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Indocyanine green identification for tumor infiltration or metastasis originating from hepatocellular carcinoma

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ABSTRACT

INTRODUCTION: The indocyanine green-photodynamic eye (ICG-PDE) system is useful to detect small hypervascular liver tumors, hepatocellular carcinoma (HCC), on the liver surface. This system may be also applied to improve determining the location of metastasis or tumor thrombus (TT). We herein report three case reports. ICG was administered preoperatively for functional testing and images of the tumor were observed during hepatectomy using a PDE camera.

CASE SERIES: The patient in case 1 exhibited advanced HCC with TT in the portal trunk. The TT in the right portal vein was clearly fluorescent by ICG-PDE and the right portal vein was adequately transected to remove TT. The patient in case 2 exhibited a large HCC in the right liver and the right adrenal gland was simultaneously swollen with enhancement. By confirming the fluorescent spot in the right adrenal gland, the metastasized lesion was completely resected. The patient in case 3 previously underwent central bi-segmentectomy, and lymph node metastasis and TT in the vena cava was observed during one-year follow-up. Although it was difficult to detect the definite margin of these lesions by the outline appearance, both lesions could be clearly observed with strong fluorescence and were completely resected.

DISCUSSION AND CONCLUSION: ICG-PDE is a useful tool for detecting the precise tumor location even in extrahepatic tumor lesions, such as metastases or tumor thrombus, which is useful for deciding which parts to resect.

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1. Introduction

In the field of hepatic resection for liver malignancy, tumor palpation and intraoperative ultrasonography (IOUS) are essential tools to determine tumor locations on preoperative imaging [1]. To improve the diagnostic accuracy of hepatocellular carcinoma (HCC) on the surface of the liver, other diagnostic tools are necessary because detection of small HCCs on the surface is often difficult by ultrasonography. In case of HCC with tumor thrombus (TT) in the main portal trunk, the tip of TT cannot be observed from the outside. Furthermore, extrahepatic metastases in lymph nodes or adrenal glands cannot be confirmed by the outer appearance as well. Indocyanine green (ICG) has usually been used to examine the hepatic functional reserve [2]. After intravenous administration, ICG imme-



Fig. 1. The ICG-PDE camera system used in this series. Figure was referred to the picture of our previous reports [8].

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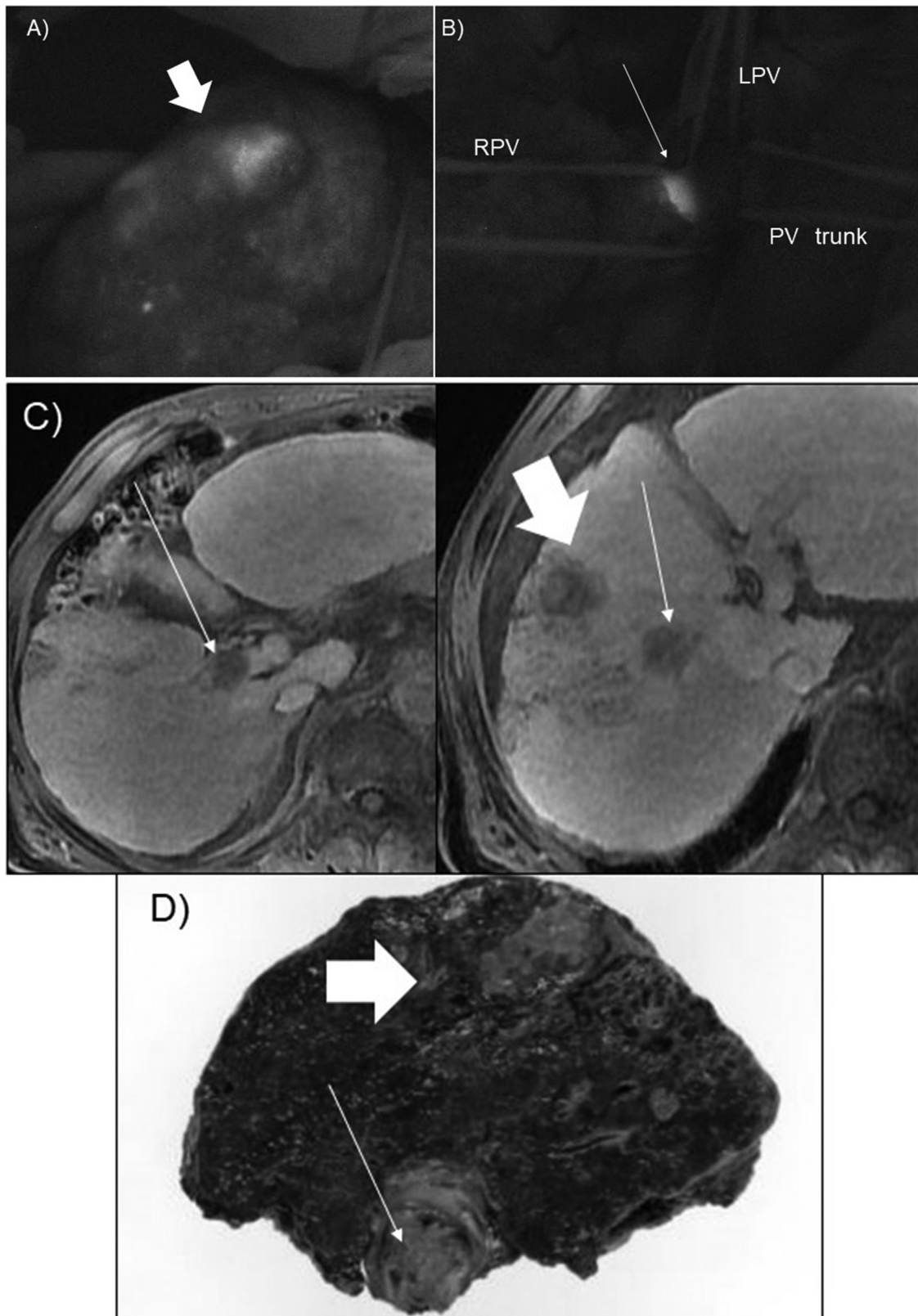


Fig. 2. Representative image of the ICG-PDE system during operation in case 1, which showed fluorescence of the main HCC (A; thick arrow) and portal vein tumor thrombus in the right portal vein (B; thin arrow). The portal vein was taped; RPV, right portal vein, LPV, left portal vein. C; The preoperative MRI showed main tumor (thick arrow) and tip of thrombus (thin arrow). D; Resected specimen showed main tumor (thick arrow) and tip of thrombus (thin arrow).

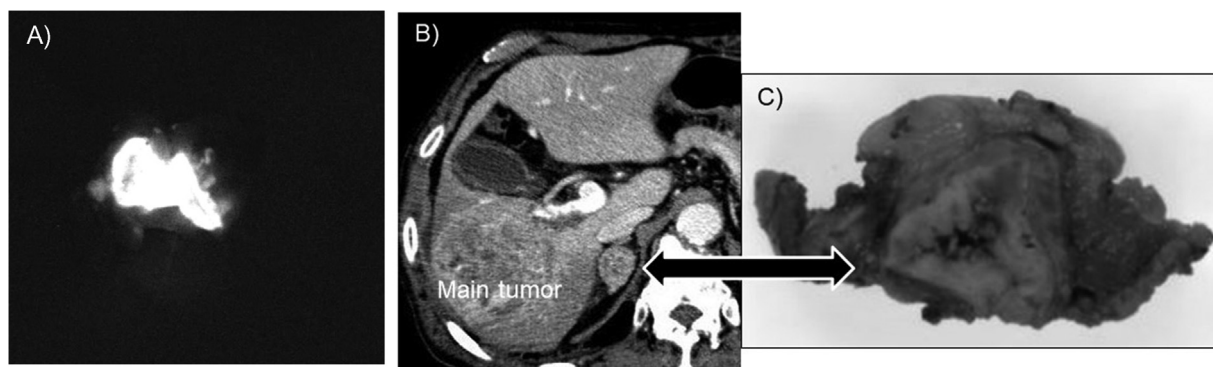


Fig. 3. A; The resected adrenal gland was strongly fluorescent and was diagnosed as a metastatic gland by histological examination. The preoperative CT and resected specimen showed metastasis of HCC in adrenal gland (B and C; double-headed arrow).

diately combines with serum protein, and this conjugated ICG is specifically taken up by the liver and immediately excreted into bile without being metabolized [3]. ICG has also been applied to detect sentinel lymph nodes in cases of breast carcinoma using a new medical imaging system with an infrared light detector, the so-called ICG-photodynamic eye (PDE) [4]. Although near-infrared light cannot usually be seen, the fluorescent materials in tissues can be clearly detected using a detector for near-infrared radiation because the ICG accumulated in tissue fluoresces under excitation by light from a laser. Applying this approach to detect ICG fluorescence improves the specificity of ICG detection compared with dye injection detected on macroscopic observation [5]. ICG-PDE has also recently been applied to detect liver tumors during hepatectomy because ICG remains inside only the liver tumor for several days after administration but not in the liver parenchyma [6]. The diagnostic accuracy, limitations and clinical applications of ICG-PDE have already been clarified, and the combination of ICG-PDE with enhanced US demonstrated high diagnostic accuracy in our previous report [7]. We hypothesize that extrahepatic metastases or the extent of TT in the hepatic vessel could be easily observed by ICG-PDE because these may take up ICG as well as primary lesions.

We herein report three patients with extrahepatic and non-parenchymal infiltration or metastasis of HCC detected by ICG-PDE to indicate the usefulness of this diagnostic tool. Five co-author surgeons contributed patient managements and intraoperative supports. Two contributed photodynamic eye identification and two contributed the main perioperative managements. Two chairmen and directors of each department performed the main operators in all operations, which were precisely described in Author's contribution section. The PROCESS Statement: Preferred Reporting of Case Series in Surgery. International Journal of Surgery 2016 by Agha RA, Fowler AJ, Rammohan S, Barai I, Orgill DP and the PROCESS Group [7]. This case series has been registered to research registry 3518 (Research Registry Unique Identifying Number) in January 06, 2018.

2. Patients and procedures

All HCC patients who were scheduled for surgery between 2010 and 2012 were selected. Consent for presentation was obtained from each patient during this period. Patient demographics and surgical data were retrieved from both institutional databases. ICG was intravenously injected several days before hepatectomy to examine the routine ICG retention rate at 15 min in order to evaluate hepatic functional reserve, as a necessary step in deciding on operative indications [8]. In general, 10 ml of diluted ICG (0.5 mg/kg of ICG dissolved in distilled water) is intravenously injected for this test. During laparotomy, under slightly dark conditions, a PDE camera system (Hamamatsu Photonics, Hamamatsu, Japan) (Fig. 1)

was applied to detect ICG fluorescence [9]. This system irradiated the ICG combined with serum protein with infrared light (wavelength, 750–830 nm). The excited ICG fluoresced at a wavelength of 845 nm, which was detected by the PDE detector. First, to determine tumor location, the surface of the whole liver was observed. In the next step, suspicious lesions detected on preoperative imaging were examined as described above. All patients were followed-up by blood tumor marker levels per a month and imaging analysis every 6 months.

3. Case

3.1. Case 1

A 66-year old man presented with advanced HCC with TT in the portal trunk. The alpha-feto protein (AFP) level was not increased as 2.5 ng/mL (Normal range was within 10 ng/mL at institute). The patient exhibited well reserved liver function and right hepatectomy was scheduled. The TT in the right portal vein TT was clearly visible by ICG-PDE (Fig. 2A and B). By confirming the tip of TT, the bifurcation of the right portal vein was transected and repaired by suturing after removal of the TT. Histological examination revealed HCC with thrombus. These could be compared to preoperative images and specimen as Fig. 2C and D. The specimen showed a chronic hepatitis with highly fibrosis as a pre-cirrhotic status. Preoperative diagnosis of HCC was mainly performed by the imaging analysis without biopsy and the final diagnosis was eventually performed by the histological examination for resected specimens.

3.2. Case 2

An 84-year-old man had a large HCC in the right liver and right hepatectomy was scheduled. The patient exhibited well reserved liver function. The AFP level was not increased as 3.5 ng/mL. Simultaneously, the right adrenal gland was swollen and enhanced, and adrenal metastasis was therefore suspected. By confirming the fluorescent spot in the right adrenal gland (Fig. 3A), the adrenal gland was also resected and histological examination revealed metastasis of HCC. The comparative preoperative CT image and resected specimen of metastatic adrenal gland tumor (Fig. 3B and C). The specimen showed a chronic hepatitis, but not in the cirrhotic status. Preoperative diagnosis of HCC was mainly performed by the imaging analysis without biopsy and the final diagnosis was eventually performed by the histological examination for resected specimens.

3.3. Case 3

A 76-year old woman who underwent central bisegmentectomy one year ago. During the follow-up, lymph

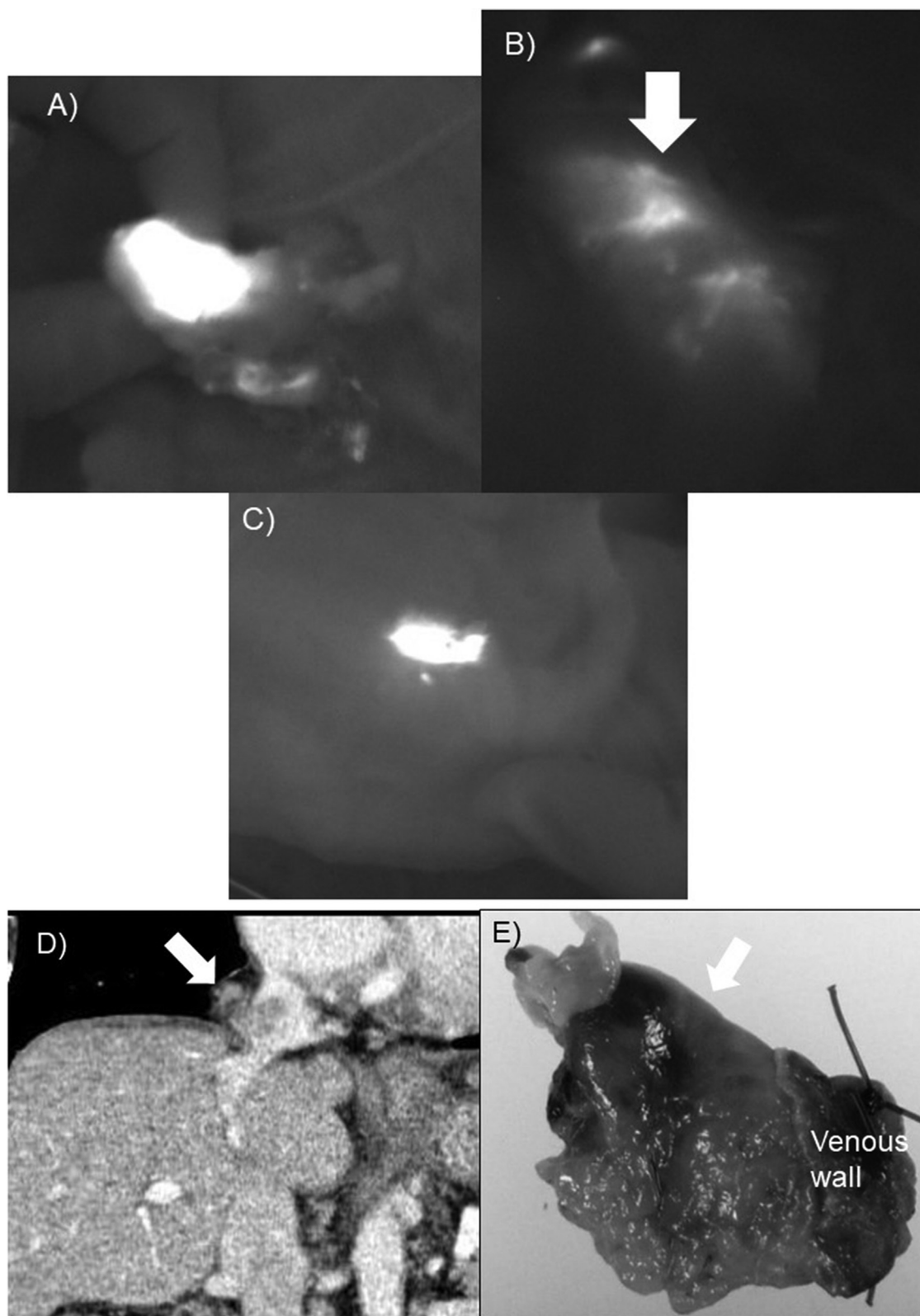


Fig. 4. The fluorescent tissue was locally resected and was diagnosed as a metastatic lymph node of HCC by histological examination. A metastatic lesion could be seen in the vena cava wall (B; thick arrow) and the tumor thrombus in the vena cava could be resected (C). The preoperative CT and resected metastatic TT of HCC in vena cava (D and E; thick arrow).

node metastasis from HCC was detected in the right diaphragm and a filling defect mass was observed in the supra-hepatic vena cava via the right infra-phrenic vein. The AFP level was highly increased as 5853 ng/mL at the time of tumor relapse. As

there were no other metastases, resection of the metastatic node and tumor thrombectomy were performed. The location of the metastatic node and TT in the vena cava could not be observed by the outline appearance because of postoperative adhesive

connective tissue; however, the fluorescent metastatic node lesion and the venous wall were visualized by ICG-PDE (Fig. 4A and B). Thus, the TT could be completely resected, which was also confirmed by ICG-PDE (Fig. 4C). Histological examination revealed a TT of well-differentiated HCC as well as the primary HCC. The comparative preoperative CT image and resected specimen of TT attached wall of vena cava (Fig. 4D and E). The specimen showed a mild chronic hepatitis. Although the liver specimen was not obtained, the appearance of the remnant liver was not cirrhotic during operation. Preoperative diagnosis of TT originated from HCC was performed by AFP level and imaging analysis without biopsy and the final diagnosis was eventually performed by the histological examination for resected specimens.

4. Discussion

Recently, ICG-PDE has been widely applied to detect lymph nodes via the lymphatic duct in the fields of breast and digestive surgery [4,10] or to detect vascular flow in surgery [5,11]. The PDE system is useful for observing real-time alterations of albumin-conjugated ICG. In the field of liver surgery, ICG-PDE has also been used to detect hypervascular tumors on the liver surface, hepatic segmentation, biliary leakage and status for biliary surgery [6,12]. Thus, the usefulness and reliability of ICG-PDE in this field have been clarified. A limitation of this test is that the depth of tissue detectable by ICG-PDE is approximately less than 10 mm. ICG that has combined with serum protein in the liver usually washes out within several hours, but remains trapped for a long period within liver tumors, particularly HCC [6,12]. The mechanisms underlying retention in malignancies have been reported by Ishizawa et al. [13] The near-infrared ray detector for the ICG-PDE system has become compact and inexpensive [5].

With the above background, we expected that the metastasized lesions from HCC or other hypervascular liver tumors could be well detected by the ICG-PDE system as well. HCC mostly recurs in the liver, but lymph node or other organ metastases are relatively rare [14]. It may be difficult to detect metastases buried in the tissue because HCC itself is not hard tumor. In the case of lymph node metastasis, resection of only the metastatic node is desired because extended node dissection leads to massive lymphorrhoea or ascites in patients with chronic injured liver. Therefore, a diagnostic detection tool is also required as well as for primary diagnosis. Satou et al. reported that the positive predictive value of ICG fluorescent imaging for extrahepatic metastasis of 24 lesions of HCC was 100% and the negative predictive value was 50, respectively [15]. In our series, metastases of moderately differentiated HCC to the lymph nodes or adrenal glands could be clearly observed with the ICG-PDE system. It can be applied to confirm the remaining tumor tissues. Furthermore, the TT of HCC was often observed in the portal vein, hepatic vein and bile duct [16]. In the case of PVTT, the surgeon can confirm the extended area of TT by touch palpation or outline appearance as an expansion of the portal vein. However, TT from HCC is also soft tissue and it is sometimes difficult to judge by these procedures. Therefore, we attempted ICG-PDE for detection of the intravascular TT extension in our series. As a result, the strong fluorescent lesion could be clearly detected and we could precisely open the veins at the tip of the TT. After resection of the TT, it was possible to detect the extension of thrombosis with this procedure as well. Accumulation of ICG might be observed in cirrhotic liver as a pseudo-positive signal [17] and, however, all cases did not showed histological cirrhosis in the present series. ICG-PDE is usually only applied as a diagnostic tool during operation and, however, this could not be applied as a preoperative diagnosis or a post-operative surveillance in case the liver biopsy was available because diagnos-

tic accuracy was low in comparison with other imaging diagnosis and histological examinations.

According to recent reports, the fluorescence patterns of liver tumors vary among homogeneous strong staining, heterogeneous weak staining, staining surrounding the tumor or no staining [13,18]. Among the liver malignancies, hypervascular tumors, such as HCC, some cholangiocarcinoma and neuroendocrine tumors may show strong staining by ICG retention [8]. In cases where the main tumors do not demonstrate strong fluorescence, it may also be difficult to detect the metastatic lesions as well. Among accessory lesions in the liver, cysts and hemangiomas were strongly identifiable from ICG-PDE, thus false-positive diagnoses must be ruled out [8]. After performing ICG-PDE to detect the metastatic lesions, it may be necessary to compare with the fluorescence pattern of the main tumor as in the presented case.

5. Conclusions

Future applications of ICG-PDE have recently been proposed. One approach is for tumor detection during laparoscopic hepatectomy [19]. Development of a laparoscopy-exclusive ICG-PDE system is expected. Such laser-application tools could be improved for future approaches. In conclusion, we have demonstrated that ICG-PDE allows for easy examination of the metastatic tumor distribution of HCC after hepatectomy and potentially facilitates decision-making for tumor resection. This new imaging modality may be useful for detecting metastatic or intravascular extensions of HCC.

Conflict of interest

The authors have no conflicts of interest to disclose.

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The authors have no extra or intra-institutional funding to declare.

Ethical approval

An ethical approval was not required at institute and nation policy in Japan.

Consent

Obtained signed consent in all regarding any clinical and research examination using each patient information before operation. This consent was obtained as paper documents.

The chief of ethics committee at University of Miyazaki stated that exhaustive attempts have been made to contact the families and that the paper has been sufficiently anonymised not to cause harm to the patients or their families.

Last author is a dean of university of medicine at Nagasaki and the first author is a chief director and professor and, therefore, we declare the head of our medical team and university hospital accepts responsibility for their consents.

Author contribution

All authors contributed patient managements and intraoperative supports equally in this case report. The principle author was an author and chairman, and was the main operators in technical parts. All authors approved the final version of the manuscript to be submitted.

Registration of research studies

This case series has been registered to researchregistry3518 (Research Registry Unique Identifying Number) in January 06, 2018.

Guarantor

Takeshi Nagayasu.

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