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

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Study protocol

Keywords: Oligometastatic prostate cancer, neoadjuvant radiation therapy, radical prostatectomy, SBRT, safety, feasibility

Posted Date: March 24th, 2020

DOI: <https://doi.org/10.21203/rs.3.rs-18507/v1>

Abstract

Background

The systemic therapy is currently recommended for patients with oligometastatic prostate cancer, however the prognosis has not been satisfactory. Therefore, it is necessary to explore more effective treatment to improve the prognosis. Oligometastatic prostate cancer is a special subgroup in patients with advanced cancer. The paradigm of treatment is shifting to a more aggressive approach. Stereotactic body radiotherapy (SBRT) is an emerging treatment alternative for patients with oligometastases with minimal toxic effects. What's more, accumulating studies have proved safety as well as feasibility of radical prostatectomy and local or metastasis-directed radiotherapy for oligometastatic patients. The aim of this phase I prospective trial is to demonstrate the early evidence of safety and feasibility of metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy for treating oligometastatic prostate cancer

Methods

The patients with oligometastatic prostate cancer received 1 month of neoadjuvant androgen deprivation therapy (ADT) followed by metastasis-directed radiation and abdominal or pelvic radiotherapy. Then offer radical prostatectomy at the interval of 4-8 weeks after radiotherapy and adjuvant ADT for 2 years. The primary endpoints of the study are safety as assessed by CTCAE 5.0 grading scale and intraoperative and postoperative day-30 morbidity. Secondary endpoints include the positive rate of post-operative edge, biochemical progression-free survival (bPFS), postoperative continence and sexual function recovery, quality of life (QoL), overall survival (OS) and adverse reactions of ADT.

Discussion

This is the first, phase I trial assessing the safety and feasibility of metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy treatment for patients with oligometastatic prostate cancer. If positive, the results of this trial may help to design subsequent phase II trials exploring the role of metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy in the randomized controlled study.

Background

Prostate cancer (PCa) is the most common malignancy in men with an incidence rate of 29.3%. It is also the leading cause of death among cancer entities with a mortality rate of 7.6% globally [1]. Traditionally, radical prostatectomy is recommended as the standard therapy for localized prostate cancer. However, if the patients present with evidence of metastasis even if it is a single positive lymph node, aggressive treatments are precluded and systemic therapies such as androgen deprivation therapy (ADT) or chemotherapy are strongly recommended [2, 3]. The current paradigm for treatment of advanced PCa is shifting towards more aggressive approach. The last two decades have witnessed a 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). The emerging evidence indicate that the various aggressive approaches might provide survival benefits to patients with lymph node-positive and metastatic PCa [4–8].

Oligometastatic prostate cancer has been proposed as an intermediate stage of cancer spread between the localized disease and the widespread metastases. The curative treatment of oligometastatic prostate cancer actually requires a 3-step method: firstly, local consolidate therapy for the primary tumor; secondly, metastasis-directed therapy and; thirdly, systemic ADT or chemotherapy. With the development of DaVinci Robotic System, RALP has become more clinically significant for tumor control, functional outcomes and complication manipulation for locally advanced prostate cancer [9, 10]. As an increasingly safe and effective treatment, the value of metastasis-directed radiation therapy remains promising for oligometastatic Pca [10]. In this study, we propose the use of radiation therapy for local as well as distant metastatic lesions thus changing the current status of oligometastasis into advanced prostate cancer for further treatment.

For patients with locally advanced prostate cancer, multimodality approach including radical prostatectomy with lymph node dissection and adjuvant long-term ADT plus radiotherapy is strongly recommended to minimize the recurrence risk [2, 3]. In addition, adverse pathological features from radical surgery can identify patients who are likely to benefit from adjuvant radiotherapy. The phase III randomized controlled trials have demonstrated that locally advanced PCa patients can benefit from adjuvant radiotherapy in terms of tumor control and biochemical progression [11–13]. Randomized clinical trials of other malignancies such as rectal cancer have demonstrated safety and efficacy of neoadjuvant radiotherapy with tolerable toxicities [14]. Compared to postoperative radiation, preoperative therapy has the following advantages. Firstly, there is improved oxygenation of target tissues in neoadjuvant setting that decreases the radio-resistance without altering the blood supply of prostate [14]. Secondly, the neoadjuvant radiation requires a lower dose to achieve the equivalent level of tumor control which helps in reducing potential side effects [15]. Thirdly, pre-operative radiation can decrease viable cancer cells at the time of radical prostatectomy and sterilize extra-prostatic clonogenic stem cells in close proximity to the gland leading to reduction in probability of local recurrence [16]. Furthermore, the metastasis-directed radiation can decrease the total tumor burden of oligometastatic PCa patients. Pre-operative radiation partially increases down-staging, and incorporation with neoadjuvant ADT further decreases the tumor stage and also aims micro-metastasis. Furthermore, the duration of treatment becomes shorter when radiation is given preoperatively.

Therefore, randomized controlled trials are required to address the promising effects of metastasis-directed radiation and neoadjuvant hormone and radiation therapy plus radical prostatectomy for oligometastatic prostate cancer. Hereby, we present a phase I study in order to demonstrate early evidence of safety and efficacy of the intervention.

Methods/design

This study was approved by the Ethics committee of the Shanghai Changhai Hospital (CHEC2019-110) and is registered on ChiCTR (CHiCTR1900025743). This is a phase I, prospective, single-arm study.

The main objective of the phase I trial is to determine whether metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy for the treatment of oligometastatic prostate cancer is safe and well tolerated, by assessing the occurrence of radiotherapy-related complications along with intra operative and postoperative day-30 morbidity.

Objectives

Primary endpoint The primary endpoints of the study were safety of radiotherapy as assessed by CTCAE 5.0 grading scale along with intraoperative and postoperative day-30 morbidity. The radiotherapy-related complications encompassed the genitourinary (GU) toxicity, gastrointestinal (GI) toxicity and erectile dysfunction (ED), while intraoperative and postoperative day-30 morbidity consisted of the operation time, intraoperative blood loss, rate of conversion to open surgery, fibrosis in the radiotherapy area, etc.

Secondary endpoints The secondary endpoints comprised of the positive rate of post-operation incisional edge, biochemical progression-free survival (bPFS), postoperative continence and recovery of sexual function, quality of life (QoL), overall survival (OS) and adverse reactions of ADT.

Inclusion criteria

- Age 18–75 years at the time of registration
- Histologically confirmed adenocarcinoma of the prostate without small cell features
- Oligometastatic prostate cancer assessed by emission computed tomography (ECT), magnetic resonance imaging (MRI), Ga-68 Prostate-Specific Membrane Antigen(PSMA) PET/CT, Ga-68 PSMA PET/MR
- < 5 oligometastases (including bone, lymph nodes above renal artery level, distant organ metastasis), and/or lymph nodes below renal artery level metastasis, tumor clinical stage cTx, Nx according to AJCC TNM 2017
- Expected survival time > 5 years
- World Health Organization (WHO) performance status 0–1
- Written informed consent according to International Council for Harmonization/ Good Clinical Practice (ICH/GCP) regulations before registration and prior to any trial specific procedures

Exclusion criteria

- Any previous or ongoing treatment of prostate cancer including radiotherapy, ADT, chemotherapy, focal treatment, etc.
- Patients who have previously undergone transurethral prostatectomy or excision
- Patients who underwent other abdominal surgery within last 3 months
- Patients who had undergone transrectal prostatic biopsy within last 2 weeks

- Patients with history of long-term use of anticoagulant and anti-platelet aggregation drugs and stopped anticoagulant less than 1 week before registration
- Patients with other malignancies, acute or chronic infections such as human immunodeficiency virus (HIV) (+), hepatitis C virus (HCV) (+) and / or positive syphilis
- Severe or active co-morbidity that is 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, patient compliance, or may cause high risk treatment-related complications for the patient
- Patients who have participated in other clinical trials within last three months
- Patients who have refused to undergo RALP
- Unsuitable to participate in this clinical trial as per the judgement of the investigator

Intervention

In this trial, patients with oligometastatic prostate cancer are registered to receive the following treatment: ADT, radiotherapy and RALP. The trial schedule is illustrated in Fig. 1. Patients with oligometastatic prostate cancer receive 1 month of neoadjuvant ADT (nADT) followed by metastasis- directed radiation and abdominal or pelvic radiotherapy. Then offer RALP at the interval of 4–8 weeks after radiation, and adjuvant ADT for 2 years.

1. ADT

Both neoadjuvant and adjuvant ADT comprised of an oral antiandrogen (bicalutamide 50 mg once daily) plus goserelin given subcutaneously 14 days after the initiation of bicalutamide as either 10.8 mg with a second shot 3 months later or 3.6 mg with a second shot 1 month later.

2. Radiation therapy

2.1 Radiotherapy for oligometastases

For oligometastases, the method and timing of radiotherapy varies depending on the location of metastasis.

For pelvic oligometastatic lesions, IMRT is administered simultaneously with prostate radiotherapy. The gross tumor volume (GTV1) of oligometastases is based on imaging examination: 68-Ga PSMA PET/CT, CT, MRI, ECT, etc. Planning target volumes (PTVs) for GTV1 are delineated with an additional 5 mm margin. Dose segmentation varies depending on the surrounding organs at risk (OARs) and tumor size. Firstly 49.5 Gy with 22 fractions or 50 Gy with 25 fractions is the recommended dose segmentation.

For non-pelvic oligometastatic lesions, SBRT will be administered. The gross tumor volume (GTV1) of oligometastases relied on imaging examination. PTV-GTV1: GTV1 relied on 3–5 mm uniform expansion. 6-8Gy per fraction with 5 fractions is the recommended dose segmentation which depends on the surrounding OARs and tumor size. If the oligometastases cause obvious symptoms, then SBRT is

considered before prostate radiotherapy. If the oligometastases do not cause obvious symptoms, then prostate radiotherapy comes before SBRT. Dose guidelines to OARs in SBRT treatment is based upon AAPM Task Group 101 [17].

2.2 Radiotherapy for prostate gland and pelvic or retroperitoneal metastatic lymph node (GTVnd)

After the IMRT is administered, all patients have to undergo a contrasted CT simulation of the pelvis or abdomen of 5-mm-slice thickness in a supine position. Then, CT images will be transferred to the treatment planning system for contouring the target volume and OARs. Critical normal structures encompass the small bowel, bladder, femoral head, rectum, spinal cord, prostatic urethra (if visualised), bulb of urethra, kidney, etc. OARs should be contoured according to the pelvic normal tissue contouring guidelines of Radiation Therapy Oncology Group (RTOG) [18]. This protocol offers dose guidelines to OARs based on previous published RTOG trials [19].

The gross tumor volume (GTV2) is contoured based on the MRI. GTV2 consist of the prostate and seminal vesicle glands. GTVnd is further confirmed by medical imaging, whether CT, MRI, 68-Ga PSMA PET/CT, etc. The clinical tumor volume (CTV) compromises of a 5 mm margin to the GTV2, 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 iliac lymph nodes, external iliac lymph nodes, internal iliac lymph nodes, S1-S3 levels presacral lymph nodes and obturator lymph nodes. The superior border of the retroperitoneal area is 2–3 cm above the positive lymph nodes though not crossing the renal artery level. PTV-GTV2: GTV2 is based on a 5–10 mm uniform expansion, but 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 be also delineated with an additional 5 mm margin separately.

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

Dose escalation

Dose escalation is 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 is adopted (Fig. 2). Briefly, three participants are initially allocated the starting dose cohort. If no dose-limiting toxicity (DLT) is observed in any of the three participants, the dose can be escalated and the three new patients can be enrolled to receive the next level of radiation dose. Even if one participant develops DLT, then additional three participants will be allocated 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 maximal tolerable dose (MTD). In this trial, DLTs are defined as any Grade III/IV toxicities.

3. Radical prostatectomy

Surgery can be scheduled 4–8 weeks after the completion of radiation therapy, via a robot-assisted laparoscopic approach and extended pelvic/retroperitoneal lymph node dissection should be performed.

Follow-up

68-Ga PSMA PET/CT should be conducted before registration, radiotherapy, surgery, and 1 year after the surgery. The prostate specific antigen (PSA) level of the participants should 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 include clinical assessment, contrast-enhanced MRI, CT, ECT or 68-Ga PSMA PET/CT. For tumour progression, treatment alternatives can be evaluated inter-disciplinarily considering abiraterone acetate, enzalutamide, reradiation therapy, chemotherapy or others.

Statistical analysis

Normally distributed continuous data is described by means of $\pm$ SD and 95% confidence intervals. Non-normal distributional continuous data is described by the median and range. Qualitative ones are described by percentage. bPFS and OS are estimated using the Kaplan-Meier method. Univariate and multivariable hazard ratios are calculated using the Cox proportion hazard model. For comparisons between the baseline variables, the χ^2 test and Fisher's exact test were performed. P values < 0.05 are considered statistically significant. Statistical analyses can be performed using SPSS software v18.0 or higher.

Discussion

For patients with oligometastatic prostate cancer, multimodality approach including consolidate local treatment, metastasis-directed therapy and systemic hormonal therapy might be the best to minimize the risk of recurrence.

Some other metastatic cancers have shown improved clinical outcomes with local aggressive approach for primary tumor and the cytoreductive radical prostatectomy may derive similar benefits in oligometastatic PCa by delaying the aggressive tumor burden [20–23]. Several retrospective studies have found that the safety and efficacy of radical prostatectomy in limited metastatic PCa with complication rates is comparable to locally advanced Pca [9, 24–27]. The first multicenter retrospective study include 106 patients with M1a-b PCa reported perioperative complication (all Clavien 1–3) rates of 29% [9]. 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 pre-operative radiotherapy over post-operative radiation in other malignancies [28, 29].

Neoadjuvant radiotherapy, to some extent, could increase down-staging before radical prostatectomy and decrease the complexity of the surgery.

Furthermore, increasingly large number of data has shown that adoption of SBRT as 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 CTCAE 5.0 criteria of adverse effects and > 95.5% local control rates.

Based on these promising results, our trial may represent an optimal treatment modality for oligometastatic prostate cancer. To acknowledge, 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 maximize the total tumor control outcomes while minimizing perioperative as well as long-term complications.

Conclusion

Metastasis-directed radiation and neoadjuvant hormone and radiation therapy followed by radical prostatectomy for treating oligometastatic prostate cancer is worth exploring.

Abbreviations

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

Declarations

Acknowledgements

None.

Funding

This study is sponsored by National Key Research and Development Program of China (2017YFC0113104), China Health Promotion Foundation THC2015001 and First Affiliated Hospital of

Navy Medical University “234 Subject Climbing Program”.

Availability of data and materials

Materials and methods are available in the ChiCTR.

Authors' 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.

Ethics approval and consent to participate

Signature of the informed consent will be obtained from all patients before inclusion in the study. This study was approved by the Ethics committee of the Shanghai Changhai Hospital (CHEC2019-110) and is registered on ChiCTR (CHiCTR1900025743).

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Time Course	1M	1-2W	5-8W	4-8W	1D	2Y
ADT						
RT		RT for O	RT for P			
RP						

- ADT: androgen deprivation therapy
- RT: radiation therapy
- RP: radical prostatectomy

Figure 1

Treatment schedule in the protocol. M: month; W: week; D: day; Y: year.

Figure 2

Graphical depiction of traditional 3+3dose escalation methods for the clinical trials. DLT, dose limiting toxicity; MTD, maximum tolerance dose; Pt, patient; Pts, patients.