

Real-Time Detection of Hepatic Micrometastases From Pancreatic Cancer by Intraoperative Fluorescence Imaging

Preliminary Results of a Prospective Study

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BACKGROUND: Recently, a highly sensitive fluorescent imaging technique was developed for the real-time identification of hepatic tumors. The authors applied this procedure for the intraoperative detection of radiographically occult hepatic micrometastases from pancreatic cancer. **METHODS:** Forty-nine consecutive patients with pancreatic cancer who underwent surgical intervention were examined. Preoperative clinical images had not revealed any hepatic metastases. On the day before surgery, indocyanine green was injected intravenously. During the operation, the liver was observed with a near-infrared camera system, and abnormal fluorescent foci were examined by frozen-section histology. The patients with hepatic micrometastases were judged to have unresectable disease and underwent only palliative surgery followed by systemic chemotherapy using gemcitabine. **RESULTS:** Abnormal hepatic fluorescence at least 1.5 mm in greatest dimension without any apparent tumor was observed in 13 patients. Among them, histologic examination confirmed micrometastases in 8 of 49 patients (16%). All patients with hepatic micrometastases had clinical T3 or T4 disease and high serum CA19-9 levels ($P = .042$). On follow-up computed tomography images that were obtained within 6 months after surgery, the patients with hepatic micrometastases manifested hepatic overt metastases (7 of 8 patients; 88%) more frequently than the patients without hepatic micrometastases (4 of 41 patients; 10%; $P < .001$). Regardless of histologic confirmation, the positive predictive value of abnormal fluorescence for the manifestation of hepatic relapse within 6 months was 77% (10 of 13 patients), and the negative predictive value was 97% (35 of 36 patients). **CONCLUSIONS:** Indocyanine green-fluorescent imaging can detect hepatic micrometastases of pancreatic cancer during surgery. The hepatic micrometastases seem to have an adverse clinical impact identical to that of evident distant metastases. *Cancer* 2012;118:2813-9. © 2011 American Cancer Society.

KEYWORDS: pancreatic neoplasms, liver neoplasms, neoplasm metastasis, neoplasm staging, diagnostic imaging.

INTRODUCTION

Pancreatic cancer often has a poor prognosis, and surgical resection is the only potential curative treatment for this disease. However, even after radical resection, patients who have rapid recurrence frequently have been encountered.¹⁻⁴ In some of these patients, distant micrometastases probably already were present at the time of surgery.⁵ Several authors have described lymph node or hepatic micrometastases from pancreatic cancer and their clinical impact.⁶⁻⁸ However, the presence of most of these micrometastases was confirmed only after surgery.⁵⁻¹⁰

Advanced imaging modalities, including multidetector computed tomography (CT) and contrast-enhanced magnetic resonance imaging (MRI), have enabled high-resolution diagnostic imaging of hepatic diseases; however, some small lesions still may go undetected.¹¹⁻¹⁴ Recently, a highly sensitive fluorescent imaging technique using a near-infrared camera system has been developed and has made it possible to identify small hepatic tumors during surgery.^{15,16} We applied

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this technique to pancreatic cancer treatment to detect hepatic micrometastases, which may not be detected by conventional preoperative or intraoperative diagnostic modalities; herein, we report the preliminary results of our procedure.

MATERIALS AND METHODS

Patients

From July 2009 to December 2010, patients with 52 pancreatic cancer underwent surgical interventions at Niigata City General Hospital. One patient who underwent an emergency laparotomy for intra-abdominal bleeding was excluded from this study, and 2 other patients with neuroendocrine carcinoma also were excluded. The remaining 49 patients with invasive ductal carcinoma were examined for hepatic micrometastases. Of these patients, 36 were admitted for the purpose of curative intent resection, and the other 13 were admitted for palliative bypass surgery. Two patients with stage IV disease received systemic chemotherapy with gemcitabine before surgery.¹⁷ No patients received neoadjuvant radiotherapy. Thirty-four patients had obstructive jaundice with a total bilirubin level ≥ 3 mg/dL at the initial presentation, and all of them underwent endoscopic or percutaneous biliary decompression before surgery. All patients were examined routinely preoperatively with abdominal imaging with multidetector CT and/or MRI. In all patients, no apparent hepatic metastases were evident.

This study was conducted in accordance with the ethical standards of Niigata City General Hospital and was approved by the institution's ethics committee. The objective, technique, and risk involved in this method were explained to the patients in detail, and informed consent was obtained from all patients before the procedure.

Procedure

The Photo Dynamic Eye (PDE; Hamamatsu Photonics, Hamamatsu, Japan) fluorescence system was used for intraoperative imaging. On the day before laparotomy, 25 mg of indocyanine green (ICG) diluted with distilled water to a concentration of 2.5 mg/mL were injected into a peripheral vein.

During surgery, we performed gross inspection and intraoperative ultrasonography (US) of the liver to reveal the extent to which the cancer had spread. Subsequently, we used the PDE system for further examination. The camera head was positioned 15 to 20 cm above the liver

Table 1. Outcome of Patients Presented According to Fluorescent Findings by Photo Dynamic Eye Examination During Surgery

Variable	Abnormal Hepatic Fluorescence		<i>P</i> ^a
	Positive	Negative	
No. of patients	13	36	
Hepatic micrometastases			
Histologically confirmed	8	NE	
Not confirmed	5	NE	
Manifestation of hepatic overt metastases after surgery^b			<.001 ^c
Present	10 (7 vs 3) ^d	1	
Absent	3 (1 vs 2) ^d	35	

Abbreviations: NE, not examined.

^a Fisher exact test.

^b Assessed on computed tomography scans within 6 months after surgery.

^c Significant at the *P* < .05 level.

^d Numbers in parentheses indicate patients who had histologic confirmation of hepatic micrometastases (*n* = 8) versus patients who did not have histologic confirmation of hepatic micrometastases (*n* = 5).

surface with the surgical lights turned off. The image thus obtained was displayed on a television monitor in the operation room. Hepatic foci with abnormal fluorescence were suspected to be micrometastases and examined histopathologically with a frozen section technique.

Patients with histologically confirmed hepatic micrometastases were judged as unresectable cases regardless of the initial surgical intent. Those patients underwent only surgical exploration or palliative bypass and subsequently received systemic chemotherapy using gemcitabine (1000 mg/m² on days 1, 8, and 15 of a 28-day cycle).¹⁷ All 49 patients were followed up with CT imaging at 6 months (and, if needed, at 3 months) after surgery to examine for the manifestation of overt hepatic metastases.

Statistical Analysis

The probabilities of the presence or absence of hepatic micrometastases were compared using the Fisher exact test or the chi-square test for categorical variables (Tables 1 and 2). The Mann-Whitney *U* test was used to calculate the association between the presence of micrometastases and preoperative serum cancer antigen 19-9 (CA 19-9) and carcinoembryonic antigen levels. All statistical evaluations were performed with the SPSS 16.0J software package (SPSS Japan Inc., Tokyo, Japan). *P* values < .05 were considered statistically significant.

Table 2. Association Between Hepatic Micrometastases and Other Clinical Variables

Variable	No. of Patients		<i>P</i> ^a
	With Hepatic Micrometastases (n = 8)	Without Hepatic Micrometastases (n = 41)	
Sex			.440
Men	3	24	
Women	5	17	
Age, y			1.00
<70	3	15	
≥70	5	26	
Tumor location^b			.410
Pancreatic head	7	28	
Pancreatic body or tail	1	13	
Primary clinical tumor classification^b			.002^c
cT1 or cT2	0	20	
cT3 or cT4	8	21	
Clinical lymph node status^b			1.00
cN0	5	27	
cN1	3	14	
Initial intent of surgery			1.00
Curative resection	6	31	
Palliative surgery	2	10	
Manifestation of hepatic overt metastases after surgery^d			<.001^c
Present	7	4	
Absent	1	37	

^a Fisher exact test.^b According to the American Joint Committee on Cancer Staging Manual, 6th ed.¹⁸^c Significant at the *P* < .05 level.^d Assessed on computed tomography scans within 6 months after surgery.

RESULTS

Intraoperative Gross Examination

No adverse events related to ICG-PDE examination, including preoperative injection of ICG resulting in allergic reaction, or caused by intraoperative observation with the near-infrared camera were evident in any of the patients. At laparotomy, no hepatic tumors were identified on gross inspection or intraoperative US in any of the 49 patients. Peritoneal metastases were discovered in 5 patients.

Benign Fluorescent Foci

In the PDE examination, fluorescent foci were observed not only in neoplastic lesions but also in benign, bile-secreting foci, which contained ICG. The extrahepatic biliary ducts and gallbladder were identified by their relatively dim fluorescence in all patients. In 29 patients, biliary cysts at the hepatic surface had bright fluorescent

spots. These non-neoplastic fluorescent foci with benign biliary pools could be distinguished easily on gross inspection and palpation during surgery.

In addition, in 2 patients, round fluorescent lesions <2 mm in greatest dimension were identified on the hepatic surface and were resected for examination. In the collected specimens, small, yellowish-white nodules were recognized just below the fluorescence. Initially, metastatic tumors from pancreatic cancer were suspected macroscopically; however, intraoperative frozen-section histology confirmed the diagnosis of biliary hamartoma in these lesions.

Detection of Hepatic Micrometastases

Excluding the benign foci described above, distinct fluorescent lesions were discovered on the hepatic surface in 13 of the 49 patients (27%) by PDE examination. The fluorescent areas ranged from a small spot 1.5 mm in

greatest dimension to a wedge-shaped segment $>3\text{ cm}^3$ (Fig. 1A,B). In all 13 patients, abnormal hepatic fluorescence was identified in multiple locations (ranging from 2 to >20), and 31 biopsy samples, approximately 1 cm in thickness, were collected from the lesions (Fig. 1C,D). In 11 of the 13 patients, no tumor could be detected on gross examination, even in the cut biopsy samples (Fig. 1E). In 1 patient, a wedge-shaped, segmental fluorescence region was observed in the left lateral section of the liver (Fig. 1D). On careful re-examination with US and palpation, we were able to identify a 3-mm-thick, sclerosing portal triad at the right median edge of the fluorescence area, and we resected a specimen (Fig. 1F). In another patient, a small, white hepatic tumor (1.5 mm in greatest dimension) was identified in the cut specimen just below the fluorescent spot, and we suspected it was a micrometastasis.

Histologic examination confirmed metastatic carcinoma in 17 specimens from 8 patients (8 of 49 patients; 16%), including the 2 patients in whom micrometastases were macroscopically suspected on the cut specimens, as described above (Table 1). All micrometastases were adenocarcinoma and were observed as small cell clusters in the hepatic parenchyma or invasive cancer nests around the portal triad (Fig. 1G,H).

False-Positive Fluorescence

Despite abnormal fluorescence in the PDE observations, histologic examination did not confirm hepatic metastases in the biopsy specimens from 5 of 13 patients. These were judged as false-positive foci. Of the patients who had false-positive fluorescence, 2 patients subsequently underwent curative resection, and 3 patients underwent palliative surgery.

Clinical Significance of Hepatic Micrometastases

All 8 patients with hepatic micrometastases had clinical T3 (cT3) or cT4 disease (Table 2). The preoperative serum levels of CA 19-9 in the patients with hepatic micrometastases (range, 9.1-16,479.5 U/mL; median, 788.5 U/mL) were significantly higher than those in the patients without micrometastases (range, 1.0-4182.0 U/mL; median, 70.8 U/mL; $P = .042$). However, there was no association between serum carcinoembryonic antigen levels and the presence of hepatic micrometastases (data not shown).

Of the 8 patients who had hepatic micrometastases, 6 initially underwent surgery with curative intent; however, because of their micrometastases, ultimately, it

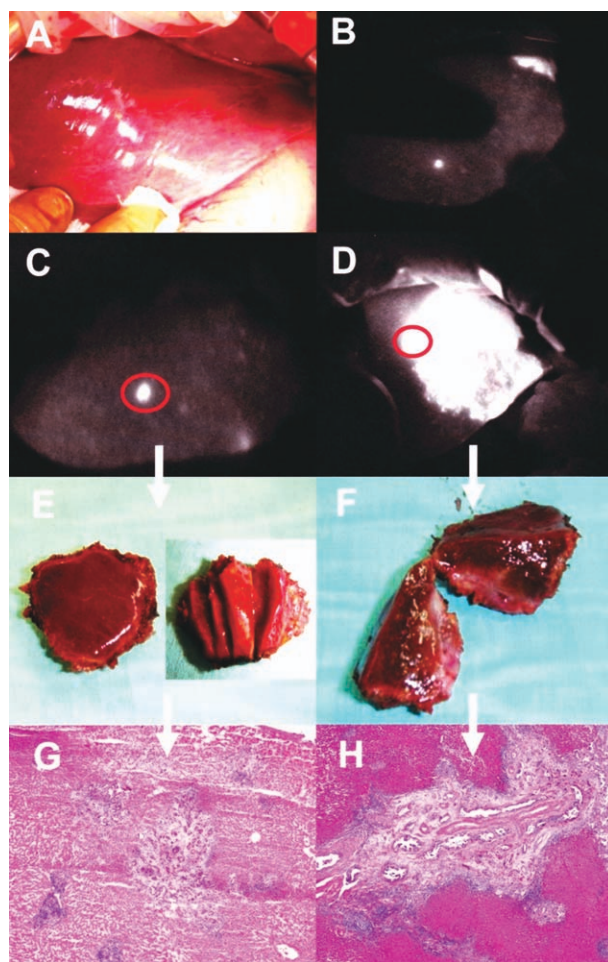


Figure 1. Although no liver tumor was detected by (A) intraoperative gross inspection, (B) Photo Dynamic Eye imaging revealed 2 fluorescent foci in the lateral segment of the liver. (C-F) Fluorescent lesions in the liver were resected and sectioned. (E) No tumor was evident in the cut specimen; however, (G) histologic examination revealed micrometastases in the hepatic parenchyma. (F) Careful reexamination identified the thickened portal triad at the median edge of the fluorescence, from which the biopsy specimen was collected. (H) Invasive adenocarcinoma was confirmed in the portal triad.

was determined that they had unresectable disease. Eventually, 27 patients underwent palliative surgery only, because it was determined that they had unresectable disease at the intraoperative final staging. The other 22 patients underwent radical resection, including pylorus-preserving pancreaticoduodenectomy in 16 patients, distal pancreatectomy in 5 patients, and total pancreatectomy in 1 patient. After radical resection, 8 patients received adjuvant chemotherapy with oral administration of S-1 (80 mg/m² per day), and 4 patients received a regimen of gemcitabine.^{17,19} No patients received adjuvant radiotherapy.

In the follow-up CT examination within 6 months after surgery, the patients with hepatic micrometastases manifested overt hepatic metastases more frequently than the patients without micrometastases (7 of 8 patients [88%] vs 4 of 41 patients [10%]; $P < .001$) (Table 2). The only patient without apparent hepatic metastases on the follow-up CT despite the presence of micrometastases died of peritoneal metastases 10 months after surgical exploration. In this patient, we could not identify any distinct clinical or histologic features compared with the other 7 patients with micrometastases, in whom overt metastases manifested later. By contrast, hepatic relapses were identified on the follow-up CT in 4 patients in whom histologic examination did not confirm micrometastases during surgery. Among these 4 patients, 3 had false-positive hepatic fluorescence. By stratifying patients into 3 groups according to hepatic fluorescence status—positive fluorescence with histologically confirmed hepatic micrometastases, false-positive fluorescence, and negative fluorescence—we observed a significant difference in the probabilities of hepatic recurrence among the groups (7 of 8 patients [88%], 3 of 5 patients [60%], and 1 of 36 patients [3%], respectively; $P < .001$) (Fig. 2). Therefore, the positive predictive value of PDE examination for hepatic relapse within 6 months was 77% (10 of 13 patients), and the negative predictive value was 97% (35 of 36 patients). Regardless of histologic confirmation of the micrometastases, abnormal hepatic fluorescence discovered on PDE examination was associated significantly with the manifestation of overt hepatic metastases ($P < .001$) (Table 1).

DISCUSSION

Assessing metastatic spread is very important in the treatment of pancreatic cancer. However, even with advanced preoperative imaging and careful intraoperative examination, some small hepatic metastases may be overlooked.^{11,20} In this preliminary study, we were able to detect unapparent hepatic micrometastases from pancreatic cancer by performing intraoperative fluorescent imaging. Hepatic micrometastases were observed in approximately one-sixth of the patients in our series, although no hepatic tumors had been detected on preoperative imaging studies in those patients.

ICG-fluorescence imaging is used for the real-time study of blood, lymphatic, or biliary flow.^{15,16,21} Intravenously injected ICG binds to serum proteins and fluoresces in near-infrared light. The protein-bound ICG is

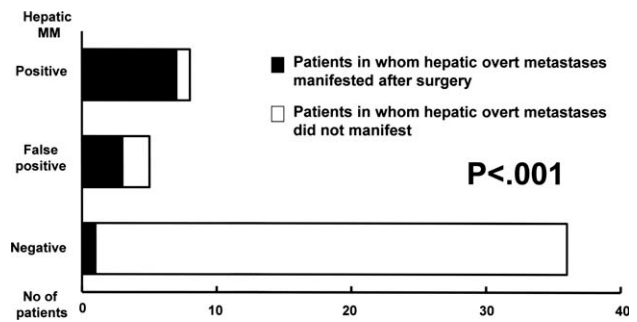


Figure 2. The manifestation of hepatic overt metastases on follow-up computed tomography studies within 6 months after surgery is illustrated. The fluorescent status of patients was categorized as 1) positive fluorescence with histologically confirmed micrometastases (MM), 2) false-positive fluorescence without MM, or 3) negative fluorescence.

excreted into the bile juice through hepatocytes. Therefore, hepatic lesions with biliary retention can be identified because they exhibit fluorescence. Ishizawa et al reported the feasibility and usefulness of this technique for detecting hepatic tumors during liver surgery.¹⁵ In their report, 2 fluorescing patterns of hepatic tumors were described: hepatocellular carcinoma tumors fluoresced uniformly, whereas metastatic liver tumors from colorectal cancer fluoresced at the rim. In the current study, hepatic micrometastases from pancreatic cancer fluoresced in various patterns and size. However, in all of the lesions, the area of the fluorescing foci was considerably larger than the actual tumor volume, indicating that the metastatic cancer cells themselves did not fluoresce. This finding may be understood as follows: Metastatic cancer cells at the portal triad obstruct local biliary flow, after which stagnant bile around the metastases emits light under infrared illumination. The fluorescent hepatic area may reflect the extent of bile stasis caused by the micrometastasis. To clarify the fluorescing mechanism of hepatic micrometastases, additional case series studies and basic research are required.

The current study demonstrated several clinically significant aspects of hepatic micrometastases from pancreatic cancer. Not surprisingly, hepatic micrometastases were identified frequently in patients with advanced disease, as measured by high cT classification and high serum CA 19-9 levels. Several authors already have documented a significant association between preoperative CA 19-9 values and the identification of subradiographic, unresectable pancreatic cancer, and our results have substantiated their findings.^{22,23} Thus, patients with pancreatic cancer who have elevated CA 19-9 levels need elaborate

examination for unapparent hepatic metastases. In contrast, elaborate examination is not needed for hepatic micrometastases in cT1 or cT2 pancreatic cancer.

The hepatic micrometastases we detected during surgery subsequently evolved into overt metastases at the high rate of 88% within 6 months after the operation. Therefore, hepatic micrometastases seem to have an adverse clinical impact as do preoperatively confirmed overt distant metastasis. Pancreatic cancer with hepatic micrometastases does not warrant radical resection.²⁴⁻²⁷ In addition, because systemic chemotherapy failed to prevent deterioration of hepatic disease, some liver-directed treatments may be needed for pancreatic cancer with hepatic micrometastases.²⁸⁻³²

It is noteworthy that we observed hepatic recurrence after surgery in 60% of the patients who had false-positive hepatic fluorescence on PDE examination. This finding leads us to hypothesize that some of the cases of false-positive fluorescence were not “true” false-positives and, instead, were either extremely small micrometastases that could not be detected by histologic examination or the result of inadequate collection of biopsy samples. Regardless, the possibility of short-term hepatic relapse may deserve consideration in patients with abnormal fluorescence of the liver even when histologic examination does not confirm the diagnosis. Conversely, patients without abnormal fluorescence on PDE examination are estimated to be at a low risk of hepatic recurrence after surgery because of its high negative predictive value.

The ICG-fluorescent imaging system has several technical limitations. First, because of the permeation limit of near-infrared light, this method cannot be used to identify deep hepatic lesions. Previous studies reported that the permeation limit of near-infrared light in human tissue is up to 1 cm.^{15,33,34} Therefore, the utility of this technique is limited to superficial hepatic tumors. However, small lesions at the hepatic surface are likely to be missed by other imaging methods, such as CT, MRI, or US, because of partial volume effects or poor near-field resolution; whereas those conventional modalities are better at detecting deep hepatic lesions. Therefore, ICG-fluorescent examination seems to have complementary merits over other imaging techniques and, thus, is worth performing to examine the entire liver in detail. Second, because there is no way to confirm false-negative findings in detecting micrometastases, it may be difficult to precisely assess the sensitivity of this method. In addition, a false-positive result may be obtained because benign bile stasis appears as a similar fluorescent area. Despite these

limitations, we believe that the ICG-fluorescent imaging technique is feasible and fulfills the demand of clinical oncologists for cancer staging during pancreatic surgery. Furthermore, this technique is beneficial for patients with pancreatic cancer because it can be used to prevent unnecessary radical resection.³⁵ To date, this imaging technique involving the use of a commercially available system can be applied only during open laparotomy; however, its future applications in laparoscopic examination may enable the development of a less invasive procedure to detect hepatic micrometastases.³⁶

In conclusion, ICG-fluorescent imaging has the ability to detect hepatic micrometastases from pancreatic cancer during surgery. The hepatic micrometastases confirmed by this technique should be treated in the same manner as evident hepatic metastases from pancreatic cancer.

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CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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