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

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Scientific summary

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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 (Quantitative-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 $\approx 20$ 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.

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This report

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