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: NCT05746806 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 5.0 (24.01.2025)

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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5.0	25.01.2025	no	Adaption ADT	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 5.0 (24/01/2025) 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 INVESTIGATOR:

The local Investigator has approved the protocol version 5.0 (24/01/2025) 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. 5.0 date 24.01.2025
Trial registration:	NCT05746806
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)

	Treatment related 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: 36 Months
Study Schedule:	First-Participant-In: Q4 2022 Last-Participant-Out: Q1 2028
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Study Centre(s):	Multi-centre study with 5 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

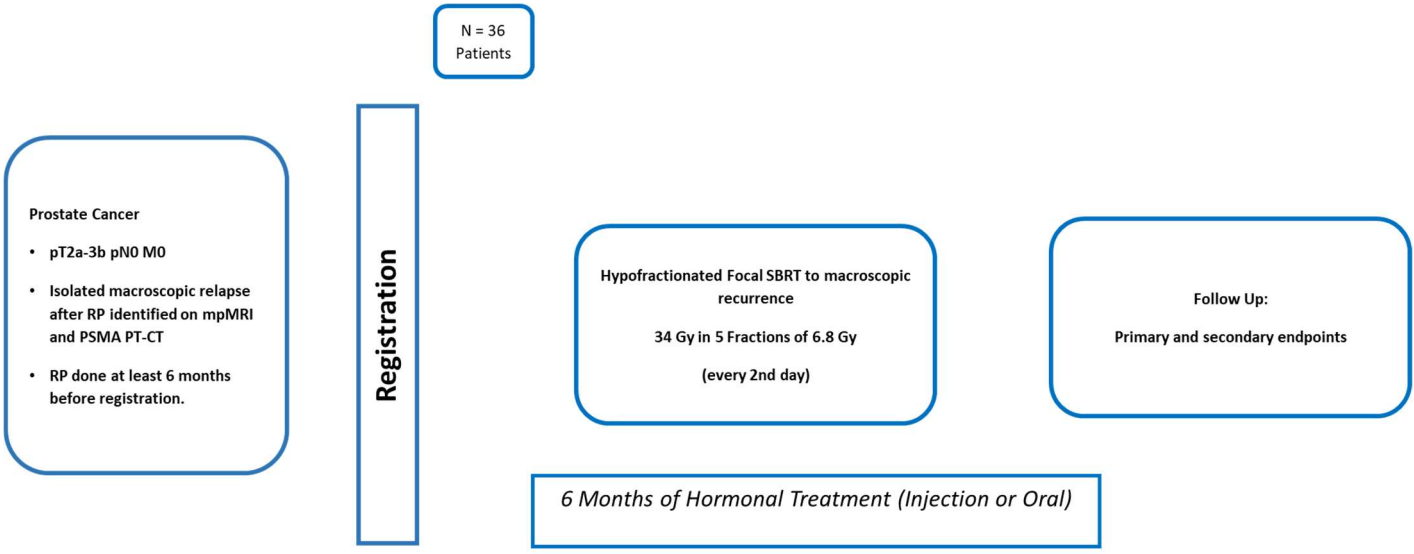
This is a single arm, prospective phase II multicenter study.

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	V41 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 42.5 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 according to institutional policy. Intramuscular, subcutaneous, or oral forms are all allowed."
- 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. The accesses to SecuTrial are created individually for each person. Login details for the online database will be sent to authorized persons. Each PI will confirm the accuracy and completeness of the data at the end of the study.

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 4 weeks prior registration					
Eligibity Check	x						
Signed informed consent	x						
Record prior history	x						
Visits							
Physical Examination		x	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 center 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.

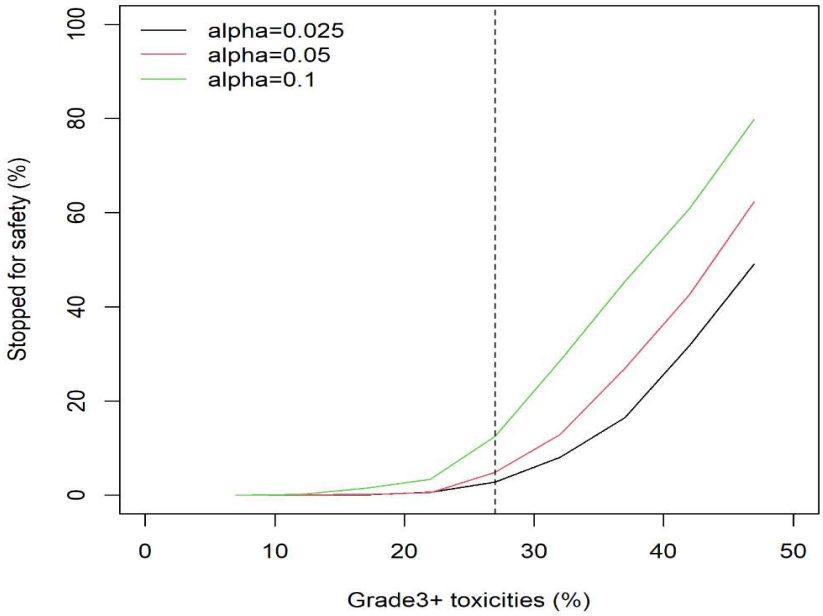
Patients may be withdrawn at any time from trial treatment at the discretion of the treating physician or the investigator due to a SAE, or based on any other relevant medical condition. The patient then will be transferred to the follow-up phase and continue to receive the follow-up assessments as scheduled.

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.

In this trial only treatment (ADT and radiotherapy) related (serious) adverse events need to be collected.

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 treatment related SAEs are documented and reported via SAE form and eCRF immediately and to be sent (within a maximum of 24 hours) to the Sponsor-Investigator of the study via Email to hypofocalsrt@insel.ch.

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.

11 REFERENCES

1. Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. *N Engl J Med*. 2016;375(15):1415-1424. doi:10.1056/NEJMoa1606220
2. Han M, Partin AW, Zahurak M, Piantadosi S, Epstein JI, Walsh PC. Biochemical (prostate specific antigen) recurrence probability following radical prostatectomy for clinically localized prostate cancer. *J Urol*. 2003;169(2):517-523. doi:10.1097/01.ju.0000045749.90353.c7

3. Gandaglia G, Briganti A, Clarke N, et al. Adjuvant and Salvage Radiotherapy after Radical Prostatectomy in Prostate Cancer Patients. *Eur Urol*. 2017;72(5):689-709. doi:10.1016/j.eururo.2017.01.039
4. Bolla M, Poppel H Van, Collette L, et al. Postoperative radiotherapy after radical prostatectomy: a randomised controlled trial (EORTC trial 22911). 2005;366:572-578.
5. Bolla M, van Poppel H, Tombal B, et al. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet (London, England)*. 2012;380(9858):2018-2027. doi:10.1016/S0140-6736(12)61253-7
6. Thompson IMJ, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathologically advanced prostate cancer: a randomized clinical trial. *JAMA*. 2006;296(19):2329-2335. doi:10.1001/jama.296.19.2329
7. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant Radiotherapy for Pathological T3N0M0 Prostate Cancer Significantly Reduces Risk of Metastases and Improves Survival: Long-Term Followup of a Randomized Clinical Trial. *J Urol*. 2009;181(3):956-962. doi:10.1016/j.juro.2008.11.032
8. Wiegel T, Bottke D, Steiner U, et al. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol Off J Am Soc Clin Oncol*. 2009;27(18):2924-2930. doi:10.1200/JCO.2008.18.9563
9. Kneebone A, Fraser-Browne C, Duchesne GM, et al. Adjuvant radiotherapy versus early salvage radiotherapy following radical prostatectomy (TROG 08.03/ANZUP RAVES): a randomised, controlled, phase 3, non-inferiority trial. *Lancet Oncol*. 2020;21(10):1331-1340. doi:10.1016/S1470-2045(20)30456-3
10. Parker CC, Clarke NW, Cook AD, et al. Timing of radiotherapy after radical prostatectomy (RADICALS-RT): a randomised, controlled phase 3 trial. *Lancet (London, England)*. 2020;396(10260):1413-1421. doi:10.1016/S0140-6736(20)31553-1
11. Sargos P, Chabaud S, Latorzeff I, et al. Adjuvant radiotherapy versus early salvage radiotherapy plus short-term androgen deprivation therapy in men with localised prostate cancer after radical prostatectomy (GETUG-AFU 17): a randomised, phase 3 trial. *Lancet Oncol*. 2020;21(10):1341-1352.

doi:10.1016/S1470-2045(20)30454-X

12. Vale CL, Fisher D, Kneebone A, et al. Adjuvant or early salvage radiotherapy for the treatment of localised and locally advanced prostate cancer: a prospectively planned systematic review and meta-analysis of aggregate data. *Lancet (London, England)*. 2020;396(10260):1422-1431. doi:10.1016/S0140-6736(20)31952-8
13. Boike TP, Lotan Y, Cho LC, et al. Phase I dose-escalation study of stereotactic body radiation therapy for low- and intermediate-risk prostate cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2011;29(15):2020-2026. doi:10.1200/JCO.2010.31.4377
14. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531-1543. doi:10.1016/S1470-2045(19)30569-8
15. Chen LN, Suy S, Uhm S, et al. Stereotactic body radiation therapy (SBRT) for clinically localized prostate cancer: the Georgetown University experience. *Radiat Oncol*. 2013;8:58. doi:10.1186/1748-717X-8-58
16. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer : A Systematic Review and Meta-Analysis of Over 6 , 000 Patients Treated On Prospective Studies. *Radiat Oncol Biol*. 2019;104(4):778-789. doi:10.1016/j.ijrobp.2019.03.051
17. King CR, Brooks JD, Gill H, Presti JCJ. Long-term outcomes from a prospective trial of stereotactic body radiotherapy for low-risk prostate cancer. *Int J Radiat Oncol Biol Phys*. 2012;82(2):877-882. doi:10.1016/j.ijrobp.2010.11.054
18. Kotecha R, Djemil T, Tendulkar RD, et al. Dose-Escalated Stereotactic Body Radiation Therapy for Patients With Intermediate- and High-Risk Prostate Cancer: Initial Dosimetry Analysis and Patient Outcomes. *Int J Radiat Oncol Biol Phys*. 2016;95(3):960-964. doi:10.1016/j.ijrobp.2016.02.009
19. Meier RM, Bloch DA, Cotrutz C, et al. Multicenter Trial of Stereotactic Body Radiation Therapy for Low- and Intermediate-Risk Prostate Cancer: Survival and Toxicity Endpoints. *Int J Radiat Oncol Biol Phys*. 2018;102(2):296-303. doi:10.1016/j.ijrobp.2018.05.040
20. Zilli T, Franzese C, Bottero M, et al. Single fraction urethra-sparing prostate cancer SBRT: Phase I results of the ONE SHOT trial. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2019;139:83-86. doi:10.1016/j.radonc.2019.07.018

21. Bauman G, Ferguson M, Lock M, et al. A Phase 1/2 Trial of Brief Androgen Suppression and Stereotactic Radiation Therapy (FASTR) for High-Risk Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2015;92(4):856-862. doi:10.1016/j.ijrobp.2015.02.046
22. Callan L, Bauman G, Chen J, et al. A Phase I/II Trial of Fairly Brief Androgen Suppression and Stereotactic Radiation Therapy for High-Risk Prostate Cancer (FASTR-2): Preliminary Results and Toxicity Analysis. *Adv Radiat Oncol*. 2019;4(4):668-673. doi:10.1016/j.adro.2019.07.007
23. Foerster R, Zwahlen DR, Buchali A, et al. Stereotactic Body Radiotherapy for High-Risk Prostate Cancer: A Systematic Review. *Cancers (Basel)*. 2021;13(4). doi:10.3390/cancers13040759
24. Murthy V, Gupta M, Mulye G, et al. Early Results of Extreme Hypofractionation Using Stereotactic Body Radiation Therapy for High-risk, Very High-risk and Node-positive Prostate Cancer. *Clin Oncol (R Coll Radiol)*. 2018;30(7):442-447. doi:10.1016/j.clon.2018.03.004
25. Widmark A, Gunnlaugsson A, Beckman L, et al. Ultra-hypofractionated versus conventionally fractionated radiotherapy for prostate cancer: 5-year outcomes of the HYPO-RT-PC randomised, non-inferiority, phase 3 trial. *Lancet (London, England)*. 2019;394(10196):385-395. doi:10.1016/S0140-6736(19)31131-6
26. Zilli T, Jorcano S, Bral S, et al. Once-a-week or every-other-day urethra-sparing prostate cancer stereotactic body radiotherapy, a randomized phase II trial: 18 months follow-up results. *Cancer Med*. 2020;9(9):3097-3106. doi:10.1002/cam4.2966
27. Brenner DJ, Martinez AA, Edmundson GK, Mitchell C, Thames HD, Armour EP. Direct evidence that prostate tumors show high sensitivity to fractionation (low alpha/beta ratio), similar to late-responding normal tissue. *Int J Radiat Oncol Biol Phys*. 2002;52(1):6-13. doi:10.1016/s0360-3016(01)02664-5
28. Miralbell R, Roberts SA, Zubizarreta E, Hendry JH. Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional datasets: α/β = 1.4 (0.9-2.2) Gy. *Int J Radiat Oncol Biol Phys*. 2012;82(1):e17-24. doi:10.1016/j.ijrobp.2010.10.075
29. Barra S, Belgioia L, Marcenaro M, et al. Moderate hypofractionated radiotherapy after prostatectomy for cancer patients: toxicity and clinical outcome. *Cancer Manag Res*. 2018;10:473-480. doi:10.2147/CMAR.S146131

30. Cozzarini C, Fiorino C, Deantoni C, et al. Higher-than-expected severe (Grade 3-4) late urinary toxicity after postprostatectomy hypofractionated radiotherapy: a single-institution analysis of 1176 patients. *Eur Urol*. 2014;66(6):1024-1030. doi:10.1016/j.eururo.2014.06.012
31. Cozzarini C, Fiorino C, Di Muzio N, et al. Hypofractionated adjuvant radiotherapy with helical tomotherapy after radical prostatectomy: planning data and toxicity results of a Phase I-II study. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2008;88(1):26-33. doi:10.1016/j.radonc.2008.03.021
32. Fersino S, Tebano U, Mazzola R, et al. Moderate Hypofractionated Postprostatectomy Volumetric Modulated Arc Therapy With Daily Image Guidance (VMAT-IGRT): A Mono-institutional Report on Feasibility and Acute Toxicity. *Clin Genitourin Cancer*. 2017;15(4):e667-e673. doi:10.1016/j.clgc.2017.01.025
33. Ippolito E, Cellini N, Digesù C, et al. Postoperative intensity-modulated radiotherapy with simultaneous integrated boost in prostate cancer: a dose-escalation trial. *Urol Oncol*. 2013;31(1):87-92. doi:10.1016/j.urolonc.2010.10.005
34. Katayama S, Striecker T, Kessel K, et al. Hypofractionated IMRT of the prostate bed after radical prostatectomy: acute toxicity in the PRIAMOS-1 trial. *Int J Radiat Oncol Biol Phys*. 2014;90(4):926-933. doi:10.1016/j.ijrobp.2014.07.015
35. Krause S, Sterzing F, Neuhof D, Edler L, Debus J, Herfarth K. Hypofractionated helical intensity-modulated radiotherapy of the prostate bed after prostatectomy with or without the pelvic lymph nodes - the PRIAMOS trial. *BMC Cancer*. 2012;12:504. doi:10.1186/1471-2407-12-504
36. Kruser TJ, Jarrard DF, Graf AK, et al. Early hypofractionated salvage radiotherapy for postprostatectomy biochemical recurrence. *Cancer*. 2011;117(12):2629-2636. doi:10.1002/cncr.25824
37. Lewis SL, Patel P, Song H, et al. Image Guided Hypofractionated Postprostatectomy Intensity Modulated Radiation Therapy for Prostate Cancer. *Int J Radiat Oncol Biol Phys*. 2016;94(3):605-611. doi:10.1016/j.ijrobp.2015.11.025
38. Massaccesi M, Cilla S, Deodato F, et al. Hypofractionated intensity-modulated radiotherapy with simultaneous integrated boost after radical prostatectomy: preliminary results of a phase II trial. *Anticancer Res*. 2013;33(6):2785-2789.
39. Arcangeli S, Gambardella P, Agolli L, et al. Stereotactic body radiation therapy

salvage reirradiation of radiorecurrent prostatic carcinoma relapsed in the prostatic bed. *Tumori*. 2015;101(2):e57-9. doi:10.5301/tj.5000251

40. Ballas LK, Luo C, Chung E, et al. Phase 1 Trial of SBRT to the Prostate Fossa After Prostatectomy. *Int J Radiat Oncol Biol Phys*. 2019;104(1):50-60. doi:10.1016/j.ijrobp.2018.12.047
41. Caroli P, Colangione SP, De Giorgi U, et al. (68)Ga-PSMA-11 PET/CT-Guided Stereotactic Body Radiation Therapy Retreatment in Prostate Cancer Patients with PSA Failure after Salvage Radiotherapy. *Biomedicines*. 2020;8(12). doi:10.3390/biomedicines8120536
42. Detti B, Bonomo P, Masi L, et al. CyberKnife stereotactic radiotherapy for isolated recurrence in the prostatic bed. *World J Urol*. 2016;34(3):311-317. doi:10.1007/s00345-015-1613-5
43. Francolini G, Jereczek-Fossa BA, Di Cataldo V, et al. Stereotactic radiotherapy for prostate bed recurrence after prostatectomy, a multicentric series. *BJU Int*. 2020;125(3):417-425. doi:10.1111/bju.14924
44. Jereczek-Fossa BA, Rojas DP, Zerini D, et al. Reirradiation for isolated local recurrence of prostate cancer: Mono-institutional series of 64 patients treated with salvage stereotactic body radiotherapy (SBRT). *Br J Radiol*. 2019;92(1094):20180494. doi:10.1259/bjr.20180494
45. Olivier J, Basson L, Puech P, et al. Stereotactic Re-irradiation for Local Recurrence in the Prostatic Bed After Prostatectomy: Preliminary Results. *Front Oncol*. 2019;9:71. doi:10.3389/fonc.2019.00071
46. Sampath S, Frankel P, Vecchio B Del, et al. Stereotactic Body Radiation Therapy to the Prostate Bed: Results of a Phase 1 Dose-Escalation Trial. *Int J Radiat Oncol Biol Phys*. 2020;106(3):537-545. doi:10.1016/j.ijrobp.2019.11.005
47. Scher N, Bauduceau O, Bollet M, et al. Stereotactic prostate focal reirradiation therapy for local recurrence: preliminary results of Hartmann Oncology Radiotherapy Group. *BJR open*. 2019;1(1):20180027. doi:10.1259/bjro.20180027
48. Zerini D, Jereczek-Fossa BA, Fodor C, et al. Salvage image-guided intensity modulated or stereotactic body reirradiation of local recurrence of prostate cancer. *Br J Radiol*. 2015;88(1052):20150197. doi:10.1259/bjr.20150197
49. Ferlay J, Soerjomataram I, Dikshit R, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J cancer*. 2015;136(5):E359-86. doi:10.1002/ijc.29210

50. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol Off J Am Soc Clin Oncol*. 2010;28(7):1117-1123. doi:10.1200/JCO.2009.26.0133
51. Han M, Partin AW, Pound CR, Epstein JI, Walsh PC. Long-term biochemical disease-free and cancer-specific survival following anatomic radical retropubic prostatectomy. The 15-year Johns Hopkins experience. *Urol Clin North Am*. 2001;28(3):555-565. doi:10.1016/s0094-0143(05)70163-4
52. Chun FK-H, Graefen M, Zacharias M, et al. Anatomic radical retropubic prostatectomy-long-term recurrence-free survival rates for localized prostate cancer. *World J Urol*. 2006;24(3):273-280. doi:10.1007/s00345-006-0058-2
53. Amling CL, Blute ML, Bergstralh EJ, Seay TM, Slezak J, Zincke H. Long-term hazard of progression after radical prostatectomy for clinically localized prostate cancer: continued risk of biochemical failure after 5 years. *J Urol*. 2000;164(1):101-105.
54. Bianco FJJ, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology*. 2005;66(5 Suppl):83-94. doi:10.1016/j.urology.2005.06.116
55. Swanson GP, Hussey MA, Tangen CM, et al. Predominant treatment failure in postprostatectomy patients is local: analysis of patterns of treatment failure in SWOG 8794. *J Clin Oncol Off J Am Soc Clin Oncol*. 2007;25(16):2225-2229. doi:10.1200/JCO.2006.09.6495
56. Pound CR, Partin AW, Eisenberger MA, Chan DW, Pearson JD, Walsh PC. Natural history of progression after PSA elevation following radical prostatectomy. *JAMA*. 1999;281(17):1591-1597. doi:10.1001/jama.281.17.1591
57. Thompson IM, Tangen CM, Paradelo J, et al. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol*. 2009;181(3):956-962. doi:10.1016/j.juro.2008.11.032
58. Mahal BA, Hoffman KE, Efstathiou JA, Nguyen PL. National trends in the recommendation of radiotherapy after prostatectomy for prostate cancer before and after the reporting of a survival benefit in March 2009. *Clin Genitourin Cancer*. 2015;13(3):e167-72. doi:10.1016/j.clgc.2014.12.005
59. Fossati N, Karnes RJ, Cozzarini C, et al. Assessing the Optimal Timing for Early Salvage Radiation Therapy in Patients with Prostate-specific Antigen Rise After

Radical Prostatectomy. *Eur Urol*. 2016;69(4):728-733. doi:10.1016/j.eururo.2015.10.009

60. Stephenson AJ, Scardino PT, Kattan MW, et al. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2007;25(15):2035-2041. doi:10.1200/JCO.2006.08.9607
61. Tendulkar RD, Agrawal S, Gao T, et al. Contemporary Update of a Multi-Institutional Predictive Nomogram for Salvage Radiotherapy After Radical Prostatectomy. *J Clin Oncol Off J Am Soc Clin Oncol*. 2016;34(30):3648-3654. doi:10.1200/JCO.2016.67.9647
62. Dal Pra A, Cury FL, Souhami L. Combining radiation therapy and androgen deprivation for localized prostate cancer-a critical review. *Curr Oncol*. 2010;17(5):28-38. doi:10.3747/co.v17i5.632
63. Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. *N Engl J Med*. 2017;376(5):417-428. doi:10.1056/NEJMoa1607529
64. Carrie C, Magné N, Burban-Provost P, et al. Short-term androgen deprivation therapy combined with radiotherapy as salvage treatment after radical prostatectomy for prostate cancer (GETUG-AFU 16): a 112-month follow-up of a phase 3, randomised trial. *Lancet Oncol*. 2019;20(12):1740-1749. doi:10.1016/S1470-2045(19)30486-3
65. Panebianco V, Villeirs G, Weinreb JC, et al. Prostate Magnetic Resonance Imaging for Local Recurrence Reporting (PI-RR): International Consensus - based Guidelines on Multiparametric Magnetic Resonance Imaging for Prostate Cancer Recurrence after Radiation Therapy and Radical Prostatectomy. *Eur Urol Oncol*. Published online February 2021. doi:10.1016/j.euo.2021.01.003
66. De Visschere PJL, Standaert C, Fütterer JJ, et al. A Systematic Review on the Role of Imaging in Early Recurrent Prostate Cancer. *Eur Urol Oncol*. 2019;2(1):47-76. doi:10.1016/j.euo.2018.09.010
67. Vargas HA, Wassberg C, Akin O, Hricak H. MR imaging of treated prostate cancer. *Radiology*. 2012;262(1):26-42. doi:10.1148/radiol.11101996
68. Barchetti F, Panebianco V. Multiparametric MRI for recurrent prostate cancer post radical prostatectomy and postradiation therapy. *Biomed Res Int*. 2014;2014:316272. doi:10.1155/2014/316272

69. Rouvière O, Vitry T, Lyonnet D. Imaging of prostate cancer local recurrences: why and how? *Eur Radiol*. 2010;20(5):1254-1266. doi:10.1007/s00330-009-1647-4
70. Casciani E, Polettini E, Carmenini E, et al. Endorectal and dynamic contrast-enhanced MRI for detection of local recurrence after radical prostatectomy. *AJR Am J Roentgenol*. 2008;190(5):1187-1192. doi:10.2214/AJR.07.3032
71. Panebianco V, Barchetti F, Sciarra A, et al. Prostate cancer recurrence after radical prostatectomy: the role of 3-T diffusion imaging in multi-parametric magnetic resonance imaging. *Eur Radiol*. 2013;23(6):1745-1752. doi:10.1007/s00330-013-2768-3
72. Kitajima K, Hartman RP, Froemming AT, Hagen CE, Takahashi N, Kawashima A. Detection of Local Recurrence of Prostate Cancer After Radical Prostatectomy Using Endorectal Coil MRI at 3 T: Addition of DWI and Dynamic Contrast Enhancement to T2-Weighted MRI. *AJR Am J Roentgenol*. 2015;205(4):807-816. doi:10.2214/AJR.14.14275
73. Litwin MS, Tan H-J. The Diagnosis and Treatment of Prostate Cancer: A Review. *JAMA*. 2017;317(24):2532-2542. doi:10.1001/jama.2017.7248
74. Wiegel T, Lohm G, Bottke D, et al. Achieving an undetectable PSA after radiotherapy for biochemical progression after radical prostatectomy is an independent predictor of biochemical outcome--results of a retrospective study. *Int J Radiat Oncol Biol Phys*. 2009;73(4):1009-1016. doi:10.1016/j.ijrobp.2008.06.1922
75. Bottke D, Bartkowiak D, Siegmann A, et al. Effect of early salvage radiotherapy at PSA < 0.5 ng/ml and impact of post-SRT PSA nadir in post-prostatectomy recurrent prostate cancer. *Prostate Cancer Prostatic Dis*. 2019;22(2):344-349. doi:10.1038/s41391-018-0112-3
76. Ghosh A, Heston WDW. Tumor target prostate specific membrane antigen (PSMA) and its regulation in prostate cancer. *J Cell Biochem*. 2004;91(3):528-539. doi:10.1002/jcb.10661
77. Eiber M, Maurer T, Souvatzoglou M, et al. Evaluation of Hybrid ^{68}Ga-PSMA Ligand PET/CT in 248 Patients with Biochemical Recurrence After Radical Prostatectomy. *J Nucl Med*. 2015;56(5):668-674. doi:10.2967/jnumed.115.154153
78. Afshar-Oromieh A, Holland-Letz T, Giesel FL, et al. Diagnostic performance of (68)Ga-PSMA-11 (HBED-CC) PET/CT in patients with recurrent prostate cancer: evaluation in 1007 patients. *Eur J Nucl Med Mol Imaging*. 2017;44(8):1258-1268.

doi:10.1007/s00259-017-3711-7

79. Miksch J, Bottke D, Krohn T, et al. Interobserver variability, detection rate, and lesion patterns of (68)Ga-PSMA-11-PET/CT in early-stage biochemical recurrence of prostate cancer after radical prostatectomy. *Eur J Nucl Med Mol Imaging*. 2020;47(10):2339-2347. doi:10.1007/s00259-020-04718-w
80. Bluemel C, Krebs M, Polat B, et al. 68Ga-PSMA-PET/CT in Patients With Biochemical Prostate Cancer Recurrence and Negative 18F-Choline-PET/CT. *Clin Nucl Med*. 2016;41(7):515-521. doi:10.1097/RLU.0000000000001197
81. Cirillo S, Petracchini M, Scotti L, et al. Endorectal magnetic resonance imaging at 1.5 Tesla to assess local recurrence following radical prostatectomy using T2-weighted and contrast-enhanced imaging. *Eur Radiol*. 2009;19(3):761-769. doi:10.1007/s00330-008-1174-8
82. Fendler WP, Eiber M, Beheshti M, et al. (68)Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging: version 1.0. *Eur J Nucl Med Mol Imaging*. 2017;44(6):1014-1024. doi:10.1007/s00259-017-3670-z
83. Fowler JF. The radiobiology of prostate cancer including new aspects of fractionated radiotherapy. *Acta Oncol*. 2005;44(3):265-276. doi:10.1080/02841860410002824
84. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated Radiation Therapy for Localized Prostate Cancer: An ASTRO, ASCO, and AUA Evidence-Based Guideline. *J Urol*. Published online October 2018. doi:10.1016/j.juro.2018.10.001
85. Hickey BE, James ML, Daly T, Soh F-Y, Jeffery M. Hypofractionation for clinically localized prostate cancer. *Cochrane database Syst Rev*. 2019;9(9):CD011462. doi:10.1002/14651858.CD011462.pub2
86. Jackson WC, Silva J, Hartman HE, et al. Stereotactic Body Radiation Therapy for Localized Prostate Cancer: A Systematic Review and Meta-Analysis of Over 6,000 Patients Treated On Prospective Studies. *Int J Radiat Oncol Biol Phys*. 2019;104(4):778-789. doi:10.1016/j.ijrobp.2019.03.051
87. Brand DH, Tree AC, Ostler P, et al. Intensity-modulated fractionated radiotherapy versus stereotactic body radiotherapy for prostate cancer (PACE-B): acute toxicity findings from an international, randomised, open-label, phase 3, non-inferiority trial. *Lancet Oncol*. 2019;20(11):1531-1543. doi:10.1016/S1470-2045(19)30569-8
88. Wolf F, Sedlmayer F, Aebersold D, et al. Ultrahypofractionation of localized

prostate cancer : Statement from the DEGRO working group prostate cancer. *Strahlenther Onkol*. 2021;197(2):89-96. doi:10.1007/s00066-020-01723-8

89. Lehrer EJ, Kishan AU, Yu JB, et al. Ultrahypofractionated versus hypofractionated and conventionally fractionated radiation therapy for localized prostate cancer: A systematic review and meta-analysis of phase III randomized trials. *Radiother Oncol J Eur Soc Ther Radiol Oncol*. 2020;148:235-242. doi:10.1016/j.radonc.2020.04.037
90. Trial D, Sampath S, Frankel P, et al. Stereotactic Body Radiation Therapy to the Prostate Bed : Results of a Phase 1. *Radiat Oncol Biol*. 2020;106(3):537-545. doi:10.1016/j.ijrobp.2019.11.005
91. Francolini G, Alicja B, Fossa J, et al. Stereotactic or conventional radiotherapy for macroscopic prostate bed recurrence : a propensity score analysis. *Radiol Med*. 2022;(0123456789). doi:10.1007/s11547-022-01465-w

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).