In vivo study to determine the efficacy of sentinel node mapping in patients with colon carcinoma using near-infrared laparoscopy after submucosal injection

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Primary objective: To study the faesibility of SLNM in patients with histological proven colon cancer using NIR-laparoscopy.Secondary objectives: To study the incidence of micrometastasis with the use of ICG and RT-PCRTo determine the number of...

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

Summary

ID

NL-OMON37962

Source
ToetsingOnline

Brief title
SLNM in patients with CRC

Condition

- Malignant and unspecified neoplasms gastrointestinal NEC
- Gastrointestinal therapeutic procedures

Synonym
colon cancer, colon carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Olympus,stichting digestieve chirurgie

Intervention

Keyword: colon cancer, sentinel node, submucosal tracer injection

Outcome measures

Primary outcome

- identification rate of SLN

- Number of false-negative SLNs

- Number of patients who are upstaged by ultrastaging techniques

- Number and status of aberrant lymph nodes

- Accuracy: conformity of the SLN status and the regional node status

- Number of positive SLNs which are the only positive nodes found.

- Number and status of SLNs detected only by the near-infrared scope in vivo

and ex vivo

- Number and status of SLNs detected only with Patent Blue ex vivo

- Number and status of SLNs detected by the near-infrared

scope and patent blue in vivo and ex vivo

Secondary outcome

faesibility of the technique

Study description

Background summary

For more than 100 years, radical lymphadenectomy has been the diagnostic and

therapeutic gold standard for the management of metastatic nodal disease, despite well-known morbidities such as lymphedema and nerve damage. (Saha et al. 245S-9S) Whereby lymph node status is the most important factor in the selection of patients for adjuvant chemotherapy.(Bilchik and Trocha 219-23;Saha et al. 245S-9S)

Recurrences occur in 20% of the patients without lymph node metastases. (Kelder et al.;Saha et al. 245S-9S) Most likely due to inadequate lymph node resection and/or missed nodal metastases on histologic examination.(Bilchik and Trocha 219-23;Saha et al. 245S-9S) With the conventional H&E staining micrometastases are not detected. They can be detected using IHC or RT-PCR but these ultrastaging techniques are labour and cost intensive, so it*s highly impractical to ultrastage all the nodes in a given specimen.
Several studies indicate that micrometastases are correlated with a significantly poorer prognosis.(Bilchik et al. 568-75;Cote et al. 613-20;Iddings et al. 1386-92;Liefers et al. 223-28) We speculate that although no recommendation for adjuvant chemotherapy is given for patients with colon cancer with stage I/II at this time, a subgroup yet to be defined would probably benefit from adjuvant chemotherapy.

The primary purpose of SLNM in colon cancer is to upstage tumors whose metastasis would remain undetected by conventional pathological mains and to identify aberrant lymphatic drainage.

Several studies concerning the feasibility of SLN mapping in colon carcinoma have been published. The conclusion of the Meta-analysis published by Des Guetz et al. is that lymphatic mapping appears to be readily applicable. (Des et al. 1304-12) The global sensitivity and specificity of the SLNM were, respectively, 70% and 81%. (Des et al. 1304-12) In the series of CRCs, more than half of the patients were found to have T3-T4 tumours. With CRCs, it was previously shown that massive lymph node involvement was the cause of the high false negative rate of SLNM (Doekhie et al. 854-62). The studies with the highest false negative rates have also tended to have the greatest proportion of T3-T4 tumours in their study cohorts. Better results in such patients populations is reported in those studies which specifically excluded those with evident lymph node disease intraoperatively (Tuech et al. 158-61) In our study we will stratify patients according to their T stage. Before routinely using this technique in CRC it has to be improved. The dyes used in these studies are patent blue/ isosulfan blue, radioisotope tracers or a combination of one of these three. In our study we have the possibility to use several tracers such as; blue dye (patent blue), radioactive (human serum albumin, technetium) or fluorescent tracers (ICG). Patent blue and radioactive colloid is mostly used in European studies. So they are well known and safe. ICG is also well known in the use for other purposes. It has one big advantage. ICG has a peak spectral absorption at 800-810 nm in blood plasma and blood. Wavelengths in the 800 nm range penetrate relatively deeply into living tissue compared to visible light, so SLN staining can also be accurately assessed in mesenteric adipose tissue.

The particle size of ICG is 7,3 nm. The lymphatic collection process is strongly related to particle size. Particles smaller than 4-5 nm will penetrate capillary membranes and therefore may not migrate through the lymphatic channel. Particles larger than 4-100 nm show the most rapid dispersal from interstitial space into lymphatic vessels, yet have significant retention in the lymph node. Particles larger than 500nm have a much slower rate of clearance from the interstitial space with significantly less accumulation in lymph nodes. The 40 nm beads were considered to be the most appropriate size for SN detection in rats (Nakajima et al. 353-56). To obtain the optimal particle size we might make a conjugate with Nanocoll ® (95% of the particles < 80 nm).
For the visualisation of indocyanine green we will have the premiere of using the first near-infrared laparoscope in Europe (Olympus Corp., Tokyo, Japan). This scope is being designed specific for this study. It consist of a regular scope with a special light source and light filters.

Hypoteses:
1) Intra-operative lymphatic mapping and sentinel lymphadenectomy is feasible in colon cancer.
2) the sentinel lymph node (SLN) status reflects the regional node status
3) focused analysis of the SLN improves staging accuracy
4) micrometastasis have prognostic importance

Study objective

Primary objective:
To study the faesibility of SLNM in patients with histological proven colon cancer using NIR-laparoscopy.

Secondary objectives:
To study the incidence of micrometastasis with the use of ICG and RT-PCR
To determine the number of false-negative SLNs
To evaluate the efficiency of minimal invasive surgery for harvesting sentinel lymph nodes.
To determine the accuracy of the technique

Study design

cross-sectional study

Intervention

Colonoscopy will be performed at the operating room when patients are under general anesthesia. When the tumor is localized, their will be one injection with the fluorescent tracer at the base of the tumor. Prior to the

administration n of the fluorescent tracer, there will be an injection with a small amount of saline to guarantee correct placement of the needle. After injection of the fluorescent tracer there wil be flushed with a small amount of saline. Afterwards laparoscopic access will be obtained in the traditional fashion and abdominal exploration shall be performed to rule out intra-abdominal metastasis. The involved segment is mobilized carefully without disruption of the lymphatic channels and blood vessels. The segment will be inspected for fluorescent nodes with the Near-Infrared laparoscope. These nodes will be marked with a suture. After mobilization is completed the involved segment of the colon and the regional lymph nodes will be resected through a minilaparotomy like the conventional method.
Ex vivo the specimen will be searched for fluorescent spots by the NIR camera system for fluorescent nodes missed in vivo. Ex vivo identified fluorescent nodes will be marked with a suture in another colour than sutures used in vivo.
Thereafter, the specimen is opened at the anti-mesenteric side. After the tumour is identified 0.5 - 2 ml of Patent Blue V dye is injected into the submucosa circumferential to the tumour, using a tuberculin syringe. The injection sites are then gently massaged for five minutes to push the tracer into the lymphatic vessels. Blue coloured sentinel nodes are identified and marked with a suture in a different colour then the in vivo and ex vivo used sutures.
Hereafter the whole specimen will be placed in formalin for 24-48 hours.

Study burden and risks

The treatment of the malignancy will be performed conform the conventional method.
Yet prospective studies are needed to evaluate the potential benefit of systematic chemotherapy in patients with micrometastases. At this moment we are evaluating if it*s favorable to randomize patients with micrometastases for adjuvant chemo.

Contacts

Public
Vrije Universiteit Medisch Centrum

De Boelelaan 1117
Amsterdam 1081HV
NL
Scientific
Vrije Universiteit Medisch Centrum

De Boelelaan 1117

Amsterdam 1081HV
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 (IC)
- Age 18 years and older
- Patients histologically or radiologically suspicion of colon cancer
- Regular Pre-operative work-up
- Surgical resection of the tumor

Exclusion criteria

- gross lymph node involvement
- distant metastases
- advanced disease with invasion of adjacent structures
- prior colorectal surgery
- metastatic or T4 disease discovered during intraoperative staging
- contraindications to laparoscopy
- rectal cancer
- allergy to iodine
- Patients at higher risk for anaphylactic reactions

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	17-08-2009
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	31-12-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2012
Application type:	Amendment
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

No registrations found.

In other registers

Register	ID
CCMO	NL24613.029.08