6. Landsman ML, Kwant G, Mook GA, Zijlstra WG. Light-absorbing properties, stability, and spectral stabilization of indocyanine green. *J Appl Physiol.* 1976;40:575–83.
7. Guyer DR, Puliafito CA, Monés JM, Friedman E, Chang W, Verdooner SR. Digital indocyanine-green angiography in chorioretinal disorders. *Ophthalmology.* 1992;99:287–91.
8. Ogata F, Azuma R, Kikuchi M, Koshima I, Morimoto Y. Novel lymphography using indocyanine green dye for near-infrared fluorescence labeling. *Ann Plast Surg.* 2007;58:652–5.
9. Kitai T, Inomoto T, Miwa M, Shikayama T. Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. *Breast Cancer.* 2005;12:211–5.
10. Rubens FD, Ruel M, Fremes SE. A new and simplified method for coronary and graft imaging during CABG. *Heart Surg Forum.* 2002;5:141–4.
11. Raabe A, Nakaji P, Beck J, et al. Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. *J Neurosurg.* 2005;103:982–9.
12. Ishizawa T, Tamura S, Masuda K, et al. Intraoperative fluorescent cholangiography using indocyanine green: a biliary road map for safe surgery. *J Am Coll Surg.* 2008;208:e1–4.
13. Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N. Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. *Br J Surg.* 2010;97:1369–77.
14. Makuuchi M, Kosuge T, Takayama T, et al. Surgery for small liver cancers. *Semin Surg Oncol.* 1993;9:298–304.
15. Ishizawa T, Hasegawa K, Aoki T, et al. Neither multiple tumors nor portal hypertension are surgical contraindications for hepatocellular carcinoma. *Gastroenterology.* 2008;134:1908–16.
16. Verbeek FP, van der Vorst JR, Schaafsma BE, et al. Image-guided hepatopancreatobiliary surgery using near-infrared fluorescent light. *J Hepatobiliary Pancreat Sci.* 2012;19:626-637.
17. Arita J, Takahashi M, Hata S, et al. Usefulness of contrast-enhanced intraoperative ultrasound using Sonazoid in patients with hepatocellular carcinoma. *Ann Surg.* 2011;254:992–9.
18. Liver Cancer Study Group of Japan. Classification of primary liver cancer. 5th ed. Kanehara: Tokyo; 2008.
19. International Working Party. Terminology of nodular hepatocellular lesions. *Hepatology.* 1995;22:983–93.
20. Subramanian A, Tamayo P, Mootha VK, et al. Gene set enrichment analysis: a knowledge-based approach for interpreting genome-wide expression profiles. *Proc Natl Acad Sci USA.* 2005;102:15545–50.
21. Cairo S, Armengol C, De Reyniès A, et al. Hepatic stem-like phenotype and interplay of Wnt/beta-catenin and Myc signaling in aggressive childhood liver cancer. *Cancer Cell.* 2008;14:471–84.
22. de Graaf W, Häusler S, Heger M, et al. Transporters involved in the hepatic uptake of (99m)Tc-mebrofenin and indocyanine green. *J Hepatol.* 2011;54:738–45.
23. Huang L, Vore M. Multidrug resistance p-glycoprotein 2 is essential for the biliary excretion of indocyanine green. *Drug Metab Dispos.* 2001;29:634–7.
24. Kitao A, Zen Y, Matsui O, et al. Hepatocellular carcinoma: signal intensity at gadoxetic acid-enhanced MR Imaging–correlation with molecular transporters and histopathologic features. *Radiology.* 2010;256:817–26.
25. Fox I, Brooker L, Heseltine D, Essex H, Wood E. New dyes for continuous recording of dilution curves in whole blood independent of variations in blood oxygen saturation. *Am J Physiol.* 1956;187:599–606.
26. Speich R, Saesseli B, Hoffmann U, Neftel KA, Reichen J. Anaphylactoid reactions after indocyanine-green administration. *Ann Intern Med.* 1988;109:345–6.
27. Wang LV. Multiscale photoacoustic microscopy and computed tomography. Nat Photonics. 2009;3:503–9.
28. Kaneko J, Inagaki Y, Ishizawa T, et al. Photodynamic therapy for human hepatoma-cell-line tumors utilizing biliary excretion properties of indocyanine green. *J Gastroenterol.* 2013. doi:10.1007/s00535-013-0775-4.

Liver Cancer

Liver Cancer 2014;3:6–8
DOI: 10.1159/000343853
Published online: February 28, 2014

2235-1795/14/0031-0006$39.50/0
www.karger.com/lic

Editorial

The Beginning of a New Era of Digestive Surgery Guided by Fluorescence Imaging

Takeaki Ishizawa[a,b] Norihiro Kokudo[a]

[a]Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, [b]Department of Gastroenterological Surgery, Cancer Institute Ariake Hospital, Japanese Foundation for Cancer Research, Tokyo, Japan

There has been a dramatic increase in the use of fluorescence imaging for visualizing biological structures during surgery; a MEDLINE search with the keywords "fluorescence imaging" and "surgery" yielded year-on-year increases in the number of publications, which reached more than 1,200 articles in 2012 (fig. 1). Use of fluorescence imaging in surgical settings started at the beginning of the 21st century with angiography using indocyanine green (ICG) as a source of fluorescence during coronary artery bypass grafting [1], and this was followed by sentinel node navigation in breast cancer surgery [2] and intraoperative angiography for cerebral aneurysm [3] in the mid 2000s. Since near-infrared imaging systems became commercially available for open surgery in 2005 and for laparoscopic surgery in 2011, the application of fluorescence-guided surgery has further accelerated.

Among the numerous fluorescent probes available for in vivo imaging, ICG remains the mainstay in the clinical setting. The safety of ICG has been established over more than 50 years of clinical usage. Its fluorescent properties (excitation 750–810 nm, emission around 830 nm) mean that the signal is not absorbed by hemoglobin or water, which confers advantages in visualizing deep-lying structures. In the field of hepatobiliary surgery, the fact that ICG is excreted in bile is a very useful pharmacological characteristic. For example, ICG-fluorescence imaging enables delineation of the bile ducts following intravenous ICG injection (fluorescence cholangiography) [4–6]. Using ICG, intraoperative identification of both primary and secondary hepatic malignancies is possible through visualization of the biliary excretion disorders that exist in hepatocellular carcinoma tissues and in non-cancerous hepatic parenchyma compressed by metastatic tumors [7–10]; this approach may lead to the development of photodynamic treatment [11]. Currently available techniques can also be used to assess portal uptake in hepatic segments with venous occlusion during liver resec-

Norihiro Kokudo, MD, PhD

Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo
7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655 (Japan)
Tel. +81 3 5800 8841, E-Mail KOKUDO-2SU@h.u-tokyo.ac.jp

Liver Cancer 2014;3:6–8
DOI: 10.1159/000343853
Published online: February 28, 2014

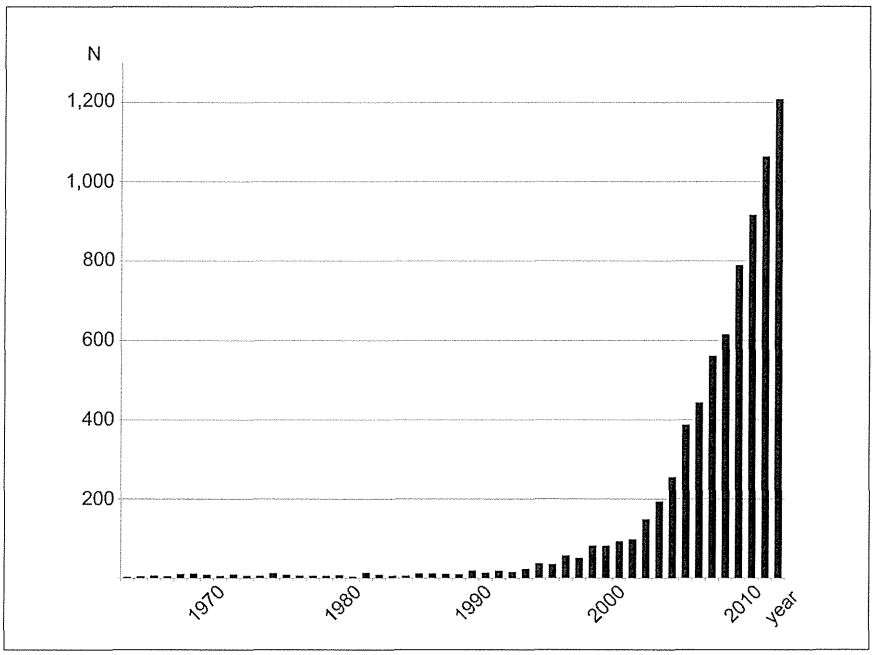

Fig. 1. Annual number of publications (N) on fluorescence imaging in the field of surgical treatment. A MEDLINE search was carried out using the keywords "fluorescence imaging" and "surgery" (accessed on 19 December 2013). The number of publications started to increase dramatically from about 2000.

tion or transplantation [12]. Another clinically available fluorescent probe is 5-aminolevulinic acid; however, its application to digestive surgery has rarely been evaluated.

In basic and preclinical studies, many novel fluorescent probes have been developed to enhance ICG-based fluorescence imaging to delineate biliary and vascular anatomy and to detect cancerous tissues other than hepatocellular carcinoma. Among these techniques, intraoperative fluorescence imaging of pancreatic leaks has the potential to reduce the incidence and severity of postoperative pancreatic fistulas [13]. Novel fluorescence imaging systems are also being actively developed to allow simultaneous identification of two or more structures with different fluorescence probes [14]; furthermore, fluorescence goggle systems worn by the operating surgeon should soon be able to provide real-time visual information on the surgical field [15]. The history and techniques of fluorescence-guided surgery are well-summarized in a recent review article by Vahrmeijer et al. [16] and are also described in detail in the book *Fluorescent Imaging: Treatment of Hepatobiliary and Pancreatic Diseases* [17]. In addition, the first international symposium on fluorescence-guided surgery, held in February 2014, promoted the sharing of cutting-edge knowledge for further development of these exciting new techniques.

Conventionally, intraoperative diagnosis and decision-making have been based on surgeons' visual inspection and palpation, with the aid of ultrasonography and radiation. Fluorescence imaging will open a new era of surgery, in which more detailed information on vascular anatomy and cancer status will be rapidly available for surgeons to view when needed, enhancing the safety and efficacy of digestive surgery.

Liver Cancer 2014;3:6–8
DOI: 10.1159/000343853
Published online: February 28, 2014

References

1 Rubens FD, Ruel M, Fremes SE: A new and simplified method for coronary and graft imaging during CABG. Heart Surg Forum 2002;5:141–144.
2 Kitai T, Inomoto T, Miwa M, Shikayama T: Fluorescence navigation with indocyanine green for detecting sentinel lymph nodes in breast cancer. Breast Cancer 2005;12:211–215.
3 Raabe A, Nakaji P, Beck J, Kim LJ, Hsu FP, Kamerman JD, Seifert V, Spetzler RF: Prospective evaluation of surgical microscope-integrated intraoperative near-infrared indocyanine green videoangiography during aneurysm surgery. J Neurosurg 2005;103:982–989.
4 Ishizawa T, Bandai Y, Kokudo N: Fluorescent cholangiography using indocyanine green for laparoscopic cholecystectomy: an initial experience. Arch Surg 2009;144:381–382.
5 Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N: Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 2010;97:1369–1377.
6 Kokudo N, Ishizawa T: Clinical application of fluorescence imaging of liver cancer using indocyanine green. Liver Cancer 2012;1:15–21.
7 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.
8 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.
9 van der Vorst JR, Schaafsma BE, Hutteman M, Verbeek FP, Liefers GJ, Hartgrink HH, Smit VT, Löwik CW, van de Velde CJ, Frangioni JV, Vahrmeijer AL: Near-infrared fluorescence-guided resection of colorectal liver metastases. Cancer 2013;119:3411–3418.
10 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 2013(in press).
11 Kaneko J, Inagaki Y, Ishizawa T, Gao J, Tang W, Aoki T, Sakamoto Y, Hasegawa K, Sugawara Y, Kokudo N: Photodynamic therapy for human hepatoma-cell-line tumors utilizing biliary excretion properties of indocyanine green. J Gastroenterol 2013(in press).
12 Kawaguchi Y, Ishizawa T, Miyata Y, Yamashita S, Masuda K, Satou S, Tamura S, Kaneko J, Sakamoto Y, Aoki T, Hasegawa K, Sugawara Y, Kokudo N: Portal uptake function in veno-occlusive regions evaluated by real-time fluorescent imaging using indocyanine green. J Hepatol 2013;58:247–253.
13 Yamashita S, Sakabe M, Ishizawa T, Hasegawa K, Urano Y, Kokudo N: Visualization of the leakage of pancreatic juice using a chymotrypsin-activated fluorescent probe. Br J Surg 2013;100:1220–1228.
14 Ashitate Y, Stockdale A, Choi HS, Laurence RG, Frangioni JV: Real-time simultaneous near-infrared fluorescence imaging of bile duct and arterial anatomy. J Surg Res 2012;176:7–13.
15 Liu Y, Zhao YM, Akers W, Tang ZY, Fan J, Sun HC, Ye QH, Wang L, Achilefu S: First in-human intraoperative imaging of HCC using the fluorescence goggle system and transarterial delivery of near-infrared fluorescent imaging agent: a pilot study. Transl Res 2013;162:324–331.
16 Vahrmeijer AL, Hutteman M, van der Vorst JR, van de Velde CJ, Frangioni JV: Image-guided cancer surgery using near-infrared fluorescence. Nat Rev Clin Oncol 2013;10:507–518.
17 Kokudo N, Ishizawa T(eds): Fluorescent imaging: treatment of hepatobiliary and pancreatic diseases. Basel, Karger, 2013.

Surg Endosc
DOI 10.1007/s00464-014-3468-z

NEW TECHNOLOGY

Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy

Hiroki Kudo · Takeaki Ishizawa · Keigo Tani · Nobuhiro Harada · Akihiko Ichida · Atsushi Shimizu · Junichi Kaneko · Taku Aoki · Yoshihiro Sakamoto · Yasuhiko Sugawara · Kiyoshi Hasegawa · Norihiro Kokudo

Received: 26 July 2013 / Accepted: 24 January 2014

Abstract
Background Although laparoscopic hepatectomy has increasingly been used to treat cancers in the liver, the accuracy of intraoperative diagnosis may be inferior to that of open surgery because the ability to visualize and palpate the liver surface during laparoscopy is relatively limited. Fluorescence imaging has the potential to provide a simple compensatory diagnostic tool for identification of cancers in the liver during laparoscopic hepatectomy.
Methods In 17 patients who were to undergo laparoscopic hepatectomy, 0.5 mg/kg body weight of indocyanine green (ICG) was administered intravenously within the 2 weeks prior to surgery. Intraoperatively, a laparoscopic fluorescence imaging system obtained fluorescence images of its surfaces during mobilization of the liver.
Results In all, 16 hepatocellular carcinomas (HCCs) and 16 liver metastases (LMs) were resected. Of these, laparoscopic ICG fluorescence imaging identified 12 HCCs (75 %) and 11 LMs (69 %) on the liver surfaces distributed over Couinaud's segments 1–8, including the 17 tumors that had not been identified by visual inspections of normal color images. The 23 tumors that were identified by fluorescence imaging were located closer to the liver surfaces than another nine tumors that were not identified by fluorescence imaging (median [range] depth 1 [0–5] vs. 11 [8–30] mm; $p < 0.001$).
Conclusions Like palpation during open hepatectomy, laparoscopic ICG fluorescence imaging enables real-time identification of subcapsular liver cancers, thus facilitating estimation of the required extent of hepatic mobilization and determination of the location of an appropriate hepatic transection line.

Keywords Indocyanine green · Fluorescence imaging · Laparoscopic hepatectomy · Hepatocellular carcinoma · Liver metastasis

Over the past few years, the role of laparoscopic hepatectomy for surgical treatment of cancers in the liver has been expanded worldwide [1, 2]. Although laparoscopic hepatectomy has potential advantages over open hepatectomy in reducing blood loss, postoperative pain, and length of hospital stay, there are still concerns that small subcapsular lesions may be missed during surgery because of the limited ability to visualize and palpate liver surfaces that laparoscopy provides. In order to further enhance the accuracy of laparoscopic hepatectomy and facilitate complicated procedures such as segmentectomies [3], novel imaging techniques that can compensate for the drawbacks of laparoscopic diagnostic tools need to be developed.

Recently, intraoperative fluorescence imaging techniques using indocyanine green (ICG) were developed [4, 5] and surgeons began to use them clinically to delineate cancers in the liver during open hepatectomy [6]. In this technique, ICG that has previously been administered intravenously for preoperative liver function assessment is used as a fluorescent source during surgery. Intraoperatively, cancers in the liver can be identified through

Electronic supplementary material The online version of this article (doi:10.1007/s00464-014-3468-z) contains supplementary material, which is available to authorized users.

H. Kudo · T. Ishizawa (✉) · K. Tani · N. Harada · A. Ichida · A. Shimizu · J. Kaneko · T. Aoki · Y. Sakamoto · Y. Sugawara · K. Hasegawa · N. Kokudo
Hepato-Biliary-Pancreatic Surgery Division, Department of Surgery, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: tish-tky@umin.ac.jp

Published online: 25 February 2014

visualization of ICG, which remains only in the cancerous tissues of hepatocellular carcinoma (HCC) and non-cancerous hepatic parenchyma compressed by liver metastases (LMs) [4, 7]. Laparoscopic fluorescence imaging systems have become commercially available from 2011, this technique can now also be used during laparoscopic hepatectomy. The aim of the present study was to develop techniques for ICG fluorescence imaging and to evaluate its efficacy in the setting of laparoscopic hepatectomy.

Materials and methods

This study was conducted with the approval of the Institutional Ethics Review Board of Tokyo University, and is registered in the UMIN-CTR (UMIN000001075, https://center.umin.ac.jp/ctr/index.htm). Informed consent was obtained from all patients.

Patients

Seventeen patients who were to undergo total laparoscopic hepatectomy or laparoscopic-assisted hepatectomy (laparoscopic mobilization of the liver followed by open hepatic transection) for HCC ($n = 10$) or LM (colorectal cancer [$n = 6$] and uterine cancer [$n = 1$]) at The University of Tokyo Hospital from April 2012 to April 2013 were studied.

Intraoperative indocyanine-green fluorescence imaging

The technical details of ICG fluorescence imaging have been described previously [4]. Briefly, 0.5 mg/kg of ICG (Diagnogreen; Daiichi Sankyo, Tokyo, Japan) is administered intravenously for liver function testing, ideally within the 2 weeks prior to surgery. At the time of surgery, ICG that is retained in cancerous tissues and/or non-cancerous compressed liver parenchyma around tumors is used as a fluorescence source.

The laparoscopic fluorescence imaging system consists of a charge-coupled device camera (410,000 pixels in total) and a xenon light source that can limit the wavelengths to between 690 and 790 nm during fluorescent imaging (Olympus Medical Systems, Tokyo, Japan). The camera imaging head is also equipped with a cutoff filter. Intraoperatively, full-color images can be converted to fluorescent images easily and quickly by using switches on the camera head to shift the light source and cutoff filter [8].

The intraoperative procedure was as follows. Following abdominal insufflation, a 30° laparoscope was introduced through a 12-mm camera port. Fluorescence images of the liver surface were obtained by converting full-color images to fluorescent images during and after completion of hepatic mobilization. Intraoperative ultrasonography with a flexible laparoscopic probe (BK Medical, Herlev, Denmark, or Hitachi-Aloka Medical, Tokyo, Japan) was also used to screen the whole liver. In principle, additional resections of lesions newly detected by ICG fluorescence imaging were considered only if these lesions were also identified by contrast-enhanced ultrasonography, in which perfluorobutane microbubbles appear as hypoechoic nodules on Kupffer phase images (Sonazoid; GE Healthcare, Oslo, Norway) [9, 10].

Following resection, the surgical specimens were sliced open in the operation room and the distances between liver surface and tumor boundaries measured. All specimens were formalin-fixed and submitted for pathological diagnosis.

Statistical analysis

Continuous data were expressed as median (range). Quantitative and categorized variables were compared using the Wilcoxon rank-sum test and Fisher's exact test, respectively. p values < 0.05 were considered to denote statistical significance. Statistical analysis was performed using the JMP software (version 9.0.0; SAS Institute, Cary, NC, USA).

Results

Among the 16 HCCs and 16 LMs resected from the 17 patients, six exposed/protruding tumors were detected by visual inspections of normal color images during the laparoscopic procedures. Laparoscopic ICG fluorescence imaging identified 12 HCCs (75 %) and 11 LMs (69 %) distributed over Couinaud's segments 1–8 on the liver surfaces (Table 1), facilitating estimation of the extent of hepatic mobilization needed for subsequent parenchymal transection (Fig. 1 and supplementary video 1) and determination of an appropriate hepatic transection line (Fig. 2 and supplementary video 2). Intraoperative contrast-enhanced ultrasonography identified all 32 tumors as hypoechoic lesions on Kupffer phase images.

The 23 tumors identified by fluorescence imaging were larger and closer to a hepatic surface than the nine tumors that were not identified by this technique (Table 1). There were no significant differences between the two groups in interval between intravenous administration of ICG and surgery (3 [1–19] days vs. 3 [2–10] days; $p = 0.530$) and preoperative ICG retention rate at 15 min (6.4 [3.4–19.5] vs. 6.4 [4.2–14.7] %; $p = 0.514$). No adverse reactions to the ICG were encountered.

Table 1 Results of indocyanine-green fluorescence imaging for identification of cancers in the liver

	Identifiable tumors		Non-identifiable tumors		*p* value
	HCC ($n = 12$)	LM ($n = 11$)	HCC ($n = 4$)	LM ($n = 5$)	
Location					
Segment 1	1	1	0	0	
Segment 2	2	0	0	1	
Segment 3	1	3	0	0	
Segment 4	1	0	1	0	
Segment 5	1	2	1	1	
Segment 6	3	3	1	1	
Segment 7	2	1	1	0	
Segment 8	1	1	0	2	
Diameter [mm; (range)]	18 (3–65)		7 (3–20)		0.018
Depth [mm; (range)]	1 (0–5)		11 (8–30)		<0.001

HCC hepatocellular carcinoma, *LM* liver metastases

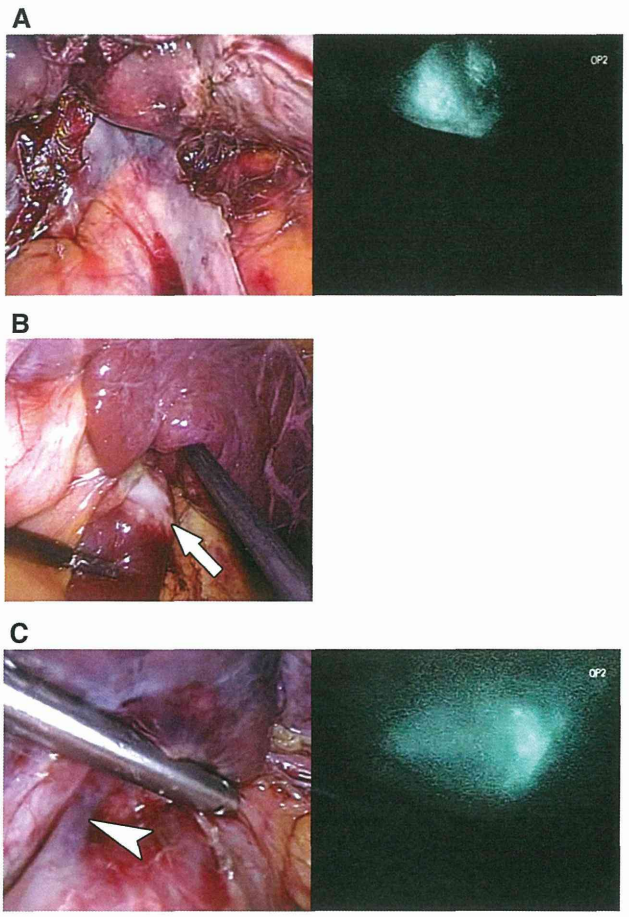

Fig. 1 Fluorescence images (*right*) and corresponding color images (*left*) of liver cancers during hepatic mobilization. **A** The right lobe of the liver is mobilized and fluorescence imaging used to confirm the exact location of a hepatocellular carcinoma in segment 7. **B**, **C** Identification of colorectal liver metastasis located in segment 1. Although the tumor is exposed on the ventral surface of Spiegel's lobe (*arrow in* **B**), it is identifiable from the dorsal aspect only by using fluorescence imaging (**C**). Based on the fluorescence images, the caudate vein (*arrowhead in* **C**) is divided and Spiegel's lobe completely mobilized preparatory to hepatic transection

Discussion

Visual inspection, palpation, and ultrasonography are essential diagnostic tools for ensuring accurate resection of hepatic malignancies. During open hepatectomy, palpation can supplement visual inspection and compensate for drawbacks in intraoperative ultrasonography by identifying small lesions located just beneath the liver surface. In contrast, during laparoscopic hepatectomy, information obtained by palpation using laparoscopic forceps is extremely limited compared with the direct manipulation possible during open surgery.

In the present series, irrespective of the tumor-bearing hepatic segments, during mobilization of the liver laparoscopic ICG fluorescence imaging identified all HCCs and LMs that were 5 mm or closer to the liver surface. Of the 23 tumors visualized by fluorescence imaging, 17 were not identifiable by visual inspection of normal laparoscopic color images. Information provided by fluorescence imaging helped surgeons to determine the required extent of hepatic mobilization and set a dissection line for parenchymal transection during the laparoscopic procedures. These findings suggest that fluorescence imaging has the potential to be used as an additional tool for identifying subcapsular tumors during laparoscopic hepatectomy.

The major advantage of fluorescence imaging is that at any time during laparoscopic procedures surgeons can confirm the locations of liver cancers to be resected by simply using a switch on the camera imaging head to convert normal color images to fluorescence images, as is the case for fluorescence cholangiography during cholecystectomy [11]. Although intraoperative ultrasonography also enables real-time identification of liver cancers during laparoscopic procedures [12], probe insertion requires an extra trocar and surgeons usually need two separate TV monitors—one for viewing the ultrasonographic images and another for the laparoscopic images.

Inability to visualize deeply-located tumors is the major limitation of ICG fluorescence imaging. In our series, it identified none of the cancers located 8 mm or more from the liver surface, consistent with findings of previous studies of ICG fluorescence imaging of liver cancers in open hepatectomy [4] and fluorescence cholangiography [11]. Size of cancerous lesions may also affect tumor detectability by fluorescence imaging. However, in the present

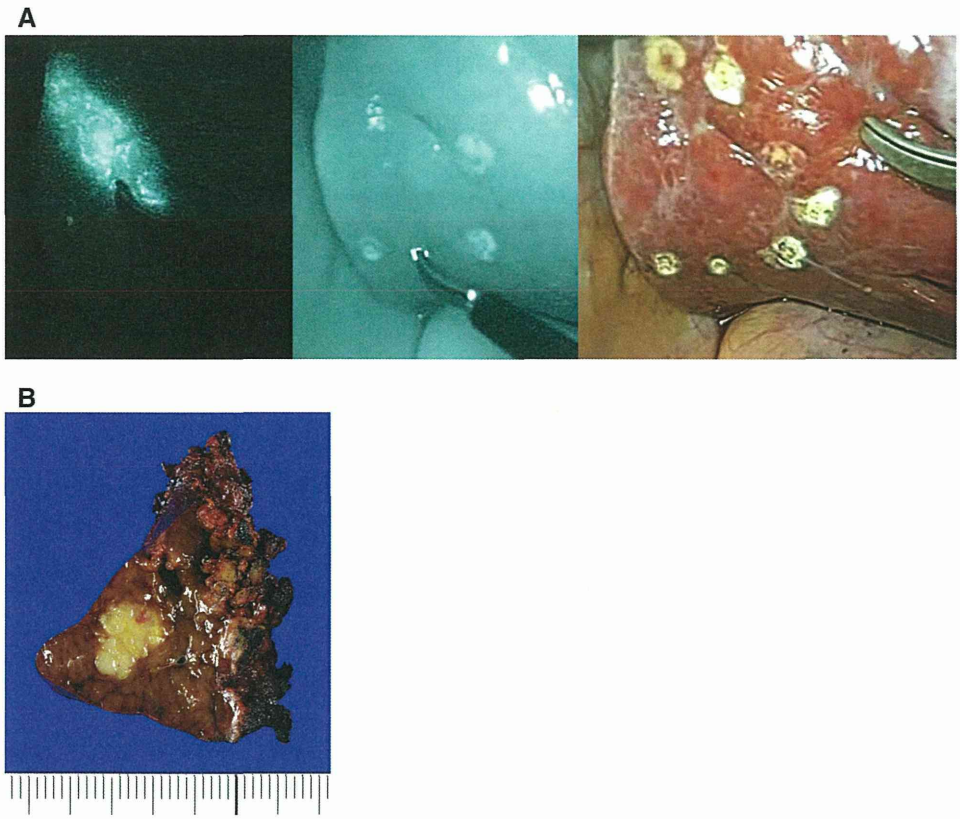

Fig. 2 Determination of a hepatic transection line using fluorescence imaging. **A** Boundaries of a colorectal metastasis located in segment 6 are confirmed by fluorescence imaging (*left*), after which a minimal hepatic transection line is marked by electric cautery on the liver surface using near-infrared images without a long-pass filter (*middle*) and normal color images (*right*). **B** Cut surface of the resected specimen

series, even 3-mm cancers were detected by fluorescence images provided they were located just beneath the liver surfaces. At present, intraoperative ultrasonography is a mandatory diagnostic tool during laparoscopic and open hepatectomy. Thus, we expect that laparoscopic ICG fluorescence imaging could complement visual inspection and ultrasonography by identifying small subcapsular tumors.

Conclusions

ICG fluorescence imaging is easy to perform and facilitates identification of subcapsular hepatic malignancies during laparoscopic procedures. If the sensitivity of laparoscopic fluorescence imaging systems to near-infrared light is improved, the present technique may also be useful for confirming surgical margins from the raw surface of the liver during parenchymal transection.

Disclosures Drs. Kudo, Ishizawa, Tani, Harada, Ichida, Shimizu, Kaneko, Aoki, Sakamoto, Sugawara, Hasegawa, and Kokudo have no conflicts of interest or financial ties to disclose.

Funding/support This work was supported by grants from the Takeda Science Foundation (Ishizawa), the Kanae Foundation for the Promotion of Medical Science (Ishizawa), and the Ministry of Education, Culture, Sports, Science and Technology of Japan (Ishizawa; Nos. 23689060 and 23249067).

References

1. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I et al (2009) The international position on laparoscopic liver surgery: the Louisville Statement, 2008. Ann Surg 250(5):825–830
2. Edwin B, Nordin A, Kazaryan AM (2011) Laparoscopic liver surgery: new frontiers. Scand J Surg 100:54–65
3. Ishizawa T, Gumbs AA, Kokudo N, Gayet B (2012) Laparoscopic segmentectomy of the liver: from segment I to VIII. Ann Surg 256:959–964
4. Ishizawa T, Fukushima N, Shibahara J, Masuda K, Tamura S, Aoki T et al (2009) Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 115:2491–2504
5. Gotoh K, Yamada T, Ishikawa O, Takahashi H, Eguchi H, Yano M et al (2009) A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. J Surg Oncol 100:75–79
6. Verbeek FP, van der Vorst JR, Schaafsma BE, Hutteman M, Bonsing BA, van Leeuwen FW et al (2012) Image-guided hepatopancreatobiliary surgery using near-infrared fluorescent light. J Hepatobiliary Pancreat Sci 19:626–637
7. van der Vorst JR, Schaafsma BE, Hutteman M, Verbeek FP, Liefers GJ, Hartgrink HH et al (2013) Near-infrared fluorescence-

guided resection of colorectal liver metastases. Cancer 119: 3411–3418
8. Ishizawa T, Zuker NB, Kokudo N, Gayet B (2012) Positive and negative staining of hepatic segments by use of fluorescent imaging techniques during laparoscopic hepatectomy. Arch Surg 147:393–394
9. Arita J, Takahashi M, Hata S, Shindoh J, Beck Y, Sugawara Y et al (2011) Usefulness of contrast-enhanced intraoperative ultrasound using Sonazoid in patients with hepatocellular carcinoma. Ann Surg 254:992–999
10. Takahashi M, Hasegawa K, Arita J, Hata S, Aoki T, Sakamoto Y et al (2012) Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. Br J Surg 99:1271–1277
11. Ishizawa T, Bandai Y, Ijichi M, Kaneko J, Hasegawa K, Kokudo N (2010) Fluorescent cholangiography illuminating the biliary tree during laparoscopic cholecystectomy. Br J Surg 97:1369–1377
12. Viganò L, Ferrero A, Amisano M, Russolillo N, Capussotti L (2013) Comparison of laparoscopic and open intraoperative ultrasonography for staging liver tumours. Br J Surg 100:535–542