Sentinel node and organ sparing surgery in stage I colon carcinoma (SENTRY trial)

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

Summary

ID

NL-OMON56976

Source
ToetsingOnline

Brief title
SENTRY

Condition

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

Synonym
colon cancer, colon carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Meander Medisch Centrum
Source(s) of monetary or material Support: Meander Medisch Centrum

Intervention

Keyword: Colon carcinoma, fluorescence-guided surgery., organ-preserving surgery, sentinel lymph nodes

Outcome measures

Primary outcome

The aim of this study is to reduce the need for colectomy and its* associated morbidity and mortality in patients with high-risk pT1 or low-risk pT2 colon carcinoma after endoscopic polypectomy by performing an endoscopy-assisted laparoscopic wedge resection and SLN biopsy.

The primary outcome of phase II is percentage of successful wedge resections and SLN biopsies.

The primary outcome of phase III is 3-year proportion of recurrences (recurrence at the site of the excised primary cancer or the adjacent mesocolon, lymph node metastases or distant metastases) in which wedge resection and SLN biopsy will be compared to standard segmental resection. The 3-year (locoregional) recurrence was chosen as the primary outcome since 92% of recurrence occurs during this time period.

Secondary outcome

Phase II:

- Proportion of patients with preference for standard and experimental treatment, and without preference

- Procedure time of organ-sparing surgery vs segmental resection

- Intraoperative complications

- Percentage of patients with a positive SLN

Phase III:

- 90-days postoperative morbidity (Clavien-Dindo classification)

- 90-days postoperative mortality

- 5-year proportion of recurrences

- 3-year overall survival

- 5-year overall survival

- Quality of life

- Costs

- Upstaging of SLNs due to ultrastaging

Study description

Background summary

Since the introduction of a Dutch nation-wide population screening programme for colorectal cancer in 2014, an increase in incidence of T1-T2 tumours was observed, with a subsequent increase in local excisions (e.g. transanal endoscopic microsurgery and full-thickness resection) and polypectomies. The risk of lymph node metastasis is relatively small in cT1-2 colon carcinoma. Diagnostic accuracy of CT abdomen is very limited, for which reason a formal oncological colonic resection has to be performed for definitive nodal staging based on pathological examination of the draining mesocolon. However, segmental resections after radical local excision of early cancers will overtreat 80 to 90% of patients depending on the histological risk profile since they do not have lymph node metastases. Colonic resections are associated with substantial morbidity and mortality.
To reduce the number needed to treat for colonic resection in early colon cancer, risk stratification is applied based on histopathological examination of locally excised lesions. In low-risk T1 lesions, colonic resections are already omitted. We hypothesise that sentinel lymph node (SLN) biopsy can identify patients with lymph node metastases in high-risk T1 and low-risk T2 tumours. In our experience, during a pilot study (n = 10), the SLN procedure

was a successful, fast and safe procedure.
The SLN procedure would be combined with an endoscopy-assisted limited wedge-resection to further reduce local recurrence risk. The wedge resection is a safe procedure to remove polyps and small tumours and has been performed in multiple Dutch hospitals. Wedge resection can efficiently be performed since the SLN already requires an intraoperative colonoscopy. The (local) recurrence risk of node-negative pT1-2 patients after SLN biopsy and wedge resection after endoscopic polypectomy should outweigh the risk of segmental colonic resection. Thereby, patients can be offered a watchful waiting strategy after a negative SLN procedure.
This sequential phase II and III study compares the combined SLN procedure and wedge resection with segmental colectomy for patients with early-stage colon carcinoma (high-risk T1 and low-risk T2) after endoscopic polypectomy. This would be an innovating step towards organ preserving colon cancer treatment.

Study objective

The aim of this study is to reduce the need for colectomy and its* associated morbidity and mortality in patients with high-risk pT1 or low-risk pT2 colon carcinoma after endoscopic polypectomy by performing a (robot-assisted) laparoscopic wedge resection and SLN biopsy sentinel node biopsy and wedge resection of the scar.

Study design

The SENTRY trial is designed to determine the oncological safety of an organ-preserving approach with local excision combined with SLN procedure and watchful waiting in case of a tumour negative sentinel node. Based on experiences in organ preserving approaches in rectal cancer, it was decided that a classical RCT design will likely result in slow accrual because of clear patient preferences and lack of equipoise. These issues can be overcome by a randomised patients* preference trial (RPPT) design. Oncological safety will be determined using a non-inferiority design.
Therefore, we will conduct a prospective multicentre, non-inferiority, randomised patients* preference trial. Eligible patients will be assigned to either segmental colectomy (standard of care) or an experimental treatment with wedge resection and sentinel node procedure including watchful waiting in case of negative sentinel node, according to patients* preference or 1:1 randomisation in case the patient has no clear preference.
Patients* preference does lead to a substantial proportion of patients refusing randomisation. However, patients* preference does not affect the primary outcome of an RPPT, but increased participation (ranging 48-100%) which improves external validity compared to a classic RCT since specific patient groups might me more likely to not participate in a RCT. Furthermore, participants of the patients* preference cohort have fewer crossovers and loss to follow-up compared to participants in the randomised cohort. Therefore,

internal validity is improved and results can be better interpreted.
The study is designed as a sequential phase II-III study, in which the feasibility of sentinel node biopsy and allocation according to patients* preferences will be evaluated in phase II, the first 80 patients. The feasibility is fulfilled if a SLN is detected in >=80% of patients. We will subsequently proceed with the phase III trial to determine the non-inferiority on the primary endpoint. Based on the preliminary data of the phase II trial, we might adapt our power calculation. If <80% of SLNs are detected during phase II, the study will be stopped. The study will not be paused to evaluate the stopping rule since temporarily halting the study could result in confusion in the including centres. More importantly, the DSMB can quickly evaluate the stopping rule after the inclusion of the 40th patient (in experimental group) since it is an intraoperative outcome.

Intervention

1. Patients are identified at the outpatient clinic after multidisciplinary consultation and asked for participation in the study.
2. Patients will be planned for endoscopic-assisted wedge resection.
3. Mechanical bowel preparation (MBP) will take place one day prior to surgery.

Sentinel lymph node identification
4. After achieving abdominal access and inspection of the abdomen, a colonoscopy will be performed. Subsequently the gastroenterologist will create four blebs around the tumour with 0.9% NaCl. Thereafter, the gastroenterologist will inject ICG in the four blebs in order to minimise spill of ICG.
5. The available near-infrared camera system is used to visualise the SLN, which will be harvested. If multiple SLNs appear, the first four SLNs will be harvested.

Wedge resection
6. A suture is placed with intraluminal endoscopic visualisation at the base of scar of the tumour.
7. Traction is given on the suture to enable positioning of a linear stapler.
8. The patency of the colonic lumen and total inclusion of the scar is checked by the gastroenterologist before stapling.
9. After stapling, the resected specimen is removed in an endobag after which the gastroenterologist and surgeon check the colon for signs of bleeding or perforation before ending the procedure.
An instructional video of wedge resection is available at www.limeric.nl

Postoperative procedures
10. Postoperative care on the ward will be according to SOC.
11. Pathological examination will be done using haematoxylin & eosin (H&E). If the SLN is negative, the SLN will be examined using serial slicing and subsequent IHC.
12. If all SLNs are negative, an adjusted watchful waiting follow-up schedule

is followed.
13. If a SLN contains (micro)metastases (metastases >= 0.2 mm), a complementary segmental resection and adjuvant chemotherapy will be advised by multidisciplinary team if performance status allows. Treatment will always be a shared decision between physician and patients.

Study burden and risks

Potential benefits associated with participation:
The wedge resection and SLN biopsy would result in less invasive surgery as no segmental colectomy will be performed. One of the most important complications of segmental colectomy is anastomotic leakage which is associated with substantial morbidity, ICU admittance and longer length of stay. In case of a wedge resection, there is also a staple line but no anastomosis between two bowel segments after vascular ligation of mesenteric vessels. Therefore, the risk of leakage is expected to be neglegible. Fewer complications would also lead to reduced mortality.
Furthermore, a limited resection will be performed compared to segmental resection which should improve postoperative bowel function due to the organ-sparing nature of the surgery. Short-term this would reduce postoperative ileus. Long-term might improve defaecation as patients undergoing segmental colectomy often experience altered defaecation patterns.
The length of stay will be shorter due to the afore mentioned benefits. The hospital stay of patients in the LIMERIC-I was most often one day, or two days in the other cases. This is shorter than segmental colectomy. Due to more experience with wedge resections, we expect that patients might even be treated in day care.
The reduced hospital stay and fewer complications likely benefits both patients and society since it improves quality-of-life and reduces costs.

Potential risk associated with participation:
One of the considerations of the wedge resection and SLN identification is the risk of missed lymph node metastases. We estimate that the SLN procedure using submucosal injection and improved near-infrared camera systems has a sensitivity of 80% for the detection of lymph node metastases in the study population (stage I), thereby accepting that we will miss 20% of metastasis in a population with an overall absolute risk of 10%, accounting for 2% absolute risk that a lymph node metastasis remains undetected. Furthermore, tumour deposits (TDs) could potentially be missed when patients are treated with the SLN procedure and wedge resection. However, in a large cohort of 103.755 patients, only 111 of 24,927 patients (0.45%) with stage I disease were TD-positive.

Furthermore, subjects in the intervention arm of this study will be administered ICG. ICG has a well-established safety profile and the risk of anaphylaxis for ICG is reported to be about 1 per 42,000. In case an anaphylactic reaction does take place, we will have the medication, necessary

for counteracting an anaphylactic reaction, present in the operation room.

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 (IC)
- Aged 18 years and older
- Fit for both organ-sparing surgery and colectomy
- Pathologically confirmed high-risk T1 or low-risk T2 adenocarcinoma of the colon after R0/R1/Rx endoscopic resection
- The resection scar after local excision is expected to be clearly recognized at endoscopy, either by a tattoo or by detecting a scar in the colorectal segment where no other polypectomies were performed
High-risk features for T1-T2 colorectal carcinoma are:

- Poor differentiation grade or undifferentiated (WHO classification of tumours: exhibits glandular structures in <50%)
- Positive tumour budding (tumour budding grade 2-3)
- Presence of lymphovascular invasion (The presence of cancer cells within endothelial-lined channels)

Exclusion criteria

- Lesion located <25cm from the anus based on endoscopic measurement
- Distant metastasis
- Mucinous or signet ring cell carcinoma
- Lynch syndrome
- Other primary malignancy treated within 5 years prior to diagnosis of colon cancer, except for curatively treated prostate, breast, skin and cervical cancer
- Tumours that comprised >50% of the colon circumference before endoscopic resection
- Tumours involving the ileocaecal valve
- Pregnancy, lactation or a planned pregnancy during the course of the study
- Known allergy to any of the compounds used for SLN identification (ICG, Iodine or Sodium iodide)
- Previous colonic surgery (excluding appendectomy).
- Contra-indication for laparoscopic or robotic surgery
- Severe kidney- or liver failure
- Hyperthyroidism or an autonomously functioning thyroid adenoma

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruiting

Start date (anticipated):	12-12-2024
Enrollment:	325
Type:	Actual

Ethics review

Approved WMO Date:	26-08-2024
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL84875.100.23