LAVA: Liver resection surgery versus thermal Ablation for colorectal liVer metAstases.

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Metastases
Study type	Interventional

Summary

ID

NL-OMON45285

Source
ToetsingOnline

Brief title
LAVA

Condition

- Metastases
- Hepatobiliary therapeutic procedures

Synonym
Liver metastases, tumor growth in the liver

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: NIHR

Intervention

Keyword: Colorectal liver metastases, Liver resection surgery, Thermal ablation

Outcome measures

Primary outcome

• Disease free survival (measured from randomisation) at 2 years

post-randomisation

Secondary outcome

• Overall survival at 2 and 5 years

• Local and distant recurrence of disease at 2 years

• Disease free survival (measured from end of intervention) at 2 years

post-randomisation

• Use of subsequent therapies for treatment failure

• Health related quality of life (QoL)

• Complications during treatment

• Post treatment complications

• Length of intensive therapy unit (ITU) and inpatient stay

• Cost effectiveness (UK only)

• Explore the association between tumour markers and recurrence

Study description

Background summary

Bowel cancer is the UK*s second biggest cancer killer. About 30% of people with colorectal cancer develop liver metastases. Liver resection is effective in improving the life expectancy in people with colorectal liver metastases (CLM). However, only about 7% to 20% of people with colorectal liver metastases

undergo liver resections because of age or comorbidities of the patient or because of the extent of cancer spread. Increasing the number of patients who can undergo potentially curative therapy for liver alone metastases is a main NHS goal for improving the outcome for bowel cancer patients in the UK. In light of this, specialist liver resection centres are carrying out more extensive and complex resections including elderly patients with major co-morbidity. This more extensive surgery in patients with co-morbidity is associated with an increased morbidity and mortality (high risk patients).
Thermal ablation is a lower risk alternative modality for treatment of CLM and involves destruction of cancer by heat. Thermal ablation includes established modalities such as radiofrequency ablation (RFA) or microwave ablation (MWA). Thermal ablation may be associated with a lower chance of cure. A systematic review of ablative methods in patients with CLM concluded that there is a group of patients in whom the risk and benefits of surgical resection are less evident and that good quality evidence is required for the clinical outcome and cost effectiveness of thermal ablation in comparison to surgery in these high risk patients.
Thermal ablation is currently used for patients with colorectal liver metastases not suitable for surgical resection and not for patients with a possibility of curative liver resection surgery because of high local recurrence rates with thermal ablation. Multiple studies have highlighted the superiority of surgery to ablation for preventing recurrence within the liver. A recent series from Nishiwada et al showed a 13% recurrence after surgery as opposed to 46% after thermal ablation. Other newer modalities of thermal ablation include laser ablation and high intensity focused ultrasound (HIFU).
To determine the evidence for thermal ablation, a NIHR (National Institute for Health Research) HTA (Health Technology Assessment) funded systematic review of literature was commissioned and subsequently published in February 2014 (Loveman et al). We have reviewed this information along with subsequently published literature. There are no adequately powered trials comparing surgery with ablation therapy in patients with colorectal liver metastases. The systematic review identified one non-randomised study in which the survival in patients with radiofrequency ablation (RFA) was similar to liver resection surgery despite the RFA group having more comorbidities or more extensive liver metastases. An exploratory cost-effectiveness analysis performed by the group on the basis of this non-randomised study showed that radiofrequency ablation has the potential to be cheaper and might result in better health-related quality of life. Another non-randomised study published since this systematic review has also shown that patients undergoing RFA have survival comparable to surgery despite having more extensive liver metastases. Similarly, an underpowered randomised controlled trial showed no difference in survival between MWA and liver surgery in resectable CLM. However, in another non-randomised study published after the systematic review by Loveman et al, people who were eligible for surgery but preferred RFA had poorer survival than those undergoing surgery.

Study objective

The aim of this research is to compare the effectiveness and cost-effectiveness of thermal ablation versus liver resection surgery in high surgical risk patients eligible for liver resection.

Study design

A prospective, UK and Netherlands multi-site, parallel-group, randomised trial with an internal pilot investigating the effectiveness and cost-effectiveness of liver resection surgery versus thermal ablation in high surgical risk patients eligible for liver resection. High surgical risk patients are defined as those with a high risk of post operative morbidity, mortality and reduced long term survival due to the age of the patient, their history of concurrent medical problems (co-morbidity), or the need for extensive liver resection surgery of a poor prognosis cancer.

Intervention

Liver resection will be carried out within regional centres according to individual centre protocol. The majority of patients will have undergone resection of the primary cancer. Patients may be offered open or laparoscopic liver resection depending on site and stage of disease. In selected cases, the liver first approach may be considered.
For thermal ablation, RFA or MWA will be used according to local availability and expertise. Ablation maybe performed at laparoscopic or open surgery if the percutaneous approach is contra-indicated.

Study burden and risks

Current evidence suggests that thermal ablation has lower complication rates and better health-related quality of life than surgery. Thermal ablation is also less expensive than liver resection, which will result in cost savings to NHS. Ablation therapy has the potential to decrease the pain after treatment and time taken for recovery from cancer therapy which will decrease the number of work days lost by the patient and their carer resulting in a financial impact on patients, their carers, and their employers.
The major concern about thermal ablation is the high incidence of local recurrence. As a result it would be anticipated that it will not offer similar cancer related outcomes as liver resection surgery. However in patients who are high risk but would currently be considered for liver resection the short and long term outcomes after surgery are likely to be poorer than the normal surgical cohort and hence thermal ablation for this group may produce comparable results.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Aged >= 18 years
2. Able to provide written informed consent
3. MDT diagnosis of colorectal liver metastases considered to be resectable or ablatable with curative intent
4. Resected colorectal primary or plan for primary resection with curative intent
5. Meets one or more of the following criteria:
i) Considered high risk for surgery due to age e.g. age greater than 70 years.
ii) Major co-morbidities as judged by the treating clinician. e.g. previous Transient Ischaemic Attack (TIA), major cerebrovascular accidents (CVA), myocardial infarction (MI), severe chronic airway disease, previous pulmonary embolism (PE), chronic kidney disease.
iii) Liver metastases with poor prognosis e.g. requiring down staging with chemotherapy prior to definitive treatment, poor response after chemotherapy but still resectable and ablatable,

curable extra-hepatic disease , multiple synchronous metastases, previous treated lung metastases (resection or ablation).
iv) High risk surgery, e.g. need two staged resection or ALPPS or portal vein embolization, small anticipated remnant liver volume.
v) Recurrence of colorectal liver metastases following previous surgery or ablation
6. Suitable candidate for either liver resection surgery or thermal ablation as judged by the MDT
7. Able and willing to comply with the terms of the protocol including QoL questionnaires

Exclusion criteria

1. Incurable extra-hepatic metastases
2. Not a suitable candidate for liver resection surgery
3. Not a suitable candidate for thermal ablation
4. Concurrent malignant disease (except basal cell carcinoma)
5. Planned simultaneous resection of primary and liver metastases
6. Pregnancy

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-07-2017
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	12-04-2017
Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	13-12-2017
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ISRCTN	ISRCTN52040363
CCMO	NL58444.068.16

Study results

Date completed:	31-08-2018
Actual enrolment:	5

Summary results
Trial is onging in other countries