# The influence of micrometastases on prognosis and survival in stage I-II colon cancerpatients: the EnRoute+ study

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The purpose of the study is to delineate the upstaging percentage of pN0 patients by detection of micrometastases (pN0micro+) and evaluate the benefits from adjuvant chemotherapy on disease recurrence in pN0micro+ CC patients.

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|---|---|
| **Ethical review** | Approved WMO |
| **Status** | Will not start |
| **Health condition type** | Malignant and unspecified neoplasms gastrointestinal NEC |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON36641

**Source**
ToetsingOnline

**Brief title**
EnRoute+ study

### Condition

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

**Synonym**
colon cancer, large intestine cancer

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Jeroen Bosch Ziekenhuis
**Source(s) of monetary or material Support:** KWF en NWO aanvragen pending

## Intervention

**Keyword:** adjuvant chemotherapy, colon cancer, micrometastasis

## Outcome measures

### Primary outcome

Primary endpoint is 3-year DFS in study groups (proportion of patients without local or distant recurrence, or second primary colorectal cancer, during the defined period of time).

### Secondary outcome

Secondary endpoints are rate of upstaging in pN0 colonic cancer patients (total number pN0micro+ patients x 100 / total number pN0 colon cancer patients) and 3-year overall survival.

# Study description

### Background summary

Colorectal cancer is the second most commonly diagnosed malignancy in men and women in the Netherlands with increasing incidence due to growth and ageing of the general population. The presence of lymph node metastases remains the most reliable prognostic predictor and the gold indicator for adjuvant treatment in colon cancer (CC). Interestingly, in a large percentage of patients without lymph node metastases in the surgical specimen, who are therefore not subjected to adjuvant chemotherapy, represent with disease recurrence. In about 10% of the patients with stage I (Dukes A) and 15-30% with stage II (Dukes B) disease recurrent locoregional or distant metastases develop within 5 years. One possible factor could be the presence of occult lymph node metastases at the time of presentation and surgical resection. Evidence has emerged showing a significant amount of nodal metastases being smaller than 2 mm or less (<0.2 mm isolated tumor cells [ITC]; 0.2 - 2mm micrometastasis [MM]) and they are likely to be missed during conventional gross pathological specimen examination. Focused examination methods, such as more extensive nodal examination by serial sectioning or step sectioning, or molecular detection of metastatic nodal cells by immunohistochemistry (IHC) or reverse transcriptase-polymerase chain reaction (RT-PCR), increase the likelihood of finding these occult tumour

deposits. However, these focused examination methods are expensive and time consuming, and therefore not applicable to all lymph nodes derived from the surgical specimen. By using sentinel lymph node mapping (SLNM) the nodes at highest risk of harbouring tumour deposits can be potentially detected and more thoroughly examined. The ex vivo SLNM procedure is technically easy, as the procedure is executed extracorporally by injection peritumoral blue dye subserosally or submucosally after which gentle massage of the injection site is performed. Blue coloured lymph nodes are excised or marked by sutures. The ex vivo SLNM procedure is characterized by a high accuracy of 90-100%, and negative predictive value of 80-100%. A rate of 19-57% upstaging is observed. Current knowledge about the prognostic relevance of nodal micrometastases and isolated tumor cells has adequately been reviewed in 2004 separately by Iddings and Nicastri. They concluded that a suggestion of prognostic relevance could be made for micrometastatic disease related to worsened disease-free survival (DFS) and overall survival (OS). The meta-analysis performed by Iddings showed a decreased 3-year DFS and OS of respectively 78% and 78% in pN0micro+ patients compared to 90% and 97% in pN0micro- patients. A solid conclusion, however, could not be made because of the lack of well-designed, well powered, controlled clinical trials. Data from other solid organ malignancies like breast cancer links micrometastatic disease to a worsened prognosis. Several prospective trials are currently recruiting. However, an randomized, controlled clinical trial of significant magnitude is needed to answer this clinically relevant question.
Adjuvant chemotherapy is only offered to high risk stage I-II colon cancer patients in the Netherlands at present. Stage I-II CC patients without risk factors are thought to do not benefit from adjuvant treatment. Individual randomized trials did not show a survival benefit in stage II colon cancer patients. The results of meta-analyses and systematic reviews show at the most a slight disease-free survival benefit of adjuvant chemotherapy in stage II disease. However, to stress out the importance of further investigation, stage I-II CC patients do suffer from disease recurrence and their overall 5-year survival is just around 70-80%. Even stage II CC patients without risk factors have been shown in several studies to benefit from adjuvant treatment. It is because of these results that in Eastern countries and the United States stage II CC patients with or without micrometastatic disease do receive adjuvant treatment. Thus, there is an international need for better delineation of high-risk stage I-II CC patients who should be offered adjuvant treatment.

## Study objective

The purpose of the study is to delineate the upstaging percentage of pN0 patients by detection of micrometastases (pN0micro+) and evaluate the benefits from adjuvant chemotherapy on disease recurrence in pN0micro+ CC patients.

## Study design

EnRoute+ is an open label, multicenter, randomized controlled clinical trial. A centrally-performed, computer-generated randomization procedure is instituted. Eligible patients are randomly assigned at a 1:1 ratio to receive treatment respectively without or with chemotherapy using block-randomisation per participating center. Design, flow chart and follow up are presented in Figures 1-3.
Study groups are defined according the randomisation group and pathological examination result.
group A pN0micro+ with chemotherapy
group B pN0micro+ without chemotherapy
group C pN0micro- without chemotherapy

### Intervention

Detection of micrometastases in pN0 colon cancer patients through ex vivo sentinel lymph node mapping procedure and fine pathology by serial sectioning and immunohistochemistry. pN0micro+ patients will be randomised to receive adjuvant chemotherapy or no adjuvant treatment. Adjuvant chemotherapy will be according to the CAPOX scheme (capecitabine/oxaliplatin) and capecitabine monotherapy.

### Study burden and risks

No additional risks for patients is introduced by the ex vivo SLNM procedure as the complete procedure is performed extracorporally. Participation in the randomization study brings risks and discomfort common to adjuvant systemic chemotherapeutic treatment as given to patients with stage III colon cancer (CAPOX scheme or capecitabine monotherapy). Dose limiting toxicities of oxaliplatin/capecitabine include diarrhoea, abdominal pain, nausea, stomatitis and hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia). Most adverse reactions are reversible and do not require permanent discontinuation of therapy, although doses may need to be withheld or reduced. A potential negative effect on prognosis can be expected in patients not receiving adjuvant chemotherapy.

## 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

- histological proven colon cancer, clinically localized, judged potentially resectable for cure, without intraoperatively gross nodal involvement
- radiological suspicion of colon cancer, clinically localized, judged potentially resectable for cure, without intraoperatively gross nodal involvement
- patients free of disseminated disease
- written informed consent

## Exclusion criteria

- previous chemotherapy
- high risk pN0 patient according to: less then 10 lymph nodes detected in resected specimen, or invasion in other organs (T4NxMx), or colon perforation at presentation, or obstruction at presentation, or angioinvasion at pathological examination.
- clinically positive nodal tumours or advanced disease (stage III / Dukes C)
- haematology (within 7 days before start of chemotherapy treatment): Hb <= 6,2 mmol/l, WBC <= 3,0 x 109/L, platelets <= 100 x 109/L
- renal function (within 7 days before start of chemotherapy treatment): creatinine < 1,25 UL or < 125 µmol/l; creat.clearance < 60 ml/min.(Cockcroft-Gault formula)
- liver function (within 7 days before start of treatment): bilirubin >= 1,5 UL, ASAT >= 2,5 UL, ALAT >= 2,5 UL, gamma-GT >= 2,5 UL, ALP >= 5 UL,
- other current serious illness or medical conditions: severe cardiac illness (NYHA class III-IV) ,

significant neurologic or psychiatric disorders, uncontrolled infections, active DIC, other serious underlying medical conditions that could impair the ability of the patient to participate in the study
- known hypersensitivity to study drugs
- definite contraindications for the use of corticosteroids
- use of immunosuppressive or antiviral drugs
- any other experimental drugs within a 4-week period prior to start of surgery and adjuvant chemotherapy and throughout the study period
- pregnancy or lactation

# Study design

## Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Open (masking not used) |

**Primary purpose:** Diagnostic

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Will not start |
| Start date (anticipated): | 01-07-2010 |
| Enrollment: | 1000 |
| Type: | Anticipated |

## Medical products/devices used

| | |
|---|---|
| Product type: | Medicine |
| Brand name: | eloxatin |
| Generic name: | oxaliplatin |
| Registration: | Yes - NL intended use |
| Product type: | Medicine |
| Brand name: | Xeloda |
| Generic name: | capecitabine |

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|---|---|
| Registration: | Yes - NL intended use |

## Ethics review

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| Approved WMO Date: | 26-07-2010 |
| Application type: | First submission |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 06-09-2010 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 13-10-2010 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 20-12-2010 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 05-01-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 08-03-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 04-04-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 05-04-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

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| Approved WMO Date: | 19-04-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 24-05-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 13-07-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 17-08-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 21-12-2011 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |
| Approved WMO Date: | 07-11-2012 |
| Application type: | Amendment |
| Review commission: | METC Brabant (Tilburg) |

# 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 | EUCTR2010-018612-32-NL |
| CCMO | NL31438.028.10 |