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Long-term follow-up after near-infrared fluorescence-guided resection of colorectal liver metastases: A retrospective multicenter analysis

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Abstract

Background: Several studies demonstrated that intraoperative near-infrared fluorescence (NIRF) imaging using indocyanine green (ICG) identifies (sub)capsular colorectal liver metastases (CRLM) missed by other techniques. It is unclear if this results in any survival benefit. This study evaluates long-term follow-up after NIRF-guided resection of CRLM using ICG.

Methods: First, patients undergoing resection of CRLM with or without NIRF imaging were analyzed retrospectively. Perioperative details, liver-specific recurrence-free interval and overall survival were compared. Second, the prognosis of patients in whom additional metastases were identified solely by NIRF was studied.

Results: Eighty-six patients underwent resection with NIRF imaging and 87 without. In significantly more patients of the NIRF imaging cohort additional metastases were identified during surgery (25% vs. 13%, $p = 0.04$). Tumors identified solely by NIRF imaging were significantly smaller compared to additional metastases identified also by inspection, palpation or intraoperative ultrasound (3.2 ± 1.8 mm vs. 7.4 ± 2.6 mm, $p < 0.001$). Liver-specific recurrence-free survival at 4 years was 47% with NIRF imaging and 39% without (hazard ratio at multivariate analysis 0.73, 95% CI 0.42–1.28, $p = 0.28$). Overall survival at 4 years was 62% and 59%, respectively ($p = 0.79$). No liver recurrences occurred within 3 years follow-up in 52% of patients in whom additional metastases were resected based on only NIRF imaging.

Conclusions: This study suggests that NIRF imaging identifies significantly more and smaller tumors during resection of CRLM, preventing recurrences in a subset of patients. Given its safety profile and low expense, routine use can be considered until tumor targeting fluorescent tracers are clinically available.

Keywords: Indocyanine green; Cancer; Liver neoplasms; Surgery; Prognosis; Fluorescence imaging

Introduction

Intrahepatic recurrence rates after resection of colorectal liver metastases (CRLM) remain high, despite improvements in preoperative imaging modalities and

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chemotherapy regimens.[1–3] The majority of patients develop recurrence within 12 months, suggesting that tumors were missed previously.[4] Indeed, current pre- and intraoperative imaging techniques have low sensitivity for subcentimeter lesions in the liver.[5–7] Near-infrared fluorescence (NIRF; wavelengths 700–900 nm) imaging with targeted or non-targeted fluorescent tracers empowers surgeons to improve contrast between structures and aids in differentiating malignant from benign tissue.[8] In general, NIRF imaging has the potential to improve clinical outcomes by improving radical resection rates and visualizing more malignant lesions, but most published studies are proof-of-concept designs. To date, randomized controlled trials have been performed only with 5-aminolevulinic acid (5-ALA) to guide brain surgery.[9] 5-ALA leads to intracellular accumulation of fluorescent protoporphyrin IX (emission peak at 635 nm, outside NIR) in malignant gliomas. Actually, the benefits of 5-ALA were evident in observational studies even before the start of a randomized controlled trial. Fluorescence imaging of malignant glioma had 85% sensitivity and 100% specificity, overall survival (OS) strongly correlated with residual intraoperative fluorescence, and no safety issues were recorded.[10,11] Not unexpectedly, the randomized study had to be terminated prematurely due to 20% higher progression-free survival in the 5-ALA arm at 6 months.

Parallels can be drawn between 5-ALA for glioma surgery and indocyanine green (ICG, emission peak at 820 nm) for resection of CRLM, even though the diseases and consequences are different. NIRF imaging using ICG identifies (sub)capsular micrometastases missed by conventional modalities in up to 17% of CRLM patients.[12–17] In addition, screening of resection margins can detect residual tumor, enabling complete removal of all tumor tissue (R0 resection).[17,18] Intravenous administration of ICG is safe; adverse reactions are reported in less than 1 in 40,000 patients.[19] ICG is widely used for clinical applications (e.g. to test liver function prior to major liver surgery).

It seems unjustifiable to randomize patients into a control arm without NIRF imaging when previous studies have already shown that NIRF imaging identifies additional tumors in the context of an excellent safety profile. However, before NIRF imaging can be accepted and implemented in routine clinical practice, the optical imaging community must show long-term benefits, while also addressing safety and cost-effectiveness.[20] A key unanswered question is whether the (micro)metastases additionally identified by NIRF are indicative of otherwise undetectable, widespread metastases in the liver or if patients are in fact cured by resecting these lesions. This multicenter study is the first to report long-term follow-up after NIRF-guided resection of CRLM. In addition, perioperative data and post-operative outcomes were compared with a cohort of patients that underwent resection of CRLM without intraoperative NIRF imaging.

Patients and methods

Patients

All patients undergoing resection of CRLM with or without NIRF imaging at Leiden University Medical Center (LUMC, Leiden, the Netherlands) between January 2010 and June 2016 were included and termed ‘analysis 1’. Patients received ICG and underwent NIRF imaging only if a NIRF imaging system and operator were available, if patients were willing to participate and if none of the exclusion criteria was met. Exclusion criteria consisted of contraindications for ICG: eGFR < 55; pregnancy; breastfeeding; hyperthyroidism; or an allergy to iodine, shellfish, or ICG. Patients with an eGFR < 55 or hyperthyroidism that underwent resection of CRLM without NIRF imaging were excluded to prevent selection bias. The local institutional review board approved the studies. All patients receiving ICG provided informed consent. Patients with a prior history of metastatic disease were excluded from analysis. Demographics, patient characteristics, Fong’s clinical risk score for predicting recurrence after hepatic resection of CRLM,[21] perioperative and long-term follow-up data were collected. Patients were divided into 2 cohorts: a control cohort that underwent standard resection and an experimental cohort that underwent NIRF-guided resection.

Intraoperative NIRF imaging (analysis 1)

Patients in the NIRF cohorts received a dose of 10 or 20 mg ICG 1 or 2 days prior to surgery. Four different NIRF imaging systems were used: Mini-FLARE® (Frangioni Laboratory, Harvard Medical School, Boston, MA, USA, see Fig. 1),[22] Kit-FLARE® (FLARE Foundation, defunct, previously Wayland, USA), Artemis (Quest Innovations BV, Middenmeer, the Netherlands),[23] and Storz HD laparoscope (KARL STORZ GmbH & Co. KGm, Tuttlingen, Germany).

Preoperative workup and surgical procedure (analysis 1)

All patients underwent computed tomography (CT) to detect hepatic and/or extrahepatic metastases. In selected cases, when deemed necessary by the medical team, magnetic resonance imaging (MRI) or positron emission tomography (PET) was performed. The protocol for imaging of CRLM was updated several times and new scanners were acquired by the hospitals during the period 2010–2016. Since 2015 Primovist-enhanced and diffusion weighted MRI was performed. Chemotherapy treatment was divided into 3 categories: (1) no chemotherapy, (2) neoadjuvant chemotherapy was defined as chemotherapy treatment specifically aimed to decrease hepatic tumor load prior to the planned liver surgery and (3) adjuvant

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