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Complete List of Authors:	Mathier, Etienne; Inselspital University Hospital Bern, Department of Radiation Oncology Althaus, Alexander; Inselspital University Hospital Bern, Department of Radiation Oncology Zwahlen, Daniel; Kantonsspital Winterthur, Department of Radiation Oncology Lustenberger, Jens; University Hospital Basel, Department of Radiation Oncology Zamboglou, Constantinos; German Oncology Center, European University Cyprus, Limassol, Cyprus De Bari, Berardino; Réseau hospitalier neuchâtelois, Department of Radiation Oncology Aebersold, Daniel M.; Inselspital University Hospital Bern, Department of Radiation Oncology Zilli, Thomas; Oncological Institute of Southern Switzerland, EOC, Bellinzona, Switzerland, Department of Radiation Oncology; Università della Svizzera italiana Shelan, Mohamed; Inselspital University Hospital Bern, Department of Radiation Oncology
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HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II trial.

Etienne Mathier[1#], Alexander Althaus[1#], Daniel R. Zwahlen[2], Jens Lustenberger[3], Constantinos Zamboglou[4], Berardino De Bari[5], Daniel M. Aebersold [1], Thomas Zilli[6*], Mohamed Shelan [1*]

[#]Equal contribution as first authors

[*]Equal contribution as last authors

Affiliations

[1]Department of Radiation Oncology, Bern University Hospital and University of Bern, Inselspital, Freiburgstrasse 18, 3010 Bern

[2] Department of Radiation Oncology, Kantonsspital Winterthur, Winterthur, Switzerland

[3] Department of Radiation Oncology, University Hospital of Basel, Basel, Switzerland

[4] German Oncology Center, European University Cyprus, Limassol, Cyprus

[5]Department of Radiation Oncology, Réseau hospitalier neuchâtelois, La Chaux-de-Fonds, Switzerland

[6] Department of Radiation Oncology, Oncological Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; Università della Svizzera Italiana, Lugano, Switzerland

* Correspondence:

Mohamed Shelan, MD

Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

Tel: +41 31 632 26 32

Email: mohamed.shelan@insel.ch

ABSTRACT

Background: Despite radical prostatectomy (RP) and radiotherapy (RT) being established treatments for localized prostate cancer, a significant number of patients experience recurrent disease. While conventionally fractionated RT is still being used as a standard treatment in the postoperative setting, ultra-hypofractionated RT has emerged as a viable option with encouraging results in patients with localized disease in the primary setting. In addition, recent technological advancements in RT delivery and precise definition of isolated macroscopic recurrence within the prostate bed using Prostate-Specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) and multiparametric magnetic resonance imaging (mpMRI) allow the exploration of ultra-hypofractionated schedules in the salvage setting using five fractions.

Methods: In this single-arm prospective phase II multicenter trial, 36 patients with node-negative prostate adenocarcinoma treated with radical prostatectomy (RP) at least 6 months before trial registration, tumor stage pT2a-3b, R0-1, pN0, or cN0 according to the UICC TNM 2009 and evidence of measurable local recurrence within the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months, will be included. The patients will undergo focal ultra-hypofractionated salvage RT (sRT) with 34 Gy in 5 fractions every other day to the site of local recurrence in combination with 6 months of Androgen deprivation therapy. The primary outcome of this study is biochemical relapse-free survival at 2 years. Secondary outcomes include acute side effects (until 90 days after the end of RT) of grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE version 5), progression-free survival, metastasis-free survival, late side effects, and the quality of life (based on EORTC QLQ-C30, QLQ-PR25).

Discussion: We propose that focal ultra-hypofractionated sRT is a valid treatment concept to conventional sRT because of its possible advantageous therapeutic ratio combined with the reduced number of fractions and the precisely defined target volume sparing the adjacent organs at risk.

Trial registration: ClinicalTrials.gov NCT05746806. Registered on February 28, 2023. Cantonal Ethics Committee Number: KEK-BE 2022-01026.

Strengths of this study:

First prospective clinical trial investigating the efficacy and safety of ultra-hypofractionated Salvage radiotherapy to isolated local recurrence within the prostate bed after radical prostatectomy.

Both mpMRI and PSMA PET/CT are used to precisely identify the site local recurrence and radiotherapy planning.

Limitations of this study:

Not a randomized controlled trial, and the results will be regenerated in a larger clinical trial.

Study status: Open for accrual.

Funding: Debiopharm AG and Berger-Janser Stiftung

Keywords: ultra-hypofractionated salvage radiotherapy; SRT; local recurrence; prostatic cancer.

1 Background

Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones for the treatment of localized prostate cancer (PC) [1]. However, around 30% to 60% of patients undergoing RP will develop recurrent disease [2, 3]. Various large randomized controlled studies have shown the effectiveness of postoperative RT in men who have a high risk of local recurrence following RP, such as pT3 tumor or positive resection margins [4–8]. In the era of high-sensitivity prostate-specific antigen (PSA) and prostate-specific membrane antigen-positron emission tomography and computed tomography (PSMA-PET/CT) as a standard staging examination in recurrent PC, new data suggest a comparable oncological results if patients are treated early with salvage RT (sRT) compared to immediate adjuvant RT [9–12]. Nevertheless, the aforementioned trials and those involving patients receiving sRT due to macroscopic tumor recurrence in the prostate bed were conducted with conventionally fractionated RT, typically 2 Gy per fraction [4–12].

Recently, ultra-hypofractionated RT has been utilized as a valid therapeutic option in patients with low- or intermediate-risk as a definitive treatment. Published data with fair follow-up periods demonstrating excellent biochemical control management with a favorable toxicity profile [13–20]. Moreover, the evidence on ultra-hypofractionated in high-risk individuals is emerging, and many significant studies have reported favorable findings [21–26]. Ultra-hypofractionation is used to treat patients with PC due to its low α/β value which is thought to be around 1.5 Gy [27, 28]. It is anticipated that increasing the dose per fraction would increase the therapeutic ratio and, thus, the potential tumor control. Nevertheless, considering the low toxicity rates reported [29–37], using moderate hypofractionation in the postoperative setting with a daily RT dose of up to 3 Gy per fraction does not seem to corroborate this concern. However, the evidence on postoperative ultra-hypofractionated RT to the prostate bed is still in its early stages.

Further improvement in the oncological outcomes can be expected through technological developments in RT delivery and precise targeting of the local relapses in the prostate bed. A sRT using an ultra-hypofractionated schedule delivered in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric magnetic resonance imaging (mpMRI) in combination with short-term androgen deprivation therapy for 6 months, may represent a valid treatment strategy to improve the therapeutic ratio in these patients (shorter overall treatment time, better sparing of organs at risk while delivering higher biological-equivalent dose into the target volume).

The main objective of this prospective single-arm trial is to explore the efficacy and safety of ultra-hypofractionated sRT delivered in 5 fractions to the site of local recurrence within the prostate bed after RP, where mpMRI and PSMA PET/CT are used to precisely identify the local recurrence.

2 METHODS

The Hypo Focal sRT Trial protocol was constructed using the SPIRIT reporting guidelines [29].

2.1 Regulatory Approval

Following permission from the regional ethics committees (KEK-BE 2022-01026), the research is registered with ClinicalTrials.gov (NCT05746806) and the Swiss National Clinical Trials Portal. Both the sponsor-investigator and the trial statistician have given their approval to the protocol version 3.0 (dated 11.11.2022), and they hereby confirm that they will conduct the study in accordance with the protocol, the most recent version of the World Medical Association Declaration of Helsinki, the ICH-GCP guidelines, and the requirements that are legally applicable in their respective jurisdictions.

2.2 Study Population

- Inclusion criteria:

1. Before registration and before any trial-specific procedures, written informed consent in accordance with ICH/GCP rules is required.

2. Minimum age to register is eighteen years old.

3. Performance level 0-1 according to WHO.

4. Lymph node negative adenocarcinoma of the prostate treated with RP at least 6 months before trial registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009.

5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, biopsy confirmation is recommended.

6. Patient must have non-metastatic (N0, M0) disease, as defined by a lack of nodal or distant metastases seen on PSMA PET/CT scan.

7. Patients are required to have non-castrate levels of serum testosterone (more than or equal to 50 ng/dL).

8. Patients must not have had bilateral orchiectomy, LHRH agonists, antiandrogens, or any combination of these in the past.

9. Absence of any psychological, family, sociological, or geographic situation that would make it difficult for the patient to adhere to the research protocol and follow-up plan; the patient should be informed of these factors before registering for the trial.

- Exclusion criteria:

1. PSA levels (> 0.4 ng/mL) that persist 4–20 weeks after RP.
2. Previous diagnosis of hematologic or primary solid malignancy during the preceding three years previous to registration, except for curatively managed localized non-melanoma skin cancer.
3. Use of substances known to alter PSA levels, such as androgen deprivation therapy and any kind of androgen suppression medication, within four weeks of the commencement of the trial treatment phase.
4. Bilateral hip prosthesis.
5. Co-morbidities that are severe or active and that are likely to have an effect on whether or not sRT is advisable.
6. Treatment with any experimental treatment or involvement in a clinical trial within the last thirty days (with the exception of concurrent participation in the biobank research, which is permitted) is required for eligibility to register.

2.3 Patient and public involvement

There was no patient or public participation in the research design, methodology, conduction, or reporting of this trial.

2.4 Recruitment and screening

Authorized investigators are the only ones who will be able to register patients for the study. The following tasks need to be completed before registering for the study:

- Fill in the patient screening (used for monitoring potentially eligible patients and will be destroyed after the end of the accrual period. Screening list is not a part of the CRFs), enrolment and identification lists.
- Check the eligibility criteria.
- Obtain signed and dated written informed permission from the patient before performing any protocol-specific procedure in accordance with ICH/GCP and local regulations.

- Patients must complete the pre-treatment of quality-of-life assessment per protocol.

Only electronic case report forms (eCRF) will be used. The use of worksheets is allowed if the copies of the templates are documented in the trial master file (TMF). The used worksheets must be kept with the patient charts. Registration is done via the Internet 'https://secutrial.insel.ch'. SecuTrial (interactive Systems) will be used as a database. In case of problems, investigators can phone the study coordinator from Monday through Friday. It is advised that investigators get in touch with CTU Bern's data management if they have any technical issues. Sites must deliver a copy of the finished personnel list to the Sponsor in order to acquire permission for online registration/data input. The online database's login information will be supplied to approved users.

2.5 Study design and sample size

This is a single-arm, prospective, phase II multicenter study. According to the published prospective trials and retrospective series reporting the outcome of the normo-fractionated sRT, we define biochemical relapse-free survival at 2 years of 60% as poor and of 80% as the promising outcome that would justify further investigation [30–33]. We will therefore test the null hypothesis that the biochemical relapse-free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%, not taking into account patients lost to follow-up. The null hypothesis will be rejected if at least 27 patients show biochemical relapse-free survival at 2 years. We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects (grade 3 or higher) is larger than 27%; the proportion observed would be tested using one-sample binomial exact tests with a one-sided alpha of 5%. **Figure 1** shows a summary of the study design and schedule.

2.6 Outcomes

- Primary outcome

- Biochemical relapse-free survival at 2 years.

- Secondary outcome

- Acute side effects (until 90 days after the end of RT) of grade 3 or higher based on CTCAE v5
- Progression-free survival
- Metastasis-free survival
- Late side effects
- Quality of life (based on EORTC QLQ-C30, QLQ-PR25)

2.7 Study Intervention

2.6.1. Pre-registration imaging

Within 3 months prior to registration, either PSMA PET/CT is mandatory to exclude regional or distant metastasis. Both ^{18}F- and ^{68}Ga-PSMA tracers are allowed. A mpMRI of the prostate bed acquired within 3 months before registration is mandatory to define the extension of local recurrence.

2.6.2. Radiation treatment (SBRT)

2.6.2.1. Patient's positioning, immobilization, data acquisition and simulation:

Determining the gross tumor volume (GTV), the planned target volume (PTV), and the essential structures requires a treatment-planning CT scan with the patient in the same position as during treatment. The patients will be placed in the supine position for the entire process. Support for the knees and legs is strongly advised. On a flat table, each patient will be placed in the treatment position while being immobilized by a unique device. It is advised that patients be treated and scanned while having a comfortably full bladder. For prostate bed RT, it is advised to have an empty rectum. An example of a bladder and rectal protocol: An empty rectum is provided by using a rectal enema ± 60 minutes before planning CT. After emptying the rectum and bladder, the patient is asked to drink the amount of 500-750 ml of water. The planning CT is then performed after ca. 40 minutes. The patient repeats the bladder filling procedure during the entire treatment course. An endorectal balloon can be used for repositioning purposes as per local institutional standards.

Radiopaque fiducial markers (mandatory for robotic-based treatments) may be implanted in the prostate bed one week before the planning CT scan at the discretion of the treating center. During the planning and performance of the treatment, the patient's location will be reproduced employing skin markings

and orthogonal laser beams. The pelvis should be scanned during the treatment planning CT scan, at least from the lower portion of the second lumbar vertebra (L2) to the lower half of the ischial tuberosities. The CT scan must cover the full target volume and all organs at risk (OAR). A CT slice should be no thicker than 2 mm. On every CT slice that shows the GTV, PTV, and OAR, these structures must be highlighted. Morphological and topographical information given by clinical examination, mpMRI and PET/CT must be integrated to delineate the target volumes. Rigid or deformable co-registration is allowed.

2.6.2.2. Volumes:

2.6.2.2.1 Definition of target volumes (refer to Appendix 2 & 3):

- **The Gross Tumor Volume of the suspicious local recurrence (GTV)** is defined by the physician as all known gross disease *before any treatment* as defined by the CT/MRI images and PET scan using rigid or deformable fusion and/or clinical information.
- **The Planning Target Volume (PTV)** will provide the GTV a margin to account for daily treatment setup variations and internal motion brought on by breathing or movement during treatment. The PTV should surround the GTV with a 5 mm margin on all sides.

2.6.2.2.1 Organs at risk (OAR):

The delineation of the **OAR** should be done following the RTOG guidelines; the normal pelvis atlas on the RTOG/NRG Oncology website provides examples of normal tissue contours [34].

The bladder is defined by its external wall, with a thickness of 5 mm delineated on each slide, from the dome to the bladder neck and the start of the vesicourethral anastomosis (VUA).

The VUA and distal urethra are delineated from the bladder neck to the distal urethra using mpMRI sequences, and a 2-mm isotropic margin is added around these structures to create a planning organ at risk volume (PRV).

The rectum is defined by its external wall, with a thickness of 5 mm from the recto-sigmoid junction to ischial tuberosities.

The femoral heads are delineated from the top of the hip joint to the small trochanter, while the bowel bag is delineated from the most inferior small or large bowel loop to 1 cm above the planning target volume (PTV) for coplanar beam plans, or more if non-coplanar beams or tomotherapy plans are used.

It is suggested that dose constraints be adhered to; however, if this is not practicable, the dose per fraction or target coverage may be adjusted to comply with the constraint. **Table 1** shows the dose constraints for OARs.

Table 1: Dose constraints for OARs.

Organ at risk	Dose Constraint	Aim
Rectal Wall	V18.1 Gy V29 Gy V36 Gy	< 50% < 20% < 1 cc
Bladder Wall	V18.1 Gy V 37 Gy	< 40% < 10 cc
PRV_VUA and distal Urethra	V36 Gy	< 1 cc
Femoral heads	V14.5 Gy	< 5%
Penile bulb	V29.5 Gy	< 50%
Bowel	V18.1 Gy V30 Gy	< 5 cc < 1 cc

2.6.2.2.3 Treatment techniques

It is required to apply rotating techniques or intensity-modulated RT (IMRT). Only dosimetry produced by inversed treatment planning is, by definition, regarded as IMRT. Step-and-Shoot, Sliding-Window, and Volumetric Modulated Arc therapy (VMAT), as well as MRI-guided radiation therapies (MRIdian® or Elekta Unity®), may be employed for performing IMRT. Treatment with Cyberknife® is allowed.

2.6.2.2.4 Dose computation

- Any treatment planning system that can compute 3D doses using a convolution strategy will be used. Any combination of coplanar or non-coplanar fields tailored to give the required dosage while limiting radiation to the normal tissue OAR may be used to treat the PTV. The best conformal plan will be created in compliance with volume definitions by using 3D planning to identify field configurations. A treatment strategy will be developed for each patient based on

a volumetric dose analysis, which includes DVH analyses of the PTV and crucial OAR. Each field must be treated every other day.

- PTVs should be drawn in all relevant planes. The dosage distribution should be shown at least in the plane containing the beam axes.
- The Dose Volume Histogram (DVH) produces a 3-dimensional representation of dose distribution. The dosage to the PTVs and other normal tissues at risk will be assessed using DVH.

2.6.2.2.5 Equipment and tool

- Linear accelerator, tomotherapy and Cyberknife are allowed.

2.6.2.2.6 Dose prescription

A total dose of 34 Gy (80% of the maximal dose) will be delivered in 5 fractions and fractions every second day (NTD2Gy 80 Gy α/β=1.5Gy for tumor control and 66.6 Gy α/β=3Gy for late toxicity). Treatment will be prescribed to the periphery of the target (80% of the dose (=34Gy), should cover 90% of the PTV) covering the PTV. A maximal dose of 40 Gy is allowed to GTV. The priority will be given with respect to dose constraints over PTV coverage.

2.6.2.2.7 Treatment Verification

Daily patient setup must be done using laser alignment to reference labels on the patient's skin. Daily cone-beam CT setup and online patient position modification are required. If numerous targets are irradiated with different isocenters, a CBCT must be performed before each treatment for each isocenter. According to institutional policy, patient immobilization devices may be employed.

2.6.2. Androgen deprivation therapy

For a total of six months, each patient should take a three-monthly formulation of an LHRH-agonist or antagonist. Prevention with an antiandrogen is indicated for at least 5 days before the initial injection of the agonist in the case of an LHRH-agonist flare and should not be sustained for more than 15 days of the first-month duration.

- Androgen deprivation therapy (ADT) should start no later than the 1st SBRT fraction and no earlier than 2 weeks before the start of RT.
- Palliative ADT should not be initiated for biochemical progression until clinical progression has been demonstrated. In the event of symptom progression, palliative ADT is required. In the event

of asymptomatic clinical progression, men who are well-informed are permitted to delay ADT until symptomatic progression occurs (EAU 2023 guidelines) [35]. Generally, we would only begin ADT in asymptomatic individuals if traditional imaging confirmed clinical progression. As a result, we would not advocate initiating ADT for PET-positive lesions that do not seem suspicious on conventional imaging (CT/MRI/bone scintigraphy).

- ADT-related toxicity should be managed, according to Nguyen et al. [36].

2.8 Study procedures

The study procedures and the schedule of assessments are presented in **Table 2.**

Table 2: Schedule of assessments

Required investigation	Inclusion		Treatment	1 Month after RT	3 Months after RT	6 Months after RT	Every 6 Months till the end of 2nd year after RT, then once per year till 60 months
	Within 12 weeks prior to registration	Within 2 weeks prior to registration			Within 2 weeks prior to registration		
Eligibility Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x		x	x	x	x
Biochemistry (Blood Samples) *							
PSA		x		x	x	x	x
Testosterone		x		x	x	x	x
Radiology							
PSMA PET	x						
MRI	x						
Radiotherapy							
Treatment planning			x				
Record Planning results			x				
Adverse Events							
Baseline toxicity		x					
Acute toxicity			x	x	x		
Late toxicity						x	x
EORTC QoL questionnaire							
QLQ-C30		x		x	x	x	x

QLQ-PR25		x		x	x	x	x

2.9 Planned Analysis

For descriptive statistics, the categorical variables will be presented as frequency and percentage, the normally distributed continuous variables will be presented as mean and standard deviation, and the non-normally distributed continuous variables will be presented as median and interquartile range.

The time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with a 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.

The probability of biochemical relapse-free survival and metastasis-free survival will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be fit to assess the effects of treatment and baseline clinical and pathologic features (such as PSA, PSA doubling time, Gleason score etc.) on biochemical relapse-free survival and metastasis-free survival).

2.10 Handling of missing data and drop-outs.

All registered patients should have comprehensive baseline data. In repeated-measures analysis, all patients who have had at least one outcome evaluation may be evaluated. Based on the missing at-random technique, models will automatically adjust for missing data. We will undertake multiple imputations for patients who have no outcome data at all. Patient drop-outs will be accounted for in the time-to-event analysis via censoring.

3 Discussion

External beam RT is a well-established treatment for organ-confined prostate cancer, with comparable cure rates to radical prostatectomy [37]. Hypofractionation employs a higher dose-per-fraction while reducing the number of fractions offering a clinical benefit in terms of tumor control in tumors with a low alfa/beta ratio (e.g. prostate cancer) and favorable toxicity, allowing for higher patient comfort [38]. Based on the results of ten prior randomized trials, there is compelling evidence suggesting that moderatehypofractionation RT is not inferior to standard normofractionation RT schedules as a definitive

treatment for primary PC[39]. This evidence led to the integration of moderate hypofractionation schedules into the list of valid treatment options in the NCCN guidelines [40]. In addition, recent advancements in the field of RT, including IMRT/rotational techniques, image-guided RT (IGRT), and stereotactic RT (SBRT), have permitted the gradual integration of ultra-hypofractionation in the treatment of localized PC. SBRT for PC has generated adequate data in terms of tumor control, patient-reported quality of life, and minimal toxicity [14, 16, 25] to support its introduction in clinical practice. In addition, the prostate cancer-working group of the German Society of Oncology (DEGRO) and the NCCN Guidelines approve the use of SBRT in the treatment of localized low and intermediate-risk prostate cancer and propose its use in clinical trials for patients with the localized high-risk disease [41, 42].

The evidence of ultra-hypofractionation has recently been supported by two randomized studies (HYPO-RT-PC [25], PACE-B trial [14]), which compare its usage to conventional fractionation. Nevertheless, only HYPO-RT-PC provided information on the outcomes of long-term tumor and toxicity control. A randomized systematic review and meta-analysis of phase 3 studies evaluating SBRT with normo- and hypo-fractionated regimens were published in 2020. It was determined that the ultra-hypofractionated regimens had comparable 5-year disease-free survival outcomes, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, in comparison to hypofractionated regimens and conventional RT [43]. In 2022, the toxicity outcome of the PACE B Trial was published, showing no significant differences between the five fractions of SBRT and conventional RT [44].

The use of moderate hypofractionation is gaining more popularity as a standard treatment in the postoperative setting [45]. Retrospective and prospective single-arm studies support a safe toxicity profile and promising biochemical control rates with hypofractionation [45]. According to newly released findings from the phase III clinical study NRG-GU003 evaluating hypofractionated postoperative prostate bed RT(HYPORT) to conventional post-prostatectomy RT for men with prostate cancer, treatment with HYPORT did not cause a rise in patient-reported GI or genitourinary (GU) toxicity for study subjects, with a comparable biochemical disease control at the 2-year follow-up [46].

Prakish et al. [47] did a theoretical feasibility study of SBRT following RP depending on the NTCP (Normal Tissue Complication Probability) model, using individuals who had been managed with conventional EBRT for biochemical recurrence after prostatectomy. The goal was to show that SBRT could be used safely and effectively in this clinical situation. A dose of 30 Gy was delivered to the PTV in five fractions, translating to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5 Gy, in accordance with RTOG standards to define postprostatectomy volumes. To predict the probability of late rectal and/or bladder toxicity, the NTCP model was used. According to the NTCP model, the average

incidence of grade ≥ 2 late rectal toxicity was assessed to be 0.28%, and that of late grade 2 toxicity on the bladder neck was determined to be as low as 0.00013%, while the average incidence of late urinary symptoms exacerbation was calculated to be 4.81 %. The author's conclusion is that employing SBRT after surgery looks viable and may provide a safe, practical therapeutic alternative for individuals in both the adjuvant and salvage following biochemical failure, taking into account the limitations of the NTCP model.

Sampath et al. examined the use of stereotactic dose-escalated RT on prostate beds in a prospective phase 1 research, which revealed a crude rate of biochemical control of 42% in the overall population [48]. Patients received care using dose fractionation regimens of 35 Gy, 40 Gy, and 45 Gy in five fractions each. The authors emphasized that raising the dosage to 45 Gy was possible without increasing the number of adverse events but that there was no observed improvement in PSA control when compared to 40 Gy in 5 fractions. Similarly, a recent propensity score study comparing salvage SBRT and conventional RT for macroscopic prostate bed recurrence revealed similar bRFS and PFS rates across the two modalities. On the other hand, a reduced incidence of toxicity was verified for patients receiving focal stereotactic sRT compared to conventionally fractionated sRT, with acute GI and GU adverse events recorded in 4.4% against 44.4% ($p < 0.001$) and 28.9% against 46.7% ($p = 0.08$) of participants, and late GI and GU side effects reported in 0% versus 13.3% ($p = 0.04$) and 6.7% versus 22.2% ($p = 0.03$) of patient populations, respectively [49]. The authors argue that salvage SBRT is a desirable substitute for conventional sRT in this situation due to the approach's favorable therapeutic ratio and the less number of required fractions. Additionally, the prospective phase 2 SCIMITAR trial reported the quality of life and toxicity outcome of 100 patients who received postoperative ultra-hypofractionated SBRT delivered in 5 fractions [50]. Acute and late grade 2 GU toxicities were both 9%, while acute and late grade 2 GI toxicities were 5% and 0%, respectively. Three patients had grade 3 toxicity (n = 1 GU, n = 2 GI) [50].

The expected results from the Hypo-Focal sRT trial will provide the first prospective evidence for the focal hypofractionated RT in the salvage setting and can be used as a basis for a large multicenter phase 3 trial. In addition to the assumed improvement in efficacy and toxicity profile due to precise customization of the treatment target volumes, the application of a focal hypofractionated RT is expected to achieve cost-effectiveness benefits. Due to the very short treatment course (unlike conventional RT treatments, which can take up to 7 weeks), hypofractionated focal sRT leads to greater patient convenience and comfortability.

Study status:

Open and currently accruing since February 20, 2023.

The approximate recruitment will be completed by March 2024.

Abbreviations:

AE	Adverse Event
ADC	Apparent diffusion coefficient
ADT	Androgen deprivation therapy
ASR/DSUR	Annual Safety Report / Development Safety Report
ASTRO	American Society for Radiation Oncology
ASCO/AUA	American Society of Clinical Oncology/ American Urological Association
ASTRO	American Society for Therapeutic Radiology and Oncology
BASEC	Business Administration System for Ethical Committees
bRFS	Biochemical relapse-free survival
CA	Clinical approval
CBCT	Cone Beam CT
CEC	Clinical ethics committee
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical trials unit
CTV	Clinical target volume
DCE	Dynamic contrast enhancement
DEGRO	German Society of radiation oncology
DFS	Disease free survival
DRE	Digital rectal examination
DVH	Dose-volume histogram
DWI	Diffusion-weighted imaging
EAU	European Association of Urology

EORTC	European Organisation for Research and Treatment of Cancer
18F	Fluorine-18
FADP	Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)
FOPH	Federal Office of Public Health
18F-DCFPYL	Pylarify - piflufolastat Fluorine-18
eCRF	Electronic Case Report Form
68Ga	Gallium-68
GCP	Good Clinical Practice
GTV	Gross tumor volume
GI	Gastrointestinal
GU	Genitourinary
HR	Hazard ratio
HRA	Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)
ICH	International Conference on Harmonisation
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
LHRH	Luteinizing hormone-releasing hormone
LHRHa	Luteinizing hormone-releasing hormone agonist
MFS	Metastasis free survival
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCI	National cancer institute
NTCP	Normal tissue complication probability
NTD	Normalized total dose
NCCN	National comprehensive cancer network
OAR	Organs at risk
OS	Overall survival
OSEM	Ordered subset expectation maximization
PET/CT	Positron electron computed tomography
PFS	Progression-free survival
PI	Principal Investigator
PRV	Planning organ at risk volume

PSA	Prostate-specific antigen
PSF	Point-spread-function
PSMA	Prostate-specific membrane antigen
PTV	Planning target volume
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SAE	Serious Adverse Event
SBRT	Stereotactic body radiotherapy
SI	Signal intensity
sRT	Salvage radiotherapy
TLC	Thin layer chromatography
TMF	Trial master file
TNM	Tumor Nodes Metastases
TOF	Time of flight
UICC	Union internationale contre le cancer
UPN	Unique Patient Number
VUA	Vesicourethral anastomosis
WHO	World health organization
QLQ	Quality of life questionnaire
QoL	Quality of life

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Funding and publication: Debiopharm AG and Berger-Janser Stiftung support this clinical trial financially. The funders did not and will not play any part in the study design, collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication. The results will be published in the name of the Hypo-FOCAL-SRT trial in a peer reviewed international journal on behalf of all collaborators. All presentations and publications, including abstracts, relating to the trial must be authorized by the Hypo-FOCAL-SRT trial steering committee. Participating centers should ask for the approval of the trial steering committee to use any data related to the patients registered in the trial.

Availability of data and materials: The dataset analyzed during the current study is available from the corresponding author on reasonable request.

Declarations

Ethical approval, protocol registration, and consent to participate: The study was got a permission from the regional ethics committees (KEK-BE 2022-01026), the research is registered with ClinicalTrials.gov (NCT05746806) and the Swiss National Clinical Trials Portal. Written, informed consent to participate is and will be obtained from all participants before participating in the trial.

Consent for publication: Not applicable.

Conflict of Interest: The authors declare that they have no competing interests.

Figure ligands:

Figure 1: Summary of the study design and schedule.

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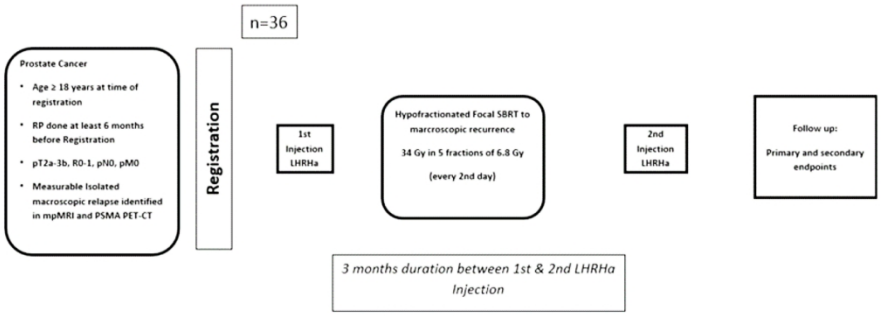

Figure 1: Summary of the study design and schedule.

159x65mm (300 x 300 DPI)

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	Reporting Item		Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1: 1-3	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4: 86-87	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4: 86-87	
Protocol version	#3	Date and version identifier	4: 88-89	

Funding	#4	Sources and types of financial, material, and other support	19: 393-400	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19: 389-392	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	19: 389-392	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19: 389-392	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19: 389-392	
Introduction			3: 52-82	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3: 52-82	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3: 52-82	
Objectives	#7	Specific objectives or hypotheses	3: 52-82	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3: 80 -82	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4: 86-91	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 5: 92-130	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11: 178-286	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7-11: 178-286	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-11: 178-286	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11: 178-286	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7: 169: 177	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6: 151-163	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6: 151-163	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 6: 131-149	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	Not controlled trial
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	Not controlled trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	Not controlled trial
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	Not controlled trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A	Not controlled trial
Methods: Data collection, management, and analysis				

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5, 6: 131-149	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5, 6: 131-149	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13: 290-303	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13: 290-303	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13: 290-303	

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13: 305-310	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5: 131-149	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A	No interim analysis
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7: 173	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	No auditing
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4: 86-91	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	4: 86-91	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4: 94-95	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	This is not an ancillary study
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5, 6: 131-149	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19: 387-390	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5, 6: 131-149	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6: 159-163	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19: 393-400	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19: 393-400	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A	No public access to the full protocol
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	19: 404-407	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	This is not an ancillary study

It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-

BMJ Open

HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II Study - Clinical Trial Protocol.

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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Oncology
Keywords:	Radiation oncology < RADIOTHERAPY, Prostatic Neoplasms, Urological tumours < ONCOLOGY

HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II Study - Clinical Trial Protocol.

Etienne Mathier[1#], Alexander Althaus[1#], Daniel R. Zwahlen[2], Jens Lustenberger[3], Constantinos Zamboglou[4], Berardino De Bari[5], Daniel M. Aebersold [1], Matthias Guckenberger[6], Thomas Zilli[7*], Mohamed Shelan [1*]

[#]Equal contribution as first authors

*Equal contribution as last authors

Affiliations

[1]Department of Radiation Oncology, Bern University Hospital and University of Bern, Inselspital, Freiburgstrasse 18, 3010 Bern

[2] Department of Radiation Oncology, Kantonsspital Winterthur, Winterthur, Switzerland

[3] Department of Radiation Oncology, University Hospital of Basel, Basel, Switzerland

[4] German Oncology Center, European University Cyprus, Limassol, Cyprus

[5]Department of Radiation Oncology, Réseau hospitalier neuchâtelois, La Chaux-de-Fonds, Switzerland

[6] Department of Radiation Oncology, University Hospital Zürich, University of Zurich, Switzerland

[7] Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; Facoltà di Scienze Biomediche, Università della Svizzera Italiana, Lugano, Switzerland

* Correspondence:

Mohamed Shelan, MD

Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

Tel: +41 31 632 26 32

Email: mohamed.shelan@insel.ch

ABSTRACT

Introduction: Despite radical prostatectomy (RP) and radiotherapy (RT) being established treatments for localized prostate cancer, a significant number of patients experience recurrent disease. While conventionally fractionated RT is still being used as a standard treatment in the postoperative setting, ultra-hypofractionated RT has emerged as a viable option with encouraging results in patients with localized disease in the primary setting. In addition, recent technological advancements in RT delivery and precise definition of isolated macroscopic recurrence within the prostate bed using Prostate-Specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) and multiparametric magnetic resonance imaging (mpMRI) allow the exploration of ultra-hypofractionated schedules in the salvage setting using five fractions.

Methods and analysis: In this single-arm prospective phase II multicenter trial, 36 patients with node-negative prostate adenocarcinoma treated with radical prostatectomy (RP) at least 6 months before trial registration, tumor stage pT2a-3b, R0-1, pN0, or cN0 according to the UICC TNM 2009 and evidence of measurable local recurrence within the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months, will be included. The patients will undergo focal ultra-hypofractionated salvage RT (sRT) with 34 Gy in 5 fractions every other day to the site of local recurrence in combination with 6 months of Androgen deprivation therapy. The primary outcome of this study is biochemical relapse-free survival at 2 years. Secondary outcomes include acute side effects (until 90 days after the end of RT) of grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE version 5), progression-free survival, metastasis-free survival, late side effects, and the quality of life (based on EORTC QLQ-C30, QLQ-PR25).

Ethics and dissemination: The study has received ethical approval from the Ethics Commission of the Canton of Bern (KEK-BE 2022-01026). Academic dissemination will occur through publications and conference presentations.

Trial registration: ClinicalTrials.gov NCT05746806. Registered on February 28, 2023.

Strengths and limitations of this study:

- Innovative trial evaluating focal SBRT combined with short-term ADT for treating isolated local recurrence after RP.
- Treatment planning is precisely defined based on PSMA PET imaging and mpMRI.
- Potential for improved efficacy and toxicity profile of salvage radiotherapy.
- Non-randomized trial; further research will be required.
- Small sample size.

Study status: Open for accrual.

Funding: Debiopharm AG and Berger-Janser Stiftung

Keywords: ultra-hypofractionation; SBRT; local recurrence; prostate cancer; salvage radiotherapy.

BACKGROUND

Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones for the treatment of localized prostate cancer (PC) [1]. However, around 30% to 60% of patients undergoing RP will develop recurrent disease [2, 3]. Various large randomized controlled studies have shown the effectiveness of postoperative RT in men who have a high risk of local recurrence following RP, such as pT3 tumor or positive resection margins [4–8]. In the era of high-sensitivity prostate-specific antigen (PSA) and prostate-specific membrane antigen-positron emission tomography and computed tomography (PSMA-PET/CT) as a standard staging examination in recurrent PC, new data suggest comparable oncological results if patients are treated early with salvage RT (sRT) compared to immediate adjuvant RT [9–12]. Nevertheless, the aforementioned trials and those involving patients receiving sRT due to macroscopic tumor recurrence in the prostate bed were conducted with conventionally fractionated RT, typically 2 Gy per fraction [4–12].

Recently, ultra-hypofractionated RT, using usually >5 Gy or higher per fraction, was assessed as a valid therapeutic option in patients with low- or intermediate-risk as a definitive treatment. Published data with fair follow-up periods demonstrated excellent biochemical control management with a favorable toxicity profile [13–20]. Moreover, the evidence on ultra-hypofractionated in high-risk individuals is emerging, and many significant studies have reported favorable findings [21–26]. Ultra-hypofractionation is used to treat patients with PC due to its low α/β value which is thought to be around 1.5 Gy [27, 28]. It is anticipated that increasing the dose per fraction would increase the therapeutic ratio and, thus, the potential tumor control. Nevertheless, considering the low toxicity rates reported [29–37], using moderate hypofractionation in the postoperative setting with a daily RT dose of up to 3 Gy per fraction does not seem to corroborate this concern. However, the evidence on postoperative ultra-hypofractionated RT to the prostate bed is still in its early stages.

Further improvement in the oncological outcomes can be expected through technological developments in RT delivery and precise targeting of the local relapses in the prostate bed. A sRT using an ultra-hypofractionated schedule delivered in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric magnetic resonance imaging (mpMRI) in combination with short-term androgen deprivation therapy for 6 months, may represent a valid treatment strategy to improve the therapeutic ratio in these patients (shorter overall treatment time, better sparing of organs at risk while delivering higher biological-equivalent dose into the target volume).

The main objective of this prospective single-arm trial is to assess the efficacy and safety of ultra-hypofractionated sRT delivered in 5 fractions to the site of local recurrence within the prostate bed with target delineation based on PSMA PET and MRI.

METHODS/DESIGN

The Hypo Focal sRT Trial protocol was constructed using the SPIRIT reporting guidelines [29]. Following permission from the regional ethics committees (KEK-BE 2022-01026), the research is registered with ClinicalTrials.gov (NCT05746806) and the Swiss National Clinical Trials Portal. Both the sponsor-investigator and the trial statistician have given their approval to the protocol version 3.0 (dated 11.11.2022).

Study Population

- Inclusion criteria:

1. Before registration and before any trial-specific procedures, written informed consent in accordance with ICH/GCP rules is required.

2. Minimum age to register is eighteen years old.

3. Performance level 0-1 according to WHO.

4. Lymph node negative adenocarcinoma of the prostate treated with RP at least 6 months before trial registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009.

5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, biopsy confirmation is recommended.

6. Patient must have non-metastatic (N0, M0) disease, as defined by no evidence of nodal or distant metastases seen on PSMA PET scan.

7. Patients must have a testosterone level > 50 ng/dL.

8. Patients must not have had bilateral orchiectomy, LHRH agonists, antiandrogens, or any combination of these in the past.

9. Absence of any psychological, family, sociological, or geographic situation that would make it difficult for the patient to adhere to the research protocol and follow-up plan; the patient should be informed of these factors before registering for the trial.

- Exclusion criteria:

1. PSA levels (> 0.4 ng/mL) that persist 4–20 weeks after RP.
2. Previous diagnosis of hematologic or primary solid malignancy during the preceding three years previous to registration, except for curatively managed localized non-melanoma skin cancer.
3. Use of substances known to alter PSA levels, such as androgen deprivation therapy and any kind of androgen suppression medication, within four weeks of the start of the trial treatment phase.
4. Bilateral hip prosthesis.
5. Co-morbidities that are severe or active and that are likely to have an effect on whether or not sRT is advisable.
6. Treatment with any experimental treatment or involvement in a clinical trial within the last thirty days (with the exception of concurrent participation in the biobank research, which is allowed) is required for eligibility to register.

Study design and sample size

This is a single-arm, prospective, phase II multicenter study. According to the published prospective trials and retrospective series reporting the outcomes of the normo-fractionated sRT, we define biochemical relapse-free survival at 2 years of 60% as poor and of 80% as the promising outcome that would justify further investigation [30–33]. We will therefore test the null hypothesis that the biochemical relapse-free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%, not taking into account patients lost to follow-up. We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects (grade 3 or higher) is larger than 27%; the proportion observed would be tested using one-sample binomial exact tests with a one-sided alpha of 5%. **Figure 1** shows a summary of the study design and schedule.

Outcomes

Primary outcome

- Biochemical relapse-free survival at 2 years

Secondary outcome

- Acute side effects (until 90 days after the end of RT) of grade 3 or higher based on CTCAE v5
- Progression-free survival
- Metastasis-free survival
- Late side effects
- Quality of life (based on EORTC QLQ-C30, QLQ-PR25)

Study Intervention

Pre-registration imaging

Within 3 months prior to registration, PSMA PET/CT is mandatory to exclude regional or distant metastasis. Both ^{18}F- and ^{68}Ga-PSMA tracers are allowed. A mpMRI of the prostate bed is required within 3 months before registration is mandatory to define the extension of local recurrence.

Radiation treatment (SBRT)

Patient's positioning, immobilization, data acquisition and simulation:

Determining the gross tumor volume (GTV), the planned target volume (PTV), and the essential structures requires a treatment-planning CT scan with the patient in the same position as during treatment. The patients will be placed in the supine position for the entire process. Support for the knees and legs is strongly advised. On a flat table, each patient will be placed in the treatment position while being immobilized by a unique device. It is advised that patients be treated and scanned while having a comfortably full bladder. For prostate bed RT, it is advised to have an empty rectum. An example of a bladder and rectal protocol: An empty rectum is provided by using a rectal enema ± 60 minutes before planning CT. After emptying the rectum and bladder, the patient is asked to drink the amount of 500-750 ml of water. The planning CT is then performed after 40 minutes. The patient repeats the bladder filling procedure during the entire treatment course. An endorectal balloon can be used for repositioning purposes as per local institutional standards.

Radiopaque fiducial markers (mandatory for robotic-based treatments) may be implanted in the prostate bed one week before the planning CT scan at the discretion of the treating center. During the planning and performance of the treatment, the patient's location will be reproduced employing skin markings

and orthogonal laser beams. The pelvis should be scanned during the treatment planning CT scan, at least from the lower portion of the second lumbar vertebra (L2) to the lower half of the ischial tuberosities. The CT scan must cover the full target volume and all organs at risk (OAR). A CT slice should be no thicker than 2 mm. On every CT slice that shows the GTV, PTV, and OAR, these structures must be highlighted. Morphological and topographical information given by clinical examination, mpMRI and PET/CT must be integrated to delineate the target volumes. Rigid or deformable co-registration is allowed.

Treatment Volumes:

Definition of target volume (refer to Supplementary material 1):

- **The Gross Tumor Volume of the suspicious local recurrence (GTV)** is defined by the physician as all known gross disease *before any treatment* as defined by the CT/MRI images and PET scan using rigid or deformable fusion and/or clinical information.
- **The Planning Target Volume (PTV)** will provide the GTV a margin to account for daily treatment setup variations and internal motion brought on by breathing or movement during treatment. The PTV should surround the GTV with a 5 mm margin on all sides.

Organs at risk (OAR):

The delineation of the **OAR** should be done following the RTOG guidelines; the normal pelvis atlas on the RTOG/NRG Oncology website provides examples of normal tissue contours [34].

The bladder is defined by its external wall, with a thickness of 5 mm delineated on each slide, from the dome to the bladder neck and the start of the vesicourethral anastomosis (VUA).

The VUA and distal urethra are delineated from the bladder neck to the distal urethra using mpMRI sequences, and a 2-mm isotropic margin is added around these structures to create a planning organ at risk volume (PRV).

The rectum is defined by its external wall, with a thickness of 5 mm from the recto-sigmoid junction to ischial tuberosities.

The femoral heads are delineated from the top of the hip joint to the small trochanter, while the bowel bag is delineated from the most inferior small or large bowel loop to 1 cm above the planning target volume (PTV) for coplanar beam plans, or more if non-coplanar beams or tomotherapy plans are used.

It is suggested that dose constraints be adhered to; however, if this is not practicable, the dose per fraction or target coverage may be adjusted to comply with the constraint. **Table 1** shows the dose constraints for OARs.

Table 1: Dose constraints for OARs.

Organ at risk	Dose Constraint	Aim
Rectal Wall	V18.1 Gy V29 Gy V36 Gy	< 50% < 20% < 1 cc
Bladder Wall	V18.1 Gy V 37 Gy	< 40% < 10 cc
PRV_VUA and distal Urethra	V36 Gy	< 1 cc
Femoral heads	V14.5 Gy	< 5%
Penile bulb	V29.5 Gy	< 50%
Bowel	V18.1 Gy V30 Gy	< 5 cc < 1 cc

Treatment techniques

It is required to apply rotating techniques or intensity-modulated RT (IMRT). Only dosimetry produced by inversed treatment planning is, by definition, regarded as IMRT. Step-and-Shoot, Sliding-Window, and Volumetric Modulated Arc therapy (VMAT), as well as MRI-guided radiation therapies (MRIdian® or Elekta Unity®), may be employed for performing IMRT. Treatment with Cyberknife® is allowed.

Dose prescription

A total dose of 34 Gy (80% of the maximal dose) will be delivered in 5 fractions and fractions every second day (NTD2Gy 80 Gy α/β=1.5Gy for tumor control and 66.6 Gy α/β=3Gy for late toxicity). Treatment will be prescribed to the periphery of the target (80% of the dose (=34Gy), should cover 90% of the PTV) covering the PTV. A maximal dose of 40 Gy is allowed to GTV. The priority will be given with respect to dose constraints over PTV coverage.

Androgen deprivation therapy

For a total of six months, each patient will be treated with a three-monthly formulation of an LHRH-agonist or antagonist. Prevention with an antiandrogen is indicated for at least 5 days before the initial injection of the agonist in the case of an LHRH-agonist flare and should not be sustained for more than 15 days of the first-month duration.

- Androgen deprivation therapy (ADT) should start no later than the 1st SBRT fraction and no earlier than 2 weeks before the start of RT.
- Palliative ADT should not be initiated for biochemical progression until clinical progression has been demonstrated. In the event of symptom progression, palliative ADT is required. In the event of asymptomatic clinical progression, men who are well-informed are permitted to delay ADT until symptomatic progression occurs (EAU 2023 guidelines) [35]. Generally, we would only begin ADT in asymptomatic individuals if traditional imaging confirmed clinical progression. As a result, we would not advocate initiating ADT for PET-positive lesions that do not seem suspicious on conventional imaging (CT/MRI/bone scintigraphy).
- ADT-related toxicity should be managed, according to Nguyen et al. [36].

Study procedures

The study procedures and the schedule of assessments are presented in **Table 2.**

Table 2: Schedule of assessments

Required investigation	Inclusion		Treatment	1 Month after RT	3 Months after RT	6 Months after RT	Every 6 Months till the end of 2nd year after RT, then once per year till 60 months
	Within 12 weeks prior to registration	Within 2 weeks prior to registration			Within 2 weeks prior to registration		
Eligibility Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x		x	x	x	x
Biochemistry (Blood Samples) *							
PSA		x		x	x	x	x

Testosterone		x		x	x	x	x
Radiology							
PSMA PET	x						
MRI	x						
Radiotherapy							
Treatment planning			x				
Record Planning results			x				
Adverse Events							
Baseline toxicity		x					
Acute toxicity			x	x	x		
Late toxicity						x	x
EORTC QoL questionnaire							
QLQ-C30		x		x	x	x	x
QLQ-PR25		x		x	x	x	x

Planned Analysis

For descriptive statistics, the categorical variables will be presented as frequency and percentage, the normally distributed continuous variables will be presented as mean and standard deviation, and the non-normally distributed continuous variables will be presented as median and interquartile range.

The time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with a 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.

The probability of biochemical relapse-free survival and metastasis-free survival will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be fit to assess the effects of treatment and baseline clinical and pathologic features (such as PSA, PSA doubling time, Gleason score etc.) on biochemical relapse-free survival and metastasis-free survival).

Study status

Open and currently accruing since February 20, 2023.

The approximate recruitment will be completed by October 2024.

Patient and public involvement

- Patients were not involved in the idea conception of this trial.
- Patients were not involved in the design of this study nor in recruitment of the study.

Ethics and dissemination

The study has been submitted and approved by ethics commission of Canton of Bern. A written informed consent will be obtained from the study participants. Academic dissemination will occur through publication and confer- ence presentations.

DISCUSSION

External beam RT is a well-established treatment for organ-confined prostate cancer, with comparable cure rates to radical prostatectomy [37]. Hypofractionation employs a higher dose-per-fraction while reducing the number of fractions offering a clinical benefit in terms of tumor control in tumors with a low alfa/beta ratio (e.g. prostate cancer) and favorable toxicity, allowing for higher patient comfort [38]. Based on the results of ten prior randomized trials, there is compelling evidence suggesting that moderate hypofractionation RT is not inferior to standard normofractionation RT schedules as a definitive treatment for primary PC[39]. This evidence led to the integration of moderate hypofractionation schedules into the list of valid treatment options in the NCCN guidelines [40]. In addition, recent advancements in the field of RT, including IMRT/rotational techniques, image-guided RT (IGRT), and stereotactic RT (SBRT), have permitted the gradual integration of ultra-hypofractionation in the treatment of localized PC. SBRT for PC has generated adequate data in terms of tumor control, patient-reported quality of life, and minimal toxicity [14, 16, 25] to support its introduction in clinical practice. In addition, the prostate cancer-working group of the German Society of Oncology (DEGRO) and the NCCN Guidelines approve the use of SBRT in the treatment of localized low and intermediate-risk prostate cancer and propose its use in clinical trials for patients with the localized high-risk disease [41, 42].

The evidence of ultra-hypofractionation has recently been supported by two randomized studies (HYPO RT-PC) [25], PACE-B trial [14]), which compare its usage to conventional fractionation. Nevertheless, only HYPO-RT-PC provided information on the outcomes of long-term tumor and toxicity control. A randomized systematic review and meta-analysis of phase 3 studies evaluating SBRT with normo- and

hypo-fractionated regimens were published in 2020. It was determined that the ultra-hypofractionated regimens had comparable 5-year disease-free survival outcomes, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, in comparison to hypofractionated regimens and conventional RT [43]. In 2022, the toxicity outcome of the PACE B Trial was published, showing no significant differences between the five fractions of SBRT and conventional RT [44].

The use of moderate hypofractionation is gaining more popularity as a standard treatment in the postoperative setting [45]. Retrospective and prospective single-arm studies support a safe toxicity profile and promising biochemical control rates with hypofractionation [45]. According to newly released findings from the phase III clinical study NRG-GU003 evaluating hypofractionated postoperative prostate bed RT (HYPORT) to conventional post-prostatectomy RT for men with prostate cancer, treatment with HYPORT did not cause a rise in patient-reported GI or genitourinary (GU) toxicity for study subjects, with a comparable biochemical disease control at the 2-year follow-up [46].

Prakish et al. [47] did a theoretical feasibility study of SBRT following RP depending on the NTCP (Normal Tissue Complication Probability) model, using individuals who had been managed with conventional EBRT for biochemical recurrence after prostatectomy. The goal was to show that SBRT could be used safely and effectively in this clinical situation. A dose of 30 Gy was delivered to the PTV in five fractions, translating to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5 Gy, in accordance with RTOG standards to define postprostatectomy volumes. To predict the probability of late rectal and/or bladder toxicity, the NTCP model was used. According to the NTCP model, the average incidence of grade ≥ 2 late rectal toxicity was assessed to be 0.28%, and that of late grade 2 toxicity on the bladder neck was determined to be as low as 0.00013%, while the average incidence of late urinary symptoms exacerbation was calculated to be 4.81 %. The author's conclusion is that employing SBRT after surgery looks viable and may provide a safe, practical therapeutic alternative for individuals in both the adjuvant and salvage following biochemical failure, taking into account the limitations of the NTCP model.

Sampath et al. examined the use of stereotactic dose-escalated RT on prostate beds in a prospective phase 1 research, which revealed a crude rate of biochemical control of 42% in the overall population [48]. Patients received care using dose fractionation regimens of 35 Gy, 40 Gy, and 45 Gy in five fractions each. The authors emphasized that raising the dosage to 45 Gy was possible without increasing the number of adverse events but that there was no observed improvement in PSA control when compared to 40 Gy in 5 fractions. Similarly, a recent propensity score study comparing salvage SBRT and conventional RT for macroscopic prostate bed recurrence revealed similar bRFS and PFS rates across the two modalities. On the other hand, a reduced incidence of toxicity was verified for patients receiving focal stereotactic sRT

compared to conventionally fractionated sRT, with acute GI and GU adverse events recorded in 4.4% against 44.4% (p< 0.001) and 28.9% against 46.7% (p= 0.08) of participants, and late GI and GU side effects reported in 0% versus 13.3% (p = 0.04) and 6.7% versus 22.2% (p = 0.03) of patient populations, respectively [49]. The authors argue that salvage SBRT is a desirable substitute for conventional sRT in this situation due to the approach's favorable therapeutic ratio and the less number of required fractions. Additionally, the prospective phase 2 SCIMITAR trial reported the quality of life and toxicity outcome of 100 patients who received postoperative ultra-hypofractionated SBRT delivered in 5 fractions [50]. Acute and late grade 2 GU toxicities were both 9%, while acute and late grade 2 GI toxicities were 5% and 0%, respectively. Three patients had grade 3 toxicity (n = 1 GU, n = 2 GI) [50].

The expected results from the Hypo-Focal sRT trial will provide the first prospective evidence for the focal hypofractionated RT in the salvage setting and can be used as a basis for a large multicenter phase 3 trial. In addition to the assumed improvement in efficacy and toxicity profile due to precise customization of the treatment target volumes, the application of a focal hypofractionated RT is expected to achieve cost-effectiveness benefits. Due to the very short treatment course (unlike conventional RT treatments, which can take up to 7 weeks), hypofractionated focal sRT leads to greater patient convenience and comfortability.

Abbreviations:

AE	Adverse Event
ADC	Apparent diffusion coefficient
ADT	Androgen deprivation therapy
ASR/DSUR	Annual Safety Report / Development Safety Report
ASTRO	American Society for Radiation Oncology
ASCO/AUA	American Society of Clinical Oncology/ American Urological Association
ASTRO	American Society for Therapeutic Radiology and Oncology
BASEC	Business Administration System for Ethical Committees
bRFS	Biochemical relapse-free survival
CA	Clinical approval
CBCT	Cone Beam CT
CEC	Clinical ethics committee
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events

CTU	Clinical trials unit
CTV	Clinical target volume
DCE	Dynamic contrast enhancement
DEGRO	German Society of radiation oncology
DFS	Disease free survival
DRE	Digital rectal examination
DVH	Dose-volume histogram
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
18F	Fluorine-18
FADP	Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)
FOPH	Federal Office of Public Health
18F-DCFPYL	Pylarify - piflufolastat Fluorine-18
eCRF	Electronic Case Report Form
68Ga	Gallium-68
GCP	Good Clinical Practice
GTV	Gross tumor volume
GI	Gastrointestinal
GU	Genitourinary
HR	Hazard ratio
HRA	Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)
ICH	International Conference on Harmonisation
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
LHRH	Luteinizing hormone-releasing hormone
LHRHa	Luteinizing hormone-releasing hormone agonist
MFS	Metastasis free survival
mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCI	National cancer institute
NTCP	Normal tissue complication probability

NTD	Normalized total dose
NCCN	National comprehensive cancer network
OAR	Organs at risk
OS	Overall survival
OSEM	Ordered subset expectation maximization
PET/CT	Positron electron computed tomography
PFS	Progression-free survival
PI	Principal Investigator
PRV	Planning organ at risk volume
PSA	Prostate-specific antigen
PSF	Point-spread-function
PSMA	Prostate-specific membrane antigen
PTV	Planning target volume
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SAE	Serious Adverse Event
SBRT	Stereotactic body radiotherapy
SI	Signal intensity
sRT	Salvage radiotherapy
TLC	Thin layer chromatography
TMF	Trial master file
TNM	Tumor Nodes Metastases
TOF	Time of flight
UICC	Union internationale contre le cancer
UPN	Unique Patient Number
VUA	Vesicourethral anastomosis
WHO	World health organization
QLQ	Quality of life questionnaire
QoL	Quality of life

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Ethical approval, protocol registration, and consent to participate: The study received a permission from the regional ethics committees (KEK-BE 2022-01026), the research is registered with ClinicalTrials.gov (NCT05746806) and the Swiss National Clinical Trials Portal. Written, informed consent to participate is and will be obtained from all participants before participating in the trial.

Patient Consent for publication: obtained.

Competing interests statement: None declared.

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Figure ligands:

Figure 1: Summary of the study design and schedule.

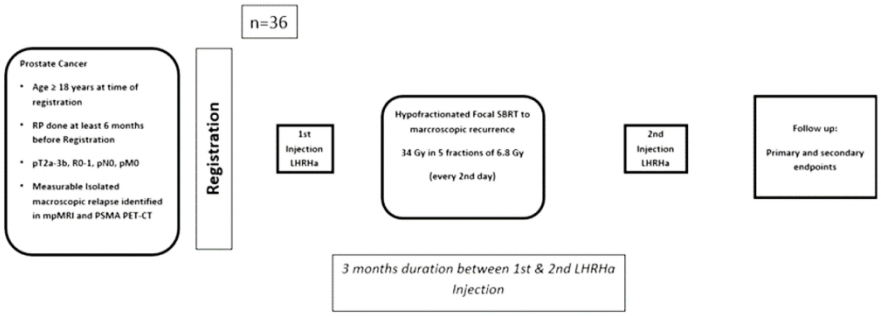

Figure 1: Summary of the study design and schedule.

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A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy

(HypoFocal SRT Trial)

Study Type: Other Clinical Trial according to ClinO, Chapter 4

Risk Categorisation: Risk category A according to ClinO, Art. 61

Study Registration: Clinicaltrials.gov: XXXX
Cantonal Ethics Committee Number: KEK-BE 2202-01026

Sponsor-Investigator Mohamed Shelan, MD

Department of Radiation Oncology, Inselspital,
Bern University Hospital and University of Bern, Bern, Switzerland.
Phone: +41 31 632 24 31
Fax: +41 31 632 85 67
E-mail: mohamed.shelan@insel.ch

Investigated Intervention: treating isolated prostate bed macroscopic recurrence after radical prostatectomy using ultrahypofractionated radiotherapy.

Protocol ID
Version and Date: Version 3.0 (11/11/2022)

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	30.05.2022		Initial version	
2.0	11.09.2022	no	Amended upon request of the ethics committee	MS
3.0	11.11.2022	no	Amended upon request of the ethics committee	MS

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PROTOCOL SIGNATURE FORM

Study Title	A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy

The Sponsor-Investigator has approved the protocol version 3.0 (11/11/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor Investigator:

Name: Dr. med. Mohamed Shelan

Date: _____ Signature: _____

PROTOCOL SIGNATURE FORM FOR LOCAL INSESTIGATOR:

The local Investigator has approved the protocol version 3.0 (11/11/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements

Local Principal Investigator at study site:

Site:

Principal Investigator:

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ADC	*Apparent diffusion coefficient*
ADT	*Aandrogen deprivation therapy*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
ASTRO/ ASCO/AUA	*American societies of radiation oncology, medical oncology and urology*
BASEC	*Business Administration System for Ethical Committees*
bRFS	*Biochemical relapse free survival*
CA	*Clinical approval*
CBCT	*Cone Beam CT*
CEC	*Clinical ethics committee*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTU	*Clinical trials unit*
CTV	*Clinical target volume*
DCE	*Dynamic contrast enhancement*
DEGRO	*German society of radiation oncology*
DFS	*Disease free survival*
DRE	*Digital rectal examination*
DVH	*Dose volume histogram*
DWI	*Diffusion-weighted imaging*
EAU	*European association of urology*
EORTC	*European organisation for research and treatment of cancer*
^{18}F	*Fluorine-18*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
FOPH	*Federal Office of Public Health*
^{18}F- DCFPYL	*Pylarify - piflufolastat Fluorine-18*
eCRF	*Electronic Case Report Form*
^{68}Ga	*Gallium-68*
GCP	*Good Clinical Practice*
GTV	*Gross tumor volume*
GI	*Gastrointestinal*
GU	*Genitourinary*
HR	*Hazard ratio*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
IGRT	*Image guided radiotherapy*
IMRT	*Intensity modulated radiotherapy*

LHRH	*Luteinizing hormone releasing hormone*
LHRHa	*Luteinizing hormone releasing hormone agonist*
MFS	*Metastasis free survival*
mpMRI	*Multiparametric magnetic resonance imaging*
MRI	*Magnetic resonance imaging*
NCI	*National cancer institute*
NTCP	*Normal tissue complication probability*
NTD	*Normalized total dose*
NCCN	*National comprehensive cancer network*
OAR	*Organs at risk*
OS	*Overall survival*
OSEM	*Ordered subset expectation maximization*
PET/CT	*Positron electron computed tomography*
PFS	*Progression-free survival*
PI	*Principal Investigator*
PRV	*Planning organ at risk volume*
PSA	*Prostate specific antigen*
PSF	*Point-spread-function*
PSMA	*Prostate-specific membrane antigen*
PTV	*Planning target volume*
RP	*Radical prostatectomy*
RT	*Radiotherapy*
RTOG	*Radiation therapy oncology group*
SAE	*Serious Adverse Event*
SBRT	*Stereotactic body radiotherapy*
SI	*Signal intensity*
SRT	*Salvage radiotherapy*
TLC	*Thin layer chromatography*
TMF	*Trial master file*
TNM	*Tumor Nodes Metastases*
TOF	*Time of flight*
UICC	*Union internationale contre le cancer*
UPN	*Unique Patient Number*
VUA	*Vesicourethral anastomosis*
WHO	*World health organization*
QLQ	*Quality of life questionnaire*
QoL	*Quality of life*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Mohamed Shelan, MD
Study Title:	A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy
Short Title / Study ID:	HypoFocal-SRT
Protocol Version and Date:	Ver. 3.0 date 11.11.2022
Trial registration:	www.clinicaltrials.gov. Registration will be completed after the Ethic committee approval
Study category and Rationale	Category A Ultrahypofractionated radiotherapy is not a standard of care in patients with local recurrence after radical prostatectomy. However, based on published data from retrospective series and phase I trial using a similar or higher fractionation scheme to the one used in this trial, toxicity is not expected to be higher than in case of normofractionated salvage radiotherapy. In terms of tumor control outcome, a benefit of hypofractionation can be expected due to the low α/β value of prostate cancer.
Clinical Phase:	Phase II
Background and Rationale:	Radical prostatectomy and radiotherapy (RT) are the considered as backbones for treating localized disease[1]. However radical prostatectomy, 30 – 60% of patients will develop recurrent disease[2,3]. Several large randomized controlled trials have shown a benefit of postoperative radiation therapy in patients with a high risk of local recurrence after RPE, e.g. pT3 disease or positive resection margins[4–8]. In the era of high sensitivity PSA and PSMA-PET/CT, there has been additional evidence suggesting a similar oncological outcome if patients are treated with early salvage radiotherapy in case of a rising PSA after RPE instead of immediate adjuvant radiotherapy[9–12]. However, the above mentioned studies as well as the studies including patients receiving salvage radiotherapy in case of a macroscopic tumor recurrence in the prostate bed were done with conventionally fractionated radiotherapy, usually in 2 Gy per fraction[4–12]. In the setting of definite radiotherapy to the prostate, ultrahypofractionated radiotherapy has been used as a treatment option in patients with low or intermediate risk for a long time and there are published data with a reasonable follow up that shows excellent biochemical control with low high grade toxicity rates[13–20]. In addition, data on ultrahypofractionated in high-risk patients are emerging with several large trials being published with encouraging results[21–26]. The rationale for using ultrahypofractionated in patients treated for prostate cancer is the estimated low α/β value of around 1.5 Gy[27,28]. Therefore, using a larger fraction dose is expected to improve the therapeutic ratio and consequently the probability of tumor control. Although Data on moderate hypofractionation in the setting of postoperative radiotherapy with a fraction dose of up to 3 Gy per fraction does not seem to support this concern, given the low toxicity rates that were reported in several analyses[29–38]. However, data on postoperative

	ultrahypofractionated radiotherapy to the prostate bed remains immature. The rates of acute and late toxicities following ultrahypofractionated radiotherapy to the prostate bed were reported in retrospective and phase I studies are within the above mentioned ranges. The rate of acute ≥ G2 GI and GU toxicities range from 0 – 50 % and 0 – 33.3 % and for late ≥ G2 GI and GU toxicities from 0 – 11.5 % and 0 – 38.5 %[39–48]. This data suggests that SBRT to the prostate bed can be applied with toxicity rates similar to that of normofractionated or mildly hypofractionated radiotherapy Further improvement in the oncological outcomes can be expected through technological developments in radiotherapy delivery and precise targeting of the local relapses in the prostate bed. A SRT using a ultrahypofractionated schedule delivered precisely in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric MRI (mpMRI) may represent a valid treatment strategy to improve the therapeutic ratio in these patients (short overall treatment time, better sparing of surrounding heathy tissues, increased dose to the target volume). Rationale for combining ADT to SRT - The benefit of ADT to salvage radiation has been demonstrated in two randomized phase III trials, RTOG 9601 and GETUG 16, which provided evidence of improved metastasis-free and overall survival and durable biochemical disease control with bicalutamide for 24 mo and ADT using LHRH agonists for 6 months, respectively. - These studies support the current National Comprehensive Cancer Network (NCCN) guidelines to consider combination of 6–24 months of hormonal therapy with SRT in this setting.
Objective(s):	The main objective of the trial is to explore the efficacy and safety of combining short-term ADT over 6 months to focal ultrahypofractionated SRT delivered in 5 fractions to the site of local recurrence within the prostate bed after radical prostatectomy where mpMRI and PSMA PET/CT are used to precisely identify the local recurrence and compare it to previously published literature.
Outcome(s):	Primary endpoints: - Biochemical relapsefree survival at 2 years Secondary endpoints: - Acute side effects (till 90 days after end of radiation) of grade 3 or higher based on CTCAE v5 - Clinical progression-free survival - Metastasis-free survival - Late side effects - Quality of life (based on EORTC QLQ-C30, QLQ-PR25)
Study design:	This a single arm, prospective, phase II multicenter study
Inclusion / Exclusion criteria:	**Inclusion criteria:** 1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures 2. Age ≥ 18 years at time of registration 3. WHO performance status 0-1 4. Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy (RP) at least 6 months before trial

	registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009. 5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, a biopsy confirmation is recommended. 6. Patient must have non-metastatic (N0, M0) disease, as defined by a lack of nodal or distant metastases seen on PSMA PET/CT scan 7. Patients must have non-castrate levels of serum testosterone (≥50 ng/dL). 8. Patients must not have previously received hormonal therapy (LHRH agonists, antiandrogen, or both, or bilateral orchiectomy). 9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial **Exclusion criteria:** 1. Persistent PSA (> 0.4 ng/mL) 4 to 20 weeks after RP 2. Previous hematologic or primary solid malignancy within 3 years prior registration with the exception of curatively treated localized non-melanoma skin cancer 3. Usage of products known to affect PSA levels within 4 weeks prior to start of trial treatment phase including any form of androgen suppression agents and androgen deprivation therapy 4. Bilateral hip prosthesis 5. Severe or active co-morbidity likely to impact on the advisability of SRT 6. Treatment with any experimental drug or participation within a clinical trial within 30 days prior to registration (exception: concurrent participation in the biobank studies is allowed)
Measurements and procedures:	**Investigations to be performed within 12 weeks prior to registration:** - Physical examinations including Digital rectal examination (DRE) - Multi-parametric MRI - PSMA PET/CT. **Investigations during trial treatment phase** - Planning CT - Multi-parametric MRI if not yet performed - Serum PSA - Total testosterone, - Assessment of recurrences in case of suspected progression **During follow-up:** - Physical examinations - Digital rectal examination (if suspected clinical progression), - serum PSA - Total testosterone - Assessment of recurrences with PSMA PET/CT imaging (local, regional, distant) **All adverse events are collected throughout the trial.**

Control Intervention (if applicable):	This is a single arm study. Control intervention is not applicable.
Number of Participants with Rationale:	It is planned to enrol a total of 36 patients in the trial (see statistical considerations for rationale).
Study Duration:	Expected accrual time: 18 Months
Study Schedule:	First-Participant-In: Q4 2022 Last-Participant-Out: Q4 2027
Investigator(s):	**Dr. med. Mohamed Shelan** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 29 70 E-Mail:mohamed.shelan@insel.ch **Prof. Dr. med. Daniel M. Aebersold** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 24 31 E-Mail:daniel.aebersold@insel.ch **Jens Lustenberger** Department of Radiation Oncology Unispital Basel E-Mail: jens.lustenberger@usb.ch **Prof. Dr. Daniel R. Zwahlen** Department of Radiation Oncology Kantonsspital Winterthur Phone: 079 553 25 63 E-Mail:daniel.zwahlen@ksw.ch **Prof. Dr. med. Thomas Zilli** Clinica di Radio-Oncologia Istituto Oncologico della Svizzera Italiana-Ente Ospedaliero Cantonale (IOSI-EOC) Phone: 091/811 96 35 E-Mail: Thomas.Zilli@eoc.ch **Dr. med. Alexander Althaus** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 29 70 Email: alexander.althaus@insel.ch **Dr. med. Hendrik Gabriel Rathke** Department of Nuclear Medicine Inselspital, Bern University Hospital Bern, Switzerland. Email:hendrik.rathke@insel.ch
Study Centre(s):	Multi-centre study. At least 4 recruiting centers in Switzerland.
Statistical Considerations:	According to the published prospective trials and retrospective series reporting the outcome of the normofractionated SRT, we define

	biochemical relapse free survival at 2 years of 60% as poor and of 80% as promising outcome that would justify further investigation. We will therefore test the null hypothesis that the biochemical relapse free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%. The null hypothesis will be rejected if at least 27 patients show biochemical relapse free survival at 2 years. We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects is larger than 27%, the proportion observed that will be tested using one-sample binomial exact tests with a one-sided alpha of 5%. Time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

2.1 Disease background

Prostate cancer is the most common non-cutaneous malignancy in men. An estimated 1.1 million patients per year worldwide were diagnosed with prostate cancer, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases occurring in more developed regions. Prostate cancer is the fifth leading cause of cancer death in men, representing 6.6% of the total male cancer mortality [49].
The most common curative therapeutic modalities for localized prostate cancers include radical prostatectomy (RP) and radiotherapy with or without androgen deprivation therapy. Although there is a wide variability between treatment site and risk groups, approximately 50% of all men with localized prostate cancer undergo RP [50]. After RP, between 30-60% of men can develop a biochemical relapse within 5 years [51–54]. The site of relapse in prostate cancer patients after RP is predominantly local, with a low incidence of distant failures [55]. Within patients with biochemical relapse the actuarial rate of bone metastasis is 37% and 65% at 5 years and 10 years, respectively. The median time to development of bone metastasis after biochemical relapse is 8 years and the median time between development of bone metastasis and death is 5 years [56].

2.2 Therapy background

2.2.1 The use of adjuvant and salvage radiotherapy after radical prostatectomy

Adverse pathological factors after prostatectomy, such as positive surgical margins, extracapsular extension, or seminal vesicle invasion, increase the likelihood of disease recurrence. Three randomized clinical trials have demonstrated the benefits of adjuvant radiotherapy after RP for patients with adverse pathological features [5,8,57]. The most consistent findings were an improvement in biochemical relapse free survival across all three trials and improvements in loco-regional and clinical relapse free survival in the two trials that reported these outcomes. Although there was an improvement in overall survival in one of the studies [57], the use of adjuvant radiotherapy is not unanimously accepted [58]. Two of these studies have included patients with a detectable prostate-specific antigen (PSA) at the time of adjuvant treatment; therefore, these patients received salvage treatment by definition. As such, many clinicians offer salvage radiotherapy (SRT) to patients with biochemical progression instead of adjuvant radiotherapy. The main advantage of salvage versus adjuvant radiotherapy is the avoidance of a potential overtreatment in cases that would never relapse after surgery, even in the presence of high-risk pathological features [59]. Recently, prospective randomized trials, systematic review, and meta-analysis suggest that adjuvant radiotherapy does not improve event-free survival in men with localized or locally advanced prostate cancer. Until data on long-term outcomes are available, early salvage treatment would seem the preferable treatment policy as it offers the opportunity to spare many men radiotherapy and its associated side-effects [9,10,12].
Predictors of response to salvage radiotherapy were examined by Stephenson et al. [60] and they found that high Gleason score, high pre-radiotherapy PSA, negative RP surgical margins, short PSA doubling time, and seminal vesicle involvement were independently associated with adverse outcomes. A contemporary update of the original Stephenson predictive nomogram including patients treated with early SRT (at a PSA ≤ 0.2 ng/mL) showed that early SRT at low PSA levels after RP is associated with improved freedom from biochemical relapse and distant metastases rates [61].

2.2.2 Optimizing salvage radiotherapy with androgen deprivation therapy

Prospective studies have shown that androgen deprivation therapy (ADT) combined with primary radiotherapy for intermediate- and high-risk prostate cancers improves overall survival [62]. The combination of ADT to radiation in the postoperative setting was for long time a matter of debate. Recently the results of prospective phase III randomized were published demonstrating a benefit of the combined treatment[63,64].
In the RTOG 9601, 771 men with an elevated serum PSA following radical prostatectomy were randomly assigned to radiation plus the anti-androgen bicalutamide for two years or radiation alone. The first interim results at a median follow up of 7 years were negative for the primary endpoint, overall survival; however, the latest report at a median follow-up of 12.6 years showed an actuarial 10-year overall survival of 82% for salvage radiation plus ADT and 78% for salvage radiation plus placebo (HR: 0.75; 95% CI: 0.58-0.98) [63].

The GETUG-AFU 16 is a phase III study that randomized men with biochemical failure after surgery to salvage radiation alone versus salvage radiation combined with 6 months of LHRH agonists. The 10 years results showed that SRT combined with short-term androgen suppression significantly reduced risk of biochemical or clinical progression and death compared with salvage radiotherapy alone. The results of the GETUG-AFU 16 trial confirm the efficacy of androgen suppression plus radiotherapy as salvage treatment in patients with increasing PSA concentration after RP for prostate cancer [64].
Finally, it is worth to mention that, the current National Comprehensive Cancer Network (NCCN) guidelines recommend a duration of 6–24 months of ADT combined SRT.

2.3. Role of new imaging modalities in identifying local recurrence after RP

2.3.1 The role for MRI in the identification of prostate cancer recurrence after RP

In men with biochemical recurrence following local treatment with curative intent for prostate cancer, it is important to identify those who will likely benefit from local salvage therapy. Imaging should provide a step-by-step multimodal approach that facilitates both local and systemic staging. Clinical guidelines recommend the use of both nuclear medicine imaging (positron emission tomography [PET] / computed tomography [CT] scans) and magnetic resonance imaging (MRI) to assess local recurrence and distant metastases [65,66] Multiparametric MRI (mpMRI) is accurate in early detection of prostate cancer local recurrence after RT and RP [66]. T2w sequences very accurately represent the postsurgical anatomy. In most cases, a local recurrence differs from normal postoperative inflammation and fibrosis. Fibrotic tissue has a lower signal intensity (SI) than recurrent tissue [67]. Recurrent tissue can have various forms, including curly, semi-circular, nodular, and plaque-like masses. In the case of asymmetric perianastomotic soft-tissue thickening with an SI in between the SIs for pelvic muscle and the surrounding adipose tissue, a local recurrence is likely to be present [68]. Functional criteria are based on diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE), which represent the cellularity and vascularity of the tissue, respectively.
DWI has good diagnostic accuracy in detecting local recurrence after RP when combined with other sequences[68]. Quite often, there is geometric distortion caused by susceptibility artefacts due to surgical clips. Local recurrence after RP, like primary tumours, shows high SI on high b-value DWI and low ADC values. In the case of artefact-altered DWI, DCE MRI is of particular importance[69]. DCE imaging plays the dominant role in the detection of RP recurrence. This technique has high sensitivity [70–72]; even tiny recurrence “foci” that may not be visible on T2WI tend to show significant enhancement in the early arterial phase, often with contrast wash-out [66]. In addition, post-RP recurrences enhance sooner and faster than normal postoperative changes [73].

2.3.2 Role of PSMA PET CT in Identification of local recurrence

In case of PSA recurrence, SRT is the only curative option, resulting in approximately 60% of the patients re-achieving an undetectable PSA. After 5 years, 80% of these men are free from progression[74]. The pre-SRT PSA level is a significant factor of progression, with more favorable results for patients with low PSA levels (0.5 ng/mL or less)[61,75]. Accordingly, European guidelines (EAU) recommend early SRT at a PSA <0.5 ng/mL. At the same time, use of restaging PSMA PET/CT is recommended by the 2021 EAU guidelines for patients with a relapsing PSA > 0.2 ng/mL. However, for clinical and imaging purposes, it is important to distinguish between two types of local recurrence and relapse outside tumor bed.

At PSA levels <1 ng/mL, most imaging methods are not suitable to detect the correlate for disease progression. Therefore, up to 20% of patients with SRT to the prostate bed (with or without including original seminal vesicle) without morphological correlate will be treated locally without actual local recurrence [74]Prostate-specific membrane antigen (PSMA) is a cell surface protein with high expression in majority of prostate cancer [76]. 68Ga-PSMA has been used since 2012 as PSMA-ligand in recurrent prostate cancer [77–79]. Especially at low PSA levels, the detection rate of 68Ga-PSMA-11-PET/CT is significantly higher in comparison to other imaging methods. In a retrospective analysis for patients with biochemical progression after RP, Afshar-Oromieh et al. found that 69% of the patients had at least one positive lesion indicating prostate cancer recurrence. The detection rates were 43% for PSA levels ≤0.2 ng/mL, 58% for PSA >0.2 to ≤0.5 ng/mL and 72% for PSA >0.5 to ≤1.0 ng/mL. Tumor detection was clearly associated with PSA level and higher Gleason scores [78]. Bluemel et al. analyzed the impact of 68Ga-PSMA-11-PET/CT in patients with PSA failure and negative F-18-choline-PET/CT. Of 125 patients, 32 patients with negative F-18-choline-PET/CT received an additional 68Ga-PSMA-11-PET/CT, which detected sites of recurrence in 43.8% [80].

The most common site of postoperative local recurrence, accounting for 57%–62% of relapse cases, is the vesicourethral anastomosis (VUA), which comprises the membranous urethra, bladder neck, and surrounding soft tissue [81]. Other typical local relapse sites are the lateral surgical margins (seminal vesicle bed) or remnant deferens, accounting for 25%–27% of cases [82], and the retrovesical region (topography of rectoprostatic/Denonvilliers fascia) in 8%–21% of cases [81]At PSMA PET/CT, local recurrence appears more often as focal ill-defined hypo-attenuating soft tissue with moderate PSMA uptake but can also simply appear as focal unilateral radiotracer uptake within the fibrotic tissue. It is important to point out that in most cases, postoperative local recurrence relies only on the PET component of the hybrid imaging because of the known lack of soft-tissue contrast in the pelvic region at CT [77].

2.4 Investigational treatment

2.4.1 Hypofractionated stereotactic body radiotherapy to the site of recurrence

External beam radiation therapy is one of the standard treatments for organ-confined prostate cancer, with cure rates similar to those of RP. Hypofractionation uses a higher dose-per-fraction of radiation, which reduces the number of fractions and the total duration of treatment, allowing greater comfort for the patient and lower costs, in addition to providing a therapeutic advantage in terms of tumor control and toxicity, as the α/β of prostate cancer is lower than that of adjacent healthy tissues[83]. In 2018, a group of experts from the American Societies of Radiation Oncology, Medical Oncology, and Urology (ASTRO/ASCO/AUA) concluded that there is sufficiently robust evidence to justify using moderate hypofractionation in prostate cancer as common clinical practice[84]. A recent Cochrane review indicated that moderate prostate cancer hypofractionation (with fractions up to 3.4 Gy) provides oncological outcomes in terms of overall survival (OS), disease-free survival (DFS), and metastasis-free survival (MFS) similar to conventional fractionation, without a significant increase in acute or late toxicity [85].
In addition, technical advances in the field of radiotherapy in recent years, such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic radiotherapy (SBRT), have enabled the progressive implementation of extreme hypofractionation (defined by fractions of at least 6 Gy) in various scenarios of localized prostate cancer treatment. The use of SBRT in prostate cancer has provided sufficient evidence in terms of tumor control results, quality of life reported by the patient, and low toxicity [25,86,87] to back its implementation in daily clinical practice. Moreover, the prostate cancer working group of the German Society of Oncology (DEGRO) but also the NCCN endorses the use of SBRT in the treatment of localized low and intermediate-risk prostate cancer, recommending its use in clinical trials in patients with the localized high-risk disease[88-48].
The recent publication of two randomized trials comparing the use of extreme hypofractionation versus conventional fractionation (HYPO-RT-PC [25], PACE-B trial[87]) has been crucial in supporting its use, although only the Scandinavian study (HYPO-RT-PC) reported results of long-term tumor and toxicity control. In 2020, a randomized systematic review and meta-analysis of phase III trials were published comparing SBRT with normofractionated and hypofractioned regimens. It concluded that the ultra-hypofractionated regimens obtained similar 5-year disease-free survival results, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, when compared to hypofractionated regimens and conventional radiotherapy [47].

Use of moderate hypofractionation is becoming a standard even in the postoperative setting. Retrospective and prospective single arm studies support a safe toxicity profile and a promising biochemical control rates with hypofractionation (PMID: 29178983). The recently reported results of the phase III clinical trial NRG-GU003 comparing hypofractionated post-operative prostate bed radiotherapy (HYPORT) to the conventional post-prostatectomy radiotherapy for men with prostate cancer determined that treatment with HYPORT yielded no increase in patient-reported genitourinary (GU) or gastrointestinal (GI) toxicity for trial participants, with a similar biochemical disease control at the 2 year follow-up.
To demonstrate the viability and safety of the use of SBRT in this clinical scenario, Repka et al [50]conducted a theoretical feasibility study of SBRT after RP based on the NTCP (Normal Tissue Complication Probability) model, using patients who had previously been treated by conventional EBRT for biochemical recurrence after prostatectomy. Using the presimulation CT, RTOG recommendations were applied to define postprostatectomy volumes, and a dose of 30 Gy was prescribed to the PTV in five fractions, corresponding to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5

Gy. The NTCP model was applied to estimate the risk of late rectal and/or bladder toxicity. According to the NTCP model, the mean of grade≥2 late rectal toxicity was estimated at 0.28% and of late grade 2 toxicity on the bladder neck at 0.00013%, while the calculated average for the exacerbation of late urinary symptoms was 4.81%. The conclusion by the authors, considering the limitations of the NTCP model, is that using SBRT after surgery seems feasible and may offer a safe, convenient treatment option for patients in both the adjuvant and salvage after biochemical failure.
A prospective phase I study by Sampath et al. tested the usage of stereotactic dose-escalated radiotherapy on prostate bed in and showed a crude rate of biochemical control of 42% in the overall population [90]. Patients were treated with dose fractionation schedules of 35, 40 and 45 Gy in five fractions. Authors underlined that dose escalation to 45 Gy was feasible without increasing the rate of adverse events, but no improvement in PSA control was reported if compared to 40 Gy in 5 fractions. Furthermore, a recent propensity score analysis comparing focal stereotactic SRT and conventional radiotherapy for macroscopic prostate bed recurrence showed comparable bRFS and PFS rates between the two modalities. On the other hands, a lower rate of toxicity was confirmed for patients undergoing focal stereotactic SRT compared to conventional fractionated SRT, with acute GI and GU adverse events reported in 4.4% versus 44.4% ($p< 0.001$) and 28.9% versus 46.7% ($p= 0.08$) of patients, and late GI and GU adverse events reported in 0% versus 13.3% ($p = 0.04$) and 6.7% versus 22.2% ($p = 0.03$) of patients, respectively [91]. Considering the favorable therapeutic ratio of this approach and the lower number of fractions needed, the authors suggested stereotactic is an attractive alternative to conventional SRT in this setting

2.5 Rationale for performing the trial

Radical prostatectomy and radiotherapy (RT) are the considered as backbones for treating localized disease[1]. However radical prostatectomy, 30 – 60% of patients will develop recurrent disease[2,3]. Several large randomized controlled trials have shown a benefit of postoperative radiation therapy in patients with a high risk of local recurrence after RPE, e.g. pT3 disease or positive resection margins[4–8]. In the era of high sensitivity PSA and PSMA-PET/CT, there has been additional evidence suggesting a similar oncological outcome if patients are treated with early salvage radiotherapy in case of a rising PSA after RPE instead of immediate adjuvant radiotherapy[9–12]. However, the above mentioned studies as well as the studies including patients receiving salvage radiotherapy in case of a macroscopic tumor recurrence in the prostate bed were done with conventionally fractionated radiotherapy, usually in 2 Gy per fraction[4–12].

In the setting of definite radiotherapy to the prostate, ultrahypofractionated radiotherapy has been used as a treatment option in patients with low or intermediate risk for a long time and there are published data with a reasonable follow up that shows excellent biochemical control with low high grade toxicity rates[13–20]. In addition, data on ultrahypofractionated in high-risk patients are emerging with several large trials being published with encouraging results[21–26]. The rationale for using ultrahypofractionated in patients treated for prostate cancer is the estimated low α/β value of around 1.5 Gy[27,28]. Therefore, using a larger fraction dose is expected to improve the therapeutic ratio and consequently the probability of tumor control.

Although Data on moderate hypofractionation in the setting of postoperative radiotherapy with a fraction dose of up to 3 Gy per fraction does not seem to support this concern, given the low toxicity rates that were reported in several analyses[29–38]. However, data on postoperative ultrahypofractionated radiotherapy to the prostate bed remains immature. The rates of acute and late toxicities following ultrahypofractionated radiotherapy to the prostate bed were reported in retrospective and phase I studies are within the above mentioned ranges. The rate of acute ≥ G2 GI and GU toxicities range from 0 – 50 % and 0 – 33.3 % and for late ≥ G2 GI and GU toxicities from 0 – 11.5 % and 0 – 38.5 %[39–48]. This data suggests that SBRT to the prostate bed can be applied with toxicity rates similar to that of normofractionated or mildly hypofractionated radiotherapy

Further improvement in the oncological outcomes can be expected through technological developments in radiotherapy delivery and precise targeting of the local relapses in the prostate bed. A SRT using a ultrahypofractionated schedule delivered precisely in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric MRI (mpMRI) may represent a valid treatment strategy to improve the therapeutic ratio in these patients (short overall treatment time, better sparing of surrounding heathy tissues, increased dose to the target volume).

Rationale for combining ADT to SRT

- The benefit of ADT to salvage radiation has been demonstrated in two randomized phase III trials, RTOG 9601 and GETUG 16, which provided evidence of improved metastasis-free and overall survival and durable biochemical disease control with bicalutamide for 24 mo and ADT using LHRH agonists for 6 months, respectively.
- These studies support the current National Comprehensive Cancer Network (NCCN) guidelines to consider combination of 6–24 months of hormonal therapy with SRT in this setting.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

We hypothesize that focal SRT in combination with short-term ADT may further prolong or prevent progression, and improve the success of SRT for relapsing patients with a macroscopic relapse after RP. Through better definition and optimization of the target volumes sparing adjacent normal tissue, an improvement in the toxicity profile can be expected.

The main objective of the trial is to explore the efficacy and safety of combining 6 months short-term ADT to focal hypofractionated SRT delivered in 5 fractions where mpMRI and PSMA-PET CT are used to precisely identify the local recurrence and compare it to the published literature.

3.2 Primary and secondary endpoints

Primary endpoints:

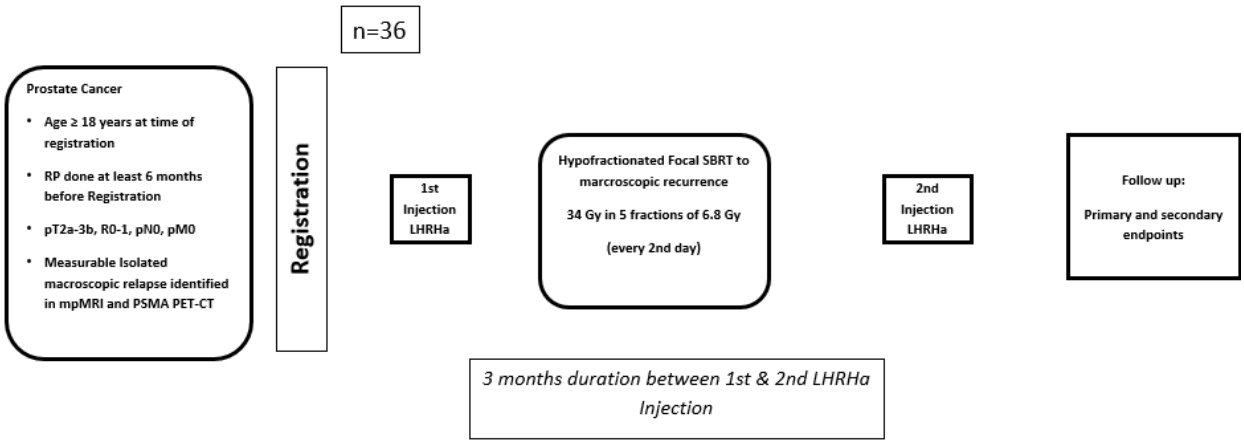
- Biochemical relapse free survival at 2 years

Secondary endpoints:

- Acute side effects (until 90 days after end of radiation) of grade 3 or higher based on CTCAE v5
- Progression-free survival
- Metastasis-free survival
- Late side effects
- Quality of life (based on EORTC QLQ-C30, QLQ-PR25)

3.3 Study design

This is a single arm, prospective phase II multicenter study.



3.4. Study intervention

3.4.1 Pre-registration imaging

Within 3 months prior to registration either, PSMA PET/CT is mandatory to exclude regional or distant metastasis. Both 18F- and 68G-PSMA tracers are allowed. A mpMRI of the prostate bed acquired within 3 months before registration is mandatory to define the extension of local recurrence.

3.4.2 Radiation treatment (SBRT)

3.4.2.1 Patient's positioning, immobilization, data acquisition and simulation:

A treatment planning CT scan, with the patient in the same position as during treatment, is required to define the clinical target volume (GTV), the planning target volume (PTV) and the critical structures. Patients will be positioned in supine position. Leg and knee support is highly recommended. Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. It is recommended that patients are scanned/simulated and treated with comfortably full bladder. An empty rectum is recommended for prostate bed radiotherapy. An example of a bladder and rectal protocol: An empty rectum is provided by using a rectal enema +/- 60 minutes before planning CT. After emptying rectum and bladder the patient is asked to drink the amount of 500-750 ml of water. The planning CT is then performed after ca. 40 minutes. The patient repeats the bladder filling procedure during the entire treatment courses. An endorectal ballon can be used for repositioning purposes as per local institutional standards.

Radiopaque fiducial markers (mandatory for robotic-based treatments) may be implanted in the prostate bed 1 week before the planning CT scan at the discretion of the treating center.

The position of the patient will be reproduced using skin marks and orthogonal laser beams during treatment preparation and execution. The treatment planning CT scan should include at least the pelvis from the lower part of the second lumbar vertebra (L2) to the lower part of the ischial tuberosities. The entire target volume and all organs at risk (OAR) must be included in CT scan. CT slice thickness should be ≤ 2 mm. The GTV, PTV and OAR must be outlined on all CT slices in which these structures are visible.

Morphological and topographical information given by clinical examination, mpMRI and PET/CT, must be integrated to delineate the target volumes. Rigid or deformable co-registration is allowed.

3.4.2.2 Volumes

3.4.2.2.1 Definition of target volumes (refer to appendix 2 & 3):

- The Gross Tumor Volume of the suspicious local recurrence (GTV) is defined by the physician as all known gross disease *before any treatment* as defined by the CT/MRI images and PET scan using rigid or deformable fusion) and/or clinical information.

- The Planning Target Volumes (PTV) will provide margin around the GTV to compensate for variability in daily treatment set-up and internal motion due to breathing or motion during treatment. The PTV should encompass the GTV with a margin of 5 mm in all directions.

3.4.2.2.2 Organs at Risk (OAR)

- *Delineation:*

The OAR should be delineated according to the RTOG guidelines. For more details please see RTOG/NRG Oncology web site to view the normal pelvis atlas for examples of normal tissue contours (http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx).

Bladder: this organ is defined by the external wall (5-mm thickness), delineated on each slide, from the dome to the bladder neck and the start of the VUA.
VUA and distal urethra: from the bladder neck to the distal urethra inside the penile bulb using the mpMRI sequences. A 2-mm isotropic margin is added around these structures to create a PRV volume.
Rectum: defined by the external wall from the recto-sigmoid junction to ischial tuberosities (5-mm thickness).
Femoral heads: delineated from the top of the hip joint to the small trochanter.
Bowel bag: from the most inferior small or large bowel loop to 1 cm at minimum above PTV for coplanar beam plans, or more if non-coplanar beams or tomotherapy plans are used.

- *Dose constraints to OAR:*

It is strongly recommended that dose constraints are not exceeded. If a dose constraint cannot be achieved due to overlap of the target with an OAR or PRV, the dose per fraction can be lowered or the target coverage compromised in order to meet the constraint.

Organ at risk	Dose constraint	Aim
Rectal wall	V18.1 Gy V29 Gy V36 Gy	<50% <20% <1cc
Bladder wall	V18.1 Gy V37 Gy	<40% <10cc
PRV_VUA and distal urethra	V36 Gy	<1cc

Femoral heads	V14.5 Gy	<5%
Penile bulb	V29.5 Gy	<50%
Bowel	V18.1 Gy V30 Gy	<5cc <1cc

3.4.2.3 Treatment technique.

Intensity modulated radiotherapy (IMRT) or use of rotational techniques is mandatory. By definition only dosimetry obtained by inversed treatment planning is considered as IMRT. IMRT may be performed by using Step-and-Shoot-Technique, Sliding-Window-Technique or Volumetric Modulated Arc Therapy (VMAT), including MRI-guided radiation therapy systems (MRIdian® or Elekta Unity®). Treatment with Cyberknife® is allowed (implant of radiopaque fiducial markers 1 week before the planning CT scan is mandatory).

3.4.2.4 Dose computation.

- Any treatment planning system, capable of 3D-dose computation using a convolution algorithm, will be used. The PTV may be treated with any combination of coplanar or non-coplanar fields shaped to deliver the specified dose while minimizing dose to the normal tissue OAR. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical OAR. Each field is to be treated daily.

- The PTVs should be outlined in all relevant planes. The dose distribution should be shown at least in the plane through the beam axes.

- Dose distribution is obtained in a 3-dimensional pattern with Dose Volume Histogram (DVH). DVH are to be used for assessing dose to the PTVs and all normal tissues at risk.

3.4.2.5. Equipment and tools.

- Both a linear accelerator, tomotherapy and Cyberknife is allowed.

3.4.2.6 Dose prescription.

A total dose of 34 Gy (80% of the maximal dose) will be delivered in 5 fractions and fractions every second day (NTD_{2Gy} 80 Gy α/β=1.5Gy for tumor control and 66.6 Gy α/β=3Gy for late toxicity). Treatment will be prescribed to the periphery of the target (80% of the dose (=34Gy), should cover 90% of the PTV) covering the PTV. A maximal dose of 40 Gy is allowed to GTV. The priority will be given to the respect of dose constraints over PTV coverage.

3.4.2.7 Treatment Verification.

Daily patient set-up shall be performed using laser alignment to reference marks on the skin of the patient. Daily cone-beam CT set-up and on-line correction of patient's position is mandatory. If multiple targets will be irradiated with multiple isocenters, a CBCT prior to every treatment for every isocenter is mandatory. Patient immobilization devices can be used according to the institutional policy.

3.4.3 Androgen deprivation therapy

- All patients should receive an LHRH-agonist or antagonist for a duration of 6 months using 3 monthly formulations. In case of LHRH-agonist flare prevention with an anti-androgen is

recommended for at least 5 days prior to the first injection of the agonist and should not be continued for longer than 15 days of the 1st month duration.

- ADT should start no later than the 1st SBRT fraction and no earlier than 2 weeks before the start of radiotherapy.
- Palliative ADT should not be started for biochemical progression without documented clinical progression. In case of symptomatic progression, palliative ADT is mandatory. In case of clinical asymptomatic progression, delayed ADT until progression to a symptomatic state is allowed in well-informed men (EAU 2016 guidelines). In general, we would recommend to start ADT in asymptomatic patients only if conventional imaging would confirm clinical progression. So we would not recommend the start of ADT for PET-positive lesions not suspicious on conventional imaging (CT/MRI/bone scintigraphy).
- ADT-related toxicity should be managed according to Nguyen et al. Eur Urol. 2015 May;67(5):825-36.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Inclusion criteria:

1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures
2. Age ≥ 18 years at time of registration
3. WHO performance status 0-1
4. Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy (RP) at least 6 months before trial registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009.
5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, a biopsy confirmation is recommended.
6. Patient must have non-metastatic (N0, M0) disease, as defined by a lack of nodal or distant metastases seen on PSMA PET/CT scan
7. Patients must have non-castrate levels of serum testosterone (≥50 ng/dL).
8. Patients must not have previously received hormonal therapy (LHRH agonists, antiandrogen, or both, or bilateral orchiectomy).
9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Exclusion criteria:

1. Persistent PSA (> 0.4 ng/mL) 4 to 20 weeks after RP
2. Previous hematologic or primary solid malignancy within 3 years prior registration with the exception of curatively treated localized non-melanoma skin cancer
3. Usage of products known to affect PSA levels within 4 weeks prior to start of trial treatment phase including any form of androgen suppression agents and androgen deprivation therapy
4. Bilateral hip prosthesis
5. Severe or active co-morbidity likely to impact on the advisability of salvage RT
6. Treatment with any experimental drug or participation within a clinical trial within 30 days prior to registration (exception: concurrent participation in the biobank studies is allowed

4.2 Recruitment and screening:

Patient registration will only be accepted from authorized investigators.

Prior to registration, the following steps have to be taken:

- Fill in the patient screening (used for monitoring potentially eligible patients, and will be destroyed after the end of the accrual period. Screening list is not a part of the CRFs), enrollment and identification lists.
- Check the eligibility criteria
- Obtain signed and dated written informed consent from the patient prior to any protocol-specific procedure according to ICH/GCP and local guidelines.
- Patients must complete the pre-treatment of quality of life assessment per protocol

Only electronic case report forms (eCRF) will be used. The use of worksheets is allowed if the copies of the templates are documented in the trial master file (TMF). The used worksheets must be kept with the patient charts.

Registration is done via Internet 'https://secutrial.insel.ch'. SecuTrial (interActive Systems) will be used as database. In case of problems investigators can phone the study coordinator from Monday through Friday. For technical difficulties, investigators are recommended to contact data management of CTU Bern

E-mail: datamanagement@ctu.unibe.ch

In order to receive authorization for online registration/data entry, sites must send a copy of the completed staff list to the Sponsor. Login details for the online database will be sent to authorized persons.

4.3 Study procedures

Schedule of assessments (Table 1)

Required investigation	Inclusion		Treatment	1 Months after RT	3 Months after RT	6 Months after RT	Every 6 Months till end of 2nd year after RT then once per year till 60 months
	Within 12 weeks prior registration	Within 2 weeks prior registration					
Eligibity Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x		x	x	x	x
Biochemistry (Blood Samples)*							
PSA		x		x	x	x	x
Testosterone		x		x	x	x	x
Radiology							
PSMA PET	x						
MRI	x						
Radiotherapy							
Treatment planning			x				
Record Planning results			x				
Adverse Events							
Baseline toxicity		x					
Acute toxicity			x	x	x		
Late toxicity						x	x
EORTC QoL questionnaire							
QLQ-C30		x		x	x	x	x
QLQ-PR25		x		x	x	x	x

*** Blood samples**

The obtained blood samples are used only for PSA and testosterone values. The measurement for this labs is conducted within the local hospital laboratory of each participating centre and the rest samples will be disposed afterwards. No blood will be collected or stored or used for other research purposes within the frame of this trial.

4.4 Withdrawal and discontinuation

Patients have the right to discontinue their participation in the trial for any reason and at any time, without prejudice to further treatment. Patients who refuse further trial treatment will be transferred to follow-up phase and continue to receive the follow-up assessments as scheduled. Patients who withdraw their consent (i.e. refuse further data collection), will be informed that all data and samples collected until the time point of their withdrawal will be kept coded and used. For the patient's security, a last examination should be performed.

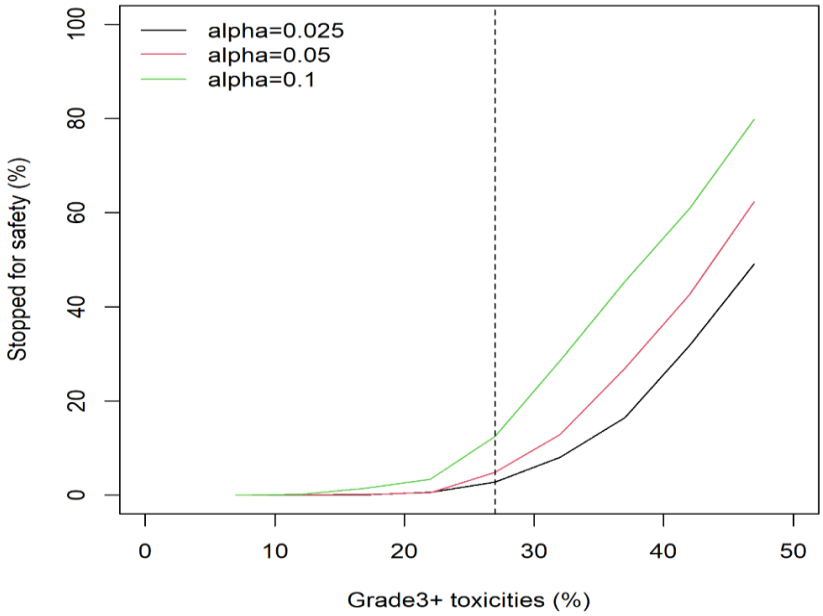
Patients may be withdrawn at any time from trial treatment at the discretion of the treating physician or the investigator due to a SAE, or based on any other relevant medical condition. The patient then will be transferred to the follow-up phase and continue to receive the follow-up assessments as scheduled.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

According to the published prospective trials and retrospective series reporting the outcome of the normofractionated SRT, we define biochemical relapse free survival at 2 years of 60% as poor and of 80% as promising outcome that would justify further investigation. We will therefore test the null hypothesis that the biochemical relapse free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%, not taking into account patients lost to follow-up. The null hypothesis will be rejected if at least 27 patients show biochemical relapse free survival at 2 years.

We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects (grade 3 or higher) is larger than 27%, the proportion observed that will be tested using one-sample binomial exact tests with a one-sided alpha of 5%.



Time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.

The probability of biochemical relapse free survival and metastasis-free survival will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be fit to assess the effects of treatment and baseline clinical and pathologic features (such as PSA, PSA doubling time, Gleason score etc) on biochemical relapse free survival and metastasis free survival

5.2. Definition of endpoints

5.2.1 Biochemical relapse free survival (primary endpoint)

The initial PSA at time of registration will be the starting point. Freedom from biochemical progression is counted from the day of registration to the day of either first recorded biochemical progression as defined below, clinical progression or death due to clinical progression. Patients not experiencing a biochemical or clinical failure or death due to clinical progression are censored at time of last assessment.
A biochemical recurrence is defined by any confirmed PSA rise above 0.20 ng/mL with a confirmatory rise at least 2 weeks later. For those patients whose PSA does not drop below 0.20 ng/mL at time of first response assessment at 3 months are considered as non-responders to treatment and are considered to have a biochemical recurrence in case a second measurement at least 2 weeks later confirms a rising PSA above this level.

5.2.2 Metastasis-free survival:

Metastasis-free survival is defined as time between registration and the appearance of a metastatic recurrence (any M1) as suggested by PET-CT or death due to any cause. Patients without any of the events of interest (including those with biochemical relapse only) are censored at the date of the last follow-up. Second cancers are not considered events in terms of this endpoint. In case of biochemical progression, re-staging will be made with PET-CT imaging preferably with the same tracer used before registration. In case of negative PET findings at biochemical relapse, a new PET imaging should be repeated on a 6-montly basis or earlier in case clinically indicated.

5.2.3 Clinical progression-free survival:

Clinical progression-free survival is defined as time between registration and the appearance of a new recurrence (any N1 or M1) as suggested by PET-CT, symptoms related to progressive PC, or death due to any cause.

- A local recurrence is defined as the appearance of evidence of a recurrence within the prostate bed. Confirmation of the recurrence by biopsy is recommended, whenever possible.
- A regional nodal recurrence is defined as a radiographic (PET-CT) evidence of a lymphadenopathy in the pelvis in a patient without the diagnosis of hematologic/lymphatic disorder associated with lymphadenopathy or if there is histopathological evidence. Histologic confirmation is not required although recommended, especially in the absence of biochemical recurrence.
- Distant recurrence is defined as the appearance of distant metastases (M1a, M1b, M1c) outside the pelvis evidenced by PET-CT. Patients without any of the events of interest (including those with biochemical relapse only) are censored at the date of the last follow-up.
- Second cancers are not considered events in terms of this endpoint. Detailed analysis per subsite of recurrence (local, regional and distant) with time-to-event analysis will be performed In case of biochemical progression, re-staging will be made with PET-CT imaging preferably with the same tracer used before registration. In case of negative PET findings at biochemical relapse, repeat PET imaging should be repeated on a 6-montly basis or earlier in case clinically indicated.

5.2.4 Acute and late toxicity:

Radiotherapy toxicity will be assessed according to NCI CTCAE v5.0. Special attention shall be given to diarrhea, fecal incontinence, proctitis, rectal hemorrhage, rectal pain, hematuria, urinary frequency, urinary urgency, urinary retention, urinary incontinence, cystitis non-infective and erectile dysfunction. Acute toxicity is defined as occurring during treatment and up to 3 months after completion of treatment. Late toxicity is defined as occurring later than 3 months after end of treatment.

5.2.5 Quality of life:

All patients registered into this trial are to complete QoL questionnaires at the defined timepoints (see table 1). A longitudinal design is used. Patients are asked to complete a QoL questionnaire.
The EORTC QoL questionnaire (QLQ) C-30 Core questionnaire (version 3) and the prostate cancer module EORTC QLQ PR25 will be used. The QoL questionnaire including all these instruments will be provided for the major languages spoken in the participating centers.

5.3. Handling of missing data and drop-outs

We expect that all registered patients have complete baseline data. All patients that have at least one outcome assessment can be considered in repeated-measures analyses. Models will implicitly correct for missing data based on the missing at random mechanism. If there are patients with no outcome data at all, we will perform multiple imputations. For the time-to-event analysis, patient drop-outs will be accounted for by censoring.

6 Regulatory Aspects and Safety

6.1 Local regulations / Declaration of Helsinki

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

If the SAE occurs at one of the study sites, the coordinating Investigator reports the events to the Ethics Committee concerned, within 15 days.

Follow up of (Serious) Adverse Events

All subjects with SAE must be followed up for outcome. The Ethics Committee must be informed according regulations.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

6.4 Radiation

If the permitted dose guidance value (5 mSv per year if no direct benefit is expected for the participants) is exceeded at any time, the local Investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known (see ClinO, Art. 44).

6.5 Pregnancy

Since this cohort only consists of male patients, pregnancy of the participant is not possible. However, patients are counselled regarding strict birth control for at least 6 months after treatment for themselves and their partners.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The sponsor-investigator has the right to close this study (or, if applicable, individual segments thereof, e.g., recruitment) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
- Safety findings from this study, e.g., SAEs,
- Results of parallel clinical studies,
- Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity, or reproduction toxicity),
- If the study conduct, e.g., recruitment rate, drop-out rate, data quality, protocol compliance, does not suggest a proper completion of the trial within a reasonable time frame.

The Investigator has the right to close his centre at any time. For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties,
- All affected institutions, e.g., IEC(s) or IRB(s), competent authority, study centre, head of study centre must be informed as applicable according to local law,
- The Investigator will retain all study materials unless notification will be given by the sponsor for destruction,
- In case of a partial study closure, ongoing patients, including those in post study follow-up, must be cared for in an ethical manner.

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38)

Essential documents will be archived safely and securely in such a way that ensures that they are readily available upon authorities' request. Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital.

After termination of the study, all study files must be archived according to the Ordinance on Clinical Trials in Human Research (ClinO), Art. 45:

"[1] The sponsor must retain all data relating to the clinical trial … at least for ten years after the completion or discontinuation of the clinical trial.

[2] The investigator must retain all documents required for the identification and follow-up of participants, and all other original data, for at least ten years after the completion or discontinuation of the clinical trial.

6.8 Insurance

Insurance will be provided by the University Hospital of Bern, Inselspital. A copy of the certificate is filed in each investigator site file and the trial master file.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

7.1.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html).

The protocol will be approved by the Local, Regional or National Ethics Committees.

7.1.2 Subject identification

Trial-related data of the patient will be provided in a coded manner to the Sponsor. The names of the patients will not be disclosed to the University Hospital Bern, Switzerland. A sequential UPN will be attributed to each patient registered into the trial. Identification of patients must be guaranteed at the center. In order to avoid identification errors the UPN have to be provided on the CRF. Use the patient screening, enrollment and identification list. Patient confidentiality will be maintained according to applicable legislation. Patients must be informed of, and agree to, data transfer and handling, in accordance with local regulations.

7.1.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered. This must be done in accordance with the national and local regulatory requirements.

7.2 Risk-benefit assessment

This trial investigates the use of ultrahypofractionated SRT for patients with biochemical progression after prostatectomy who developed isolated local recurrence with no evidence of metastasis. For this group of patients, conventional SRT is the standard of care. Previous studies have shown that ultrahypofractionated RT is safe and can be considered as standard of care in treatment of primary prostate cancer. The use of ultrahypofractionated SRT was reported in various retrospective series and phase I trials.

Patients presenting disease progression with radiological evidence of disease either loco-regionally and/or systemically (bone and/or lymph nodes) could undergo biopsy depending on clinical judgment, i.e. if the risks of the biopsy procedure are clinically acceptable. This will be discussed with patients at an individual basis.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

The investigators will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP (E6) and regulatory and institutional requirements for the protection of confidentiality of subjects. SecuTrial (interActive Systems) will be used as database. The principal investigator, sub-investigator, and clinical research nurses or coordinators will have access to the records.

The principal investigators will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

8.2.1 Case Report Forms

The CRFs will be electronic (eCRF). All data requested on the CRFs must be recorded and the recorded data should be consistent with the source documents or the discrepancies should be explained. The Investigator should ensure the accuracy, completeness, and timeliness of the data reported in the CRF and all other required reports. Generally, the CRFs should be completed within one week of completion of a patient visit.

8.2.2 Specification of source documents

Source documents must be available at the site to document the existence of the study participants and must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Where source documents for specific entries in the CRF are not available, this must be explicitly documented in a note to file. Any data recorded directly in the CRF will be considered as source data. Any change or correction to source data should be dated, initialed, and explained (if necessary) and should not obscure the original entry. The use of worksheets is allowed if the copies of the templates are documented in the trial master file (TMF). The used worksheets must be kept with the patient charts.
For all data captured in the CRF, the location of the source should be documented on a list of source documents, which will be stored in the investigator site file at each study site. Only the local investigator, the responsible study nurse team, the study monitor and the authorities can access this document.

8.2.3 Record keeping / archiving

Essential documents (written and electronic), including images and radiotherapy plans must be retained for a period of at least 10 years from the completion or premature termination of the trial. The investigators should take measures to prevent accidental or premature destruction of these documents.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

The investigator ensures anonymity of the patients; patients will not be identified by names in any documents. Signed informed consent forms and patient enrollment log will be kept strictly confidential to enable patient identification at the site.

8.4 Retention and destruction of study data

All study data are archived for 10 years after study termination or premature termination of the study.

9 MONITORING AND REGISTRATION

For quality control of the study conduct and data retrieval, all study sites will be visited on-site by appropriately trained and qualified monitors. Any findings and comments will be documented in site visit reports and communicated to the local PI and to the sponsor as applicable. Investigators at the participating study sites will support the monitor in his/her activities. Prior to study start (first participant enrolled) a plan detailing all monitoring-related procedures will be developed.

All source data and relevant documents will be accessible to monitors and questions of monitors are answered during site visits.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

Debiopharm AG and Berger-Janser Stiftung support financially this clinical trial.

The results will be published in the name of the Hypo-FOCAL-SRT trial in a peer reviewed international journal on behalf of all collaborators. All presentations and publications, including abstracts, relating to the trial must be authorized by the Hypo-FOCAL-SRT trial steering committee (all co-investigators listed in the protocol). Participating centers should ask for the approval of the trial steering committee to use any data related to the patients registered in the trial.

The investigators declare that they have no conflict of interest.

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12 APPENDICES

Appendix 1 TNM Classification according to UICC 2009

T - Primary tumor
pT: pathological tumor classification
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically unapparent tumor not palpable or visible by imaging
T1a Tumor incidental histological finding in 5% or less of tissue resected
T1b Tumor incidental histological finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined within the prostate
T2a Tumor involves one half of one lobe or less
T2b Tumor involves more than one half of one lobe but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostate capsule
T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes
cN: clinical regional lymph node classification
pN: pathological regional lymph node classification
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M - Distant metastases
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Nonregional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Appendix 2 Pre-registration imaging (PSMA PET CT):

For the detection of local recurrence using hybrid imaging several, PSMA-tracers are clinically available, such as ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCFPYL (Pylarify - piflufolastat F 18). Imaging is usually performed as a whole-body PET/CT for the detection of local recurrence and distant metastases.

Imaging protocol should contain:

- The radiochemical purity of the radiotracer should be greater than or equal to 95% in high performance liquid chromatography (HPLC) and Thin Layer Chromatography (TLC))
- Free ^{18}F-fluoride or ^{68}Ga-eluate should be the major impurity.
- i.v. application of the radiotracer is beneficial
- regarding the specific tracer a tracer-individual uptake period from application to imaging is recommended:
    - 60 min p.i. for ^{68}Ga-PSMA-11
    - 90-120 min p.i. for ^{18}F-PSMA-1007
    - 60 min p.i. for ^{18}F-DCFPYL
- PET scans should be acquired in the 3D mode
    - with an acquisition time of 1.5 min/bed position
    - by continues bed movement or
    - using a whole-body PET/CT scanner.
- Emission data using bed position PET/CT scanners should be corrected for scatter and attenuation and reconstructed iteratively with an OSEM algorithm (2 iterations and 21 subsets) followed by a postreconstruction smoothing gaussian filter.
- Whole body PET images at Inselspital Bern using the Siemens Quadra or Siemens Biograph Vision 600 will be reconstructed with the same reconstruction parameters for both systems in 3D with a zoom factor of 1.0. Emission data need to be corrected for randoms, scatter and decay, and reconstruction with the vendor's time of flight (TOF) point-spread-function (PSF) algorithm with 4 iterations and 5 subsets.

Image interpretation: Focal uptake of ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCFPYL higher than the surrounding background and not associated with physiologic uptake is considered suggestive of malignancy. Typical pitfalls in PSMA ligand PET imaging need to be known (e.g., celiac and other ganglia for ^{18}F-PSMA-1007, fractures and degenerative changes for all fluorinated radiotracers, and perfusion effects in inflammatory lymph nodes for all tracers).

Appendix 3 Pre-treatment imaging (mpMRI)

In order to define the extension of macroscopic local recurrence, a mpMRI of the pelvis with i.v. Gadolinium is mandatory after biochemical progression upon RP

MRI should preferably be performed on a 3T MR unit; if not available a 1.5T MR unit can also be accepted. There is no need for an endorectal coil. MRI should cover the entire pelvis from the aortic bifurcation to the inferior border of the pubic symphysis. Ideally, air in the rectum should be minimized by emptying the rectum by applying local guidelines. The following sequences should be performed:

- Coronal T2-weighted sequence with isotropic voxels (1mm) covering the entire pelvis allowing reconstruction in the axial and sagittal plane.
- Axial T2-weighted high resolution covering the former prostatic bed including seminal vesicles (3mm slice thickness, no gap)
- Dynamic axial T1-weighted sequence (Dotarem®) including prostatic bed and seminal vesicles with high spatial resolution and slice thickness of 3mm.
- A T1-weighted sequence before administration of Gadolinium has to be added.
- Diffusion-weighted MRI (DW-MRI) in the axial plane covering the entire pelvis with slice thickness of 4mm and b-values of 0, 500 and 1000 sec/mm^2 in order to detect lymph node metastases and local recurrence.
- Diffusion-weighted MRI (Zoomit) with limited field of view (former prostate and seminal vesicle bed) and b-values of 0, 500, 1000 and 2000 sec/mm^2.
- Axial T1-weighted fat saturated sequence covering the entire pelvis (4mm slice thickness).

Image interpretation: Local recurrence is defined as the following: soft tissue mass on T1- and T2-weighted sequences with early contrast medium enhancement on DCE-MRI. DW-MRI is analyzed qualitatively: tumor recurrence shows a high signal intensity focal lesion on the high b-value image corresponding to a low signal intensity lesion on the corresponding Apparent Diffusion Coefficient (ADC) map (impeded diffusion due to high cellularity).

SPIRIT Checklist for *Trials*

Complete this checklist by entering the page and line numbers where each of the items listed below can be found in your manuscript.

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	Reporting Item		Page and Line Number	Reason if not applicable
Administrative information				
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1: 1-3	
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	4: 86-87	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	4: 86-87	
Protocol version	#3	Date and version identifier	4: 88-89	

Funding	#4	Sources and types of financial, material, and other support	19: 393-400	
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	19: 389-392	
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	19: 389-392	
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19: 389-392	
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	19: 389-392	
Introduction			3: 52-82	
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3: 52-82	

Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	3: 52-82	
Objectives	#7	Specific objectives or hypotheses	3: 52-82	
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	3: 80 -82	
Methods: Participants, interventions, and outcomes				
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	4: 86-91	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	4, 5: 92-130	
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7-11: 178-286	
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	7-11: 178-286	

Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	7-11: 178-286	
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7-11: 178-286	
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7: 169: 177	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6: 151-163	
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6: 151-163	
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6, 6: 131-149	

Methods: Assignment of interventions (for controlled trials)				
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	N/A	Not controlled trial
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N/A	Not controlled trial
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N/A	Not controlled trial
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N/A	Not controlled trial
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A	Not controlled trial
Methods: Data collection, management, and analysis				

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	5, 6: 131-149	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	5, 6: 131-149	
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13: 290-303	
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13: 290-303	
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13: 290-303	

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13: 305-310	
Methods: Monitoring				
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	5: 131-149	
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	N/A	No interim analysis
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	7: 173	
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N/A	No auditing
Ethics and dissemination				

Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	4: 86-91	
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	4: 86-91	
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	4: 94-95	
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N/A	This is not an ancillary study
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	5, 6: 131-149	
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	19: 387-390	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	5, 6: 131-149	

Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6: 159-163	
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	19: 393-400	
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	19: 393-400	
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N/A	No public access to the full protocol
Appendices				
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	19: 404-407	
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A	This is not an ancillary study

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Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075846.R2
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Complete List of Authors:	Mathier, Etienne; Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern Althaus, Alexander; Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern Zwahlen, Daniel; Kantonsspital Winterthur, Department of Radiation Oncology Lustenberger, Jens; University Hospital Basel, Department of Radiation Oncology Zamboglou, Constantinos; German Oncology Center, European University Cyprus, Limassol, Cyprus De Bari, Berardino; Réseau hospitalier neuchâtelois, Department of Radiation Oncology Aebersold, Daniel M.; Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern Guckenberger, Matthias; University Hospital Zurich, Zilli, Thomas; Oncological Institute of Southern Switzerland, EOC, Bellinzona, Switzerland, Department of Radiation Oncology; Università della Svizzera italiana Shelan, Mohamed; Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern
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HypoFocal SRT Trial: Ultra-hypo fractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy - Single-arm phase II Study - Clinical Trial Protocol.

Etienne Mathier[1#], Alexander Althaus[1#], Daniel R. Zwahlen[2], Jens Lustenberger[3], Constantinos Zamboglou[4], Berardino De Bari[5], Daniel M. Aebersold [1], Matthias Guckenberger[6], Thomas Zilli[7*], Mohamed Shelan [1*]

[#]Equal contribution as first authors

*Equal contribution as last authors

Affiliations

[1] Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, Switzerland

[2] Department of Radiation Oncology, Kantonsspital Winterthur, Winterthur, Switzerland

[3] Department of Radiation Oncology, University Hospital of Basel, Basel, Switzerland

[4] German Oncology Center, European University Cyprus, Limassol, Cyprus

[5]Department of Radiation Oncology, Réseau hospitalier neuchâtelois, La Chaux-de-Fonds, Switzerland

[6] Department of Radiation Oncology, University Hospital Zürich, University of Zurich, Switzerland

[7] Department of Radiation Oncology, Oncology Institute of Southern Switzerland, EOC, Bellinzona, Switzerland; Facoltà di Scienze Biomediche, Università della Svizzera Italiana, Lugano, Switzerland

* Correspondence:

Mohamed Shelan, MD

Department of Radiation Oncology, Inselspital, Bern University Hospital, University of Bern, 3010 Bern, Switzerland

Tel: +41 31 632 26 32

Email: mohamed.shelan@insel.ch

ABSTRACT

Introduction: Despite radical prostatectomy (RP) and radiotherapy (RT) being established treatments for localized prostate cancer, a significant number of patients experience recurrent disease. While conventionally fractionated RT is still being used as a standard treatment in the postoperative setting, ultra-hypofractionated RT has emerged as a viable option with encouraging results in patients with localized disease in the primary setting. In addition, recent technological advancements in RT delivery and precise definition of isolated macroscopic recurrence within the prostate bed using Prostate-Specific Membrane Antigen-Positron Emission Tomography (PSMA-PET) and multiparametric magnetic resonance imaging (mpMRI) allow the exploration of ultra-hypofractionated schedules in the salvage setting using five fractions.

Methods and analysis: In this single-arm prospective phase II multicenter trial, 36 patients with node-negative prostate adenocarcinoma treated with radical prostatectomy (RP) at least 6 months before trial registration, tumor stage pT2a-3b, R0-1, pN0, or cN0 according to the UICC TNM 2009 and evidence of measurable local recurrence within the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months, will be included. The patients will undergo focal ultra-hypofractionated salvage RT (sRT) with 34 Gy in 5 fractions every other day to the site of local recurrence in combination with 6 months of Androgen deprivation therapy. The primary outcome of this study is biochemical relapse-free survival at 2 years. Secondary outcomes include acute side effects (until 90 days after the end of RT) of grade 3 or higher based on Common Terminology Criteria for Adverse Events (CTCAE version 5), progression-free survival, metastasis-free survival, late side effects, and the quality of life (based on EORTC QLQ-C30, QLQ-PR25).

Ethics and dissemination: The study has received ethical approval from the Ethics Commission of the Canton of Bern (KEK-BE 2022-01026). Academic dissemination will occur through publications and conference presentations.

Trial registration: ClinicalTrials.gov NCT05746806. Registered on February 28, 2023.

Strengths and limitations of this study:

- Innovative trial evaluating focal SBRT combined with short-term ADT for treating isolated local recurrence after RP.
- Treatment planning is precisely defined based on PSMA PET imaging and mpMRI.
- Potential for improved efficacy and toxicity profile of salvage radiotherapy.
- Non-randomized trial; further research will be required.
- Small sample size.

Study status: Open for accrual.

Funding: Debiopharm AG and Berger-Janser Stiftung

Keywords: ultra-hypofractionation; SBRT; local recurrence; prostate cancer; salvage radiotherapy.

BACKGROUND

Radical prostatectomy (RP) and radiotherapy (RT) are cornerstones for the treatment of localized prostate cancer (PC) [1]. However, around 30% to 60% of patients undergoing RP will develop recurrent disease [2, 3]. Various large randomized controlled studies have shown the effectiveness of postoperative RT in men who have a high risk of local recurrence following RP, such as pT3 tumor or positive resection margins [4–8]. In the era of high-sensitivity prostate-specific antigen (PSA) and prostate-specific membrane antigen-positron emission tomography and computed tomography (PSMA-PET/CT) as a standard staging examination in recurrent PC, new data suggest comparable oncological results if patients are treated early with salvage RT (sRT) compared to immediate adjuvant RT [9–12]. Nevertheless, the aforementioned trials and those involving patients receiving sRT due to macroscopic tumor recurrence in the prostate bed were conducted with conventionally fractionated RT, typically 2 Gy per fraction [4–12].

Recently, ultra-hypofractionated RT, using usually >5 Gy or higher per fraction, was assessed as a valid therapeutic option in patients with low- or intermediate-risk as a definitive treatment. Published data with fair follow-up periods demonstrated excellent biochemical control management with a favorable toxicity profile [13–20]. Moreover, the evidence on ultra-hypofractionated in high-risk individuals is emerging, and many significant studies have reported favorable findings [21–26]. Ultra-hypofractionation is used to treat patients with PC due to its low α/β value which is thought to be around 1.5 Gy [27, 28]. It is anticipated that increasing the dose per fraction would increase the therapeutic ratio and, thus, the potential tumor control. Nevertheless, considering the low toxicity rates reported [29–37], using moderate hypofractionation in the postoperative setting with a daily RT dose of up to 3 Gy per fraction does not seem to corroborate this concern. However, the evidence on postoperative ultra-hypofractionated RT to the prostate bed is still in its early stages.

Further improvement in the oncological outcomes can be expected through technological developments in RT delivery and precise targeting of the local relapses in the prostate bed. A sRT using an ultra-hypofractionated schedule delivered in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric magnetic resonance imaging (mpMRI) in combination with short-term androgen deprivation therapy for 6 months, may represent a valid treatment strategy to improve the therapeutic ratio in these patients (shorter overall treatment time, better sparing of organs at risk while delivering higher biological-equivalent dose into the target volume).

The main objective of this prospective single-arm trial is to assess the efficacy and safety of ultra-hypofractionated sRT delivered in 5 fractions to the site of local recurrence within the prostate bed with target delineation based on PSMA PET and MRI.

METHODS/DESIGN

The Hypo Focal sRT Trial protocol was constructed using the SPIRIT reporting guidelines [29]. Following permission from the regional ethics committees (KEK-BE 2022-01026), the research is registered with ClinicalTrials.gov (NCT05746806) and the Swiss National Clinical Trials Portal. Both the sponsor-investigator and the trial statistician have given their approval to the protocol version 3.0 (dated 11.11.2022).

Study Population

- Inclusion criteria:

1. Before registration and before any trial-specific procedures, written informed consent in accordance with ICH/GCP rules is required.

2. Minimum age to register is eighteen years old.

3. Performance level 0-1 according to WHO.

4. Lymph node negative adenocarcinoma of the prostate treated with RP at least 6 months before trial registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009.

5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, biopsy confirmation is recommended.

6. Patient must have non-metastatic (N0, M0) disease, as defined by no evidence of nodal or distant metastases seen on PSMA PET scan.

7. Patients must have a testosterone level > 50 ng/dL.

8. Patients must not have had bilateral orchiectomy, LHRH agonists, antiandrogens, or any combination of these in the past.

9. Absence of any psychological, family, sociological, or geographic situation that would make it difficult for the patient to adhere to the research protocol and follow-up plan; the patient should be informed of these factors before registering for the trial.

- Exclusion criteria:

1. PSA levels (> 0.4 ng/mL) that persist 4–20 weeks after RP.
2. Previous diagnosis of hematologic or primary solid malignancy during the preceding three years previous to registration, except for curatively managed localized non-melanoma skin cancer.
3. Use of substances known to alter PSA levels, such as androgen deprivation therapy and any kind of androgen suppression medication, within four weeks of the start of the trial treatment phase.
4. Bilateral hip prosthesis.
5. Co-morbidities that are severe or active and that are likely to have an effect on whether or not sRT is advisable.
6. Treatment with any experimental treatment or involvement in a clinical trial within the last thirty days (with the exception of concurrent participation in the biobank research, which is allowed) is required for eligibility to register.

Study design and sample size

This is a single-arm, prospective, phase II multicenter study. According to the published prospective trials and retrospective series reporting the outcomes of the normo-fractionated sRT, we define biochemical relapse-free survival at 2 years of 60% as poor and of 80% as the promising outcome that would justify further investigation [30–33]. We will therefore test the null hypothesis that the biochemical relapse-free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%, not taking into account patients lost to follow-up. We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects (grade 3 or higher) is larger than 27%; the proportion observed would be tested using one-sample binomial exact tests with a one-sided alpha of 5%. **Figure 1** shows a summary of the study design and schedule.

Outcomes

Primary outcome

- Biochemical relapse-free survival at 2 years

Secondary outcome

- Acute side effects (until 90 days after the end of RT) of grade 3 or higher based on CTCAE v5
- Progression-free survival
- Metastasis-free survival
- Late side effects
- Quality of life (based on EORTC QLQ-C30, QLQ-PR25)

Study Intervention

Pre-registration imaging

Within 3 months prior to registration, PSMA PET/CT is mandatory to exclude regional or distant metastasis. Both ^{18}F- and ^{68}Ga-PSMA tracers are allowed. An mpMRI of the prostate bed is required within 3 months before registration is mandatory to define the extension of local recurrence.

Radiation treatment (SBRT)

Patient's positioning, immobilization, data acquisition and simulation:

Determining the gross tumor volume (GTV), the planned target volume (PTV), and the essential structures requires a treatment-planning CT scan with the patient in the same position as during treatment. The patients will be placed in the supine position for the entire process. Support for the knees and legs is strongly advised. On a flat table, each patient will be placed in the treatment position while being immobilized by a unique device. It is advised that patients be treated and scanned while having a comfortably full bladder. For prostate bed RT, it is advised to have an empty rectum. An example of a bladder and rectal protocol: An empty rectum is provided by using a rectal enema ± 60 minutes before planning CT. After emptying the rectum and bladder, the patient is asked to drink the amount of 500-750 ml of water. The planning CT is then performed after 40 minutes. The patient repeats the bladder filling procedure during the entire treatment course. An endorectal balloon can be used for repositioning purposes as per local institutional standards.

Radiopaque fiducial markers (mandatory for robotic-based treatments) may be implanted in the prostate bed one week before the planning CT scan at the discretion of the treating center. During the planning and performance of the treatment, the patient's location will be reproduced employing skin markings

and orthogonal laser beams. The pelvis should be scanned during the treatment planning CT scan, at least from the lower portion of the second lumbar vertebra (L2) to the lower half of the ischial tuberosities. The CT scan must cover the full target volume and all organs at risk (OAR). A CT slice should be no thicker than 2 mm. On every CT slice that shows the GTV, PTV, and OAR, these structures must be highlighted. Morphological and topographical information given by clinical examination, mpMRI and PET/CT must be integrated to delineate the target volumes. Rigid or deformable co-registration is allowed.

Treatment Volumes:

Definition of target volume (refer to Supplementary material 1):

- **The Gross Tumor Volume of the suspicious local recurrence (GTV)** is defined by the physician as all known gross disease *before any treatment* as defined by the CT/MRI images and PET scan using rigid or deformable fusion and/or clinical information.
- **The Planning Target Volume (PTV)** will provide the GTV a margin to account for daily treatment setup variations and internal motion brought on by breathing or movement during treatment. The PTV should surround the GTV with a 5 mm margin on all sides.

Organs at risk (OAR):

The delineation of the **OAR** should be done following the RTOG guidelines; the normal pelvis atlas on the RTOG/NRG Oncology website provides examples of normal tissue contours [34].

The bladder is defined by its external wall, with a thickness of 5 mm delineated on each slide, from the dome to the bladder neck and the start of the vesicourethral anastomosis (VUA).

The VUA and distal urethra are delineated from the bladder neck to the distal urethra using mpMRI sequences, and a 2-mm isotropic margin is added around these structures to create a planning organ at risk volume (PRV).

The rectum is defined by its external wall, with a thickness of 5 mm from the recto-sigmoid junction to ischial tuberosities.

The femoral heads are delineated from the top of the hip joint to the small trochanter, while the bowel bag is delineated from the most inferior small or large bowel loop to 1 cm above the planning target volume (PTV) for coplanar beam plans, or more if non-coplanar beams or tomotherapy plans are used.

It is suggested that dose constraints be adhered to; however, if this is not practicable, the dose per fraction or target coverage may be adjusted to comply with the constraint. **Table 1** shows the dose constraints for OARs.

Table 1: Dose constraints for OARs.

Organ at risk	Dose Constraint	Aim
Rectal Wall	V18.1 Gy V29 Gy V36 Gy	< 50% < 20% < 1 cc
Bladder Wall	V18.1 Gy V 37 Gy	< 40% < 10 cc
PRV_VUA and distal Urethra	V36 Gy	< 1 cc
Femoral heads	V14.5 Gy	< 5%
Penile bulb	V29.5 Gy	< 50%
Bowel	V18.1 Gy V30 Gy	< 5 cc < 1 cc

Treatment techniques

It is required to apply rotating techniques or intensity-modulated RT (IMRT). Only dosimetry produced by inversed treatment planning is, by definition, regarded as IMRT. Step-and-Shoot, Sliding-Window, and Volumetric Modulated Arc therapy (VMAT), as well as MRI-guided radiation therapies (MRIdian® or Elekta Unity®), may be employed for performing IMRT. Treatment with Cyberknife® is allowed.

Dose prescription

A total dose of 34 Gy (80% of the maximal dose) will be delivered in 5 fractions and fractions every second day (NTD2Gy 80 Gy α/β=1.5Gy for tumor control and 66.6 Gy α/β=3Gy for late toxicity). Treatment will be prescribed to the periphery of the target (80% of the dose (=34Gy), should cover 90% of the PTV) covering the PTV. A maximal dose of 40 Gy is allowed to GTV. The priority will be given with respect to dose constraints over PTV coverage.

Androgen deprivation therapy

For a total of six months, each patient will be treated with a three-monthly formulation of an LHRH-agonist or antagonist. Prevention with an antiandrogen is indicated for at least 5 days before the initial injection of the agonist in the case of an LHRH-agonist flare and should not be sustained for more than 15 days of the first-month duration.

- Androgen deprivation therapy (ADT) should start no later than the 1st SBRT fraction and no earlier than 2 weeks before the start of RT.
- Palliative ADT should not be initiated for biochemical progression until clinical progression has been demonstrated. In the event of symptom progression, palliative ADT is required. In the event of asymptomatic clinical progression, men who are well-informed are permitted to delay ADT until symptomatic progression occurs (EAU 2023 guidelines) [35]. Generally, we would only begin ADT in asymptomatic individuals if traditional imaging confirmed clinical progression. As a result, we would not advocate initiating ADT for PET-positive lesions that do not seem suspicious on conventional imaging (CT/MRI/bone scintigraphy).
- ADT-related toxicity should be managed, according to Nguyen et al. [36].

Study procedures

The study procedures and the schedule of assessments are presented in **Table 2.**

Table 2: Schedule of assessments

Required investigation	Inclusion		Treatment	1 Month after RT	3 Months after RT	6 Months after RT	Every 6 Months till the end of 2nd year after RT, then once per year till 60 months
	Within 12 weeks prior to registration	Within 2 weeks prior to registration			Within 2 weeks prior to registration		
Eligibility Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x		x	x	x	x
Biochemistry (Blood Samples) *							
PSA		x		x	x	x	x

Testosterone		x		x	x	x	x
Radiology							
PSMA PET	x						
MRI	x						
Radiotherapy							
Treatment planning			x				
Record Planning results			x				
Adverse Events							
Baseline toxicity		x					
Acute toxicity			x	x	x		
Late toxicity						x	x
EORTC QoL questionnaire							
QLQ-C30		x		x	x	x	x
QLQ-PR25		x		x	x	x	x

Planned Analysis

For descriptive statistics, the categorical variables will be presented as frequency and percentage, the normally distributed continuous variables will be presented as mean and standard deviation, and the non-normally distributed continuous variables will be presented as median and interquartile range.

The time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with a 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.

The probability of biochemical relapse-free survival and metastasis-free survival will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be fit to assess the effects of treatment and baseline clinical and pathologic features (such as PSA, PSA doubling time, Gleason score etc.) on biochemical relapse-free survival and metastasis-free survival).

Further subgroup analysis will follow after finalizing the accrual (R0 vs. R1), (pN0 vs. cN0) and based the location of the recurrence.

Study status

Open and currently accruing since February 20, 2023.

The approximate recruitment will be completed by October 2024.

Patient and public involvement

- Patients were not involved in the idea conception of this trial.
- Patients were not involved in the design of this study nor in recruitment of the study.

Ethics and dissemination

The study has been submitted and approved by ethics commission of Canton of Bern. A written informed consent will be obtained from the study participants. Academic dissemination will occur through publication and conference presentations.

DISCUSSION

External beam RT is a well-established treatment for organ-confined prostate cancer, with comparable cure rates to radical prostatectomy [37]. Hypofractionation employs a higher dose-per-fraction while reducing the number of fractions offering a clinical benefit in terms of tumor control in tumors with a low alfa/beta ratio (e.g. prostate cancer) and favorable toxicity, allowing for higher patient comfort [38]. Based on the results of ten prior randomized trials, there is compelling evidence suggesting that moderate hypofractionation RT is not inferior to standard normofractionation RT schedules as a definitive treatment for primary PC[39]. This evidence led to the integration of moderate hypofractionation schedules into the list of valid treatment options in the NCCN guidelines [40]. In addition, recent advancements in the field of RT, including IMRT/rotational techniques, image-guided RT (IGRT), and stereotactic RT (SBRT), have permitted the gradual integration of ultra-hypofractionation in the treatment of localized PC. SBRT for PC has generated adequate data in terms of tumor control, patient-reported quality of life, and minimal toxicity [14, 16, 25] to support its introduction in clinical practice. In addition, the prostate cancer-working group of the German Society of Oncology (DEGRO) and the NCCN Guidelines approve the use of SBRT in the treatment of localized low and intermediate-risk prostate cancer and propose its use in clinical trials for patients with the localized high-risk disease [41, 42].

The evidence of ultra-hypofractionation has recently been supported by two randomized studies (HYPO RT-PC) [25], PACE-B trial [14]), which compare its usage to conventional fractionation. Nevertheless, only HYPO-RT-PC provided information on the outcomes of long-term tumor and toxicity control. A randomized systematic review and meta-analysis of phase 3 studies evaluating SBRT with normo- and hypo-fractionated regimens were published in 2020. It was determined that the ultra-hypofractionated regimens had comparable 5-year disease-free survival outcomes, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, in comparison to hypofractionated regimens and conventional RT [43]. In 2022, the toxicity outcome of the PACE B Trial was published, showing no significant differences between the five fractions of SBRT and conventional RT [44].

The use of moderate hypofractionation is gaining more popularity as a standard treatment in the postoperative setting [45]. Retrospective and prospective single-arm studies support a safe toxicity profile and promising biochemical control rates with hypofractionation [45]. According to newly released findings from the phase III clinical study NRG-GU003 evaluating hypofractionated postoperative prostate bed RT (HYPORT) to conventional post-prostatectomy RT for men with prostate cancer, treatment with HYPORT did not cause a rise in patient-reported GI or genitourinary (GU) toxicity for study subjects, with a comparable biochemical disease control at the 2-year follow-up [46].

Prakish et al. [47] did a theoretical feasibility study of SBRT following RP depending on the NTCP (Normal Tissue Complication Probability) model, using individuals who had been managed with conventional EBRT for biochemical recurrence after prostatectomy. The goal was to show that SBRT could be used safely and effectively in this clinical situation. A dose of 30 Gy was delivered to the PTV in five fractions, translating to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5 Gy, in accordance with RTOG standards to define postprostatectomy volumes. To predict the probability of late rectal and/or bladder toxicity, the NTCP model was used. According to the NTCP model, the average incidence of grade ≥ 2 late rectal toxicity was assessed to be 0.28%, and that of late grade 2 toxicity on the bladder neck was determined to be as low as 0.00013%, while the average incidence of late urinary symptoms exacerbation was calculated to be 4.81 %. The author's conclusion is that employing SBRT after surgery looks viable and may provide a safe, practical therapeutic alternative for individuals in both the adjuvant and salvage following biochemical failure, taking into account the limitations of the NTCP model.

Sampath et al. examined the use of stereotactic dose-escalated RT on prostate beds in a prospective phase 1 research, which revealed a crude rate of biochemical control of 42% in the overall population [48]. Patients received care using dose fractionation regimens of 35 Gy, 40 Gy, and 45 Gy in five fractions each. The authors emphasized that raising the dosage to 45 Gy was possible without increasing the number of

adverse events but that there was no observed improvement in PSA control when compared to 40 Gy in 5 fractions. Similarly, a recent propensity score study comparing salvage SBRT and conventional RT for macroscopic prostate bed recurrence revealed similar bRFS and PFS rates across the two modalities. On the other hand, a reduced incidence of toxicity was verified for patients receiving focal stereotactic sRT compared to conventionally fractionated sRT, with acute GI and GU adverse events recorded in 4.4% against 44.4% ($p< 0.001$) and 28.9% against 46.7% ($p= 0.08$) of participants, and late GI and GU side effects reported in 0% versus 13.3% ($p = 0.04$) and 6.7% versus 22.2% ($p = 0.03$) of patient populations, respectively [49]. The authors argue that salvage SBRT is a desirable substitute for conventional sRT in this situation due to the approach's favorable therapeutic ratio and the less number of required fractions. Additionally, the prospective phase 2 SCIMITAR trial reported the quality of life and toxicity outcome of 100 patients who received postoperative ultra-hypofractionated SBRT delivered in 5 fractions [50]. Acute and late grade 2 GU toxicities were both 9%, while acute and late grade 2 GI toxicities were 5% and 0%, respectively. Three patients had grade 3 toxicity ($n = 1$ GU, $n = 2$ GI) [50].

The expected results from the Hypo-Focal sRT trial will provide the first prospective evidence for the focal hypofractionated RT in the salvage setting and can be used as a basis for a large multicenter phase 3 trial. In addition to the assumed improvement in efficacy and toxicity profile due to precise customization of the treatment target volumes, the application of a focal hypofractionated RT is expected to achieve cost-effectiveness benefits. Due to the very short treatment course (unlike conventional RT treatments, which can take up to 7 weeks), hypofractionated focal sRT leads to greater patient convenience and comfortability.

Abbreviations:

AE	Adverse Event
ADC	Apparent diffusion coefficient
ADT	Androgen deprivation therapy
ASR/DSUR	Annual Safety Report / Development Safety Report
ASTRO	American Society for Radiation Oncology
ASCO/AUA	American Society of Clinical Oncology/ American Urological Association
ASTRO	American Society for Therapeutic Radiology and Oncology
BASEC	Business Administration System for Ethical Committees
bRFS	Biochemical relapse-free survival
CA	Clinical approval
CBCT	Cone Beam CT

CEC	Clinical ethics committee
ClinO	Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTU	Clinical trials unit
CTV	Clinical target volume
DCE	Dynamic contrast enhancement
DEGRO	German Society of radiation oncology
DFS	Disease free survival
DRE	Digital rectal examination
DVH	Dose-volume histogram
DWI	Diffusion-weighted imaging
EAU	European Association of Urology
EORTC	European Organisation for Research and Treatment of Cancer
18F	Fluorine-18
FADP	Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)
FOPH	Federal Office of Public Health
18F-DCFPYL	Pylarify - piflufolastat Fluorine-18
eCRF	Electronic Case Report Form
68Ga	Gallium-68
GCP	Good Clinical Practice
GTV	Gross tumor volume
GI	Gastrointestinal
GU	Genitourinary
HR	Hazard ratio
HRA	Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)
ICH	International Conference on Harmonisation
IGRT	Image-guided radiotherapy
IMRT	Intensity-modulated radiotherapy
LHRH	Luteinizing hormone-releasing hormone
LHRHa	Luteinizing hormone-releasing hormone agonist
MFS	Metastasis free survival

mpMRI	Multiparametric magnetic resonance imaging
MRI	Magnetic resonance imaging
NCI	National cancer institute
NTCP	Normal tissue complication probability
NTD	Normalized total dose
NCCN	National comprehensive cancer network
OAR	Organs at risk
OS	Overall survival
OSEM	Ordered subset expectation maximization
PET/CT	Positron electron computed tomography
PFS	Progression-free survival
PI	Principal Investigator
PRV	Planning organ at risk volume
PSA	Prostate-specific antigen
PSF	Point-spread-function
PSMA	Prostate-specific membrane antigen
PTV	Planning target volume
RP	Radical prostatectomy
RT	Radiotherapy
RTOG	Radiation therapy oncology group
SAE	Serious Adverse Event
SBRT	Stereotactic body radiotherapy
SI	Signal intensity
sRT	Salvage radiotherapy
TLC	Thin layer chromatography
TMF	Trial master file
TNM	Tumor Nodes Metastases
TOF	Time of flight
UICC	Union internationale contre le cancer
UPN	Unique Patient Number
VUA	Vesicourethral anastomosis
WHO	World health organization
QLQ	Quality of life questionnaire

QoL	Quality of life

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Patient Consent for publication: obtained.

Competing interests statement: None declared.

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Figure ligands:

Figure 1: Summary of the study design and schedule.

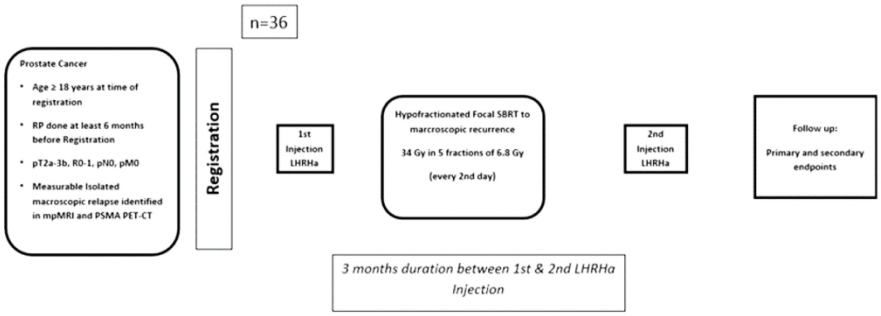

Figure 1: Summary of the study design and schedule.

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INSELSPITAL UNIVERSITÄTSSPITAL BERN HÔPITAL UNIVERSITAIRE DE BERNE | UCI UNIVERSITY CANCER CENTER INSELSPITAL

A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy

(HypoFocal SRT Trial)

Study Type:	Other Clinical Trial according to ClinO, Chapter 4
Risk Categorisation:	Risk category A according to ClinO, Art. 61
Study Registration:	Clinicaltrials.gov: XXXX Cantonal Ethics Committee Number: KEK-BE 2202-01026
Sponsor-Investigator	Mohamed Shelan, MD Department of Radiation Oncology, Inselspital, Bern University Hospital and University of Bern, Bern, Switzerland. Phone: +41 31 632 24 31 Fax: +41 31 632 85 67 E-mail: mohamed.shelan@insel.ch
Investigated Intervention:	treating isolated prostate bed macroscopic recurrence after radical prostatectomy using ultrahypofractionated radiotherapy.
Protocol ID Version and Date:	Version 3.0 (11/11/2022)

Change history

Version Nr	Version date	Modified without version change	Description, comments	Control
1.0	30.05.2022		Initial version	
2.0	11.09.2022	no	Amended upon request of the ethics committee	MS
3.0	11.11.2022	no	Amended upon request of the ethics committee	MS

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PROTOCOL SIGNATURE FORM

Study Title	A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy

The Sponsor-Investigator has approved the protocol version 3.0 (11/11/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements.

Sponsor Investigator:

Name: Dr. med. Mohamed Shelan

Date: _____ Signature: _____

PROTOCOL SIGNATURE FORM FOR LOCAL INSESTIGATOR:

The local Investigator has approved the protocol version 3.0 (11/11/2022) and confirm hereby to conduct the study according to the protocol, current version of the World Medical Association Declaration of Helsinki, and ICH-GCP guidelines as well as the local legally applicable requirements

Local Principal Investigator at study site:

Site:

Principal Investigator:

Date: _____ Signature: _____

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GLOSSARY OF ABBREVATIONS

AE	*Adverse Event*
ADC	*Apparent diffusion coefficient*
ADT	*Aandrogen deprivation therapy*
ASR/DSUR	*Annual Safety Repot / Development Safety Report*
ASTRO/ ASCO/AUA	*American societies of radiation oncology, medical oncology and urology*
BASEC	*Business Administration System for Ethical Committees*
bRFS	*Biochemical relapse free survival*
CA	*Clinical approval*
CBCT	*Cone Beam CT*
CEC	*Clinical ethics committee*
ClinO	*Ordinance on Clinical Trials in Human Research (in German: KlinV, in French: OClin, in Italian: OSRUm)*
CRF	*Case Report Form*
CTCAE	*Common Terminology Criteria for Adverse Events*
CTU	*Clinical trials unit*
CTV	*Clinical target volume*
DCE	*Dynamic contrast enhancement*
DEGRO	*German society of radiation oncology*
DFS	*Disease free survival*
DRE	*Digital rectal examination*
DVH	*Dose volume histogram*
DWI	*Diffusion-weighted imaging*
EAU	*European association of urology*
EORTC	*European organisation for research and treatment of cancer*
^{18}F	*Fluorine-18*
FADP	*Federal Act on Data Protection (in German: DSG, in French: LPD, in Italian: LPD)*
FOPH	*Federal Office of Public Health*
^{18}F- DCFPYL	*Pylarify - piflufolastat Fluorine-18*
eCRF	*Electronic Case Report Form*
^{68}Ga	*Gallium-68*
GCP	*Good Clinical Practice*
GTV	*Gross tumor volume*
GI	*Gastrointestinal*
GU	*Genitourinary*
HR	*Hazard ratio*
HRA	*Human Research Act (in German: HFG, in French: LRH, in Italian: LRUm)*
ICH	*International Conference on Harmonisation*
IGRT	*Image guided radiotherapy*
IMRT	*Intensity modulated radiotherapy*

LHRH	*Luteinizing hormone releasing hormone*
LHRHa	*Luteinizing hormone releasing hormone agonist*
MFS	*Metastasis free survival*
mpMRI	*Multiparametric magnetic resonance imaging*
MRI	*Magnetic resonance imaging*
NCI	*National cancer institute*
NTCP	*Normal tissue complication probability*
NTD	*Normalized total dose*
NCCN	*National comprehensive cancer network*
OAR	*Organs at risk*
OS	*Overall survival*
OSEM	*Ordered subset expectation maximization*
PET/CT	*Positron electron computed tomography*
PFS	*Progression-free survival*
PI	*Principal Investigator*
PRV	*Planning organ at risk volume*
PSA	*Prostate specific antigen*
PSF	*Point-spread-function*
PSMA	*Prostate-specific membrane antigen*
PTV	*Planning target volume*
RP	*Radical prostatectomy*
RT	*Radiotherapy*
RTOG	*Radiation therapy oncology group*
SAE	*Serious Adverse Event*
SBRT	*Stereotactic body radiotherapy*
SI	*Signal intensity*
SRT	*Salvage radiotherapy*
TLC	*Thin layer chromatography*
TMF	*Trial master file*
TNM	*Tumor Nodes Metastases*
TOF	*Time of flight*
UICC	*Union internationale contre le cancer*
UPN	*Unique Patient Number*
VUA	*Vesicourethral anastomosis*
WHO	*World health organization*
QLQ	*Quality of life questionnaire*
QoL	*Quality of life*

1 STUDY SYNOPSIS

Sponsor / Sponsor-Investigator	Mohamed Shelan, MD
Study Title:	A single arm phase II trial of ultrahypofractionated focal salvage radiotherapy for isolated prostate bed recurrence after radical prostatectomy
Short Title / Study ID:	HypoFocal-SRT
Protocol Version and Date:	Ver. 3.0 date 11.11.2022
Trial registration:	www.clinicaltrials.gov. Registration will be completed after the Ethic committee approval
Study category and Rationale	Category A Ultrahypofractionated radiotherapy is not a standard of care in patients with local recurrence after radical prostatectomy. However, based on published data from retrospective series and phase I trial using a similar or higher fractionation scheme to the one used in this trial, toxicity is not expected to be higher than in case of normofractionated salvage radiotherapy. In terms of tumor control outcome, a benefit of hypofractionation can be expected due to the low α/β value of prostate cancer.
Clinical Phase:	Phase II
Background and Rationale:	Radical prostatectomy and radiotherapy (RT) are the considered as backbones for treating localized disease[1]. However radical prostatectomy, 30 – 60% of patients will develop recurrent disease[2,3]. Several large randomized controlled trials have shown a benefit of postoperative radiation therapy in patients with a high risk of local recurrence after RPE, e.g. pT3 disease or positive resection margins[4–8]. In the era of high sensitivity PSA and PSMA-PET/CT, there has been additional evidence suggesting a similar oncological outcome if patients are treated with early salvage radiotherapy in case of a rising PSA after RPE instead of immediate adjuvant radiotherapy[9–12]. However, the above mentioned studies as well as the studies including patients receiving salvage radiotherapy in case of a macroscopic tumor recurrence in the prostate bed were done with conventionally fractionated radiotherapy, usually in 2 Gy per fraction[4–12]. In the setting of definite radiotherapy to the prostate, ultrahypofractionated radiotherapy has been used as a treatment option in patients with low or intermediate risk for a long time and there are published data with a reasonable follow up that shows excellent biochemical control with low high grade toxicity rates[13–20]. In addition, data on ultrahypofractionated in high-risk patients are emerging with several large trials being published with encouraging results[21–26]. The rationale for using ultrahypofractionated in patients treated for prostate cancer is the estimated low α/β value of around 1.5 Gy[27,28]. Therefore, using a larger fraction dose is expected to improve the therapeutic ratio and consequently the probability of tumor control. Although Data on moderate hypofractionation in the setting of postoperative radiotherapy with a fraction dose of up to 3 Gy per fraction does not seem to support this concern, given the low toxicity rates that were reported in several analyses[29–38]. However, data on postoperative

	ultrahypofractionated radiotherapy to the prostate bed remains immature. The rates of acute and late toxicities following ultrahypofractionated radiotherapy to the prostate bed were reported in retrospective and phase I studies are within the above mentioned ranges. The rate of acute ≥ G2 GI and GU toxicities range from 0 – 50 % and 0 – 33.3 % and for late ≥ G2 GI and GU toxicities from 0 – 11.5 % and 0 – 38.5 %[39–48]. This data suggests that SBRT to the prostate bed can be applied with toxicity rates similar to that of normofractionated or mildly hypofractionated radiotherapy Further improvement in the oncological outcomes can be expected through technological developments in radiotherapy delivery and precise targeting of the local relapses in the prostate bed. A SRT using a ultrahypofractionated schedule delivered precisely in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric MRI (mpMRI) may represent a valid treatment strategy to improve the therapeutic ratio in these patients (short overall treatment time, better sparing of surrounding heathy tissues, increased dose to the target volume). Rationale for combining ADT to SRT - The benefit of ADT to salvage radiation has been demonstrated in two randomized phase III trials, RTOG 9601 and GETUG 16, which provided evidence of improved metastasis-free and overall survival and durable biochemical disease control with bicalutamide for 24 mo and ADT using LHRH agonists for 6 months, respectively. - These studies support the current National Comprehensive Cancer Network (NCCN) guidelines to consider combination of 6–24 months of hormonal therapy with SRT in this setting.
Objective(s):	The main objective of the trial is to explore the efficacy and safety of combining short-term ADT over 6 months to focal ultrahypofractionated SRT delivered in 5 fractions to the site of local recurrence within the prostate bed after radical prostatectomy where mpMRI and PSMA PET/CT are used to precisely identify the local recurrence and compare it to previously published literature.
Outcome(s):	Primary endpoints: - Biochemical relapsefree survival at 2 years Secondary endpoints: - Acute side effects (till 90 days after end of radiation) of grade 3 or higher based on CTCAE v5 - Clinical progression-free survival - Metastasis-free survival - Late side effects - Quality of life (based on EORTC QLQ-C30, QLQ-PR25)
Study design:	This a single arm, prospective, phase II multicenter study
Inclusion / Exclusion criteria:	**Inclusion criteria:** 1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures 2. Age ≥ 18 years at time of registration 3. WHO performance status 0-1 4. Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy (RP) at least 6 months before trial

	registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009. 5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, a biopsy confirmation is recommended. 6. Patient must have non-metastatic (N0, M0) disease, as defined by a lack of nodal or distant metastases seen on PSMA PET/CT scan 7. Patients must have non-castrate levels of serum testosterone (≥50 ng/dL). 8. Patients must not have previously received hormonal therapy (LHRH agonists, antiandrogen, or both, or bilateral orchiectomy). 9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial **Exclusion criteria:** 1. Persistent PSA (> 0.4 ng/mL) 4 to 20 weeks after RP 2. Previous hematologic or primary solid malignancy within 3 years prior registration with the exception of curatively treated localized non-melanoma skin cancer 3. Usage of products known to affect PSA levels within 4 weeks prior to start of trial treatment phase including any form of androgen suppression agents and androgen deprivation therapy 4. Bilateral hip prosthesis 5. Severe or active co-morbidity likely to impact on the advisability of SRT 6. Treatment with any experimental drug or participation within a clinical trial within 30 days prior to registration (exception: concurrent participation in the biobank studies is allowed)
Measurements and procedures:	**Investigations to be performed within 12 weeks prior to registration:** - Physical examinations including Digital rectal examination (DRE) - Multi-parametric MRI - PSMA PET/CT. **Investigations during trial treatment phase** - Planning CT - Multi-parametric MRI if not yet performed - Serum PSA - Total testosterone, - Assessment of recurrences in case of suspected progression **During follow-up:** - Physical examinations - Digital rectal examination (if suspected clinical progression), - serum PSA - Total testosterone - Assessment of recurrences with PSMA PET/CT imaging (local, regional, distant) **All adverse events are collected throughout the trial.**

Control Intervention (if applicable):	This is a single arm study. Control intervention is not applicable.
Number of Participants with Rationale:	It is planned to enrol a total of 36 patients in the trial (see statistical considerations for rationale).
Study Duration:	Expected accrual time: 18 Months
Study Schedule:	First-Participant-In: Q4 2022 Last-Participant-Out: Q4 2027
Investigator(s):	**Dr. med. Mohamed Shelan** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 29 70 E-Mail:mohamed.shelan@insel.ch **Prof. Dr. med. Daniel M. Aebersold** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 24 31 E-Mail:daniel.aebersold@insel.ch **Jens Lustenberger** Department of Radiation Oncology Unispital Basel E-Mail: jens.lustenberger@usb.ch **Prof. Dr. Daniel R. Zwahlen** Department of Radiation Oncology Kantonsspital Winterthur Phone: 079 553 25 63 E-Mail:daniel.zwahlen@ksw.ch **Prof. Dr. med. Thomas Zilli** Clinica di Radio-Oncologia Istituto Oncologico della Svizzera Italiana-Ente Ospedaliero Cantonale (IOSI-EOC) Phone: 091/811 96 35 E-Mail: Thomas.Zilli@eoc.ch **Dr. med. Alexander Althaus** Department of Radiation Oncology Inselspital, Bern University Hospital Bern, Switzerland. Phone: 031 632 29 70 Email: alexander.althaus@insel.ch **Dr. med. Hendrik Gabriel Rathke** Department of Nuclear Medicine Inselspital, Bern University Hospital Bern, Switzerland. Email:hendrik.rathke@insel.ch
Study Centre(s):	Multi-centre study. At least 4 recruiting centers in Switzerland.
Statistical Considerations:	According to the published prospective trials and retrospective series reporting the outcome of the normofractionated SRT, we define

	biochemical relapse free survival at 2 years of 60% as poor and of 80% as promising outcome that would justify further investigation. We will therefore test the null hypothesis that the biochemical relapse free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%. The null hypothesis will be rejected if at least 27 patients show biochemical relapse free survival at 2 years. We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects is larger than 27%, the proportion observed that will be tested using one-sample binomial exact tests with a one-sided alpha of 5%. Time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.
GCP Statement:	This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, the ICH-GCP or ISO EN 14155 (as far as applicable) as well as all national legal and regulatory requirements.

2 BACKGROUND AND RATIONALE

2.1 Disease background

Prostate cancer is the most common non-cutaneous malignancy in men. An estimated 1.1 million patients per year worldwide were diagnosed with prostate cancer, accounting for 15% of the cancers diagnosed in men, with almost 70% of the cases occurring in more developed regions. Prostate cancer is the fifth leading cause of cancer death in men, representing 6.6% of the total male cancer mortality [49].
The most common curative therapeutic modalities for localized prostate cancers include radical prostatectomy (RP) and radiotherapy with or without androgen deprivation therapy. Although there is a wide variability between treatment site and risk groups, approximately 50% of all men with localized prostate cancer undergo RP [50]. After RP, between 30-60% of men can develop a biochemical relapse within 5 years [51–54]. The site of relapse in prostate cancer patients after RP is predominantly local, with a low incidence of distant failures [55]. Within patients with biochemical relapse the actuarial rate of bone metastasis is 37% and 65% at 5 years and 10 years, respectively. The median time to development of bone metastasis after biochemical relapse is 8 years and the median time between development of bone metastasis and death is 5 years [56].

2.2 Therapy background

2.2.1 The use of adjuvant and salvage radiotherapy after radical prostatectomy

Adverse pathological factors after prostatectomy, such as positive surgical margins, extracapsular extension, or seminal vesicle invasion, increase the likelihood of disease recurrence. Three randomized clinical trials have demonstrated the benefits of adjuvant radiotherapy after RP for patients with adverse pathological features [5,8,57]. The most consistent findings were an improvement in biochemical relapse free survival across all three trials and improvements in loco-regional and clinical relapse free survival in the two trials that reported these outcomes. Although there was an improvement in overall survival in one of the studies [57], the use of adjuvant radiotherapy is not unanimously accepted [58]. Two of these studies have included patients with a detectable prostate-specific antigen (PSA) at the time of adjuvant treatment; therefore, these patients received salvage treatment by definition. As such, many clinicians offer salvage radiotherapy (SRT) to patients with biochemical progression instead of adjuvant radiotherapy. The main advantage of salvage versus adjuvant radiotherapy is the avoidance of a potential overtreatment in cases that would never relapse after surgery, even in the presence of high-risk pathological features [59]. Recently, prospective randomized trials, systematic review, and meta-analysis suggest that adjuvant radiotherapy does not improve event-free survival in men with localized or locally advanced prostate cancer. Until data on long-term outcomes are available, early salvage treatment would seem the preferable treatment policy as it offers the opportunity to spare many men radiotherapy and its associated side-effects [9,10,12].
Predictors of response to salvage radiotherapy were examined by Stephenson et al. [60] and they found that high Gleason score, high pre-radiotherapy PSA, negative RP surgical margins, short PSA doubling time, and seminal vesicle involvement were independently associated with adverse outcomes. A contemporary update of the original Stephenson predictive nomogram including patients treated with early SRT (at a PSA ≤ 0.2 ng/mL) showed that early SRT at low PSA levels after RP is associated with improved freedom from biochemical relapse and distant metastases rates [61].

2.2.2 Optimizing salvage radiotherapy with androgen deprivation therapy

Prospective studies have shown that androgen deprivation therapy (ADT) combined with primary radiotherapy for intermediate- and high-risk prostate cancers improves overall survival [62]. The combination of ADT to radiation in the postoperative setting was for long time a matter of debate. Recently the results of prospective phase III randomized were published demonstrating a benefit of the combined treatment[63,64].
In the RTOG 9601, 771 men with an elevated serum PSA following radical prostatectomy were randomly assigned to radiation plus the anti-androgen bicalutamide for two years or radiation alone. The first interim results at a median follow up of 7 years were negative for the primary endpoint, overall survival; however, the latest report at a median follow-up of 12.6 years showed an actuarial 10-year overall survival of 82% for salvage radiation plus ADT and 78% for salvage radiation plus placebo (HR: 0.75; 95% CI: 0.58-0.98) [63].

The GETUG-AFU 16 is a phase III study that randomized men with biochemical failure after surgery to salvage radiation alone versus salvage radiation combined with 6 months of LHRH agonists. The 10 years results showed that SRT combined with short-term androgen suppression significantly reduced risk of biochemical or clinical progression and death compared with salvage radiotherapy alone. The results of the GETUG-AFU 16 trial confirm the efficacy of androgen suppression plus radiotherapy as salvage treatment in patients with increasing PSA concentration after RP for prostate cancer [64].
Finally, it is worth to mention that, the current National Comprehensive Cancer Network (NCCN) guidelines recommend a duration of 6–24 months of ADT combined SRT.

2.3. Role of new imaging modalities in identifying local recurrence after RP

2.3.1 The role for MRI in the identification of prostate cancer recurrence after RP

In men with biochemical recurrence following local treatment with curative intent for prostate cancer, it is important to identify those who will likely benefit from local salvage therapy. Imaging should provide a step-by-step multimodal approach that facilitates both local and systemic staging. Clinical guidelines recommend the use of both nuclear medicine imaging (positron emission tomography [PET] / computed tomography [CT] scans) and magnetic resonance imaging (MRI) to assess local recurrence and distant metastases [65,66] Multiparametric MRI (mpMRI) is accurate in early detection of prostate cancer local recurrence after RT and RP [66]. T2w sequences very accurately represent the postsurgical anatomy. In most cases, a local recurrence differs from normal postoperative inflammation and fibrosis. Fibrotic tissue has a lower signal intensity (SI) than recurrent tissue [67]. Recurrent tissue can have various forms, including curly, semi-circular, nodular, and plaque-like masses. In the case of asymmetric perianastomotic soft-tissue thickening with an SI in between the SIs for pelvic muscle and the surrounding adipose tissue, a local recurrence is likely to be present [68]. Functional criteria are based on diffusion-weighted imaging (DWI) and dynamic contrast enhancement (DCE), which represent the cellularity and vascularity of the tissue, respectively.
DWI has good diagnostic accuracy in detecting local recurrence after RP when combined with other sequences[68]. Quite often, there is geometric distortion caused by susceptibility artefacts due to surgical clips. Local recurrence after RP, like primary tumours, shows high SI on high b-value DWI and low ADC values. In the case of artefact-altered DWI, DCE MRI is of particular importance[69]. DCE imaging plays the dominant role in the detection of RP recurrence. This technique has high sensitivity [70–72]; even tiny recurrence “foci” that may not be visible on T2WI tend to show significant enhancement in the early arterial phase, often with contrast wash-out [66]. In addition, post-RP recurrences enhance sooner and faster than normal postoperative changes [73].

2.3.2 Role of PSMA PET CT in Identification of local recurrence

In case of PSA recurrence, SRT is the only curative option, resulting in approximately 60% of the patients re-achieving an undetectable PSA. After 5 years, 80% of these men are free from progression[74]. The pre-SRT PSA level is a significant factor of progression, with more favorable results for patients with low PSA levels (0.5 ng/mL or less)[61,75]. Accordingly, European guidelines (EAU) recommend early SRT at a PSA <0.5 ng/mL. At the same time, use of restaging PSMA PET/CT is recommended by the 2021 EAU guidelines for patients with a relapsing PSA > 0.2 ng/mL. However, for clinical and imaging purposes, it is important to distinguish between two types of local recurrence and relapse outside tumor bed.

At PSA levels <1 ng/mL, most imaging methods are not suitable to detect the correlate for disease progression. Therefore, up to 20% of patients with SRT to the prostate bed (with or without including original seminal vesicle) without morphological correlate will be treated locally without actual local recurrence [74]Prostate-specific membrane antigen (PSMA) is a cell surface protein with high expression in majority of prostate cancer [76]. 68Ga-PSMA has been used since 2012 as PSMA-ligand in recurrent prostate cancer [77–79]. Especially at low PSA levels, the detection rate of 68Ga-PSMA-11-PET/CT is significantly higher in comparison to other imaging methods. In a retrospective analysis for patients with biochemical progression after RP, Afshar-Oromieh et al. found that 69% of the patients had at least one positive lesion indicating prostate cancer recurrence. The detection rates were 43% for PSA levels ≤0.2 ng/mL, 58% for PSA >0.2 to ≤0.5 ng/mL and 72% for PSA >0.5 to ≤1.0 ng/mL. Tumor detection was clearly associated with PSA level and higher Gleason scores [78]. Bluemel et al. analyzed the impact of 68Ga-PSMA-11-PET/CT in patients with PSA failure and negative F-18-choline-PET/CT. Of 125 patients, 32 patients with negative F-18-choline-PET/CT received an additional 68Ga-PSMA-11-PET/CT, which detected sites of recurrence in 43.8% [80].

The most common site of postoperative local recurrence, accounting for 57%–62% of relapse cases, is the vesicourethral anastomosis (VUA), which comprises the membranous urethra, bladder neck, and surrounding soft tissue [81]. Other typical local relapse sites are the lateral surgical margins (seminal vesicle bed) or remnant deferens, accounting for 25%–27% of cases [82], and the retrovesical region (topography of rectoprostatic/Denonvilliers fascia) in 8%–21% of cases [81]At PSMA PET/CT, local recurrence appears more often as focal ill-defined hypo-attenuating soft tissue with moderate PSMA uptake but can also simply appear as focal unilateral radiotracer uptake within the fibrotic tissue. It is important to point out that in most cases, postoperative local recurrence relies only on the PET component of the hybrid imaging because of the known lack of soft-tissue contrast in the pelvic region at CT [77].

2.4 Investigational treatment

2.4.1 Hypofractionated stereotactic body radiotherapy to the site of recurrence

External beam radiation therapy is one of the standard treatments for organ-confined prostate cancer, with cure rates similar to those of RP. Hypofractionation uses a higher dose-per-fraction of radiation, which reduces the number of fractions and the total duration of treatment, allowing greater comfort for the patient and lower costs, in addition to providing a therapeutic advantage in terms of tumor control and toxicity, as the α/β of prostate cancer is lower than that of adjacent healthy tissues[83]. In 2018, a group of experts from the American Societies of Radiation Oncology, Medical Oncology, and Urology (ASTRO/ASCO/AUA) concluded that there is sufficiently robust evidence to justify using moderate hypofractionation in prostate cancer as common clinical practice[84]. A recent Cochrane review indicated that moderate prostate cancer hypofractionation (with fractions up to 3.4 Gy) provides oncological outcomes in terms of overall survival (OS), disease-free survival (DFS), and metastasis-free survival (MFS) similar to conventional fractionation, without a significant increase in acute or late toxicity [85].
In addition, technical advances in the field of radiotherapy in recent years, such as intensity-modulated radiotherapy (IMRT), image-guided radiotherapy (IGRT), and stereotactic radiotherapy (SBRT), have enabled the progressive implementation of extreme hypofractionation (defined by fractions of at least 6 Gy) in various scenarios of localized prostate cancer treatment. The use of SBRT in prostate cancer has provided sufficient evidence in terms of tumor control results, quality of life reported by the patient, and low toxicity [25,86,87] to back its implementation in daily clinical practice. Moreover, the prostate cancer working group of the German Society of Oncology (DEGRO) but also the NCCN endorses the use of SBRT in the treatment of localized low and intermediate-risk prostate cancer, recommending its use in clinical trials in patients with the localized high-risk disease[88-48].
The recent publication of two randomized trials comparing the use of extreme hypofractionation versus conventional fractionation (HYPO-RT-PC [25], PACE-B trial[87]) has been crucial in supporting its use, although only the Scandinavian study (HYPO-RT-PC) reported results of long-term tumor and toxicity control. In 2020, a randomized systematic review and meta-analysis of phase III trials were published comparing SBRT with normofractionated and hypofractioned regimens. It concluded that the ultra-hypofractionated regimens obtained similar 5-year disease-free survival results, with late gastrointestinal and genitourinary toxicity of <15% and <21%, respectively, when compared to hypofractionated regimens and conventional radiotherapy [47].

Use of moderate hypofractionation is becoming a standard even in the postoperative setting. Retrospective and prospective single arm studies support a safe toxicity profile and a promising biochemical control rates with hypofractionation (PMID: 29178983). The recently reported results of the phase III clinical trial NRG-GU003 comparing hypofractionated post-operative prostate bed radiotherapy (HYPORT) to the conventional post-prostatectomy radiotherapy for men with prostate cancer determined that treatment with HYPORT yielded no increase in patient-reported genitourinary (GU) or gastrointestinal (GI) toxicity for trial participants, with a similar biochemical disease control at the 2 year follow-up.
To demonstrate the viability and safety of the use of SBRT in this clinical scenario, Repka et al [50]conducted a theoretical feasibility study of SBRT after RP based on the NTCP (Normal Tissue Complication Probability) model, using patients who had previously been treated by conventional EBRT for biochemical recurrence after prostatectomy. Using the presimulation CT, RTOG recommendations were applied to define postprostatectomy volumes, and a dose of 30 Gy was prescribed to the PTV in five fractions, corresponding to an equivalent dose in 2 Gy fractions (EQD2) of 64.3 Gy, assuming an α/β value of 1.5

Gy. The NTCP model was applied to estimate the risk of late rectal and/or bladder toxicity. According to the NTCP model, the mean of grade≥2 late rectal toxicity was estimated at 0.28% and of late grade 2 toxicity on the bladder neck at 0.00013%, while the calculated average for the exacerbation of late urinary symptoms was 4.81%. The conclusion by the authors, considering the limitations of the NTCP model, is that using SBRT after surgery seems feasible and may offer a safe, convenient treatment option for patients in both the adjuvant and salvage after biochemical failure.
A prospective phase I study by Sampath et al. tested the usage of stereotactic dose-escalated radiotherapy on prostate bed in and showed a crude rate of biochemical control of 42% in the overall population [90]. Patients were treated with dose fractionation schedules of 35, 40 and 45 Gy in five fractions. Authors underlined that dose escalation to 45 Gy was feasible without increasing the rate of adverse events, but no improvement in PSA control was reported if compared to 40 Gy in 5 fractions. Furthermore, a recent propensity score analysis comparing focal stereotactic SRT and conventional radiotherapy for macroscopic prostate bed recurrence showed comparable bRFS and PFS rates between the two modalities. On the other hands, a lower rate of toxicity was confirmed for patients undergoing focal stereotactic SRT compared to conventional fractionated SRT, with acute GI and GU adverse events reported in 4.4% versus 44.4% ($p< 0.001$) and 28.9% versus 46.7% ($p= 0.08$) of patients, and late GI and GU adverse events reported in 0% versus 13.3% ($p = 0.04$) and 6.7% versus 22.2% ($p = 0.03$) of patients, respectively [91]. Considering the favorable therapeutic ratio of this approach and the lower number of fractions needed, the authors suggested stereotactic is an attractive alternative to conventional SRT in this setting

2.5 Rationale for performing the trial

Radical prostatectomy and radiotherapy (RT) are the considered as backbones for treating localized disease[1]. However radical prostatectomy, 30 – 60% of patients will develop recurrent disease[2,3]. Several large randomized controlled trials have shown a benefit of postoperative radiation therapy in patients with a high risk of local recurrence after RPE, e.g. pT3 disease or positive resection margins[4–8]. In the era of high sensitivity PSA and PSMA-PET/CT, there has been additional evidence suggesting a similar oncological outcome if patients are treated with early salvage radiotherapy in case of a rising PSA after RPE instead of immediate adjuvant radiotherapy[9–12]. However, the above mentioned studies as well as the studies including patients receiving salvage radiotherapy in case of a macroscopic tumor recurrence in the prostate bed were done with conventionally fractionated radiotherapy, usually in 2 Gy per fraction[4–12].

In the setting of definite radiotherapy to the prostate, ultrahypofractionated radiotherapy has been used as a treatment option in patients with low or intermediate risk for a long time and there are published data with a reasonable follow up that shows excellent biochemical control with low high grade toxicity rates[13–20]. In addition, data on ultrahypofractionated in high-risk patients are emerging with several large trials being published with encouraging results[21–26]. The rationale for using ultrahypofractionated in patients treated for prostate cancer is the estimated low α/β value of around 1.5 Gy[27,28]. Therefore, using a larger fraction dose is expected to improve the therapeutic ratio and consequently the probability of tumor control.

Although Data on moderate hypofractionation in the setting of postoperative radiotherapy with a fraction dose of up to 3 Gy per fraction does not seem to support this concern, given the low toxicity rates that were reported in several analyses[29–38]. However, data on postoperative ultrahypofractionated radiotherapy to the prostate bed remains immature. The rates of acute and late toxicities following ultrahypofractionated radiotherapy to the prostate bed were reported in retrospective and phase I studies are within the above mentioned ranges. The rate of acute ≥ G2 GI and GU toxicities range from 0 – 50 % and 0 – 33.3 % and for late ≥ G2 GI and GU toxicities from 0 – 11.5 % and 0 – 38.5 %[39–48]. This data suggests that SBRT to the prostate bed can be applied with toxicity rates similar to that of normofractionated or mildly hypofractionated radiotherapy

Further improvement in the oncological outcomes can be expected through technological developments in radiotherapy delivery and precise targeting of the local relapses in the prostate bed. A SRT using a ultrahypofractionated schedule delivered precisely in 5 fractions and limited only to the site of isolated macroscopic recurrence in the prostate bed as defined by PSMA-PET and multiparametric MRI (mpMRI) may represent a valid treatment strategy to improve the therapeutic ratio in these patients (short overall treatment time, better sparing of surrounding heathy tissues, increased dose to the target volume).

Rationale for combining ADT to SRT

- The benefit of ADT to salvage radiation has been demonstrated in two randomized phase III trials, RTOG 9601 and GETUG 16, which provided evidence of improved metastasis-free and overall survival and durable biochemical disease control with bicalutamide for 24 mo and ADT using LHRH agonists for 6 months, respectively.
- These studies support the current National Comprehensive Cancer Network (NCCN) guidelines to consider combination of 6–24 months of hormonal therapy with SRT in this setting.

3 STUDY OBJECTIVES AND DESIGN

3.1 Hypothesis and primary objective

We hypothesize that focal SRT in combination with short-term ADT may further prolong or prevent progression, and improve the success of SRT for relapsing patients with a macroscopic relapse after RP. Through better definition and optimization of the target volumes sparing adjacent normal tissue, an improvement in the toxicity profile can be expected.

The main objective of the trial is to explore the efficacy and safety of combining 6 months short-term ADT to focal hypofractionated SRT delivered in 5 fractions where mpMRI and PSMA-PET CT are used to precisely identify the local recurrence and compare it to the published literature.

3.2 Primary and secondary endpoints

Primary endpoints:

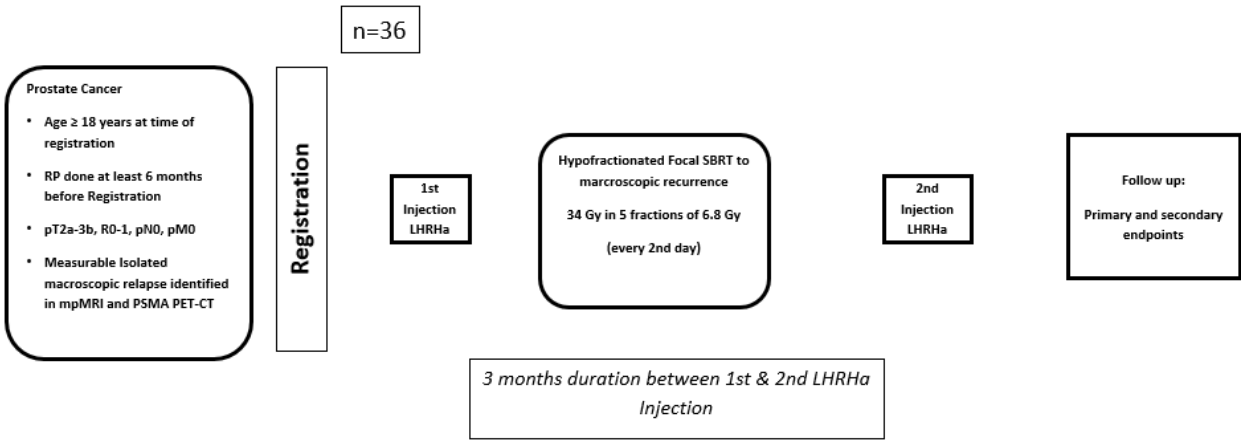
- Biochemical relapse free survival at 2 years

Secondary endpoints:

- Acute side effects (until 90 days after end of radiation) of grade 3 or higher based on CTCAE v5
- Progression-free survival
- Metastasis-free survival
- Late side effects
- Quality of life (based on EORTC QLQ-C30, QLQ-PR25)

3.3 Study design

This is a single arm, prospective phase II multicenter study.



3.4. Study intervention

3.4.1 Pre-registration imaging

Within 3 months prior to registration either, PSMA PET/CT is mandatory to exclude regional or distant metastasis. Both 18F- and 68G-PSMA tracers are allowed. A mpMRI of the prostate bed acquired within 3 months before registration is mandatory to define the extension of local recurrence.

3.4.2 Radiation treatment (SBRT)

3.4.2.1 Patient's positioning, immobilization, data acquisition and simulation:

A treatment planning CT scan, with the patient in the same position as during treatment, is required to define the clinical target volume (GTV), the planning target volume (PTV) and the critical structures. Patients will be positioned in supine position. Leg and knee support is highly recommended. Each patient will be positioned in an individualized immobilization device in the treatment position on a flat table. It is recommended that patients are scanned/simulated and treated with comfortably full bladder. An empty rectum is recommended for prostate bed radiotherapy. An example of a bladder and rectal protocol: An empty rectum is provided by using a rectal enema +/- 60 minutes before planning CT. After emptying rectum and bladder the patient is asked to drink the amount of 500-750 ml of water. The planning CT is then performed after ca. 40 minutes. The patient repeats the bladder filling procedure during the entire treatment courses. An endorectal ballon can be used for repositioning purposes as per local institutional standards.

Radiopaque fiducial markers (mandatory for robotic-based treatments) may be implanted in the prostate bed 1 week before the planning CT scan at the discretion of the treating center.

The position of the patient will be reproduced using skin marks and orthogonal laser beams during treatment preparation and execution. The treatment planning CT scan should include at least the pelvis from the lower part of the second lumbar vertebra (L2) to the lower part of the ischial tuberosities. The entire target volume and all organs at risk (OAR) must be included in CT scan. CT slice thickness should be ≤ 2 mm. The GTV, PTV and OAR must be outlined on all CT slices in which these structures are visible.

Morphological and topographical information given by clinical examination, mpMRI and PET/CT, must be integrated to delineate the target volumes. Rigid or deformable co-registration is allowed.

3.4.2.2 Volumes

3.4.2.2.1 Definition of target volumes (refer to appendix 2 & 3):

- The Gross Tumor Volume of the suspicious local recurrence (GTV) is defined by the physician as all known gross disease *before any treatment* as defined by the CT/MRI images and PET scan using rigid or deformable fusion) and/or clinical information.

- The Planning Target Volumes (PTV) will provide margin around the GTV to compensate for variability in daily treatment set-up and internal motion due to breathing or motion during treatment. The PTV should encompass the GTV with a margin of 5 mm in all directions.

3.4.2.2.2 Organs at Risk (OAR)

- *Delineation:*

The OAR should be delineated according to the RTOG guidelines. For more details please see RTOG/NRG Oncology web site to view the normal pelvis atlas for examples of normal tissue contours (http://www.rtog.org/CoreLab/ContouringAtlases/MaleRTOGNormalPelvisAtlas.aspx).

Bladder: this organ is defined by the external wall (5-mm thickness), delineated on each slide, from the dome to the bladder neck and the start of the VUA.
VUA and distal urethra: from the bladder neck to the distal urethra inside the penile bulb using the mpMRI sequences. A 2-mm isotropic margin is added around these structures to create a PRV volume.
Rectum: defined by the external wall from the recto-sigmoid junction to ischial tuberosities (5-mm thickness).
Femoral heads: delineated from the top of the hip joint to the small trochanter.
Bowel bag: from the most inferior small or large bowel loop to 1 cm at minimum above PTV for coplanar beam plans, or more if non-coplanar beams or tomotherapy plans are used.

- *Dose constraints to OAR:*

It is strongly recommended that dose constraints are not exceeded. If a dose constraint cannot be achieved due to overlap of the target with an OAR or PRV, the dose per fraction can be lowered or the target coverage compromised in order to meet the constraint.

Organ at risk	Dose constraint	Aim
Rectal wall	V18.1 Gy V29 Gy V36 Gy	<50% <20% <1cc
Bladder wall	V18.1 Gy V37 Gy	<40% <10cc
PRV_VUA and distal urethra	V36 Gy	<1cc

Femoral heads	V14.5 Gy	<5%
Penile bulb	V29.5 Gy	<50%
Bowel	V18.1 Gy V30 Gy	<5cc <1cc

3.4.2.3 Treatment technique.

Intensity modulated radiotherapy (IMRT) or use of rotational techniques is mandatory. By definition only dosimetry obtained by inversed treatment planning is considered as IMRT. IMRT may be performed by using Step-and-Shoot-Technique, Sliding-Window-Technique or Volumetric Modulated Arc Therapy (VMAT), including MRI-guided radiation therapy systems (MRIdian® or Elekta Unity®). Treatment with Cyberknife® is allowed (implant of radiopaque fiducial markers 1 week before the planning CT scan is mandatory).

3.4.2.4 Dose computation.

- Any treatment planning system, capable of 3D-dose computation using a convolution algorithm, will be used. The PTV may be treated with any combination of coplanar or non-coplanar fields shaped to deliver the specified dose while minimizing dose to the normal tissue OAR. Field arrangements will be determined by 3D planning to produce the optimal conformal plan in accordance with volume definitions. The treatment plan used for each patient will be based on an analysis of the volumetric dose including DVH analyses of the PTV and critical OAR. Each field is to be treated daily.

- The PTVs should be outlined in all relevant planes. The dose distribution should be shown at least in the plane through the beam axes.

- Dose distribution is obtained in a 3-dimensional pattern with Dose Volume Histogram (DVH). DVH are to be used for assessing dose to the PTVs and all normal tissues at risk.

3.4.2.5. Equipment and tools.

- Both a linear accelerator, tomotherapy and Cyberknife is allowed.

3.4.2.6 Dose prescription.

A total dose of 34 Gy (80% of the maximal dose) will be delivered in 5 fractions and fractions every second day (NTD_{2Gy} 80 Gy α/β=1.5Gy for tumor control and 66.6 Gy α/β=3Gy for late toxicity). Treatment will be prescribed to the periphery of the target (80% of the dose (=34Gy), should cover 90% of the PTV) covering the PTV. A maximal dose of 40 Gy is allowed to GTV. The priority will be given to the respect of dose constraints over PTV coverage.

3.4.2.7 Treatment Verification.

Daily patient set-up shall be performed using laser alignment to reference marks on the skin of the patient. Daily cone-beam CT set-up and on-line correction of patient's position is mandatory. If multiple targets will be irradiated with multiple isocenters, a CBCT prior to every treatment for every isocenter is mandatory. Patient immobilization devices can be used according to the institutional policy.

3.4.3 Androgen deprivation therapy

- All patients should receive an LHRH-agonist or antagonist for a duration of 6 months using 3 monthly formulations. In case of LHRH-agonist flare prevention with an anti-androgen is

recommended for at least 5 days prior to the first injection of the agonist and should not be continued for longer than 15 days of the 1st month duration.

- ADT should start no later than the 1st SBRT fraction and no earlier than 2 weeks before the start of radiotherapy.
- Palliative ADT should not be started for biochemical progression without documented clinical progression. In case of symptomatic progression, palliative ADT is mandatory. In case of clinical asymptomatic progression, delayed ADT until progression to a symptomatic state is allowed in well-informed men (EAU 2016 guidelines). In general, we would recommend to start ADT in asymptomatic patients only if conventional imaging would confirm clinical progression. So we would not recommend the start of ADT for PET-positive lesions not suspicious on conventional imaging (CT/MRI/bone scintigraphy).
- ADT-related toxicity should be managed according to Nguyen et al. Eur Urol. 2015 May;67(5):825-36.

4 STUDY POPULATION AND STUDY PROCEDURES

4.1 Inclusion and exclusion criteria, justification of study population

Inclusion criteria:

1. Written informed consent according to ICH/GCP regulations before registration and prior to any trial specific procedures
2. Age ≥ 18 years at time of registration
3. WHO performance status 0-1
4. Lymph node negative adenocarcinoma of the prostate treated with radical prostatectomy (RP) at least 6 months before trial registration. Tumor stage pT2a-3b, R0-1, pN0 or cN0 according to the UICC TNM 2009.
5. Evidence of measurable local recurrence at the prostate bed detected by PSMA PET/CT and mpMRI within the last 3 months. In case of unclear local recurrence, a biopsy confirmation is recommended.
6. Patient must have non-metastatic (N0, M0) disease, as defined by a lack of nodal or distant metastases seen on PSMA PET/CT scan
7. Patients must have non-castrate levels of serum testosterone (≥50 ng/dL).
8. Patients must not have previously received hormonal therapy (LHRH agonists, antiandrogen, or both, or bilateral orchiectomy).
9. Absence of any psychological, familial, sociological or geographical condition potentially hampering compliance with the study protocol and follow-up schedule; those conditions should be discussed with the patient before registration in the trial

Exclusion criteria:

1. Persistent PSA (> 0.4 ng/mL) 4 to 20 weeks after RP
2. Previous hematologic or primary solid malignancy within 3 years prior registration with the exception of curatively treated localized non-melanoma skin cancer
3. Usage of products known to affect PSA levels within 4 weeks prior to start of trial treatment phase including any form of androgen suppression agents and androgen deprivation therapy
4. Bilateral hip prosthesis
5. Severe or active co-morbidity likely to impact on the advisability of salvage RT
6. Treatment with any experimental drug or participation within a clinical trial within 30 days prior to registration (exception: concurrent participation in the biobank studies is allowed

4.2 Recruitment and screening:

Patient registration will only be accepted from authorized investigators.

Prior to registration, the following steps have to be taken:

- Fill in the patient screening (used for monitoring potentially eligible patients, and will be destroyed after the end of the accrual period. Screening list is not a part of the CRFs), enrollment and identification lists.
- Check the eligibility criteria
- Obtain signed and dated written informed consent from the patient prior to any protocol-specific procedure according to ICH/GCP and local guidelines.
- Patients must complete the pre-treatment of quality of life assessment per protocol

Only electronic case report forms (eCRF) will be used. The use of worksheets is allowed if the copies of the templates are documented in the trial master file (TMF). The used worksheets must be kept with the patient charts.

Registration is done via Internet 'https://secutrial.insel.ch'. SecuTrial (interActive Systems) will be used as database. In case of problems investigators can phone the study coordinator from Monday through Friday. For technical difficulties, investigators are recommended to contact data management of CTU Bern

E-mail: datamanagement@ctu.unibe.ch

In order to receive authorization for online registration/data entry, sites must send a copy of the completed staff list to the Sponsor. Login details for the online database will be sent to authorized persons.

4.3 Study procedures

Schedule of assessments (Table 1)

Required investigation	Inclusion		Treatment	1 Months after RT	3 Months after RT	6 Months after RT	Every 6 Months till end of 2nd year after RT then once per year till 60 months
	Within 12 weeks prior registration	Within 2 weeks prior registration					
Eligibity Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x		x	x	x	x
Biochemistry (Blood Samples)*							
PSA		x		x	x	x	x
Testosterone		x		x	x	x	x
Radiology							
PSMA PET	x						
MRI	x						
Radiotherapy							
Treatment planning			x				
Record Planning results			x				
Adverse Events							
Baseline toxicity		x					
Acute toxicity			x	x	x		
Late toxicity						x	x
EORTC QoL questionnaire							
QLQ-C30		x		x	x	x	x
QLQ-PR25		x		x	x	x	x

*** Blood samples**

The obtained blood samples are used only for PSA and testosterone values. The measurement for this labs is conducted within the local hospital laboratory of each participating centre and the rest samples will be disposed afterwards. No blood will be collected or stored or used for other research purposes within the frame of this trial.

4.4 Withdrawal and discontinuation

Patients have the right to discontinue their participation in the trial for any reason and at any time, without prejudice to further treatment. Patients who refuse further trial treatment will be transferred to follow-up phase and continue to receive the follow-up assessments as scheduled. Patients who withdraw their consent (i.e. refuse further data collection), will be informed that all data and samples collected until the time point of their withdrawal will be kept coded and used. For the patient's security, a last examination should be performed.

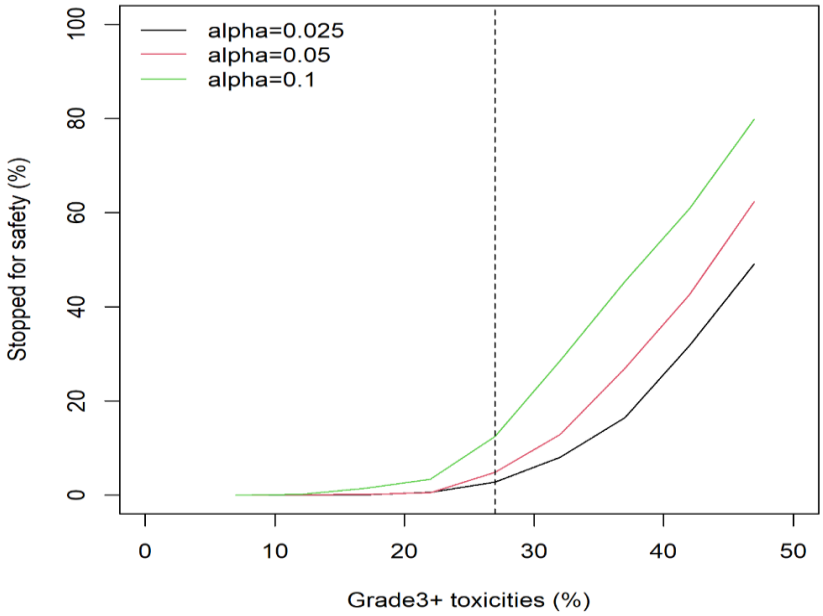
Patients may be withdrawn at any time from trial treatment at the discretion of the treating physician or the investigator due to a SAE, or based on any other relevant medical condition. The patient then will be transferred to the follow-up phase and continue to receive the follow-up assessments as scheduled.

5 STATISTICS AND METHODOLOGY

5.1. Statistical analysis plan and sample size calculation

According to the published prospective trials and retrospective series reporting the outcome of the normofractionated SRT, we define biochemical relapse free survival at 2 years of 60% as poor and of 80% as promising outcome that would justify further investigation. We will therefore test the null hypothesis that the biochemical relapse free survival at 2 years is lower than 60% against the alternative that it is at least 80%. Based on a one-sample binomial exact test with a one-sided alpha of 5%, 36 patients are required to reach a power of 80%, not taking into account patients lost to follow-up. The null hypothesis will be rejected if at least 27 patients show biochemical relapse free survival at 2 years.

We will control the safety of the intervention during the trial by assessing acute side effects (grade 3 or higher) at 90 days after 12 and 24 patients. The trial will be stopped if there is evidence that the proportion of patients with acute side effects (grade 3 or higher) is larger than 27%, the proportion observed that will be tested using one-sample binomial exact tests with a one-sided alpha of 5%.



Time-to-event outcomes will be analyzed using Kaplan-Meier-curves, the proportion of responders at 1 and 2 years, and the restricted mean survival time at 1 and 2 years with 95% confidence interval. Binary outcomes will be reported using absolute and relative frequencies with 95% confidence intervals.

The probability of biochemical relapse free survival and metastasis-free survival will be estimated using the Kaplan-Meier method. Cox proportional hazards models will be fit to assess the effects of treatment and baseline clinical and pathologic features (such as PSA, PSA doubling time, Gleason score etc) on biochemical relapse free survival and metastasis free survival

5.2. Definition of endpoints

5.2.1 Biochemical relapse free survival (primary endpoint)

The initial PSA at time of registration will be the starting point. Freedom from biochemical progression is counted from the day of registration to the day of either first recorded biochemical progression as defined below, clinical progression or death due to clinical progression. Patients not experiencing a biochemical or clinical failure or death due to clinical progression are censored at time of last assessment.
A biochemical recurrence is defined by any confirmed PSA rise above 0.20 ng/mL with a confirmatory rise at least 2 weeks later. For those patients whose PSA does not drop below 0.20 ng/mL at time of first response assessment at 3 months are considered as non-responders to treatment and are considered to have a biochemical recurrence in case a second measurement at least 2 weeks later confirms a rising PSA above this level.

5.2.2 Metastasis-free survival:

Metastasis-free survival is defined as time between registration and the appearance of a metastatic recurrence (any M1) as suggested by PET-CT or death due to any cause. Patients without any of the events of interest (including those with biochemical relapse only) are censored at the date of the last follow-up. Second cancers are not considered events in terms of this endpoint. In case of biochemical progression, re-staging will be made with PET-CT imaging preferably with the same tracer used before registration. In case of negative PET findings at biochemical relapse, a new PET imaging should be repeated on a 6-montly basis or earlier in case clinically indicated.

5.2.3 Clinical progression-free survival:

Clinical progression-free survival is defined as time between registration and the appearance of a new recurrence (any N1 or M1) as suggested by PET-CT, symptoms related to progressive PC, or death due to any cause.

- A local recurrence is defined as the appearance of evidence of a recurrence within the prostate bed. Confirmation of the recurrence by biopsy is recommended, whenever possible.
- A regional nodal recurrence is defined as a radiographic (PET-CT) evidence of a lymphadenopathy in the pelvis in a patient without the diagnosis of hematologic/lymphatic disorder associated with lymphadenopathy or if there is histopathological evidence. Histologic confirmation is not required although recommended, especially in the absence of biochemical recurrence.
- Distant recurrence is defined as the appearance of distant metastases (M1a, M1b, M1c) outside the pelvis evidenced by PET-CT. Patients without any of the events of interest (including those with biochemical relapse only) are censored at the date of the last follow-up.
- Second cancers are not considered events in terms of this endpoint. Detailed analysis per subsite of recurrence (local, regional and distant) with time-to-event analysis will be performed In case of biochemical progression, re-staging will be made with PET-CT imaging preferably with the same tracer used before registration. In case of negative PET findings at biochemical relapse, repeat PET imaging should be repeated on a 6-montly basis or earlier in case clinically indicated.

5.2.4 Acute and late toxicity:

Radiotherapy toxicity will be assessed according to NCI CTCAE v5.0. Special attention shall be given to diarrhea, fecal incontinence, proctitis, rectal hemorrhage, rectal pain, hematuria, urinary frequency, urinary urgency, urinary retention, urinary incontinence, cystitis non-infective and erectile dysfunction. Acute toxicity is defined as occurring during treatment and up to 3 months after completion of treatment. Late toxicity is defined as occurring later than 3 months after end of treatment.

5.2.5 Quality of life:

All patients registered into this trial are to complete QoL questionnaires at the defined timepoints (see table 1). A longitudinal design is used. Patients are asked to complete a QoL questionnaire.
The EORTC QoL questionnaire (QLQ) C-30 Core questionnaire (version 3) and the prostate cancer module EORTC QLQ PR25 will be used. The QoL questionnaire including all these instruments will be provided for the major languages spoken in the participating centers.

5.3. Handling of missing data and drop-outs

We expect that all registered patients have complete baseline data. All patients that have at least one outcome assessment can be considered in repeated-measures analyses. Models will implicitly correct for missing data based on the missing at random mechanism. If there are patients with no outcome data at all, we will perform multiple imputations. For the time-to-event analysis, patient drop-outs will be accounted for by censoring.

6 Regulatory Aspects and Safety

6.1 Local regulations / Declaration of Helsinki

The study will be carried out in accordance to the protocol and with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, the Swiss Law and Swiss regulatory authority's requirements. The CEC and regulatory authorities will receive annual safety and interim reports and be informed about study stop/end in agreement with local requirements.

6.2 (Serious) Adverse Events and notification of safety and protective measures

An Adverse Event (AE) is any untoward medical occurrence in a patient or a clinical investigation subject which does not necessarily have a causal relationship with the trial procedure. An AE can therefore be any unfavourable or unintended finding, symptom, or disease temporally associated with a trial procedure, whether or not related to it.

A Serious Adverse Event (SAE) (ClinO, Art. 63) is any untoward medical occurrence that

- Results in death or is life-threatening,
- Requires in-patient hospitalisation or prolongation of existing hospitalisation,
- Results in persistent or significant disability or incapacity, or
- Causes a congenital anomaly or birth defect

Both Investigator and Sponsor-Investigator make a causality assessment of the event to the trial intervention, (see table below based on the terms given in ICH E2A guidelines). Any event assessed as possibly, probably or definitely related is classified as related to the trial intervention.

Relationship	**Description**
Definitely	Temporal relationship Improvement after dechallenge* Recurrence after rechallenge (or other proof of drug cause)
Probably	Temporal relationship Improvement after dechallenge No other cause evident
Possibly	Temporal relationship Other cause possible
Unlikely	Any assessable reaction that does not fulfil the above conditions
Not related	Causal relationship can be ruled out
*Improvement after dechallenge only taken into consideration, if applicable to reaction	

Both Investigator and Sponsor-Investigator make a severity assessment of the event as mild, moderate or severe. Mild means the complication is tolerable, moderate means it interferes with daily activities and severe means it renders daily activities impossible.

Reporting of SAEs (see ClinO, Art. 63)

All SAEs are documented and reported immediately (within a maximum of 24 hours) to the Sponsor-Investigator of the study.

If it cannot be excluded that the SAE occurring in Switzerland is attributable to the intervention under investigation, the Investigator reports it to the Ethics Committee via BASEC within 15 days.

If the SAE occurs at one of the study sites, the coordinating Investigator reports the events to the Ethics Committee concerned, within 15 days.

Follow up of (Serious) Adverse Events

All subjects with SAE must be followed up for outcome. The Ethics Committee must be informed according regulations.

Notification of safety and protective measures (see ClinO, Art 62, b)

If immediate safety and protective measures have to be taken during the conduct of the study, the investigator notifies the Ethics committee of these measures, and of the circumstances necessitating them, within 7 days.

6.3 (Periodic) safety reporting

An annual safety report (ASR/DSUR) is submitted once a year to the local Ethics Committee by the Investigator (ClinO, Art. 43 Abs).

6.4 Radiation

If the permitted dose guidance value (5 mSv per year if no direct benefit is expected for the participants) is exceeded at any time, the local Investigator notifies the Ethics Committee via BASEC within 7 working days of it becoming known (see ClinO, Art. 44).

6.5 Pregnancy

Since this cohort only consists of male patients, pregnancy of the participant is not possible. However, patients are counselled regarding strict birth control for at least 6 months after treatment for themselves and their partners.

6.6 Amendments

Substantial changes to the study setup and study organization, the protocol and relevant study documents are submitted to the Ethics Committee for approval before implementation. Under emergency circumstances, deviations from the protocol to protect the rights, safety and well-being of human subjects may proceed without prior approval of the Ethics Committee. Such deviations shall be documented and reported to the Ethics Committee as soon as possible.

Substantial amendments are changes that affect the safety, health, rights and obligations of participants, changes in the protocol that affect study objective(s) or central research topic, changes of study site(s) or of study leader and sponsor (ClinO, Art. 29).

A list of all non-substantial amendments will be submitted once a year to the competent EC together with the ASR.

6.7 (Premature) termination of study

The sponsor-investigator has the right to close this study (or, if applicable, individual segments thereof, e.g., recruitment) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
- Safety findings from this study, e.g., SAEs,
- Results of parallel clinical studies,
- Results of parallel animal studies (e.g., toxicity, teratogenicity, carcinogenicity, or reproduction toxicity),
- If the study conduct, e.g., recruitment rate, drop-out rate, data quality, protocol compliance, does not suggest a proper completion of the trial within a reasonable time frame.

The Investigator has the right to close his centre at any time. For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties,
- All affected institutions, e.g., IEC(s) or IRB(s), competent authority, study centre, head of study centre must be informed as applicable according to local law,
- The Investigator will retain all study materials unless notification will be given by the sponsor for destruction,
- In case of a partial study closure, ongoing patients, including those in post study follow-up, must be cared for in an ethical manner.

Upon regular study termination, the Ethics Committee is notified via BASEC within 90 days (ClinO, Art. 38).

Upon premature study termination or study interruption, the Ethics Committee is notified via BASEC within 15 days (ClinO, Art. 38).

A final report is submitted to the Ethics Committee via BASEC within a year after completion or discontinuation of the study, unless a longer period is specified in the protocol (ClinO, Art. 38)

Essential documents will be archived safely and securely in such a way that ensures that they are readily available upon authorities' request. Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital.

After termination of the study, all study files must be archived according to the Ordinance on Clinical Trials in Human Research (ClinO), Art. 45:

"[1] The sponsor must retain all data relating to the clinical trial … at least for ten years after the completion or discontinuation of the clinical trial.

[2] The investigator must retain all documents required for the identification and follow-up of participants, and all other original data, for at least ten years after the completion or discontinuation of the clinical trial.

6.8 Insurance

Insurance will be provided by the University Hospital of Bern, Inselspital. A copy of the certificate is filed in each investigator site file and the trial master file.

7 FURTHER ASPECTS

7.1 Overall ethical considerations

7.1.1 Patient protection

The responsible investigator will ensure that this study is conducted in agreement with either the Declaration of Helsinki (Tokyo, Venice, Hong Kong, Somerset West and Edinburgh amendments) or the laws and regulations of the country, whichever provides the greatest protection of the patient.
The protocol has been written, and the study will be conducted according to the ICH Harmonized Tripartite Guideline for Good Clinical Practice (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/good-clinical-practice.html).

The protocol will be approved by the Local, Regional or National Ethics Committees.

7.1.2 Subject identification

Trial-related data of the patient will be provided in a coded manner to the Sponsor. The names of the patients will not be disclosed to the University Hospital Bern, Switzerland. A sequential UPN will be attributed to each patient registered into the trial. Identification of patients must be guaranteed at the center. In order to avoid identification errors the UPN have to be provided on the CRF. Use the patient screening, enrollment and identification list. Patient confidentiality will be maintained according to applicable legislation. Patients must be informed of, and agree to, data transfer and handling, in accordance with local regulations.

7.1.3 Informed consent

All patients will be informed of the aims of the study, the possible adverse events, the procedures and possible hazards to which he/she will be exposed, and the mechanism of treatment allocation. They will be informed as to the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician.

It is the responsibility of the individual investigator to translate the enclosed informed consent document. The translated version should be dated and version controlled.

It will be emphasized that the participation is voluntary and that the patient is allowed to refuse further participation in the protocol whenever he/she wants. This will not prejudice the patient's subsequent care. Documented informed consent must be obtained for all patients included in the study before they are registered. This must be done in accordance with the national and local regulatory requirements.

7.2 Risk-benefit assessment

This trial investigates the use of ultrahypofractionated SRT for patients with biochemical progression after prostatectomy who developed isolated local recurrence with no evidence of metastasis. For this group of patients, conventional SRT is the standard of care. Previous studies have shown that ultrahypofractionated RT is safe and can be considered as standard of care in treatment of primary prostate cancer. The use of ultrahypofractionated SRT was reported in various retrospective series and phase I trials.

Patients presenting disease progression with radiological evidence of disease either loco-regionally and/or systemically (bone and/or lymph nodes) could undergo biopsy depending on clinical judgment, i.e. if the risks of the biopsy procedure are clinically acceptable. This will be discussed with patients at an individual basis.

8 QUALITY CONTROL AND DATA PROTECTION

8.1 Quality measures

For quality assurance the sponsor, the Ethics Committee or an independent trial monitor may visit the research sites. Direct access to the source data and all study related files is granted on such occasions. All involved parties keep the participant data strictly confidential.

8.2 Data recording and source data

The investigators will maintain appropriate medical and research records for this trial, in compliance with ICH-GCP (E6) and regulatory and institutional requirements for the protection of confidentiality of subjects. SecuTrial (interActive Systems) will be used as database. The principal investigator, sub-investigator, and clinical research nurses or coordinators will have access to the records.

The principal investigators will permit authorized representatives of the Sponsor and regulatory agencies to examine (and when required by applicable law, to copy) clinical records for the purposes of quality assurance reviews, audits, and evaluation of the study safety and progress.

8.2.1 Case Report Forms

The CRFs will be electronic (eCRF). All data requested on the CRFs must be recorded and the recorded data should be consistent with the source documents or the discrepancies should be explained. The Investigator should ensure the accuracy, completeness, and timeliness of the data reported in the CRF and all other required reports. Generally, the CRFs should be completed within one week of completion of a patient visit.

8.2.2 Specification of source documents

Source documents must be available at the site to document the existence of the study participants and must include the original documents relating to the study, as well as the medical treatment and medical history of the participant. Where source documents for specific entries in the CRF are not available, this must be explicitly documented in a note to file. Any data recorded directly in the CRF will be considered as source data. Any change or correction to source data should be dated, initialed, and explained (if necessary) and should not obscure the original entry. The use of worksheets is allowed if the copies of the templates are documented in the trial master file (TMF). The used worksheets must be kept with the patient charts.
For all data captured in the CRF, the location of the source should be documented on a list of source documents, which will be stored in the investigator site file at each study site. Only the local investigator, the responsible study nurse team, the study monitor and the authorities can access this document.

8.2.3 Record keeping / archiving

Essential documents (written and electronic), including images and radiotherapy plans must be retained for a period of at least 10 years from the completion or premature termination of the trial. The investigators should take measures to prevent accidental or premature destruction of these documents.

8.3 Confidentiality and coding

Trial and participant data will be handled with uttermost discretion and is only accessible to authorised personnel who require the data to fulfil their duties within the scope of the study. On the CRFs and other study specific documents, participants are only identified by a unique participant number.

The investigator ensures anonymity of the patients; patients will not be identified by names in any documents. Signed informed consent forms and patient enrollment log will be kept strictly confidential to enable patient identification at the site.

8.4 Retention and destruction of study data

All study data are archived for 10 years after study termination or premature termination of the study.

9 MONITORING AND REGISTRATION

For quality control of the study conduct and data retrieval, all study sites will be visited on-site by appropriately trained and qualified monitors. Any findings and comments will be documented in site visit reports and communicated to the local PI and to the sponsor as applicable. Investigators at the participating study sites will support the monitor in his/her activities. Prior to study start (first participant enrolled) a plan detailing all monitoring-related procedures will be developed.

All source data and relevant documents will be accessible to monitors and questions of monitors are answered during site visits.

10. FUNDING / PUBLICATION / DECLARATION OF INTEREST

Debiopharm AG and Berger-Janser Stiftung support financially this clinical trial.

The results will be published in the name of the Hypo-FOCAL-SRT trial in a peer reviewed international journal on behalf of all collaborators. All presentations and publications, including abstracts, relating to the trial must be authorized by the Hypo-FOCAL-SRT trial steering committee (all co-investigators listed in the protocol). Participating centers should ask for the approval of the trial steering committee to use any data related to the patients registered in the trial.

The investigators declare that they have no conflict of interest.

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12 APPENDICES

Appendix 1 TNM Classification according to UICC 2009

T - Primary tumor
pT: pathological tumor classification
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
T1 Clinically unapparent tumor not palpable or visible by imaging
T1a Tumor incidental histological finding in 5% or less of tissue resected
T1b Tumor incidental histological finding in more than 5% of tissue resected
T1c Tumor identified by needle biopsy (e.g., because of elevated PSA)
T2 Tumor confined within the prostate
T2a Tumor involves one half of one lobe or less
T2b Tumor involves more than one half of one lobe but not both lobes
T2c Tumor involves both lobes
T3 Tumor extends through the prostate capsule
T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b Tumor invades seminal vesicle(s)
T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
N - Regional lymph nodes
cN: clinical regional lymph node classification
pN: pathological regional lymph node classification
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 Regional lymph node metastasis
M - Distant metastases
Mx Distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
M1a Nonregional lymph node(s)
M1b Bone(s)
M1c Other site(s)

Appendix 2 Pre-registration imaging (PSMA PET CT):

For the detection of local recurrence using hybrid imaging several, PSMA-tracers are clinically available, such as ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCFPYL (Pylarify - piflufolastat F 18). Imaging is usually performed as a whole-body PET/CT for the detection of local recurrence and distant metastases.

Imaging protocol should contain:

- The radiochemical purity of the radiotracer should be greater than or equal to 95% in high performance liquid chromatography (HPLC) and Thin Layer Chromatography (TLC))
- Free ^{18}F-fluoride or ^{68}Ga-eluate should be the major impurity.
- i.v. application of the radiotracer is beneficial
- regarding the specific tracer a tracer-individual uptake period from application to imaging is recommended:
    - 60 min p.i. for ^{68}Ga-PSMA-11
    - 90-120 min p.i. for ^{18}F-PSMA-1007
    - 60 min p.i. for ^{18}F-DCFPYL
- PET scans should be acquired in the 3D mode
    - with an acquisition time of 1.5 min/bed position
    - by continues bed movement or
    - using a whole-body PET/CT scanner.
- Emission data using bed position PET/CT scanners should be corrected for scatter and attenuation and reconstructed iteratively with an OSEM algorithm (2 iterations and 21 subsets) followed by a postreconstruction smoothing gaussian filter.
- Whole body PET images at Inselspital Bern using the Siemens Quadra or Siemens Biograph Vision 600 will be reconstructed with the same reconstruction parameters for both systems in 3D with a zoom factor of 1.0. Emission data need to be corrected for randoms, scatter and decay, and reconstruction with the vendor's time of flight (TOF) point-spread-function (PSF) algorithm with 4 iterations and 5 subsets.

Image interpretation: Focal uptake of ^{68}Ga-PSMA-11, ^{18}F-PSMA-1007, and ^{18}F-DCFPYL higher than the surrounding background and not associated with physiologic uptake is considered suggestive of malignancy. Typical pitfalls in PSMA ligand PET imaging need to be known (e.g., celiac and other ganglia for ^{18}F-PSMA-1007, fractures and degenerative changes for all fluorinated radiotracers, and perfusion effects in inflammatory lymph nodes for all tracers).

Appendix 3 Pre-treatment imaging (mpMRI)

In order to define the extension of macroscopic local recurrence, a mpMRI of the pelvis with i.v. Gadolinium is mandatory after biochemical progression upon RP

MRI should preferably be performed on a 3T MR unit; if not available a 1.5T MR unit can also be accepted. There is no need for an endorectal coil. MRI should cover the entire pelvis from the aortic bifurcation to the inferior border of the pubic symphysis. Ideally, air in the rectum should be minimized by emptying the rectum by applying local guidelines. The following sequences should be performed:

- Coronal T2-weighted sequence with isotropic voxels (1mm) covering the entire pelvis allowing reconstruction in the axial and sagittal plane.
- Axial T2-weighted high resolution covering the former prostatic bed including seminal vesicles (3mm slice thickness, no gap)
- Dynamic axial T1-weighted sequence (Dotarem®) including prostatic bed and seminal vesicles with high spatial resolution and slice thickness of 3mm.
- A T1-weighted sequence before administration of Gadolinium has to be added.
- Diffusion-weighted MRI (DW-MRI) in the axial plane covering the entire pelvis with slice thickness of 4mm and b-values of 0, 500 and 1000 sec/mm^2 in order to detect lymph node metastases and local recurrence.
- Diffusion-weighted MRI (Zoomit) with limited field of view (former prostate and seminal vesicle bed) and b-values of 0, 500, 1000 and 2000 sec/mm^2.
- Axial T1-weighted fat saturated sequence covering the entire pelvis (4mm slice thickness).

Image interpretation: Local recurrence is defined as the following: soft tissue mass on T1- and T2-weighted sequences with early contrast medium enhancement on DCE-MRI. DW-MRI is analyzed qualitatively: tumor recurrence shows a high signal intensity focal lesion on the high b-value image corresponding to a low signal intensity lesion on the corresponding Apparent Diffusion Coefficient (ADC) map (impeded diffusion due to high cellularity).

SPIRIT
STANDARD PROTOCOL ITEMS: RECOMMENDATIONS FOR INTERVENTIONAL TRIALS

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Page No [line No]
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1 [1-3]
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	5 [94-98]
	2b	All items from the World Health Organization Trial Registration Data Set	5 [94-98]
Protocol version	3	Date and version identifier	5 [94-98]
Funding	4	Sources and types of financial, material, and other support	18 [353-354]
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	18 [349-352]
	5b	Name and contact information for the trial sponsor	18 [353-354]
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18 [349-355]
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	18 [349-355]
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	4 [61-89]
	6b	Explanation for choice of comparators	4 [61-89]
Objectives	7	Specific objectives or hypotheses	4 [90-92]

Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	4 [90-92]
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	6 [137-148]
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	5,6 [99-135]
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	7,8,9,10 [158-246]
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	7,8,9,10 [158-246]
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	7,8,9,10 [158-246]
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	7,8,9,10 [158-246]
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	7 [149-157]
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	6 [137-148] See figure 1
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	6 [137-148]
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	6 [137-148]
Methods: Assignment of interventions (for controlled trials)			
Allocation:			NA

Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	NA
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	NA
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	NA
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	NA
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	NA
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	6,7 [137-158]
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	6,7 [137-158]
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	11 [247-263]
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	11 [247-263]

	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	11 [247-263]
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	6 [137-148]
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	NA
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	6 [137-148]
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	NA
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	5 [94-98]
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	5 [94-98]
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	5 [101-102]
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	NA
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	6 [137-148]
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	18 [360]
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	6 [137-148]

Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	6 [145-148]
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	2 [45-47]
	31b	Authorship eligibility guidelines and any intended use of professional writers	18 [349-352]
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	NA
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	18 [349-352]
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA