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Efficacy of focal high-dose-rate brachytherapy in the treatment of patients diagnosed with low or favourable intermediate-risk prostate cancer—a protocol for a randomised controlled trial

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ABSTRACT

Introduction Prostate cancer (PCa) is men's second most predominant cancer worldwide. Because the prostate-specific antigen test is used in diagnostics, PCa is more often diagnosed in the early stages, making radical treatment of the disease possible. However, it is estimated that over a million men worldwide suffer from radical treatment-related complications. Thus, focal treatment has been proposed as a solution, which aims to destroy the predominant lesson that determines the progression of the disease. The main objective of our study is to compare the quality of life and efficacy of patients diagnosed with PCa before and after the treatment with focal high-dose-rate brachytherapy and to compare results with focal low-dose-rate brachytherapy and active surveillance.

Methods and analysis 150 patients diagnosed with low-risk or favourable intermediate-risk PCa who meet the inclusion criteria will be enrolled in the study. Patients are going to be randomly assigned to the study groups: focal high-dose-rate brachytherapy (group 1), focal low-dose-rate brachytherapy (group 2) and active surveillance (group 3). The study's primary outcomes are quality of life after the procedure and time without biochemical disease recurrence. The secondary outcomes are early and late genitourinary and gastrointestinal reactions after the focal high-dose and low-dose-rate brachytherapies and evaluation of the importance and significance of in vivo dosimetry used for high-dose-rate brachytherapy.

Ethics and dissemination Bioethics committee approval was obtained before this study. The trial results will be published in peer-reviewed journals and at conferences.

Trial registration number Vilnius regional bioethics committee; approval ID 2022/6-1438-911.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ A randomised prospective study comparing the standard of care (active surveillance) versus two focal treatment options (low-dose and high-dose-rate brachytherapy).
⇒ The quality of life and biochemical recurrence-free survival will be compared during the study.
⇒ In vivo dosimetry for high-dose-rate brachytherapy will be implemented to ensure high-dose conformality.
⇒ Clear outcome measures will be used in the trial to increase the study results' validity and reliability.
⇒ There are several limitations to the current study, including selection bias, the inability to blind participants and the possibility that unmeasured confounding factors could still influence the study's results despite randomisation balancing known and unknown variables between the groups.

INTRODUCTION

Prostate cancer (PCa) is the second most predominant cancer and fifth on the list of the leading cause of death between malignancies among men worldwide.[1] Early diagnosis of PCa and timely applied effective treatment methods made it possible to increase the 5-year survival rate of patients with PCa from 65% described in the European cancer registry (EUROCARE)-3 study to 83% described in the EUROCARE-5 study.[2 3] This improvement is associated with the use of prostate-specific antigen (PSA) testing in the diagnosis of PCa. Because the PSA test is used in diagnostics, PCa is more often diagnosed in the early stages without local or distant advance, making radical treatment of the disease possible.[4]

Several standard radical treatment options are available for patients diagnosed with PCa—radical prostatectomy (RP), external body radiation therapy (EBRT) and brachytherapy (BT). However, it is estimated that over a million men worldwide have undergone radical treatment after PSA

screening receiving a negative results and suffering from treatment-related complications such as impotence, urinary incontinence and secondary cancers caused by radiation therapy.[5] For example, in a study by *Resnick et al*, authors compared RP with EBRT and found that patients treated with either method had worse erectile and urinary functional status after the treatment.[6] The side effects were more predominant in the RP group at 2 and 5 years (ORs in the RP group were 6.22 (95% CI (1.92 to 20.29)) and 5.10 (95% CI (2.29 to 11.36)), respectively, for incontinence, and 3.46 (95% CI (1.93 to 6.17)) and 1.96 (95% CI (1.05 to 3.63)), respectively, for erectile dysfunction). Similar results were obtained in the Scandinavian Prostate Cancer Group Study Number 4 (SPCG-4).[7] The observed incidence rate of incontinence during the median 12.2-year follow-up was 27% and 41% at 4 and 12 years, respectively (p=0.608). However, incontinence among men allocated in the watchful-waiting group was rarer (4% and 10% at 4 and 12 years, respectively).

The active surveillance (AS) has been offered as one of the methods to reduce the frequency of adverse effects caused by radical treatment of clinically insignificant low or intermediate-risk PCa. Comparing AS with RP in a group of patients diagnosed with localised PCa, it was observed that RP did not statistically significantly reduce the risk of death from PCa (HR 0.63, 95% CI (0.36 to 1.09), p=0.09).[8] Similar results were obtained in another large-scale *ProtecT* study, in which the 10-year follow-up showed that the PCa-related mortality of patients included in the AS group was not statistically significantly different from that of patients treated with EBRT or RP (PCa-related deaths per 1000 person-year for AS, RP and EBRT with 95% CI, respectively, 1.5 (0.7 to 3.0), 0.9 (0.4 to 2.2), 0.7 (0.3 to 2.0), p=0.48).[9] On the other hand, the risk of disease progression was higher in the AS group comparing with RP and RBRT (112, 46 and 46 men, respectively, p<0.001). Nevertheless, the *National Comprehensive Cancer Network* has included AS in its official guidelines,[10] and it is now widely used in very low-risk and low-risk PCa and is often considered in cases of an intermediate-risk PCa. However, the risk of PCa progression, the cost of repeated biopsies included in the AS protocol, the risk of complications associated with the biopsies and the deterioration of quality of life (QoL) due to the anxiety associated with a non-curable disease suggested brought up a different approach to the treatment of low-risk or intermediate-risk PCa.

The focal treatment aimed to destroy the predominant lesson that determines the progression of the disease, leaving clinically insignificant changes in the prostate tissue untreated, is still in the stage of clinical trials.[11] The clinical effect is achieved using thermal ablation, focused ultrasound waves, electroporation or ionising radiation.[12 13] At the moment, the most studied and verified techniques for focal treatment of PCa are high-intensity focused ultrasound ablation, cryotherapy and low-dose-rate (LDR) BT.[14–16]

Like all new treatment methods that find their way into medical practice, focal treatment raises many questions—what is the ideal patient for this treatment option, what should be the optimal monitoring protocol, what will be the survival rate without disease progression after applied focal treatment, etc.[17]

High-dose-rate (HDR) BT has been used as a monotherapy or a boost before or after external beam radiation therapy for the treatment of intermediate and high-risk PCa yielding good results.[18–20] A recent study by Morton *et al* showed a two-fraction (2×13.5 Gy 1 week apart) superiority to a single fraction (1×19 Gy) HDR implant.[21] In the single fraction group, the 5-year biochemical-free survival and cumulative incidence of local failure rates were 73.5% and 29%, respectively. Meanwhile, in the two-fraction group, these rates were significantly higher—95% (p=0.001) and 3% (p<0.001), respectively. In the following paper, authors report two-fraction implant superiority to one fraction while comparing genitourinary (GU) toxicity (prevalence of one-fraction grade 1, 2 and 3 toxicities at 5 years versus two fraction were as follows: 29% vs 14%, 29% vs 21%, 0% vs 0% (p=0.017)).[22] The authors summarise that the single-fraction regime is inferior in whole gland treatment and should not be used.

However, there is not much research on the usage of HDR BT in focal PCa treatment, or the results of clinical studies are still awaited. One of the first studies to use HDR BT in focal treatment was conducted by Peters *et al*. A non-randomised single-arm study enrolled 30 patients with intermediate or low-risk PCa.[23] During the procedure, a single dose of 19.1 Gy (17.9–20.5 Gy) was delivered to 95% of the clinical tumour volume (CTV). The average duration of follow-up of the subjects was 4 years. No treatment-related GU and gastrointestinal (GI) toxicities higher than grades 2 and 1 were observed during the study. When changes in QoL were evaluated, no statistically significant difference was observed compared with the beginning of treatment. Biochemical relapse-free survival (based on Phoenix criteria (PSA nadir+2 ng/mL) at 4 years was 70%, and metastasis-free survival was 93%. In the case of disease progression, the authors observed that in 78% of cases, PCa was found outside the focal irradiation zone. This fact is agreeable in the context of focal BT because in another study investigating the causes of PCa progression after whole-gland monobrachytherapy with a single fraction of 19 Gy to the entire prostate volume, 88% of disease progressions were detected at sites of pre-existing lesions.[24] It should be noted that during focal BT, Peters *et al* used more needles to deliver the radioactive source to the PCa area, allowing steeper dose gradients to be achieved. Another consideration is the average dose delivered to the CTV. During focal BT, the mean CTV dose was 37.5 Gy. Meanwhile, Mendez *et al*, in the article on the causes of recurrences after total prostate BT, calculated that the average dose of the CTV of the subjects who had a fixed recurrence was 29.1 Gy.

These observations allow us to assume that the tumour environment enters a 'hot' zone during focal BT, where it is destroyed more efficiently.

As it is clear from previous studies, the precise determination of the dose that was delivered to the CTV during the focal HDR BT is essential in order to achieve disease control. Significant technological progress in both therapy delivery equipment and dose calculation algorithms[25] led to an increase in the effectiveness of HDR BT.[26 27] With the introduction of more accurate imaging methods, the target of irradiation can be identified and defined more accurately and in more detail, and a higher dose can be delivered to the target even in the presence of healthy critical organs. However, due to the complexity of the BT procedure itself and inaccuracies in the introduction of needles, there is a risk that the actual dose distribution will not be as planned, and due to large dose gradients, minor inaccuracies may lead to incomplete destruction of the tumour or severe damage to critical organs.[28 29] This situation arises because dosimetry methods have not been developed enabling the registration of the delivered dose under the real conditions in vivo (in the patient's body or organ).[30] Moreover, there is a significant increase in interest in in vivo dosimetry in BT and the development of methods enabling real-time monitoring of the delivered dose.[28]

No randomised, prospective studies compare focal HDR BT with focal LDR BT and AS. The published results of single-arm studies evaluating the safety and effectiveness of focal HDR BT are not comprehensive and do not provide valuable recommendations for clinicians.[23 31] In a recent literature review, the authors emphasise that prospective clinical trials comparing standard of care (AS) with focal therapy are needed for focal therapy to become the standard of care in the treatment of patients diagnosed with non-metastatic low and intermediate-risk PCa.[11] Additionally, clinical studies using in vivo dosimetry with focal HDR BT to ensure dose conformity and adequacy are lacking, or results are still pending. The results of this study would allow a much more accurate selection of patients for whom focal BT can be applied and would allow us to evaluate the changes in their QoL compared with other treatment methods. Based on the results of this clinical trial, it will be possible to achieve better control of localised low and favourable intermedium-risk PCa, avoid damage to adjacent organs and improve patients' QoL.

Therefore, we have raised a few hypotheses:

- The QoL after performed HDR/LDR focal BT is not inferior to active surveillance (non-inferiority trial).
- Survival without biochemical disease progression after focal HDR BT delivered in one fraction of 19 Gy is not inferior to focal LDR BT (non-inferiority trial).
- Using in vivo dosimetry during HDR, focal BT increases the accuracy of dose delivery (proof-of-concept).

In order to check the above hypotheses, the main goals of this study were set:

- To evaluate the QoL of patients who were treated using focal HDR BT and compare results with focal LDR BT and AS.
- To evaluate the progression-free survival after the focal HDR BT and compare results with focal LDR BT and AS.

Secondary goals are:

- To evaluate early and late GU and GI reactions after the performed focal HDR BT and compare results with focal LDR BT.
- To evaluate the importance and significance of in vivo dosimetry to focal HDR BT.

Thus, the primary endpoints of the trial are:

Quality of life: the study will measure and compare the QoL scores in patients treated with focal HDR BT, focal LDR BT and active surveillance using validated questionnaires.

Progression-free survival: the study will evaluate progression-free survival in patients following focal HDR BT, focal LDR BT and AS.

Secondary endpoints:

Early and late GU/GI reactions: the study will assess the incidence and severity of early and late GU and GI toxicities in patients treated with focal HDR BT, focal LDR BT.

In vivo dosimetry: the study will evaluate the importance and significance of in vivo dosimetry in focal HDR BT.

METHODS AND ANALYSIS

Here, we describe a randomised prospective cohort study designed for patients diagnosed with low-risk and favourable intermediate-risk PCa treated at the National Cancer Institute in Vilnius, Lithuania. We are planning to start recruitment in September 2022. Patients will be evaluated at the beginning of the study and then every 6 months afterward for 5 years. We are planning to complete the recruitment of the patients by September 2027. The planned duration of the study is 10 years.

Eligibility criteria

- 40 to 75 years old.
- Multiparametric MRI (mpMRI) was performed, and the tumour was verified by transrectal ultrasound (TRUS)—mpMRI fusion-guided biopsy together with systemic biopsy.
- Histologically confirmed low-risk or favourable intermediate-risk PCa from mpMRI visible lesions only that meet the following criteria and there are no diseases found in systemic biopsy:
  - PSA≤10 ng/mL.
  - International Society of Urological Pathology (ISUP) grading score ≤ 2.
  - T1–T2b.
- Less than 25% of biopsy columns were affected.
- The size of the prostate does not exceed 60 cm^3.
- Index lesion is larger than 0.5 cm^3 or 6 mm in diameter.

- International prostate symptom score (IPSS) score is not greater than 18 points.
- Agrees to participate in the study and signs the consent form.

Patients who underwent previous radical PCa treatment, have proven extracapsular extension of disease, or have metastatic tumours will be excluded from the study.

Data collection

The following medical data will be collected during the investigation: patient age; morphology, TNM classification and tumour stage; comorbidities; PSA values; MRI and US images; PCA3, TMPRSS2:ERG and other biomarkers in urine; uroflowmetry results; physical examination results; delivered dose to the CTV; the actual dose that was measured using in vivo dosimetry; average and the maximal dose delivered to the CTV; other dosimetric parameters such as V150, V200 and others, dose to organs at risk; the number of needles used during the procedure; answers to the provided questioners.

Evaluation of QoL

The subject's QoL will be evaluated using European Organisation for Research and Treatment of Cancer Quality of Life of Cancer Patients questionnaire (QLQ-C30) and an additional module for PCa patients (PR25).[32 33] The primary emphasis will be placed on the global health status when analysing QLQ-C30 responses. However, the analysis will also include physical, emotional and social functioning as well as the domains of fatigue and pain symptoms. Additionally, urinary symptoms will be our main focus while analysing QLQ-PR25 responses (incontinence, and bowel symptoms, together with sexual activity and functioning, will also be analysed).

Additionally, the subject's erectile function will be evaluated using the international index of erectile function-5 questionnaire and urinary function will be evaluated using the IPSS and interpreting the results of uroflowmetry.[34 35]

Evaluation of progression-free survival and time to recurrence

Progression-free survival and time to recurrence will be assessed using standard tests performed on subjects diagnosed with PCa, such as PSA, PSA doubling time (PSADT), an mpMRI examination and a systematic and targeted biopsy guided by TRUS-MRI fusion images. We will assume that the disease progresses when there is a confirmation of the progression after the performed TRUS-MRI fusion-guided focal and/or a systematic 12-needle biopsy. Subjects are referred for biopsy when:

- Negative PSA dynamics are observed during the follow-up visits, and the PSADT is less than 3 years.
- After the planned follow-up mpMRI examination, there is a suspicion of progression.
- The clinician suspects progression after the digital rectal examination.

Evaluation of early and late GU and GI reactions

Early and late GI and GU radiation toxicities after the performed focal treatment in HDR LDR groups will be evaluated using the Radiation Therapy Oncology Group criteria.[36]

Evaluation of the importance of in vivo dosimetry

Evaluation of the significance and importance of the in vivo dosimetry is performed by observing the actual dose of ionising radiation administered to the patient during the focal HDR BT procedure and comparing it with the actual prescribed dose. Measurements will be performed using a dosimetric system created in the applied physics department of Vilnius University.

Description of the groups

Subjects diagnosed with a low-risk or favourable intermediate-risk PCa (PSA ≤10 ng/mL, ISUP ≤2, tumour size T1–T2b) and who meet other inclusion criteria will be randomly assigned to one of the three groups:

- Active surveilance group
  - This is a control group and a standard approach proposed in clinical practice for patients diagnosed with low-risk or favourable intermediate-risk PCa.
- Focal LDR BT group.
  - It is a standard treatment method within the framework of clinical trials. The effectiveness and safety of focal LDR BT are well-studied and described in the scientific literature.[37 38]
  - Focal LDR BT is performed under general or spinal anaesthesia, under TRUS control, implanting ^{125}I radioactive seeds into the tumour tissue.
  - A senior radiation oncologist will perform the fusion of the patient's prebiopsy mpMRI and acquired ultrasound images during the procedure. The radiological extent of the index lesion will be defined as the focal gross tumour volume (fGTV), while the focal planning target volume (fPTV) will be created as a 5 mm isotropic expansion of the fGTV.
  - A planned dose to be administered by the implanted seed is 145 Gy to the fPTV, which complies with safe dosimetric plan parameters.
- Focal HDR BT group.
  - This study group will be compared with the rest of the groups.
  - Focal HDR BT is performed under general or spinal anaesthesia, under TRUS control, inserting special hollow needles into the tumour and delivering radioactive iridium 192 isotope through special catheters.
  - A senior radiation oncologist will perform the fusion of the patient's prebiopsy mpMRI and acquired ultrasound images during the procedure. The radiological extent of the index lesion will be defined as fGTV, while the fPTV will be created as a 5 mm isotropic expansion of the fGTV.

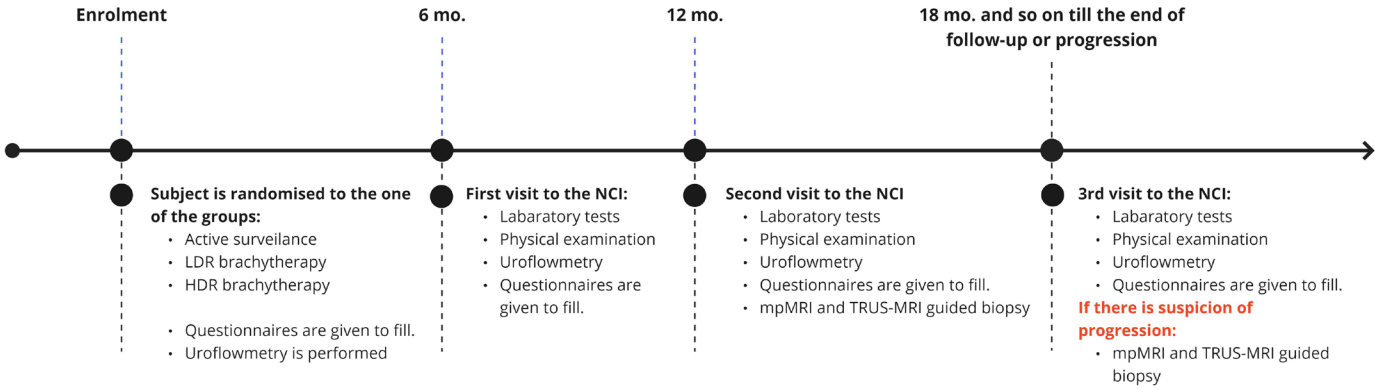

Figure 1 A detailed flowchart of the investigation. HDR, High-dose rate; LDR, low-dose-rate; mpMRI, multiparametric MRI; TRUS-MRI, Transrectal ultrasound - MRI fusion-guided biopsy; NCI, National Cancer Institute;

- During focal HDR BT, a single dose of 19 Gy is administered to the fPTV located in the prostate in compliance with the safe dosimetric parameters of the plan.
- During the procedure, the delivered dose will be monitored by in vivo dosimeters.

In the case of disease progression, the subject's participation in the biomedical study is terminated, and he continues to be treated according to the standards of PCa treatment. A detailed scheme of the investigation is presented in figure 1.

Treatment quality assurance

Treatment quality assurance (QA) involves several steps to ensure that the radiation dose delivered to the patient is safe and accurate. The QA procedure includes:

- Treatment planning verification is made before every treatment delivery. The treatment plan is verified to ensure that the dose distribution is consistent with the intended treatment.
- Pretreatment imaging verification. Before treatment, imaging is performed to verify the source position's accuracy and ensure that the treatment plan is properly aligned with the patient's anatomy.
- Patient follow-up. The patient is monitored after the treatment to assess the response to the performed treatment and related side effects.

Additionally, for LDR BT:

- Source strength verification is performed before seed implantation.
- Treatment delivery verification is performed during the seed implantation to ensure that it is in the correct position.
- After the procedure, post-treatment imaging is performed with a pelvic CT scan to verify the source positions.

Data evaluation and sample size

Statistical data analysis will be performed using the data analysis software package SPSS. Means, SD, median, minimum and maximum values will be calculated to assess quantitative characteristics. Frequencies and percentages of values will be calculated for qualitative characteristics. The χ^2 test will be used to assess the correlation of study parameters with clinical pathological parameters. Differences between groups will be considered statistically significant if $p<0.05$.

ORs with CIs will be calculated using one-way logistic regression analysis. A multivariate logistic regression model will be applied to assess the probability of the influence of the research parameters. The multivariate logistic regression analysis model will include those parameters that are statistically significant after univariate analysis.

Survival data are analysed using the Kaplan-Meier method, and survival probabilities are presented graphically. The log-rank test is used to compare survival.

One hundred and fifty-nine subjects are planned to be enrolled in the study. The number of patients that needed to be enrolled in the study was calculated using G-Power software. An 80% statistical weight and 5% statistical significance (p 0.05) were chosen. The effect size was set to 25%. Powering was done to detect difference at 5-year time point. The distribution between groups is planned in the ratio of 1:1:1.

ETHICS AND DISSEMINATION

Bioethics committee approval was obtained before this study (approval ID 2022/6-1438-911). Therefore, patients will only be enrolled in the study after signing the informed consent form. Before signing the consent form, investigators will provide all the information about the study aims and objectives and give the patient time to decide if he wants to participate in the ongoing study ensuring to the patient that the participation is done by free will and there will be no penance if the patient decides not to participate. In addition, the investigators will answer all the questions related to the ongoing study that will arise to the patient. Informed consent will be signed in two duplicates—one will stay with the patient, the other with the investigator.

If the subject learns that a treatment method he does not want will be applied to him, he will be able to terminate his participation in the study of his own free will.

After withdrawal from the study at this stage, the subject will receive the standard treatment.

During the study, personal data will be collected. The unique identification number will code the identities of the participants. Only the principal investigator will have the principal list of participants where the identification number is associated with the participant's identity. Additionally, anonymised data will be available only to the study personnel. Personal identifiers will not be used in the data analysis.

Patients and the public were not involved in the design of this trial, nor will they be involved in the conduction of the trial. However, we are planning to disseminate the results to patient groups and relevant stakeholders via planned scientific publications. We will also make the study findings available to healthcare providers and policymakers to inform decision-making.

The results of this investigation will be published in peer-reviewed journals important in the field of this work (eg, 'Journal of Clinical Oncology' and others) and/or presented at relevant scientific meetings. Additionally, the investigation will contribute to the preparation of doctoral thesis.

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