

8th July 2023

To
Chief Editor
World Journal Of Gastrointestinal Surgery

Re: Manuscript NO.: 85750, Review

Dear Sir / Madam

Many thanks for soliciting peer review for our review manuscript on utility of indocyanine green in abdominal surgery. We are appreciate of peer reviewers comments and herewith submit point by point response to and have made necessary changes in the manuscript files too. We hope that this is satisfactory.

Reviewer #1:

There is an increasing body of literature on this topic and much effort has been devoted to evaluating the efficacy of the clinical use of ICG in the surgical settings. This review article seems informative and educational. Nonetheless, several potentially important issues would need to be addressed.

Comment 1: p.11, Biliary Mapping During Laparoscopic Cholecystectomy) The term “CBD injury” is not appropriate. Instead, “Bile duct injury” should be used. The common and right hepatic ducts are also susceptible to injury during laparoscopic cholecystectomy.

Response 1: Thanks for this suggestion. We have done this at all the relevant places. We have introduced the acronym BDI for bile duct injury. The statement now reads as - “Bile duct injury (BDI) is an uncommon but significant complication associated with cholecystectomy as it reduces patient’s quality of life and exposes surgeon to litigation.”

Comment 2: p.11, Biliary Mapping During Laparoscopic Cholecystectomy, Is the ICG cholangiography superior to conventional intraoperative cholangiography? If so, what is the advantage of the ICG method?

Response 2: Thanks for this comment. The manuscript states that IOC (intraoperative cholangiography) is considered the current gold standard. However, ICG is good for the extrahepatic biliary tree and also avoids radiation exposure. Our group published a meta-analysis on this topic comparing IOC with ICG use in cholecystectomy surgery and concluded that both techniques have their own advantages and drawbacks – this was published in Surgical Endoscopy (PMID – 33398590). We have edited the following statement – “ICG NIR FI has been found to only be useful in discerning the extrahepatic biliary tree, while intraoperative cholangiography is useful for evaluating the intrahepatic biliary tree.”

Comment 3: p.19, Lymphatic mapping, The lymphatic mapping has been attempted to identify the main feeding vessels and lymphatics for appropriate lymph node dissection in colon cancer surgery as well as to find the sentinel lymph nodes to minimize the resection area. These two concepts of the procedure should be discriminated and the evidence should be distinctively described.

Response 3: Many thanks for this useful and insightful comment. We have added the following – “In patients with CRC, ICG is useful for two purposes. Firstly, ICG dye injection guides lymphatic mapping to facilitate harvesting of the draining lymph nodes for oncological resection during colorectal resection. Secondly, ICG dye injection helps identify the SLN and provide information to surgeons for resection and is an area of ongoing research initiatives.”

In addition, the section contains two separate paragraphs to provide details of each of the above two use of ICG.

Comment 4: p.20, Ureteral visualization, Is there any evidence for using ICG-coated ureteral catheter to visualize the ureter intraoperatively?

Response 4: This comment is a testament of an astute reviewer who is indeed a subject matter expert. We have not come across any such clinical application of ICG whereby it is coated on a tube or stent. However, there is emerging evidence related to ICG-coated nanostructures or membranes that can have potential clinical applications in the near future (PMID - 36246765 and PMID - 36015366). In our manuscript, we have mentioned on page 21 about ICG-coated silicon Foleys urinary catheters being used in cadavers (citation 97). Thus, it is a matter of time when ICG coated tubes or materials will be available for clinical application. We have covered most of the potential future use/application in the section "future direction". We have added the following in this section of the manuscript -

"ICG coating of the tubes and stents can be made possible with potential future clinical application in surgery. For example, ICG-coated ureteral stents can be useful in colorectal, gynecological, and urological procedures."

Comment 5: p.20, Identification of Peritoneal Metastasis, The authors say "Peritoneal metastases occur in 30-40% of colorectal cancer patients". Is the proportion of peritoneal metastasis really so high?

Response 5: Many thanks for this observation. This rate seems to be high to us too. However, we have double checked the citation from where this information is cited (annals of surgery paper, citation 118). In addition, we have found two more papers (one old and one less old) that also kind of echoes similarly high rates. Both papers are given below:

1. Chu DZ, Lang NP, Thompson C, et al. Peritoneal carcinomatosis in nongynecologic malignancy. A prospective study of prognostic factors. *Cancer* 1989; 63:364-367.

2. Verwaal VJ, van Ruth S, de Bree E, et al. Randomized trial of cytoreduction and hyperthermic intraperitoneal chemotherapy versus systemic chemotherapy and palliative surgery in patients with peritoneal carcinomatosis of colorectal cancer. *J Clin Oncol* 2003; 21:3737–3743.)

As the above two manuscripts are more than 2 decades old, we have checked additional more recent literature. A relatively recent review paper also summarizes peritoneal metastases incidence for synchronous metastases as 5-8% and metachronous metastases as 4-19% with a footnote that these rates are an underestimation due to the limitation of routine imaging modalities to detect peritoneal disease and non-performance of routine autopsies of colorectal cancer patients. Thus, we have edited the statement to clarify synchronous and metachronous peritoneal metastases –

“Peritoneal metastases occur in up to 30% of colorectal cancer patients (metachronous more than synchronous), and 75% of ovarian cancer patients present with peritoneal disease on diagnosis.”

Reviewer #2:

The authors have done a nice and comprehensive work on the review of ICG applications in surgery. ICG has myriad of applications. The language and grammar appears adequate. There are few suggestions to further improve the manuscript.

Comment 1: ICG visualization needs special Apparatus / equipment which adds to cost or not available everywhere. This can be discussed.

Response 1: Many thanks for this pertinent comment. We agree that availability, accessibility, affordability, and adoption remain an issue that needs medico-industrial complex collaboration. We have added the following in discussion section under “future direction” heading – “ICG has myriad clinical applications and many emerging applications. Despite this, the accessibility, availability, affordability, and adoption remain an unmet need that needs to be met by collaborative initiatives

of the medico-industrial complex. To begin with, standardized evidence base guidelines need to be developed, disseminated, and implemented for safe adoption in routine clinical practice.”

Comment 2: Pharmacokinetics and pharmacodynamics along with ICG Toxicity can be mentioned in brief.

Response 2: This is an important issue and we apologize for having not emphasized this in our review. We have added the pertinent details. In the introduction section we have added the following –

“After intravenous injection, ICG binds to plasma proteins and has a half-life of three minutes. As the lymph is rich in protein content, lymphatics and lymph nodes can be easily mapped after ICG injection. In general, ICG is safe at dose below 0.5mg/Kg body weight, however adverse reactions like nausea, pyrexia, and anaphylaxis may occur.”

Comment 3: Biliary surgery- Bilio-enterostomy – Check about any studies for it

Response 3: We have added two subheadings for the biliary section and included one recent publication of use in choledochal cyst surgery for resection and other conference abstract showing utility in detection of intraoperative bile leak during hepaticojejunostomies. The following is added –

Choledochal cyst excision:

The utility of ICG is also explored in identification of pancreatico-biliary junction and distal end of bile duct in a patient with choledochal cyst scheduled for laparoscopic excision. The authors innovated a novel method of exploiting the protein affinity of ICG by mixing ICG with the patient’s own bile juice aspirated from the gallbladder during surgery.

Bilio-enteric anastomosis:

In patients undergoing hepaticojejunostomy for a variety of indications, ICG is shown to increase the detection of intra-operative bile leak from the anastomosis, thus allowing surgeons to reinforce the suture line and reducing the risk of post-operative biliary fistulas.

Comment 4: Must mention Current status in urologic surgery. It has role in skin flaps too which needs to be discussed.

Response 4: The scope of our paper is clarified in the title as “gastrointestinal surgery” and thus we have not included other applications like ophthalmology, plastic surgery, and urology. However, in the colorectal section, we have included ICG application for ureteral and urethral identification. We hope this is acceptable.

Comment 5: Majority of studies happened in Laparoscopic cholecystectomy and Colo-rectal surgeries. Their discussion can be expanded based on existing literature.

Response 5: Many thanks for your comment. We have added some sections relating to colorectal surgery application and biliary surgery application in line with comments from two reviewers. We hope that this is satisfactory.

Thanking you

Sincerely

A/Prof Vishal G Shelat

Senior Consultant

Department of General Surgery

Tan Tock Seng Hospital

Singapore 308433