

Efficacy of Hepatic Segmental Visualization Using Indocyanine Green Photodynamic Eye Imaging

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Abstract

Background To clarify the usefulness of identification of hepatic segmentation stained with an indocyanine green–photodynamic eye (ICG–PDE) system, we sequentially investigated the matching of visualization during hepatectomy in 40 patients at two institutions between 2009 and 2017.

Methods A low dose of ICG was administered into the portal flow to stain the estimated segments of the liver to be resected during hepatectomy, and segmentation images were observed using a PDE camera. Intraoperative ICG–PDE could be carried out for all patients without side effects.

Results Complete segmental identification of the liver by blue dye stain and ICG–PDE was achieved in 30 (75%) and 35 (88%) patients, respectively, but the prevalence between them was not significantly different ($p = 0.302$). ICG–PDE segmentation in the estimated area was incomplete in three patients, and complete failure (no staining) was observed in two patients. The border between the posterior section and the caudate was identified in two patients.

Conclusion This preliminary study showed ICG–PDE to be a useful tool for clearly determining liver segmentation to estimate the area for resection.

Introduction

In the surgical procedure for primary liver carcinomas, anatomical resection without tumor exposure is necessary to attain high curability and longer survival in comparison with those by non-anatomical resection. During

hepatectomy, intraoperative ultrasonography (IOUS) is an essential tool to identify the intrahepatic vasculature as landmarks for anatomical hepatectomy. In the 1980s, Makuuchi et al. developed a new procedure called “tattooing” for ultrasonically guided puncture and dye injection [1]. This staining technique has been conventionally applied for anatomical hepatectomies. Indocyanine green (ICG) has usually been used to examine hepatic functional reserve and was also applied for detection in a new medical imaging system using an infrared light detector, the ICG–photodynamic eye (PDE) system [2]. The distribution of subtly fluorescing materials in tissues can be precisely detected using a near-infrared radiation system. Applying this approach to detect ICG fluorescence improves the specificity of hepatic segmental detection compared with dye injection detected visually. With intravenous injection of ICG, clearer detection of segmental fluorescence at the transected liver becomes possible in comparison with

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conventional dye injection [3]. We hypothesized that surgery using ICG–PDE navigation would be feasible as an alternative or reliable method of “tattooing” to achieve anatomical hepatectomy. For this purpose, we assessed the use of ICG–PDE in 40 patients with malignant hepatobiliary diseases who underwent anatomical hepatic resections and examined the feasibility and limitations of this modality.

Methods

Patient Background

Study participants comprised 40 patients with hepatobiliary diseases who were scheduled for surgery and admitted to two institutions, the Division of Surgical Oncology at Nagasaki University Hospital (NUH) between November 2009 and March 2015, and the Division of Hepato-biliary-pancreas Surgery, University of Miyazaki Faculty of Medicine (UM) between April 2015 and April 2017. The study protocols followed the ethical principles of the Declaration of Helsinki 2008 and were approved by the Human Ethics Review Board at NUH (#1805215, May 22, 2018) and UM (#O-0305, April 5, 2018). Informed consent for data collection was obtained by the opt-out procedures for 1 month. The Chi-square test was used to compare categorical variables. Two-tailed P values < 0.05 were considered significant.

IOUS and ICG–PDE Procedures

All IOUS was performed by surgeons, and the intrahepatic vasculature was identified during the operation. Under dark conditions, a PDE camera system (Hamamatsu Photonics, Hamamatsu, Japan) was used to detect ICG fluorescence. This system irradiates the ICG combined with serum protein with infrared light (wavelength 750–830 nm). The excited ICG fluoresces at a wavelength of 845 nm, which is then detected by the PDE detector. Under IOUS, 5 mL of ICG diluted with 100 mL of distilled water (0.25 mg/mL) was injected into the portal vein under the arterial clamp to supply the area estimated for liver resection. After detection of tumor location and estimated resected area by IOUS, staining with blue dye injection was simultaneously performed with conjugated methylene blue dye and the ICG solution, and the injected area was compared with the fluorescence area (Fig. 1a, b). To avoid influences of arterial flow, the proper artery was transiently clamped, and the targeted portal vein was precisely injected by a long 22-gauge needle under the ultrasonography. Injection speed was carefully checked by confirming ultrasonography to inject adequate area or to avoid back-flow to

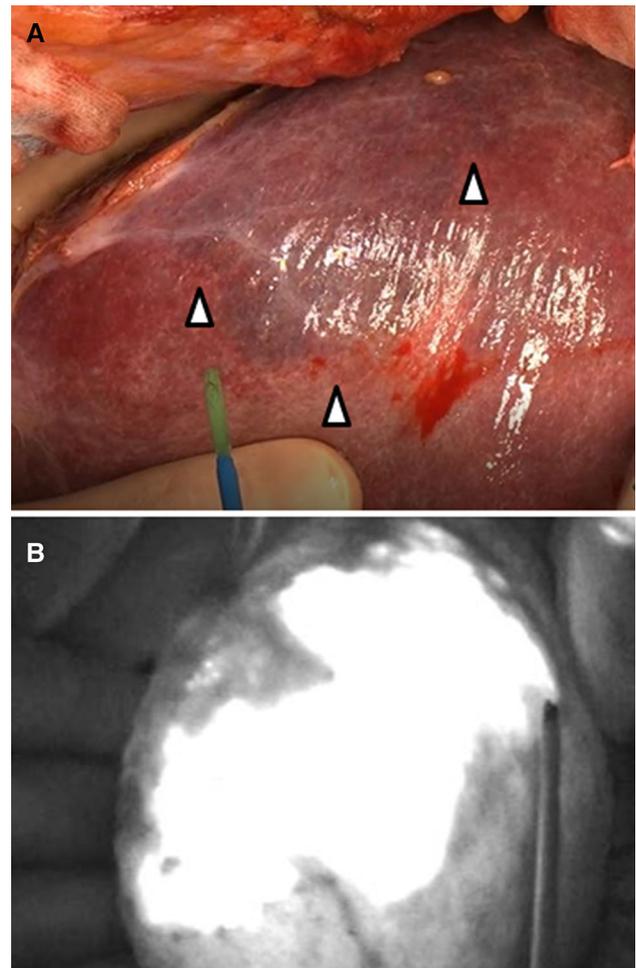


Fig. 1 Representative comparison images showing identification of an area of portal perfusion by conventional blue dye (a) and the ICG–PDE system (b) during surgery. The demarcation line of the blue dye is indicated by arrowheads

inadequate portal area. The area of fluorescing liver was marked by diathermy (Fig. 2a, b with video). Blue dye segmentation was firstly confirmed, and then, ICG segmentation was performed, sequentially. After confirming stained area, arterial clamp was released.

Results

Each patient data are shown in Table 1. During the intraoperative ICG–PDE, no ICG-related side effects such as anaphylaxis occurred. Complete segmental identification of the liver by comparison with the resected specimen by blue staining and ICG–PDE was attained in 30 (75%) and 35 (88%) patients, respectively. The difference in segmentation was not significant between the two staining methods ($p = 0.302$). However, partial failure of ICG–PDE to identify segmentation in the estimated area was observed in

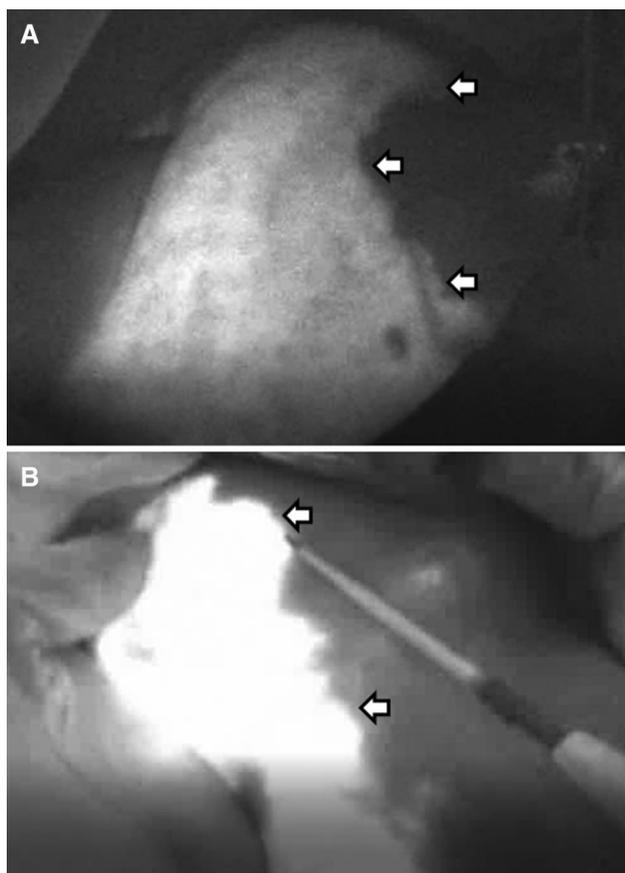


Fig. 2 Representative image showing identification by the ICG–PDE system during surgery. A clear segmental area is shown at the liver surface. The demarcation line (arrow) between the right and left liver (a) and that between the posterior and anterior sectors (arrow) (b) are shown along with an associated video

three patients and complete failure was observed in three patients. The border between the posterior section and the caudate lobe was identified in two patients.

Discussion

Although ICG–PDE has also been attempted to detect intrahepatic tumor locations [4], its usefulness and reliability for liver segmentation have not been fully clarified yet. ICG fluorescence was strongly detected due to vascular retention, but this staining is applicable only at the liver surface. Application of ICG–PDE to segmentation by portal injection of ICG is a new procedure that has remarkably advanced identification. According to accomplish the precise area for segmental stain [2], it is necessary to puncture the adequate portal veins and to inject by using fine needle and confirmation under careful examination of

IOUS. Although tattooing or blue dye segmentation has been used for some time now [2], visualization of the stained area is sometimes difficult, and the dye cannot immediately be seen clearly, particularly in an injured liver. The present results indicated that the prevalence of complete segmentation identification using ICG–PDE might be more frequent but not significantly different from blue dye staining. The usefulness of ICG–PDE segmentation compared with the conventional dye method has not been well reported so far. Although the difference in identified staining between blue dye and ICG–PDE has not been fully explained and indicated in the previous reports, it is speculated that because the blue dye is water soluble, it therefore washes out more rapidly than does ICG. ICG combines with lipoprotein in the blood, which is conjugated in hepatocytes for some period of time. Therefore, the accumulated ICG would remain longer than would blue dye; however, the precise mechanism for this still remains unclear. Another reason might relate to contrast ability because the color blue is difficult to identify visually in some patients with a chronically injured liver presenting a darker color in comparison with normal liver perfusion. In 5 of the 40 patients, ICG–PDE partially or completely failed despite successful portal injection. The injected solution sometimes back-flowed into the non-estimated blood flow. ICG–PDE segmentation was also applied in the present patient series as a counterstain for non-stained areas to confirm the segment to be resected in 1 case, and this might be a good application of this technique. We did not perform ICG–PDE in laparoscopy cases in the present series. In recent years, ICG–PDE has been used to provide clear imaging for the identification of tumor locations [5]. As it is possible to inject ICG into the portal vein via the percutaneous transhepatic route under intraoperative ultrasonography, segmentation by ICG–PDE would appear to be a useful modality to remarkably identify the transection area for laparoscopic anatomical hepatectomy. To clarify the feasibility of ICG–PDE segmentation and explain the difference between it and blue dye segmentation, it will be necessary to examine the technique in a larger number of patients.

Conclusion

We showed that the ICG–PDE system allows easy examination of the liver for detection of the extent of the area to be resected following portal vein injection of ICG, and this new imaging modality could become a standard procedure in combination with preoperative simulation before

Table 1 Summary of characteristics and procedures in patients who underwent ICG–PDE segmentation

No.	Age	Gender	Liver disease	Background liver	Hepatectomy segment	ICG stain	Blue dye stain
1	60	F	CCC	NASH	8	Failure	Failure
2	69	M	CLM	N	8	Partial	Failure
3	78	M	HCC	LC	6	Complete	Complete
4	75	M	HCC	LC	56	Complete	Complete
5	77	M	HCC	LC	8	Complete	Complete
6	69	F	HCC	CVH	67	Complete	Complete
7	50	F	CLM	N	67	Complete	Complete
8	73	F	HCC	CVH	78	Complete	Complete
9	45	M	HCC	CVH	5	Complete	Complete
10	61	M	HCC	CVH	4	Complete	Complete
11	78	F	HCC	CVH	78	Complete	Complete
12	63	M	HCC	CVH	67	Complete	Complete
13	78	F	CCC	N	234	Complete ^a	Failure
14	56	M	CCC	OJ	234	Complete ^a	Failure
15	76	M	HCC	CVH	67	Partial (6)	Failure
16	81	M	HCC	CVH	67	Failure	Failure
17	61	M	CCC	CVH	58	Complete	Complete
18	59	F	CLM	N	6	Complete	Complete
19	78	F	CCC	OJ	234	Complete ^b	Failure
20	60	M	Benign	N	5678	Complete	Complete
21	68	M	CCC	OJ	234	Complete ^a	Complete ^b
22	78	M	HCC	CVH	8	Complete	Complete
23	72	F	HCC	LC	67	Complete	Complete
24	68	M	HCC	N	6	Complete	Complete
25	85	M	HCC	CVH	56	Complete	Complete
26	74	M	HCC	N	8	Complete	Complete
27	72	M	HCC	CVH	8	Complete	Complete
28	68	M	HCC	CVH	6	Complete	Complete
29	66	F	CLM	CASH	234	Complete	Complete
30	54	M	CLM	CASH	234	Complete	Complete
31	70	M	CCC	LC	67	Partial (6)	Failure
32	65	M	HCC	LC	8	Complete	Complete
33	61	M	HCC	LC	48	Complete	Complete
34	72	F	HCC	CVH	8	Complete	Complete
35	61	M	HCC	CVH	48	Complete	Partial
36	64	M	CLM	N	6	Complete	Complete
37	74	F	HCC	CVH	8 Ventral part	Complete	Complete
38	72	F	HCC	NASH	56	Complete	Partial
39	70	M	HCC	CVH	8	Complete	Complete
40	84	M	HCC	CVH	5	Complete	Complete

Age 68.6 ± 9.1 years (range 45–85), *M* male, *F* female

HCC hepatocellular carcinoma, *CCC* cholangiocarcinoma, *CLM* colorectal liver metastasis, *N* normal, *CVH* chronic viral hepatitis, *LC* liver cirrhosis due to *CVH*, *OJ* obstructive jaundice, *CASH* chemotherapy-associated steatohepatitis, *NASH* non-alcoholic steatohepatitis

Partial (6); segment 6 was only stained

^aThe border of caudate was detected

^bThe border of caudate was not clearly detected

hepatectomy. Therefore, next steps include additional investigation in a larger cohort of patients to compare resected specimens and improvement in the injection technique to determine accurate segmentation in comparison with conventional blue dye injection.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Informed consent Informed consent for data collection was obtained by the opt-out procedures for 1 month.

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