Editorial

Future applications of fusion-fluorescence imaging during laparoscopic procedures

Babs G. Sibinga Mulder, Alexander L. Vahrmeijer, J. Sven D. Mieog

Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands

Correspondence to: J. Sven D. Mieog. Department of Surgery, Leiden University Medical Center, Leiden, The Netherlands. Email: j.s.d.mieog@lumc.nl.

Provenance: This is a Guest Editorial commissioned by Editor-in-Chief Jia-Fu Ji, MD, FACS (Department of Gastrointestinal Surgery, Peking University School of Oncology & Beijing Cancer Hospital, Beijing, China).

Comment on: Terasawa M, Ishizawa T, Mise Y, *et al.* Applications of fusion-fluorescence imaging using indocyanine green in laparoscopic hepatectomy. Surg Endosc 2017. [Epub ahead of print].

Received: 28 August 2017; Accepted: 31 August 2017; Published: 21 September 2017.

doi: 10.21037/tgh.2017.09.03

View this article at: http://dx.doi.org/10.21037/tgh.2017.09.03

Image-guided surgery in hepatobiliary surgery using near-infrared fluorescence (NIRF) is a relatively novel imaging technique that can aid in real-time demarcation of tumors, liver mapping and cholangiography (1). NIRF imaging, using indocyanine green (ICG), can be especially valuable during hepatic minimally invasive procedures, because surgeons are deprived of tactile feedback. This technique proved to be feasible for detection and resection of hepatocellular carcinoma (HCC) as well as metastases, all with different fluorescence patterns (2). The feasibility of fusion-fluorescence imaging using ICG during laparoscopic hepatectomy for identification of hepatic tumors and segmental boundaries was described in *Surgical Endoscopy* by Terasawa *et al.* (3). The authors describe a cohort of 41 patients undergoing laparoscopic hepatectomy using the PINPOINT^{TM} imaging system (NOVADAQ, Toronto, Canada) (4), providing simultaneously monochromatic fluorescence images under near-infrared light illumination, colour images under white-light illumination and fusion images. Eighty-five percent of the detected malignant tumors were identified with NIRF imaging, of which 49% could only be detected with NIRF, although no information about the detection of these tumors on the preoperative imaging was mentioned by the authors. Hepatic segments were successfully identified and resected in 12 patients with the aid of fusion imaging (5). The fusion images, made up of pseudocolour-fluorescence signals on white-light colour images, enables the surgeon to continue the surgical procedure without shifting between the NIR and white light channels, receiving information about the tumor location, segmental boundaries and bile duct anatomy. Laparoscopic camera systems, enabling real time overlay fluorescence become increasingly available for clinical use.

NIRF imaging using ICG in liver surgery has been studied extensively over the last few years and the added value of this technique is clear (1,6). However, the overall survival and disease-free survival of patients in whom additional hepatic metastases are detected with NIRF imaging using ICG, did not differ from the patients who underwent surgery without NIRF imaging. In some patients repeated procedures can be prevented due to the additional detection of lesions with NIRF imaging (7).

As described in this study, for the detection of the deeply seated tumors the laparoscopic procedure should be complemented with other techniques, due to the limited depth-penetration of NIRF imaging. With the introduction of the gadoxetic acid-enhanced liver MRI, very small (<1 cm) metastases can be identified preoperatively (8). Subsequently, the surgeon and radiologist can use intraoperative (contrast-enhanced) ultrasonography during the surgery for the detection of these deeper seated lesions. The false positivity rate of contrast-enhanced ultrasonography remains relatively high (9). Furthermore, ICG is not tumor specific and due to the learning curve distinction between malignant and benign fluorescence patterns can be difficult, therefore the false positivity rate can be high (10,11). The use of NIRF imaging using ICG is limited to the liver since ICG is not tumor specific, therefore

demarcation of other tumor types is not possible (12). Although, NIRF fusion images during laparoscopy has a lot of potential, NIRF imaging using ICG is only used in the hepatobiliary surgery for tumor demarcation, liver mapping and bile duct anatomy and for perfusion of anastomoses.

Tumor specific fluorescent tracers could partly overcome these shortcomings and offer new possibilities for the laparoscopic systems providing NIRF fusion images. The first-in-human trials with tumor specific fluorescent tracers against folate receptor in metastatic ovarian cancer and against CEA in pancreatic cancer are showing promising results [(13); Hoogstins CE, Sibinga Mulder BG, Mieog JS, *et al.* Image-guided surgery in patients with pancreatic cancer: a clinical trial using SGM-101, a novel carcinoembryonic antigen-targeting, near-infrared fluorescent agent (unpublished data)]. In ongoing clinical trials antibody-based targeting ligands against vascular endothelial growth factor-A (VEGF-A) and epidermal growth factor receptor (EGRF) are used in patients with breast, colon or head-and-neck cancer. The use of tumor specific targets can potentially increase tumor detection rates, including possible micrometastases, and radical resection rates. Because tumor specific fluorescent targets only bind to specific receptors, false positivity rates could be decreased.

Additionally, new NIR fluorophores will become available and are currently tested in clinical trials, such as ZW800-I (Curadel Surgical Innovations, Wayland, MA, USA). The favourable characteristics of ZW800-I, emission at a wavelength range of 800 nm, small size, low toxicity and excretion through the kidneys, make this a very suitable fluorophore for the current available laparoscopic systems (800 nm), enabling visualisation of the ureters and perfusion of anastomoses without making the liver fluorescent. The majority of these new fluorophores and tumor specific fluorescent tracers are studied in patients using open space camera systems, due to the wider availability of these fluorescence camera's, higher sensitivity and more extensive functions of the camera systems.

Still, the maximal depth penetration of a fluorescence signal is limited to 1 cm (14), therefore NIRF imaging should be combined with other techniques, such as radionuclides. Tumor specific ligands can easily be conjugated to fluorophores, but can also be linked to radioactive isotopes. Ideally, these tumors specific preoperative PET/SPECT-scans provide information about tumor extension and allow surgical planning. During surgery the tumor can be NIRF guided approached and resected. The combination of radionuclide and fluorescence imaging can be even of more value in patients who are neoadjuvantly treated, discrimination between chemotherapy induced fibrotic tissue and vital cancer cells is more difficult on both preoperative radiologic imaging as during surgery. Clinical trials investigating both radionuclide and fluorescence imaging in patients are currently ongoing. The first *ex vivo* results show that combination of these techniques is feasible (15).

As above described, deeper seated tumors could be visualized using intraoperative ultrasound, preferably contrast-enhanced ultrasound as described in the study of Terasawa *et al.* In the far future the limited depth penetration problem might even be solved with the use of multispectral optoacoustic tomography (MSOT) or photoacoustic imaging (16,17). Depth penetration is extended to approximately 5cm, but these techniques are still in an early stage.

Although the use of ICG in hepatobiliary surgery has extensively been described, this study of Terasawa *et al.* clearly demonstrates the benefit and value of laparoscopic NIRF guided surgery, and encourages to investigate NIRF imaging in a broader patient cohort, using different kinds of fluorophores and optimizing laparoscopic systems for this application.

Acknowledgements

Funding: This work was supported by the Bas Mulder Award (grant UL2015-7665) from the Dutch Cancer Society.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Majlesara A, Golriz M, Hafezi M, et al. Indocyanine green fluorescence imaging in hepatobiliary surgery. Photodiagnosis Photodyn Ther 2017;17:208-15.
2. Boogerd LS, Handgraaf HJ, Lam HD, et al. Laparoscopic detection and resection of occult liver tumors of multiple cancer types using real-time near-infrared fluorescence guidance. Surg Endosc 2017;31:952-61.
3. Terasawa M, Ishizawa T, Mise Y, et al. Applications of fusion-fluorescence imaging using indocyanine green in laparoscopic hepatectomy. Surg Endosc 2017. [Epub ahead of print].

4. Kono Y, Ishizawa T, Tani K, et al. Techniques of Fluorescence Cholangiography During Laparoscopic Cholecystectomy for Better Delineation of the Bile Duct Anatomy. Medicine (Baltimore) 2015;94:e1005.
5. Ishizawa T, Zuker NB, Kokudo N, et al. Positive and negative staining of hepatic segments by use of fluorescent imaging techniques during laparoscopic hepatectomy. Arch Surg 2012;147:393-4.
6. Kudo H, Ishizawa T, Tani K, et al. Visualization of subcapsular hepatic malignancy by indocyanine-green fluorescence imaging during laparoscopic hepatectomy. Surg Endosc 2014;28:2504-8.
7. Handgraaf HJM, Boogerd LSF, Höppener DJ, et al. Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: A retrospective multicenter analysis. Eur J Surg Oncol 2017;43:1463-71.
8. Jhaveri KS, Fischer SE, Hosseini-Nik H, et al. Prospective comparison of gadoxetic acid-enhanced liver MRI and contrast-enhanced CT with histopathological correlation for preoperative detection of colorectal liver metastases following chemotherapy and potential impact on surgical plan. HPB (Oxford) 2017. [Epub ahead of print].
9. Takahashi M, Hasegawa K, Arita J, et al. Contrast-enhanced intraoperative ultrasonography using perfluorobutane microbubbles for the enumeration of colorectal liver metastases. Br J Surg 2012;99:1271-7.
10. Yokoyama N, Otani T, Hashidate H, et al. Real-time detection of hepatic micrometastases from pancreatic cancer by intraoperative fluorescence imaging: preliminary results of a prospective study. Cancer 2012;118:2813-9.
11. Ishizawa T, Fukushima N, Shibahara J, et al. Real-time identification of liver cancers by using indocyanine green fluorescent imaging. Cancer 2009;115:2491-504.
12. Hutteman M, van der Vorst JR, Mieog JS, et al. Near-infrared fluorescence imaging in patients undergoing pancreaticoduodenectomy. Eur Surg Res 2011;47:90-7.
13. Hoogstins CE, Tummers QR, Gaarenstroom KN, et al. A Novel Tumor-Specific Agent for Intraoperative Near-Infrared Fluorescence Imaging: A Translational Study in Healthy Volunteers and Patients with Ovarian Cancer. Clin Cancer Res 2016;22:2929-38.
14. Frangioni JV. New technologies for human cancer imaging. J Clin Oncol 2008;26:4012-21.
15. Hekman MC, Boerman OC, de Weijert M, et al. Targeted Dual-Modality Imaging in Renal Cell Carcinoma: An Ex Vivo Kidney Perfusion Study. Clin Cancer Res 2016;22:4634-42.
16. McNally LR, Mezera M, Morgan DE, et al. Current and Emerging Clinical Applications of Multispectral Optoacoustic Tomography (MSOT) in Oncology. Clin Cancer Res 2016;22:3432-9.
17. Zackrisson S, van de Ven SMWY, Gambhir SS. Light in and sound out: emerging translational strategies for photoacoustic imaging. Cancer Res 2014;74:979-1004.

doi: 10.21037/tgh.2017.09.03
Cite this article as: Sibinga Mulder BG, Vahrmeijer AL, Mieog JS. Future applications of fusion-fluorescence imaging during laparoscopic procedures. Transl Gastroenterol Hepatol 2017;2:76.

