

Complete Removal of Adrenal Metastasis in Hepatocellular Carcinoma Using Indocyanine Green Fluorescent Imaging

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Abstract. *Aim: Our aim was to confirm the utility of Indocyanine green (ICG) fluorescence imaging for intraoperative detection of adrenal hepatocellular carcinoma (HCC) metastasis. Case Report: An 83-year-old man with a right adrenal HCC metastasis was admitted after complete remission of primary HCC and a metachronous left adrenal metastasis. He was treated with ICG fluorescence-guided limited resection to preserve adrenal function. ICG was administered intravenously at a dose of 0.5 mg/kg, 6 days before the operation. After removal of the entire suspicious metastatic HCC, ICG fluorescence imaging clearly demonstrated two illuminated lesions. The lesions were separately resected using an energy device. Finally, there were no ICG fluorescent lesions which meant residual tumor. Histopathological examination confirmed adrenal metastasis of moderately differentiated HCC in the initial specimen and the additional resected specimens. Three months after the operation, adrenal function was well preserved without recurrence of HCC. Conclusion: ICG fluorescence imaging is essential for complete resection of adrenal HCC metastasis.*

Indocyanine green (ICG), primarily used to evaluate functional reserve mainly before hepatectomy (1-3), is also used during surgical navigation as it can produce fluorescence upon illumination with near-infrared light (4-6). Several ICG-photodynamic eye (PDE) systems are available for both open and laparoscopic surgery (7-9). In liver surgery, ICG-PDE

systems are used to observe areas of ischemia and congestion as well as bile duct anatomy (4-9). Furthermore, ICG-PDE systems are useful for the detection of hepatocellular carcinoma (HCC), mainly for lesions on the liver surface (5-9). Although the mechanism of ICG accumulation in HCC cells is not fully known, HCC cells can incorporate ICG similar to hepatocytes but fail to secrete it into bile (5-7).

Several studies have recently demonstrated that ICG-PDE systems are a convenient approach for intraoperative detection of extrahepatic HCC metastases, including those in the lungs, adrenal glands, lymph nodes, as well as in portal vein tumor thrombosis and peritoneal dissemination (10-14). Only a small number of studies have reported the utility of ICG-PDE systems in the detection of adrenal metastases of HCC (10, 11). Small metastatic nodules are difficult to recognize with the naked eye or a standard laparoscopic view. Additionally, some metastatic HCCs have ill-defined borders with invasive features. For such cases, laparoscopic ICG-PDE systems are beneficial in detecting metastases and determining the extent of metastases that should be removed.

In an autopsy study of 398 patients with HCC, extrahepatic metastases were found in 39.1% of the patients while lung, bone, and adrenal metastases were at the rate of 74.5%, 24.8%, and 19.1%, respectively (15). Surgical resection is the first-choice treatment for adrenal metastases of HCC because of the high cure rate (16, 17) and partial resection is recommended to preserve adrenal function. Chemoembolization, ablation therapy by alcohol injection, radiofrequency or microwave, and radiotherapy are used alone or in combination for patients who are not suitable for surgical resection (17-20).

We herein present a patient with HCC to illustrate the utility of limited tumor resection using an ICG-PDE system to preserve right adrenal function. The patient developed left adrenal HCC metastasis that was treated by radiofrequency

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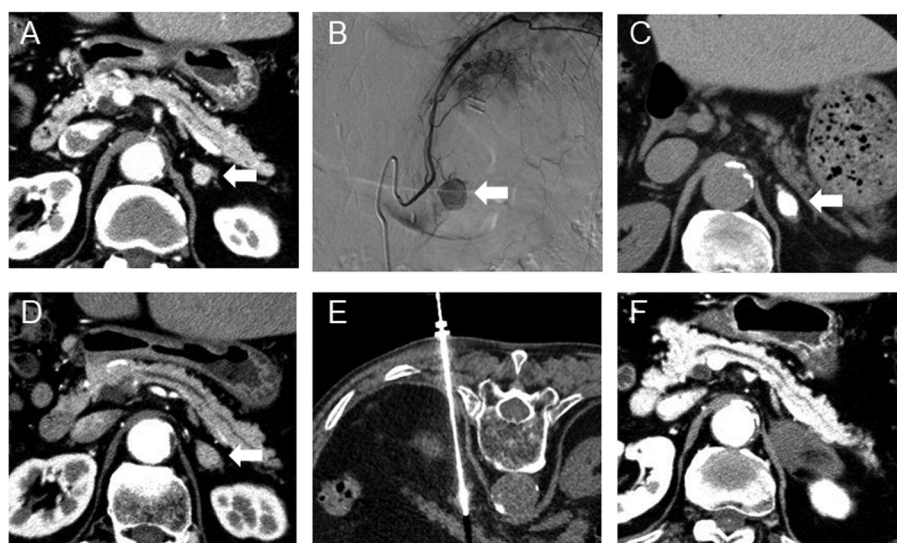


Figure 1. Serial images of the left adrenal metastasis during treatment. Early enhancement of the tumor, 15 mm in diameter, in the arterial phase of contrast-enhanced computed tomography (CT) (A) and tumor staining in digital subtraction angiography (B). (C) Dense lipiodol uptake is observed by non-contrast CT obtained one week after transarterial chemoembolization (TACE). (D) Recurrence at the treated site is observed in the arterial phase of contrast-enhanced CT performed ten months after TACE. (E) CT-guided radiofrequency ablation (RFA). (F) Follow-up contrast-enhanced CT obtained 14 months after RFA shows a hypoattenuating area with enhancement.

ablation (RFA) following chemoembolization. The treatment led to the complete destruction of the left adrenal gland, however, he later developed a solitary right adrenal HCC metastasis, which was successfully resected using an ICG-PDE system. The latter allowed the functional preservation of the right adrenal gland.

Case Report

An 83-year-old male patient underwent right hepatectomy for HCC (T3N0M0, stage III) (21) about five years earlier at another hospital. Two years and five months later, he was diagnosed with left adrenal metastasis and treated with transarterial chemoembolization (TACE) *via* the left inferior phrenic artery (Figures 1A-C). One year later he developed recurrent metastasis at the same site (Figure 1D). Computed tomography (CT)-guided RFA following TACE was successful (Figure 1E). The patient was determined to achieve complete tumor response, however, the left adrenal function was considered lost because of the complete destruction of the gland (Figure 1F). One year later, he developed a HCC metastatic lesion on the right adrenal (Figure 2A). Despite the two TACE procedures *via* the right inferior phrenic artery within a six-month period (Figure 2B), CT images showed an extra-adrenal HCC lesion with partial lipiodol accumulation and enhancement of the remnant tumor, suggesting local recurrence on follow-up images after TACE (Figures 2C-F).

Surgical partial resection of the right adrenal metastasis, 18mm in diameter, was performed to avoid the loss of adrenal function, and ICG-PDE-guided limited resection was planned. Briefly, 0.5 mg/kg ICG was administered intravenously six days prior to the surgery for simultaneous evaluation of liver function. Laboratory data before the surgery (Table I) indicated nonB/nonC hepatitis with diabetes mellitus and good liver function. Intraoperative findings were as follows: i) laparotomy was performed using the previous inverted L incision, ii) intraoperative ultrasonography suggested adrenal metastasis located on the right side of inferior vena cava, iii) no other metastases were observed inside or outside the liver. Distinguishing the HCC metastasis from the surrounding inflammatory fibrotic tissue and adrenal gland was difficult. Therefore, a laparoscopic near-infrared light camera system with a xenon light source and laparoscope (Karl Storz, Tuttlingen, Germany) was used for ICG fluorescent imaging. Briefly, the camera detected light on a wavelength of <820 nm. The camera head was positioned 20-30 cm away from the site, and the output intensity of near-infrared light was 4 mW/cm². The tumor, which was vaguely detectable by normal observation (Figure 3A), was clearly identified as a fluorescent tumor upon illumination (Figure 3D). The tissue around the tumor was hard to dissect because of the two previous TACE procedures. Clips and an energy device were used to ligate and dissect between the tumor and the surrounding tissue. After the removal of the entire metastatic HCC tumor, no other tumors were detected by endoscopic observation and intraoperative

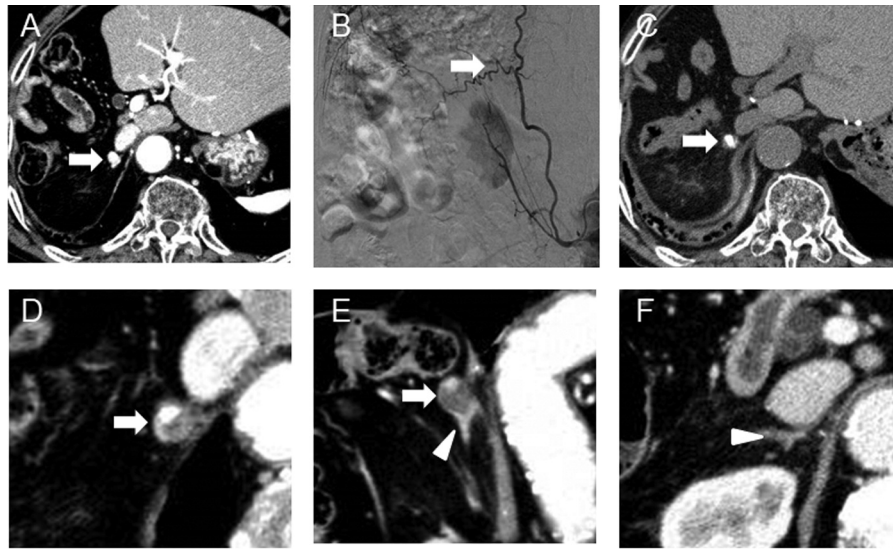


Figure 2. Serial images of the right adrenal metastasis during treatment. (A) Pretreatment contrast-enhanced CT image. (B) Subtraction angiography image before TACE. (C) Non-contrast CT image one week after TACE. Contrast-enhanced axial (D) and coronal (E) CT images in portal phase seven months after TACE. (F) Contrast-enhanced CT image one month after surgery. HCC metastasis (arrow) and adrenal gland (arrowhead).

Table I. Laboratory data.

Total protein	8.0	g/dl	White blood cell	6.5	$\times 10^3/\mu\text{l}$
Albumin	3.9	g/dl	Neutrocytes	63.7	%
Total bilirubin	0.7	mg/dl	Red blood cell	4.41	$\times 10^6/\mu\text{l}$
Direct bilirubin	0.2	mg/dl	Hemoglobin	12.3	g/dl
AST	23	U/l	Platelet	133	$\times 10^3/\mu\text{l}$
ALT	18	U/l			
LDH	259	U/l	HBs-Ag	(-)	
ALP	51	U/l	HBs-Ab	(-)	
γ -GTP	17	U/l	HCV-Ab	(-)	
ChE	279	U/l			
BUN	18.2	mg/dl	PT activity	68.5	%
Creatinine	1.06	mg/dl	APTT	36.6	s
Total cholesterol	206	mg/dl			
LDL	140	mg/dl	ICG R15	15.9	%
HDL	44	mg/dl			
TG	99	mg/dl	AFP	1.7	ng/ml
NH3	83	$\mu\text{g/dl}$	PIVKA-II	17	AU/ml
CRP	0.43	mg/dl	AFP-L3	<0.5	%
FBS	114	mg/dl	ACTH	37.8	pg/ml
Hb A1c	6.4	%	Cortisol	10.71	$\mu\text{g/dl}$

ALT: Alanine transaminase; AST: aspartate aminotransferase; γ -GTP: γ -glutamyl transpeptidase; LDH: lactate dehydrogenase; ALP: alkaline phosphatase; BUN: blood urea nitrogen; CRP: C-reactive protein; LDL: low-density lipoprotein cholesterol; HDL: high-density lipoprotein cholesterol; TG: triglyceride; FBS: fasting blood glucose; Hb: hemoglobin; HBs-Ag: Hepatitis B virus surface antigen; HCV-Ab: hepatitis C virus antibody; PT: prothrombin time; APTT: activated partial thromboplastin time; ICG R15: indocyanine green retention rate at 15 min; AFP: alpha-fetoprotein; PIVKA-II: protein induced by vitamin K absence or antagonist-II; ACTH: adrenocorticotrophic hormone.

ultrasonography (Figure 3B), however, the ICG-PDE system clearly demonstrated two additional ICG fluorescent areas (Figure 3E), which were individually resected using the energy device. Final assessment showed that there were no ICG

fluorescent lesions, indicating the absence of any probable residual tumors (Figures 3C and F). The operative time was 160 minutes, and the intraoperative bleeding amount was 30 g. Histopathological examination confirmed adrenal metastasis of

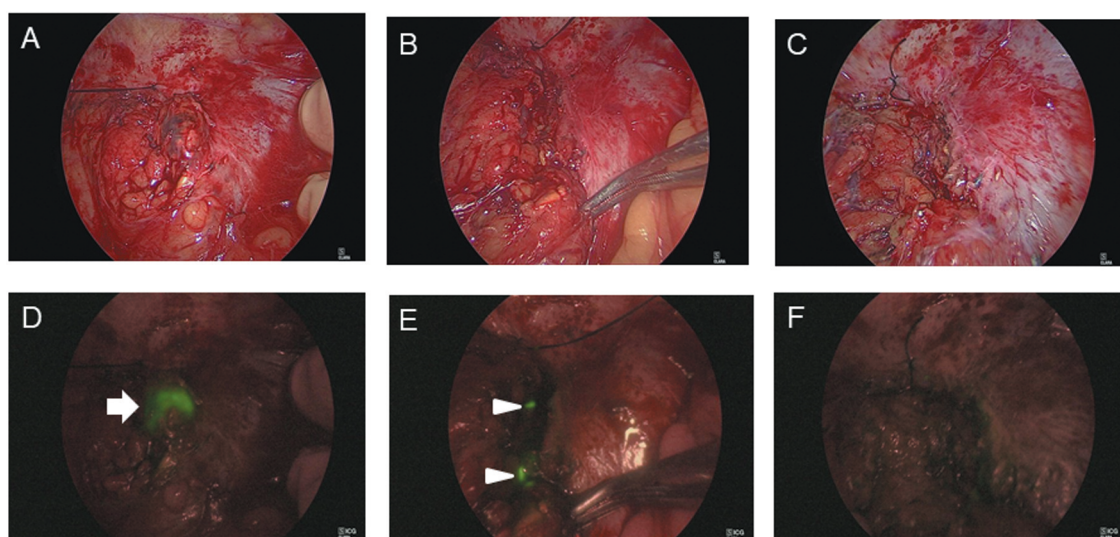


Figure 3. Intraoperative findings using indocyanine green (ICG) fluorescence endoscopy. Right adrenal metastasis prior to resection: (A) without ICG, (D) with ICG. After subtotal resection of right adrenal metastasis: (B) without ICG, (E) with ICG. After complete resection of right adrenal metastasis: (C) without ICG, (F) with ICG. An initial illuminated HCC metastasis (arrow) and two residual illuminated HCC metastases (arrowhead).

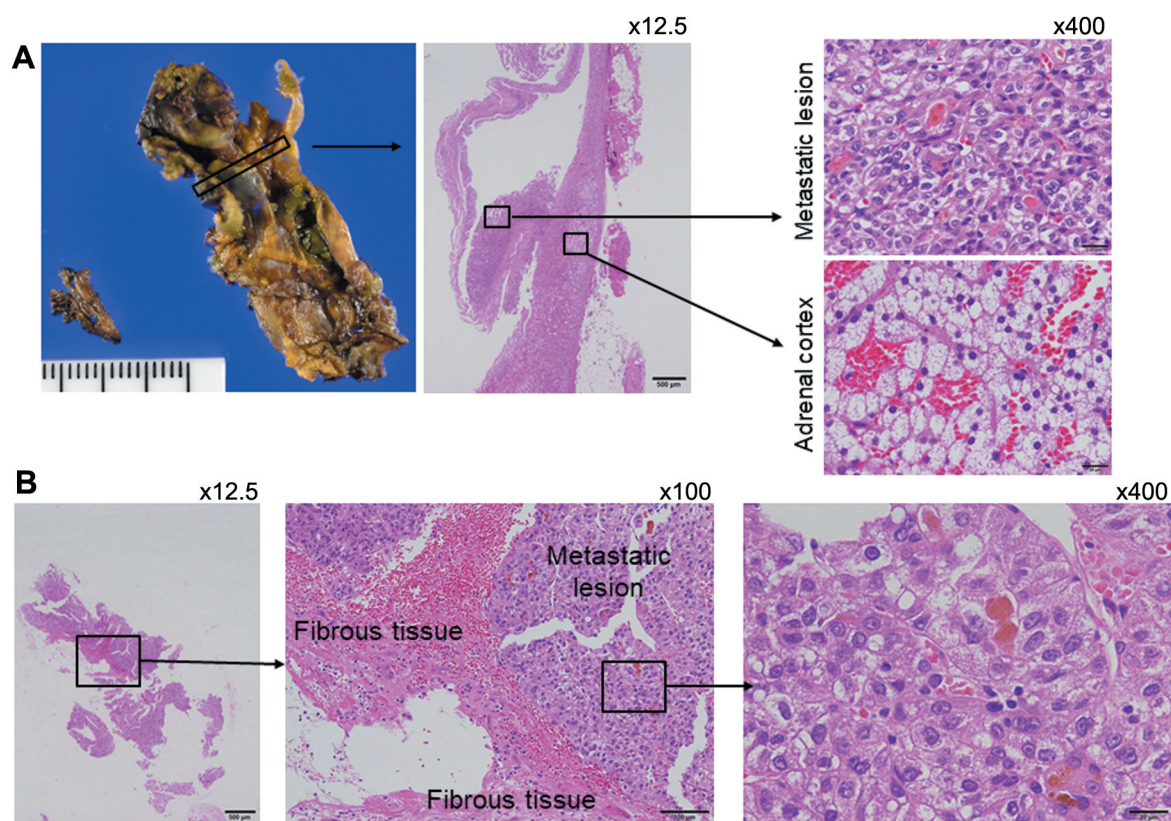


Figure 4. Macroscopic and histopathological findings of the initial and additionally resected specimens. (A) Moderately differentiated hepatocellular carcinoma with bile production (arrowhead) extending to the adrenal gland. (B) Moderately differentiated hepatocellular carcinoma with bile production (arrowhead) and surrounding fibrous tissue identified in sections of additionally resected small lesion using ICG fluorescence.

moderately differentiated HCC in the initial and additional resected specimens (Figure 4). Three months after the operation, adrenal function was well preserved without steroid hormone replacement and the patient has been doing well without HCC recurrence during follow-up.

Discussion

We herein presented a patient with a solitary right adrenal HCC metastasis, which developed after the complete remission of a left adrenal HCC metastasis that was treated with CT-guided RFA following TACE. The metastasis was treated twice with TACE without sufficient control. Therefore, ICG-PDE guided limited resection of the right adrenal metastasis was planned, with priority to preserve adrenal function. Maintaining adrenal function is challenging when using ablation therapy or radiotherapy because successful treatment without damage to the adrenal gland may not be possible (18-20). Since the metastasis in the present patient exhibited extra-adrenal growth, partial adrenal resection was considered. The cure rate with TACE, which was also performed to preserve adrenal function, is very low (19, 20). In the present patient, the therapeutic efficacy of the two TACE procedures for bilateral adrenal metastases was insufficient to control adrenal metastases.

HCC cells in extrahepatic metastases uptake ICG similar to hepatocytes and intrahepatic HCC cells (7). ICG secretion from extrahepatic metastatic cells into the surrounding tissue may be severely impaired compared to that from HCC cells into the intrahepatic bile duct. For extrahepatic HCC metastases, ICG fluorescent imaging has a high positive predictive value of 100% and a high sensitivity of 92%; however, its negative predictive value is low (at 50%) (10). There are two items for ICG-PDE systems: i) open and ii) laparoscopic surgery (7-9). For deeply seated organs, including adrenal glands, laparoscopic items are more convenient even for open surgery.

In the present patient, no tumor was observed by macroscopic observation, palpation, or intraoperative ultrasonography following the complete removal of the suspicious tumor. However, the ICG-PDE system clearly demonstrated two ICG fluorescent lesions in the connective tissue. We used near-infrared imaging with ICG, which is able to detect strong fluorescence and thus allow us to clearly distinguish the boundaries between the fluorescent and the surrounding tissue. The two additional fluorescent lesions were removed using the energy device. All resected specimens included moderately differentiated HCC with free margins using histological examination. Most parts of the adrenal gland could be preserved; therefore, the adrenal function was well maintained after the operation. Recent studies have demonstrated that laparoscopic surgical navigation with near-infrared fluorescence imaging using ICG is useful in patients requiring total or partial adrenalectomy. Additionally, intraoperative intravenous administration of

ICG can clearly delineate the vascular anatomy of adrenal neoplasms and enhance the borders between the tumor and the normal tissue (22, 23).

In liver, well-differentiated and moderately differentiated HCCs are described as cancerous-type ICG fluorescent lesions, including those with total and partial fluorescence uptake (24). In contrast, poorly differentiated HCCs are defined as those with rim fluorescence reflecting ICG uptake in the surrounding liver tissue but not in the HCC itself (24). Outside the liver, well-to-moderately differentiated HCCs are fluorescent whereas poorly differentiated HCCs are not fluorescent. As the tissue penetration of near-infrared light is limited to 5-10 mm (5), detection of tumors in deeper sites using this approach is difficult. Regenerative or necrotic extrahepatic HCCs caused by spontaneous regression or local therapy are also challenging to detect. In patients with tumors that are difficult to detect by ICG fluorescence, other approved fluorescence imaging agents, including the porphyrin precursor 5-aminolevulinic acid might be useful (25). The fluorescence of 5-aminolevulinic acid exhibits high specificity with low sensitivity in detecting liver tumors.

In patients with intrahepatic HCC, Ishizawa *et al.* (9) have recently proposed that ICG at a dose of 0.5 mg/kg body weight should be administered within two weeks before surgery. Additionally, the authors have recommended not to administer ICG one day before surgery to decrease the incidence of false-positive nodules. For patients with extrahepatic HCC, the currently recommended interval ranges from 1 to 5 days (10). However, the duration of ICG retention in extrahepatic HCC might be longer than expected and ICG administration immediately before surgery can be permissible because of lack of uptake by the background tissue.

In conclusion, limited tumor resection using the ICG-PDE systems is useful not only for the complete removal of adrenal HCC metastasis but also for the preservation of adrenal function.

Conflicts of Interest

The Authors have no conflicts of interest.

Authors' Contributions

KY and TB identified the concept and wrote the draft of the article. YK examined pathological findings. All Authors treated the patient and collected data. All Authors read and approved the final version of the manuscript.

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