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Intraoperative ICG-based imaging of liver neoplasms: a simple yet powerful tool. Preliminary results

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Abstract

Background Detecting small nodules that are grossly unidentifiable remains a major challenge in liver resection for cancer. Novel developments in navigation surgery, especially indocyanine green (ICG)-based fluorescence imaging, are making a clear breakthrough in addressing this issue. ICG is almost routinely administered during the preoperative stage in hepatobiliary surgery. However, its full potential has yet to be realized, partly because there are no precise guidelines regarding the optimal dose or timing of ICG injections before liver surgery. The main goal of this study was to design an algorithm for the management of ICG injections to achieve optimal liver staining results.

Methods Twenty-seven consecutive, unselected patients undergoing liver resection for cancer were enrolled and underwent preoperative liver function assessment by the LiMON test. Extra ICG i.v. injections at different doses and timings were performed. In vivo intraoperative analysis of the stain detected by near-infrared fluorescence imaging of the liver and ex vivo analysis of each resected nodule was performed and compared to the pathological analysis.

Results (i) The success rate of ICG injections in terms of liver staining was 92.6%; (ii) in the absence of or with 7 or more days from a previous ICG injection, the best dose to inject before the operation was 0.2 mg/kg, and the best timing was between 24 and 48 h before the scheduled surgery; and (iii) the ICG fluorescence patterns observed in the tumors were total fluorescence staining (41% of the cases), partial fluorescence staining (15%), rim fluorescence staining surrounding the tumor (30%), and no staining (15%).

Conclusions This study is a building block for the characterization of liver nodules and the search for additional surface lesions undetected by preoperative radiological work-up—a crucial task for the successful treatment of liver cancer at an early stage using a safe, minimally invasive, and inexpensive technique.

Keywords Fluorescence imaging · Intraoperative imaging · Indocyanine green · Liver cancer · Navigation surgery

Liver resection plays a leading role in the treatment of hepatocellular carcinoma (HCC) and metastases of colorectal carcinoma (CRC). One of the main challenges in liver surgery remains the intraoperative diagnosis of small tumors, especially those with indistinct margins, which can be detected only by microscopic examination; hence, these grossly unidentifiable liver cancers may be overlooked during the intraoperative and even the pathological analysis. Therefore, intraoperatively identifying small tumors is a task of paramount importance for the successful treatment of liver cancer at an early stage.

Recent developments in intraoperative imaging techniques using indocyanine green (ICG) are enhancing the accuracy of liver resection and the pathological diagnosis of small liver cancers. ICG-based fluorescence imaging is based on the principle that protein-bound ICG emits light with a peak wavelength of approximately 835 nm when illuminated with near-infrared (NIR) light (750–810 nm) [1]. In the past 15 years, ICG-based fluorescence imaging has

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become a widespread and useful tool in several medical and surgical specialties. Published studies have promoted it as an effective intraoperative method for evaluating visceral perfusion before anastomosis [1], visualizing biliary anatomy during complex cholecystectomies [2], detecting lymphatic flow in the extremities [3], finding sentinel lymph nodes in patients with melanoma and breast cancer [4–6], and facilitating nodal dissection in gastric cancer [7]. In contrast, in hepatobiliary surgery, the state of the art with regard to ICG-based fluorescence imaging considers ICG mainly as a simple reagent for the preoperative evaluation of hepatic function.

The comparatively limited use of ICG-based fluorescence imaging in hepatobiliary surgery with respect to other surgical specialties is slightly puzzling considering that this technique is highly suitable for this branch of surgery because of the exclusive biliary excretion of ICG. During the development of fluorescence cholangiography, ICG was found to accumulate in HCC tissue and in noncancerous hepatic parenchyma around adenocarcinoma foci. The first application of this imaging technique was reported in 2009 in seminal studies by Ishizawa et al. [8] and Gotoh et al. [9]. Because its application in hepatobiliary surgery is still in its infancy (the existing studies have tested different doses and timings), clear guidelines regarding the best dose, timing, and site for administering ICG are still missing and would be very welcome in light of its extensive potential clinical advantages compared to its simple and inexpensive use [10, 11].

This study reports the preliminary findings of the first step of a project whose overarching goal is to evaluate the usefulness of ICG-based fluorescence imaging for the intraoperative identification of liver nodules, especially those that are grossly unidentifiable. More specifically, the project comprises the following three steps: (i) identification of the best dose and timing of ICG injections focusing on the preoperative liver function evaluation test to correctly differentiate nodule and liver tissue; (ii) the characterization of liver nodules compared with the preoperative diagnosis, radiological features, intraoperative in vivo and ex vivo staining patterns, and final pathological report for each nodule; and (iii) the identification of additional surface lesions undetected by preoperative radiological analysis.

Materials and methods

Ethics/study approval

Informed consent was obtained from each patient included in the study. Experimental protocols conform to the ethical guidelines of the 1975 Declaration of Helsinki (6th revision, 2008) as reflected in the prior approval by the Institutional Review Committee of the Department of Clinical and Experimental Sciences at the University of Brescia. The protocols also meet the Italian Guidelines for clinical research.

Patients

The subjects comprised 27 patients (7 women and 20 men, mean age of 68.2 ± 9.0 years) with liver tumors who had undergone liver resection at Brescia University Hospital (Spedali Civili di Brescia) in Italy between November 2016 and April 2017. Contraindications to ICG injection (e.g., allergy to iodinated contrast medium, thyroid dysfunction) were the only exclusion criteria [12].

Before surgery, all patients underwent abdominal ultrasonography (US), contrast-enhanced helical computed tomography (CT), or magnetic resonance imaging (MRI) examinations. Table 1 summarizes the main characteristics of the patients and the surgical procedures. Twenty-four patients underwent the LiMON test, a noninvasive measurement of liver function based on ICG elimination after i.v. injection. Liver tumors included HCC, cholangiocarcinoma (CCC), and CRC. A normal liver was observed in 30% of the patients. All surgical procedures were performed by specialized liver surgeons.

Table 1 Patient cohort ($n = 27$) and surgical procedures

	HCC	CCC	CRC	Total	Percentage
Patients	19	3	5	27	–
Male	17	1	4	22	81.5
Female	2	2	1	5	18.5
Liver characteristics					
Cirrhosis	12	0	1	13	48.1
Chronic hepatitis	4	1	0	5	18.5
Chemo dysfunct.	0	1	0	1	3.7
Normal liver	3	0	5	8	29.7
ICG R15 < 10%	15	2	5	22	91.6
Nodules					
Single	15	0	4	19	70.4
Multiple	4	1	3	8	29.6
Superficial	6	2	3	11	40.7
Deep	13	0	3	16	59.3
Surgical procedure					
Hemihepatectomy	4	1	1	6	22.2
Bisegmentectomy	3	0	3	6	22.2
Segmentectomy	10	1	0	11	40.8
Limited resection	2	0	2	4	14.8

HCC hepatocarcinoma, *CCC* cholangiocarcinoma, *CRC* colorectal liver metastases

Administration of ICG

Before surgery, 24 out of 27 patients (88.9%) underwent conventional liver function tests and measurements of the ICG retention rate after 15 min (ICGR15—LiMON test) as a necessary step to confirm that the patient could undergo liver resection. The ICG plasma disappearance rate (PDR, %/min) and ICGR15 (%/min) were measured in all patients instantaneously and noninvasively by pulse spectrophotometry after the i.v. injection of a bolus of 0.5 mg/kg of ICG dye (Table 1) [13, 14].

To design an algorithm for setting the best dose and timing of ICG injections as a fluorescence source for intraoperative in vivo and ex vivo specimen analysis, the following steps were undertaken. First, the study group reviewed the existing relevant literature and found that different doses and timings were employed in the available series. Second, before starting to enroll the 27 consecutive patients, the study group experimented with a small number of cases. This pilot stage enabled the exclusion of doses and timings that were clearly not ideal (e.g., the dose was too strong and stained the entire liver, or the timing of the ICG injection was too far away from the scheduled surgery, resulting in no staining). Third, based on what has been learned from both the literature review and the outcome of the pilot stage, the following algorithm was proposed and implemented using the timing of the previous LiMON test as the relevant threshold:

i. No extra ICG injections before the scheduled surgery were performed if the LiMON test had been performed *within* 7 days before the scheduled operation;
ii. When the LiMON test had been performed 7 or more days before the scheduled surgery or had not been performed at all, only 0.2 mg/kg of ICG dye (in distilled water) was injected 24–48 h before the scheduled operation.

ICG-based fluorescence imaging system

The fluorescence imaging system uses an intraoperative infrared camera system that activates ICG with emitted light at a wavelength of 750 nm and filters out light with a wavelength below 810 nm. Both Karl Storz equipment (a NIR/ICG system based on the IMAGE1 Spies camera platform) and Striker equipment (a 1588 Advanced Imaging Modalities [AIM] platform with a specific mode named endoscope near-infrared visualization [ENV]) were employed. Data were transmitted to a personal computer, and fluorescence images were created and stored.

Intraoperative examination

On the day of surgery, after laparotomy, the liver was routinely examined by visual inspection, manual palpation, and intraoperative ultrasonography (IOUS). After mobilization of the liver, the camera imaging head was positioned at a fixed distance of 15 cm above the liver surface to keep the intensity of the emitted signal constant, the surgical lights were turned off, and fluorescence images of the liver surfaces were displayed on a television monitor in the operating room. Newly detected HCCs or metastases were resected whenever possible.

Back-table examination of liver nodules

Once the liver resection was completed, the nodules were sectioned on the back table, and their fluorescence activities were examined by the same infrared photodynamic eye (PDE) camera to study the different patterns of ICG staining. More specifically, surgical specimens were cut to include each tumor's maximum diameter based on gross inspection immediately after liver resection. The cut surfaces were grossly examined and subsequently investigated using the fluorescence imaging system without referring to the pre- or intraoperative findings. Any fluorescing lesions were marked with needles for subsequent microscopic examination if they were larger than 5 mm in size.

Finally, the following data were recorded in a database by senior medical residents participating in this study: patients' demographic characteristics, preoperative imaging procedure (US vs. CT vs. MRI), preoperative diagnosis, ICG dose, ICG injection time, R15, tumor diameter, tumor location and distance from the liver surface, type of liver resection, intensity of tumor ICG staining, type of ICG tumor staining, and final pathological diagnosis.

The intensity and type of ICG tumor staining were analyzed and assessed independently by the lead surgeon (GLB) and two senior medical residents (MSA and SM) belonging to the surgical team. More specifically, the three specialized surgeons independently examined the intraoperative images of the liver surface and the postoperative images of the surgical specimens of the liver nodules on the back table and assessed whether the tissues could be categorized with one of the following three types of fluorescence proposed by Ishizawa et al. [8]:

(i) *Total fluorescence*, in which all of the cancer tissues showed a uniform fluorescence (Fig. 1);
(ii) *Partial fluorescence*, in which part of the cancer tissues showed fluorescence (Fig. 2); or
(iii) *Rim fluorescence*, in which the cancer tissues were negative for fluorescence, but the surrounding liver parenchyma showed fluorescence (Fig. 3).

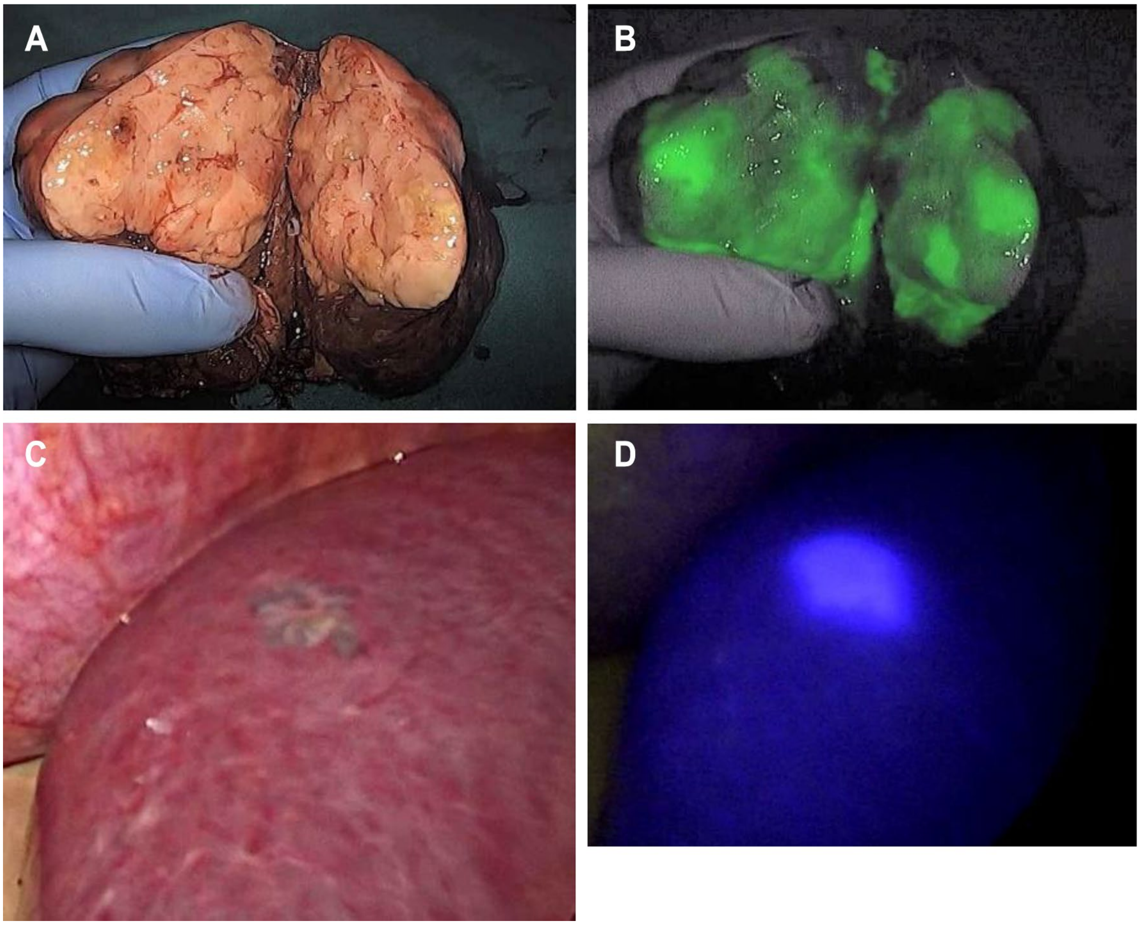

Fig. 1 Two cases of total fluorescence type. Well-differentiated HCC are displayed with white light in panels **A** and **C**, and with PDE-fluorescence imaging using Stryker equipment in panel **B** and Storz equipment in panel **D**

Pathological examination of the surgical specimens

Nodular lesions identified macroscopically and fluorescent lesions detected by the PDE camera were further processed for microscopic examination. All surgical specimens were formalin-fixed, stained with hematoxylin only and then examined by experienced pathologists. All grossly identified nodules were microscopically evaluated irrespective of the presence or absence of ICG fluorescence.

Results

Optimal dose and timing of ICG injections before liver surgery

Intraoperative ICG–PDE imaging was carried out for all patients undergoing liver surgery for cancer without side effects. The key finding was that the best dose and timing of ICG injections for patients who had undergone the LiMON test 7 or more days before the scheduled surgery was 0.2 ml/kg administered 24–48 h before the scheduled surgery.

Correct differentiation between liver parenchyma and tumor tissue was obtained in 25 out of 27 cases, which amounts to a remarkable 92.6% success rate. The procedure failed in only two cases: the ICG retention rate in the whole liver was too much in one case and too little in the other case, with all the liver parenchyma completely stained and completely free from staining, respectively. The dose and interval between ICG injections and the scheduled surgery were key determinants of the remaining background fluorescence signal in the liver and of the fluorescence in or surrounding the tumor. Liver staining in the patient who received an i.v. ICG injection of 0.5 mg/kg the day before the scheduled surgery was too strong to identify the nodules from the rest of the parenchyma (Fig. 4). In contrast, liver staining was practically nil in the other patient who had received the same injection 7 days before surgery (Fig. 5).

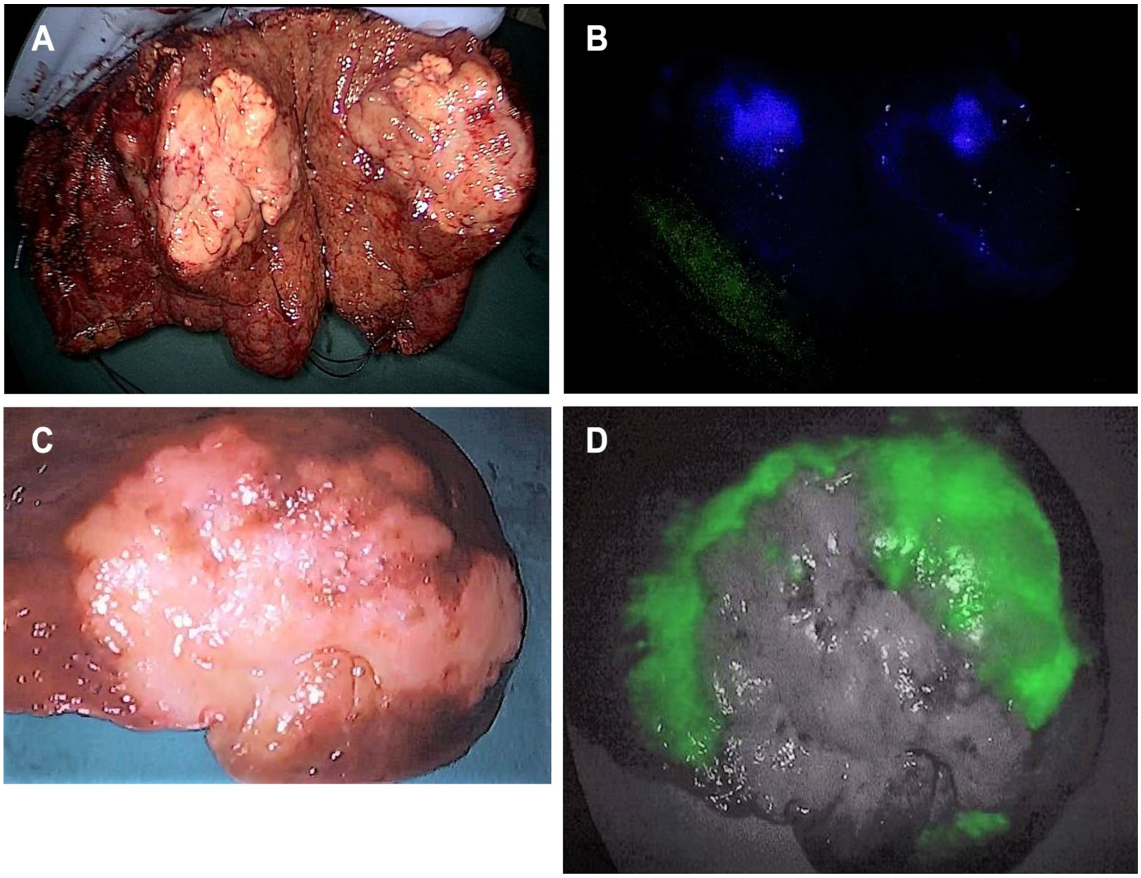

Fig. 2 Two cases of partial fluorescence type. A poorly differentiated HCC is displayed with white light in panel **A**, and with PDE-fluorescence imaging using Storz equipment in panel **B**. A CCC is displayed with white light in panel **C** and with PDE-fluorescence imaging using Stryker equipment in panel **D**

Cancer detection using ICG-based fluorescence imaging of surgical specimens

All but one tumor were completely resected with negative margins. In only one case, a new, small, superficial nodule that was undetected by the preoperative work-up was evident. Final histological examination revealed a benign lesion (biliary cyst). Some nodules were not visible by fluorescence imaging before resection, mainly because of the deep location of the tumor itself (12 cases, 44.4%) (Table 2). Postresection bile leakage spots were observed in 2 cases and sutured. The postoperative leakage rate was 14.8% (4 out of 27 patients).

The independent assessments of the three specialized liver surgeons based on the in vivo intraoperative images and the ex vivo postoperative surgical specimen images delivered a unanimous consensus on the ICG-based fluorescence patterns: total fluorescence in 11 patients (approximately 41%), partial fluorescence in 4 patients (approximately 15%), rim fluorescence in 8 patients (approximately 30%), and no staining in 4 patients (approximately 15%). Total and partial fluorescence were predominantly observed in patients with HCC. Rim fluorescence was observed in 4 out of 6 patients with metastases, whereas cholangiocarcinoma showed no predominant fluorescence pattern (Table 3).

It is important to underline that there were no differences in the enhancement pattern of the ICG-based fluorescence imaging between the in vivo intraoperative examination of the liver surface and the ex vivo back-table analysis of the surgical specimens.

Discussion

From a theoretical point of view, ICG-based fluorescence imaging is a simple tool and may turn out to be a powerful method for the following:

i. Precisely identifying the local extent of tumor spread, which is particularly valuable in laparoscopic surgery, in which no tactile sensation is available;

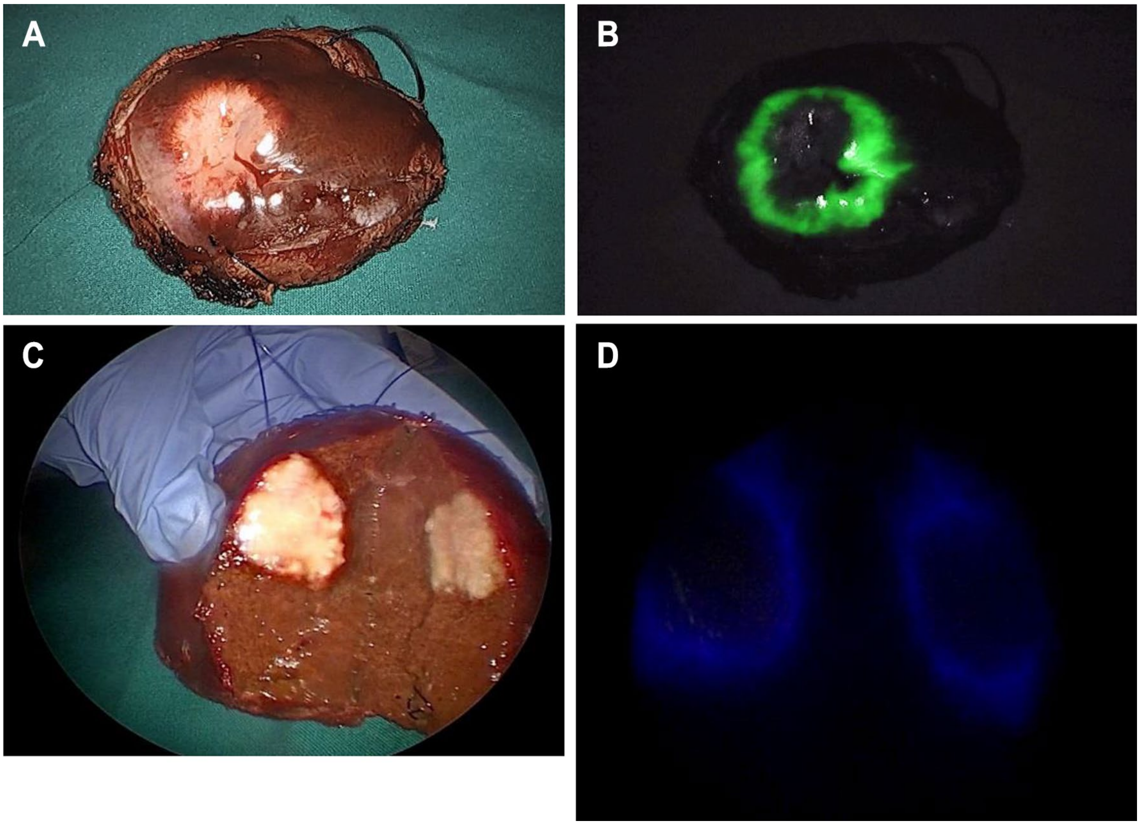

Fig. 3 Two cases of rim fluorescence type. CRC are displayed with white light in panels **A** and **C**, and with PDE-fluorescence imaging using Stryker equipment in panel **B** and Storz equipment in panel **D**

ii. Checking the radicality of the resection (once the resection is done, no residual ICG-based fluorescence should be detected along the resection line);
iii. Detecting new malignant nodules that had not been detected by preoperative radiological imaging; and
iv. Ruling out the malignant nature of suspicious superficial nodules appearing on preoperative radiological imaging.

Further possible intraoperative advantages of ICG-based fluorescence imaging, such as biliary anatomy visualization, identification of biliary leakage along the resection line [15], and liver segmental anatomy staining by intraportal injection [16, 17], were not analyzed in this study.

The mechanisms that mediate the preferential accumulation of ICG in HCC by comparison to normal liver tissue have recently been elucidated by immunohistochemical staining and gene expression analysis. In differentiated HCC tissues, the expression levels of portal uptake transporters of ICG (organic anion transporting polypeptide 8 and Na+/taurocholate cotransporting polypeptide) were well preserved, but functional or morphological biliary excretion disorders were present, leading to the retention of ICG in cancerous tissues at the time of surgery when preoperative i.v. injections were performed. However, in poorly differentiated HCC, portal uptake transporters were downregulated in cancerous tissues, but the biliary excretion of ICG by surrounding noncancerous hepatic parenchyma was also disordered, resulting in rim-type fluorescence. The rim-type fluorescence signal in metastases has been reported to be caused by immature hepatocytes with decreased bile excretion ability surrounding the tumor [8, 18, 19].

The series presented in this study was unselected; thus, only a minority of cases were ideal for ICG staining (only 11.1% of patients had small and superficial liver nodules). However, in this subgroup, ICG-based fluorescence was simply and effectively identified, with a 100% success rate. At the same time, control of the resection line once the specimen was removed revealed some residual fluorescence in two cases, and further resection was performed. Final histological examination revealed no residual tumor in the enlarged specimens; however, the resection margin in the first specimen was < 1 mm. This may suggest that the rim of fluorescence surrounding the tumor represents the correct resection line, allowing a free margin. Further studies focusing on selected cases are warranted.

In one only case of normal liver, a nodule undetected by preoperative imaging was found and resected, and it turned

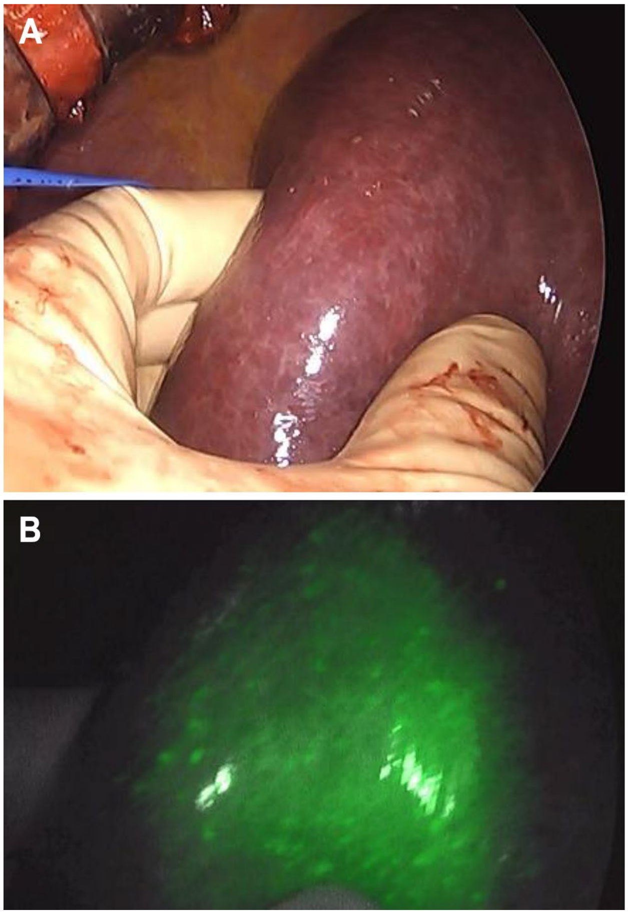

Fig. 4 Full staining of the liver. The image of the surgical specimen is displayed with white light in panel **A** and with PDE-fluorescence imaging using Stryker equipment in panel **B**

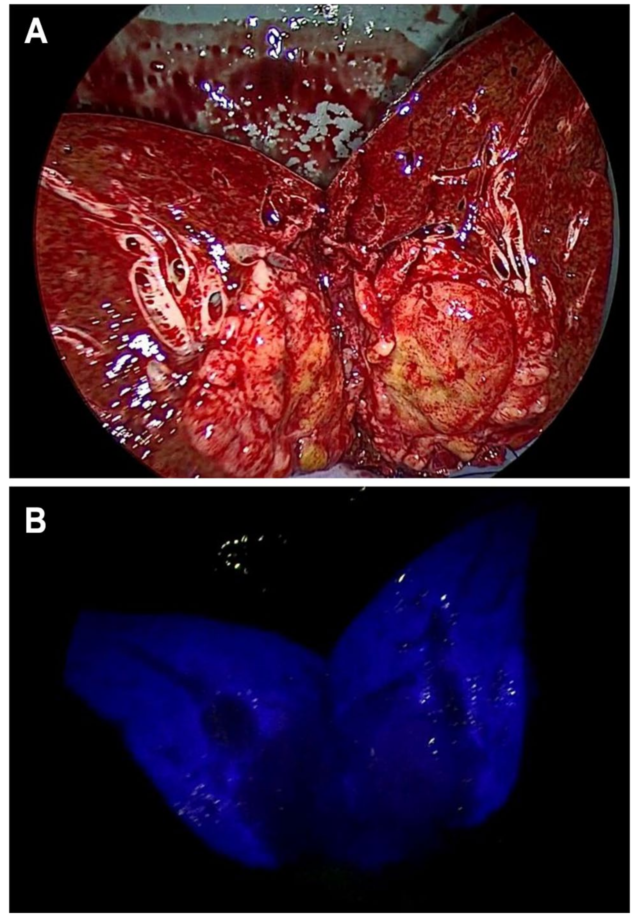

Fig. 5 No staining of the nodule. The image of the surgical specimen is displayed with white light in panel **A** and with PDE-fluorescence imaging using Storz equipment in panel **B**

out to be a benign nodule. It was observed that cirrhotic livers showed many small (1–2 mm) areas of ICG retention, which may be related to benign areas of reduced biliary excretion, whereas normal livers do not display the same pattern. There were no cases of suspicious superficial nodules in cirrhotic livers; thus, it was not possible to rule out the malignant nature of those nodules. Moreover, normal liver parenchyma was observed in only 29.7% of the cases. It is unknown if cirrhosis or other hepatic diseases might change the identification patterns of lesions with ICG-based fluorescence imaging and, hence, in this study, it is not possible to address this issue in a statistically meaningful way. For this reason, we are conducting another study that focuses on the analysis of nonneoplastic parenchyma fluorescence. Some areas retaining ICG will be resected and examined, and correlations with liver function, liver appearance on MRI, and liver histological features will be analyzed in depth.

There are two main concerns regarding this study. One concern pertains to the limited sample size. However, the current sample includes all patients who were enrolled during the 6-month period. More patients are going to be enrolled, and more observations are going to be added to the sample in the coming months with the ultimate goal of implementing a prospective study.

The other shortcoming is the lack of standardization of the analysis of the fluorescence signal. This is a

Table 2 Tumor visualization rate related to tumor size and location

Staining	Nodule depth				Total (percentage)
	< 0.7 cm		> 0.7 cm		
	Nodule size		Nodule size		
	< 2 cm	> 2 cm	< 2 cm	> 2 cm	
Yes	3	12	0	0	15 (55.6%)
No	0	2	6	4	12 (44.4%)

Nodule depth measures the distance of the nodule from the Glisson's capsule at CT scan. This distance is recommended by the producers of the NIR equipment (Storz and Stryker), which have been employed in this study

Table 3 ICG patterns of staining in tumors

	HCC	CCC	CRC	Total	Percentage
Patients	19	2	6	27	–
Pattern of staining					
Total fluorescence	10	0	1	11	40.8
Partial fluorescence	3	1	0	4	14.8
Rim fluorescence	3	1	4	8	29.6
None	3	0	1	4	14.8
Margin+	0	0	1	1	3.7
More lesions	0	1	1	2	7.4
Biliary visualization	1	1	0	2	7.4

HCC hepatocarcinoma, *CCC* cholangiocarcinoma, *CRC* colorectal liver metastases

well-known limitation that has been acknowledged since the seminal contributions of Ishizawa et al. [8] and Gotoh et al. [9]. Future technological software developments, one of which is currently ongoing at IRCAD in Strasbourg (France), will enable the quantification of ICG-based fluorescence signals in the near future.

In conclusion, advances in imaging systems will increase the use of fluorescence imaging as an intraoperative navigation tool that can enhance the safety and accuracy of open and laparoscopic hepatobiliary surgery. ICG-based fluorescence imaging is a promising method for routine intraoperative imaging during hepatic resection. Considering the dire consequences of undetected small nodules and metastases and the fact that ICG-based fluorescence imaging is a safe, easy, and relatively inexpensive intraoperative tool, further research to assess its clinical advantages is warranted.

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Author contributions GLB developed the original idea and methodology of the project and made substantial contributions to the manuscript. MSA wrote the first draft of the paper and incorporated the conceptual feedback sent by the coauthors. SM, SB, BM, PP, and EA collected intraoperative images and performed the literature search and review. NP, FG, and MB made scientific contributions to the project and critically revised the manuscript.

Compliance with ethical standards

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