Indocyanine Green Fluorescence Image-guided Laparoscopic Hepatectomy Enabled Resection of a Tumor Invisible With Ultrasonography

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Abstract. *Background:* Ultrasonography (US) is widely used for pre-operative detection of liver tumors. However, US does not have high resolution and very small tumors, tumors located near the liver surface, or those in cirrhotic livers are often not detected. *Case Report:* A 47-year-old woman with a previous surgery for sigmoid colon cancer (T3N1bM0 Stage3b) showed a liver tumor on the surface of segment 2 by contrast-enhanced computed tomography (CT) and gadoliniummethoxybenzyl-diethylenetriamine-pyridine-tauroic acid (Gd-EOB-DTPA) magnetic resonance imaging (MRI). However, preoperative US could not identify a tumor lesion at the same site. The most likely preoperative diagnosis was metastasis from her sigmoid colon cancer and laparoscopic liver resection was performed. Intraoperative ultrasonography (IOUS) did not identify the tumor, but it was visualized with indocyanine green (ICG) fluorescence at the surface of segment 2. Laparoscopic liver resection was performed under fluorescence guidance. Pathological examination showed a pseudotumor with negative margins. *Conclusion:* ICG fluorescence imaging can allow visualization of liver tumors that are undetectable on US.

Intraoperative ultrasonography (IOUS) is widely used for observing liver anatomy, staging tumors, guiding tumor resection, and detecting additional lesions in up to 20% of patients (1). Laparoscopic liver resection has gained widespread acceptance worldwide. Many reports have shown the feasibility, safety, and benefits of laparoscopic surgery over open liver resection.

Intraoperative ultrasonography (IOUS) in laparoscopic liver resection is more important compared with open liver surgery because the information obtained by palpation using laparoscopic forceps during liver resection is extremely limited. However, ultrasonography cannot reveal tiny tumors and liver tumors near the liver surface or cirrhotic livers.

Currently, indocyanine green (ICG) fluorescence imaging is widely used in various surgical fields (2). In liver surgery, Aoki *et al.* reported the first demonstration of anatomical liver resection using fluorescence guidance with ICG (3). ICG fluorescence can intraoperatively identify tumors invisible with other imaging modalities (4).

In the present report we describe a case in which ICG fluorescence-guided laparoscopic resection of a tumor invisible with IOUS was performed.

Case Report

A 47-year-old woman had a surgery for sigmoid colon cancer one year previous to her presentation with a lesion in the liver segment 2 observed with contrast-enhanced CT (Figure 1A). gadoliniummethoxybenzyl-diethylenetriamine-pyridine-tauroic acid (Gd-EOB-DTPA) magnetic resonance imaging (MRI) imaging showed early ring enhancement of approximately 15 mm in size at segment 2, and a neoplastic lesion with reduced uptake in the hepatocyte phase (Figure 1B). Abdominal ultrasound (US) did not detect the lesions that were seen on CT and MRI.

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Figure 1. Preoperative computed tomography, magnetic resonance gadoliniummethoxybenzyl diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) magnetic resonance imaging (MRI), and ultrasonography image. (A) Preoperative abdominal computed tomography (CT) scan imaging. Contrast CT shows poor contrast area (white arrows). (B) Preoperative MRI EOB imaging. The neoplastic lesion in segment 2 has a ring enhancement contrast effect (white arrows).

Figure 2. Intraoperative findings: a tumor in segment 2. Near-infrared fluorescence image; fluorescence was detected on the liver surface (white arrow).

Figure 3. Macroscopic image of the tumor. Fluorescent microscopy image ($\times 200$ magnification; bar=200 μm).

No swollen lymph nodes, ascites, or peritoneal metastases were observed. The level of carcinoembryonic antigen (CEA) was 1.3 ng/ml, carbohydrate antigen 19-9 (CA19-9) was 4.0 U/ml and alpha fetoprotein was 0.6 ng/ml.

Final diagnosis. The patient was clinically diagnosed with liver metastases from sigmoid colon cancer.

Treatment. Explain to the patient and obtain consent. It is also approved by the Showa University Hospital Ethics Committee. ICG 0.5 ml/kg was intravenously administered two days before laparoscopic partial liver resection. The tumor in segment 2 was invisible under IOUS. However, it was detected in the same segment by ICG fluorescence using a PINPOINT Endoscopic

Fluorescence Imaging System (Stryker, Kalamazoo, MI, USA) (Figure 2). Liver parenchymal transections were carefully performed under fluorescence guidance enabling the surgical margin to be secured. The operation time was 1 h and 58 min, and blood loss was very small. No visible mass or nodules were observed macroscopically by ICG fluorescence on the resected surface tissue. Pathological examination diagnosed a pseudotumor which was a metastases of sigmoid colon cancer.

Discussion

Laparoscopic IOUS is a useful tool for detecting liver tumors with a performance similar to open IOUS (5). However, laparoscopic IOUS has some drawbacks, such as intrinsic

human tremor that prevent accurate depiction of lesions, restrictive movement with only 4 degrees of freedom, and a 2-dimensional view. These drawbacks limit the utility of laparoscopic IOUS in complex liver resections and may increase the risk of not detecting small tumors.

Currently, ICG is used for fluorescence-guided surgery in various organs (2). Our team was the first report on anatomical liver section using fluorescence imaging with ICG in 2008 (3). Subsequently ICG fluorescence imaging is used for the detection of liver tumors, defining surgical margins (4), biliary tract surgery (6), and bile leakage.

ICG has a fluorescence peak at wavelength of approximately 830 nm when irradiated with excitation light with a wavelength of approximately 760 nm. There are many clinical imaging systems compatible with ICG fluorescence (7, 8). Both colorectal cancer and hepatocellular carcinoma have been shown to accumulate ICG (9). ICG fluorescence helps to identify the tumors that cannot be identified by ultrasonography. The present study, showed the treatment of a tumor that could not be identified by preoperative and intraoperative ultrasonography. Therefore, we attempted to identify the tumor using ICG fluorescence and were able to perform complete laparoscopic partial liver resection with accurate and safe surgical margins under fluorescence guidance. Pathological diagnosis showed the tumor as a pseudotumor. Under a fluorescence microscopy, the pseudotumor showed diffuse fluorescence (Figure 3).

ICG fluorescence has some disadvantages, such as the inability of fluorescence signals to visualize tumors deeply localized below the liver surface. Furthermore, there is a high rate (about 40%) of false positives. Based on the pathological findings, the targeted tumor in the present case was a pseudotumor, although the preoperative diagnosis was metastatic colorectal liver tumor. However, the present study showed that ICG can allow the detection of tumors in the liver that are invisible with IOUS. Furthermore ICG fluorescence has a higher detection rate for small tumors or tumors near the surface of the liver than IOUS (10). Therefore, ICG is useful for fluorescence-guided surgery of otherwise invisible liver tumors near the surface.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

K.O., R.M.H., and T.A performed the operation and wrote the article; Y.T., T.K., T.K., Y.W., H.S., T.Y., H.D., T.A., S.G., K.Y., M.W., A.F., Y.E., K.O., M.M. provided technical support and conceptual advice.

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