Protocol for the CoNoR Study: A prospective multi-step study of the potential added benefit of two novel assessment tools in colorectal liver metastases technical resectability decision-making

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ABSTRACT

Introduction Liver resection is the only curative treatment for colorectal liver metastases (CLM). Resectability decision-making is therefore a key determinant of outcomes. Wide variation has been demonstrated in resectability decision-making, despite the existence of criteria. This paper summarises a study protocol to evaluate the potential added value of two novel assessment tools in assessing CLM technical resectability: the Hepatica preoperative MR scan (MR-based volumetry, Couinaud segmentation, liver tissue characteristics and operative planning tool) and the LiMAx test (hepatic functional capacity).

Methods and analysis This study uses a systematic multistep approach, whereby three preparatory workstreams aid the design of the final international case-based scenario survey:
Workstream 1: systematic literature review of published resectability criteria.
Workstream 2: international hepatopancreatobiliary (HPB) interviews.
Workstream 3: international HPB questionnaire.
Workstream 4: international HPB case-based scenario survey.

The primary outcome measures are change in resectability decision-making and change in planned operative strategy, resulting from the novel test results. Secondary outcome measures are variability in CLM resectability decision-making and opinions on the role for novel tools.

Ethics and dissemination The study protocol has been approved by a National Health Service Research Ethics Committee and registered with the Health Research Authority. Dissemination will be via international and national conferences. Manuscripts will be published.

Registration details The CoNoR Study is registered with ClinicalTrials.gov (registration number NCT04270851). The systematic review is registered on the PROSPERO database (registration number CRD42019136748).

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This study uses a large-scale international survey to assess the impact of novel assessment tools on decision-making around technical resectability of colorectal liver metastases (CLM).
⇒ This study uses multiple workstream methodologies to evaluate perceived benefit and change in decision-making by hepatopancreatobiliary professionals as the result of novel tools.
⇒ A justification for our methodology is that a large international study on CLM decision-making recently highlighted the need for a large-scale international assessment of variability.
⇒ A limitation of our methodology is that the change in decision-making is measured in a simulated multidisciplinary team setting, which may not correlate with real-life clinical decision-making.
⇒ Another limitation is that it is unknown if changes in decision-making translate into patient benefit.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cause of cancer death in the UK, resulting in approximately 16 000 deaths per year.3 Death is usually due to metastatic disease, with the most common site being the liver (colorectal liver metastases (CLM)). There is an incidence of 15%–20% CLM at initial diagnosis of CRC2 with up to 50% of patients ultimately developing CLM.3–6

Surgical resection is the only potentially curative treatment for CLM,2 offering a realistic chance of cure in selected patients.8 Surgical resection converts the median survival from 6 to 13 months9 without surgery to 3.6 years10 following resection, and the overall 5-year survival from 10%9 to in excess
of 50%, respectively. Advances in chemotherapy and hepatic surgery have expanded the pool of candidates for potentially curative resection. Approximately 30% of patients presenting with CLM are initially deemed resectable; after systemic chemotherapy, this increases to 40%. Outcomes in these ‘downsized’ cases are similar to those initially presenting with resectable disease.

Adequate patient selection for curative surgery requires precise assessment of technical resectability (can all the disease be removed?), a plan for an optimal surgical strategy (how should all the disease be removed?) and a detailed assessment of the underlying disease biology and trajectory (if the disease is all removed, will the patient benefit?)—often referred to as oncological resectability.

The Americas Hepato-Pancreato-Biliary Association (AHPBA) Consensus Conference on the treatment of CLM recognised that resectability is dependent on both technical and oncological factors. This study protocol focuses exclusively on the issue of technical resectability; the separate matter of oncological resectability is not discussed further.

Technical resectability refers to the feasibility of a planned hepatic resection, in light of the expectation that a margin-negative resection can be achieved with a successful postoperative recovery. The optimal histological margin has been defined as ≥1 mm. The ongoing debate over the impact of margin negativity on outcomes is not addressed further in this protocol.

Technical resectability in the liver is no longer defined by what can be resected but instead, by what functional liver is left behind. The future liver remnant (FLR) must have sufficient hepatic arterial and portal venous inflow, venous outflow, biliary drainage, and be of sufficient quantity and quality to sustain function and support postoperative regeneration. It is therefore essential that high-quality cross-sectional imaging is used to establish the location of the CLM relative to the hepatic vascular and biliary anatomy, determining the proximity and involvement of these structures with the highest degree of accuracy.

It is recommended by the AHPBA consensus statement that CLM technical resectability decision-making should be based on the following four criteria as applied to the anticipated FLR, subsequent to a multifaceted analysis of liver anatomy, histology and function, analysed in a multidisciplinary setting:

1. Assessment of FLR volume
   Preoperative estimation of FLR volume via imaging-based volumetry has become an important assessment tool when planning major resections. CT volumetry has been widely used for this purpose. It is traditionally performed by manual contour tracing, usually by a clinician. Manual methods are operator dependent and require considerable time; therefore, automated and semiautomated measurement methods have been developed to increase efficiency. MRI volumetry has also been shown to produce reliable measurements, with a strong correlation demonstrated between CT and MRI-based measurements.

   This ability to accurately predict FLR volume has improved the ability to determine technical resectability, within the limitation that volume alone is not an ideal assessment of function or predictor of outcome. FLR function is decreased in the presence of parenchymal disease, despite equal volume to healthy liver, and may result in impaired liver regeneration.

2. Assessment of FLR function
   Accurate preoperative assessment of liver function is crucial in view of its impact on postoperative regeneration. Clinicians frequently rely on non-specific laboratory assessments of liver function, such as solitary values (eg, serum bilirubin) or aggregate scores (eg, model for end-stage liver disease). In cases of difficult resectability decision-making, more advanced assessments of liver function can be sought, for example, indocyanine green (ICG) excretion. ICG excretion provides a global estimate of liver function, although it is neither widely available nor universally accepted as an accurate assessment of FLR function, given its assumption of homogeneous liver function and its inability to calculate regional function specific to the FLR.

   The surgical strategy may need to be adapted in the presence of impaired liver function, either to increase the volume of the FLR or to perform a less extensive resection.

3. Assessment of FLR inflow
   The surgical strategy may need to be adapted in the presence of impaired liver function, either to increase the volume of the FLR or to perform a less extensive resection.

   The AHPBA consensus document states that one of the few accurate tests available for the assessment of the functional and regenerative capacity of the FLR is portal vein embolisation (PVE). This technique was developed to improve the size and function of the FLR by occluding the ipsilateral portal vein, leading to an increase in volume by a combination of hypertrophy and hyperplasia.

   The capacity for regeneration in the otherwise healthy liver is significant; PVE results in increased FLR volume in 60% of patients with an average volume increase of 12%. Non-cirrhotic liver hypertrophies at a rate of about 12–21 cm³/day at 2 weeks, compared with just 9 cm³/day for a cirrhotic liver, and the growth rate can be used to predict the probability of liver failure and major complications.

   The FLR’s ability to hypertrophy in response to PVE is thus a highly reliable indicator of FLR function of the FLR. This plays a limited role in overall functional
assessment, however, due to the use of PVE in only highly selected cases.

Recent studies have demonstrated that despite the existence of guidelines on resectability criteria, there is a surprisingly high level of disagreement between surgeons when assessing the resectability of individual cases.\textsuperscript{43–46} Resectability decision-making determines the treatment intent: a curative versus palliative approach.\textsuperscript{44} Disagreement between experts on resectability therefore leads to inconsistencies in the treatments offered to patients.\textsuperscript{43–47}

National case-based surveys assessing CLM resectability in Canada and the Netherlands have reported substantial disagreement between liver surgeons.\textsuperscript{44 46} The first international survey reported high inter-rater agreement between liver surgeons in low-complexity cases, but low inter-rater agreement in high-complexity cases.\textsuperscript{43} There was minimal to no inter-rater agreement regarding therapeutic treatment decisions overall. Potential factors put forward to explain these decision-making discrepancies included the differing interpretation of the current guidelines, geographical variations (noted to be an influencing factor in the subgroup analysis) and the recognised lack of high-evidence studies.\textsuperscript{43}

In view of the inconsistencies in CLM technical resectability decision-making despite the existence of guidelines, there is a role for novel assessment tools to potentially improve consistency in the selection of both appropriate patients and operative strategies for CLM hepatic resection.

The two novel assessment tools assessed in this study are:

1. Hepatica MR scan
   Given the clear guidelines that decision-making in CLM technical resectability is dependent upon the accurate imaging assessment of FLR volume, function, vascular inflow, outflow and biliary drainage, along with the proximity of tumour to and potential involvement of major vascular and biliary structures, there is a potential role for advanced MRI in preoperative assessment.

   The Hepatica preoperative planning scan has been developed using a suite of advanced MRI techniques. It comprises the Liver MultiScan, designed to quantitatively characterise liver tissue via three metrics: fat fraction, iron load (T2*) and fibroinflammation (cT1), combined with a virtual operative planning three-dimensional reconstruction model developed during the Hepatica Study.\textsuperscript{56–58} The metrics provided from the Hepatica scan include the relative volume of each Couinaud segment to calculate the predicted FLR, and the liver tissue characteristics (liver fat and fibroinflammation) of each Couinaud segment. Version 1 of the Hepatica scan will be used in the CoNoR Study workstream 4 international case-based survey. Any feedback received from the international hepatopancreatobiliary (HPB) community regarding potential modifications that would increase its utility in CLM technical resectability decision-making will be taken into account in the development of version 2.

2. Liver Maximum capacity (LiMAx) test

The LiMAx test was developed as a novel clinical evaluation of liver function, aimed at overcoming the difficulties in accurately assessing preoperative liver function prior to hepatic resection.\textsuperscript{53} It is based on the metabolism of a $^{13}$C-labelled substrate by the hepatocyte-specific enzyme system P450 CYP1A2, the activity of which is not influenced by drugs or genetic variations.\textsuperscript{54} is distributed ubiquitously throughout the liver, and shows a clear discrimination between normal and abnormal liver function independent of cholestasis.\textsuperscript{56} The intravenous administration of $^{13}$C-methacetin results in a significant alteration of the normal expired breath $^{13}$CO$_2$/$^{12}$CO$_2$ ratio,\textsuperscript{57} detected by breath analysis performed by an infrared spectroscopy-based device.

The LiMAx test has been prospectively evaluated in preoperative and postoperative hepatectomy assessment as an adjunct to standard preoperative and postoperative assessment in hepatectomy.\textsuperscript{58} Resection of a specific percentage of functional liver volume was found to lead to an equivalent reduction in LiMAx value and residual LiMAx values correlated with residual liver volume ($r=0.94; p<0.001$). Multivariate analysis revealed LiMAx on postoperative day 1 to be the only predictor of liver failure ($p=0.003$) and postoperative mortality ($p=0.004$). Postoperative mortality rates have been demonstrated to be statistically significantly correlated with preoperative LiMAx results.\textsuperscript{59} Subsequent assessments confirmed the accuracy of the LiMAx test in determining liver function capacity in the perioperative management of liver resection.\textsuperscript{59 60} The LiMAx test has therefore been shown to represent an accurate surrogate of liver function capacity, to be an accurate predictor of postoperative liver failure and mortality,\textsuperscript{59 58–60} and to be unaffected by age and gender.\textsuperscript{61}

This novel technique is undergoing a National Institute of Clinical Excellence medical technology appraisal,\textsuperscript{62} where potential utility has been identified in the LiMAx test being used to predict and monitor postoperative outcome in liver resection.

An algorithm has been developed for using the test in evaluating patients before liver surgery\textsuperscript{58 59 63} whereby LiMAx values could help to guide the number of segments being safely resected. There is therefore potential for the information provided by the LiMAx test to augment preoperative CLM technical resectability decision-making.

**Exploratory work**

The workstream 3 international questionnaire was designed as exploratory work to guide the preparation of the workstream 4 international survey. The aim was to explore the opinions of the international HPB community in order to evaluate the following: appropriate cases for inclusion in the workstream 4 international survey, opinions on the potential utility of the novel tests, feasibility and feedback on the proposed survey design. Participation was increased by study endorsement and
dissemination via a number of international professional associations.

One hundred ninety-seven responses were received from 37 countries across all continents. The geographical locations of the respondents are shown in figure 1; the countries where respondents work are shown in figure 2. The workstream 3 questionnaire questions are shown in online supplemental file 1.

Ninety per cent of respondents were consultant/attending grade. Over 95% of respondents identified the following scenarios as leading to difficult technical resectability decisions: recurrent disease post-liver resection, post-chemotherapy downsizing, post-PVE and tumours in close proximity to ducts/vessels. There was significant variation in the percentage FLR at which respondents felt these decisions became difficult, across all proposed scenarios. Over 60% of respondents thought that either of the novel tests would likely impact their clinical practice by resulting in more cases being judged as resectable, and by better informing preoperative discussions with patients.

METHODS AND ANALYSIS

Aim
To evaluate the potential added value of two novel assessment tools (Hepatica and LiMAX) in CLM technical resectability decision-making.

Primary outcome measures
The added value of Hepatica and LiMAX in CLM technical resectability decision-making, assessed by measuring the following in HPB experts:
1. Proportion of (net) change in resectability decision-making resulting from the novel tests.
2. Proportion of (net) change in planned operative strategy resulting from novel tests.

Secondary outcome measures
1. Variability in CLM resectability decision-making.
2. Opinions on the role of novel tools in CLM resectability decision-making.

Study design
This is a multistep systematic approach of systematic review, international expert interviews, international questionnaire and international case-based survey. This multistep study design is shown in figure 3.

The preparatory workstreams (1–3) facilitate the design of the final workstream (4)—the international case-based scenario survey. The workstream 4 survey questions are shown in online supplemental file 2.

Investigators
The CoNoR Study is led by a dedicated clinical research fellow, as part of a university-registered thesis. The PhD supervisory team provide the relevant expertise in...
surgical cancer research, hepatobiliary surgery, medical oncology and imaging science, with additional research and statistical support available as required. Additional clinical HPB input is provided by an advisory panel of international HPB surgeons.

**Study setting**
The study is sponsored by the University of Manchester and will be performed at the University of Manchester Imaging Centres, Manchester University Foundation Trust and The Christie National Health Service (NHS) Foundation Trust. Participant identification will take place at the joint Christie-Manchester University Foundation Trust HPB multidisciplinary team meeting, with support from Basingstoke and North Hampshire Hospital as a further Participant Identification Centre.

**Inclusion criteria**
Patients with liver metastases of colorectal origin deemed to represent ‘difficult technical resectability decision-making’ by a panel of HPB surgeons.

**Data collection**
Data collection will include the study test results (Hepatica MR scan and LiMAx test), performed directly by the clinical research fellow, and the results of standard preoperative assessments. Informed consent will be taken for the research team to access preoperative assessments from the medical records. All clinicians involved in the treatment of the study participants will be blinded to the results of the study tests. All other aspects of treatment will remain unchanged and proceed as per standard care. In the event of ongoing difficulties in performing study tests due to local COVID-19-related amendments to research practice guidance, the fall-back recruitment plan will be to use pre-existing LiMAx test results and Hepatica scan results in the workstream 4 survey.

**Data management**
The NHS code of confidentiality will be observed, with only the clinical care team and team directly involved in the research having access to any identifiable data. Data will be collected and stored in accordance with the General Data Protection Regulation (GDPR) and Data Protection Act 2018. The University of Manchester, as data controller for this study, takes responsibility for the protection of any personal information collected by this study. All researchers will be appropriately trained in data protection.

**Survey participant recruitment (HPB experts to complete the survey)**
Invitations to participate in the survey will be distributed via the same methods as used for the workstream 3 questionnaire: via email to the membership list of endorsing organisation (listed below), via promotion on social media via Twitter and via snowball sampling to increase sample size. As this preliminary use of the same recruitment methodology resulted in 197 completed questionnaires, it is anticipated that the maximum number of participants will be 200. The likely outcome is that there will be fewer participants in view of the increased length of time taken to complete this more extensive survey. Recruitment will therefore continue for as long as feasible within the study timeline, up to a maximum number of 200 participants.

**Statistical analysis**
Statistical support will be provided where required by the University of Manchester Cancer Data Science Team. The main analysis will be at the conclusion of workstream 4, determining the added value of Hepatica and LiMAx as compared with standard preoperative assessments for aiding decision-making in CLM technical resectability. This analysis will occur at several levels.

The Canadian national HPB network study demonstrated that agreement on CLM technical resectability was moderate to poor for half of the clinical scenarios provided, one of which demonstrated no agreement. The international survey reported high levels of inter-rater agreement between liver surgeons in low-complexity cases (median score of 1.0, indicating 100% agreement), but low inter-rater agreement in high-complexity cases (median score of 0.71, IQR 0.35–0.82).

We will report the level of agreement between experts on resectability for the workstream 4 scenarios, and analyse for any change in level agreement following the addition of the results of the novel tools. We will also compare the proportion of experts who believe each scenario to be resectable before and after the results from the novel tools, and analyse this for any statistically significant change. We will additionally report the proportion of experts who changed their operative plan following the addition of the results from the novel tools, and analyse the responses to report the main themes in any changes observed (ie, two-stage hepatectomy to one-stage).

**Quality assurance**
The quality of this study has been assessed by the following means:

- Independent review by the Manchester Cancer Research Centre Educational Committee.
- External review by National Institute for Health and Care Research (NIHR) specialty lead for CLM (representing Association of Upper Gastrointestinal Surgeons, Great Britain and Ireland Hepato Pancreato Biliary Association, and Bowel Cancer UK).
- External review by the scientific committee of the European-African Hepato-Pancreato-Biliary Association.
- External review by the scientific committee of the International Hepato-Pancreato-Biliary Association.
- Independent review as part of the registration process for ClinicalTrials.gov, a publicly accessible database of worldwide research studies, maintained by the National Library of Medicine at the National Institutes for Health (USA) (NCT04270851).
Study timetable
The study timetable is shown in table 1 below:

<table>
<thead>
<tr>
<th>Time period</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study set-up and approvals (all workstreams)</td>
<td>01 Oct 2019–01 Jun 2021</td>
</tr>
<tr>
<td>Workstream 1 systematic review</td>
<td>01 May 2019–31 Dec 2020</td>
</tr>
<tr>
<td>Workstream 2 expert interviews</td>
<td>01 May 2019–31 Dec 2020</td>
</tr>
<tr>
<td>Workstream 3 international questionnaire</td>
<td>01 Feb 2020–31 Jan 2021</td>
</tr>
<tr>
<td>Workstream 4 international survey</td>
<td>01 Dec 2022–31 Mar 2023</td>
</tr>
<tr>
<td>Data analysis and write-up</td>
<td>31 Mar 2023–31 Jul 2023</td>
</tr>
</tbody>
</table>

The anticipated study timetable outlined in table 1 remains subject to ongoing adjustments related to the impact of COVID-19.

Endorsing organisations (no funding contribution)
The endorsing organisations are shown in table 2 below:

<table>
<thead>
<tr>
<th>AUGHIS</th>
<th>Association of Upper Gastrointestinal Surgeons</th>
</tr>
</thead>
<tbody>
<tr>
<td>GBHPBA</td>
<td>Great Britain and Ireland Hepato Pancreato Biliary Association</td>
</tr>
<tr>
<td>BCUK</td>
<td>Bowel Cancer UK</td>
</tr>
<tr>
<td>E-AHPBA</td>
<td>European-African Hepato-Pancreato-Biliary Association</td>
</tr>
<tr>
<td>CHPBA</td>
<td>Canadian Hepato-Pancreato-Biliary Network</td>
</tr>
<tr>
<td>AHPBA</td>
<td>Americas Hepato-Pancreato-Biliary Association</td>
</tr>
<tr>
<td>IHPBA</td>
<td>International Hepato-Pancreato-Biliary Association</td>
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</tbody>
</table>

Patient and public involvement
The Public Programmes Team at the Manchester University NHS Foundation Trust hosted a discussion group for the CoNoR Study with eight members of the NIHR Manchester Biomedical Research Centre-funded Cancer Research Advisory Panel on 24 May 2019. The eight attending members were all patients/carers with personal experience of CLM treatment, four of whom had personal experience of both study tests via participation in the related CLiFF Study.66 This event was attended by the principal investigator and principal supervisor to actively seek and hear the views of the patient and public representatives. The group reviewed the participant information sheet (PIS) and discussed the study proposal. They unanimously agreed that this area of research was important, found no feasibility or acceptability issues with the study and thought it likely that they would take part if asked. The only modification suggested by the panel was a unanimous request for a reduction in the volume of GDPR information included within the PIS; however, it was explained via feedback that including the GDPR information within the document is now mandatory.

Dissemination
This study will be submitted for presentation at national or international surgical conferences. Manuscript(s) will be prepared following close of the study.

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Contributors The original study concept was conceived by KLP. The study design was developed by KLP, AGR, DO’R and LM. The present protocol was written by KLP and AGR. Study set-up was carried out by KLP, LM, AGR, DO’R, MR, FKSW and RF. Data collection and analysis for workstream 3 were performed by KLP and LM. All authors (KLP, DO’R, JY, MB, LM, RPJ, FB, MR, FKSW, RF and AGR) contributed to the revision and preparation of this manuscript.

Funding This work has received funding from the following sources: the Manchester Foundation Trust Hepatopancreaticobiliary Surgical Research charitable funds; the Christie NHS Foundation Trust charitable funds; the Royal College of Surgeons of England Fellowship scheme; National Institute for Health Research Manchester Biomedical Research Centre; and Perspectum. There are no applicable award or grant numbers for any of these funding sources.
Competing interests None declared.

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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REFERENCES


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