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Study Protocol

A feasibility randomized controlled trial testing the use of indocyanine green fluorescence image-guidance in liver surgery compared to standard liver surgery alone in reducing microscopic positive tumor margin resection rate with an embedded qualitative study: the I-FIGS study protocol

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Abstract

Indocyanine green fluorescence image-guidance (I-FIGS) is gaining global popularity in liver surgery for various applications. However, its true clinical value in reducing microscopic positive margins (R1-resection rate) remains uncertain. To address this, a multi-center randomized controlled trial (RCT) comparing I-FIGS with standard liver surgery is needed. However, due to a lack of essential information on potential R1 reduction rate, sample size, methodology, intervention delivery and patient experience, a feasibility RCT protocol has been developed to determine the viability of conducting a full-scale RCT. The aim of the study is to conduct a feasibility RCT (fRCT) with an embedded qualitative study to gather all the necessary information for a full-scale RCT. Adult patients undergoing elective liver surgery for colorectal liver metastasis (CRLMs), hepatocellular carcinoma (HCC) or peripheral cholangiocarcinoma will be eligible for the study. Forty patients will be randomly assigned to either the control group (standard liver surgery) or the intervention group (standard liver surgery + I-FIGS). Patients in the I-FIGS group will receive intravenous injection of 0.03–0.05 mg/kg indocyanine green (ICG) dye 2–4 hours before the surgery. Data will be collected on demographics, screening, recruitment and retention rates, adherence to study methods, intraoperative details, postoperative histology, and experiences of both surgeons and patients. Interviews will be conducted with selected patients and surgeons to explore their experiences with the intervention. The protocol has been approved by the West-Midlands-Solihull Research Ethics Committee and registered with [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT05616039). The results will be disseminated through academic publications, congresses, newsletters and other platforms.

Keywords: indocyanine green (ICG), liver surgery, fluorescence guided surgery

INTRODUCTION

Liver resection is the mainstay of treatment for liver tumors—both hepatocellular carcinomas (HCC) and metastases from colorectal cancer (CRLM) [1]. The main aim of liver surgery is complete removal of tumor (R0 resection) leaving adequate future liver remnant. R1 resection can lead to increased tumor recurrence, reduced overall survival, higher local complications, and a negative impact on the patient's quality of life [2]. To achieve R0 resection, it is essential to accurately identify the tumor location and its boundaries intra-operatively, so that the whole tumor can be removed without compromising resection margins, and therefore oncological outcomes [2]. Currently, surgeons plan the type of liver resection based on preoperative

cross-sectional imaging (computed tomography and magnetic resonance imaging) of the liver, intra-operative bimanual palpation and intra-operative ultrasound (IOUS). However, these have limitations in detecting small superficial tumors, deep-seated tumors and accurately marking of tumor margins. Another limitation is that this does not provide a real-time visual clue on transection margins [3, 4]. Therefore, a robust real-time navigation tool is needed to complement pre-operative images and IOUS to accurately identify liver tumors and resection margins.

Indocyanine green (ICG) fluorescence image-guided surgery (I-FIGS) has increasingly been applied as an intraoperative navigation tool in liver surgery. ICG is a relatively inert dye that binds to albumin intravascularly when injected intravenously and is selectively absorbed by the hepatocytes, secreted into bile,

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Table 1. Trial assessments.

| Assessments | Pre-operative (2 weeks prior to surgery) | Intra-operative | Post-operative | Follow-up (6 weeks post-surgery) |
|---|--|-----------------|----------------|--|
| Demographic characteristics | x | | | |
| Indication for liver resection | x | | | |
| Number and size of tumors based on pre-operative imaging | x | | | |
| Type of liver resection (Modified G-K classification) | x | x | | |
| IOUS findings (Number/size/location of tumors) | | x | | |
| I-FIGS findings (Change of transection margins/additional tumors) | | x | | |
| Surgeons' perspective | | | x | |
| Surgical outcomes | | | | |
| • Type of liver resection | | x | | |
| • Operative duration | | | | |
| • Complications | | | | |
| Length of stay | | | x | |
| Postoperative complications | | | x | x |
| Safety reporting | x | x | x | x |
| Histopathology Report: | | | | |
| • Diagnosis | | | | x |
| • Number of tumors | | | | |
| • Size of tumors | | | | |
| • Differentiation | | | | |
| • Resection margin status | | | | |

and rapidly cleared by the liver. Liver tumors—CRLMs and HCCs retain ICG longer than the rest of the liver parenchyma due to biliary excretion disorders in the tumor cells. Albumin-bound ICG emits fluorescence peaking at 840 nm under illumination with near-infrared light, thus providing a contrast between liver parenchyma and liver tumor, making it easy to visualize the tumor and demarcate its boundaries [5]. It is gaining attention in accurate identification of resection margins, identifying the tumor/s location and picking up other tumors not identified by preoperative investigations, surgeons naked eye, palpation or IOUS [6].

To conclusively establish the role of I-FIGS in liver surgery, further high-quality clinical studies are required to ascertain its role in accurate identification of resection margin and reduction of R1 resection rates. Therefore, the aim of our fRCT is to gather the necessary operational and feasibility data to inform the design of a definitive RCT to determine the additional value of I-FIGS to standard liver surgery.

METHODS

Trial design

This is a fRCT to gather information on the intervention and the feasibility of conducting a full-scale RCT. Patients will be randomly allocated into two groups.

Control group (standard liver surgery)

In this group, tumor/s, resection margin identification, and the type and number of liver resections will be based on naked eye examination, palpation and IOUS. All the intra-operative findings will be recorded on a pre-designed proforma. These details include the type of surgical approach (open, laparoscopic, robotic and hand-assisted), the location of tumor/s, number and size of tumors, relationship of the tumor/s to inflow and outflow of the liver, duration of surgery and estimated blood loss.

Intervention group (I-FIGS)

In this group, patients will receive intravenous ICG injection in a dose of 0.03–0.05 mg/kg 2–4 hours before surgery. ICG is readily available in the hospital pharmacy and in operating theaters. It comes in crystal form in a 25 mg vial. It will be diluted with 10 ml of water, and the required dose as per the weight of the patient will be prepared freshly and given at least 2–4 hours before surgery. The surgical planning will be carried out as per the standard approach using naked eye and IOUS. As for standard surgery, all intra-operative findings will be recorded on the pre-designed proforma. Once this is all recorded, ICG cameras will be switched on, and the additional findings (additional lesions detected, additional resections carried out) and change to surgical plan (change to the line of parenchymal transection) will be noted. ICG cameras-SPY Portable Handheld Imager for open surgery and PINPOINT Endoscopic Fluorescence Imaging System (Stryker) for laparoscopic surgery are readily available in theaters and will be made available for every procedure.

Trial setting

The fRCT will be conducted at University Hospitals Plymouth, NHS Trust (UHPNT). Liver resection/s will be performed by consultant Hepatopancreatobiliary (HPB) surgeons in both groups. The final histopathology report will be issued by pathologists at UHPNT.

Participant eligibility criteria

Inclusion criteria

- All adult patients (>18 years) requiring elective open/laparoscopic liver resection/s for CRLMs, HCCs and peripheral cholangiocarcinoma will be included in the study.

Exclusion criteria

- Patients allergic to iodine/contrast or shellfish.
- Patients with suspected hilar cholangiocarcinoma.

Table 2. Objectives and outcomes.

| Objectives | Outcome measures | Timepoint(s) of evaluation of this outcome measure |
|--|---|---|
| <p>Primary objective</p> <p>1) To assess the research methods used to compare I-FIGS and standard surgery with standard surgery alone and to identify surgical outcome measures to inform the sample size calculation for the definitive planned RCT.</p> <p>2) To determine the most clinically relevant primary outcomes for the definitive trial</p> <p>3) To explore the experiences of the study participants, and the experiences of the surgeons who have delivered the intervention.</p> | <p>i) Rates of screening and recruitment</p> <p>ii) Retention rate</p> <p>iii) Feasibility of trial processes and procedures</p> <p>iv) Adherence rates to study methods and procedures (Consent, randomization, intervention, data collection)</p> <p>v) Microscopic positive resection margin rate</p> <p>vi) Number of additional tumors detected by I-FIGS</p> <p>vii) Change in the surgical plan in the I-FIGS group</p> <p>viii) Duration of surgery</p> <p>ix) Complication rates (intra-operative and post-operative)</p> <p>x) Length of hospital stay</p> <p>Narratives of study participants will be explored leading to themes to inform suggestions and recommendations for the definitive RCT.</p> | <p>During the study period</p> <p>6 weeks after the surgery</p> <p>At the time of surgery</p> |
| <p>Secondary objectives</p> <p>To assess the potential barriers and challenges with the delivery of the intervention for the definitive planned RCT</p> | <p>i) Ease and simplicity of the participant documentation through the study (Participant information sheet, consent form, data collection sheet).</p> <p>ii) Accuracy of data collection, processing, and storage.</p> <p>iii) Access to basic services (Libraries, literature support).</p> <p>iv) Availability of equipment and expertise required for the research project.</p> <p>v) Adequate software to randomize, record, process and store research data.</p> | <p>During the study period</p> |

- Patients requiring emergency liver surgery.
- Pregnant patients.

Trial procedures

Recruitment

Potential participants will be identified at the regional HPB multidisciplinary team meeting at UHPNT. As routine, all potential participants will be informed about their diagnosis via a telephone appointment approximately 2–3 weeks before the surgery. They will be informed about the research study via a separate telephone conversation 1–2 days after the first appointment as advised by our patient public involvement (PPI) group. A patient information leaflet will be sent to them via email/post. A routine face-to-face clinic appointment will be scheduled in the next 1–2 weeks at UHPNT. Patients will be verbally consented for the study and demographic data will be collected during this visit. Following this, patients will be randomly allocated to either the control group or the intervention group. Patients will be formally consented for the study on the morning of the surgery along with the routine consent for surgery.

The randomization scheme

The patients who consent to participate in the study will be randomized into two groups by a secure sealed envelope web-based randomization system (<https://www.sealedenvelope.com/simple-randomiser/v1/>). Randomization will be completed in a 1:1 ratio using random permuted blocks.

Trial assessments

Sample size calculation

As this is a feasibility study, a formal sample size calculation is not appropriate. We aim to recruit 40 patients to provide operational experience to conduct a larger definitive trial; to provide

reasonable robust estimates of our feasibility outcomes, and the variability of the proposed outcomes to inform future sample size calculation.

OBJECTIVES AND OUTCOMES

Data management

Collection of data and study materials

The participants in both the groups will be assessed and data collected pre-operatively, during the surgery and 6 weeks postoperatively. The data will be collected independently for both groups in a prospective manner over 18 months (November 2022–April 2024) on the REDcap database. It will include participant's demographic characteristics and the outcomes that will be measured to achieve the respective objectives of the study.

Statistical analysis

A detailed statistical analysis plan will be finalized before the trial database is locked. The trial will be reported in accordance with the CONSORT 2010 statement extension to pilot and feasibility trials [7]. There will be no formal hypothesis testing, instead the focus will be on presenting summary statistics with appropriate confidence intervals, to meet listed study objectives. Descriptive statistics will be reported for the feasibility outcomes: recruitment, retention, and adherence rates (reported with 95% confidence intervals), completeness of data collection, intervention delivery and fidelity. Baseline and follow-up data for candidate primary and secondary outcomes will be summarized overall and by trial arm. Data will inform a potential definitive study. Variability in candidate primary measures will be calculated, and a sample size (power calculation) for the definitive trial will be estimated for each. Adverse events will be summarized descriptively.

Embedded qualitative study

This component of the fRCT explores the experiences of the study participants and the experiences of the surgeons who have delivered the intervention. The aim is to generate recommendations and address unknowns including experiences of recruitment, retention, practical implementation and further refinement of the intervention and outcome measures for the design of the future RCT.

An exploratory inductive qualitative design with semi-structured interviews will be used for the qualitative study. This will involve a face-to-face, controlled and open interaction between the participants and the researchers.

Six to ten participants (three to five from intervention and control arm each) and four to five surgeons will be interviewed to explore their experiences of receiving and delivering the intervention.

All qualitative interviews will be conducted by the chief investigator/co-investigator. The duration of the interviews will last around 30–45 minutes. The interview proceedings will be audio recorded with the participant's consent and will be deleted following transcription.

Thematic analysis will be performed using the NVivo 12 qualitative analysis software programme. Data extracts will be coded and categorized into themes, following the Braun and Clarke six-steps thematic analysis guide.

The result of this study will be reported in accordance with the Consolidated criteria for reporting qualitative research checklist.

ETHICS AND DISSEMINATION

Research ethics approval

The protocol has been approved by the West Midlands-Solihull Research Ethics Committee. The trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) in United Kingdom. Trial Registration number is NCT05616039. The results of the study will be presented to the scientific community through publications, conferences or other means.

Patient and public involvement

Patients of the public were involved in the design and conduct of this trial. Patients acknowledged the need and usefulness of I-FIGS in liver surgery. They gave valuable suggestions that informed protocol development of the fRCT, priority of research questions and selection of outcome measures.

CONFLICT OF INTEREST STATEMENT

Authors Rahi Karmarkar, Jos Latour, Joanne Hosking, Pavith Jayaraj and Somaiah Aroori have no conflicts of interest and no financial ties to disclose.

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AUTHOR CONTRIBUTIONS

The first draft of the protocol was prepared by Rahi Karmarkar and Somaiah Aroori. Dr. Joanne Hosking helped develop statistical part of the study. Prof. Jos Latour and Somaiah Aroori commented on previous versions of the manuscript. All authors read and approved the final manuscript.

DATA AVAILABILITY

Data sharing is not applicable to this article as no new data was created or analyzed in this study protocol.

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