Fluorescence Molecular Endoscopy and Molecular Fluorescence-guided Surgery of locally advanced rectal cancer using cetuximab-IRDye800CW: a single-center feasibility safety study.

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The study consists of and endoscopic part (1) and an intraoperative part (2).1) Endoscopic part: to determine the feasibility and safety of molecular fluorescence endoscopy using the fluorescent tracer cetuximab-IRDye800CW targeting the epidermal...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Interventional

Summary

ID

NL-OMON50556

Source
ToetsingOnline

Brief title
TRACT-II: Fluorescence Endoscopy and Surgery of Rectal Cancer

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal neoplasms malignant and unspecified

Synonym
Rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: KWF

Intervention

Keyword: Endoscopy, Fluorescence, Rectal cancer, Surgery

Outcome measures

Primary outcome

General main study parameter:

- Evaluating vital parameters, ECG, adverse events (AE), serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSAR) for safety assessment;

Main study parameter for endoscopy part:

- Macroscopic fluorescent signal levels (tumor-to-background ratio) observed by NIR fluorescence imaging correlated to histology between tumor and normal rectal tissue.

Main study parameter for surgical part:

- Macroscopic fluorescent signal levels (tumor-to-background ratio) observed by NIR fluorescence imaging correlated to histology for resection margins.

Secondary outcome

General secondary study parameters:

- Quantification of fluorescence through analyses of spectroscopy measurements;

- Fluorescence distribution on a microscopic level for assessment of tracer localization and distribution in normal rectal tissue and LARC.

Secondary study parameter for endoscopy part:

- Histological information and in vivo cellular detection of the fluorescent

tracer cetuximab-IRDye800CW (CLE; optionally);

Study description

Background summary

Treatment of patients with locally advanced rectal cancer (LARC) is multidisciplinary and consists of neoadjuvant chemoradiotherapy (nCRT) followed by surgical removal of the rectal tumor and potentially tumor positive lymph nodes.(1)
1) After surgery, in 15 to 27% of patients that received nCRT no tumor cells can be detected during histopathological examination.(2-7) In today*s clinical practice, all of these patients with a pathological complete response (pCR) are operated upon, with substantial morbidity and mortality. The 5-year survival is 83.3% for patients with a pCR, and 65.6% for those without pCR.(4) Response after nCRT is currently evaluated using magnetic resonance imaging (MRI). However, as MRI cannot differentiate between molecular characteristics of tissue, prediction of treatment response can be inaccurate. In patients with a potential cCR on MRI, additionally a high-definition white-light (HD-WL) endoscopy is performed with biopsies of the previous tumor location. If both MRI and HD-WL endoscopy confirm a potential cCR, patients can also be treated with a watch-and-wait approach, including frequent follow-up with HD-WL endoscopy and MRI.(8) This potentially prevents extensive surgical procedures for patients in which this is not required. However, MRI and HD-WL endoscopy often remain insufficient for identification of cCR. Therefore, novel imaging methods are needed for accurate prediction of treatment response in order to select patients. We believe fluorescence molecular endoscopy (FME) could be a promising technique for evaluation of treatment response.
2) During surgery, tumor-negative resection margins are of great prognostic value. Currently, surgeons rely on visual and tactile inspection for differentiation between malignant and healthy tissue. When in doubt, a frozen section can be obtained, which is time consuming and poses a high risk of sampling error. However, 14.7% of patients still have tumor-positive resection margins, increasing the risk of local recurrence and worsening outcome.(9) Therefore, there is a need for novel imaging techniques that can be used intraoperatively to improve margin assessment. We believe molecular fluorescence-guided surgery (MFGS) could be a promising technique for evaluation of resection margins.

Study objective

The study consists of and endoscopic part (1) and an intraoperative part (2).
1) Endoscopic part: to determine the feasibility and safety of molecular fluorescence endoscopy using the fluorescent tracer cetuximab-IRDye800CW targeting the epidermal growth factor receptor (EGFR) in patients with LARC.
2) Surgical part: to determine the feasibility and safety of molecular fluorescence-guided surgery using the fluorescent tracer cetuximab-IRDye800CW targeting EGFR for intraoperative evaluation of resection margins.

Study design

The study design is similar to the previously approved study for molecular fluorescence endoscopy of patients with LARC (NL43407.042.13). The current study is a non-randomized, non-blinded, prospective, single-center feasibility, safety study in patients with locally advanced rectal cancer that require surgical excision.15 patients will receive an intravenous injection of first 75 mg unlabeled cetuximab followed by 15 mg cetuximab-IRDye800CW. Furthermore, 3 patients will be included that will not receive the tracer.
1) For the endoscopy part patients will undergo a fluorescence endoscopy procedure that is scheduled after nCRT. This fluorescence endoscopy procedure will be performed in the operation theater previously to surgery after the patient is anesthetized or will be performed during restaging. Fluorescence signals of tumor and normal rectal tissue will be compared. Confocal laser endomicroscopy will optionally be used to obtain in vivo histological information. Multi-diameter single fiber reflectance, single fiber fluorescence (MDSFR-SFF) spectroscopy will be performed to quantify fluorescence signals on biopsies taken from tumor and normal tissue.
2) The surgical part of the study will be conducted during surgery, directly after the endoscopy. Surgery will be performed according to standard clinical care, decisions will not be based on fluorescence imaging. There will be at least two imaging moments: previously to resection of the tumor (tumor and lymph node detection) and after resection of the tumor (evaluation of the resection plane). MDSFR-SFF spectroscopy will be used to quantify fluorescence signals from the fresh surgical specimen.
Thereafter, extensive ex vivo analyses will be performed in order to correlate fluorescence signals with histology, and to gain more insight in tissue distribution of the tracer.

Intervention

Tracer administration: the EGFR-targeted fluorescent tracer cetuximab-IRDye800CW will be administered intravenously 3 days prior to the endoscopy/surgery procedure at the UMCG. Afterwards patients will be monitored for one hour by measurements of vital parameters (i.e. heartrate, blood pressure and temperature) and ECG for potential side-effects. Additionally, three patients will be included that won't receive the tracer as a negative control.

1) Endoscopy procedure: three days after tracer injection patients will undergo a sigmoidoscopy at the surgical theater after the patient is anesthetized or during restaging. First, the gastroenterologist will use routine high-definition white-light (HD-WL) inspection, followed by fluorescence inspection. Confocal laser endomicroscopy (CLE; optionally) may be performed to obtain in vivo histological information of suspicious lesions. Additionally, biopsies will be taken from the tumor (max. 8), from normal tissue (max. 4) and from additional fluorescence lesions when present (max 4). Quantification of fluorescence using spectroscopy will be performed either in vivo or ex vivo on biopsies, depending on the lesions.
2) Surgical procedure: the surgical procedure will be performed according to standard clinical care. Fluorescence inspection will be performed before resection of the tumor for detection of lymph nodes, and after resection for evaluation of the resection planes. MDSFR/SFF spectroscopy can be performed in vivo in case a positive resection margin is suspected based on fluorescence signals. Additionally, biopsies can be taken when fluorescence is detected in additional lesions and/or the resection plane.

Study burden and risks

Burden: Patients do not need to make extra visits to the UMCG if the tracer administration for both the endoscopy and surgery procedure can be scheduled on the day of admission for the surgery. If this is not possible due to logistics, we will try to schedule the tracer administration on the same day of outpatient clinic visits. However, if we cannot arrange this the patients will need to make an extra visit for the tracer administration which will take about 2-3 hours. The endoscopy will take place at the surgical theater after the patient is anesthetized or the procedures will be scheduled during restaging after nCRT which is part of the normal clinical workflow. Hereby we ensure that the endoscopy is not an extra burden for the patients. Prior to the endoscopy procedures, patient will have to undergo bowel cleaning by a phosphate enema.
Risks: The intravenous injection and the use of a cannula are known to carry a small risk of infection and hematoma. Theoretically, a possible SAE for injection of cetuximab-IRDye800CW could be an allergic and anaphylactic reaction. Therefore, tavegil, adrenalin and prednisone will always be present at the site of the injection. However, this is considered a very low risk and was not seen in previously injected patients. No preclinical or clinical study reported higher than grade 2 adverse events.
The study procedures will prolong a standard endoscopy with approximately 15 minutes, due to fluorescence imaging, confocal laser endomicroscopy and biopsies. The risks of the investigational endoscopy procedures are comparable to the minimal risks of a standard clinical sigmoidoscopy. These superficial biopsies that will be taken pose a small risk of bleeding. Most bleedings coagulate spontaneously. If not, which is very uncommon, the gastroenterologist has several tools to coagulate the small bleeding.
Next to this, the operation time may be prolonged with approximately 15

minutes, due to fluorescence imaging. Therefore, the time under general anesthesia will be prolonged. Additional biopsies from the resection surface or other fluorescence lesions can only be taken if judged as safe by both surgeons operating the patient. Therefore, no additional risk will be expected for the patient, since also the tracer is already administered to the patient because of the endoscopy procedure.
Benefit: Patients will have not benefit from this study directly. Surgery will be planned and performed according to standard clinical care. During surgery, no decisions will be made based on the fluorescence imaging. The benefit of this study will be the establishment of usefulness of cetuximab-IRDye800CW during endoscopy for prediction of treatment response and evaluation of resection margins for future patients.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

- Locally advanced rectal cancer, in multi-disciplinary colorectal oncology meeting agreed on long course neoadjuvant chemoradiotherapy, followed by surgical removal of the primary tumor;
- Age >= 18 years;
- Written informed consent.

Exclusion criteria

- Medical or psychiatric conditions that compromise the patient*s ability to give informed consent;
- Concurrent uncontrolled medical conditions;
- Pregnancy or breast feeding. A negative pregnancy test must be available for women of childbearing potential (i.e. premenopausal women with intact reproductive organs and women less than two years after menopause);
- Received an investigational drug within 30 days prior to the dose of cetuximab-IRDye800CW;
- History of infusion reactions to cetuximab or other monoclonal antibodies;
- Had within 6 months prior to enrollment: myocardial infarction, cerebrovascular accident, uncontrolled cardiac heart failure, significant liver disease, unstable angina pectoris;
- Patients receiving Class IA (quinidine, procainamide) or Class III (dofetilide, amiodarone, sotalol) antiarrhythmic agents;
- Evidence of QT prolongation on an ECG made within three months prior to inclusion (greater than 440 ms in males or greater than 450 ms in females);
- Magnesium, potassium and calcium lower than the lower limit of normal range, determined within three months prior to inclusion.

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	13-11-2020
Enrollment:	18
Type:	Actual

Medical products/devices used

Generic name:	A clinical therapeutic endoscope;a fluorescence fiber bundle to perform fluorescence endoscopy;a MDS
Registration:	Yes - CE outside intended use

Ethics review

Approved WMO Date:	10-04-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-06-2017
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	05-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-08-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	27-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2017-001229-42-NL
ClinicalTrials.gov	NCTnummervolgt.
CCMO	NL61406.042.17

Study results

Date completed:	31-12-2022
Actual enrolment:	13