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Real-Time Navigation Guidance Using Fusion Indocyanine Green Fluorescence Imaging in Laparoscopic Non-Anatomical Hepatectomy of Hepatocellular Carcinomas at Segments 6, 7, or 8 (with Videos)

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

CDEG Yu Zhou
BC Ye Lin
BE Haosheng Jin
D Baohua Hou
BCD Min Yu
BCDE Zi Yin
ABCDEG Zhixiang Jian

Department of General Surgery, Guangdong General Hospital, Guangdong Academy of Medical Sciences, Guangzhou, Guangdong, P.R. China

Corresponding Author: Zhixiang Jian, e-mail: jzx_118@163.com
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Background: The right area and posterior area of the liver are considered relatively unfavorable portions for laparoscopic hepatectomy (LH) due to the limited gross inspection and poor tactile feedback. Fusion indocyanine green fluorescence fusion imaging (ICGFI) may be a reliable real-time navigation tool for LH. The aim of the present study was to evaluate the usefulness of ICGFI for laparoscopic non-anatomical hepatectomy in patients with hepatocellular carcinoma at the right area and posterior area.

Material/Methods: We conducted a retrospective comparison of surgical and perioperative outcomes for 21 hepatocellular carcinoma patients who had undergone LH with fusion ICGFI guidance and 21 matched patients who underwent the procedure without the guidance of ICGFI between November 2017 to August 2018.

Results: Preoperative characteristics were comparable between the groups. Tumor fluorescence images were clearly displayed in all 21 ICGFI patients, providing precise information about tumor location. Laparoscopic parenchymal transection could be performed safely and quickly through tracing the fusion ICGFI on the cutting surface. Operation time was significantly reduced in the ICGFI group. Postoperative complications were comparable between the groups. There was no positive margin in either group.

Conclusions: These preliminary data suggest that fusion ICGFI may be a useful tool that provides real-time navigation for non-anatomical LH. It may assist in the safe and accurate completion of LH for tumors located at the right posterior areas. Further studies are needed to fully clarify the advantages and disadvantages of ICGFI in LH, including short-term perioperative outcomes and long-term prognosis.

MeSH Keywords: Hepatectomy • Indocyanine Green • Laparoscopy

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Background

Laparoscopic hepatectomy (LH) is widely accepted and routinely performed worldwide in selected candidates. While anatomical liver resection is the recommended method, non-anatomical resection is also performed [1]. Due to the lack of a complete hepatic overview and tactile feedback during laparoscopic hepatectomy (LH), extreme care must be taken around the margins [2]. The disadvantages are more obvious for tumors in right and posterosuperior areas (segments 6–8) due to the limited visualization and the difficulty of handling the laparoscopic devices.

During non-anatomical laparoscopic hepatectomies (LHs), accurate localization of the tumor is critical in order to achieve clear margins. Intraoperative laparoscopic ultrasound (IOUS) can be helpful, but it is not real-time. An indocyanine green (ICG)-based fluorescence fusion imaging (ICGFI) technique was recently developed to safely enable truly real-time views of liver lesions during hepatectomies [3–5]. Recent studies have described the application of fusion indocyanine green fluorescence imaging (ICGFI) in liver surgery, reporting that it showed great potential with regard to real-time navigation for hepatectomy [5–8]. Herein, we report our preliminary experience with the application of fusion ICGFI during non-anatomical LHs. We focused on hepatocellular carcinomas (HCCs) of the right posterior areas, and we also retrospectively compared fusion ICGFI-guided LHs with procedures utilizing IOUS guidance alone in a matched cohort.

Material and Methods

Administration of ICG

To provide a fluorescent source, ICG was injected intravenously at a dose of 0.25 mg/kg body weight 3–5 days before surgery. According to our experience, injection of ICG at a dose of 0.25 mg/kg 3–5days before surgery is associated with the highest success rate and the best visualization effect. Fusion ICGFI was obtained using the PINPOINT™ imaging system (NOVADAQ, Toronto, Canada). The details of this system have been described in previous reports [7].

Patients

Fusion ICGFI was used in 21 consecutive HCC patients undergoing LH for tumors in right posterior areas at Guangdong General Hospital in China from November 2017 to August 2018. The 21 cases were individually matched at a 1: 1 ratio to patients who underwent LH with IOUS guidance alone between January 2015 and October 2017. Sex, hepatitis background, age (±5 years), tumor size (±0.5 cm), tumor number, tumor segment, tumor depth (±0.5 cm, measured in CT or MRI images), and the chief surgeon were matched. For tumors of ICG cases adjacent to major vessels (≤0.5 cm from the trunk of hepatic veins, or the first branches of right portal vein), the relationships with major vessels were also matched (≤0.5 cm from the same vessels). When more than 1 control patient was matched, the best-matched case according to operation difficulty was selected through discussion by 3 experienced laparoscopic surgeons (Ye Lin, Haosheng Jin, and Baohua Hou). The study was approved by the Medical Ethics Review Committee of Guangdong General Hospital.

Statistical analysis

The perioperative outcomes in the 2 groups were statistically analyzed and compared using SPSS version 24.0 (IBM, Armonk, NY). Data are reported as medians and ranges. The chi-square test was used to compare categorical variables and the Mann-Whitney U test or paired-samples *t* test was used to compare continuous variables, and $p<0.05$ was considered statistically significant.

Results

Clinical characteristics and perioperative outcomes in the 2 groups are summarized in Table 1. Preoperative characteristics were comparable between the 2 groups. We found that operation time was significantly reduced in the ICGFI group. Postoperative complications were comparable between the groups, and there were no positive margins in either group.

Tumor fluorescence images were clearly displayed in all 21 ICGFI patients, providing precise information about tumor location. Two exemplar case reports are presented, and videos depicting these 2 representative cases are attached.

Patient 1 (Video 1)

A 68-year-old man with hepatitis B virus (HBV) was detected by preoperative CT and MRI to have an irregular tumor in segment 8 measuring 5.5×5.0 cm in diameter (Figure 1A). ICG was injected intravenously at a dose of 0.25 mg/kg body weight 5 days before surgery. A small area of ICGFI was detected on the liver surface. No other superficial ICGFI were found. The resection line on the surface of the liver was marked using monopolar electrocautery after IOUS scanning. The parenchyma was dissected with ultrasonic scalpel. As the parenchymal transection proceeds, ICG fluorescence appeared on the transection surface, and we were thus able to confirm the intraparenchymal boundary by observing ICG fluorescence on the cut surface (Figure 1B). We kept ICG fluorescence localized on the cut surface of the resected part during liver resection.

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Table 1. Clinical characteristics and perioperative outcomes of the 20 matched patients.

Variables	ICGFI group (n=21)	IOUS group (n=21)	P
Age years (≥60/<60)	5/16	5/16	1.000*
Clinical characteristics			
Sex (Male/Female)	15/6	15/6	1.000*
HBsAg positive (n,%)	15, 71.4%	15, 71.4%	1.000*
Liver cirrhosis (n,%)	9, 42.9%	9, 42.9%	1.000*
Child-Pugh (A/B/C)	18/3/0	18/3/0	1.000*
Tumor size cm (median, range)	3.1 (1.8–5.5)	3.2 (1.2–5.5)	0.881#
Tumor number (median, range)	1 (1–2)	1 (1–2)	1.000*
Tumor location			1.000*
Segment 6	9	9	
Segment 7	7	7	
Segment 8	4	4	
Segment 5/6	1	1	
Operative outcomes			
Clearly ICGFI of tumor boundary (n,%)	21, 100%	–	–
Operation time min (median, range)	180 (150–330)	210 (135–375)	0.038#
Blood loss ml (median, range)	50 (10–500)	50 (10–700)	0.610#
Blood perfusion (n,%)	0, 0%	0, 0%	–
Postoperative outcomes			
Intra-abdominal hemorrhage (n,%)	0, 0%	0, 0%	–
Bile leakage (n,%)	0, 0%	1, 4.8%	1.000*
Wound infection (n,%)	0, 0%	0, 0%	–
Liver failure ISGLS Grade (A/B/C)	3/1/0	2/1/0	0.714*
Pathological results			
Hepatocellular carcinoma	21, 100%	21, 100%	1.000*
R0 resection (n,%)	21, 100%	21, 100%	1.000*
Minimal margin width mm (n, median, range)	7.0 (3.0–11.0)	8.0 (2.0–15.0)	0.180#

* Fisher's exact test; # paired-sample *t* test. ICGFI – indocyanine green fluorescence imaging group; IOUS – intraoperative ultrasound; HBsAg – hepatitis B surface antigen; HBV – hepatitis B virus; cm – centimeter; min – minute; ml – milliliter.

With the guidance of ICGFI, the operation allows fluent execution. The tumor was removed with a safe margin (Figure 1C).

Patient 2 (Video 2)

A 70-year-old man with HBV cirrhosis was detected by CT and MRI to have a tumor located between hepatic segment 5 and segment 6. The tumor was small (2.1×1.8 cm) (Figure 1D). Because the tumor was deep, no clear-formed ICG fluorescence was detected on the liver surface. IOUS was routinely used to localize the tumor. The parenchyma was dissected. We observed weak fluorescence on the cutting surface due to ICG retention in the liver parenchyma. Clear ICG fluorescence appeared during parenchymal transection (Figure 1E), which provided information about the precise location of the tumor. Because the tumor was adjacent to major vessels, the ICG fluorescence margin was compromised in order to preserve those vessels, and a little ICG fluorescence was left on the residual liver. The tumor was removed with a safe margin (Figure 1F).

Discussion

ICG fluorescence facilitates the identification of tumors by enabling the visualization of impaired biliary excretion of ICG around tumor tissues. It is important to highlight that the border

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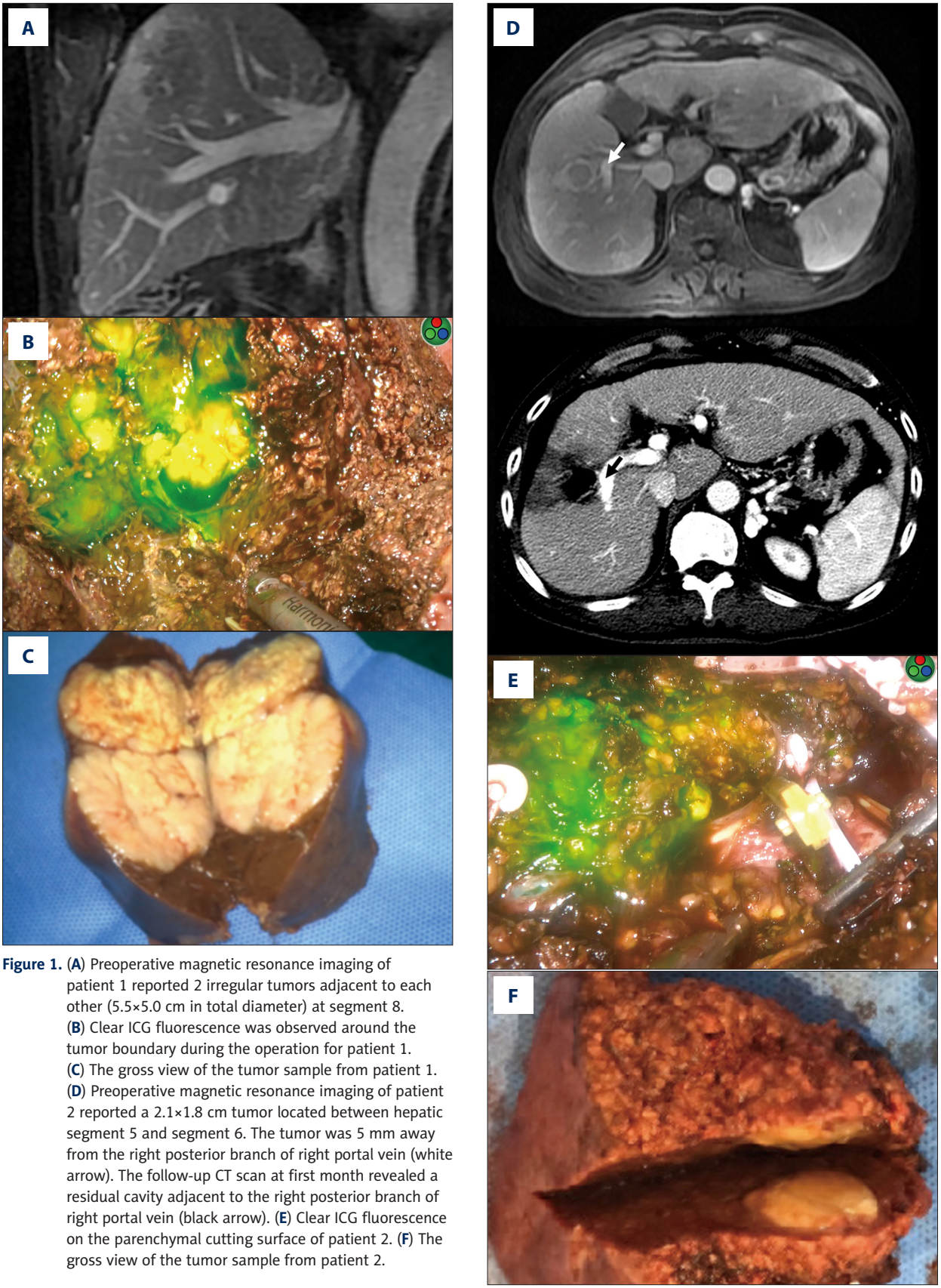

Figure 1. (**A**) Preoperative magnetic resonance imaging of patient 1 reported 2 irregular tumors adjacent to each other (5.5×5.0 cm in total diameter) at segment 8. (**B**) Clear ICG fluorescence was observed around the tumor boundary during the operation for patient 1. (**C**) The gross view of the tumor sample from patient 1. (**D**) Preoperative magnetic resonance imaging of patient 2 reported a 2.1×1.8 cm tumor located between hepatic segment 5 and segment 6. The tumor was 5 mm away from the right posterior branch of right portal vein (white arrow). The follow-up CT scan at first month revealed a residual cavity adjacent to the right posterior branch of right portal vein (black arrow). (**E**) Clear ICG fluorescence on the parenchymal cutting surface of patient 2. (**F**) The gross view of the tumor sample from patient 2.

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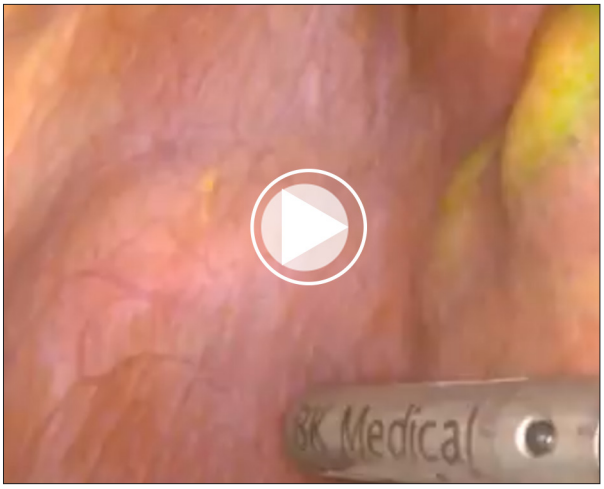
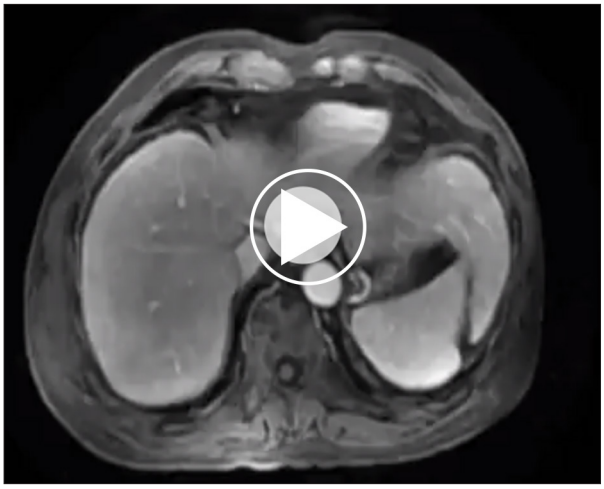


Video 1. Video of surgical procedure for patient 1.



Video 2. Video of surgical procedure for patient 2.

of ICG fluorescence does not equal the boundary of the tumor, as it is wider than the tumor margin [9,10]. Therefore, this mechanism ensures a safe margin, provided that fluorescence can be kept localized in the resected liver. Based on our preliminary experience, the main clinical benefit of ICGFI in non-anatomical LH is the real-time visualization of safe boundaries, which is highly beneficial in the management of deep lesions or those located in unfavorable regions. In the current study, no visible fluorescence at the residual liver could ensure a surgical margin of at least 6 mm, which is slightly less than the ≥8-mm margin reported previously, but it is in accordance with the 5–10-mm tissue penetration depth of ICG fluorescence [11,12]. Further research is needed to provide more data about the minimal margin width in ICGFI-guided tumorectomies. Also, we must add that not all non-anatomical LHs can be performed completely by tracing the ICG fluorescence margin alone. As in the Patient 1, margin width is usually compromised due to the need to preserve vessels, and this also applies to IOUS-guided resections.

Clinical application of the PINPOINT™ imaging system for laparoscopic liver resection has been reported in a few studies. Takahashi et al. [8] reported their initial experience and the potential utility of ICG during liver surgery. They investigated the efficiency of ICGFI in detecting superficial tumors and found ICGFI was a good adjunct to ultrasound in demonstrating superficial lesions, and ICGFI also could provide real-time feedback to the surgeon about the margins of superficial tumors for resection or ablation. Terasawa et al. [7] evaluated the usefulness of fusion ICGFI in 41 patients who received laparoscopic hepatectomy, and the results revealed that fusion imaging enhances the feasibility of intraoperative ICGFI in identification of hepatic tumors and segmental boundaries. Ueno et al. [6] reported their experience in ICGFI-guided segmental hepatectomy in 5 cases by using a novel technique in which the ICG was injected into the artery of the target segment through a catheter inserted from the right femoral artery in a hybrid operating room.

The previous reports mostly focused on the visualization effect and reliability of fusion ICGFI in superficial lesions and segmental staining [7,8]. In addition, in the previous reports, the sizes of lesions for tumorectomy or partial hepatectomy were usually small on average, and the locations of lesions were distributed from segment 1 to segment 8 [7]. Laparoscopic left lateral lobectomy has become a routine procedure, and tumorectomy for lesions of the left lobe is a relatively easy procedure [11,13]. Here, we focused on ICGFI-guided tumorectomy or partial hepatectomy for tumors of the right posterosuperior areas. The tumor sizes of our present study were relatively large, and we included both superficial and deep lesions. Through the surgical details provided in our attached operation videos, we found that fusion ICGFI was a good navigational tool that provides information on tumor location and boundaries during parenchymal transection. For deep tumors, the ICGFI can provide clear navigation information that makes the transection surface easier to control, without the need for repeated IOUS scanning. We also compared the safety and efficacy between fusion ICGFI-guided liver resection and IOUS-guided liver resection. We found that, with the help of fusion ICGFI, the tumorectomy for tumors of right posterosuperior areas could be performed more efficiently and with safe margins.

Notably, IOUS is still necessary. Because the tissue penetration depth of ICG-emitted fluorescence is only approximately 5–10 mm, IOUS scanning should be routinely performed to identify the tumor location before liver resectioning. The margin widths were comparable in the 2 groups in the present study, given that the cases were carefully matched and that we did not intentionally seek a margin >1 cm in these cases. However, accumulating evidence suggests that a wide surgical margin can significantly improve the prognosis in patients with HCC. Under this requirement, ICG can be used concurrently to avoid positive margins arising due to error, and IOUS is still necessary because the tissue penetration depth of ICG-emitted fluorescence is only approximately 5–10 mm.

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Our department is an experienced high-volume center for LH. All control cases were operated on within the last 3 years – a period *after* which LH technology had become firmly established and laparoscopic procedures for tumors in right posterior superior areas had become routine. Therefore, aspects of our results such as the reduction of operation time in the ICGFI group were not due to a learning curve effect. On the other hand, except for the significant difference in operation time, other outcomes were similar between the 2 group of patients. Although we found ICGFI is a useful navigation tool to avoid positive margins, the R0 resection rate was 100% in both groups. The equal R0 rates of these groups were mainly due to our sufficient experience in laparoscopic liver resection and the relatively small sample size of the current study. Further studies with larger sample sizes are need to learn more about the perioperative advantages and long-term outcome of ICGFI-guided LH.

For anatomical segmental hepatectomies, the ICG is usually injected either intravenously after clamping the Glissonian sheaths flowing in the cancer-bearing hepatic segment, or directly into the vessel branches supplying blood flow to the tumor-bearing hepatic segment [5,6]. But for tumor imaging, the ICG should be administered intravenously prior to the operation. The time between ICG administration and surgery should not be too long or too short. An inadequate interval can lead to ICG retention in normal liver tissues, but the tumor imaging will be too weak or even disappear after a long interval. The optimal regimen of ICG administration for intraoperative cancer imaging has not been established. In their initial experiences with fusion ICGFI in hepatectomy with the use of the PINPOINT™ imaging system, Terasawa et al. [7] injected ICG intravenously at a dose of 0.5 mg/kg within 2 days before surgery, Takahashi et al. [8] injected 7.5 mg ICG 2 days before surgery. In our experience, injection of ICG at a dose of 0.25 mg/kg 3–5 days before surgery was associated with the highest success rate and the best visualization effect. If the time interval exceeded 7 days, the ICG fluorescence of liver tumors might disappear. Further study is still needed to determine the optimal regimen of ICG administration, especially in patients with impaired liver function.

Although the current study was focused on non-anatomical hepatectomy, it is notable that the guidance of anatomical hepatectomy is an essential application for ICG [5,7,14]. When the laparoscopic Glissonian approach is used, ICG is usually injected intravenously after clamping the Glissonian sheaths to exclude the anatomical segment. The intersegmental transection plan can be clearly displayed via segmental mapping with ICG. Other techniques to establish segmental ICG staining have also been reported [6]. Segmental mapping with ICG appears to be a promising technique in anatomical LH.

Conclusions

Fusion ICGFI is a helpful real-time navigation tool for the identification of tumors and boundaries during non-anatomical LH, but a single application of ICGFI has the clear limitation that the tissue penetration depth of fluorescence is limited. Further studies are needed to fully clarify the advantages and disadvantages of ICGFI in LH, including both short-term perioperative outcomes and long-term prognoses.

Conflict of interest

None.

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