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Safety and Efficacy Study of Neoadjuvant Radiohormonal Therapy for Oligometastatic Prostate Cancer: Protocol of an Open-Label, Dose-Escalation, Single-Centre Phase I/II Clinical Trial

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Abstract

Background: The optimal treatment for oligometastatic prostate cancer (OMPC) is still on its way. Accumulating evidence has proven the safety and feasibility of radical prostatectomy and local or metastasis-directed radiotherapy for oligometastatic patients. The aim of this trial is to demonstrate the safety and feasibility outcomes of metastasis-directed neoadjuvant radiotherapy (naRT) and neoadjuvant androgen deprivation therapy (naADT) followed by robotic-assisted radical prostatectomy (RARP) for treating OMPC.

Methods: The present study will be conducted as a prospective, open-label, dose-escalation, phase I/II clinical trial. The patients with oligometastatic PCa will receive 1 month of naADT, followed by metastasis-directed radiation and abdominal or pelvic radiotherapy. Then, radical prostatectomy will be performed at intervals of 4-8 weeks after radiotherapy, and ADT will be continued for 2 years. The primary endpoints of the study are safety profiles, assessed by the Common Terminology Criteria for Adverse Events (CTCAE) 5.0 grading scale, and perioperativemorbidities, assessed by the Clavien-Dindo classification system. The secondary endpoints include positive surgical margin (pSM), biochemical recurrence-free survival (bPFS), radiological progression-free survival (RPFS), postoperative continence, and quality of life (QoL) parameters.

Discussion: The optimal treatment for OMPC is still on its way, prompting investigation for novel multimodality treatment protocol for this patient population. Traditionally, radical prostatectomy has been recommended as one of the standard therapies for localized prostate cancer, but indications have expanded over the years as recommended by NCCN and EAU guidelines. RP has been carried out in some centres for OMPC patients, but its value has been inconclusive, showing elevated complication risks and limited survival benefit. Neoadjuvant radiotherapy has been proven safe and effective in colorectal cancer, breast cancer and other various types of malignant tumors, showing potential advantages in terms of reducing metastatic

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stem-cell activity, providing clinical downstaging, and reducing potential intraoperative risks. Existing trials have shown that naRT is well tolerated for high-risk and locally-advanced prostate cancer. In this study, we hope to further determine the optimal irradiation dose and patient tolerance for genitourinary, gastrointestinal and systemic toxicities with the design of 3+3 dose escalation; also, final pathology can be obtained following RP to further determine treatment response and follow-up treatment plans.

Trial registration: Chinese Clinical Trial Registry, ChiCTR1900025743. http://www.chictr.org.cn/showprojen.aspx?proj=43065.

Keywords
prostate cancer, oligometastatic, neoadjuvant radiation therapy

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Introduction

Prostate cancer (PCa) is the most common malignancy in men, with an incidence rate of 29.3%. It is also one of the leading cause of death among cancer entities, with a mortality rate of 7.6% globally.[1] Traditionally, radical prostatectomy has been recommended as the standard therapy for localized PCa. However, if patients present with evidence of metastasis, systemic therapies such as androgen deprivation therapy (ADT) or chemotherapy are strongly recommended.[2,3] The current paradigm for the treatment of advanced PCa is shifting towards a more comprehensive approach. The last 2 decades have witnessed great progress in surgical and radiation techniques, such as robotic-assisted laparoscopic radical prostatectomy (RALP), intensity modulated radiation therapy (IMRT) and stereotactic body radiotherapy (SBRT). Emerging evidence indicates that various comprehensive approaches might provide survival benefits to patients with lymph node-positive and metastatic PCa.[4-8]

Oligometastatic PCa has been proposed as an intermediate stage of cancer spread between localized disease and widespread metastases. Ongoing clinical trials including ongoing multi-institutional randomized Phase II trial (NCT01751438) conducted by MD Anderson Cancer Center and SWOG/NCTN Phase III trial (NCT03678025), have been conducted to compare the additional value of local treatment on the basis of initial best systemic therapy for de novo metastatic prostate cancer. In this setting, the multimodality treatment paradigm of oligometastatic PCa requires local consolidated therapy for the primary tumour by surgery or radiotherapy, metastasis-directed therapy, and systemic ADT or chemotherapy. With the development of the daVinci Robotic System, RALP has become more clinically significant for tumour control.[9,10] As an increasingly safe and effective treatment, metastasis-directed radiation therapy remains promising for oligometastatic PCa.[2]

For patients with locally advanced PCa, a multimodality approach including radical prostatectomy with lymph node dissection with/without adjuvant long-term ADT plus radiotherapy is one of the recently developed treatments to reduce recurrence risk.[2,3] In addition, adverse pathological features from radical surgery can identify patients who are likely to benefit from adjuvant radiotherapy. Phase III randomized controlled trials have demonstrated that locally advanced PCa patients can benefit from adjuvant radiotherapy in terms of tumour control and biochemical progression.[11] Randomized clinical trials of other malignancies, such as rectal cancer, have demonstrated the safety and efficacy of neoadjuvant radiotherapy with tolerable toxicities.[3,14-16] What's more, neoadjuvant SBRT may lead to severe toxicity as reported by some studies on nonmetastatic high-risk or locally advanced prostate cancer.[12,13] But neoadjuvant conventional fractionation radiotherapy is still underexplored.

Hereby, we present a phase I study to demonstrate early evidence of the safety and efficacy of the intervention.

Methods and Analysis

Ethics and Dissemination

This study was approved by the Ethics Committee of Shanghai Changhai Hospital (CHEC2019-110) and is registered on ChiCTR (CHiCTR1900025743). All clinical data will be collected by the researcher. Findings of the study will be submitted for publication in peer-reviewed scientific journals and presented at relevant medical conferences. Written informed consent was obtained according to the International Council for Harmonization/Good Clinical Practice (ICH/GCP) regulations before registration and prior to any trial-specific procedures.

Study Design

This study will be conducted as a phase I, prospective, open-label, dose-escalation, single-arm study. The development of the study protocol followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines. The protocol is reported according to the SPIRIT (Additional file 1). Written informed consent including treatment programs, benefits, the possible risks and treatment measures for the risk and all possible elements essential before conducting this clinical trial will be

obtained from eligible patients after initial evaluation with 68Ga-PSMA-PET/CT. Consecutive radiological images with 68Ga-PSMA-PET/CT or whole-body MRI will be scheduled before registration, radiotherapy, and surgery, as well as 1 year after surgery. The prostate-specific antigen (PSA) and testosterone levels of the participants will be checked monthly. After the completion of treatment during the study, participants will be given a follow-up every 3 months or as needed clinically in the first 2 years, every 6 months in the next 3 years, and annually thereafter. Follow-up examinations will include clinical assessments and contrast-enhanced MRI, CT, ECT or 68-Ga PSMA PET/CT. For tumour progression, treatment alternatives can be evaluated interdisciplinarily considering abiraterone acetate, enzalutamide, reradiation therapy, chemotherapy or others.

Recruitment

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

Study Participants

Inclusion Criteria

- Aged 18 years or over at the time of registration
- Histologically confirmed adenocarcinoma of the prostate without small cell features
- Oligometastatic PCa assessed by Ga-68 prostate-specific membrane antigen (PSMA), PET/CT
- <5 oligometastases (including bone, lymph nodes above the renal artery level) and/or lymph node metastasis below the renal artery level, tumour clinical stage cTx, Nx according to AJCC TNM 2017
- Expected survival time >5 years
- World Health Organization (WHO) performance status 0-1
- Be willing to give written informed consent.

Exclusion Criteria

- Any previous or ongoing treatment for PCa, including radiotherapy, ADT, chemotherapy, focal treatment, etc.
- Patients who have previously undergone transurethral resection or enucleation of the prostate.
- Patients who have undergone other abdominal surgery within the last 3 months
- Patients who have undergone transrectal prostatic biopsy within the last 2 weeks
- Patients with a history of long-term anticoagulant use and anti-platelet drug use and who stopped anticoagulant therapy less than 1 week before registration
- Patients with other malignancies and acute or chronic infections such as human immunodeficiency virus (HIV) (+), hepatitis C virus (HCV) (+) and/or positive syphilis
- Severe or active comorbidities likely to impact the advisability of radiotherapy
- Any other serious underlying medical, psychiatric, psychological, familial, or geographical condition, which, according to the judgement of the investigator, may affect the planned staging, treatment and follow-up or patient compliance or may cause high-risk treatment-related complications for the patient
- Patients who have participated in other clinical trials within the last 3 months
- Patients who refuse to undergo RALP
- Patients unsuitable for participation in this clinical trial as per the judgement of the investigator.

Interventions

All subjects will receive 1 month of naADT followed by naRT for 4-7 weeks. Then, RALP will be performed at intervals of 5-14 weeks after radiation, and adjuvant ADT will be performed for 2 years.

Androgen Deprivation Therapy. Pre- and post-operative ADT will comprise an antiandrogen (bicalutamide 50 mg/d, oral) plus LHRH agonist (goserelin3.6 mg, monthly or 10.8 mg, trimonthly, subcutaneous injection) 14 days after the initiation of bicalutamide.

Radiation Therapy. For oligometastases, the method and timing of radiotherapy will vary depending on the metastasis location.

For pelvic oligometastatic lesions, IMRT will be administered simultaneously with prostate radiotherapy. The gross tumour volume (GTV1) of oligometastases is based on imaging examination: 68-Ga PSMA PET/CT. The planning target volumes (PTVs) for GTV1 are delineated with an additional 5 mm margin. Dose segmentation will vary depending on the surrounding organs at risk (OARs) and tumour size. First, 65 Gy with 25 fractions or 50 Gy with 25 fractions will be the recommended dose segmentation.

For non-pelvic oligometastatic lesions, SBRT will be administered. The gross tumour volume (GTV1) of oligometastases relies on imaging examination. PTV-GTV1: GTV1 relies on 5-8 mm uniform expansion. 6-8 Gy per fraction with 5 fractions is the recommended dose segmentation, which will depend on the surrounding OARs and tumour size. The dose guidelines for OARs in SBRT are based upon AAPM Task Group 101.[17]

After IMRT is administered, all patients will undergo a contrasted CT simulation of the pelvis or abdomen with a slice thickness of 5 mm. Then, the CT image data will be transferred to the treatment planning system for contouring the target volume and OARs. The critical normal structures encompass the small bowel, bladder, femoral head, rectum, spinal cord, prostatic urethra (if visualized), bulb of the urethra, kidney, etc. OARs should be contoured according to the pelvic normal tissue contouring guidelines of the Radiation Therapy

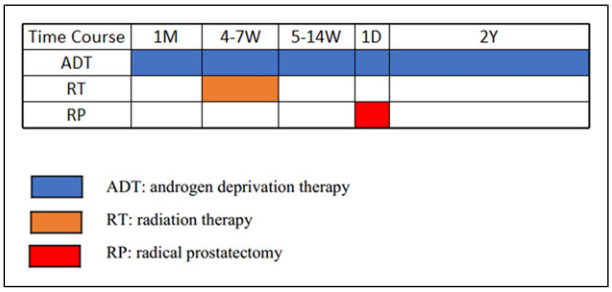

Figure 1. Treatment schedule in the protocol.
Abbreviations: M: Month; W: Week; D: Day; Y: Year.

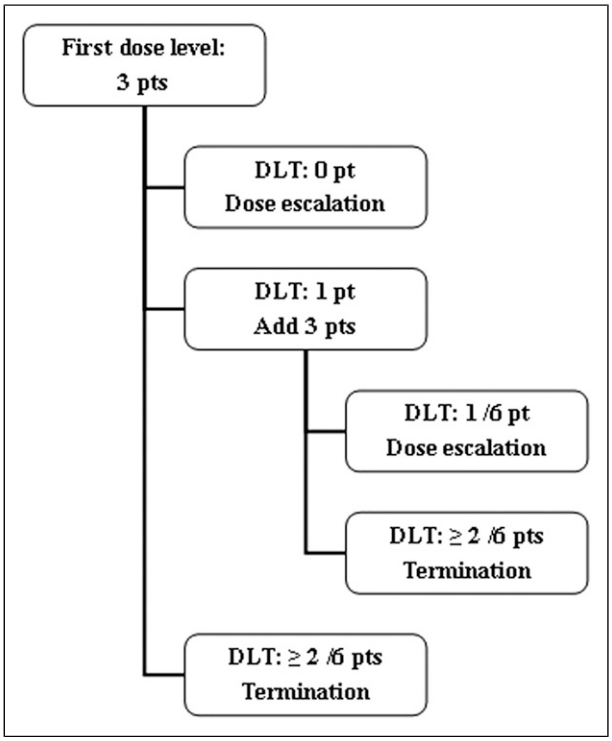

Figure 2. Graphical depiction of traditional 3 + 3 dose-escalation methods for clinical trials.
Abbreviations: DLT, Dose-limiting toxicity; MTD, Maximum tolerable dose; Pt, patient; Pts, Patients.

Oncology Group (RTOG).[18] This protocol offers dose guidelines for OARs based on previously published RTOG trials.[19]

The gross tumour volume (GTV2) will be contoured based on MRI. GTV2 consists of the prostate and seminal vesicle glands. GTVnd consisting of pelvic/retroperitoneal metastatic lymph nodes will be further confirmed by medical imaging: MRI, 68-Ga PSMA PET/CT, etc. The clinical tumour volume (CTV) compromises a 5 mm margin to the GTV2, GTVnd, and pelvic/retroperitoneal lymphatic drainage area.

The upper border of the whole pelvic field extends to the L5-S1 interspace in the N1 subgroup. The pelvic lymphatic drainage area includes the bilateral iliac lymph nodes, external iliac lymph nodes, internal iliac lymph nodes, presacral lymph nodes of the S1-S3 levels and obturator lymph nodes. The superior border of the retroperitoneal area is 2-3 cm above the positive lymph nodes but does not cross the renal artery level. PTV-GTV2: GTV2 is based on a 5-10 mm uniform expansion but on only 5 mm for the posterior part to reduce any rectal irradiation. PTV-GTVnd for GTVnd should be delineated with an additional 5 mm margin, and PTV-CTV for CTV should also be delineated with an additional 5 mm margin separately.

Four radiation dose levels are planned for dose escalation: 39.6 Gy, 45 Gy, 50.4 Gy, and 54 Gy in 22 fractions, 25 fractions, 28 fractions, and 30 fractions, respectively. Radiation therapy will be delivered in 5 fractions per week. The initial 2 dose levels will target the whole pelvis/retroperitoneum, whereas the latter 2 dose levels will act as a subsequent boost for the prostate, seminal vesicles and pelvic/retroperitoneal metastatic lymph nodes, which will be added after reaching 45 Gy.

Dose Escalation. Dose escalation will be conducted with 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 (Figures 1 and 2). Briefly, 3 participants will be initially allocated to the starting dose cohort. If no Dose-limiting toxicity (DLT) is observed in any of the 3 participants, the dose can be escalated, and the 3 new patients can be enrolled to receive the next level of radiation dose. Even if one participant develops DLT, then an additional 3 participants will be allocated to the same dose cohort. If there are multiple observations of DLT at any given dose level, dose escalation will be stopped, and the previous dose level will be identified as the maximal tolerable dose (MTD). In this trial, DLTs are defined as any grade III/IV toxicities.

Radical Prostatectomy. Surgery can be scheduled 5-14 weeks after the completion of radiation therapy, via a robot-assisted transperitoneal approach on da Vinci Si system, and extended pelvic/retroperitoneal lymph node dissection will be performed, including obturator, internal iliac, external iliac, common iliac, presacral, as well as radiologically-identified retroperitoneal positive nodes up to the level of the renal arteries.

Study Endpoints

The primary endpoints of the study are treatment-induced acute and late toxicities, as assessed by the CTCAE 5.0 grading scale, along with intraoperative and postoperative 30-day morbidity assessed by Clavien-Dindo classification system. Radiotherapy-related complications encompass acute and late genitourinary (GU) toxicity, gastrointestinal (GI) toxicity and erectile dysfunction (ED), while intraoperative and postoperative 30-day morbidity consists of the operation time, intraoperative blood loss, rate of conversion to open surgery, fibrosis in the radiotherapy area, etc. Late RT-induced toxicity will be followed from 3 months after RT to up to 2 years postoperatively; surgery-related comorbidities (e.g., incontinence)

will be followed up to 2 years postoperatively; ADT-related adverse events, will be followed up to 2 years postoperatively. The secondary endpoints comprise the positive postoperative incisal edge rate, biochemical progression-free survival (bPFS), postoperative continence and recovery of sexual function, overall survival (OS) and adverse reactions of ADT, as well as quality of life (QoL) evaluation, which will be documented using Italian UCLA Prostate Cancer Index and SF-12 scale.[20]

Determination of Sample Size

The study is a dose-escalation study with 4 dose levels. Three to 6 patients will be allocated to each dose level cohort. Therefore, the minimal and maximum sample sizes for the study are 12 and 24, respectively.

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 semi-annual basis. A planned interim analysis will be performed by the principle investigator when the median postoperative follow-up reaches 1 year.

Statistical Analysis

Normally distributed continuous data will be described by means and ±SD as well as 95% confidence intervals. Non-normally distributed continuous data will be described by median and range. Qualitative data will be described as percentages. BFS and RPFS will 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<.05 will be considered statistically significant.

Patient and Public Involvement

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

Discussion

Metastasis-directed radiation can decrease the total tumour burden of oligometastatic PCa patients. Preoperative radiation partially increases downstaging, and the incorporation of neoadjuvant ADT further decreases the tumour stage and aims to promote micrometastasis. Furthermore, the duration of treatment becomes shorter when radiation is given preoperatively.

For patients with oligometastatic PCa, a multimodality approach including consolidated local treatment, metastasis-directed therapy and systemic hormonal therapy might be the best option to minimize the risk of recurrence. Artificial intelligence (AI) has shown promising value in terms of predicting survival and treatment response in the near future of radiological diagnosis. Also, because radiotherapy is a crucial component in our treatment modality, toxicity is often challenging to predict. AI may also show its potential advantages in terms of predicting treatment-induced adverse effect. In order to achieve a more accurate initial evaluation, 68Ga-PSMA-PET/CT was recommended for initial evaluation in our protocol, with or without whole-body MRI, in which perfusion imaging contrast uptake, ADC of MRI, liquid biopsy biomarkers and PSMA uptake activity were adopted as potential biomarkers, in order to achieve a higher reetection rate of the bone lesions from PSMA-PET/CT, as well as a higher soft tissue resolution of the primary from whole-body MRI.[21,22]

Some other metastatic cancers have shown improved clinical outcomes with a local aggressive approach for primary tumours, and cytoreductive radical prostatectomy may derive similar benefits in oligometastatic PCa by delaying the aggressive tumour burden.[23,24] Several retrospective studies have found that the safety and efficacy of radical prostatectomy in oligometastatic PCa with complication rates is comparable to those of locally advanced PCa.[9,25-27] The first multicentre retrospective study that included 106 patients with M1a-b PCa reported perioperative complication (all Clavien 1-3) rates of 29%.[6] Gandaglia et al. reported 7-year clinical progression-free rates of 45% and cancer-specific mortality-free survival rates of 82% in a cohort of 11 patients with oligometastatic PCa.[25] Studies have shown the advantages of preoperative radiotherapy over postoperative radiation in other malignancies.[28,29] Compared to postoperative radiation, preoperative therapy has the following advantages. First, there is improved oxygenation of target tissues in the neoadjuvant setting that decreases radioresistance without altering the blood supply of the prostate.[3] Second, neoadjuvant radiation requires a lower dose for achieving the equivalent level of tumour control, which helps reduce potential side effects.[4] Third, preoperative radiation can decrease viable cancer cells at the time of radical prostatectomy and can sterilize extraprostatic clonogenic stem cells in close proximity to the gland, leading to a reduction in the probability of local recurrence.[5]

Furthermore, an increasingly large amount of data has shown that the adoption of SBRT as a metastasis-directed therapy for metastatic lesions of oligometastatic PCa provides excellent local control with minimal toxicity.[30-33] All of these studies reported zero (0%) grade 3 toxicities using the CTCAE 5.0 criteria of adverse effects and >95.5% local control rates. In the HORRAD trial and STAMPEDE trial, radiotherapy to the prostate alone for patients with low burden metastatic disease has been discussed with improved survival.[34,35] However, salvage RP may still be necessary for these patients, should treatment failure be observed. Whether or not neoadjuvant radiohormonal therapy may be a better solution is worthwhile to be explored, which is different from salvage radical prostatectomy after external beam radiotherapy in terms of lower overall dose of irradiation, better coverage of clinically-visible lesions, as well as a shorter interval between

RT and RP, presenting a novel treatment modality for oligometastatic PCa. To the best of our knowledge, our study is the first prospective trial to assess the safety and feasibility of metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy for oligometastatic PCa. Our project is expected to be well tolerated with minimal Grade 3 or above acute or late toxicities, with comparable perioperative comorbidities, pSM and continence recovery, compared with RP for locally-advanced PCa reported in the literature. Efficacy data in terms of postoperative PSA, treatment response, tumor regression grade, BFS and RPFS may also provide useful information for future design of randomized controlled trials (RCT). Therefore, RCT are required to address the promising effects of metastasis-directed radiation and neoadjuvant hormone and radiation therapy plus radical prostatectomy for oligometastatic PCa.

Appendix

Abbreviations

ADT	Androgen deprivation therapy
bPFS	Biochemical progression-free survival
ED	Erectile dysfunction
ECT	Emission computed tomography
DLT	Dose-limiting toxicity
ICH/GCP	International Council for Harmonization/Good Clinical Practice
IMRT	Intensity modulated radiation therapy
GI	Gastrointestinal
GTV	Gross tumour volume
GTVnd	Pelvic or retroperitoneal metastatic lymph node
GU	Genitourinary
MRI	Magnetic resonance imaging
MTD	Maximal tolerable dose
OARs	Organs at risk
OS	Overall survival
PCa	Prostate cancer
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
Pt	Patient
Pts	Patients
PTV	Planning target volume
QoL	Quality of life
RALP	Robotic-assisted laparoscopic radical prostatectomy
RP	Radical prostatectomy
RT	Radiation therapy
RTOG	Radiation Therapy Oncology Group
SBRT	Stereotactic body radiotherapy
WHO	World Health Organization

Author Contributions

Study conception: H.J.Z, S.C.R Initial Study design: X.Z.Z., Y.T.X. and Y.F.C. Revision of study design and protocol: H.J.Z, S.C.R, X.Z.Z., Y.T.X. and Y.F.C. Study coordination: X.Z.Z., Y.T.X., Y.S.Y. Y.F.C. and L.G.J. Drafting the manuscript: X.Z.Z., Y.Y., and Y.T.X. Professionally stylistic ameliorations of the English language: M.E. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

This study was approved by the Ethics Committee of Shanghai Changhai Hospital of Shanghai Changhai Hospital (CHEC2019-110) and is registered on ChiCTR (CHiCTR1900025743).

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Supplemental Material

Supplemental material for this article is available online.

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