# The application of indocyanine green fluorescence as imaging modality during robotic liver surgery

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The indocyanine green (ICG) is a safe and highly available fluorophore that emits a fluorescence signal after being illuminated by a specific laser source (Near Infrared Light). This signal has the potential to enhance the visualization of biological structures and to improve the understanding of an organ's perfusion (1).

While, the identification of the extrahepatic biliary anatomy and the vascular assessment of anastomotic site during visceral surgery has already gained momentum in the surgical community, the application of ICG in liver surgery is still in its explorative phase (2).

Initially adopted in 1985 as a reagent for estimating hepatic function, intraoperative application of the ICG did not begin until the late 2000s (3). Currently the three main fields of ICG applications in liver surgery are: the intraoperative visualization of the biliary tree, the identification of liver tumors and finally demarcation of the hepatic segment boundaries (4).

The biliary anatomy identification relies on the exclusive hepatic metabolism of the ICG, which is excreted from the biliary tree approximately 30 minutes after the intravenous injection. This property allows a clear visualization of the biliary tree in several challenge scenarios, such as in case of difficult cholecystectomy, centrally located liver or biliary tract (Klatskin) tumors and finally in case of anomalous biliary confluence during major hepatectomies (5).

Despite the potential benefits in terms of reducing biliary leaks, there is still some debate regarding the ideal time for intravenous injection of ICG, which can result in an unclear visualization of the biliary tree (if administered too late) or a fluorescence background-effect of the liver parenchyma (if administered too early). The ICG offers evident benefits compared to the intraoperative cholangiogram, in fact the process is not time consuming and is not associated with exposure to ionizing radiation, it also does not require a dissection of the Calot triangle and the cannulation of the cystic duct (6).

During the early experience in liver surgery, ICG was observed to accumulate in the cancerous tissues of hepatocellular carcinoma (HCC) and in the no-cancerous hepatic parenchyma around adenocarcinoma foci (7). Practically in the case of HCCs, the ICG is strongly captured and retained by malignant hepatocytes, while its secretion is highly impaired thus leading to "total-type" fluorescent pattern.

Conversely due to the high necrotic component, colo-rectal liver metastases (CRLMs) are visualized as "rim-type" patterns, as the ICG is retained by a group of hepatocytes surrounding the necrotic nodule. In the cholangio-carcinomas (CCCs), the ICG is not fully uptake by the biliary duct cells and it is partly retained due to alterations in the biliary delivery process, thus creating a "partial-type" image.

Unfortunately, although tumor behavior is a promising and interesting field of investigation, there are no accepted guidelines for differentiating malignant lesions based on the fluorescent model. Intrinsic vascularization, nodal behavior in the portal phase and timing of intravenous injection can both modify the final distribution of ICG within liver tumors (8).

The potential is enormous, ICG fluorescence can be

used for the detection of small superficial malignant nodules not detected preoperatively, or to guarantee a complete tumor resection such as absence of fluorescence to the liver remnant and finally to evaluate the resection margin as distance from the fluorescent tumoral border during the parenchymal transection (9).

These capabilities can overcome the limitations in tumor detection found in patients undergoing multiple cycles of chemotherapy or cirrhotic liver and in the case of laparoscopic surgery in which the execution of intraoperative ultrasound is both challenging and time-consuming.

According to the literature, the tumor detectability varies from 70% to 92% even in large laparoscopic series (10,11) but unfortunately the technique is associated with a high-false positive rate (40%) (8). These results open the way for a broad debate and several questions still remain unsolved. Should all newly detected tumors be removed? Or maybe just the one associated with a strong fluorescent signal? Do we still need regular use of IOUS?

The boundaries of hepatic segments can be identified prior to the liver transection, with the rationale to increase the number of anatomical resections and therefore improve the oncologic outcomes (12).

The dye-staining techniques allow identification of the portal vein territory, by injecting the ICG solution into the corresponding tumor-bearing portal pedicle (positive staining) or by injecting into a systemic vein after clamping of the corresponding tumor-bearing portal pedicle (negative staining) (13).

The ICG-staining method has achieved great consensus by providing good results in both cirrhotic *vs*. no-cirrhotic livers, it has achieved a high rate of identification of the borders of the liver segment (90%) thus overcoming the historical limits of the indigo-carmine solution (13). Unfortunately, there is no standardized technique in the ICG injection method (14). In this dynamic scenario, the robotic surgery has spread rapidly thanks to the opportunity to integrate different sources of information and technologies into the same platform. The software for near-infrared light visualization (FireFly™) is integrated into the robotic system and it can easily be activated from the surgeon's console. This approach allows for a real-time visualization of anatomical structures and it pushes surgeons towards true real image-guided surgery.

In our experience, application of ICG during robotic liver surgery, reduced postoperative bile leakage (P=0.023) post-

hepatectomy liver failure (P=0.035) and readmission rate (P=0.023) compared to patients undergoing standard robotic liver resection (without ICG). The R1 resection rate was zero among patients undergoing ICG application, while the overall resection margin was lower (13 *vs*. 22 mm, P=0.018) confirming the usefulness in terms of parenchymal-sparing. The adoption of the ICG increased the number of tumors detected compared to those discovered during preoperative work-up (34 *vs*. 28) but unfortunately only six out of eight (75%) of newly discovered tumors were malignant at the final histopathology. These tumors, ranging from 3 to 8 mm, were all located within 8 mm of the liver surface. The postoperative observation of the liver specimen trough photodynamic emission camera revealed a total of 37 tumors, therefore three more than the intraoperative use of ICG. The oncologic outcomes of the two groups of patients (ICG *vs*. no-ICG) were similar in terms of overall (89% *vs*. 87%) and disease-free survival (72.5% *vs*. 69%) (6).

According to our experience, we observed a good correlation between the rim-type and fluorescent-type pattern and CRLMs and well-differentiated HCCs, in the meantime the partial-type showed a great heterogeneity to the final histopatological diagnosis. The staining method was assessed by an internal questionnaire which confirmed that the negative technique was easier to adopt and also it provided a greater satisfaction and comfort to the surgeon than the positive one (4). The clarity of the images was judged superior after the negative staining technique although it required a longer time for the demarcation of the territory to be visible on the surface of the liver (375 *vs*. 90 seconds).

However, our studies have important drawbacks such as the small sample size, the short follow-up period and the single-institutional settings but it represents the first comparative study that addresses the application of ICG in robotic liver surgery.

In conclusions, the ICG is a tantalizing approach that presents some drawbacks in terms of limited penetration depth (up to 8 mm) and high-false positive rate in terms of tumor identification; more over it is still not clear what the ideal dose and timing of injection are. Numerous studies are currently addressing the usefulness of ICG as photodinamyc therapy for the treatment of HCC, and cancer-specific fluorophores will soon be available which will pave the way for the adoption of image-guided surgery (15).

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.

## Footnote

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