Sentinel lymph node identification in colon cancer using the hybrid tracer ICG-99mTc-nanocoll

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Aim of the study is to develop an intraoperative technique for SLN mapping in colon cancer which is suitably in daily practice in colon surgery in an average hospital setting.

Ethical review	Approved WMO
Status	Completed
Health condition type	Gastrointestinal conditions NEC
Study type	Interventional

Summary

ID

NL-OMON46140

Source
ToetsingOnline

Brief title
SLN in colon cancer using ICG-99mTc-nanocolloid

Condition

- Gastrointestinal conditions NEC
- Gastrointestinal neoplasms malignant and unspecified
- Gastrointestinal therapeutic procedures

Synonym
Colon cancer, sentinel lymph node

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: CCA VUmc,Olympus

Intervention

Keyword: Colon cancer, Fluorescence, Imaging, SLN

Outcome measures

Primary outcome

Number of patients upstaged with the SLN procedure

Secondary outcome

- Preoperative detection rate of SLNs by SPECT/CT scan

- Adaptive value of preoperative localization of SLNs by SPECT/CT imaging

during the surgical procedure.

- Number of injection failures

- Duration of SLN procedure

- Implementation of the SLN procedure in the conventional surgical procedure

- Adaptive value and capability of the SLN procedure for the surgeon

- Adaptive value of gamma-probe in detection of the SLNs

- Number and location of SLNs detected by NIR fluorescence imaging

- Visualization of lymphatic vessels and the possibility of differentiation

between first and second echelon lymph nodes.

- Pathological status of the detected SLNs.

- Optimale time-frame for SPECt-CT scan after 99mTc-nanocoll injection.

Study description

Background summary

Colon cancer is one of the leading causes of cancer related deaths in the Western World. In the Netherlands there are over 10.000 new cases of colon

cancer each year which will increase to more than 14.000.
Due to the introduction of nationwide screening programs the incidence of stage I and II disease is expected to increase. Local excision of the primary tumor is an attractive treatment option but is only oncological safe in the absence of lymph node metastasis. The current standard preoperative imaging modalities (CT and MRI) are not able to distinguish nodal involvement. As a result all patients need to be treated with a resection of the primary tumor and appropriate en-bloc resection of associated lymph nodes. Fifty precent of the diagnosed patients suffers from a stage I/II disease. The extensive surgical approach leads to over-treatment and unnecessary exposure of surgery-related morbidity in especially these patients with early CRC. However, the 5-year survival rates for patients with stage I and II colon carcinoma are respectively 90% and 75%. Unfortunately, up to 30% stage I/II patients will nonetheless develop distant metastases and eventually die from colorectal carcinoma. This is probably caused by understaging of the LNs since occult tumor cells and micrometastasis, associated with disease recurrence and poor survival, but easily missed during routine hisptopathological examination (single-section haematoxylin and eosin staining). Ideally, all lymph nodes should be examined with serial sectioning and additional immunohistochemistry or reverse transcriptase RT-PCR for more accurately staging. Unfortunately, these techniques are expensive and time-consuming which make them not preferable in daily practice. Apart from insufficient pathologic examination of the LNs, lymphatic drainage patterns are variable or can be aberrant from conventional resection margins which lead to incomplete lymphadenectomy. The aim of this project is to design an easy and widely applicable method to improve lymph node metastases detection techniques.

Drawbacks of current lymph node staging
Better detection and pathologic staging of the lymph nodes will contribute significantly to a better survival of colon cancer patients. There are a number of drawbacks in the current lymph node staging technique which makes it difficult to classify and stage patients accurately and withhold the optimal postoperative treatment.
First, on standard preoperative imaging it is often difficult to determine if lymph nodes contain metastases. During surgery, the lymph nodes are too small (± 0.5 mm diameter) and therefore not visible to the naked eye. Moreover, the pathologist identifies the lymph nodes by palpation. Because of the very small size of the lymph nodes from CRC, they are easily missed. Second, understaging of the lymph nodes by histopathological examination may also contribute to inadequate staging. Usually, the lymph nodes are cut in two parts and only one slice from both halves is examined.
(Micro-)metastases outside these slices are missed. Ideally, all lymph nodes should be examined on different levels by cutting the lymph nodes in several parts. Although staging can be improved by addition of advanced pathological staging techniques like immunohistochemistry or RT-PCR, these additional techniques are too expensive and time consuming to analyze all lymph nodes. This is therefore not feasible in every day practice.

The sentinel lymph node (SLN) concept could offer a solution. This procedure aims to identify the first 1-4 lymph nodes that have the most direct drainage from the primary tumor and therefore contain the highest risk of harboring metastases even when located outside the resection area. Identification of the SLN allows the pathologist to examine these few nodes with additional histopathological techniques as mentioned above.

Sentinel lymph node procedure in colon cancer

The SLN procedure is a diagnostic staging procedure in multiple types of cancer like melanoma and breast cancer. A SLN with metastatic disease is an indication for additional extensive surgery or adjuvant postoperative chemotherapy. However, a negative SLN would justify a wait and see policy. Treatment of breast cancer and melanoma patients with the SLN procedures has proven to be a safe and valuable technique. Since the introduction of the SLN procedure, it changed the treatment of these cancers and improved the quality of life of these patients dramatically.

Many studies already support its feasibility but the sensitivity rates are low and variable. Van der Pas et al. (1) showed in meta-analysis that after selection of high-quality studies, an increase of sensitivity up to 90% is possible when the SLN technique would be standardized and patients selection refined.

First, colon and rectal cancer should be separated since the majority of patients with rectal cancer receive neoadjuvant therapy which might obliterate lymphatic flow. Secondly there are some technical difficulties which counteract clinical implementation of SLN mapping in CRC. The current most used optical dyes are patent blue or isolfan blue which have been used in an in vivo and ex vivo settings. Both blue dyes cannot be seen through fatty tissue and easily diffuse trough the true SLN and stain regional lymph nodes. Also the injection technique varies between studies.

Using radioactive tracers presents the problem of signal interference of the injection site. The very strong signal of the injection site *overshines* the signal of the SLNs which are located near the tumor which makes SLN detection impossible. Besides that, the limitation to visualize the lymph nodes and his corresponding lymphatic vessels during surgery itself makes radioactive tracers alone less attractive.

Ideally the SLN procedure should be performed in vivo to overcome the problem of aberrant lymphatic drainage. Subserosal injection of dye can be easily performed in vivo but tumor margins are not very clear during this approach. Subsequently, dye injection occurs easily to far from the tumor or into the site which do not exactly match the lymphatic drainage from the malignancy. An endoscopic submucosal injection allows for better tumor visualization which results in more accurate dye administration and lymphatic drainage pattern towards the SLN. Although an additional pre- or perioperative colonoscopy is necessary this disturbs and prolongs the surgical procedure.

SLN detection with a near-infrared (NIR)-imaging and the fluorescent dye Indocyanine Green (ICG) is a new and promising technique which may have the characteristic to solve all the problems inherent to use of blue dye and radioactive tracers. NIR-light penetrates deeply into fat tissue compared with

visible light or blue dye. It can be used during the surgical procedure and can be seen during the operation. This provides the opportunity for the surgeon to localize the lymph node in the abdomen and makes sure there is an adequate resection.
Preliminary results
Our research group investigates the applicability of the SLN procedure in colorectal cancer since 2011. To identify the SLN we use the Near-Infrared (NIR) dye Indocyanin Green (ICG). Great advantage of the NIR-dye compared to conventional light or blue dye is the better penetration depth which makes deeper located structures visible.
To investigate the feasibility of SLN detection with the NIR technique, we started in a goat model (2). In this study we identified SLNs after injection with the fluorescent dye Indocyanin Green dissolved in saline (0.9%) and human albumin (200 mg/ml) with a new developed laparoscopic NIR fluorescence imaging system. Hereafter we performed a feasibility study to establish the SLN technique in colon cancer patients with no signs of (lymph node) metastases. We compared two injection techniques. In fourteen

Study objective

Aim of the study is to develop an intraoperative technique for SLN mapping in colon cancer which is suitably in daily practice in colon surgery in an average hospital setting.

Study design

The study will be a prospective non-randomized trial in which we use the hybrid tracer 99mTc-Nanocoll-ICG to detect the SLN in patient with colon cancer. The study will focus on upstaging and applicability in daily practice.
When this SLN technique is accurate and feasible if will be used in a large randomized clinical trial.

Intervention

Patients will be injected with the tracer 99mTc-Nanocoll-ICG respectively 5 or 14 hrs before surgery. The tracer will be administrated by colonoscopy performed by the gastroenterologist and injected at the base of the tumor in submucosal layer. After tracer administration, patients undergo a SPECT-CT scan just before the surgical procedure. The SLN procedure will be performed during the conventional resection in a adjusted sequence. First the segment will be inspected for fluorescent nodes with the Near-Infrared- laparoscope (Olympus Corporation, Tokyo, Japan). Fluorescent nodes are marked with a suture. Secondly, the segment will be inspected with the gamma-probe. Radioactive nodes are marked with a suture too. Thereafter the number of fluorescent and/or radioactive nodes found in vivo will be compared with the number of nodes found by preoperative imaging. After removal the specimen, it will be inspected for

fluorescent and/or radioactive nodes which are not detected inside the body. These nodes will also be marked with a suture. To confirm if the intraopertive marked SLN are the same as seen on preoperative SPECT/CT, an additional SPECT/CT of the specimen will be performed. The entire specimen will be submitted for pathologic examination. The SLNs will be taken out first and fluorescence and radioactivity will be confirmed by using the NIR-laparoscope and gamma-probe. All non-marked regional lymph nodes found will also examined for fluorescence and radioactivity. All identified SLNs and regional lymph nodes will be stained with hematoxylin-eosin (H&E). If the sentinel lymph nodes are negative after routine H&E staining, they will be sliced in multiple parts and examined with H&E staining and immunohistochemistry with the specific marker CAM5.2 and CK19.
Metastases between 0.2 mm and 2.0 mm will be referred to as micrometastases (N1mi). Metastases smaller than 0,2 mm will be described as isolated tumor cells (N0i+). Lymph nodes which are not fluorescent or radioactive will be screened according to the SLN protocol too.
Patients will be considered as N+ when metastases are found after multislicing & staining. These patients are eligible for adjuvant chemotherapy. There are no treatment implications for patients in which we found micrometastases or isolated tumor cells. Follow-up of patients will be five years.
Ten patients will be included.

Study burden and risks

Additional risks for the patients are negligible. The overall risk of colon perforation due to the colonoscopy is
<0.002%. The effective dose for patients will be 1.25 mSv in total; 0.5 mSv from 100 MBq 99mTc-nanocoll-ICG and 1.5 mSv from the low-dose SPECT-CT scans. The effective dose for the gastroenterologist will be 2 uSv/hr when a distance of 50 cm from the patients will be maintained. The mean duration of a colposcopy is 30 minutes. The effective dose for the surgeon will be less than 0,1 mSv/hr for each patient. Other medical professionals who contact the patient will not receive more than 0.008 mSv during the treatment of one patient for each patient. The maximum allowed effective dose for these persons is 1 mSv/year. We will not exceed this amount. All medical professionals involved in the study will not exceed the maximum allowed radiation of 1000 uSv/year.

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
Age 18 years and older
Preoperative tumor stage colon cancer (Tis-T1-T2)
Laparoscopic surgical resection of the tumor
Regular pre-operative work-up

Exclusion criteria

- Patients younger than 18 years
- Patients who are legally or mentally incapable or unable to give informed consent
- Gross lymph node involvement
- Invasion of the tumour in surrounding tissue
- Distant metastases
- Tumours > 5 cm estimated during preoperative diagnostics
- T3 / T4 or metastatic disease discovered during intraoperative staging
- Contraindications to laparoscopic surgery
- Patients at higher risk for anaphylactic reactions
- Pregnancy

- Recent myocardial infarction
- Allergy for iodine
- Claustrophobia
- Rectal carcinoma

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-10-2016
Enrollment:	10
Type:	Actual

Medical products/devices used

Generic name:	Coloscopy
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	99mTechnetium-Nanocoll
Generic name:	99mTechnetium-Nanocoll
Product type:	Medicine
Brand name:	ICG-Pulsion
Generic name:	Indocyanin Green
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	21-04-2016
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-03-2017
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
EudraCT	EUCTR2016-001020-56-NL
CCMO	NL57102.029.16