Fodor *et al. Radiation Oncology* (2025) 20:134
https://doi.org/10.1186/s13014-025-02713-9

Radiation Oncology

STUDY PROTOCOL

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Comprehensive one-day management of prostate cancer patients: PRO-FAST single-fraction ablative, urethral-sparing, HDR-like, robotic SBRT

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Abstract

Background Radiotherapy (RT) is a standard curative treatment for prostate cancer (PCa) and there is growing evidence of the high efficacy of moderate and ultra-hypofractionated RT. Reducing treatment duration to one week or less is a major advance, but very few studies have explored single-fraction therapy. This study evaluates the feasibility, safety, and efficacy of single-fraction stereotactic body RT (SBRT) while delivering the entire procedure in one day, with a potentially high benefit in terms of patient comfort and therapy cost and logistics.

Methods This prospective, non-randomized monocentric trial uses Robotic Radiosurgery (CyberKnife v.7 system) to deliver a single 24 Gy fraction to the prostate (± seminal vesicles) with a "urethral sparing HDR-like" technique, and target tracking. The first phase will enroll 13 PCa patients following Simon's optimal design. Treatment is to be stopped if ≥ 2 patients develop ≥ G3 toxicity (CTCAE v5.0) within a month from RT end; otherwise, 52 more patients will be added, totaling 65. To account for minimal drop-out, 5 extra patients will be enrolled, reaching 70. All procedures are performed in a single day, including fiducial implantation, imaging acquisition, contouring, planning, dosimetry quality control, and treatment. Apart from treatment feasibility in terms of one-month acute toxicity, secondary endpoints include late toxicity, biochemical and clinical control.

Discussion Few others have investigated the 24 Gy single-fraction schedule using different delivery modalities (not including tracking), which has proved to be non-inferior to 5 fraction SBRT. Our approach aims to maintain (and possibly improve) the previously reported acute, subacute and late toxicity as well as disease control, adding evidence in favor of single-fraction delivery. Another significant goal of the study is the demonstration that all the complex treatment procedures can be safely delivered in a single day. This would be especially appealing for patients far from radiotherapy centers and those with work commitments not allowing daily hospital visits. The study of response to RT can also provide useful information about PCa radiobiology. Planned additional analyses may help in better

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assessing the clinical value of PSMA PET/CT in the selection of high-risk patients with true limited disease, and in identifying radiomic features associated to outcome.

Trial registration: The study was prospectively registered at clinicaltrials.gov (NCT 05936736).

Keywords Prostate cancer, Stereotactic body radiotherapy, Single fraction, PSMA PET/CT, T2 weighted MRI, Clinical prospective trial

Background

The main treatments for prostate cancer (PCa) are radical prostatectomy (RP), radiotherapy (RT)- external beam (EBRT) or brachytherapy (BT)-, and active surveillance (AS), with similar 10-year survival, but worse 6-year quality of life after RP [1–3]. AS aims to avoid overtreatment and delay side effects (incontinence, erectile dysfunction, infertility, urinary/rectal toxicity), though patient selection and follow-up remain debated [1, 4]. Even though treatments for early-stage PCa are well established, approaches could still be optimized. NCCN PCa risk groups guide therapy: low-risk (LR) patients have a low risk of dying from PCa, while the risk increases for intermediate (IR), high- (HR) and very high- (VHR) patients without treatment [1, 4].

Five-year biochemical control with EBRT or BT -low-dose rate (LDR, permanent seeds) or high-dose rate (HDR, temporary source)- is ~ 85% [1, 4]. For IR/HR cases, RT is combined with androgen deprivation therapy (ADT) of varying duration [1, 4]. HDR-BT is typically given in 2–4 fractions over 2 days, but single-session regimens are under study [5, 6].

EBRT doses increased from 60 to 66 Gy before the 1990s, when the 2-dimensional (2D) techniques limited the deliverable doses, to over 78 Gy today. PROTECT trial patients received 74 Gy/37 fr, but phase III trials show that doses > 78 Gy improve biochemical control, reduce metastases, and enhance survival [3, 7–12].

Modern high-tech RT machines enabled IGRT (Image Guided RadioTherapy) -IMRT (Intensity Modulated RadioTherapy) and therefore the delivery of Moderate Hypofractionation (MH), which reduces therapy from 8 to 4–5 weeks. Phase III trials confirmed MH is non-inferior to conventional RT, now standard per NCCN/ESMO [1, 4, 13–17]. Radiobiological studies have demonstrated the PCa's low α/β ratio (1.5–2 Gy), which makes it sensitive to high doses per fraction, sparing nearby organs-at-risk (OARs) like rectum and bladder (which have an $\alpha/\beta = 3$–4 Gy) [18–21], although recent reports suggest a low α/β (0.6–2 Gy) also for OARs [22]. New evidence, including phase III trials (such as HYPO-RT-PC and PACE B) supports the non-inferiority of ultrahypofractionation (UH, > 5 Gy/fraction) [23–30]. NCCN approved UH (defined as ≥ 5 Gy/fraction by ASTRO/ASCO/AUA) for all risk groups [1, 31]. Regimens range from 35–50 Gy in up to 7 fractions, including a 4-fraction SBRT mimicking HDR-BT, reducing urethral dose and boosting intraprostatic peaks [25].

A 2018 phase I/II study tested a single 19 Gy SBRT fraction [32], though 19 Gy HDR-BT showed lower 5-year biochemical control (66–73%) [5, 6, 33–35]. A phase II trial comparing 45 Gy/5 fr vs. 24 Gy/1 fr showed similar outcomes [36]. The 24 Gy/1 fr was proposed due to a phase III trial observing that 24 Gy is effective for 5-year metastasis control [37]. Some authors suggest that PCa's dose sensitivity should be considered as a range, not a fixed value, and that the possibility of repopulation should be considered [38–40].

This study aims to assess the feasibility, safety, and efficacy of single-fraction radical PCa SBRT, with all procedures completed in one day. The use of continuous target tracking may further reduce toxicity by allowing smaller margins compared to non-tracking methods [41].

Methods/design

Aim, design, and setting of the study

This is a monocentric single-arm prospective study. It follows Simon's optimal two-stage design [42], enrolling 13 patients in the first phase. Treatment will be halted if two or more patients experience ≥ G3 toxicity and/or biochemical recurrence within a month. Otherwise, the study will proceed to the second phase, enrolling at least 52 additional patients, for a total of 65. Treatment consists of a single 24 Gy fraction using the "urethral sparing HDR-like" technique. The study is based on the hypothesis that if the proportion of patients free from cumulative acute ≥ G3 toxicity (Common Terminology Criteria for Adverse Events, CTCAE v5.0) one month post-treatment is < 85%, the treatment will be discontinued, whereas if > 95%, the treatment will be considered safe. Assuming minimal or no dropouts—given that the primary endpoint is toxicity at one month—five patients additional will be enrolled, bringing the total to 70 patients.

If toxicity remains low and biochemical control is comparable to literature and historical data from our institution, this protocol will be adopted as a standard departmental treatment. The project was registered at clinicaltrials.gov (NCT05936736) and approved by institutional Ethics Committee (identification number 27/INT//2023).

Study population

Participant characteristics and eligibility criteria are summarized in Table 1.

For low-risk patients, prostate multiparametric magnetic resonance imaging (mpMRI) is considered sufficient for staging, as in our institution the radiologist also reports on lymph node status. For favorable-intermediate risk patients, a bone scan could be added. If the patient has unfavorable intermediate, high or very high-risk disease, and up to the first visit has not yet undergone PSMA PET/CT, essential for enrollment in the study, it will be scheduled as soon as possible. A contrast-enhanced MRI will be required in case of suspicious bone lesions on PET. Uroflowmetry is mandatory regardless of the risk group.

Patients who agree to participate in the study and meet the inclusion and exclusion criteria will be scheduled for the treatment within the following two weeks to allow all departments preparation time.

Daily delivery: organizational issues

On the scheduled day, the patient, in the morning before coming to the hospital, gives himself an enema, to ensure an empty rectum. He then begins the cascade procedures at approximately 8:15 AM in the Urology department with the insertion of a urinary catheter to identify the urethra, followed immediately by the insertion of 4 gold fiducials, which serve for tracking. The fiducials are implanted in a Urology Department operating room used for biopsies, by skilled urologists, who have already implanted hundreds of patients. The rules of a sterile fiducial implantation are observed and prophylactic antibiotic administration is not standard practice.

The patient then goes to Radiology, where, after emptying his bladder (removing the cap from the catheter) drinks 250 ml of water and waits about 15 min, to ensure a semi-full bladder. Subsequently, the simulation CT (approximately 10:30) and MRI (approximately 11:00) are performed, the latter only as T2 2D and T2 3D sequences that allow good identification of the fiducials and contouring of the prostate.

After image fusion, the structures are automatically generated using the CyberKnife® (Accuray Incorporated, Sunnyvale, CA, USA) atlas or other validated AI programs, and then manually corrected and approved by the Radiation Oncologist.

At noon, planning begins and continues until the treatment planning is considered satisfactory with respect to PTV planning coverage and critical organ sparing.

Around 2 pm the QA, which lasts 45–60 min, begins; then, after a new bladder emptying/filling procedure, following the same scheme as in the morning, the patient is treated. The treatment session length is approximately 35–40 min, capable of delivering the 24 Gy with continuous tracking.

After treatment end, the urinary catheter is removed, and the patient fills out the study questionnaires before being discharged.

Table 1 Eligibility criteria

Eligibility	Criteria
Inclusion criteria	Histological diagnosis of prostate adenocarcinoma, ISUP Grade Groups 1–5 (Gleason scores from 3 + 3 to 5 + 5) Age ≥ 18 years Signed informed consent Prostate cancer risk group: from low- to very-high risk, according to NCCN 2019 classification Negative lymph nodes confirmed with PSMA PET/CT and/or contrast-enhanced pelvic MRI as per NCCN guidelines, within 3 months for unfavorable intermediate/high-risk patients Clinical M0 confirmed by PSMA PET/CT, bone scan, and/or pelvic MRI, as per NCCN guidelines, required for suspected cases and all unfavorable intermediate/high-risk patients within 3 months Acceptable Uroflowmetry: peak urinary flow ≥ 15 ml/s (preferably), post void residue (PVR) ≤ 50 cc. If lower, uroflowmetry must improve to ≥ 12 ml/s after 3 months of neoadjuvant hormone therapy + alpha-blockers for prostate volume reduction Performance status ECOG ≤ 2 No prior pelvic radiotherapy Other Requirements: ability to complete quality-of-life questionnaires (EORTC QLQ-C30, EORTC QLQ-PR25, IPSS, IIEF-5, EPIC-26)
Exclusion criteria	Severe Systemic Disease Mental or other disorders preventing the patient from providing informed consent History of invasive cancer (except non-melanoma skin cancer) unless disease-free for ≥ 3 years (e.g., Carcinoma in Situ of the Oral Cavity or Bladder) Lymph node involvement (N1) Presence of distant metastases (M1) IPSS Score > 20 Uroflowmetry: peak flow ≤ 11 ml/sec and/or PVR > 100 ml Active urinary or gastrointestinal inflammatory diseases (e.g., Ulcerative Colitis, Crohn's Disease) Overactive bladder Inability to implant fiducial markers Inability or refusal to insert a bladder catheter for treatment planning Inability to undergo MRI for treatment planning Contraindication for hormonal therapy in patients with unfavorable-intermediate, high, or very high-risk disease Noncompliance with the dose constraints specified in the treatment plan

ISUP International Society of Urological Pathology; *NCCN* National Comprehensive Cancer Network; *PSMA PET/CT* Prostate Specific Membrane Antigen Positron Emission Tomography/ Computed Tomography; *MRI* Magnetic Resonance Imaging; *PVR* Post Void Residue; *ECOG* Eastern Cooperative Oncology Group; *EORTC* European Organisation for Research and Treatment of Cancer; *QLQ* Quality of Life Questionnaire; *IPSS* International Prostate Symptom Score; *IIEF* International Index of Erectile Function; *EPIC* Expanded Prostate Cancer Index Composite

Study overview

The research project comprises several tasks:

1. Technological assessment – a pre-clinical investigation of procedure feasibility using an ablative dose delivered with CyberKnife is conducted to establish protocol procedures.
2. Patient enrollment, delivery of the cascade procedure and patient monitoring—patients are enrolled according to the inclusion and exclusion criteria. Maximum acute toxicity at the end of treatment, 1 and 3 months after radioablation is evaluated to modulate the accrual throughout phase I of the study, to verify the toxicity in the first 13 patients.
3. Outcome analysis – local, regional and distant relapse are investigated through PSA trend, new PSMA PET/CT and possible biopsy, in case of biochemical recurrence. Prostate cancer specific survival and overall survival will be calculated at the end of the planned 5-year follow-up.
4. Late toxicity incidence will be registered until the end of follow-up.
5. Radiology and Radiomics tasks—imaging features extracted from pre-radioablation simulation CT/MRI—are quantitatively and semi-quantitatively analyzed to identify imaging markers of radiation response.
6. Identification of clinical and dosimetric factors that influence the outcome.

Phase I study

The project refers to a prospective, non-randomized, monocentric interventional clinical study of a single-fraction radiotherapy treatment for prostate cancer which involves the recruitment of 13 patients for the first phase of the study according to the optimal design of a Simon scheme [42]. This number was derived by considering the hypothesis that the proportion of patients free from cumulative acute toxicity ≥ G3 (CTCAE v5.0 scale) [43] one month after the end of treatment should be < 85% to suspend the treatment and > 95% to consider the treatment as safe. The treatment will be interrupted if ≥ G3 toxicities are recorded within a month in two or more patients.

Phase II study

If fewer than two patients experience ≥ G3 acute toxicity, the study will proceed to the second phase, which requires the enrollment of at least 52 more patients, for a total of 65 patients. The treatment involves the delivery of a single fraction of 24 Gy using the "urethral sparing HDR-like" technique. Assuming a minimal, if any, dropout rate, we plan to enroll an additional 5 patients in total, bringing the total number of patients to 70 (65 required + 5 for potential dropouts).

In the absence of subsequent high toxicity and worsened biochemical control compared to literature data and historical treatments in the Radiation Oncology Department, IRCCS San Raffaele, this prescription will be considered safe and adopted as an alternative to the standard for the department.

Imaging, contouring and treatment planning

All the procedures described above have been designed to be carried out in a single day, from the first to the last, thus, the MRI is acquired in supine position, with a Combifix™ (CIVCO Radiotherapy), only as T2 2D and T2 3D sequences, to quickly identify fiducials and the prostate, shortening the time required for the procedure as much as possible. The purpose is to improve target definition beyond CT resolution. Rigid and/or deformable registration, based on fiducial identification, considering translations and rotations, will be performed between MRI sequences and treatment planning non-contrast enhanced CT images.

Automatic Gross tumor volume (GTV) delineation starts on the CT scan and is corrected after MRI-CT fusion by a radiation oncologist and then double-checked by a second radiation oncologist. The clinical target volume (CTV) coincides with GTV and is expanded by 0.2 cm in all directions except for rectum (0 cm) to create the planning target volume (PTV). Plans are elaborated on the CyberKnife Treatment Planning System (Precision®, Accuray, Sunnyvale, CA), using a non-coplanar and non-isocentric approach. Pre-specified dose constraints for organs at risk and planning objectives for target are based on the conversion for one fraction of the HDR-like prostate SBRT protocol developed by Fuller et al. [25] giving greater weight to urethral sparing, and on stereotactic radiosurgery constraints [44] (see Table 2). Further optimization of dosimetric parameters will be performed as experience increases during the study.

Treatment delivery and follow-up

Radioablation is performed on the same day as the fiducial implantation, simulation and planning, thus also avoiding marker migration. Treatment delivery is carried out using a realtime fiducial-based target tracking (Synchrony®). Total system accuracy of the robotic stereotactic radioablation/ motion tracking has been reported as submillimetric [45, 46], which allows the use of smaller margins compared with conventional linac radiosurgery.

Table 2 Planning objectives and constraints for organs at risk

Organ	Volume	Dose (Gy)
PTV (V 100)	D 0.03 cc	48 Gy (200%)
	V 150%	≥ 1%
Planning-PTV	95%	95%
	95%	90%
Rectum	Dose max (0.03 cc)	ALARA* (≤ 24 Gy)
	D 1	ALARA* (≤ 18 Gy)
	D 50	< 11 Gy
Rectal mucosa	D 0.03 cc	ALARA* (≤ 18 Gy) (75% of prescription dose)
	D 1	≤ 13.5 Gy
	D 50	< 8.5 Gy
Urethra	D 0.03 cc	ALARA* (≤ 22 Gy) (90% of total dose)
	D 1	ALARA* (≤ 21 Gy)
Bladder	D 0.03 cc	ALARA* (≤ 24 Gy) (100% of the prescribed dose)
	D 1	ALARA* (≤ 21 Gy)
	D 50	< 12 Gy
Penile bulb	D 0.03 cc	≤ 100% of prescription dose
	Less than 3 cc	14 Gy
Femoral heads	D 0.03 cc	15 Gy
Bowel loops	D 0.03 cc	12 Gy (small bowel)- 15 Gy (large bowel)

ALARA As low as reasonably achievable (as closed as possible to the desired value, in parenthesis, even if unreachable)

The rigid body created by the fiducials changes as the nearby organs fill, and the robot makes real-time corrections within specific limits for the three spatial directions and rotations (6D). If the limit is exceeded by 1°, the treatment is stopped for medical intervention. The most common situation (though still not observed in single-fraction treatments) is the presence of abdominal gas. Its movement is clearly visible in orthogonal images. Our approach is active, and the gas is eliminated with a catheter- a 2 min procedure.

ADT will be prescribed from the first day of treatment for 6 and 24 months, according to the guidelines for unfavorable intermediate- and high-risk patients, respectively [1]. Patients with unacceptable uroflowmetry may receive 3–6 months of neoadjuvant hormone therapy to improve urinary flow and become eligible for enrollment. Post-treatment radiation side effects as well as quality-of-life questionnaires are regularly collected as follow-up is scheduled on a regular basis over 5 years (at one, three, 6, 12, 18, 24, 36, 48 and 60 months).

Endpoints of the study

Phase I endpoints

Primary endpoint of the phase I study is identification of the impact of single-fraction treatment on ≥ G3 acute toxicity (at one month, CTCAE v5.0), which is an indicator of late toxicity in prostate cancer [47, 48]. A 15% acute ≥ G3 toxicity related to radioablation is considered too high, and the study will be aborted.

Phase II endpoints

Primary endpoint is the evaluation of one-month acute toxicity in the entire patient sample to confirm the first phase results.

Secondary endpoints include biochemical control, biochemical relapse-free survival, local relapse-free survival, regional relapse-free survival (nodal), distant metastasis-free survival, clinical relapse-free survival (local, regional and distant), cancer specific-survival, overall survival, late toxicity, quality-of-life (with EORTC QLQ C30 e QLQ-PR25, IPSS, IEEF-5, EPIC 26 questionnaires) [49–53], modeling of organ movements during treatment, identification of clinical, imaging and laboratory prognostic factors for an aggressive prostate cancer phenotype, evaluation of radiomic features on CT and MRI images in relation to clinical and histological parameters and their predictive role regarding treatment response.

Radiomic features, belonging to four families (fractal, statistical, textural, and morphological), will be extracted from 2D and 2.5D images of simulation CT and MRI images according to the specific recommendation of the International Biomarker Standardization Initiative (IBSI) [54]. Appropriate filters will be applied to the images prior to feature extraction to optimize the radiomic workflow. Feature selection and modeling will be

performed using iterative methods specifically developed for this study. Feature values will be normalized before final analysis using software that includes a statistical module, allowing correlation between the extracted outputs and the CT and MRI parameters of patients enrolled in the study, along with clinical and efficacy data.

Ethical aspects

The study is conducted according to the Declaration of Helsinki/Tokyo and to Good Clinical Practice guidelines. The protocol has been presented to and approved by the ethics committee of the IRCCS San Raffaele Scientific Institute, Milan, Italy. Patients signing the written informed consent for participation in the trial after a complete explanation of the objectives and modalities of the study, will be included.

Discussion

The accumulated knowledge over decades of RT for PCa, along with technological advances in EBRT (from 2D to IGRT-IMRT) and BT, have shown that PCa's biology differs slightly from other tumors, highlighting the need to better understand the dose–response relationship. Over 20 years ago, researchers explored the α/β ratio for PCa, considering tumor repopulation. They found it to be low-lower than nearby organs at risk- supporting higher doses per fraction in fewer sessions [18–21, 55].

Radiation dose escalation and increase in target volumes, as well as the addition of ADT, must undergo a cost–benefit analysis [12, 47, 48, 56–58]. Prospective randomized trials of moderate and ultra-hypofractionation have demonstrated their non-inferiority compared to conventional fractionation [13–17, 29, 30]. The HYPO-RT-PC trial allowed conformal techniques and used wide margins (7 mm) and demonstrated the non-inferiority of ultra-hypofractionation in terms of 5-year biochemical control (84% in both arms) and long-term toxicity [29]. PACE-B showed SBRT in 5 fractions is non-inferior to conventional IMRT, with similar GI toxicity and slightly higher ≥ G2 GU toxicity (26.9% vs. 18.3%, $p < 0.001$) [30]. This small increase is acceptable given the major benefit of reducing treatment from nearly eight weeks to just one, helping patients and healthcare systems. Meta-analyses of numerous prospective phase II studies, including thousands of patients, nonetheless demonstrate very limited long-term toxicity [27, 28].

The PROTECT trial demonstrated that after an initial decline genitourinary and erectile quality of life after RT returns to levels similar to active monitoring (AM) [3]. In contrast, quality of life after surgery remains significantly worse at 2 and 6 years [3]. In an era in which therapeutic alternatives are selected also on the basis of quality of life, and surgery has a significant impact even in its modern, robotic form [59], PACE-A trial demonstrated that SBRT was associated with less patient-reported urinary incontinence and sexual dysfunction, and slightly more bowel toxicity than prostatectomy [60].

Therefore, SBRT, which is even more convenient than MHRT, could represent the future of PCa RT. The continuous reduction of margins—and consequently of treatment volumes—thanks to the increasing precision with IGRT, and real-time tracking during treatment, is expected to further reduce toxicity [61, 62]. We therefore have a rationale for pushing the ultra-hypofractionation further, and the question is: how short can this treatment be? Based on its low alpha/beta ratio, PCa is probably the one that is most suitable for single-fraction treatments.

In 2018, the ONE-SHOT multicenter phase I/II trial started, using a 19 Gy single fraction SBRT [32]. However, a 19 Gy single fraction of HDR BT obtained a biochemical control of only 66–73% at 5 years—below the 82–85% target for PCa RT [5, 33–35]. Beyond the limitations of dose equivalence models between BT and EBRT, LDR and HDR BT have established a reference for disease control and toxicity outcomes, which are a reference regardless of technique. Thus, the results of 19 Gy single-fraction HDR BT caused concern.

Greco et al. published the results of a phase II randomized trial comparing 45 Gy in 5 fractions over 5 days versus 24 Gy in 1 fraction, showing similar biochemical control and toxicity [36]. Previously, Zelefsky et al. phase III trial had already shown that 24 Gy is needed for effective 5-year local control of PCa metastases [37]. Further confirmation of the feasibility of delivering a single-fraction high dose, ablative treatment (SDRT) comes from the ABRUPT study, which, using the same SDRT approach as the Greco et al. trial, reported no ≥ G3 side effects with 18 months of follow-up [63]. Interestingly, all these results were obtained without applying any tracking technique, suggesting that better results may still be expected once intra-fraction motion is counteracted through continuous tracking, as included in our approach [41, 61, 62].

It was observed that the 4-year biochemical relapse-free survival of the PROSINT 24-Gy SDRT (77%) is similar to the 73.5% 5-year rate reported after 19-Gy high-dose-rate (HDR) single-fraction BT (SFBT) [64]. However, almost 2/3 of PROSINT patients were unfavorable IR, vs 30% in the SFBT study [5]. In the past decade, since AS became the primary recommendation for LR patients—who previously accounted for nearly 60% of those undergoing surgery or RT—the risk profile has shifted toward higher-risk cases. This shift presents two issues. First, the use of ADT- which was not allowed in the PROSINT trial and is generally not prescribed alongside BT for LR and favorable IR patients–would be necessary for unfavorable IR

and HR cases [1]. Second, the POP-RT study showed that RT targeting the pelvic lymph nodes improves biochemical disease control and reduces recurrences and distant metastases [56]. However, this effect is significant only in younger patients (≤66 years) [56].

Long-term results from the GETUG-AFU 18 study further show that dose escalation leads to improved disease outcomes and increased survival [12], supporting the long-term results of BT, and leading Prada to increase the prescription dose from 19 to 20.5 Gy [5, 6].

The SBRT schedule of 24 Gy in 1 fraction to the whole prostate has an equivalent 2 Gy dose (EQD2) of 174.86 Gy (assuming an α/β for PCa of 1.5 Gy), while the 38 Gy/4 fractions schedule corresponds to an EQD2 of 119.43 Gy. These doses are not equivalent for the linear-quadratic model, though its accuracy is limited at very high doses. A single dose equivalent to 38 Gy/4 fractions would be around 19–20 Gy, as used in the European "ONE SHOT" trial [32]. However, HDR BT studies—despite good results with 38 Gy/4 fractions—have failed to achieve high long-term biochemical control with a single 19 Gy fraction [5, 6, 33–35, 64–67]. The likely reason is that fractionated treatments allow for cumulative DNA damage (single and double-strand breaks), which must be compensated with higher doses in single-fraction schedules. Dose-escalation studies (19 vs 19.5 vs 20 Gy) have addressed this shortcoming [64–67]. A single 20.5 Gy dose shows acceptable toxicity, but 6-year biochemical control is only 82%, which, although comparable to historical conformal RT or BT, may be suboptimal for LR and IR PCa in an era allowing dose escalation [6]. Prada's group estimated that to achieve 90% 5-year biochemical control in LR and IR disease, at least 22 Gy in a single fraction would be needed [68].

Based on these findings, also taking into account the biologic aggressiveness of the disease, the radiosensitivity, the expected pattern of relapse and the integration with ADT, we have designed a study delivering a single-fraction dose expected to be sufficient for disease control in most patients [37, 68]. The HDR-like approach will allow for dose escalation within the target volume, similar to a BT treatment [25]. Fuller's method will be modified to prioritize urethral sparing, ensuring that doses do not exceed those used in BT to date [6]. Additionally, selection of patients with unfavorable IR, HR, and VHR disease will be based on negative PSMA PET/CT findings. Although not a perfect tool, it may be adequate to identify patients with clinically significant disease burden, who would instead be directed to an alternative treatment including WPRT [69]. Given the current distribution of patients treated with RT, with few LR, the final sample should allow us to understand whether the selection tool was suitable for the characterization of a disease with good prognosis, as previous research seems to suggest [69].

For many patients, the duration of treatment with CFRT—or even MHRT, lasting 2 and 1 month respectively—is cumbersome, and significantly impacts quality of social life, due to travel distance to the treatment center or work commitments. Treatments delivered in 4–7 fractions have shortened the overall treatment time to 1–2 weeks, but the gold standard remains LDR BRT, where the implant is performed in a single procedure and the patient stays in the hospital for just over 24 h. By removing needles—and therefore anesthesia—from the workflow, an ideal treatment could potentially be delivered in a single day.

The modern concept of precision medicine must maximize the use of advanced technology while also becoming cost-effective. The aim of our study is to streamline all steps of a complex stereotactic treatment—from the implantation of fiducial markers, enabling sub-millimetric delivery accuracy through real-time tracking, to the precise identification of the target and organs at risk, including structures within the target, such as the urethra. This can be achieved by selecting only the imaging sequences truly necessary for accurate fusion and delineation during simulation. At the same time, we will establish planning models and dose constraints to render the treatment both tolerable and effective. Demonstrating the feasibility of this approach could increase patient interest in a modern, high-precision treatment option, ensuring good quality of life (which will be verified, for further confirmation). Modern and promising radiomic analyses will be included in the study, along with the attempt to identify clinical and dosimetric differences between responders and non-responders, contributing to a better understanding of radiobiologic effects and behavior of the irradiated PCa. The ultimate goal is to identify those tumors which achieve complete response and those needing more extensive treatment.

With the aim of reducing the number of fractions, several other studies, some already mentioned above, are recruiting patients to study schedules shorter than the classic 4–5 fractions (see Table 2). Besides PROSINT, ONE SHOT and ABRUPT, the only single-fraction trials, there are studies that have tested the two and three fractions.

Clinicaltrials.gov ID	Title	Status	Treatment	Primary objective	Patient's nr	Study start	Estimated completion date
Single fraction trials							
NCT02570919	Phase II Study of Ultra-high-dose Hypofractionated vs. Single-dose Image-Guided Radiotherapy for Prostate Cancer (PROSINT)	Completed	IGRT 24 Gy single dose Vs IGRT 45 Gy in 5 fractions of 9 Gy delivered in 5 consecutive days	5-year adverse events measured by Common Toxicity Criteria for Adverse Effects v4.0	30	01/09/2015	31/12/2017
NCT04147806	A Pilot Study of Ultra-High-Dose Hypofractionated or Single-Dose Radiotherapy for Intermediate Risk Prostate Cancer (PROSINT)	Active, not recruiting	IGRT 24 Gy single dose single fraction IGRT vs IGRT 45 Gy in 5 fractions of 9 Gy in five consecutive days	Comparison of treatment related adverse events as measured by Common Toxicity Criteria for Adverse Effects v4.0 over a 5 year time frame	30	01/08/2016	13/07/2026
NCT03294889	ONE-SHOT Trial—Ultra-hypofractionated Single-dose SBRT for Prostate Cancer	Recruiting	Ultra-hypofractionated single-fraction SBRT with urethra-sparing with image-guidance and intra-fractional control motion with the Calypso® system 19 Gy in a single fraction to the whole prostate gland ± proximal seminal vesicles 17 Gy in a single fraction to the urethra planning-risk volume (PRV)	Clinical performance: Acute GU and GI G ≥ 3 toxicity during the first 3 months according to CTCAE v.4.03 (Phase I). Three-year biochemical relapse free survival (bRFS and its 97.5% one-sided confidence interval (CI) determined with KM method. Expected value: 96% if not included in this interval, the efficacy of the experimental treatment will be questioned). (Phase II)	45	01/09/2017	01/10/2030
NCT04004312	Single fraction SBRT for prostate cancer	Recruiting	Phase I study of radical 19 Gy single fraction SBRT in low- and favorable intermediate-risk prostate cancer with placement of the SpaceOAR hydrogel prior to treatment	To assess 3 month acute gastro-intestinal and genito-urinary toxicity	12	07/11/2018	20/12/2026

Clinicaltrials.gov ID	Title	Status	Treatment	Primary objective	Patient's nr	Study start	Estimated completion date
NCT04035642	Phase II Study of Single-Dose Image-Guided Radiotherapy (SDRT) for Prostate Cancer (PROSINT II)	Recruiting	IGRT 24 Gy Single dose	Number of patients with treatment-related adverse events assessed by CTCAEv4.0 over 5 years Concentration of serum PSA at 5 years Changes in PSA biochemical parameter measurements (Phoenix Definition) at 5 years	200	01/06/2019	06/2026
NCT04831983	ABlative Radiotherapy (for) Unfavorable Prostate Tumors (ABRUPT)	Recruiting	Image-guided, volumetric modulated radiotherapy (IGRT-VMAT) in a single session (SDRT) of 21 Gy to the whole gland with a simultaneous boost of 24 Gy to the macroscopic PI-RADS driven (4–5) tumour(s). ADT will be prescribed concomitantly, as per standard of care	To assess treatment related GI and GU toxicity with CTCAE v5.0 scale at 60 months	30	15/04/2021	01/04/2029
NCT05936736	24 Gy in One Fraction Urethral-sparing "HDR Like" SBRT for Prostate Cancer (PROFAST)	Recruiting	24 Gy in one fraction, urethral sparing HDR like SBRT for patients with localized prostate cancer delivered with Robotic radiosurgery and tracking (negative PSMA PET/CT for unfavorable intermediate and high-risk patients	Incidence of acute toxicity G ≥ 3 as maximum toxicity within a month of the end of SBRT, using CTCAE v5.0 scale	70	08/11/2023	05/2030
Two fraction trials							
NCT03588819	Stereotactic MRI-Guided Radiation for Localized Prostate Cancer (2SMART)	Unknown status	26 Gy in 2 fractions to the prostate and DIL dose of up to 32 Gy in 2 fractions of MR-guided SABR delivered 1 week apart	To determine the prostate-specific quality of life (QOL) using the Expanded Prostate Cancer Index Composite (EPIC) at 5 years	30	23/04/2018	23/04/2024

Clinicaltrials.gov ID	Title	Status	Treatment	Primary objective	Patient's nr	Study start	Estimated completion date
NCT06027892	Two-fraction Versus Five-fraction Stereotactic Radiotherapy for Localized Prostate Cancer (SABR-Dual)	Recruiting	Two-fraction SBRT to 27 Gy, with the option to boost a high-grade lesion to 30 Gy vs 5-fraction SBRT to 40 Gy, with the option to boost a high-grade lesion to 45 Gy	Five-year biochemical relapse-free survival	562	29/12/2022	12/2032
NCT05864196	Two Fraction Prostate SBRT With DIL SIB	recruiting	Two-fraction SBRT with an MRI directed, dominant intraprostatic lesion, simultaneous integrated boost (SIB) based on genomic classification in the treatment of low and intermediate risk prostate cancer	Number of ≥ GU and GI G2 toxicities based on the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 up to 5 years after the treatment	80	17/07/2023	06/2026
NCT05616650	Focal Therapy With Stereotactic Body Radiation Therapy (SBRT) for Patients With a Single Prostate Tumor	Recruiting	Focal SBRT to the tumor focus within the prostate, to a dose of 26 Gy in two fractions with the second fraction performed within 8 days of the first fraction, with response assessed by biopsy and imaging, including 18F-DCFPyL PET/CT	The primary objective is the pathologic complete response rate on biopsy at two years. This will be defined by a negative biopsy at 2 years post-treatment	42	19/10/2023	01/12/2028
NCT05600400	Improving Sexual Quality of Life-Randomized Trial of Two vs Five MRI Guided SABR Treatments for Prostate Cancer (iSMART)	Recruiting	Two weekly fractions of 13.5 Gy vs Five every other day fractions of 8 Gy	Prostate Cancer Patient's Quality of Life Function will be measured to determine from baseline to 5 years beyond treatment Expanded Prostate Cancer Index Composite questionnaires will be scored and analyzed	144	01/03/2024	06/2029

Clinicaltrials.gov ID	Title	Status	Treatment	Primary objective	Patient's nr	Study start	Estimated completion date
NCT06518226	Two-Fraction Ultrahypofractionated Radiotherapy With Focal Boost for Intermediate Risk, Localized Prostate Cancer (TURBO)	Recruiting	Ultrahypofractionated MRgRT to the prostate in 2 fractions of 12 Gy, with a focal boost of 13.5 Gy to the GTV, administered over the course of 8 days vs MRgRT to the prostate in 5 fractions of 7.25 Gy to the prostate without focal boost, administered over the course of 16–18 days	Incidence of acute G ≥ 2 GU physician-reported toxicity scored using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 scale. Scores will be retrieved from the hospital information system at 90 days after treatment	160	28/03/2024	01/02/2031
NCT06638541	Dose dE-eScalaTion IN prostATe radIOtherapy usiNg an MR-Linac in 2 Fractions (DESTINATION 2)	Recruiting	Arm 1 (Uniform dose) will receive 27 Gy in 2 fractions to the whole prostate + seminal vesicles (SV), the CTV, with 0 mm CTV-PTV margin. Arm 2 (De-escalated dose) will use two dose levels: The benign prostate (on MRI) will receive 20 Gy in 2 fractions with a 0 mm PTV margin The intraprostatic tumour mass(es) as seen on MRI will receive 27 Gy in 2 fractions. A 4 mm GTV-PTV margin will be added to the MR visible tumour to form PTV 27 Gy	To describe the absolute risk and relative risk reduction of acute GU toxicity (CTCAE v5) when delivering de-escalated two fraction prostate SBRT compared to uniform dose two fraction prostate SBRT for intermediate risk prostate cancer, at 12 weeks	54	01/11/2024	01/11/2026
NCT06835725	Phase II Randomized Trial of 2 Versus 5 Fraction Prostate Stereotactic Ablative Radiotherapy for Intermediate Risk Prostate Cancer (ADAPT-25)	Not yet recruiting	27 Gy delivered to the prostate gland (CTV) in 2 fractions over 2 weeks vs 40 Gy delivered to the prostate gland (CTV) in 5 fractions over 2 weeks	Freedom from G ≥ 2 GU and GI toxicity at 4 years	100	30/04/2025	30/04/2033
Three fraction trials							

Clinicaltrials.gov ID	Title	Status	Treatment	Primary objective	Patient's nr	Study start	Estimated completion date
NCT06117059	The PRECISION Study: 3 Fractions of Prostate SBRT and RayPilot HypoCath Image Guidance (PRECISION)	Recruiting	3 fractions of prostate SBRT with image guidance using the RayPilot HypoCath system given on 3 consecutive days	Number of GU and GI ≥ G2 toxicities based on the RTOG and Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 at 12 weeks after treatment	100	01/11/2024	01/11/2027
NCT02623647	A Phase I-II Study on Stereotactic Body Radiotherapy in 3 Fractions for Low/Int Risk Prostate Cancer (eHYPO)	Unknown status	A single-arm, nonrandomized SBRT, 40 Gy for 3 fractions	G ≥ 2 GU toxicity according to CTCv4.0 (Hematuria- a disorder characterized by laboratory test results that indicate blood in the urine; Urinary incontinence—a disorder characterized by inability to control the flow of urine from the bladder.) at 1 year	150	11/2015	03/2021
NCT05851547	Dose Escalation For INtraprostatic LEsions (DEFINE)	Recruiting	Stereotactic body radiotherapy to 27 Gy in 3 fractions to uninvolved regions of the prostate gland on alternating days and up to 39 Gy in 3 fractions to mpMRI-defined intraprostatic lesions, with concurrent/ adjuvant androgen deprivation therapy (6 months for intermediate risk, 24 months for high risk)	Number of patients with G ≥ 2 GU and GI toxicity as measured by CTCAEv5.0 and RTOG radiation toxicity scale up to 2 years	54	23/11/2023	06/2028

Optimal dose and fraction numbers have not yet been established, and dose-escalation/ fractions de-escalation studies continue to be designed. The single dose is currently being investigated in the phase I dose escalation study testing 19 Gy. So far, there have been several phase II studies whose results remain limited in terms of number of cases and median follow-up time, but published data show the feasibility of the treatment.

Our study project will add (to the promising but still limited body of literature) new knowledge about the use of single-fraction SBRT for PCa patients, reflecting the current real-world case distribution, with numerous patients at unfavorable IR and HR, but with disease confined to the prostate, selected through PSMA PET/CT imaging. For the first time, to our knowledge, the delivery will be carried out under a tracking guide, permitting a safe reduction of the applied margins. The most ambitious goal is to perform, in the selected patients, all phases needed for treatment delivery in a single day, demonstrating the feasibility of the treatment in a short time frame, similarly to LDR BT, but without the need for anesthesia and hospitalization of the patient and without radiation protection issues. This approach could be particularly useful for patients located at significant

distances from the treatment centers or those with work commitments that cannot be postponed. It will also be important to identify the predictive factors (of disease, dosimetric and radiomic), for the best selection of patients who can undergo this treatment. Once knowledge and expertise have been consolidated, this approach might be offered to suitable patients. In addition, single-fraction prostate SBRT might be offered in oligometastatic patients, alongside the treatment of synchronous distant metastases, in order to treat all the active disease sites in a short treatment time frame, without interfering with necessary systemic treatments.

Abbreviations

ADT	Androgen deprivation therapy
3D-CRT	Three-dimensional conformal RT
bRFS	Biochemical relapse-free survival
BRT	Brachytherapy
CFRT	Conventional fractionated radiotherapy
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical tumor volume
ECOG	Eastern Cooperative Oncology Group
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	Expanded prostate cancer index composite
GTV	Gross tumor volume
HYPO-RT-PC	Hypofractionated radiotherapy for prostate cancer
LDR	Low-dose-rate
LHRH	LH-Releasing Hormone
IGRT	Image Guided Radiotherapy
IMRT	Intensity modulated RT
IPSS	International Prostate Symptom Score
IIEF	International Index of Erectile Function
MHRT	Moderately hypofractionated radiotherapy
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
PCa	Prostate cancer
PET/CT	Positron Emission Tomography/Computed Tomography
PTV	Planning tumor volume
PSA	Prostate Specific Antigen
PSMA	Prostate-specific Membrane Antigen
RT	Radiotherapy
SBRT	Stereotactic body RT
SDRT	Single-dose ablative radiotherapy
SRS	Stereotactic radiosurgery
VMAT	Volumetric-modulated arc-therapy
WPRT	Whole pelvis radiotherapy

Author contributions

A F, Prof. N DM, P M, C F, Prof. C B, R M and Prof. A C contributed to the study conception and design. The first draft of the manuscript was written by A F and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Data availability

The data that support the findings of this study (anonymized individual participant data) are available on request from the corresponding author to researchers who provide a methodologically sound proposal. Requests made to the corresponding author (AF) will be evaluated by the Lombardy Territorial Ethics Committee 1.

Declarations

Ethics approval and consent to participate

All procedures performed in the present study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies using animals performed by any of the authors. This study has been approved by the Institutional Scientific Board of the IRCCS San Raffaele Scientific Institute (registration number 27/INT//2023). All participants will sign an Informed Consent.

Consent for publication

Not applicable.

Competing interests

Miriam Torrisi and Roberta Tummineri received a speaker honorarium from Accuray Inc. independently from the current work. Laura Giannini received a research fellowship from AIRC: IG 25951-project "Toward clinical use of PET in selecting patients with pancreatic cancer for local treatment intensification". Miriam Torrisi received a research grant from the Next Generation EU (PNRR-MCNT2-2023-12378239), with a project entitled "Radio-immunotherapy in solid tumors" (CUP Code: C43C24000320005). The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript. The remaining authors declare no conflicts of interest.

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Received: 21 May 2025 Accepted: 11 August 2025
Published online: 27 August 2025

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