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Intraoperative indocyanine green fluorescence navigation facilitates complete removal of lymph node metastases from hepatocellular carcinoma

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Abstract: Indocyanine green (ICG) is a fluorescent dye that selectively accumulates in primary hepatocellular carcinoma (HCC) as well as in extrahepatic metastases of HCC. Reported here is a case of metachronous lymph node (LN) metastases from HCC that were resected using ICG fluorescence navigation. A man in his 70s was referred to this department for suspected LN metastasis from HCC. Computed tomography revealed an enlarged suprapancreatic LN. After a laparotomy, an ICG fluorescence imaging system intraoperatively revealed strong fluorescence of this LN, which was then easily resected. An examination after the removal of the LN revealed fluorescence from the adjacent lymphatic tissue as well, so an additional resection was performed. Pathologically, both LNs were confirmed to be metastases from HCC. In this case, some lymphatic tissue metastases from HCC could not be identified prior to surgery, but intraoperative use of ICG fluorescence navigation facilitated their complete removal.

***Keywords*:** hepatocellular carcinoma, LN metastasis, indocyanine green, fluorescence navigation surgery

Indocyanine green (ICG) has been used for perfusion diagnosis of tissue and navigation to locate sentinel lymph nodes (LNs) since ICG emits light with a peak wavelength of approximately 800 nm when excited with near-infrared light. Recent studies have indicated that ICG fluorescence imaging was useful at detecting primary HCC and extrahepatic metastases from HCC (*1-3*). Reported here is a case where ICG fluorescent navigation was intraoperatively used to detect LN metastases of HCC that could not be identified prior to surgery.

A man in his 70s was referred to this department for resection of LN metastasis of HCC. He had a history of hepatitis C infection, but a sustained virologic response was achieved with interferon treatment. He had undergone left lateral segmentectomy for HCC 26 years ago and distal gastrectomy for gastric cancer 16 years ago. Transcatheter arterial chemoembolization was performed twice for intrahepatic recurrence in segment VI 12 months ago and in segments IV & VIII 6 months ago. Nevertheless, the serum levels of alpha-fetoprotein (AFP) and protein induced by vitamin K absence or antagonist-II (PIVKA-II) gradually increased (AFP: 1751 ng/mL, PIVKA-II: 172 mAU/mL). Thus, further examination was performed. Contrast-enhanced dynamic computed tomography revealed no intrahepatic recurrence and a swollen suprapancreatic LN that had increased in size from 11 mm to 16 mm over the last 3 months (Figure 1A and 1B). This LN was highly enhanced in the arterial phase, which accorded with the metastasis of HCC. Positron emission tomography-computed tomography revealed the accumulation of fluorine-18 deoxyglucose in this LN (Figure 1C). SUVmax was 2.05. There was no evidence of recurrence in any other regions, and resection of this LN was scheduled.

ICG (Diagnogreen, Daiichi Sankyo, Tokyo, Japan) was injected intravenously at a dose of 0.5 mg/kg body weight, 1 day before surgery. After a laparotomy and sharp dissection of severe adhesions, a swollen LN was palpated in the suprapancreatic area. Exploration with a near-infrared light camera system (PINPOINT®, Stryker Corporation, Kalamazoo, MI) revealed strong fluorescence from this LN (Figure 2A). After the resection of this LN, the abdominal cavity was explored with the ICG camera again. The cranial side of the resected area was still emitting fluorescence (Figure 2B), so an additional resection was performed. After fluorescence was no longer observed (Figure 2C), surgery was concluded.

Hematoxylin and eosin staining of resected specimens revealed that the normal LN structure was replaced by atypical cells (Figure 3A). Immunohistochemical analysis indicated that these cells were positive for

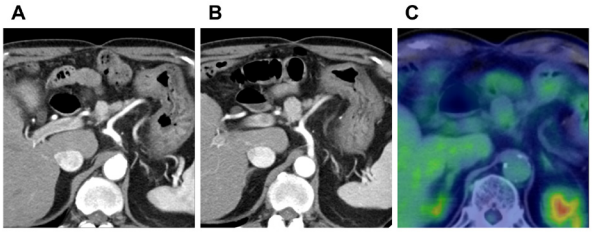

Figure 1. (A) CE-CT revealed a swollen LN 11 mm in diameter with enhancement in the arterial phase (arrow). **(B)** Three months later, CE-CT revealed enlargement of this LN, which was now 16 mm in diameter, with enhancement in the arterial phase (arrow). **(C)** PET-CT revealed FDG accumulation in this LN. CE-CT: contrast-enhanced computed tomography, PET-CT: positron emission tomography-computed tomography, FDG: fluorine-18 deoxyglucose, LN: lymph node.

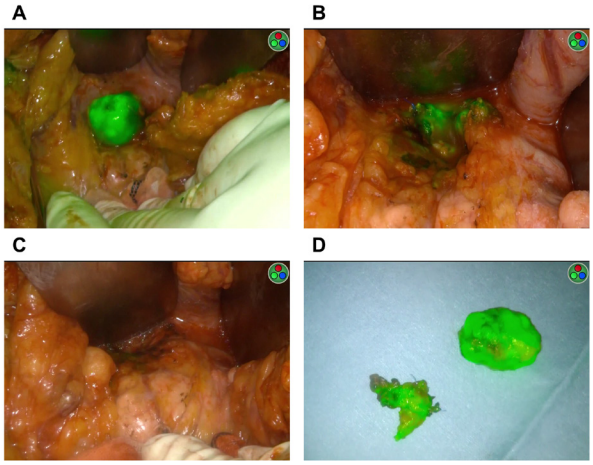

Figure 2. ICG fluorescence imaging using the PINPOINT® camera system. (A) A swollen LN with a strong fluorescent signal. **(B)** After the resection of the swollen LN, the strong fluorescent signal remained. **(C)** After the additional resection, no fluorescent signal was detected. **(D)** ICG fluorescence image of the resected specimens. ICG: Indocyanine green.

Glypican-3 and Hep Par1 and negative for CK7 and CK20 (Figure 3B). Based on these results, the resected LNs were pathologically confirmed to be metastases of HCC. Soon after surgery, elevated tumor markers returned to normal levels (AFP: 33 ng/mL, PIVKA-II: 10 mAU/mL) (Figure 4). No recurrence of HCC has been detected for more than 2 years after surgery.

Extrahepatic recurrence of HCC is relatively rare compared to intrahepatic recurrence. The common sites of extrahepatic metastases are the lungs, bones, and LNs (*4*). LN metastasis is found in 3-8% of patients with HCC. An effective standard treatment for LN metastasis has yet to be established, and the prognosis of LN metastasis is generally poor. As a result of 2 phase III studies (the SHARP trial and the Asia Pacific trial), sorafenib has been regarded as the standard treatment for advanced (unresectable or metastatic) HCC (*5,6*). However, sorafenib has not been found to provide a significant survival benefit according to a subgroup analysis of patients with LN metastasis. Although the clinical significance of surgical resection of LN metastasis

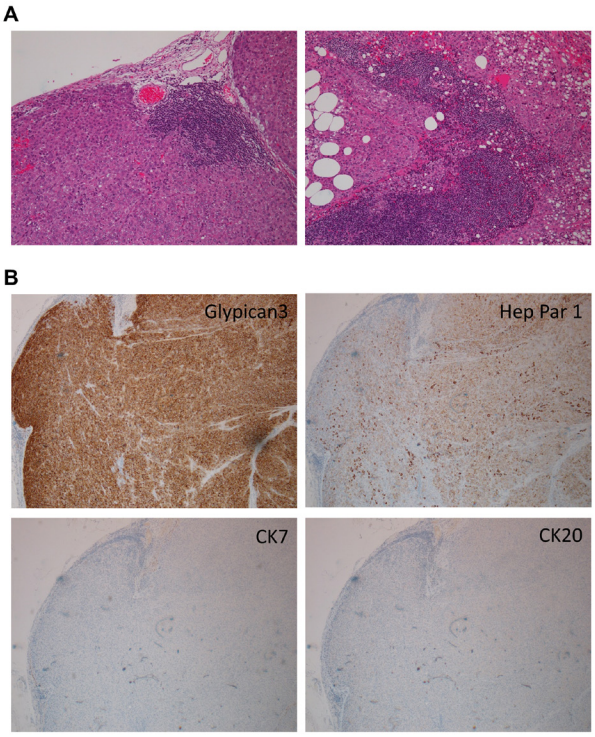

Figure 3. (A) Pathological findings for the resected LNs: both LNs contained metastatic hepatocellular carcinoma cells (left; swollen LN, right; additional resected LN, hematoxylin and eosin staining, ×100). **(B)** Immunohistochemistry of the resected LN (×40). The LN was positive for Glypican-3 and Hep Par 1 and negative for CK7 and CK20 (×40). LN: lymph node.

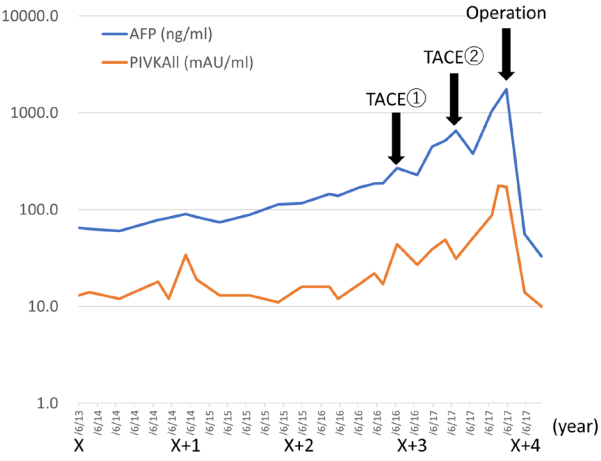

Figure 4. Changes in serum AFP and PIVKA-II levels. Serum AFP and PIVKA-II levels rapidly decreased within the normal range. AFP: alpha-fetoprotein, PIVKA-II: protein induced by vitamin K absence-II.

remains controversial, some studies have reported that the resection of LN metastasis was associated with long-term survival, and especially in patients with resectable or controllable intrahepatic lesions (*7,8*). In the current case, no other recurrent lesions were detected, so complete resection of LN metastasis should allow a longer survival.

ICG is a fluorescent dye that emits light with a peak

wavelength of approximately 800 nm when excited with near-infrared light and was initially used to evaluate liver function and cardiac output. As real-time fluorescent imaging systems have developed, ICG has been used for perfusion diagnosis of tissue and navigation to locate sentinel LNs. In addition, recent studies have revealed that ICG fluorescence imaging was useful at detecting primary HCC and extrahepatic metastases from HCC because of the selective uptake and the prolonged retention of ICG (*1-3,9*).

An accurate diagnosis of LN metastases is essential for determination of the appropriate surgical procedure. However, preoperative imaging studies using modalities such as CT and MRI assess LN metastases based on criteria like size and shape. In patients with HCC, hilar or peripancreatic LNs are often swollen because of accompanying liver inflammation. Therefore, distinguishing between swelling of benign LNs and malignant LNs is difficult. Moreover, determining whether a small LN is metastatic or not is even more difficult. Since multimodal diagnosis for the N-staging of gastric cancer has a reported accuracy of only 50-90% (*10*), preoperative diagnosis of LN metastasis from HCC presents a challenge.

Hence, more sensitive and specific methods of diagnosis should be developed. Satou *et al*. reported that 14 (93%) out of 15 LN metastases from HCC were detectable with ICG fluorescent imaging (*3*). In the current case, lymphatic metastases that were not evident prior to surgery were identified. Although ICG fluorescence imaging has a drawback in that it cannot detect fluorescence from a deep lesion, it could be a useful tool with which to detect LN metastases.

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References

1. Gotoh K, Yamada T, Ishikawa O, Takahashi H, Eguchi H, Yano M, Ohigashi H, Tomita Y, Miyamoto Y, Imaoka S. A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. J Surg Oncol. 2009; 100: 75-79.
2. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T, Hasegawa K, Beck Y, Fukayama M, Kokudo N. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer. 2009; 115: 2491-2504.
3. Satou S, Ishizawa T, Masuda K, Kaneko J, Aoki T, Sakamoto Y, Hasegawa K, Sugawara Y, Kokudo N. Indocyanine green fluorescent imaging for detecting extrahepatic metastasis of hepatocellular carcinoma. J Gastroenterol. 2013; 48:1136-1143.
4. Kudo M, Izumi N, Kubo S, Kokudo N, Sakamoto M, Shiina S, Tateishi R, Nakashima O, Murakami T, Matsuyama Y, Takahashi A, Miyata H, Takayama T. Report of the 20th Nationwide Follow-up Survey of Primary Liver Cancer in Japan. Hepatol Res. 2020; 50:15-46.
5. Llovet JM, Ricci S, Mazzaferro V, *et al*. Sorafenib in advanced hepatocellular carcinoma. N Engl J Med. 2008; 359:378-390.
6. Cheng AL, Kang YK, Chen Z, *et al*. Efficacy and safety of sorafenib in patients in the Asia-Pacific region with advanced hepatocellular carcinoma: A phase III randomised, double-blind, placebo-controlled trial. Lancet Oncol. 2009; 10:25-34.
7. Kobayashi S, Takahashi S, Kato Y, Gotohda N, Nakagohri T, Konishi M, Kinoshita T. Surgical treatment of lymph node metastases from hepatocellular carcinoma. J Hepatobiliary Pancreat Sci. 2011; 18:559-566.
8. Hasegawa K, Makuuchi M, Kokudo N, Izumi N, Ichida T, Kudo M, Ku Y, Sakamoto M, Nakashima O, Matsui O, Matsuyama Y; Liver Cancer Study Group of Japan. Impact of histologically confirmed lymph node metastases on patient survival after surgical resection for hepatocellular carcinoma: Report of a Japanese nationwide survey. Ann Surg. 2014; 259:166-170.
9. Ishizawa T, Masuda K, Urano Y, Kawaguchi Y, Satou S, Kaneko J, Hasegawa K, Shibahara J, Fukayama M, Tsuji S, Midorikawa Y, Aburatani H, Kokudo N. Mechanistic background and clinical applications of indocyanine green fluorescence imaging of hepatocellular carcinoma. Ann Surg Oncol. 2014; 21:440-448.
10. Vergadis C, Schizas D. Is accurate N - staging for gastric cancer possible? Front Surg. 2018; 5:41.

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