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Review

Fluorescence guided surgery in liver tumors: applications and advantages

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Summary. The use of fluorescence-guided surgery for benign and malignant hepatobiliary (HPB) neoplasms has significantly increased and improved imaging methods creating new interesting perspectives. A major challenge in HPB surgery is performing radical resection with maximal preservation of the liver parenchyma and obtaining a low rate of complications. Despite the developments, visual inspection, palpation, and intraoperative ultrasound remain the most utilized tools during surgery today. In laparoscopic and robotic HPB surgery palpation is not possible. Fluorescence imaging enables identification of subcapsular liver tumors through accumulation of indocyanine green (ICG), after preoperative intravenous injection, in cancerous tissues of hepatocellular carcinoma and in noncancerous hepatic parenchyma, around intrahepatic cholangiocarcinoma and liver metastases, and it can also be used for visualizing extrahepatic bile duct anatomy and hepatic segmental borders, increasing the accuracy and the easiness of open and minimally invasive hepatectomy. (www.actabiomedica.it)

Key words: liver, fluorescence, indocyanine-green, surgery, tumors

Introduction

Since its approval (1954) by U.S. Food and Drug Administration, Indocyanine green (ICG) has been widely employed in many different clinical settings. At the beginning, it has been helpful to evaluate cardiac output and liver function.

In the 1970s, protein-bound ICG was found to emit fluorescence, peaking at about 840 nm, under illumination with near-infrared light (750–810 nm) (1).

Then ICG was initially clinically used for ocular fundus angiography in the early 1990s (2). With the advances in technology over the recent years, ICG fluorescence imaging has received significant interest for use in various surgical procedures, i.e. to detect lymphatic flow in the extremities (3), sentinel lymph nodes in patients with breast (4) and gastrointestinal cancers (5), to evaluate blood flow during coronary artery bypass grafting (6) and clipping of cerebral artery aneurysms (7).

Primary liver cancer and liver metastases of colorectal cancer are among the most common leading causes of cancer-related death worldwide (8) and surgery represents one of the main treatments to obtain the best results in overall and disease free survival.

Over the last few decades, imaging technologies in hepatobiliary (HPB) surgery such as ultrasonography (US), computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) have become indispensable tools for preoperative planning in surgical procedures. During interventions, in liver surgery, the surgeon must recog-

nize vital anatomical structures and, in case of tumor, discriminate between lump and healthy tissue by visual inspection and palpation. Although in some cases intraoperative imaging modalities such as US or cholangiography can be applied. Irradical (R1) oncologic resections and iatrogenic surgical injuries are still major issues in hepatobiliary surgery.

Real-time visualization of the liver and localization of hepatic tumors can help surgeons to perform therapeutic liver resections even with sparing parenchyma hepatectomies, thereby reducing post-operative complications.

During development of fluorescence cholangiography, it has been observed that ICG accumulates in primary tumor liver cells and around adenocarcinoma mass, thereafter a new imaging technique has taken place.

ICG fluorescence imaging (FI) technique helps to guide the hepatic surgical procedures and provides the surgeon with real-time visualization of the fluorescent structures of interest that would be invisible under conventional white light. The extrahepatic bile duct anatomy and liver tumors can be emphasized, and hepatic segments highlighted, based on the fluorescence property of ICG and its biliary excretion.

The aim of this paper is to report useful aspects in the practice about this imaging technique in HPB surgery, and showing the concept and the technical bases of fluorescence imaging, by summarizing its practical and technical aspects, and describe the features of the images that can be obtained, and the limitations of its use in hepatic surgery.

Useful indocyanine green features

Indocyanine green, is a hydrosoluble molecule (disulfonated heptamethine indocyanine) with the characteristics of fluorescent dye. Its metabolic properties of intravascular confinement, binding plasma and bile high molecular weight proteins (eg. albumin, lipoproteins), that are not metabolized, and do not alter protein structure, avoid the toxicity of intravenous administration and maintain efficacy at low doses (9,10). Furthermore, thanks to its rapid and biliary excretion, via an active transport system, to its spectral proprieties, and to the development of suitable imaging systems, application of ICG fluorescence has been extended to several surgical fields.

Characteristically, under the action of light, depending on wavelengths, the level of energy of the molecules rises; as soon as the level returns to its basal state, light is emitted. The difference between excitation and emission wavelengths is exploited thanks to cameras equipped with interferential filters to obtain the images.

Fluorescent light is largely attenuated by hemoglobin and water as it traverses biological tissues. Hemoglobin strongly attenuates all wavelengths less than 700 nm (which corresponds in fact to the entire visible spectrum excepting deep red). Water is transparent in visible and near-infrared light but attenuates wavelengths over 900 nm. Therefore, there is a "window" of wavelengths at the limit between deep red and near infrared (700–900 nm) where tissue transparency is maximal. This is one of the reasons why ICG fluorescence can be detected in the near-infrared zone from as deep as 10 mm from the surface of tissues (11).

In hepatic surgery, the ICG dye has been used to evaluate hepatic function and more recently to outline hepatectomy strategies for oncologic resections (12,13) and to plan hepatectomy in living donor hepatic transplantation (14).

After its intravenous or direct intrabiliary injection (15), imaging techniques based on near-infrared ICG fluorescence, allow the visualization of bile ducts (16-18), as well as primary and metastatic liver tumors during surgery (19,20).

Basically, ICG is administered intravenously before, or even during surgery, in a variable interval time, and lights up the liver surface when illuminated with a near-infrared source intraoperatively. Several studies have reported that an intravenous preoperative ICG administration of 0.25–0.5 mg/kg from 12 hours to 14 days helps to identify tumors by intraoperative fluorescence (21,22). After the injection, tumoral and non-tumoral hepatocytes rapidly take up ICG. Normally ICG is excreted in the bile and disappears from healthy liver parenchyma within a few hours (23). On the other hand, ICG remains fixed in tumoral hepatocytes and in pathological areas of the liver, particularly around non-hepatocellular tumors, where hepatocytes are underactive. The features of the camera allow the detection of

hepatocellular (tumor fluorescence) and non-hepatocellular tumors (peri-tumoral fluorescence), thanks to fluorescent light emitted by withheld ICG.

Apparatus Fluorescence imaging system

Apparatus for fluorescence imaging system (FIS) is a mobile system, which provides real time quantitative fluorescent imaging (Fig. 1). The system includes an infrared camera and an amplifier. The camera simultaneously provides the functions of fluorescence excitation with a laser (LED emitting an infrared radiance) over the operative field, and fluorescence image acquisition is ensured by a captor, which filters the light, so that only near infrared wavelengths can be seen.

The camera and cable do not need to be sterilized. The screen and amplifier are placed sufficiently far away, thanks to the length of the cable; so that a non-sterile person can hold the infrared camera above the sterile operative field.

ICG based imaging

ICG most important uses during hepatobiliary surgery for tumors are: cholangiography, liver mapping, and intra and post-operative tumor detection.

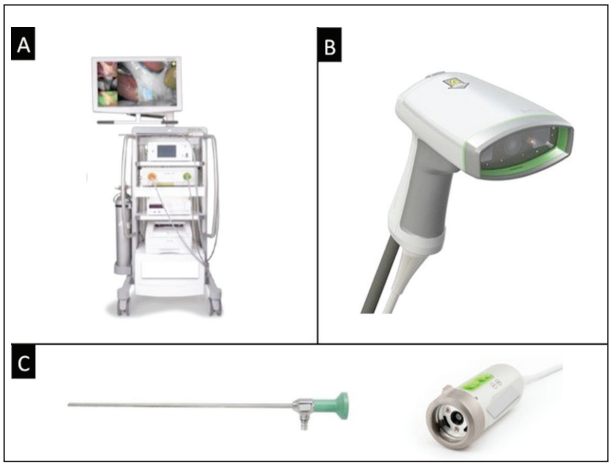

Figure 1. Fluorescence imaging system. The camera includes a laser and a captor: the laser emits a radiance that induces the excitation of fluorescence of the ICG molecules, while the captor filters the light so that near-infrared wavelengths can be seen on the screen. 1A: The system is integrated into a laparoscopic column. 1B: open surgery bundle. 1C: laparoscopic surgery bundle

The main application of fluorescence imaging (FI) ICG-based is the visualization and the study of biliary anatomy. Because of its biliary excretion starting approximately 30 min after intravenous injection, ICG biliary imaging allows a clear visualization of the biliary anatomy, which is useful during difficult cholecystectomies and during resections of centrally located liver tumors and hilar cholangiocarcinoma (17,24). In case of intra-hepatic cholangiography FI-ICG based is limited by depth of the tissue (5–10 mm) (25), nevertheless ICG cholangiography can detect bile duct leakages during hepatectomies, that are missed by other routine tests, like shown by Keiburi et al. in a controlled trial (26).

Anatomic segmentectomy is an essential surgical technique in hepatectomy, balancing cancer curability and postoperative hepatic function. Delineation of liver segments can help surgeons to perform resections based on the exact segmental liver anatomy (27). For this purpose, intra-operative contrast-enhanced ultrasound remains the gold standard for liver mapping (28). Hepatic segments can be identified prior to resection by a dye-staining technique, in which indigo-carmine solution is injected into the corresponding portal branch under US guidance, and segments boundaries are defined as blue staining of hepatic surfaces. However, portal hypertension, in the case of liver cirrhosis, might obstruct conventional liver mapping by US. In contrast, FI allows accurate visualization even in the case of liver cirrhosis (29).

One of the disadvantages to ICG-FI is that tracking the stained plane during dissection of the liver parenchyma is difficult. The fluorescent dye within the targeted segment gradually disappears and is necessary a repeated injection of ICG or temporally clamping the hepatic artery for reducing washout of the dye and permanently visualize the segment. Additionally, a small amount of ICG circulates through the body after injection into the portal vein branch, which eventually stains the entire liver. To avoid these problems, intermittent periods of inflow clamping using the Pringle maneuver are recommended (30). This obtains continuous fluorescence imaging during the operation and allows persistent visualization of the segmental boundaries (31).

Detection of lesions by fluorescence is based on the contrast between tumoral or peri-tumoral fluores-

cent tissues and the rest of the non-fluorescent liver tissue. The observation that hepatocellular carcinoma (HCC) and colorectal metastases (CLL) were detectable by infrared light after ICG was administered intravenously as part of a routine pre-surgical liver function test has been employed in the clinical setting of intraoperative detection of liver tumors (20,32). Moreover, fluorescence patterns are related to the type of cancer and its grade of differentiation (22). Moreover, fluorescence patterns are related to the type of cancer and its grade of differentiation. Injured bile excretion in HCC cells means that ICG is retained, therefore well-differentiated HCCs can be detected by strong, homogenous fluorescence emissions. In contrast, in poorly-differentiated HCCs and metastases ICG is retained in the parenchyma cytoplasm. This means that poorly-differentiated HCCs and CLL produce rim type fluorescence patterns (Fig. 2).

A single dose of ICG (generally 0.5 mg/kg) for routine liver function tests, administered within 14 days prior to surgery, is sufficient to identify tumors by fluorescence imaging.

Normal liver tissue can rapidly uptake ICG, which it is usually eliminated in bile; however, severely cirrhotic liver tissue may not be able to eliminate ICG.

Among limits for viewing tumors using FIS-ICG, there's limited depth of infrared light penetration and tissue thickness. Both affect the fluorescence intensity. Infrared light can only penetrate 5–10 mm of tissue and deeper lesions cannot be visualized. Kudo et al. (33) showed that tumors located 8 mm or more from the liver surface could not be identified, both resected liver metastasis and HCCs. Kudo in his study, evidenced that only tumors that were 5 mm or closer to the liver surface were observable by ICG-FIS.

The study from Peloso A., et al. in 2013 (34) gives preliminary clinical evidence that the intraoperative use of ICG fluorescence can improve detection of CLL, particularly in case of very small lesions, which are frequently missed with conventional imaging modalities.

Literature data highlight the usefulness of fluorescence guided surgery to detect new tumors not diagnosed by preoperative imaging. Handgraaf et al., in their retrospective analysis (35), observed that the percentage of patients in whom additional lesions were identified during surgery was significantly higher by near infrared fluorescence imaging in addition to inspection, palpation or intraoperative ultrasound and the diameter of the lesions identified by fluorescence were smaller than lesions detected by conventional diagnostic procedures.

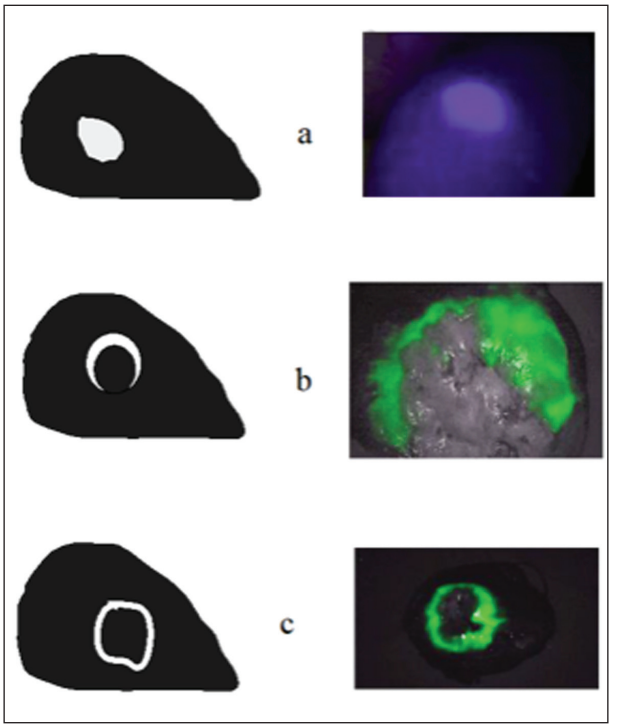

Figure 2. Schematic visualization of liver lesions by FIS. A - homogeneous fluorescence (tipical aspect of well differentiated HCC); B - partial fluorescence (visualized in moderately differentiated HCC); C - peri-tumoral fluorescence (fluorescent ring in poorly differentiated HCC, colorectal liver metastasis, cholangiocarcinomas)

On the other hand, malignant tumors cannot be distinguished from benign tumors, thus leading to a high false positive rate.

Conclusions

The development of more specific molecular tracers should help finding new indications for the application of fluorescence guided surgery. Molecular information provided by this technique could present a paradigm change in decision-taking during resection.

On the other side there has been a steady growth in commercially marketed systems, each with their

own differentiated performance characteristics and specifications (36).

Intraoperative fluorescence imaging will develop into an essential navigation tool, particularly in laparoscopic and robotic liver surgery. This trend will allow surgeons to personalize the procedures according to cancer spread, anatomical variations, and risks of complications.

In these perspectives, procedural protocols should be uniformed for different fields of application. Timing of injection and optimal dosage of ICG are important issues for the standardization of the technique. Some authors have suggested to inject ICG before surgery, and time interval ranged from 1 to 14 days, while others proposed an intraoperative injection (37,38). Most authors prefer to inject ICG 24 hours before surgery, in order to consistently reduce physiological hepatic uptake and to allow the drug to concentrate in the tumor, and 0.5 mg/kg represents the most commonly used dose.

Even administration routes of ICG were differently applied, related to preoperative or intraoperative ICG use (e.g. portal vein or right vein of the stomach, central venous catheter, or peripheral vein) (39).

ICG-fluorescence imaging can be used safely and easily to identify liver tumors, hepatic segments, and extrahepatic bile ducts, in real time during open and minimally invasive surgery.

Despite the various benefits of FI-ICG based in hepatobiliary surgery, there are some drawbacks; these include limited tissue penetration and poor specificity. Intraoperative US remains the goal standard for detection of deeper tumors and FI-ICG based is complemental.

In the literature the high incidence of false positives in tumors detection (about 40%) (19,40) is evident, mostly in liver cirrhosis.

Further clinical studies are required to assess the sensitivity and specificity of FI-ICG based during hepatobiliary surgery.

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