Liver resection surgery compared with thermal ablation in high surgical risk patients with colorectal liver metastases: the LAVA international RCT

Brian Davidson,[1*] Kurinchi Gurusamy,[1]
Neil Corrigan,[2] Julie Croft,[2] Sharon Ruddock,[2]
Alison Pullan,[2] Julia Brown,[2] Maureen Twiddy,[3,4]
Jaqueline Birtwistle,[3] Stephen Morris,[5]
Nick Woodward,[6] Steve Bandula,[7]
Daniel Hochhauser,[8] Raj Prasad,[9]
Steven Olde Damink,[10] Marielle Coolson,[10]
K van Laarhoven[11] and Johannes HW de Wilt[11]

[1]Royal Free Campus, Division of Surgery and Interventional Science, University College London, London, UK
[2]Clinical Trials Research Unit, Leeds Institute of Clinical Trials Research, University of Leeds, Leeds, UK
[3]Leeds Institute of Health Sciences, University of Leeds, Leeds, UK
[4]Institute of Clinical and Applied Health Research, Faculty of Health Science, University of Hull, Hull, UK
[5]Department of Applied Health Research, University College London, London, UK
[6]Radiology, Royal Free Hospital, London, UK
[7]Radiology, University College Hospital, London, UK
[8]Cancer Institute, University College London, London, UK
[9]Surgery and Transplantation, Leeds Teaching Hospital, Leeds, UK
[10]General Surgery, Maastricht University, Maastricht, the Netherlands
[11]Surgery, Radboud University Medical Centre, Nijmegen, the Netherlands

*Corresponding author b.davidson@ucl.ac.uk

Declared competing interests of authors: Julia Brown is a member of Health Technology Assessment (HTA) Mental, Psychological and Occupational Health Methods Group, HTA Clinical Trials Committee, HTA Prioritisation Committee Methods Group and HTA Funding Committee Policy Group. Stephen Morris was formerly a member of the National Institute for Health Research (NIHR) Health Services and Delivery Research (HSDR) Research Funding Board, the NIHR HSDR Commissioned Board, the NIHR HSDR Evidence Synthesis Sub Board, the NIHR Unmet Need Sub Board, the NIHR HTA Clinical Evaluation and Trials Board, the NIHR HTA Commissioning Board, the NIHR Public Health Research (PHR) Research Funding Board and the NIHR Programme Grants for Applied Research (PGfAR) expert subpanel. Maureen Twiddy is a member of the Research for Patient Benefit North East and Yorkshire Advisory Panel. Brian Davidson is chairperson of the London NIHR Research for Patient Benefit panel.

Daniel Hochhauser reports Medical Research Council CASE studentship with Merck Serono (Darmstadt, Germany). Kurinchi Gurusamy reports grants from NIHR, Cancer Research UK Multidisciplinary Award, UK Oncology Nursing Society, University College London and Wellcome Trust/Department of Health and Social Care – Health Innovation Challenge Fund 4 – Smart Surgery, during the conduct of the study.

Published April 2020
DOI: 10.3310/hta24210

Scientific summary

The LAVA international RCT

Health Technology Assessment 2020; Vol. 24: No. 21
DOI: 10.3310/hta24210

NIHR Journals Library www.journalslibrary.nihr.ac.uk

Scientific summary

Background

Main trial background

Bowel cancer (colorectal cancer) is the second biggest cause of cancer-related death in the UK and the fourth most common cancer. Just under 16,000 colorectal cancer patients die each year in the UK. The main cause of death is the development of colorectal liver metastases. About 20% of patients have liver metastases at presentation and another 30% develop liver metastases subsequently. Surgical resection of colorectal liver metastases is considered the only potentially curative treatment. Therefore, specialist liver resection centres are carrying out more extensive and complex liver resections, including in elderly patients and those with major comorbidities. This more extensive surgery in elderly patients and those with comorbidities (i.e. high-risk patients) is associated with increased morbidity and mortality.

Thermal ablation has lower complication rates and is associated with better health-related quality of life than surgery, but is used mainly when potentially curative surgery is not possible. There has been no adequately powered randomised controlled trial comparing ablation with surgery in patients with colorectal liver metastases. Some retrospective studies have shown that there is a higher rate of local recurrence following thermal ablation than following surgery. Because of this and the lack of long-term data on cancer outcomes, the majority of clinicians feel that it would be unethical to randomise low-risk patients to ablation or surgery, despite the short-term benefits of lower complication rates, less pain and lower costs associated with patients undergoing ablation. Although some non-randomised studies did not justify these concerns and demonstrated equivalent survival between radiofrequency ablation and liver resection despite patients undergoing radiofrequency ablation having more comorbidities or more extensive cancer, another non-randomised study supported these concerns and demonstrated that radiofrequency ablation was associated with poorer 5-year survival than surgery. The only difference between the patient groups in the second study was that treatment followed patient preference for radiofrequency ablation or surgery.

However, with high-risk patients, there is significant uncertainty as to the benefits of surgery, and the majority of clinicians feel that there is equipoise between these modalities for this patient group. Survival rates in this patient group are 1.5–2 times lower than in low surgical risk patients. In this randomised controlled trial, we planned to compare the clinical effectiveness and cost-effectiveness of ablation with that of surgery in this high-risk group of patients. If this research showed equivalent results of thermal ablation and surgery in this group, then thermal ablation could be considered standard of care as it is associated with reduced pain, morbidity, mortality and hospital stay. The data would also provide justification for a subsequent clinical trial on low-risk patients.

Pilot study background

Recruitment to randomised controlled trials with very different treatment arms can be difficult and recruitment to surgical trials is particularly challenging. Qualitative research can identify aspects of the trial design that hinder recruitment and possible solutions, so qualitative work was embedded into the LAVA (Liver Resection Surgery Versus Thermal Ablation for Colorectal LiVer MetAstases) pilot study. Previous studies have shown that patient-related (e.g. difficulties of informed consent, understanding randomisation and preference for certain treatments) and clinician-related (e.g. concern about impact on the doctor–patient relationship, clinical equipoise and how the trial is presented to patient) factors affect recruitment. To anticipate these issues, a training manual was developed based on published guidance and supplemented by research findings. This provided advice about presenting the trial, the evidence base for the LAVA trial, and a step-by-step guide to help recruiters present the information in an unbiased way. The manual was presented at the study launch meeting, a copy was given to each local principal

investigator at site initiation, and this was followed up with telephone-based support. The qualitative substudy aimed to understand barriers to recruitment from the perspective of patients and staff.

Objectives

Pilot study and main trial objectives

The aim of the research is to compare the clinical effectiveness and cost-effectiveness of thermal ablation with that of liver resection surgery in high surgical risk patients who are eligible for liver resection. The main trial primary outcome was disease-free survival at 2 years post randomisation.

The internal pilot study objective was to assess the feasibility of recruitment. The assessments around the interventions were to assess the quality of the ablations and the quality of liver resection surgery in terms of completeness of resection. In addition, the computed tomography scan findings relating to ablation outcomes were centrally reviewed to ensure quality of reporting.

Qualitative study objectives

The aims of the qualitative study during the internal pilot were to explore patients' and clinicians' acceptability of the trial and recruitment processes to inform recruitment and follow-up strategies for the main trial.

Methods

Study design

This was an international (UK and the Netherlands), multisite, open, pragmatic, parallel-group, randomised controlled trial design with an internal pilot. Participants were randomised via Clinical Trials Research Unit telephone or web-based 24-hour randomisation systems on a one-to-one basis to receive either surgical resection or thermal ablation. The trial aim was to recruit 330 participants over a 48-month period. During the internal pilot, 15 centres were required to open for recruitment and 45 participants had to be recruited for the main trial to be considered feasible. It was agreed with the funders at the grant application stage that, if this recruitment target was not met by the end of the pilot, trial continuation would be discussed with the Trial Steering Committee and Data Monitoring and Ethics Committee.

Settings and participants

Participants were recruited from tertiary hepatopancreatobiliary centres in the UK and in the Netherlands. Patients were eligible if they were aged $\geq$ 18 years with a specialist multidisciplinary team diagnosis of colorectal liver metastases that were considered to be resectable or ablatable with curative intent, or were considered to be high risk for surgery by meeting at least one of the following criteria: at high risk because of their age, at high risk because they have major comorbidities as judged by the treating clinician, liver metastases leading to poor prognosis or at high risk because of tumour burden or anticipated small volume of residual liver. Exclusion criteria included incurable extrahepatic metastases that were not suitable for liver resection surgery or thermal ablation, concurrent malignant disease (except basal cell skin carcinoma), planned simultaneous resection of primary and liver metastases, and pregnancy.

Intervention and control

Patients were randomised using minimisation incorporating a random element to surgical resection or thermal ablation to be carried out as per standard practice. The minimum ablation and surgical standards were defined in the Site Standard Operation Procedures and ablation criteria were based on Cardiovascular and Interventional Radiological Society of Europe guidance provided to the centres.

Outcomes

Primary outcome
Disease-free survival at 2 years post randomisation.

Secondary outcomes
Overall survival, timing and site of recurrence, additional therapy after treatment failure, quality of life, complications, length of hospital stay, costs, trial acceptability, and disease-free survival measured from the end of the intervention. It was also planned that 5-year survival data would be documented through record linkage.

Follow-up of participants
Participants would have been reviewed in clinics at 3, 6, 12, 18 and 24 months post randomisation, where they would have received follow-up investigations (computed tomography scans of the chest, abdomen and pelvis) as a minimum and blood tests to check the levels of tumour markers.

Statistical methods

Analysis methods: statistical
Owing to the small sample size and early closure of the trial, it was not possible to perform any of the original planned analysis for the main trial. The intention for the main trial was to assess the difference in disease-free survival at 2 years. The non-inferiority hypothesis would have been tested using an appropriate survival model to incorporate random effects with respect to research sites, and including adjustment for the stratification factors. Differences in rates, such as complication rates and recurrence rates, would have been analysed using multilevel logistic regression incorporating random effects with respect to research site, and would have included adjustment for the stratification factors.

Analysis methods: qualitative study
In-depth, semistructured telephone or face-to-face interviews were conducted with recruiters (i.e. consultants, interventional radiologists and nursing staff), and face-to-face interviews were conducted with patients. Interviews were audio-recorded, transcribed verbatim, anonymised and analysed thematically. This allowed the interpretation of key issues faced by recruiters, and reasons for non-consent from the perspective of patients and staff to be examined. Participant information sessions (recruiter consultation encounters) were audio-recorded (with permission) and were examined using the Q-QAT (Quanti-Qualitative Appointment Timing) approach to allow the analysis of how information was presented by recruiters and received and understood by patients. All patients eligible for the trial and all staff involved in trial recruitment were eligible for interview, with a planned sample size of ≈20 patients (i.e. consenters, decliners and those withdrawing post randomisation) and 15 staff. An iterative approach to sampling was planned, with earlier interviews to be used to inform later recruitment until data saturation was reached.

Sample size
A total of 330 participants were required to demonstrate non-inferiority of thermal ablation with respect to resection in terms of the primary end point (2-year disease-free survival) with 80% power at the 2.5% one-sided level of significance, assuming a median time to event of 14 months in the resection group and a non-inferiority margin for thermal ablation of 4 months, allowing for a 5% drop-out rate.

Results

Patient recruitment
The trial opened in 17 sites (UK, $n = 13$; and the Netherlands, $n = 4$) during the internal pilot phase. Of the 366 patients with colorectal liver metastases screened, 59 were eligible for the trial. Only nine

participants were randomised during the 12-month internal pilot phase, compared with the anticipated recruitment of 45 participants. The trial was stopped early; therefore, the participants were followed up within the trial for 3 months post randomisation. These patients were subsequently followed as per the usual follow-up regimen in the hospital.

Assessing barriers to recruitment and actions taken to increase recruitment

In September 2017, 6 months following commencement of the 1-year pilot phase, sites had identified fewer eligible patients than expected. Closer examination identified that some sites were misapplying the inclusion and exclusion criteria, and the chief investigator visited each site and met with clinical colleagues to remedy these misunderstandings. However, this did not lead to improvements in recruitment. Interviews with staff revealed that, when potentially eligible patients were identified, the specialist multidisciplinary team generally rejected their inclusion in the trial. Few patients (decliners or consenters) consented to be interviewed, so little can be gleaned from their perspective, but there was some evidence from staff interviews that recruiting surgeons struggled to maintain equipoise when presenting the trial.

Prior to study launch, the qualitative study team developed a training manual to help with study introduction, and this was discussed at each site initiation meeting. Follow-up teleconferences were arranged following each site set-up to identify early challenges and to go through the training manual with recruiting staff. However, it was many months between training and the identification of potentially eligible patients; therefore, much of the initial learning was lost. During interviews with staff, we explored training needs, but most sites refused training as they considered that they had a strong track record of recruiting to trials and felt that training was not needed, or had not identified any eligible patients and felt that it was premature to judge if additional training were needed.

Qualitative study results

Thirteen of the 15 planned staff interviews were conducted and these were analysed as intended.

Invitations were sent to 41 staff (i.e. consultants, radiologists and research nurses) at 12 sites, and all of those who consented were interviewed. Interviews took place between November 2017 and February 2018. We conducted in-depth, semistructured interviews that were informed by a topic guide developed in conjunction with patient and public involvement representatives and the existing literature on the barriers (clear obstacles and hidden challenges) to recruitment. All interviews were audio-recorded with permission. The 13 interviews generated 268 minutes of rich audio data.

The original aim was to conduct interviews with up to 20 patients: consenters, decliners and those dropping out post randomisation. Despite regular reminders to sites, significant recruitment problems were encountered. All eligible patients were to be invited to take part in an interview, but only three sites forwarded details of any patients who were willing to be approached for interview. Evidence from conversations with staff and staff interviews suggests that gatekeeping by nurses was an issue, with some nurses being reluctant to approach patients who had already consented for the trial, citing concerns about patient burden (i.e. not wanting to lose a patient who was showing interest in taking part in the trial). Four patients initially consented to interview (all of whom declined trial involvement), but two subsequently declined an interview because of health problems.

Ten sites consented to record recruitment sessions but, despite regular reminders and reassurances that the recordings would remain confidential, only two sites provided any recordings for analysis [six recordings were from one site (one clinician) and one recording was from a second clinician at another site]. A commonly cited barrier to recording the sessions was that the study voice recorder was held by the research nurse, who was not always available when clinicians met with patients.

Conclusions

The feasibility of recruitment in the patient population was not demonstrated during the pilot stage of the trial and, therefore, the trial closed early to recruitment on completion of the pilot stage. The main reasons for the poor recruitment into the trial included fewer than anticipated participants who were eligible for both surgery and ablation, clinician unconscious bias towards surgery, patient preference for one treatment or the other, and lack of dedicated research nurses who could identify and recruit participants to the trial. There were insufficient numbers recruited to allow useful comparison between the two interventions.

Lessons learned

There were several lessons learned during this trial. Studies comparing two very different treatment modalities will benefit from a feasibility study to provide a better estimate of the number of participants eligible for the trial and resolve any misconceptions about participant eligibility. In the absence of a feasibility study, a longer and more intensive phase of internal pilot study would be required to resolve the issues, which might be in the form of more extensive training to avoid unconscious bias of the recruiters and training the referring clinicians so that the patient does not have a preconceived idea of treatment. It is probably prohibitively expensive to have dedicated trial nursing staff for a trial of this nature with an anticipated recruitment of four or five participants per centre per year; therefore, sufficient time should be allowed to identify appropriately trained staff through National Institute for Health Research (NIHR) Research Networks.

With hindsight, it would have been better to conduct the qualitative research interviews prior to recruitment starting to prospectively identify and resolve any difficulties, as well as during the initial months of recruitment. Once set up, the buy-in by the majority of clinicians participating in the specialist multidisciplinary team is critical to the screening and identification of trial candidates and this can be truly judged only once clinicians start to screen patients.

The uncertainty about the relative benefits and harms of thermal ablation compared with liver resection in high surgical risk patients with colorectal liver metastases will remain for the next decade. Surgeons and other members of the specialist multidisciplinary team should be aware of the ongoing lack of evidence to guide the choice of liver resection or thermal ablation in patients with colorectal liver metastases, especially in those who are in a high surgical risk group.

Trial registration

This trial is registered as ISRCTN52040363.

Funding

This project was funded by the NIHR Health Technology Assessment programme and will be published in full in *Health Technology Assessment*; Vol. 24, No. 21. See the NIHR Journals Library website for further project information.

Health Technology Assessment

HTA/HTA TAR

ISSN 1366-5278 (Print)

ISSN 2046-4924 (Online)

Impact factor: 3.819

Health Technology Assessment is indexed in MEDLINE, CINAHL, EMBASE, The Cochrane Library and the Clarivate Analytics Science Citation Index.

This journal is a member of and subscribes to the principles of the Committee on Publication Ethics (COPE) (www.publicationethics.org/).

Editorial contact: journals.library@nihr.ac.uk

The full HTA archive is freely available to view online at www.journalslibrary.nihr.ac.uk/hta. Print-on-demand copies can be purchased from the report pages of the NIHR Journals Library website: www.journalslibrary.nihr.ac.uk

Criteria for inclusion in the *Health Technology Assessment* journal

Reports are published in *Health Technology Assessment* (HTA) if (1) they have resulted from work for the HTA programme, and (2) they are of a sufficiently high scientific quality as assessed by the reviewers and editors.

Reviews in *Health Technology Assessment* are termed 'systematic' when the account of the search appraisal and synthesis methods (to minimise biases and random errors) would, in theory, permit the replication of the review by others.

HTA programme

Health Technology Assessment (HTA) research is undertaken where some evidence already exists to show that a technology can be effective and this needs to be compared to the current standard intervention to see which works best. Research can evaluate any intervention used in the treatment, prevention or diagnosis of disease, provided the study outcomes lead to findings that have the potential to be of direct benefit to NHS patients. Technologies in this context mean any method used to promote health; prevent and treat disease; and improve rehabilitation or long-term care. They are not confined to new drugs and include any intervention used in the treatment, prevention or diagnosis of disease.

The journal is indexed in NHS Evidence via its abstracts included in MEDLINE and its Technology Assessment Reports inform National Institute for Health and Care Excellence (NICE) guidance. HTA research is also an important source of evidence for National Screening Committee (NSC) policy decisions.

This report

The research reported in this issue of the journal was funded by the HTA programme as project number 13/153/04. The contractual start date was in January 2016. The draft report began editorial review in January 2019 and was accepted for publication in December 2019. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the reviewers for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

This report presents independent research funded by the National Institute for Health Research (NIHR). The views and opinions expressed by authors in this publication are those of the authors and do not necessarily reflect those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care. If there are verbatim quotations included in this publication the views and opinions expressed by the interviewees are those of the interviewees and do not necessarily reflect those of the authors, those of the NHS, the NIHR, NETSCC, the HTA programme or the Department of Health and Social Care.

Published by the NIHR Journals Library (www.journalslibrary.nihr.ac.uk), produced by Prepress Projects Ltd, Perth, Scotland (www.prepress-projects.co.uk).