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Evaluation of the inflammatory response to minilaparotomy compared to conventional laparotomy in the surgical resection of colorectal cancer including its influence on long term survival and local recurrence

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Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Mr Charles Evans

Contact details
c/o Mr Kumar's secretary
3rd Floor St James Wing
St Georges Hospital
Blackshaw Road, Tooting
London
United Kingdom
SW17 0RE
+44 (0)798 081 7254
charliemedic@hotmail.com

Additional identifiers

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N0236173867

Study information

Scientific Title
Evaluation of the inflammatory response to minilaparotomy compared to conventional laparotomy in the surgical resection of colorectal cancer including its influence on long term survival and local recurrence

Study objectives
To compare standard surgical approach to minilaparotomy in patients undergoing surgical resection for colorectal cancer. Once group will have surgery in the conventional manner and the other will have it performed using a mini-laparotomy. A mini-laparotomy being where the incision, through which the abdominal cavity is entered to reach the cancer, is 15cm or less; whereas conventionally a cut is made along the entire length of the abdomen.

We aim to show that there is a reduced inflammatory response to the mini-laparotomies by measuring inflammatory markers (cytokines) from blood samples taken before and after surgery.

We believe that a reduced acute inflammatory response post surgery has benefits for the patient in both the short term with regards to improved recovery times to mobilisation and restoration of bowel function and the longer term with relation to rates of local recurrence of the tumour and overall prognosis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Not provided at time of registration

Study design
Randomised controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Cancer: Colorectal

Interventions
HYPOTHESES TO BE TESTED IN THIS STUDY:

ONE:
Null Hypothesis: There is no difference in the postoperative levels of immunosupression as a result of mini-laparotomy compared to conventional laparotomy when excising colorectal cancers.

Alternative Hypothesis: There are reduced levels of immunosupression following surgical resection of a colorectal cancer via a mini-laparotomy compared to a conventional laparotomy.

TWO:
Null Hypothesis: There is no benefit in terms of reduced rates of local recurrence, development of metastases and improved long-term survival when excising colorectal tumours using a mini-laparotomy compared to conventional laparotomy.

Alternative Hypothesis: There are reduced rates of local recurrence, development of metastases and improved long-term survival when colorectal cancers are resected using a mini-laparotomy compared to conventional laparotomy.

THREE:
Null Hypothesis: Surgical excision of colorectal cancers via a mini-laparotomy allows the same clearance margins for the cancers specimen as when performed using conventional laparotomy.

Alternative Hypothesis: There is a difference in the clearance margins for colorectal cancer specimens resected via a mini-laparotomy compared to a conventional laparotomy.

FOUR:
Null Hypothesis: Spillage of tumour cells in to the blood circulation on mobilisation of colorectal cancers during surgical excision is no different when the operation is performed using a mini-laparotomy or conventional laparotomy.

Alternative Hypothesis: There is a difference in the number of tumour cells spilt into the blood when a colorectal cancer is mobilised during surgical excision via mini-laparotomy compared to conventional laparotomy.

STUDY DESIGN

A full literature review using PubMed and Medline was made. Information was gathered from studies investigating immunosupression and surgery, studies comparing laparascopic resection of colorectal cancers to open surgery and work done at St Georges Hospital by Mr A.G. Heriot and Mr A.G. Prabhudesai investigating imunosupression and colorectal cancer. Advice was obtained from Professor D. Kumar (consultant colorectal surgeon at St Georges Hospital) and Professor A.G. Daigleish (consultant oncologist at St Georges Hospital) with input from other specialists in both fields. Statistical advice from Mr Jan Poloneicki (statistician) was taken to ascertain the number of patients that would be needed to make sure any information collected would statistically be significant.
From all the data collected, previous studies performed and upon the advice given it was felt the best way to answer the above hypotheses was to perform a prospective, randomised study on sixty patients diagnosed with colorectal cancer.

Patients would be randomly split into two groups using a block number randomisation. One group would have surgery in the conventional way with a full laparotomy; i.e. any incision length greater than 15cm dependant on patient size and access required. The other group would have surgery in the identical manner, with the same pre-operative preparation and post operative care except surgery would be performed via a mini-laparotomy; i.e. an incision length of 15cm or less.

To answer the first hypothesis regarding post operative immune suppression it was felt that by measuring the acute inflammatory markers, cytokines IL-1b, interlukin-2 (IL-2), TNF-a and IL-6, in venous blood samples both pre and post operatively it is possible to determine the inflammatory response to surgery and subsequent immunosupression. Blood samples taken at 1

day pre operatively and 3 hours, days 1 and 5 post operative would allow accurate assessment of the inflammatory response to surgery which at its maximum has been shown to last 6-9 days. The above cytokines were chosen because they have been shown in numerous studies to be released in response to tissue injury, with systemic levels that correlate with the magnitude of the trauma and inversely relate to the degree of immune suppression.

To answer the second hypothesis correlating immune suppression with rates of local recurrence, development of metastases and long term survival additional cytokines will need to be measured pre operatively and post operatively including 2 months after surgery when the acute inflammatory response is known to have ended. From previous work performed at St Georges it has been shown that increased post-operative levels of the immunosuppressive cytokine -10 (IL-10) appears to be related to the development of distant metastases and patients with high post operative levels of the proinflammatory cytokine interferon gamma (IFN-g) developed local recurrence later than those with low levels. By measuring these cytokines both before and 2 months after surgery it will be possible to see if the mini-laparotomy has any influence on underlying pro and anti inflammatory cytokine levels with subsequent influence on disease progression.

In order to measure the cytokine levels heparinised venous blood samples will be obtained and they will be detected using enzyme linked immunosorbent assay (ELISA) techniques (see below for details). Quantitative values of the cytokines will also be measured using real-time PCR.

The cancer specimens, post-surgical resection, are reviewed by the histopathology department so an accurate staging of the tumour can be made, checking for its degree of invasion locally and distally. Margins of clearance from the tumour to the excision edge are also measured. These measurements will enable it to be assessed if there is any significant difference between those resected through a mini-laparotomy and the conventional technique, answering the third hypothesis,

In order to assess the extent of tumour cell spillage during mobilisation of the cancer during surgery venous blood samples can be taken from patients during the operation before and after mobilisation or attempted mobilisation of the tumour. Also blood spilled into the abdominal cavity during the operation can be taken with a heparinised syringe. These samples can then have the tumour cells extracted by spinning the samples using centrifugation and then magnetically labelling the cancer cells which can then be identified via microscopy. It then should be possible to assess if by performing a mini-laparotomy there is any difference in the number of tumour cells spilled from the cancer compared to when using the conventional approach.

PATIENT SELECTION

Patients with colorectal cancer diagnosed at St Georges Hospital from the 1st of November 2004 will be assessed for suitability for entry into the study. It must have been agreed by the patient and clinician that surgical resection of the cancer is appropriate and that the patient is willing to undergo surgery.

Once the decision is made for surgery to go ahead the patient will be introduced to the chief investigator of the study, preferably in the same clinic or when the patient first is available / willing to have a discussion. In the initial interview the study will be explained including the full implications to the patient, the risks, the additional inconveniences and investigations along with the potential benefits. If at that time the patient wishes to consider involvement a full information sheet will be given including a contact number of the chief investigator so that any

further questions can be answered. Once the patient has had time to consider inclusion in to the study or not and is agreement an informed consent form will be signed.

STEPS IN STUDY WITH REGARDS TO PATIENT

Pre Operation:
Patient will receive the same pre operative investigations and bowel preparation as per current protocols at St Georges Hospital, which ever group they have been allocated to. An additional venous blood sample will be taken 1 day pre operation of 20 mls.

Operation Day:
All patients will undergo surgery with general anaesthetic whilst placed in the supine or lithotomy position. All patients in the mini-laparotomy group will undergo surgery that uses conventional surgical techniques and instruments via a small abdominal incision. The incision will be of 15cm or less and its position on the abdomen will be determined by the need to facilitate the most straightforward resection. The other group will undergo the resection of colorectal tumours using conventional open procedures with conventional techniques and instruments. The abdominal incision they will receive will be greater than 15cm, as is conventional practice.

Venous blood samples of 8mls will be taken from the patient during the operation before and after mobilisation of the tumour. 10mls of blood spilt into the abdominal cavity will be collected in a heparinised syringe. Total blood loss would also be recorded.

Post Operation:
Patients will have post operative care using the conventional practice as directed by each specific consultants request within St Georges Hospital colorectal unit with diet being resumed as soon as bowel function returns clinically. Postoperative times to standing, walking, passage of flatus and urinary catheter removal will be recorded as well as post operative analgesic requirements. When patients were fully ambulatory they would be discharged.
Additional venous blood samples of 20mls would be taken at 3 hours, day 1 and day 5 post operations.
In routine general surgical outpatient clinic 2 months after surgery a final venous blood sample of 20 mls would be taken, completing the patients involvement in the study.

BIOLOGICAL SPECIMENS

The venous blood samples taken from patients in order to measure cytokine levels will, once collected be diluted and be left for 24 hours incubated in 24-well plates at 37 degrees Celsius in 5% carbon dioxide and either stimulated with lipopolysaccharide or left unstimulated. The cells within the blood will then be separated off using micro centrifugation and the remaining cell-free supernatant stored at -70 degrees Celsius until analysis. Batches of collected samples will then be tested for cytokines by using ELISA. (For methodology please see reference Heriot et al 2002 British Journal of Cancer 82 (5), 1009-1012.) Quantitative, absolute values of cytokine levels will be also measured by using real time PCR techniques (see Wheelan et al (2003) Journal of Immunological Methods 278 261-269).

The intra operative venous blood samples including the spilled blood within the abdominal cavity will be diluted and subjected to differential density centrifugation. The cancer cells will then be labelled with an immunomagnetic antibody so that they can be separated off and identified by microscopic examination.

The colorectal cancer specimens will be sent to the histopathology department where they will be fixed, sliced, mounted onto slides and stained so that the pathologists can review them to give accurate staging of the tumour and measure clearance margins.

ELIMINATING BIAS

This study is clearly unable to be a blind trial as both clinicians and patients will know which procedure is being performed from the onset. However this is a randomised, prospective study. The data being collected is objective data, directly from the measurement of cytokine levels, counting tumour cells and measuring clearance margins with no element for researcher bias.

TIMETABLE FOR RESEARCH

Having studied the data from St Georges Hospital approximately 500 patients were diagnosed with colorectal cancer in the last five years. Not all of these patients will have been treated with surgery and of the remaining group not all would have had the appropriate criteria for admission into this study. However it is estimated that it will take approximately twelve months to recruit sixty patients, needing a further three months to complete all sample collection.
During this time it will have been feasible to perform the majority of experiments with a last batch awaiting the final samples. This would leave four months to analyse the data and interpret it. At least two publications in scientific journals are planned from the data obtained and a completed report is intended to contribute to my MD thesis.

Intervention Type
Other

Phase
Not Specified

Primary outcome(s)
The primary outcome measure is the amount of acute inflammatory markers (the cytokines IL-6, IL-2, IL-1beta and TNF-alpha) measured from venous blood samples taken 1 day pre operation, day 1, day 5 and 2 months post surgery in the two groups.

Key secondary outcome(s))
Not provided at time of registration

Completion date
01/08/2006

Eligibility

Key inclusion criteria
IDENTIFICATION OF PATIENTS

Patients with colorectal cancer diagnosed at St Georges Hospital from the 1st November 2004 will be considered for this study. It must have been agreed by the patient and clinician that surgical resection of the cancer is appropriate and that the patient is willing to undergo surgery at St Georges Hospital.

APPROACHING PATIENTS
Once the decision is made for surgery to go ahead the patient will be introduced to the chief investigator of the study, who is a member of the colorectal team, preferably in the same clinic or when the patient is first available / willing to have a discussion. A face to face discussion will be held with the patient and or any friend / relative that they wish to be involved.

RECRUITING PATIENTS
In the initial interview the study will be explained including the full implications to the patient, the risks, the additional inconveniences and investigations along with the potential benefits. If at that time the patient wishes to consider involvement a full information sheet will be given including a contact number of the chief investigator if there are any further questions.
Once the patient has had time to consider inclusion in to the study or not and is in agreement an informed consent form will be signed. It should be noted that there will be no delay in arranging a date for surgery while the patient considers their involvement in the study.

Inclusion criteria:
1. Clinical diagnosis of adenocarcinoma of the colon/rectum
2. 18 years old or older
3. Willing to consent & surgically resectable tumours

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
Not Specified

Key exclusion criteria
1. Patients with intestinal obstruction or perforation
2. Concurrent or previous malignant tumours or familial adenomatous polyposis
3. Patients with known metastases
4. Patients with gross psychiatric illness & pts with pre-existing inflammatory bowel disease

Date of first enrolment
01/01/2005

Date of final enrolment
01/08/2006

Locations

Countries of recruitment

United Kingdom

England

Study participating centre
c/o Mr Kumar's secretary
London
United Kingdom
SW17 0RE

Sponsor information

Organisation
Record Provided by the NHSTCT Register - 2006 Update - Department of Health

Funder(s)

Funder type
Government

Funder Name
St George's Healthcare NHS Trust (UK)

Funder Name
No External Funding

Funder Name
NHS R&D Support Funding

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/02/2009		Yes	No
Plain English results				No	Yes