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Indocyanine Green Fluorescence Navigation in Liver Surgery

A Systematic Review on Dose and Timing of Administration

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Background: Indocyanine green (ICG) fluorescence has proven to be a high potential navigation tool during liver surgery; however, its optimal usage is still far from being standardized.

Methods: A systematic review was conducted on MEDLINE/PubMed for English articles that contained the information of dose and timing of ICG administration until February 2021. Successful rates of tumor detection and liver segmentation, as well as tumor/patient background and imaging settings were also reviewed. The quality assessment of the articles was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN).

Results: Out of initial 311 articles, a total of 72 manuscripts were obtained. The quality assessment of the included studies revealed usually low; only 9 articles got qualified as high quality. Forty articles (55%) focused on open resections, whereas 32 articles (45%) on laparoscopic and robotic liver resections. Thirty-four articles (47%) described tumor detection ability, and 25 articles (35%) did liver segmentation ability, and the others (18%) did both abilities. Negative staining was reported (42%) more than positive staining (32%). For tumor detection, majority used the dose of 0.5 mg/kg within 14 days before the operation day, and an additional administration (0.02–0.5 mg/kg) in case of longer preoperative interval. Tumor detection rate was reported to be 87.4% (range, 43%–100%) with false positive rate reported to be 10.5% (range, 0%–31.3%). For negative staining method, the majority used 2.5 mg/body, ranging from 0.025 to 25 mg/body. For positive staining method, the majority used 0.25 mg/body, ranging from 0.025 to 12.5 mg/body. Successful segmentation rate was 88.0% (range, 53%–100%).

Conclusion: The time point and dose of ICG administration strongly needs to be tailored case by case in daily practice, due to various tumor/patient backgrounds and imaging settings.

Keywords: ICG fluorescence, indocyanine green, liver segmentation, liver surgery, tumor detection

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As of today, surgical resection is still considered the gold standard treatment, as much as feasible, for patients with liver malignancies and selected benign diseases. In the last decades, liver surgery has dramatically developed, becoming a standardized and safe operation with perioperative mortality rates 1.0% and 2.0% even for advanced laparoscopic and open liver resections, respectively.[1] Improvements in preoperative evaluation, patient selection, advances in surgical technique and technology are the main reasons of this enhancement.[2,3] The cornerstone for a successful oncologic liver surgery relies on obtaining a R0 resection margin and preserving a proper healthy liver parenchyma to achieve better short- and long- term outcomes.[4,5] To achieve these goals, the application of intraoperative navigation tools has been required as a part of the progressive developments in liver surgery. In fact, the need of the real time visualization of precise liver anatomy, in particular during minimally invasive surgery (MIS), has encouraged the implementation of such instruments, potentially helpful for a proper and safe liver transection.

When performing anatomic liver resections, the borders of liver segments should be clearly identified in practice. Generally, hepatic veins are considered essential to define hepatic segments and can be mapped by intraoperative ultrasonography (IOUS). However, as recently emphasized by some authors, major hepatic veins are not sufficient for guiding anatomic resections, due to the 3D irregular shape of liver segments.[6,7] In this context, indocyanine green (ICG) fluorescence has proven to be a high potential navigation tool during liver surgery, allowing real-time 3D identification of both liver neoplasms and segmental boundaries.[8–11]

The fluorescence characteristics of ICG, which is metabolized by the liver and excreted through the bile ducts, has made this tool particularly helpful for liver surgeon as real time navigation system.[12] Many studies already reported the strong effectiveness of ICG applied to the tumor detection, either on liver surfaces or surgical specimens, in particular to identify preoperatively unknown lesions.[13,14] Furthermore, beside its broad availability, ICG has proven to be extremely safe and cost-effective, encouraging its widespread use in the last few years.[15,16] However, although using ICG fluorescence during liver surgery, specific limitations must be taken into account, including low penetration depth (up to 10 mm) and the lack of reliability in patients suffering from chronic liver disease.[17–19] Hence, due to the high variability in liver

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metabolization in patients with cirrhosis, the optimal usage of ICG fluorescence is still one step away from its standardization.[13,18,20]

Although reports assessing effectiveness and usefulness of ICG are steadily increasing, its application in liver surgery is still in an early phase. However, in light of not only its potentially wide clinical benefits but also its simple and affordable use, clear standardization on the optimal dose and timing of administration of ICG would be of great help for further spreading its application worldwide. Therefore, in this study, we aimed to review existing evidences and discuss clinical applications of ICG fluorescence as real-time navigation tool for tumor detection and liver segmentation, to find out the optimal dose and timing of administration in liver surgery.

METHODS

Search Strategy

This systematic review was performed for all articles published until February 2021 following the rules of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[21] PubMed and Medline databases were searched for original English articles on applications of ICG in the setting of clinical studies on liver surgery. Publications were selected based on the following medical subject headings (MeSH): ((ICG fluorescence[Title]) OR (indocyanine green[Title])) AND ((liver[Title]) OR (liver surgery[Title]) OR (liver resection[Title])). Search terms were discussed with all authors before the search.

Inclusion and Exclusion Criteria

Following the primary search, articles were systematically reviewed. Inclusion criteria for this systematic review were: English language studies, full-text articles, human studies, and studies regarding ICG fluorescence as real-time navigation tool for tumor detection and liver segmentation. Moreover, reports were included only when dose and timing of ICG administration were clearly described. Comparative studies, case series, and case reports which met these inclusion criteria were included. Exclusion criteria were as follows: studies involving animal experiments, studies published in languages other than English, conference abstracts, editorials, expert opinions, and review papers. The number of patients included and the different surgical approaches in the studies were not exclusion criteria when these articles could be considered relevant or add a great value to the completeness of the systematic review.

Review Workflow

Anatomic, cadaveric, and surgical studies on application of ICG fluorescence in liver surgery were identified. Firstly, articles not related to the topic and duplicates were excluded according to the title and the abstract. The articles from the same center representing the same application (tumor detection/liver segmentation) or setting (MIS/open) were considered as duplications. In the presence of duplications, the study that contained a larger number of patients was kept and the others were excluded in the final count. After initial screening, full-text versions of the selected manuscripts were obtained. Two independent reviewers evaluated the included manuscripts in full text format (T.W. and A.B.C.). Subsequently, full-text of the selected studies were collected and reviewed. Based on references of the included studies, hand-searched articles, which were thought to be helpful for the topic, were reviewed and included in the review process. Disagreements on articles selection were resolved by discussion and consensus among the authors. The final review of the articles was performed by February 27, 2021.

Primary objective was to review and discuss the two main clinical applications of ICG fluorescence in liver surgery, namely tumor detection and liver segmentation. Besides, dose and timing of ICG administration for both applications have been reviewed and summarized. Secondary objectives were defined as rates of tumor detection and successful liver segmentation, as well as false-positive rate and penetration depth of ICG fluorescence in tumor detection when available. Furthermore, the following valuables were systematically collected: number of cases, type of near-infrared (NIR) camera, type of diseases, and rate of liver cirrhosis in the studies.

Quality Assessment

The quality assessment was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN).[22] A worksheet table presenting the extracted data was completed to comprehend the observations in the selected studies.

RESULTS

Study Selection

A total of 311 articles were obtained (Fig. 1, Flow Chart). Of these, 219 articles were discarded in the initial checking as these were not relevant with our topic or duplicates. There were no randomized controlled trials. Subsequently, 10 comparative studies, 57 case-series, and 25 case reports were identified after the first screening. After reviewing and analyzing the full texts of the articles, the following articles were finally selected: 62 articles (8 comparative studies, 39 case series, 15 case reports) focused on the topic. In addition, 10 hand-searched articles (7 case series, 2 case reports, and 1 correspondence article) were added for their relevance to the aim of the study. Finally, a total of 72 articles were reviewed for the present study and all the variables are shown in Supplementary material 1, http://links.lww.com/SLA/D667.

The quality assessment of the included studies resulted in low due to small number of cases and large bias. However, we decided to give a high value to 9 articles due to their clinical relevance and contribution to this topic based on the SIGN methodology as shown in Supplementary material 1, http://links.lww.com/SLA/D667. In total 20 articles were judged as acceptable, whereas 43 studies were categorized as low quality, yet all the selected articles contained the information of dose and timing of ICG administration (Supplementary material 1, http://links.lww.com/SLA/D667).

Types of Near-Infrared Camera and Number of Cases

The authors in the reviewed articles used various NIR cameras in their study (Fig. 2). Major productions (manufacturers) were PINPOINT system/1588 Advanced Imaging Modalities Platform (Stryker Co., Kalamazoo, MI) for MIS (23 articles, 29.9%), and Photodynamic Eye (Hamamatsu Photonics Co., Shizuoka, Japan) for open surgery (21 articles, 27.3%). In 12 articles (15.6%), other productions or the newly developed fluorescence systems were used in the authors' institutes. For robotic procedure, Firefly system (Intuitive Surgical Inc., Sunnyvale, CA) was used in all 5 articles (6.4%).

In a total of 72 articles, 40 articles (55%) focused on open resections, whereas 27 articles (38%) and 5 articles (7%) focused on laparoscopic and robotic liver resections, respectively (Fig. 3A). In majority of the articles (45 articles, 62%), the patient number was <30 (Fig. 3B).

Application of ICG in Liver Resection

For the application of ICG, 34 articles (47%) described tumor detection ability, while 25 articles (35%) described liver segmentation ability, and the remained 13 articles (18%) described both applications (Fig. 3C). From a total of 38 articles on liver segmentation, 16 articles (42%) described the negative staining method,

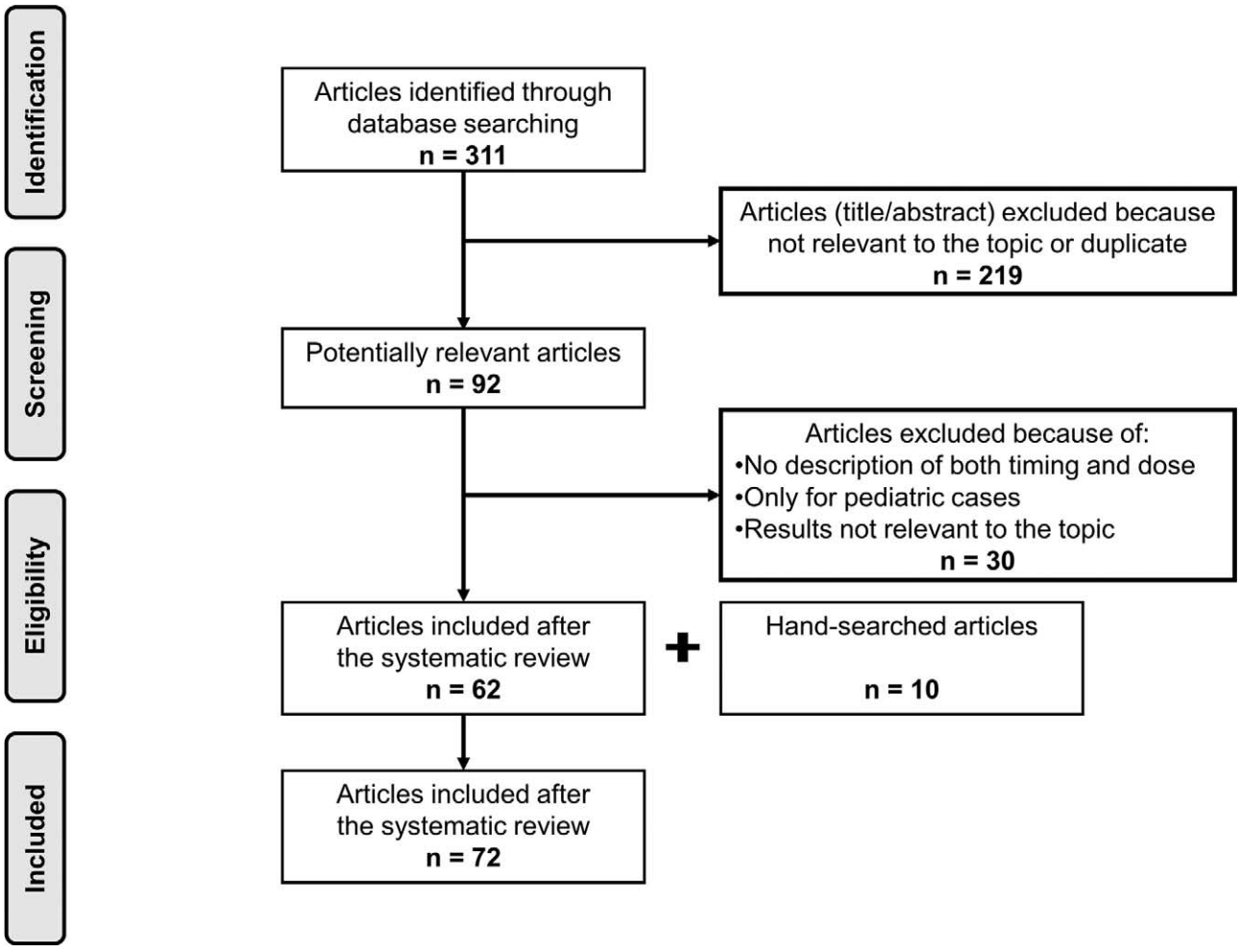

FIGURE 1. PRISMA flow diagram for study selection.

whereas 12 articles (32%) described the positive staining method, and the remained 10 articles (26%) described both methods (Fig. 3D).

Dose and Timing of ICG for Tumor Detection

For tumor detection, the clear-cut data of both dose and timing were available in 40 articles of the 47 studies. Majority of the articles presented the ICG dose of 0.5 mg/kg (Fig. 4). The timing of administration has been variously described. Generally, ICG was administered within 14 days before the operation day, especially within 3 days in the majority of the studies. An additional administration (0.02–0.5 mg/kg) was described as an option in case of the long interval between the administration and operation day.[23] Additionally, we performed a subanalysis to stratify the results by calculating the median values of ICG dose and timing from 13 articles that described the rates of cirrhotic patients including >15 subjects. We divided the 13 articles into high liver cirrhotic rate (high-LC) group (n = 6), which included LC patients more than 50%, and low liver cirrhotic rate (low-LC) group (n = 7), which included LC patients <50%. In the analysis, the median value (range) of the ICG dose and timing was 25 (2–25) mg/body and 7 (1–14) days before surgery in the high-LC group, and 25 (5–25) mg/body and 4 (2–8) days before surgery in the low-LC group (when 0.5 mg/kg was converted at 50 kg body weight) (Supplementary material 2, http://links.lww.com/SLA/D668). Finally, median tumor detection rate was reported to be 87.4% (43%–100%), and median false-positive rate was reported to be 10.5% (0%–31.3%) (Supplementary material 1, http://links.lww.com/SLA/D667).

Dose and Timing of ICG for Liver Segmentation

For negative staining method, the ICG was injected intravenously in the all 26 articles. The majority used 2.5 mg/body, and the dose ranged from 0.025 to 25 mg/body (Fig. 5A). For positive staining method, the ICG was directly injected to portal venous branches in 21 articles of the 22 articles. The majority used 0.25 mg/body, which is approximately one-tenth of that of the negative staining. The dose ranged from 0.025 to 12.5 mg/body (Fig. 5B). Successful segmentation rate was reported to be 88.0% (53%–100%) using intraoperative ICG fluorescence navigation (Supplementary material 1, http://links.lww.com/SLA/D667). The practical scheme was developed precisely in accordance with the results of the systematic review (Fig. 6).

DISCUSSIONS

This systematic review aimed to develop a broad view of clinical applications of this game-changer—ICG fluorescence imaging for surgical navigation—focusing on the optimal dose and timing

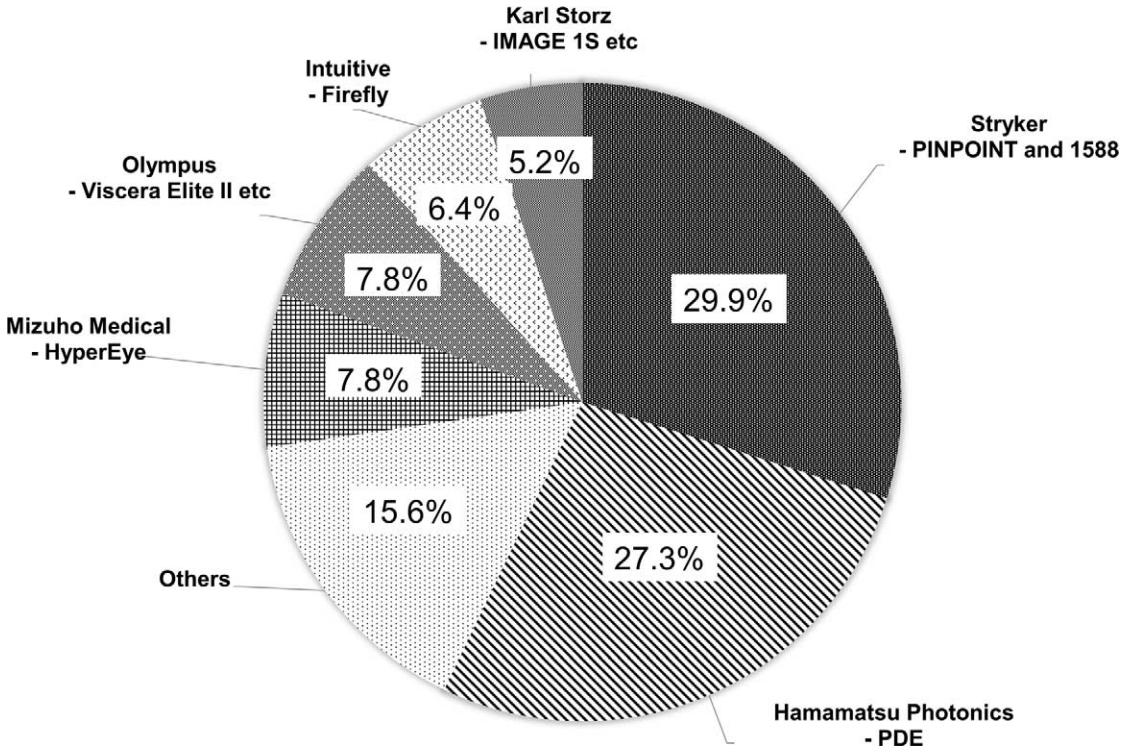

FIGURE 2. Rate of different near-infrared cameras used in selected studies.

of administration in hepatobiliary surgery. Initially, we considered that the Delphi survey among the experts was the best way as Dip et al demonstrated for establishing the consensus statement on general use of NIR fluorescence imaging and ICG guided surgery in their article.[24] However, in liver resection, where the surgical approach/technique, level of experts, and preferability of ICG fluorescence guidance can be significantly varied among worldwide experts, we began to consider that an intensive evidence search should be prioritized before establishing such a worldwide expert consensus. On the other hand, the latest consensus article by Wang et al described the preferred dosage and timing in tumor detection, liver segmentation, cholangiography, and biliary mapping in transplantation.[10] However, an issue is that the preferred dosage and timing by Wang et al are not necessarily ''optimal'' but just ''most used'' ones in the previous publications according to the results of our present review. In addition, designs and characteristics of the previous studies contains high heterogeneity (ie, rate of cirrhosis, type of neoplasms, age, and tumor associated factors), which eventually affect the intraoperative observability of ICG fluorescent emission and make it problematic to create the consensus statement for ICG usage in liver surgery. Contrarily, the present review enables us to read every single dose and timing in the previous publications. Thus, this is a comprehensive review to assist clinical decision making and to clarify the future direction of ICG fluorescence-guided liver surgery.

One of the noteworthy features of this study is to review and discuss the two main applications of ICG fluorescence in liver surgery. Indeed, ICG-fluorescence offers a simple and safe method for visualization of liver tissue enabling identification of hepatic tumors and liver segmentation during laparoscopic and open liver resections.

Firstly, tumor detection is relatively well-established application during the previous years. ICG fluorescence has been primarily used to visualize liver lesions, even allowing the identification of liver neoplasms that could not be detected using intraoperative ultrasonography.[14,25–27] In majority of the studies, ICG fluorophore was injected for preoperative liver function test (0.5 mg/kg body) within 14 days before surgery.[28,29] Furthermore, in 27 articles of the 40 articles, ICG was injected within 3 days before surgery (Fig. 4). However, there supposed to be institutions that do not perform routine ICG retention test or administer ICG fluorophore more than 14 days before surgery. Kobayashi et al suggested 2.5 mg ICG can be additionally injected one day before surgery without increasing the false positive rate in case of no ICG retention test or interval beyond 14 days from the first injection.[9] In cirrhotic or fibrotic liver with impaired liver function, slower metabolic elimination of ICG is considered to lead increased false positive rate of tumor detection.[13] Indeed, we found that the articles including the highest rate of cirrhotic patients tended to present longer interval between ICG administration and surgery over 7 days.[20,30] However, the correlation between preoperative liver function test (ie, ICG retention rate at

15 minutes, and so on) and the diagnostic accuracy of ICG-fluorescence is still unknown in the previous literature.[23,25,30] Further studies are needed to determine the optimal interval for obtaining a higher specificity of ICG-fluorescence imaging. Besides, liver metabolism may be gradually impaired by aging as well.[13] However, we believe that future mechanistic studies are needed to confirm the true impact of aging on the ICG metabolism of the liver. For the moment, a tailored ICG administration can be achieved by considering these patient-related aspects shown in Supplementary material 1, http://links.lww.com/SLA/D667.

Another aspect to take into account is the ICG staining pattern of tumors and its penetration through liver tissue. Generally, total or partial fluorescence staining pattern is predominantly observed in patients with hepatocellular carcinoma. Rim fluorescence staining

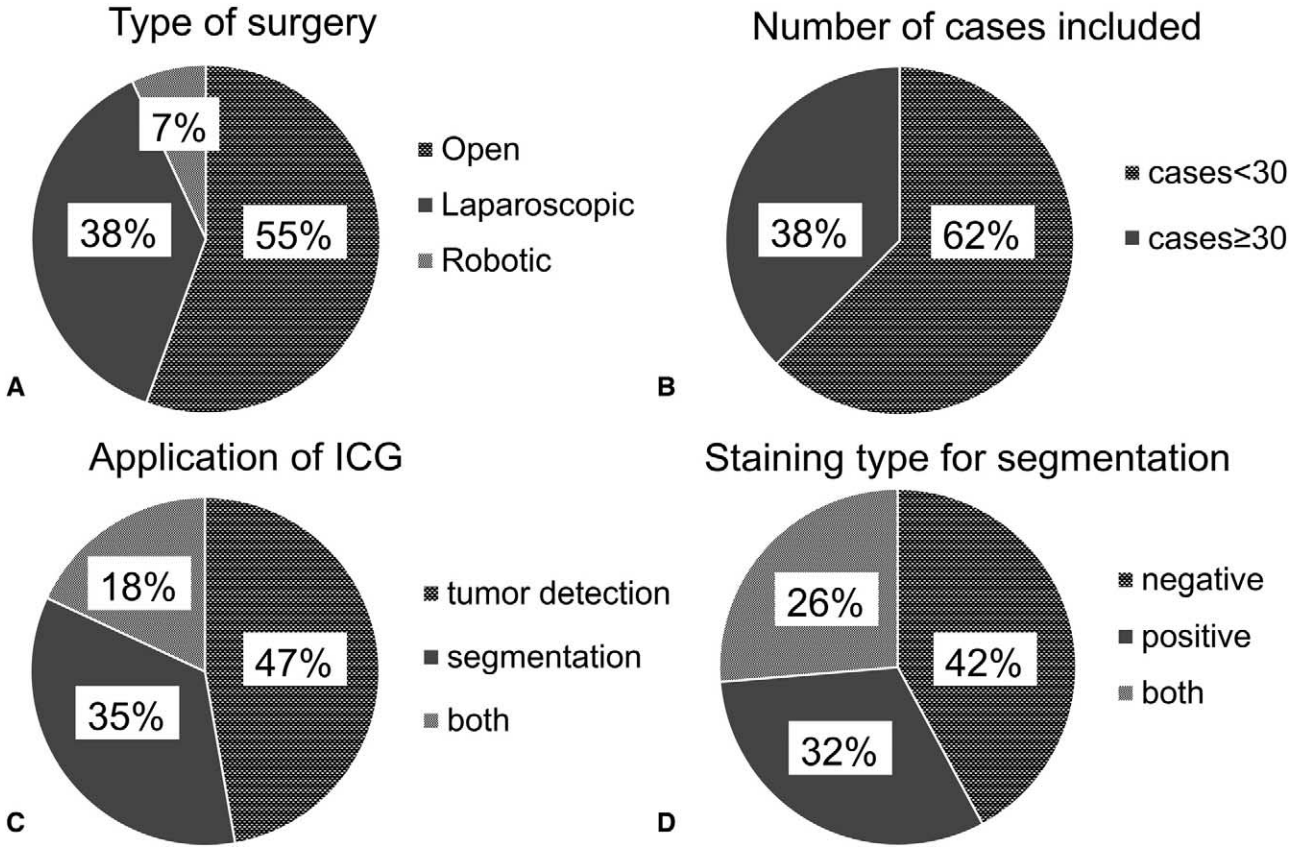

FIGURE 3. Rate of different variables in selected studies. (A) Rate of type of surgery, (B) rate of studies with more and less than 30 cases, (C) rate of application of ICG fluorescence, and (D) rate of staining technique for liver segmentation are represented with the circle graphs.

pattern is observed mainly in metastases, whereas cholangiocarcinoma shows no predominant staining pattern.[23] As to penetration depth of ICG fluorescence, tumors located deeper than 8 to 13 mm from the liver surface are presently considered not well identifiable using ICG fluorescent imaging.[13,31] Indeed, Boogerd et al reported that most of the tumors undetected by IOUS were superficially located, whereas those missed by ICG fluorescence were deeply located. This suggests the potential complementary role of both tools.[32] Indeed, the value of ICG fluorescence in tumor detection for deeper tumors seems to be limited to achieving a proper tumor margin in the proximity of the tumor.[18]

Another noteworthy finding is that the ICG fluorescent visualization is differed among the fluorescent imaging systems.[9] This could be the tremendous bias when trying to make a standardization of dose and timing of ICG administration. However, it was not clearly described in the article by Wang et al.[10] Thus, we reported the types of surgery (MIS or open) and NIR cameras used in the included studies given the significance of intraoperative setting of ICG imaging system.[32] For imaging devices, there are mainly 6 leading companies providing NIR cameras in the field of ICG fluorescence guided surgery (Fig. 2). Photodynamic Eye (Hamamatsu Photonics Co) and HyperEye Medical System (Mizuho Medical Co., Ltd) are mainly used in the open liver setting, enabling to contrast in black and white (or fluorescent emission in white light image) between normal liver parenchyma and tumorous/ischemic area. The ability of black and white mode can be demonstrated in particular when detecting the biliary system to avoid biliary injury or bile leakage.[33] Overlay mode is available in PINPOINT/SPY PHI (Stryker Co) and HyperEye Medical System (Mizuho Medical Co., Ltd. Tokyo, Japan) which allow fluorescence visualization and white light imaging simultaneously, preventing the surgeon from continuously switching from one to another. Furthermore, it enables to clearly demarcate intersegmental plane in the raw surface of liver parenchyma which is a huge advantage during minimally invasive anatomic resection.[34] The recent products, 1688 AIM (Stryker Co) and Image 1S Rubina (Karl Storz SE & Co. KG, Tuttlingen, Germany), have the overlay technology but was not used in the articles at the moment of the present review. Viscera Elite II (Olympus Corp., Tokyo, Japan) and Firefly (Intuitive Surgical Inc.) have the fusion image mode between green fluorescence and grayscale background images, which is also considered useful during liver parenchymal transection.[5,35] In addition, multiple color mode enables a quantitative assessment of tissue perfusion. This mode can be used in anastomotic perfusion,[36] sentinel lymph node mapping,[37] or plastic and reconstructive surgery,[38] but scarcely used in liver resection. However, we believe it is a future research topic to assess precise surgical margin, liver parenchymal perfusion, and lymph node metastases from primary liver cancer using this type of mode. The major commercially available laparoscopic fluorescent systems are summed up in Supplementary material 3, http://links.lww.com/SLA/D669. In anatomic liver resections, the overlay mode with the high-resolution image is supposed to be the preferable function to make the identification of intersegmental/sectional planes feasible even in deeper liver parenchyma.[34,39] This concept should be further investigated in future studies.

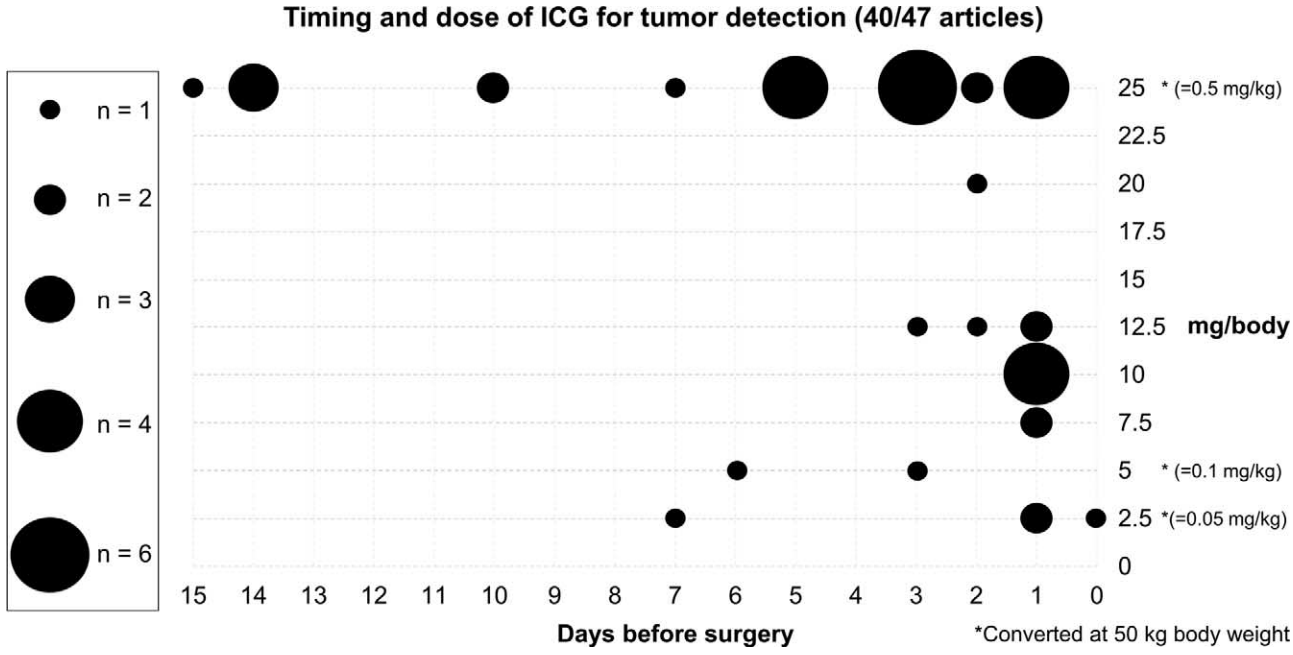

FIGURE 4. Timing and dose of ICG administration reported for intraoperative tumor detection.

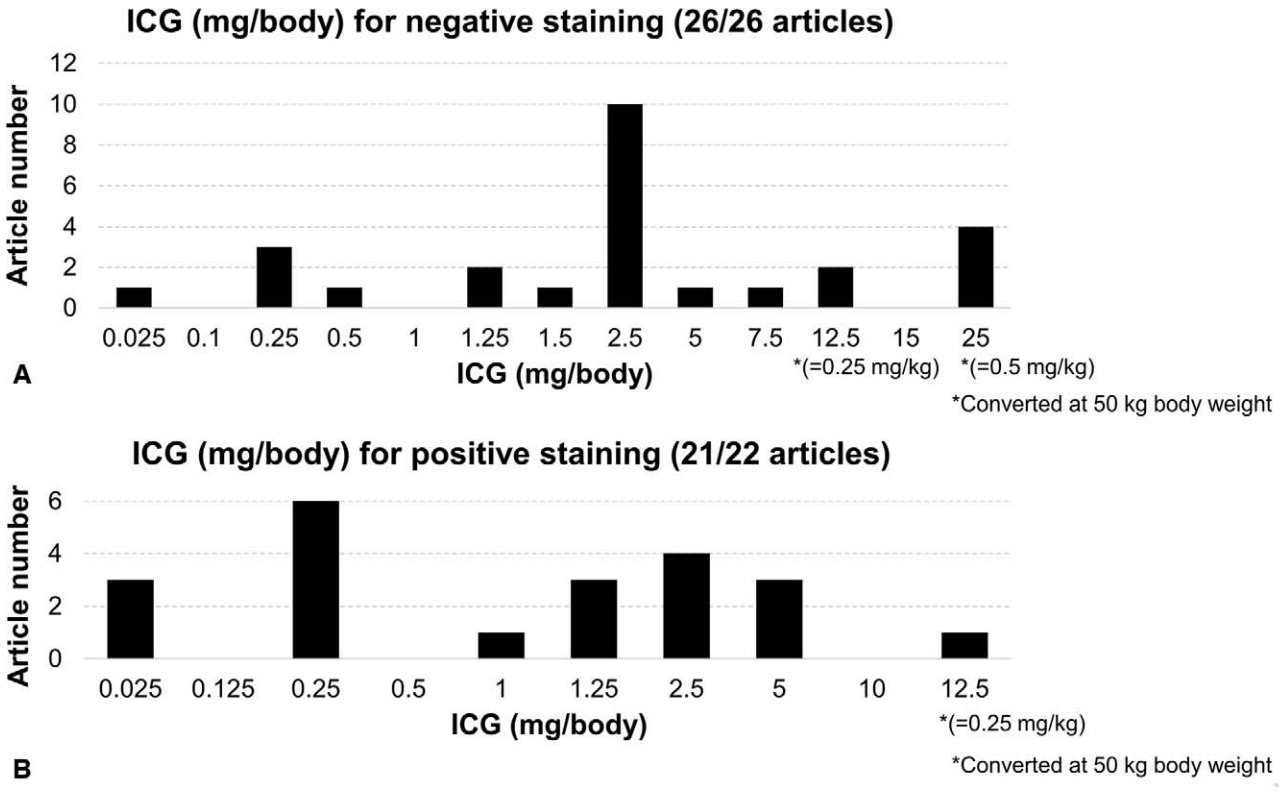

FIGURE 5. Dose of intraoperative ICG administration reported for liver segmentation. Doses in (A) negative staining and (B) positive staining techniques were introduced in 26 and 21 articles, respectively.

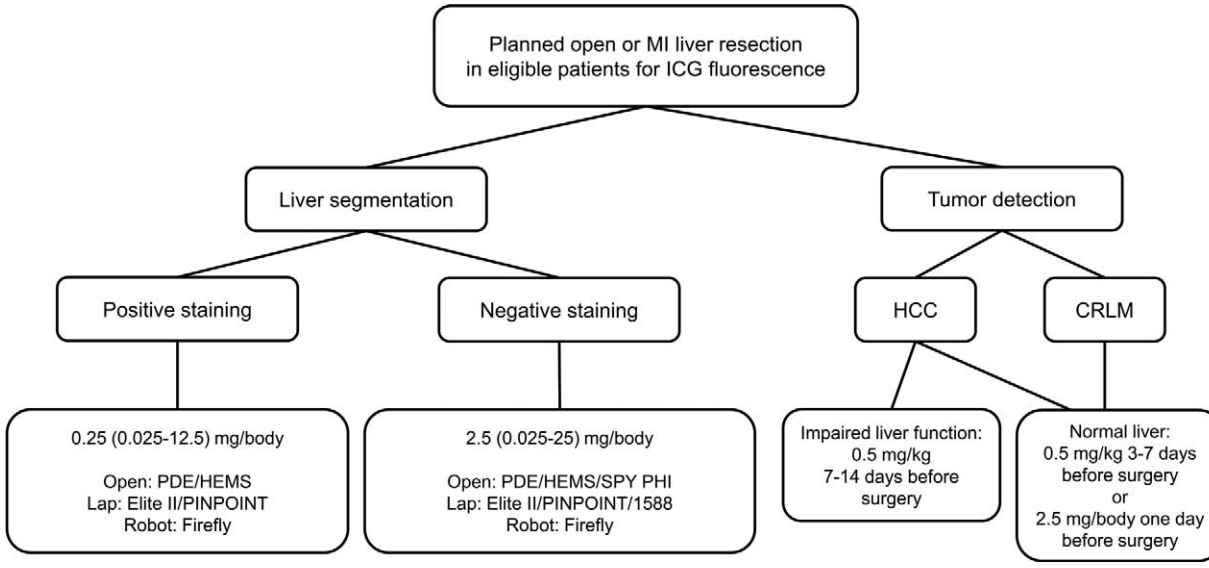

FIGURE 6. Practical scheme of ICG fluorescence for open and minimally invasive liver resections.

As previously mentioned, the other main application of ICG fluorescence in hepatobiliary surgery is the realization of transection planes during anatomic liver resection. Aoki et al firstly described their technique of direct portal injection of 5 mg/body ICG for liver segmentation in 2008.[40] The success rate of segmentation was 94.3% in open liver resection. Subsequently, Ishizawa et al reported the application of positive and negative staining method in laparoscopic anatomic liver segmentectomies.[41] Consequently, 40 articles on intraoperative liver segmentation for anatomic liver resections have been published until 2021.

As for ICG staining method of liver segmentation, Kobayashi et al described different types of staining as follows:[42] single, multiple, or counterstaining staining technique (referred to positive staining in the present review), and negative staining or paradoxical negative staining technique (referred to negative staining in the present review). For positive and negative staining, the ICG for injection powder should be first dissolved with the sterile water, whereas isotonic saline should be used to further dilute the ICG solution (eg, 100-fold dilution) to avoid hemolysis (Drugs. com: https://www.drugs.com/pro/indocyanine-green.html). In addition, some authors mixed indigo carmine with the ICG solution for positive staining as it enables the liver segmentation also with naked eyes.[42] In ICG negative staining, intersegmental/sectional planes can be visualized not only on the liver surfaces but also on the raw surfaces during liver transection using the fluorescence images after systemic intravenous injection of ICG.[43] Negative staining is supposed to be a favorable technique for hemihepatectomy, sectionectomy, and anterolateral segmentectomies using preferably Takasaki's extrahepatic Glissonean approach.[10]

On the contrary, ICG positive staining means the direct injection of ICG into the portal branches responsible for resected territories or surrounding territories to see clear demarcation planes. Some authors described the detailed technique of positive staining as follows: the portal branches of tumor-bearing liver segments are targeted and punctured under ultrasound guidance with an 18- to 22-gauge spinal or percutaneous transhepatic cholangiodrainage needle introduced through the abdominal wall.[41] The direction of the needle is assisted by the needle hole in a dedicated laparoscopic ultrasound probe (provided by BK Medical, Herlev, Denmark). Subsequently, a small amount of ICG (eg, 1 mL of 0.025 mg/mL) is injected into the portal branch slowly for avoiding the risk of ICG retrograde flow into neighboring segments with undesired staining without clamping the hepatic artery.[44] As to dose of positive staining, it should be considered depending on the segmental volume to be resected.[45] Positive staining requires the expertise for manipulating IOUS and needle puncture, especially in MIS setting.[46] In fact, Marino reported that negative staining (vs positive staining) seemed to provide a higher demarcation (90% vs 85%), better scores in terms of general quality of fluorescence image (65% vs 59%), and comfort/satisfaction of the surgeon during technique (51% vs. 42%) in robotic-assisted liver resection, evaluating the questionnaire completed by the operators.[5] However, some experts argued the priority of positive staining in right superior segments (ie, segment 7 and 8) compared to negative staining technique in hepatobiliary surgery.[10] Berardi et al presented the favorable short-term outcomes of their 86 cases who underwent laparoscopic anatomic parenchymal sparing liver resections using the Glissonean approach from the liver hilum and the negative staining approach performed in the Japanese referral center of laparoscopic liver resection.[12] In their article, negative staining technique was achieved in all segmentectomies (posterosuperior segmentectomies accounted for 31%), although the feasibility of their technique should be further investigated in future well-controlled trials.

One of the most important findings of the present review is the limits of tumor detection and liver segmentation. Indeed, the lowest rate of tumor identification is 43% reported by Kose et al, and only 4% (3/82) of the deeply located tumors could be detected using ICG fluorescent imaging in their article.[47] Contrarily, the lowest rate of liver segmentation is 53% reported by Xu et al[45] Xu et al summarized the failure of positive and negative staining in laparoscopic liver resections based on different reasons. In the case of positive staining, the failure could occur due to the retrograde flow, unequal blood flow that disseminated ICG into the different downstream areas, or puncturing wrong branches or hepatic venous tributaries. Whereas, negative staining could be gradually contaminated due to collateral circulation because of single portal vein clamping, presence of aberrant circulation feeding undesired segments (ie, accessory left hepatic artery or inferior phrenic artery among others), or multiple

portal branch supplies. To prevent the contaminations, the authors recommended to precisely investigate the portal tree and clamping the specific Glissonean pedicles. Indeed, Berardi et al reported no remarkable contamination in their negative staining technique from the hilum, in which the precise confirmation was repeated intraoperatively with the 3D simulation, IOUS, and doppler until the correct Glissonean pedicles were achieved to clamp.[12] One more noteworthy thing is that Berardi et al used relatively small amount of ICG dose (0.5 mg/body) for their negative staining technique to avoid the contamination.[12] However, future well-designed trial is necessarily required to identify proper dose for anatomic liver resections.

Some limitations of the present review should be addressed. Firstly, we could not reach the clear-cut results of the optimal dose and timing of ICG injection in the present review. One of the reasons is the study design of the included studies which are mostly case series with a small number of patients containing heterogeneity. Thus, as abovementioned, we performed a sub-analysis to stratify the dose and timing according to the rate of cirrhotic patients in the articles. This result may partially imply that the authors tended to employ the longer interval between ICG injection and surgery in cirrhotic patients than in noncirrhotic patients. As a consequence, we confined our main statement to the data summary on the current practical usage of ICG in liver resection as shown in Supplementary material 1, http://links.lww.com/SLA/D667. Next, articles on hepatoblastomas that possess similar features to HCC were excluded in the present studies, because they are the most common pediatric malignancies usually diagnosed under 3 years of age.[48] However, ICG usage in case of bile duct obstruction and preoperative portal vein embolization (PVE) could be the matters. Some authors demonstrated that preoperative systemic ICG administration could result in identifying noncancerous liver parenchyma affected with bile ducts obstruction and the consecutive altered biliary excretion by allowing visualization of the ICG fluorescence retained in the cholestatic regions. This application could lead to giving aid in sparing liver parenchyma for resection of the tumor with bile duct infiltration or thrombosis.[49,50] Preoperative PVE is a part of routine clinical practice for liver surgeries. In the case of preoperative PVE, the transection plane can be easily visualized after ICG systemic injection without liver manipulation as a negative staining method.[51] As a consequence, the transection plane was tended to shift towards the left or right side of the liver due to the hypertrophy of the non-PVE side and hypotrophy of the PVE side of the liver.[52] Lastly, the usefulness of ICG fluorescence for resections of extra hepatic diseases and lymph node metastases are the key issues. Satou et al reported that extrahepatic metastases from HCC accumulate ICG after intravenous injection emitting fluorescence upon being illuminated with NIR light.[53] Contrarily, Liberale et al demonstrated the equivocal role of ICG fluorescence in the detection of peritoneal metastases due to colorectal cancer.[54] Especially, mucinous adenocarcinoma showed a specific fluorescence distribution as indicated by a hyperfluorescent peripheral rim and hypofluorescent center in contrast to non-mucinous adenocarcinoma which ubiquitously expresses hyperfluorescent emission. However, there are no notable reports of ICG usage on lymphatic mapping on primary liver cancer especially cholangiocarcinoma due to the complexity in lymphatic drainage in the liver, although ICG fluorescent lymphatic mapping has been introduced in many gastrointestinal surgeries.[55] This topic was also mentioned as one of the future directions in the Asia-Pacific expert panel meeting for the use of ICG fluorescence imaging in hepatobiliary surgery.[10] Future clinical studies are warranted to clarify the dose and timing for the extrahepatic disease of liver malignancies and to investigate standard sentinel lymph node protocol for cholangiocarcinoma in combination with ICG fluorescence imaging.

In conclusion, ICG fluorescent navigation is complemental technique to identify subcapsular tumors or intersegmental/sectional planes in anatomic resections. When combined with preoperative 3D reconstruction and IOUS, it can be solid real-time navigation tool to make a huge difference in accuracy of liver resections. However, best time point and dose of ICG administration for tumor identification and liver segmentation remains unclear due to various patient backgrounds and imaging settings in the previous studies.[56–101] Thus, its administration strongly needs to be tailored case by case in daily practice.

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