OPtimizing Preoperative EndoRectal BrachyTherapy (OPPER-BT)

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Establishment of an image-guided brachytherapy procedure that is feasible for a multicenter randomized trial

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

Summary

ID

NL-OMON45506

Source
ToetsingOnline

Brief title
OPPER-BT

Condition

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

Synonym
adenocarcinoma of the rectum, Rectal cancer, rectal tumor

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: KWF/Alpe d'HuZes UL 2014-6311

Intervention

Keyword: brachytherapy, image guidance, rectal cancer

Outcome measures

Primary outcome

To establish an image-guided brachytherapy procedure for rectal cancer that is feasible for use in a multicenter randomized trial.

The protocol will be declared feasible and robust for multicenter use if in both institutes 4/5 patients have been treated without defined violations. The following events are considered violations:

* Patients not completing the brachytherapy (i.e. 4 fractions) due to non-compliance

* Geographic miss of the tumor bed (as determined by review by PI)

* Inability to reproduce the planning position of the applicator during the treatment (as determined by review by PI)

* Inappropriate assignment of the planned first dwell position on the planning CT data set (more than 4 times the slice thickness; i.e. more than 8 mm in cranial caudal direction)

* Incorrect calculation of the indexer length on treatment days

* Improper channel assignment during a daily treatment

* Inappropriate assignment of the channel rotational position (more than ± 5o, or more than 1.5 mm misalignment between x-ray markers in channels 1 and 5 as seen on a daily radiograph)

* Planning criteria not met:

o 90% of the clinical target volume will receive at least 90% of the

prescribed dose (D90> 23,4 Gy).

o Organs at risk: cumulative D2cc (EQD2, using */*=3): bladder < 90 Gy;

sigmoid < 75 Gy, bowel < 75 Gy.

Secondary outcome

* Evaluation of willingness of patients to undergo an image-guided

brachytherapy procedure.

* Refinement of repeated quantitative MR imaging for response monitoring for

later use in the randomized trial.

* Definition of an optimal PA procedure for histological analysis of whole

mount slides, for later use in the randomized trial

* Development of methods for registration of MRI data to pathology slides

Study description

Background summary

Preoperative external beam radiotherapy (EBRT) for rectal cancer has shown to be effective in reducing local recurrence, but comes at a price of acute and late toxicity. In order to reduce toxicity without compromising oncological outcome, high dose rate (HDR) endorectal brachytherapy (BT) has been introduced in a single center phase II study, with excellent results. Based on the smaller irradiated volume, less toxicity (both acute and late effects) can be expected with BT compared to EBRT.
At present in the Netherlands, brachytherapy for rectal cancer is given at the LUMC and NKI-AVL as definitive treatment after external-beam radiotherapy. Further optimization to allow image guided brachytherapy is necessary before the technique can be implemented nationwide in a multi-center setting. For this optimization we will perform a pilot study as described below. The brachytherapy technique will be optimized, and we will develop methods to correlate MRI changes, pathology changes and dose distribution in normal tissue. The pilot study will be used to develop feasible methods and generate

hypotheses that will be tested in a multicenter randomized phase III study.

Study objective

Establishment of an image-guided brachytherapy procedure that is feasible for a multicenter randomized trial

Study design

The study will be carried out in the departments of radiotherapy of the LUMC and the Netherlands Cancer Institute (NKI). A total of 20 patients will be included and receive HDR endorectal BT in 4 fractions of 6.5 Gy. The first 5 patients will receive BT at the LUMC. In this group, the BT procedure will be optimized and the subsequent 5 patients will then be treated at the LUMC to validate this updated procedure. After that, 5 patients in LUMC and 5 in NKI-AVL will be treated according to the definitive protocol to evaluate feasibility in multi-center setting. In the LUMC, 2 other radiation oncologists will be involved for the last five patients to test the procedure. The protocol will be declared feasible and robust for multicenter use if in both institutes 4/5 patients have been treated without defined violations.

Intervention

HDR endorectal brachytherapy: 4 fractions of 6.5 Gy within 7 days. TME surgery will be performed 8 weeks after the first fraction of radiotherapy.

Study burden and risks

Endoscopy and marker placement
The endoscopy and fiducial marker placement will last about 30 minutes. 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.

Imaging
Patients will undergo the multi-parametric MRI exam 3 additional times in this study. In this exam 15 ml of the contrast agent Dotarem (Gadoteric acid, concentration 0.5M) is administered intravenously. No adverse effects are known of the administration of a second dose one week after the regular exam. The repeat of the MRI exam causes a negligible risk for the patient.

Endorectal brachytherapy
Expected complications of endorectal brachytherapy are limited. As reported by Vuong et al., proctitis grade 3 occurs in all patients, but resides before

surgery. Based on the results of Vuong, no increased risk of local recurrence is expected. Reduced long-term toxicity will be the major benefit for participating patients.

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
* Clinically T1-2N1 or T3N0 with > 5 mm extramural invasion or T3N1 tumor
* No threatened or involved mesorectal fascia on MRI
* Eligible for 5x5 Gy according to the Dutch guidelines
* Cranial edge of the tumor below sigmoid curvature on MRI
* Caudal margin of the tumor above dentate line (endoscopic observation)
* Tumors with an adequate (>2 cm) lumen to allow the positioning of the applicator (e.g. non

obstructive tumor)
* WHO performance status 0-2 (Appendix B)
* Age > 18 years

Exclusion criteria

* Extramesorectal (e.g. iliac, lateral) pelvic lymph node involvement
* Previous pelvic irradiation
* Extension of tumor into the anal canal
* 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.
* Contra-indications for a MRI exam with Gadolinium according to the institutional policy
* Pregnancy

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-10-2017
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Intracavitary mold applicator set;part # 189.011
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	25-04-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	08-02-2018
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

No registrations found.

In other registers

Register	ID
CCMO	NL60244.058.16