Standard moderately hypofractionated radiotherapy vs. ultra-hypofractionated focal lesion ablative microboost in prostate cancer, Hypo-FLAME 3.0

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To demonstrate superiority of whole gland SBRT with a simultaneous integrated focal boost 35/50 Gy in 5 fractions (Hypo-FLAME) regarding 5-year bDFS compared to the current standard moderately hypofractionated schedule of 62 Gy in 20 fractions of 3....

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

Summary

ID

NL-OMON56327

Source
ToetsingOnline

Brief title
Hypo-FLAME 3.0

Condition

- Reproductive neoplasms male malignant and unspecified

Synonym
prostate cancer

Research involving
Human

Sponsors and support

Primary sponsor: Antoni van Leeuwenhoek Ziekenhuis

Source(s) of monetary or material Support: KWF & Kom op tegen Kanker (België)

Intervention

Keyword: hypofractionation, prostate cancer, radiotherapy, stereotactic radiotherapy

Outcome measures

Primary outcome

Biochemical disease free survival (bDFS) will be defined at time from randomization until biochemical failure (defined by the Phoenix consensus definition PSA > nadir + 2 ng/mL) [12]. Biochemical outcome data will be obtained by performing a PSA test at day 90, month 6 and every 6 months up to 3 years and after that every year up to 5 years. Death without biochemical recurrence is not considered an event

Secondary outcome

Acute and late GU and GI toxicity according to the CTCAE v5.0.

Patient-Reported Outcome Measures (PROMs) will be assessed up to 3 years using the International Prostate Symptom Score (IPSS) questionnaire, the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire and the EPIC-26 questionnaire.

Disease-free survival

Distant metastases-free survival Prostate cancer-specific survival Overall survival

Study description

Background summary

External beam radiotherapy (EBRT) is one of the standard treatment options for patients with localized prostate cancer (PCA). Based on the outcome of randomized trials, moderately hypofractionated radiotherapy (19-25 fractions of 2.5-3.4 Gy) is considered equivalent to conventional fractionated schemes with 35-39 fractions of 2 Gy. A schedule of 20 fractions to a dose of 60-62 Gy is adopted as standard of care for all risk-groups [1]. Driven by the success of moderate hypofractionation, there is a strong trend towards extreme hypofractionation, also called stereotactic body radiotherapy (SBRT), reducing the number of fractions even further. The schedule mostly used is 5 fractions of 7-7.25 Gy. Its effectiveness, equivalence to standard EBRT schedules, has been demonstrated for low and favourable intermediate risk (IM) patients [2] [3].
For unfavourable IM (here defined as IM with ISUP grade 3) and high-risk (HR) PCA the outcome of EBRT can be further improved by dose escalation. Because of dose-limiting toxicity, the maximal dose of EBRT for conventionally fractionated schemes was approximately 80 Gy. Initially hypofractionation was considered as a potential way to escalate the biologically effective dose (BED) above 80 Gy, however, this proved not to be the case. With hypofractionation, a saturation in dose effect seems to be present at a BED of 80 Gy [4]. Recently, the multi-centre phase III FLAME trial broke the *80 Gy barrier* and showed that in mainly HR PCA patients, treated with a conventional fractionation schedule, focal boosting of the intraprostatic lesion to a total dose of 95 Gy improves biochemical disease-free survival (bDFS) [5]. However, given the advantages of hypofractionation in terms of patient comfort and costs, the FLAME schedule is not ideal as the standard treatment.
For unfavourable IM and HR PCA patients the value of SBRT has not yet been established [1] [2]. The FLAME trial showed that higher than standard BED is a prerequisite for optimal bDFS [5]. Furthermore, post SBRT biopsies results suggest a dose response relationship with better outcome of dose levels above 40 Gy [6] [7]. Therefore, probably a higher than standard dose SBRT is necessary for these patients. A recent meta-analysis suggests diminishing results from increased fraction sizes in SBRT [8]. So, the question remains whether dose escalation in SBRT will indeed improve treatment outcome.
With standard SBRT to the whole prostate, dose escalation is limited to 40 Gy because of unacceptable toxicity [9][10]. In line with FLAME, we conducted the Hypo-FLAME trial investigating focal dose escalation in SBRT. In the phase II Hypo-FLAME trial, 100 patients with IM or HR PCA were treated with SBRT 35 Gy in 5 weekly fractions to the whole prostate with a focal boost up to 50 Gy. The acute toxicity rates, the primary endpoint, were low and similar to standard SBRT indicating this schedule can be safely applied [11]. Given this was a phase II trial, no conclusions on oncological outcome can be drawn.
Shortening of the overall treatment time (OTT) has been suggested to play a

role in SBRT efficacy and 5 fractions delivered every other day this is internationally accepted as standard [9]. We therefore initiated the phase II Hypo-FLAME 2.0 trial, investigating the feasibility of a reduction in the OTT of the Hypo-FLAME schedule from 29 to 15 days with acute toxicity as primary endpoint. The accrual of this trial is completed and a first analysis of the primary endpoint shows low toxicity figures, well in the range of what was expected. We expect to submit the analysis for publication by the end of 2022. At present, it is unknown what the oncological efficacy of the Hypo-FLAME schedule is compared to the standard of care in unfavourable IM and HR prostate cancer. Therefore, we will conduct a Phase III multi-centre randomized trial, in which 484 patients with unfavourable IM or HR PCA will be randomized between:
1. Standard treatment; moderately hypofractionated radiotherapy 62 Gy in 20 fractions of 3.1 Gy
2. Experimental treatment; SBRT 5x7Gy with an iso-toxic integrated focal boost up to 50 Gy (Hypo-FLAME).

Study objective

To demonstrate superiority of whole gland SBRT with a simultaneous integrated focal boost 35/50 Gy in 5 fractions (Hypo-FLAME) regarding 5-year bDFS compared to the current standard moderately hypofractionated schedule of 62 Gy in 20 fractions of 3.1 Gy. bDFS will be assessed, using the Phoenix consensus definition [12].

Study design

A Phase III multi-centre randomized trial, in which 484 patients with unfavourable IM or HR PCA who meet the selection criteria will be randomized (1:1) to one of the following arms:
1. Standard treatment; moderately hypofractionated radiotherapy 62 Gy in 20 fractions of 3.1 Gy
2. Experimental treatment; SBRT 5x7Gy with an iso-toxic integrated focal boost up to 50 Gy (Hypo-FLAME) in 15 days (2 fractions per week).

Intervention

Radiotherapy

Study burden and risks

Theoretically the Hypo-FLAME schedule could be less effective and/or more toxic than the current standard treatment. Given the favourable results reported in the literature and scientific conferences so far, the favourable results within the Hypo-FLAME and Hypo-FLAME 2.0 trials and the quality assurance and accreditation program that is part of Hypo-FLAME 3.0 the risk is considered minor and acceptable.

A possible benefit of participation is that half of the patients will be treated with only 5 instead of 20 treatments.

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

• Men >= 18 years with histologically confirmed prostate adenocarcinoma
• No evidence of lymph node or distant metastases N0M0.
• MRI visible tumor on mpMRI (PI-RADS v2 >= 4).
• Intermediate- or high-risk PCa, defined as at least one of the following risk criteria
- clinical stage cT2c-T3a (UICC TNM 8th edition) [13]
- Imaging stage T2c, T3a or T3b with less than 5 mm invasion in the seminal vesicles (as defined on mp MRI)

- >= Gleason score 4+3, (ISUP Grade groups 3,4 or 5)
- PSA >= 20 ng/mL
• World Health Organization (WHO) performance score <= 2
• International prostate symptoms score (IPSS score) < 15
• PSA <= 30 ng/mL
• Prostate volume <= 90 cc on MRI
• Ability to give written informed consent and willingness to return for follow* up

Exclusion criteria

• Prior pelvic radiotherapy
• TURP (transurethral prostate resection) within 6 months from start treatment
• On-line image guidance based on either fiducial markers or high-quality CBCT or MRI according to local guidelines not feasible. For example: Unsafe to have gold fiducial marker implantation, if gold fiducial markers are used for image guidance. Distorted images on MR because of hip protheses prohibit accurate MR image guidance, if MR is used for image guidance.
• Contraindications to MRI according to local hospital guidelines

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):	26-04-2023
Enrollment:	352

Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	14-03-2023
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	11-10-2023
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	14-03-2024
Application type:	Amendment
Review commission:	METC NedMec

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
ClinicalTrials.gov	NCT05705921
CCMO	NL80431.041.22