BMJ Open

Stereotactic body radiotherapy (SBRT) versus androgen deprivation therapy (ADT) for oligometastatic prostate cancer: protocol for a prospective randomised control clinical trial

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To cite: Zhao X, Wang T, Ye Y, *et al*. Stereotactic body radiotherapy (SBRT) versus androgen deprivation therapy (ADT) for oligometastatic prostate cancer: protocol for a prospective randomised control clinical trial. *BMJ Open* 2022;**12**:e051371. doi:10.1136/bmjopen-2021-051371

► Prepublication history for this paper is available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-051371).

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Received 18 March 2021
Accepted 11 August 2022

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ABSTRACT

Introduction The systemic therapy, especially androgen deprivation therapy (ADT), is currently recommended for patients with oligometastatic prostate cancer (PCa). However, the results have not been satisfactory including adverse reactions and castration resistance. Therefore, it is necessary to explore more effective treatment to prolong biochemical progression-free survival (bPFS) and delay the start of hormonal therapy for treating oligometastatic PCa. Stereotactic body radiotherapy (SBRT) is an emerging treatment alternative for patients with oligometastases with high local control rates and minimal toxic effects. This prospective trial aims to demonstrate whether SBRT for the oligometastases of hormone-sensitive PCa can delay the start of ADT and prolong the time from inception of the study to castration-resistant prostate cancer (CRPC).

Methods and analysis Patients with ≤3 oligometastatic recurrences, diagnosed on Ga-68 prostate-specific membrane antigen PET/CT, will be randomised in a 1:1 ratio between arm A (ADT only) and arm B (SBRT for oligometastases only). SBRT is conducted by CyberKnife with prescription dose 30–50 Gy in 3–5 fractions. One of the primary endpoints is ADT-free survival of arm B, the other is the time from inception of the study to CRPC. The secondary endpoints include radiotherapy-related toxicity, ADT-related toxicity, bPFS, local PFS and overall survival. Toxicity will be assessed using the National Cancer Institute Common Toxicity Criteria V.5.0.

Ethics and dissemination This protocol was approved by the institutional review board of Shanghai Changhai Hospital (CHEC2020-101). This is a randomised control clinical trial comparing SBRT to ADT for men with oligometastatic PCa. The study will be performed in compliance with applicable local legislation and in accordance with the ethical principles developed by the World Medical Association in the Declaration of Helsinki 2013. Study results will be disseminated through conferences and peer-reviewed scientific journals.

Trial registration number Clinicaltrials.gov identifier:NCT04599686.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised trial comparing androgen deprivation therapy versus stereotactic body radiotherapy for oligometastatic prostate cancer.
⇒ In this protocol, before and after treatment Ga-68 prostate-specific membrane antigen PET/CT shall be performed in all patients.
⇒ The limitation is monocentric, with a relatively small sample size.

INTRODUCTION

Prostate cancer (PCa) is one of the most frequent malignancies in men. The main reason for death among patients with PCa is distant metastasis.[1] Longlife androgen deprivation therapy (ADT) by means of surgical or medical castration, or in combination with other agents (docetaxel, abiraterone, etc), is considered as the mainstay of treatment for metastatic PCa.[1] However, hormonal therapy can lead to many adverse reactions and loss of quality of life (QoL). Decreased sexual appetite and sexual dysfunction are the most common side effects of hormonal therapy. Osteoporosis, cognition hypofunction, anaemia, hot flash, mammary swelling pain and feminisation also occur in many patients, which greatly trouble them. What's more, longlife ADT inclusive of abiraterone can lead to castration-resistant prostate cancer (CRPC) in most patients after 33–36 months.[2 3] So, seeking a new treatment to delay the start of ADT is necessary urgently.

The metastatic PCa behaves as a spectrum of disease progression, which presents an oligometastatic state with limited metastases and a wide metastatic state with a lot of metastases. System therapy was not considered curative treatment for most metastases. It is encouraging that patients with oligometastases would benefit

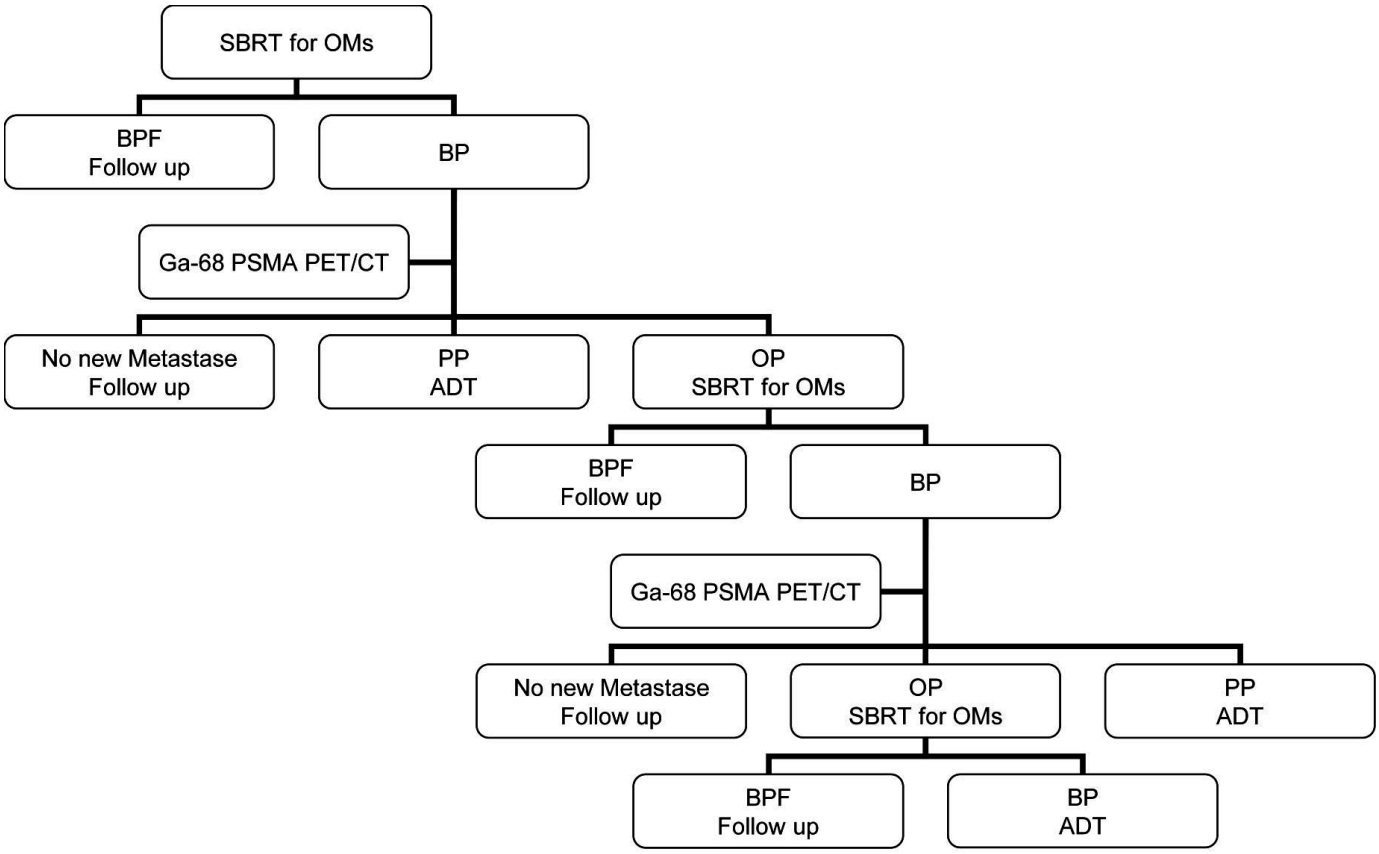

Figure 1 Treatment schedule of arm B in the protocol. ADT, androgen deprivation therapy; BP, biochemical progression; BPF, biochemical progression free; OMs, oligometastases; OP, oligprogression; PP, polyprogression; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiotherapy.

from local therapy, especially radiation therapy.[4] Stereotactic body radiation therapy (SBRT) were currently used in treatment of bone or lymph nodes metastases, which can achieve high dose for target and low dose for normal organ or tissue. What's more, SBRT was convenient for patients with limited number of radiation therapy performed with CyberKnife or linear accelerator, which had optimistic efficacy and tolerable toxicity.[5–7] CyberKnife was a successful surgical robot with many advantages, especially real-time tracking technique.[8 9] Based on previous studies, SBRT has been shown very promising on the treatment of oligometastases from PCa.[10–13]

Some studies show that system therapy is the standard treatment for oligometastatic PCa, but some studies argue that local therapy for oligometastases can decrease disease progression and delay hormone therapy. However, it is unknown which is the best treatment for oligometastatic PCa, system therapy alone or SBRT alone. Therefore, we have designed this prospective randomised control trial to investigate whether SBRT alone for oligometastases can delay the start of ADT and prolong the time from inception of the study to CRPC.

Methods and analysis

Study design

This is a prospective, two arms, randomised control clinical trial. The development of the study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The protocol has been prepared in accordance with the SPIRIT.

The main objective of the trial is to determine whether SBRT for the oligometastases of hormone-sensitive PCa can prolong biochemical progression-free survival (bPFS) and delay the start of ADT in arm B(SBRT for oligometastases only). Then the study also explores whether patients in arm B can prolong the time from inception of the study to CRPC, compared with arm A(ADT only). The definition of CRPC are as follows: castrate serum testosterone<50 ng/dL or 1.7 nmol/L plus either: (1) biochemical progression: three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA >2 ng/mL or (2) radiological progression: the appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using Response Evaluation Criteria in Solid Tumours.[14] The planned start and end dates for the study were 11 November 2020 and 1 October 2025, respectively.

Recruitment

Patients who refer to the outpatient department of the trial site and meet the inclusion criteria are recommended to participate in this trial by the physicians in charge of the study.

Table 1 The schematic diagram for data collections and assessment

Test items	Screening	Before SBRT or ADT	Follow-up
Demographics	●	●	●
Medical history	●	●	●
Physical examination	●	●	●
Concomitant symptoms	●	●	●
PSA	●	●	●
Testosterone		●	●
Blood routine	●	●	●
Ga-68 PSMA PET/CT	●	○	○
SPECT	○	●	○
Contrast-enhanced CT	○		○
Contrast-enhanced MRI	○		○
Blood biochemistry	●	●	○
Coagulation function	●	●	○
Biopsies of the prostate	●		
Adverse effects		●	●
Combined drug record	●	●	●

● represents required items ; ○represents selected items.
ADT, androgen deprivation therapy; PET, positron emission tomography; PSA, prostate specific antigen; PSMA, prostate-specific membrane antigen; SBRT, stereotactic body radiotherapy; SPECT, single-photon emission computed tomography.

Study participants

Inclusion criteria

- ≤80 years old at the time of registration.
- Histologically confirmed adenocarcinoma of the prostate without small cell features.
- PCa treated with curative intent (radical prostatectomy, primary radiotherapy or a combination of both).
- Ga-68 prostate-specific membrane antigen (PSMA) PET/CT evidence of one to three metastases (bone or lymph node) within 6 weeks of enrolment, if the position of oligometastases is judged by the doctor to be in the same radiotherapy area, the number of metastases can be appropriately increased to 5. The diameter of the target was 1.0–5.0 cm. The protocol would not only allow M1a lymph node metastases but also include oligorecurrences in pelvic nodes.
- Without ADT treatment.
- PSA <50 ng/mL before enrolment.
- Eastern Cooperative Oncology Group (ECOG) performance status 0–2.
- Written informed consent according to International Council for Harmonization/Good Clinical Practice regulations before registration and before any trial-specific procedures.

Exclusion criteria

- Any previous or ongoing treatment of oligometastases including radiotherapy, ADT, chemotherapy, focal treatment, etc.
- Patients with organ metastases, unstable lesions with spinal or long bone metastases.
- ≥4 metastases or ≥6 metastases if the metastases are in the same radiotherapy area.
- Histologically confirmed neuroendocrine tumour or small cell carcinoma of the prostate.
- Severe or active comorbidity was likely to impact the advisability of SBRT like severe liver or kidney dysfunction, etc.
- Patients with other malignancies, or acute or other severe infections, with ulcerative colitis, inflammatory bowel disease, etc.
- Patients who have participated in other clinical trials for less than 3 months.
- Unsuitable to participate in this clinical trial judged by the investigator.

Dropout or suspension of the trial

- The occurrence of grade III/IV adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) V.5.0.
- Requests from patients to withdraw from the trial.
- Lost to follow-up.
- Other potential situations that necessitate the termination of the trial.

Interventions

Baseline evaluation

Patients with clinically confirmed oligometastatic PCa who are eligible for this trial will be evaluated for baseline characteristics. The evaluation will include demographics, medical history, concomitant diseases and medications, physical exam, vital signs, concomitant symptoms, routine blood tests, Ga-68 PSMA PET/CT in enrolled patients. Baseline characteristics of the included patients will be collected within 2 weeks prior to the initiation of enrolment. Then, participants will be randomised with a 1:1 allocation to receive ADT only (arm A) or SBRT for oligometastases only (arm B).

Arm A

The ADT regimen for patients in arm A includes bicalutamide 50 mg orally once daily for 2 weeks and goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will be administered subcutaneously either at a dose of 3.6 mg every 4 weeks or at a dose of 10.8 mg every 12 weeks. Abiraterone with prednisone should be given with concurrent steroid.

Arm B

SBRT

For oligometastatic lesions, SBRT will be administered, which would be performed with CyberKnife. The gross tumour volume (GTV) of oligometastases relied on imaging examination. Planning target volume for GTV is delineated with an additional 5–8 mm margin. A total of 30–50 Gy with 3–5 fractions is the recommended dose segmentation, which depends on the surrounding organs at risk (OARs) and tumour location. Dose guidelines to OARs in SBRT treatment are based on AAPM Task Group 101.[15]

Biochemical progression

Biochemical progression is defined as a ≥20% increase in prostate specific antigen (PSA) from nadir (and the increasing value ≥2 ng/mL). After SBRT treatment, Ga-68 PSMA PET/CT shall be conducted if patients develop biochemical progression. If no new lesion occurs, patients will check serum PSA regularly. If new lesions occur, the treatment depends on whether the disease state is oligoprogression or polyprogression. Oligprogression is defined as the number of new metastases ≤3, and the time interval between the diagnosis of new metastases and the last disease progression is more than 1 year. Polyprogression is defined as the number of new metastases >3, or the time interval between the diagnosis of new metastases and the last disease progression is less than 1 year.

First, patients in arm B will receive SBRT for the oligometastases. Second, when the disease progresses oligprogression in the follow-up, SBRT will be applied for the treatment of oligometastases. Third, when their disease progresses oligprogression in the follow-up again, SBRT will be applied for the treatment of oligometastases. However, patients will receive ADT when their disease progresses, no matter oligprogression or polyprogression. What's more, patients will receive ADT once their disease progresses extensively (figure 1).

Outcomes and measurements

The primary objective of this trial is to assess the ADT-free survival of arm B and the time from randomisation to CRPC in both arms. The secondary endpoints include radiotherapy-related toxicity, ADT-related toxicity, bPFS, local PFS (LPFS) in arm B, overall survival (OS) in both arms. Toxicity will be assessed via CTCAE V.5.0. QoL of two arms is very important in the study. QoL will be measured using Karnofsky Performance Status Scale,[16] the Expanded Prostate Cancer Index Composite (EPIC)[17] and the 5-level EQ-5D instrument.[18]

Data collection

The schematic diagram for data collections and evaluations of efficacy and safety is shown in table 1. Physicians will evaluate all the pretreatment data, baseline data and follow-up information of patients, which will be checked again by the researchers not involved in the study to promote data accuracy and completeness. What's more, all the research data of patients will be strictly confidential. When treatment and follow-up data need to be reviewed by the ethics committee or searched by authorised researchers, it will be retrieved from the database.

Follow-up

After SBRT or ADT treatment, participants will be monthly evaluated for serum PSA and testosterone levels. All patients will be evaluated for Ga-68 PSMA PET/CT 1 year after treatment. Contrast-enhanced CT, contrast-enhanced MRI or ECT will be evaluated when necessary. If patients develop biochemical progression, Ga-68 PSMA PET/CT will be considered.

Statistical analysis

Sample size

The time from randomisation to CRPC is the primary objective. It is estimated that long-term ADT inclusive of abiraterone leads to CRPC in most patients after 33–36 months. There will be a 1:1 randomisation between arm A and arm B. In order to detect a 36-month difference in the studied endpoint from 33 to 69 months, each group needs at least 45 samples while α is 0.05 and the test efficiency is 80%. Assuming a 10% rate of loss to follow-up, 50 patients of each group will be recruited considering the time from randomisation to CRPC.

Data analysis

The primary endpoint ADT-free survival of arm B and the time from randomisation to CRPC will be calculated using Kaplan-Meier actuarial analyses. Preplanned subgroup analysis will conduct based on stratification variables using the log-rank test. bPFS, LPFS and OS will also be estimated using the Kaplan-Meier method. Univariate and multivariable hazard ratios will be calculated using the Cox proportional hazard model. P values <0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS 18.0 (IBM Corporation,Armonk, NY, USA). Toxicity data of both arms will be summarised.

Biological specimens

Informed consent will be obtained from the participants prior to the acquisition of biological specimens, including blood and tissue samples, which will be stored for subsequent exploratory biomarker research.

Patient and public involvement

Patients or the public were not involved in the design of the present study.

Ethics and dissemination

Eligible patients will be well informed of the purpose and schedule of this study. Signed informed consent forms will be obtained from all patients before inclusion in the study. The study is approved by the ethics committee of the Shanghai Changhai Hospital (CHEC2020-101), and registered on Clinicaltrials.gov identifier: NCT04599686. The researcher will collect all clinical data. Findings of the study will be submitted for publication in peer-reviewed scientific journals and presented at relevant medical conferences.

DISCUSSION

The mainstay of metastatic hormone-sensitive PCa remains systemic therapy, either with ADT alone or in combination with other agents (docetaxel, abiraterone, etc). However, ADT can have troublesome toxicity and lead to CRPC. So, any effort to delay the start of hormonal therapy would be an advantage to the patient.

Some clinical trials are exploring alternate methods to postpone ADT. STOMP trial is a randomised phase II trial comparing surveillance with metastasis-directed surgery or SBRT for oligometastatic PCa recurrence.[19] Another phase II randomised trial is ORIOLE comparing observation with stereotactic ablative radiation for oligometastatic PCa.[20] However, we think surveillance for oligometastatic patients is a negative treatment attitude. So, the control group in our clinical trial will receive ADT, while experimental group will receive SBRT.

Currently, clinical studies on radiotherapy for oligometastases showed a promising result. Gianluca *et al* conducted a retrospective study in which 40 patients with PCa with 47 isolated lymph node metastases were treated with SBRT.[12] With a mean follow-up of 30.18 months, the 2-year bPFS was 44%. What's more, 16 (40 %) patients were free from ADT at the last follow-up (mean value 26.18 months; range 3.96–59.46). Siva *et al* analysed 33 patients with 50 oligometastases who received stereotactic abative body radiotherapy. They obtained 2-year freedom from ADT was 48% in 22 patients not on ADT.[13]

Although these studies collectively suggested the role of SBRT in the management of oligometastatic PCa, there was no data of prospective randomised controlled study on SBRT comparing to ADT with oligometastatic PCa. Simultaneously, many questions remain to be resolved, for example, what kind of clinical features are suitable for inclusion in the SBRT group. A persuasive perspective on the impact of SBRT on the oligometastases will be obtained through correlation of clinical efficacy and number of tumours, tumour location, pathological type, immune response and genomic susceptibility characterisation. These have motivated us to evaluate the SBRT in oligometastatic PCa. The clinical trial may be the first step making the therapeutic purposes from palliative intent therapy to curative intent therapy for patients with oligometastatic PCa. What's more, this study will give us a meaningful answer which is the better treatment for oligometastatic patients with PCa: system therapy or local therapy. The time from enrolment to CRPC is the important endpoints to judge whether SBRT for oligometastases can delay hormone therapy.

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Contributors Study conception: HZ and XG. Initial study design: XZ and JL. Revision of study design and protocol: HZ, XG, XZ, JL, YY and TW. Study coordination: all authors. Drafting the manuscript: XZ, TW and YY. All authors read and approved the final manuscript.

Funding This study is sponsored by the First Affiliated Hospital of Naval Medical University "234 Subject Climbing Program" (2019YPT004) , the First Affiliated Hospital of Naval Medical University "Youth Startup Fund" (2020QNB10). The funding body had no role in the design of the study and will have no role in the collection, analysis or interpretation of the data as well as in writing the manuscript or the decision to submit the report for publication.

Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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