HERBERT II: external beam radiation therapy followed by high-dose rate endorectal brachytherapy (HDRBT) in elderly early rectal cancer patients not undergoing surgery: A randomized multicenter phase III study

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To assess the added value of a brachytherapy boost after external beam radiotherapy in elderly, frail patients with rectal cancer.

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

Summary

ID

NL-OMON55855

Source
ToetsingOnline

Brief title
HERBERT II

Condition

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

Synonym
rectal cancer

Research involving

Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: KWF/Alpe d□Huzes 2013-6311

Intervention

Keyword: Brachytherapy, Elderly, Rectal cancer

Outcome measures

Primary outcome

Complete clinical response (cCR) at 26 weeks after EBRT for the control group

and at 26 weeks after the last brachytherapy fraction for the intervention

group.

Secondary outcome

• Acute and late toxicity (CTCAE v5)

• HRQL and functional status at 1 and 2 year

• Sustainability of response at 2 years

• Overall survival at 2 years

Study description

Background summary

The incidence of rectal cancer in elderly patients is increasing due to screening and aging of the population. While TME surgery with or without pre-operative radio(chemo)therapy is the standard treatment for rectal cancer, the risk of surgical complications and post-operative mortality rises with increasing age and comorbidity. Postoperative complications occur in approximately 50% in patients older than 75 years and one-month postoperative mortality in patients aged 75-95 with an American Society of Anaesthesiology classification of II-IV ranges from 5.4%-28.0%. At 6 months, this results in an overall mortality of 13.4% in patients aged 75-85 increasing and almost 30% in

patients of 85-95 years. Because patients who are unfit for surgery, are usually also unfit for chemotherapy, they are often offered palliative radiotherapy to reduce symptoms. There are however indications that patients might benefit from a more radical approach using radiotherapy alone.
To achieve local control with radiotherapy alone high doses must be delivered. With standard doses external beam chemoradiotherapy (EBRT, 45-50 Gy) a complete pathologic response (pCR) is observed in approximately 16%. Dose response analyses indicate that doses as high as 92 Gy (EQD2) are needed to achieve pCR in 50% of patients. To further escalate the dose without exceeding normal tissue tolerance, local boosts on the tumour can be applied with various techniques. The attraction of intracavitary irradiation, either by contact therapy or by endoluminal brachytherapy lies in the ability to deliver a localised high dose with rapid fall-off and sparing of adjacent normal tissues. Combining EBRT with intracavitary irradiation in such a way that the chances of local control are increased without causing excessive toxicity, therefore seems a promising option.
In medically inoperable rectal cancer patients, there is no standard treatment schedule for radiotherapy. This led to the initiation of a dose escalation study in this patient group by the LUMC, called the HERBERT trial. The treatment schedule consisted of 13 fractions of 3 Gy EBRT, followed by high dose rate endoluminal brachytherapy (HDREBT) 6 weeks later. The brachytherapy was given in 3 fractions with the starting dose level being 3x5 Gy, prescribed at the depth of the tumor. Eventually, 38 patients have been included and the maximum tolerated dose has been reached at a level of 3x7 Gy, with clinical grade 3 proctitis being the dose limiting factor. In total, clinical response could be evaluated in 33 patients. Seven patients (21%) had a complete response after EBRT, whereas an additional 13 achieved a complete response after the brachytherapy, resulting in 60% complete responders in total. None of the patients demonstrated progressive disease in the evaluation 6 weeks after the EBRT. However, of the 5 patients with stable disease (SD), none reached a complete response. Patient reported bowel symptoms showed a marked increase at the end of EBRT and two weeks after HDREBT. Acute grade 2 and 3 proctitis occurred in 68.4% and 13.2% respectively while late grade 2 and >=3 proctitis occurred in 52% and 36%. Endoscopic evaluation mainly showed erythema and telangiectasia. In three patients frank haemorrhage or ulceration occurred. Most severe toxicity was observed 12-18 months after treatment.
Based on this study, it was concluded that for elderly patients with rectal cancer, definitive radiotherapy can provide good tumour response but has a substantial risk of toxicity. The potential benefit and risks of a HDREBT boost above EBRT alone must be further evaluated.

Study objective

To assess the added value of a brachytherapy boost after external beam radiotherapy in elderly, frail patients with rectal cancer.

Study design

A total of 110 patients will be included and receive EBRT in 13 fractions of 3 Gy to the mesorectum. Patients will then be evaluated and if there is no progressive disease they will be randomized between no further treatment or a HDR endorectal brachytherapy boost to the primary tumour in 3 fractions of 7 Gy, given one a week. The first fraction of brachytherapy should take place within an interval of 11-15 weeks after EBRT.

Intervention

Control group of EBRT (13 fractions of 3 Gy) alone versus intervention group EBRT + HDREBT (13 fractions of 3 Gy + 3 fractions of 7 Gy). For patients randomized to the intervention group, the HDR boost will be given at least 10 weeks after end of EBRT.

Study burden and risks

Patients included in this study will receive multiple additional examinations. Prior to the EBRT treatment, all patients will receive a sigmoidoscopy during which reference markers will be placed to mark the tumor borders. The expected complication risks of the endoscopy and the marker placement are very limited. A very low rate of pain, bleeding or infectious complications has been reported in previous transrectal marker placement or rectal marker placement studies. Similar results have been found in the recently performed REMARK study with gold fiducial markers. The endoscopy and fiducial marker placement will last about 30 minutes.
Patients will undergo the multi-parametric MRI exam 3 additional times in this study. The repeat of the MRI exam causes a negligible risk for the patient.
Patients in the intervention group will receive endoluminal brachytherapy. The brachytherapy fractions will be delivered using a endorectal applicator (Intracavitary Mold Applicator, Elketa, Veenendaal, The Netherlands) with a diameter of 2 centimeter, consisting of a central flexible tube with 8 catheters arranged around the circumference of a central tube. Patients in both the control and the intervention groups will fill in questionnaires about their experiences with the treatment and to evaluate the willingness of patients to receive endoluminale brachytherapy. Expected complications of endoluminal brachytherapy are limited. However, the HERBERT study demonstrated 35% late grade 3 toxicity after the whole treatment. At the same time, increased tumor control is expected in patients undergoing brachytherapy.

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

• Adenocarcinoma of the rectum
• WHO performance status 0-3
• Frail patients unfit for surgery or refusing surgery (see §4.3)
• Tumors with a sufficient lumen to allow the positioning of the flexible, multichannel applicator
• Signed informed consent prior to start of protocol specific procedures

Exclusion criteria

• Extramesorectal (e.g. iliac, lateral) pelvic lymph node involvement
• 4 or more lymph nodes > 1 cm disease on MRI (gross N2 disease)
• M1 disease
• Extension of tumour into the anal canal
• Tumor > 2/3 of the circumference
• Previous pelvic irradiation

• Prior chemotherapy
• Prior surgery for rectal cancer, except local excision > 3 months before start of EBRT
• Contra-indication for endoscopic placement of gold-markers such as coagulopathy (prothrombin time < 50% of control; partial thromboplastin time > 50 seconds) or anticoagulantia (marcoumar, sintrom or new oral anticoagulants) that cannot be stopped.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	24-07-2021
Enrollment:	110
Type:	Actual

Ethics review

Approved WMO

Date:	25-05-2020
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	11-08-2021
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 26642
Source: Nationaal Trial Register
Title:

In other registers

Register	ID
CCMO	NL69261.058.19
Other	NL7795
OMON	NL-OMON26642