INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0189 PRINCIPAL INVESTIGATOR: Udo Rudloff, M.D., PhD

STUDY TITLE: Prospective Randomized Trial Comparing Gastrectomy, Metastasectomy plus Systemic Therapy versus Systemic Therapy Alone: GYMSSA Trial

Continuing Review Approved by the IRB on 02/27/12
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Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

Gastric Cancer (stomach cancer) is a rare cancer. In most cases, by the time it has been diagnosed, it has spread to other organs in the body (metastasized) and the chance of a cure is very small. The standard treatment for gastric cancer is a combination of chemotherapy drugs. In this study, we want to see if removing all of the tumors first and then giving chemotherapy slows the growth of the cancer better than giving chemotherapy alone. In addition, we want to know how participants in each group feel during treatment; how well they are able to do their usual activities and how they rate their health. In order to gather this information, all participants will be asked to complete quality of life (QOL) questionnaires designed to show how people feel at the beginning of the study and about every 4 months during the study.

Why are you being asked to take part in this study?

You have cancer of the stomach which has spread to a few other organs in your body. Based on your CT scans, we think that we could remove all of your tumors. You have met all of the eligibility criteria for this study and so we feel that this procedure would be safe for you.

How many people will take part in this Study?

Approximately 136 people with gastric cancer will participate in this study.

Description of Research Study

This study is a randomized study; participants will be assigned to 2 different groups by chance (like flipping a coin). Half of the participants will be assigned to have surgery first and then chemotherapy; the other half will be assigned to have chemotherapy alone. This study has several stages as shown in the table below.

Stage	Timeframe	Location	Events
Work up	1-2 weeks	Inpatient and out patient	Scans, x-rays, labs, laparoscopy, QOL questionnaire, other tests as needed
Randomization	Following laparoscopy		
Surgery and recovery {for patients randomized to receive surgery + chemo}	4-16 weeks	In-patient, ICU and out-patient	Number of days in the hospital and length of recovery will depend on the size and location of tumors
Chemotherapy – will begin either within 2 weeks of randomization {chemo only arm} or 6-8 weeks following surgery {surgery + chemo group}.	24 weeks	NIH Clinical Center Day Hospital or home oncology clinic	Physician visit, chemotherapy, labs every 2 weeks. Scans every 8 weeks, QOL questionnaire every 16 weeks
Follow up	Every 3 months for 2 years, then every 6 months for 3 years then yearly thereafter	NIH Clinical Center as possible	Includes physician visit, labs, scans and QOL questionnaires.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for 6 months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- Abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

What will happen if you take part in this research study?

Before you begin the study

Once we have determined that it is safe for you to participate in this study, you will have a laparoscopy. This is a minor surgical procedure that uses a laparoscope, inserted through the abdominal wall, to examine the inside of the abdomen. A laparoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue to be checked under a microscope for signs of disease. The laparoscopy is to see how much tumor you have in your abdomen. If you have too much disease, you will not be able to participate in the study.

After we have the results of the laparoscopy, you will be randomized to either receive surgery followed by chemotherapy or chemotherapy alone.

During the study

Surgery

If you are randomized to the surgery + chemotherapy group:

In order to remove all of the tumors in your abdomen, you will need to have a **major** operation. This will include removing the tumor as well as a large part of your stomach. If you have tumors in your liver, the tumors and some of the surrounding normal tissue will be removed, if you have tumors on other organs they will be removed along with some of the normal surrounding tissue. If you have tumors in your peritoneum (the thin film of tissue that covers all of your abdominal organs) this will be removed and you will undergo a procedure called Continuous Hyperthermic Peritoneal Perfusion (CHPP) while you are in the operating room (see below).

After the operation you will be admitted to the Intensive Care Unit (ICU) where you will be monitored closely for 1-4 days. As with any major operation, you may have a breathing tube and be connected to a breathing machine for 1-2 days following the operation. You will have a tube in your stomach, a catheter (tube) in your bladder and several IVs during this period. As soon as you are able, you will be helped to get out of bed, to cough and take deep breaths and to walk. Once your bowel function has returned to normal, you will be allowed to eat – this usually takes 4-7 days.

When your condition is stable, you will be transferred to the regular patient care unit until you are ready to be discharged to home, usually 7-21 days following the operation. Throughout your hospitalization, you will receive pain medications, IV fluids, antibiotics, and blood transfusions as necessary.

CHPP (for patients with tumor in the peritoneum only)

Near the end of the operation, after the tumors have been removed, two catheters (or thin tubes) will be put in your abdomen. You will receive 3 chemotherapy drugs, 5-FU (also called 5-fluorouracil), leucovorin (LV), and oxaliplatin. The 5-FU and LV will be injected into your vein. The oxaliplatin will be diluted in a heated solution and will be given to you through one catheter and drained out through another, bathing the inside of your abdomen with oxaliplatin. This chemotherapy solution will be washed through your abdomen over 35 minutes at a temperature of about 108.6 degrees, which is 10 degrees above your normal body temperature. After your abdomen has been bathed for 90 minutes, the chemotherapy will be rinsed out and the catheters will be removed. During this procedure we will carefully monitor your

temperature. If your body temperature goes up during the procedure, we will use cooling blankets and ice packs to keep your body temperature normal.

If you have small tumors in your lung which can be removed, you will have surgery to remove the tumors after you recover from the abdominal surgery. Your physician and the Thoracic surgeon will explain the surgery to you and you will be given a separate consent to sign. After the operation to remove the tumors in your lung, you will be admitted to the ICU and then transferred to the regular patient care unit just as described above. You will be hospitalized for about 1-3 weeks depending on the location of your tumors.

Chemotherapy

If you are randomized to the chemotherapy group, you will begin treatment within 2 weeks following the laparoscopy. If you are randomized to the surgery group, you will receive chemotherapy about 6-16 weeks following the operation(s). The drugs are given in your vein over 2 days every 2 weeks (one cycle) for 12 cycles (about 6 months). You may receive the chemotherapy in the day hospital here at the NIH Clinical Center or at home with your referring oncologist. While you are receiving the drugs, you will need to have your blood drawn about once a week (more if you are having certain side effects), and you will need to see your doctor about every 2 weeks, right before the chemotherapy drugs are given, and you will have scans about every 8 weeks while you are on the chemotherapy. You will also be asked to keep a diary of all of the side effects you may have.

You will receive 4 chemotherapy drugs, 5-Fluorouracil (5-FU), leucovorin (LV), oxaliplatin, and irinotecan. These drugs are commonly given together for patients with colon cancer who have metastases in the liver and peritoneum and they have been effective in shrinking the tumors. The main side effects of these drugs when given together include, diarrhea, which can be severe, ulceration of the mouth, low blood counts, sensitivity to cold in the hands, feet and mouth, allergic reaction and fatigue. Your oncologist and chemotherapy nurse will review all of the side effects with you and discuss additional medications you may receive to help prevent or control the side effects. It is also possible that you may lose your fertility following this treatment. If your side effects are severe or your tumors grow while you are taking the chemotherapy, the drugs will be stopped and your physician will discuss additional treatment options with you.

Additional side effects are listed in the table in the Risks or Discomforts section.

Follow up

Once you have completed surgery and/or chemotherapy you will return to the NIH Clinical Center for follow up about every 3 months for 2 years, then every 6 months for 3 years and yearly thereafter. If you are not able to return to the NIH Clinical Center, you will be contacted by phone.

Health Related Quality of Life Forms (HRQOL)

At several points during this study, we will ask you to complete 2 health related quality of life questionnaires. This will take about 15 minutes and we will ask that you complete the questionnaires by yourself. We will ask you to do this before you have your laparoscopy and then every 16 weeks for the first 2 years, then every 6 months for the next three years and yearly thereafter. You can decide not to complete the questionnaires at any point and this will not affect your treatment.

What other choices do I have if I do not take part in this study?

Instead of being in this study, you have these options**:**

- Getting chemotherapy or surgery for your cancer without being in a study
- Taking part in another experimental study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

What side effects or risks can I expect from being in this study?

As described above, the main side effects of the chemotherapy include, diarrhea, which can be severe, ulceration of the mouth, low blood counts, sensitivity to cold in the hands, feet and mouth, allergic reaction, fatigue and loss of fertility. These risks are listed in the tables below.

The operation to remove the gastric tumor and any other tumors throughout your abdomen is likely to be quite extensive and may incorporate CHPP as well. The risks from this operation and general anesthesia include:

Likely

- Pain
- Temporary slowing or stopping of bowel function, known as an ileus. This could take several days to resolve and may require that the tube in your nose that drains your stomach stay in place longer
- Laboratory studies of the liver, particularly bilirubin may be elevated. This may be due to handling or removing part of the liver during surgery or it may be as a result of one of the chemotherapy drugs. This usually does not cause any symptoms and resolves in a few days.
- This surgery may also cause changes in your bowel pattern, either constipation or diarrhea. Fluid may develop in your abdomen, known as ascites. This may go away on its own, or may need to be drained if it becomes too uncomfortable.

Less Likely

- Leakage of bowel contents may occur from an area where the bowel was sewn together or from any area of your bowel due to the effects of the chemotherapy, the increased temperature during CHPP, or from the surgery itself. This may cause an infection in your abdomen that may be life threatening and may require an additional operation to repair the leak. Rarely this will cause openings to form from the bowel through the skin or into the abdomen (fistulas) that may require you to stay in the hospital longer, may require antibiotics, or require a second operation to repair.
- The chemotherapy in your abdomen may also cause irritation to structures surrounding the abdomen, particularly the lining of your lungs. This irritation may result in a condition called "pleural effusion" which means that the lung lining is irritated. This may cause pain and some fluid may collect between the lining and the lung. The fluid usually resolves by itself, but on occasion it may need to be drained with a needle and syringe, if it is causing difficulty breathing.
- Bleeding which might require transfusions or a second operation to correct
- Blood clots that have the risk of moving to the lungs causing difficulty breathing
- Infection in the abdomen, where the incision was made, or in the lungs (pneumonia). All types of infections would be treated with antibiotics.

Rare but serious:

- Heart failure, lung failure, kidney failure, liver failure, blood clots in your extremities or lungs and stroke This may require treatment in the ICU including need for a breathing machine, dialysis, and blood pressure medications.
- Damage to the various organs of your body which may cause your death.

Risks: Oxalipaltin + 5-FU/LV		
Likely – these may be mild to severe	Less Likely – these may be mild to severe	Rare but Serious
• Tingling of the mouth, lips, hands and feet - Sensitivity to cold in the mouth, hands and feet • Nausea, vomiting, diarrhea, loss of appetite, weight loss, constipation, abdominal pain • Ulceration of the mouth • Decrease in blood counts including white blood cells (which increase the risk of infection), red cells (which may cause fatigue and weakness) and platelets (which increase the risk of bleeding). • Tiredness, insomnia, muscle aches, dizziness • Changes in taste and smell • Cough, shortness of breath	• Hair loss • Tumor lysis syndrome (A change in certain chemicals in the blood, which may cause damage to organs, including the kidneys, heart, and liver.) • Flushing, runny nose, eye irritation, headache, fever • Rash – particularly on the hands and feet • Changes in lab values that cause no symptoms and may or may not require treatment • Hiccups • Mood changes	• Low blood pressure • Blood clots • Severe allergic reaction • Death

Risks: Irinotecan + 5-FU/LV		
Likely – these may be mild to severe	Less Likely – these may be mild to severe	Rare but Serious
• Diarrhea, this can be mild to severe and can occur immediately following the drug or several days later • Runny nose, tearing eyes, abdominal cramping, increased salivation • Nausea, vomiting, constipation, loss of appetite, weight loss • Decrease in blood counts including white blood cells (which increase the risk of infection), red cells (which may cause fatigue and weakness) and platelets (which increase the risk of bleeding). • Tiredness, insomnia, fever, muscle aches, pain, dizziness • Cough, shortness of breath • Changes in taste and smell • Hair loss	• Rash – particularly on the hands and feet • Changes in lab values that cause no symptoms and may or may not require treatment	• Low blood pressure • Blood clots • Death

Potential Benefits of Participation

Are there benefits to taking part in this study?

It is possible that we may be able to remove all of your tumors and that the chemotherapy will keep them from returning but we don't know if this will happen.
The aim of this study is to see if undergoing surgery before chemotherapy will keep people cancer free longer than chemotherapy alone. We don't know if this is the case. We hope that you will get personal medical benefit from taking part in this study, but we cannot be certain. Because there is not much information about this treatment, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at the NIH Clinical Center at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH).
- If you receive chemotherapy from your local oncologist, that treatment will be billed to your insurance company and you will be responsible for all co-payments and other charges not covered by your insurance company.

- Medicines that are not part of the study treatment and are not given at the Clinical Center will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:
- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. The following link contains details on this process *http://ethics.od.nih.gov/procedures/COI-Protocol-Review-Guide.pdf*. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

OTHER PERTINENT INFORMATION

1. **Confidentiality.** When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

   The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. **Policy Regarding Research-Related Injuries.** The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. **Payments.** The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. **Problems or Questions.** If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, **Udo Rudloff**, M.D., PhD, Building 10, Room **4-5950** Telephone: 301-496-3098.

   You may also call the Clinical Center Patient Representative at 301-496-2626.

5. **Consent Document.** Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:

A. Adult Patient's Consent

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study.

Signature of Adult Patient/Legal Representative Date

Print Name

B. Parent's Permission for Minor Patient.

I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study.

(Attach NIH 2514-2, Minor's Assent, if applicable.)

Signature of Parent(s)/Guardian Date

Print Name

C. Child's Verbal Assent (If Applicable)

The information in the above consent was described to my child and my child agrees to participate in the study.

Signature of Parent(s)/Guardian Date Print Name

THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM FEBRUARY 27, 2012 THROUGH FEBRUARY 26, 2013.

Signature of Investigator Date

Print Name

Signature of Witness Date

Print Name