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

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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 (PSMA) PET/CT, will be randomized 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 30-50Gy 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 progression-free-survival (LPFS), and overall survival (OS). Toxicity will be assessed using the National Cancer Institute Common Toxicity Criteria V5.0.

Ethics and dissemination

This protocol was approved by the institutional review board of Shanghai Changhai Hospital (CHEC2020-101). This is a randomized control clinical trial comparing SBRT to ADT for men with oligometastatic PCa. The study will be performed in compliance with applicable local legislation and 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; Pre-results.

Strengths and Limitations of this study

- This is a randomized trial comparing ADT versus SBRT for oligometastatic PCa.
- It will seek a biomarker of subgroup oligometastatic prostate cancer patients to delay the start of hormonal therapy.
- In this protocol, pre and after-treatment Ga-68 PSMA 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 PCa patients 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, anemia, hot flash, mammary swelling pain, and feminization also occur in many patients, which greatly trouble them[2]. What's more, longlife ADT can lead to castration-resistant prostate cancer (CRPC) in most patients after 18-24 months[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 from local therapy, especially radiation therapy[4]. Recently, due to the advantages of stereotactic body radiation therapy (SBRT), including precise delivery, abrupt dose fall-off outside targets, and high local dose conformation, it has been commonly used in selected patients with bone or lymph nodes metastases, with high local control (LC) rates and acceptable toxicity[5 6]. High doses could be precisely delivered to an extracranial target within the body, either as a single dose or a small limited number of radiation fractions[7]. It can be performed either with a traditional linear accelerator or a robotic arm (CyberKnife®). CyberKnife was developed in the 1990s at Stanford (Accuray Inc., Sunnyvale, CA, USA)[8], which represented an innovation of traditional stereotactic surgery. Given the real-time tracking, beam angles could be simultaneously corrected intrafractionally via pre-identified patient's breathing patterns[9]. Based on previous studies, SBRT has been shown very promising on the treatment of oligometastases from PCa[10 11].[13,14]

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 randomized 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 study was approved by the Ethics committee of the Shanghai Changhai Hospital (CHEC2020-101) and has been registered on Clinicaltrials.gov (NCT045996860. This is a prospective, two arms, randomized control clinical trial. The development of the study protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The protocol has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

The main objective of the trial is to determine whether SBRT for the oligometastases of hormone-sensitive PCa can prolong bPFS and delay the start of ADT in arm B. Then the study also explores whether patients in arm B can prolong the time from inception of the study to CRPC, compared to arm A.

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.

Study participants

Inclusion Criteria

- ≤80 years old years 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.
- Without ADT treatment.
- PSA< 50ng/ml before enrollment.
- ECOG performance status 0–2.
- Written informed consent according to International Council for Harmonization/ Good Clinical Practice (ICH/GCP) 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.
- 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 tumor or small cell carcinoma of the prostate.
- Severe or active co-morbidity 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 three 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 enrollment. Then, participants will be randomized with a 1:1 allocation to receive ADT only (arm A) or SBRT for oligometastases only (arm B).

Arm A

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

Arm B

SBRT

For oligometastatic lesions, SBRT will be administered. The gross tumor volume (GTV) of oligometastases relied on imaging examination. Planning target volume (PTV) for GTV is delineated with an additional 5-8 mm margin. 30-50Gy with 3-5 fractions is the recommended dose segmentation which depends on the surrounding

organs at risk (OARs) and tumor location. Dose guidelines to OARs in SBRT treatment are based upon AAPM Task Group 101[12].

Biochemical progression

Biochemical progression is defined as a ≥ 20% increase in 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 micro-progression or extensive progression. Micro-progression is defined as the number of new metastases ≤ 2, and the time interval between the diagnosis of new metastases and the last disease progression is more than 1 year. Extensive progression is defined as the number of new metastases > 2, or the time interval between the diagnosis of new metastases and the last disease progression is less than 1 year.

Patients in arm B will receive SBRT for the oligometastases firstly. When the disease progresses micro-progression in the follow-up, SBRT will be applied for the treatment of oligometastases, secondly. When their disease progresses micro-progression in the follow-up again, SBRT will be applied for the treatment of oligometastases, thirdly. However, patients will receive ADT when their disease progresses, no matter micro-progression or extensive progression. 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 randomization to CRPC in both arms. The secondary endpoints include radiotherapy-related toxicity, ADT-related toxicity, bPFS, local progression-free-survival (LPFS) in arm B, overall survival (OS) in both arms. Toxicity will be assessed via CTCAE v5.0.

Data collection

The schematic diagram for data collections and evaluations of efficacy and safety is shown in Table 1. Physicians will evaluate all the pre-treatment 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 authorized researchers, it will be retrieved from the database.

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	●	○	●
ECT	○	●	○
Contrast-enhanced CT	○		○
Contrast-enhanced MRI	○		○
Blood biochemistry	●	●	○
Coagulation	●	●	○

function			
Biopsies of the prostate	●		
Adverse effects		●	●
Combined drug record	●	●	●

●：Required items；○：Selected items

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

It is estimated that the median delay to start palliative ADT after metastasis-directed therapy is approximately 12 months. There will be a 1:1 randomization between arm A and arm B. In order to detect a 12-month difference in the studied endpoint from 12 to 24 months, each group needs at least 7 samples while α is 0.05 and the test efficiency is 90%. Assuming a 20% rate of loss to follow-up, a total of 18 patients will be accrued. In this experiment, 50 patients of each group will be recruited considering the time from randomization to CRPC.

Data analysis

The primary endpoint ADT-free survival of arm B and the time from randomization to CRPC will be calculated using Kaplan-Meier actuarial analyses. Pre-planned 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. For comparisons between the baseline variables, the $\chi 2$ test and Fisher's exact test will be performed. P values< 0.05 will be considered statistically significant. Statistical analysis will be performed with SPSS (IBM Corp, Somers, NY, USA).

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.

Currently, clinical studies on radiotherapy for oligometastases showed a promising result. Gianluca et al conducted a retrospective study in which 40 PCa patients with 47 isolated lymph node metastases were treated with SBRT[13]. 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). Shankar et al. analyzed 33 patients with 50 oligometastases who received stereotactic body radiotherapy (SABR). They obtained 2-year freedom from ADT was 48% in 22 patients not on ADT[14].

Although these studies collectively suggested the role of SBRT in the management of oligometastatic PCa, there was no data of prospective randomized 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 tumors, tumor location, pathological type, immune response, and genomic susceptibility characterization. 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 PCa patients: system therapy or local therapy. The time from enrollment to CRPC is the important endpoints to judge whether SBRT for oligometastases can delay hormone therapy.

Abbreviations

SBRT: Stereotactic body radiotherapy; ADT: Androgen deprivation therapy; PCa: Prostate cancer; bPFS: Biochemical progression-free survival; CRPC: Castration-resistant prostate cancer; PSMA: Prostate-specific membrane antigen; LPFS: Local progression-free-survival; OS: Overall survival; QoL: Quality of life; LC: Local control; ASTRO: American Society for Therapeutic Radiology and Oncology; ACR: American College of Radiology; ICH/GCP: International Council for Harmonization/Good Clinical Practice; CTCAE: Common Terminology Criteria for Adverse Events; LHRHa: Luteinizing hormone-releasing hormone agonist; GTV: Gross tumor volume; PTV: Planning target volume; OARs: Organs at risk; OMs:

Oligometastases; BPF: Biochemical progression-free; BP: Biochemical progression; EP: Extensive progression; MP: Micro-progression.

Acknowledgments

Not applicable.

Author Contributions

Study conception: H.J.Z and X.G. Initial Study design: X.Z.Z. and J.L. Revision of study design and protocol: H.J.Z, X.G., X.Z.Z., J.L. Y.S.Y, and T.W. Study coordination: All authors. Drafting the manuscript: X.Z.Z., T.W., and Y.S.Y. All authors read and approved the final manuscript.

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Competing interest statement

The authors declare that they have no competing interests.

Patient consent for publication

Not applicable.

Provence and peer review

Not commissioned; externally peer-reviewed.

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Figure legend

Fig. 1 Treatment schedule of Arm B in the protocol. OMs: oligometastases; BPF: biochemical progression-free; BP: biochemical progression; EP: extensive progression; MP: micro-progression.

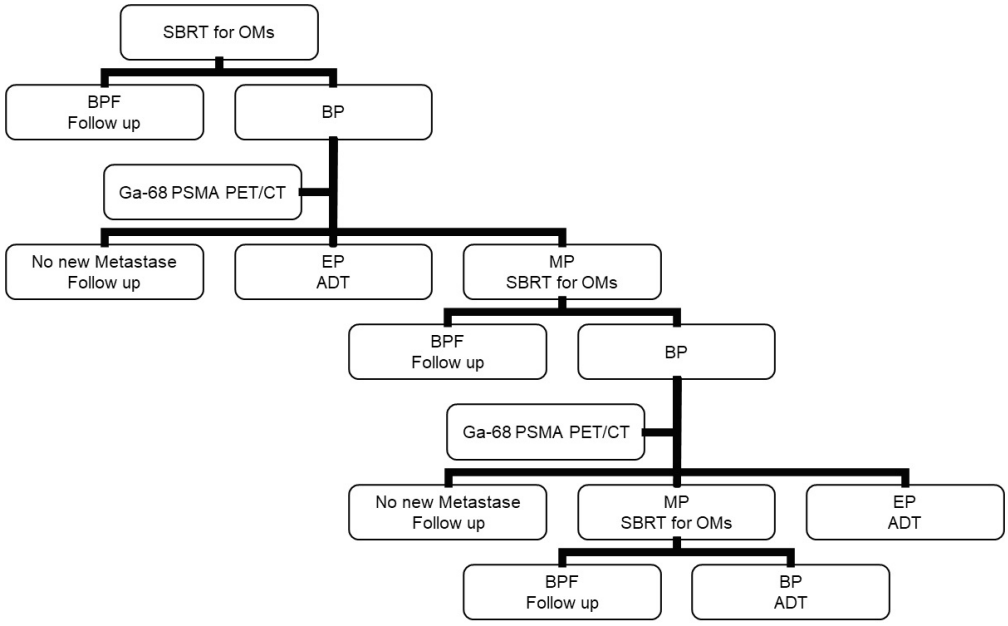

Fig. 1 Treatment schedule of Arm B in the protocol. OMs: oligometastases; BPF: biochemical progression-free; BP: biochemical progression; EP: extensive progression; MP: micro-progression.

254x167mm (120 x 120 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2and 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	6

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10,11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8,9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	10,11

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10,11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11,12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if	12

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2,12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	N/A

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

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

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

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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 (PSMA) PET/CT, will be randomized 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 30-50Gy 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 progression-free-survival (LPFS), and overall survival (OS). Toxicity will be assessed using the National Cancer Institute Common Toxicity Criteria V5.0.

Ethics and dissemination

This protocol was approved by the institutional review board of Shanghai Changhai Hospital (CHEC2020-101). This is a randomized control clinical trial comparing SBRT to ADT for men with oligometastatic PCa. The study will be performed in

compliance with applicable local legislation and 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; Pre-results.

Strengths and Limitations of this study

- This is a randomized trial comparing ADT versus SBRT for oligometastatic PCa.
- In this protocol, pre and after-treatment Ga-68 PSMA 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 PCa patients 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, anemia, hot flash, mammary swelling pain, and feminization 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 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.[10,11,12,13]

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 randomized 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 study was approved by the Ethics committee of the Shanghai Changhai Hospital (CHEC2020-101) and has been registered on Clinicaltrials.gov (NCT045996860. This is a prospective, two arms, randomized control clinical trial. The development of the study protocol followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The protocol has been prepared in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT).

The main objective of the trial is to determine whether SBRT for the oligometastases of hormone-sensitive PCa can prolong bPFS and delay the start of ADT in arm B. Then the study also explores whether patients in arm B can prolong the time from inception of the study to CRPC, compared to arm A. 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 one 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 RECIST(Response Evaluation Criteria in Solid Tumours).[14] The planned start and end dates for the study were November 11, 2020 and October 1, 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.

Study participants

Inclusion Criteria

- ≤80 years old years 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< 50ng/ml before enrollment.
- ECOG performance status 0–2.
- Written informed consent according to International Council for Harmonization/ Good Clinical Practice (ICH/GCP) 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 tumor or small cell carcinoma of the prostate.
- Severe or active co-morbidity 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 three 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 enrollment. Then, participants will be randomized 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 50mg PO once daily for 2 weeks and goserelin acetate, a gonadotropin-releasing hormone agonist. The latter will be administered subcutaneously either at a dose of 3.6mg every 4 weeks or at a dose of 10.8mg 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 tumor volume (GTV) of oligometastases relied on

imaging examination. Planning target volume (PTV) for GTV is delineated with an additional 5-8 mm margin. 30-50Gy with 3-5 fractions is the recommended dose segmentation which depends on the surrounding organs at risk (OARs) and tumor location. Dose guidelines to OARs in SBRT treatment are based upon AAPM Task Group 101.[15]

Biochemical progression

Biochemical progression is defined as a ≥ 20% increase in 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.

Patients in arm B will receive SBRT for the oligometastases firstly. When the disease progresses oligprogression in the follow-up, SBRT will be applied for the treatment of oligometastases, secondly. When their disease progresses oligprogression in the follow-up again, SBRT will be applied for the treatment of oligometastases, thirdly. 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 randomization to CRPC in both arms. The secondary endpoints include radiotherapy-related toxicity, ADT-related toxicity, bPFS, local

progression-free-survival (LPFS) in arm B, overall survival (OS) in both arms. Toxicity will be assessed via CTCAE v5.0. Quality of life of two arms is very inmportant in the study. Quality of life will be measured using Karnofsky Performance Status Scale,[16] the Expanded Prostate Cancer Index Composite (EPIC)[17] and the 5-level EQ-5D (EQ-5D-5L) 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 pre-treatment 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 authorized researchers, it will be retrieved from the database.

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	●	○	●
ECT	○	●	○
Contrast-enhanced CT	○		○
Contrast-enhanced MRI	○		○
Blood biochemistry	●	●	○

Coagulation function	●	●	○
Biopsies of the prostate	●		
Adverse effects		●	●
Combined drug record	●	●	●

●：Required items；○：Selected items

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 randomization 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 randomization 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 randomization to CRPC.

Data analysis

The primary endpoint ADT-free survival of arm B and the time from randomization to CRPC will be calculated using Kaplan-Meier actuarial analyses. Pre-planned 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 (IBM Corp, Somers, NY, USA). Toxicity data of both arms will be summarized.

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 randomized phase II trial comparing surveillance with metastasis-directed surgery or SBRT for oligometastatic prostate cancer recurrence.[19] Another phase II randomized trial is ORIOLE comparing observation with stereotactic ablative radiation for oligometastatic prostate cancer.[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 PCa patients 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). Shankar et al. analyzed 33 patients with 50 oligometastases who received stereotactic body radiotherapy (SABR). 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 randomized 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 tumors, tumor location, pathological type, immune response, and genomic susceptibility characterization. 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 PCa patients: system therapy or local therapy. The time from enrollment to CRPC is the important endpoints to judge whether SBRT for oligometastases can delay hormone therapy.

Abbreviations

SBRT: Stereotactic body radiotherapy; ADT: Androgen deprivation therapy; PCa: Prostate cancer; bPFS: Biochemical progression-free survival; CRPC: Castration-resistant prostate cancer; PSMA: Prostate-specific membrane antigen; LPFS: Local progression-free-survival; OS: Overall survival; QoL: Quality of life; LC:

Local control; ASTRO: American Society for Therapeutic Radiology and Oncology; ACR: American College of Radiology; ICH/GCP: International Council for Harmonization/Good Clinical Practice; CTCAE: Common Terminology Criteria for Adverse Events; LHRHa: Luteinizing hormone-releasing hormone agonist; GTV: Gross tumor volume; PTV: Planning target volume; OARs: Organs at risk; OMs: Oligometastases; BPF: Biochemical progression-free; BP: Biochemical progression; PP: Polyprogression; OP: Oligprogression.

Acknowledgments

Not applicable.

Author Contributions

Study conception: H.J.Z and X.G. Initial Study design: X.Z.Z. and J.L. Revision of study design and protocol: H.J.Z, X.G., X.Z.Z., J.L. Y.S.Y, and T.W. Study coordination: All authors. Drafting the manuscript: X.Z.Z., T.W., and Y.S.Y. All authors read and approved the final manuscript.

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Competing interest statement

The authors declare that they have no competing interests.

Patient consent for publication

Not applicable.

Provence and peer review

Not commissioned; externally peer-reviewed.

Data sharing

The authors certify that this manuscript reports original clinical trial data (Clinicaltrials.gov identifier: NCT04599686). Individual participant data including baseline characteristics,treatment information and follow-up data on toxicity, survival and disease control will be shared.

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Figure legend

Fig. 1 Treatment schedule of Arm B in the protocol. OMs: oligometastases; BPF: biochemical progression-free; BP: biochemical progression; PP: polyprogression; OP: oligprogression.

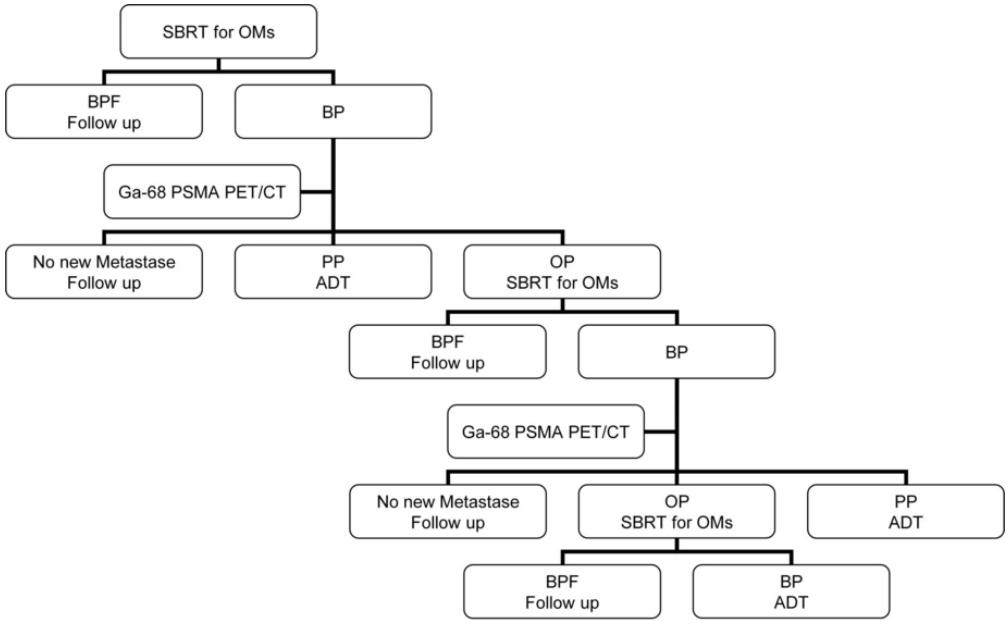

Fig. 1 Treatment schedule of Arm B in the protocol. OMs: oligometastases; BPF: biochemical progression-free; BP: biochemical progression; PP: polyprogression; OP: oligprogression.

38x24mm (600 x 600 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A
Protocol version	#3	Date and version identifier	N/A
Funding	#4	Sources and types of financial, material, and other support	14
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	2and 14

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N/A
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N/A
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	5,6
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	N/A
Objectives	#7	Specific objectives or hypotheses	6
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	6
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be	6

		obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	6,7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	8,9
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N/A
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	10,11
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	8,9
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	9
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	10,11
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	N/A

Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	11
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the	10,11

		protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	10,11
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	10
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11,12
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11,12
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11,12
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	10
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	10
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	10
Auditing	#23	Frequency and procedures for auditing trial conduct, if	12

		any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	2,12
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N/A
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	12
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	12
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	12
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	14
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	N/A
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N/A
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy:	#31b	Authorship eligibility guidelines and any intended use of	N/A

authorship		professional writers	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A