



# Navigation surgery using indocyanine green fluorescent imaging for hepatoblastoma patients

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## Abstract

**Background** Technology for detecting liver tumors and identifying the bile ducts using indocyanine green (ICG) has recently been developed. However, the usefulness and limitations of ICG navigation surgery for hepatoblastoma (HB) have not been fully clarified. We herein report our experiences with surgical navigation using ICG for in HB patients.

**Methods** In 5 HB patients, 10 ICG navigation surgeries were performed using a 10-mm infrared fluorescence imaging scope after the injection of 0.5 mg/kg ICG intravenously. The surgical and clinical features were collected retrospectively.

**Results** Navigation surgery using ICG was performed for primary liver tumors in 4 cases, and the timing of ICG injection was  $90.5 \pm 33.7$  h before the operation. All tumors exhibited intense fluorescence from the liver surface. ICG navigation for the primary liver tumor was useful for detecting the residual tumor at the stump and invasion to the diaphragm during surgery. Six lung surgeries using ICG navigation were performed. The timing of ICG injection was  $21.8 \pm 3.4$  h before the operation. The size of the metastatic tumor was  $7.4 \pm 4.1$  mm (1.2–15 mm). Of 11 metastatic tumors detected by computed tomography (CT), 10—including the smallest tumor (1.2 mm)—were able to be detected by ICG from the lung surface. The depth of the 10 ICG-positive tumors from the lung surface was  $0.9 \pm 1.9$  mm (0–6 mm), and the depth of the single ICG-negative tumor was 12 mm. One lesion not detected by CT showed ICG false positivity.

**Conclusion** Navigation surgery using ICG for patients with HB was useful for identifying tumors and confirming complete resection. However, in ICG navigation surgery, we must be aware of the limitations with regard to the tumor size and the depth from the surface.

**Keywords** Indocyanine green · Hepatoblastoma · Navigation surgery

## Introduction

Hepatoblastoma (HB) is the most common malignant liver tumor in childhood. Chemotherapy including cisplatin has been shown to be effective, and adjuvant chemotherapy is usually given to HB patients [1, 2]. However, the best way

to achieve a cure is complete resection of the tumor, which leads to a good oncologic outcome, even in cases of lung metastasis [3].

In visualization by indocyanine green (ICG), injected ICG is taken up by tumor cells, such as HB cells, and normal hepatocytes. In the normal hepatocytes, ICG is excreted into the bile and disappears within a few hours [4]. However, in tumor cells, excretion is inhibited, and ICG persists. This ICG can then be detected using a camera with a fluorescent light. Technology for detecting liver tumors and identifying the bile ducts during liver surgery using ICG has recently been developed [5]. A few papers on HB have described the detection of lung and pleural metastasis and liver resection [6–8]. However, the usefulness and limitations of ICG navigation surgery for HB have not been fully clarified.

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We herein report our experiences with surgical navigation using ICG for primary tumor resection and metastasectomy of the lung in HB patients and limitation associated with this navigation surgery.

## Materials and methods

Ten ICG navigation surgeries were performed in five HB patients at the Department of Pediatric Surgery, Kyushu University, between February 2017 and May 2018. Among these five HB patients, one showed PRETEXT II, three showed PRETEXT III and one showed PRETEXT IV statuses. Two of the patients had lung metastasis: one with multiple lung metastases at the diagnosis and the other with lung recurrence after liver resection and chemotherapy.

Regarding ICG navigation surgery, ICG was injected intravenously at 0.5 mg/kg body weight for all cases preoperatively, and the liver tumor and lung metastatic tumors were examined using a 10-mm endoscopic ICG near-infrared fluorescence imaging system (D-LIGHT P, Karl Storz, Germany) intraoperatively. The clinical and pathological data were collected. The tumor size and the depth of the tumor from the liver and lung surface were measured using preoperative computed tomography (CT) images (minimum slice interval: 0.5 mm).

This study was performed according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labour and Welfare of Japan on July 30, 2003 (revised 2008), and complied with the 1964 Declaration of Helsinki (revised 2008). This study was approved by the Ethics Committee in our institution (28–119).

## Results

The clinical data of the HB patients who underwent ICG navigation are shown in Table 1. Navigation surgery using ICG was performed for primary liver tumors in four HB cases. Extended right hepatectomy was performed for three patients and liver transplantation for one patient. The timing of ICG injection was  $90.5 \pm 33.7$  h before the operation. The size of the liver tumors was  $75.0 \pm 41.8$  mm (40–135 mm). All liver tumors were visible from the liver surface and exhibited intense fluorescence using ICG detection (Fig. 1a). ICG navigation for liver surgery was useful for detecting the residual tumor at the resection stump, especially surrounding the inferior vena cava (IVC) (Fig. 2a–c) and the invasion of the tumor into the diaphragm during surgery. No fluorescence was detected in the residual liver after resection, and all tumors were shown to be completely resected by a pathological examination.

Six navigation surgeries using ICG were performed for metastatic lung tumors in two cases. Both patients initially underwent bilateral lung partial resection. When recurrence was recognized in both cases after resection, left upper lobectomy and re-partial resection were performed in one patient each. The timing of ICG injection was  $21.8 \pm 3.4$  h before lung resection. A total of 11 metastatic tumors were detected by preoperative CT, and the size of the metastatic tumors was  $7.4 \pm 4.1$  mm (1.2–15 mm). The operation time of partial resection was  $142.2 \pm 26.6$  min (101–174 min). Of the 11 metastatic lung lesions detected by preoperative CT, 10 were able to be detected by ICG from the lung surface (Fig. 1b). The depth of the 10 ICG-positive tumors from the lung surface was  $0.9 \pm 1.9$  mm (0–6 mm), and the depth of the single ICG-negative tumor was 12 mm, making it the deepest lesion (Fig. 3). This tumor was confirmed to be ICG-positive using a resected sample after surgery. Of the 10 tumors detected using ICG, 2 were not palpable from the lung surface during surgery because the size of tumors was very small and the lung tissue had been damaged due to adhesion between the lung surface and the chest wall (Fig. 4). All 11 tumors detected by preoperative CT were shown to consist of HB cells according to pathological examinations. One lesion not detected by CT showed ICG false positivity and exhibited weak fluorescence, and no HB cells were recognized on a pathological examination of a resected sample. In one case (Case 1) that underwent left upper lobectomy, ICG-positive lesion except one tumor detected CT was none and no tumor except one tumor detected CT was shown according to a pathological examination for resected left upper lobe. Therefore, no lesions showed false negativity in this case.

No adverse events concerning ICG injection were observed in all cases.

## Discussion

We performed ICG navigation surgery for liver resection and metastasectomy of the lung in HB patients. ICG navigation was useful for detecting lung metastasis even if the tumor was not palpable and for confirming complete resection of primary liver tumors. Only three papers about ICG navigation surgery for HB patients were already published. The first paper is about 2 cases of liver resection and one case of pulmonary metastasis resection. The second paper is about ten cases of pulmonary metastasis resection. The last paper is the case report about peritoneal metastasis resection in HB. They also reported the usefulness of ICG navigation surgery for HB patients.

The timing and dosage of ICG have already been reported in other studies. Kitagawa et al. reported that 0.5 mg/kg body weight ICG was injected intravenously 24 h before lung

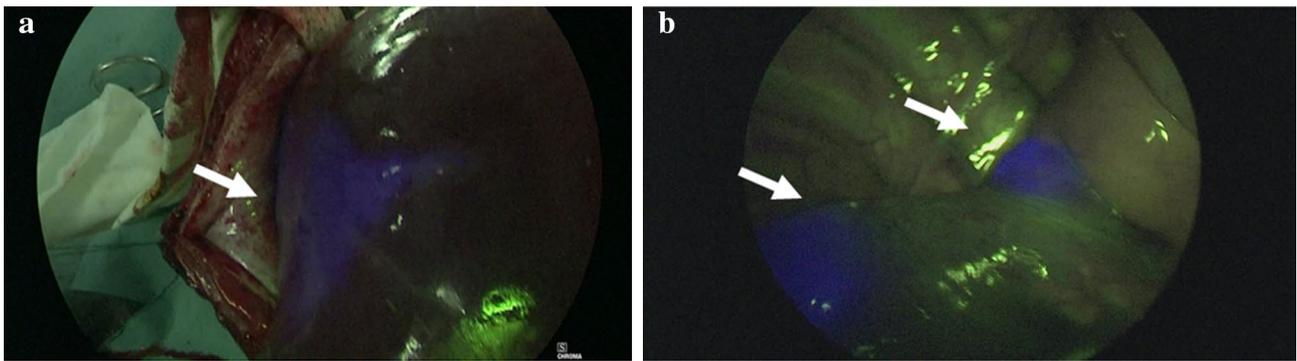
**Table 1** Clinical findings of the HB patients who underwent ICG navigation surgery

Case	Sex	Age (months)	PRE-TEXT	Surgical procedure	Open or endoscopic	AFP (ng/dL) at surgery	The number of the tumor (CT)	ICG positive lesion	Reoperation	Tumor size	Tumor depth from organ surface	Palpable or not	ICG dosage	Timing of ICG injection before surgery (h)	Operation time (min)	Usefulness
<i>Liver resection</i>																
1	M	35	III	Extended right hepatectomy	Open	80,013	1	1	-	70 mm	0 mm	-	0.5 mg/kg	138	363	Detection resection stump and invasion to the diaphragm
2	M	33	IV	Liver transplantation	Open	100,687	1	1	-	135 mm	0 mm	-	0.5 mg/kg	60	353	Detection resection stump and invasion to the diaphragm
3	M	32	III	Extended right hepatectomy	Open	509.9	1	1	-	55 mm	0 mm	-	0.5 mg/kg	76	436	Detection resection stump
4	F	12	III	Extended right hepatectomy	Open	35.6	1	1	-	40 mm	0 mm	-	0.5 mg/kg	88	399	Detecting resection stump and surrounding IVC
<i>Lung resection</i>																
1	M	34	III	Left lung partial resection	Open	52,185	2	2	-	10 mm, 15 mm	0 mm, 0 mm	Yes	0.5 mg/kg	19	174	
1	M	34	III	Right lung partial resection	VATS	52,185	2	3	-	5 mm, 10 mm	0 mm, 0 mm	Yes	0.5 mg/kg	18	147	
1	M	36	III	Left upper lobe lobectomy	Open	1010	1	0	Yes	10 mm	12 mm	Yes	0.5 mg/kg	20	177	

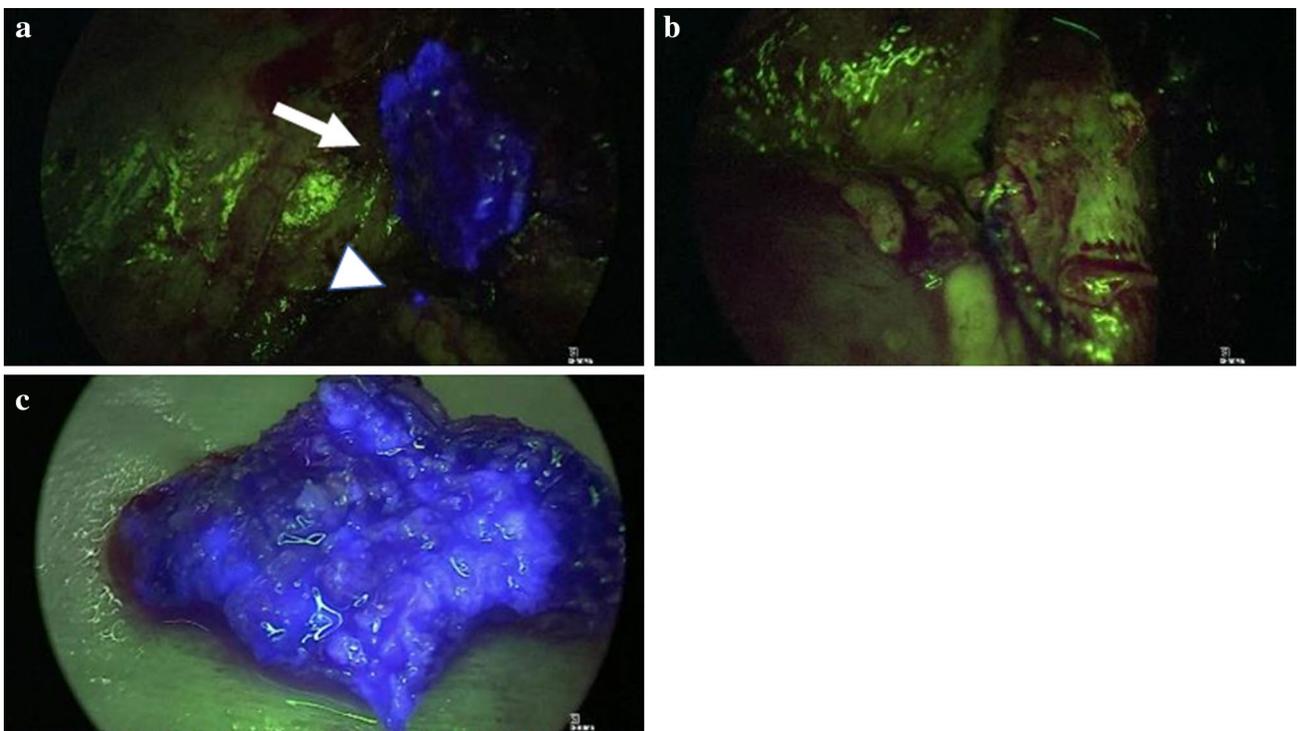
Table 1 (continued)

Case	Sex	Age (months)	PRE-TEXT	Surgical procedure	Open or endoscopic	AFP (ng/dL) at surgery	The number of the tumor (CT)	ICG positive lesion	Reoperation	Tumor size	Tumor depth from organ surface	Palpable or not	ICG dosage	Timing of ICG injection before surgery (h)	Operation time (min)	Usefulness
5	F	29	II	Right lung partial resection	Open	2553	2	2	–	9 mm, 9 mm	6 mm, 0 mm	Yes	0.5 mg/kg	23	151	
5	F	30	II	Left lung partial resection	Open	2553	2	2	–	7 mm, 3 mm	0 mm, 0 mm	Yes	0.5 mg/kg	24	138	
5	F	34	II	Right lung partial resection	Open	90	2	2	Yes	2.5 mm, 1.2 mm	1.5 mm, 1.5 mm	No	0.5 mg/kg	27	101	

M male, F female, VATS video-assisted thoracic surgery



**Fig. 1** **a** The primary liver tumor showed fluorescence using ICG navigation in Case 4 (white arrow). **b** The fluorescence of the two tumors of the lung during the VATS procedure in Case 1 (white arrow)



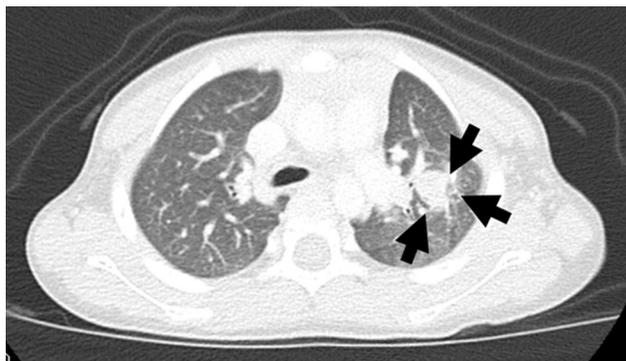
**Fig. 2** **a** ICG navigation detected the residual tumor surrounding the IVC (white arrow) and a spilled small tumor fragment in Case 4 (white arrowhead). **b** No fluorescence was recognized in front of the

IVC after resection. **c** The resected sample was detected using ICG navigation showing strong fluorescence

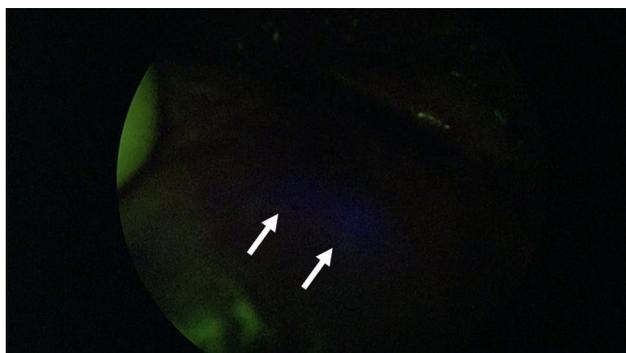
resection, and Yamamichi et al. reported injecting the same dosage intravenously 4 days before liver resection and 24 h before lung resection [6, 7]. In cases of lung surgery, normal lung cells are unable to take up ICG. In the current study, we injected ICG 18–27 h before surgery for lung resection, and lung metastasis was clearly detected in all cases. In contrast, for liver surgery, normal liver cells are able to take up ICG, similar to HB cells, although the washout timing differs between tumor cells and normal liver cells. Therefore, the timing of the ICG injection is important for accurately

detecting HB. We injected ICG 60–138 h before surgery for liver resection and did not note any marked difference in the sensitivity of the ICG intensity by the timing of ICG injection. However, comparing the ICG intensity by the timing of injection was difficult. In the future, the most suitable timing of ICG injection will need to be examined after the accumulation of more HB cases with ICG navigation.

Several types of equipment are available for ICG detection during navigation surgery, such as a charge-coupled device (CCD) camera [6] and a telescopic detector [5]. We



**Fig. 3** CT image showing the tumor without ICG detection. This was the deepest tumor from the lung surface (12 mm deep)



**Fig. 4** ICG navigation detected two tumors measuring 1.2 and 2.5 mm in diameter that were not palpable from the lung surface

used a telescopic detector in the current study. We think that the sensitivity of the ICG intensity is high when using the telescopic detector because the tip of the scope is quite close to the tumors. Moreover, ICG navigation surgery using the telescopic detector in endoscopic surgery also has an advantage over open surgery because the surgical field can be perfectly darkened and thus increase the sensitivity of ICG. In the current study, one VATS surgery had already been performed via an ICG navigation approach, and the tumor had been clearly detected. Palpation was found to be important to detect HB metastatic lung tumors. Therefore, open surgery has some advantages over thoracoscopic surgery when performing lung metastatectomy for HB patients. In the future, the detection of lung tumors using ICG is thus considered to be more sensitive than detecting such tumors using palpation in HB patients. As a result, thoracoscopic surgery using ICG navigation may become the standard surgical approach for the treatment of HB patients, and this phenomenon is expected to lead to the performance of less invasive treatment for HB patients.

The limited detectability of ICG for metastatic lung lesions may be associated with the relationship between the

tumor size and the distance from the organ surface. However, these limitations were not clearly identified in the present study, although the minimum detectable tumor size was 1.2 mm. Kitagawa et al. previously reported that they were able to detect a metastatic tumor of 0.062 mm in diameter in the lung of an HB patient [6], but they did not mention the tumor depth from the lung surface. A previous study reported that navigation surgery using ICG could not detect the tumors located at a depth of more than 10 mm from the organ surface, and that finding was similar to our present findings [9].

In HB, complete resection is the rule for achieving the best oncologic outcome [3]. However, huge HB in the liver sometimes shows invasion to the IVC and major vessels, and whether or not complete resection has been achieved can be unclear during surgery. Two of our patients showed attachment to the diaphragm, and one had a residual tumor around the IVC during surgery. All patients were evaluated using ICG navigation and additional resection was performed for the residual tumor around the IVC in case 4. It is easy to confirm the presence of residual tumors using the ICG navigation.

Concerning other detecting methods for tiny metastatic tumors, preoperative CT guide marking and an Augmented Reality navigation system have been previously reported [10, 11]. However, patients who undergo preoperative CT examinations must be moved to the surgical room from the CT room. Therefore, ICG navigation surgery has an advantage over these techniques with regard to convenience.

In conclusion, navigation surgery using ICG for patients with HB was useful for identifying tumors and confirming complete resection. In the future, the suitable timing of the ICG injection and limitations with regard to the depth from the organ surface and the tumor size will be explored after the accumulation of more HB cases with ICG navigation.

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## Compliance with ethical standards

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

## References

1. Hiyama E, Hishiki T, Watanabe K, Ida K, Yano M, Oue T, Iehara T, Hoshino K, Koh K, Tanaka Y, Kurihara S, Ueda Y, Onitake Y (2015) Mortality and morbidity in primarily resected hepatoblastomas in Japan: experience of the JPLT (Japanese Study Group for Pediatric Liver Tumor) trials. *J Pediatr Surg* 50:2098–2101
2. Tajiri T, Kimura O, Fumino S, Furukawa T, Iehara T, Souzaki R, Kinoshita Y, Koga Y, Suminoe A, Hara T, Kohashi K, Oda Y, Hishiki T, Hosoi H, Hiyama E, Taguchi T (2012)

- Surgical strategies for unresectable hepatoblastomas. *J Pediatr Surg* 47:2194–2198
3. Hishiki T, Watanabe K, Ida K, Hoshino K, Iehara T, Aoki Y, Kazama T, Kihira K, Takama Y, Taguchi T, Fujimura J, Honda S, Matsumoto K, Mori M, Yano M, Yokoi A, Tanaka Y, Fuji H, Miyazaki O, Yoshimura K, Takimoto T, Hiyama E (2017) The role of pulmonary metastasectomy for hepatoblastoma in children with metastasis at diagnosis: results from the JPLT-2 study. *J Pediatr Surg* 52:2051–2055
  4. Branch RA (1982) Drugs as indicators of hepatic function. *Hepatology* 2:97–105
  5. Graves C, Ely S, Idowu O, Newton C, Kim S (2017) Direct gallbladder indocyanine green injection fluorescence cholangiography during laparoscopic cholecystectomy. *J Laparoendosc Adv Surg Tech A* 27:1069–1073
  6. Kitagawa N, Shinkai M, Mochizuki K, Usui H, Miyagi H, Nakamura K, Tanaka M, Tanaka Y, Kusano M, Ohtsubo S (2015) Navigation using indocyanine green fluorescence imaging for hepatoblastoma pulmonary metastases surgery. *Pediatr Surg Int* 31:407–411
  7. Yamamichi T, Oue T, Yonekura T, Owari M, Nakahata K, Umeda S, Nara K, Ueno T, Uehara S, Usui N (2015) Clinical application of indocyanine green (ICG) fluorescent imaging of hepatoblastoma. *J Pediatr Surg* 50:833–836
  8. Yamada Y, Hoshino K, Mori T, Kawaida M, Abe K, Takahashi N, Fujimura T, Kameyama K, Kuroda T (2018) Metastasectomy of hepatoblastoma utilizing a novel overlay fluorescence imaging system. *J Laparoendosc Adv Surg Tech A* 28:1152–1155
  9. Kitai T, Inomoto T, Miwa M, Shikayama T (2005) Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer* 12:211–215
  10. Nara K, Oue T, Uehara S, Ueno T, Ibuka S, Nakahata K, Zenitani M, Umeda S, Yamamichi T, Honda O, Okuyama H (2016) Efficacy of CT-guided localization followed by video-assisted thoracoscopic surgery in children with tiny pulmonary nodules. *Asian J Endosc Surg* 9:328–331
  11. Souzaki R, Ieiri S, Uemura M, Ohuchida K, Tomikawa M, Kinoshita Y, Koga Y, Suminoe A, Kohashi K, Oda Y, Hara T, Hashizume M, Taguchi T (2013) An augmented reality navigation system for pediatric oncologic surgery based on preoperative CT and MRI images. *J Pediatr Surg* 48:2479–2483

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