Fluorescence Molecular Endoscopy of locally advanced esophageal carcinoma using bevacizumab-800CW to evaluate dose response after neoadjuvant chemoradiotherapy: a single-center feasibility study.

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

Summary

ID

NL-OMON48982

Source
ToetsingOnline

Brief title
Fluorescence endoscopy of esophageal carcinoma

Condition

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

Synonym
esophageal cancer, locally advanced esophageal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: SurgVision bv.,unrestricted research grant SurgVision

Intervention

Keyword: bevacizumab-800CW, Endoscopy, Fluorescence, Locally advanced esophageal cancer

Outcome measures

Primary outcome

The primary endpoints of this study include

• Discrimination of tumorous and non-tumorous tissue based on in vivo and ex

vivo fluorescence measurements from bevacizumab-800CW gained during

fluorescence endoscopy procedures;

• The safety of bevacizumab-800CW through monitoring vital signs, the injection

site and evaluating possible (severe) adverse events (SAE/AEs).

Secondary outcome

Secondary study parameters/endpoints

• The correlation of in vivo and ex vivo fluorescent signals to

histopathological analysis results.

• Quantification of fluorescent signal by MDSFR/SFF spectroscopy;

• The localization and distribution of bevacizumab-800CW fluorescent signal at

cell level observed in-vivo by CLE;

• Assessment of the (sub-)cellular distribution of bevacizumab-800CW by ex-vivo

fluorescence microscopy.

• The variation in fluorescence intensity between FME before and after nCRT.

• The correlation of in vivo and ex vivo OFDI measurements to histopathological analysis results.

• Differentiate between positive and negative lymphnodes based on SFR/SFF spectroscopy measurements

• The correlation of in vivo measurements to cytology results.

• Safety evaluation of (serious) adverse events and suspected unexpected serious adverse events related to SFR/SFF

• The most optimal dose of bevacizumab-800CW for fluorescence molecular endoscopy.

Other study parameters

• Patient characteristics (age, sex, history, morbidity, nCRT completed, treatment outcome, prognosis, basic vital signs before and after tracer administration).

• surgical specimen characteristics (according to standard reports from pathologists).

Study description

Background summary

For locally advanced esophageal cancer (EC), neoadjuvant chemoradiotherapy (nCRT) for 5 weeks followed by esophagectomy and lymphadenectomy, if necessary, is standard of care. It is reported that the pathological complete response (pCR) rate after nCRT ranges from 16% to 43%, with a median of 26.5% [1]. According to current clinical guidelines, patients who achieved pCR still go for surgery even though those patients who achieved pCR may not benefit from

surgery. Besides, about 50% of EC patients may have post-operative complications including pneumonia, anastomotic leakage, recurrent laryngeal nerve paralysis, which lead to low health-related quality of life (HQoL) [2,3]. The golden standard to test the pathological response is by pathological assessment of the surgical specimen and thus after surgery. Theoretically, if pCR after nCRT can be predicted accurately before surgery by advanced imaging techniques, patients could have a wait-and-see. The wait-and-see procedure includes regular follow-up and salvage surgery if recurrence is present. Therefore, molecular fluorescence endoscopy (FME) using near-infrared fluorescence (NIRF) tracer bevacizumab-800CW targeting vascular endothelial growth factor combined with high-definition white light (HD-WL) endoscopy is expected to be a promising technique to monitor pCR and fill the gap.

Study objective

The primary objective of this study is to determine the safety and feasibility of fluorescence molecular endoscopy using the fluorescent tracer bevacizumab-800CW for identification of pathological complete response after neoadjuvant chemoradiotherapy in patients with a locally advanced esophageal carcinoma.

Secondary Objectives
• To quantify fluorescence intensity in vivo and ex vivo with multi-diameter single-fiber reflectance, single-fiber fluorescence (MDSFR-SFF) spectroscopy;
• To correlate and validate both the in vivo and ex vivo measured fluorescence signals with histopathological analysis and IHC staining;
• To validate the (sub)-cellular location of fluorescent signals obtained during FME with Confocal laser endomicroscopy (CLE);
• To assess the (sub)-cellular location of bevacizumab-800CW by ex vivo fluorescence microscopy;
• To compare the fluorescence intensity and tumor-to-background ratio (TBR) of the fluorescent tracer bevacizumab-800CW before and after nCRT;
• To correlate in vivo and ex vivo Optical Frequency Domain Imaging (OFDI) images to histopathological analysis;
• Validation of Single fiber reflection / single fiber fluorescence (SFR/SFF) spectroscopy to distinguish between positive and negative lymph nodes;
• Correlation of SFR/SFF spectroscopy measurements to cytology results.
• The safety of using SFR/SFF spectroscopy during ultrasound-guided FNA by monitoring (serious) adverse events related to this measurement.
• To determine the most optimal dose of bevacizumab-800CW for fluorescence molecular endoscopy.

Study design

This current study is a non-randomized, non-blinded, prospective and single-center feasibility study. Thirty patients previously diagnosed with a

locally advanced EAC scheduled to undergo neoadjuvant chemoradiotherapy followed by surgery in the University Medical Center Groningen (UMCG) will be included in this study.

For this study, patients will undergo generally two endoscopic procedures at different time-points: (1) before the start of nCRT, which is optional for included patients and (2) after nCRT but before surgery as part of the normal clinical workflow. The second endoscopy will be arranged on the day of admission.

During the standard clinical endoscopie, HD-WL and EUS will be used to identify and stage the cancer. Afterwards, fluorescence molecular endoscopy is performed, followed by MDSFR/spectroscpie measurements on both fluorescent and normal tissue and OFDI imaging of the esophagus and finally confocal laser endomicroscopie (CLE). All fiberbundels or probes can be inserted through the working channel of the clinical endoscope.
Besides the endoscopic measurements, also fluorescent measurements will be performed on the resected surgical specimen.

An interim analysis will be performed after the first 5 patiënts to evaluate the primary endpoints before continuing the study.

NB. Patients enrolled in our clinical trial may also be enrolled in the PRIDE study.
The PRIDE study (NL62881.041.17) is an ongoing multicenter observational study directed by the UMCU. The primary objective is to evaluate pCR after nCRT in locally advanced esophageal cancer, by integrating magnetic resonance imaging (MRI) in conjunction with combined 18F-fluorodeoxyglucose positron emission tomography and computed tomography (18F-FDG PET-CT) scans acquired prior to, during and after administration of nCRT.

Intervention

Patients will undergo optimally two fluorescence endoscopies: before and after nCRT.
The patients involved will receive an intravenous administration of bevacizumab-800CW at the dosage of 4.5mg three days before the endoscopy procedure. Vital signs, such as heart rate, blood pressure, temperature and respiratory rate will be measured before injection, directly after injection and an hour after injection

Endoscopy procedure
Both endoscopies will be performed by dedicated endoscopists. The endoscopy will start with HD-WL endoscopy to focus on the lesion, followed by inserting different fibers through the working channel of the clinical endoscope, FME and CLE will be conducted to observe the fluorescence signals macroscopically (FME) and, microscopically (CLE). MDSFR-SFF spectroscopy will be conducted to

quantify the fluorescence signals in vivo and ex vivo. An OFDI catheter will be introduced to perform optical frequency domain imaging (OFDI). Subsequently, EUS is performed. If fine needle aspiration (FNA) biopsy is taken, SFR/SFF spectroscopy measurements will be performed on the lymph nodes.
In addition, biopsies will be taken during the endoscopy procedure. A maximum of 16 biopsies will be taken in order to directly correlate fluorescence with histology: 8 from the tumor, at most 4 from normal tissue and 4 from additional fluorescence lesions when present.

Study burden and risks

Time investment
Two extra visits to UMCG are needed for patients involved in this study. The extra visits include the first and the second tracer administration which takes about two hours each time. The first endoscopy will be planned during a standard clinical gastroscopy and the second during patient submission for the surgery.

Risks
The administration risks of bevacizumab-800CW are reported in the IMPD (version 5.0, Jan. 2018, section 2.4, page 44). No adverse events were reported from previous administrations with bevacizumab-800CW with more than 120 patients included. Due to fluorescence imaging (FME+ MDSFR/SFF+ CLE) and OCT, the endoscopy will be prolonged for 20 to 30 minutes. As the fiber of FME or MDSFR/SFF, SFR/SFF, OCT, CLE or OCT can be inserted through the working channel of HD-WL endoscope, the risks of fluorescence imaging is comparable to HD-WL endoscopy. The biopsy procedure may cause some bleeding which often can be treated by the gastroenterologist. The intravenous injection and the use of a cannula are known to carry a small risk of infection and hematoma.

Benefit
There is no direct diagnostic or treatment benefit for the patients as all procedures are processed following standard clinical guidance. No decisions according to clinical care will be based on study results.

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 esophageal carcinoma (cT1b-4a N0-3 M0) in multi-disciplinary esophageal oncology meeting agreed on long course neoadjuvant chemoradiotherapy, followed by esophagectomy;
- Age >= 18 years;
- Written informed consent.

Exclusion criteria

- Patients with psychological diseases or medical issues who are not able to sign informed consent form;
• 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);
• Irradical endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of primary tumor prior to start of neoadjuvant chemoradiotherapy
• Received a different investigational drug within 30 days prior to the dose of bevacizumab-800CW;
• History of infusion reactions to bevacizumab or other monoclonal antibodies;

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-11-2018
Enrollment:	41
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	08-05-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-08-2018
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-12-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-02-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	29-07-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-08-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-09-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	10-04-2020
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	EUCTR2018-001580-23-NL
ClinicalTrials.gov	NCT03558724
CCMO	NL65856.042.18

Study results

Date completed:	17-10-2022
Actual enrolment:	25