PSMA-PET guided hypofractionated salvage prostate bed radiotherapy of biochemical failure after radical prostatectomy for prostate cancer

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Reproductive neoplasms male malignant and unspecified
Study type	Interventional

Summary

ID

NL-OMON52569

Source
ToetsingOnline

Brief title
PERYTON

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
Prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Koningin Wilhelmina Fonds

Intervention

Keyword: hypofractionation, prostate cancer, PSMA-PET/CT or PSMA-PET/MRI, salvage radiotherapy

Outcome measures

Primary outcome

The primary endpoint will be the 5-year progression-free survival (PFS) after

treatment.

Progression is defined as biochemical progression, clinical progression,

loco-regional or distant progression or start with hormonal therapy, whichever

occurs first.

Secondary outcome

The secondary objectives are: acute and late toxicity, Quality of Life (QoL),

PCa-specific mortality, metastasis-free survival and overall survival at 5

years.

Study description

Background summary

Prostate cancer (PCa) is the most common malignancy in men and a major cause of cancer deaths. Most of the cases are diagnosed as organ-confined diseases, where radical prostatectomy is one of the primary treatment options. After radical prostatectomy approximately 15-40% of men develop a biochemical recurrence (BR) within 5 years.
The standard treatment of post-prostatectomy BR is salvage external beam radiation therapy (sEBRT). sEBRT can provide long-term disease control; with 5 year biochemical progression-free survival (bPFS) up to 60% and with most treatment failures in the first 2 years after sEBRT.

We hypothesize two potential causes for failure of the treatment.

First, the second BR may result from the possible presence of (occult) oligometastases, for which local sEBRT is inappropriate. For most patients, the only evidence of recurrent disease after radical prostatectomy is an increased serum prostate-specific -antigen (PSA) level - a marker also used for metastatic diseases - because radiographic detection of recurrent disease has historically been difficult. Consequently, discriminating between local recurrence and metastasis is impossible, leading to unnecessary local treatment in patients with metastatic disease.
The identification of oligometastases can be improved by using PSMA-PET/CT or PSMA-PET/MRI, which has improved the detection of recurrent PCa at low PSA levels. Patients with oligometastases can thus be detected at an early stage and excluded from local salvage radiotherapy to avoid unnecessary toxicity.

Secondly, the currently applied radiation dose for local sEBRT may be low and insufficient. Like in primary PCa, also in post-operative sEBRT, a dose-effect relationship has been reported, indicating a 2.0% improvement in bPFS for each additional Gy. This may offer an opportunity to lower BR by increasing the radiotherapy dose. Therefore, in non-metastatic patients, dose escalation to the prostate bed may improve the bPFS. Recent studies have shown that the α/β-ratio for PCa cells may be lower than that of surrounding normal tissues, perhaps as low as 1.5 Gy. This means that PCa cells are more sensitive to fraction dose than the surrounding normal tissues, leading to the rationale for increasing the dose-per-fraction (hypofractionation) instead of the total dose. In doing so, the biological dose to the tumour cells, but not to the surrounding normal tissues, will increase.
Besides an increase in therapeutic gain by reducing the biochemical recurrence rate, hypofractionated schedules for prostate cancer could lead to economic and logistic advantages.

We will perform a prospective open phase III randomized trial to compare the 5-year progression-free survival in patients receiving sEBRT of 35 x 2Gy and patients receiving hypofractionated sEBRT of 20 x 3Gy.

Study objective

The main goal of this project is to investigate whether the oncologic outcome in patients with post-prostatectomy recurrent PCa can be improved, by increasing the biological effective radiation dose using a hypofractionated schedule of 20 x 3 = 60 Gy.

Study design

The study is designed as a prospective open phase III randomized multicenter trial.

Intervention

All eligible patients will be randomized to one of the following two treatment arms:
Arm 1 = Conventional sEBRT to apply a total dose of 70 Gy in 35 daily fractions of 2 Gy during 7 weeks.
Arm 2 = Hypofractionated sEBRT to apply a total dose of 60 Gy in 20 fractions of 3 Gy during 4 weeks.

Study burden and risks

Patients will be randomised into two groups. Patients participating in the conventional arm will follow the standard treatment regimen of 35 fractions, the experimental treatment will be delivered in 20 fractions. Patients participating in the experimental arm of the study will visit the hospital less frequently during the treatment phase (20 times), compared to the standard treatment (35 times). Unlike non-study patients, all patients participating in the study will complete side effect and QoL questionnaires at baseline, at the end of the treatment and the follow-up. The follow up is the same in both treatment arms.
The expected toxicity profile of postoperative RT in both arms consists of acute and late urinary (urge, frequency, nocturia and possibly incontinence) and gastrointestinal complaints (urge, frequency, rectal bleeding, loss of mucous and possibly incontinence), fatigue, and erectile dysfunction (if preserved after prostatectomy). Given the difference in α/β-ratios between PCa and late responding normal tissue, the use of hypofractionation will increase the biological effective dose to prostate cancer but not to the organs at risk (bladder and rectum). Calculating the biologically equivalent dose assuming an α/β of 4Gy for bladder and
rectum, the use of 20 x 3Gy equals an EQD2 of 70Gy, which is equal to the 70Gy of the standard arm. Nevertheless, a slight increase in the acute toxicity in the experimental arm might be expected due to the short overall treatment time.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

• Patients with prostate adenocarcinoma treated with radical prostatectomy;
• Tumour stage pT2-4, R0-1, pN0, or cN0, cNx according to the UICC TNM 2009, only with Gleason score available;
• No lymph node or distant metastases. A recent PSMA-PET scan (< 60 days) without evidence of lymph node or distant metastases;
• PSA progression after prostatectomy defined as two consecutive rises with the final PSA > 0.1 ng/mL or 3 consecutive rises. The first value must be measured at least 6 weeks after radical prostatectomy;
• PSA at inclusion < 1.0 ng/mL;
• WHO performance status 0-2 at inclusion;
• Age at inclusion between 18 and 80 years;
• Written (signed and dated) informed consent prior to registration.

Exclusion criteria

• Prior pelvic irradiation, (chemo)hormonal therapy or orchiectomy;
• Previous or concurrent active invasive cancers other than superficial non-melanoma skin cancers;
• Patients with positive nodes or with distant metastases based on the surgical specimen of lymphadenectomy or the following minimum diagnostic workup: PSMA-PET/CT or PSMA-PET/MRI, 60 days prior to registration;
• Double-sided metallic hip prosthesis;
• Inability or unwillingness to understand the information on trial-related topics, to give informed consent or to fill out QoL questionnaires.

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:	Recruiting
Start date (anticipated):	04-09-2020
Enrollment:	538
Type:	Actual

Ethics review

Approved WMO Date:	23-06-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-06-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-07-2022

Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-07-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL73639.042.20