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ORIGINAL ARTICLE

Optimization of indocyanine green angiography for colon perfusion during laparoscopic colorectal surgery

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Abstract

Aim: This study aims to evaluate the extrinsic effects of conditional factors affecting quantitative parameters and to establish the optimization of indocyanine green (ICG) angiography using in vitro experiments and a prospective observational study.

Method: In vitro experiments were performed to evaluate the correlation between conditional factors such as camera distance, surrounding lighting, fluorescence emission sources and ICG doses. The fluorescence intensity was measured from the ICG-containing test tube in each condition. In the clinical study, ICG angiography was applied to patients with colorectal cancer (n = 164). The quantitative perfusion parameters were the maximal fluorescence intensity (F_{MAX}), slope, $T_{1/2MAX}$ and perfusion time ratio (TR). Camera position, distance to colon, fluorescence emission source, surrounding lighting, site of angiography and ICG specific mode were considered as conditional factors and compared with the quantitative parameters to identify the optimal condition of ICG angiography.

Results: The fluorescence intensity had an inverse correlation with distance, and the transitional zone was shown at a distance of 4–5 cm by slope differential. F_{MAX}, $T_{1/2MAX}$ and slope were affected significantly by camera distance, site of angiography, fluorescence emission source and ICG mode as conditional factors. On multivariate analysis, F_{MAX} was independently associated with spectral ICG mode with red inversion, laser mode and camera distance. Conversely, TR was not related to any conditional factors.

Conclusion: Since quantitative parameters of ICG angiography are influenced by various conditions, a standardized protocol is required. The application of ICG specific modes with a constant distance of 4–5 cm can provide optimized fluorescence images.

KEYWORDS
colorectal surgery, fluorescein angiography, indocyanine green, laparoscopy, perfusion imaging

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INTRODUCTION

Anastomotic leakage is a major complication that is reported as much as 10%–20% after colorectal surgery [1,2]. Insufficient mesenteric arterial flow can induce ischaemic changes and anastomotic complications [3]. Colonic perfusion can be determined by the bowel colour change, persistent peristalsis, or intentional bleeding of the colonic marginal artery, but these methods are too subjective to estimate colon perfusion [4].

Intra-operative angiography using a near-infrared (NIR) camera system was introduced as an objective perfusion assessment [5-7]. Since indocyanine green (ICG) yields fluorescence in the NIR spectrum, intravenous ICG injection can enable real-time colon perfusion status to be visualized [8] Using ICG fluorescence angiography, surgeons have been able to detect the hypoperfusion segments and change the planned transection line, which can decrease the risk of anastomotic complications [9-11].

However, it is still challenging to establish a standardized protocol for ICG angiography and quantitative analysis to identify adequate perfusion status [6,12]. Quantitative parameters were calculated using fluorescence intensity and fluorescence enhancing time [13]. Fluorescence intensity can be affected by various conditional factors, such as surrounding light, fluorescence emission sources, or distance between the colon and camera [8,10]. The protocols for ICG angiography have also been varied between centres and surgeons in previous studies [14]. So, a standardized protocol is required to establish the quantitative analysis of ICG angiography as an objective method for evaluating perfusion status.

Thus, this study aims to evaluate the extrinsic effects of conditional factors affecting quantitative parameters of ICG angiography using in vitro experiments and a prospective observational study. Furthermore, we would like to establish an optimized protocol for ICG angiography in laparoscopic colorectal surgery.

> **What does this paper add to the literature?**
>
> Various conditional factors affect the quantitative parameters of perfusion significantly. An optimized protocol can be suggested as a constant distance (4–5 cm) using indocyanine green (ICG) specific modes like Spectra A or laser (ENV) modes that can improve the quality and consistency of quantitative analysis in laparoscopic ICG angiography.

METHOD

Patients

We prospectively enrolled 164 patients who underwent laparoscopic colorectal surgery between July 2015 and May 2019 at Pusan National University Yangsan Hospital. The inclusion criteria were patients aged 19–80 years who had sigmoid colon and rectal cancer and underwent laparoscopic surgery using an NIR camera system. Either anterior resection or low anterior resection was performed according to the cancer location.

The exclusion criteria were haemodynamic instability, emergency surgery or pregnancy. Patients who underwent surgery without colonic anastomosis were also excluded. All patients enrolled in the study had no history of allergies or adverse effects to either the contrast agent used for CT or the iodine-containing drugs. We used clinical data from the prospectively collected database and the recorded surgical videos. We defined the anastomotic complications as leakage, colonic necrosis, pelvic abscess and stricture requiring endoscopic or surgical treatment. If postoperative anastomotic complications were suspected, pelvic CT and sigmoidoscopy were performed. This study was conducted after receiving the approval of the Institutional Review Board (IRB no. 05-2020-103) of the Pusan National University Yangsan Hospital. Written informed consent was obtained from all patients.

Indocyanine green angiography and quantitative analysis

All patients underwent intra-operative ICG angiography before colon transection. ICG (Diagnogreen Inj. 25 mg, Daiichi Sankyo) was diluted in 10 ml distilled water and injected by the anaesthesiologist attending the surgery. Using a dose of 0.25 mg/kg, the ICG was injected slowly for 10 s. Colon perfusion was monitored for 2 min after ICG injection, and for a further 3 min if the angiogram was not visible after 2 min. The change in fluorescence intensity was measured sequentially to produce time–fluorescence intensity graphs using video analysis and a modelling tool (MATLAB R2019a, MathWorks) [15]. From the graphs, we analysed quantitative parameters such as maximal fluorescence intensity (F_{MAX}), time to half of F_{MAX} ($T_{1/2MAX}$), fluorescence rising slope (slope = F_{MAX}/T_{MAX}) and perfusion time ratio (TR = $T_{1/2MAX}/T_{MAX}$) (Figure 1A).

Conditional factors

The distance between the colon and camera was calculated using the formula $l = kw_r$ (Figure 1B), where l is the length between the lens and the subject, k is a coefficient and w_r is distance on the ruler lying underneath the colon. When fluorescence angiography was performed outside the abdominal cavity, the distance was measured directly with a surgical ruler. In cases of extra-abdominal ICG angiography, the colon was extracted from the abdominal cavity through a transumbilical mini-laparotomy site. After dividing the colonic mesentery, ICG angiography was performed, leaving the operation room lights turned either on (light) or off (dark). Intra-abdominal ICG angiography was performed with the dark condition. We used two different camera systems using a xenon lamp (IMAGE1 S™, Karl Storz) or laser (1588 AIM camera system, Stryker). For ICG image modes of the laparoscopic NIR camera system, we used the conventional ICG mode (blue

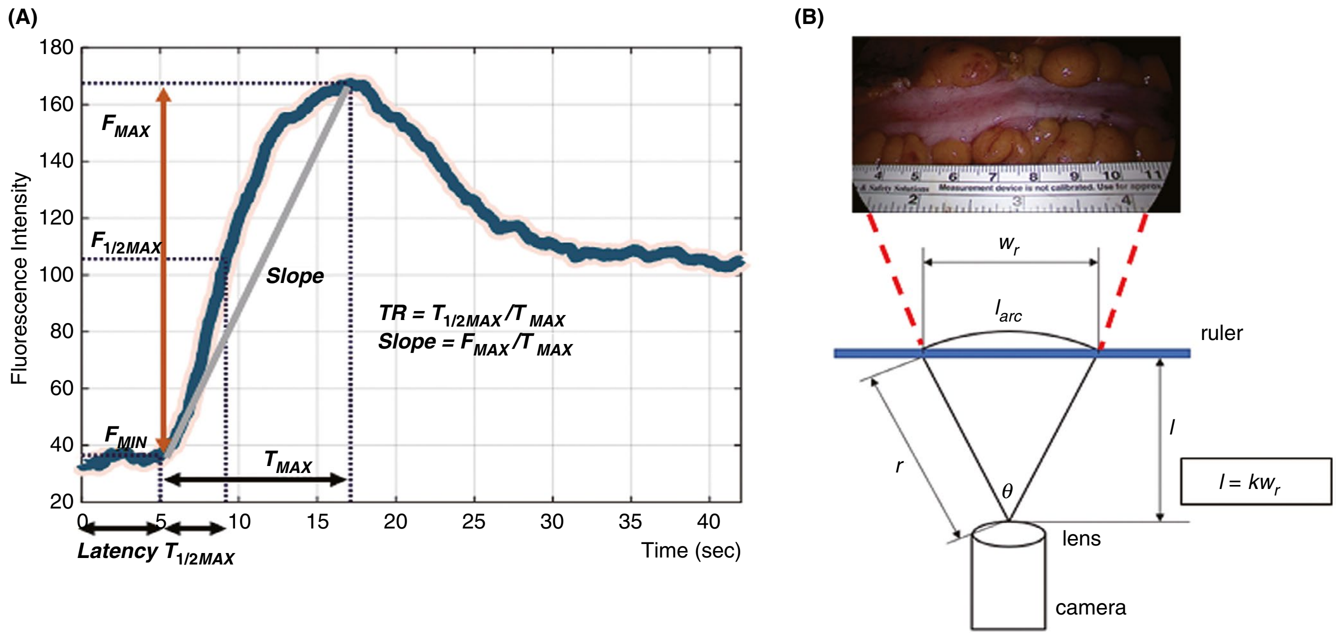

FIGURE 1 The parameters of quantitative analysis for ICG angiography and the distance calculation formula. (A) The time–fluorescence curve of ICG angiography for quantitative analysis was obtained to demonstrate the parameters. *F* stands for fluorescence intensity and *T* is perfusion time. F_{MAX}, $T_{1/2MAX}$, slope and perfusion time ratio (TR) are included in analysing the clinical data. (B) The distance calculation formula has been applied to measure the distance between the colon and camera. The length of the surgical ruler (Flexi-ruler) shown in the camera image was the indicator, and coefficient *k* was estimated as 0.8

colour) and Spectra A mode with red inversion (light cyan colour) for the xenon lamp camera system and the endoscopic NIR visualization (ENV) mode (green colour) for the laser camera system (Figure 2).

In vitro study

We designed a series of in vitro experiments that explored the extrinsic effects of various conditional factors including distances, dilution concentrations of ICG, fluorescence emission sources, and lighting of surrounding conditions. First, we made a linear actuator device that could move the subject 0–15 cm away from the camera with constant velocity. The device consisted of a step motor, two limiter switches, a camera holder and a plate (Figure 3A). The plate moved at a speed of 0.33 cm/s, and the frame rate of the camera was 30 fps, so the subject was photographed using the NIR camera system while moving it by 0.011 cm per frame. We used two different fluorescence emission sources: a xenon lamp (300 W xenon light source, Karl Storz) and a laser (L10 LED light source, Stryker). With the laser, we used the ENV modes 3 and 5. The device was covered with a black box to demonstrate the 'dark' surrounding condition that could represent either intra-abdominal ICG angiography or extra-abdominal ICG angiography without room lights. Without the box, the 'light' surrounding condition was demonstrated, which represented extra-abdominal ICG angiography with the room lights on (Figure 3B). Diluted ICG solutions were prepared with dilution concentrations of 0.01 and 0.05 mg/ml in the test tubes (Figure 3C). From the recorded video, we analysed the fluorescence intensity from different distances with different conditional settings.

Statistics

The mean values of each parameter were compared using either an independent *t* test or Mann–Whitney *U* test according to the results of the Kolmogorov–Smirnov test. The correlation between the distance and each parameter was analysed using either Pearson correlation analysis or Spearman's rank correlation analysis according to the distribution of data. Quantitative parameters on ICG image modes were compared using one-way ANOVA with the Bonferroni test for post hoc analysis. Multivariate analysis was performed with a binary logistic regression model using a forward condition analysis. The covariance input criterion was less than 0.1 and the elimination criterion was less than 0.05. All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 23.0, for Windows (SPSS, IBM). The results of continuous variables were expressed as mean ± standard deviation. All results with a *P* value less than 0.05 were considered significant.

RESULTS

Clinical data analysis

The clinical characteristics are shown in Table 1. Ten out of 164 (6.1%) patients had major anastomotic complications. The anastomotic complications were colonic necrosis (n = 1), anastomotic leak (n = 6), anastomotic stricture (n = 1), delayed pelvic abscess (n = 1) and delayed anastomotic dehiscence during intensive care for respiratory failure (n = 1). The transection line was changed in 11

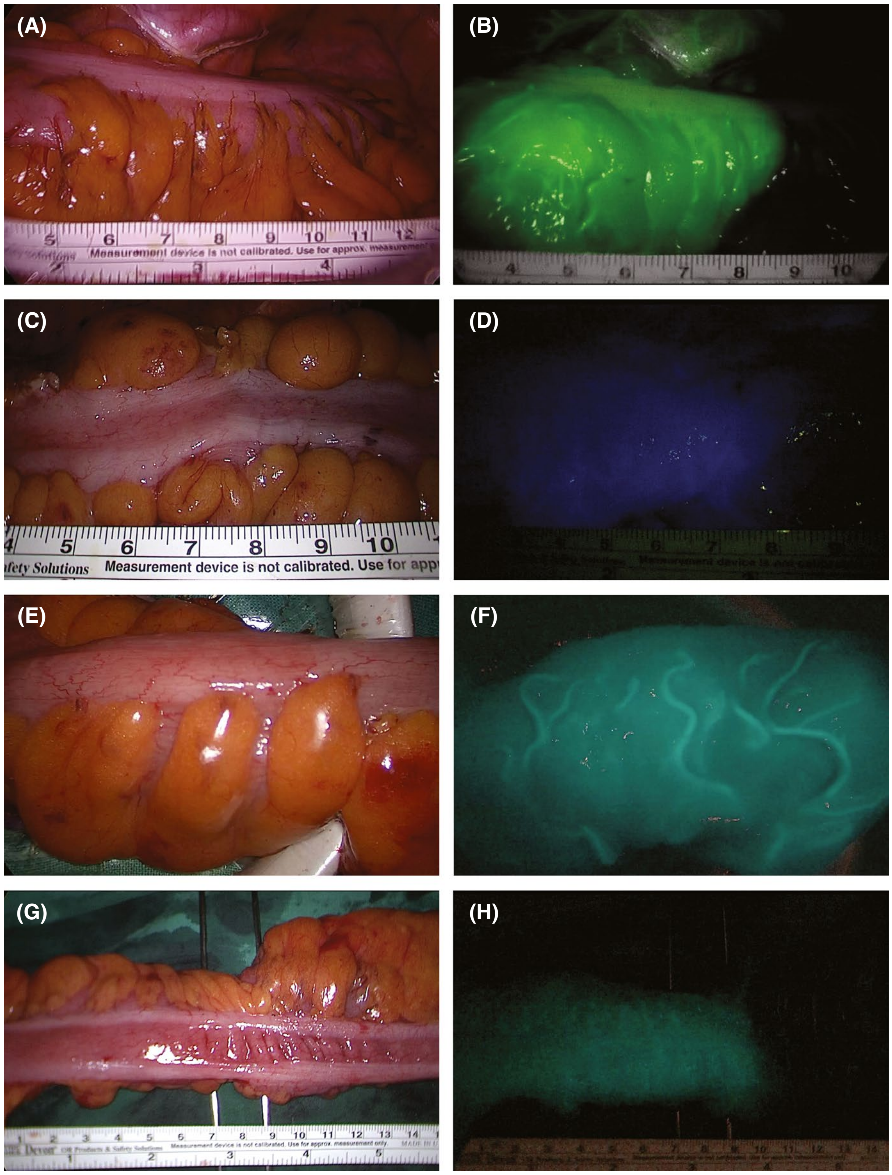

FIGURE 2 Conditional factors that affect the ICG angiography of quantitative analysis. Various conditional factors have been tried to standardize the protocol for ICG angiography. (A), (B) Intra-abdominal ICG angiography with a xenon lamp as the fluorescence emission source is demonstrated. (C), (D) Intra-abdominal ICG angiography with a laser as the fluorescence emission source is shown. (E), (F) Extra-abdominal ICG angiography and (G), (H) extra-abdominal ICG angiography with distances as far as 18 cm were tried

patients (6.7%) based on ICG angiography, and anastomotic leakage occurred in one patient among them.

Conditional factors of ICG angiography are shown in Table 2. The correlation between distance and each quantitative parameter was estimated (Figure 4A–D). The distance from the colon to the laparoscopic camera was statistically related to F_{MAX}, $T_{1/2MAX}$ and slope but did not influence TR. In particular, F_{MAX} tended to decrease when the distance increased, and it was statistically significant ($P < 0.001$). Intra-abdominal or extra-abdominal ICG angiography also showed different quantitative parameter levels (Figure 4E–H). F_{MAX} and slope were significantly higher in intra-abdominal ICG angiography, but $T_{1/2MAX}$ and TR were statistically similar. However, the mean distance of intra-abdominal ICG angiography was 6.24 cm, while extra-abdominal ICG angiography was 8.56 cm, which was statistically significant ($P < 0.001$). Thus, in the intra-abdominal condition, the closer distance affected elevated F_{MAX} and slope. The fluorescence emission source also affected F_{MAX}, $T_{1/2MAX}$ and slope, but not TR (Figure 4I–L).

A subgroup with extra-abdominal ICG angiography was analysed to compare each parameter with the room lights on and off. F_{MAX} tended to display a higher value when the room lights were on (62.25 ± 25.41 AU) compared to when the room lights were off (58.67 ± 25.43 AU). However, all parameters, including F_{MAX}, were not statistically significant according to room lights ($P = 0.618$).

In the xenon camera system, the F_{MAX} of conventional ICG mode (blue colour) and Spectra A mode with red inversion (light cyan colour) showed significant differences (48.29 ± 16.29 AU vs. 75.62 ± 29.14 AU, respectively, $P < 0.001$). However, there was no statistical difference between Spectra A mode and laser (ENV) mode (82.06 ± 29.39 AU, $P = 0.521$).

On multivariate analysis, F_{MAX} (>70 AU) was independently associated with Spectra A mode, laser (ENV) mode and close distance (<8 cm) (Table 3). Conversely, TR (<0.6) was not affected by any conditional factors.

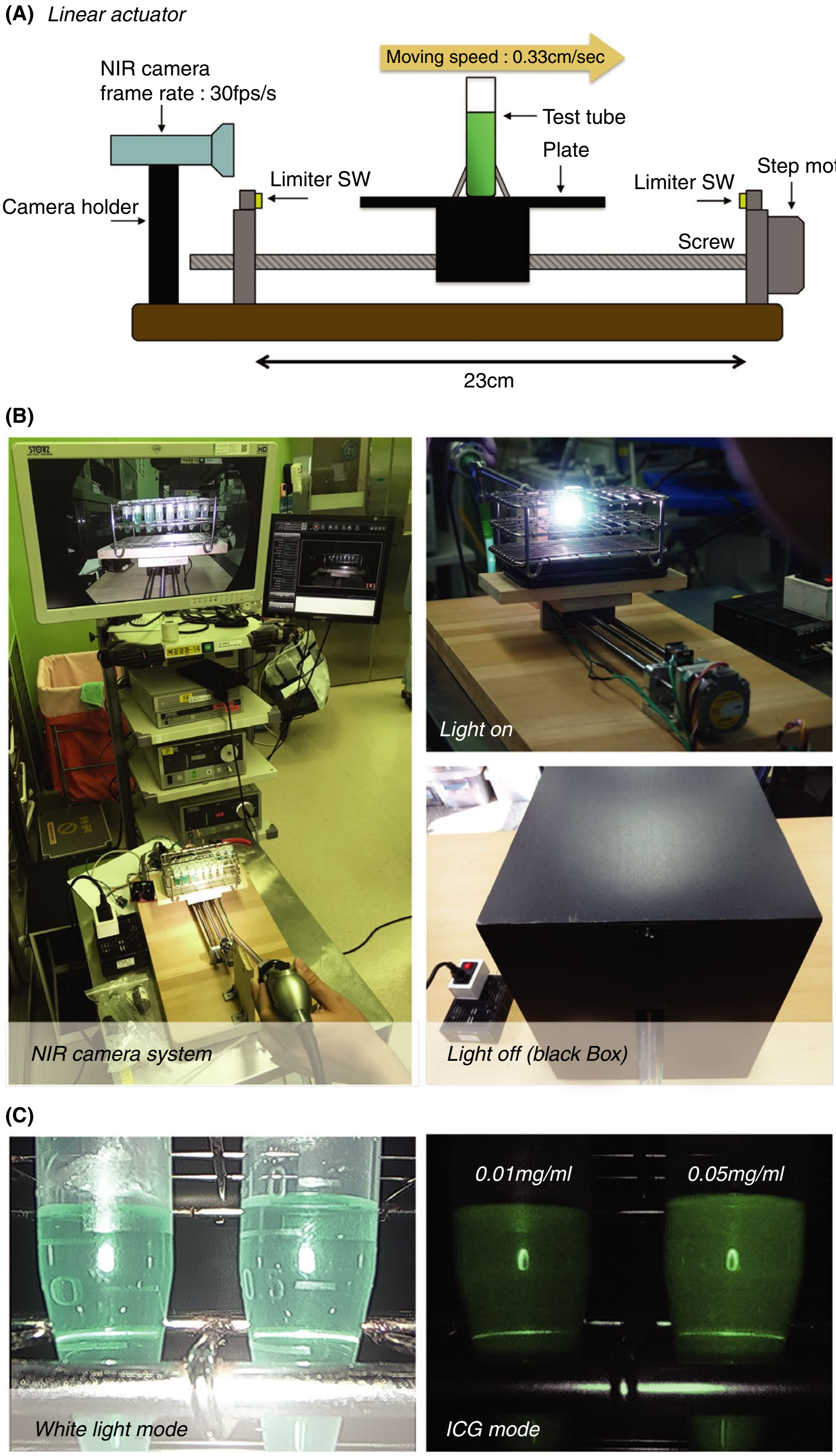

FIGURE 3 In vitro study for conditional factors influencing the parameters of quantitative analysis. (A) A device named 'Linear actuator' in which a subject moves away with constant velocity (0.33 cm/s) was fabricated so that the fluorescence intensity could be recorded constantly from 0 to 15 cm. By changing camera systems, different fluorescence emission sources were implemented. We covered this device with the black-coloured box to demonstrate the dark surrounding conditions. (B) Combining the device with the NIR system, in vitro experiments were demonstrated. Without covering the black box, the light surrounding condition is made. By covering the device with the black box, dark surroundings are made. (C) We used a test tube to reduce the reflected light, which may interfere with the detection of fluorescence intensity

In vitro experiments

The fluorescence intensity graphs had an inverse correlation with distance (Figure 5A). When the fluorescence emission source was farther away, the estimated fluorescence intensity was lower. The decreasing slopes were steep (high slope region) in a distance within 4–5 cm, after which the slopes were almost flat (low-intensity region). This transitional section was obtained around 4–5 cm (Figure 5B). In various conditions, the graphs appeared as similar patterns of the transitional section where the optimal distance of fluorescence intensity was. The fluorescence intensity graphs were compared by altering the surrounding lighting and fluorescence emission sources (Figure 5C). The fluorescence slope of the laser camera was steeper and affected more easily by distance than the xenon camera. When the surrounding lights were turned on, the fluorescence intensity tended to be higher than in dark conditions.

TABLE 1 Clinical characteristics of patients (n = 164)

Patient characteristics	*n* (%)
Age ≥65 years	80 (48.8)
Sex	
Male	115 (70.1)
Female	49 (29.9)
BMI ≥ 25 kg/m^2	53 (32.3)
Hypertension	69 (42.1)
Diabetes mellitus	37 (22.6)
Smoking	38 (23.2)
Type of surgery	
Anterior resection	61 (37.2)
Low anterior resection	103 (62.8)
Cancer stage	
0–2	108 (65.9)
3–4	56 (34.1)
ASA score	
1–2	152 (92.7)
3–4	12 (7.3)
Cancer obstruction	38 (23.2)
Preoperative radiation therapy	9 (5.5)
IMA ligation	
High ligation	120 (73.2)
Low ligation	44 (26.8)
Anastomosis level	
≥5 cm	106 (64.6)
<5 cm	58 (35.4)
Splenic flexure mobilization	130 (79.3)
Diverting ileostomy	55 (33.5)
Transection line change	11 (6.7)
Anastomotic complications	10 (6.1)

Abbreviations: ASA, American Society of Anesthesiologists; BMI, body mass index; IMA, inferior mesenteric artery.

DISCUSSION

ICG angiography protocols have been introduced for the objective assessment of colon perfusion [3,7,17,18,19,20,21] and are summarized in Table 4. All studies have described the intravenous dose of ICG and the NIR system. However, conditional factors such as distance and surrounding lighting varied from one to another. Recent meta-analysis studies on anastomotic leakage after ICG angiography have reviewed the papers but they considered different camera systems and ICG dose as their limitation, which would influence the diverse results [22]. They also commented that many previous studies were not standardized with the protocol for ICG angiography, including the dosage of ICG injected during surgery [23]. In this prospective observational cohort, the quantitative parameters of colon perfusion were significantly affected by conditional factors, including distance, surrounding light and fluorescence emission source. To standardize and optimize the ICG angiography protocol for quantitative analysis, we performed a series of in vitro experiments to explore how conditional factors affect the fluorescence intensity during ICG angiography.

TABLE 2 Conditional factors of ICG angiography for laparoscopic colorectal surgery (n = 164)

Conditional factors	Values
Camera distance (cm), mean ± SD	7.22 ± 1.95
Site of angiography, *n* (%)	
Intra-abdominal ICG angiography	103 (62.8)
Extra-abdominal ICG angiography	61 (37.2)
Surrounding lighting, *n* (%)	
Light off (dark)	145 (88.4)
Light on (light)	19 (11.6)
Fluorescence emission source, *n* (%)	
Xenon (Storz)	102 (62.2)
Laser (Stryker)	62 (37.8)
ICG mode, *n* (%)	
Conventional ICG (Storz)	22 (13.4)
Spectra A mode with red inversion (Storz)	80 (48.8)
ENV mode (Stryker)	62 (37.8)

Abbreviations: ENV, endoscopic near-infrared visualization; ICG, indocyanine green.

First, the distance from the camera to the subject affects the fluorescence intensity inversely. In the quantitative analysis, F_{MAX} tends to decrease when the distance increases between the laparoscopic camera and ICG test tube. A previous similar experiment for influencing environmental factors was conducted with ICG cholangiography [24]. Their experiment was based on different concentrations of ICG and distance from the laparoscopic camera to ICG dyed bile duct. The results were similar to ours: as the distance increased, the fluorescence intensity decreased. They also commented that maintaining the same distance might be necessary to obtain the optimal fluorescence signal. To standardize the various conditions that may affect the fluorescence intensity of ICG, we have designed a much more sophisticated in vitro experiment for fluorescence intensity under various conditions including wide distance range, dilute ICG solutions, surrounding light and fluorescence emission source. Interestingly, the fluorescence intensity graph patterns commonly show the inflection point around 4–5 cm, where the steep decreasing slope turns almost flat in a horizontal manner in most conditions. Thus, we considered that this transitional section could be one of the candidates for an optimal distance zone for ICG angiography.

In the high slope region, the camera becomes too close to visualize all the fields of view of the subject at a distance of 0–4 cm. In other words, the field of view is too small to properly analyse ICG angiography when the camera is too close. Also, a steep slope indicates that fluorescence intensity is very sensitive to slight changes in distance. Thus, a very small tremor of the handheld camera can make noise that interferes with quantitative analysis in clinical practice.

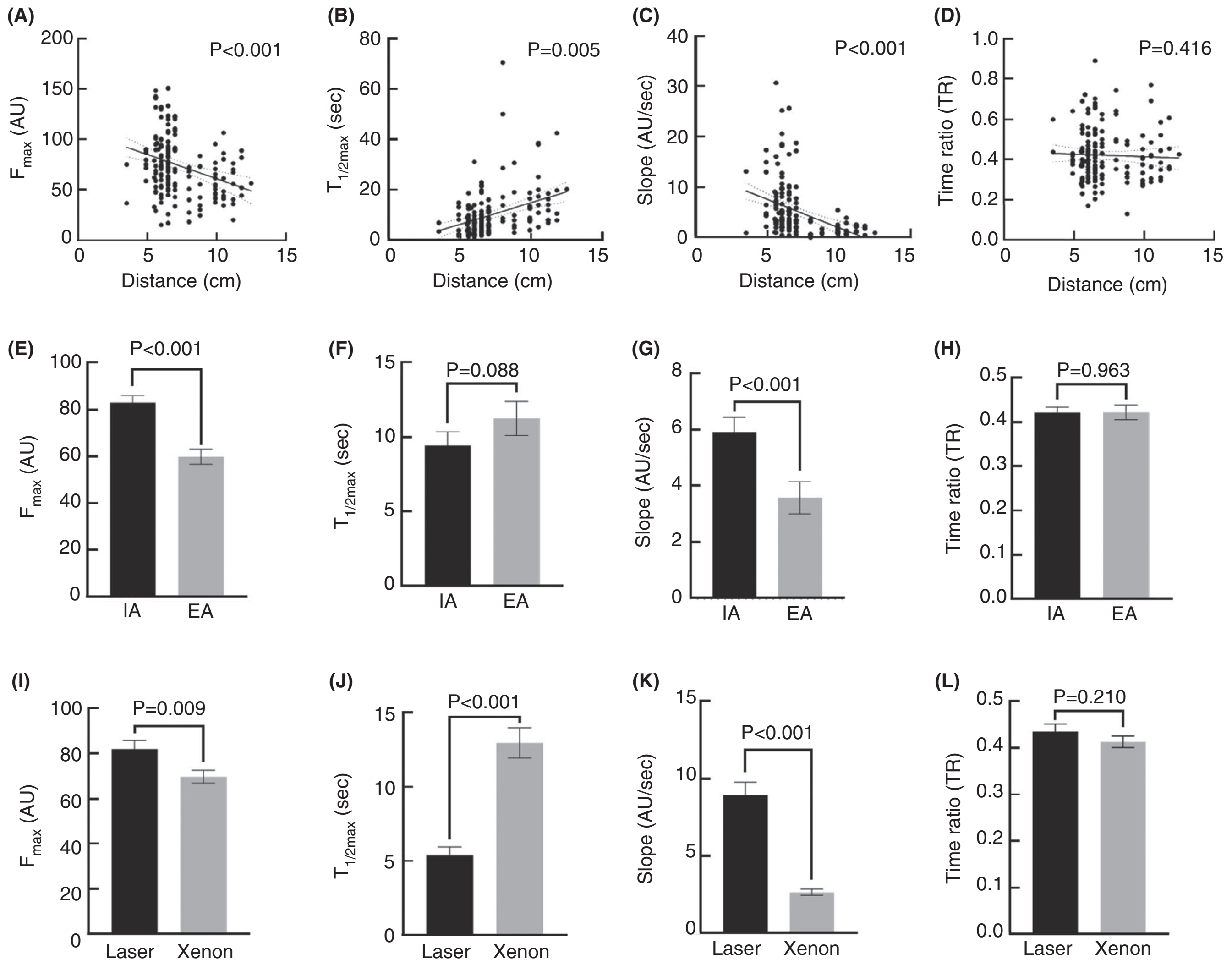

FIGURE 4 Clinical data analysis as the correlation between the parameters of quantitative analysis and conditional factors. F_{MAX}, $T_{1/2MAX}$, slope and TR are analysed with different conditional factors. (A)–(D) Scatter plots of distance and each quantitative parameter are shown. F_{MAX}, $T_{1/2MAX}$ and slope are related to distance change with statistical significance (P < 0.001, P = 0.005 and P < 0.001, respectively). (E)–(H) The parameters are compared from intra-abdominal ICG angiography and extra-abdominal ICG angiography. IA stands for intra-abdominal ICG angiography, while EA is for extra-abdominal. F_{MAX} (83.05 and 59.78 AU, respectively) and slope (5.90 and 3.57 AU/s, respectively) are statistically relevant; both are higher with intra-abdominal ICG angiography. (I)–(L) With different fluorescence emission sources, F_{MAX}, $T_{1/2MAX}$ and slope are closely related. F_{MAX} (82.07 and 69.73 AU, respectively) and slope (8.94 and 2.66 AU/s, respectively) are higher with laser as the fluorescence emission source, and $T_{1/2MAX}$ is lower with laser (5.40 and 12.97 s, respectively). Overall, TR is less affected by changes of the surrounding conditions (P = 0.416, P = 0.963 and P = 0.210, respectively)

Moreover, in the low-intensity region above 5–6 cm from the subject, it is too dark to photograph which indicates less effective sections for obtaining a proper level of fluorescence intensity. From the technological point of view, the energy decreases in inverse proportion to the square of the distance in the radiation area. Additionally, if the fluorescence intensity is too dark, low-light noise is relatively emphasized and the quality of the image deteriorates. In our experiments, the best shooting distance is considered as 4–5 cm, wherein the slope is placed between high slope and low-intensity regions. Therefore, we would suggest that 4–5 cm is the optimal distance of ICG angiography for quantitative analysis.

We have assumed that F_{MAX} might be higher in dark conditions because fluorescence looks brighter in a dark field. The results of in vitro study have shown that the fluorescence intensity is higher in a surrounding light-on condition. This can be explained by room lights containing a similar wavelength of the NIR spectrum which can interfere with the fluorescence intensity of ICG. Not only our results but also a previous basic study recommended turning off shadowless lights during ICG fluorescence because of the existence of an additional NIR spectrum among the room lights [8]. Thus, we would also like to suggest that ICG angiography should be performed with all surrounding lights off during extra-abdominal ICG angiography.

In our clinical data, F_{MAX} in intra-abdominal ICG angiography was much higher than that of the extra-abdominal procedure. This clinical result is the opposite of the in vitro study; this can be explained by the fact that the mean distance is statistically closer in

TABLE 3 Univariate and multivariate analysis for clinical and conditional factors associated with F_{MAX} parameter (n = 164)

Factors	Total	Univariate		Multivariate		
	n	*n* (%)	*P* value	HR	95% CI	*P* value
Age (years)						
<65	84	51 (60.7)	0.090			
≥65	80	38 (47.5)				
Preoperative radiation						
No	155	81 (52.3)	0.032			
Yes	9	8 (88.9)				
IMA ligation level						
High	120	64 (53.3)	0.691			
Low	44	25 (56.8)				
Anastomotic complications						
No	154	85 (55.2)	0.350			
Yes	10	4 (40.0)				
Fluorescence emission source						
Xenon	102	48 (47.1)	0.017			
Laser	62	41 (66.1)				
ICG image mode						
Conventional	22	3 (13.6)	<0.001	1		
Red inversion	80	45 (56.3)		6.552	1.749–24.538	0.005
Laser (ENV)	62	41 (66.1)		7.556	1.862–30.663	0.005
Surrounding light						
Off	145	81 (55.9)	0.258			
On	19	8 (42.1)				
Distance (cm)						
≥8	40	12 (30.0)	<0.001	1		
<8	124	77 (62.1)		2.488	1.033–5.989	0.042

Abbreviations: ENV, endoscopic near-infrared visualization; F_{MAX}, maximal fluorescence intensity; HR, hazard ratio; ICG, indocyanine green; IMA, inferior mesenteric artery.

the intra-abdominal ICG angiography (P < 0.001). Thus, we speculate that distance has a greater influence on fluorescence intensity than surrounding lighting.

In this study, the fluorescence emission source affected F_{MAX}, $T_{1/2MAX}$ and slope with statistical significance. In particular, F_{MAX} was higher with a laser source than a xenon lamp. In the xenon camera system, the original blue fluorescence image can be translated to light cyan colour by red inversion mode, and this ICG dedicated mode can express brighter fluorescence like a laser camera. On multivariate analysis, ICG specific mode and laser (ENV) mode were analysed as an independent factor for improving fluorescence intensity.

ICG angiography helps surgeons visualize the colon perfusion that is related to anastomotic leakage during laparoscopic colorectal surgery [21,25,26]. According to previous studies on ICG angiography from our institute, quantitative parameters including $T_{1/2MAX}$, slope and TR are associated with the prediction of anastomotic leakage [12,13]. In this study, we have found that TR was analysed as a stable quantitative parameter independent of conditional factors such as distance and fluorescence emission sources. Because TR is composed of the element of time rather than the level of fluorescence intensity, it can overcome the interference of extrinsic environmental factors. However, the slope and F_{MAX} are based on the amount of fluorescence intensity change and are affected by conditional factors, so these parameters show a significant difference according to the external environmental conditions. This phenomenon can act as a hidden obstacle to quantitative analysis of perfusion status. Therefore, an optimized and standardized protocol of ICG angiography can serve as a basis for establishing the reliability of the quantitative perfusion analysis.

This study has several limitations. First, this was a small sample size study of a single cohort. Although the clinical data were collected for a prospective observational study, there is unequal size sampling within each different conditional group. This is due to consecutive trials for establishing an optimal protocol to obtain an improved quality of fluorescence intensity. Second, we have considered five different conditional factors; nevertheless, there may be more categories of conditional factors such as different ICG dosage and advanced fluorescence modes. We are looking for optimal ICG

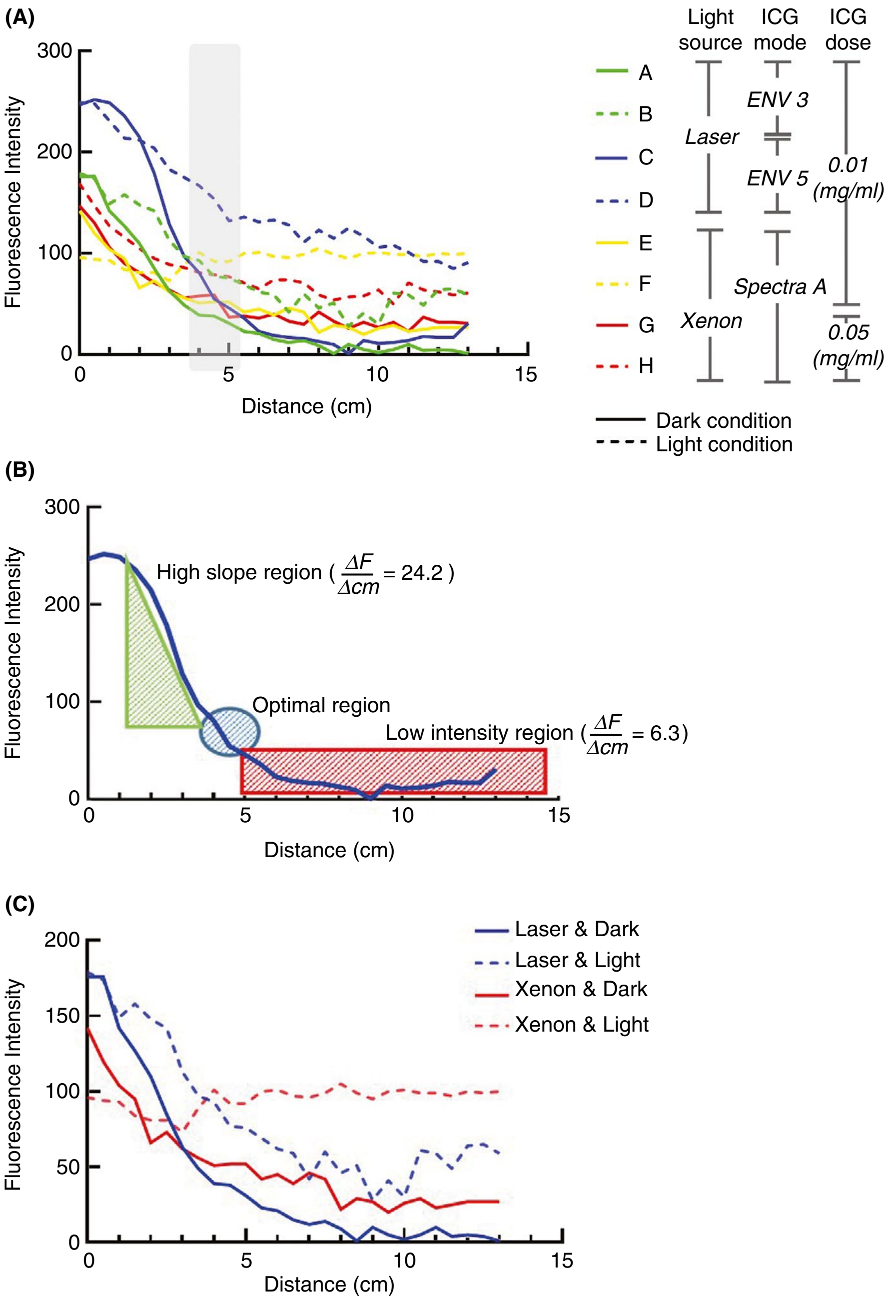

FIGURE 5 Distance–fluorescence curves of ICG fluorescence intensity of the in vitro study. Distance–fluorescence curves are drawn with various conditions: fluorescence emission source, ICG mode, ICG dosage and surrounding lighting (solid line as dark condition and dotted line as the light condition which was performed without covered box). (A) Despite various conditions A–H, the patterns of the distance–fluorescence curve are similar in that, as the distance gets further, the detected fluorescence intensity is lower. (B) Closer than 4 cm, the slope of the curve is steep ($\Delta F/\Delta cm = 24.2$); when the distance gets further than 5 cm, the slope becomes almost flat ($\Delta F/\Delta cm = 6.3$). All curves have a common transitional area within 4–5 cm as an optimal zone to analyse the fluorescence images. (C) Comparison of fluorescence emission sources is shown with different coloured curves (blue as laser and red as xenon lamp), and comparison of surrounding lighting is shown with different shapes of the curves. As the distance gets further, the fluorescence intensity tends to stay as high as 50 to 100 AU in light conditions, while the fluorescence almost disappears in darkened surroundings

dosage for angiography; however, it is necessary to establish standardization of conditional factors ahead of the ICG dosage optimization study. As far as we know, there is no standard use of ICG dose for fluorescence angiography for colon perfusion [18]. So, we expect that this work can be a scaffold for future studies for the standardization of ICG angiography. Finally, this study was conducted based on the laparoscopic NIR system currently available in the operating room of our institution. In perspective, new camera systems will be introduced with the complementarity of the conditional factors. In particular, many instruments using not only ICG but also hyperspectral images and laser speckle contrast images are being developed to minimize the external influence of distance and room light. Along with developing the new image system, additional studies should be conducted to update the standardization protocol of angiography with advanced technology.

CONCLUSION

In conclusion, conditional factors, including distance, surrounding light and fluorescence emission source, significantly affect the quantitative parameters, especially F_{MAX}, $T_{1/2MAX}$ and slope. The standardization protocol of ICG angiography can improve the quality and consistency of quantitative analysis, and we would like to suggest a protocol with an optimal distance of 4–5 cm using ICG specific modes.

TABLE 4 Research protocols for intra-operative ICG angiography

Reference	Patients	Types of surgery	Intravenous dose of ICG	Distance (cm)	Extra-/intra-abdominal angiography	Surrounding light	Fluorescence emission source	NIR system
Aiba et al. 2021 [16]	110	Colorectal resection	0.1 mg/kg	5	Extra-peritoneal	Off	Xenon	OPAL1 (Karl Storz)
Benčurik et al. 2020 [17]	100	Laparoscopic or robotic LAR	0.2 mg/kg	–	Extra-peritoneal	–	Xenon laser	SPIES (Karl Storz) Firefly (Intuitive)
Watanabe et al. 2020 [18]	236	Laparoscopic LAR	0.25 mg/kg	–	Extra-peritoneal	–	Xenon laser	D-light P (Karl Storz) 1588 AIM (Stryker)
De Nardi et al. 2020 [19]	240	Laparoscopic left-sided colorectal resection	0.3 mg/kg	–	–	–	Xenon	Image1 (Karl Storz)
Son et al. 2019 [13]	86	Laparoscopic AR or LAR	0.25 mg/kg	–	Extra- or intra-peritoneal	Off	Xenon	Image1 S (Karl Storz)
Ogino et al. 2019 [3]	74	Colorectal surgery	Bolus 5 mg	15	Extra-peritoneal	–	LED	Photodynamic Eye System (Hamamatsu)
Morales-Conde et al. 2020 [20]	192	Colorectal surgery	Bolus 15 mg	5	Extra-peritoneal	–	Xenon laser	Image1 S (Karl Storz) 1588 AIM (Stryker)
Chang et al. 2019 [7]	110	–	Bolus 5 mg	–	Extra-peritoneal	Off	Laser	SPY Elite System (Stryker)
Boni et al. 2017 [21]	42	Laparoscopic LAR	0.2 mg/kg	–	–	–	Xenon	Image1 (Karl Storz)

Abbreviations: AR, anterior resection; ICG, indocyanine green; LAR, low anterior resection; LED, light emitting diode; NIR, near infrared.

INFORMED CONSENT

Informed consent was obtained from all individual participants included in the study.

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CONFLICT OF INTERESTS

The authors declare no conflicts of interest.

AUTHOR CONTRIBUTIONS

Conceptualization: SGM. Formal analysis: SGM, AHM. Investigation: SGM, AHM, PSH, KNS. Methodology: SGM, PSH, KNS, LIY. Project administration: LIY. Writing—original draft: SGM, AHM, PSH. Writing—review and editing: SGM, AHM.

ETHICAL STATEMENT

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

Research data are not shared.

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