PROTECT: on-line adaptive proton therapy for cervical cancer to reduce the impact on morbidity and the immune system

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Primary objective:- To determine the difference in mean dose (Gy) to pelvic bones (whole pelvic contour), and the difference in the mean V15Gy-bowelbag volume in cc (according to EMBRACE bowel bag definition) between photon and proton therapy in…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms female malignant and unspecified
Study type	Observational invasive

Summary

ID

NL-OMON51896

Source
ToetsingOnline

Brief title
PROTECT

Condition

- Reproductive neoplasms female malignant and unspecified

Synonym
cervical cancer

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: VARIAN - HPTC

Intervention

Keyword: bone marrow sparing, cervical cancer, proton therapy, toxicity

Outcome measures

Primary outcome

Mean dose (Gy) to pelvic bones and the mean V15Gy -bowel bag volume (cc)

Secondary outcome

- Compare (IMRT/VMAT) photon with Proton Therapy (IMPT) on:

o Dosimetric parameters (target volumes and organs at risk)

o Clinical outcomes (response after 3 months, overall survival, pelvic- and

distant recurrence-free survival)

o Health-related quality of life (EORTC QLQC30 and EORTC QLQCX24/EN24)

o Safety & tolerability, grade >=2 according to NCI-CTCAE version 5.0

- Determine the effect of IMPT and IMRT/VMAT on the immune system and possible

differences, as measured by the number and function of circulating leukocytes

(myeloid cells and lymphocytes).

- Evaluation of bone marrow activity using the MRI Dixon sequence.

Study description

Background summary

Rationale:
The current standard treatment for locally advanced cervical cancer is external beam radiotherapy (EBRT) with concurrent chemotherapy followed by MRI-guided intracavitary/interstitial brachytherapy. This combination of treatment modalities is very effective for locoregional control. As most patients have the prospect of long-term survival, they will also have to live with

treatment-related morbidity. This has substantial impact on many domains of their life (physical, sexual, emotional, social, economic). Since most patients are diagnosed in their early decades (peak incidence: 35-45 yrs), morbidity has a major societal impact as well.
Severe late morbidity (grade 3-4) which requires medical intervention (grade 3) and/or can be life-threatening (grade 4), occurs in 8-11% of patients and concerns most often the gastro-intestinal and urogenital tract and, less frequently, insufficiency fractures of the pelvic bones in the irradiated area. Moreover, the number and functioning of circulating leukocytes (myeloid cells and lymphocytes) can be reduced by pelvic radiotherapy, which might reduce efficacy and feasibility of adjuvant chemo/immunotherapy.
Radiotherapy-related morbidity is a result of the dose to organs at risk (OAR) and is both dose and volume dependent. With proton therapy (PT), OAR dose can be further reduced by highly localized dose-deposition using its finite range. The biggest dose reductions are observed in low-dose regions, such as bowel and bone(marrow). For treatments that included both the pelvic and para-aortic regions the dosimetric advantage of PT is even bigger.
This clinical study will be the first prospective comparative trial to directly compare adaptive photon therapy (IMRT/VMAT) with adaptive PT (IMPT) on dosimetric parameters and clinical outcomes. All participating patients will undergo the current state-of-the-art treatment for LACC (primary chemoradiation with concurrent cisplatin followed by image-guided adaptive brachytherapy). With this study design we will create a homogenous population wherein only the type of EBRT (IMRT/VMAT or IMPT) is different. Such a study will yield a wealth of information on differences in the effects on dose-volume parameters and both short-term and long-term morbidities. Moreover, it creates a unique opportunity to study the effects of both types of EBRT on local and systemic immune response.

Hypothesis:
I. Daily adaptive IMPT for locally advanced cervical cancer is clinically feasible and will be able to spare the organs at risk to a significantly greater extent than photon-based IMRT/VMAT, while maintaining coverage of the target volume.
II. There are subgroups of patients with locally advanced cervical cancer that will have a clinically relevant reduction of acute and late bowel morbidity if treated with IMPT instead of IMRT/VMAT
III. With IMPT the suppression of the number of circulating leukocytes (myeloid cells and lymphocytes) will be lower compared to IMRT/VMAT

Study objective

Primary objective:
- To determine the difference in mean dose (Gy) to pelvic bones (whole pelvic contour), and the difference in the mean V15Gy-bowelbag volume in cc (according to EMBRACE bowel bag definition) between photon and proton therapy in clinical practice.

Secondary objectives:
- Compare (IMRT/VMAT) photon with Proton Therapy (IMPT) on:
o Dosimetric parameters (target volumes and organs at risk)
o Clinical outcomes (response after 3 months, overall survival, pelvic- and distant recurrence-free survival)
o Health-related quality of life (EORTC QLQC30 and EORTC QLQCX24/EN24)
o Safety & tolerability, grade >=2 according to NCI-CTCAE version 5.0
- Determine the effect of IMPT and IMRT/VMAT on the immune system and possible differences, as measured by the number and function of circulating leukocytes (myeloid cells and lymphocytes).
- Evaluation of bone marrow activity using the MRI Dixon sequence.

Study design

Multicentre, prospective, clinical, non-randomised phase 2 trial to compare photon and proton therapy in patients with locally advanced cervical cancer who are treated with pelvic +/-peri-aortic adaptive radiotherapy combined with concurrent chemotherapy with curative intent.

Study burden and risks

The patient extra burden will be limited to two additional blood samples (61.5 mL, 8 and 12 weeks after treatment) and one additional tumour biopsy under anaesthesia at first brachytherapy session. Additional blood samples (54 ml) for immunomonitoring will be added to the standard of care blood drawing (7.5mL) at baseline, week 4 of treatment, 4 weeks and 12 months after treatment. The total volume of blood sampling will be 7.5 mL + 54 mL = 61.5 mL. An additional blood sample can cause discomfort or hematoma. The extra biopsy will be done when patient is already under general or spinal anaesthesia and can cause, although rarely, complications such as bleeding and infection. Furthermore, an extra MRI sequence (Dixon) will be added to the MRI at baseline, brachytherapy and at 12 weeks and 12 months after treatment. The MRI at these timepoints is already standard of care and will take approximately 5 minutes longer with this addition sequence. It is not standard of care to always perform a MRI 12 months after treatment, but this is very frequently done in the clinical setting. According to EMBRACE protocol (both LUMC and EMC participate in this trial) a MRI after 12 months is part of the standard follow up procedures. In daily practice, most women will have either a MRI, CT or PET-CT scan at 12 months after treatment.
An optional second MRI (only Dixon sequence) at baseline before start of treatment is encouraged but not mandatory.
Patients who will be treated with IMPT in the second, experimental phase of the trial may have longer travel time to the HPTC and an extra intake session. Although proceeding to the second phase of trial will not occur before the technical aspects of optimal PT delivery have been optimized and implemented, and whereas IMPT is already used for other tumour sites, the treatment with

IMPT for cervical cancer has not been performed yet in Holland PTC.
The benefit of participating in this study for all participating women is the satisfaction of participating in a trial in order to improve the standard of care for future cervical cancer patients. For the women who will be treated with IMPT there is the potential benefit of being treated with a more precise type of radiation therapy, with less radiation dose to the surrounding healthy organs and thereby possibly reducing the risk of acute and late bowel morbidity.
Filling in the quality of life questionnaires takes approximately 10-15 minutes and women will be asked to return these questionnaires at baseline, week 4 of treatment, end of treatment and 3-6-9-12 months after treatment. If women also participate in the EMBRACE trial (same questionnaire at the same timepoints) they can consent to use the same questionnaire for the two trials.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

- Histologically confirmed diagnosis of cervical cancer (squamous cell carcinoma, adenocarcinoma or adenosquamous carcinoma, HPV positive or negative) with an indication for curative treatment with primary chemoradiation with concurrent cisplatin followed by 3D image-guided adaptive brachytherapy.
- Indication to include the common iliac region (minimum 5, maximum 8) or the common iliac and para-aortic regions (minimum 5, maximum 10) into the elective clinical target volume of the external beam radiotherapy.
- No distant metastasis beyond the para-aortic lymph node chain as determined by diagnostic imaging (CT or PET-CT scan)
- Age > 18 years
- WHO 0-1
- Adequate systemic organ function:
o Creatinine clearance (> 50 cc/min)
o Adequate bone marrow function : white blood cells (WBCs) >=3.0 x 109/l, neutrophils >=1.5 x 109/l, platelets >=100 x 109/l
- Patients must be accessible for treatment and follow-up
- Written informed consent according to the local Ethics Committee requirements

Exclusion criteria

- Small cell cancer, melanoma and other rare histological types of the cervix.
- History of another primary malignancy that could conceivably be active evaluated by the study physician. Examples of exception include, but are not limited to:
o Malignancy treated with curative intent and with no known active disease >=5 years.
o Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Other severe diseases such as recent myocardial infarction, clinical signs of cardiac failure or clinically significant arrhythmias
- Previous pelvic or abdominal radiotherapy
- History of active primary immunodeficiency
- Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g. colitis or Crohn*s disease]
- The use of immunosuppressive drugs at baseline
- Contraindications for weekly Cisplatin (or Carboplatin)
- Contraindications for the use of MRI

Study design

Design

Study phase:	2
Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	20-05-2022
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	24-11-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO Date:	25-08-2022
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	NL77911.058.21