Review Article

Quantitative evaluation of anastomotic perfusion during colorectal surgery via indocyanine green fluorescence angiography: a narrative review

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Background and Objective: Quantitative studies of indocyanine green (ICG) are needed to optimize its evaluative potential in anastomotic perfusion during colorectal surgery. However, some limitations still existed in current studies about qualitative evaluations such as small-scale studies, the inconsistent concentration of the drug, the method of injection, etc. Therefore, this review summarized the primary quantitative parameters, image, method, and so on, during ICG fluorescence angiography aiming to further provide a theoretical basis for the application of ICG in laparoscopic colorectal surgery.

Methods: The following keywords "indocyanine green or ICG", "anastomotic perfusion", and "colorectal surgery" were applied to search for literature published from 2002 to 2022 in the PubMed, Web of Science, and Medline databases. Then, the information about ICG fluorescence angiography in quantitative evaluation of anastomotic perfusion during colorectal surgery was summarized. Through integrating the experiences derived from the literature and our research center, the crucial quantitative parameters [such as T0, Tmax, Fmax, and S (Fmax/Tmax)], image characteristics, and standard operational process for ICG fluorescence angiography were summarized.

Key Content and Findings: Firstly, quantitative parameters, including T0, Tmax, Fmax, and S (Fmax/Tmax) during the ICG fluorescence angiography could predict anastomotic leakage, and thus should be recorded. Secondly, the image curve generated by the software might differ among patients, which included a filling period, reducing period, and platform period; some patients even presented a second fluorescence intensity peak. Finally, present studies presented great heterogeneity regarding the injection dose of ICG, observation distance from the laparoscope to the anastomotic site, software, and so on, during ICG fluorescence angiography in quantitatively evaluating the intestinal blood perfusion.

Conclusions: This review points out the challenges of ICG fluorescence angiography in quantitative evaluation of anastomotic perfusion and gives some advice. However, some difficulties and issues are non-neglectable during the clinical implications of the quantitative evaluation of ICG, such as standardizing the specific cut-off value about the quantitative parameters, injection dose of ICG, observation distance from the laparoscope to the anastomotic site, software, and so on, during ICG fluorescence angiography in quantitatively evaluating the intestinal blood perfusion to eliminate heterogeneity.

Keywords: Indocyanine green (ICG); anastomotic perfusion; laparoscopy; quantitative; colorectal surgery

Submitted Oct 10, 2022. Accepted for publication Nov 21, 2022.
doi: 10.21037/atm-22-5312
View this article at: https://dx.doi.org/10.21037/atm-22-5312

Introduction

Anastomotic leakage is one of the most common complications after colorectal surgery, with an incidence of 3–29% (1-3). The etiology of anastomotic leakage is diverse, among which the most critical and direct factor is the status of anastomotic perfusion (4). Previously, anastomotic perfusion was judged by the surgeon according to the color of the anastomotic site during the operation, yet this judgment method is subjective and largely depends on the surgeons' experience with heterogeneous criteria among different surgeons. Hence, there is an urgent need to discover a more objective and visualized way to evaluate anastomotic perfusion.

With the development of laparoscopy, indocyanine green (ICG) fluorescence angiography has been successfully used to reveal anastomotic perfusion and could thus reduce the incidence of anastomotic leakage. For instance, a recent meta-analysis including 20 studies with 5,498 colorectal cancer (CRC) patients revealed that the application of ICG fluorescence angiography is associated with reducing anastomotic leakage (5). However, these studies mainly focused on the qualitative evaluation of anastomotic perfusion, which limits its application in observing the regional blood supply (6). For instance, even though the fluorescence could be detected in the anastomotic sites of patients, anastomotic leakage still could occur if the local hemodynamic condition is unstable (7). Therefore, studies aiming to quantitatively evaluate the anastomotic perfusion by ICG fluorescence angiography are currently ongoing. However, these studies are mainly single-center; the concentration of the drug, the method of injection, and the equipment used in these studies are varied; the cut-off value of ICG fluorescence and the outcome measures are also different. Therefore, it is urgent to carry out a study to conclude the shortage and difficulty about the quantitative evaluation of ICG fluorescence angiography, based on which, some advice or further directions should be indicated.

Hence, this narrative review summarized the quantitative methods of ICG fluorescence and observation parameters in the published papers and aimed to provide a theoretical basis for the standardization of quantitatively evaluating the anastomotic perfusion by ICG fluorescence angiography during laparoscopic colorectal surgery to further promote its clinical implications. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5312/rc).

Methods

The following keywords "indocyanine green or ICG", "anastomotic perfusion", and "colorectal surgery" were applied for searching the literature related to the topic of this study. Besides, any linked, published papers during the past 20 years in the PubMed, Web of Science, and Medline databases were collected, read, and cited as appropriate. Furthermore, the references in the retrieved papers were also read and referred to as needed. The search strategy is summarized in *Table 1*. The crucial quantitative parameters [such as T0, Tmax, Fmax, and S (Fmax/Tmax)], image characteristics, and standard operational process for ICG fluorescence angiography were summarized in these retrieved papers.

Discussion

ICG fluorescence angiography

Laparoscopy has evolved to be regarded as a routine colorectal surgical procedure due to its advantages of minimal associated trauma and bleeding (8,9). However, high accuracy is required for visualization during laparoscopic colorectal surgery. ICG is a non-toxic contrast medium with good biocompatibility, which has been approved by the Food and Drug Administration (FDA) in generating images (10). After ICG is injected into the human body, it binds to plasma proteins and absorbs the near-infrared (NIR) fluorophores. This further presents the fluorescence and thus develops the images (11-13). ICG fluorescence angiography has been widely used for tissue perfusion assessment, detection of cancerous lesions, lymph node tracing, and visualization of segmental organs such as the lungs and liver (14-16). Recently, the introduction of ICG fluorescence angiography to laparoscopic colorectal surgery has exhibited better visualization, and the number of studies on the use of ICG fluorescence angiography in laparoscopic colorectal surgery is increasing, which would be a hotspot in the field of colorectal surgery.

The assessment procedure of anastomotic perfusion by the ICG fluorescence angiography

The occurrence of anastomotic leakage is related to many factors, among which the perfusion and excessive tension at the anastomotic sites are two key factors affecting the incidence of anastomotic leakage (17,18). Surgeons have been able to sufficiently control the tension at the

Table 1 The search strategy

Items	Specification
Date of search	01-03-2022 to 01-07-2022
Databases and other sources searched	PubMed, Web of Science, and Medline
Search terms used	"indocyanine green or ICG", "anastomotic perfusion", "colorectal surgery"
Timeframe	01-03-2002 to 01-06-2022
Inclusion and exclusion criteria	Only papers in English were included
Selection process	W Kong collected and assembled the data. Finally, all authors reached an agreement on the manuscript

ICG, indocyanine green.

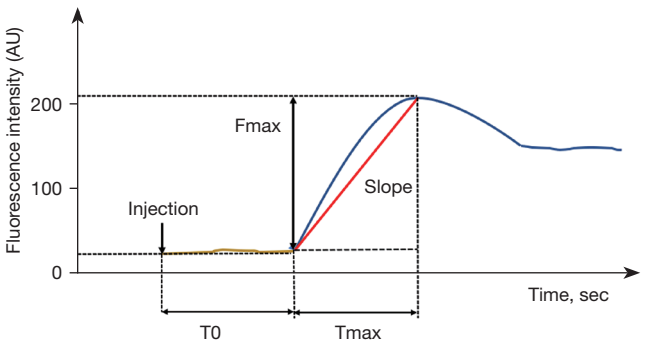

Figure 1 Quantitative parameters of ICG-NIRF. ICG-NIRF, indocyanine green-NIR fluorescence technology. NIR, near-infrared.

anastomotic sites by dissociating the mesentery or choosing the appropriate anastomotic method, but the perfusion is not able to be manually controlled; good perfusion at anastomotic sites becomes essential for the anastomotic healing (19). Therefore, evaluation of the anastomotic perfusion during laparoscopic colorectal surgery is critical.

Currently, anastomotic perfusion is judged by surgeons subjectively, which is insufficiently accurate and objective. As mentioned above, the application of ICG fluorescence angiography in laparoscopic colorectal surgery could obtain well-visualized static and dynamic images, which is a convenient and simply operated procedure. Besides, its efficacy and safety have been widely verified. In general, the operation of the ICG fluorescence angiography is as follows: 25 mg ICG is dissolved in 10 mL sterile water to acquire the mixed solution with a concentration of 2.5 mg/mL, then this solution is injected into the patient through the central peripheral vein. The classical injection timing is as follows: (I) after the devascularization; (II) before the resection of the colorectum; (III) after the anastomosis (20-22). Then, the corresponding parameters for the ICG fluorescence angiography are recorded.

Quantitative parameters of ICG-NIR fluorescence technology (NIRF)

The primary recorded parameters include (I) T0 (defined as the time from the injection of ICG solution to the development of fluorescence image); (II) Fmax (defined as the maximum ICG fluorescence value); (III) Tmax (defined as the time from the development of fluorescence image to the achievement of maximum ICG fluorescence value); (IV) S (defined as Fmax/Tmax, which means the speed of the fluorescence reaching the peak value) (*Figure 1*). Wada *et al.* (23) conducted a single-center retrospective study comprising 112 CRC patients who underwent laparoscopic colorectal surgery between August 2013 and April 2016; the parameters including Fmax, Tmax, T1/2, and the S were recorded, aiming to evaluate the correlation of these parameters with the incidence of anastomotic leakage and the intestinal function recovery after the resection. They found that Fmax might be related to the anastomotic leakage, and that Tmax might be associated with intestinal function recovery. Interestingly, a cut-off value of the Fmax (52.0) was generated in their study, and they proposed that this cut-off value of Fmax could well distinguish the patients with or without the anastomotic leakage with a sensitivity of 100.0% and specificity of 92.5%. In detail, if the value of Fmax is lower than 52.0, the incidence of anastomotic leakage would primarily increase (23). This study carried out by the Wada *et al.* was the first quantitative study to evaluate the anastomotic perfusion by laparoscopic ICG fluorescence angiography, which provides more ideas and

directions for applying ICG fluorescence angiography in colorectal surgery. Based on their precursory study, more studies that use ICG fluorescence angiography to evaluate the anastomotic perfusion quantitatively have been carried out subsequently. A prospective study by Hayami *et al.* (24) enrolled CRC patients who underwent laparoscopic colorectal surgery, and used ICG fluorescence angiography to evaluate the anastomotic leakage. They found that T0 in patients with anastomotic leakage is more prolonged than that in those without anastomotic leakage, which implies the potential value of T0 in predicting the occurrence of anastomotic leakage. Iwamoto *et al.* (25) reviewed 25 patients who underwent elective laparoscopic anterior resection for rectal cancer. They found that the mean T0 value was 37.5±17.1 seconds in patients with anastomotic leakage, which was longer than that in patients without anastomotic leakage (T0 =11±13.1 seconds). Hence, it could be concluded that (I) the the T0, Fmax, Tmax, and S are four important parameters that should be recorded during the ICG procedure; (II) the prolonged T0 might be correlated with an increased risk of anastomotic leakage and suggests that clinicians should pay more attention to the extended T0; if the T0 occurs during colorectal surgery, a preventive laparostomy should be considered.

Images during ICG-NIRF

Apart from the abovementioned quantitative parameters, the image drawn by the parameters is another essential indicator during quantitative research. The ICG quantitative curve varies among patients due to its heterogeneous ICG quantitative parameters. In the study by Park *et al.* (26), the ICG quantitative curve could be divided into 25 kinds, and each patient could be defined among these 25 kinds. In our preliminary study which aimed to apply the ICG quantitative curve in evaluating anastomotic perfusion, we found that the ICG quantitative curve in patients with satisfactory anastomotic perfusion exhibited an apparent increasing trend in the initial stage (also called the filling period), then the fluorescence intensity gradually increased to the peak value; after that, the fluorescence intensity exhibited a decreasing trend (also called the reducing period), during this period, the decreasing trend was relatively slow; finally, the fluorescence intensity decreased to a certain level and remained unchanged (this period also called platform period) (*Figure 2A-2E*). However, some patients with promising anastomotic perfusion also showed a second fluorescence intensity peak (*Figure 3A-3C*). Therefore, the shortage and limitations about the current quantitative studies are non-neglectable, such as the number of studies is few, and those available studies exhibit an internal heterogeneous study design with relatively small sample sizes and inconsistent conclusions (27,28). Therefore, a more extensive sample-size study is still needed to standardize the injection method and dose of ICG to eliminate the potential heterogeneity.

The quantitative method of ICG-NIRF in assessing the anastomotic perfusion

After injecting the ICG solution through the central or peripheral veins, the laparoscope could be fixed at a certain distance from the anastomotic sites and retained for a definite period; then, the video should be saved. If it is an open operation, then the lights in the operating room should be turned off to eliminate interference from external light. After the surgical resection, in the stored video, the region of interest (ROI) of the proximal and distal sections could be selected and evaluated by the image-analyzer software; finally, the quantitative curve of fluorescence intensity in ROI with time can be drawn according to the continuous reading results. The choice for the quantitative software of fluorescence intensity includes ROIs (Hamamatsu Photonics K.K., Shizuoka, Japan) (23,24,29-31), Image J (version 1.39 s; National Institutes of Health, Bethesda, MD, USA, available at http://rsb.info.nih.gov/ij) (32), MATLAB 2019 (MathWorks, Natick, MA, USA), and so on (26,33).

Ahn *et al.* (33) showed that the fluorescence intensity is negatively correlated with the distance (from the laparoscope to the anastomotic sites), with the best distance of 4–5 cm. Amagai *et al.* (32) reported that it is impossible to assess the whole loop of the anastomotic sites through the serosal surface during the ICG fluorescence angiography; therefore, they proposed that transanal ICG-NIR might be a more effective and detailed method for evaluating the anastomotic perfusion over the entire circumference of the anastomotic sites in detail. However, the procedure of transanal ICG-NIRF is more complex than the standard ICG-NIRF; this finding also needs a further sample-size study to verify.

Hence, challenges, including the difficulty for quantitative evaluation and judgment of the lack of a unified standard, are non-negligible during the ICG fluorescence

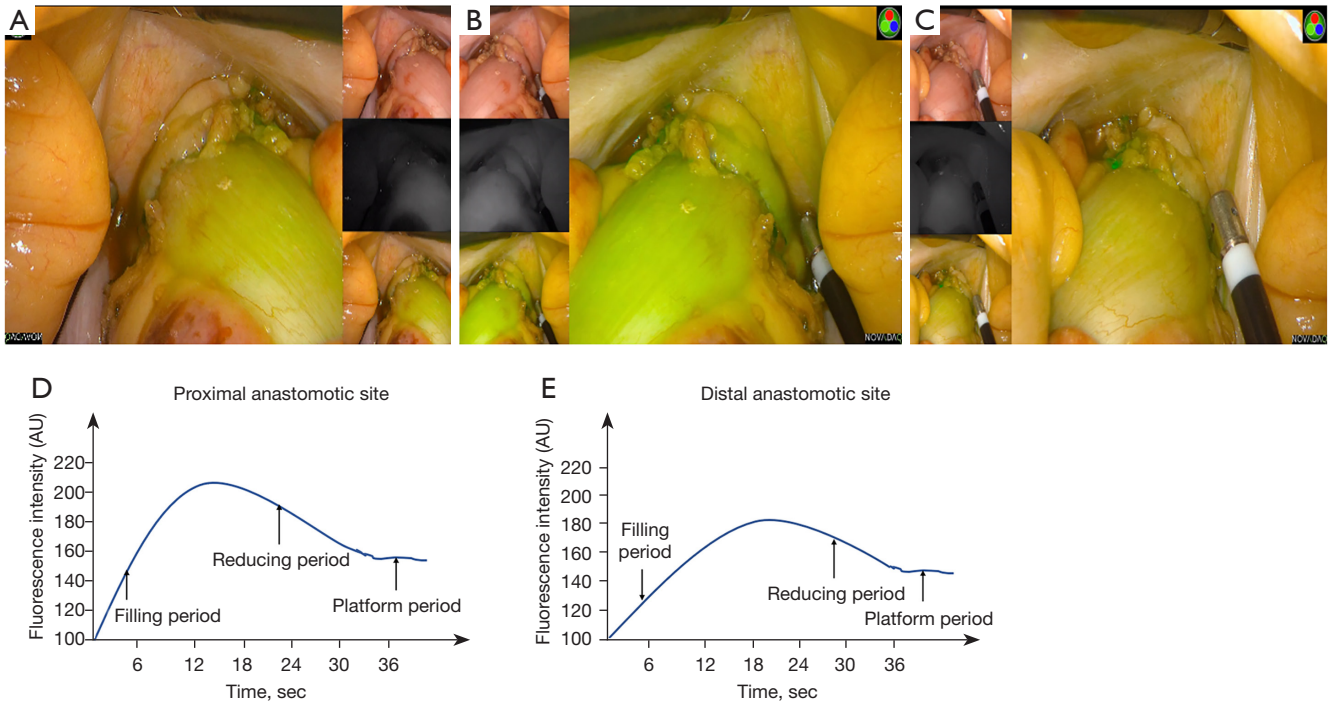

Figure 2 Representative image of ICG fluorescence angiography and the fluorescence intensity change during ICG fluorescence angiography in the anastomotic stoma of the general population. Representative image of anastomotic stoma after injecting ICG at the filling period (A), reducing period (B), and platform period (C) in the general population. Change of fluorescence intensity at proximal anastomotic site (D) and the distal anastomotic site (E) in the general population. ICG, indocyanine green.

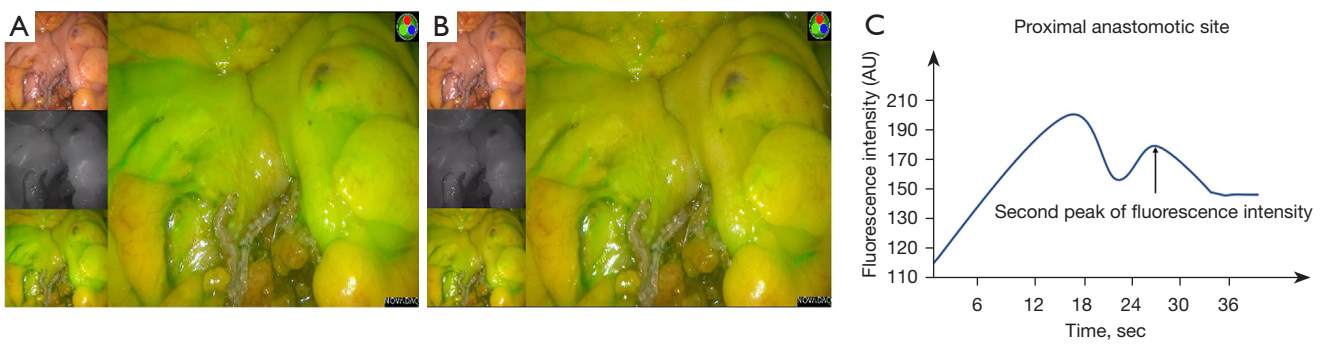

Figure 3 Representative image of ICG fluorescence angiography and the change of fluorescence intensity during ICG fluorescence angiography in the anastomotic stoma of the patients with a second peak of fluorescence intensity. Representative image of anastomotic stoma after injecting ICG at the first (A) and second (B) peak of fluorescence intensity in the patients with a second peak of fluorescence intensity. Change of fluorescence intensity at the proximal anastomotic site in the patients with a second peak of fluorescence intensity (C). ICG, indocyanine green.

quantitative study. Therefore, it is necessary to establish a standard quantitative scheme of ICG fluorescence imaging to evaluate perfusion status objectively. Furthermore, a multicenter, large-sample-size, prospective study should be carried out to determine the specific cut-off values of the quantitative parameters during ICG-NIRF to reduce the incidence of anastomotic leakage and improve the prognosis of patients receiving colorectal surgery.

Conclusions

Laparoscopic technology has been implemented in China for more than 30 years. Surgeons have been seeking new techniques to reduce the incidence of postoperative complications. Besides, traditional laparoscopic technology is gradually developing towards functional endoscopic technology. As an emerging technology, ICG fluorescence imaging technology applies the near-infrared functional endoscopy during surgery, through which surgeons can obtain real-time images of intestinal anastomotic perfusion in the surgical area, which has great application potential in the surgical treatment of CRC (34-36). Recently, studies on ICG fluorescence have mainly included qualitative and quantitative studies. Many qualitative studies have confirmed that ICG fluorescence angiography is safe and feasible in evaluating intraoperative intestinal blood perfusion (37-40). However, the qualitative studies could not draw definite conclusions based on numerical values. Therefore, quantitative research is being carried out, which is a current hot spot. The current review extrapolated that T0, Tmax, Fmax, and S (Fmax/Tmax) during the ICG fluorescence angiography could predict anastomotic leakage; however, the specific cut-off value needs further larger-sample-size studies to determine. Besides, the standardized operation process (including injection dose, observation distance, quantitative software, etc.) for ICG fluorescence angiography in quantitative evaluation of the intestinal blood perfusion is necessary to eliminate heterogeneity. The measures mentioned above could provide a theoretical basis for promoting the standardized development of ICG fluorescence quantitative research in laparoscopic colorectal surgery and subsequently improve the prognosis of these patients.

Acknowledgments

Funding: This study was supported by the Key Medical Specialty of Shanghai (No. ZK2019A15).

Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-5312/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-5312/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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(English Language Editor: J. Jones)

Cite this article as: Kong W, Wang B, Niu Q, Lin C, Fan D. Quantitative evaluation of anastomotic perfusion during colorectal surgery via indocyanine green fluorescence angiography: a narrative review. Ann Transl Med 2022;10(24):1402. doi: 10.21037/atm-22-5312

