Review Article

Advantages of using indocyanine green in liver transplantation: a narrative review

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Objective: To assess the role of indocyanine green in liver transplantation and to lay the foundation for its application in clinical practice.

Background: Liver transplantation offers the best prognosis for patients with end-stage liver disease. However, this invasive procedure involves multiple well-known challenges, including complications due to graft rejection and dysfunction, surgical risks, and critical postoperative management. Intraoperative methods to assess graft function rely on conventional methods, such as blood chemistries and Doppler ultrasound. However, these methods are limited in their abilities to assess liver conditions, predict functional outcomes of the graft, and prevent surgical complications. Thus, identifying a more effective and comprehensive detection method is necessary.

Methods: The information used to write this narrative review was collected from the references' opinions and conclusions.

Conclusions: Indocyanine green can effectively monitor blood flow during surgery, evaluate donor graft function, and monitor the recipients functional status during and after surgery. It may also help surgeons to predict the prognosis of patients throughout the liver transplantation process, from assessing patients for liver transplantation status to postoperative management. Therefore indocyanine green should be routinely used in liver transplantation to help re-organize the transplant waiting list and improve the surgical outcomes of liver transplantation patients.

Keywords: Indocyanine green (ICG); liver transplantation (LT); liver allocation; transplant assessment; surgical complications

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Introduction

The high mortality rate of end-stage liver diseases is a global health issue. In the United States, approximately 30,000 patients die from chronic liver disease each year, and the incidence of such deaths has been increasing. Liver transplantation (LT) is the only curative treatment for end-stage liver disease (1); however, the results are disappointing. The mortality rate at 30 days postoperatively is as high as 3%, which increases to approximately 7% at 90-day postoperatively (2,3). LT complications include dysfunctional grafts, unpredictable surgical complications, and delayed postoperative intervention (4-6). This review discusses indocyanine green (ICG) perfusion and related tests as complementary methods to assess graft function in real time, before, during, and after transplantation, in order to predict surgical complications.

Graft function is most commonly evaluated by the Child-Pugh score and the Model for End-Stage Liver Disease (MELD) score. However, two parameters in the Child-Pugh system, ascites and encephalopathy, are subjective. Additionally, the international normalized ratio (INR) in the two systems cannot sufficiently reflect coagulopathy and consequently liver function, and meanwhile ignores interlaboratory variation (7,8). Blood tests for liver-specific enzymes, like the ratio between concentrations of alanine aminotransferase and aminotransaminase (ALT/AST), does not express liver function accurately enough to predict surgical outcomes. Imaging methods, such as computed tomography (CT), can accurately calculate the liver volume, but cannot reflect the function of liver cells. Furthermore, CT imaging does not evaluate hepatocellular failure caused by biliary obstruction (9).

ICG is a safe, low-cost, and commonly used injectable dye that fluoresces in the near-infrared region. When excited by near-infrared light, ICG emits fluorescence that can be detected in real-time during operations. Typically, after it is intravenously injected to the patient, ICG binds to serum proteins and is rapidly uptaken by hepatic cells and tumor tissue. This NIR fluorescent probe accumulates in tumors, via the enhanced permeability and retention (EPR) effect (10), hence achieving a better tumor detection. Upon irradiation with NIR light, ICG absorbs the light at 800 nm, emitting a strong fluorescence at a wavelength of 830 nm, thus improving tumor localization. Once the fluorescence is collected by the relevant instrument, it can be displayed on the screen of the instrument after being processed by the computer for rapid image registration, so as to provide accurate surgical guidance. The molecular formula of ICG has been described by Vos *et al.* (11). Compared with visible light, near-infrared light penetrates more effectively through living tissue. ICG was approved by the Food and Drug Administration (FDA) for clinical use and has played a critical role in several applications, including assessing perfusion in colon anastomoses and breast reconstruction (12,13), detecting sentinel lymph nodes (14,15), and intraoperative localization of tumors (16). It has also been shown to successfully predict liver reserve function prior to liver resection (17). As such, ICG could be used in conjunction with traditional liver function tests. Intraoperatively, ICG offers clear visualization and assessment of liver function. Moreover, the use optical molecular imaging can help doctors assess the approximate surgical location. Combined with RGD-ICG molecular probes, it can quickly locate the surgical area. Moreover, RGD-ICG molecular probes can help doctors reduce exploration time, improve exploration efficiency, and thereby reduce operation time. These advantages in assessing liver function before and during liver resection and transplantation have led some transplant centers to commonly adopt ICG perfusion during LT. Interestingly, ICG perfusion of donor grafts can reasonably assess graft function, perform real-time intraoperative navigation, and even predict postoperative risk. In this review paper, we reviewed the data on ICG in LT. As shown in *Table 1*, using ICG has been shown to be an effective and convenient method to assess liver function compared with other methods. Based on the data, we recommend ICG as a safe, cost-effective tool that provides valuable clinical data in LT to help improve patient prognosis in end-stage liver disease. Previous literature on ICG was mainly limited to: (I) liver function reserve test (II) vascular patency and (III) tumor identification. However, to the best of our knowledge, systematic reports describing ICG's unique advantages specifically in liver transplantation are not available. These advantages are as follows: (I) ICG can make up for the insufficiency of MELD score and allow a more reasonable allocation of organs. (II) It helps evaluate the liver status and (III) reduce the rate of useless liver transplantation. The patient's prognosis (IV) can help predict early postoperative complications and provide early warning regarding the medical treatment. We present the following article in accordance with the Narrative Review reporting checklist (available at https://atm.amegroups.com/article/view/10.21037/atm-21-6650/rc).

Table 1 Method usually used in evaluation of liver function

Method	Advantage	Disadvantage
Child-Pugh score (Parameters: Albumin, Bilirubin, PT, Ascites, Encephalopathy)	Reliable and convenient	Ascites and encephalopathy are subjective, can be variable according to the doctors' judgment
		INR cannot sufficiently reflect coagulopathy and consequently liver function
		There exists interlaboratory variation
MELD score (Parameters: Creatinine, Bilirubin, INR)	Reliable and convenient	INR cannot sufficiently reflect coagulopathy and consequently liver function
MEGX test	Real-time measure	Wide interindividual variability
		Requires constant monitoring and is not suitable for patients in the initial stages of chronic hepatitis
Galactose elimination capacity test	Well reflected the metabolic function of liver	Time-consuming process
		Requires many repeated blood draws
		Affected by anaerobic respiration
Imaging modalities	Accurately calculate graft volume or residual liver volume	Inconvenient
		Liver volume does not accurately reflect liver function
Serum liver specific enzymes (Parameters: ALT, AST, GLDH)	Quick and convenient	Cannot assess liver function dynamically
		AST is not liver specific
ICG clearance test	Real-time measure, convenient and non-toxic	Decreased ICG extraction rate in patients with hyperbilirubinemia

INR, international normalized ratio; PT, Prothrombin activity; MEGX, monoethylglycinexylidide; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GLDH, glutamate dehydrogenase; MELD, model for end stage liver disease; ICG, indocyanine green.

Table 2 Sources used for this overview

PubMed search: 1966–January 2001. Key words: Indocyanine green (ICG); liver transplantation; liver allocation; transplant assessment; surgical complications. Review of the Literature; Authorship; Meta-analysis; Narrative overview
Discuss with experts in the ICG field
Information collection and surgical observation of liver transplantation patients
Author's experience of ICG in liver surgery
The author's own experience in writing ICG related research papers and reviews

ICG, indocyanine green.

Methods

We searched the PubMed database from 1966 to January 2021 using the following keywords: indocyanine green, liver transplantation, liver allocation, transplant assessment, and surgical complications. The information used to write this paper was collected from the sources listed in *Table 2*.

Discussion

Pre-transplantation benefits of ICG

Assessing the status of LT candidates by ICG clearance test

The primary limitation of LT is the shortage of donor livers.

Long wait times significantly reduce patient survival before and after transplantation (18). Depending on the condition of the recipient, proper organ allocation is important to improve the overall transplantation survival rate. The MELD score accurately predicts the short-term survival and mortality risk in patients with end-stage liver disease and is widely used for liver distribution worldwide (19), but it is ineffective in 15–20% of patients (20). Ecochard *et al.* added metabolic liver function tests to improve the prediction accuracy of the MELD score; in a study of 560 cirrhotic patients listed for transplantation, the ICG clearance rate was evaluated. This improved the prognostic and survival evaluation with high sensitivity and specificity, indicating that an ICG clearance test can be used as a pre-transplant receptor test program to assist MELD scoring, hence more effectively distribute organs (21). For patients with acute liver failure (ALF), the plasma disappearance rate of indocyanine green (ICG-PDR) exhibited a close relationship with the patient's survival rate, which suggests that ICG can help surgeons determine whether patients are good candidates for LT (22). Moreover, ICG-PDR is a safe and non-invasive test that can be conveniently performed at the patient's bedside.

Evaluating the graft's function by ICG retention rate

Due to recent advances in surgery and improved perioperative care, LT offers many patients the best prognosis, making this surgery widely accepted worldwide and further increasing the demand for donor livers (23,24). In order to meet the demand, many transplantation centers have expanded the criteria for transplant donation, including the use of marginal donor livers with steatosis, chronic hepatitis, and even tumors for critical cases (25). Assessing the function of these potential grafts is the first step in LT. Although each transplantation center appropriately prioritizes this analysis of donor liver function, there still exists a lack of accurate, quantitative methods.

Tang *et al.* performed ICG clearance testing on 90 brain-dead donors before liver procurement, including 45 cases of livers with varying degrees of cirrhosis, acute hepatic necrosis, hepatocellular carcinoma and/or hepatitis B virus (HBV)-associated cirrhosis. The results showed that the ICG retention rate at 15 minutes (ICGR15) >11.0% had significantly lower 3-month graft survival rates (26). Zarrinpar *et al.* measured ICG-PDR in 53 donors, including 11 with poor-quality livers, and observed that ICG-PDR was the only effective donor predictor of 7-day graft survival (27). Wang *et al.* investigated the 15-minute detection rate of ICG (ICGR15D) in 106 liver donors, including 22 cases of mild fatty liver and 20 cases of moderate to severe fatty liver. The study found that the ICGR15D increased according to the severity of donor fatty liver, and those with >20% of fatty degeneration (ICGR15D 4.5±1.1) had a higher risk of transplantation failure and postoperative complications (28). Therefore, ICG can be used as a pre-transplant graft function evaluation factor to predict the prognosis of transplant patients. Globally, ICG clearance represent the most common test used to perioperatively evaluate liver function in case of liver resection surgery and liver transplantation (29). To determine ICG clearance, the standard method used is the *ex vivo* photometric analysis of several arterial blood samples obtained in a short time frame (15 min) following the intravenous injection of ICG. ICGPDR and ICGR15 are the two parameters usually used to evaluate ICG clearance. For donors with long ICG clearance time, pre-transplant treatment, such as antiviral therapy, can be considered, which may effectively preempt transplant failure.

Intraoperative function of ICG

Preventing biliary complications through ICG fluorescence cholangiography

Biliary complications are the Achilles heel of LT, with incidence rates ranging from 23–43.8% in different transplantation centers. The two most common complications are bile leaks (8.5–46%) and strictures (14.7–37.5%), with resulting mortality rates of 1–3% (30-32). Abnormal bile duct anatomy around the hilum and postoperative inflammatory reactions associated with biliary complications, make these challenges more severe. Fluorescence imaging technology provides the ability to visualize biliary structures through the liver hilar fat and surrounding tissues. Furthermore, it makes it easier to identify the cystic duct without a tedious dissection of Calot's triangle (33). Since 2008, this approach has been increasingly adopted (34).

Mizuno *et al.* conducted a study of 108 donors and recipients undergoing living-donor liver transplantation (LDLT), with a mean follow-up time of 58 months. In the control group (without ICG imaging guidance), six patients had postoperative bile leaks (5.6%), 15 had biliary strictures (13.9%), and 3three donors had bile leaks (2.7%). In the ICG fluorescence cholangiography

group, there were no biliary complications in the donors or recipients (35). It was observed that ICG biliary fluorescence imaging made it easier for surgeons to identify the demarcation of the biliary tree in the donor, thereby preventing biliary complications (36). Hong *et al.* reported the use of ICG near-infrared fluorescence cholangiography to assist during a pediatric LDLT case. They found the optimal bile duct division point by real-time ICG fluorescence cholangiography and reported no biliary complications following surgery (37). Nonetheless, optimizing cholangiography may require the development of individualized standards based on the patient's metabolic status, which is a direction that requires further research.

Preventing vascular complications by using ICG with ultrasound

LT-related vascular complications usually include hemorrhage, stenosis, thrombosis, and anastomoses. Although rare, these complications have a mortality rate of 13% in LDLT (13%) and a mortality rate of 7% in various series of deceased donor liver transplantation (DDLT) (4,38-40). Without timely intervention arterial thrombosis alone results in a mortality rate of greater than 50% (41). Insufficient anastomoses and stenosis are highly associated with these complications. Although intraoperative Doppler ultrasound (IDUS) is used to ensure effective vascular reconstruction in LDLT, it cannot visualize the anastomosis in real time (42). Kubota *et al.* used ICG for imaging of reconstructed vessels in three patients who had undergone LDLT. They demonstrated that, in addition to monitoring bile production in the transplanted liver graft, ICG can help the surgeon clearly visualize the reconstructed hepatic artery and portal vein (42). ICG fluorescence has been shown to be a valuable adjunct to ultrasound to guarantee the patency of reconstructed vessels.

Observing reperfusion of graft

Primary graft dysfunction (PGD) is a clinical situation that comprises initial poor function (IPF) and primary non-function (PNF), and when accompanied by reperfusion injury, PGD results in irreversible graft failure (43,44). Traditionally, there has been no effective method to assess and predict graft dysfunction intraoperatively after graft implantation. More recently, ICG imaging has been used to evaluate liver parenchymal perfusion. Figueroa *et al.* used ICG fluorescence imaging to analyze graft perfusion. They assessed perfusion in 72 patients during LT and found that an abnormal intraoperative ICG fluorescence pattern (non-homogeneous fluorescence) accompanied the high occurrence of PGD after LT (45). LT hypoperfusion caused by portal vein thrombosis can be detected by ICG imaging. After performing ICG fluorescence imaging to confirm graft perfusion, Kawaguchi *et al.* observed insufficient perfusion on the segmental surface, which was ultimately diagnosed as portal vein thrombosis (46). Hepatic venous outflow obstruction of the graft can lead to a reduction in portal uptake and sinusoidal perfusion, resulting in necrosis or insufficient regeneration of related veno-occlusive regions (VOR), and ultimately leading to graft dysfunction (47,48). In order to prevent postoperative graft dysfunction caused by VOR, major hepatic vein tributaries sometimes need to be reconstructed (49). Although preoperative three-dimensional computed tomography (CT) can estimate the relative regional liver volumes with postoperative VOR, it cannot alert the surgeon in real time if the patient requires venous reconstruction. Hashimoto *et al.* evaluated the decrease of sinusoidal perfusion in VOR in the remnant liver after LT by detecting ICG using near-infrared spectroscopy. There is a notable difference in ICG detection between VOR and non-VOR, but there also exists patient-to-patient differences (50). On this basis, Kawaguchi *et al.* directly used the fluorescence imaging function of ICG to observe the surface of the graft. The imaging clearly identifies VOR from non-VOR, and provides ICG intake values which can effectively help doctors decide whether they need to reconstruct hepatic vein tributaries (51).

Monitoring portal venous flow by ICG elimination rate

Insufficient graft size is a major issue that is often accompanied by poor surgical outcomes and patient death; however, has been shown to be acceptable given adequate portal blood pressure (PVP) (52,53). This situation can be effectively alleviated by regulating portal venous flow (PVF). However, some conditions such as cirrhosis with collaterals of the portal vein, would prevent PVP from correctly reflecting the optimal PVF. Therefore, it is necessary to establish a reliable indicator to predict the optimal PVF during LDLT. Hori *et al.* used the ICG elimination rate (kICG) to confirm that optimal PVF can be achieved during LDLT. They observed significant improvements in the LT outcomes when the final PVP <15 mmHg and kICG >3.1175×10^{-4} g. The kICG/graft-weight value is a reliable intraoperative predictor and indicator, according to which surgeons can adjust the PVF via surgery or other means to ensure the safety of the transplantation (54).

Postoperative function of ICG

Predicting early mortality and complications by ICG clearance rate

Graft dysfunction is the primary indication for early re-transplantation, and LT mortality is usually caused by vascular thrombosis, sepsis, and acute rejection, among other complications. Moreover, the recurrence of hepatocellular carcinoma (HCC) after LT, is rather common with a rate of about 10–15% (55). Several risk factors play a role in HCC recurrence and patient's survival. For instance, the more the size and number of tumors exceeds Milan criteria, the greater the risk. Microvascular invasion is closely related to HCC recurrence and reduces the survival of patients. In addition, poor tumor differentiation is also a related risk factor for postoperative recurrence. However, recipient's tumor marker alpha-fetoprotein (AFP) prior to transplantation is negatively correlated with the prognosis of LT (56). Hepatic artery thrombosis (HAT) alone results in a re-transplantation rate of up to 75% (57) and mortality rate of around 50% (41). Thus, predicting early graft dysfunction can provide treating physicians with necessary information to promptly adjust postoperative treatments, in order to improve the survival rate of patients. Du *et al.* retrospectively analyzed 178 patients who underwent LDLT, and their results showed that a minimum ICG clearance rate constant K (m-KICG) <0.100/minute was the strongest predictor of early graft loss after postoperative day 3 (sensitivity, 100%; specificity, 97.2%) (58). Olmedilla *et al.* conducted a prospective analysis between the ICG-PDR and early graft function after LT, and showed that the survival rate was significantly lower when the 1-hour plasma disappearance value was below 10.8%/minute (59). Klinzing *et al.* analyzed ICG-PDR within 6 hours after Intensive Care Unit (ICU) admission and calculated the MELD score before LT; they found that when MELD >25 and ICG-PDR <20%/minute, the ICU stay time and hospital mortality were significantly longer. They suggested that ICG-PDR can help predict the outcome and risk stratification after LT and create an optimal intensive care management strategy to avoid early postoperative complications (such as acute rejection, sepsis etc.) (60). Levesque *et al.* measured ICG-PDR in 72 LT recipients in the first 5 days after LT and found that a ICG-PDR cutoff level of approximately 12.85%/minute predicts serious complications. The sequential changes of ICG-PDR indicated early severe complications with low values of around 8.8%±4.5%/minute, and acute rejection activity with a progressive reduction value from 25.5%±4.8% to 10.3%±2.5%/minute (61).

As described before, HAT is the most severe complication after LT. Doppler ultrasonography, which has a high sensitivity (approximately 92%), is the first choice to investigate HAT. Levesque *et al.* used ICG-PDR in conjunction with ultrasonography, and observed that a low value of ICG-PDR with abnormal ultrasound images was usually an indicator of HAT occurrence. Additionally, they found that with a normal value of ICG-PDR, angiography was unnecessary in emergency situations, suggesting that ICG-PDR may be more sensitive than angiography (62). Sun *et al.* also investigated ICG-PDR in 115 LT patients, and found that hepatic arterial complications and rates of pneumonia were higher in the ICG-PDR <18%/minute group compared to a control (63). Collectively, these studies show that the ICG clearance rate can provide a reliable, convenient, and low-cost postoperative test to predict mortality and surgical complications. According to the ICG clearance rate results, doctors can detect, prevent, or alleviate complications. ICG-PDR may be a good additional tool for physicians to use in their treatment plan.

Detecting graft function and regeneration by ICG clearance tests

Measuring the early function of grafts after LT can help strengthen clinical management and further improve transplant outcomes. Some laboratory indicators such as the aspartate aminotransferase (AST), alanine aminotransferase (ALT), pH, and prothrombin time (PT) can reflect the function of the graft to a certain extent, but they are not representative. ICG clearance tests can be used as complementary tests to predict graft functionality by evaluating functional hepatocyte levels and effective hepatic blood flow. Vos *et al.* reported that ICG-PDR can accurately predict early graft function (64). Hori *et al.* assessed the reliability of KICG (ICG elimination rate constant) value up to 28 days after LDLT. In the first 24 hours after LT, there were already significant differences between recipients with or without good graft function, reflecting different effective hepatic blood flow rates, which is crucial for liver regeneration (65). Liver regeneration after LDLT closely affects the transplant response in both donors and recipients. Jochum *et al.* used functional tests such as galactose elimination capacity (GEC), lidocaine half-life and ICG half-life as biomarkers to evaluate liver regeneration in the first 3 months after LT in both donors and recipients. The results showed that ICG and GEC

differed significantly between donors (ICG, –9.1%; GEC, +59.3%) and recipients (ICG, –63.7%; GEC, +16.3%), and the lidocaine half-life showed no significant changes (66), which suggests that ICG can be reliably used to test postoperative liver regeneration.

Evaluating optimal systemic hemodynamics by ICG kinetics

Systemic hemodynamic changes cause long-term portal hypertension in patients with advanced cirrhosis. Even after transplantation, this situation is difficult to alleviate (67). PVF is affected by systemic hemodynamics, and excessive PVP can cause LT failure. Timely and accurate assessment of systemic hemodynamics to regulate PVF is important for the success of transplantation.

Conclusions

To assess liver function and prevent surgical complications, ICG offers many advantages in LT compared to other available approaches. It is effective at low doses, metabolized rapidly, and has no known limitations in assessing liver function compared to other methods, with the exception of detecting hyperbilirubinemia. Unlike existing methods, such as ultrasound or biochemical testing, ICG testing can be conveniently performed at the patient's bedside in real-time.

ICG is a non-toxic, low cost, widely available, and effective fluorescent dye. It emits light in the near-infrared spectrum, which permits relatively deep tissue penetration. Following intravenous injection, ICG attaches to plasma proteins and allows for easy detection of blood perfusion in real-time. Moreover, ICG is efficiently and selectively taken up by hepatocytes, and can accurately predict liver function preoperatively, intraoperatively, and postoperatively. Preoperatively, ICG detection and clearance rates can provide clinical data on the status of potential surgical candidates, which can help expedite the waiting list. Additionally, ICG can accurately evaluate graft function, so that grafts predicted to be high-risk or ineffective can be avoided. Intraoperatively, surgeons can use ICG to detect anastomosis of the bile duct and blood vessels, which can help prevent biliary leaks and other related complications. Postoperatively, ICG clearance rate can predict early mortality and complications, evaluate graft function and regeneration, and help avoid failures caused by post-transplant complications. The metabolic function of ICG combined with PVF can quantify liver regeneration postoperatively to prevent early complications and help perform appropriate perioperative interventions and management. ICG kinetics evaluate the optimal systemic hemodynamics to increase the success of transplantation.

In short, ICG can be used for various stages of LT, offering unique advantages. We suggest ICG can and should be routinely used in LT to help re-organize the transplant waiting list and improve the surgical outcomes of LT patients.

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Footnote

Reporting Checklist: The authors have completed the Narrative Review reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-21-6650/rc

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