Lanorec study: Lateral Nodal Recurrence in rectal Cancer

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To investigate whether a standardized multidisciplinary treatment of rectal cancer patients with enlarged lateral lymph nodes will decrease the amount of local recurrences. Secondary outcomes are morbidity, quality of life and functional outcomes.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Malignant and unspecified neoplasms gastrointestinal NEC
Study type	Observational invasive

Summary

ID

NL-OMON52811

Source
ToetsingOnline

Brief title
LaNoReC

Condition

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

Synonym
Lateral lymph node recurrence in rectal cancer, metastasised rectal cancer

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: KWF subsidie

Intervention

Keyword: lateral nodal recurrence, rectal cancer

Outcome measures

Primary outcome

To investigate whether optimal irradiation and indicated lateral lymph node dissections (LLNDs) can reduce the lateral local recurrence rate to 6%, as described in the literature. Patients who cannot undergo nerve sparing LLND or minimally invasive TME due to the extensiveness of their tumor will drop out of the main cohort and enter the registration arm together with Asian patients treated in Asia who follow the exact same protocol.

Secondary outcome

To evaluate the morbidity, quality of life and functional quality of patients by questionnaires.

Study description

Background summary

The complexity of rectal cancer treatment increases towards the level of the sphincter. Tapering of the mesorectum imposes that the circumferential resection margin (CRM) is more easily involved (R1 resections) than in higher tumors. In addition, the pelvic nerves, the sphincter complex and reproductive organs are close by in low rectal cancers, which can lead to morbidity and reduced quality of life. Oncological and functional outcomes are highly dependent on available expertise and cooperation within the multi-disciplinary team.
Distal, locally advanced, rectal cancer has the tendency to spread to lateral lymph nodes. Previous research has shown that patients with enlarged lateral lymph nodes have a considerable chance of local recurrence, e.g. 19.5% in 5 years1. Western surgeons have always relied on (chemo)radiotherapy ((C)RT) to sterilize the lateral compartment containing the internal iliac and obturator lymph nodes. Eastern surgeons however treat enlarged lateral lymph nodes with a

lateral lymph node dissection (LLND), which is technically challenging to perform and associated with nerve function disorders. Furthermore, most Western clinicians consider lateral nodal disease to represent metastatic disease, not amendable to cure2. Recently, the Lateral Node Study consortium undertook a multi-center study with 12 centers from seven countries, collecting data over a 5-year period, including all consecutive patients operated for a cT3 or cT4 rectal cancer1,3. In all patients, MRI*s were re-reviewed by a standardized protocol, examining lateral pelvic nodes, defining these according to size and the presence of malignant features and relating these to the development of locally recurrent disease.

In the first publication of the consortium with a total of 1216 patients, it was shown that a pre- treatment lateral lymph node (LLN) size of * 7 mm results in an unacceptably high incidence of lateral local recurrence of 19.5%, despite (C)RT with total mesorectal excision (TME)1. Within the consortium, several centers performed LLND*s after (C)RT, which resulted in a significantly lower rate of lateral local recurrence of 5.7% in nodes * 7 mm ($p = 0.042$). Furthermore, LLN enlargement did not influence distant metastases rate, suggesting it is a local issue, which requires to be addressed through targeted treatment in the pelvis, rather simply representing a marker of poor prognosis and distant disease.
To assess the value of restaging MRI, patients who underwent (C)RT and had a restaging MRI were then selected, leaving 741 for analyses: 651 had (C)RT+TME, 90 underwent (C)RT+TME+LLND. In total, 96 patients (14.7%) had nodes * 7 mm in short-axis on primary MRI (pre-SA). At 3 years after surgery, there were no lateral local recurrences in 28 patients (29.2%) with nodes that had a short-axis of * 4 mm on restaging MRI (post-SA). There was an important difference between the nodes that had a short-axis of * 4 mm on restaging MRI (post-SA). And, there was an important difference between the nodes located in the internal iliac compartment versus the ones in the obturator compartment. In the internal iliac nodes, there was only a 22% chance of becoming * 4 mm. Pre-SA * 7 mm, post-SA > 4 mm in the internal iliac compartment resulted in a 5-year lateral local recurrence rate of 52.3%. Adding LLND to (C)RT+TME in these malignant internal nodes, resulted in a significantly lower 8.7% lateral recurrence rate ($p = 0.0071$). In the nodes in the obturator compartment, the chance of becoming * 4 mm was 36%, but even in the nodes * 6 mm (63%) there was a 0% chance of lateral local recurrence. If the nodes however remained post-SA > 6 mm, the chance of lateral local recurrence was 17.8%. This was reduced to 0% after a LLND3.

The major drawback from this multi-center study is its retrospective nature. The institutional protocols stated that the lateral nodal compartments would always be included in the irradiation volume in these types of rectal cancers. However, whether this was practiced for each individual patient was impossible to find out. It might be that the internal iliac were not always included in the irradiation volume, explaining the low response rate and the high lateral local recurrence rate. Also, although it was reconstructed from the operation

reports that all patients had a complete formal LLND, surgery was not standardized, not guaranteeing clearance of all nodes with formal anatomical landmarks and boundaries of the dissection. So, we don*t know which part of the high local recurrence rates in enlarged nodes is due to inadequate application of radiotherapy, and which part is due to not performing (adequate) lateral lymph node dissections. Moreover, functional outcome and quality of life data are not known for this cohort of patients. Therefore, a national prospective registration study is presented here, aiming to standardize radiotherapy and surgery, and to assess quality of life outcome after this treatment.

Study objective

To investigate whether a standardized multidisciplinary treatment of rectal cancer patients with enlarged lateral lymph nodes will decrease the amount of local recurrences.

Secondary outcomes are morbidity, quality of life and functional outcomes.

Study design

Please also see the flowchart in the protocol.

Briefly, patients with rectal cancer and 1/more LNN of >7.0mm in the internal iliac or obturator compartment can be included. They will undergo standardised radiotherapy and chemotherapy, according protocol. After 6 weeks a new MRI scan will be made, and the short-axis of the LNN in the internal iliac/obturator compartment will be measured again.

If a LLN in the internal iliac compartment <4mm and a clinical complete response (cCR) => Watch & Wait + FU
If a LLN in the internal iliac compartment <4mm and NO clinical complete response (cCR) => TME
If a LLN in the internal iliac compartment > 4mm and NO clinical complete response (cCR) => TME + referral to VUmc for LLND

If a LLN in the obturator compartment <6mm and a clinical complete response (cCR) => Watch & Wait
If a LLN in the obturator compartment <6mm and NO clinical complete response (cCR) => TME
If a LLN in the obturator compartment >6mm and NO clinical complete response (cCR) => TME + referral to VUmc for LLND

Patients with extensive tumors and/or lateral nodal disease which means that they cannot undergo minimally invasive TME surgery and/or nerve sparing LLND surgery will drop out of the main study cohort and enter the registration study. They require invasive and extensive surgery to ensure goed resection

margins. These patients will be followed in the registration cohort.

Patients will undergo follow-up according to local protocol, except that they will have an additional MRI after 2yrs (this appointment is not extra, but the MRI imaging is suggested instead of other options such as X-thorax/endoscopy). Before irradiation and after 6, 12, 36 months a quality of life questionnaire will be obtained

Intervention

Standardised radiotherapy and selective lateral lymph node dissection in high risk patients.

Study burden and risks

The potential benefit resulting from participation is improvement in oncological outcome, mainly by the reduction of lateral local recurrence. A local recurrence is associated with significant morbidity and disease related mortality. More than half of the patients with a local recurrence can only be treated palliatively. Another advantage is that patients will be closely monitored with frequent follow-up visits, with one extra MRI for local recurrence monitoring.

The potential risks are mostly associated with the performance of a LLND. The main peroperative complication is bleeding. In the last years, this was mainly performed via open surgery, but nowadays laparoscopic LLND is gaining interest. A recent meta-analysis showed that laparoscopic LLND has similar efficacy in oncological outcomes and postoperative complications to conventional (open) surgery. Yet, laparoscopic LLND resulted also in advantages of reduced intraoperative blood loss and shorter postoperative hospital stay.

The most important postoperative complication is a LLND is urinary dysfunction, caused by autonomic nerve injury during surgery. However, complete preservation of autonomic nerves during LLND reduces the incidence of dysfunction by 4-8%. Moreover, recent research showed no significant difference in percentages of urogenital dysfunction between patients who underwent TME + LLND and patients who underwent TME alone (i.e. 79% vs 68% in 343 patients).

The main goal of this study is to ensure quality control of LLND*s, by performance of the procedure by experienced surgeons and video analysis. As described in chapter 5.4, surgery will be centralized and surgeons will go through an intensive training and proctoring program, to ensure a standardized procedure is performed to reduce per- and postoperative complications.

The burdens for patients taking part in this study are not great that patients who do not take part, except if they undergo a LLND procedure (see above). Then

there are added positives that the local recurrence chance should be reduced.

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

In order to be eligible to participate in this study, a subject must meet all of the following criteria:
- patients with rectal cancer
- at least one enlarged lateral node; with a short-axis of *7mm on the iliac or obturator compartment, measured on MRI

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study:
- Patients younger than 18 years old
- Patients with previous pelvic radiotherapy
- Patients that have undergone a lateral lymph node dissection for a previous pelvic malignancy
- Patients with synchronous distant metastases
- Synchronous colon cancer with a higher stage than the rectal cancer
- Other malignancies in the previous 3 years which could affect oncological outcomes (these patients must first be discussed with the research team before inclusion)
- Patients with an absolute contra-indication for general anaesthesia
- Patients with familiar adenomatous polyposis (FAP)
- Pregnancy

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-11-2020
Enrollment:	145
Type:	Actual

Ethics review

Approved WMO

Date:	03-11-2020

Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-05-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2022
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	NL72626.029.20
Other	NL8593