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Research Article

Fluorescence-Guided Surgery with Indocyanine Green for Hepatoblastoma in a Child

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- Hepatoblastoma; Pulmonary metastases; Indocyanine green; Surgical navigation; Child

Abstract

Purpose: Complete resection of the primary lesion and lung metastases is important for the treatment of hepatoblastoma in children. Surgical navigation using Indocyanine green (ICG) is effective in identifying micro-lung metastatic lesions.

Method: We examined eight procedures performed on six cases of hepatoblastoma lung metastases. In all cases, ICG (0.5 mg/kg) was intravenously administered 24 hours before surgery to identify the lesion.

Results: Our cases included five males and one female, and the age at surgery ranged from 6 months to 12 years, and the affected side was the right side for five cases, the left side for one case, and both sides (including recurrent surgery) for two cases. The number of excised specimens was 34. Of those, 23 had tumor cells and 33 were ICG-positive. Of the 33 specimens, 23 were ICG-positive and had tumor cells, while 10 specimens were ICG-positive with no tumor cells. In addition, 18 out of 34 specimens were positive on preoperative computed tomography, and tumor cells were observed in all of them. There were 16 specimens that were negative on computed tomography but positive for ICG, of which six specimens showed tumor cells.

Conclusion: Fluorescence-guided surgery is useful for visualizing micro-lung metastases that cannot be detected by imaging modalities. However, there are some false positives. Therefore, it is necessary to develop a technique for recognizing true micro-lung metastases.

ABBREVIATIONS

CT: Computed Tomography; ICG: Indocyanine green; JPLT: Japanese Study Group for Pediatric Liver Tumor

INTRODUCTION

Hepatoblastoma is the most common type of liver tumor occurring in children, with an incidence of 1.5-2.0 per million children in Japan [1]. According to the Japanese Study Group for Pediatric Liver Tumor (JPLT), the 3-year survival rate for completely resected cases and microscopic residual group was 87.7%, but the 3-year survival rate for incompletely resected macroscopic disease and unresectable cases was 55.8% [2]. Clinical trials have shown that complete resection of the primary lesion and lung metastases are important for the treatment of hepatoblastoma [3].

Localized lung metastatic lesions were confirmed by preoperative image evaluation, intraoperative visual inspection, and palpation. A few recent studies have reported that fluorescence-guided surgery using Indocyanine green (ICG) is effective in identifying micro-lung metastatic lesions [4-7]. This is the first report describing the sensitivity and specificity of ICG-guided surgery in children with lung metastases of hepatoblastoma. We examined its effectiveness and characteristics in cases.

MATERIALS AND METHODS

Six patients with lung metastases of hepatoblastoma who underwent surgery at our center were included. Based on the JPLT-3 protocol, which is currently in progress, lung metastases was defined as "one or more lesions with a major axis of more than 1 cm or at least two lesions with a major axis of more than 5 mm in the chest CT examination at the first visit." ICG-guided surgery was performed twice in two cases; therefore, eight operations were performed in total. In all cases, ICG (0.5 mg/kg; Diagono Green ®, Daiichi Sankyo in Japan) was intravenously administered 24 hours before surgery. Surgery was performed under general anesthesia and isolated lung ventilation. The tumor was confirmed by preoperative computed tomography (CT), and location of tumor was identified by visual inspection and palpation during surgery. During the surgery, the entire surgical field was observed with a Photodynamic Eye (PDE®, Hamamatsu Photonics, Japan), and all lesions detected in the preoperative image were identified. ICG fluorescence was detected during

surgery with a charge-coupled device camera and confirmed by all surgeons and assistants. All tumors that were identified by inspection and palpation and ICG fluorescence were wedge-shape resected. . A Photodynamic Eye was used again to re-confirm that the resected specimens were fluorescing.

There were no specific exclusion criteria. All procedures used in this research were approved by the Ethical Committee of the National Center for Child Health and Development. For specimens resected by ICG-guided surgery, retrospective data on preoperative CT findings, palpable mass, ICG uptake, and histopathological findings were extracted from medical and surgical records. We calculated the specificity, sensitivity, and positive and negative predictive values of ICG-guided surgery using Microsoft Excel.

RESULTS

The age at surgery was 6 months to 12 years; the right side was affected in five cases, left side in one case, and both sides in two cases (including recurrent surgery). Of the eight procedures, two were performed for recurrent lung lesions. Table 1 summarizes the treatment strategies of our six cases and eight procedures. Hepatectomy was performed in four out of six cases (Cases 2, 3, 4, and 6), and liver transplantation was performed in two cases (Cases 1,5). In both patients who underwent liver transplantation, the lung metastases had been resected before liver transplantation (Cases 1 and 5). One patient had recurrence in the right lung twice after liver transplantation (Case 1).Two of the four patients might be judged to be difficult to perform hepatectomy and scheduled for liver transplantation. ICG-guided surgery was performed to control external hepatic metastatic lesions in these two cases (Cases 2 and 3).In one case, hepatectomy was performed three times for recurrent hepatoblastoma and ICG-guided surgery was performed for resection of both liver and lung tumor in fourth operation. (Case 4). However, numerous fluorescent lung lesions were observed (Figure 1). Therefore, chemotherapy was prioritized over resection, and eight palpable lesions were resected for detecting pathological diagnosis.In the remaining case, a recurrent liver tumor was observed after hepatectomy, and partial liver resection was performed. After that, ICG-guided surgery was performed for lung metastases 5 years later (Case 6).

As a special case, a nodule 4 mm in size was visualized by preoperative CT, but no ICG fluorescence was observed in the operative findings, and the tumor was not palpated. We carefully monitored this lesion without excision (one lesion of Case 5, data not shown). No recurrence occurred at this lesion.

The thirty four lung tissues resected by ICG-guided surgery were classified according to preoperative CT findings, tumor palpation, and intraoperative ICG fluorescence findings (Figure 2). Preoperative CT showed 18 tumor lesions including 17 ICG-positive specimens and 1 ICG-negative specimen, all of which were palpable during operation.All 18 specimens histologically had viable cells. On the other hand, 16 of the resected specimens were not visualized using preoperative CT. All lesions were palpated and ICG-positive, but only 6 were histologically positive for viable cells while 10 were negative.As a result of histopathological examination of the 34 specimens, viable cells were found in 23 specimens (68%). Of the 34 specimens, 33 were ICG-positive, of which 23 (70%) had viable cells and 10 (30%) had no viable cells. The sensitivity, specificity, and positive and negative predictive values of ICG-guided surgery were 100%, 9%, 70%, and 100%, respectively, and the false positive rate (ICG negative among resected neoplastic lesions) was 91%. The false negative rate (ICG positive among resected neoplastic lesions) was 0% (Table 2). CT examination had the sensitivity, specificity, and positive and negative predictive value of 74%, 91%, 94%, and 63%, respectively; a false positive rate of 9%; and a false negative rate of 26% (Table 3). In addition, 18 specimens (53%) were positive on preoperative CT images among 34 specimens, and one of these specimens was positive on the CT image but

Table 1: Treatment strategies of six cases of hepatoblastoma lung metastases.

Case	PRETEXT	Lung metastases pre-surgery	Chemotherapy pre-surgery	Timing of lung metastatic resection	Lung metastatic resection procedure	Liver transplantation
1	IV	+	+	After living-donor liver transplantation *	Partial right lung resection	+
1 (rec)	IV	+	+	After living-donor liver transplantation	Partial right lung resection	+
2	IV	+	+	Before excision of the primary liver tumor	Partial right lung resection	-
3	II	-**	+	Before excision of the primary liver	Partial bilateral lung resection	-
3 (rec)	IV	+	+	After excision of the primary liver	Partial right lung resection	-
4	IV	+	+	After excision of the primary liver	Partial right lung resection	-
5	IV	+	+	Before living-donor liver transplantation	Partial bilateral lung resection	+
6	IV	+	+	After resection of recurrent liver tumor	Partial left lung resection	-

Rec: recurrence
Note: *Partial lung resection (no indocyanine green administration) was performed before liver transplantation.
**Computed tomography showed 1.5-mm large nodules on both sides.

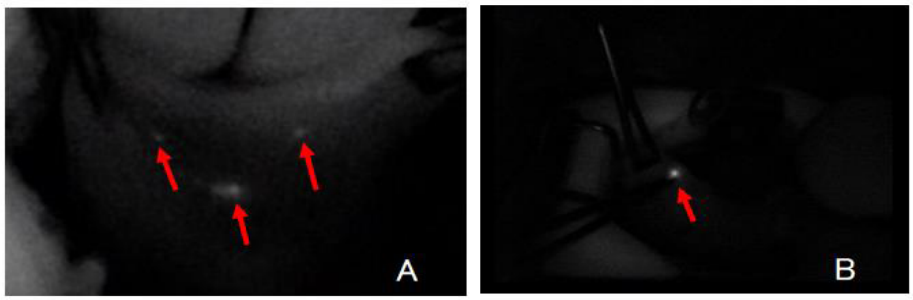

Figure 1 Numerous micro-fluorescent lesions on the surface of the lung.
In case 4, numerous ICG-positive lesions were observed during the operation. A: S3 ICG-positive lesions (arrow), B: S8 ICG-positive lesion (arrow). ICG: Indocyanine green

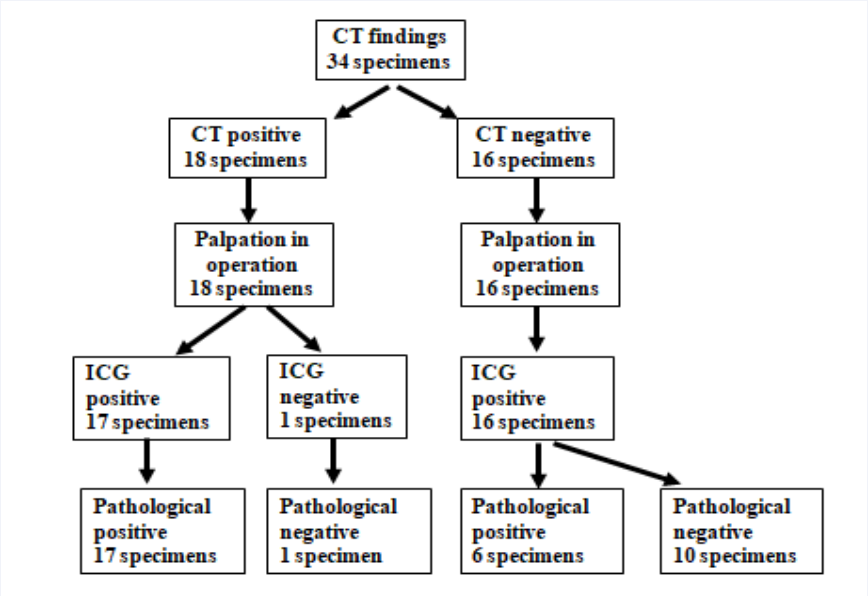

Figure 2 Characteristics of 34 resected specimens.
Thirty-four partial lung tissues detected by ICG fluorescence were resectedand classified according to CT findings, palpable mass, and fluorescence emission. Tumor cells in each specimen were pathologically examined.
Tumor cells were found in all 18 specimens with positive CT, intraoperative, and ICG findings. Of the 16 specimens with negative CT findings, positive intraoperative findings, and positive ICG findings, six were positive for tumor cells. No tumor cells were found in the remaining 10 lesions with negative CT findings, positive intraoperative findings, and positive ICG findings. No lesions were negative CT findings, palpable mass, and negative ICG findings. ICG: Indocyanine green, CT: Computed Tomography

Table 2: Indocyanine green(ICG) navigation and histopathological findings.

	Pathologically positive	Pathologically negative	Total
ICG positive	23 specimens	10 specimens	33 specimens
ICG negative	0 specimen	1 specimen	1 specimen
Total	23 specimens	11 specimens	34 specimens

ICG: Indocyanine green

negative on ICG. However, there were 16 ICG-positive specimens, of which six had viable cells (38%) (Figure 2).

Table 4 shows the pathological findings of the 10 false-positive ICG samples. Fibrous tissue, including small blood vessels was found in two specimens. The other two specimens showed inflammatory cell infiltration and macrophage accumulation (Figure 3). In addition, granulation surrounding the suture used for the first operation was observed (Figure 4). The other six cases were determined to be alveolar tissue.

DISCUSSION

ICG is used to estimate liver function, as the administered ICG

Table 3: Computed Tomography (CT) and histopathological findings.

	Pathologically positive	Pathologically negative	Total
CT positive	17 specimens	1 specimen	18 specimens
CT negative	6 specimens	10 specimens	16 specimens
Total	23 specimens	11 specimens	34 specimens

CT: Computed Tomography

Table 4: Pathological findings of Indocyanine green false positives.

Case	side	Lung area	Pathological findings
1	right	S4	Fibrous tissue containing small blood vessels
		S5	Fibrous tissue containing small blood vessels
2	right	S2	Alveolar tissue
		S2/3	Alveolar tissue (containing blood vessels)
		S6	Alveolar tissue (thickening of blood vessel wall and infiltration of inflammatory cells
3 (rec)	right	S5	Thickening of blood vessel wall, accumulation of macrophages, and thread
4	right	S3	Alveolar tissue
		S3	Alveolar tissue
		S5	Alveolar tissue
		S5	Alveolar tissue

Rec: recurrence

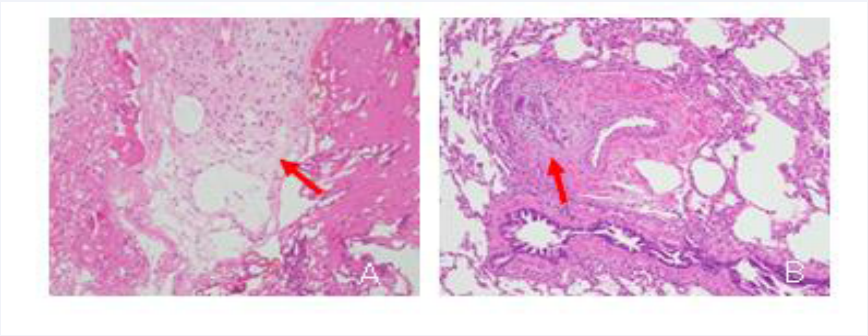

Figure 3 Pathological findings of ICG false positive lesions.
A: Fibrous tissue, including small blood vessels, and foci of foamy histiocytes (arrow).B:Granulation surrounding the suture used for the first operation was observed.ICG: Indocyanine green

Figure 4 Operative findings of ICG false positive lesions.
Similar to ICG-positive tumor lesions (arrow), purple-coloredVicryl thread ® also fluoresces (arrowhead).ICG: indocyanine green

is taken into the liver as a foreign substance and excreted in bile. In liver cirrhosis and liver tumors, excretion is delayed, resulting in a difference in contrast between normal and neoplastic tissues. By intravenous ICG administration before surgery, ICG accumulates in impaired liver tissue or tumor tissue. Tissue that taken ICG is excited by infrared rays at wavelength of 750-800 nm and fluoresces [8,9]. This phenomenon has already been clinically applied in adults for the evaluation of the hepatectomy range and resection margin of hepatocellular carcinoma [10,11] and biliary angiography of hepatectomy [12]. In the field of pediatric surgery, there are some reports that ICG-guided surgery is useful for visualizing micro-lung metastases that cannot be detected by alternative imaging modalities [4,5]. In our cases six specimens of our resected 34 specimens were not visualized by preoperative CT, but identified by positive ICG, and all lesions had viable cells confirmed by histopathology examination.

From our data, we consider that the rule of partial lung resection using ICG should be as follows: (1) positive CT findings and palpation and ICG-positive lesions were found to have viable cells in all cases, so they should be resected. (2) Positive CT findings and palpation and ICG-negative lesions or negative CT findings and palpation and ICG-positive lesions were found in some cases without viable cells. These cases were after chemotherapy and pathological findings suggest chemotherapeutic change. We consider excision is appropriate in these cases because excision of all metastatic suspicious lesions leads to improved prognoses of lung metastases of hepatoblastoma. (3) Positive CT findings, negative palpation, and ICG-negative lesions are rare. It is difficult to resect lesions because both palpation and ICG are negative. Indications only by CT must be considered a false positive; therefore, careful follow-up is necessary. (4) Negative CT findings, negative palpation and ICG-positive lesions were assumed to be absent but were found in a case with repeated local and metastatic recurrence. In case 5, ICG-guided surgery was attempted under thoracotomy at the recurrence. Numerous fluorescent nodules were found on the surface of the lung. Some nodules were excised as much as possible, but it was difficult to excise all the fluorescent nodules because of the possibility of total pneumonectomy. Therefore, we expected subsequent chemotherapy to be effective. However, in this case, liver tumors and metastases are uncontrollable. We were able to show the pathological results of uncontrolled case but could not perform radical resection using ICG.

In adults, the specificity and sensitivity of ICG-guided surgery has already been observed for the identification of extrahepatic metastatic lesions of hepatocellular carcinoma. Satou et al. examined 28 extrahepatic lesions (including 5 lung lesions) and showed that the sensitivity, specificity, positive predictive value, and negative predictive value of ICG were 92%, 100%, 100%, and 50%, respectively [13]. In our experience, ICG-guided surgery has an excellent sensitivity of 100%, but the false positive rate can be as high as 91%. Based on this result, the final evaluation of lung metastases should be made by combining preoperative CT examination, intraoperative palpation, and ICG fluorescence. Furthermore we considered four patterns as described above and decided the indications for excision.

Regarding the cause of false positives in ICG-guided surgery, Kitagawa et al [5] explained that it is difficult to prepare appropriate specimen slides because the resected lesions are too small to detect histopathological findings. Another reason is also a possibility of fluorescence emission from tissues other than hepatoblastomas, such as thromboses, and normal alveolar cells [5]. Our results show that fibrous scar tissue, macrophage accumulation, Vicryl threads, adhesions, and atelectasis after chemotherapy treatment can be false positives (Table 4 and Figures 3, 4). From these findings, we speculated that lung metastatic lesions composed of viable cells may change into fibrous scar tissue or aggregation of macrophages after chemotherapy treatment. Therefore, false positive lesions should be considered due to be the possibility of ICG fluorescence.

The reasons for false negatives in ICG-guided surgery are related to the difficulty of identifying micro-lung lesions with a depth ≥10 mm from the lung surface, different degrees of absorption between tissues, or tissue adhesion that prevents the identification of ICG fluorescence [4,13]. In our study, there was only one false-negative case. We consider false negatives are quite rare because intraoperative diagnosis of resected specimens is performed immediately with a Photodynamic Eye. Our resected specimens after excision were all ICG-positive.

A major factor that affects fluorescence is the timing of ICG administration. In children, previous studies reported that effective administration advocate 24 hours [5] or 3-4 days [4] before surgery. Optimal recommendations have not been decided. A report describing the case of an adult patient recommended an optimal interval is at least two days between ICG administration and surgery because ofa good contrast between the liver parenchyma and tumor [13,14]. At our institution, based on previous reports, ICG was administered 24 hours before excision of lung metastases and 2-3 days before excisions of liver tumor.

CONCLUSION

ICG-guided surgery has been proven useful for identifying extrahepatic lesions, and the metastatic lung tissue contrast of hepatoblastomas is extremely high because normal lung tissue does not uptake ICG. There were some cases with micro-lung metastases that could not be visualized by CT but were clearly visualized using ICG-guided surgery. However, the false positive rate is high. Therefore, the development of a new procedure is necessary to improve the accuracy of ICG-guided surgery for detecting true metastatic lesions.

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