INFORMED CONSENT FORM

UOC of Radiation Oncology Policlinico Universitario A. Gemelli IRCCS

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THUNDER 2: The use of imaging to define the best therapeutic approach in rectal cancer with MRI-guided radiation therapy

INFORMATION SHEET

Dear patient,

A medical-scientific research entitled "THUNDER 2: the use of imaging to define the best therapeutic approach in rectal cancer with MRI-guided radiotherapy" is planned in this University Hospital. This research is being conducted exclusively in this institution. In order to realise this research we need the cooperation and availability of people who, like you, meet the scientific requirements needed for the analysis to be carried out. However, before you make the decision to accept or decline to participate, please read this document carefully, taking as much time as necessary, and ask us for clarification if you do not understand or need further clarification. Furthermore, if you want, you can also ask your family or a doctor for advice before making your decision.

WHAT IS THE PURPOSE OF THE STUDY?

The general purpose of this study is to obtain an increase in the rate of complete response in patients with locally advanced rectal cancer undergoing chemoradiotherapy treatment. The principle is to personalize treatment, based on disease characteristics visualized by imaging obtained during treatment on MRIdian, a hybrid radiotherapy machine that take advantages of magnetic resonance images.
Using a volumetric reduction index during treatment, patients will be stratified into "patients with a high probability of complete response" and "patients with a low probability of complete response".
The first group will undergo conventional radio-chemotherapy treatment; for the second group, instead, a radiotherapy dose escalation at the site of disease will be considered through a simultaneous overdosage technique under the guidance of cine-MRI images (4-8 images per second).
This radiotherapy dose escalation is intended to increase the rate of complete responses in patients with locally advanced rectal cancer, reducing the risk of local recurrence and the rate of extensive surgery.

WHAT DOES YOUR PARTICIPATION IS THE STUDY IMPLY?

If you decide to participate in the study, the experimental design of this research requires that you receive the standard preoperative radiochemotherapy necessary for your condition. The therapy consists of administering radiation therapy at a total dose of 55Gy over 5 weeks, every day except for Saturdays and Sundays, combined with the administration of either an oral chemotherapy drug, capecitabine, or an infusion drug, 5-fluorouracil, for the duration of radiation therapy. The treatment will perform on MRIdian, which, as previously described, is a hybrid radiation therapy machine.
The innovation is, at the 10th fraction of treatment, the opportunity to perform dose escalation on the disease area alone will be considered, based on an evaluation of the acquired MRI images. The evaluation is intended to select a category of patients who could benefit from such dose escalation, as they have radioresistant disease.
You will be closely monitored during therapy for evaluation of any acute toxicities. At the end of chemo-radiotherapy treatment, after approximately 6-8 weeks, you will undergo a clinical-instrumental reassessment. At this point, if the response to treatment will be greater or complete, as happens in about

15% of cases, a new instrumental re-evaluation after 12-14 weeks will be setted. If instead the response to treatment will be partial, stable or disease progression surgery will be planned.
Overall the study will be conducted for 3 years and 63 patients will participate in this research. These 63 patients will be chosen from among all those affected by the same disease as you.
If you agree to participate in this study, you will undergo an initial examination to verify that your condition meets the criteria required by the study. During this visit (which may be performed by Prof. Maria Antonietta Gambacorta, Prof. Vincenzo Valentini, Dr. Giuditta Chiloiro, Dr. Barbara Corvari or Dr. Elisa Meldolesi) an objective examination, an evaluation of your general condition and an evaluation of your laboratory, endoscopic, biopsy and radiological tests will be performed. In addition, questionnaires will be administered to evaluate your quality of life. These visits will be repeated at the end of the radiochemotherapy treatment, at 6 weeks after the end of the radiochemotherapy, 1-2 months after surgery and then periodically as required by the frequency of follow-up (every 3 months for the first year, every 6 months up to 5 years and then annually).
You are requested to cooperate as follows:
1. In the period prior to treatment you have to undergo clinical and instrumental investigations necessary to characterize your disease as indicated by the Multidisciplinary Team and according to guidelines.
2. During the radiotherapy treatment you should avoid exposure to sunlight in the irradiated area, take the prescribed support therapies, follow the dietary instructions that will be given to you; you have to undergo the examinations and tests that will be indicated to you.
Participation in the trial does not entail any additional costs for you.

WHAT ARE THE RISKS OF PARTICIPATING IN THE STUDY?

Participation in the study may involve some risks related to the administration of a dose of radiotherapy higher than the standard treatment.
These possible side effects are divided into early and late toxicities. Early side effects, could occur during or within six months after radiochemotherapy treatment. The possible late side effects could occur six months after the end of radiochemotherapy treatment.
An increase in acute radiotherapy dose could cause an increase in the risk of altered blood values, skin toxicity on irradiated areas, especially perianal, a flare-up of hemorrhoidal pathology, rectorrhage, proctitis up to fistulisation, enteritis (abdominal pain, diarrhoea, flatulence), cystitis, urethritis, pelvic pain and in women vulvovaginitis.
Increased radiotherapy dose in chronic could cause increased risk of skin dystrophy, lymphedema, stress urinary incontinence, urethral stenosis and obstruction, chronic hemorrhagic cystitis, resting urinary incontinence, intestinal malabsorption, adhesions, chronic proctitis, fecal urgency, fecal incontinence, anal stenosis, chronic enterocolitis, worsening of the adherential picture, ulcers, fistulas or necrosis of the small intestine, sacroiliitis, sacral plexopathy, necrosis of the femoral heads, vaginal fistulas in women.
The facility and investigators are covered by an appropriate insurance policy for any damages that may result from the trial.
If data become available that may affect your willingness to continue participating in the study, you will be informed promptly.
If you are a woman of reproductive age, and you cannot exclude the possibility of pregnancy during the study, you should not participate in this trial because harmful effects to the embryo/fetus cannot be excluded.

WHAT ARE THE BENEFITS YOU MAY RECEIVE BY PARTICIPATING IN THE STUDY?

In inviting you to participate in this study, we inform you that you will receive a radiochemotherapy treatment that represents the standard for your stage of disease. The study aims to test if it is possible to identify, thanks to technology and advances in scientific research, a group of patients who can benefit from an

increase in the dose of radiotherapy on the disease, in order to maximize the rate of complete response to treatment. The information we will gain from this study, however, will help us to improve the treatment of patients who, like you, have locally advanced rectal neoplasia. You will also be notified of any new information that becomes available during the course of the study if it may affect your decision to continue participating in the study.

INVESTIGATIONS YOU WILL UNDERGO DURING THE STUDY

The study includes endoscopic examinations (rectoscopy and colonoscopy), radiological examinations (magnetic resonance imaging and computed tomography) and laboratory examinations (blood count, liver function, kidney function, coagulation study, tumor markers), which are routine for this type of treatment. You will also be asked to complete quality of life questionnaires before treatment and during scheduled follow-ups.

WHAT HAPPENS IF YOU DECIDE NOT TO PARTICIPATE IN THE STUDY

You are free to not participate in the study. In this case, you will receive all the standard therapies for your condition, without any penalty, and the doctors will continue to follow you with due care. If you do not agree to participate in this study, you will receive traditional treatment, i.e., combination external radiation therapy with concomitant chemotherapy, followed by surgery after a standard interval of 8-10 weeks. During the treatment, regardless of your decision to participate in the study, you will undergo the standard radiotherapy check-ups, hematological examinations and clinical examination, periodically. The clinical examinations you will undergo before, during, and at the end of treatment will not differ from those commonly performed for the type of disease you have.

WHAT HAPPENS IN CASE OF DAMAGE

This study is insured under Lloyd's policy no. A1202049545-LB. This policy provides a maximum damages of €1,000,000 per patient, with a limit of €7,500,000 per protocol.
The policy is exclusively operative for damages which have occurred no later than 36 months from the end of the trial for which a claim for compensation has been presented no later than the end of the trial.
The exceeding of the above limits and the previous restrictions do not however affect your right to seek compensation directly from the person responsible for the damage. By signing this informed consent you are not waiving any of your legal rights.
Before participating in this trial, if you have an insurance policy, you should check with your insurer that your participation will not affect it.

STUDY DISCONTINUATION

Your participation in this research program is completely voluntary and you may withdraw from the study at any time.
Similarly, the trial may be terminated if the physician determines that any unintended effects have occurred.

INFORMATION FOR FEMALE SUBJECTS OF CHILDBEARING AGE

If you are a woman of childbearing age, you should be aware that the standard radiochemotherapy treatment you will receive will lead to an early menopause. If you are a woman of childbearing age and think you may become pregnant during the trial, you should not undergo standard radiochemotherapy and therefore participate in this study because harmful effects on the conceived fetus cannot be excluded due to standard radiochemotherapy. If you still want to participate, you must undertake not to become pregnant during the trial period and, if you should still be fertile after treatment (highly unlikely event), for 5 years after the last dose of chemotherapy provided by the treatment you will undergo. In the unlikely event that you become pregnant after the chemotherapy, there may be a high risk of miscarriage and malformation of the fetus. If you become pregnant, you must inform the doctor in charge of the trial immediately. Therefore choose freely, based on the information above and your moral convictions, whether or not to participate in the trial that is proposed.

INFORMATION FOR MALE SUBJECTS WHO HAVE A SPOUSE/PARTNER OF CHILDBEARING AGE

If you are a man of childbearing age, you should be aware that the standard radiochemotherapy treatment you will receive may induce early hypogonadism. If you have a spouse/partner of childbearing age and think you may become pregnant during the trial, you should not participate in this study because the standard radiation chemotherapy treatment to which you will be subjected has been shown to have toxic effects on your sperm fluid and therefore on your sperm function and therefore on the fetus eventually conceived. We therefore urge you to inform your spouse/partner of this. If you still intend to participate, you must agree not to have your partner initiate a pregnancy during the trial period and for at least 5 years after taking the last administration of radio-chemotherapy treatment.

CONFIDENTIALITY OF PERSONAL DATA

Pursuant to Legislative Decree no. 196 of June 30, 2003 "Code for the protection of personal data", we inform you that your personal data will be collected and stored electronically and will be used exclusively for scientific research purposes, in an anonymous way.
You have the right to know what information will be stored and to update or modify erroneous data. Access to such data will be protected by the principal investigator. Regulatory authorities and medical personnel in charge of monitoring and verifying procedures will be able to inspect the archive. By signing the informed consent form, you are authorizing access to this data. The results of the study in which you participate may be published, but your identity will always remain confidential.

INFORMATION ABOUT STUDY RESULTS

If you request it, at the end of the study you may be informed about the results of the study in general and in particular those that concern you.

ADDITIONAL INFORMATION

If you agree, it may be helpful to inform your primary care physician of your participation in this trial to avoid interference with any other medications you may be prescribed and/or treatments you may be receiving.

For further information and communications during the study will be available the following staff Prof. Maria Antonietta Gambacorta, Prof. Vincenzo Valentini, Dr. Giuditta Chiloiro, Dr. Elisa Meldolesi and Dr. Barbara Corvari. These representatives will be available at the Radiotherapy Department of the Fondazione Policlinico Universitario A. Gemelli and can be reached by phone at 06-30154981 from Monday to Friday during working hours.

The protocol of the study that has been proposed to you has been drawn up in accordance with the Standards of Good Clinical Practice of the European Union and the current revision of the Declaration of Helsinki and

has been approved by the Ethics Committee of this structure. You can report any facts you deem appropriate to highlight, with regard to the trial that concerns you, to the Ethics Committee of this structure.

DECLARATION OF CONSENT

I, the undersigned: _____
declare that I have received from Dr. _____

full explanations regarding the request for participation in the experimental study in question, as reported in the information sheet attached hereto, a copy of which has been given to me beforehand.

I also declare that I have been able to discuss these explanations, to have asked all the questions I deemed necessary and have received satisfactory answers, as well as to have had the opportunity to inform me about the details of the study with a person of my choice.

I therefore freely agree to participate in the trial, having fully understood the meaning of the request and having understood the risks and benefits involved.

I have also been informed of my right to have free access to the documentation relating to the clinical-scientific trial and to the evaluation expressed by the Ethics Committee.

_____ _____

Date Patient's signature

Date Signature of the doctor who informed the patient

[In case the patient cannot read and/or sign].

I, the undersigned: _____

testify that Dr. _____

has exhaustively explained to Mr. _____

the characteristics of the experimental study in question, as reported in the information sheet attached hereto, and that the same, having had the opportunity to ask all the questions he considered necessary, has freely accepted to join the study.

_____

Date

_____

Signature of independent witness