Informed Consent

2-fraction Stereotactic Body Proton Therapy (SBPT) with Magnetic Resonance Imaging (MRI) Guidance in Localized Prostate Cancer: A single-arm Phase II Non-randomized Trial

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Informed Consent Form
(for participation in research)

Research Title	**:**	2-fraction Stereotactic Body Proton Therapy (SBPT) with Magnetic Resonance Imaging (MRI) Guidance in Localized Prostate Cancer: A single-arm Phase II Non-randomized Trial
Principal Investigator	**:**	**Dr. Poon Ming Chun, Darren (Associate Director, Comprehensive Oncology Center)**
Centre/Site	**:**	**HKSH Comprehensive Oncology Centre, 11/F, HKSH Eastern Building, 3 Tung Wong Road, Shau Kei Wan, Hong Kong** **Tel: (852) 2917 1200**

This document has two parts:

Part I: Information Sheet	(information you should know about the research)
Part II: Certificate of Consent	(your agreement to take part in the research)

The Chinese version of this document is only a translation of the English original. In case of discrepancy, the English original shall prevail.

A copy of the signed Informed Consent Form will be provided for your record.

PART I: Information Sheet

1. Introduction

HKSH has established the first Proton Therapy (PT) Center in Hong Kong, which began offering PT treatment in July 2023. Proton therapy is an advanced and precise form of radiation treatment that has demonstrated safety and effectiveness. However, PT is an extremely costly therapy requiring significant capital investment, which limits access for patients with unfavorable socioeconomic status.

To improve accessibility, this study explores reducing the treatment duration of Stereotactic Body Proton Therapy (SBPT) from 5 fractions to 2 fractions. Recent trials show two-fraction prostate stereotactic body ablative radiotherapy (SABR) is safe and feasible, with GI/GU toxicity comparable to five-fraction SABR using MR-guided radiotherapy. While 2-fraction SBPT may lower costs and enhance access, its safety and effectiveness compared to standard 5-fraction SBPT are not fully established. This study aims to demonstrate that 2-fraction SBPT is safe, feasible, and effective for treatment prostate cancer. Additionally, as this is a new technique using MR guidance and real-time tumor tracking, the study will provide valuable insights for further improvement.

This is a clinical trial, a type of research study designed to evaluate new treatments. Your study doctor/research representative will explain the trial details to you. Participation is entirely voluntary, and only those who choose to participate will be included. Please take time to make your decision, and feel free to discuss with your family, friends, or healthcare team. If you have any questions, your study doctor is available to provide further clarification.

You are being invited to participate because you have been diagnosed with localized prostate cancer and have chosen proton therapy as part of your treatment.

The Research Ethics Committee of HKSH has approved this research.

2. Purpose of the research

To demonstrate that 2-fractions of SBPT is safe, feasible, and results in similar toxicity profile as compared to 5-fraction SBPT. Clinician-reported adverse event (AEs) and patient-reported quality-of-life (QOL) will be assessed to evaluate outcomes.

3. Type of Research Intervention

This is a single-arm, non-randomized clinical trial involves MRI-guided SBPT as the external radiation therapy approach. Real-time tumor tracking will be performed using on-board orthogonal X-ray imaging to ensure precision and accuracy during treatment.

4. Participant selection and Study Duration

A total of 35 prostate cancer patients treated at HKSH using proton therapy will be prospectively recruited.

To participate this study, you meet the following criteria:

1. Be male over the age of 18 with histologically confirmed low or intermediate risk prostate cancer according to National Comprehensive Cancer Network (NCCN ver 5.0) guideline.
2. Have an Eastern Cooperative Oncology Group (ECOG) score < 2.

3. Be able to undergo anMR simulation scan without absolute contraindications (e.g. cardiac implantable electronic device),
4. Be able to complete the QOL questionnaire

You will be excluded if you have:
1. A history of inflammatory bowel disease or cancers other than prostate cancer.
2. A history of receiving pelvic radiotherapy, chemotherapy, or radical prostatectomy, cryosurgery, or other focal therapies (e.g., high-intensity focused ultrasound (HIFU) for prostate cancer.
3. A history of bladder neck or urethral stricture.
4. Undergone transurethral resection of the prostate (TURP) within 8 weeks prior to SBPT.
5. Unilateral or bilateral hip replacements.
6. Nodal or distant metastases indicated by CT, MRI, and/or prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans.
7. Received prior androgen deprivation therapy (ADT) lasting more than 6 months.

The duration of this study is 8 years with 5 years follow-up time for each participant.

5. Voluntary Participation and Withdrawal

Participation in this research is entirely voluntary. You can choose whether to participate, and you may withdraw at any time, even after agreeing to participate, without affecting your medical care.

If you decided to withdraw, please inform the principal investigator or the research representative. The study team will guide you through a safe withdrawal process, assess any radiation-related risks, and discuss the most appropriate follow-up care and tests for your situation. The principal investigator or research representative may also terminate your participation if they believe it is in your best interest.

6. Procedures and Protocol

If you choose to participate in this study, you will follow the 2-fraction SBPT protocol outlined in Figure 1, which details the steps, locations, and timing of the procedures.

Step 1: Rectal Spacer and Fiducial Marker Implantation

Before radiotherapy simulation, you will undergo implantation of a rectal spacer (a biodegradable gel, absorbed by the body in about 6 - 12 months, to reduce radiation exposure to the rectum) and fiducial markers (small objects implanted into the prostate for positional verification). This procedure, also used for 5-fraction SBPT, will be performed at HKSH or the Chinese University of Hong Kong (CUHK).

After the implantation, 2–3 week waiting period is required to ensure no severe complications (e.g., severe bleeding, infection, or rectal/urethral injury) occur. If severe complications arise and remain unresolved within this period, the waiting time may be extended at the principal investigator's discretion.

Step 2: Treatment Simulation and Planning

You will attend a treatment planning session at HKSH, where CT and MRI scans will be conducted in the treatment position. These scans will guide proton therapy planning, with the process and quality checks taking approximately 2 weeks.

Step 3: Treatment Delivery

You will receive 2 proton therapy sessions, each lasting about 1 hour, with at least 6 days between sessions, and both completed within 2 weeks.

Step 4: Follow-Up Visits

After completing the treatment, you will attend 12 follow-up consultations at HKSH:

- First Year: Visits at 1, 3, 6, and 12 months.
- Subsequent Years: Visits every 6 months until 5 years post-treatment (a 1-month scheduling flexibility is allowed).

At each visit:

- A blood test will measure your Prostate-Specific Antigen (PSA) level to guide follow-up management accordingly such as the potential use of ADT
- You will complete the QOL questionnaire assessing urinary function, bowel habits, sexual function, and hormonal function.

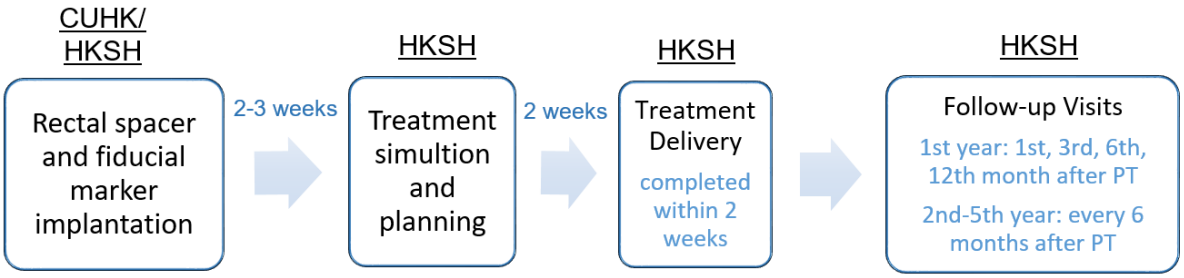

Figure 1: Study flow chart

7. Side Effects & Risks

Participating may involve side effects, which your healthcare team and research representatives will monitor closely. Not all potential side effects are known, and their severity can range from mild to serious. Appropriate medical care will be provided to manage side effects, some of which may be temporary and resolve after treatment, while others may be chronic, long-lasting, or permanent. In rare cases, side effects can be life-threatening or result in death.

If you experience any side effects, discuss them with your doctor. If intolerable side effects occur (as determined by the principal investigator) during the 2-fraction SBPT treatment or 5 years follow-up, HKSH will provide necessary medical care at no cost.

Currently evidence shows no significant difference in the incidence of side effects between 2-fraction and 5-fraction prostate cancer radiotherapy. General risks and side effects related to radiation are listed below:

- *Common temporary side effects:*
  - Tiredness, sleepiness, nausea and/or poor appetite.
  - Skin reaction) e.g., dryness, redness, itchiness, darkening, and moist desquamation, similar to sunburn).
  - Temporary hair loss in the treated area.
  - Bowel inflammation causing cramps and/or diarrhea.
  - Bladder, rectal, or anal inflammation causing pain, irritation, discharge and/or bleeding.
- *Uncommon temporary effects include:*
  - Skin blistering and peeling.
  - Depression of blood counts, increasing infection and bleeding risk, especially in patients with large irradiated area.
- *Common long term side effects include:*
  - Skin dryness, fibrosis and/or discoloration.
  - Swelling of genitalia and/or leg.
  - Radiation damage to bowel causing irregular bowel habits and/or chronic diarrhea.
  - Bladder damage, resulting in reduced capacity and increased urination frequency.
  - Testicular damage, leading to reduced sperm counts or sterility.
  - Impotence and/or sexual dysfunction.
- *Uncommon long term side effects include:*
  - Permanent hair loss in the treated area.
  - Scarring and stiffness of skin and soft tissue in the treated area.
  - Severe radiation damage to the bowel, causing obstruction, ulceration, bleeding, and/or malabsorption (surgery or colostomy may be required in severe cases).
  - Severe bladder damage causing pain, blood in urine, and/or recurrent urinary infections (surgical intervention may be required in severe cases).
  - Fistula between the bowel or bladder and other organs.
  - Bone damage, potentially causing fractures.
  - Nerve damage, causing pain, loss of strength or sensation in legs, and/or difficulty controlling stool or urine passage.

Reproductive risk: You should not father a child nor donate sperm during the study or for the first 3 months after completing therapy, as radiation may affect an unborn baby. You and/or your partner must use birth control during this period. Consult your study doctor about approved birth control methods and duration.

Relapse risk: As this is a clinical trial, the risk of cancer relapse is not yet fully known. However, the disease-free survival rate is expected to be comparable to stereotactic body radiation therapy (SBRT), which exceeds 91% over a 5 years for patients with low- and intermediate-risk prostate cancer.

Additional risks:
- Increased severity of side effects in area previously treated with radiation.
- Very rare occurrences of radiation-induced cancer.
- Extremely rare, life-threatening complications from proton therapy, with a mortality rate of less than 1%.

8. **Potential Benefits**

Participants may experience health benefits, although these cannot be guaranteed. This study aims to evaluate if 2-fraction SBPT are as safe and effective as 5-fraction PT, potentially offering a shorter treatment course with similar outcomes. The study's results may also advance PT treatment for prostate cancer, benefiting future patients.

9. Financial Costs & Reimbursements

This research is supported by HKSH. As a participant, you will not incur costs for the following trial-related procedures and services:

1. *Treatment-Related Costs*:
    - Proton Therapy Simulation, Treatment Planning and Treatment Delivery: Includes CT and MR simulation fees, MRI-guided positional verification, consumables (e.g., rectal spacer, fiducial markers, rectal balloons), and 2 fractions of SBPT.
2. *Follow-Up Care:*
    - Consultations at 1, 3, 6, and 12 months in the first year, and very 6 months thereafter for up to 5 years post-treatment.
3. *Supportive Care:*
    - Medications for intolerable side effects related to trial (as determined by the Principal Investigator) will be provided at no cost during the follow-up period.
    - For intermediate-risk patients, ADT (Androgen Deprivation Therapy) for 4-6 months will be provided at no cost, based on the investigator's discretion and/or your preference.

You and/or your insurance will be responsible for standard-of-care tests and procedures your doctor would provide outside of this study. You will not receive payment for your time or expenses unrelated to the study.

10. Confidentiality

Your anonymized or personal information will be used by the research team for this study. All data, including treatment details, side effects, and outcomes, will be securely stored in a password-protected database managed by HKSH. Physical copies of your data will also be kept in a locked cabinet in a restricted area at HKSH. Your personal information will remain confidential, even if the study results are published.

Only authorized team members, such as doctors and researchers involved in the study, can access your data. Security measures, including:

- Secure logins with usernames and passwords.
- Restricted data transfers within the hospital's network.
- Added security during data transfers.
- Password and Key to the locked cabinet managed by the principal investigator.

The HKSH Research Ethic Committee (REC) will be granted direct access to subject's original medical records for verification for clinical trial procedures and/or data, without violating your confidentiality. By signing the written informed consent form, you authorize the research team and REC to use

your anonymized data and access your medical records as needed, following all legal and ethical guidelines.

11. Sharing the Results

The research results may be published on scientific journal, or presented at conferences for academic purpose and knowledge exchange.

12. Alternatives to Participating

You have the following treatment options without participating in this study:

- Standard radiation therapy over a 7.5-8 week (38 fractions, 5 per week)
- Hypofractionated radiation therapy with MR-Linac over 2.5 week (5 fractions, 2 per week)
- Standard proton therapy
- Surgery
- Hormone therapy
- No treatment (close monitoring recommended, with treatment advised if disease progression occurs).

Surgery or radiotherapy provide similar outcome, but differ in potential complications. Surgery is invasive, requiring general anesthesia, and carries risks such as infection, bleeding, urinary incontinence, impotence, etc. Radiotherapy does not require surgery or general anesthesia.

Discuss your options with your study doctor before deciding whether to participate.

13. Who to Contact

You may contact the research officer Wong Oi Lei, Ph.D. at (852) 2835 5550 to clarify any questions, concerns, input or complaints about the study, which may arise later. You may also ask questions regarding your rights and obligations as a patient and as a participant in this research.

If you experience a research-related injury or become ill as a result of taking part in this research, please consult the principal investigator, Dr. Poon Ming Chun, Darren at (852) 2917 1200 or contact the research officer mentioned above.

This research has been reviewed and approved by the Research Ethics Committee of HKSH Medical Group, which is a committee to conduct ethical review on research studies. If you wish to find out more about the Committee, please contact (852) 2835 8426.

PART II: Certificate of Consent

Participant: _____ *(name in print)*

I have read the information in Part I, or it has been read and explained to me. I have had the opportunity to ask questions about it. All questions (if any) have been answered to my satisfaction.
I consent voluntarily to participate in this research.

Participant's signature _____ (*thumb print if cannot sign*)

Date _____ (*day / month / year)*

Statement by researcher/person* taking consent

The above-named participant has read the information in Part I, or I have read and explained it to him/her. The participant has been given the opportunity to ask questions about the research. All questions (if any) have been answered to the best of my ability. I am satisfied that the participant understands its contents.

I confirm that no pressure has been exerted on the participant to coerce him/her to take part in the research, and he/she gave the consent freely and voluntarily.

A copy of this signed Informed Consent Form has been provided to the participant.

Researcher/person* taking consent _____ *(name in print)*

_____ *(signature)*

Date _____ *(day / month / year)*

* person refers to the nurse/staff designated by the Investigator to the study