/laparotomic surgeries for acute intestinal ischemia and hence perform patient-tailored surgeries, avoiding unnecessary or underestimated resections. In a word,

we can use ICG to weigh the extent of the resection or avoid it. Prospective studies are needed to optimize the use of this tool at its best: in particular, more extensive and randomized trials **are required to assess when and how the intraoperative use of ICG-fluorescence can remarkably impact on surgical decision-making and patient outcome.**

A "grey-zone" related to ICG-guided surgery, especially in perfusion assessment field, is the need to measure the fluorescence signal in an objective manner, in order to accomplish adequate clinical decision-making. In most of the studies, the evaluation of bowel perfusion with ICG is based on the surgeon's subjective visual quantification of fluorescence, which results in a large inter-observer variation. This limitation may be overcome identifying univocal reporting benchmarks and an objective cut-off based on the fluorescence signal pattern. This is an area of active research where dedicated software for digital imaging analysis is under development.[4,11] So far, they have been tested in pre-clinical studies and still need to be fully validated, thereby enabling the standardization of clinical trials and the achievement of significant results. **Other limitations of the qualitative assessment of the intestinal viability with the ICG (e.g. the fluorescence or brightness of the green varies depending on the distance between the intestinal wall and the camera) are minor limitations that can be overcome by the operator's surgical skills and experience.**

In the end, ICG fluorescence in intestinal ischemia is a promising technique, but not still exploited at its best. In our opinion, the assessment of intestinal viability is one of those fields that could benefit most from the development and spread of green fluorescence in acute setting.

Is the future green and bright?

There is increasing evidence that the use of ICG fluorescence during abdominal surgery could facilitate intra-operative decision-making and change surgical strategies. Nevertheless, it does not play a pivotal role in all acute surgical diseases.

Acute appendicitis is one of the main indications for urgent surgery worldwide, but ICG use in this field is still in its early stage. Some preliminary studies showed that ICG could be a useful method for assessing appendix stump vascularization. Dye-guided surgery might represent one of the decision-making modalities for patients with complicated acute appendicitis to manage the appendicular base with the different devices, eventually reducing postoperative complications and the use of endo-staplers in well-selected patients[16]. However, ICG importance in this case might be limited by the fact

that appendicectomy is burdened by a low rate of morbidity, mortality and post-operative complications, although not absent.

Intraurethral injection of ICG is an effective adjunct for ureteral identification during minimally invasive surgery, especially in the case of acute inflammatory processes where the anatomy may be significantly distorted. However, in these cases, the real challenge is the identification of the ureter itself, which is necessary for this approach; once identified, its course is usually easier to follow, therefore intraureteral injection might represent an over-precaution with an inconvenient cost/benefit ratio.

Another topic that is still a matter of debate and promising expectation is the use of ICG fluorescence in trauma surgery. In trauma patients, ICG has been used mainly to assess the viability of bowel or parenchymatous organs, to evaluate the perfusion-related tissue impairment in an extremity or craniofacial trauma and, lastly, to reassess the efficacy of surgical procedures performed in terms of vascularization. [10] Nevertheless, literature about this topic is limited and to understand the real contribution of ICG to trauma surgery more controlled studies are needed.

CONCLUSIONS

ICG is a safe, feasible and effective aid, even in the field of emergency surgery. Its use could facilitate intra-operative decision-making, change surgical strategy and improve patient outcome. We strongly believe that the elective and routinary use of the dye is the best way to acquire the necessary skills and experience to be exploited within emergency procedures. Despite these promising evidences, the literature is sparse, small, and heterogeneous; thus, new randomized controlled trials are needed to unequivocally demonstrate the benefits of routinary fluorescence-guided surgery in emergency setting.

~~Again, we congratulate the authors on their successful work. Reading the aforementioned paper, we felt stimulated to begin further research in the field of fluorescence-guided surgery, especially in the emergency setting.~~

~~Emergency surgery has a notoriously higher complication rate than elective surgery, resulting in an increase in perioperative mortality, length of hospital stay and care-related costs. Therefore, why do not extensively use ICG even in emergency surgery?~~

~~By guiding the operator's action, the primary goal of using ICG fluorescence in surgery is a significant reduction in complications, while also reducing total healthcare costs.~~

~~We thank the authors of the manuscript for their precious job and hope in future clinical trials focused on this issue.~~

CONFLICT OF INTEREST: Perini D. and Martellucci J. certify that there is no actual or potential conflict of interest in relation to this editorial and they state that there are no financial interests or connections, direct or indirect, or other situations that might raise the question of bias in the work reported or the conclusions, implications, or opinions stated – including pertinent commercial or other sources of funding for the individual author(s) or for the associated department(s) or organization(s), personal relationships, or direct academic competition.

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