A pilot study to assess the safety and feasibility of fluorescent sentinel lymph node identification in colon carcinoma using submucosal bevacizumab-800CW

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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-OMON51330

Source
ToetsingOnline

Brief title
IBIZA-1(pilot)

Condition

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

Synonym
colon carcinoma, intestinal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Meander Medisch Centrum
Source(s) of monetary or material Support: Meander Medisch Centrum

Intervention

Keyword: Bevacizumab-800CW, Colon carcinoma, Fluorescence, Sentinel lymph node

Outcome measures

Primary outcome

1. Identification rate of SLN(s) or lymph node metastases with

bevacizumab-800CW, Defined as the number of patients in which a SLN or lymph

node metastases were detected due to fluorescence during surgery and/or

pathology assessment / total number of procedure

2. Rate of adverse events related to bevacizumab-800CW (injection).

Defined as the number of adverse events related towards bevacizumab-800CW /

total number of procedures (n, %).

Secondary outcome

3. Amount of fluorescence in lymph node metastases compared to lymph node

without metastases

4. False-negative SLNs:

The SLNs are negative whereas the non-sentinel nodes (NSNs) were positive

(number).

5. True-negative SLNs:

Both the SLNs and NSNs are negative (number).

6. Sensitivity:

The number of patients with a positive SLN / the total number of node positive

patients (n, %).

7. Upstaging:

The number of patients with SLNs positive for micro- or macrometastases by serial slicing and IHC / the number of patients who were node negative by H&E examination (n, %).

8. Aberrant lymph node status:

The number of patients with aberrant lymph nodes, and the status of these lymph nodes considering micro- or macrometastases.

9. Accuracy:

(The total number of patients with a positive SLN + the number of patients with a true-negative SLN) / number of patients with an identified SLN (n, %).

10. Negative predictive value (NPV):

The number of true negative SLNs / (true negative + false negative SLNs).

11. Number of SLN identified:

Number of SLN identified (number).

Study description

Background summary

The current gold standard for the treatment of colon carcinoma consists of the surgical en-bloc resection of the colonic segment including the adjacent mesocolon containing the draining lymph nodes. Analysis of these lymph nodes is important, since lymph node status is one of the most important prognostic factors determining the use of adjuvant chemotherapy. Although patients with tumour stage I and II do not have lymph node metastases, 15-20% develop recurrent disease. Several studies suggest that ultrastaging techniques such as immunohistochemistry (IHC) or reverse transcriptase polymerase chain reaction (RT-PCR) using multilevel slicing results in upstaging of 14-18% of patients, due to newly found (micro)metastasis. Furthermore, several studies indicate

that these micrometastases are correlated with a significantly poorer prognosis, subsequently suggesting that this subgroup of patients might benefit of adjuvant chemotherapy. Therefore, the most recent Dutch guidelines advice the use of adjuvant chemotherapy in this *upstaged* group, although evidence is still lacking.
However, ultrastaging techniques are labour-intensive and costly, and therefore not suitable for analyses of all lymph nodes that have been collected during segmental colectomy. Sentinel lymph node (SLN) identification in colon carcinoma has been proposed to overcome this problem by identifying the first order draining lymph node(s) of the tumour, which have the highest chance of containing metastatic tumour cells. Several studies aimed at SLN identification in colon carcinoma have been published, however, early studies using radio-guided or blue-dye guided SLN identification, showed relatively high rates of false negatives with consequent low sensitivity rates. Since mesocolon is rather fatty tissue, visualization of conventional dyes is difficult.
Indocyanine green (ICG), which can be visualized using near infrared (NIR), has been put forward since it is known to penetrate relatively deep into living tissue.
Nevertheless, results of SLN identification using ICG remain unsatisfying with high false-negative rates and low sensitivity. Most likely this is due to the fact that these studies also included large cT3-cT4 tumours and patients with massive lymph node involvement. Which are factors known to interfere with lymph drainage patterns. Furthermore, subserosal injections were frequently used, while it is suggested that submucosal injections might result in better sensitivity of the procedure. In the FLUOR-SLN-ICG pilot study, we successfully conducted SLN identification in patients with ICG. We want to expand the pilot study using a tumour-targeted tracer: bevacizumab-800CW. Bevacizumab-800CW can be preoperatively administered, binds to tumour and metastases, thus allowing more time for uptake in patients with larger tumour and lymph node metastases. Therefore this prospective study aims to assess the safety and feasibility of lymph node identification using bevacizumab-800CW in patients with cT1-3N0-2 tumours, using peritumoral submucosal injections.

Study objective

The primary outcome parameters are identification rate of SLN(s) or lymph node metastases with bevacizumab-800CW, defined as the number of patients in which a SLN or lymph node metastasis was detected due to fluorescence during surgery and/or pathology assessment divided by the total number of procedures.
Furthermore the rate of adverse events related towards bevacizumab-800CW will be measured. This is defined as the number of adverse events related towards bevacizumab-800CW/total number of procedures.
Secondary outcome parameters include: amount of fluorescence in lymph node metastases compared to lymph node without metastases, false-negative SLNs, true-negative SLNs, sensitivity, upstaged patients, aberrant lymph node status, accuracy, negative predictive value and number of SLNs identified.

Study design

This is a single-centre, open-label, non-randomized cohort safety and feasibility study.

Intervention

1. Patients are identified at the outpatient clinic and asked for participation in the study.
2. Patients will be planned for laparoscopic/robot-assisted surgical colectomy according to standard of care (SOC).
3. 2-4 days before surgery, a colonoscopy is performed by the gastroenterologist to submucosally inject a maximum of 4.5mg bevacizumab-800CW around the tumour. The patient is observed during one hour after injection of bevacizumab-800CW. Before the colonoscopy, mechanical bowel preparation (MBP) will take place according to hospital protocol.
4. During segmental colectomy, a NIR camera is used to visualize the SLN, which will be marked using a stitch. If an aberrant lymph node is visualized, this node will be harvested.
5. Segmental colectomy with procurement of the adhering mesocolon will be performed according SOC.
6. After extraction of the specimen, ex-vivo examination of the specimen using the NIR camera will be performed.
7. Postoperative management will be according SOC.
8. Pathological examination will be done using haematoxylin & eosin (H&E). If no lymph node metastases are found, the lymph nodes will be examined using serial slicing and subsequent IHC.
9. Resected specimens or formalin-fixed paraffin embedded blocks of tissue will also be examined in the UMC Groningen for the presence of NIR. This process will not interfere with standard working procedures related to clinical care.
In case no SLN can be detected with intraoperative fluorescence, we will be able to detect (ex vivo) fluorescence with specially designed cameras present at the UMCG. These cameras can detect bevacizumab-800CW while more than >16.000x diluted. This allows for *ex-vivo* SLN identification if there is any clinically relevant fluorescence present in the lymph nodes, while no intraoperative fluorescence is detected. Therefore, these results then still can be translated to the clinic when optimised systems become available.

Study burden and risks

This study is a non-therapeutic, diagnostic feasibility study, aimed at identification of the SLN with bevacizumab-800CW. Furthermore, although micrometastasis are associated with poor prognosis, it is yet unknown whether the treatment of micrometastasis with adjuvant chemotherapy will result in any clinical benefit. However, the most recent Dutch guidelines advice the use of adjuvant chemotherapy in this *upstaged* group and thus will receive adjuvant

chemotherapy.

The potential benefits or harms for the patient are based upon the difference in staging compared to standard staging techniques. With negative lymph nodes after H&E, additional ultrastaging techniques will be performed. If micrometastases are detected in the lymph nodes this will not result in any clinical consequences, due to the lack of evidence for effectivity of adjuvant chemotherapy in these patients. However, if ultrastaging techniques result in detection of lymph nodes with macrometastases, these patients will be offered adjuvant chemotherapy. Furthermore, aberrant lymph nodes will be excised and analysed as the other lymph nodes. Potentially resulting in treatment with adjuvant chemotherapy, while, this would not be given if the aberrant node would not be excised.

Since patients will receive an additional colonoscopy, preceded by an additional MBP, patient have an additional risk of complications associated with MBP and colonoscopy. Risks associated with MBP that have been described are hypovolemia, electrolyte imbalances, renal failure and discomfort for the patient. Furthermore, risks associated with colonoscopy that have been described are perforations and post-colonoscopy bleeding. However, reported risks have shown to be low with 0.05% and 0.98% for perforations and postcolonoscopy bleeding respectively. More importantly, these complications are mostly related to polypectomies and would be resolved immediately since injection is performed during surgery. The risk of comparable procedures such as endoscopic tattooing is low (<0.22% complication rate) and are routinely performed. Bevacizumab-800CW has a low-risk safety profile, see for further elaboration (Chapter 11 of study protocol: Potential issues of concern). Since we will only inject a small amount of tracer, we expect these risks are negligible.

Consequently, the potential benefit of this study is a potential better oncological outcome for patients who will be offered adjuvant chemotherapy since ultrastaging techniques delivered micrometastases, who would otherwise not be found. Potential risk of this study is the risks associated with MBP and colonoscopy.

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

- Oral and written informed consent (IC)
- Aged 18 years and older
- Pathologically confinmed and/or suspected cT1-3N0-2M0 colon carcinoma

Exclusion criteria

- Distant metastasis
- Suspicion of cT4 disease based on pre-operative assessment
- Metastatic or T4 disease discovered during intraoperative staging
- Pregnancy, lactation or a planned pregnancy during the course of the study
- Previous colon surgery, excluding appendectomy.
- Contra-indication for laparoscopic/robotic surgery
- Inadequately controlled hypertension with or without current antihypertensive medication.
- Within 6 months prior to inclusion: myocardial infarction, TIA, CVA, pulmonary embolism, unstable angina pectoris, or uncontrolled chronic hepatic failure.
- Regarding bevacizumab: Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised

antibodies. Or an allergy for its components (Trehalose dehydrate, sodium phosphate, polysorbate 20, water for injections)

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):	19-09-2022
Enrollment:	5
Type:	Actual

Ethics review

Approved WMO Date:	12-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	13-07-2022
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2021-006700-32-NL
CCMO	NL80013.100.21