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Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single-centre, phase I clinical trial

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Abstract

Introduction

Patients with locally advanced prostate cancer are at high risk of recurrence after definitive treatment. There are emerging data that radical prostatectomy can delay the progression of castration resistance and potentially prolong survival. Neoadjuvant radiation therapy improves local control and has shown survival benefit with favorable toxicity profile in several other malignancies. We have designed this trial to investigate whether this combination, which theoretically maximizes local control, is a safe and feasible approach for treating locally advanced prostate cancer.

Methods and analysis

This study is a phase I, open-label study to investigate the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy by a traditional 3+3 dose-escalation design with 4 planned radiation dose levels (39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F). Locally advanced prostate cancer patients with positive pelvic and/or retroperitoneal lymph nodes will be recruited. The primary objective is to determine the adverse events and maximal tolerable dose neoadjuvant of radiotherapy. 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 (ref. CHEC2019-070 & CHEC2019-082). 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

ChiCTR1900022716 & ChiCTR1900022754; Pre-results.

Strengths and Limitations of this study

- This protocol describes a phase I study with a traditional 3+3 dose-escalation design.
- This study is expected to provide safety and feasibility profile to inform future prospective trials on preoperative radiotherapy in locally advanced prostate cancer.
- This study is monocentric, with relatively small sample size.

Introduction

Prostate cancer is a major health problem worldwide, accounting for one fifth of newly-diagnosed malignancies in men. The number of prostate cancer patients in China have been continuously mounting and shows no sign at present of ceasing to rise, with approximately 99, 322 new diagnoses in the year 2018.[1] Radical prostatectomy, commonly performed in a laparoscopic or robot-assisted fashion, is the first-line active treatment for localized prostate cancer.[2] Patients with locally advanced prostate cancer are at higher risk of recurrence, and the optimal treatment approach is still controversial. Current National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines all recommend radiation therapy plus long-term androgen deprivation therapy (ADT) as a primary treatment option.[3 4] Increasingly, surgery-based multimodality treatment (MDT) has become a feasible approach for treating high-risk localized and locally advanced prostate cancer.[5] Whether individual patient may benefit from surgery remains to be elucidated, and a prospective phase III randomized controlled trial (RCT) comparing radical prostatectomy against radiation therapy and ADT for locally advanced prostate cancer patients is currently recruiting[6].

However, there is evidence that patients might benefit from maximizing local control with a combination of radiation therapy and surgery. Results from three phase III RCTs suggest improved biochemical progression-free survival and metastasis-free survival from immediate post-operative radiation therapy.[7-9] We argue that similar survival benefits could be achieved through radiation therapy plus ADT in a neoadjuvant setting. Theoretically, the additional advantages of neoadjuvant radiation therapy include: 1) potential down-staging of the tumors, decreased rate of positive surgical margins, and

lower incidence of positive lymph nodes, 2) decreased hypoxia-induced radio-resistance because of unaltered prostatic blood supply, and 3) potential decrease in dosage and radiation-related toxicity. Indeed, the superiority of preoperative over postoperative chemoradiotherapy in terms of improved local control and reduced toxicity has been demonstrated by the phase III CAO/ARO/AIO-94 study in locally advanced rectal cancer.[10] In addition, given the considerable overlap of the radiation target volume, dose, and schedule, the safety profile of preoperative radiotherapy for locally advanced prostate cancer and rectal cancer is roughly comparable. Therefore, we hypothesize that neoadjuvant radiation therapy is a safe and feasible approach for treating locally advanced prostate cancer.

Methods and analysis

Study design

This is a phase I, single-arm, single-centre observational study in Shanghai Changhai Hospital. The participants enrolled will be assigned to one of the four groups receiving 39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F of preoperative radiation therapy plus ADT. A traditional 3+3 dose escalation design will be utilized to determine the maximal tolerable dose (MTD) of radiation therapy. Participants will then undergo robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND), followed by post-operative ADT for at least 2 years. The trial schedule is illustrated in Figure 1. The trial is approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082) and is prospectively registered at the Chinese Clinical Trial Registry

(ChiCTR1900022716 & ChiCTR1900022754). This trial protocol is structured and reported in accordance with the SPIRIT 2013 statement.[11 12]

Recruitment

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

Study participants

Inclusion Criteria

- Men between 18 and 75 years of age.
- A diagnosis of prostate cancer confirmed by biopsy pathology.
- Locally advanced disease with positive pelvic lymph node(stage N1M0, ChiCTR1900022716) or positive retroperitoneal lymph node(stage M1a, ChiCTR1900022754), as determined by contrast-enhanced CT, bone scan, and/or MRI.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
- An expected life expectancy of at least 5 years.
- Patients who are well-informed of the current treatment options and willing to participate in the trial.
- Signed, written informed consent.

Exclusion Criteria

A patient may not enter the study if ANY of the following applies:

- Lymph node metastases spreading beyond pelvic and retroperitoneal nodes.
- Presence of bone metastasis or distant organ metastasis.
- Prior exposure to any treatment for prostate cancer, including surgery, radiotherapy, chemotherapy, hormone therapy, focal therapy, etc.
- Prior transurethral enucleation or resection of the prostate.
- Any abdominal surgery performed within 3 months prior to enrollment.
- A transrectal prostate biopsy performed within 2 weeks prior to enrollment.
- Sustained use of anticoagulation and antiplatelet drugs.
- Any other previous or concurrent malignancies.
- Disease complicated by other severe systemic diseases which, in the judgment of the investigators, are likely to interfere with the treatment, assessment or compliance associated with this trial.
- Participation in any other trial which is ongoing or has been completed within 3 months.
- Any contraindication for radiation therapy or surgery.

Dropout or suspension of the trial

- 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.
- Disease progression.
- Other potential situations that necessitate the termination of the trial.

Interventions

Baseline evaluation

Patients with histologically confirmed locally advanced prostate cancer who are eligible for this study will be evaluated for baseline characteristics. The evaluation will include demographics, medical history, concomitant diseases and medications, physical exam, vital signs, digital rectal exam, routine blood tests, high-resolution MRI of the pelvis, and bone scan in selected patients. Baseline characteristics of the included participants will be collected within two weeks prior to the initiation of ADT.

Neoadjuvant radiation therapy plus ADT

The ADT regimen for this trial includes bicalutamide 50mg PO once daily 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.

Intensity modulated radiation therapy (IMRT) will be administered 4 months after the initiation of preoperative ADT. All patients shall undergo a contrasted CT simulation of the pelvis or abdomen of 5-mm-slice thickness in a supine position. The CT images will then be transferred to the treatment planning system for contouring the target volume and organs at risk (OARs)

and planning. Critical normal structures include the small bowel, bladder, femoral head, rectum, spinal cord, prostatic urethra (if visualised), bulbous urethra, kidney, etc. OARs shall be contoured according to the pelvic normal tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG).[13] This protocol offers dose guidelines to OARs based upon prior published RTOG trials.[14-16]

The gross tumor volume (GTV) is contoured based on MRI. GTV includes prostate and seminal vesicle glands. GTV of the pelvic or retroperitoneal metastatic lymph node (GTVnd) is further confirmed by imaging. The clinical tumor volume (CTV) includes GTV, GTVnd, pelvic/ retroperitoneal lymphatic drainage area. The superior border of the whole pelvis field extends to the L5-S1 interspace for N1 subgroup. The pelvic lymphatic drainage area includes bilateral total iliac lymph nodes, extra-iliac lymph nodes, intra-iliac lymph nodes, S1-S3 levels presacral lymph nodes and obturator lymph nodes. The superior border of the retroperitoneal field is 2-3 cm above the positive lymph nodes not exceeding renal artery level. The primary gross tumor volume (pGTV) is 5-10mm outwards for GTV in any direction, but only 5 mm in the posterior to reduce rectal irradiation. pGTVnd for GTVnd shall be delineated with an additional 5mm margin and pCTV for CTV shall be delineated with an additional 5mm margin separately.

Four radiation dose levels were planned: 39.6 Gy, 45 Gy, 50.4 Gy, and 54 Gy. Radiation therapy will be delivered in 5 1.8-Gy fractions per week. The initial two dose levels target whole pelvis/ retroperitoneum, whereas in the latter two dose levels a subsequent boost to the prostate, seminal vesicles and pelvic/ retroperitoneal metastatic lymph nodes were added after reaching 45 Gy.

Dose escalation

Dose escalation will be conducted in a 3+3 design with dose levels of 39.6, 45, 50.4, and 54 Gy in 22, 25, 28 and 30 fractions respectively. A traditional 3+3 dose-escalation design will be adopted (Figure 2). Briefly, three participants will initially be allocated into the starting dose cohort. If no dose-limiting toxicity (DLT) is observed in any of the three participants, the dose will be escalated and three new patients will be enrolled to receive the next level of radiation dose. If one participant develops any DLT, an additional three participants will be allocated into the same dose cohort. If there are multiple observations of DLT at any given dose level, the dose escalation will be stopped and the previous dose level will be identified as the MTD. In this trial, DLTs are defined as any Grade III/IV toxicities.

Robot-assisted radical prostatectomy

Surgery will be scheduled 8 weeks after the completion of radiation therapy, via a robot-assisted laparoscopic approach. Extended pelvic lymph node dissection (ePLND) will be performed. All surgical procedures will be performed by a single highly experienced robotic surgeon (R.S.).

Post-operative treatment

Participants will receive long-term post-operative ADT for at least 2 years. The regimen will remain the same. Participants will be monthly evaluated for serum PSA level at their local primary healthcare facilities. They will be followed up every 3 months for the first year and every 6 months for the following year. Upon tumor progression, salvage treatment including but not limited to abiraterone acetate/prednisone treatment, chemotherapy, and surgery, will be administered to the trial participants upon documented progression in accordance with standard clinical practice.

Outcomes and Measurements

The primary objective of this trial is to determine the adverse events and MTD of radiotherapy. Adverse events throughout the study will be assessed via CTCAE v5.0 by research physicians or nurses. Secondary endpoints include perioperative safety profile, efficacy of neoadjuvant treatment, rates of positive surgical margins, biochemical recurrence-free survival, overall survival, and functional outcomes.

Determination of sample size

The study is a dose-escalation study which implements a traditional 3+3 design with 4 dose levels. Three to six participants will be allocated to each dose level cohort. Therefore, the maximum per protocol sample size for this trial is 24.

Data Management and Monitoring

The institutional review board of Shanghai Changhai Hospital will monitor the reporting of adverse events and the quality of collected data on a semiannual basis. A planned interim analysis will be performed by the principle investigator when median post-operative follow-up reached 1 year.

Statistical analysis

All characteristics will be described by the frequency for classified variables, mean±SD and 95% confidence intervals for normally distributed continuous data, and the median and range for non-normal distributional continuous data. Should any statistical hypothesis testing be used, a two-tailed test is

preferred and the significance level threshold(α) is set as 0.05. Statistical analyses will be performed using the R software v3.6.0 or higher.[17]

Biological specimens

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

Patient and public involvement

Patients or public have not been 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. Written informed consent will be obtained by research physicians or nurses if patients decide to participate. All clinical data will be confidentially collected by research members. Findings of the study will be disseminated through publication in peer-reviewed scientific journals as well as relevant medical conferences.

Discussion

The idea for maximizing cancer local control originates from the “seed and soil” hypothesis, which postulates that the growth of disseminating tumor

cells is driven by factors secreted by the primary tumor.[18] It has been demonstrated in metastatic prostate cancer that aggressive subclones persist in primary tumor site and can seed to metastatic lesions, leading to a vicious cycle of metastatic disease.[19 20] Furthermore, overall survival benefits can be observed in metastatic prostate cancer patients who have been treated with radiotherapy plus ADT compared to ADT alone.[21] These data collectively suggest a role of maximizing local control in the management of locally advanced and metastatic prostate cancer.

Currently, clinical trials on preoperative radiation therapy for prostate cancer have focused primarily on men with high-risk localized disease. To the best of our knowledge, there are two published modern-era trials that evaluated preoperative radiation therapy in localized prostate cancer. Koontz et al. conducted a phase I clinical trial in 13 men with high-risk localized prostate cancer evaluating long-course preoperative radiation therapy followed by radical prostatectomy.[22] The reported two-year biochemical recurrence-free survival was 67%. Glicksman et al. recently reported the long-term results of their phase I pilot study of 15 patients.[23] At a median follow-up of 12.2 years, 7 patients were free from biochemical relapse and 6 patients were metastasis-free. These have motivated us to assess this treatment combination in locally advanced disease. Despite the limitations, the impact of this study has the potential to drive a paradigm shift in the management of locally advanced prostate cancer.

Acknowledgments

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Author Contributions

YTX, XZ, YC, HZ, and SR were involved in literature search, study conception, protocol development, conduct of the study, and manuscript writing. XL was involved in the conduct of the study. YW was involved in writing the manuscript. SR is the principle investigator. YTX, XZ, and YC are the trial coordinators. All authors contributed to and approved the final version of the manuscript.

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This study has been approved by the institutional review board of Shanghai Changhai Hospital. (ref. CHEC2019-070 & CHEC2019-082)

Provenance and peer review

Not commissioned; externally peer reviewed.

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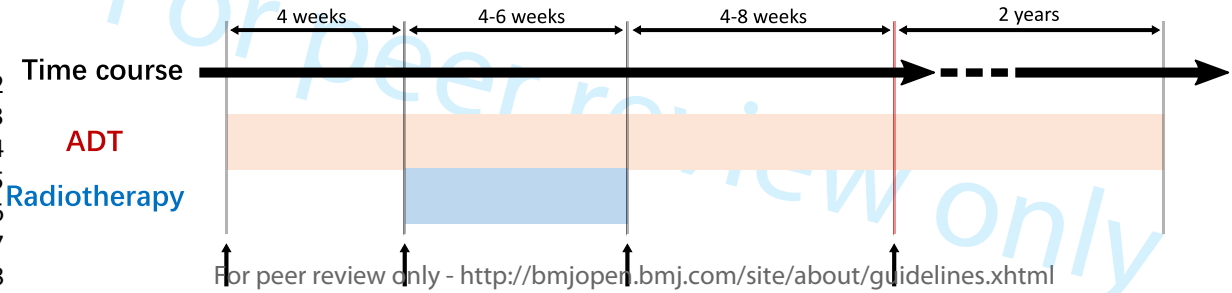
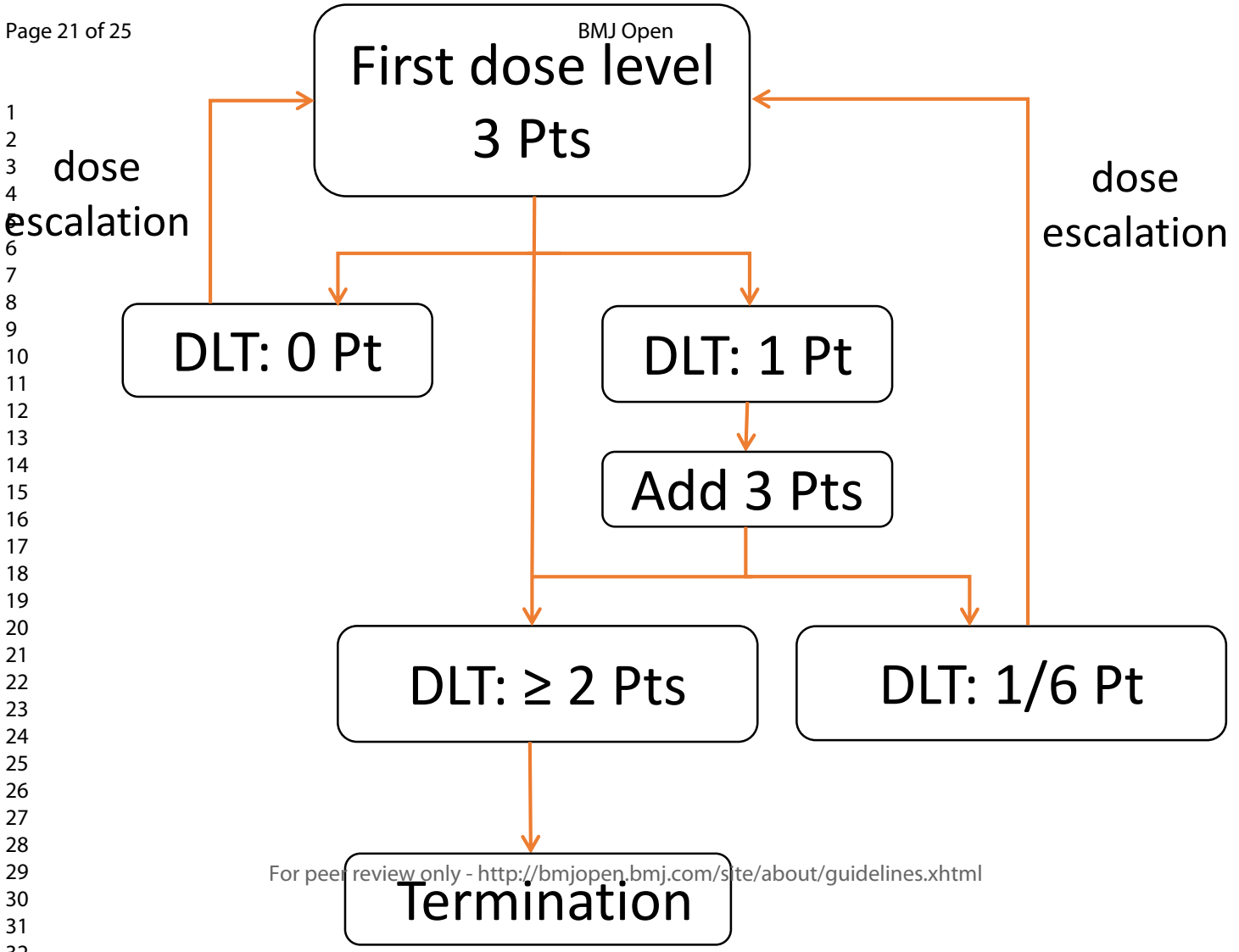
Figure Legends

Figure 1. Schedule of the study. ADT, androgen deprivation therapy.

Figure 2. Graphical depiction of the 3+3 dose-escalation study design. DLT, dose-limiting toxicity. Pt, participant.





SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 6-7
	2b	All items from the World Health Organization Trial Registration Data Set	Not included in the manuscript. Available on the registration website.
Protocol version	3	Date and version identifier	Not included in the manuscript.
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, Page 15
	5b	Name and contact information for the trial sponsor	Not applicable.
	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	Not applicable.
	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)	Page 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	Page 5-6.
	6b	Explanation for choice of comparators	Not applicable (single-arm)
Objectives	7	Specific objectives or hypotheses	Page 12
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, noninferiority, exploratory)	Page 11.
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 obtained	Page 5-6.
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)	Page 7-9 ; Page 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-12.
	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)	Page 8-11.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 7-9.
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	Page 11.
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)	Page 6-11 ; Figure 1-2.

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	Page 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA

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	✓
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	✓
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓

Methods: Data collection, management, and analysis

Data collection methods	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 protocol	Page 11-12.
	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	Not included in the manuscript.

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	Page 12
Statistical methods	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	Page 12-13.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 13.
	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)	NA
Methods: Monitoring			
Data monitoring	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	Page 13.
	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	Page 12.
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	Page 12.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 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)	Not included in the manuscript.

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 13.
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	Page 13.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not included in the manuscript.
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	Not included in the manuscript.
Dissemination policy	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	Page 13.
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not included in the manuscript.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not included in the manuscript.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included in the manuscript.
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	Page 13.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single-centre, phase I clinical trial

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Assessing the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy for treating locally advanced prostate cancer: protocol for an open-label, dose-escalation, single-centre, phase I clinical trial

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Abstract

Introduction

Patients with locally advanced prostate cancer are at high risk of recurrence after definitive treatment. There are emerging data that radical prostatectomy can delay the progression of castration resistance and potentially prolong survival. Neoadjuvant radiation therapy improves local control and has shown survival benefit with favorable toxicity profiles in several other malignancies. We have designed this trial to investigate whether this combination, which theoretically maximizes local control, is a safe and feasible approach for treating locally advanced prostate cancer.

Methods and analysis

This study is a phase I, open-label study to investigate the safety and feasibility of neoadjuvant hormone and radiation therapy followed by robot-assisted radical prostatectomy by a traditional 3+3 dose-escalation design with 4 planned radiation dose levels (39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F). Locally advanced prostate cancer patients with positive pelvic and/or retroperitoneal lymph nodes will be recruited. The primary objective is to determine the adverse events and maximal tolerable dose neoadjuvant of radiotherapy. 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 (ref. CHEC2019-070 & CHEC2019-082). 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

ChiCTR1900022716 & ChiCTR1900022754; Pre-results.

Strengths and Limitations of this study

- This protocol describes a phase I study with a traditional 3+3 dose-escalation design.
- This study is expected to provide safety and feasibility profile to inform future prospective trials on preoperative radiotherapy in locally advanced prostate cancer.
- This study is monocentric, with relatively small sample size.

Introduction

Prostate cancer is a major health problem worldwide, accounting for one fifth of newly-diagnosed malignancies in men. The number of prostate cancer patients in China have been continuously mounting and shows no sign at present of ceasing to rise, with approximately 99, 322 new diagnoses in the year 2018.[1] Radical prostatectomy, commonly performed in a laparoscopic or robot-assisted approach, is a first-line curative treatment option for localized prostate cancer.[2] Patients with locally advanced prostate cancer are at higher risk of recurrence, and the optimal treatment is still controversial. Current National Comprehensive Cancer Network (NCCN) and European Association of Urology (EAU) guidelines all recommend radiation therapy plus long-term androgen deprivation therapy (ADT) as a primary treatment option.[3 4] Increasingly, surgery-based multimodality treatment (MDT) has become a feasible approach for treating high-risk localized and locally advanced prostate cancer.[5] Whether individual patients may benefit from surgery remains to be elucidated, and a prospective phase III randomized controlled trial (RCT) comparing radical prostatectomy against radiation therapy and ADT for locally advanced prostate cancer patients is currently recruiting[6].

However, there is evidence that patients might benefit from maximizing local control with a combination of radiation therapy and surgery. Results from three phase III RCTs suggest improved biochemical progression-free survival and metastasis-free survival from immediate post-operative radiation therapy.[7-9] We argue that similar survival benefits could be achieved through the use of radiation therapy and ADT in a neoadjuvant setting. Theoretically, the additional advantages of neoadjuvant radiation therapy include: 1) potential down-staging of the tumors, decreased rate of positive surgical

margins, and lower incidence of positive lymph nodes, 2) decreased hypoxia-induced radio-resistance because of unaltered prostatic blood supply, and 3) potential decrease in dosage and radiation-related toxicity. Indeed, the superiority of preoperative over postoperative chemoradiotherapy in terms of improved local control and reduced toxicity has been demonstrated by the phase III CAO/ARO/AIO-94 study in locally advanced rectal cancer.[10] In addition, given the considerable overlap of the radiation target volume, dose, and schedule, the safety profile of preoperative radiotherapy for locally advanced prostate cancer and rectal cancer is roughly comparable. Therefore, we hypothesize that neoadjuvant radiation therapy is a safe and feasible approach for treating locally advanced prostate cancer.

Methods and analysis

Study design

This is a phase I, single-arm, single-centre observational study in Shanghai Changhai Hospital. The participants enrolled will be assigned to one of the four groups receiving 39.6 Gy/22F, 45 Gy/25F, 50.4 Gy/28F, and 54 Gy/30F of preoperative radiation therapy plus ADT. A traditional 3+3 dose escalation design will be utilized to determine the maximal tolerable dose (MTD) of radiation therapy. Participants will then undergo robot-assisted radical prostatectomy (RARP) and extended pelvic lymph node dissection (ePLND), followed by post-operative ADT for at least 2 years. The trial schedule is illustrated in Figure 1. The trial is approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082) and is prospectively registered at the Chinese Clinical Trial Registry

(ChiCTR1900022716 & ChiCTR1900022754). This trial protocol is structured and reported in accordance with the SPIRIT 2013 statement.[11 12]

Recruitment

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

Study participants

Inclusion Criteria

- Men between 18 and 75 years of age.
- Biopsy confirmed prostate adenocarcinoma without neuroendocrine differentiation, signet cell, or small cell features.
- Locally advanced disease with positive pelvic lymph node(stage N1M0, ChiCTR1900022716) or positive retroperitoneal lymph node(stage M1a, ChiCTR1900022754), as determined by contrast-enhanced CT, bone scan, ~~and/or~~ MRI, and/or 68Ga-PSMA PET/CT.
- Eastern Cooperative Oncology Group (ECOG) performance status 0-1.
- An expected life expectancy of at least 5 years.
- Patients who are well-informed of the current treatment options and willing to participate in the trial.
- Signed, written informed consent.

Exclusion Criteria

A patient may not enter the study if ANY of the following applies:

- Lymph node metastases spreading beyond pelvic and retroperitoneal nodes.
- Presence of bone metastasis or distant organ metastasis.
- Prior exposure to any treatment for prostate cancer, including radiotherapy, chemotherapy, hormone therapy, focal therapy, etc.
- Prior transurethral enucleation or resection of the prostate.
- Any abdominal surgery performed within 3 months prior to enrollment.
- Sustained use of anticoagulation and antiplatelet drugs.
- Any other previous or concurrent malignancies.
- Disease complicated by other severe systemic diseases which, in the judgment of the investigators, are likely to interfere with the treatment, assessment or compliance associated with this trial.
- Participation in any other trial which is ongoing or has been completed within 3 months.
- Any contraindication for radiation therapy or surgery.

Dropout or suspension of the trial

- 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.

- Disease progression.
- Other potential situations that necessitate the termination of the trial.

Interventions

Baseline evaluation

Patients with histologically confirmed locally advanced prostate cancer who are eligible for this study will be evaluated for baseline characteristics. The evaluation will include demographics, medical history, concomitant diseases and medications, physical exam, vital signs, digital rectal exam, routine blood tests, high-resolution MRI of the pelvis, ~~and~~ bone scan, and 68Ga-PSMA PET/CT. Baseline characteristics of the included participants will be collected within two weeks prior to the initiation of ADT.

Neoadjuvant radiation therapy plus ADT

The ADT regimen for this trial includes bicalutamide 50mg PO once daily 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.

Intensity modulated radiation therapy (IMRT) will be administered 4 weeks after the initiation of preoperative ADT. All patients shall undergo a contrasted CT simulation of the pelvis or abdomen of 5-mm-slice thickness in a supine position. The CT images will then be transferred to the treatment planning system for contouring the target volume and organs at risk (OARs) and planning. Critical normal structures include the small bowel, bladder, femoral head, rectum, spinal cord, prostatic urethra (if visualised), bulbous urethra, kidney, etc. OARs shall be contoured according to the pelvic normal

tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG).[13] This protocol offers dose guidelines to OARs based upon prior published RTOG trials.[14-16]

The gross tumor volume (GTV) is contoured based on MRI. GTV includes prostate and seminal vesicle glands. GTV of the pelvic or retroperitoneal metastatic lymph node (GTVnd) is further confirmed by imaging. The clinical tumor volume (CTV) includes GTV, GTVnd, pelvic/ retroperitoneal lymphatic drainage area. The superior border of the whole pelvis field extends to the L5-S1 interspace for N1 subgroup. The pelvic lymphatic drainage area includes bilateral total iliac lymph nodes, extra-iliac lymph nodes, intra-iliac lymph nodes, S1-S3 levels presacral lymph nodes and obturator lymph nodes. The superior border of the retroperitoneal field is 2-3 cm above the positive lymph nodes not exceeding renal artery level. The primary gross tumor volume (pGTV) is 5-10mm outwards for GTV in any direction, but only 5 mm in the posterior to reduce rectal irradiation. pGTVnd for GTVnd shall be delineated with an additional 5mm margin and pCTV for CTV shall be delineated with an additional 5mm margin separately.

Four radiation dose levels were planned: 39.6, 45, 50.4, and 54 Gy. Radiation therapy will be delivered in 5 1.8-Gy fractions per week. The initial two dose levels target whole pelvis/ retroperitoneum, whereas in the latter two dose levels a subsequent boost to the prostate, seminal vesicles and pelvic/ retroperitoneal metastatic lymph nodes were added after reaching 45 Gy.

Dose escalation

Dose escalation will be conducted in a 3+3 design with dose levels of 39.6, 45, 50.4, and 54 Gy in 22, 25, 28 and 30 fractions respectively. A traditional 3+3 dose-escalation design will be adopted (Figure 2). Briefly, three participants will initially be allocated into the starting dose cohort. If no dose-limiting

toxicity (DLT) is observed in any of the three participants, the dose will be escalated and three new patients will be enrolled to receive the next level of radiation dose. If one participant develops any DLT, an additional three participants will be allocated into the same dose cohort. If there are multiple observations of DLT at any given dose level, the dose escalation will be stopped, and the previous dose level will be identified as the MTD. In this trial, DLT is defined as (1) any grade 4+ toxicity, (2) any grade 3 toxicity except urinary incontinence, erectile dysfunction, and responsive diarrhea, (3) grade 2+ fistula, (4) any grade colonic or rectal perforation, or (5) any grade intraoperative rectal injury.

Robot-assisted radical prostatectomy

Surgery will be scheduled within 4–8 weeks after the completion of radiation therapy, via a robot-assisted laparoscopic approach. Extended pelvic lymph node dissection (ePLND) will be performed. All surgical procedures will be performed by one single highly experienced robotic surgeon (R.S.).

Post-operative treatment

Participants will receive long-term post-operative ADT for at least 2 years. The regimen will remain the same. Participants will be monthly evaluated for serum PSA and testosterone level at their local primary healthcare facilities. They will be followed up every 3 months for the first year and every 6 months for the following year. Upon tumor progression, salvage treatment including but not limited to abiraterone acetate/prednisone treatment, chemotherapy, and surgery, will be administered to the trial participants upon documented progression in accordance with standard clinical practice.

Outcomes and Measurements

The primary objective of this trial is to determine the adverse events and MTD of radiotherapy. Adverse events throughout the study will be assessed via CTCAE v5.0 by research physicians or nurses.

Secondary endpoints include perioperative safety profile, efficacy of neoadjuvant treatment, rates of positive surgical margins, biochemical recurrence-free survival, overall survival, and functional outcomes. Perioperative complications will be measured by Clavien-Dindo classification within 30 postoperative days. Continence will be measured by patient-reported pads used per day. Quality of life will be measured using Karnofsky Performance Status Scale,[17] the Functional Assessment of Cancer Therapy-Prostate (FACT-P, version 4) instrument,[18] and the 5-level EQ-5D (EQ-5D-5L) instrument.[19]

Determination of sample size

The study is a dose-escalation study which implements a traditional 3+3 design with 4 dose levels. Three to six participants will be allocated to each dose level cohort. Therefore, the maximum per protocol sample size for this trial is 24.

Data Management and Monitoring

The institutional review board of Shanghai Changhai Hospital will monitor the reporting of adverse events and the quality of collected data on a

semiannual basis. A planned interim analysis will be performed by the principal investigator when median post-operative follow-up reached 1 year.

Statistical analysis

All characteristics will be described by the frequency for classified variables, mean±SD and 95% confidence intervals for normally distributed continuous data, and the median and range for non-normal distributional continuous data. Should any statistical hypothesis testing be used, a two-tailed test is preferred and the significance level threshold (α) is set as 0.05. Statistical analyses will be performed using the R software v4.0.0 or higher.[20]

Biological specimens

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

Patient and public involvement

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

Ethics and dissemination

This study was approved by the institutional review board of Shanghai Changhai Hospital (ref. CHEC2019-070 & CHEC2019-082). The study will be performed in compliance with applicable local legislation and in accordance with the ethical principles in the Declaration of Helsinki 2013. Eligible patients will be well informed of the purpose and schedule of this study. Written informed consent will be obtained by research physicians or nurses if patients decide to participate. All clinical data will be confidentially collected by research members. Findings of the study will be disseminated through publication in peer-reviewed scientific journals as well as relevant medical conferences.

Discussion

The idea for maximizing cancer local control originates from the "seed and soil" hypothesis, which postulates that the growth of disseminating tumor cells is driven by factors secreted by the primary tumor.[21] It has been demonstrated in metastatic prostate cancer that aggressive subclones persist in primary tumor site and can seed to metastatic lesions, leading to a vicious cycle of metastatic disease.[22 23] Furthermore, overall survival benefits can be observed in metastatic prostate cancer patients who have been treated with radiotherapy plus ADT compared to ADT alone.[24] These data collectively suggest a role of maximizing local control in the management of locally advanced and metastatic prostate cancer.

Currently, clinical trials on preoperative radiation therapy for prostate cancer have focused primarily on men with high-risk localized disease. To the best of our knowledge, there are two published modern-era trials that evaluated preoperative radiation therapy in localized prostate cancer. Koontz et al. reported a phase I clinical trial in 12 men with high-risk localized prostate cancer who had completed long-course preoperative radiation therapy followed by radical prostatectomy.[25] Radiation therapy was dose-escalated with dose levels of 39.6, 45, 50.4, and 54 Gy in 5 1.8-Gy fractions per week. The pelvic lymph nodes were treated up to 45 Gy with any additional dose given to the prostate and seminal vesicles. The superior border of the whole pelvis field extended to the L5-S1 interspace. Two patients developed urethral strictures requiring dilation. The reported two-year biochemical recurrence-free survival was 67%. Glicksman et al. recently reported the long-term results of their phase I pilot study of 15 patients.[26] Patients received 25 Gy in 5 consecutive daily fractions to the prostate only. At a median follow-up of 12.2 years, 7 patients were free from biochemical relapse and 6 patients were metastasis-free. These results have motivated us to assess this treatment combination in locally advanced disease. Despite the limitations, the impact of our study has the potential to drive a paradigm shift in the management of locally advanced prostate cancer.

Acknowledgments

We wish to acknowledge Dr. Jin Fan (Department of Radiation Oncology, Fudan University Shanghai Cancer Center) for providing support on protocol development.

Author Contributions

YTX, XZ, YC, HZ, and SR were involved in literature search, study conception, protocol development, conduct of the study, and manuscript writing. XL was involved in the conduct of the study. YW was involved in writing the manuscript. SR is the principal investigator. YTX, XZ, and YC are the trial coordinators. All authors contributed to and approved the final version of the manuscript.

Funding

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Competing interests

None declared.

Patient consent for publication

Not required.

Ethics approval

This study has been approved by the institutional review board of Shanghai Changhai Hospital. (ref. CHEC2019-070 & CHEC2019-082)

Provenance and peer review

Not commissioned; externally peer reviewed.

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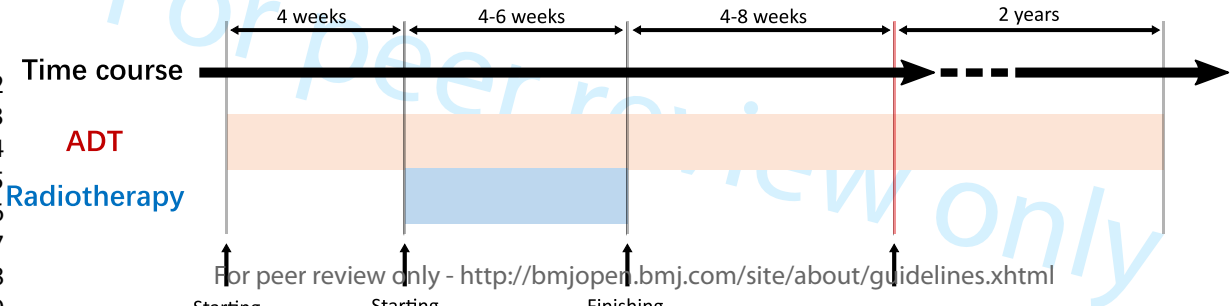
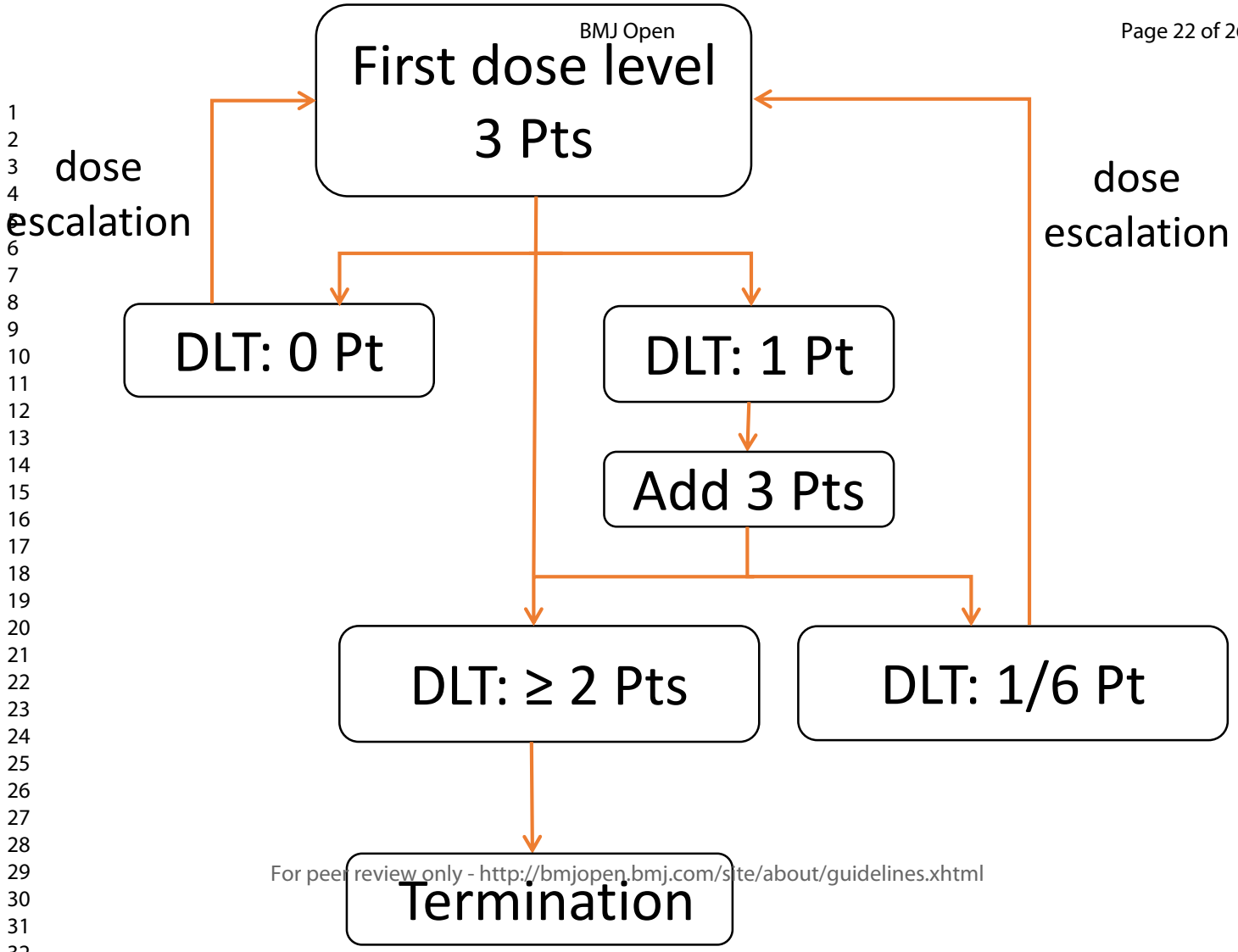
Figure Legends

Figure 1. Schedule of the study. ADT, androgen deprivation therapy.

Figure 2. Graphical depiction of the 3+3 dose-escalation study design. DLT, dose-limiting toxicity. Pt, participant.





SPIRIT

STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	Page 1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	Page 6-7
	2b	All items from the World Health Organization Trial Registration Data Set	Not included in the manuscript. Available on the registration website.
Protocol version	3	Date and version identifier	Not included in the manuscript.
Funding	4	Sources and types of financial, material, and other support	Page 15
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	Page 1, Page 15
	5b	Name and contact information for the trial sponsor	Not applicable.
	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	Not applicable.
	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)	Page 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	Page 5-6.
	6b	Explanation for choice of comparators	Not applicable (single-arm)
Objectives	7	Specific objectives or hypotheses	Page 12
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, noninferiority, exploratory)	Page 11.

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 obtained	Page 5-6.
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)	Page 7-9 ; Page 11
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	Page 9-12.
	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)	Page 8-11.
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	Page 11.
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	Page 7-9.
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	Page 11.
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)	Page 6-11 ; Figure 1-2.

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	Page 12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	NA
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	✓
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	✓
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	✓
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	✓
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	✓
Methods: Data collection, management, and analysis			
Data collection methods	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 protocol	Page 11-12.
	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	Not included in the manuscript.

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	Page 12
Statistical methods	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	Page 12-13.
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	Page 13.
	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)	NA
Methods: Monitoring			
Data monitoring	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	Page 13.
	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	Page 12.
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	Page 12.
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	Page 12.
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	Page 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)	Not included in the manuscript.

Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	Page 13.
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	Page 13.
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	Page 13.
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	Page 15.
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	Not included in the manuscript.
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	Not included in the manuscript.
Dissemination policy	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	Page 13.
	31b	Authorship eligibility guidelines and any intended use of professional writers	Not included in the manuscript.
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	Not included in the manuscript.
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	Not included in the manuscript.
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	Page 13.

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.