# Sentinel lymph node identification in colon and rectal cancer using a radioactive and fluorescent tracer

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Aim of the present study is to investigate if a combination of a radioactive and fluorescent tracer can increase the sensitivity and specificity of the SLNM technique in colon and rectal cancer by utilizing the radioactive component for preoperative...

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| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Gastrointestinal conditions NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON41306

**Source**
ToetsingOnline

**Brief title**
SLN in colon and rectal cancer using a multimodal tracer

### Condition

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

**Synonym**
Colorectal 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, Imaging, Rectal cancer, SLN

## Outcome measures

### Primary outcome

Identification rate of SLNM with preoperative PET/CT imaging and intraoperative NIR fluorescence imaging in patients with colon and rectal cancer.

### Secondary outcome

• Preoperative detection rate of SLNs by PET/CT scan

• Number of SLNs seen by PET/CT scan at different time points after tracer injection

• Adaptive value of preoperative localization of SLNs by PET/CT imaging during the surgical procedure.

• Number and location of SLNs detected by NIR fluorescence imaging in vivo and ex vivo

• Determination of the optimal volume of 89Zr-Nanocoll

• Determination of the optimal preoperative injection time for 89Zr-Nanocoll

• Visualization of lymphatic vesselsand the possibility of differentiation between first and second echelon lymph nodes.

• Pathological status of the detected (S)LNs.

• Amount of metastasis in positive lymph nodes.

- Differences in kinetics of the tracer between colon and rectal cancer

- Differences in detection rate of the SLN between colon and rectal cancer

# Study description

**Background summary**

Colorectal cancer (CRC) is one of the leading causes of cancer related deaths in the Western World. In the Netherlands there are over 10.000 new cases each year. This number will increase to more than 14.000 caused by more awareness of the disease, aging, growing population and nationwide screening programmes which will start this year. Complete resection of the primary tumour and accurate staging of the lymph nodes are the determining factors in patient survival. Nowadays, 50% of the patients with colorectal carcinoma are diagnosed with a stage I or II tumour, which are node negative by definition. The 5-year survival rates for patients with stage I and II colorectal carcinoma are respectively 90% and 75%. Up to 20-30% stage I/II patients will nonetheless develop distant metastases and the majority will eventually die from colorectal carcinoma. It is possible that in this group of patients, small lymph node metastases have been missed, resulting in understaging. This may be due to an inadequate surgical lymphadenectomy or insufficient pathological examination. Metastatic nodes can be missed when not enough lymph nodes are being examined. For accurate staging a minimum of 7-14 lymph nodes is recommended. This is also the mean number of nodes we examine at the VU University Medical Center. However, some authors suggest that when examining only 14 lymph nodes metastases will be missed. Therefore about 40 lymph nodes need to be examined for a 85% probability that the patient is node negative.Better detection and pathologic staging of the lymph nodes could contribute to a better survival of colorectal cancer patients. With conventional H&E staining, micrometastases are not detected. They can be detected by multislicing and immunohistochemical staining (IHC). However, these ultrastaging techniques are labour and cost intensive, so it is highly impractical to ultrastage all the nodes in a given specimen. A solution for better detection, harvesting and optimalization for histopathological examination is the sentinel lymph node (SLN) procedure. This procedure aims to identify the first draining lymph node(s) from the primary tumour, which have the highest risk of harbouring metastases. These SLNs can be analyzed with the more sensitive histopathologic techniques as mentioned above. Since the introduction of the SLN principle by Morton, the SLN procedure has become a diagnostic staging procedure in multiple types of cancer like melanoma and breast cancer. Identification of the SLN provides information about the rest of the lymph nodes. A SLN with metastasis is an indication for additional adjuvant postoperative chemotherapy. However, a negative SLN would justify a wait and see policy. Recently we have published a meta-analysis of 52 studies with 3767 SLN procedures; 2961 colon and 806 rectum carcinoma. We noticed that between the studies there were big differences in used technique, type and amount of dye, number of performed procedure, patient selection and pathological examination of the harvested nodes. The mean overall detection rate was 0.94 (0.95% CI0.92-0.95), at pooled sensitivity 0.76 (0.72-0.80). In a

subgroup of 8 high methodological quality showed a higher detection rate and sensitivity in colon cancer patients (resp. 0.96, 0.95% CI 0.90-0.95 en 0.90 (0.86-0.93) and rectum cancer (resp. 0.95 (0.75-0.90) and 0.82 0.60-0.93)). We concluded that for implementation, the SLN procedure needs optimization and standardization. Therefore we made a view recommendations:
1. Colon and rectal cancer should be considered as a distinct type of cancer, as it has a different pattern of spread and recurrence. Secondly, there is a wide variation in the used SLNM techniques.
2. Standardization of the used tracer, injection and harvesting technique.
Identification of the SLNs in colorectal cancer is usually guided by the in vivo or ex vivo injection of blue dyes, a radioactive tracer or a combination of both. Most experience with the SLNM technique has been reported with blue dye. The particle size of blue dye is relatively small so its passages quickly through the lymphatic vessels and nodes. As a result, all lymph nodes will stain in a few minutes. This makes it impossible to identify the true SLN. Another drawback is the limited tissue penetration depth which makes it impossible to detect SLNs in the fatty mesocolon.
Using only radioactive tracer presents the problem of signal interference of the injection site so we are not able to distinguish between the injection spot and the SLNs. SLN mapping with a near-infrared (NIR) dye is a new and promising technique. In breast cancer and melanoma is has shown excellent results. NIR-dyes 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 make sure there is an adequate resection. In the last year, we included 27 patients with CRC by which a SLNM procedure is performed using the NIR dye Indocyanin Green (ICG). Out of this study we concluded that a submucosal injection technique at the base of the tumour was superior compared to a subserosal peritumoral injection. Although we found fluorescent nodes in all patients, the techniques needs improvement. Penetration depth in fatty tissue is better with ICG than blue dye, but still limited. Fluorescent guidance to the region of interest could benefit from additional guidance provoked by a radioactive component. Preoperative injection of a tracer which consist of a fluorescent and radioactive component would allow for preoperative planning and intraoperative detection of the SLNs.
Preoperative imaging of the SLNs using PET/CT provides useful preoperative anatomic information regarding the location. It can produce a road map to detect all SLNs even if there is an unusual pattern of lymph drainage from the primary tumour. Pharmacokinetics and biodistribution can also be monitored accurately with preoperative imaging. The multimodal SPECT-tracer ICG-99mTc-NanoColl is already used in SLNM in prostate cancer. The authors experienced the value of the real-time fluorescence guidance in areas where accurate gamma tracing was hindered by background signals. The preoperative imaging performed with SPECT/CT provided anatomic information which improved the SLN detection accuracy to 98%. Out of results from SLNM in floor and mouth tumours, we know that the resolution of gamma-or SPECT camera is not always sufficient to visualize and localize SLNs. Probably because of the *shine-through* of the injection site (i.e. primary tumour) which makes detection of

SLNs near the tumour impossible. Intraoperative gamma-probe detection also fails if it can not differentiate between SLN and injection site. The department of Otolaryngology and Nuclear Medicine & PET research of VU University Medical Center Amsterdam (Prof.dr. G.A.M.S. van Dongen and Prof.dr. R. de Bree) have developed a new PET/CT-tracer 89Zr-Nanocoll.
Preliminary results showed that preoperative detection and localization of SLNs with PET/CT was superior compared to SPECT/CT. Another advantage of the 89 Zr-nanocoll compared to the common used SPECT-tracer 99m Tc-Nanocoll is the longer half-life.
For so far, we do not know the kinetics of the tracer in colorectal carcinoma. Therefore we prefer a tracer which can be detected long after administration.

**Study objective**

Aim of the present study is to investigate if a combination of a radioactive and fluorescent tracer can increase the sensitivity and specificity of the SLNM technique in colon and rectal cancer by utilizing the radioactive component for preoperative imaging (PET/CT) and guidance to the SLNs by using the near infrared fluorescence imaging of the nodes during the surgical procedure. The results of this study (scan protocol, amount of conjugate etc.) will be the fundamental part to set up a new trial with larger number of patients.

**Study design**

Single center prospective pilot study

**Intervention**

The proposed study is a prospective feasibility study to demonstrate the feasibility of SLN mapping by using a radioactive and fluorescent tracer.

Study setting:
The proposed study will be conducted at the VU University Medical Center in Amsterdam, The Netherlands. Patients who meet the inclusion criteria will be asked to participate during their standard appointment at the outdoor patient clinic.

Administration of 89Zr-Nanocoll and ICG
The 89Zr-Nanocoll tracer will be administered by colonoscopy ± 48 hrs before start of the operation. The day before tracer administration the sigmoid will be cleaned with Klean-Prep 4L or Moviprep 2L. For injection we use a colonoscopic sclerosing needle. An earlier performed *paste-test* showed that at least 90% of the radioactivity will be administrated. A total of 0.5-4.0 ml, maximum 20 MBq 89Zr-Nanocoll will be administrated in 1-4 injections at the base of the tumour, depending on the size of the tumour. Indocyanin Green 25 mg (Pulsion, Munich, Germany) will be diluted in 9 ml 0.9% saline and 1 ml 200

g/l human albumin. This will be administrated during surgery by colonoscopy when the patient is under general anesthesia. Therefore patient will receive two enemas the day before surgery.

Patients will undergo three PET/ CT scans during this study, independent of the used tracer.
The first will take place directly after tracer administration. The second one ± 24 hrs after tracer administration and the third just before the surgical procedure, respectively ± 48 hrs after tracer administration.

The PET/CT images will be compared with respect to the total number and location of foci and, if visible, lymphatic vessels. During surgery, PET/CT images will be visible on an extern monitor. The images of the SLNs identified with PET/CT scan will be used as guidance for localization of the SLNs during surgical exploration, which makes it easier to identify the nodes.
All patients will undergo laparoscopic surgery. Laparoscopic access will be obtained in the traditional way and abdominal exploration shall be performed to rule out the intra-abdominal metastasis. The involved colonic segment will be localized and mobilized. The SLN procedure will then be performed.
First the segment will be inspected for fluorescent nodes with the NIR-laparoscope. Fluorescent nodes are marked with a suture.
Thereafter the PET/CT images will be used as a roadmap, to detect SLNs which are not visible with the NIR laparoscope. These nodes will also be marked with a suture in a different colour then the fluorescent nodes. The involved segment of the colon and regional lymph nodes will be resected like the conventional way.
Ex vivo the surgical specimen will be inspected for fluorescent and radioactive nodes which are not detected during surgery. All the identified nodes will be taken out ex vivo and stored separately. The number of identified nodes during the surgical procedure will be compared with the number of nodes found by the PET/CT scans.
The entire specimen will be submitted for pathologic examination. All identified fluorescent and/or radioactive nodes will be stained with hematoxylin-eosin (H&E). If the fluorescent or radioactive SLNs are negative after routine H&E staining, they will be sliced in multiple parts and examined with IHC with the specific marker CAM5.2.
The pathologist uses palpation to identify the remaining non-fluorescent and/ or radioactive lymph nodes. Nodes found by palpation will be screened for fluorescence by the NIR-laparoscope and radioactivity by placing them on the tip of a gamma-probe.
Lymph nodes with metastasis will be analysed with the the Q-prodit; an interactive video morphometry system (Leica, Cambridge, UK) to determine the amount of tumour tissue.

## Study burden and risks

All participating patients will receive conventional resection of the tumour

and follow-up according to normal standards in our hospital. The main goal of this study is to optimize the SLN mapping technique in colon cancer. If we are able to identify the true SLN this could lead to better staging and survival of patients with this type of cancer. Patients undergo one or two colonoscopies for injection of the tracers and three additional PET/CT scans. Because of the colonscopy ± 48 hrs before surgery, patients stay in the hospital will be prolonged with one day. The additional risks and exposure to radiation for participating patients are calculated and can be considered as negligible.

## 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
- Age 18 years and older

- Colon cancer (Tis-T1-T2-T3)
- Laparoscopic surgical resection of the tumour
- Regular pre-operative work-up
- Rectal cancer with no indication for neoadjuvant treatment
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### 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
- 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 cancer with indication for neoadjuvant therapy

## Study design

### Design

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

### Recruitment

NL

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|---|---|
| Recruitment status: | Will not start |
| Start date (anticipated): | 01-07-2014 |
| Enrollment: | 12 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Generic name: | Coloscopy |
| Registration: | Yes - CE intended use |
| Product type: | Medicine |
| Brand name: | 89Zirconium-Nanocoll |
| Generic name: | 89Zirconium-Nanocoll |
| Product type: | Medicine |
| Brand name: | ICG-Pulsion |
| Generic name: | Indocyanin Green |
| Registration: | Yes - NL outside intended use |

# Ethics review

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| Approved WMO Date: | 27-06-2014 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 15-01-2015 |
| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-09-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 14-10-2015 |
| Application type: | Amendment |
| Review commission: | METC Amsterdam UMC |
| Approved WMO Date: | 21-01-2016 |
| 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 | EUCTR2014-000304-96-NL |
| CCMO | NL47648.029.14 |