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Systemic chemotheRapy and the liVEr-fiRSt approach compared to index colorectal resection for colorectal cancer presenting with synchronous liver metastases (the RVERS trial)

Submission date 12/07/2012	**Recruitment status** Stopped	[X] Prospectively registered
		[ ] Protocol
Registration date 09/10/2012	**Overall study status** Stopped	[ ] Statistical analysis plan
		[ ] Results
Last Edited 07/10/2013	**Condition category** Cancer	[ ] Individual participant data
		[ ] Record updated in last year

Plain English summary of protocol

Background and study aims

Bowel cancer is the third most common cancer in the United Kingdom and the liver is the most common site to which bowel cancer spreads. About a third of patients with bowel cancer will already have secondary tumours in the liver (called metastases) at the time that the bowel cancer is diagnosed. In this situation, the standard treatment is to remove the bowel cancer first by surgery, give chemotherapy and then about three to four months later, remove the liver tumours. This is known as the classic approach. The limitation with this is that the liver tumours are untreated during the period of bowel cancer surgery and the patient may have to wait several months for chemotherapy. An alternative approach, known as the reverse strategy, is to give chemotherapy as the first treatment for patients with bowel cancer with tumours in the liver, then remove the liver tumours and finally the bowel cancer. The reasoning behind this approach is that chemotherapy treats the whole body and tumours in both the liver and the bowel. The liver tumours are thought to be responsible for spread of bowel cancer to other sites so the reason for operating on these first is to reduce the chance of spread. Finally, it is the bowel surgery which is associated with unpleasant side effects such as the possibility of requiring a colostomy (stoma bag) and for men the possibility of impaired sexual function, and in some patients treated with the reverse approach the chemotherapy means that if the bowel tumour responds completely, surgical removal may not be necessary. This watch and wait policy if there has been a complete response, cannot be used if the bowel tumour has been the target of surgery before any other treatment.

Who can participate?

Patients over the age of 18 presenting with bowel cancer that has spread to the liver.

What does the study involve?

Participants will be randomly allocated to receive either the standard treatment or the newer reverse approach. In both options, both the bowel cancer and the liver tumour are treated; the difference lies in the sequence of treatment.

What are the possible benefits and risks of participating?
Both strategies are known to be safe but it is not known whether one is better than the other. The benefits are that we may establish that one strategy is better than the other. There is no additional risk from participation.

Where is the study run from?
This study is run by the liver surgery unit of the Manchester Royal Infirmary in collaboration with the Clinical Trials Unit of the Christie Hospital NHS Foundation Trust. The participating hospitals are St James Hospital, Leeds and Queens Medical Centre, Nottingham (UK).

When is the study starting and how long is it expected to run for?
It is anticipated that recruitment will start in mid 2013, for two years. The study observation period will be for a year after enrolment in the study.

Who is funding the study?
NIHR Health Technology Assessment Programme (UK).

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Version 3.9

Study information

Scientific Title
Systemic chemotherapy and the liver-first approach compared to index colorectal resection for colorectal cancer presenting with synchronous liver metastases: a randomised controlled trial (the RVERS trial)

Acronym
RVERS

Study objectives
In patients with colorectal cancer with synchronous liver-only metastases, a "reverse" or liver-first sequence of best-evidenced neoadjuvant chemotherapy, liver resection and (bowel resection preceded by adjuvant chemo(radio)therapy for rectal tumours) reduces the risk of cancer progression compared to the current standard management sequence of bowel resection (with chemoradiotherapy for rectal lesions), neoadjuvant chemotherapy followed by liver resection with adjuvant chemotherapy as the final step.

Ethics approval required
Old ethics approval format

Ethics approval(s)
National Research Ethics Committee, North West - Greater Manchester West

Study design
Non-blinded multi-centre randomised controlled trial.

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Colorectal cancer

Interventions
For patients with colorectal cancer with synchronous hepatic metastases, the study compares the classic approach of bowel cancer surgery first, followed by neoadjuvant chemtoherapy and then liver resection to the reverse approach of systemic chemotherapy first, followed by liver

resection as the first surgical intervention, adjuvant chemotherapy and then colorectal resection as the final surgical intervention.

Updated 07/10/2013: The trial did not commence due to funding being declined.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
Is there disease-free survival 12 months after enrolment into protocol with the new "reverse" approach to the management of patients with colorectal cancer with synchronous liver metastases compared with classical management

Secondary outcome measures
1. Disease progression in patients who are not disease-free at the end of protocol:
The most sensitive measure of change is likely to involve a metric incorporating tumour size. There is evidence that CT-based volumetric assessment of metastases (seeded region growing method, slice-based segmentation or threshold-based segmentation) is more accurate for assessment of disease progression than the RECIST 1.1 method of largest axial diameter. It is acknowledged that although RECIST criteria provide an objective means of assessment of solid tumour response to treatment, there is a risk of inter-observer bias. Further, RECIST criteria may be insufficient to assess response to treatment in patients with colorectal liver metastases treated by biologic agents such as bevacizumab. Thus, disease progression at end of protocol will be assessed by RECIST 1.1 criteria and compared to volumetric assessment.
2. Timelines for completion of treatment protocol:
This is defined as the amount of time in days from enrolment to completion of full protocol. In the reverse protocol, patients may complete the protocol without rectal cancer resection if there is a complete oncological response and a watch and wait policy is adopted.
3. Failure to complete treatment protocol:
This is defined as drop-out prior to completion of allocated arm. It will be further categorised as due to disease progression, patient choice or un-related to colorectal cancer (for example myocardial infarction) and will be recorded as the timepoint in days from enrolment.
4. Resection margin status:
R0 bowel resection and R0 liver resection (no residual cancer status after colorectal resection and after liver resection).
5. Complication and treatment-related morbidity profiles:
Complications will be recorded prospectively according to the criteria defined above (see treatments) and assessed at the end of the study. Complication profiles in patients in the reverse arm will be compared to those in the classic arm. The morbidity associated with each intervention step will be recorded separately. Morbidity will include unplanned re-admission and re-operation rates. Requirement for non-elective surgery for colonic complications (obstruction, perforation, bleeding) will be recorded. Resection margin status for both colorectal and liver resection will be recorded.
6. Avoidance of stoma after colorectal surgery:
Use of stoma (either temporary or permanent) will be recorded.
7. Mortality:
Overall and cancer-related mortality in either arm after enrolment will be recorded. All-cause mortality will be determined using the Demographics Batch Service (DBS) to access the national

electronic database of the UK NHS (National Health Service).
8. Cost of care:
Health service costs in either arm will be assessed.
9. In-patient and critical care occupancy:
A record will be made of in-patient and critical care occupancy associated with intervention.
10. Quality of life:
Quality of life will be assessed using the European Organization for Research and Treatment of Cancer QLQ-LMC21 questionnaire which has been validated for assessment of patient-reported outcomes during treatment of colorectal liver metastases. The questionnaire will be completed by patients at time of enrolment and after completion of protocol.

Overall study start date
01/10/2013

Completion date
01/10/2015

Reason abandoned (if study stopped)
Lack of funding/sponsorship

Eligibility

Key inclusion criteria
In order to be eligible for inclusion, patients must fulfil the following criteria:
1. Over 18 years of age
2. Able to give informed consent
3. Have a histological diagnosis of colorectal cancer
4. No prior history of malignancy
5. Have radiological evidence on either contrast-enhanced computed tomography or contrast-enhanced magnetic resonance scanning of hepatic metastases at the time of diagnosis of the primary tumour or within 3 months thereof. (Liver metastases should not be biopsied)
6. Liver metastatic burden feasible for surgical resection as agreed by an appropriately constituted multi-disciplinary team or to be downstageable for resection by neoadjuvant chemotherapy
7. Computed tomographic and/or 18fluoro-deoxyglucose positron emission tomographic (FDG-PET) of the absence of pulmonary metastases
8. Magnetic resonance scan assessment of rectal primary tumours
9. World Health Organisation performance status (PS) 0, 1 or 2 (see Appendix 2) and considered by both multidisciplinary team and a specialist oncologist to be suitable for chemotherapy.
10. Baseline laboratory tests (within 1 week prior to randomisation):
neutrophils ¡Ý 1.5 x109/l and platelet count ¡Ý 100 x109/serum bilirubin ¡Ü 1.25 x upper limit of normal (ULN), alkaline phosphatase ¡Ü 5 x ULN and serum transaminase (either AST or ALT) ¡Ü 2.5 x ULN, estimated creatinine clearance (Cockcroft; appendix VIII) >50ml/min or measured GFR (EDTA clearance) >50 ml/min
11. For women of childbearing potential, negative pregnancy test and adequate contraceptive. Adequate contraception for men.
12. Consent to allow surplus pathological material to be analysed for translational research projects (patients may decline participation in this supplementary component and still participate in the main trial).

Participant type(s)

Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
120

Key exclusion criteria
1. Patients who are under 18 years of age
2. Patients who are unable to give informed consent
3. Patients who are unfit for the chemotherapy regimens in this protocol, for example: severe uncontrolled concurrent medical illness (including poorly-controlled angina or very recent myocardial infarction, i.e. in previous 3 months) likely to interfere with protocol treatments
4. Any psychiatric or neurological condition which is felt likely to compromise the patient's ability to give informed consent or to comply with oral medication
5. Partial or complete bowel obstruction not amenable to resolution by stent or diversion
6. Pre-existing neuropathy (> grade 1)
7. Patients requiring on-going treatment with a contraindicated concomitant medication
8. Patients with another previous or current malignant disease
9. Patients with known hypersensitivity reactions to any of the components of the study treatments
10. Patients with brain metastases
11. Female patients who are lactating
12. Patients who have received prior chemotherapy with oxaliplatin
13. Patients with a personal or family history suggestive of dihydropyrimidine dehydrogenase (DPD) deficiency or with known DPD deficiency

Date of first enrolment
01/10/2013

Date of final enrolment
01/10/2015

Locations

Countries of recruitment
England

United Kingdom

Study participating centre

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Sponsor information

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Central Manchester University Hospitals NHS Foundation Trust (UK)

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Sponsor type
Hospital/treatment centre

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ROR
https://ror.org/00he80998

Funder(s)

Funder type
Government

Funder Name
NIHR Health Technology Assessment programme - HTA (UK)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration