

YIA applicant

PRECLINICAL OPTIMIZATION AND CLINICAL TRANSLATION OF NEAR-INFRARED FLUORESCENCE IMAGING OF COLORECTAL LIVER METASTASES USING INDOCYANINE GREEN

J.R. van der Vorst¹, M. Hutteman¹, J.S.D. Mieog², G.J. Liefers¹, H.H. Hartgrink¹, V.T.H.B.M Smit¹, K.E. De Rooij¹, I.M. Mol¹, B.E. Schaafsma¹, E.L. Kaijzel¹, P.J.K. Kuppen¹, J.V. Frangioni², C.J.H. Van de Velde¹, C.W.G.M. Lowik¹, A.L. Vahrmeijer¹

¹LUMC, Leiden, Netherlands ²Beth Israel Deaconess Medical Center, Boston, USA
(j.r.van_der_vorst@lumc.nl)

Introduction: Near-infrared (NIR) fluorescence imaging using indocyanine green (ICG) is a promising technique to obtain real-time assessment of the extent and number of colorectal liver metastases during liver surgery. The current study aims to optimize dosage and timing of ICG administration.

Methods: The Mini-FLARE imaging system was used for real-time identification of liver tumors in 18 rats. Liver tumors were measured at 24, 48, 72 or 96 hours after administration of 0.04, 0.08, or 0.16 mg ICG (0.13, 0.26 or 0.53 mg / kg, respectively). Guided by these results, intraoperative identification of liver metastases was performed in 22 patients undergoing liver resection. NIR fluorescence imaging was performed 24 or 48 hours after administration of 10 or 20 mg ICG (approximately 0.26 mg / kg, respectively). After intraoperative imaging, resection specimens were sliced to examine internal fluorescent patterns using the Mini-FLARE imaging system. Subsequently, frozen tissue sections were measured for fluorescence using the Nuance multispectral imager.

Results: Using NIR fluorescence imaging and ICG, all colorectal liver metastases (N = 34), could be identified in all rats. Average tumor-to-liver (TLR) ratio over all groups was 3.0 ± 1.2 . Liver signal was lower in the 72 h time group compared to other time points, resulting in a significantly higher TLR. ICG dose did not significantly influence TLR, but a trend was found favoring the 0.08 mg dose group. Clinically, during intraoperative NIR fluorescence imaging, all superficially located metastases (< 1 cm beneath liver capsule) were identified (N = 44). Median TLR was 7.4 (range: 1.9 - 18.7) and no significant differences between time-points or doses were found. Liver signal was comparable to pre-injection signal at 24 to 48 hours post-injection, eliminating the need to test other time-points. In all patients, a fluorescent rim around the tumor was found, as described in earlier studies. Using fluorescence microscopy, this clear fluorescent rim was localized in stromal tissue in the transition area between tumor and normal liver tissue in all liver metastases. In this area, multiple cell types that are involved in tissue inflammation (e.g. granulocytes, lymphocytes) were found. In four patients, additional small (2 - 8 mm) metastases were identified using NIR fluorescence that were otherwise missed preoperatively and intraoperatively using only visual inspection and ultrasound

Conclusions: This study demonstrates that colorectal cancer liver metastases can be clearly identified during surgery using ICG and the Mini-FLARE imaging system. NIR fluorescence imaging has the potential to improve intraoperative detection of in particular small and superficially located liver metastases and can therefore be seen as an addition to the conventional imaging modalities.