Advanced imaging in HIPEC for peritoneal carcinomatosis of colorectal origin; a feasibility study

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Primary Objective:-Evaluate tumour detection sensitivity and specificity with the following image enhancement modalities:1 *narrow-band imaging*, (NBI)2 *near-infrared indocyanin green imaging*, (ICG)3 *5-aminolevulinic acid fluorescent imaging*, (5...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Peritoneal and retroperitoneal conditions
Study type	Observational invasive

Summary

ID

NL-OMON44157

Source
ToetsingOnline

Brief title
Advanced imaging techniques for detection of peritoneal carcinomatosis

Condition

- Peritoneal and retroperitoneal conditions
- Metastases
- Gastrointestinal therapeutic procedures

Synonym
Peritoneal Carcinomatosis, Peritoneal Metastases

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Colorectal metastases, HIPEC, Imaging

Outcome measures

Primary outcome

To evaluate the sensitivity of Narrow Band Imaging, Three-dimensional imaging, Near-infrared Indocyanin Green Imaging, 5-ALA fluorescent imaging and Indigo Carmine Blue Spray Dye Chromoendoscopy in the detection of malignant lesions.

To evaluate if more malignant lesions are found with NBI, 3D, NIR-ICG, 5-ALA and SDCE, compared to conventional white light laparoscopy.

Secondary outcome

Operating time

Blood loss

Peritoneal carcinomatosis index (PCI) score

(Serious) adverse events

Patient characteristics

Tumour characteristics

Study description

Background summary

Peritoneal carcinomatosis (PC) of colorectal origin occurs in 13 per cent of the patients at time of diagnosis and 25% of the patients develop PC at recurrence[. Prognosis for PC without aggressive therapy is very poor. Without treatment, median survival is approximately 3 months. Cytoreductive surgery

(CRS) combined with hyperthermic intraperitoneal chemotherapy (HIPEC) has been reported to have good results on survival of metastasized gastro-intestinal and gynaecological carcinomas. Median survival of patients with PC of colorectal origin has improved with 21-30 months with up to 40% 5 year survival.

CRS combined with HIPEC is a procedure that has high rates of morbidity and mortality. A multi-institutional study was performed of 1.290 (523 with primary colorectal adenocarcinoma) patients who were treated by open CRS and HIPEC for non-ovarian malignancies. Overall morbidity and mortality rates were 33.6% and 4,1% respectively. A careful decision has to be made whether it is worth for patients to undergo an operation with such high rates of morbidity and mortality.

The peritoneal carcinomatosis index (PCI) is an important tool for predicting survival and for determining whether complete resection is possible. The peritoneum is divided into 13 regions. To each region a score of 0 through 3 is given according to tumour size found. A study showed a difference in survival between patients with a PCI <15 and =/>15. Significance difference was observed in both disease-free-survival and overall survival (p=0,0009 and p=0,013 and respectively) between both groups. It has been demostrated that the survival after CRS and HIPEC was correlated to the extent of disease and the completeness of removing all malignant lesions.

Staging the extent of disease has shown to be viable to assess if patients should undergo such an invasive procedure. The benefits of the oncologic outcomes have to be weighed against the high rates of morbidity and mortality. After staging the procedure can only be successful if all malignant lesions larger than 2 millimetres are resected prior to chemotherapy cleansing. Image enhanced modalities such as narrow-band imaging, autofluorescent imaging, photodynamic diagnosis with 5-ALA, near-infrared imaging with ICG and spray-dye chromoendoscopy with ICB have shown in different medical fields of speciality to improve lesion detection, especially of smaller, flatter and harder detectable lesions. Therefore we should investigate these imaging modalities to improve survival for patients by having a more complete cytoreduction.

Study objective

Primary Objective:
-Evaluate tumour detection sensitivity and specificity with the following image enhancement modalities:

1 *narrow-band imaging*, (NBI)
2 *near-infrared indocyanin green imaging*, (ICG)
3 *5-aminolevulinic acid fluorescent imaging*, (5-ALA)
4 *spray-dye chromoendoscopy with Indigo Carmine* (ICB)

Study design

The proposed study is a prospective feasibility study to demonstrate which imaging modality is most suited for detecting peritoneal metastases.
This study will take place at the VU University Medical Center by the department of gastro-intestinal surgery.
The duration of the study is determined by the time period in which the sample size can be operated. We perform around 30 HIPEC procedures per year and hope to include at least 20 patients in that period.

Preoperative procedure
In the outdoor patient clinic all subjects who meet inclusion criteria will be informed and asked for oral and written informed consent. Patients are instructed about the procedure, the alternatives and the adverse events. After being informed by the physician, the patient receives the patient-information-letter. Any additional questions will be answered by the physician or the executive investigator. Patients have a minimal time for reflection and consultation of one week.
Preoperative screening by the department of Anaesthesiology takes place in the outdoor patient clinic as well.
In the hospital the preoperative care is conducted as stated by the *general protocol for preoperative care* of the VU Medical Center department of surgery. Six hours prior to surgery the patients have to be sober and 2 hours before surgery no more water is allowed as well.
Three hours prior to anaesthesia 5-aminolevulinic acid (5-ALA) is administered orally. The dose depends on the body weight (20mg/kg). ICG (0,25mg/kg bodyweight with a maximum of 5mg/kg bodyweight) is intravenously administered on the ward, 3 hours prior to surgery.

Intraoperative procedure
Patients are placed in the supine position and receive general anaesthesia. The surgical procedure will be either performed by laparoscopy or laparotomy (open procedure), depending on the extent of disease and patient history. If the procedure is started laparoscopically a 12mm-trocar and rigid laparoscope are placed after a periumbilical incision is made. Two more 5mm-trocars are introduced to assist the laparoscope. If the procedure is started by laparotomy, a midline incision is made from xyfoid to the pubic bone.

The peritoneum surrounding the larger peritoneal metastases is inspected systematically, according to the Peritoneal Carcinomatosis Index (PCI). The peritoneum is first inspected by conventionalWL. Next the peritoneum is inspected using the advanced imaging modalities in a computer-generated rotating different order:
A. Narrow-band imaging (NBI)
B1. Near-infrared imaging with intravenous fluorescent Indocyanin Green infusion (NIR-ICG)

B2. Photodynamic diagnosis with orally administered 5-ALA (5-ALA)
C. Spray-dye chromoendoscopy with Indigo Carmine Blue (SDCE)
The techniques are used in a computer-generated randomly different order. This is achieved by use of the online available Sealed Envelope program.

Per imaging modality (WL, , NBI, NIR-ICG, 5-ALA and SDCE) photographs are taken of possibly malignant lesions. The photographs will be systematically sorted according to the Peritoneal Carcinomatosis Index (PCI) and per imaging modality. After the regions of interest have been evaluated with every imaging modality, biopsies will be taken of each potentially malignant lesion. A maximum of five biopsies of apparent healthy tissue will be taken for negative control. Biopsies of healthy peritoneum will be taken within 2cm proximity of a potentially malignant lesion. By taking biopsies after all the imaging modalities have been applied, less biopsies are needed and therefore decreases the risk of bleeding.

NBI can be initiated by changing the settings on the laparoscopic tower. No invasive extra procedures is needed for this modality. When the peritoneum is inspected by laparotomy, the NBI laparoscopic camera is used in an open fashion.
For the imaging technique SDCE (technique C), ICB is sprayed onto the peritoneum to enhance tissue architecture. A sterile catheter is introduced to spray the ICB onto the peritoneum. After evaluation of the peritoneum with SDCE, the ICB is rinsed and aspirated.
Patients will receive either intravenous indocyanin green three hours prior to surgery (NIR-ICG) or 5-aminolevulinic acid (5-ALA) orally three hours prior to surgery (techniques B1 and B2).
If patients receive ICG three hours prior to surgery, it is intravenously administered (0,25 mg/kg bodyweight, diluted in sterile water with a maximum dose of 5mg/kg bodyweight) on the ward. During surgery either the laparoscope will be set to near-infrared, or an open near-infrared camera system will be usedfor fluorescent imaging of the ICG
If 5-ALA is chosen, patients will be asked to drink 5-ALA, dissolved in water, three hours prior to surgery for optimal distribution and optimal fluorescent imaging. The laparoscope is set correctly for optimal wavelength emission. Either the laparoscopic system will be used in an open fashion, or an open camera system will be used.

The peritoneum is inspected by the operating physician (Dr. Tuynman or Dr. Meijerink). Two independent surgeons/fellows of gastro-intestinal surgery will review the photographs taken per imaging modality after the procedure in order to assess interrater variability ..

After the surgical procedure, all photos and biopsies will be sorted according to the PCI region and image enhancement technique used. The pathologist will blindly inspect biopsies for malignancy. The results of the pathologic report will be correlated to the different imaging modalities. For each modality the next will be checked:

-Is the photograph taken of the potential malignant lesion correlated to a positive pathologic finding (e.g. malignant tissue found in biopsy)?
-Is the photograph taken of the potential malignant lesion correlated to a negative pathologic finding (e.g. no malignant tissue found in biopsy)?
-Is the photograph taken of the potential healthy tissue correlated to a positive pathologic finding (e.g. malignant tissue found in biopsy)?
-Is the photograph taken of the potential healthy tissue correlated to a negative pathologic finding (e.g. no malignant tissue found in biopsy)?

Not all image enhancement modalities will be used in the first twenty patients. The patients will be divided into two groups. Half the patients will receive ICG for near-infrared imaging and the other half will receive 5-ALA for photodynamic diagnosis. This is due to possible background interference when ICG and 5-ALA would be used simultaneously. Simultaneous use of ICG and 5-ALA is also avoided due to possible interaction of these substances. After the first twenty patients a trend toward which modalities have superior tumour detection properties should be visible. The imaging modality with the best tumour detection properties (e.g. increased sensitivity compared to WL and comparable specificity) is than selected for further investigation. In this second phase of the study, all regions of the peritoneum, according to the PCI, will be visualised.

If any of the image enhancement modalities proves to be of no value, the modality will be eliminated from the study prematurely. This will be determined by the project leader. This decision will be based upon ease of use, consuming of operating time, lack of fluorescence/non-fluorescence.

Postoperative procedure
Postoperative care is given as stated by the VU University Medical Center *general protocol for postoperative care*
Additional postoperative care is necessary for patients who underwent CRS followed by HIPEC as stated in the *HIPEC protocol*. This includes 2 days of postoperative monitoring on the I.C.U. or M.C.U.

Study burden and risks

Added risk
Participation in this trial adds four extra proceedings*:
1) The use of different imaging modalities may increase operating time and time under narcosis.
2) Possible adverse reaction to ICG, possible decrease in kidney or liver function
3) Possible adverse reaction to ICB
4) Possible adverse reaction to 5-ALA
5) Extra biopsies of unhealthy and healthy tissue will be taken
6) The absence of knowledge

* Four extra proceedings because patients will receive either ICG or 5-ALA.

Frequency/damage
The chance for damage as a result of this study is estimated at low risk. This is because we have anticipated for the potential risks by excluding the patients with enlarged chance for adverse events as a result of ICG, ICB or 5-ALA usage:
2) Patients with kidney and/or liver insufficiency are excluded. Patients with iodine allergy are excluded.
3) Patients with hypertension, cardiac ischemia and heart function insufficiency are excluded. Patients with prior hypersensitivity reaction to ICB are excluded.
4) Patients with acute or chronic porphyria are excluded. Patients with prior hypersensitivity reaction to 5-ALA or porphyrins are excluded.
Patients receive ICG, ICB or 5-ALA either intraoperatively or during admission. Patients are closely monitored and if any adverse event occurs, appropriate measures according to the substance*s SPC can be taken immediately.

Known risks
1) Increased time under narcosis. Extra time under narcosis is estimated at 15 minutes.
- We believe that these 15 minutes on top of the average operating time of 360 minutes will not cause any damage for the patient.
2) In 1/10.000 patients an anaphylactic or urticarial hypersensitivity reaction can occur as a result of intravenous ICG injection.
- The damage caused by this adverse event is moderate and reversible.
- If an anaphylactic reaction occurs, the anaesthesiologist can anticipate immediately
3) ICB may cause a transient elevation of blood pressure and reflex bradycardia if administered intravenously or orally. In patients with an eGFR< 10 mL/min clearance may be delayed.
- The damage caused by this adverse event is light and immediately reversible.
- Patients with known unstable hypertension, cardiac ischemia and heart insufficiency are excluded. Patients with an eGFR< 55 mL/min are excluded from this trial.
4) 5-ALA can cause phototoxic affects to the skin and eyes 24 hours after administration by direct sunlight.
- The damage caused by this adverse event is moderate and reversible.
- Patients will not be exposed to direct sunlight 24 hours after 5-ALA has been administered
5) Bleeding can occur as a result of biopsies
- The damage cause by this adverse event is light and reversible.
- Any bleedings can be coagulated by the operating physician.

No additional physical, psychological or social burdening is caused by this trial for the study subjects.

Synthesis:
We hypothesize that this study will benefit the patients. Better tumour visualisation will correlate to a prolonged survival. Intravenous ICG has already been widely used in different fields of surgery and is FDA approved. Very little adverse events have been reported, especially in low doses.
Only one case has been described in literature on the use of spray-dye indigo carmine onto the peritoneum. We do not know how much of the dye will diffuse over the serosa of the peritoneum. After spraying and visualizing the lesion, the dye is rinsed of the peritoneum and aspirated. We therefore hypothesize that very little indigo carmine will be taken up in to the bloodstream.
5-ALA causes hypersensitive skin and eyes 24 hours after administration. Therefore patients are not exposed to direct sunlight directly after administration of 5-ALA.
During surgery the patients are under constant surveillance of the anaesthesiologist and its assistants. If an adverse event occurs, such as a change in blood pressure, change of heart frequency or respiratory failure, the anaesthesiologist will intervene.
We believe the potential risks of participating in this study are acceptable and do not weigh up to the benefits.

After structured risk analysis according to NFU standards, we conclude that the damage possibly caused by this study is light and the chance is low; therefore negligible risk.

Contacts

Public
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1081HZ
NL
Scientific
Vrije Universiteit Medisch Centrum

Boelelaan 1117
Amsterdam 1081HZ
NL

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
-Age 18 years and older
-Elective cytoreductive surgery followed by HIPEC
-Regular preoperative work-up
-Laparoscopic or open approach

Exclusion criteria

-ASA score higher than 3
-Patients who have had prior major open abdominal surgery
-Contraindicattions for ICG, 5-ALA or ICB
-Medication that interacts with ICG, 5-ALA or ICB
-Chronic kidney failure (eGFR < 55)
-Chronic liver failure (ASAT, ALAT, AF or yGT > 2 times normal value)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-05-2016
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Gliolan
Generic name:	5-aminolevulinic acid
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	ICG-Pulsion
Generic name:	Indocyanin Green
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Indigo Carmine
Generic name:	Indigotindisulfonate Sodium Injection
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

ID: 27102
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
EudraCT	EUCTR2014-003932-38-NL
CCMO	NL50797.029.15
OMON	NL-OMON27102

Study results

Date completed:	15-05-2018
Actual enrolment:	28