

STUDY PROTOCOL

Open Access



# Functional imaging guided stereotactic ablative body radiotherapy (SABR) with focal dose escalation and bladder trigone sparing for intermediate and high-risk prostate cancer: study protocol for phase II safe trial

Almudena Zapatero<sup>1\*</sup>, Pablo Castro<sup>2</sup>, María Roch<sup>2</sup>, Pablo Rodríguez Carnero<sup>3</sup>, Sara Carroceda<sup>1</sup>, Alexandra Elena Stoica Rosciupchin<sup>1</sup>, Sergio Honorato Hernández<sup>2</sup>, Leopoldo Cogorno<sup>4</sup>, Alfonso Gómez Iturriaga<sup>5</sup> and David Büchser García<sup>1</sup>

## Abstract

**Background** Stereotactic ablative body radiotherapy (SABR) is an emerging treatment alternative for patients with localized low and intermediate risk prostate cancer patients. As already explored by some authors in the context of conventional moderate hypofractionated radiotherapy, focal boost of the index lesion defined by magnetic resonance imaging (MRI) is associated with an improved biochemical outcome. The objective of this phase II trial is to determine the effectiveness (in terms of biochemical, morphological and functional control), the safety and impact on quality of life, of prostate SABR with MRI guided focal dose intensification in males with intermediate and high-risk localized prostate cancer.

**Methods** Patients with intermediate and high-risk prostate cancer according to NCCN definition will be treated with SABR 36.25 Gy in 5 fractions to the whole prostate gland with MRI guided simultaneous integrated focal boost (SIB) to the index lesion (IL) up to 50 Gy in 5 fractions, using a protocol of bladder trigone and urethra sparing. Intra-fractional motion will be monitored with daily cone beam computed tomography (CBCT) and intra-fractional tracking with intraprostatic gold fiducials. Androgen deprivation therapy (ADT) will be allowed. The primary endpoint will be efficacy in terms of biochemical and local control assessed by Phoenix criteria and post-treatment MRI respectively. The secondary endpoints will encompass acute and late toxicity, quality of life (QoL) and progression-free survival. Finally, the subgroup of high-risk patients will be involved in a prospective study focused on immuno-phenotyping.

**Discussion** To the best of our knowledge, this is the first trial to evaluate the impact of post-treatment MRI on local control among patients with intermediate and high-risk prostate cancer undergoing SABR and MRI guided focal intensification. The results of this trial will enhance our understanding of treatment focal intensification through the

\*Correspondence:  
Almudena Zapatero  
almudena.zapatero@salud.madrid.org

Full list of author information is available at the end of the article



© The Author(s) 2024. **Open Access** This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>. The Creative Commons Public Domain Dedication waiver (<http://creativecommons.org/publicdomain/zero/1.0/>) applies to the data made available in this article, unless otherwise stated in a credit line to the data.

employment of the SABR technique within this specific patient subgroup, particularly among those with high-risk disease, and will help to clarify the significance of MRI in monitoring local responses. Hopefully will also help to design more personalized biomarker-based phase III trials in this specific context. Additionally, this trial is expected to be incorporated into a prospective radiomics study focused on localized prostate cancer treated with radiotherapy.

**Trial registration** Clinicaltrials.gov identifier: NCT05919524; Registered 17 July 2023.

**Trial Sponsor** IRAD/SEOR (Instituto de Investigación de Oncología Radioterápica / Sociedad Española de Oncología Radioterápica).

**Study setting** Clinicaltrials.gov identifier: NCT05919524; Registered 17 July 2023.

**Trial status** Protocol version number and date: v. 5/ 17 May-2023. Date of recruitment start: August 8, 2023. Date of recruitment completion: July 1, 2024.

**Keywords** Prostate cancer, High-risk prostate cancer, SABR, SBRT, Ultrahypofractionation, Extreme hypofractionation, Magnetic resonance imaging, MRI, Focal boost, Biochemical control

## Background

Dose intensification has shown to potentially improve long-term control, particularly in intermediate and high-risk prostate cancer patients. Hence, it is crucial to intensify efforts in minimizing the dose to organs at risk. Employing advanced image-guided radiation therapy (IGRT) techniques and optimizing dosage to the rectum and urinary structures has become essential to accomplish this objective.

Focal boost to index lesions (ILs) represents an interesting strategy for dose escalation. This approach is based on the clinical and pathologic evidence showing that the ILs might be the nucleus of the tumor aggressiveness and post-treatment recurrence [1, 2]. The clinical benefits of and tolerance of focal boost to the ILs have been previously reported [3]. The oncological benefit was demonstrated in the phase 3 FLAME trial [4] where patients were randomized to receive standard radiation therapy of 77 Gy in 35 fractions, with or without a focal boost to 95 Gy. Results indicated an improved biochemical-free survival with the IL boost at 5-years, with no adverse impact on toxicities and quality of life (QoL). Other studies have also reported excellent morphological and functional results with highly selected focal radiation dose intensification [5].

Nevertheless, it remains uncertain whether the benefit of ILs boost persist in the context of ultrahypofractionated radiation therapy (UHRT). In this setting, several phase I/II studies have presented preliminary findings on early toxicities with a focal boost ranging from 40 to 55 Gy over 5-fraction prostate stereotactic ablative radiotherapy (SABR) [6–8].

However, most of the evidence with UHRT has been reported in low- and intermediate-risk prostate cancer, while there is very limited data in high-risk disease [9]. At present, the largest available randomized evidence for UHRT comes from HYPO-RT-PC [10], a non-inferiority phase III clinical trial that randomized 1,200 prostate cancer patients to UHRT (42.7 Gy in 7 fractions) versus

conventional fractionated radiation therapy (78 Gy in 39 fractions)—including 126 high-risk patients. Although equally effective, UHRT was however related with increased urinary toxicity that could potentially been lower if a genuine SABR technique had been employed. Other reported prospective studies of SABR in high-risk prostate cancer are small size phase II trials with preliminary results [9, 11]. An individual patient meta-analysis of 344 patients with high-risk prostate cancer treated with SABR has shown promising efficacy [12]. Further controlled prospective studies are needed to verify these results and investigate the optimal dose and target volume in this scenario.

The present study is a prospective single arm phase II (proof of concept) trial designed to evaluate the effectiveness, safety and impact on quality of life of focal dose intensification to ILs using SABR technology and UHRT in intermediate and high-risk prostate cancer patients. The hypothesis of this study is that the combination of prostate SABR with imaging guided focal dose intensification on the ILs, together with partial preservation of the prostatic urethra and bladder trigone, would lead to a higher probability of local control without a significant increase in toxicity or even lower complications compared to standard clinical practice. The results will help determine the design of subsequent based phase III trials in the exclusive SABR setting in high-risk disease, the value of MRI in monitoring response, and hopefully the impact of immune phenotyping in the individualized approach of SABR dose intensification in localized prostate cancer.

## Methods: design, participants, interventions and outcomes/design

This is a prospective single arm phase II (proof of concept) trial, approved by the Ethics Committee of the Hospital Universitario de La Princesa, Health Research Institute in Madrid (2023.5222) and registered on clinicaltrials.gov (NCT05919524). To ensure and adequate

enrolment in accordance with the chronogram, all patients with localized prostate cancer will initially be visited by the trial investigators.

The aim is to evaluate the effectiveness, safety and impact on quality of life of MRI guided focal dose intensification to ILs using SABR technology and UHRT in intermediate and high-risk prostate cancer patients including partial sparing of the bladder trigone and urethra. An interim analysis in the first 5 cases will be carried out by the PI to assess the safety of the trial, through the analysis of acute urinary and rectal toxicity as a surrogate variable for late toxicity. This analysis will be accessible to all investigator and the sponsor of the trial.

The high-risk patients in this study will be prospectively included (following screening and informed consent) in a translational study of biomarkers (Immune Phenotype Of Metastatic Prostate Cancer: Immuno-PROfiling; grant from Health Research Fund -FIS- PI21/01111).

## Objectives

### **Co-primary endpoints and measures**

- Biochemical progression-free survival, from time of inclusion until biochemical failure defined by the Phoenix Consensus Conference recommendation from the Radiation Therapy Oncology Group - American Society for Radiation Oncology (RTOG-ASTRO): A rise by 2 ng/ml or more above the nadir prostate specific antigen (PSA) confirmed by a second observation taken 3–4 weeks later.
- Local control defined as the disappearance of suspicious images (ILs) on mpMRI performed 6–9 months after the end of radiotherapy.

### **Secondary endpoints and measures**

- Incidence and severity of acute urinary treatment-related adverse events graded according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 scale. Every urinary event occurring within 3 months from treatment completion will be defined as “acute event”. All adverse events will be recorded and graded according to CTCAE V5.0 scale (graded from 0 to 5 with greater values representing worse outcomes) [Time Frame: 90 days].
- Incidence and severity of acute rectal treatment-related adverse events graded according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 scale.
- This paragraph follows the prior. Every rectal event occurring within 3 months from treatment completion will be defined as “acute event”. All adverse events will be recorded and graded

according to CTCAE V5.0 scale (graded from 0 to 5 with greater values representing worse outcomes) [Time Frame: 90 days].

- Incidence and severity of late urinary treatment-related adverse events graded according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 scale. Every urinary event occurring after 3 months from treatment completion will be defined as “late event”. All adverse events will be recorded and graded according to CTCAE V5.0 scale (graded from 0 to 5 with greater values representing worse outcomes) [Time Frame: 2 years].
- Incidence and severity of late rectal treatment-related adverse events graded according to CTCAE (Common Terminology Criteria for Adverse Events) v5.0 scale. Every rectal event occurring after 3 months from treatment completion will be defined as “late event”. All adverse events will be recorded and graded according to CTCAE V5.0 scale (graded from 0 to 5 with greater values representing worse outcomes) [Time Frame: 2 years].
- Patient reported outcomes and quality of life assessment. Impact on Quality of life affecting the genitourinary, gastrointestinal, sexual and hormonal domains using the EPIC-26 short form, the International Prostate Symptom Score (IPSS) and the Expanded Prostate Index Composite-26. [Time Frame: 2 years]

## Eligibility criteria

### **Inclusion criteria**

- Signed written informed consent obtained by the investigators of this study according to ICH/GCP regulations before registration and prior to any trial procedure.
- ECOG 0–1
- Minimum age 18 years.
- Histologically confirmed adenocarcinoma of the prostate.
- Primary localized Prostate cancer, cN0 and cM0, intermediate or high-risk disease according to NCCN 2023.
- Tumor clinical stage cT2-T3a with visible index lesion on pretreatment MRI. MRI pre-treatment is mandatory.
- Desirable prostate volume in MRI (not mandatory) < 80 cc or > 80 cc if urinary function is preserved and is dosimetrically feasible.
- IPSS (International Prostate Symptom Score) ≤ 18; alfa blockers allowed.

### Exclusion criteria

- Unresolved previous prostatitis, symptomatic urethral stenosis.
- Bilateral hip prosthesis.
- Previous surgery at the prostate level (transurethral resection of the prostate or adenectomy) within the past 6 months.
- Prior pelvic RT.
- Evidence of T3b or T4 clinical stage or N1 or M1 (presence of distant metastases).
- Severe or active co-morbidity likely to impact on the advisability of SABR.
- Previous malign neoplasia unless in remission for at least 3 years from registration with the exception of non-melanoma skin cancer.

### Intervention

#### Radiation dose

- 36.25 Gy in 5 sessions of 7.25 Gy (EQD2 of 85 Gy with an alpha/beta of 1.5) to the whole prostate gland + seminal vesicles + margin (planned target volume1, PTV1), every other day. Weekly sessions will be permitted on an exceptional basis for selected patients with a prostate volume exceeding 80 cc and IPSS values ranging between 15 and 18 (without adjusting for overall treatment duration).
- Simultaneous “isotoxic” focal boost of up to 50 Gy in 5 sessions to the index lesion + margin (PTV2), prioritizing critical organ restriction criteria at all times.
- Additional urethra and bladder trigone sparing constrains.

### Protocol design and procedures

Once adenocarcinoma of the prostate is histologically confirmed, patients will be staged with multiparametric MRI of the prostate consisting of T2 in axial, coronal and sagittal planes, axial T1 non-contrast of the pelvis, diffusion weighted imaging (DWI), and T1 dynamic contrast-enhanced sequences (DCE), using a body-phased array coil. The acquisition and imaging protocol will be consistent with the European Society of Urogenital Radiology recommendations [13]. A prostate imaging reporting and data system (PI-RADS version 2.1) score of at least 3 is required for the lesion to be deemed appropriate for focal intensification, with confirmatory target biopsies conducted on equivocal MRI findings. The MRI images acquired will serve as the substrate for patient inclusion in the study and will provide a reference basis for the

subsequent definition of treatment volumes (prostate gland and ILs) in treatment planning.

After obtaining informed consent, a minimum of three gold fiducial seeds will be implanted in the prostate through ultrasound-guided trans-rectal pre-loaded needles, along with recto-prostatic spacer at physician discretion (optional). Between 7 and 15 days after fiducial implantation, a computed tomography (CT, slice thickness of 2 mm) and a new MRI study of the prostate that included axial T2 weighted images, DWI and a T2\* gradient recalled echo images will be performed in radiotherapy supine position (flat table top with an indexed knee and ankle immobilization device) for treatment planning following a comfortably full bladder and an empty rectum protocol. To help with the contouring of the urethra, a 12 French Foley non-radiopaque catheter will be inserted before the CT simulation. A matching point registration (based on fiducials) of planning CT and MRI will be used for prostate and tumor delineation. In those patients treated with neoadjuvant hormone therapy for more than 3 months, we will use a second diagnostic mpMRI registration to add prostate and tumor delineation.

The clinical target volume (CTV) will include the prostate and one-third of seminal vesicles for favorable intermediate risk and two-third of seminal vesicles for unfavorable intermediate and high-risk patients. A margin of 3 mm posteriorly and 5 mm in all the other directions will be added to create the planning target volume for the prostate (PTV-P) and 2–3 mm in all directions for the mpMRI visible index lesion (PTV-IL), except for interfase GTV-rectum/urethra that will be (0–1 mm). ESTRO ACROP consensus guideline for CT-MRI target volume delineation will be used for contouring [14]. Organs at risk (OAR) will be contoured according to RTOG guidelines and will include the bladder and rectum as solid organs, the rectum PRV (rectum + margin 2–3 mm), the urethra PRV (Foley catheter with a 1–2 mm isotropic ring expansion), the bulbar urethra, the bladder trigone [15] and femoral heads. Table 1 summarizes the dose constraints for the OAR. Indeed, the criteria for further excluding the patient from the trial is not the location of the IL, but rather the consideration of mandatory organ-at-risk (OAR) constraints.

### Dose prescription, treatment delivery and quality control

Radiation treatment will consist on 5 fractions of 7.25 Gy (every other day) to the whole prostate gland and the seminal vesicles with a simultaneous “isotoxic” focal boost of up to 50 Gy in 5 sessions to the ILs, prioritizing critical organ restriction criteria at all times. We have selected this dose schedule to further escalate dose to the tumor lesion to an EQD2Gy (equivalent dose in 2 Gy fractions) above 125–150 Gy (alpha/β 1.5), while maintaining an EQD2Gy of 85 Gy to the whole prostate.

**Table 1** Summary of time schedules, events and follow-up

Study Procedure	Screening visit	During SABR Protocol treatment		Follow-up		
		During SABR treatment	End of SABR treatment	Year 1–2 First month and every 3months	Years 3 Every 6 months	End of study
Medical history and physical examination	X			X	X	X
Informed consent	X					
Concomitant medications	X		X	X	X	X
Bood counts, Serum chemistry PSA/Testosterona	X			X	X	X
Urinary or rectal comorbidities	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X
Prostate MRI	X			X	X*	
Standard imaging work up	X#					
PET-TC (PSMA or Choline in High Risk)	X#					
QoL questionaires	X		X	X	X	X
Urinary and rectal events and grades	X	X	X	X	X	X
Survival	X		X	X	X	X

\*: at 3 months and 6–12 months when required

#: At screening and when required

The treatment will be administered using an electron Linear Accelerator (Linac) named TrueBeam with Volumetric Modulated Arc Therapy (VMAT) technique employing complete arcs of 36 degrees. The treatment design will be conducted using an inverse optimization process integrated into specific PC-software (Treatment Planning System, TPS) that models the mechanical and dosimetric properties of the linac. The procedure will be conducted with filter-free energy to minimize treatment times as much as possible, utilizing the highest available energy, specifically 10 FFF (Flattening Filter Free), and a maximum rate of 2400 MU/min (Monitor Units per minute). The fiducial markers will serve as a reference for daily mobility control IGRT prior treatment using cone beam CT (CBCT) technology, and intra-fractional tracking during treatment using KV acquisitions every 20° of arc rotation. Images acquired daily through pre-treatment and during-treatment will help monitor and quantify uncertainties associated with positioning, allowing assessment of treatment volume safety margins. Also on a daily basis, a verification of the isocenter position of the kV On-Board Imager (OBI) imaging system will be performed using the Machine Performance Check device with a tolerance of 0.5 millimeters.

An alternative calculation to the dose distribution provided by the TPS will be performed prior to treatment. The discrepancy in point dose should not exceed 3%. Additionally, in the comparison between dose distributions, it will be ensured that 95% of the analyzed points meet the gamma criterion of 3%/3 mm less than 1. Furthermore, it will be verified that the linac delivers the treatment correctly and that dose distributions are

equivalent to those calculated by the TPS. This verification is carried out using a high-resolution detector array.

#### Systemic therapy

Short- (6 months) or long-term (18–28 months) androgen deprivation therapy (ADT) will be allowed for unfavourable intermediate and high-risk tumours, respectively, in agreement with clinical guidelines and following a protocol of risk adapted ADT. Since the publication in 2022 of the results of the meta-analysis from the STAMPEDE platform [16], we also incorporate doublet with ADT and Abiraterone-prednisone in selected high and very high-risk patients.

#### Outcomes: clinical and toxicity assessment and follow-up

Clinical assessment is planned at baseline, weekly during radiation treatment, at 3, 6, 9 and 12 months follow-up and every 6 months thereafter until 5 years. Prostate-specific antigen (PSA) values, serum testosterone level and a complete blood count will be obtained at each visit. Biochemical control will be assessed through PSA measurements. A post-radiotherapy MRI study is mandatory for local control assessment, and is planned at six months following radiation treatment and repeated 3–6 months later in those cases in which a complete response is not achieved. The high-risk patients in this study will be prospectively included (following screening and informed consent) in a translational study of biomarkers (Immune Phenotype Of Metastatic Prostate Cancer: Immuno-PROfiling; grant from Spanish Health Research Fund -FIS- PI21/01111). Toxicity and perceived quality of life in the urinary, digestive, and hormonal domains will be evaluated using specific assessment scales (EORTC/

RTOG and CTCAEs) and validated specific questionnaires (IPSS/EPIC 26) prior to treatment and during follow-up (Table 2). Prostate biopsy will be performed in clinically selected cases according to standard practice.

## Statistical analysis

### Sample size

Based on limited published results of SABR in high-risk patients, the aim of this trial is to demonstrate that the success rate (increase biochemical free survival) using focal intensification in high-risk prostate cancer, will reach 85%, with a minimum of 65%. Since the goal is to establish that the success rate exceeds a pre-established lower limit, this is a non-inferiority study, employing a one-sided analysis. The assumed success rate in the sample is 0.85. Using alpha and beta levels of 0.05 and 0.2 (contrast power of 0.8) and a one-sided test, a sample of 23 patients will be required to demonstrate that the lower limit of the 95% confidence interval for the success rate is greater than or equal to 0.50. The G\*Power 3.1 software was employed for the calculations. It is expected that the recruitment target of 27 patients, accounting for a 15% margin for potential losses, will be easily met within the estimated two-year recruitment period. Depending on preliminary results, a decision and amend will be

consider to extend the enrollment to achieve recruitment goal of 50 patients and a 5 years endpoint analysis.

## Definitions and statistical analysis

The co-primary endpoints are the biochemical-disease-free survival and the MRI- defined local control. Biochemical failure was defined according to the Phoenix definition (PSA > 2 ng/mL above the currently observed PSA nadir). An image complete response is defined as disappearance of all morphological and functional lesions in MRI 6 to 12 months after radiotherapy.

No confirmatory biopsy is required. Secondary endpoints included acute and late toxicity and QoL assessment. Urinary and rectal toxicity will be calculated using the maximal recorded toxicity per patient and date of occurrence for actuarial calculation.

Descriptive statistics will be used to summarize demographic and tumor and treatment characteristics as well as acute and late toxicity and QoL outcomes. The Kaplan-Meier method will be used to determine biochemical relapse free and toxicity-free survival rates and medians and the log-rank test for survival rates. The chi2 or Fisher exact test will be used to evaluate differences in patient and treatment characteristics for categorical variables. The t-test, analysis of variance, or Mann-Whitney test will be used, depending on the type and distribution of the variables, to evaluate differences in patient and treatment characteristics for continuous data. The three domains of EPIC scores and sub scores (urinary [function/bother], bowel [function/bother] and sexual [function/bother]) and IPSS will be analyzed to estimate differences in QoL score change from baseline, adjusting by baseline score. A decreased of >0.5 standard deviation (SD) of baseline values for each domain score will be considered clinically relevant (mild change). A change > 1 (SD) of baseline values will be considered moderately relevant (moderate change) and a change of > 2 SD will be considered a severe change. All statistical analysis will be performed with SAS 9.4. P-values less than 5% will be considered as significant.

**Table 2** Summary of dose constrains

Structure	Dosimetric parameter	Constrains per protocol
PTV1	D98% (Dnear min)	> 95% (34.44 Gy)
CTV1– PRV Urethra	D98% (Dnear min)	> 95% (34.44 Gy)
	D95% (Dnear min)	> 100% (36.25 Gy)
PTV2	V95% (47.5 Gy)	> 95%
	V105% (52.5 Gy)	< 5%
Rectum	Maximum dose (0.03 cc)	≤ 39 Gy
	Median dose	≤ 18.1 Gy
	V18Gy	≤ 50%
	V29Gy	≤ 20%
	V36Gy	< 1 cc (alternative 2 cc)
PRV Rectum	Maximum dose (0.03 cc)	≤ 41 Gy
Bladder	Maximum dose (0.03 cc)	≤ 39 Gy
	V18.1 Gy	≤ 40%
	V36Gy	≤ 10%
	V37Gy	< 5 cc (alternative 10 cc)
PRV Urethra	Maximum dose (0.03 cc)	≤ 35.25 Gy (alternative 36.25 Gy)
Bulbar Urethra	Maximum dose (1 cc)	≤ 40 Gy
Bladder trigone	Maximum dose (0.1 cc)	≤ 38 Gy
Sigma Bowel	V20Gy	< 1%
Penile bulb	Maximum dose (0.03 cc)	< 40 Gy
	V21.6 Gy	< 3 cc
Femoral Heads	V14.5 Gy	≤ 5%
	Maximum dose (0.03 cc)	< 32.4 Gy

## Discussion

There is substantial clinical evidence backing the escalation of radiation therapy doses, demonstrating enhanced biochemical disease-free survival in patients with prostate cancer across all risk groups. This improvement is particularly notable in those with intermediate and high-risk tumors [17, 18]. The utilization of UHRT employing the SABR technique, which enables the delivery of elevated radiation doses in 5 or fewer fractions, has proven to be a secure, efficient, and convenient approach in treating clinically localized prostate cancer. SABR has been predominantly explored in low- and intermediate-risk prostate cancer patients, yielding excellent outcomes

[10, 19, 20, 21] However, several interrogations persist concerning the optimal dose, target volumes and timing. Interestingly, a relevant question that needs further exploration is the effectiveness of SABR in high-risk patients, especially given the limited number of studies addressing this particular aspect [7, 9, 11, 12, 22–24].

Given the potential for dose escalation to improve long-term disease control even in the context of extreme hypofractionation, efforts to further minimize doses to organs at risk and enhance overall tolerance should be actively pursued. Based on pathological investigations that suggest that the presence of IPLs serves as a robust indicator of tumor aggressiveness and post-radiotherapy local recurrence [1, 2], a focal dose boost to IPLs has been proposed as a potential way of individualized dose intensification aimed to improve local control and increase biochemical disease-free survival (bDFS) without compromising the sparing of organs at risk (OARs). Several contemporary studies [3, 4], have demonstrated the feasibility and applicability of this treatment, along with good safety and patient tolerance. We recently reported an excellent morphological and functional MRI response in a phase II trial of MRI-guided focal boost using VMAT hypofractionated technique [5]. The oncological benefit of focal DIL boost is now confirmed in the phase 3 FLAME trial that has shown improved biochemical-free survival with IL boost at 5 years, without affecting toxicities and QoL [4].

Since the value of dose intensification in high-risk prostate cancer is well established [17, 18, 25], it becomes evident that the next step should include the exploration of the advantages of both, UHRT with SABR and an individualized focal dose intensification on index lesions.

In this phase II proof of concept trial, we aimed to assess whether the integration of three strategies -UHRT SABR with focal dose intensification on the prostatic IL and a preservation of the prostatic urethra and bladder trigone-, would lead to a higher probability of local control in intermediate and high-risk prostate cancer patients, without a significant increase in toxicity compared to standard clinical practice. To our knowledge this is the first trial to assess the impact on local control and monitoring of post treatment MRI. This trial is also anticipated to be included in a prospective radiomics study focused in prostate cancer treated with radiotherapy. The information derived from this trial together with the results of the sub analysis of biomarkers in high risk disease, will help to design more personalized designs of subsequent phase III trials in the exclusive RT setting for the treatment of high-risk disease.

**Trial Sponsor** IRAD/SEOR (Instituto de Investigación de Oncología Radioterápica / Sociedad Española de Oncología Radioterápica).

## Abbreviations

ADT	Androgen deprivation therapy
bDFS	biochemical disease-free survival
CBCT	cone beam computed tomography
CT	Computerized tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical target volume
EPIC 26	Expanded Prostate Index Composite-26
EQD2	Equivalent total doses in 2-Gy fractions
ESTRO/ACROP	European Society for Radiotherapy and Oncology/ Advisory Committee for Radiation Oncology Practice
IGRT	Image-Guided Radiation Therapy
IL	Index lesion
IPSS	International Prostate Symptom Score
MRI	magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
OAR	Organs at risk
PRV	Planning organ at risk volume
PSA	Prostatic specific antigen
PTV	Planning target volume
QoL	quality of life
RTOG-ASTRO	Radiation Therapy Oncology Group - American Society for Radiation Oncology
SABR	Stereotactic ablative radiation therapy
SBRT	Stereotactic body radiation therapy
SD	standard deviation
SIB	Simultaneous integrated focal boost
UHRT	Ultra hypofractionated radiation therapy
VMAT	Volumetric Modulated Arc Therapy

## Author contributions

Study conception: AZ, PC. Initial Study design: AZ, PC. Revision of study Design and protocol: AZ, PC, MR, PRC, LC, SC AGI, DB Study coordination: AZ, PC, MR AGI. Participating centers: Hospital Universitario de La Princesa, Radiation Oncology Department, Health Research Institute, Madrid and Hospital Universitario Cruces, Department of Surgery and Radiology and Physical Medicine, University of the Basque Country UPV/EHU, Biobizkaia Health Research Institute Drafting the manuscript: AZ, PC, AGI, All authors read and approved the final manuscript.

## Funding

This study was supported by funding from from Instituto De Investigación En Oncología Radioterápica (IRAD), Spain, Sociedad Española de Oncología Radioterápica (SEOR) and Janssen. We thank the Scientific Committee.

## Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Declarations

### Ethics approval and consent to participate

This research complies with the Helsinki declaration and has been approved by the Ethics committee of the Hospital Universitario de La Princesa, Health Research Institute, Madrid (2023.5222). Trial registration: Clinicaltrials.gov identifier: NCT05919524; Registered 17 July 2023. Signature of the informed consent will be obtained from all patients before inclusion in the study.

### Consent for publication

Not applicable.

### Competing interests

The authors declare that they have no competing interests. The analysis and monitoring of the data will be performed by a external and independent CRO.

### Author details

<sup>1</sup>Radiation Oncology Department, Hospital Universitario de la Princesa, Health Research Institute IIS- IP, Diego de León 62, 28006 Madrid, Spain

<sup>2</sup>Medical Physics Department, Hospital Universitario de la Princesa, Health Research Institute IIS- IP, Madrid, Spain

<sup>3</sup>Radiology Department, Hospital Universitario de la Princesa, Health Research Institute IIS-IP, Madrid, Spain

<sup>4</sup>Urology Department, Hospital Universitario de la Princesa, Health Research Institute IIS-IP, Madrid, Spain

<sup>5</sup>Department of Surgery and Radiology and Physical Medicine, Hospital Universitario Cruces, University of the Basque Country UPV/EHU, Biobizkaia Health Research Institute, Bizkaia, Spain

Received: 24 January 2024 / Accepted: 5 April 2024

Published online: 03 May 2024

## References

- Huang CC, Deng F-M, Kong MX, Ren Q, Melamed J, Zhou M. Re-evaluating the concept of dominant/index tumor nodule in multifocal prostate cancer. *Virchows Archiv*. 2014; 464: 589–94. <https://doi.org/10.1007/s00428-014-1557-y>.
- Arrayeh E, Westphalen AC, Kurhanewicz J, Roach M, Jung AJ, Carroll PR et al. Does local recurrence of prostate cancer after radiation therapy occur at the site of primary tumor? results of a longitudinal MRI and MRSI study. *Int J Radiat Oncol Biol Phys* 2012; 82: e787–93. <https://doi.org/10.1016/j.ijrobp.2011.11.030>.
- Darren MC, Poon J, Yuan B, Yang, Linda GW, Kerkmeijer d, Amar U. Kishan E, Vedang Murthy f, Alison Tree g, Almudena Zapatero h, Oi Lei Wong. Magnetic resonance imaging-guided focal boost to intraprostatic lesions using External Beam Radiotherapy for localized prostate Cancer: a systematic review and Meta-analysis. *Eur Urol Oncol*. 2022. <https://doi.org/10.1016/j.euo.2022.10.001>.
- Kerkmeijer LGW, Groen VH, Pos FJ, et al. Focal boost to the intraprostatic tumor in external beam radiotherapy for patients with localized prostate cancer: results from the FLAME randomized phase III trial. *J Clin Oncol*. 2021;39:787–96.
- Zapatero A, Roch M, Castro Tejero P, Büchser D, Martin de C, Vidales S, González, et al. MRI-guided focal boost to dominant intraprostatic lesion using volumetric modulated arc therapy in prostate cancer. Results of a phase II trial. *Br J Radiol*. 2022;95:20210683.
- Alayed Y, Davidson M, Liu S, et al. Evaluating the tolerability of a simultaneous focal boost to the gross tumor in prostate SABR: a toxicity and quality-of-life comparison of two prospective trials. *Int J Radiat Oncol Biol Phys*. 2020;107:136–42.
- Herrera FG, Valerio M, Berthold D, et al. 50-Gy stereotactic body radiation therapy to the dominant intraprostatic nodule: results from a phase 1a/b trial. *Int J Radiat Oncol Biol Phys*. 2019;103:320–34.
- Andrew M, McDonald MC, Dobelbower ES, Yang GM, Clark R, Jacob RY, Kim, et al. Prostate stereotactic body radiation therapy with a focal simultaneous integrated boost: Acute toxicity and dosimetry results from a prospective trial. *Adv Radiat Oncol*. 2019;4:90–5. <https://doi.org/10.1016/j.adro.2018.09.007>.
- Aquibul Hannan S, Salamekh NB, Desai A, Garant MR, Folkert, et al. SABR for high-risk prostate cancer: a prospective multilevel MRI-based dose escalation trial. *Int J Radiat Oncol Biol Phys*. 2022;113:290–301. <https://doi.org/10.1016/j.ijrobp.2021.10.137>.
- Anders Widmark A, Gunnlaugsson L, Beckman C, Thellenberg-Karlsson M, Hoyer M, Lagerlund, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet*. 2019;394:385–95. [https://doi.org/10.1016/S0140-6736\(19\)31131-6](https://doi.org/10.1016/S0140-6736(19)31131-6).
- Alayed Y, Cheung P, Vesprini D, et al. SABR in high-risk prostate cancer: outcomes from 2 prospective clinical trials with and without elective nodal irradiation. *Int J Radiat Oncol Biol Phys*. 2019;104:36–41. [PubMed: 30445172].
- van Ritchell NY, Jiang DB, Fuller A, Loblaw T, Jiang AJ, Katz et al. Stereotactic body radiotherapy for high-risk localized Carcinoma of the prostate (SHARP) Consortium: analysis of 344 prospectively treated patients, International. *J Radiation Oncology\*Biophysics\*Volume 110, Issue 3, 2021, Pages 731-737, ISSN 0360-3016*, <https://doi.org/10.1016/j.jrobp.2021.01.016>.
- Barentsz JO, Richenberg J, Clements R, Choyke P, Verma S, Villeirs G. et al. ESUR prostate Mr guidelines 2012. *Eur Radiol*. 2012;22:746–57. 1007/ s00330-011-2377-y. <https://doi.org/10.1007/s00330-011-2377-y>.
- Salember C, Villeirs G, De Bari B, Hoskin P, Pieters BR, Van Vulpen M, et al. ESTRO ACROP consensus guideline on CT- and MRI- based target volume delineation for primary radiation therapy of localized prostate cancer. *Radiother Oncol*. 2018; 127: 49–61. <https://doi.org/10.1016/j.radonc.2018.01.014>
- Ghadjar P, Zelefsky MJ, Spratt DE, Munck af Rosenschöld P, Oh JH, Hunt M, et al. Impact of dose to the bladder trigone on long-term urinary function after high dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys*. 2014;88:339–44. <https://doi.org/10.1016/j.ijrobp.2013.10.042>.
- Attard G, Murphy L, Clarke NW, Cross W, Jones RJ, Parker CC, et al. Systemic therapy in advancing or metastatic prostate cancer: evaluation of drug efficacy (STAMPEDE) investigators. Abiraterone acetate and prednisolone with or without enzalutamide for high-risk non-metastatic prostate cancer: a meta-analysis of primary results from two randomised controlled phase 3 trials of the STAMPEDE platform protocol. *Lancet*. 2022;399(10323):447–60. [https://doi.org/10.1016/S0140-6736\(21\)02437-5](https://doi.org/10.1016/S0140-6736(21)02437-5). Epub 2021 Dec 23. PMID: 34953525; PMCID: PMC8811484.
- Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol*. 2009;74:1405–18. <https://doi.org/10.1016/j.ijrobp.2008.10.091>.
- Almudena Zapatero, Francisco Valcarcel, Felipe A. Calvo, Rosa Alga's, Amelia Béjar, Javier Maldonado, and Salvador Villa Risk-Adapted Androgen Deprivation and Escalated Three-Dimensional Conformal Radiotherapy for Prostate Cancer: Does Radiation Dose Influence Outcome of Patients Treated With Adjuvant Androgen Deprivation? A GICOR Study *J Clin Oncol* 23:6561-6568, 2005 DOI: 10.1200/JCO.2005.09.662
- Hannan R, Tumati V, Xie XJ, et al. Stereotactic body radiation therapy for low and intermediate risk prostate cancer—results from a multi-institutional clinical trial. *Eur J Cancer*. 2016;59:142–51.
- Alayed Y, Quon H, Ong A, et al. Accelerating prostate stereotactic ablative body radiotherapy: Efficacy and toxicity of a randomized phase II study of 11 versus 29 days overall treatment time (PATRIOT). *Radiother Oncol*. 2020;149:8–13.
- Wee Loon Ong MD, Patrick Cheung MD, Hans Chung MD, William Chu MD, Jay Detsky MD, Stanley Liu MD o Boost or Not to Boost: Pooled Analyses From 2-Fraction SABR Trials for Localized Prostate Cancer, *Int J Radiation Oncol Biol Phys*, Vol. 117, No. 5, pp. 1153–1162, Marvaso G, Gugliandolo SG, Bellerba F, Gandini S, Corrao G, Volpe S et al. Phase II prospective trial Give Me Five short-term high precision radiotherapy for early prostate cancer with simultaneous boost to the dominant intraprostatic lesion: the impact of toxicity on quality of life (AIRC IG-13218). *Med Oncol*. 2020;37(8):74. <https://doi.org/10.1007/s12032-020-01397-3> PMID: 32725443.
- Giorgia Timon, Delia Ciardo, Alessia Bazani, Giulia Marvaso, Giulia Riva, Stefania Volpe, et al. Short-term high precision radiotherapy for early prostate cancer with concomitant boost to the dominant lesion: an interim analysis and preliminary results of Phase II trial AIRC-IG-13218. *British Journal of Radiology*, Volume 91, Issue 1089, 1 September 2018, 20160725, <https://doi.org/10.1259/bjr.20160725>.
- Marvaso G, Gugliandolo SG, Bellerba F, Gandini S, Corrao G, Volpe S, et al. Phase II prospective trial "Give Me Five" short-term high precision radiotherapy for early prostate cancer with simultaneous boost to the dominant intraprostatic lesion: the impact of toxicity on quality of life (AIRC IG-13218). *Med Oncol*. 2020 Jul 28;37(8):74. <https://doi.org/10.1007/s12032-020-01397-3> PMID: 32725443.
- Ian Pollack FM, China E, Bossart D, Kwon MC, Abramowitz C, Lynne M, Jorda B, Marples VN, Patel X, Wu I, Reis MT, Studenski. Javier Casillas, Radka Stoyanova, Phase I trial of MRI-Guided prostate Cancer lattice Extreme Ablative Dose (LEAD) Boost Radiation Therapy. *Int J Radiation Oncology\*Biophysics\*Volume 107, Issue 2, 2020, Pages 305-315, ISSN 0360-3016*, <https://doi.org/10.1016/j.jrobp.2020.01.052>.
- Morris WJ, Tyldesley S, Rodda S, et al. Androgen suppression combined with elective nodal and dose escalated radiation therapy (the ASCENDE-RT trial): an analysis of survival endpoints for a randomized trial comparing a low-dose-rate brachytherapy boost to a dose-escalated external beam boost for high- and intermediate-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2017;98:275–85. [PubMed: 28262473].

## Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.