Effectiveness of focal therapy in men with prostate cancer (ENFORCE)

Published: 04-12-2023
Last updated: 30-11-2024

We hypothesize that a significant proportion of the patients will benefit more from focal therapy as compared to usual care in terms of morbidity and quality of life, without compromising oncological effectiveness. Primary objective: To study the...

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

Summary

ID

NL-OMON55975

Source
ToetsingOnline

Brief title
ENFORCE

Condition

- Reproductive neoplasms male malignant and unspecified
- Prostatic disorders (excl infections and inflammations)
- Male genital tract therapeutic procedures

Synonym
Prostate carcinoma; prostate carcinoma

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Zorginstituut Nederland - Veelbelovende Zorg

Intervention

Keyword: Focal therapy, Prostate carcinoma, Randomized controlled trial

Outcome measures

Primary outcome

Main study parameter/endpoint

• Oncological effectiveness (non-inferiority), defined as treatment failure, i.e. the need for retreatment with salvage treatment (RP or RT) in the focal therapy group and as biochemical recurrence followed by salvage treatment in the usual care group. Follow-up will be for at least 48 months so that more data on (metastasis-free) survival can be collected for oncological effectiveness

• Quality of life (superiority), measured with EPIC-26 questionnaires at 12 months follow-up

Secondary outcome

Secondary study parameters/endpoints (if applicable)

• Metastasis-free survival (validated surrogate endpoint of overall survival)

• Generic health-related quality of life at baseline, 3, 6, 12, 24, 36, 48 and 60 months using validated questionnaires (EPIC-26, EORTC QLQ-PR25 for sexual symptoms, ICIQ, IPSS, SHIM IIEF-5, EuroQoL 5D)

• Oncologic safety

• Disease progression

• Disease-specific mortality

• All-cause mortality

• Operating time

• Hospital care stay

• Pathology results

• Adverse events

• Cost-effectiveness

Study description

Background summary

In the Netherlands, most men with PCa are treated with radical whole-gland treatment, i.e. prostatectomy or radiotherapy. The burden of complications such as incontinence and erectile dysfunction associated with radical treatment is considerable [1].
A recent systematic review by our group has shown that focal therapy of PCa seems to reduce the burden of treatment side-effects in men with intermediate-risk disease, maintaining their quality of life without compromising oncological effectiveness [2]. The costs of side-effects that can be prevented are estimated at ¤5456 per patient, resulting in total expected cost savings of about ¤22 million per year in The Netherlands. Furthermore, exploration of the benefit-risk balance under patients showed that they are willing to sacrifice some survival for an improvement in quality of life (QoL) [3, 4].
Focal therapy comprises a modern alternative to selectively treat a specific part of the prostate while preserving the rest of the gland. There is, however, a lack of high-quality evidence, and numerous papers therefore recommend to perform a multicenter randomized controlled trial (RCT). The RCT should have long-term follow-up, predefined assessment of cancer-specific and health-related QoL outcome measures, and economic evaluations to inform policymakers regarding cost-effectiveness. This RCT on focal therapy versus usual care is urgently needed to enable focal therapy to overgrow the experimental status, provide the evidence needed for guidelines, and make this available for selected patients who benefit from this strategy. Because of its promising results in other countries, focal therapy is increasingly requested by patients, but due to the lack of high-quality evidence, it is not reimbursed yet. This has been designated by both the PCa patient support group and physicians as a failure of both the market and the funding agencies.
At present, all devices that are used in the proposed study are CE approved and no safety issues were reported in IDEAL stage 1 and 2a studies [4-7]. For high-risk PCa, local radical therapy has been found to significantly improve oncological endpoints [8]. However, for low- and intermediate-risk localized PCa, the different recommended options by guidelines (radical prostatectomy

(RP), radiotherapy (RT), or active surveillance (AS)) have similar short- to medium-term oncological outcomes in randomized studies [9]. A PROZIB database [10] search and a KWF report showed that about 65% of the intermediate-risk patients that are eligible for focal therapy currently undergo either RP or RT. Furthermore, brachytherapy is only used to a limited extent (7%) in intermediate-risk patients in the Netherlands, and since it is not offered as a treatment option in the participating hospitals in this proposal, we do not include this option in our study.

Active surveillance is mainly used for low-risk patients rather than for the intermediate-risk patients we are aiming for in this study. Our systematic review concluded that more high-quality evidence is required before focal therapy can become available as a standard treatment [2]. The majority of focal therapy studies were prospective development IDEAL stage 2a studies (feasibility studies), showing the limited adverse impact on functional outcomes and favorable oncological outcomes. Overall, focal therapy studies reported a median of 95% pad-free at 1-year and 85% of the patients had no clinically significant cancer in the treated area, respectively. High-quality multi-center comparative clinical trials, however, appear to be lacking. The appropriate management of patients with recurrent PCa following focal therapy has been an ongoing point of discussion. Marra et al. [11] showed that evidence from assessments of salvage treatments after focal therapy failure is low and is derived from four retrospective salvage series. Available salvage options after focal therapy include RP and RT. Overall oncological outcomes are acceptable, although biochemical recurrence is slightly higher compared to primary PCa treatment, probably because of the higher aggressiveness of recurrent/persistent PCa. Functional outcomes and complications are not markedly worse compared to primary treatment [12]. Salvage RP and salvage RT, therefore, seem feasible treatment options with acceptable oncological control and functional outcomes. Thus, re-treatment with salvage radiotherapy or salvage surgery remains a clinical option after focal therapy failure.

Experience from other countries and our qualitative research on this topic taught us that many patients will consciously opt for an initial focal therapy to maintain their quality of life and because they can be treated later when deemed necessary with the other options [13].

All patients included in our trial will undergo intensive follow-up. Patients undergoing focal therapy will undergo quarterly PSA measurement and yearly prostate MRI, followed by a prostate biopsy after 12 months and thereafter if indicated based on the MRI. Since focal therapy is a one-time intervention, there will be no patients left in treatment or that require alternative fallback treatments. Ablation devices can be returned after the completion of the trial. The disposables are single-use and are depreciated. There are no specific costs associated with the discontinuation of focal treatment after the trial.

We, therefore, aim to perform a high-quality multi-center RCT to provide the evidence needed to decide on reimbursement and implementation of focal therapy in patients with intermediate-risk, unilateral clinically localized PCa in the Netherlands. This study is funded by a national grant (Veelbelovende Zorg) from

the Dutch Health Institute (Zorginstituut Nederland).

Study objective

We hypothesize that a significant proportion of the patients will benefit more from focal therapy as compared to usual care in terms of morbidity and quality of life, without compromising oncological effectiveness.

Primary objective: To study the oncological effectiveness and quality of life of focal therapy versus usual care (i.e. radical prostatectomy or radiotherapy) in patients with intermediate-risk, unilateral clinically localized PCa.

Secondary objectives: To study the cost-effectiveness of focal therapy versus usual care (i.e. radical prostatectomy or radiotherapy) in patients with intermediate-risk, unilateral clinically localized PCa.

Primary endpoints:
- Oncological effectiveness (non-inferiority), defined as treatment failure, i.e. the need for retreatment with salvage treatment (RP or RT) in the focal therapy group and as biochemical recurrence followed by salvage treatment in the usual care group. Follow-up will be for at least 48 months so that more data on (metastasis-free) survival can be collected for oncological effectiveness
- Quality of life (superiority), measured with the EPIC-26 questionnaire at 12 months follow-up

Secondary endpoints:
- Metastasis-free survival as a validated surrogate endpoint of overall [11].
- Health-related quality of life at baseline, 3, 6, 12, 24, 36, 48 and 60 months using validated questionnaires (EPIC-26, EORTC QLQ-PR25 scale for sexual symptoms, ICIQ, IPSS, SHIM IIEF-5, and EuroQol 5D). The patients in which focal treatment fails will also be followed and their outcomes will be measured.
- Oncologic safety
- Disease progression
- Disease-specific mortality and all-cause mortality
- Operating time
- Hospital care stay
- Pathology results
- Adverse events
- Cost-effectiveness

Study design

We will perform a prospective, multi-center randomized controlled trial in 356 men with localized intermediate PCa. Patients will be randomized to either:
a) Focal treatment with ultrasound ablation (HIFU/TULSA) or irreversible

electroporation (IRE) (n=178)
b) Usual care comprising of either radical prostatectomy (RP) or radiotherapy (RT) (n=178).

This multi-center study will be coordinated by the Radboudumc.
Patients will be recruited by the treating physician of the urology department from patients presenting in the participating center i.e. Prosper network (Radboudumc, Canisius Wilhelmina Ziekenhuis (CWZ) Nijmegen, Catharina Ziekenhuis Eindhoven (CZE)), Isala klinieken Zwolle, St Antonius ziekenhuis Nieuwegein, Amsterdam UMC (within the prostate cancer network, including AVL), and Embraze network (Amphia Breda, Admiraal de Ruiter ziekenhuis (ADRZ) Goes, Bravis ziekenhuis Roosendaal, Erasmus Medisch Centrum (EMC) Rotterdam, Elizabeth-TweeSteden Ziekenhuis (ETZ) Tilburg).
Focal therapy will be performed in the 5 centers in which the focal equipment (i.e. Radboudumc, Isala, St Antonius, Amsterdam UMC, HIFU kliniek) is available and patients will be referred from the other participating centers in the region; usual care and follow-up measurements will be performed in all participating centers in this trial.

Intervention

1. After the patient has signed for informed consent, a baseline visit (V1) will be scheduled with the urologist and a clinical PhD student. At this visit, questions about the trial will be answered and baseline measurements will be performed; the patient will be asked to complete some questionnaires (EPIC-26, EORTC QLQ-PR25 scale for sexual symptoms, ICIQ, IPSS, SHIM IIEF-5, and EuroQol 5D).
2. Randomization. The patient*s urologist (and interventional radiologist) will be notified about the result of randomization. Patients will be scheduled for surgery/focal therapy/radiotherapy within 6 weeks. Patients who randomize for focal therapy will be referred to the closest participating focal therapy center.
3. Patients will be scheduled for focal therapy (HIFU/TULSA/IRE) or radical prostatectomy/radiotherapy within 6 weeks. Patients who randomize for focal therapy will be referred to the closest participating focal therapy centre. A detailed and standardized operation report is kept. If during follow-up the medical condition of the patient warrants medical attention, the study physician will refer the patient to his/her local physician for further management. If the local physician decides to perform an alternative intervention (e.g. salvage RP or salvage RT for patients first treated with focal therapy) during the follow-up period, the patient will be classified as cross-over and followed up as planned.
4. Patients will be followed for minimum 36 months, up to a maximum of 60 months over the entire study period. The clinical follow-up takes place at 6 weeks, and 3, 6, 12, 24, 36, 48 and 60 months after randomization. Clinical follow-up in both arms consist of pre- and posttreatment PSA measurements and adverse events monitoring. Conferring to international consensus guidelines

follow-up will include laboratory tests including tumor marker (PSA) and clinical examination every 3 months for the first year and every 12 months hereafter. The extra follow-up due to the RCT comprises the assessment of quality of life questionnaires at baseline at 3, 6, 12, 24, 36, 48 and 60 months. Because PSA is not reliable in focal therapy, the patients in the focal therapy arm will have an additional annual MRI-scan performed at 12, 24, 36, 48 and 60 months after the initial treatment as well as a biopsy at 12 months (targeted both at the ablation zone and random). In case recurrence or residual disease is suspected based on the follow-up MRI at 24, 36, 48 or 60 months, both targeted and random biopsy will be performed. The MRI follow-up scheme is according to the international consensus meeting on focal therapy in prostate cancer [13]. Patients who have a significant in-field tumor recurrence (ISUP grade 2 (Gleason 3+4) with >=4 mm tumour length, or any focus of ISUP grade >=3 in the treated area after focal treatment during the follow-up, detected with MRI and subsequent random/targeted biopsy [13], will return to the clinical standard pathway comprising of salvage radical prostatectomy or salvage radiotherapy. Treatment failure in radical prostatectomy or radiotherapy is based on biochemical recurrence and subsequently patients will be treated according to the available guidelines. The Phoenix criteria are used to define biochemical recurrence in postradiation therapy, which requires an increase in PSA of at least 2 ng/mL above the postradiation PSA nadir, whereas biochemical recurrence post-RP is defined as at least two PSA values that are 0.2 ng/mL or higher. Patients who fail RP will undergo salvage radiotherapy. Patients who fail RT will undergo a form of treatment, for example, salvage prostatectomy. The effects of these re-treatments will also be followed and measured.

Study burden and risks

Possible complications associated with focal therapy are hemorrhage, inflammation, minute risk of perforation of urethra or bladder, and fistula formation. The use of MRI-guidance may have a burden of local heating and noise, risks of contrast reactions against gadolinium, or serious unexpected events and patient burden in form of time investment.
These drawbacks are outweighed by potential benefits for patients, since focal therapy has a lower chance on developing impotence and incontinence when comparing it to the standard treatment of radical prostatectomy of radiotherapy.
At present, all devices that are used in the proposed study are CE approved and no safety issues were reported in IDEAL stage 1 and 2a studies [5-8].
Marra et al. [9] showed that evidence from assessments of salvage treatments after focal therapy failure is low and is derived from four retrospective salvage series. Available salvage options after focal therapy include RP and RT. Overall oncological outcomes are acceptable, although biochemical recurrence is slightly higher compared to primary PCa treatment, probably because of the higher aggressiveness of recurrent/persistent PCa. Functional outcomes and complications are not markedly worse compared to primary treatment [10]. Salvage RP and salvage RT, therefore, seem feasible treatment options

with acceptable oncological control and functional outcomes. Thus, re-treatment with salvage radiotherapy or salvage surgery remains a clinical option after focal therapy failure.
All patients included in our trial will undergo intensive follow-up. Patients undergoing focal therapy will undergo quarterly PSA measurement and yearly prostate MRI, followed by a prostate biopsy after 12 months and thereafter if indicated based on the MRI. Since focal therapy is a one-time intervention, there will be no patients left in treatment or that require alternative fallback 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 with unilateral clinically significant intermediate-risk PCa ór dominant

unilateral clinically significant intermediate-risk and small contralateral low-risk (ISUP 1) disease:
• Gleason score of 7 (3 + 4 or 4 + 3; ISUP grade 2/3)
• PSA level of <= 20 ng/ml
• Clinical stage <= T2b disease
• Life expectancy of >= 10 years
• Men with a prostate size <= 5 cm in sagittal length and <= 6 cm in axial length
• Fit, eligible, and normally destined for radical surgery or radiotherapy
• No concomitant cancer
• No previous treatment of their prostate
• An understanding of the Dutch language sufficient to receive written and verbal information about the trial, its consent process and the study questionnaires

Exclusion criteria

A potential subject who meets any of the following criteria will be excluded from participation in this study: • Unfit for general anesthesia or radical surgery • Low volume low-risk disease (<=4mmGleason score of <= 6 / ISUP grade 1) • High-risk disease (Gleason score of >= 8 / ISUP grade >3) • Clinical T3 disease (extracapsular PCa) • Men who have received previous active therapy for PCa. • Men with evidence of extraprostatic disease. • Men with an inability to tolerate a transrectal ultrasound. • Cardiac pacemaker • Metal implants/stents in the urethra or prostate. • ASA >=4 • Prostatic calcification/cysts that interfere with effective delivery of TULSA/HIFU based on CT. • Men with renal impairment and a glomerular filtration rate (GFR) of < 30 ml/minute/1.73 m2. • Unable to give consent to participate in the trial, as judged by the attending clinicians

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):	06-02-2024
Enrollment:	356
Type:	Actual

Medical products/devices used

Generic name:	Nanoknife/TULSA-PRO/Focal One Robotic Focal HIFU
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	04-12-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-03-2024
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL83913.091.23