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MIRRORS study – robotic surgery for advanced ovarian cancer

Submission date
19/01/2021

Recruitment status
No longer recruiting

Registration date
21/01/2021

Overall study status
Completed

Last Edited
05/07/2023

Condition category
Cancer

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[ ] Results
[ ] Individual participant data
[ ] Record updated in last year

Plain English summary of protocol

See: https://www.cancerresearchuk.org/about-cancer/find-a-clinical-trial/a-study-looking-at-robotic-surgery-for-ovarian-cancer-mirrors (added 16/03/2021)

Background and study aims
The researchers are looking to find out whether robotic surgery is able to remove as much tumour as open surgery with improved patient outcomes in women with advanced ovarian cancer who have received chemotherapy before surgery. The current standard treatment for advanced ovarian cancer involves surgery and chemotherapy. The aim of surgery is to assess how far the cancer has spread (staging) and to remove as much visible disease as possible as this is associated with improved survival. Ovarian cancer surgery is usually performed through a vertical incision on the tummy (abdomen) from the just above the pubic bone to above the navel and sometimes up towards the bottom of the breastbone. A larger incision is required if there are tumour deposits in the upper parts of the abdomen.
Robotic surgery is a development of 'keyhole' laparoscopic surgery in which computer-aided mechanical assistance is used to support wristed instruments within the abdomen. Surgery is performed by the surgeon who is seated close by at a 3D console. An assistant is by the patient's bedside. The surgery is not automated and is still entirely performed by the surgeon but with mechanical assistance.

Performing surgery through smaller cuts is less painful and has been found to enhance recovery with reduced length of stay in hospital, reduced blood loss, so avoiding blood transfusion, infections and blood clots in the legs or lungs. Larger more complex operations generally carry greater risks of surgical complications, and such complications may delay or prevent women from re-starting their chemotherapy. However, it is impossible to remove large cysts or masses through such keyhole incisions and so this form of surgery is not suitable for everyone with ovarian cancer.

Since 2009, over 1300 gynaecological oncology robotic operations have been performed at the Royal Surrey for various indications, and they have by far the greatest experience in the UK. Robotic surgery has been found to be associated with a lower number of complications than standard laparoscopic keyhole surgery or open surgery, but has not been performed for many women with ovarian cancer. The role of robotic surgery in ovarian cancer treatment is uncertain

but it has the potential to lessen the impact and reduce the adverse effects of surgery for some women. Through this study the researchers want to help establish if this is true and if so what may its role be in advanced ovarian cancer. This initial feasibility study will focus on the ability to recruit patients, acceptability, quality of life, the rate at which it is possible to remove all visible tumour and the rate of conversion to open surgery. Ultimately the researchers would like to determine whether, in selected patients, robotic surgery offers improved quality of life and recovery with equivalent overall and progression-free survival.

Who can participate?
Women referred to the Royal Surrey NHS Foundation Trust, Guildford with stage IIIc –IVb advanced ovarian cancer who have undergone neoadjuvant chemotherapy. Participants need to be 18 years or older, have a pelvic mass ≤ 8 cm and, following discussion in a multidisciplinary team meeting, are not expected to require open surgery for another reason such liver surgery.

What does the study involve?
The study involves doing an initial laparoscopy at the beginning of the interval debulking surgery operation to assess the extent of disease and inform the decision regarding whether to proceed with maximal debulking surgery by robotic or open surgery. The surgery will then proceed by one of these two routes. If there is disease that cannot be removed robotically after starting by this route but can be removed via an open incision the surgery will be converted to an open procedure if it is safe to do so. The aim of the surgery whether by robotic or open is to remove all visible disease safely. The study also involves questionnaires relating to recovery and quality of life. As part of the study the researchers will collect data regarding surgical findings, operating parameters and recovery including patient questionnaires and an audio-recorded interview looking at recovery time, complications, quality of life and experience of being in the study.

The researchers will also record the operating time and interval between surgery and starting chemotherapy. The questionnaires will be done before and after surgery. The final questionnaire will be done at the 3-month review. After this point there will be no further questionnaires but the researchers will record how whether there is any sign of recurrence. This is the same as they do for all patients to monitor treatment and will not require anything except attending usual follow up appointments.

MIRRORS Indocyanine Green (ICG) dye study
Women recruited for the study who are not allergic to iodine ICG dye and do not have severe kidney problems can be included. Participants do not have to be involved in this part of the study to be enrolled in the main MIRRORS study.

ICG is an intravenous fluorescent dye used in medical diagnostics. In the Gynaecological oncology department it is currently used to assess lymph nodes. It is also given through a drip for angiography in ophthalmology to look for new blood vessel formation in the back of the eye in age-related macular degeneration. Peritoneal inflammation (peritoneum is the tissue that lines the abdominal cavity) and cancer also causes this abnormal formation of new blood vessels. As part of this study the researchers are investigating the use of ICG fluorescence dye to look at the blood vessel pattern in the peritoneum. They are looking to see what the blood vessel pattern is around tumour deposits. Following injection of ICG, the peritoneal surfaces of the abdominal and pelvic cavity will be searched under normal white light in order to identify any tumour deposits. The abdominal cavity will then be examined under near-infrared light which makes the dye fluoresce, looking for areas of abnormal vasculature (blood vessels) and peritoneal metastases (cancer that has spread). All visibly abnormal areas will be removed and sent to histopathology as standard surgical practice. The ICG will not be used to guide where

biopsies are taken or tissue is removed, only clinically abnormal tissue or lymph nodes will be removed regardless of the effect of the ICG on them. The researchers will observe and record whether or not any lesions that are removed fluoresced under near-infrared light.

Surgery for ovarian cancer involves surgically removing all visible tumour. All tissue samples that are removed are sent to the Histology laboratory where they are used to assess the tumour's spread and response to chemotherapy. As part of the study the researchers are collecting a small piece of this tissue to compare the differences between tumours requiring open surgery and those who are able to have surgery robotically. Tumour characteristics may relate to how aggressive the tumour is or how well it responds to chemotherapy. One factor in particular the researchers would like to explore is the immune environment of the tumour. This is because there is evidence that tumours with increased numbers of infiltrating lymphocytes (white blood cells that fight infections and cancer) have a better prognosis. The findings will be correlated with anonymised clinical information.

What are the possible benefits and risks of participating?
As part of this study participants will be offered robotic minimally invasive surgery for their interval debulking procedure with or without the addition of the use of the ICG dye (if they choose to be part of this part of the study). This is not routinely available outside of the study. Having surgery by a minimally invasive route may lead to a quicker recovery. On the other hand it may not. Participants will be contributing to ovarian cancer research with the aim to not only treat ovarian cancer but improve the quality of life of women living with ovarian cancer.

Both open and robotic surgery carry risks of surgical complications and each approach requires a general anaesthetic. Complications of this type of surgery include the risk of infections in the urine, wound or chest, injury to other organs such as the bowel, bladder or ureters. Breathing, heart and other cardiovascular problems can occur, either related directly or indirectly to surgery (due to underlying medical conditions being exacerbated by the stress of surgery). This would include heart attacks, stroke and heart rhythm problems (e.g. palpitations) and clots in the legs or lungs. Due to the nature of advanced ovarian cancer, bowel surgery can be necessary either to remove tumour deposits or due to extensive adhesions (bowel stuck together). Separation of bowel that is stuck together can result in injury requiring repair. Occasionally the formation of a stoma is needed (an opening on the abdomen connected to one end of the small or large bowel over which a bag is worn on the abdomen). This stoma may be temporary or permanent. Severe anaesthetic complications including allergic reactions can result in a longer hospital stay, as can complications such as wound breakdown and hernias. It is possible for injuries to present late or go unnoticed at the time of surgery possibly because the injury is very small or has occurred outside the surgical field of view. Very rarely complications occur that require another operation for example if bleeding or infection in the abdomen develops. There is a very small risk of a severe allergic reaction to ICG dye. This affects fewer than 1 in every 10,000 patients. Such reactions would most likely occur while being closely monitored in the hospital.

Where is the study run from?
Royal Surrey NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
April 2019 to November 2021

Who is funding the study?
GRACE (Gynae-oncology Research and Clinical Excellence) (UK)

Who is the main contact?
Miss Christina Uwins
Christina.Uwins@nhs.net

Study website
https://grace-charity.org.uk/research/mirrors-study/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
261933

ClinicalTrials.gov number
NCT04402333

Secondary identifying numbers
CPMS 44849, IRAS 261933

Study information

Scientific Title
Minimally invasive robotic surgery, role in optimal debulking ovarian cancer, recovery and survival

Acronym
MIRRORS

Study objectives
In selected cases of ovarian cancer, following neoadjuvant chemotherapy, minimally invasive robotic surgery provides maximal debulking surgery and improved patient outcomes.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/04/2020, London - Riverside Research Ethics Committee (Level 3 Block B, Whitefriars, Lewins Mead, Bristol, BS1 2NT, UK; +44 (0)207 104 8340; riverside.rec@hra.nhs.uk), REC ref: 20/LO/0262

Study design
Non-randomized; Both; Design type: Treatment, Management of Care, Surgery, Cohort study

Primary study design
Interventional

Secondary study design
Non randomised study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
https://grace-charity.org.uk/research/mirrors-study/

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

Interventions

The researchers are looking to find out in women with advanced ovarian cancer who have received chemotherapy before surgery whether robotic surgery is able to remove as much tumour as open surgery with improved patient outcomes. Suitable participants will be identified during the multidisciplinary team meeting (MDT). To be eligible for the study women will need to have received three cycles of chemotherapy, be medically fit for surgery, have a pelvic mass ≤8 cm and no disease that requires open surgery (such as a requirement for liver surgery).

All screened patients will have the following anonymised basic information collected:
1. Date of birth/age
2. Ethnicity
3. Reason not eligible
4. Reason for declining if eligible but declined

After initial contact by telephone, the participant's information sheet, consent form, study questionnaires and an introductory letter will be sent with the clinic invitation letter prior to potential participants attending clinic. The study will then be talked through in clinic and consent confirmed. Consent for surgical procedures is a two-stage process where consent is taken in the clinic following discussion of the options, the patient then has their consent confirmed on the morning of surgery. Participants are free to withdraw at any time from the trial without giving reasons and without prejudicing their further treatment.

After signing the MIRRORS consent form participants will be invited to complete baseline questionnaires at this same appointment.

Participants identified as suitable and willing to have robotic interval debulking surgery as part of the study will be consented for both open surgery and robotic-assisted laparosopic surgery.

All participants who join the study are free to change their mind and withdraw at any time during the study. The decision will not affect their care in any way. The anonymised data that has been collected up to the point of withdrawing can still be used in the final analysis of the results. However, if they do not want this to happen the researchers will destroy the data. Participants GP will be informed that they are taking part in the study and consent for informing the GP forms part of the study consent form.

At the time of surgery, the standard practice for advanced ovarian cancer would be to proceed with an extended vertical cut on the abdomen to remove as much tumour as possible. Participants who have agreed to be in the study will start the surgery with an initial assessment with a camera inserted through the belly button. This visual assessment will be used to determine whether it is feasible to proceed with surgery robotically or whether full debulking surgery to zero macroscopic residual disease would be best carried out through an open surgical approach. If an open surgical approach is considered the optimum treatment for the patient and they have consented for this, then this will be done. If there is disease that cannot be removed robotically after starting by this route, but can be removed via an open incision the surgery will be converted to an open procedure if it is safe to do so. If there are any complications, we may also need to convert to open surgery. The aim of the surgery whether by robotic or open is to remove all visible disease safely.

Following surgery, a contrast CT of the chest abdomen and pelvis will be done to confirm current disease status. This is the current standard practice.

The study will also involve questionnaires relating to recovery and quality of life and pain (These are established validated questionnaires), two are from the European Organisation for Research

and Treatment of Cancer "EORTC QLQ C30" & "EORTC QLQ OV28" Another is the Hospital Anxiety and Depression Scale which was originally developed by Zigmond and Snaith in 1983 and is used to assess levels of anxiety and depression that a person is experiencing. Lastly the researchers will be using a simple 11-point pain scale (0-10) to assess participants' pain.

These questionnaires will be done at baseline (provided at the post MDT visit) Day 1 post-surgery, 3-4 weeks post-surgery and at 3 months post-surgery. Lastly, a qualitative interview will be conducted 3-6 weeks post-surgery ideally at the first follow up visit (3-4 weeks post-surgery). The aim of this interview is to provide an insight into women's experiences of taking part in the study.

Study participants will be followed up during their normal scheduled appointment times as per the standard care. There will be no additional screening bloods or investigations beyond that already done as part of the surgical workup. If necessary questionnaires can be completed by telephone (included in the study consent form).

After the 3-month follow-up appointment participants will not need to fill in any more questionnaires but the researchers will continue to record how they are doing and whether there is any sign of recurrence. This is the same as they do for all of our patients to monitor treatment and will not require participants to do anything except attend their usual follow up appointments.

There is no comparison arm to the study. The researchers will however follow-up study participants who following diagnostic laparoscopy are found to require open surgery as well as those who have robotic interval debulking surgery. This is to ensure that the intervention (robotic interval debulking surgery) does not have a worse impact on the participant's recovery and quality of life compared to standard treatment.

Intervention Type
Procedure/Surgery

Primary outcome measure
Recruitment: number of patients consented compared to the number identified by multidisciplinary team as eligible for inclusion in the study expressed as a percentage. Assessed at 1 year (recruitment period)

Secondary outcome measures
1. Quality of life following surgery assessed using European Organisation for Research and Treatment of Cancer (EORTC) validated quality of life questionnaire (QLQ) for ovarian cancer (QLQ-C30/QLQ-OV28) at baseline, Day 1 post op, 3-4 weeks post op, 3months +/- 7 days post op
2. Mental wellbeing assessed using hospital anxiety and depression scale (HADS) at baseline, Day 1 post op, 3-4 weeks post op, 3months +/- 7 days post op
3. Pain assessed using a numeric rating scale (NRS11) at baseline, Day 1 post op, 3-4 weeks post op, 3months +/- 7 days post op
4. Surgical complications from quarterly reports submitted to sponsor assessed at close of trial - 15 months +/- 7 days (recruitment + follow up period)
5. Rate of conversion to open surgery (percentage of patients converted to open surgery after being deemed suitable for robotic interval debulking surgery following initial diagnostic laparoscopy), assessed at 1 year 3 months (once the last recruited patient has undergone surgery)
6. Robotic interval debulking maximal macroscopic debulking rate (R=0) (percentage of patients

undergoing robotic interval debulking surgery who achieve maximal macroscopic debulking i.e. no macroscopic residual disease present [R=0 rate]), assessed at 1 year 3 months (once last recruited patient has undergone surgery)
7. Overall survival, measured in months from the date of surgery, assessed at close of trial - 15 months +/- 7 days (recruitment + follow up period), reassessed at 5 years to a maximum of 10 years
8. Progression-free survival, measured in months from the date of surgery until the date of first documented progression, assessed at close of trial - 15 months +/- 7 days (recruitment + follow up period) reassessed at 5 years to a maximum of 10 years
9. Cost of robotic minimally invasive interval debulking surgery to the hospital compared to a similar open procedure measured in British Pounds (GBP), assessed at close of trial - 15 months +/- 7 days (recruitment + follow up period)

Overall study start date
03/04/2019

Completion date
03/11/2021

Eligibility

Key inclusion criteria
1. Adult women ≥18 years with stage III and IV ovarian cancer undergoing neoadjuvant chemotherapy
2. Considered suitable for IDS
3. ≤8 cm pelvic mass
4. Open surgery not required for other surgical speciality intervention

MIRRORS ICG inclusion criteria - same as above

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Female

Target number of participants
Planned Sample Size: 20; UK Sample Size: 20

Total final enrolment
23

Key exclusion criteria

1. Extensive disease requiring liver and upper gastro-intestinal surgical support will exclude patients if an open surgical approach is considered necessary
2. Lacking capacity to the extent they are unable to understand or complete trial documentation /questionnaires

MIRRORS ICG exclusion criteria:
Severe renal insufficiency GFR <55 ml/min, known allergy to iodine or ICG and hyperthyroidism

Date of first enrolment
26/06/2020

Date of final enrolment
25/06/2021

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Royal Surrey County Hospital NHS Foundation Trust
Egerton Road
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GU2 7XX

Sponsor information

Organisation
Royal Surrey County Hospital NHS Foundation Trust

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
http://www.royalsurrey.nhs.uk/

ROR
https://ror.org/050bd8661

Funder(s)

Funder type
Charity

Funder Name
GRACE (Gynae-oncology Research And Clinical Excellence)

Results and Publications

Publication and dissemination plan
1. The study protocol is currently being prepared for publication from the original document provided to sponsors
2. Patient information leaflet and study pathway can be found at https://grace-charity.org.uk/research/mirrors-study/
3. Planned publication in a high-impact peer-reviewed journal and presentation at an international conference planned around 1 year after the trial end date

Intention to publish date
03/11/2023

Individual participant data (IPD) sharing plan
The datasets generated during from this current study will be available upon request from Miss Christina Uwins (Christina.Uwins@nhs.net) as raw anonymised data following the publication of the findings and upon reasonable request for up to 5 years following completion of the study. Participants have given their consent for the information collected from this study to be used to support other research in the future and to be shared anonymously with other researchers.

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Plain English results			05/07/2023	No	Yes