Editorial Commentary

Indocyanine green fluorescence imaging technology in minimally invasive liver resection

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Comment on: Marino MV, Podda M, Fernandez CC, *et al.* The application of indocyanine green-fluorescence imaging during robotic-assisted liver resection for malignant tumors: a single-arm feasibility cohort study. HPB (Oxford) 2020;22:422-31.

Received: 29 April 2020; Accepted: 12 May 2020; Published: 25 January 2021.

doi: 10.21037/ls-20-88

View this article at: http://dx.doi.org/10.21037/ls-20-88

The recent introduction of smart fluorescence imaging technology has initiated a paradigm shift in surgery with significant potential to enhance safety and surgical outcome with a concomitant reduction in health care expenses (1). In particular, the ICG fluorescence imaging system under infrared light has found a myriad of surgical applications e.g. the identification of sentinel lymph nodes in both gastrointestinal and lung malignancies, the evaluation of adequate perfusion after cardiovascular grafting apart from several applications in the field of liver surgery (2-6). In 2008, we were the first to demonstrate the use of ICG fluorescence in hepatic segmentation mapping during anatomical liver resections (ALRs) (2). ICG uptake by hepatocytes and its biliary excretion are the basis for the characteristic ability of ICG to demarcate hepatic segments (2). Subsequently, the role of ICG as real time cholangiography was reported by Ishizawa *et al.* (3) and further reports about the value of ICG in intraoperative identification of subcapsular hepatic lesions (4) and the securing of surgical margins (5) as followed. A significant advancement in ICG fluorescence imaging was achieved by the recent addition of near-infrared fluorescence (NIR). This combination constitutes a novel real time navigation system during both open and laparoscopic (2,7) as well as robotic hepatobiliary surgery (8).

Marino *et al.* report the first case series evaluating the application of ICG fluorescence imaging in robotic-assisted hepatic resections. Using the Da Vinci Robotic Xi™ Surgical System (Intuitive Surgical Inc.®, Sunnyvale, CA, USA), they performed 40 consecutive ALRs by either systemic venous ICG injection (2.5 mg) after clamping the portal vein to the tumor-bearing segment (negative staining technique) or direct portal puncture and injection of 0.25 mg/mL (total 2.5 mg) of ICG (positive staining technique). Both, the positive and negative staining technique were preceded by dissection of the designated Glissonian pedicle. In addition, ICG retention test was performed 5 days before surgery. The positive staining technique required a higher number of attempts to insert the needle into the portal branch for ICG injection, and the demarcation rate of liver segment boundaries by the positive and negative staining technique was 80% and 95%, respectively. The negative staining technique mostly provided uniform and reproducible staining even in patients with cirrhosis, whereas in the positive staining technique, ICG gradually spread widely to the entire liver after injection, and the boundaries of the target segments became indistinct during surgery. R0 resection could be achieved in all cases, and ICG fluorescence imaging detected six new malignant lesions that were missed by white-light exploration and intraoperative

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ultrasonography (IOUS). Seven further lesions were not identified by intraoperative ICG fluorescence but only ICG fluorescence of the resected specimens and by microscopic examination. Analysis of the features of these lesions revealed the depth of their location as the common factor. Regarding the fluorescence pattern of liver tumors at intraoperative inspection, full correspondence between the total-types and well-differentiated HCC, as well as between CRLM and rim-types was found. The 2-year overall and disease-free survival rates were 84% and 65%, respectively. In the majority of cases during major hepatectomy, ICG fluorescence cholangiography indicated the confluence of the left and right hepatic duct at the hepatic hilum. Extrahepatic biliary structures were not visualized by ICG fluorescence cholangiography in a few cases caused by obstructive jaundice or liver dysfunction.

Marino *et al.* described four key points. ICG fluorescence imaging was helpful to perform safe and accurate robotic ALRs with (I) the clear identification of liver segment mapping, (II) the detection of subcapsular hepatic tumors, (III) securing surgical margins and (IV) intraoperative cholangiography.

The clear identification of liver segment mapping

Recently, laparoscopic hepatic surgery has been rapidly expanding due to the inherent advantages of a minimally invasive approach. With the development of surgical skills and devices, laparoscopic liver resection can be performed for any segment of the liver (9). However, just like in the open approach, laparoscopic ALR requires segmental liver mapping. The application of ICG staining in robotic-assisted hepatectomies emphasizes the continued necessity for segmental liver mapping.

In 1985, Makuuchi pioneered in open ALR achieved through IOUS guided indigocarmine injection into the portal pedicle supplying the territory harboring the malignancy (10). Indigocarmine injection can stain all segments, but its early wash-out (within a few minutes) limit its ability to delineate the intersegmental planes for accurate parenchymal transection. Alternatively, the Glissonean approach was first described by Takasaki *et al.* (11) in which the designated portal branch is dissected and ligated, marking the target segment as an area of ischemia. However, demarcation of the intersegmental plane of cleavage is difficult to visualize with this technique. In contrast, ICG fluorescence under infrared light, could not only identify the surface demarcation of the hepatic segment but also the intersegmental planes (2,12). We have reported that this technological innovation holds promise as real-time navigation during ALR.

Ishizawa *et al.* demonstrated two available options for ICG staining, the so called, positive or negative staining techniques for segment delineation using a laparoscopic ICG fluorescence imaging system during minimally invasive hepatic resections (7). Laparoscopic positive segmental staining entails portal puncture through the liver surface using a long needle under sonographic guidance. Slow injection of ICG solution into the portal vein avoiding too much pressure is warranted. Otherwise, back flow of ICG into branches supplying neighboring segments and their undesired fluorescence may occur. If the portal radicles to the segment are multiple or too small rendering direct puncture difficult or impossible, the portal branch of the adjacent hepatic segment can be punctured and injected with ICG to identify the segment boundary (13) (counter staining technique). Marino *et al.* described that the positive staining technique is more challenging and therefore required more attempts to successfully insert the needle into the portal branch for ICG injection. This finding raises an important aspect. Although the positive staining technique is the original concept used by Makuuchi *et al.* and our study group, who first described ICG for liver segmentation in open surgery, transfer of this concept into the laparoscopic setting represented a significant challenge. Creating an accurate trajectory passing first through the abdominal wall, then through the laparoscopic IOUS probe on the liver surface visualized on the laparoscopic monitor and lastly through a vessel visualized on the sonography screen is definitely challenging. This drove us to develop the simple and convenient "preoperative positive staining" technique for laparoscopic ALR in which we percutaneously inject 0.025 mg/mL ICG under B mode trans-abdominal US guidance after general anesthesia induction and immediately prior to induction of the pneumoperitoneum (12). This preoperative positive staining is effective and simple. It creates both a segment mapping on the liver surface and intersegmental planes enhancing the safety and accuracy of laparoscopic ALR.

The role of positive staining becomes evident when considering segmentectomies or subsegmentectomies especially of the posterosuperior hepatic segments as laparoscopic Glissonian dissection (as part of the negative staining technique) of third and 4th order portal branches is difficult and associated with the risk of biliary and vascular

injury. Therefore, the possibility to puncture the distally located Glissonian pedicle directly either under trans abdominal or laparoscopic ultrasound guidance without the need for prior Glissonian dissection represents an attractive staining alternative. In fact, one of the advantages of robotic-assisted hepatic resections is the facilitated minimally invasive access to the so called difficult segments (posterosuperior segments). The integration of both the Firefly mode and ultrasonography into the robotic platform might play a role in overcoming the challenges encountered during the positive staining method.

As for the dosage of ICG, 0.025 mg/mL has been stated as suitable for positive staining (7,12). According to Marino *et al.* the dye (dosage of ICG; 0.25 mg/mL) gradually disappeared from the target segment to diffuse into the whole background liver. This phenomenon may be related to the relatively high dose they used.

In the negative staining technique, dissection of the Glissonian pedicle is performed. After its clamping and interruption of blood flow to the cancer-bearing portal territory, intravenous ICG is administered. In the negative staining technique, the target area is identified by its lack of ICG fluorescence. Marino *et al.* described that the negative staining technique provided uniform and reproducible staining even in patients with cirrhosis. However, when performing negative staining technique in patients with cirrhosis, it is difficult to access to Glissonian sheath. Thus, caution to avoid biliary injury and intraoperative bleeding is warranted. In both, the positive and the negative staining technique, the plane between the fluorescent and the non-fluorescent parenchyma can be easily seen on both the hepatic surface and during intersegmental parenchymal transection. ICG fluorescence usually remains visible throughout the whole surgical intervention (12).

In the near future, we need further study to refine the IOUS guided surgical puncture method during minimally invasive surgery.

Detection of subcapsular hepatic tumor

Intraoperative identification and localization of subcapsular liver tumors by the NIR fluorescence imaging system is one of the important functions of ICG. ICG clearance into the biliary system is impaired in malignant hepatocytes or liver tissue compressed by tumor. This retention property facilitates tumor detection after preoperative intravenous ICG injection (4). With NIR fluorescence imaging in laparoscopic hepatectomy, detection rates between 77.8% and 100% are quoted (4,5,14-16). Marino *et al.* report 11.5% newly detected lesions which could not be detected by either preoperative CT and MRI or IOUS. This result is in concordance with the findings of other authors stating that NIR fluorescence imaging is particularly useful to detect lesions after chemotherapy (16-18) and also new lesions that have not been identified by other diagnostic modalities (4,14-17,19). However, as mentioned by the authors, there were three false positive lesions whose pathology turned out to be benign such as hemangioma and steatosis. Indeed, NIR fluorescence imaging is associated with a relatively high false-positive rate of 38–50% (4,14,15). Moreover, tumors located deeply within the liver parenchyma are difficult to visualize (4). Yet, with the continuous development of new florescent target-specific tracers e.g., antibodies, the drawback of the high false positive rate could be overcome and thus become an integral part in the diagnosis and treatment of hepatic malignancies.

Secure the surgical margin

The authors achieved an R0 resection in all cases. A previous report from our study group along with reports from several other authors provides evidence for the usefulness of NIR fluorescence imaging in securing an adequate surgical margin during parenchymal transection (5,19-21). The fluorescence exhibited either within or around the lesions provides very valuable visual guidance during hepatic transection. The authors state that they readjusted their planned transection line in 12 out of 40 cases. NIR fluorescence imaging serves to determine and modify the transection plane making sure not to expose tumor fluorescence (5). Absence of residual fluorescence in the liver bed after tumor resection is an indicator of reduced risk of surgical margin positivity. Therefore, frequent verification of the complete removal of all fluorescent tumor tissue is warranted.

Intraoperative cholangiography

The biliary excretion of ICG render it useful for intraoperative cholangiography permitting detection of biliary leakage and real-time delineation of biliary tract anatomy especially during biliary reconstruction. The implementation of NIR fluorescence cholangiography for intraoperative visualization of biliary anatomy during hepatic and transplant surgery was first reported by Ishizawa

in 2009 (3). In 2019, Dip *et al.* provided statistical evidence for the superiority of NIR fluorescence cholangiography over while light alone in laparoscopic cholecystectomy in terms of extra hepatic biliary delineation (22). The first report of NIR fluorescence cholangiography during robotic cholecystectomy by Buchs *et al.* (23) confirmed its usefulness in identification of biliary structures specially that the NIR fluorescence camera is integrated in the robotic platform. Fluorescence cholangiography is simple and convenient and creates a real-time anatomical roadmap guiding biliary dissection to avoid injury. However, obstructive jaundice and hepatic dysfunction affecting biliary excretion of ICG limit its utility as real-time intraoperative cholangiography. Furthermore, the optimal dosage and timing for ICG injection are yet to be determined.

In conclusion, ICG fluorescence imaging technology constitutes an excellent intraoperative navigational tool enhancing the safety and accuracy of open, laparoscopic and robotic hepatic surgery. The implementation of ICG fluorescence imaging in the robotic approach could be facilitated by the integration of IOUS in the robotic platform, the fully wristed dexterity of its instrumentation and microdissection capabilities and therefore potentially overcome the challenges of laparoscopic liver resection.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the editorial office, *Laparoscopic Surgery*. The article did not undergo external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/ls-20-88). The authors have no conflicts of interest to declare.

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

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doi: 10.21037/ls-20-88
Cite this article as: Aoki T, Koizumi T, Mansour DA, Tomioka K, Murakami M. Indocyanine green fluorescence imaging technology in minimally invasive liver resection. Laparosc Surg 2021;5:13.