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 (PT2 Trial)

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Introduction

Proton therapy (PT) is an advanced form of external beam radiotherapy (EBRT) that offers significant potential to enhance the therapeutic ratio compared to photon radiotherapy, owing to its unique Bragg peak beam characteristics. This advantage applies to a wide range of oncological applications. However, PT requires substantial capital investment, rendering it an expensive treatment option and limiting access for patients with socioeconomic challenges.

In addition to technological advancements, such as the development of compact particle accelerators and gantry-free treatment solutions, hypofractionation—reducing the number of treatment fractions per PT course—offers a practical strategy to improve access, lower treatment costs, and maintain clinical outcomes without compromising efficacy (1–3). Hypofractionation also benefits patients from remote areas by reducing the duration of time they must spend away from home, thereby minimizing financial and psychosocial burdens on their support networks (3).

Given the low α/β ratio assumed for prostate cancer and the higher α/β ratios for organs at risk, the linear-quadratic model suggests that larger doses per fraction may improve the therapeutic ratio, theoretically supporting ultrahypofractionation in clinical practice. Ultrahypofractionated radiotherapy using photon beams, known as Stereotactic Body Radiation Therapy (SBRT), has been demonstrated to be safe and effective, with Level 1 evidence from phase III randomized clinical trials such as the PACE-B study (4, 5) and the HYPO-RT-PC trial (6, 7). These findings underpin the National Comprehensive Cancer Network (NCCN) guidelines (Version 4.2023), which recognize SBRT as a standard-of-care treatment option for localized prostate cancer across all risk groups (https://www.nccn.org/guidelines/guidelines-detail?category=1&id=1459, last accessed February 6, 2024).

Ultrahypofractionated PT, referred to here as Stereotactic Body Proton Therapy (SBPT) with treatment reduced to five fractions, is being investigated for localized prostate cancer. Preliminary results indicate promising outcomes with no significant increase in toxicities compared to traditionally fractionated or moderately hypofractionated PT. For example, Kubes et al. (2019) reported outcomes for 200 prostate cancer patients (low-risk: n=93; intermediate-risk: n=103) treated with extreme hypofractionated SBPT delivering 36.25 Gy (Relative Biological Effectiveness, RBE) in five fractions, with a median follow-up of 30 months. Late gastrointestinal (GI) Grade 2 (G2) toxicity occurred in 5.5% of patients, and late genitourinary (GU) G2 toxicity in 4%, with no

Grade 3 (G3) or higher toxicities observed. Prostate-specific antigen (PSA) relapse was noted in 1.08% of low-risk patients and 6.5% of intermediate-risk patients (8). In a 2023 update, Kubes et al. reported on a larger cohort (n=853) with a median follow-up of 62.7 months, showing 5-year biochemical disease-free survival (bDFS) rates of 96.5%, 93.7%, and 91.2% for low-, favorable intermediate-, and unfavorable intermediate-risk groups, respectively. Cumulative late toxicity (CTCAE v4.0) included GI G2 in 9.1% and G3 in 0.5%, and GU G2 in 4.3%, with no G3 toxicity. PSA relapse occurred in 6.8% of patients (9). Recent trials support 2-fraction prostate stereotactic ablative radiotherapy (SABR): The phase III SABR-DUAL demonstrated non-inferiority versus 5-fractions in low/favorable-IR disease using MRI planning with rectal spacers (10). FORT phase II showed non-inferiority in GI/GU toxicity between 2- and 5-fraction MRI-guided SBRT (11). HERMES, a single-arm phase II trial, confirmed feasibility of 2-fraction SABR for IR/low-tier HR patients using 1.5T MR-Linac (12). Collectively, these studies suggest the use of 2-fractionation scheme with similar efficiency to the 5 fractionated SABR.

The efficacy of SBRT for localized prostate cancer can be further enhanced with advanced image guidance using magnetic resonance imaging (MRI), or MR-guided radiotherapy (MRgRT), facilitated by recently introduced MRI-integrated linear accelerators (MR-LINACs) (13, 14). Preliminary clinical outcomes of MR-guided SBRT at our institution are encouraging and add to the growing evidence base (15). Moreover, emerging evidence suggests that radiotherapy for localized prostate cancer can be safely and effectively delivered in fewer than five fractions using SBRT (16). Ongoing pilot MRgRT studies, such as NCT03588819 (2SMART) and NCT04984343 (FORT), are investigating treatment efficacy by reducing fractions from five to two (11). Encouraging interim results have recently been published, indicating safety and comparable acute toxicity profiles to 5-fraction SBRT (17, 18).

In this study, we hypothesize that 2-fraction (2-fx) SBPT is safe and feasible in clinical practice, with similar rates of severe adverse events in low- and intermediate-risk prostate cancer patients compared to moderately hypofractionated PT and 5-fx SBPT, when guided by planning MRI acquired before and during the PT course. Furthermore, reducing the treatment to two fractions could decrease treatment costs by approximately 50%, significantly improving affordability and increasing access to this advanced treatment for more patients.

Methods/Design

This is a phase II, single-arm, non-randomized trial to evaluate clinician-reported and

patient-reported gastrointestinal (GI) and genitourinary (GU) toxicities at baseline and up to 5 years post-treatment in men with low- or intermediate-risk prostate cancer (PCa) receiving 2-fraction (offline) Stereotactic Body Proton Therapy (SBPT) guided by planning magnetic resonance imaging (MRI). We plan to enroll 35 patients, with an anticipated accrual rate of 1–3 patients per month. SBPT will deliver 25 Gy in 2 fractions to the prostate ± seminal vesicles, with an optional simultaneous dose boost to intraprostatic lesions. Treatments will be administered with at least 6 days between fractions, ideally completed within 2 weeks.

Objectives

Primary Objective: To demonstrate that 2-fraction SBPT is safe and feasible, resulting in similar toxicity rates compared to 5-fraction SBRT. Clinician-reported Grade 2 or higher (G2+) GU and GI toxicities, based on the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 (v5.0), will be assessed. Patient-reported GI and GU symptoms post-treatment, and changes in scores compared to pre-SBPT baseline, will also be evaluated.

Primary Endpoint

The primary endpoint is clinician-reported G2+ GU and GI adverse events (AEs) at 3 months and 24 months post-SBPT, as assessed by NCI-CTCAE v5.0. G2+ GU and GI AEs within 3 months post-SBPT are classified as acute toxicities, while those occurring after 3 months are considered late toxicities.

Secondary Endpoints

1. Changes in patient-reported GI and GU symptoms, measured using the Expanded Prostate Cancer Index Composite (EPIC) questionnaire, from baseline to 3 months post-SBPT.
2. Changes in patient-reported GI and GU symptoms, measured using the EPIC questionnaire, from baseline to 24 months post-SBPT.
3. Assessment of disease progression, including biochemical failure (BF), local failure (LF), regional failure (RF), and distant metastasis (DM), and time-to-progression (TTP), defined as the first occurrence of BF, LF, RF, or DM.
4. Clinician-reported G2+ GU and GI late events (LEs) at 5 years post-SBPT, based on NCI-CTCAE v5.0.

Inclusion Criteria

- Men aged ≥ 18 years with histologically confirmed low- or intermediate-risk prostate cancer per NCCN guidelines.
- Eastern Cooperative Oncology Group (ECOG) performance status < 2.
- Ability to undergo MRI simulation scans without absolute contraindications, such as cardiac implantable electronic devices.
- Ability to complete the EPIC questionnaire.

Exclusion Criteria

- History of inflammatory bowel disease or other cancers (except prostate cancer).
- Prior pelvic radiotherapy, chemotherapy, radical prostatectomy, cryosurgery, or focal therapy (e.g., high-intensity focused ultrasound [HIFU]) for prostate cancer.
- History of bladder neck or urethral stricture.
- Transurethral resection of the prostate (TURP) < 8 weeks prior to SBPT.
- Prostate volume > 100 cc on MRI.
- Unilateral or bilateral hip replacements.
- Nodal or distant metastases, as indicated by CT, MRI, or prostate-specific membrane antigen (PSMA) positron emission tomography (PET) scans.
- Previous androgen deprivation therapy (ADT) lasting more than 6 months.

Patient Selection, Study Enrollment, Randomization, and Blinding

Patients with biopsy-confirmed prostate cancer, who have chosen to receive proton therapy, will be informed of their eligibility for this study. Clinicians or research nurses/assistants will explain the informed consent form in person. Patients who agree to participate must sign the consent form, and a copy will be provided to them. This study involves no randomization or blinding; patients are aware of their treatment.

Interventions

Radiation Treatment Planning

Following consent and eligibility confirmation, patients will undergo rectal spacer and fiducial marker (Visicoil, IBA Dosimetry GmbH, Schwarzenbruck, Germany) implantation per the institutional protocol, prior to simulation scans and treatment planning. After 2–3 weeks, without severe complications from implantation, patients

will undergo same-day CT and subsequent MRI simulation scans (on a 1.5T or 3T MRI simulator dedicated for radiotherapy and proton therapy applications) per the institutional protocol. Treatment will target the prostate ± seminal vesicles, delivering 25 Gy in 2 fractions, with at least 6 days between treatments, completed within 2 weeks, at the treating physician's discretion.

Contours

1. The clinical target volume (CTV1) will encompass the entire prostate, as defined by the non-contrast axial planning CT scan, for low-risk patients. For intermediate-risk patients, CTV2 will include the entire prostate plus the proximal two-thirds of the seminal vesicles, in addition to CTV1. MRI will be co-registered with the planning CT to assist with target contouring.
2. An optional boost volume may be defined for intraprostatic lesions identified by clinical imaging (e.g., MRI, PSMA-PET), at the oncologist's discretion.
3. The rectum will be contoured from the bottom of the ischial tuberosities to the sigmoid flexure.
4. Normal structures, including the bladder, urethra (delineation at the treating physician's discretion), femoral heads, and penile bulb, will also be contoured. Urethral delineation may use T2 sequences, contouring on axial slices where visible, and/or on the sagittal plane from the bladder to the penile urethra.

Treatment Dose Planning Parameters

A setup error of 2 mm and a range uncertainty of 3% will be applied in robust planning. The CTV will receive a prescribed dose of 25 Gy in 2 fractions. The volume of the CTV receiving the prescription dose (V25 Gy) must be ≥ 95% and not exceed 125% (hotspot). No more than 10% of the urethra volume should receive > 27 Gy.

Table 1: Dose constraints used in the planning of the 2-fraction regimen

Structure	Dose Metric	Planning Dosimetric Criterion
CTV1	V25 Gy	> 95%
	Dmax	< 27.5 Gy
CTV2	V20 Gy	> 95%
Urethra	D10%	< 27 Gy
Bowel	V12 Gy	< 5 cm^3
Femoral head_L	V14 Gy	< 10 cm^3

Femoral head_R	V14 Gy	< 10 cm^3
Bladder	V20.8 Gy	< 5 cm^3
	V14.6 Gy	< 15 cm^3
	Dmax	< 27Gy
Penile Bulb	V19.5 Gy	< 50%
Rectum	V20.8 Gy	< 1 cm^3
	V17.6 Gy	< 4 cm^3
	V13 Gy	< 7 cm^3
	Dmax	< 27Gy

Adaptive Planning

1. The need for adaptive planning will be assessed for all participants.
2. Daily MR images will be rigidly registered to the planning CT by aligning relevant anatomy (bladder, rectum, prostate ± seminal vesicles).
3. Organs at risk (OARs) will be auto-contoured on the MR, and CTV simulation contours will be rigidly copied to the MR scan.
4. CTV1/CTV2 and OAR contours will be reviewed and manually adjusted if necessary.
5. The original plan will be recalculated on a synthetic CT generated from the daily setup MR to verify compliance with planning dose parameters.
6. Adaptive planning will be performed if treatment dose parameters fail to meet planning or protocol-mandated criteria.

Treatment Delivery and Gating

1. A short MRI scan (~25 seconds) will be used for setup and to assess bladder filling and rectal position.
2. A long MRI scan (~3 minutes) will be used for adaptive planning assessment.
3. Orthogonal X-ray images will align bony anatomy with the planning CT at the patient's imaging position.
4. Final couch shifts, based on fiducial marker positions, will be applied before treatment delivery.
5. The fiducial marker with minimal migration will be selected for real-time image-guided particle therapy (RGPT), using a 1–1.5 mm tracking boundary during treatment.

Concomitant Medication and Supportive Care Guidelines

1. Androgen deprivation therapy (ADT) for 4–6 months may be administered to intermediate-risk patients, at the investigator's discretion and/or patient preference, in neoadjuvant (up to 2 months pre-SBPT), concurrent, or adjuvant (post-SBPT) settings.
2. Patients experiencing increased urinary frequency or urgency may receive medications (e.g., anticholinergics, alpha-blockers like tamsulosin) at the radiation oncologist's discretion, with documentation in the patient chart.
3. Rare serious bowel symptoms (e.g., rectal urgency, tenesmus, diarrhea) may be managed with medications (e.g., diphenoxylate, loperamide) at the radiation oncologist's discretion, documented in the patient chart.

Follow-Up Phase

Post-SBPT, patients will be followed at 1, 3, 6, and 12 months in the first year, then every 6 months until 5 years post-treatment. At each visit, patients will complete the EPIC questionnaire (in English or validated Chinese versions), assessing four domains: urinary symptoms (subdomains: incontinence, irritative/obstructive), sexual symptoms, bowel symptoms, and hormonal symptoms, scored from 0 (worst) to 100 (best). PSA levels will be measured at each follow-up (±1 month window).

Clinician-Reported Adverse Events

Adverse events (AEs) will be reported using NCI-CTCAE v5.0. GU toxicities include urinary frequency, urgency, incontinence, obstruction, retention, pain, bladder spasm, cystitis (noninfective), and hematuria. GI toxicities include proctitis, diarrhea, fecal incontinence, rectal hemorrhage, stenosis, ulcer, and small-intestinal obstruction. Erectile dysfunction and fatigue will also be graded. Clinical discretion may guide management, such as diphenoxylate/loperamide for diarrhea/rectal symptoms, phenazopyridine for bladder irritation, anticholinergics/alpha-blockers for urinary symptoms, and phosphodiesterase inhibitors (e.g., sildenafil) for erectile dysfunction. All AEs and G3+ serious adverse events (SAEs) will be recorded and followed until resolution or stabilization.

Data Management and Safety Monitoring

A secure database, maintained by HKSH, will store all treatment, toxicity, efficacy, and AE data, accessible only to clinicians, investigators, and core research team members.

Security measures include firewall technology, role-based access, user authentication (ID/password), and restricted data transfer within hospital systems. Data will be retained for at least 10 years post-study.

Statistical Analysis

Sample Size and Accrual

We hypothesize that ≤5% of patients will experience G2+ GI or GU late toxicities (≥3 months) up to 2 years post-treatment. A sample size of 32 patients, using a one-stage binomial design, tests the null hypothesis that the G2+ GI or GU toxicity rate is ≥15%, with 80% power and a 5% significance level. The target sample size is increased to 35 to account for a 10% non-compliance rate (e.g., rejection, cancellation, treatment violation, dropout/loss to follow-up). The projected accrual rate is 1–3 patients/month, with study completion expected in 12–30 months.

Data Analysis

Analysis of Primary Endpoints

GI and GU toxicities will be evaluated throughout follow-up, with occurrence dates recorded. Proportions of patients with G2+ GI, GU, or both toxicities will be calculated at baseline and each follow-up. Fisher's exact tests will compare categorical data.

Early Stopping Guidelines/Interim Futility Analysis

An interim futility analysis will occur when half the patients complete 6 months of follow-up. If the G2+ GI or GU toxicity rate exceeds 20%, the treatment strategy will be deemed unacceptable, and results will be reported to the Institutional Review Board (IRB) for review, potentially leading to early study termination.

Analysis of Secondary Endpoints

Patient-reported EPIC score changes will be calculated as baseline scores minus follow-up scores at 1, 3, 6, and 12 months (year 1), then every 6 months (years 2–5). Longitudinal analysis using linear mixed-effects models, adjusted for age, baseline domain score, NCCN risk level, Gleason score, baseline PSA, and T-stage, will assess each domain. Race will not be included, as most participants are expected to be Chinese.

Analysis of variance (ANOVA) will compare EPIC score changes at 2 years. Missing data impact will be evaluated using multiple strategies, including adjustments for patient characteristics (missing at random [MAR]), joint models (missing not at random [MNAR]), pattern mixture models, and sensitivity analyses.

For oncological outcomes (BF, LF, RF, DM), Gray's cumulative incidence method will account for death as a competing risk. Overall survival (OS) will be estimated using the Kaplan–Meier method. Cox regression will provide hazard ratios (HRs) for TTP, and Fine and Gray's regression will address competing risks. Adjusted HRs and 95% confidence intervals will be reported, adjusting for baseline PSA, EPIC scores, ADT use, age, Gleason score, and T-stage as appropriate.

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