BRIEF REPORT

First in-human intraoperative imaging of HCC using the fluorescence goggle system and transarterial delivery of near-infrared fluorescent imaging agent: a pilot study

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Surgical resections remain the primary curative interventions for hepatocellular carcinoma (HCC). However, lack of real-time intraoperative image guidance confines surgeons to subjective visual assessment of the surgical bed, leading to poor visualization of small positive nodules and the extension of diffuse HCC. To address this problem, we developed a wearable fluorescence imaging and display system (fluorescence goggle) for intraoperative imaging of HCCs in human patients. In this pilot study, both intravenous (IV) and transarterial hepatic (TAH) delivery of indocyanine green (ICG) were explored to facilitate fluorescence goggle-mediated HCC imaging. The results show that all primary tumors in patients (n = 4) who received TAH delivery of ICG were identified successfully by the fluorescence goggle. In addition, 6 satellite tumors were also detected by the goggle, 5 of which were neither identifiable via preoperative magnetic resonance imaging (MRI) and computed tomography (CT) nor by visual inspection and palpation. In the group (n = 5) that received ICG intravenously, only 2 of 6 tumors visible by preoperative MRI or CT were identified with the fluorescence goggle, demonstrating the limitation of this delivery route for a non-tumor-selective imaging agent. Comparative analysis shows that the HCC-to-liver florescence contrast detected by the goggle was significantly greater in patients that received TAH than IV delivery of ICG ($P = 0.013$). This pilot study demonstrates the feasibility of using the fluorescence goggle to identify multifocal lesions and small tumor deposits using TAH ICG delivery in HCC patients. (Translational Research 2013;162:324–331)

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Conflicts of Interest: All authors have read the journal's policy on conflicts of interest and have none to declare.

This study is based on work supported by the Mallinckrodt Institute of Radiology Development Fund and, in part, by the U.S. National Institutes of Health (NIH) grants R01 CA171651 and U54 CA136398 (Network for Translational Research). Y. Liu was supported by the U.S. Department of Defense (DoD) Breast Cancer Research Program Predoctoral Award (W81XWH-11-1-0059). W. Akers was supported by award no. K01RR026095 from the National Center for Research Resources. The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH and the DoD.

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Submitted for publication February 17, 2013; revision submitted May 2, 2013; accepted for publication May 9, 2013.

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1931-5244/$ - see front matter

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http://dx.doi.org/10.1016/j.trsl.2013.05.002

Abbreviations: CT = computed tomography; HCC = hepatocellular carcinoma; ICG = indocyanine green; IUS = intraoperative ultrasonography; IV = intravenous; LCI = Liver Cancer Institute; MRI = magnetic resonance imaging; NIR = near infrared; TAH = transarterial hepatic; PET = positron emission tomography; FDA = Food and Drug Administration; H&E = hematoxylin and eosin

AT A GLANCE COMMENTARY

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Background

Surgical resections remain a primary curative intervention for hepatocellular carcinoma. To ensure complete removal of the primary and satellite tumors, real-time image guidance is needed in the operating room. The new goggle device developed for this study has the potential to address this need by using a low-cost and compact system for eyepiece graphical display of the fluorescent dye-stained hepatocellular carcinoma.

Translational Significance

The new fluorescence goggle system is simple, cheap, and applicable to high- and low-resource clinical centers. In combination with a molecular probe, it guides accurate tumor resection with tumor-free surgical margins.

Hepatocellular carcinoma (HCC) is the third most predominant cause of cancer-related death worldwide.[1,2] To date, the standard of care for HCC is still far from satisfactory, and the prognosis of HCC is poor. Intraoperative ultrasonography (IUS) is currently used in the operating room to assist surgical resection of HCC. However, IUS is primarily a structural imaging modality that does not provide satisfactory contrast for small tumors and satellite foci.[3-6] The detection of superficially located nodules are particularly difficult to achieve with IUS.[7] In addition, current imaging systems typically rely on graphic display of imaging results on computer monitors, which may distract the surgeon from focusing on the surgical site.

To address these challenges and to complement current clinical modalities, we developed a wearable real-time fluorescence imaging and display system—the fluorescence goggle.[8] The fluorescence information of tissues is imaged and displayed directly in the goggle eyepiece worn by a surgeon. The point of view of the goggle is also synchronized with the wearer's head movement and gaze direction.[8]

In this pilot study, the fluorescence goggle was designed specifically to work with near-infrared (NIR) fluorescent contrast agents. Because of the regulatory hurdles to bring tumor-targeted NIR molecular probes to the clinic, most clinical studies have relied on the use of indocyanine green (ICG), which is approved for human use.[9-13] In general, ICG accumulates in the tumor largely by enhanced permeability and retention effect or other mechanisms after intravenous (IV) administration.[9,10] Although a small molecule, the binding of ICG to blood proteins increases the net size of the dye, which favors retention around porous vascular regions. Moreover, ICG can be cleared faster from a healthy liver than from tumors, which further enhances the contrast. However, poor tumor specificity, unpredictable pharmacokinetics, and cross-patient variability[10] are major limitations to the use of ICG for cancer imaging.

Unlike the hepatic parenchyma, which receives only 25% of its blood supply through the hepatic artery, the hepatic artery is the primary source of blood supply for HCC.[1,2] Thus, HCC presents a unique pathophysiology that favors selective delivery of nonspecific therapeutic and imaging agents to the target malignancies through transarterial hepatic (TAH) injection. This delivery route enables high tumor uptake with attendant reduction in systemic toxicity.[1,2] In light of this, we hypothesized that transarterial delivery of ICG would facilitate rapid and selective uptake of ICG in HCC, providing high imaging contrast between the tumors and normal hepatic tissue. The fluorescence goggle demonstrated the feasibility of using both routes to image HCC intraoperatively, with the TAH ICG delivery route providing higher contrast in tumors than the IV method.

MATERIALS AND METHODS

Fluorescence goggle system. The goggle system was developed at Washington University in St. Louis, MO, and was approved by the Washington University in St. Louis Human Research Protection Office (FWA00002284) for use at the Liver Cancer Institute (LCI) at Zhongshan Hospital, Fudan University, China. The configuration of the fluorescence goggle used in this study is similar to the previously reported system,[8] except that the NIR light source now consists of 4 high-power light-emitting diodes (no. H2A1-H760, Roithner Lasertechnik), and a short-pass emission filter (775 nm; no. NT64-615, Edmund Optics) was used in the clinical system. The average irradiance of

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