



Universiteit
Leiden
The Netherlands

Image-guided cancer surgery : the value of near-infrared fluorescence imaging during oncologic and gastrointestinal procedures

Verbeek, F.P.R.

Citation

Verbeek, F. P. R. (2015, June 3). *Image-guided cancer surgery : the value of near-infrared fluorescence imaging during oncologic and gastrointestinal procedures*. Department of Surger, Faculty of Medicine, Leiden University Medical Center (LUMC), Leiden University. Retrieved from <https://hdl.handle.net/1887/33206>

Version: Corrected Publisher's Version

License: [Licence agreement concerning inclusion of doctoral thesis in the Institutional Repository of the University of Leiden](#)

Downloaded from: <https://hdl.handle.net/1887/33206>

Note: To cite this publication please use the final published version (if applicable).

Cover Page



Universiteit Leiden



The handle <http://hdl.handle.net/1887/33206> holds various files of this Leiden University dissertation.

Author: Verbeek, Floris Paul Reinier

Title: Image-guided cancer surgery : the value of near-infrared fluorescence imaging during oncologic and gastrointestinal procedures

Issue Date: 2015-06-03

Chapter 1

General introduction and thesis outline

Based on:

Hutteman M, Verbeek FP, Vahrmeijer AL. Application of Fluorescence Imaging to Hepatopancreatobiliary Surgery. *Published in: Fluorescence Imaging in the Treatment of Hepatobiliary and Pancreatic Diseases: Techniques and Future Perspectives. Frontiers of Gastrointestinal Research*, vol 31, pp 1–9. DOI: 10.1159/000348602, Karger Basel, 2013

Handgraaf HJ, Verbeek FP, Hutteman M, Vahrmeijer AL. Identification of metastatic liver cancer. *Published in: Fluorescence Imaging for Surgeons: Concepts and Applications*, 2015, DOI 10.1007/978-3-319-15678-1_16, Springer International Publishing Switzerland 2015

INTRODUCTION

Over the last century, remarkable advances have been made in the treatment of cancer. The improvement of chemotherapy, hormonal therapy and targeted systemic therapies has considerably improved patient prognosis. Despite these developments, surgery remains the cornerstone of primary treatment, especially in patients where the disease is localized and distant metastases are absent. The prognosis and quality of life of these patients depends in particular on the extent and quality of the surgical treatment. At present, residual of malignant cells (or so called R1 resection) remains a substantial issue in cancer surgery. In contrast to the many imaging modalities that can be used preoperatively for diagnosis, staging, and surgical planning (i.e. CT, MRI, PET and SPECT), real-time, intraoperative imaging modalities to assess the extent of disease and to determine adequate resection margins are lacking^{1,2}. As a consequence, surgeons still have to rely only on visual appearance and palpation to discriminate between tumor tissue and normal tissue. Misidentification of residual disease can result in a local recurrence, and subsequent deprived prognosis. Since this situation has not been changed for many decades, there is a need for a diagnostic tool that can discriminate tumor tissue from normal tissue during surgery.

NEAR-INFRARED FLUORESCENCE IMAGING

Optical imaging using near-infrared (NIR) fluorescence is a relatively new technique that has emerged as a promising intraoperative imaging modality²⁻⁴. NIR fluorescence imaging has several characteristics that are advantageous for implementation in a surgical setting². First, the wavelength of NIR light is between 700 to 900 nanometers, which is invisible to the human eye, and therefore does not alter the look of the surgical field. At this wavelength, light has relatively low tissue absorbance, resulting in high tissue penetration (up to several millimeters) and low autofluorescence³⁻⁶. Second, only low concentrations of a non-ionizing tracer are needed and no direct tissue contact is employed in NIR fluorescence imaging making it an inherently safe technique⁷. Finally, images can be acquired within a few milliseconds and this technique can be easily combined with zoom lenses using a “hands-free” setup, which allows the surgeon to operate under real-time image guidance⁸⁻¹⁰. The introduction of minimally invasive techniques has increased the need for additional intraoperative imaging modalities. For example, NIR fluorescence imaging has already been used during robot-assisted laparoscopic surgery for several indications¹¹⁻¹⁴.

Multiple NIR imaging systems have been developed for both open and laparoscopic surgery¹⁵⁻²¹. Several of these systems are commercially available^{7,15}. Optimized

imaging systems have the ability to provide a real-time overlay of the NIR fluorescence signal with visible color images. This provides the NIR fluorescence signal in relation to the surgical anatomy, enabling true image-guidance. Along with the introduction of image-guided surgery, several minimal invasive alternatives have been validated to replace the conventional open approach^{22,23}. For several indications the laparoscopic approach shows a more favorable outcome than open surgery with regard to postoperative pain, hospital stay and blood loss²⁴⁻²⁷. However, minimally invasive surgery also limits visualization and palpability of the surgical field. NIR fluorescence imaging could therefore contribute to this field of surgery by providing additional information.^{20,28-31}

Besides intraoperative imaging systems, for NIR fluorescence image-guided surgery, a NIR fluorescent contrast agent (i.e. fluorophore or “probe”) is also needed to visualize specific structures that need to be resected (e.g. tumor tissue) or should be spared (e.g. bile ducts). Indocyanine green (ICG) and Methylene blue are currently the only NIR fluorophores that are registered with the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for clinical application, albeit for other indications. ICG has been used since the 1950s to measure cardiac output, hepatic function, and retinal perfusion. The absorbance of ICG is around 800 nm, and adverse events following administration are rare, making it a safe contrast agent. Most studies report ICG doses between 1 and 10 mg for intraoperative imaging applications, but intravenous injection up to 25 mg has been reported to be safe³². After intravenous injection, ICG is cleared rapidly by the liver and almost completely excreted into bile. Methylene blue is also currently applicable for clinical use and at certain concentrations has fluorescent properties. However, its emission peak lies around 700 nm, which is less optimal due to higher tissue absorbance and higher auto-fluorescence. Both ICG and MB are non-targeted dyes as their chemical structures do not allow conjugation to tissue-specific ligands. Novel NIR fluorescent probes are being developed, to permit targeted imaging³³⁻³⁵. An ideal fluorophore should be simply to conjugate to tumor specific antibodies or ligands, have a high quantum yield (brightness) and low background uptake^{1,36}. Currently, multiple first-in-human trials are ongoing to allow broad clinical implementation of this new generation of dyes.

OUTLINE OF THE THESIS

This thesis is divided in three parts. **The first part** focusses on the intraoperative evaluation of surgical margins using NIR fluorescence imaging in both preclinical and clinical settings. **The second part** of this thesis focusses on the clinical imple-

mentation of fluorescence guided Sentinel Lymph Node Biopsy. **In part three**, NIR fluorescence imaging is used to visualize vital structures during abdominal surgery.

Part I: Intraoperative evaluation of surgical margins

Chapter 2 describes the use of a novel fluorophore (ZW800-1) that is conjugated to the ligand cRGD that targets integrins. The aim of the current study was to intra-operatively identify both colorectal tumors and ureters in orthotopic animal models using cRGD-ZW800-1. Moreover, as cRGD-ZW800-1 is cleared renally, minimal background uptake in the gastrointestinal tract was observed and ureteral visualization was feasible after a single injection. The characteristics of this NIR probe allow fluorescence guidance within 2 hours after administration to detect the extent of the primary tumor as well as the sites of disseminated disease whilst minimizing the risk of damage to ureters. **Chapter 3** describes the intraoperative identification of breast cancer using NIR fluorescence and the intravenous administration of methylene blue. **Chapter 4** gives an overview of the preclinical development and clinical applications of NIR fluorescence imaging during open and laparoscopic hepatopancreatobiliary surgery.

Part II: Sentinel lymph node imaging

Chapter 5 evaluates the diagnostic accuracy of NIR fluorescence for SLN mapping in breast cancer patients when used in addition to conventional techniques. This study describes a multicenter experience with the Fluorescence-Assisted Resection and Exploration (FLAREtm) imaging system, developed by the group of professor Frangioni (Harvard Medical School, Boston, MA, USA). Patients were enrolled in the Dana-Farber / Harvard Cancer Center (Boston, MA, USA) and the Leiden University Medical Center (Leiden, the Netherlands). In **Chapter 6** the ability to combine both radioactive and NIR fluorescence guidance for SLN mapping in breast cancer is demonstrated. A hybrid radioactive and fluorescence tracer was used which permits both preoperative imaging and intraoperative guidance after a single injection. In **Chapter 7** the same hybrid tracer is used for SLN mapping in melanoma patients. **Chapter 8** describes feasibility of SLN mapping using NIR fluorescence and ICG in patients undergoing radical cystectomy with lymphadenectomy for bladder cancer. In **Chapter 9** the application of NIR fluorescence imaging using different tracers for SLN mapping in vulvar cancer patients was investigated.

Part III: Vital structure imaging

Chapter 10 demonstrates the first successful clinical use of NIR fluorescence imaging using low dose methylene blue for the identification of the ureters during lower abdominal surgery. In **Chapter 11** ICG dose and timing for NIR cholangiography were optimized during open hepatopancreatobiliary surgery. Subsequently, these results were validated during laparoscopic cholecystectomies using a laparoscopic fluorescence imaging system. This study clearly shows that a prolonged interval between ICG administration and surgery permits optimal NIR cholangiography with minimal liver background fluorescence.

Finally, in **Chapter 12** results of the studies performed in this thesis are summarized and future perspectives are described.

REFERENCES

1. Vahrmeijer AL, Hutteman M, van der Vorst JR et al. Image-guided cancer surgery using near-infrared fluorescence. *Nat Rev Clin Oncol* 2013.
2. Frangioni JV. New technologies for human cancer imaging. *J Clin Oncol* 2008; 26:4012-4021.
3. Frangioni JV. In vivo near-infrared fluorescence imaging. *Curr Opin Chem Biol* 2003; 7:626-634.
4. Tanaka E, Choi HS, Fujii H et al. Image-guided oncologic surgery using invisible light: completed pre-clinical development for sentinel lymph node mapping. *Ann Surg Oncol* 2006; 13:1671-1681.
5. Vahrmeijer AL, Frangioni JV. Seeing the invisible during surgery. *Br J Surg* 2011; 98:749-750.
6. Chance B. Near-infrared images using continuous, phase-modulated, and pulsed light with quantitation of blood and blood oxygenation. *Ann N Y Acad Sci* 1998; 838:29-45.
7. Gioux S, Choi HS, Frangioni JV. Image-guided surgery using invisible near-infrared light: fundamentals of clinical translation. *Mol Imaging* 2010; 9:237-255.
8. Troyan SL, Kianzad V, Gibbs-Strauss SL et al. The FLARE intraoperative near-infrared fluorescence imaging system: a first-in-human clinical trial in breast cancer sentinel lymph node mapping. *Ann Surg Oncol* 2009; 16:2943-2952.
9. Stockdale A, Oketokoun R, Gioux S, Frangioni JV. Mini-FLARE: A Compact and Ergonomic Dual-Channel Near-Infrared Fluorescence Image-Guided Surgery System. *World Molecular Imaging Congress, Montreal, Canada, September 2009*. 2010.
10. Verbeek FP, Troyan SL, Mieog JS et al. Near-infrared fluorescence sentinel lymph node mapping in breast cancer: a multicenter experience. *Breast Cancer Res Treat* 2014; 143:333-342.
11. Rossi EC, Ivanova A, Boggess JF. Robotically assisted fluorescence-guided lymph node mapping with ICG for gynecologic malignancies: a feasibility study. *Gynecol Oncol* 2012; 124:78-82.
12. Buchs NC, Pugin F, Azagury DE et al. Real-time near-infrared fluorescent cholangiography could shorten operative time during robotic single-site cholecystectomy. *Surg Endosc* 2013.
13. Spinoglio G, Priora F, Bianchi PP et al. Real-time near-infrared (NIR) fluorescent cholangiography in single-site robotic cholecystectomy (SSRC): a single-institutional prospective study. *Surg Endosc* 2013; 27:2156-2162.
14. Borofsky MS, Gill IS, Hemal AK et al. Near-infrared fluorescence imaging to facilitate super-selective arterial clamping during zero-ischaemia robotic partial nephrectomy. *BJU Int* 2013; 111:604-610.
15. Schaafsma BE, Mieog JSD, Hutteman M et al. The clinical use of indocyanine green as a near-infrared fluorescent contrast agent for image-guided oncologic surgery. *J Surg Oncol* 2011; in press.
16. Hirche C, Engel H, Kolios L et al. An experimental study to evaluate the fluobeam 800 imaging system for fluorescence-guided lymphatic imaging and sentinel node biopsy. *Surg Innov* 2013; 20:516-523.
17. Gotoh K, Yamada T, Ishikawa O et al. A novel image-guided surgery of hepatocellular carcinoma by indocyanine green fluorescence imaging navigation. *J Surg Oncol* 2009; 100:75-79.

18. Crane LM, Themelis G, Pleijhuis RG et al. Intraoperative multispectral fluorescence imaging for the detection of the sentinel lymph node in cervical cancer: a novel concept. *Mol Imaging Biol* 2011; 13:1043-1049.
19. Yamauchi K, Nagafuji H, Nakamura T et al. Feasibility of ICG fluorescence-guided sentinel node biopsy in animal models using the HyperEye Medical System. *Ann Surg Oncol* 2011; 18:2042-2047.
20. van der Poel HG, Buckle T, Brouwer OR et al. Intraoperative Laparoscopic Fluorescence Guidance to the Sentinel Lymph Node in Prostate Cancer Patients: Clinical Proof of Concept of an Integrated Functional Imaging Approach Using a Multimodal Tracer. *Eur Urol* 2011; 60:826-33.
21. Cahill RA, Anderson M, Wang LM et al. Near-infrared (NIR) laparoscopy for intraoperative lymphatic road-mapping and sentinel node identification during definitive surgical resection of early-stage colorectal neoplasia. *Surg Endosc* 2011.
22. Keus F, de Jong JA, Gooszen HG et al. Laparoscopic versus open cholecystectomy for patients with symptomatic cholecystolithiasis. *Cochrane Database Syst Rev* 2006;CD006231.
23. Plante M, Renaud MC, Tetu B et al. Laparoscopic sentinel node mapping in early-stage cervical cancer. *Gynecol Oncol* 2003; 91:494-503.
24. Schirmer BD, Edge SB, Dix J et al. Laparoscopic cholecystectomy. Treatment of choice for symptomatic cholelithiasis. *Ann Surg* 1991; 213:665-676.
25. Ng SS, Lee JF, Yiu RY et al. Long-term oncologic outcomes of laparoscopic versus open surgery for rectal cancer: a pooled analysis of 3 randomized controlled trials. *Ann Surg* 2014; 259:139-147.
26. Wilson RG, Macintyre IM, Nixon SJ et al. Laparoscopic cholecystectomy as a safe and effective treatment for severe acute cholecystitis. *BMJ* 1992; 305:394-396.
27. Velanovich V. Laparoscopic vs open surgery: a preliminary comparison of quality-of-life outcomes. *Surg Endosc* 2000; 14:16-21.
28. Schols RM, Bouvy ND, Masclee AA et al. Fluorescence cholangiography during laparoscopic cholecystectomy: a feasibility study on early biliary tract delineation. *Surg Endosc* 2013; 27:1530-1536.
29. Schols RM, Bouvy ND, van Dam RM et al. Advanced intraoperative imaging methods for laparoscopic anatomy navigation: an overview. *Surg Endosc* 2012.
30. Ishizawa T, Bandai Y, Harada N et al. Indocyanine green-fluorescent imaging of hepatocellular carcinoma during laparoscopic hepatectomy: An initial experience. *Asian Journal of Endoscopic Surgery* 2010; 3:42-45.
31. Verbeek FP, Schaafsma BE, Tummers QR et al. Optimization of near-infrared fluorescence cholangiography for open and laparoscopic surgery. *Surg Endosc* 2013.
32. 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.
33. Luo S, Zhang E, Su Y et al. A review of NIR dyes in cancer targeting and imaging. *Biomaterials* 2011; 32:7127-7138.
34. Choi HS, Gibbs SL, Lee JH et al. Targeted zwitterionic near-infrared fluorophores for improved optical imaging. *Nat Biotechnol* 2013; 31:148-153.
35. Weissleder R, Tung CH, Mahmood U et al. In vivo imaging of tumors with protease-activated near-infrared fluorescent probes. *Nat Biotechnol* 1999; 17:375-378.
36. Frangioni JV. The problem is background, not signal. *Mol Imaging* 2009; 8:303-304.

